THE ALKALOIDS
CHEMISTRY AND PHYSIOLOGY

Volume II

R. H. F. Manske &
H. L. Holmes

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Chemistry and Physiology

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Chemistry and Physiology

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PREFACE

It is the fond hope of the editors and contributors of this volume that the excellent reception accorded Volume I will be extended to Volume II. We are apprehensive of the chief criticism of Volume I, namely that some of the chapters were already out of date at the time of printing. Progress in certain of these fields, particularly in those of strychnine and morphine, has been so rapid, and even spectacular, that changes in page proof would not adequately have circumvented this deficiency. Accordingly, supplementary chapters have been added to this volume to bring the information in these fields and the others presented herein up to date.

We have been able to secure the cooperation of a number of competent pharmacologists to contribute chapters on a variety of physiological and pharmacological responses and these are scheduled to appear in Volume V. The intervening Volumes, III and IV, will deal with alkaloids containing the quinoline, the isoquinoline, the glyoxaline, the quinuclidine, and the steroid nuclei, as well as several other groups not so specifically characterized.

We do not agree with the criticism that the order of the chapters is not a preferred one. Plants do not elaborate alkaloids, nor do chemists determine their structure in accordance with a scheme which has its genesis in the five membered heterocycles and its apodosis in the complex polynuclear systems. The sequence of the chapters in the present and the proposed volumes is therefore often dependent upon their accessibility although whenever possible, closely related fields will be placed in sequence. It is our aim to provide a readable and comprehensive work which will include all matters of importance in alkaloid chemistry.

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CONTENTS

Acridine Alkaloids

By J. R. Price, *Division of Industrial Chemistry, C.S.I.R.O., Melbourne, Australia*

The Indole Alkaloids

By Léo Marion, *National Research Council, Ottawa, Canada*

The Erythrina Alkaloids

By Léo Marion, *National Research Council, Ottawa, Canada*

The Strychnos Alkaloids. Part II

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CHAPTER VIII

PART I

The Morphine Alkaloids. I

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I. Introduction

The interest in the opium alkaloids dates back to the seventeenth century, when attempts were made to isolate from opium the principle to which it owes its activity. During the course of these experiments many extracts were obtained and employed in medicine under the name, *Magisterium opii.*

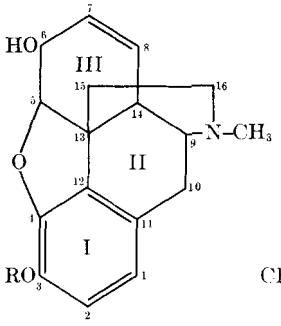
The isolation of a constitutent of opium in crystalline form was first attained, in 1803, by Derosne (47), an apothecary practicing in Paris. He diluted his sirupy extract of opium with water and precipitated the "salt of opium" with potassium carbonate. Séguin, in 1804, read a paper (48) to the Institute of France "Sur l'opium," in which he described the isolation of morphine, and the following year Sertürner (304, 305, 306) isolated both morphine and meconic acid from opium. In subsequent work (49, 52, 53, 54) he recognized the ability of morphine to neutralize acids. This "vegetable alkali" was the first member of a large group of naturally occurring substances, which later became known as the alkaloids.

Since Sertürner's characterization of morphine as a vegetable alkali, codeine, thebaine, and neopine have been isolated from the same source, while isothebaine, an aporphine base, has been found to occur in *Papaver orientale* during the flowering season. Since Derosne's time, the structures of morphine (I, R = H), codeine (I, R = CH_3), neopine (II), and thebaine (III) have been established except for the location of the ethanamine

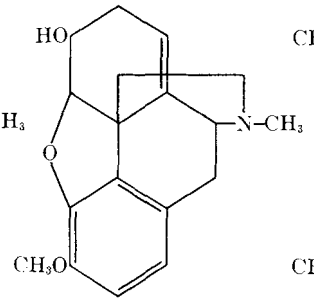
$$\left(-CH_2-CH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{N}}-CH_3\right)$$

chain, a number of degradations to, and the synthesis

of phenanthrene and various hydroxylated and alkoxylated derivatives have been effected. However, attempts to degrade these alkaloids to hydrophenanthrenes, which still retain at least part of the ethanamine chain, and to establish their structures by synthesis have failed. Until such a



R = H, CH_3, C_2H_5
I



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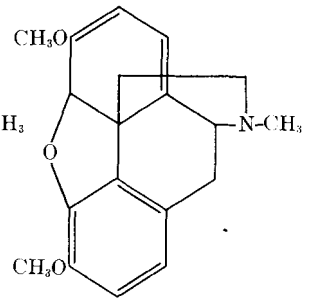


III

time as the constitution of morphine is finally settled it is obviously impractical to attempt the complete synthesis of these alkaloids or to embark on a study of the stereochemical problem. Hence it would appear that the most direct route to a knowledge of the chemistry of these interesting bases would be to examine the analytical evidence which has led to the structure accepted today, followed by a study of their reactions and rearrangement products. This will be followed in turn by a review of the attempts to synthesize various hydrophenanthrenes which might prove to be degradation products of morphine and the related bases. Finally, the physical constants of the various products of transformation and degradation, not listed elsewhere (331), have been tabulated, followed by a bibliography of the more readily available papers on the subject.

II. Elucidation of the Structure of Morphine, Codeine, and Thebaine

1. The Phenanthrene Nucleus of Morphine

Many of the early workers sensed a close relationship between morphine, codeine, and thebaine; however, little progress was made towards the elucidation of the structure of these alkaloids until about the year 1880. The first elementary analysis of morphine was reported in 1831 by Liebig (50) who considered that the base was represented by the formula $C_{34}H_{36}O_6N_2$. This was subject to much revision until 1847 when Laurent (51) arrived at the formula $C_{34}H_{38}O_6N_2$ which subsequently was shown, by molecular weight determinations (329, 330) to be the dimeric form of that accepted today, $C_{17}H_{19}O_3N$. The early work clearly demonstrated

that of the three oxygen atoms of morphine, two are in hydroxyl groups (diacetyl (276) and dibenzoyl (66, 279) derivatives), and one is phenolic (ferric chloride test, precipitation of the alkaloid from its alkaline solution by carbon dioxide and the formation of monoalkyl ethers). This phenolic hydroxyl has been alkylated by a number of methods (the monomethyl ether (I, R = CH_3) of morphine is codeine (13, 227, 233)), and several of the less familiar reagents which have proved useful for this purpose are the arylsulfonic esters (188) and trimethylphenylammonium hydroxide (227).

Methylation of morphine (227). The methohydroxide of dimethylaniline is prepared by adding 55.0 g. of the methyl benzenesulfonate of dimethylaniline to an ethanolic solution of sodium ethylate (4.5 g. sodium in 45 cc. ethanol) and removal of the sodium benzenesulfonate by filtration. The methylation of morphine is effected by adding 42.0 g. of the base to the alcoholic solution of the methohydroxide and heating the reaction mixture in an oil bath until all the ethanol is expelled and the temperature of the reaction mixture has risen to 110°, at which temperature it is maintained for 1 hour. The mixture is acidified with 15% acetic acid and the dimethylaniline removed by steam distillation.

Codeine is then liberated from its acetate by the addition of a large excess of 20% sodium hydroxide solution and the oily base (23.5 g.), which first separates, soon crystallizes. An additional 6.0 g. is recovered from the aqueous alkaline solution by extraction with benzene. Based on the amount of morphine used (9.0 g. of morphine may be recovered from the alkaline solution) the conversion to codeine is 85%.

Replacement of the second hydroxyl group by halogens and the oxidation of codeine ($C_{18}H_{21}O_3N$) to a ketone, codeinone ($C_{18}H_{19}O_3N$), amongst other reactions has clearly diagnosed the alcoholic nature of this group. The third oxygen atom is very unreactive and appears to be present in an ether type of linkage (76).

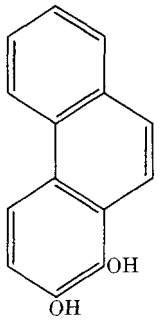
Several reactions, although quite drastic in nature, indicate that in all probability the morphine alkaloids contain a phenanthrene skeleton while the relatively high percentage of hydrogen in these bases has led to the presumption that the phenanthrene system is partially hydrogenated. The recovery of 3–4% of phenanthrene (characterized through its picrate and by its conversion to phenanthrenequinone which in turn was oxidized to diphenic acid) (12) from the zinc dust distillation of morphine can hardly be construed as direct evidence for the presence of the phenanthrene system in morphine owing to the poor yield and because of the possible secondary origin of this hydrocarbon under these pyrogenic conditions. Even the improvement in the yield of phenanthrene to 19–20% (86) through the conversion of morphine to des-*N*-methylcodeine (13, 233) prior to pyrolysis with zinc dust does not remove the second of these objections. Another phenanthrene derivative, $C_{14}H_7O \cdot OCH_3$, was obtained by heating acetylmethylmorphimethine (acetyl-des-*N*-methylcodeine) to 120° (13). Modification and extension of this reaction afforded a phenanthrene deriva-

tive (72) in moderate yield by other than pyrolytic methods. Furthermore, when morphine methiodide was boiled with acetic anhydride, a nitrogen-free, water- and alkali-insoluble phenanthrene derivative ($C_{18}H_{14}O_4$) was obtained. Hydrolysis of this nitrogen-free product with alcoholic ammonia at an elevated temperature removed two acetyl residues with the formation of morphol ($C_{14}H_{10}O_2$), a new dihydroxyphenanthrene (methylmorphol, the monomethyl ether of morphol, results in a similar fashion from the acetolysis of codeine methiodide (76) and subsequent hydrolysis (72) of the acetyl group of the resulting acetylmethylmorphol).

Morphol and methylmorphol are both soluble in alkali and give a positive color reaction with ferric chloride solution, thus indicating the phenolic nature of the two hydroxyl groups of morphol. Methylation of both morphol ($(CH_3)_2SO_4$) (285) and methylmorphol ($CH_3I + C_2H_5ONa$) (97a) yields the dimethyl ether, dimethylmorphol ($C_{16}H_{14}O_2$). Dimethylmorphol has been oxidized to a quinone (97a) but morphol itself proved to be too sensitive to air and other oxidants to undergo a similar oxidation. This difficulty was circumvented by the oxidation (H_2CrO_4) (72, 92) of diacetylmorphol and the subsequent removal (alcoholic ammonia) (72) of the two acetyl groups from the resulting diacetylmorpholquinone. The formation by diacetylmorpholquinone of a crystalline azine (with *o*-toluylenediamine) (92) would suggest that this quinone is an *ortho*-quinone of the phenanthrenequinone type. Since morpholquinone ($C_{14}H_8O_4$) contains two more oxygens than morphol ($C_{14}H_{10}O_2$) it may safely be inferred that neither of the two hydroxyls of morphol occupy positions C_9 or C_{10}. Furthermore, the oxidation ($KMnO_4$) of morpholquinone to phthalic acid (92, 93) locates the two hydroxyls in one of the terminal rings of morphol. Then the observation that morpholquinone, like alizarin, has pronounced properties as a dye for mordanted fabrics prompted early workers to conclude that the two hydroxyls of morphol occupy vicinal positions in the phenanthrene nucleus (92) (the isolation of protocatechuic acid (322) from the alkali fusion of morphine supports this conjecture). From these data morphol was considered to be IV.

The study of methylmorphenol, a second nitrogen-free cleavage product from codeine, went hand in hand with that of morphol. Codeine (I, R = CH_3) and codethylene (I, R = C_2H_5), when exhaustively ethylated and then heated with alcoholic potash, yielded methylmorphenol ($C_{15}H_{10}O_2$) and ethylmorphenol ($C_{16}H_{12}O_2$), respectively (68, 69, 85). That these two products were ethers of a phenanthrene derivative was established by removal of the alkyl groups to give the phenolic parent substance morphenol ($C_{14}H_8O_2$) (69, 88, 95) and the zinc dust distillation of these to phenanthrene (68, 69, 81, 88). Although one of the oxygen atoms of morphenol is present as an ether, yet a close relationship was sensed between morphenol and

morphol (85, 86, 87, 88, 92, 95). This conjecture proved to be well founded since morphenol was later reduced to morphol by sodium and ethanol (88), from which it would appear that the degradation process has been carried one step further in morphol than in morphenol. This relation of morphenol



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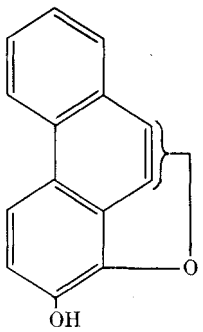
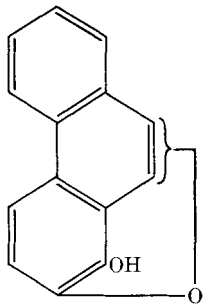
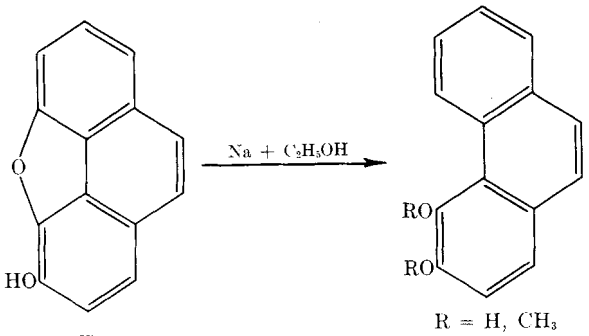


V



VI

to morphol (IV) finds expression only when morphenol is represented by V or VI. Oxidative experiments, however, demonstrated that such formulas were untenable for both morphol and morphenol since acetylmorphenol yields a quinone in which the oxide ring is still intact. This leaves only a phenanthrylene oxide of structure VII as the plausible structure for morphenol. Furthermore, on these grounds, the reduction of morphenol to morphol necessitates a relocation of the hydroxyl groups of the latter at C_3 and C_4 as in VIII (R = H). (While the marked stability of diphenylene oxide prejudiced the early workers against a structure such as VII for morphenol (9), yet the failure to isolate phthalic acid from its oxidation



VII

R = H, CH_3

VIII

(95) ($KMnO_4$ or H_2CrO_4) appears to be significant in the light of this formula.) While this oxide bridge proved to be quite resistant to many hydrolytic agents it did, in the case of morphenol methyl ether, yield to the action of fused potassium hydroxide (131). The resulting trihydroxy-

phenanthrene, when methylated (131), proved to be identical with synthetic 3,4,5-trimethoxyphenanthrene (Pschorr synthesis-2-nitro-3,4-dimethoxybenzaldehyde + sodium 3-methoxyphenylacetate) (28). This combined with the characterization of dimethylmorphol as 3,4-dimethoxyphenanthrene (97) served to locate the hydroxyls of morphol at C_3 and C_4 (VIII) and the oxide bridge of morphenol at C_4–C_5 (VII).

The hydrophenanthrene nucleus of morphine is not completely saturated but must contain one isolated ethylenic double bond since codeine decolorizes bromine slowly, is quantitatively reduced to a dihydro derivative by the absorption of one mole of hydrogen ($PdCl_2$) (173, 320) and is oxidized by potassium permanganate (291) to a dihydroxydihydrocodeine.

2. Oxazine and Isoquinoline Formulas for Morphine

The nature of the nitrogen complex of morphine and its mode of attachment to the hydrophenanthrene nucleus has proved to be the major problem in this field. The basic nitrogen of morphine and codeine is tertiary and a component of a ring since both bases react with molar proportions of methyl iodide (13, 78, 233) to give quaternary salts, while codeine methohydroxide (Ag_2O, (233) NaOH or KOH (13) on the methiodide) when heated does not lose the nitrogen atom but is converted to a new tertiary amine, des-*N*-methylcodeine (morphine methiodide does not undergo a similar Hofmann reaction when heated with alkali which may probably be attributed to phenolbetaine formation (13, 83)). This des-*N*-methylcodeine or α-methylmorphimethine contains one more center of unsaturation (76) than codeine.

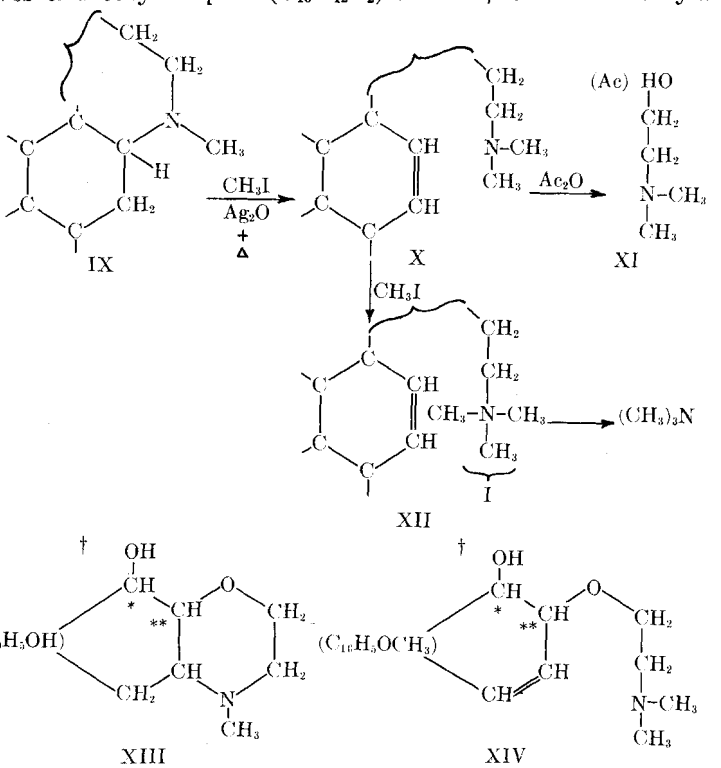
α-Methylmorphimethine (256). Three hundred and three grams of morphine is added to a methanolic solution of sodium methylate (24.0 g. sodium in 1 l. methanol) to which 250 g. dimethyl sulfate is added dropwise. When about one-quarter of the dimethyl sulfate has been added the heat of reaction becomes apparent and the remainder is added at such a rate that the reaction mixture boils gently. When the reaction subsides the mixture is heated on a steam bath for 3–4 hours. Removal of the methanol (vacuum) leaves a residue of codeine methomethyl sulfate. The salt may be degraded to α-methylmorphimethine by boiling for 10 minutes with aqueous sodium hydroxide solution (125 g. sodium hydroxide in 1500 cc. water).

The α-methylmorphimethine, which separates as a brown oil, is recovered by decantation and is washed with water. Recrystallization from toluene yields 210–225 g. (67–70%) of the base.

Elimination of the nitrogen atom was first achieved by exhaustively methylating des-*N*-ethylcodeine and degrading it by the method of A. W. Hofmann. The basic cleavage product was characterized as its chloroplatinate and regarded, at that time, as methylethylpropylamine (68, 69). The characterization of this base as methylethylpropylamine must have been a question of mistaken identity for the subsequent degradation of

des-*N*-methylcodeine methiodide (XII) has been demonstrated (75) to yield trimethylamine (characterized as its aurichloride and chloroplatinate). Such a series of reactions can only be explained if the nitrogen complex of codeine is a component of a ring as in part formula IX and bears a methyl group (75) (demethylation of codeine to norcodeine, which in contrast to the former yields a nitrosamine (179), supports the previous conclusion).

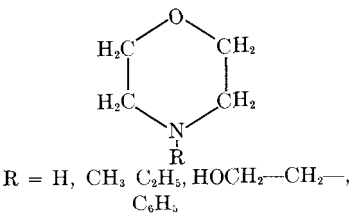
The most fruitful experiment, yet equally as misleading, in exposing the nature of the nitrogen chain of morphine was a modification of the earlier acetolysis experiments on the methiodide of morphine and codeine. It was found that acetic anhydride cleaved the nitrogen chain of des-*N*-methylcodeine (*α*-methylmorphimethine) $C_{19}H_{23}O_3N$, to give the acetyl derivatives of methylmorphol ($C_{15}H_{12}O_2$) and of *β*-ethanoldimethylamine



† Knorr was in doubt as to the location of the alcoholic hydroxyl offering ** as an alternative position to *.

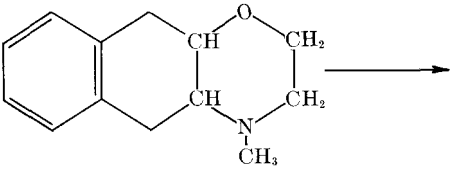
($C_4H_{11}ON$) (XI) (67, 72, 75), the latter being characterized as its aurichloride and chloroplatinate salts. Under the above conditions 50% of the *α*-methylmorphimethine is isomerized to a *β*-isomer (78), while some dimethylamine is also formed in the process (75). It is to be seen that

(a) these cleavage products account for all of the carbon atoms of α-methylmorphimethine and (b) only two of the three morphine-oxygen atoms appear in methylmorphol; a third appearing in β-ethanoldimethylamine. Hence the early workers (76) inferred that the carbon skeleton and the ethanamine chain of α-methylmorphimethine were mutually linked through the inert oxygen atom. From a consideration of the evidence so far discussed Knorr (76) proposed the first of his formulas (1889) for morphine (XIII) and methylmorphimethine (XIV). The incorporation of a hydrogenated oxazine ring in his formula for morphine led Knorr to develop a good synthesis for the morpholines (XV) (17, 77) with the view of studying the products of their degradation for comparison with those obtained from morphine under similar conditions. His greatest contribution to the support of his formula for morphine, and at the same time to its

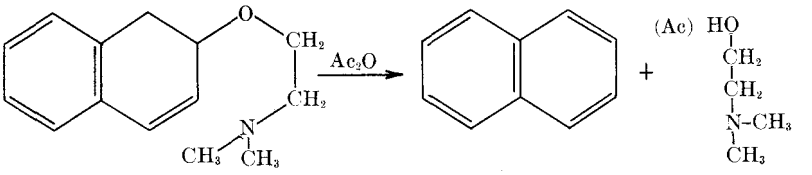


R = H, CH_3, C_2H_5, $HOCH_2—CH_2—$, C_6H_5

XV



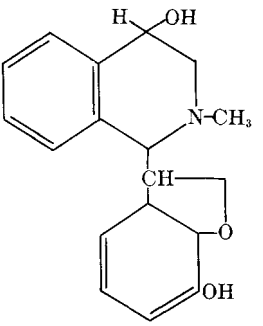
XVI



XVII

ultimate downfall, was the synthesis and degradation of naphthalanemorpholine (XVI) (91). Under conditions of acetolysis similar to those used on α-methylmorphimethine, des-*N*-methylnaphthalanemorpholine (XVII) yielded naphthalene and the acetyl derivative of β-ethanoldimethylamine. This would be striking evidence in favor of such an oxazine formula if it had not been for the marked difference in the ease of formation of this basic cleavage product from α-methylmorphimethine and the naphthalanemorpholine analog. Knorr regarded this difference as due to the great tendency of such hydroaromatic systems as the methine base (XVII) to attain a completely aromatic structure. Such a condition on the other hand was not to be found in α-methylmorphimethine where more vigorous conditions were necessary for the extrusion of the ethanamine chain.

At about the same time that Knorr published his formula for morphine, Goldschmiedt completely elucidated the structure of papaverine so that at this time it was the natural tendency to interpret all difficult structural problems of alkaloid chemistry on an isoquinoline system. Vis (317) pointed out that there was no unequivocal evidence to prove that morphine contained a phenanthrene nucleus which could not equally well be interpreted on his benzylisoquinoline structure (XVIII) as the result of a rearrangement. The one piece of evidence which tended to support such a structure

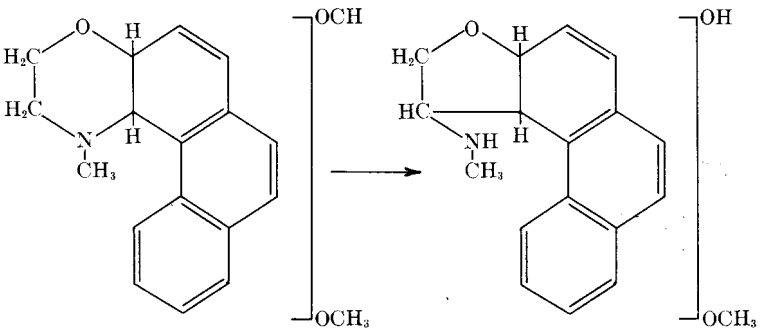


XVIII

for morphine, namely, the formation of triacetyl (235) and tribenzoyl (66) derivatives (cleavage of the oxide bridge), was later discredited (164). Furthermore, since α- and β-methylmorphimethine are not antipodes (78), it was concluded that this necessitated the existence, in these bases, of two asymmetric centers. This could only be interpreted on the Vis formula as a cleavage of the oxide bridge and subsequent closing of this linkage in the alternate steric position, which appears highly improbable. If Knorr's assumption of a morpholine ring were correct, then hydrogen chloride should cleave the ether linkage of α-methylmorphimethine with the formation of a phenanthrene derivative. His isolations of morphol in good yield (a demethylation has occurred (78, 115)) as well as secondary products resulting from the action of alkali upon β-chloroethyldimethylamine (117) critically disposed of Vis's benzylisoquinoline formula.

Freund (79, 80, 84) attacked the problem by a study of the closely related base, thebaine ($C_{19}H_{21}O_3N$), which was also considered to contain a morpholine ring system. Many of the reactions of thebaine mirror those of morphine and codeine but proceed with much greater facility and it also appears to be more subject to rearrangement by acid than the latter bases. In contrast to codeine, thebaine (β-ethanolmethylamine being the other cleavage product (80)) as well as its methiodide (β-ethanoldimethylamine being the other cleavage product (84)) is converted by boiling acetic

anhydride to the *O*-acetyl derivative of thebaol ($CH_3O(C_{14}H_8O)OCH_3$) (it is to be noted that thebaol, in contrast to methylmorphol, retains all three oxygens of thebaine and that two of them are present in methoxyl groups). Acetylthebaol may be considered as the thebaine analog of acetylmethylmorphol and like the latter may be oxidized (CrO_3) to a quinone, acetylthebaolquinone ($CH_3O(C_{16}H_8O_4)OCH_3$) (84), which gives a crystalline azine with *o*-toluylenediamine. Freund centered his attention upon the acid rearrangement products, morphothebaine and thebenine. Morphothebaine ($C_{18}H_{19}O_3N$) was first considered to be an intermediate in the formation of thebenine ($C_{18}H_{19}O_3N$). This concept, however, was later abandoned when morphothebaine could not be converted to thebenine under the conditions of the above rearrangement and when it was demonstrated that thebenine was a secondary amine (two moles of ethyl iodide are required for ethiodide formation, which on degradation afforded methyldiethylamine (84)). It must be accepted that these two bases result by different mechanisms. Thebenine contains two phenolic hydroxyls which, when protected by acetyl groups, can be oxidized to a quinone. In 1897 Freund proposed his first formula for thebaine but did not attempt to locate the methoxyl groups, although by oxidation ($KMnO_4$) of thebaolquinone (saponification of acetylthebaolquinone with sodium ethylate (84)) a product considered to be 3(?)-methoxyphthalic acid (84) was isolated. Hence one methoxyl must be in ring I and the other in ring III. The conversion of the tertiary base, thebaine, to the secondary amine, thebenine, which involved a demethylation as well, was represented by XIX and XX. Formula XX adequately accommodated the conversion of thebenine to trimethylamine and thebenol (XXI) by exhaustive methylation (two moles

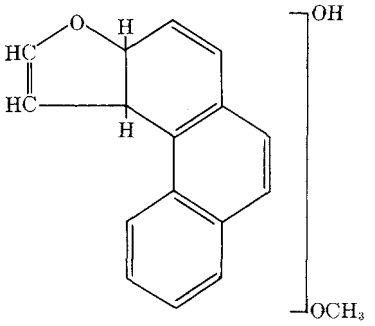


XIX XX

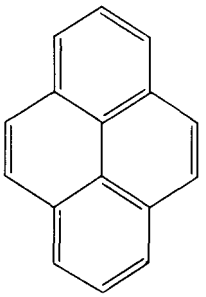
of CH_3I) and degradation of the methiodide. This formula also accommodated the erroneous statement (14, 84) that diacetylthebeninequinone was a naphthoquinone and not a phenanthrenequinone. Moreover the conversion of thebenol to pyrene (XXII) (zinc dust (84, 100) or hydriodic

acid and phosphorus (84)) was readily understandable on these formulas.

In 1899 Knorr (90, 91) revised his earlier formula for morphine but clung to his original concept of an oxazine ring system in this base. Follow-

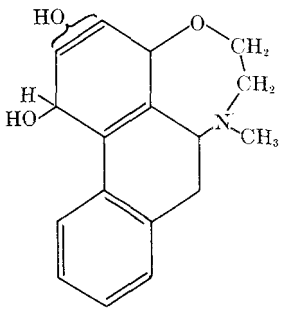


XXI

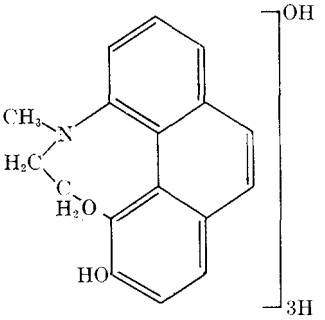


XXII

ing the trend of opinion of the time he modelled his oxazine formula XXIII in close analogy to that of papaverine, a formula having little in its favor. It could not be made to represent the conversion of thebaine to pyrene without an attendant shift of the ethanamine chain. This structure was completely disproved in the next four years.



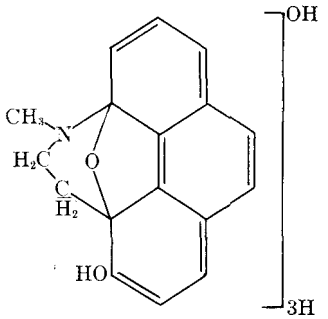
XXIII



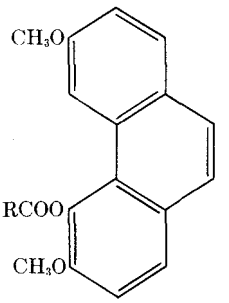
XXIV

Von Gerichten, basing his speculations largely upon observations made during a study of the morphenol degradation of the morphine alkaloids, made two tentative proposals, XXIV and XXV in 1900. In neither formula was any conjecture made as to the location of the alcoholic hydroxyl group or the saturated portion of the nucleus. While the first was but a slight modification of the Knorr formula (91, 95, note 1), the second was an entirely new innovation in the oxazine formulas for morphine. In formula XXV he expressed his belief that the phenanthrylene oxide of morphenol was of primary origin and an inherent part of the structure of morphine. It was so ingeniously fabricated that it also included a morpho-

line ring although of the mesoxazine type rather than a paroxazine as conceived by Knorr. Whereas the first formula failed to account for the formation of morphenol, the second was inadequate to explain the morphol



XXV



R = CH_3 C_6H_5

XXVI

cleavage without the assumption of a rupture of the oxide bridge, a supposition that appeared highly improbable in the light of Gräbe's work on diphenylene oxide. Obviously this formula suffered from the same inadequacies as did the other oxazine formulas and was outmoded by work that was soon to follow.

At the turn of the century Pschorr's new phenanthrene synthesis lent itself beautifully to the definite establishment of the position of the three oxygens in morphine. Morphol, through its relationship to morphenol (85, 86, 87, 88, 92, 95), was in all probability 3,4-dihydroxyphenanthrene. Pschorr's synthesis of 3,4-dimethoxyphenanthrene and its identity with dimethylmorphol confirmed this but gave no indication as to which hydroxyl group of morphol corresponded to the phenolic hydroxyl of morphine.

3,4-Dimethoxyphenanthrene (97). A solution of the diazonium salt from 10 g. α-phenyl-2-amino-3,4-dimethoxycinnamic acid (from sodium phenylacetate + 2-nitro-3,4-dimethoxybenzaldehyde followed by reduction of the nitro group) in 400 g. 13% sulfuric acid, after filtering, is treated with molecular copper powder when a lively reaction sets in with the evolution of nitrogen. This solution acts as its own indicator, for the reaction is complete when the color of the solution becomes a bluish-green.

The mixture of 3,4-dimethoxyphenanthrene-9-carboxylic acid and copper is collected on a filter and stirred in aqueous sodium hydroxide solution and filtered to remove the copper. Acidification of the alkaline solution yields an amorphous precipitate which, after clarification with Norit, is crystallized from ethanol. The yield of acid melting at 227–228° (corr.) is 70–80%.

3,4-Dimethoxyphenanthrene results from the decarboxylation of the above acid by distillation at 300 mm. pressure. The oily distillate, which soon solidified, is taken up in ether and washed with dilute ammonia to remove the unchanged acid. After removal of the ether from the dried solution the crude dimethoxyphenanthrene is fractionally distilled (298–303°, 112 mm.) and then crystallized from aqueous ethanol (m.p. 44°).

It is to be seen that the synthesis of methylmorphol would completely establish this point. The dissimilarity of the synthetic 3-hydroxy-4-methoxyphenanthrene (isomethylmorphol; from sodium phenylacetate + 2-nitro-3-methoxy-4-acetoxybenzaldehyde) (97) led to the conclusion that methylmorphol must be 3-methoxy-4-hydroxyphenanthrene. This was subsequently confirmed by synthesis of methylmorpholquinone (sodium phenylacetate + 2-nitro-3-acetoxy-4-methoxybenzaldehyde) (109). This locates beyond doubt one of the oxygen atoms of morphine (at C_3) and shows that a second one is linked, at least in part, at C_4. The evidence for the position of the third oxygen atom of morphine was obtained from thebaol, a degradation product of thebaine. Thebaol ($C_{16}H_{14}O_3$), like morphol, is a phenanthrene derivative since zinc dust distillation (84) converts it to phenanthrene. Thebaol, however, unlike morphol contains all three oxygen atoms of thebaine and a fourth oxygen appears in the β-ethanoldimethylamine (or β-ethanolmethylamine). Little was known of the structure of thebaol until it was oxidized to a methoxyphthalic acid (probably 4-methoxyphthalic acid), and a product with an odor resembling that of vanillin (probably isovanillin). One of the methoxyls is, therefore, in each of the terminal rings and one is vicinal to a hydroxyl group. The synthesis of the quinone of 3,6-dimethoxy-4-acetoxyphenanthrene (XXVI, R = CH_3) (by a Pschorr synthesis from sodium 4-methoxyphenylacetate + 2-nitro-3-acetoxy-4-methoxybenzaldehyde) (107) and its identity with that of acetylthebaol unequivocally located the three oxygen atoms in thebaol. This placed the third oxygen (the second methoxyl) of thebaine at C_5. Finally, the acid hydrolysis of thebaine to codeinone (previously prepared by the oxidation of codeine by chromic acid or potassium permanganate in acetic acid established the long sensed relationship between thebaine and morphine.

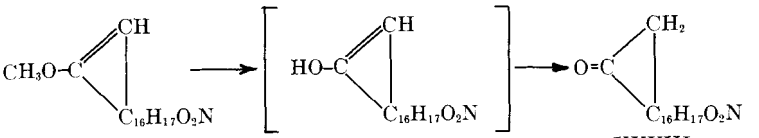
A. Codeinone from thebaine (129). A solution of 3.0 g. of thebaine in 30 cc. of 1 *N* sulfuric acid is boiled for 6–7 minutes, then cooled in an ice bath and the hydrolysis stopped by pouring the reaction mixture into 50 cc. of 10% sodium hydroxide solution. The resulting precipitate is thoroughly extracted with ether and the extract dried over potassium hydroxide. Removal of the ether gave 0.2 g. of codeinone.

B. Codeinone from codeine (334). A solution of 20 g. of codeine in 105 g. of dilute acetic acid (80 g. of water and 25 g. of acetic acid) is oxidized by the addition of a solution of 10 g. of chromic anhydride in 20 g. of water. The resulting oily precipitate is heated and stirred until a clear solution is obtained. By slowly cooling and scratching crystallization of the chromate salt is induced, and after standing in a cooling bath for 30 minutes the crystals are collected on a filter. The salt and the filtrate separately are made strongly basic with ammonia and extracted with ether. The residue after removal of the organic solvent is crystallized from alcohol; yield 40%.

Thebaine (XXVII) is the enol methyl ether of codeinone (XXVIII) (113).

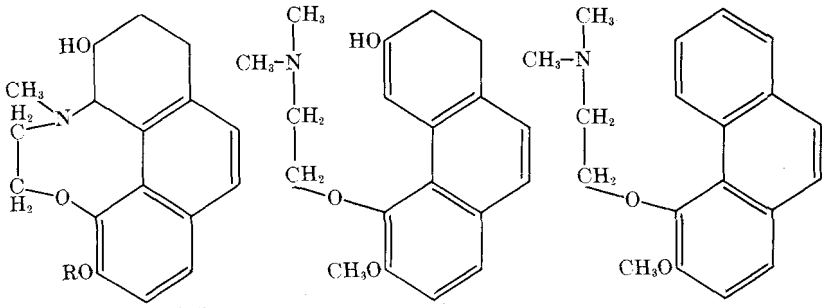
The location of the three oxygen atoms in thebaine is demonstrated

equally well by its hydrolysis to, and the acetolysis (113) of codeinone to a substance which, after methylation, proved to be identical with synthetic 3,4,6-trimethoxyphenanthrene (107).



XXVII XXVIII

Knorr's third formula (XXIX, R = H) (113), although it did locate the oxygens at C_3, C_4 and C_6, did not adequately explain the existence of the four isomeric methylmorphimethines that had been prepared by that time (120). The corresponding methine base XXX would be a dihydrophenanthrene derivative so would be expected to lose water readily to arrive at a fully aromatic system. Such an expectation could not be



R = H, CH_3

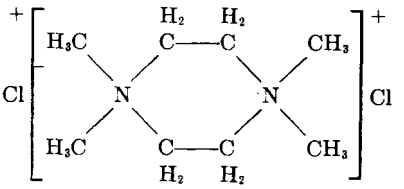
XXIX XXX XXXI

realized experimentally. Moreover, the base XXXI (120) was synthesized and it showed a marked difference from α-methylmorphimethine in its sensitivity to acetic anhydride and sodium ethylate.

Recent work (32, 35) on the catalytic reduction of α-methylmorphimethine shows that it does not contain a naphthalene system as does XXX but two isolated centers of unsaturation which have been reduced stepwise to dihydro- and a tetrahydromethylmorphimethine.

Since 1905 the results of three separate investigations (although one of them is no longer tenable) effectively discouraged the further consideration of the oxazine type of structure for morphine. Pschorr (25), to disprove the statement that the third and ether type oxygen of α-methylmorphimethine is cleaved so as to appear in the basic moiety, degraded chloromethylmorphimethine (α-methylmorphimethine in which the alcoholic hydroxyl has been replaced by chlorine) by long heating in alcohol at

100°. Methylmorphol was isolated in good yield and the primary basic moiety (β-chloroethyldimethylamine) dimerized under these conditions to *N*-dimethylpiperazine dimethochloride (XXXII).

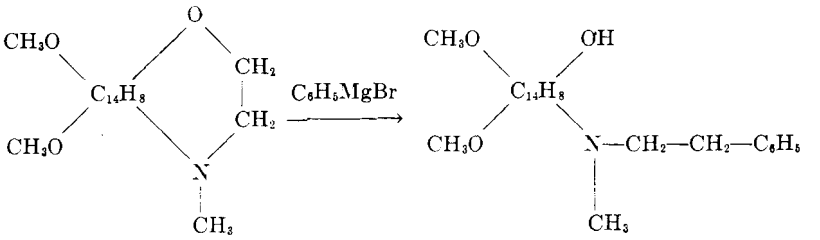


XXXII

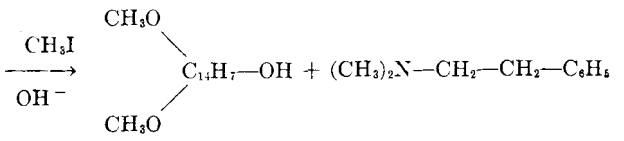
What, at first, appeared to be the most convincing evidence against the oxazine type of structure for morphine has since been shown to be invalid. This evidence involved metathebainone (called thebainone at that time) which resulted from the reduction of thebaine with stannous chloride. Diagnostic reactions disclosed that, of the three oxygens present in metathebainone, one was in a phenol group (monosodium salt and monoacetyl derivative (122)), the second in a ketone carbonyl grouping (oxime, phenylhydrazone and semicarbazone) (122), while by the Zeisel method of analysis (122) the presence of a methoxyl in the molecule was clearly established. Exhaustive methylation and Hofmann elimination on the other hand demonstrated that the nitrogen, as in thebaine, was a tertiary amine and a component of a ring. Acetolysis of the methyl ether (diazomethane (122)) of metathebainonemethine, as in the case of α-methylmorphimethine, gave dimethylmorphol and the acetyl derivative of β-ethanoldimethylamine (124). Since all three oxygen atoms of metathebainone were fully characterized, then β-ethanoldimethylamine must be of secondary origin and cannot arise from the cleavage of a β-aminoether. This evidence is no longer tenable since, in the conversion of thebaine to metathebainone, it is considered that a rearrangement involving the side chain occurs concomitantly with reduction.

Phenyldihydrothebaine ($C_{25}H_{27}O_3N$), which results from the action of phenylmagnesium bromide upon thebaine ($C_{19}H_{21}O_3N$), offers a third piece of evidence against the oxazine formulas for these bases. Although the mechanics of this reaction are not fully understood, and in spite of the anomalous properties of this substance, yet its phenolic properties would suggest that the Grignard reagent had attacked and cleaved the ether linkage in thebaine. This would be represented on the oxazine formulas by XXXIII. The Hofmann degradation of the methohydroxide of XXXIII would yield XXXIV and XXXV. The Hofmann reaction, on the contrary, when applied to this base did not eliminate the ethanamine chain but

gave a tertiary base quite analogous in properties to α-methylmorphimethine (125).



XXXIII



XXXIV XXXV

3. Pyridine Formulas for Morphine

Although von Gerichten's morphine formula proved to be unsatisfactory, his original theory that the 4,5-oxide bridge is a constituent part of morphine proved to be a popular one (120) and has since been shown to be correct (40, 43).

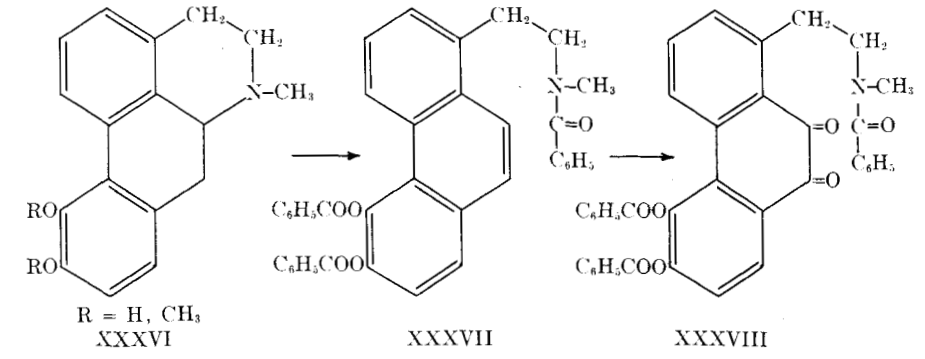
Pschorr (106) attacked the morphine structural problem through a lengthy degradation of apomorphine; his interpretation of each step being remarkably accurate. Apomorphine ($C_{17}H_{17}O_2N$) had been prepared, at that time, by heating morphine with mineral acids (55)

Apomorphine (55, 313). Five grams of morphine (or 5.0 g. of dichlorodihydrodesoxymorphine hydrochloride) and 50 cc. concentrated hydrochloric acid are heated at 130–140° in a sealed tube for 3 hours. The contents of the tube are dissolved in water and the bases precipitated by the addition of an excess of sodium carbonate and extracted into ether (morphine is quite insoluble). The base is isolated as its hydrochloride in a yield of 1.8 g. (33.8%) (1.5 g.; 37.3% from dichlorodihydrodesoxymorphine). The hydrochloride is purified by crystallization from hot water.

The free base is liberated from an aqueous solution of its hydrochloride salt by the addition of twice the theoretical amount of sodium carbonate. Apomorphine is recovered as a snow-white, nonerystalline solid, which soon turns green on the surface due to aerial oxidation.

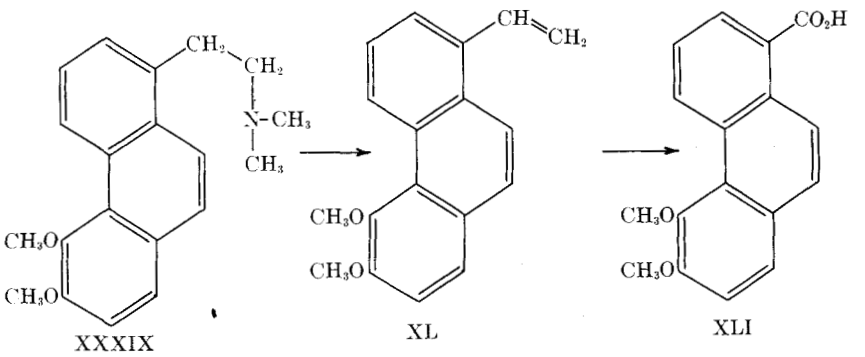
or zinc chloride (65) at 120–150° (apocodeine can be prepared in a similar way (55) or by methylation of apomorphine (106), but more advantageously by heating codeine with oxalic acid (263) or phosphoric acid (313)). The net result was the loss of the elements of a molecule of water from morphine ($C_{17}H_{19}O_3N$).

Pschorr's preparation of the dibenzoate of apomorphine discredited Dankwortt's earlier statement that apomorphine was a monophenol, and that the inert oxygen was still present in this base. Under more vigorous

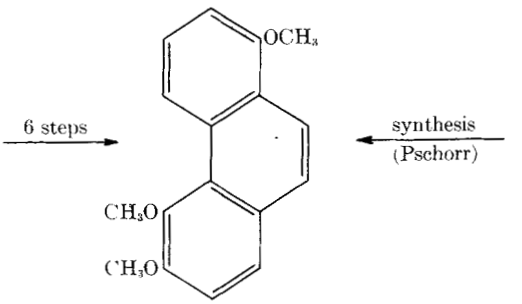


R = H, CH_3

XXXVI XXXVII XXXVIII



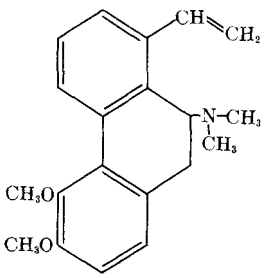
XXXIX XL XLI



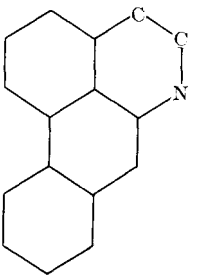
XLII

conditions of benzoylation apomorphine reacted with three mole equivalents of the reagent to give a neutral and optically inactive tribenzoyl derivative, XXXVII. Pschorr considered that the third benzoyl radical had been introduced by cleavage of a tetrahydroisoquinoline nucleus present in

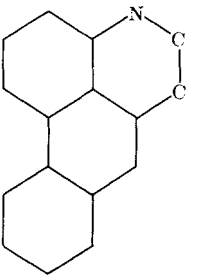
apomorphine, a reaction diagnostic for such a system. That this tribenzoyl derivative contained a phenanthrene nucleus was demonstrated by oxidation with chromic acid. Early attempts at this oxidation yielded only an



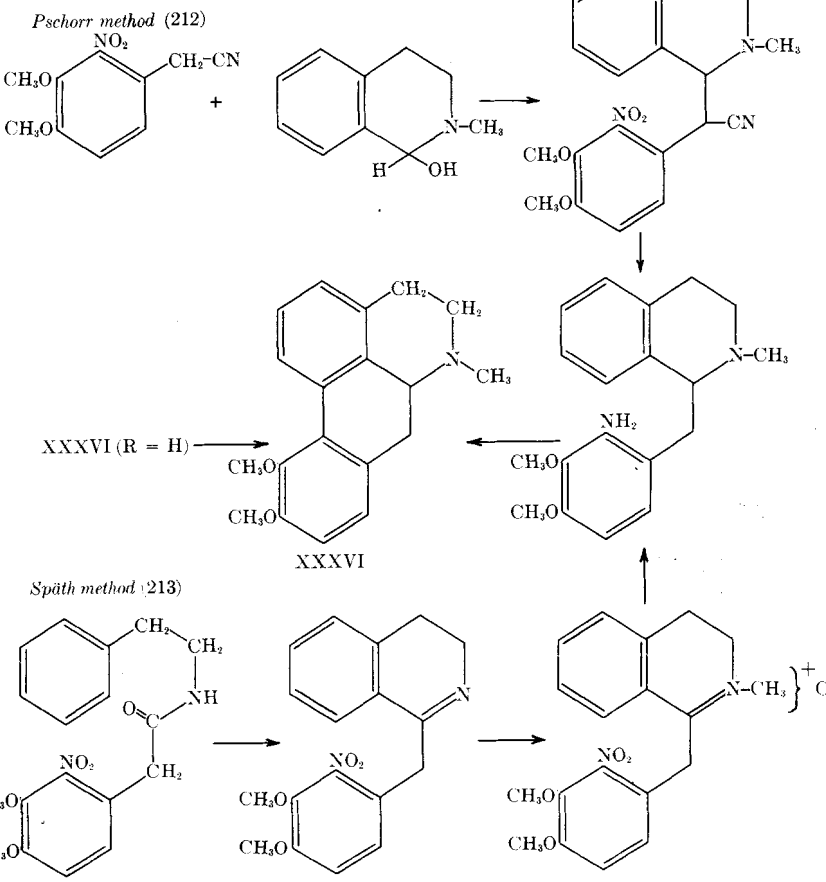
XLIII



XLIV

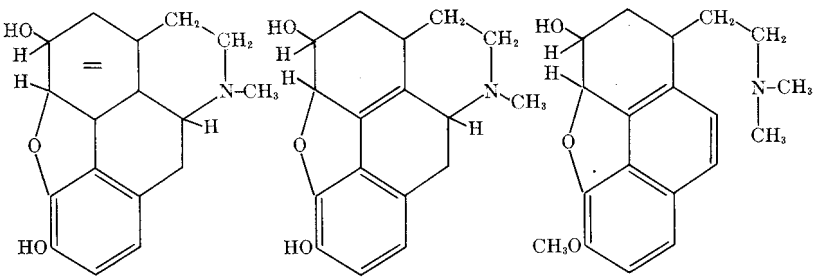


XLV



amorphous material that gave color reactions similar to those of dibenzoylmorpholquinone, but later the quinone was isolated in crystalline form and its structure shown be to XXXVIII (141).

Apomorphine is a cyclic (106) tertiary base with an *N*-methyl grouping (323) since treatment of its dimethyl ether (diazomethane in amyl alcohol (106)) with methyl iodide and subsequent degradation by the Hofmann method yielded a des-base (XXXIX) (an optically active isomethine base, XLIII, is also formed (59, 309)). Elimination of the nitrogen atom by a second Hofmann degradation left only a vinyl group as a residue from the original ethanamine chain. In an effort to locate this unsaturated grouping, the dimethoxyvinylphenanthrene was oxidized to the corresponding carboxylic acid (XLI) (106). The carboxyl group was tentatively placed at C_8, a conjecture which later proved to be correct because when the acid (142) was converted via the urethan to the amine and finally into a trimethoxyphenanthrene. The last proved to be identical with methylpseudothebaol (94). Methylpseudothebaol was shown by synthesis (a Pschorr synthesis from 2-nitro-3,4-dimethoxybenzaldehyde + sodium *o*-methoxyphenylacetate) to be 3,4,8-trimethoxyphenanthrene (143). Pschorr's structure for apomorphine (XXXVI, R = H) was not without analogy, since von Gerichten (101) had previously described substances of basic character obtained by the zinc dust distillation of morphine which he considered to be of the type XLIV or XLV. Subsequent syntheses of apomorphine dimethyl ether demonstrated that Pschorr's interpretation of his analytical work was correct in every detail (it is to be noted that if this transformation were free from rearrangements, then this would definitely locate the nitrogen atom in morphine).



XLVI XLVII XLVIII

Pschorr (106), supposing that only a molecule of water had been lost in the conversion of morphine to apomorphine and that the ring systems were the same, suggested a "pyridine formula" (XLVI) for morphine. Though Pschorr did not commit himself at the outset as to the position of the double bond in the hydroaromatic ring III, subsequently he assigned

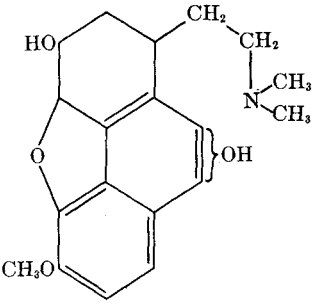
this center of unsaturation to Δ^{13-14} (140, 147). On this formulation, α-methylmorphimethine would be a naphthalene derivative.

Knorr (112), in an attempt to get further evidence for the structure of morphine by oxidative degradation, obtained a hydroxycodeine by the chromic acid oxidation of codeine at 5°.

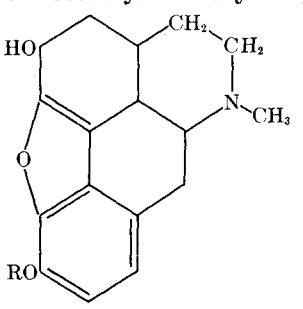
Hydroxycodeine (270). A vigorously stirred solution of 15.0 g. of codeine (m.p. 154–155°) in 80 g. of concentrated sulfuric acid and 160 g. of water is oxidized at 5° by the dropwise addition of a solution of 4.2 g. of chromic anhydride in dilute sulfuric acid (5.0 g. of sulfuric acid and 10.0 g. of water). Fifteen minutes are required for the addition of the oxidant and stirring is continued for an additional 30 minutes. Solid sodium carbonate is then added in small portions until the reaction mixture is only slightly acid to litmus. The separation of sodium sulfate makes the reaction mixture very viscous at this point. The sodium sulfate is collected and washed with a little water. The combined filtrates, after making strongly basic with 75 cc. of 20% sodium hydroxide solution, are extracted many times with chloroform. The yellow chloroform extract, after washing with water, is dried over sodium sulfate, the solvent removed and the residual brown oil dissolved in 200 cc. of hot benzene. The cold benzene solution deposits about 0.1 g. of an amorphous product melting above 300°. When the amorphous material is removed and the benzene solution concentrated to 75 cc., usually 2.3 g. of hydroxycodeine separates (m.p. 186°). Two crystallizations from benzene are sufficient to raise the melting point of the rosettes of yellow crystals to 205–206° (uncorr.); $[\alpha]_D^{22} = -115 \pm 1°$ ($l = 1$).

This hydroxycodeine (112), like codeine, was very stable to acetic anhydride; only the two alcoholic hydroxyls being acetylated. The exhaustive methylation and subsequent degradation of hydroxycodeine methiodide was completely comparable with that of codeine, the properties of the methine base being quite analogous with those of α-methylmorphimethine. While acetolysis of α-methylmorphimethine gave acetylmethylmorphol, the des-base from hydroxycodeine gave the diacetyl derivative of a hydroxymethylmorphol (130), which on oxidation (CrO_3 + HOAc) gave acetylmethylmorpholquinone (135). (This diacetyl derivative of a hydroxymethylmorphol and the corresponding quinone have been obtained from α-methylmorphimethine (134). If α-methylmorphimethine is treated in chloroform solution with phosphorus pentachloride and the resulting dichloro-compound heated with acetic anhydride, the above diacetyl derivative is obtained which can be oxidized to the respective quinone.) Since one of the oxygen atoms of the hydroxymethylmorphol has entered into quinone formation, then this hydroxyl must be at C_9 or C_{10}. Likewise the fourth oxygen of hydroxycodeine and of the methine base must occupy a similar position. The methine base afforded a method for testing the validity of Pschorr's morphine formula (XLVII), since on this formula it is to be seen that the des-base (XLIX) of hydroxycodeine is either a substituted α- or β-naphthol. Contrary to Knorr's earlier diagnosis this fourth oxygen in the des-base was not in an alcoholic hydroxyl nor in a

phenolic hydroxyl, but showed properties diagnostic for a carbonyl grouping. From these experiments it is to be seen that the newly generated hydroxyl and the nitrogen in hydroxycodeine must be linked either collectively or separately to C_9 and/or C_{10}; for, if the hydroxyl of hydroxycodeine is to become the ketone carbonyl of ketodihydromethylmorphimethine, then it must pass through an intermediate enol phase. Knorr, to obviate this objection to Pschorr's formula, located the double bond in ring III of morphine and codeine at Δ^{5-13} (L; a coumarone formula) (147). Hence the conversion of hydroxycodeine to ketodihydromethylmorphimethine finds expression in formulas LI–LIII.

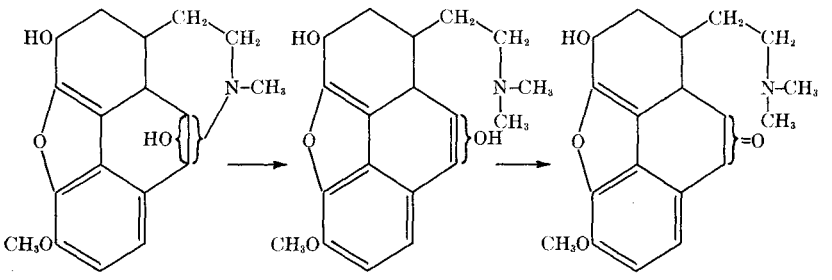


XLIX



R = H, CH_3

L



LI LII LIII

Developments in the study of the isomeric codeines soon led Knorr to abandon the hypothesis of a C_8 linkage for the carbon end of the ethanamine grouping. Many reagents such as water-free hydrogen chloride (134), phosphorus tri- and pentachlorides (11, 160, 241, 280, 282, 320), and thionyl chloride (27) smoothly replace the alcoholic hydroxyl of morphine and codeine with a halogen atom. α- and β-Chloromorphide have been related to α- and β-chlorocodide by methylation ($(CH_3)_2SO_4$ (284) or CH_2N_2 (157)) and these alpha bases may be thermally isomerized, respectively, to the β-isomers (20, 156, 202). The mechanism of the reactions leading to these isomeric chlorocodides is, as yet, obscure, and, although

the possibility of stereoisomerism (spatial disposition of the halogen at C_6) cannot be entirely neglected, yet the evidence at hand indicates an isomerism of a structural nature (the chlorine atom at C_6 or C_8) to be more likely. Hydrolysis of the chlorocodide isomers with water (57, 145, 152, 157 159, 282) or by dilute acid (136) gave a series of isomeric codeines in proportions as shown in Table 1. In a similar way three bases, isomeric

TABLE 1

PROPORTION OF ISOMERIC CODEINES FROM THE HYDROLYSIS OF THE CHLOROCODIDES*

	Isocodeine %	Pseudocodeine %	Allopseudocodeine %
α-Chlorocodide	25	45	15
β-Chlorocodide	55	10	20

* Göhlich (57) is the only one reported to have isolated codeine from the hydrolysis of the chlorocodides.

with morphine, have been isolated from the hydrolysis of α-chloromorphide (160, 281, 282). The relation of the isomeric morphines to the codeines has been demonstrated by methylation of the C_3 phenolic group in the isomorphines (152, 160, 327) and is recorded in Table 2.

Isocodeine differs from codeine solely in the configuration of the hydrogen and hydroxyl group about C_6, for this isomerism disappears when codeine (112) and isocodeine (158) are oxidized (chromic acid) to codeinone. That this is the C_6 ketone of the secondary alcohols, codeine and isocodeine, was established by degradation (acetolysis and methylation (113)) to 3,4,6-trimethoxyphenanthrene which had previously been synthesized (107). A similar series of reactions were used to show that an identical relationship exists between pseudocodeine and allopseudocodeine. These two isomers, when oxidized (chromic acid), yield the same ketone, pseudo-

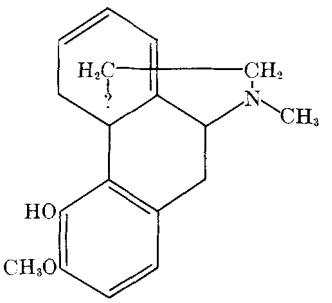
TABLE 2

RELATIONSHIP OF THE MORPHINES TO THE CODEINES

Morphine	→	Codeine
α-Isomorphine	→	Isocodeine[a]
β-Isomorphine	→	Allopseudocodeine
γ-Isomorphine[b]	→	Pseudocodeine[c]

[a] Isocodeine has been applied at various times (282) in reference to allopseudocodeine (157).
[b] The pseudo nomenclature of the codeine isomers could not be employed in the case of the isomeric morphines because this term had already been used to designate a dimer resulting from the oxidation of morphine with potassium ferricyanide solution.
[c] Pseudocodeine has, at times (150, 277), been referred to as dicodeine.

codeinone (145, 149). The position of the carbonyl group at C_8 in this ketone, which is isomeric with codeinone, was established by its degradation (alcohol on the methiodide) to the synthetic 3,4,8-trimethoxyphenanthrene (143). To prove that the nitrogen chain had suffered no rearrangement in the process of converting codeine into its isomers, the four codeines were converted through their respective chlorocodides to the same desoxycodeine (LIV) (138, 153). From this it was inferred (1) that the ethanamine chain had suffered no alteration in the above transformations and (2) that formulas involving a C_6 or C_8 attachment of the ethanamine chain for codeinone (hence also codeine which may be derived from codeinone by



LIV

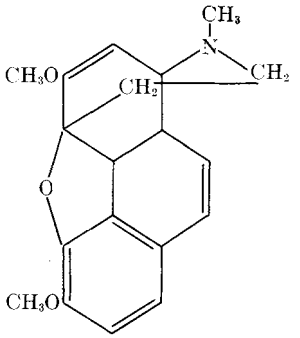
reduction (42, 331)) and pseudocodeinone are inadequate (pentavalent carbon). Although these conclusions fulfilled the purpose of discouraging further consideration of pyridine formulas of types XLVII and L, the basis for these assumptions is subject to some doubt for any deductions drawn from a series of reactions involving intermediates, whose relationships are as ill-defined as those of the chlorocodides, are subject to much skepticism (287). Since the shift of the hydroxyl from C_6 to C_8 in the conversion of codeine to pseudocodeine appears to be an allylic shift, it is not improbable that the ethanamine chain may be involved in such a rearrangement.

4. Transitional Formulas

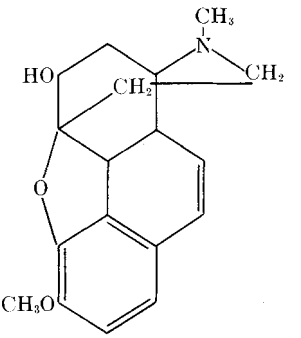
There was a period of a few years between the time of the final evidence against the oxazine formula in 1905 and the work of Knorr and Pschorr on hydroxycodeine in which little or no evidence was set forth on which to base the location of the ethanamine chain.

Freund's extensive study of thebaine afforded a possible clue to the attachment of the carbon end of the chain (79, 80, 84, 128). He converted thebaine to thebenine, in which the phenanthrene system is completely aromatic and the now secondary nitrogen is no longer a constituent of a ring. Exhaustive methylation (two moles of CH_3I) and Hofmann degrada-

tion gave rise to trimethylamine and a phenanthrene derivative, thebenol, containing an oxide ring system. Zinc dust (84) or phosphorus and hydriodic acid (84) readily converted this to pyrene. This formation of pyrene led to the conclusion that the ethanamine chain in thebenine is attached at C_5. Because of the close relationship of thebaine to thebenine it was considered that the carbon end of the side chain had suffered no modification in the process. With the ether type linkage of the ethanamine chain effectively disposed of thebaine and codeine could no longer be considered to be di- and tetrahydrophenanthrenes, but must be looked upon as tetra- and hexahydrophenanthrenes. The results of the action of phenylmagnesium bromide (other Grignards have since been used) on thebaine further confirmed von Gerichten's assumed phenanthrylene oxide system

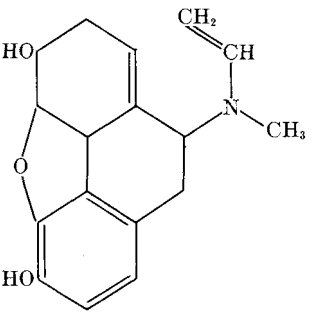


LV



LVI

for morphine and led Freund to advance LV and LVI for thebaine and codeine, respectively. It is obvious this formula for codeine is untenable in the light of Knorr and Pschorr's later experiments of hydroxycodeine.



LVII

In an effort to explain the ease with which thebaine and codeinone lose the nitrogen side chain by acetolytic cleavage, Wieland (27) enlarged on Knorr's earlier hypothesis and proposed a vinyl formula (LVII) for mor-

phine. This alkeneamine formula is in direct contradiction to the imposing array of evidence in favor of a nitrogen-heterocyclic ring in these bases. If morphine were represented by such a structure it should absorb two mole equivalents of hydrogen, a conclusion that is contrary to fact. (Wieland ascribed this inability of morphine to absorb two moles of hydrogen to the presence of "a mole of water of constitution" on the vinyl group. The preparation of anhydrous morphine proved somewhat difficult (27).) Wieland saw in this vinyl formula a ready means of explaining the formation of such diverse structures as apomorphine, morphothebaine, and thebenine. Later studies of the catalytic reduction of anhydrous morphine, however, forced Wieland (32) to retract his earlier statements regarding this hydrate form.

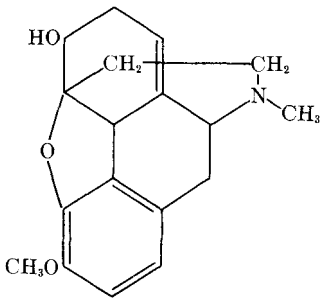
Gadamer (3, 58), on rather indirect evidence, proposed a formula which was but a slight modification of the Freund formula and involved only a translocation of the morphine double bond from Δ^{9-10} to Δ^{13-14}.

5. The Camphane and Modern Formulas

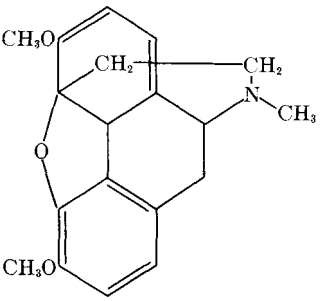
To Knorr should go the credit for the development of the structure of the morphine alkaloids, for he exerted a marked influence on the trend of thought in this field from 1889 to 1907. This influence is still felt today; for the modern formula is closely related to his sixth formula (LVIII and LIX) for these alkaloids. These minor variations are but a fuller expression of his experiments, supplemented by but a single piece of evidence.

After localizing the position of the nitrogen at C_9 or C_{10} through the degradation of hydroxycodeine and by analogy to apomorphine, only two structural features remained in doubt; first, the location of the center of unsaturation in ring III and, secondly, the point of attachment of the carbon end of the ethanamine chain. Since no direct experimental approach to these problems was possible at this time and because of a number of anomalous reactions which occur in this series, many conflicting ideas resulted. From the experimental evidence which had been presented up to this time, it appeared that the dimethylene group of the nitrogen chain is united to some part of the hydroaromatic ring III. The isomerism of codeinone and pseudocodeinone seemed to preclude its attachment at C_6 or C_8, leaving only C_5, C_7, C_{13} and C_{14} to be considered. Of these four, C_{13} and C_{14} could hardly come into consideration for the nitrogen chain is still intact even when, as in thebenine, the third ring has become completely aromatic. This left only C_5 and C_7 open for consideration. From the formation of characteristic derivatives by codeinone and pseudocodeinone with benzaldehyde, amyl nitrite, and benzenediazonium chloride Knorr (149) concluded that there must be a methylene group alpha to the carbonyl in these two keto bases, and carbon atom 7 seemed to be the

only possible position for such an active methylene group. Furthermore, the reduction of codeinone to codeine (112) (no experimental data) appeared to leave little reason to doubt the presence of such a methylene group at C_7 in codeine and narrowed the possibilities for the attachment of the carbon end of the ethanamine chain to C_5 in codeine (LVIII) and thebaine (LIX).



LVIII

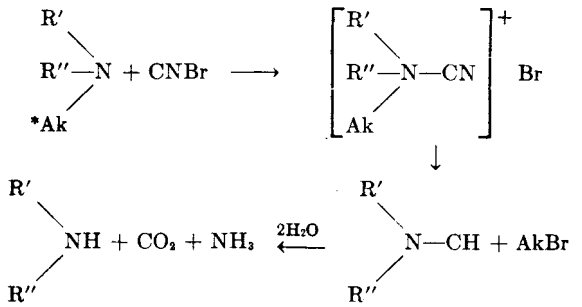


LIX

The evidence previously cited against a Δ^{13-14} double bond and the existence of a C_7 methylene group of necessity placed the double bond at Δ^{8-14} in this formula for codeine. The isomerism of α- to β- (from codeine) and of γ- to δ- (from isocodeine) methylmorphimethines was then explained as a shift of the double bond from Δ^{8-14} to Δ^{13-14}. A study of such a structure with atom models showed that such a heterocyclic seven-membered ring as in this codeine formula was under but slight strain, whereas the extra center of unsaturation of thebaine makes the strain in this ring much greater. Knorr considered that under slight provocation (e.g., acetolysis, dilute hydrochloric acid, etc.) the seven-membered hetero ring would break at one end (thebenine) or the other (morphothebaine, apomorphine) with subsequent linkage elsewhere to form stable five- or six-membered rings. This explained the varied structures and reactions of thebaine, thebenine and morphothebaine.

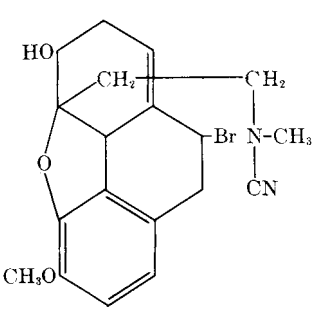
Formula LVIII, with its Δ^{8-14} double bond, explains satisfactorily the complex rearrangements of morphine and thebaine, but it fails to account for the difficulty encountered in the addition of two bromine atoms to morphine and codeine or the removal of the halogen from chloromorphide. This caused von Braun (179) to question the presence of an ethylene in morphine and codeine. His extensive study of the action of cyanogen bromide upon tertiary amines provided an experimental method for testing the presence of a Δ^{8-14} double bond (allylamine type) in both codeine and thebaine. His early investigation of this reagent with tertiary amines established that the reaction proceeded in two phases. The cyanogen bromide, like an alkyl bromide, first adds to the nitrogen to form a

quaternary salt which then loses a molecule of an alkyl bromide. Hydrolysis of the *N*-disubstituted cyanamide yields a secondary amine. The

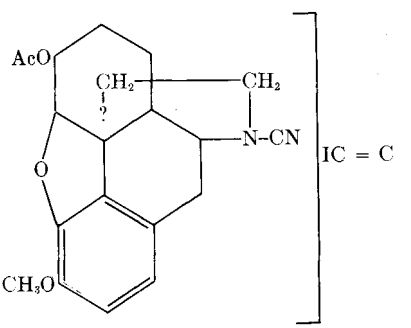


* Ak represents an alkyl residue.

intensity of the reaction in the initial stage varies with the type of substituents on the nitrogen, as does the specificity of the cleavage of the quaternary salt. Whereas the action of cyanogen bromide on an ethereal solution of trimethylamine is very vigorous even at low temperatures, the substance had to be heated with triphenylamine to convert the amine to a quaternary salt. The degree of activity, however, is not solely dependent upon the mechanical size of molecule but is, to a degree, dependent upon the chemical nature of the substituents; for it is found that allyl groups tend to increase the activity of these systems. In the second phase of this reaction, the substituent cleaved from a mixed alkylamine, as in the case of a quaternary ammonium halide, is usually the smallest residue. Here again the chemical factor, in some cases, gives precedence to such groups as allyl and isopropyl over those of smaller dimensions. If codeine were a substi-



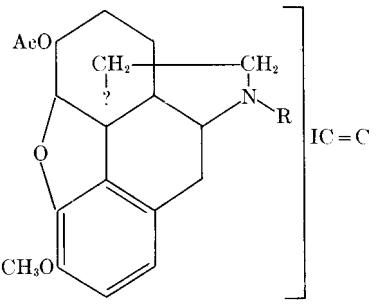
LX



LXI

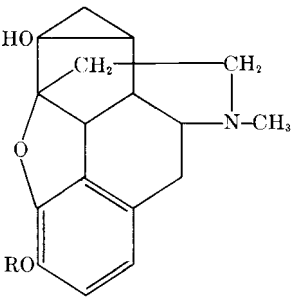
tuted allylamine (the double bond at Δ^{8-14}), it would be expected that cyanogen bromide would cleave this system (LX) in preference to the N—CH_3 grouping. On the contrary, acetylcodeine yielded methyl bromide and a neutral product, cyanoacetylnorcodeine, LXI, $C_{20}H_{20}O_4N_2$. To

show that this was no idiosyncrasy of codeine he applied this reaction to the acetyl derivative of α-methylmorphimethine, which he knew had no unsaturation β, γ to the nitrogen atom. The results were completely in accord with those for codeine. He extended this study to include many *N*-homologs (LXII) of codeine, which he prepared from norcodeine (182, 185, 195, 196, 210). It was found that cleavage of the heterocyclic ring of these *N*-substituted acetylnorcodeines was not attained until the exo-



R = aryl and saturated or unsaturated alkyl residues

LXII



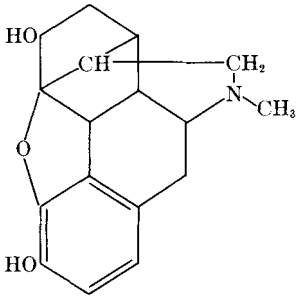
R = H, CH_3

LXIII

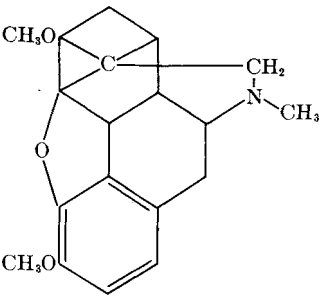
cyclic nitrogen substituent was a chain of at least five carbons (182). In contrast to this, thebaine was not demethylated by this reagent, but like dibenzoylapomorphine (this ring fission is accompanied by the loss of the elements of hydrogen bromide from the primary reaction product (186)) suffered ring fission (here, too, secondary reactions occurred (179, 205)). This would indicate that thebaine, in contrast to morphine and codeine, had a center of unsaturation β, γ to the nitrogen atom. He further confirmed his hypothesis by reducing thebaine to the tetrahydro derivative (dihydrocodeine-6-methyl ether), which, like all members of the codeine series, suffered *N*-demethylation (the reaction product was not isolated in pure state (179). This proof of the absence of a double bond β, γ to the nitrogen atom in codeine, combined with the evidence for a methylene group at C_7, added weight to his conviction that there was a three-ring in morphine and codeine (LXIII) similar to that in carane. This formulation of a three-ring admirably accounted for the observed difficulty of brominating codeine.

Freund (183), extending von Braun's representation of unsaturation in the morphine molecule, modified the carane formula to one involving a camphane nucleus (LXIV). From the study of the catalytic reduction and halogenation of phenyldihydrothebaine no good evidence could be found for the presence of ethylenic bonds in thebaine. The one piece of evidence championing this type of formula over all others was that it

explained the existence of the two *supposedly* isomeric tetrahydrodesoxycodeines (242 note 6, 320) by the alternate breaking of the C_5–C_{15} or the C_8–C_{15} bond.



LXIV

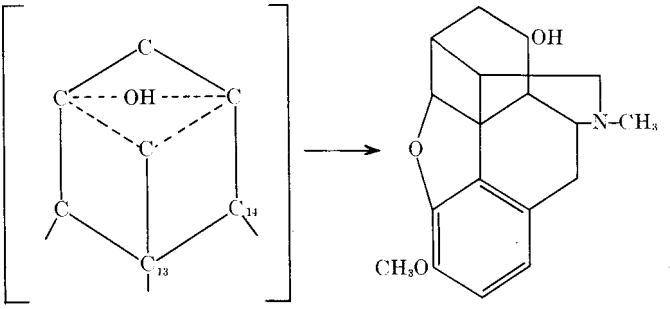


LXV

Neither of the two previous formulas offered an adequate explanation for the extrusion of the side chain on aromatization of ring III (α-methyl morphimethine → acetylmethylmorphol, thebaine → acetylthebaol). The driving force behind this change would doubtless be the tendency to produce an aromatic nucleus; for elimination of the aminoethane grouping is never observed independently of the formation of the complete phenanthrene system. It is clear that the only structural condition which could inhibit aromatic ring formation is that the side chain is attached to a quaternary carbon, namely, C_{13} or C_{14}. This precludes a further consideration of LXIV, for, in this instance, there would be a loss of the side chain without any compelling reason and an explanation other than that now advanced would have to be found. From the fact that codeine can be oxidized to codeinone, hydroxycodeine and codinal without apparent attack on an isolated ethylene, prompted Robinson (287) to conclude that morphine contained a bridge system. The two possible bridge systems that would fulfill the previous requirements are C_8–C_{15}–C_{13} or C_8–C_{15}–C_{14}. On the latter structure, the conversion of codeine to pseudocodeine would involve a ring enlargement from a cyclopropane to a cyclopentane ring, and the difference in the stability of the ring systems should be considerable so that the reverse transformation of pseudocodeine to codeine (57) would present a difficulty.[1] The codeine-pseudocodeine (LXIVb) transformation was then considered to be a type of modified geraniol-linalool rearrangement involving an intermediate cyclobutane derivative, LXIVa. The isomerism of α- (or γ-) to β- (or δ-) methylmorphimethine was ascribed to the cleavage

[1] Although it is doubtful if codeine has ever been obtained from pseudocodeine directly through the chlorocodide (20, 136, 152, 159, 280, 281, 282), yet it can be prepared by oxidation of the derived isocodeine to codeinone and its subsequent reduction to codeine. From this consideration such a statement may not be valid.

of the C_8–C_{15} bridge to form a Δ^{8-14} bond, which is conjugated with the Δ^{9-10} -styrene double bond. The failure of ε- (from pseudocodeine) and ζ- (from allopseudocodeine) methylmophimethine to undergo a similar



LXIVa LXIVb

type of isomerization seemed adequately accounted for by the fact that a conjugated system could not result directly as in the previous case by the rupture of the C_5–C_{15} bridge of these methine bases.

The complex rearrangements in the formation of morphothebaine and apomorphine were looked upon as a simultaneous cleavage of the C_{13}–C_{15} bond and the oxide bridge, while thebenine formation was thought to involve an isoborneol-camphene type of rearrangement.

These bridge formulas had two distinct advantages: they adequately explained the existence of the two supposed tetrahydrodesoxycodeines (242), and at the same time adequately accommodated the observed passivity of ring III to ozone. The one serious objection, however, that could not be discounted was the results of the catalytic reduction of the isomeric methylmorphimethines (35, 246, 251, 255). α-Methylmorphimethine absorbs stepwise two moles of hydrogen to yield a tetrahydro derivative. The dihydro derivative, identical with that from dihydrocodeine, (32, 320) demonstrates that the unsaturation in ring III (a three or a four carbon ring) is hydrogenated in preference to the styrene double bond at Δ^{9-10}. The marked difference in strain between a four carbon ring and an ethylenic double bond would lead to the expectation of a distinct break in the hydrogenation curve for tetrahydromethylmorphimethine, but no such discontinuity was observed (35). Furthermore, the reduction of β-methylmorphimethine to the above tetrahydro derivative established that the isomerism of these two methylmorphimethines must be attributed to a difference in position of the unsaturation in the two molecules (on von Braun's and Knorr's formulation for β-methylmorphimethine as a naphthalene derivative, the addition of 1 mole equivalent of hydrogen would be expected to yield a mixture of the tetrahydro derivative and starting material: on the contrary, a good yield of dihydro-β-methylmor-

phimethine resulted). Finally, it is hard to understand the relation of codeine to codeinone on a three ring formula (LXIII), for it would necessitate the opening of this ring and the introduction of an ethylenic linkage in some part of ring III, since codeinone does show evidence of unsaturation (62, 197). Although this is conceivable, the greater stability of the three ring makes its reformation during the reduction of codeinone to codeine appear highly unlikely (34).

The oxidation of codeine to dihydroxydihydrocodeine (291) and the ozonolysis of thebaine to α-thebaizone suggests the presence of at least one ethylenic linkage in these alkaloids. Robinson made adequate allowance for one ethylenic linkage in thebaine, but his formula does not account for the enol ether properties (acid hydrolysis to dihydrocodeinone) of dihydrothebaine (reduction of thebaine with H_2 + platinum black (189)). The argument that catalytic reduction might favor the rupture of a four ring in preference to an enol ether double bond appeared ill-founded; for, at that time, the reduction of the enol methyl ether of cyclohexanone with reasonable ease had been described (209).

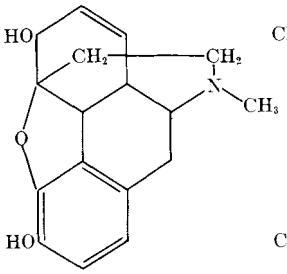
Robinson's (293, 321) experimental evidence that hydroxycodeinone

$$\begin{matrix} & & O & & \\ & & \| & & \\ -C- & & & & CH_2- \end{matrix}$$

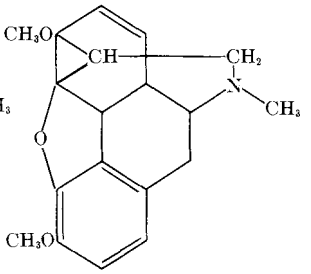
(H_2O_2 on thebaine) has no grouping, while dihydrohydroxycodeinone has, led the more recent workers in this field to revert to the Knorr type formula (LVIII).

In 1925 Wieland (34) and Robinson (321, 326) independently proposed formulas differing only in the position of the carbon end of the ethanamine chain. Wieland attacked the problem through the degradation of thebaine and concluded that the side chain must be at C_5 (LXVI) in morphine. Von Braun's comprehensive study of the action of cyanogen bromide on these alkaloids precluded every position except Δ^{7-8} for the double bond in ring III of codeine. Wieland's formula for thebaine (LXVII) conformed with hydrogenation experiments, although it did not explain its apparent enol ether system. He preferred to retain the Δ^{7-8} center of unsaturation in his thebaine formula and to represent the other unsaturation as a three-ring, which suffered fission in the hydrolysis of thebaine to codeinone. Subsequent studies of the ozonolysis of thebaine led Wieland to accept Robinson's theory for the presence and position of two ethylenic double bonds in this base (LXVIII). Dihydrothebainemethine (34) was catalytically reduced to 9, 10-dihydro-des-*N*-methyldihydrothebaine and this was followed by hydrolysis of the enol ether system. This ketone proved to be identical with that prepared from codeine by another route. The oxide bridge was reductively cleaved (aluminum amlagam) and the derived phenolic methine methohydroxide, when warmed, yielded thebenone by

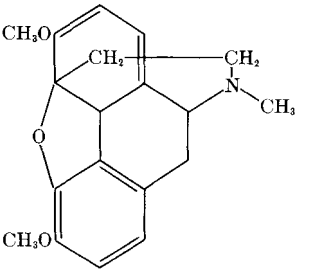
loss of trimethylamine and cyclization of the primarily formed vinyl compound. To account for this ease of cyclization Wieland considered that the side chain had to be in close proximity to the C_4 hydroxyl group. This



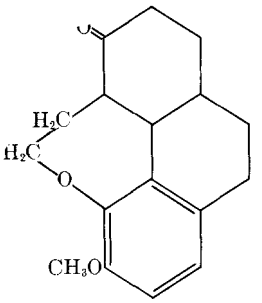
LXVI



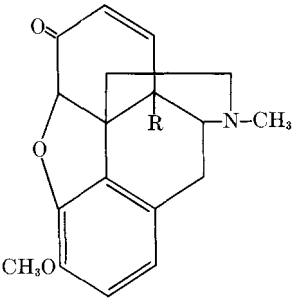
LXVII



LXVIII



LXIX

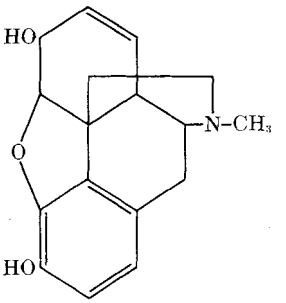


R = OH, Br
LXX

limited the positions for consideration to C_5 and C_{13}. If the side chain were attached to C_{13}, then thebenone should possess two active methylene groups, alpha to the carbonyl group. Repeated attempts clearly demonstrated that only one mole of amyl nitrite, benzaldehyde, or piperonal could be made to react with thebenone, even under the most drastic conditions. This evidence would appear to substantiate Wieland's hypothesis of a C_5 attachment for the ethanamine chain.

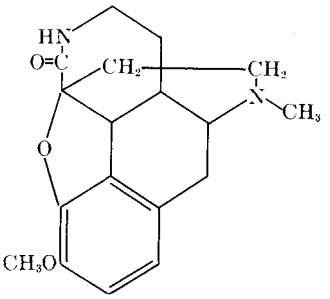
At the same time Robinson advanced arguments which seemed to favor the attachment of the nitrogen chain in morphine at C_{13}. Reviewing the work on hydroxycodeinone (128, 200, 319) he conclusively demonstrated (321) that a compound having these properties could not be an alpha-hydroxy ketone. Hydroxycodeinone was prepared by the action of hydrogen peroxide on thebaine. At this stage its formation was represented as a 1, 2 addition of the elements of hydrogen peroxide to the enol ether double bond, followed by the loss of the elements of methyl alcohol from C_6. Such a mechanism can hardly be correct for, in contrast to α-hydroxy ketones, this product was very stable to alkaline cupric and

silver solutions. In view of the difficulty in dehydrating hydroxycodeinone, the substance could hardly be a β-hydroxy ketone, thus leaving the gamma position as the only alternative for the hydroxyl group (LXX, R = OH). Bromine reacts similarly with thebaine yielding bromocodeinone which has been converted into both codeinone and hydroxycodeinone. The formation of a 6-aminopiperonal derivative by dihydrohydroxycodeinone and the failure of a similar reaction on hydroxycodeinone appears to be the strongest evidence at hand for a Δ^{7-8} double bond in both hydroxycodeinone and codeinone (and hence in codeine). Moreover, the loss of the ethanamine grouping from eserethole (289) was presented by Robinson as added support for his principle of the driving force in the aromatization of ring III. It was on this evidence that Robinson proposed LXXI for morphine. These two formulas (LXVI and LXXI) for morphine accommodated all the experimental facts equally well. The conversion of codeine to pseudocodeine may now be expressed on either formula as a true allylic

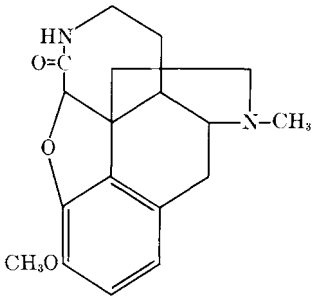


LXXI

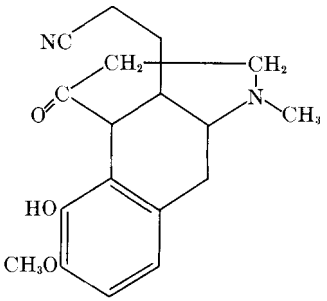
rearrangement, while sodium ethylate is considered to shift the double bond to Δ^{8-14} in the isomerization of α- to β-methylmorphimethine. There remained only the application of these two formulas to experimental test to determine the point of attachment of the carbon chain. From a series of reactions involving the Beckmann rearrangement of dihydrocodeinone oxime, Schöpf (36) has advanced evidence favoring Robinson's formula. The Beckmann rearrangement can follow one or both of two courses. First, an enlargement of ring III, LXXII-W and LXXII-R, is possible, although of no interest in this argument, and, secondly, there may be a cleavage of the ring similar to that occurring in α-benzoin oxime. The isoxime formed by the latter method of rearrangement would be a ketone on Wieland's formulation (LXXIII-W), while Robinson's formula (LXXIII-R) would represent it as an aldehyde. That the Beckmann rearrangement of dihydrocodeinone oxime actually did give an isoxime was supported by many tests. The presence of the carbonyl group was manifest by oxime



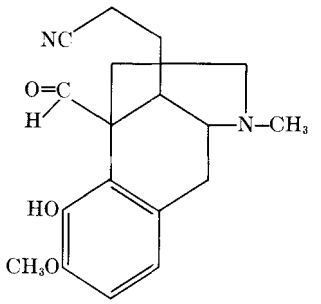
LXXII-W



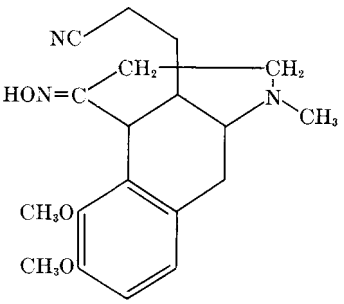
LXXII-R



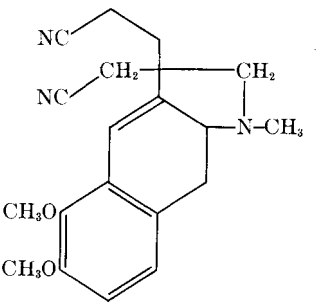
LXXIII-W



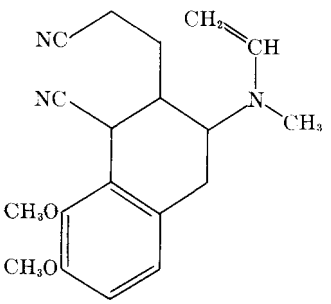
LXXIII-R



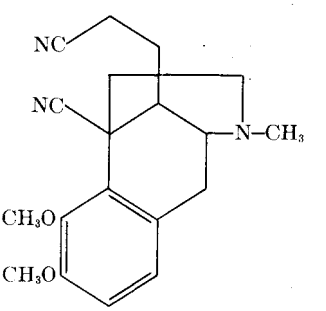
LXXIV-W



LXXV-W



LXXVI-W

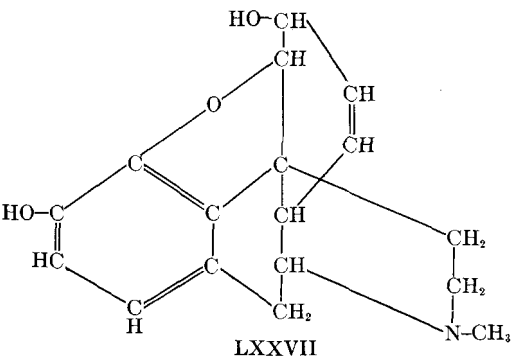


LXXV-R

formation, and that of the nitrile by hydrolysis to the acid. The solubility of this rearrangement product in alkali and its insolubility in soda attests to the cleavage of the oxide bridge and generation of a C_4 phenolic hydroxyl. It is the characterization of the carbonyl group of this isoxime as an aldehyde or a ketone that is the critical test upon which the proof for the validity of the respective formulas for morphine is based.

If LXXIII-W represents the structure of the isoxime, then the substance would be expected to condense with aldehydes at C_{15}; or if it were the aldehyde LXXIII-R, then the oxime of the isoxime would be expected to lose water with formation of a dinitrile. Actually both tests proved negative. A molecule of water was, however, removed by acetic anhydride from the oxime of the isoxime methyl ether, but this finds expression in the two alternatives. The loss of water from the ketonic formula (LXXIV-W) would be analogous to the formation of campholenonitrile from camphor oxime, while the loss of water from the aldehyde oxime would give the dinitrile LXXV-R. Two methods for the elimination of water from the keto-isoxime formula come into consideration, namely, LXXV-W and LXXVI-W.

Since the basic nitrogen of LXXV-W or LXXVI-W is not a component of a ring, it would be expected that the degradation of its quaternary base would result in a neutral naphthalene derivative; whereas LXXV-R would be expected to yield a methine base. Actually the derived product was not neutral but basic, and with properties analogous to those of α-methylmorphimethine. It is to be emphasized that while this evidence effectively disposes of Wieland's formula, yet it does not supply the needed proof to establish Robinson's formula as that of morphine.

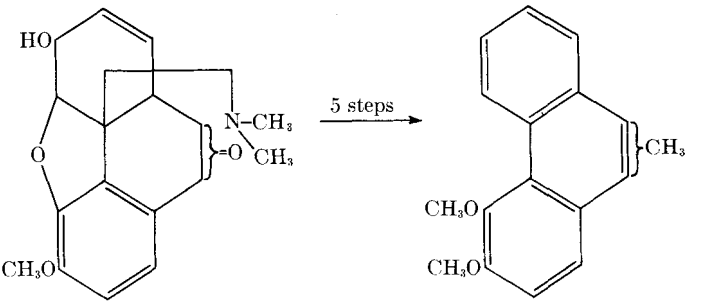


LXXVII

Emde (238) has pointed out that the asymmetric centers of the morphine molecule are in an unbranched chain (LXXVII) as arranged in glucose.

6. Problems Remaining

From the mass of accumulated evidence it must be apparent that Robinson's formula probably represents the true structure of morphine, although certain aspects of the problem have stubbornly resisted confirmation by experimental means. The key to the whole problem lies in the location of the ethanamine bridge. Several unsuccessful attempts have been made to degrade codeine and thebaine to 3, 4-dimethoxy-13- (or 14-) ethyloctahydrophenanthrene, for, if the carbon end of the chain is linked to C_{13}, then the addition of a conjugated diene to codienone, bromocodeinone or hydroxycodeinone would be sufficient to unequivocally assign the double bond to the position Δ^{7-8}. Then only the position of the nitrogen atom would remain in doubt. From the evidence at hand its attachment has been localized to either C_9 or C_{10}. A project is under way to definitely locate its position in the molecule (270, 271). It is to be seen that if the position of the newly generated hydroxyl group of hydroxycodeine is known as well as the position of the nitrogen atom with respect to this grouping, this would be sufficient to definitely assign a position to this atom in the molecule. The action of two moles of methylmagnesium iodide upon ketodihydromethylmorphimethine (LXXVIII), followed by dehydration



LXXVIII LXXIX

of the resulting tertiary carbinol and acetolysis of the doubly unsaturated methine base would yield, after saponification and methylation, either the 9- or 10-methyl derivative of 3, 4-dimethoxyphenanthrene (LXXIX). Comparison with the two possible isomers prepared by synthesis (271) would definitely locate the hydroxyl group. Hydroxycodeine does not appear to exhibit the properties of a carbinol amine, although its characterization as a β-ethanolamine has, as yet, not been achieved.

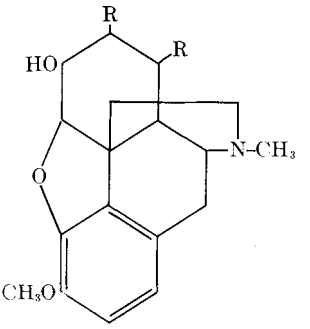
After the solution of the structural problem there still remains the question of the configuration about the five asymmetric centers of morphine.

III. The Reactions of Morphine, Codeine, and Related Products

1. Reduction

The centers most subject to reduction in morphine and related products are the double bond (at Δ^{6-7} or Δ^{7-8}), the oxide bridge and the carbonyl group, when present, while in several instances the reductive fission of a C—N bond has been realized. By careful selection of conditions and reagents it is possible, in many cases, to selectively reduce one or other of these groupings. The position of the ethylene has a pronounced influence on the course of the reduction process. When the double bond is at Δ^{6-7}, then, unless the conditions are rigorously controlled, rupture of the oxide bridge (the so-called abnormal reduction) accompanies the hydrogenation of the ethylenic linkage.

a. Catalytic Reduction. The catalytic reduction of these bases conveniently falls into two categories, depending on the constitution of the base in question. When the ethylenic linkage is located at Δ^{7-8} (orΔ^{8-14}), the hydrogen uptake ends abruptly when one mole equivalent of hydrogen has been absorbed, and the respective dihydro derivatives can be isolated in good yield. For example, morphine (169, 173), its phenolic, alcoholic (307), and its dimethyl (60) ethers, normorphine (181), the phenolic and alcoholic ethers of α-isomorphine (307), codeine (173, 320), isocodeine (192, 258, 313), neopine (290) 1-bromocodeine (201), norcodeine (181), desoxycodeine-D (314), α-chlorocodide (313), or their salts absorb one mole equivalent of hydrogen (pseudomorphine, being a dimolecular molecule, absorbs two mole equivalents of hydrogen (253) in the presence of a catalyst (platinum oxide, colloidal palladium and gum arabic or palladium



R = H. OH
LXXX

supported on barium sulfate or charcoal) to yield the respective dihydro derivatives (dihydrocodeine (LXXX) (62) but not codeine (62), dihydropseudocodeine but not dihydroisocodeine (258) have been demethylated

to dihydromorphine and dihydro-γ-isomorphine; thus establishing the relationship between these two series of dihydro bases).

Under ordinary conditions of catalytic hydrogenation, compounds of the pseudocodeine type (with the double bond at Δ^{6-7}) absorb two mole equivalents of hydrogen with reductive fission of the oxide bridge as well as saturation of the double bond. Thus C_4 phenolic tetrahydro derivatives have been obtained from β-isomorphine (258), γ-isomorphine (252), pseudocodeine (31, 192, 246, 251), and its methyl ether (257), allopseudocodeine (31, 255), and pseudocodeinone (258, 331). The same reductive mechanism obtains for ε- and ζ-methylmorphimethine but, with the presence of the second ethylenic linkage in the molecule, hexahydro derivatives result from the absorption of three mole equivalents of hydrogen (33). Abnormal reduction of this type has been used as an experimental criterion for locating the double bond of desoxycodeine-C at this position. The application of this method to the solution of the similar problem for β-chlorocodide failed due to the simultaneous reductive elimination of the halogen atom (313). This abnormal behavior towards catalytic hydrogenation may be largely suppressed for it has been found that the course of the reduction is greatly influenced by the nature of the solvent, the type of catalyst and the pH of the solution (246). By adhering closely to certain well-defined experimental conditions, β- and γ-isomorphine and their alcoholic methyl ethers (252, 258), pseudocodeine (246) and its methyl ether (257), allopseudocodeine (255), pseudocodeinone (259), and desoxycodeine-C (242, 250) have been reduced to nonphenolic (saturation of the ethylene alone) dihydro derivatives.

Dihydroallopseudocodeine (255). Twenty grams of allopseudocodeine hydrochloride in 200 cc. of glacial acetic acid and in the presence of 0.2 g. of platinum oxide absorbs 1748 cc. of hydrogen (1.34 moles). The solvent is removed under diminished pressure, water added, and the solution, when covered with a layer of ether, is made strongly alkaline with dilute sodium hydroxide solution. After several extractions, the ether yields 14.3 g. (80%) of oily dihydroallopseudocodeine which is purified as the acid tartrate. From the alkaline mother liquors 3.2 g. (18%) of tetrahydroallopseudocodeine is obtained. The crude dihydroallopseudocodeine contains traces (up to 7%) of tetrahydrodesoxycodeine, which separates in crystalline form when the oily base is taken up in 60% ethanol. The dihydro base, after purification through its acid tartrate, crystallizes from ethyl acetate-ligroin mixture and melts at 78–79°.

Intramolecular disproportionation of hydrogen in codeine (promoted by the noble metals) has proved to be the most direct route to dihydrocodeinone (336, 337, 338).

Dihydrocodeinone (337). A suspension of 25 g. of finely powdered palladium in a solution of 300 g. of codeine in 2 l. of dilute hydrochloric acid is boiled under a reflux condenser for several hours. The palladium is collected on a filter and the filtrate saturated with sodium hydroxide. The dihydrocodeinone settles out and is collected, washed with water and crystallized from ethanol, m.p. 195°; yield, 85–95%.

Reduction of the benzene nucleus of codeine or related products, as yet, has not been realized (261).

b. Electrolytic Reduction. Electrolytic reduction of a sulfuric acid solution of these bases at a lead cathode has found limited application in this field for the removal of halogen atoms and for the reduction of double bonds and carbonyl groups. Specifically, it has been used successfully in the conversion of α- and β-chlorocodide (241, 320) (also α-chloromorphide (247) and bromomorphide (248) and chlorodihydrocodide (242) to desoxycodeine-B (also desoxymorphine-A) and dihydrodesoxycodeine-C.

The reduction of pseudocodeine (31, 249) and desoxycodeine-C (242) respectively to dihydropseudocodeine and dihydrodesoxycodeine-B are typical examples where this method has been used for the reduction of ethylenic double bonds. The reduction of ketone carbonyls (e.g., codeinone $\rightarrow$ codeine) (331) proceeds with greater facility than does that of ethylenic double bonds. The introduction of the hydroxyl group into codeinone at C_{14}(?) exerts a marked influence on the course of the reduction since now hydrogenolysis of the ether bridge accompanies reduction of the ketone carbonyl and phenolic hydroxythebainol results (30).

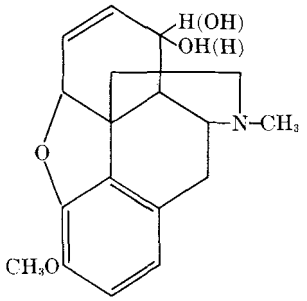
c. Reduction by Chemical Means. The course of the reduction of these bases by chemical means again appears to be largely dependent upon the position of the ethylenic linkage in the hydroaromatic ring III, for, while morphine is not attacked by sodium and alcohol or zinc and acetic acid (148), the oxide bridge of pseudocodeine (251), its methyl ether (257) and that of allopseudocodeine (255) is reductively cleaved with the formation of the respective phenolic dihydro derivatives. Apparently the susceptibility of the oxide bridge to reductive fission is not limited to those bases with an ethylenic double bond at Δ^{6-7} but may be extended, at least in some instances, to those having an unsaturated grouping or even an atom with unshared electrons stemming from C_6. The conversion of codeinone to thebainone ($HCl + SnCl_2$) and of 6-keto-13-ethyloctahydromorphenol methyl ether to 6-keto-13-ethyloctahydromorphol-3-methyl ether (AlHg) (297) as well as that of tetrahydrochloromethylmorphimethine to dihydrodesoxytetrahydro-α-methylmorphimethine (33) are but cases in point. When zinc amalgam (Clemmensen) is applied to dihydrocodeinone, the oxide bridge is ruptured and the ketone carbonyl is reduced yielding predominantly β-tetrahydrodesoxycodeine (as well as some dihydrocodeine) (62), while sodium amalgam yields dihydrothebainol. The reduction of the ketone carbonyl without rupture of the oxide bridge of codeinone can be realized with sodium hydrosulfite (331) (a similar reaction on bromocodeinone is reported to yield dihydropseudocodeinone) (201, 203).

The Emde reduction of methiodides will be considered under the section on fission around the nitrogen atom.

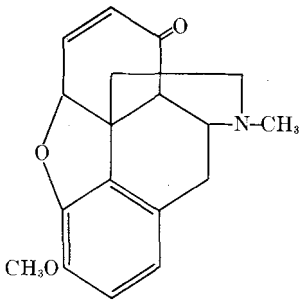
2. Oxidation

The role of oxidative degradation in the elucidation of the structure of these bases has been rather limited because of discouragingly poor yields. In spite of the poor yield the localizing of the nitrogen atom at C_9 or C_{10} is based on the degradation of one of these oxidation products of codeine (the sensitivity of the phenolic hydroxyl of morphine to oxidizing agents has centered most of the attention upon its methyl ether codeine (112)). In contrast to tropine and strychnine, specificity in the oxidation of codeine lies in the choice of conditions rather than in the selection of the oxidizing agent. At 50° chromic acid oxidizes the alcoholic hydroxyl of codeine to a carbonyl group (codeinone), while at 5° a hydrogen on C_9 or C_{10} is oxidized to a hydroxyl group.

a. Chromic Acid and Potassium Permanganate. Codeine (112, 158, 334) and isocodeine (158) are oxidized, in limited yield, by chromic acid (potassium permanganate in acetone proved less satisfactory (112)) at 50° to codeinone, while pseudocodeine (LXXXIII) (145, 149) and allopseudocodeine (LXXXIII) (145, 149) yield pseudocodeinone (LXXXIV). At lower temperatures (5°), chromic acid in sulfuric acid (112, 270) oxidizes



LXXXIII



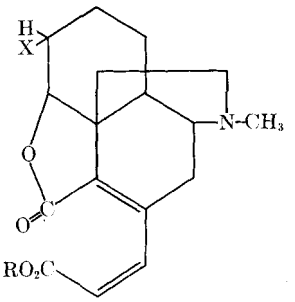
LXXXIV

a hydrogen on the hydrophenanthrene nucleus of codeine to a hydroxyl group (diacetate formation (130)). As has already been shown, this oxidative attack is centered upon a hydrogen contiguous to the nitrogen atom (C_9 or C_{10}).

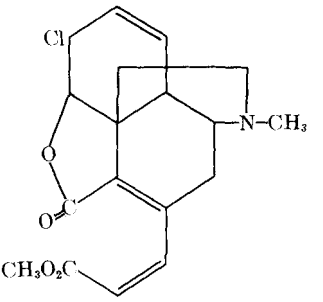
Dilute (1%) aqueous potassium permanganate attacks the ethylene in hydroaromatic ring III of codeine resulting in the glycerol, dihydroxydihydrocodeine (LXXX, R = OH; triacetate formation (291)).

b. Ozone. Morphine, codeine, and a number of related products react readily, in neutral or acid media, with two mole equivalents of ozone with the formation of aldehydes. In some instances, the ozonolysis may be interrupted at an intermediate stage (one mole of ozone), while in others it proceeds to completion. Dihydrocodeine ($C_{18}H_{23}O_3N$), dihydroethylmorphine ($C_{19}H_{25}O_3N$), α-chlorocodide and β-chlorocodide ($C_{18}H_{20}O_2NCl$)

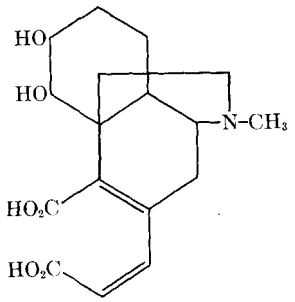
react with 1 mole equivalent of ozone (see Table III) which, on decomposition of the respective ozonides, yield α-ozodihydrocodeine ($C_{18}H_{23}O_5N_2$; LXXXV; R = CH_3, X = OH), α-ozodihydroethylmorphine ($C_{19}H_{25}O_5N$; LXXXV; R = C_2H_5, X = OH), α-ozochlorocodide (LXXXVI) and -ozochlorocodide. In each instance the formula of the ozonolysis product



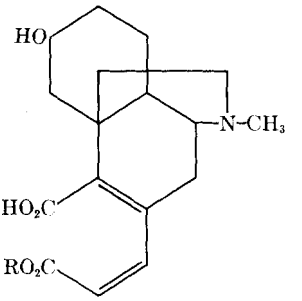
R = CH_3, C_2H_5
X = OH, Cl
LXXXV



LXXXVI



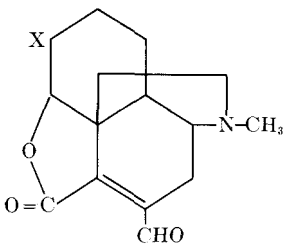
LXXXVII



R = H, CH_3, C_2H_5
LXXXVIII

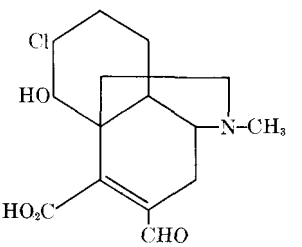
differs from that of the starting product by two oxygens. A Zeisel determination, negative tests for a phenol and formation of an acetyl derivative of the alcoholic hydroxyl as well as its replacement by chlorine (chloro-ozodihydrocodeine (LXXXV, X = Cl)) (207) were sufficient to illustrate the presence of a methoxyl group, the oxide bridge and the C_6 hydroxyl in the ozonolysis product of dihydrocodeine. The center of attack in both dihydrocodeine and dihydroethylmorphine must be the Δ^{3-4} double bond since saponification (1 *N* KOH) converts α-ozodihydrocodeine and α-ozodihydroethylmorphine to dihydromorphinic acid (LXXXVII) (named in analogy to morphinonic acid (207), prepared by heating morphine quinitrol with water (27)). The ethylenic double bond in both α-ozodihydrocodeine and α-ozodihydroethylmorphine is resistant to reduction either by electrolytic means or by gaseous hydrogen in the presence of palladium. Instead,

electrolytic reduction converted the above two bases to 5-desoxydihydromorphinic acid ($C_{17}H_{23}O_5N$) (LXXXVIII, R = H) by hydrogenolysis of the lactone and saponification of the carbomethoxy group of LXXXV. Hydrogen and palladium also hydrogenolyzed the lactone of the last two named bases to yield the respective esters, LXXXVIII (R = CH_3 and C_2H_5). On the other hand, when, as in dihydromorphinic acid, the lactone group is opened, 1 mole of hydrogen (palladium) is absorbed yielding one of the possible dihydro derivatives. A second mole of ozone on these intermediate products yields a mole of the respective glyoxylic ester (characterized as their phenylhydrazones (211) and dihydrocodinal, LXXXIX (X = OH). The course of the ozonolysis of chloroozodihydro-



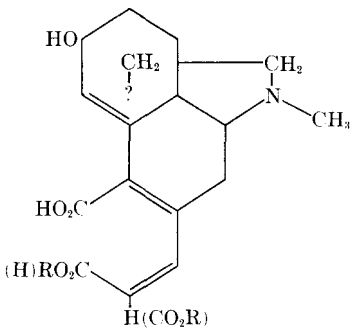
X = OH, Cl, = O

LXXXIX



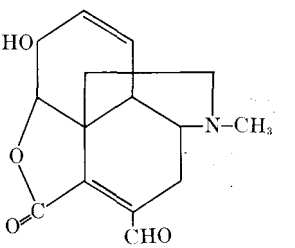
XC

codeine (and that of chlorodihydrocodide)(215) depends upon the conditions. An ethanol-acetic acid solution of the perchlorate yields chlorodi hydrocodinal, while cleavage of the lactone ring accompanies ozonolysis when the solvent is 10% acetic acid (XC). Ozo-α-chlorocodide hydro-



R = CH_3, C_2H_5

XCI



XCII

chloride, in water, gives α-chlorocodinal, the unsaturated analog of LXXXV (X = Cl) (a small amount of chlorocodinal is formed as a by-product in the ozonolysis of α-chlorocodide to ozo-α-chlorocodide (214).

Alcoholic sodium alcoholates at 0° convert α-ozodihydrocodeine into a β-isomer, which, at higher temperatures (50°), is in turn isomerized to a γ-isomer. β-Isomer formation may be considered to result from the hydrolysis of the lactone and the dehydration of the hydroxy acid to XCI (the position of C_{15} in the molecule was not assigned). The α-isomer is probably the *trans* form (about Δ^{1-2}) of XCI, the result of a transformation known to occur in ethylenes under these conditions (214).

Two moles of ozone converts morphine, codeine, dihydromorphine, and dihydrocodeinone respectively to codinal, codinal (XCII) (characterized as its phenylhydrazone), dihydrocodinal (LXXXIX, X = OH) (semicarbazone) and 6-ketodihydrocodinal (LXXXIX, X = =O) (semicarbazone).

It is reported (217) that ozone attacks the Δ^{2-3} double bond of dihydro-α-methylmorphimethine (from dihydrocodeine) with formation of an aldehydic ester (oxime and saponification to an acid), des-*N*-methyl-7, 8-dihydrocodizal-3-methyl ester. The C_6 hydroxyl of this ozonolysis product has been both acetylated and oxidized ($Na_2Cr_2O_7$) to a ketone group.

c. Other Oxidizing Agents. Attempts to gain an insight into the structure of these bases through oxidative degradation has prompted the application of a number of oxidizing agents to these alkaloids. In the main, the results have had no direct bearing on the elucidation of their structure, and, in many cases, the oxidation products were not as well characterized as those described above; in many instances their structures are still undetermined.

Molecular weight determinations have shown that morphine (66) and a number of related products (α-isomorphine (253), β-isomorphine (253), γ-isomorphine (253), dihydromorphine (253), dihydro-γ-isomorphine (253), dihydrodesoxymorphine (253), heterocodeine or morphine-6-methyl ether (253) and metathebainone (39)) undergo oxidative dimerization (74) (in yields of about 85% (15, 253)) when treated with an alkaline solution of potassium ferricyanide.

γ-*Pseudomorphine* (253). A solution of 1.0 g. of γ-isomorphine (m.p. 274°, $[\alpha]_D$ = −94°) in 1 *N* sodium hydroxide is treated with a concentrated solution of 1.2 g. of potassium ferricyanide, and the mixture neutralized with carbon dioxide. The resulting solid is collected, washed, dissolved in hot ammonium hydroxide, and crystallized by boiling off the ammonia. The white, granular crystals (85%) are dried at 160° to remove three molecules of water of crystallization; m.p. 282–283° (vac).

While the three theoretically possible products result from a similar oxidation of a mixture of morphine and γ-isomorphine, it is the mixed dimeric product, morphine-γ-isomorphine, which occurs in preponderant amount (253). Morphine methiodide, under similar conditions, yields pseudo-

TABLE 3

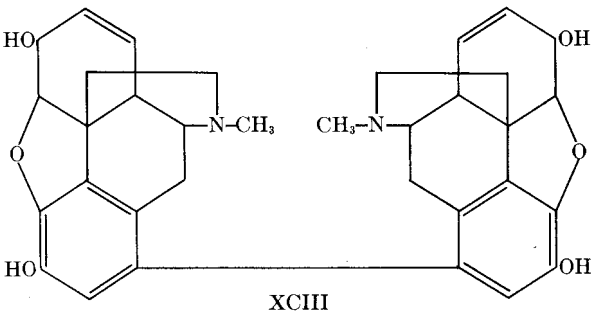
THE OZONOLYSIS OF CODEINE AND RELATED PRODUCTS

Product ozonized	Ozonolysis product	Ozone	Solvent	References
(1) α-Chlorocodide hydrochloride	Ozo-α-chlorocodide hydrochloride	3%	Water	38, 214
(2) β-Chlorocodide hydrochloride	Ozo-β-chlorocodide picrate	3%	Water	214
(3) Chlorodihydrocodide	Chlorodihydrodiconal hydroperchlorate	..	25% Formic acid	211
(4) Chlorodihydrocodide hydroperchlorate	Chlorodihydrocodinal hydroperchlorate	..	Ethanol	211
(5) Chloroozodihydrocodeine hydroperchlorate	Chlorodihydrocodinal hydroperchlorate	8%	Ethanol	211
(6) Chloroozodihydrocodeine hydroperchlorate	Chlorodihydrodiconal hydroperchlorate	..	10% Acetic acid	211
(7) Codeine	Codinal phenylhydrazone	8%	30% Formic acid	207, 214
(8) Des-*N*-methyldihydrocodeine	Des-*N*-methyl-7,8-dihydrocodizal-3-methyl ester	8%	Water	217
(9) Dihydrocodeine	Ozodihydrocodeine hydrochloride	8–10%	25% Formic acid	207
(10) Dihydrocodeinone	6-Ketodihydrocodinal semicarbazone	8%	25% Formic acid	214
(11) Dihydroethylmorphine	Ozodihydroethylmorphine hydriodide	8–10%	25% Formic acid	207
(12) Dihydromorphine	Dihydrocodinal semicarbazone	3–4%	10% Formic acid	211
(13) Dihydrooxycodeinone	..	3.8%	10% Acetic acid	211
(14) Morphine	Codinal phenylhydrazone	8%	Water	211
(15) Ozo-α-chlorocodide hydrochloride	α-Chlorocodinal phenylhydrazone	3%	Water	214
(16) α-Ozodihydrocodeine hydrochloride	Dihydrocodinal phenylhydrazone hydriodide	3%	Water	211
(17) α-Ozodihydroethylmorphine	Dihydrocodinal phenylhydrazone hydriodide	4%	10% Acetic acid	211
(18) β-Ozodihydroethylmorphine	β-Dihydrodiconal phenylhydrazone	8%	Dilute acetic acid	214
(19) γ-Ozodihydroethylmorphine	β-Dihydrodiconal phenylhydrazone	8%	Dilute acetic acid	214

morphine methiodide methohydroxide (66). The above reagent is not specific for such transformations since such oxidizing agents as air, ammoniacal cupric solutions, bromine and hydrogen peroxide-potassium cuprous

cyanide have been reported to convert morphine to pseudomorphine, if in poorer yield.

The mechanism of this reaction appears to be intimately associated with the C_3 phenolic hydroxyl and necessitates an unsubstituted C_1 position for analogous dimeric products were not formed in the case of codeine, diacetylmorphine, methylmorphimethine (15) or bromomorphine (16). In analogy with the 1-1′-union in β-dinaphthol (from β-naphthol) (39) and from the assumed location of the bromine of bromomorphine at C_2, early workers considered the union of the two morphine units of pseudomorphine to be at C_2–C_2'. The subsequent location of the halogen atom in bromomorphine at C_1 (265), although not unequivocal evidence, tends to favor a C_1–C_1' linkage (XCIII).

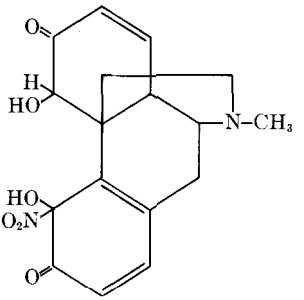


XCIII

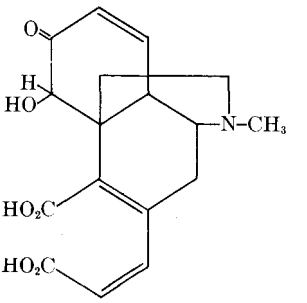
The properties of pseudomorphine and γ-pseudomorphine, however, are not altogether consistent with such structures for, while tetraacetate formation (13, 253) clearly demonstrates the presence of four free hydroxyl groups in these bases, only one of these appears to be phenolic. Pseudomorphine and γ-pseudomorphine may be methylated with sodium hydroxide and methyl iodide and the resulting monomethyl ethers are insoluble in alkali. A similar difference has been observed in the reactions of the two nitrogen atoms. Pseudomorphine monomethyl ether, when heated under pressure with two moles of methyl iodide, yields a dimethiodide which may be converted by hot ammonium hydroxide to the respective methiodide-methohydroxide (15). Pseudomorphine methiodide-methohydroxide reacts quite normally towards acetolysis with the formation of bis (1,1′)-3,4-diacetylmorphol (39). The two ethylenes in these bases react quite normally as is attested by the absorption by pseudomorphine of two mole equivalents of hydrogen (palladium on barium sulfate) (253) to give a tetrahydro derivative identical with that from the oxidation of dihydromorphine (253). Retention of the allylic ether structure in γ-pseudomorphine is also manifest by a similar reaction. Under special conditions a tetrahydro derivative may be prepared, but under normal conditions for

catalytic hydrogenation 4 moles of hydrogen are absorbed with the simultaneous hydrogenolysis of the two ether bridges (253). Catalytic reduction also affords an insight into the constitution of the main product from the oxidation of a mixture of morphine and γ-isomorphine. This oxidation product must be morphine-γ-isomorphine since, under normal conditions, it absorbs three moles of hydrogen (253).

Another oxidizing agent which gives promise of an inroad into the benzene nucleus of morphine is nitrous acid (27). The prolonged action of this reagent on an aqueous solution of morphine gives at best a 30% yield of a yellow solid (accompanied by much 2-nitromorphine) considered to be the nitrate salt of the quinitrol, XCIV. Purification of the salts of



XCIV



XCV

this quinitrol proved difficult and even in warm water an internal oxidation resulted in the generation of morphinonic acid (XCV) (207) (this acid was originally called morphinic acid but, since it gives a ketoxime (27), the name has been altered so as to reveal its true nature).

The action of hydrogen peroxide on morphine (167), codeine (167), ethylmorphine (167), dihydrocodeine (193), chlorodihydrocodide (320), isocodeine (31) and pseudocodeine (31, 193), in contrast to that on thebaine, is limited to amine oxide formation (a dimolecular amine oxide hydrate has also been described for codeine (168)), and the original bases may be regenerated by reduction of the amine oxides by sulfurous acid. The oxidation of codeine-*N*-oxide by potassium chromate to formaldehyde and norcodeine is a practical method for the *N*-demethylation of codeine and would appear to be a reaction that might bear fruitful results if applied to other alkaloids.

3. Substitution in the Benzene Nucleus

A number of reactions resulting in substitution in the benzene nucleus have been applied to morphine, codeine, and related products, and at various times C_1 and C_2 have been considered as the center of attack in these reactions. Such early observations as anhydride formation by diazo-

morphine (from nitrosation of morphine and its reduction to the amine (27)) prompted the suggestion that substitution had occurred ortho (that is at C_2) to the C_3-phenolic hydroxyl of morphine. Furthermore, the analogy of pseudomorphine formation with that of β-dinaphthol (39) and the failure of bromomorphine to form a brominated pseudomorphine appeared to support further the general assumption that substitution occurs at C_2 (16). On the other hand, bromination of dihydrothebainone *para* (at C_1) to the free phenol would appear most reasonable; so that the conversion of bromodihydrothebainone to bromodihydrocodeinone would suggest that substitution, at least in dihydrocodeinone, occurred at C_1. Recently it has been shown that, in general, substitution at C_1 is the rule.

a. Halogenation. With the exception of the bromination of morphine (which yields tetrabromo derivatives of unknown constitution (235)) and of the chlorination of codeine with chlorine or chlorine water (when intractable tars are formed (5a)), halogenation (iodination excepted) of the morphine alkaloids, under suitably chosen conditions, yields homogeneous monohalogenated derivatives. Monobromomorphine has been prepared by bromination of diacetylmorphine (heroin), followed by saponification of the brominated diacetate (16) or by the action of hydrogen peroxide on morphine hydrobromide. That substitution occurs at the same center in the bromination of morphine and codeine has been demonstrated by methylation of the former to the methiodide of bromocodeine (16). While the latter base can be prepared by the action of bromine water upon codeine (5a, 11) (the same is true for pseudocodeine (19)), the most suitable conditions for bromination (and chlorination) of codeine have proved to be the action of hydrogen peroxide on the proper hydrohalide salt (201, 265) acetylation of (16) and the replacement of the alcoholic hydroxyl by a chlorine atom established the immunity of this grouping from attack in the primary halogenation).

Bromocodeine (201). Twenty cubic centimeters of 30% hydrogen peroxide is added to a solution of 5.0 g. codeine hydrobromide in 25 cc. of 30% formic acid and the reaction mixture heated until a lively reaction sets in. When this reaction subsides the cooled mixture is made alkaline with sodium hydroxide, and an oil settles out which solidifies after long standing. The bromocodeine is collected, washed, and crystallized from ethanol (needles); m.p. 162°. The yield from large-scale runs averages about 60% (265).

Bromocodeine ($C_{18}H_{20}O_3NBr$) yields a methiodide ($C_{19}H_{23}O_3NBrI$) (16, 265) and the latter has been transformed by 10% sodium hydroxide solution into bromo-α-methylmorphimethine (16, 265). Acetolysis of this brominated methine gave bromoacetylmethylmorphol which, after saponification of the acetyl group (alcoholic alkali) and methylation of the resulting phenol ($(CH_3)_2SO_4$), proved to be identical with synthetic 1-bromo-3,4-

dimethoxyphenanthrene (Pschorr synthesis: sodium phenylacetate + 6-bromo-2-nitroveratraldehyde) (265). Hence bromination of both morphine and codeine occurred at C_1. This is apparently the only site for substitution in codeine since attempts to nitrate 1-bromocodeine failed.

b. Nitration. Two nitrocodeines ($C_{18}H_{20}O_5N_2$) and one nitromorphine have been reported in the literature. One nitrocodeine (m.p. 221°) has been prepared by nitration of codeine (5a, 163) with strong nitric acid. A supposed isomeric product (m.p. 197°; this may be an impure sample of the former for both gave aminocodeine melting at 228° (170)) was derived from α-codeine-*N*-oxide sulfonic acid by replacement of the sulfonic acid by a nitro group (strong nitric acid) and reduction of the *N*-oxide with sulfurous acid (170) (dihydrocodeine-*N*-oxide sulfonic acid in a similar way yields a nitrodihydrocodeine (193) identical with that from the direct nitration of dihydrocodeine (320), while α-dihydrocodeinesulfonic acid yields an isomeric nitrodihydrocodeine (193)).

The second nitrocodeine (m.p. 172°) was derived by methylation of nitromorphine (prepared by the prolonged action of nitrous acid on morphine (27), and at first considered to be a nitrosomorphine (222)). Electrolytic reduction of this nitrocodeine gave a new aminocodeine which crystallized with one molecule of acetone of crystallization and melted at 95–96.5° (222).

The amine from nitrocodeine (m.p. 221°) has been diazotized and converted by standard reactions to 1-bromocodeine (222) and 1-hydroxycodeine (170). This clearly illustrates that the direct nitration of codeine occurs at C_1 (cyanonorcodeine nitrates at the C_1 position since the same product results from the action of cyanogen bromide on acetylnitrocodeine (181)). The only alternative position then for the nitro group of nitromorphine is at C_2, which now makes the observed anhydride formation in the diazotized amine understandable (27). Also the possibility of rearrangements in the above series of reactions has been disposed of by the regeneration of morphine from the diazotized amine (27). 1-Nitrocodeine and nitropseudocodeine ($C_{18}H_{20}O_5N_2$) have been oxidized by nitric acid, with the loss of two carbon atoms, to nitrocodeic acid ($C_{16}H_{18}O_9N_2$) (112, 163). This aminodicarboxylic acid forms salts with mineral acids which readily dissociate in water, while esterification by the Fischer method is accompanied by the loss of the elements of a molecule of water probably resulting in a lactonic monoester. Reduction of the nitro group with tin and hydrochloric acid yields aminocodeic acid. Hot concentrated halogen acids (HCl and HI) on nitrocodeic acid and amincodeic acid eliminate the elements of a methylene group, yielding nornitrocodeic acid ($C_{15}H_{16}O_9N_2$) and noraminocodeic acid, respectively.

Diazotization of aminocodeine (m.p. 95–96.5°) affords a diazocodeine

which has been converted by standard methods to 2-bromocodeine (222) and 2-hydroxycodeine (27).

c. Acetylation. Acetic anhydride-sulfuric acid mixture introduces three acetyl residues into morphine (333) and two into codeine (164, 333), isocodeine (164a), pseudocodeine (164a), and allopseudocodeine (164a). The two acetyl residues in aceto-6-acetylcodeine show completely different properties. Only one of these can be removed by boiling alcoholic sodium hydroxide, and the resulting acetocodeine (164), like the diacetyl derivative (164, 312), yields an oxime. The resistance of one of the acetyl groups to saponification, combined with the observed failure of acetocodeine to nitrate (164), prompted the inference that the second acetyl group has substituted where nitration normally occurs. This inference has since been shown to be well founded; for a Beckmann rearrangement on the oxime of aceto-6-acetylcodeine, followed by hydrolysis of the derived acetylaminocodeine, gave 1-aminocodeine (m.p. 228°) (312).

d. Sulfonation. The sulfonic acids of a number of these bases have been prepared by sulfonation of the *N*-oxide and subsequent regeneration of the amine with sulfurous acid. The *N*-oxides of codeine (2, 167, 170), dihydrocodeine (193), chlorodihydrocodide (193), isocodeine (31), pseudocodeine (31, 193), and allopseudocodeine (31) have all been sulfonated by sulfuric-acetic acid mixture to give two isomeric amine oxide sulfonic acids (chlorodihydrocodide and dihydrocodeine proved to be the exception when only one sulfonic acid was isolated in each instance). A similar reaction upon morphine-*N*-oxide proved to be abnormal in that a dimeric dimorphine oxide hydrate sulfonic acid anhydride ($C_{34}H_{40}O_{15}N_2S_2$) was formed. Sulfurous acid, however, transformed this dimeric product into the monomeric morphinesulfonic acid hydrate ($C_{17}H_{21}O_7NS$) (2, 167).

Codeine-*N*-oxide, for example, yields a water-soluble α-codeine-*N*-oxide sulfonic acid which isomerizes in acid or alkali to an isomeric sulfonic acid exhibiting a characteristic insolubility in most organic solvents. Sulfurous acid converts these two *N*-oxide acids to the same codeinesulfonic acid (170). No nuclear alteration accompanies these transformations since replacement of the sulfonic acid group by a hydrogen atom (water in a sealed tube at 180° (170)) regenerates codeine. While the nature of the isomerism of the two *N*-oxide sulfonic acids is still obscure, it has been considered that a rearrangement from the codeine to the pseudocodeine structure may be the reason. However, the preparation of two isomeric *N*-oxide sulfonic acids from isocodeine (31), pseudocodeine (31, 193), and allopseudocodeine (31), and their difference from those from codeine, negates this hypothesis. An alternate hypothesis involving a structural isomerism, due to the position of the sulfonic acid group, has been advanced and this may find confirmation in the results of the action of nitric acid on

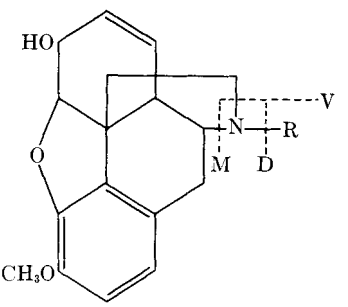
codeinesulfonic acid and on α-codeine-*N*-oxide sulfonic acid. The respective products from these reactions are 1-nitrocodeine (m.p. 221°) (170) and the so-called α-nitrocodeine (m.p. 197°) (170) (the latter may be either a labile isomer of 1-nitrocodeine or just an impure sample of this well-known 1-nitrocodeine (analyses support the latter conclusion), for both isomers yield the same 1-aminocodeine on reduction with tin and hydrochloric acid (170)).

Catalytic hydrogenation ($2H_2$ + Pd) of codeine-*N*-oxide sulfonic acid and α-codeine-*N*-oxide sulfonic acid reduces the *N*-oxide and saturates the codeine double bond yielding, respectively, dihydrocodeinesulfonic acid (available also from the catalytic reduction (H_2 + Pd) of codeinesulfonic acid and from dihydrocodeine-*N*-oxide sulfonic acid (170)) and α-dihydrocodeinesulfonic acid (nitration of the latter yields an α-nitrodihydrocodeine, while the former yields nitrodihydrocodeine identical with that from the direct nitration of dihydrocodeine (320)).

The methohydroxides of codeinesulfonic acid and dihydrocodeinesulfonic acid are readily prepared but show a marked difference in thermal stability. The ease of thermal decomposition of the methohydroxide of codeinesulfonic acid to tetramethylethylenediamine (characterized as the aurichloride (193)) and an unstable nitrogen-free product stands in marked contrast to the reluctance shown by dihydrocodeinesulfonic acid methohydroxide to undergo a similar reaction.

4. Fission Around the Nitrogen Atom

Examination of the generalized formula XCVI will disclose that cleavage about the nitrogen atom can occur in three different ways (for convenience these may be designated as type D (demethylation), type M



R = H, CH_3, C_2H_5, C_3H_7, C_4H_9, C_5H_{11}

XCVI

(methine formation) and type V (where a vinyl group results from the fission)); however, some control may be exercised over the direction of the fission by the proper choice of reagents and conditions. Fission of types

D and M is most common, yet a satisfactory experimental method for discerning between types M and V is still lacking.

a. Fission of Type D. A number of reagents such as nitrous acid (216), dimethyl azodicarboxylate (method A) (178) and chromic acid upon the *N*-oxide (method B) (184) have found limited application in type D fission, yet the most generally serviceable reagent for this fission is a chloroform solution of cyanogen bromide (method C). *N*-Demethylation by this reagent in yields ranging from 40–91% has been reported for acetylcodeine (179), acetyldihydrocodeine (179), acetylmethylmorphimethine (179), acetyltetrahydro-γ-methylmorphimethine (35), acetylnitrocodeine (181), α- and β-chlorocodide (181), desoxycodeine-C and -D (314), diacetyldihydromorphine (179), diacetylmorphine (a small amount of a second product thought to result from cleavage of type M or V has also been isolated) (179), and dihydrocodeinone (189). Application of this reaction to a series of *N*-substituted homologs of codeine has shown that fission of type D predominates over either of the other two types until the exocyclic nitrogen substituent contains five or more carbon atoms (182). Fission of type M occurs in preference to that of type D when a double bond is βγ- to the amine (Δ^{8-14}) (dibenzoylapomorphine) (186).

Norcodeine — Method A (178). To reduce the vigor of the reaction 10 cc. of dimethyl azodicarboxylate is added dropwise to a solution of 10.0 g. of codeine in 30 cc. of methanol. When the reaction is complete, the solvent is removed under vacuum (40°). The residual yellow, resinous mass is dissolved in 40 cc. of 1 *N* hydrochloric acid and warmed on a steam bath until the odor of formaldehyde can no longer be detected. When cold, the solid material is collected, washed with ice-cold water and crystallized from 50% ethanol; yield 4.0 g.

Norcodeine is generated from its hydrochloride by shaking it for 12 hours with 50 cc. of concentrated ammonium hydroxide. The crystals of norcodeine are collected, washed with ice-cold water and crystallized from acetone. The yield of norcodeine, melting at 185°, is 1.6 g.

Method B (184). When 4.0 g. of codeine-*N*-oxide is treated with a 10% aqueous solution of potassium chromate, the reaction mixture froths, becomes exothermic and turns a dark brown, and the odor of formaldehyde is easily detected. After the vigorous reaction has subsided, the reaction mixture is warmed on a steam bath until formaldehyde can no longer be detected. The cold reaction product is then poured into sufficient ethanol to dissolve the organic material; the remaining inorganic material being removed by centrifugation. The amorphous residue, resulting from evaporation of the clear, brown, alcoholic solution, yields the crystalline hydrochloride when rubbed with dilute hydrochloric acid. Crystallization from 50% ethanol yields 1.0 g. of norcodeine hydrochloride.

Method C (179). Heat is evolved when one mole of cyanogen bromide reacts with a solution of one mole of acetylcodeine in three times its weight of chloroform. When this exothermic reaction subsides, the chloroform solution is gently warmed on a steam bath for 2 hours and then evaporated to dryness. The semisolid residue is heated with 10 times the quantity of water, and the solid material collected on a funnel. To remove the last traces of acetylcodeine methobromide the solid is digested with five times its

weight of hot ethanol, and the acetylcyanonorcodeine precipitated by the careful addition of water. The yield of material, melting at 180°, is 80% of theory.

Acetylcyanonorcodeine is hydrolyzed to cyanonorcodeine by heating the acetyl derivative on a steam bath with 8–10 times its weight of hydrochloric acid (sp. g. 1.19). The hydrolysis is arrested 5 minutes after solution is effected by addition of water, and the cyanonorcodeine is recovered as a fine powder. The yield of cyanonorcodeine, melting at 240–245° is almost quantitative. The pure product is obtained by crystallization from ethanol (m.p. 263°).

An 80% yield of norcodeine is realized when 100 g. of cyanonorcodeine is refluxed with 3 kg. of 6% hydrochloric acid for 8 hours. When cold the hydrochloride separates in beautiful cyrstals, and without separating this salt the reaction mixture is made alkaline and the norcodeine extracted with chloroform. Removal of the solvent yields the demethylated base, which melts at 181°.

In 3 days it is possible to convert 100 g. of acetylcodeine to 55.0 g. of norcodeine.

b. Fission of Types M and V— Neopine. While exhaustive methylation, followed by the Hofmann elimination, has been most generally employed in fission of this nature, the Emde method has found limited application. Benzoyl chloride is an effective agent for type M rupture of the tetrahydroisoquinoline system of apomorphine (106).

The Hofmann transformation has been observed in various cases to follow one or more of three theoretically possible courses. Loss of methanol from the methohydroxide and regeneration of the starting base may occur to a small extent, but, on the whole, is of minor importance. Fission of type V has been recognized experimentally in but a single case. In the degradation of the methohydroxide of apomorphine dimethyl ether an optically active base, $C_{20}H_{23}O_2N$ (type V; isomethine) (59), was isolated as well as the expected optically inactive base, $C_{20}H_{23}O_2N$ (type M; methine base) (106). It must be emphasized here that this may not be a good example, since it no longer contains the morphine nuclear structure. The factors governing the course of these fissions are, as yet, rather obscure; however, the nature of the grouping at C_4 appears to be one of the prime factors, while the experimental conditions seem to play but a minor role. It has been observed (309) that δ-methyldihydrothebaine methyl ether follows the normal mechanism, while the parent base with a phenolic group at C_4 yields predominantly the isomethine (type V). While these cases which have been cited may prove to be the exception rather than the rule, yet fission of type V may occur more often than is realized (either as the main product of the reaction or as unidentified by-products). In the absence of good experimental criteria for the diagnosis of the type of fission occurring, a number of these transformation products have been tentatively classed as norma (methine formation) purely in analogy to that for codeine methohydroxide.

Morphine (13), bromomorphine (16), α-isomorphine (280), and the isomeric codeines ($C_{18}H_{21}O_3N$), codeine, isocodeine, pseudocodeine, and

TABLE 4

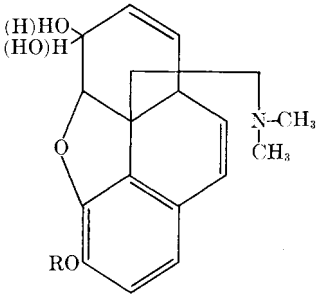
SOME METHO SALTS THAT HAVE BEEN SUBJECTED TO HOFMANN DEGRADATION

Metho salt of	Reagent	References	Metho salt of	Reagent	References
Acetocodeine[a,d]	NaOH	164	Dihydrodesoxycodeine-B[a]	TlOH	250
Allopseudocodeine[a]	NaOH	152			
Bromocodeine[a,d]	$Ba(OH)_2$	16, 148, 265	Dihydrodesoxycodeine-C[a]	TlOH	250
1-Bromodesoxycodeine-C[a]	NaOH	265			
Chlorodihydrocodeine[a]	NaOH	320	Dihydrodesoxycodeine-D[a]	KOH	62
Codeine[a,d]	NaOH	13, 78			
Codeine[c,d]	AgOH	233	Dihydrodesoxycodeine-E methyl ether[a]	KOH	197
	NaOH	13,256			
Codeine methyl ether[a,d]	NaOH	171	Dihydroisocodeine[a]	KOH	31
Desoxycodeine-A[a]	NaOH	153	Dihydropseudocodeine[a]	NaOH	246
Desoxycodeine-A methyl ether[a]	NaOH	153	Dihydropseudocodeine-A methyl ether[a]	NaOH	257
Desoxycodeine-D[a]	NaOH	314	Dihydropseudocodeine-B[a]	KOH	251
Dihydroallopseudocodeine[a]	NaOH	255			
Dihydrocodeine[a]	NaOH	32, 320	Dihydropseudocodeine-C[a]	KOH	251
Dihydrocodeinone[a]	NaOH	189			
Dimethylapomorphine[a,c,e]	KOH or NaOH	106, 133, 212	Piperidocodide[a]	NaOH	111
			Pseudocodeine[a]	NaOH	19,137, 160
α-Ethylthiocodide[a,d]	NaOH	20	Pseudocodeine methyl ether[a]	NaOH	171,175
γ-Ethylthiocodide[a]	NaOH	20			
δ-Ethylthiocodide[a]	NaOH	20	Pseudocodeinone[a]	NaOH	145
9(?)-Hydroxycodeine[a]	NaOH	130, 139, 147	Tetrahydroallopseudocodeine[a]	KOH	31
Isocodeine[a,d]	NaOH	160, 281			
Isocodeine methyl ether[a,d]	NaOH	171, 175	Tetrahydrodesoxycodeine methyl ether[a]	NaOH	320
6-Methyldihydrocodeine[a]	KOH	316	Tetrahydropseudocodeine[a]	KOH	31
Morphine[b,d]	Ac_2O	13, 93			
Neopine[c]	KOH	290			
Nitrocodeine[a]	NaOH	119			

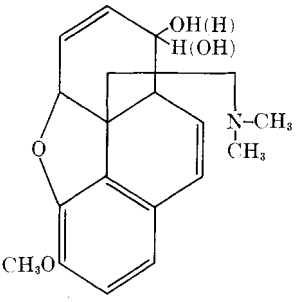
[a] Methiodide.
[b] Methohydroxide.
[c] Methomethyl sulfate.
[d] These methines may be isomerized to an isomeric methine.
[e] Isomethine formation also occurs.

allopseudocodeine, and a number of related products, form methiodides which in turn are converted by alkali (AgOH, KOH, NaOH, $Ba(OH)_2$) to the respective methohydroxides. Some of these methohydroxides, in which there is a free C_3 phenolic hydroxyl group, show a marked thermal stability (to temperatures even as high as 120°) which may be ascribed to phenol betaine formation with this hydroxyl group (13). Cleavage of morphine methohydroxide has been achieved with acetic anhydride, but the primary product (diacetyl derivative of α-morphimethine (XCVII, R = H)) is not stable to this reagent but is degraded further to diacetylmorphol. The primary product is, however, not all degraded to diacetylmorphol, but is partially isomerized to a β-isomer which yields β-methylmorphimethine methiodide upon methylation (CH_3I + $NaOCH_3$) (93).

Those methohydroxides in which the C_3 hydroxyl is protected as its methyl or ethyl ether often undergo a spontaneous transformation at room temperature (83). The methohydroxides of codeine, isocodeine, pseudo-



R = H, CH_3
XCVII

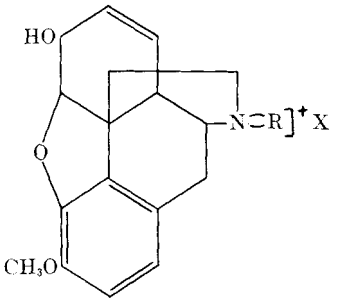


XCVIII

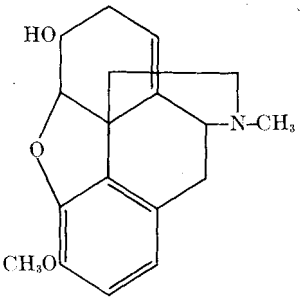
codeine, and allopseudocodeine (see also Table 4) yield respectively the α-, γ- (XCVII, R = CH_3), ε- and ζ- (XCVIII) methylmorphimethines ($C_{19}H_{23}O_3N$). The great susceptibility of the heterocyclic ring of the codeine bases to cleavage of this nature is clearly illustrated by the application of similar conditions to such compounds as XCIX (R = $-CH_2-CH_2-CH_2-$, $-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-C_6H_4-CH_2-$). In every instance fission of type M occurs in preference to cleavage of the newly generated heterocyclic ring (187).

Failure to isolate methines from the methiodides of α-chlorocodide and codeinone proved to be the two notable exceptions to this otherwise general reaction. Gentle heating of the methohydroxide of α-chlorocodide converts this to a product containing an ionizable chlorine (16), which, when made basic, is amorphous and chlorine-free (134). While chloro-α-methylmorphimethine is not directly available in this way, it can be prepared by the replacement of the hydroxyl of α-methylmorphimethine by chlorine (PCl_3 (134), PCl_5 (25)). The marked tendency of codeinone and its

methiodide to arrive at a fully aromatic phenanthrene structure has precluded the isolation of the primary methine base. The isolation of the analogous methine from pseudocodeinone, however, has been reported (145).



R = —CH_2—CH_2—CH_2—
—$(CH_2)_2$—O—$(CH_2)_2$—
—CH_2—C_6H_4—CH_2—
XCIX



C

Heat alone (127), or in combination with one of a number of chemical agents (water (104), aqueous alcohol (104), hydrogen chloride (78), acetic anhydride (76, 104), or ethanolic potassium hydroxide (104, 256)), initiates the isomerization of α-methylmorphimethine to a β-isomer (a similar isomerization of γ-methylmorphimethine to a δ-isomer (105) and of bromo-α-methylmorphimethine to a β-isomer (148) has also been realized: see Table 4).

β-Methylmorphimethine (104, 256). A solution of 20.0 g. of α-methylmorphimethine in ethanolic potassium hydroxide (20.0 g. KOH in 200 g. 60% ethanol) is refluxed for 2 hours. The viscous oil, which separates (19–20 g.) on cooling, crystallizes in prisms from ethanol; m.p. 134–135°.

β-Methylmorphimethine methomethyl sulfate is prepared by combining equal amounts of the base and dimethyl sulfate in alcohol.

β-Methylmorphimethine is also the primary product from the action of potassium hydroxide on neopine methomethyl sulfate (290). The isomerization of α- and δ-methylmorphimethine respectively to the β- and δ-isomers is considered to involve the migration of the Δ^{7-8}-ethylene into a position of conjugation (Δ^{8-14}) with the other center of unsaturation, since, when the unsaturation in ring III is more remote from the Δ^{9-10} double bond, as in ε- and ζ-methylmorphimethine, no such isomerization, under these conditions, has been observed (152).

The nature of the isomerism of α- and β-methylmorphimethine has been diagnosed as structural by hydrogenation experiments. The addition of one mole equivalent of hydrogen to α-methylmorphimethine (Ni) (35) and to β-methylmorphimethine (Ni) (35) afforded two isomeric dihydro

derivatives (dihydro-α-methylmorphimethine is identical with the methine from dihydrocodeine (32, 320); hence, the reduction of the β-isomer must involve the Δ^{9-10} double bond. The dihydro-β-methylmorphimethine is also obtained when the α-isomer is reduced with sodium and ethanol (91a), a reagent that promotes isomerization of the Δ^{7-8} double bond to Δ^{8-14} as well as reduction of the one at Δ^{9-10}, which in turn has been converted to the same tetrahydromethylmorphimethine by the absorption of one mole equivalent of hydrogen over palladium on charcoal (32, 33) (ε- and ζ-methylmorphimethine, on the contrary, yield isomeric hexahydro derivatives) (246, 255). Hence, it is obvious that the Δ^{7-8} double bond is involved in the primary phase of the reduction of α-methylmorphimethine, while the reduction of both α- and β-methylmorphimethine to dihydro-β-methylmorphimethine requires that the Δ^{9-10} double bond is the one involved and that it is the Δ^{7-8} double bond that rearranges in β-isomer formation. On this basis neopine must be C (this also accommodates the reduction of neopine to dihydrocodeine, and requires that the hydrogen adds sterically in only one and the required way (290)).

The degree of unsaturation in these methylmorphimethines is such that little chemical stimulus is required to initiate the transformation of these bases (by elimination of the ethanamine chain) to fully aromatic phenanthrenes. Characterization of the basic fragment as some modification of dimethylethylamine is sufficient to label the primary fission as one of type M (in most instances the experimental recognition of type V fission proves more difficult). Acetic anhydride (72, 75, 76) (other reagents effecting a similar aromatization of the nucleus are hydrogen chloride (78, 115) and sodium ethylate (115)) yields acetylmethylmorphol and the acetyl derivative (the ethoxy derivative when sodium ethylate is used) of β-ethanoldimethylamine as well as some dimethylamine (75) and β-methylmorphimethine (78). The recovery of β-methylmorphimethine (50%) from this acetolysis experiment clearly demonstrates the greater stability of this base over that of the α-isomer (the morphol cleavage of β-methylmorphimethine can be effected when it is heated (150°) with sodium ethylate (115)).

Acetylmethylmorphol (72, 75). Acetylmethylmorphol is prepared by heating α-methylmorphimethine with 5 times its weight of acetic anhydride at 160–200°. Most of the acetic anhydride is then distilled and the residue poured into water when a water-insoluble acetylmethylmorphol settles out; m.p. 131°. The methylmorphol is liberated when the acetyl derivative is boiled with alcoholic ammonia.

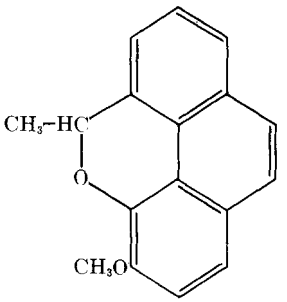
The conversion of α-methylmorphimethine methiodide (AgOH (75) or alkali (13, 81)) to the corresponding methohydroxide (β-methylmorphimethine methohydroxide is stable in boiling aqueous alkali (256)), and its subsequent degradation, undoubtedly yields trimethylamine (13) and

the primary 3-methyl-6-hydroxy-13-vinyltetrahydromorphenol, but the tendency for such a compound to arrive at a fully aromatic state is the driving force for the elimination of ethylene (characterized as its dibromide (81)) and water from this molecule with the formation of methylmorphenol. While this was the original method for preparing this phenanthrylene oxide derivative, it has since been found that substitution of sodium amylate or sodium cyclohexanolate for the alkali results in a marked improvement in the yield of methylmorphenol.

Methylmorphenol (256). The degradation is carried out in a 2-l. three-necked flask fitted with a mercury-sealed stirrer, a thermometer and a delivery tube through which any gas formed is passed into dilute hydrochloric acid. Twenty-eight grams of sodium is added slowly and with stirring to 850 cc. cyclohexanol at 110°. The temperature must then be raised to 120° (140° if the sodium cyclohexanolate begins to separate) during the addition of the β-methylmorphimethine methomethyl sulfate. When the sodium is completely dissolved, 220 g. of the above salt (or 250 g. of the same salt of the α-isomer) is added in portions over a period of 30 minutes and the stirring continued an additional 15 minutes after the last addition.

The cyclohexanol is removed with steam and the residue extracted with ether (emulsions often occur). The extract is washed with dilute hydrochloric acid and then with sodium bicarbonate solution. The residual oil, after removal of the ether, is crystallized from methanol; yield 65–70% of material melting at 64–65°.

As well, small amounts of three other products have been isolated from this reaction (315). One of these, representing about 1% of the morphine used, has the formula $C_{17}H_{14}O_2$, , is optically inactive, contains one methoxyl group and is nonphenolic. Diagnostic reactions for the presence of unsaturation or of alcoholic or ketonic groups in this molecule were negative. These data, combined with its observed conversion to pyrene and a positive test for one *C*-methyl group, suggest CI for this compound (315).



CI

Demethylation (HI) of methylmorphenol proved to be the early route to morphenol (88, 95), but subsequent work has shown that demethylation accompanies degradation when alcoholic potassium hydroxide is applied to the methiodides of β- (102, 171), γ- (281), or ε- (19) methylmorphimethine.

Morphenol (102). A mixture of 2 g. β-methylmorphimethine methiodide, 4 g. potassium hydroxide and 8 g. ethanol is heated in a sealed tube for 4–5 hours at 160°. The cold reaction mixture is poured into a slight excess of dilute sulfuric acid and extracted with ether. The morphenol is extracted, in turn, from the ether with dilute sodium hydroxide and the phenolic product recovered by acidifying the aqueous solution of the sodium salt with sulfuric acid. The crystalline morphenol is purified by conversion (acetic anhydride and sodium acetate) to and the crystallization of its diacetyl derivative (yield 70%).

The extrusion of the vinyl group and the generation of a phenanthrene structure is a general reaction, except where aromatization is blocked by hydrogenation or nuclear substituents (315). The Hofmann degradation of the methohydroxides of dihydro-α-methylmorphimethine and its γ-isomer yields isomeric nitrogen-free products ($C_{17}H_{18}O_3$) as well as trimethylamine and water (31). Tetrahydro-α-methylmorphimethine has been similarly degraded, but the nitrogen-free product was amorphous and proved difficult to purify (32, 320). Several instances of the failure of this reaction, due to the loss of methyl alcohol, have been reported and appear to be dependent upon the state of the oxygen at C_4 (309). Cases where nuclear substitution hinder aromatization of the nucleus are also known. 6-Methyldihydromethylmorphimethine (methyllithium on dihydrocodeinone followed by exhaustive methylation) (316), when subjected to a Hofmann degradation, yields 6-methyl-6-hydroxy-13-vinylhexahydromethylmorphenol which readily absorbs two mole equivalents of hydrogen (PtO_2).

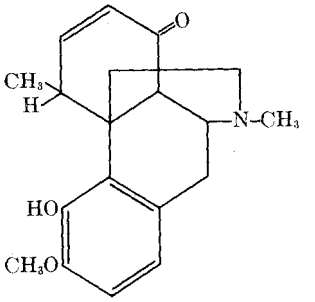
The Emde method of ring fission, while it is an important supplement to the Hofmann method, has found, as yet, but limited application in this field. The observation that α-methylmorphimethine methyl ether results from dimethylmorphine by both the Emde (325) and Hofmann methods has prompted the suggestion that morphine is a substituted β-phenylethylamine, and that hence the nitrogen atom is located at C_9 (36). Further degradation of the methochloride of α-methylmorphimethine methyl ether by the Emde method failed (325). The fission of the heterocyclic ring of dimethylapomorphine methochloride by this method proceeded quite normally to give the expected dimethyldihydroapomorphinemethine (324).

5. The Action of Organometallic Compounds

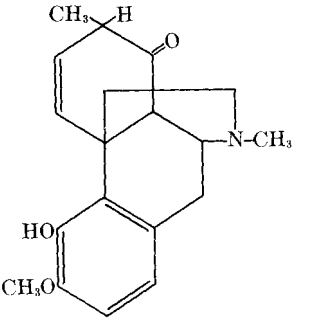
The reaction of organometallic compounds with bases of this series serves as supplementary evidence in the diagnosis of the pseudocodeine type bases (double bond at Δ^{6-7}), for those bases which undergo abnormal reduction (absorption of two mole equivalents of hydrogen with fission of the oxide bridge) invariably react with organometallic compounds.

Grignards fail to react under normal conditions with dihydrocodeinone and dihydropseudocodeinone (259) and with codeine (125) and codeinone (331), even at temperatures of from 150 to 170°. Under forcing conditions

dihydrocodeinone reacts in an abnormal way with methylmagnesium iodide to yield the phenolic ketone, methyldihydrothebainone (316) (the location of the methyl group at C_5 or C_7 is not definitely established (262)). Similarly, methylmagnesium iodide does not attack the ketone group of pseudocodeinone but the ether bridge (259) (pseudocodeine methyl ether reacts similarly (308)) yielding the phenolic ketone, methyldihydropseudocodeinone. It has not, as yet, been possible to determine whether the rupture of the ether bridge occurs by 1,2- (CII) or 1,4- (CIII) addition to the allyl ether system. This keto base fails to react with hydroxylamine and semicarbazide, and is resistant to catalytic hydrogenation and to reduction by sodium and alcohol or the Clemmensen method (259).

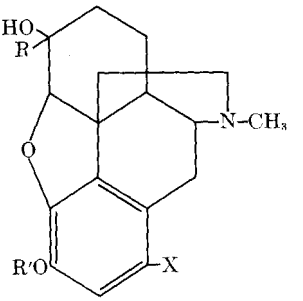


CII



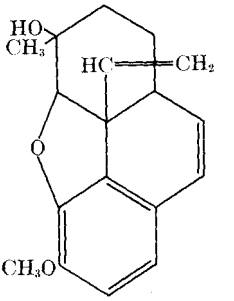
CIII

While the carbonyl groups of codeinone and dihydrocodeinone exhibit a surprising and inexplicable passivity towards organanomagnesium compounds, nevertheless, they do react with the more reactive organolithium



R = CH_3, C_2H_5, C_5H_{11}, C_6H_5
R′ = CH_3, CH_3—O—CH_2—Na
X = H, Cl, Br

CIV



CV

analogs. Methyl-lithium (ethyl-, *n*-amyl-, and phenyl-lithium have also been used) reacts vigorously and quantitatively at 0° with dihydrocodeinone and its C_1-halogen (chlorine and bromine) derivatives yielding the non-

phenolic 6-methyldihydrocodeine (the reaction with codeinone has not been as thoroughly studied) or its halogenated derivatives (CIV) (316). Demethylation at C_3 by the usual methods proved unsuccessful, but 6-methyldihydromorphine (CIV, R = CH_3, R′ = X = H) is available from the action of methyl-lithium on an ethereal solution of the sodium salt of dihydromorphinone (316). Acetylation of the tertiary hydroxyl and its replacement by halogen proved difficult in this homologue of dihydrocodeine, but by the use of a modified procedure the preparation of the acetate was achieved. In all probability phosphorus pentachloride in chloroform replaced the tertiary hydroxyl by chlorine but this labile primary product lost the elements of hydrogen chloride and the product isolated was 6-methyldesoxycodeine-C.

The reactions of the tertiary amine of 6-methyldihydrocodeine proved to be quite normal. Its methiodide is transformed by 30% potassium hydroxide solution into 6-methyldihydromethylmorphimethine, while its methohydroxide (dry distillation in vacuum) in turn afforded 6-methyl-6-hydroxy-13-vinylhexahydromethylmorphenol (CV) (this absorbed 2 mole equivalents of hydrogen over PtO_2).

Methylmagnesium iodide acts as a reducing agent upon α-chlorocodide rather than as a coupling agent (241).

6. The Codides and Morphides

a. Those Containing Chlorine and Bromine. A variety of reagents has been used to replace the alcoholic hydroxyl of a number of these bases by a chlorine or bromine atom (Table 5; fluoro compounds have not been studied and the iodo bases have been prepared in another way). By way of illustration, morphine, codeine, and their dihydro derivatives yield respectively α-chloromorphide, α-chlorocodide, chlorodihydromorphide, and chlorodihydrocodide. The primary halogen containing products of those bases embodying an allyl system may be accompanied by a β-isomer (β-chloromorphide and β-chlorocodide) (313) or may be completely converted to the latter isomer by the reagent (bromomorphide and bromocodide), or by such reagents as fuming hydrochloric acid (156, 157, 202), boiling tetralin or bromobenzene (202), or even by heating the α-isomers above their melting point (this is usually accompanied by much decomposition) (20, 202). The changes occurring throughout these two series of bases are quite comparable since the products derived from morphine and its dihydro derivative have been related to the analogous products of the codeine series by methylation (157, 282).

The observed conversion of codeine and pseudocodeine mainly to α-chlorocodide (202, 313) (it has been reported that a third isomer, chloropseudocodide, results from the action of phosphorus pentachloride on

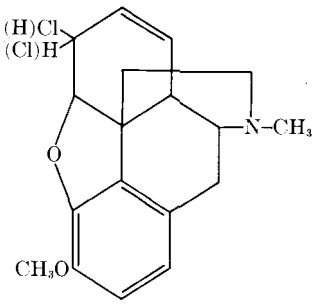
TABLE 5

SOME HALOGENO-MORPHIDES AND -CODIDES

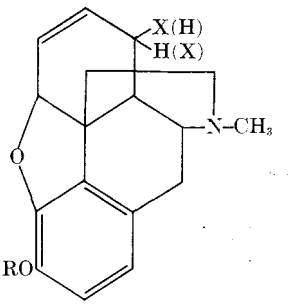
Reactant	Reagent	Product	References
Allopseudocodeine	$SOCl_2$	β-Chlorocodide	202
Bromocodeine	PCl_5	Bromochlorocodide	265
α-Chlorocodide	Conc. HCl	β-Chlorocodide	157
	Heat	β-Chlorocodide	20, 241
	Heat in tetralin	β-Chlorocodide	202
	SO_2Cl_2	Pentachlorooxycodide	313
α-Chloromorphide	Conc. HCl	β-Chloromorphide	156
Codeine	Conc. HCl	β-Chlorocodide	55, 157
	PCl_3	α-Chlorocodide	282
	PCl_5	α-Chlorocodide	11, 20, 241, 282, 320
	$SOCl_2$	α-Chlorocodide	27
	PBr_3	Bromocodide	20, 281, 282
Dihydroallopseudocodeine	PCl_5	8-Chlorodihydrocodide	313
	PBr_3	Bromine- and methoxyl-free product	313
Dihydrocodeine	PCl_5	6-Chlorodihydrocodide	62
	PBr_3	Phosphorus containing compound	313
Dihydrohydroxycodeine-B	PCl_5	Dihydrohydroxychlorocodide	311
Dihydroisocodeine	PCl_5	Phosphorus containing compound	313
	PBr_3	Phosphorus containing compound	313
Dihydromorphine	$SOCl_2$	Chlorodihydromorphide	247
Dihydropseudocodeine	PCl_5	8-Chlorodihydrocodide	313
	PCl_5	1,8-Dichlorodihydrocodide	313
	PBr_3	8-Bromodihydrocodide(?)	313
Isocodeine	$SOCl_2$	β-Chlorocodide	202
β-Isomorphine	PCl_3		281
	HBr	Bromomorphide	281
	PBr_3	Bromomorphide	281
α-Methylmorphimethine	PCl_5	Chloromethylmorphimethine	134
Morphine	Dry HCl	α-Chloromorphide	134
	Conc. HCl	β-Chloromorphide	156, 248, 313
	Conc. HCl	Dichlorodihydrodesoxymorphine	313
	PCl_3	α-Chloromorphide	280
	PCl_3	α-Chloromorphide	160
	$SOCl_2$	α-Chloromorphide	27, 248
	$SOCl_2$	Trichloromorphide	313
	PBr_3	Bromomorphide	248, 280
	PBr_5	Bromomorphide	134
Pseudocodeine	Conc. HCl	β-Chlorocodide	157
	PCl_5	α-Chlorocodide	19
	PCl_5	Pseudochlorocodide(?)	19, 149
	$SOCl_2$	α-Chlorocodide	202
Tetrahydropseudocodeine	PCl_5	Tetrahydropseudochlorocodide	31

pseudocodeine (19, 149); Table 5), while isocodeine and allopseudocodeine yield predominantly the β-isomer (202), is sufficient to demonstrate that this isomerism involves positional (αγ-shift in the allyl system) as well as possible configurational (Walden inversion) changes. Application of the same reagent, on the other hand, to the dihydro derivatives of the codeine isomers removes the possibility of positional changes in the molecule and, at the same time, clearly manifests the occurrence of configurational changes in certain of these transformations. By this reagent dihydropseudocodeine and dihydroallopseudocodeine have been converted to one of the two possible 8-chlorodihydrocodides (some 1,8-dichlorodihydrocodide occurs as a by-product) (313), while dihydrocodeine gave an isomeric 6-chlorodihydrocodide (dihydroisocodeine gave a phosphorus containing compound) (313).

The apparent impossibility of obtaining all four chlorodihydrocodides, due to the Walden inversion which is attendant upon the conversion of one of the dihydrocodeine isomers to 8-chlorodihydrocodide and to the anomalous reaction of dihydroisocodeine with phosphorus pentachloride, has materially impeded the assignment of a structure to β-chlorocodide on other than speculative grounds. Under normal conditions the catalytic reduction of α- and β-chlorocodide involves other changes in the molecule besides reduction of the ethylenic double bond. Under well-controlled conditions (the hydrochloride in acetic acid or alcoholic hydrogen chloride) (313), however, α- and β-chlorocodide have been reduced in part (besides 52% of 6-chlorodihydrocodide α-chlorocodide yields also 40% of tetrahydrodesoxycodeine and 7.5% of dihydrodesoxycodeine-D) to 6-chlorodihydrocodide and β-chlorodihydrocodide, respectively. The latter base



CVI



X = Cl, Br
R = H, CH_3

CVII

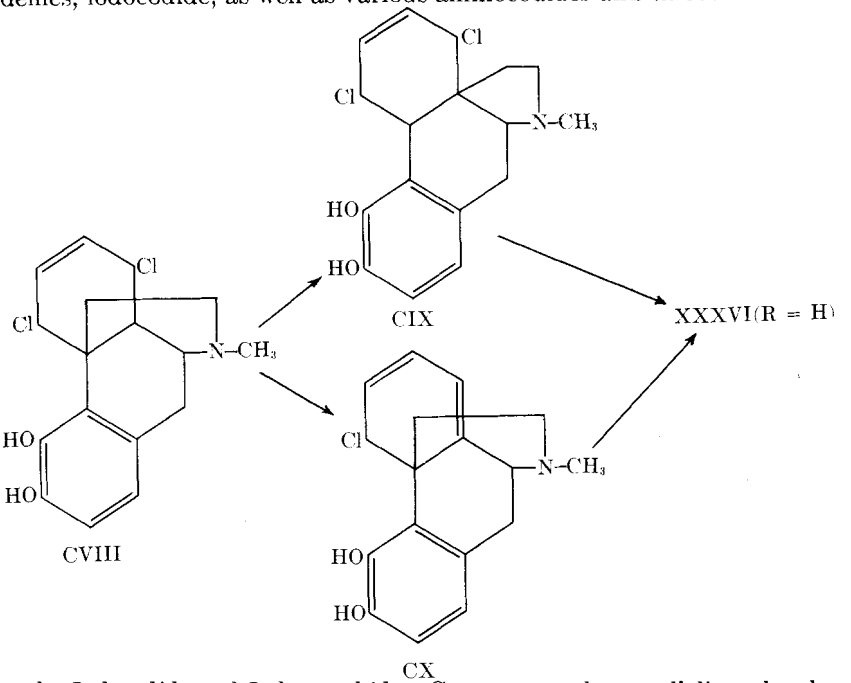
proved to be different from the known 6- and 8-chlorodihydrocodides. Hence, from the evidence at hand, α-chlorocodide is one of the stereoisomers of CVI, while various metathetical reactions suggest that β-chlorocodide (see aminocodides) has structure CVII (R = CH_3, X = Cl).

The ambiguity in the structure of β-chlorocodide (and hence of β-chloromorphide) has obscured the mechanism of formation of apomorphine from morphine (codeine and hydrochloric acid under pressure yield apomorphine and methyl chloride (55)), for it has long been considered that β-chloromorphide is an intermediate in this conversion (156). The primary product from the action of fuming hydrochloric acid on morphine is probably α-chloromorphide, which is unstable under these conditions and is isomerized to the more stable β-isomer (156, 202, 313). Under the conditions imposed for apomorphine formation, the oxide bridge (activated by the Δ^{6-7} double bond) of β-chloromorphide is cleaved with addition of the elements of hydrogen chloride resulting in the third intermediate, dichlorodihydrodesoxymorphine (CVIII) (313, 339), which in turn gives yields of apomorphine (XXXVI, R = H) equal to those from morphine (313). While the evidence is not complete yet, the first three stages in the conversion seem apparent and these are sufficient to refute the previous hypothesis of a sequence of multiple additions and eliminations of the elements of hydrogen chloride (42). While CIX may be the subsequent transitory intermediate in the formation of apomorphine, it is considered more probable that apomorphine is formed by loss of hydrogen chloride from C_8–C_{14} (CX), and that the subsequent $\alpha\gamma$-shift of the chain from C_{13} to C_8 is accompanied by loss of a second molecule of hydrogen chloride (313).

More highly chlorinated derivatives than dichlorodihydrodesoxymorphine have also been prepared from morphine (313), but their structures are still obscure. A trichloromorphide has been isolated as a by-product from the action of thionyl chloride on morphine. The product ($C_{17}H_{16}O_2NCl_3$) is phenolic and on methylation yields a trichlorocodide. Two of the halogens are probably at C_1 and C_6 (or C_8) but the location of the third one is not obvious. Sulfuryl chloride on α-chlorocodide yields *pentachlorooxycodide* ($C_{18}H_{20}O_3NCl_5$) (313). The analytical figures make it apparent that addition and not substitution has occurred.

In contrast to the chloromorphides and the chlorocodides, only one *bromomorphide* and *bromocodide* have been prepared. The failure of bromocodide to isomerize on heating (20, 313), combined with results of amination (267) and hydrolysis (159) experiments, has prompted the conclusion that the bromo series may have the same structure as the β-chloro series, although there is no reason why the α-bromo series should not exist (313). There appear, however, to be a few inconsistencies. In view of the above parallelism between the β-chloro and bromo compounds it is surprising that α-chloromorphide and bromomorphide should yield the same *iodomorphide*, while the halogen of β-chloromorphide (313) and of β-chlorocodide is indifferent, even under more vigorous conditions (see also amino-

codides). The ease with which these halogenated bases take part in metathetical reactions has been employed in the preparation of the isomeric codeines, iodocodide, as well as various aminocodides and thiocodides.



b. Iodocodide and Iodomorphide. Contrary to the parallelism that has been developed between β-chlorocodide and bromocodide, α-chloromorphide and bromomorphide exhibit a marked similarity in their reaction with potassium iodide (in dilute acetic acid) (313). The metathetical reaction of α-chloromorphide and bromomorphide with this reagent proceeds with such great ease that it has been found impossible to prepare the hydriodides of these bases in this way. Instead, the hydriodide of iodomorphide results in good yield. Iodomorphide and iodocodide belong to the same structural and stereochemical series, since the former is converted into the latter with diazomethane (313).

Iodocodide results also from the action of potassium iodide on a boiling alcoholic solution of α-chlorocodide (173a) (but not from β-chlorocodide (241)), and in limited quantities when α-chlorocodide reacts with alkylmagnesium iodides (241). Since iodocodide, like α-chlorocodide, is further converted into desoxycodeine-A by Grignard reagents, it has been postulated that iodocodide may be an intermediate in the conversion of α-chlorocodide to desoxycodeine-A (241).

Hydrolysis of iodocodide with silver acetate and acetic acid at room

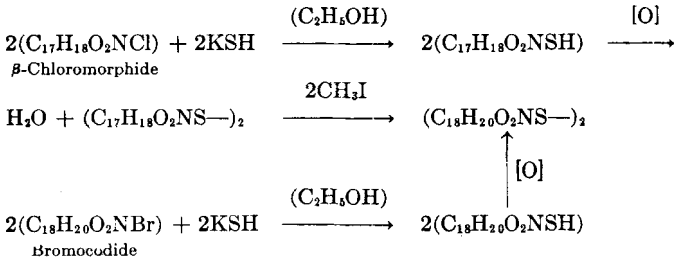
temperature yields a separable mixture of isocodeine, pseudocodeine, and allopseudocodeine (173a).

c. The Amino-codides and -morphides. Treatment of the halogenocodides and -morphides with ammonia or secondary amines effects an exchange of an amino group or disubstituted amino group for the halogen atom. While all possible combinations have not been tried, the halogen of α-chloromorphide (27, 267), bromomorphide (267), α-chlorocodide (111, 185, 267), β-chlorocodide (267) and bromocodide (267) has been replaced by an amino group upon application of such reagents as liquid ammonia (bromocodide failed to react with this reagent) (267), dimethylamine, diethylamine, and piperidine. As is well known, exchange reactions involving allyl systems of this nature may involve both configurational and positional changes. Unfortunately a physical or chemical method for the elucidation of the configuration of the amino group at C_6 or C_8, in the derived aminocodide, with respect to some arbitrarily chosen standard, is still lacking. Catalytic hydrogenation, on the other hand, does offer a possible means of locating the double bond in these products at either Δ^{6-7} or Δ^{7-8}, and hence makes it possible to assign a position to the amino group. In aminococide, diethylaminocodide, piperidomorphide, and piperidocodide, resulting from the α-series of halogen compounds, the double bond is located at Δ^{6-7}; since, under normal conditions for hydrogenation, two mole equivalents of hydrogen are absorbed yielding the respective phenolic tetrahydro derivatives. If, on the other hand, their hydrochlorides are reduced in glacial acetic acid solution, then nonphenolic dihydro derivatives result (267). Hence an allylic rearrangement has occurred and the amino group is at C_8 in all the cases cited.

If a similar α,γ-shift occurs in the formation of aminocodides from β-chlorocodide (or bromocodide), and the amino group can be indirectly located by hydrogenation experiments, then this would locate the halogen of β-chloromorphide and β-chlorocodide. The piperidomorphide and piperidocodide, resulting respectively from β-chloromorphide and its methyl ether (or bromocodide), cannot be induced to absorb more than one mole equivalent of hydrogen (267); whence, the double bond of these diacidic bases has been assigned to Δ^{7-8} and the amino group to C_6. On this basis the chlorine of β-chlorocodide is at C_8 (267).

d. Thiocodides and Thiomorphides. Attempts have been made to prepare the C_6–thio analogs of the morphine and codeine isomers by replacing the halogen of the halogenomorphides (β-chloromorphide and bromomorphide) and bromocodide by a sulfhydryl group (KSH + C_2H_5OH) (134). These attempts have been attended with failure due to the marked susceptibility of the primarily formed thioalclohol to aerial oxidation at this grouping. Bisthiomorphide, derived in this way from the halogenomor-

phides, is convertible into bis-thiocodide (obtainable also from bromocodide) by methylation with two mole equivalents of methyl iodide in the presence of sodium ethylate (134). This oxidative dimerization and methylation may be expressed as follows:



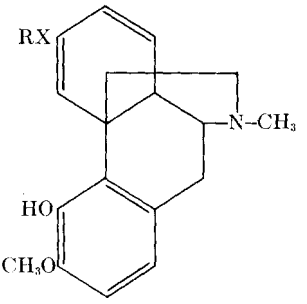
The protection of the sulfhydryl group of these transitory thiomorphides and thiocodides as their methyl and ethyl ethers reduces to some extent (see γ-ethylthiocodide) their susceptibility to oxidation by air, so that β-ethylthiomorphide as well as a number of ethylthiocodides have been prepared.

α-Ethylthiocodide (the analog of α-chlorocodide) is prepared by treatment of β-chlorocodide or bromocodide with ethylmercaptan and aqueous alkali at 100° (20, 254), while under comparable conditions α-chlorocodide yields δ-ethylthiocodide (20, 254) (the analog of β-chlorocodide). β-Ethylthiocodide, a third isomer, results when α-ethylthiocodide is heated with sodium ethylate (134) or directly when bromocodide reacts with ethylmercaptan in the presence of sodium ethylate (134) (β-ethylthiomorphide is formed in an analogous way) (22). A supposed fourth isomer, γ-ethylthiocodide, has been described in the literature, but this proved to be the sulfoxide of the β-isomer (254).

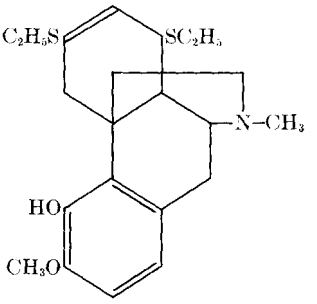
Structures have been assigned tentatively to α- and γ-ethylthiocodide but the evidence for these is more speculative than was the case for the aminocodides. Experiments designed to locate the alicyclic double bond in these two isomers by catalytic hydrogenation failed, since hydrogenolysis of the mercaptal grouping generated sufficient mercaptan to poison the catalyst (254). Under these exigencies it has been found necessary to assign a structure to the α-isomer on the basis of its relation to β-ethylthiocodide and of its reduction (Na + C_2H_5OH) to dihydrothebainol (254). Evidence for the pseudocodeine-like structure that has been assigned to β-ethylthiocodide is based on various addition and reduction reactions characteristic for such a structure.

β-Ethylthiocodide ($C_{18}H_{20}O_2NSC_2H_5$) is a weakly acidic phenol (solubility in alkali, ferric chloride test (254), formation of an acetyl derivative (21) and betaine formation when the methiodide is treated with strong

alkali (21)). The phenolic nature of this base, combined with its hydrogenation to a tetrahydro derivative without the elimination of the thioethyl grouping, justifies the assumption of two double bonds in ring III. Furthermore, the facile hydrolysis (cold 0.1 *N* hydrochloric acid) of this base (21, 245) to thebainone ($C_{18}H_{21}O_3N$; that is, loss of C_2H_4S and the gain of one oxygen atom) would suggest that it is a thioenol ethyl ether, and thus locating one of the alicyclic double bonds at either Δ^{5-6} or Δ^{6-7} and the mercaptal grouping at C_6. Position Δ^{5-6} for this double bond appears to be favored since codeine-6-methyl ether (the oxygen analog of α-ethylthiocodide) undergoes an analogous isomerization to thebainone methyl enolate (CXI, RX = OCH_3) (310), which, like β-ethylthiocodide, is hydrolyzed with facility to thebainone (310).



RX = CH_3O, C_2H_5S
CXI

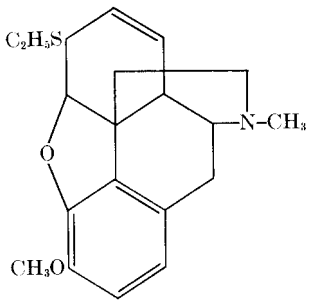


CXII

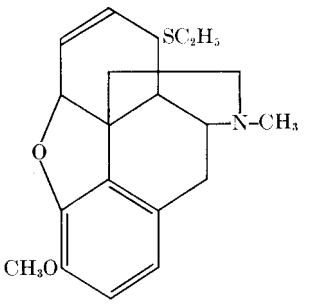
Thebainone methyl enolate (310). A solution of codeine methyl ether (m.p. 141–142°, $[\alpha]_D^{22} = -194.5°$) in absolute ethanolic sodium ethylate (80 cc. ethanol and 2.4 g. of sodium) is heated in a sealed tube at 100° for 4 hours. When cold, 150 cc. of water is added and the alcohol removed under an atmosphere of hydrogen and at diminished pressure (temperature 25°). The product separates as pink crystals and that remaining in solution is salted out by the addition of saturated ammonium chloride solution. The crystals, when collected, are washed with water and dried in vacuum; yield 9.5 g. After two crystallizations from absolute ethanol the colorless, granular crystals melt at 154–156° with some previous softening.

One mole of ethyl mercaptan will add to β-ethylthiocodide and the resulting dihydro-β-diethyldithiocodide (CXII) is still subject to acid hydrolysis (21). Ethylthiodihydrothebainone, the acid hydrolyzate, is identical with the product obtained from the 1,4-addition of ethyl mercaptan to thebainone (254). Hence, the second double bond of β-ethylthiocodide is at Δ^{7-8} and is in conjugation with that at Δ^{5-6}. On this evidence β-ethylthiocodide is considered to have the structure CXI (RX = C_2H_5S). If this structure be accepted for β-ethylthiocodide, then CXIII would logically account for the conversion of α-ethylthiocodide to the β-isomer and for its reduction to dihydrothebainol (254). From the similarity between the reactions of desoxycodeine-C and γ-ethylthiocodide,

the latter is considered to be an allylic ether and probably represented by structure CXIV (254).



CXIII



CXIV

The methiodides of α- and δ-ethylthiocodide react normally towards alkali yielding α- and δ-ethylthiomethylmorphimethine, respectively. As might be expected (α-methylmorphimethine → the β-isomer), α-ethylthiomethylmorphimethine (but not the δ-isomer) is isomerized by sodium ethylate to β-ethylthiomethylmorphimethine (not the methine of β-ethylthiocodide) (20). This isomerization probably involves a migration of the double bond from Δ^{7-8} to Δ^{8-14}. The latter methine is also available from the interaction of chloromethylmorphimethine with ethylmercaptan in the presence of sodium ethylate (20).

Further degradation of δ-ethylthiomethylmorphimethine (but not the α-isomer) yielded a crystalline tetrahydrovinylethylthiomorphenol methyl ether and trimethylamine (20).

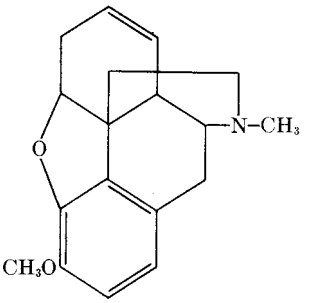
7. The Desoxycodeines

The hypothetical desoxycodeine (CXV), as the name implies, should be derived from codeine by the loss of one oxygen atom, and the oxygen atom in question is that of the alcoholic hydroxyl. Although the preparation of this desoxy base has not been realized as yet,* isomeric compounds agreeing with the required formula $C_{18}H_{21}O_2N$ have been obtained from codeine and its derivatives by elimination of a molecule of water with the accompanied addition of one molecule of hydrogen.

a. Preparation of the Desoxycodeines and Their Hydro Derivatives. A compound fitting this formula has been prepared by the reduction of an absolute ethanolic solution of α-chlorocodide (CVI) (153), β-chlorocodide (CVII; R = CH_3, X = Cl) (157), bromocodide (153), or pseudochlorocodide (149, 153) with zinc dust. The isolation of other so-called desoxycodeines ($C_{18}H_{21}O_2N$), for clarity, required that the above isomer be designated desoxycodeine-A. The action of alkylmagnesium iodides (methyl

*This true desoxycodeine-E has just been prepared by P. Karrer and G. Widmark, Helv. Chim. Acta, *34*, 34 (1951) by the lithium aluminum hydride reduction of codeine tosylate.

and ethyl) (241) on α-chlorocodide led not to the expected homodesoxycodeine but, instead, to a good yield of desoxycodeine-A and small, variable amounts of iodocodide. The halogen of iodocodide, like that of α-chlorocodide, proved to be quite labile in its reactions with alkyl magnesium



CXV

halides. The isolation of desoxycodeine-A from this reaction prompted the early workers (241) to postulate that iodocodide was an intermediate in this formation of desoxycodeine-A from α-chlorocodide.

A second isomer, desoxycodeine-B, although at first incorrectly diagnosed by Freund (320) as a dihydrodesoxycodeine, results from the electrolytic reduction of a 20% sulfuric acid solution of α-chlorocodide at a lead cathode. Freund also stated (and later verified (241)) that this base was formed by the electrolytic reduction of β-chlorocodide, chlorodihydrocodide and desoxycodeine-A. The evidence upon which the reduction product was characterized as a dihydrodesoxycodeine was based on (1) analytical data and (2) the catalytic reduction of 0.4 g. of the material (the source of which was not given). Since definite analytical proof for the presence of two hydrogen atoms in a compound of molecular weight 283 is questionable, and if the material used for the catalytic hydrogenation were from the electrolytic reduction of desoxycodeine-A or chlorodihydrocodide, then only one mole of hydrogen would be absorbed. Small and Cohen have asserted that the electrolytic reduction of α- or β-chlorocodide led actually to an isomeric desoxycodeine-B. This conclusion was substantiated by reduction of this base over Adams' platinium oxide catalyst or palladium on barium sulfate (2 moles of hydrogen absorbed) to give a quantitative yield of tetrahydrodesoxycodeine. Moreover, this reduction was also achieved in a stepwise fashion. Sodium and alcohol gave a dihydrodesoxycodeine which in turn absorbed one mole equivalent of hydrogen (PtO_2) yielding the same tetrahydrodesoxycodeine (241, 242).

Since a parallel electrolytic reduction of α-chloromorphide resulted in the formation of desoxymorphine-A (converted to desoxycodeine-A by

methylation), and the sodium-alcohol reduction of both desoxycodeines-A and -B gave rise to the same dihydrodesoxycodeine, it was speculated that desoxycodeines-A and -B are identical. This was proved when it was successfully demonstrated experimentally that desoxycodeine-B actually consists mainly of desoxycodeine-A with an uncertain amount of an extraordinarily persistent impurity (247). Minute quantities of this impurity were isolated in crystalline form and it has been suggested that it might represent a true desoxycodeine-B because it can be hydrogenated to tetrahydrodesoxycodeine, and also in the large scale catalytic reduction of the so-called desoxycodeine-B two mole equivalents of hydrogen were always absorbed. This conjecture, however, cannot be unequivocally accepted for the possibility that part of the desoxycodeine-A might be further reduced electrolytically to a dihydrodesoxycodeine must not be excluded.

Desoxycodeine-C, a nonphenolic isomer, was prepared by the treatment of chlorodihydrocodide with an absolute methanolic solution of sodium methylate at 140° for 24 hours (244). Prior to this time, this, too, had been incorrectly diagnosed as a dihydrodesoxycodeine. The C_6–methyl homolog of desoxycodeine-C has been prepared by the action of thionyl chloride upon 6-methyldihydrocodeine (CIV; R = R′ = CH_3, X = H) (316). When phosphorus pentachloride was the reagent, a simultaneous substitution occurred at C_1 yielding 1-chloro-6-methyldesoxycodeine-C (316).

Desoxycodeine-D, the second nonphenolic desoxy base to be described, was prepared by the prolonged treatment of 8-chlorodihydrocodide (from the action of phosphorus pentachloride on dihydropseudocodeine or dihydroallopseudocodeine (313)) with sodium and boiling cyclohexanol (314).

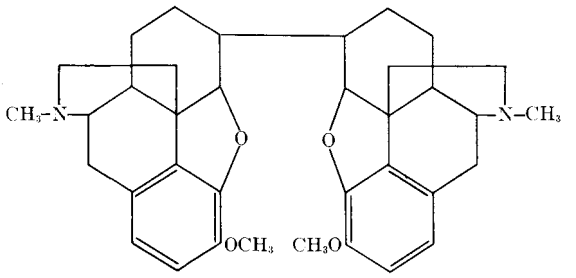
Five dihydrodesoxycodeines have been described and of these dihydrodesoxycodeine-D is nonphenolic, while dihydrodesoxycodeine-A has been shown to be a mixture of dihydrodesoxycodeines-B and -C, occurring in the constant ratio of 1 to 3 (250).

Dihydrodesoxycodeine-B and dihydrodesoxycodeine-C were prepared respectively by the electrolytic reduction of desoxycodeine-C and chlorodihydrocodide (242), while the mixture of these two dihydrodesoxy-bases (dihydrodesoxycodeine-A) resulted from the sodium and alcohol reduction of α-chlorocodide, desoxycodeine-A (153, 242), desoxycodeine-C, pseudocodeine (255), or allopseudocodeine (255), and by the electrolytic reduction of desoxycodeine-A (242). The attainment of this mixture as an apparent homogeneous compound with constant properties was the result of the extraordinary tendency of the B- and C-isomers, as well as their salts, to crystallize together. The separation into the two component dihydrodesoxycodeines was effected through fractional crystallization of the mixture itself or of their methine bases (250).

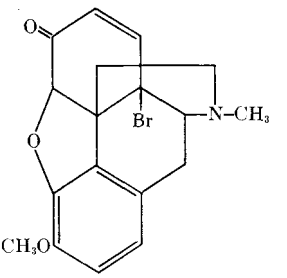
It may be recalled that Freund *et al.* (320) erroneously stated that the same dihydrodesoxycodeine is obtained from the electrolytic reduction of α- and β-chlorocodide, chlorodihydrocodide or desoxycodeine-A. Subsequent work (241, 242), however, has shown that the electrolytic reduction of α- and β-chlorocodide resulted in the formation of desoxycodeine-A containing small amounts of a persistent impurity, while chlorodihydrocodide led to dihydrodesoxycodeine-C, whereas desoxycodeine-A afforded a 1:3 mixture of the dihydrodesoxycodeines-B and -C.

Dihydrodesoxycodeine-D, the only nonphenolic dihydrodesoxy base, yet prepared, was obtained in quantitative yield from the catalytic reduction (PtO_2) of desoxycodeine-D (314) and was described as the major product from the catalytic hydrogenation (Pd on $BaSO_4$) of β-chlorocodide (62, 242) or desoxycodeine-C in glacial acetic acid (PtO_2) (247) (in both cases tetrahydrodesoxycodeine was also formed). The purification of this base was most simply accomplished through its crystalline acid tartrate.

The products obtained from the hydrogenation of α-chlorocodide or bromocodide depended largely on the experimental conditions (243). When the hydrogenation of α-chlorocodide was carried out slowly in acetic acid solution in the presence of colloidal palladium, a 95% yield of dihydrodesoxycodeine-D was realized; whereas with palladium on barium sulfate, the yield was quantitative. As the amount of catalyst and the speed of the reaction increased, the yield of dihydrodesoxycodeine-D progressively decreased to 40%, while at the same time the tetrahydrodesoxycodeine (5%) and an amorphous alkali-insoluble compound (45%) were formed. Moreover, the yield of this amorphous base could be increased to 95–100% when the catalyst was palladium on calcium carbonate, and it became the exclusive product when the catalyst was platinum oxide. Except for slightly inferior yields, the behavior of bromocodide toward catalytic hydrogenation was the same as that of α-chlorocodide.



CXVI



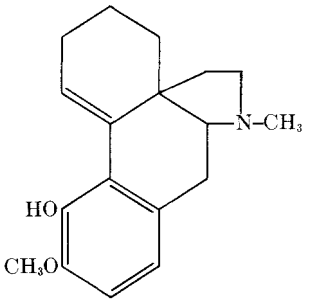
CXVII

In the early stages of this work the amorphous base was incorrectly designated as α-dihydrodesoxycodeine (320). Actually, it is bis-dihydrodesoxycodeine (CXVI) whose dimolecular nature was manifest by its forma-

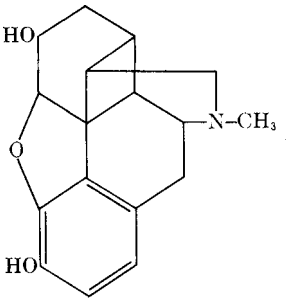
tion of a crystalline monomethiodide, $(C_{18}H_{22}O_2N)_2 \cdot CH_3I$, which in turn could be transformed into an amorphous dimethiodide, $(C_{18}H_{22}O_2N \cdot CH_3I)_2$.

The fifth dihydrodesoxy isomer, dihydrodesoxycodeine-E, was obtained from the electrolytic reduction of bromocodeinone (CXVII) at a lead cathode (197, 242).

Dihydrodesoxymetacodeine (CXVIII), isomeric with the dihydrodesoxy bases derived from the normal codeine series, was prepared by the Wolff-Kischner reduction of metathebainone (CXLI) (249).



CXVIII



CXIX

Tetrahydrodesoxycodeine is the end product of reduction of all known desoxy- and dihydrodesoxycodeines. It has also been obtained directly from the catalytic hydrogenation of α- and β-chlorocodide (the yield is largely dependent upon experimental conditions) (243). With a very active catalyst (platinum oxide), tetrahydrodesoxycodeine was the exclusive product of reduction of β-chlorocodide, whereas the α-isomer gave only bis-dihydrodesoxycodeine.

In the early literature, this base was designated as β-tetrahydrodesoxycodeine to accommodate the statement (320) that the desoxydihydrocodeine of Knorr and Waentig (153) (from the sodium-alcohol reduction of desoxycodeine-A) was actually an α-tetrahydrodesoxycodeine. This fallacious assertion was later challenged when the reduction products were shown to be the isomeric dihydrodesoxycodeines-B and -C (242, 250). This so-called α-tetrahydrodesoxycodeine has also been reported as the end product in the catalytic reduction (colloidal Pd) of β-chlorocodide (at that time erroneously called allopseudochlorocodide) (31). In this instance it proved to be a mixture of dihydrodesoxycodeine-D and the true (β-) tetrahydrodesoxycodeine (62, 242).

With the supposed isomerism of the tetrahydrodesoxycodeines as a basis, Freund advanced his bridge formula for morphine (LXIV) and regarded the isomerism to be the result of a reductive rupture of either the C_5–C_{15} or the C_8–C_{15} bond. Gulland and Robinson, adopting a similar hypothesis, represented morphine as CXIX (287). The overwhelming

evidence in favor of a double bond in the hydroaromatic ring III necessitated a modification of the bridge formula when the supposed isomerism of α- and β-tetrahydrodesoxycodeine was considered to be a steric one about C_{14}

The formation of tetrahydrodesoxycodeine in the reduction of allopseudocodeine is considered to result from the primary 1,6-addition of hydrogen followed by reduction of the derived desoxycodeine-A (255). Tetrahydrodesoxycodeine, like all the known phenolic desoxy- and dihydrodesoxycodeines, contains one-half molecule of water of crystallization. When distilled or sublimed in high vacuum, an anhydrous tetrahydrodesoxycodeine was obtained which in turn slowly changed to a second anhydrous modification. When crystallized from dilute alcohol or acetone, both anhydrous forms revert to the hemihydrate.

Desoxymorphine-A was prepared by the electrolytic reduction of α-chloromorphide (247). It proved to be the demethylated analog of desoxycodeine-A, since on treatment with diazomethane a good yield of the latter base was realized.

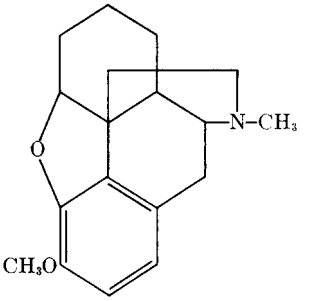
Desoxymorphine-C, most conveniently prepared by demethylation of desoxycodeine-C with sodium methylate, is the product from the treatment of chlorodihydromorphide with sodium methylate in an autoclave at 140° (247). When a glacial acetic acid solution of the hydrochloride of desoxymorphine-C is hydrogenated over platinum oxide, approximately equal amounts of dihydrodesoxymorphine-D and tetrahydrodesoxymorphine were formed. After separation of the sparingly soluble tetrahydrodesoxymorphine from the reduction product, methylation with diazomethane resulted in the formation of nonphenolic dihydrodesoxycodeine-D.

Tetrahydrodesoxymorphine is the end product in the catalytic reduction of desoxymorphine-A and -C. It has been prepared also by demethylation of tetrahydrodesoxycodeine with hydriodic acid. Furthermore, by a mechanism analogous to the formation of tetrahydrodesoxycodeine by catalytic reduction of allopseudocodeine, traces of tetrahydrodesoxymorphine have been recovered from the hydrogenation of β-isomorphine (258).

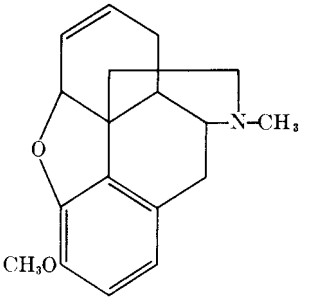
In 1900, the formation of a desoxymorphine hydrochloride by reduction of α-chloromorphide with tin and hydrochloric acid was reported (280). Attempts to repeat this work, however, have failed (247).

b. Location of the Double Bonds in the Desoxycodeines and Their Dihydro Derivatives. Structurally, the desoxycodeines and their dihydro derivatives may be classified into two groups: (a) those that retain the codeinelike hydrophenanthrylene oxide skeleton (these are nonphenolic), and (b) those that contain a phenolic hydroxyl resulting from cleavage of the 4,5-ether bridge. Among the known desoxy bases, desoxycodeines-C and -D and dihydrodesoxycodeine-D fall into category (a). In the elucidation of the

structures of these bases, the dihydro nature of dihydrodesoxycodeine-D was manifest by analysis and by its reduction to tetrahydrodesoxycodeine (sodium and methanol or by electrolytic reduction in sulfuric acid) (242). Since ring III of this compound is completely saturated, formula CXX must represent dihydrodesoxycodeine-D.



CXX



CXXI

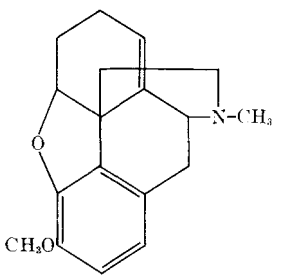
The position of the double bond in desoxycodeine-C is manifest by its pseudocodeinelike behavior towards catalytic reduction and Grignard reagents. Like pseudocodeine, desoxycodeine-C was catalytically reduced ($PtO_2 + 2H_2$) under normal conditions to tetrahydrodesoxycodeine (241), while under special conditions of hydrogenation in acid medium (desoxycodeine-C hydrochloride in glacial acetic acid with platinum oxide catalyst), selective reduction of the double bond occurred with the formation of dihydrodesoxycodeine-D and some tetrahydrodesoxycodeine (247). Furthermore, on treatment with methyl, ethyl or phenyl magnesium halides, desoxycodeine-C gave rise to methyl-, ethyl- or phenyldihydrodesoxycodeines (261). These reactions which have become diagnostic for the pseudocodeine type of structure point unequivocally to the Δ^{6-7} position for the unsaturation in desoxycodeine-C (CXXI).

6-Methyldesoxycodeine-C (316) is nonphenolic (insoluble in alkali and gives a negative test with diazosulfanilic acid), and is unsaturated towards potassium permanganate and ozone. Decomposition of the ozonide and treatment of the resulting carbonyl compound with sodium hypoiodite were sufficient to demonstrate that a methyl ketone was formed in this oxidation. Hence, the alicyclic double bond in 6-methyldesoxycodeine-C must be assigned either to position Δ^{5-6} or to Δ^{6-7}. If the double bond were at Δ^{5-6}, then this base (an enol ether) should be very susceptible to acid hydrolysis, but it was not. Absorption of two moles of hydrogen (PtO_2) by this base demonstrated its pseudocodeinelike structure and definitely located the double bond at Δ^{6-7}.

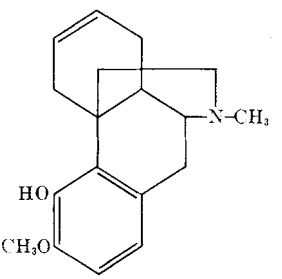
Desoxycodeine-D must also have a hydrophenanthrylene oxide structure since it absorbs but one mole equivalent of hydrogen, yielding dihydro-

desoxycodeine-D. Its mode of formation from 8-chlorodihydrocodide by elimination of the elements of hydrogen chloride suggests either Δ^{7-8} or Δ^{8-14} as the most probable site for the single center of unsaturation in this base. Several pieces of evidence favor position Δ^{8-14}. Firstly, like all methines with a Δ^{8-14} double bond that of desoxycodeine-D is not isomerized by sodium alcoholates (314), and, secondly, cyanogen bromide yields an amorphous bromine containing product (314). On the basis of this evidence, structure CXXII has been assigned to desoxycodeine-D (this is also the desoxy derivative of neopine; hence, desoxycodeine-D may logically be termed desoxyneopine).

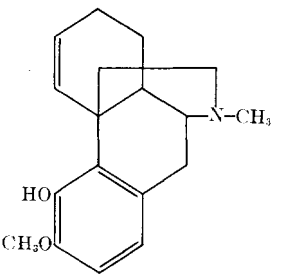
Assigning structures to the desoxy bases belonging to category (b) has proved more difficult, since no experimental approach is at hand for locating the double bonds in these bases. As a poor substitute the positions of these centers of unsaturation have been tentatively assigned through consideration of the possible mechanisms of formation of these bases. The formation of a mixture of dihydrodesoxycodeine-B and -C in the sodium and alcohol reduction of desoxycodeine-C has been regarded as the result of competing 1,2- and 1,4-addition of hydrogen, giving rise to CXXIII and CXXIV. The electrolytic reduction of chlorodihydrocodide to dihydrodesoxycodeine-C could likewise be accounted for by a 1,4-addition to the chlorine and the ether bridge oxygen with formation of a Δ^{5-6} double bond (250). The alternative hypotheses that hydrogen chloride might have been eliminated from C_6–C; or C_5–C_6 before or after the reductive opening of the oxide ring to give either CXXIII or CXXIV appear to be less probable, since chlorodihydrocodide loses hydrogen chloride only on protracted treatment with sodium methylate at 140° (241). On the basis of these arguments, dihydrodesoxycodeine-C must be assigned structure



CXXII



CXXIII



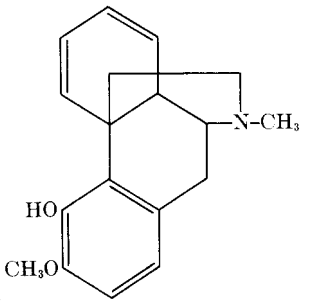
CXXIV

CXXIV, leaving the alternative formula for dihydrodesoxycodeine-B. The formation of dihydrodesoxycodeine-B by the electrolytic reduction of desoxycodeine-C must then be the result of 1,2-addition of hydrogen to the oxygen and C_5.

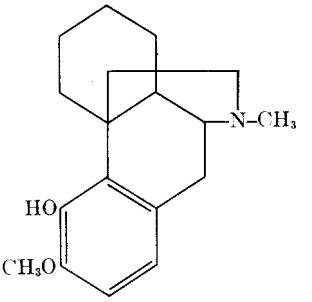
In analogy with the reduction of chlorodihydrocodide to dihydro-

desoxycodeine-C, the 1,4-addition of hydrogen to α-chlorocodide has been proposed as the mechanism for the formation of desoxycodeine-A (250). Desoxycodeine-A, therefore, would be CXXV, a structure which also would accommodate its conversion to dihydrodesoxycodeine-B and -C.

No structural formula has, as yet, been assigned to dihydrodesoxycodeine-E (197, 242). It suffices to say that it is a phenolic base, and that its degree of saturation is demonstrated through its conversion to tetrahydrodesoxycodeine by the absorption of one mole equivalent of hydrogen (Pd on $BaSO_4$) (242).



CXXV



CXXVI

The generally accepted formula for tetrahydrodesoxycodeine is CXXVI. Although its behavior as a cryptophenol (insoluble in alkali and indifferent towards acetylation and the usual methylating agents) seems difficult to bring into accord with such a structure, the proof of the presence of this phenolic hydroxyl lies in the preparation of its methyl ether (244) (conversion to the methyl ether methiodide (320) followed by high vacuum distillation of the derived methochloride). This cryptophenolic behavior of C_4 hydroxyl groups is now regarded as characteristic for all morphine derivatives having ring III completely saturated.

c. Reactions of the Desoxycodeines and Their Hydro Derivatives. The Hofmann transformation has been applied to the methiodides of desoxycodeines-A and -D, of the dihydrodesoxycodeines-B, -C and -E, and to that of tetrahydrodesoxycodeine. The methines from desoxycodeine-A and its derivatives were very unstable. Desoxycodeine-A methine was very subject to aerial oxidation, while its methyl ether was decomposed in acid medium to dimethylmorphol (153).

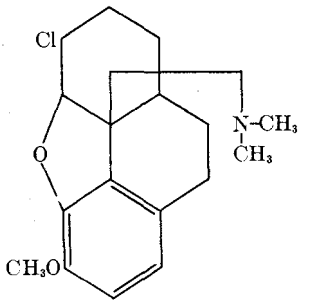
A stable methine has been prepared from desoxycodeine-D (314). As noted previously, the stability of this methine to conditions that promote isomerization of α- and γ-methylmorphimethines, respectively, to β- and δ-isomers suggests that the alicyclic double bond in desoxycodeine-D is at Δ^{8-14}.

Dihydrodesoxycodeine-A was erroneously described by early workers

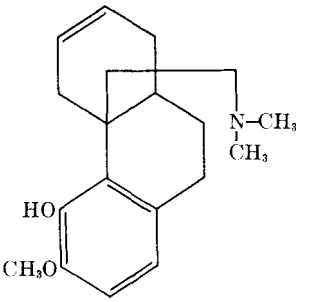
as a pure compound (153), and the physical constants of its methine were also recorded. It was the separation of this so-called methine into its component B- and C-methines which subsequently led to the separation of desoxycodeine-A into desoxycodeine-B and -C.

The product from the Hofmann reaction on dihydrodesoxycodeine-E methyl ether has been reported as an oily base which gave a crystalline hydriodide. A second Hofmann degradation yields trimethylamine and an unstable nitrogen-free product (197).

Des-*N*-methyltetrahydrodesoxycodeine, like tetrahydrodesoxycodeine, behaved as a cryptophenol. On catalytic hydrogenation (Pd on $BaSO_4$) one mole of hydrogen was absorbed yielding dihydro-des-*N*-methyltetrahydrodesoxycodeine (244), which proved to be identical with dihydrodesoxytetrahydromethylmorphimethine (prepared by the sodium and alcohol reduction of tetrahydrochloromethylmorphimethine (CXXVII) to desoxytetrahydromethylmorphimethine (CXXVIII) followed by catalytic hydrogenation) (33, 292).



CXXVII

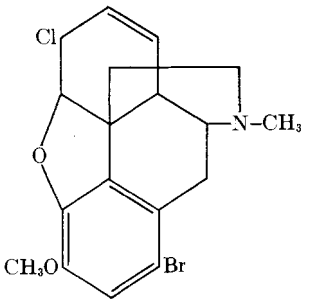


CXXVIII

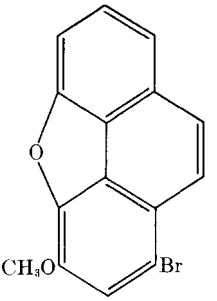
A number of brominated desoxycodeines have been prepared. On bromination of desoxycodeine-A, dibromodihydrodesoxycodeine resulted by substitution in the aromatic nucleus, while the hydrogen bromide generated in this reaction, in turn, added to the system of double bonds in ring III. The above mechanism has been verified by obtaining the same product by first adding hydrogen bromide (in glacial acetic acid) to the unsaturation in ring III of desoxycodeine followed by bromination of the resulting bromodihydrodesoxycodeine (265). On acetolysis, the des-base from dibromodihydrodesoxycodeine gave the same bromoacetylmethylmorphol as that obtained from 1-bromo-α-methylmorphimethine. Hence, the substitution in desoxycodeine-A must have occurred at C_1 and para to the C_4 hydroxyl.

When bromochlorocodide (CXXIX) was subjected to zinc and alcohol reduction, in a manner analogous to that for the preparation of desoxy-

codeine-A and α-chlorocodide, the product behaved more like a brominated desoxycodeine-C than bromodesoxycodeine-A (retention of the phenanthrylene oxide ring in this base was demonstrated by conversion of its methomethyl sulfate by alkali to bromomethylmorphenol (CXXX)). Apparently, because of the influence of the bromine atom, the ether bridge was not ruptured. The double bond in this bromodesoxycodeine-C must be at Δ^{6-7} since two moles of hydrogen were absorbed on catalytic reduction, and the hydrogenated base proved to be identical with the bromotetrahydrodesoxycodeine from the bromination of tetrahydrodesoxycodeine.



CXXIX



CXXX

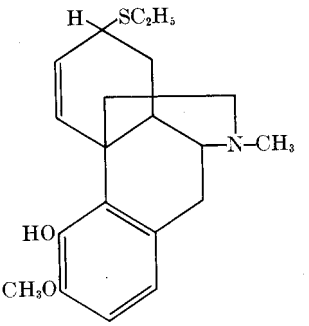
A tribromodihydrodesoxycodeine resulted from the bromination of desoxycodeine-C. Its formation probably involves addition of the halogen to the double bond as well as substitution in the aromatic nucleus (265). By catalytic reduction (PtO_2) three mole equivalents of hydrogen were absorbed, whereby two bromines were replaced by hydrogen and the ether bridge was reductively opened, giving a weakly phenolic compound isomeric with, but different from, bromotetrahydrodesoxycodeine. Further reduction with sodium and alcohol removed the last bromine, but the resulting product was not tetrahydrodesoxycodeine (265).

In the discussion on the structure of desoxycodeine-C, reference to the action of Grignards on this base has already been made. A more extensive correlation of these reactions, however, is warranted, since interesting abnormalities have been observed in the behavior of this base. On treatment with methyl magnesium iodide, desoxycodeine-C, like pseudocodeinone, took up the elements of CH_4 forming phenolic methyldihydrodesoxycodeine. Zinc dust distillation of this product gave a small yield of a crystalline hydrocarbon whose analysis agreed with that required for methylphenanthrene, but its properties were different from those of any of the known methylphenanthrenes (261). With ethyl magnesium iodide, two isomeric ethyldihydrodesoxycodeines were formed (one of the isomers was isolated only after hydrogenation).

Both methyl and ethyl derivatives were hydrogenated readily in

organic media, although the reaction was highly accelerated by traces of hydrogen chloride. Phenyldihydrodesoxycodeine (phenylmagnesium bromide on desoxycodeine-C), on the other hand, was not reduced under similar conditions. In alcoholic solution in the presence of an excess of mineral acid eight atoms of hydrogen were absorbed smoothly. It has been postulated that the newly introduced phenyl group and the double bond in ring III have been reduced in the formation of hexahydrophenyldihydrodesoxycodeine (261). If this hypothesis were correct, hexahydrophenyldihydrodesoxycodeine should be identical with cyclohexyldihydrodesoxycodeine. The preparation of the latter base from the interaction of cyclohexyl magnesium chloride and desoxycodeine-C showed that these two compounds were different. Whether the difference lies in the mode of addition of the phenyl and cyclohexyl groups or that the concept concerning the formation of hexahydrophenyldihydrodesoxycodeine was fallacious has not yet been ascertained.

Ethyl mercaptan, like organomagnesium compounds, ruptures the oxide bridge of desoxycodeine-C by an apparent 1,4-addition to the allyl ether system. The resulting ethylthiodihydrodesoxycodeine is thought to be CXXXI (254).



CXXXI

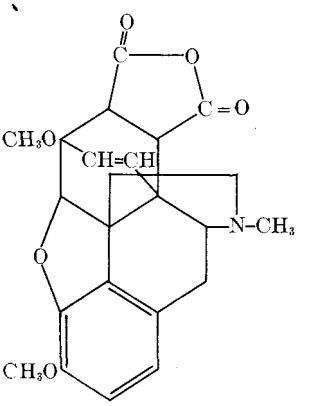
IV. The Reactions of Thebaine and Related Products

Thebaine (4) ($C_{19}H_{21}O_3N$) (6, 278) (III) occurs in *Papaver somniferum* associated with morphine, codeine, narcotine, and other alkaloids. It is also found in young plants of *Papaver orientale*, but this is gradually supplanted by isothebaine (an aporphine base) as the plant approaches maturity.

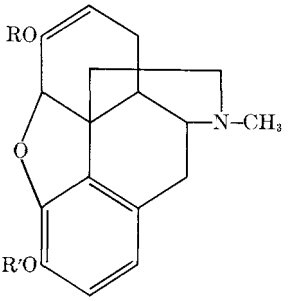
Thebaine hydrochloride is more soluble than that of codeine, so it is usually recovered from the mother liquors of the codeine preparation by addition of potassium hydroxide. The copious precipitate is collected and dissolved in dilute acetic acid, decolorized with activated charcoal, and

then powdered tartaric acid is stirred into the acetic acid solution. The crystalline thebaine bitartrate, which separates after standing for 24 hours, is collected, washed with water, and the base then liberated from its salt by the addition of ammonia. Thebaine is purified by recrystallization from ethanol (6).

Thebaine is a strong (turns litmus blue (6)), monoacidic, tertiary (see dihydrothebaine) base which contains two methoxyl groups (Zeisel) (73) but no carbonyl grouping (no oxime or phenylhydrazone) (125). The presence of two ethylenic double bonds in this base is apparent from its hydrogenation to dihydromorphine dimethyl ether (if this hydrogenation is interrupted at an intermediate stage dihydrothebaine results), thus establishing a relationship between thebaine and the previously discussed series of bases. Conjugation of the two double bonds in this base is evident from its quantitative reaction with molar amounts of various dienophiles (maleic anhydride (46, 220), *p*-benzoquinone (46, 220), and 1,4-naphthoquinone (220); the U. V. absorption spectrum has also been studied (228)). The ease of acid hydrolysis of one of the methoxyl groups of thebaine (to codeinone (129)) attests to the presence of an enol methyl ether in this base, while the resistance of the thebaine-maleic anhydride adduct (CXXXII)



CXXXII



R = CH_3, $COCH_3$
R' = H, CH_3

CXXXIII

to similar treatment unequivocally assigns the conjugated diene system to Δ^{6-7} and Δ^{8-14} (and not at Δ^{5-6} and Δ^{7-8}) (46). The hydrolysis of thebaine to codeinone (7% yield; regeneration of thebaine through the intermediate methyl ketal was not realized (129, 209)) is beset with difficulties, for, in contrast to codeine, this base exhibits a marked susceptibility to rearrangement (metathebainone, thebenine, and morphothebaine) in acid media (hence, substitution in the benzene nucleus has not proved practical).

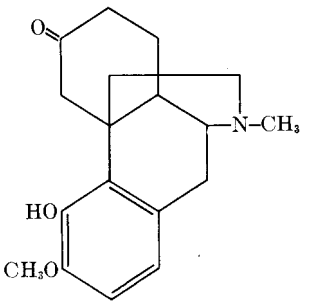
Owing to the greater degree of unsaturation in the nucleus of thebaine (a tetrahydrophenanthrene) than in codeine (a hexahydrophenanthrene),

the tendency towards aromatization of its nucleus and extrusion of the ethanamine chain is much more pronounced.

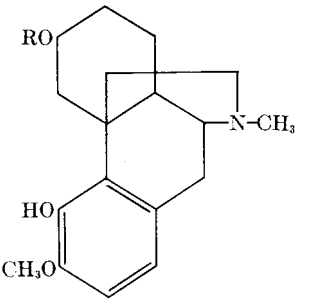
1. Reduction

a. Catalytic Reduction. Although the mechanism for the reduction of thebaine has proved to be a complex one, it has offered a second clear-cut relationship between thebaine and morphine. Tetrahydrothebaine is identical with dihydromorphine dimethyl ether (hydrogenation of codeine-6-methyl ether) (60), and on demethylation (HI, HBr, $AlCl_3$) it yields dihydromorphine (335).

The course of the reduction of thebaine is markedly dependent upon the type of catalyst and the pH of the solution (36). Reduction of the hydrochloride of this base over palladium black gave a difficultly separable mixture of nonphenolic dihydrothebaine (CXXXIII, R = R′ = CH_3) (36, 189, 191, 262), dihydrothebainone (CXXXIV) (this is favored when colloidal palladium and acetic acid are used (191) whereas with a platinum catalyst, reduction of the ketone group and the formation of dihydrothebainol (CXXXV, R = H) occur to a limited extent (191)) and tetrahydrothebaine (CXXXVI) (36, 179, 335) (platinum oxide catalyst and



CXXXIV



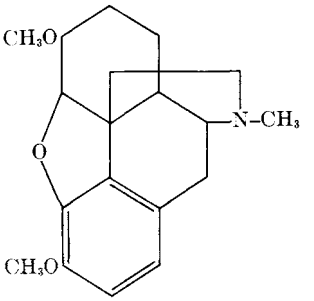
R = H, CH_3

CXXXV

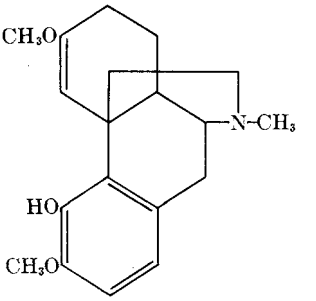
acid medium favor the reduction to tetrahydrothebaine (335). Reduction of the enol ether double bond usually proves difficult (310)). Neutral reduction (alcohol and sodium bicarbonate and palladium black) yields dihydrothebainone methyl enolate (47%) (CXXXVII), tetrahydrothebaine (18%) and dihydrothebainol methyl ether (CXXXV, R = CH_3).

In the reduction to dihydrothebaine hydrogen must have added to the Δ^{8-14} double bond of thebaine, since the sensitivity of thebaine to mineral acids is retained by the dihydro derivative (affording dihydrocodeinone) (189) (dihydromorphinone methyl enolate, the morphine analog of dihydrothebaine, results from the demethylation of the latter base at C_3 by such reagents as sodium ethylate, isopropyl or phenyl magnesium bromide (308)).

It is not to be inferred that dihydrothebaine is the intermediate in the formation of the tetrahydro derivative, for the resistance of dihydrothebaine to further reduction, on the other hand, makes it appear highly probable



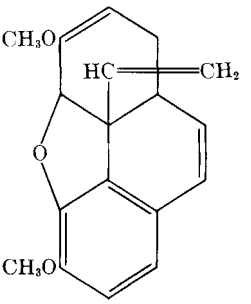
CXXXVI



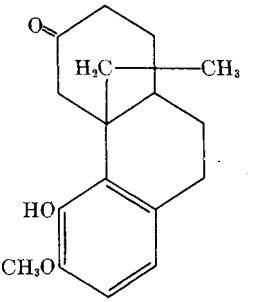
CXXXVII

that these two products are formed by different mechanisms. Under forcing conditions (36, 189) the allyl system of dihydrothebaine undergoes hydrogenolysis (1,4-addition of hydrogen), the ether of the derived intermediate (CXXXVII) suffers hydrolysis ahead of reduction (36, 209), and dihydrothebainone results (hydrogenation over palladium on calcium carbonate results in the formation of a stereoisomeric dihydroepithebainone (36, 37) amongst other products). It is believed that dihydrothebainone formation must result from the 1,6-addition of a molecule of hydrogen (C_8 and the oxide bridge) followed by 1,2-addition of a second molecule to the Δ^{7-8} double bond (310) and subsequent hydrolysis of the enol methyl ether (36, 310). Tetrahydrothebaine formation, on the other hand, must involve 1,4-addition to the conjugated system followed by reduction of the derived Δ^{7-8} double bond.

Saturation of one or both of the double bonds of thebaine removes the



CXXXVIII



CXXXIX

tedency towards aromatization of the nucleus, and, by way of illustration, dihydrothebaine may be cited. Alkali on the methiodide of this base yields the stable des-*N*-methyldihydrothebaine. A second Hofmannn

degradation eliminates the nitrogen as trimethylamine with the formation of 6-methoxy-13-vinyltetrahydromorphenol methyl ether (CXXXVIII) (189, 297). Subsequent hydrolysis of the enol methyl ether (HCl) (297) followed by saturation of the vinyl group (H_2 + Pd on charcoal) (297) and reductive cleavage (AlHg) (297) of the oxide bridge yielded 6-keto-13-ethyloctahydromethylmorphol (CXXXIX). Neither methylation of the phenol nor the reduction of the ketone of CXXXIX has been realized (297).

Reduction of the Δ^{9-10} double bond of des-*N*-methyldihydrothebaine hydrochloride (H_2 + $PdCl_2$) and hydrolysis of the enol ether (HCl) (34) yielded a ketone identical with that from the oxidation (CrO_3 + HOAc) (34) of tetrahydromethylmorphimethine. The degradation of dihydro-des-*N*-methyldihydrothebaine afforded a nitrogen-free vinyl compound which, when subjected to hydrogenolysis ($2H_2$ + Pd) and hydrolysis of the enol ether, gave a poor yield of CXXXIX (34).

b. Chemical Methods. Alkaline reduction (Na + C_2H_5OH) of thebaine cleaves the oxide bridge to give a phenolic dihydrothebaine, while acid reduction ($SnCl_2$ + HCl) involves, as well, the hydrolysis of the enol ether and, to a limited extent at least, the migration of the carbon end of the ethanamine chain to some new site.

Reduction of thebaine or codeinone by a hydrochloric acid solution of stannous chloride yields thebainone ($C_{18}H_{21}O_3N$) (CXL, X = H) (41,42).

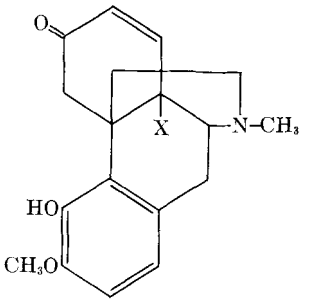
Thebainone (42). Thebaine is reduced to thebainone by the portionwise addition of 10.0 g. of the base at room temperature to a solution of 58.0 g. of stannous chloride (dihydrate) in 120 cc. of 37.2% hydrochloric acid. When the thebaine is completely in solution (usually 15 minutes), the reaction mixture is heated to 70° in a pressure flask for 15 minutes. When cold, the contents of the pressure flask is poured, with vigorous stirring, into 12 times the quantity of water, neutralized with sodium hydroxide and made alkaline with sodium bicarbonate to liberate the free base. The gelatinous precipitate is collected and well washed with warm (50°) water (the washing is continued until the filtrate no longer develops a yellow color when made alkaline). The combined filtrates are clarified with Norit, extracted with chloroform, and dried over sodium sulfate. The 9.5 g. of residue, after removal of the chloroform, is rubbed with 30 cc. of methanol, when 2.0 g. (19%) of pure metathebainone crystallizes. The mother liquor, which darkens rapidly in air, is evaporated to dryness and the remaining amorphous residue (7.0 g.) is triturated with 30 cc. of acetone. In this way 0.8 g. of thebainone (m.p. 145°) is recovered. By evaporating the acetone solution in vacuum and repeating the process with less acetone an additional 4.9 g. of less pure material (m.p. 130–140°) is recovered. Recrystallization from ethanol yields 3.4 g. of pure thebainone melting at 151–152°.

A similar experiment with 2.6 g. of codeinone afforded 1.2 g. (44%) of thebainone melting at 144–147°.

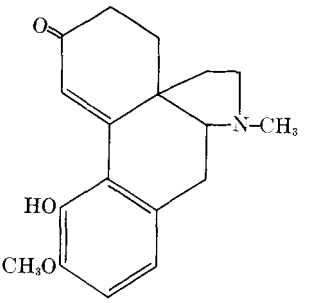
(A by-product, metathebainone (19%) (CXLI), may become the main product under suitable conditions). Contrary to what might be expected, thebainone is not an intermediate in the high temperature (100°) reduc-

tion of thebaine to metathebainone because thebainone is only resinified under these conditions (42).

Various reactions and tests indicate that thebainone is phenolic and contains an α,β-unsaturated carbonyl grouping and a methoxyl group.



X = H, OH
CXL



CXLI

For example, thebainone is soluble in alkali and is regenerated unchanged by the addition of ammonium chloride. It gives an oxime, which like thebainone (H_2 + $PdCl_2$ + HOAc) (42), is reduced ($2H_2$ + Pd on $BaSO_4$, yielding ammonia) (30) to dihydrothebainone ($C_{18}H_{23}O_3N$) (42) (further reduction of dihydrothebainone hydrochloride over platinum yielded the alcohol dihydrothebainol-B (191) which is isomeric with dihydrothebainol-A obtained by electrolytic reduction (190) or sodium amalgam reduction of dihydrothebainone). This reduction of the oxime to dihydrothebainone is characteristic of an α,β-unsaturated ketone (42) (its ultraviolet absorption spectrum confirms this (42)). Finally, a Zeisel determination on dihydrothebainone was sufficient to demonstrate the presence of one methoxyl in thebainone (189). Furthermore, no alteration in ring structure occurred during the reduction of thebaine to thebainone because dihydrothebainone has been converted to dihydrocodeinone. The stepwise bromination of dihydrothebainone at C_1, C_5 (40) and C_7 yields respectively the mono-, di- and tribromodihydrothebainones. The sodium salt of dibromodihydrothebainone loses the elements of sodium bromide and regenerates the hydrophenanthrylene oxide ring of 1-bromodihydrocodeinone. Catalytic debromination ($PdCl_2$ + gum arabic) yielded dihydrocodeinone (40).

1-Bromodihydrocodeinone (40). Dibromodihydrothebainone is prepared by the dropwise addition of 32.0 g. of bromine in 300 cc. glacial acetic acid to a well-stirred solution of 30.0 g. of dihydrothebainone (previously dried in vacuum) in 300 cc. of acetic acid maintained at 15°. The bromine is instantly decolorized. When the addition is complete, the acetic acid is removed in vacuum and the residue, after solution in a little water, is poured into an excess of ice-cold 7 *N* alkali. The nature of the pasty mass soon changes to that of the crystalline 1-bromodihydrocodeinone (80%) when gently warmed. The crude 1-bromodihydrocodeinone, when crystallized from alcohol, yields glistening needles which melt at 205–207°.

By altering the conditions for the reduction of thebaine (37, 122, 288) or codeinone (123), metathebainone (this base was called thebainone before 1931 (41)) becomes the major product. The most satisfactory conditions for this is to dissolve the thebaine in concentrated hydrochloric acid and then reduce the resulting halochromic salt at 100° with stannous chloride (37, 122, 288).

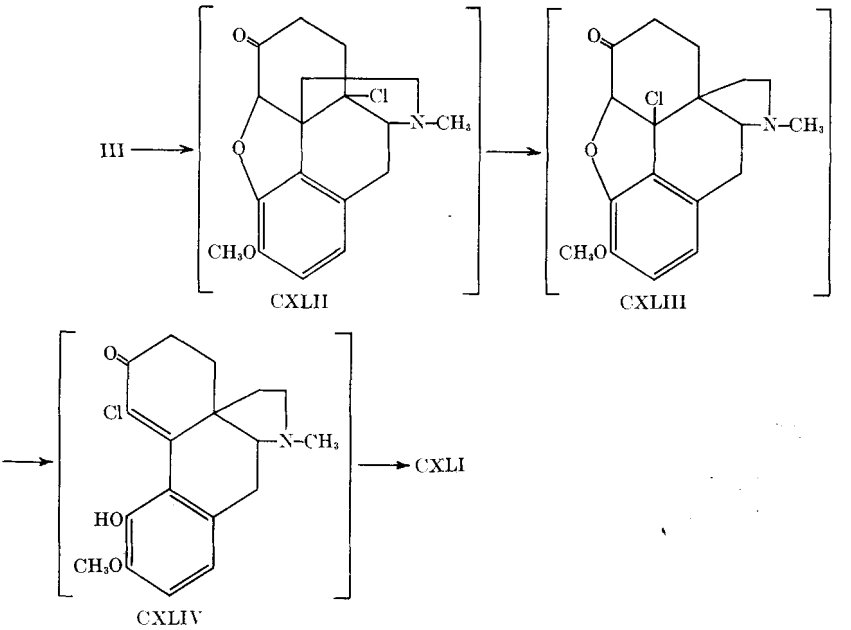
Metathebainone (37, 288). This reduction of thebaine is achieved by adding 18.6 g. of stannous chloride to a solution of 6.0 g. of thebaine in 72 g. of concentrated hydrochloric acid, and the mixture heated in a sealed tube at 100° for 20 minutes. The red-colored solution is poured into 800 cc. of water and 10% sodium hydroxide added until a permanent turbidity develops (at this point the solution is slightly acid to Congo red). The neutral point is now attained by successive additions of small amounts of sodium bicarbonate and the resulting precipitate allowed to settle overnight. The clear, orange solution is decanted, clarified twice with Norit, filtered, and extracted with chloroform and the solution dried over sodium sulfate. After removal of the chloroform the red, sirupy mass is triturated with 30 cc. of warm methanol, when a 53% recovery of the ketone is obtained. Crystallization from methanol yields prismatic crystals (m.p. 115–118°) containing one molecule of alcohol of crystallization.

The same functional groups have been shown to be present in metathebainone as are found in thebainone. Metathebainone forms an oxime and a monosodium salt, while a Zeisel determination indicates the presence of one methoxyl group (122). Exhaustive methylation and a series of two Hofmann eliminations clearly demonstrate that the nitrogen in metathebainone is tertiary and a component of a ring (acetolysis of methylmetathebainonemethine yields dimethylmorphol as well as the acetyl derivative of β-ethanoldimethylamine (124)). The halochromic reactions of this yellow base are very suggestive of an α,β-unsaturated ketone and, like salicylideneacetone, gives an intense yellow color when dissolved in water, which changes to orange upon the addition of alkali (37). With hydrochloric acid it yields an orange-red-colored solution (37) (thebainone exhibits no such halochromism in mineral acids (42)).

The most obvious structure for metathebainone would be CXL (X = H), but certain experimental observations made such a hypothesis untenable. Reduction (Pd + aqueous solution of the hydrochloride (249), or better by sodium amalgam reduction of an alkaline solution (122, 288)) of metathebainone gave dihydrometathebainone (formerly called thebainol (122)), isomeric with dihydrothebainone from the catalytic hydrogenation of thebaine. The hypothesis of a stereoisomerism about C_{14} (37) to account for this isomeric pair proved inadequate, since dihydro-epi-thebainone was isolated from the reduction of thebaine over palladium on calcium carbonate (36, 37, 249). In any event, the carbon end of the ethanamine chain of metathebainone must be attached to a quaternary carbon atom to account for the extrusion of the side chain upon aromatization of the nucleus

(dimethylmorphol formation (124)). Furthermore, if the analogy of this base with salicylideneacetone is to be maintained, then the double bond must be assigned to Δ^{5-13}, thus leaving only the quaternary carbon C_{14} for the ethanamine chain (CXLI). It is to be emphasized that such a structure has been derived solely by the elimination of other possibilities and still lacks experimental confirmation; however, such a structure does seem to accommodate the requirements of this base quite satisfactorily. The most direct evidence in support of such a structure would be the reduction of metathebainone to two stereoisomeric dihydrometathebainones. An ill-defined β-dihydrometathebainone has been reported, but it proved to be a difficultly separable mixture of dihydrometathebainone and a small amount of metathebainol (249). Metathebainol is the alcohol of metathebainone and results from the hydrogenation of metathebainone over platinum oxide catalyst at 3 atmospheres pressure (this has been dehydrated by alcoholic KOH at 160° to anhydrometathebainol (249)).

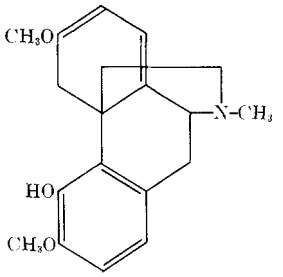
The transformation of thebaine to metathebainone might be considered to result from the simultaneous hydrolysis of the C_6 enol ether and the addition of the elements of hydrogen chloride to the Δ^{8-14} double bond



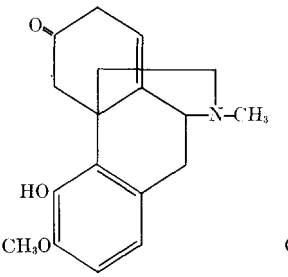
of thebaine. The remaining retropinacol rearrangement of the ethanamine chain to C_{14} and the subsequent intermediate steps necessary to account for the formation of metathebainone are schematically depicted in formulas CXLII–CXLIV (37).

Reduction of the ketone carbonyl of metathebainone and dihydrometathebainone by the Wolff-Kischner method yielded respectively dihydrodesoxymetacodeine and tetrahydrodesoxymetacodeine (249).

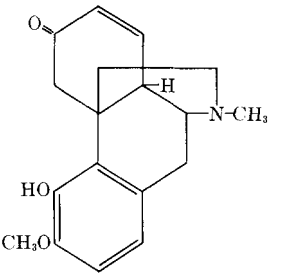
The phenolic dihydrothebaine, resulting from the alkaline reduction ($Na + C_2H_5OH$) of thebaine (89, 183, 310), must be CXLV, since catalytic hydrogenation ($H_2 + PtO_2 + C_2H_5OH$) (310) yields dihydrothebainone-Δ^{6-7}-methyl enolate, isomeric with the previously described dihydrothebainone-Δ^{5-6}-methyl enolate. This isomerism must involve only the disposition of the double bond, since the two isomeric enolates are readily hydrolyzed to dihydrothebainone (310).



CXLV



CXLVI



CXLVII

Hydrolysis of phenolic dihydrothebaine with potassium acid sulfate (310) (less satisfactory with SO_2 (310) or HCl (89)) gave a separable mixture of thebainone (CXL, X = H; 5.2%), α-thebainone (CXLVI; a trace) and β-thebainone (CXLVII; 80.7%). The isomerism of thebainone and β-thebainone cannot be ascribed to a difference in the location of the double bond, as has been assumed for the α-isomer, since the isomerism is retained in their dihydro derivatives (310). Hence, the isomerism must be attributed to a difference in the steric position of the hydrogen atom at C_{14}. The conversion of dihydro-β-thebainone through its dibromo derivative into epidihydrocodeinone and thence to the interesting epidihydrocodeine has not, as yet, been achieved.

Phenolic dihydrothebaine has been converted to the respective methyl ether methiodide which is transformed in alkali to the methine base. This methyldihydrothebainemethine is degraded by 30% potassium hydroxide to methylthebaol (125).

2. Oxidation

Proof of structure of thebaine by the classical method of oxidative degradation has failed to provide any evidence regarding its constitution. Certain gentle oxidizing agents, through attack on one or both of the double bonds of the conjugated system of thebaine, however, have provided a number of interesting oxidation products with the same number of carbon

atoms (simultaneous hydrolysis of the enol methyl ether is not considered in this statement).

a. Hydrogen Peroxide. Thebaine ($C_{19}H_{21}O_3N$) reacts in the normal way with 30% hydrogen peroxide to give the *N*-oxide (prolonged treatment with this reagent and in the absence of acid yields a yellow base, $C_{19}H_{19}O_3N$, of unknown structure (319)) from which the starting material can be regenerated with sulfurous acid (167, 231). In the presence of acetic acid the reaction with hydrogen peroxide follows a different course (achieved equally well with chromic acid (319)) leading to hydroxycodeinone ($C_{18}H_{19}O_4N$) (319). This implies the gain of one oxygen atom and the loss of a CH_2 group.

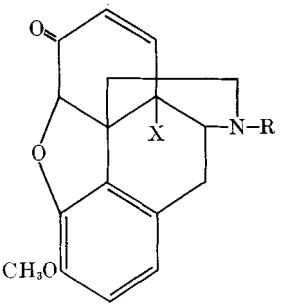
Hydroxycodeinone (319). Ten grams of thebaine is stirred with a solution of 20 cc. of cold saturated potassium dichromate and 20 cc. of sulfuric acid (sp. g. 1.215). The reaction becomes exothermic and a green homogeneous solution results. When this is boiled for 10 minutes, the odor of formaldehyde can be detected. Sodium hydroxide is then added until the chromium hydroxide, which first precipitates, is again in solution. The hydroxycodeinone separates in a short time and is collected, washed, and crystallized from alcohol containing a little chloroform; m.p. 275° (yield 3.0 g.).

Hydroxycodeinone forms an oxime and a phenylhydrazone, an acetyl and a benzoyl derivative, while analytical results indicate the presence of one methoxyl group (319) (the fourth oxygen is present in the ether bridge). Absorption of one mole of hydrogen (over Pt or Pd) and the isolation of a nonphenolic dihydrohydroxycodeinone indicate the presence of one double bond in this base (319). (This dihydrohydroxycodeinone differs from dihydro-7-hydroxycodeinone prepared from 7-isonitrosodihydrocodeinone→ 7-aminodihydrothebainone → dihydro-7-hydroxycodeinone (218).) The reduction of the oxime (30) and the phenylhydrazone (199) of hydroxycodeinone to dihydrohydroxycodeinone ($2H_2$ + colloidal Pd in HOAc; with formation of ammonia) offers some support for locating the double bond alpha,beta to the carbonyl grouping. Exhaustive methylation and degradation indicate that the nitrogen is still a tertiary amine and a component of a ring (319).

Rearrangements apparently have not accompanied this transformation because hydroxycodeinone has been related to codeinone indirectly through bromocodeinone. Bromocodeinone results from thebaine by a quite analogous reaction involving the addition of bromine to an acetic acid or chloroform solution of thebaine (addition of potassium bromide improves the yield of bromocodeinone (197)). An unstable addition product is the primary product, but this readily loses the elements of methyl bromide generating bromocodeinone ($C_{18}H_{18}O_3NBr$) (128, 197). Replacement of the bromine atom by a hydroxyl (NH_2OH) and formation of the oxime of hydroxycodeinone (128, 319, 321), establish that these two bases are similarly

constituted. The reduction (Fe + H_2SO_4) of bromocodeinone to codeinone (128) thus indirectly relates hydroxycodeinone to codeinone. (The catalytic reduction of bromocodeinone, over palladium on charcoal, to dihydrocodeinone (197) further clarifies the above relationship.)

Evidence for the location of the hydroxyl in hydroxycodeinone, at best, is very speculative and rests upon the exclusion of other possible positions. Hydroxylation of the benzene nucleus need hardly be considered since the base is insoluble in alkali (319). From the failure to detect a second ketonic group in the derived methine base it is safe to conclude that the hydroxyl is not on C_9 or C_{10}, which localizes its position as somewhere in ring III. If it were located at C_7, as originally suggested (319), then hydroxycodeinone should reduce alkaline cupric and silver solutions and might be expected to form an osazone. Hydroxycodeinone fulfilled none of these requirements (see also dihydrohydroxycodeinone). Furthermore, when the hydroxyl is assigned to C_7, this leaves only position Δ^{8-14} for the double bond, whence previous experience makes it reasonable to expect a cleavage of type M with cyanogen bromide. Application of this reagent to the acetyl derivatives of hydroxycodeinone and dihydrohydroxycodeinone did not lead to brominated secondary amines but to norhydroxycodeinone (200, 319) (CXLVIII; X = OH, R = H) and its dihydro derivative.



X = H, Br, OH, $OCOCH_3$
R = H, CH_3

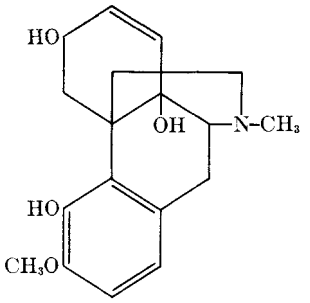
CXLVIII

Location of the hydroxyl at C_8 offers a solution to some of these difficulties, but also creates a new series of problems in their place. While it would be hard to visualize a structure for thebaine that would adequately account for the formation of such a hydroxycodeinone, a β-hydroxyketone structure of this nature fails on another count. Such a β-hydroxyketone would be expected to dehydrate readily, but, on the contrary, it is stable to 20% hydrochloric acid at temperatures as high as 120°. Location of the hydroxyl at the remaining alternative position (C_{14}) (CXLVIII;

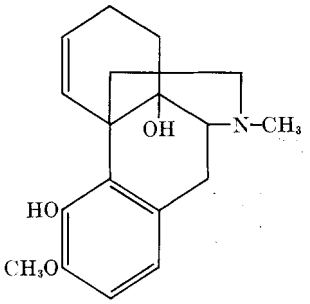
X = OH, R = CH_3) appears to be the most satisfactory structure to date, yet it, too, is inadequate in certain respects. Such a structure does not adequately account for the ease experienced in the acetylation of this hydroxyl nor for the resistance exhibited by dihydrohydroxycodeinone towards dehydration (311). However, the fact that dihydrohydroxycodeinone contains the grouping $-CH_2-CO-$, whereas hydroxycodeinone itself does not, locates the double bond at Δ^{7-8} and might be construed as evidence in favor of such a structure (321).

14-Hydroxycodeinone might be derived from thebaine by the 1,4-addition of the elements of hydrogen peroxide to the conjugated system of thebaine followed by loss of methyl alcohol from the derived hemiketal (bromocodeinone might result from thebaine in a like manner).

Reduction of hydroxycodeinone follows a pattern very similar to that for codeinone. Stannous chloride and hydrochloric acid reduce this hydroxylated base to phenolic hydroxythebainone ($C_{18}H_{21}O_4N$) (CXL, X = OH), which in turn will absorb one mole equivalent of hydrogen (catalytic hydrogenation or metal combinations) yielding the saturated ketone, dihydrohydroxythebainone (319) (the same product results from the reduction of dihydrohydroxycodeinone with sodium amalgam in alcohol, by electrolytic reduction at a lead cathode or by the Clemmensen method (319)). Rearrangement of the metathebainone type has not occurred during the conversion of hydroxycodeinone to hydroxythebainone (no halochromism is observed when hydroxythebainone is dissolved in hydrochloric or sulfuric acid (37)), since two hydrogen atoms in dihydrohydroxythebainone are replaceable by bromine atoms (40) from which dihydrohydroxycodeinone may be regenerated by re-formation of the oxide bridge with alkali and catalytic debromination of the remaining bromine atom (40).



CXLIX



CL

Zinc and acetic acid reduce the ketone group of hydroxycodeinone, in part, to a nonphenolic hydroxycodeine (30, 319), while the remainder is converted to phenolic hydroxythebainol (CXLIX) and a small amount of a chloroform-insoluble product (30). This hydroxycodeine slowly absorbs

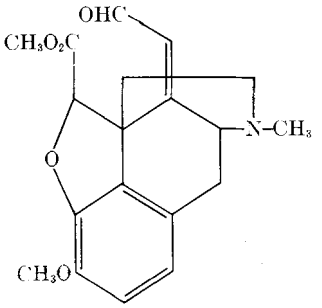
one mole equivalent of hydrogen (PtO_2 in HOAc) giving a nonphenolic dihydrohydroxycodeine-A (311). The letter "A" is used to distinguish this isomer from the two dihydrohydroxycodeines-B and -C arising from the catalytic hydrogenation of dihydrohydroxycodeinone over platinum oxide (311). No direct relationship between these B- and C-isomers and dihydro- and dihydroisocodeine has been discerned; however, comparative pharmacological studies suggest that dihydrohydroxycodeine-B is the hydroxy analog of dihydrocodeine, while the C-isomer is the counterpart of dihydroisocodeine (311). This finds further confirmation in the reaction of these two isomers with phosphorus pentachloride. Dihydrohydroxycodeine-B, like dihydrocodeine, yields the respective chlorocodide, while the C-isomers, like dihydroisocodeine, yields a phosphorus containing compound (311). Since dihydrohydroxycodeine-A differs markedly in both chemical and pharmacological properties from the isomeric B- and C-compounds, it has been inferred that a rearrangement occurred during the vigorous reduction of hydroxycodeinone to hydroxycodeine (311).

In view of the reduction ($Na+C_2H_5OH$) of the above dihydrohydroxychlorocodide to phenolic dihydrodesoxyhydroxycodeine (CL) it is inescapable that it was the C_6, and not the C_{14}, hydroxyl that was replaced by chlorine. This unexpected resistance of the tertiary hydroxyl to replacement by a halogen may be due to its steric position, situated as it is, at the juncture of two fused rings. Thionyl chloride, in contrast to phosphorus pentachloride, attacks neither the C_6 nor the C_{14} hydroxyl groups of dihydrohydroxycodeine-B but results in nuclear substitution, probably at C_1. This so-called 1(?)-chlorodihydrohydroxycodeine-B when treated with phosphorus pentachloride yields 1(?)-chlorodihydrohydroxychlorocodide.

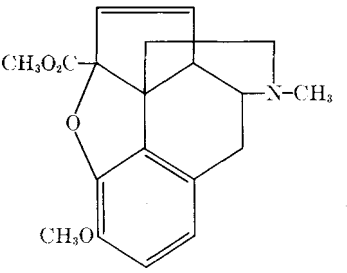
The action of phosphorus pentachloride on hydroxycodeinone (199, 311) is much more complex, leading as it does, to a mixture of six products of varying degrees of halogenation. One of these, 14-chlorocodeinoneketochloride-A (311), has been reduced catalytically to a mixture of dihydrodesoxycodeine-D and β-tetrahydrodesoxycodeine.

b. Ozone. Ozonolysis of thebaine has contributed nothing new towards the solution of the morphine structural problem. In contrast to its action on morphine and codeine, a 5% solution of ozone attacks the enol ether double bond of thebaine hydrochloride ($C_{19}H_{21}O_3N \cdot HCl$) yielding a new base, α-thebaizone ($C_{19}H_{21}O_5N$) (CLI) (38, 151). Generation of an aldehyde grouping during the ozonolysis is manifest by formation of a semicarbazone (151) and by the positive reaction of α-thebaizone with such reagents as Fehling's, Tollens', and Fuchsin solution (38). The oxidation (H_2O_2) of the aldehyde to an acid (which is accompanied by hydrolysis of the newly generated carbomethoxy group), thebaizonedicarboxylic acid (38, 211) is added support for an aldehyde carbonyl in α-thebaizone.

α-Thebaizone is stable at room temperature, but is isomerized at 200° to a β-isomer (38). In alkali it is saponified to an acid, thebaizonic acid ($C_{18}H_{19}O_5N$), and methyl alcohol (characterized as its *p*-nitrobenzoate). The double bond, remaining in α-thebaizone, exhibits a surprising passivity towards catalytic hydrogenation. Under the standard conditions for hydrogenation over platinum oxide only hydrogenolysis of the oxide bridge occurs (acetate formation) (38). The expected reduction product (iso-



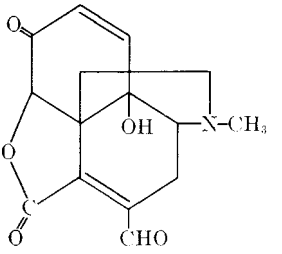
CLI



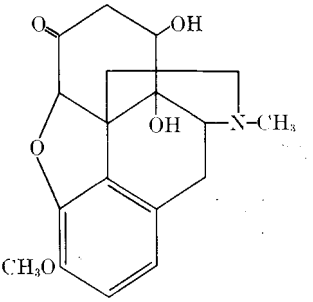
CLII

dihydrothebaizone) is obtainable only by ozonolysis of dihydrothebaine (38). Condensation of the aldehyde of CLI at C_5 and the subsequent reduction to desoxythebaizone (CLII) is effected by aluminum amalgam. This in turn may be reduced further to a dihydrodesoxythebaizone by catalytic hydrogenation (β-thebaizone does not react similarly (38)).

Metathebainone methyl ether and phenyldihydrothebaine methyl ether are unaffected by ozone (38), while it is reported that this reagent (3.8%) attacks the aromatic nucleus of dihydrohydroxycodeinone generating methyl glyoxylate and CLIII.



CLIII



CLIV

c. Other Oxidizing Agents. Manganese tetraacetate and lead tetraacetate, in contrast to ozone, attack the Δ^{8-14} double bond of thebaine (219) with the introduction of one hydroxyl and one acetoxyl group. The observed ease of hydrolysis of this acetyl residue (dilute HCl; accompanied

by hydrolysis of the enol ether) would tend to favor location of the acetoxyl at C_8 rather than at C_{14}. This conclusion is justified since the deacetylated product (CLIV), in contrast to the primary oxidation product, readily loses water (alcoholic KOH) yielding the α,β-unsaturated ketone, hydroxycodeinone (CXLVIII; X = OH, R = CH_3). Oxidation of the glycol (CLIV) proved rather unsatisfactory.

Metathebainone is oxidized by such reagents as silver nitrate and potassium ferricyanide to the isomeric dimolecular α- and β-dithebainones (39). While it is generally considered that oxidative dimerization occurs at C_1, nevertheless, the nature of this isomerism is still obscure.

3. The Action of Organometallic Compounds

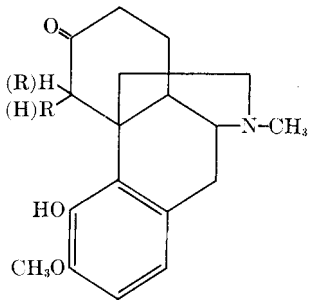
Organometallic compounds react with varying degrees of ease with thebaine, nonphenolic dihydrothebaine, and several related compounds incorporating the allyl ether bridge system (double bond at Δ^{6-7}). While these reaction products have been isolated and characterized, their structures are unknown and the mechanism of their formation is still obscure. In spite of this, these products offer an unequivocal argument refuting an oxazine structure for the morphine bases, and, when the reaction of methylmagnesium iodide with dihydrothebaine is thoroughly understood, they may supply the necessary evidence for the overthrow of the Knorr-Wieland morphine formula (309). A number of apparently anomalous reactions, however, enhance the difficulty of interpreting these reactions.

Methyl magnesium iodide (262) and a number of other Grignard reagents (C_2H_5MgI, i-C_3H_7MgBr, n-$C_5H_{11}MgBr$, C_6H_5MgBr and $C_6H_5CH_2MgCl$) (308) react slowly (extracted from a Soxhlet in 5 days) with an ethereal solution of dihydrothebaine causing cleavage of the oxide bridge as well as hydrolysis of the enol ether either during the reaction or upon decomposition of the resulting magnesium salt, with the formation of the respective phenolic alkyl- or aryldihydrothebainones. Accompanying this main product is usually a small and variable amount of an isoalkyl- or isoaryldihydrothebainone (reactions involving C_3H_7MgBr, $C_5H_{11}MgBr$, and C_6H_5–CH_2MgCl excepted) and some dihydromorphinone methyl enolate (CXXXIII; R = CH_3, R′ = H) (308) formed by the demethylating action of the reagent. The cryptophenolic property of isomethyldihydrothebainone lends itself admirably to the separation of this isomeric base from the main product. The limited supply of thebaine and its far from favorable reduction to nonphenolic dihydrothebaine would have precluded an exhaustive study of methyl- and isomethyldihydrothebainone had it not been for the observation that these products are readily available from dihydrocodeinone enol acetate (CXXXIII; R = $COCH_3$, R′ = CH_3) (308) (acetyldihydro-

hydroxycodeinone yields a similar enol acetate which reacts with methylmagnesium iodide (311)).

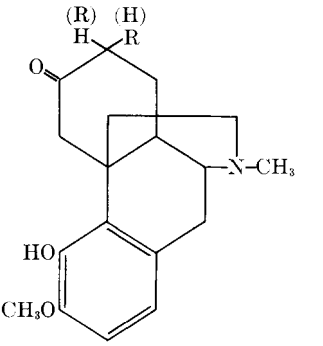
Dihydrocodeinone enol acetate (308). A solution of 15.0 g. of dihydrocodeinone and 1.5 g. of anhydrous sodium acetate in 75 cc. of acetic anhydride is boiled under reflux for 105 minutes. Most of the acetic anhydride is then removed under vacuum (water pump) at 100° and the remainder is decomposed on ice. The clear, aqueous solution is then treated cautiously with excess ammonia and the crystalline base (16.4 g.; m.p. 152–153°) collected on a funnel. The enol acetate, once crystallized from methanol, melts at 153–153.5°.

These may conceivably be stereoisomers resulting from the 1,2- (CLV) or 1,4- (CLVI) addition of the Grignard to the allylic ether bridge or they may be structural isomers arising from competing 1,2- and 1,4-addition reactions.



R = CH_3, C_2H_5, *i*—C_3H_7
n—C_5H_{11}, C_6H_5, C_6H_5—CH_2—

CLV



R = CH_3, C_2H_5, *i*—C_3H_7,
n—C_5H_{11}, C_6H_5, C_6H_5—CH_2—

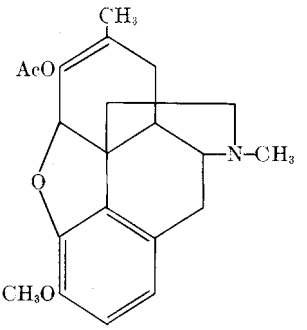
CLVI

As in dihydrothebainone, two of the hydrogen atoms (probably at C_1 and C_5) in methyldihydrothebainone and isomethyldihydrothebainone (the same is true for the higher homologs) are replaceable by bromine. The ether bridge of 1-bromomethyldihydrocodeinone and 1-bromoisomethyldihydrocodeinone was then generated in the normal way by solution in alkali (262). Removal of the second bromine (H_2 + $PdCl_2$ + gum arabic) and reduction of the ketone group (H_2 + PtO_2) of 1-bromomethyldihydrocodeinone afforded a base which, in analogy to the steric course of the reduction of codeinone, was considered to be methyldihydrocodeine. An alternative and more circuitous route leads to the same product. Methyldihydromorphinone, from the demethylation (48% HBr) of methyldihydrocodeinone, has been reduced to methyldihydromorphine and this in turn methylated (CH_2N_2) to methyldihydrocodeine (253). Because of the limited quantity of methyldihydrocodeine available, location of the methyl group by degradation to a 5- or 7-methylmethylmorphol was out of the question,

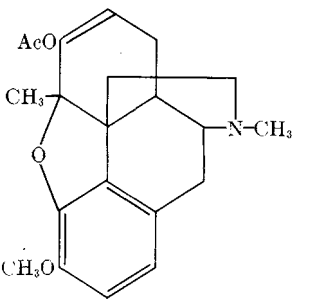
and the inferences that have been drawn regarding the structure of these isomers are conflicting.

It is known that bromination of 2-methylcyclohexanone occurs preferentially at the methylene group rather than at the methenyl grouping. This might be used as an argument for a C_7-methyl group in these compounds, since bromination of methyldihydrothebainone must have occurred at C_5 or the observed ether bridge formation would not be understandable. Assumption of such a stereoisomerism about C_7 to account for the isomeric methyl- and isomethyldihydrocodeinones would make it difficult to explain the observed condensation of ethyl oxalate with both ketones. Conversion of methyldihydrocodeinone and isomethyldihydrocodeinone to different enol acetates (from which the respective ketones can be regenerated) would seem to refute this argument. These two enol acetates might result from an enolization involving the hydrogen on C_5 in one case and that on C_7 in the other case, but their reactions with methylmagnesium iodide tend to refute such an argument since both appear to possess the characteristic allyl ether bridge system. In each case the ether bridge is cleaved and the enol acetate hydrolyzed to give the same dimethyldihydrothebainone. Hence, stereoisomerism about C_7 is excluded. Bromination of this dimethyldihydrothebainone introduces two bromine atoms. This substitution presumably occurs at C_1 and C_7 (or perbromide formation), since under no conditions could cyclization to a bromodimethyldihydrocodeinone be induced (308). This would suggest that the two methyl groups of dimethyldihydrothebainone are at C_5, and that the isomerism of methyl- and isomethyldihydrothebainone may be ascribed to a difference in steric disposition of the methyl group at C_5.

The above argument is not too convincing since the formation of



CLVII



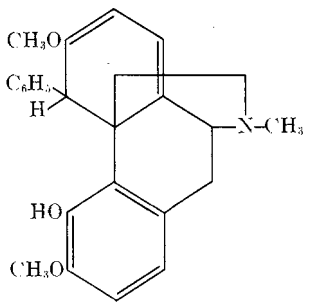
CLVIII

dimethyldihydrothebainone might equally well be accounted for by the 1,2-addition of methyl magnesium iodide to CLVII and by a 1,4-addition to CLVIII. In this case, bromination may have occurred at C_5 but ether

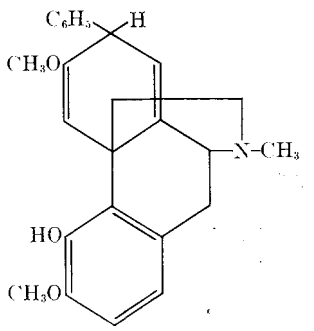
bridge formation may have been hindered by an unfavorable configuration at this position. In any event it would appear that either methyldihydrothebainone or the isomer bears a methyl group at C_5, and, if this can be definitely established, it will effectively dispose of the Knorr-Wieland type of formula; for, on such a structure, C_5 of either methyldihydrocodeinone or its isomer would be pentavalent.

Thebaine reacts somewhat more readily with Grignard reagents than does dihydrothebaine, but the mechanism of these reactions is more obscure and the question of the structure of the reaction products still remains unsettled. When thebaine ($C_{19}H_{21}O_3N$) is extracted (13 hours) out of a Soxhlet extractor into a boiling ethereal solution of methylmagnesium iodide (phenylmagnesium bromide acts similarly (125, 309)), a separable mixture of α-methyldihydrothebaine (41–49%) and δ-methyldihydrothebaine (24–26%) ($C_{20}H_{25}O_3N$) (309) results. These two isomers are strongly phenolic but differ widely in physical properties. By the proper choice of conditions, however, α-methyldihydrothebaine may be converted into the δ-isomer (10%; 100° for 24 hours) (309) or into ω- and η-methyldihydrothebaine (slow distillation under vacuum). The last two mentioned isomers are apparently the respective enantiomorphs of α- and δ-methyldihydrothebaine.

When phenylmagnesium bromide reacts with thebaine, generation of phenolic properties (sodium salt and methyl ether) (125) in the resulting phenyldihydrothebaine ($C_{25}H_{27}O_3N$) accompanies the uptake of the elements of C_6H_6. This reaction would appear to involve a 1,2- (CLXIX) or a 1,4- (CLXX) addition to the allyl ether bridge system (on the oxazine



CLIX



CLX

formula one Hofmann degradation would be expected to remove the nitrogen complex from phenyldihydrothebaine, such, however, is not the case (125)). The properties of phenyldihydrothebaine (also of α-methyldihydrothebaine) do not appear to be in accord with such structures (309).

Unlike dihydrothebaine, the enol ether of these derived bases is not hydrolyzed during their formation or in the working up of the reaction products (a Zeisel determination shows the presence of two methoxyl groups) (125). In fact, it is so stable that conditions that will hydrolyze this grouping (HCl under pressure) also demethylates the C_3 methoxyl yielding a triphenolic base (125). (Regeneration of phenyldihydrothebaine with diazomethane excludes the possibility of rearrangements. Furthermore, if the carbon end of the ethanamine chain is linked to C_{13}, it is impossible to construct a formula that does not include an enol methyl ether (309).) Phenyldihydrothebaine appears to be devoid of ethylenic double bonds, or, if present, they exhibit an abnormal and subdued reactivity as they are passive to such reagents as ozone (on methyl ether) (38), halogens (183), electrolytic reduction at a lead cathode (183), and catalytic hydrogenation (183). Hydrogenolysis (H_2 + colloidal palladium) of the nitrogen ring yielding phenyltetrahydrothebaimine (a secondary amine) sets in before hydrogenation in ring III (183). Acceptance of the inviting hypothesis of the aromatization of ring III would remove a number of these anomalies, yet this necessitates (under mild conditions) a migration of the side chain to some nonangular position and creates the problem of what to do with two hydrogen atoms if the structure is to conform with analytical figures. Furthermore, the optical activity of some of the degradation products of the methyldihydrothebaines makes it difficult to understand how ring III could be aromatic.

4. Fission Around the Nitrogen Atom

The factors controlling fission of the N–C bonds and the accompanied loss of the ethanamine chain are, in general, similar to those obtaining for codeine and related products, although a few apparently anomalous reactions have been observed.

Thebaine (and its methiodide) (80) and thebainone (as its methiodide) (42), containing, as they do, a degree of unsaturation comparable with that of codeinone, require but little chemical stimulation to promote the aromatization of the nucleus and loss of the whole nitrogen bridge (the susceptibility of these tetrahydrophenanthrene alkaloids to extrusion of the nitrogen chain is destroyed when the nucleus is reduced, or when aromatization is blocked by substituents). For example, when thebaine (but not phenyldihydrothebaine (125)) is heated with acetic anhydride (80, 84, 278) (some silver acetate is added when the methiodide is employed (80)) or benzoyl chloride (126), the respective acylthebaol (XXVI) is formed with loss of the nitrogen bridge which appears as ethanolmethylamine (aurichloride: ethanoldimethylamine is the second product when the methiodide is

employed (80)). Thebainone methiodide undergoes a similar cleavage (sodium acetate was added to the acetic anhydride), but demethylation of the acetylthebaol to 3,4,6-triacetoxyphenanthrene accompanies the primary reaction (42). Metathebainone, in contrast to thebainone, is stable to boiling acetic anhydride (226). The reason for this apparent anomaly will probably be more apparent when the structure of this base is more clearly defined. This base acts more like codeine, since metathebainonemethine methyl ether upon acetolysis yields dimethylmorphol (VIII, R = CH_3) (thebainone, on the other hand, retains all three oxygen atoms in the nonbasic moiety, after cleavage).

Although the aromatization of the hydrophenanthrene nucleus may be the driving force for the extrusion of the nitrogen complex, it does not supply the whole answer since the ethanamine chain of isophenyldihydrothebaine methyl ether methochloride is lost (at 200°) without aromatization of the nucleus. The nonbasic fragment was recovered and analytical figures indicate that it is 3,4-dimethoxy-5 (or 7)-phenyl-6-keto-5,6,7,8-tetrahydrophenanthrene (308).

The hydrogenolytic fission (colloidal Pd) of the heterocyclic ring of phenyldihydrothebaine has also been reported (183). The resulting phenyltetrahydrothebaimine is a secondary amine because it yields a nitroso derivative and it reacts with two moles of methyl iodide in the formation of its methiodide (183). Reduction of the reactive double bond of des-*N*-methylphenyldihydrothebaine and comparison of its methiodide with that of phenyltetrahydrothebaimine would determine whether ring fission had occurred at the same place in the two cases.

a. Hofmann Method. The nitrogen of thebaine and a number of related products (dihydrothebaine, dihydrothebainone, dihydrothebainol, metathebainone, phenolic dihydrothebaine, β-dihydrothebainone, hydroxycodeinone, hydroxythebainone, dihydrohydroxycodeinone, dihydrohydroxythebainone, hydroxythebainol, dihydrohydroxycodeine-B, α-thebaizone, hydroxydihydrothebaizonic acid, dihydrodesoxythebaizone, the methyldihydrothebaines and phenyldihydrothebaine (Table 6)) all react with methyl iodide yielding the respective methiodides, but their reaction towards heat and alkali is less uniform than the corresponding derivative of codeine and its related products. Furthermore, little attempt has been made to classify the type of cleavage occurring in each case. The evidence, at hand, indicates that type V fission occurs in the four isomeric methyldihydrothebaines but not in their acetyl derivatives (309) (the term des-*N*-methyl seems preferable here to the methine terminology until such time as evidence is at hand to diagnose the various fissions as to type). Fission of type M must occur in the formation of the des-base from metathebainone methyl ether, since dimethylmorphol (VIII, R = CH_3) and

TABLE 6

SOME PRODUCTS OF THE HOFMANN REACTION

Methiode of	Reagent	Basic product	Nitrogen-free product	References
Acetylhydroxy-thebainone	Alkali	Des-*N*-methylhydroxy-thebainone	..	30
Acetyl-δ-methyl-dihydrothebaine	TlOH	(-)Methyldihydrothebaine methine and δ-Methyldihydrothebaine isomethine	..	309
Des-*N*-methyldihydro-desoxythebaizonic acid	TlOH	Des-*N*-methyldihydro-desoxythebaizonic acid	Methanol	38
Des-*N*-methyldihydro-hydroxycodeinone	AgOH	Trimethylamine	Dihydrohydroxy-codeone	36
Des-*N*-methyldihydro-hydroxythebainone	KOH	Trimethylamine	..	319
Methyl ether	NaOH	Trimethylamine	Dihydrohydroxy-thebaon methyl ether	36
Des-*N*-methyldihydro-thebaine	KOH or AgOH	Trimethylamine	$C_{17}H_{16}O_3$	189, 297
Des-*N*-methyldihydro-thebaine(phenolic) methyl ether	KOH	Trimethylamine	Thebaol methyl ether + ethylene	125
Des-*N*-methyldihydro-thebainol	KOH	Trimethylamine	..	190
Des-*N*-methylhydroxy-thebainol methyl ether	AgOH	Trimethylamine	$C_{18}H_{20}O_4$	30
Des-*N*-methylmeta-thebainone	Alkali	No reaction	No reaction	37
Methyl ether	AgOH	Trimethylamine	Oily vinyl product	124
Des-*N*-methylphenyl-dihydrothebaine	KOH or $NaOC_2H_5$	Trimethylamine	Phenyldihydrothebenol	125
ethyl ether	$NaOC_2H_5$	..	α-Phenyldihydrothebenol ethyl ether	125
Methyl ether	$NaOC_2H_5$	..	α-Phenyldihydrothebenol methyl ether	125
Des-*N*-methylthebaizonic acid	..	Des-*N*-methylthebaizonic acid	Methanol	38
Dihydro-des-*N*-methyl-dihydrohydroxy-codeinone	AgOH	..	Tetrahydrohydroxy-codeone	36
Dihydro-des-*N*-methyl-dihydrohydroxy-thebainone	KOH	Trimethylamine	Tetrahydrohydroxy-thebaon	319
Methyl ether	NaOH	..	Tetrahydrohydroxy-thebaon methyl ether	36

TABLE 6 (*Continued*)

Methiode of	Reagent	Basic product	Nitrogen-free product	References
Dihydro-des-*N*-methyl-dihydrothebaine	AgOH or KOH	Trimethylamine + dihydro-des-*N*-methyldihydro-thebaine	$C_{18}H_{20}O_3$	34
Dihydro-des-*N*-methyl-dihydrothebainone	NaOH	Trimethylamine	Thebenone	34
Dihydro-des-*N*-methyl-β-dihydrothe-bainone	NaOH	Trimethylamine	β-Thebenone	310
Dihydrodesoxythebai-zone	TlOH	Des-*N*-methyldihydro-desoxythebaizonic acid	..	38
Dihydrohydroxy-codeine-B	NaOH	Des-*N*-methyldihydro-hydroxycodeine-B	..	311
Dihydrohydroxy-codeinone	KOH	Des-*N*-methyldihydro-hydroxycodeinone	..	36, 319
Dihydrohydroxy-thebainone	KOH	Des-*N*-methyldihydro-hydroxythebainone	..	319
Methyl ether	NaOH	Des-*N*-methyldihydro-hydroxythebainone methyl ether	..	36
Dihydrometathebai-none methyl ether	..	Des-*N*-methyldihydro-metathebainone methyl ether	..	37
Dihydrothebaine	NaOH or KOH	Des-*N*-methyldihydro-thebaine	..	34, 189
Dihydrothebaine (phenolic)	Alkali	No reaction	No reaction	89
Methyl ether	KOH	Des-*N*-methyldihydro-thebaine (phenolic) methyl ether	..	125
Dihydrothebainol-A	KOH	Des-*N*-methyldihydro-thebainol-A	..	190
Dihydrothebainone	KOH	Des-*N*-methyldihydro-thebainone	..	189
Methyl ether	NaOH	Des-*N*-methyldihydro-thebainone methyl ether	..	292
β-Dihydrothebainone	NaOH	Des-*N*-methyl-β-dihydrothebainone	..	310
α-Di-(meta)-thebai-none	NaOH	..	..	39
Hydroxycodeinone	$NaOC_2H_5$	Des-*N*-methylhydroxy-codeinone	..	319
Hydroxydihydrothe-baizonic acid	NaOH	Hydroxydihydrothe-baizonic acid	Methanol	38
Hydroxythebainol methyl ether	KOH	Des-*N*-methylhydroxy-thebainol methyl ether	..	30

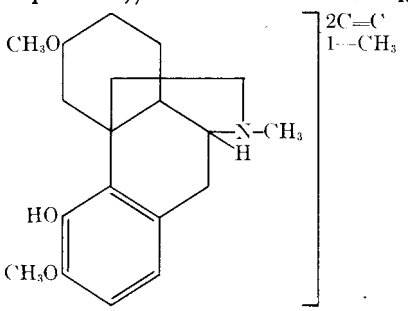
TABLE 6 (*Continued*)

Methiodide of	Reagent	Basic product	Nitrogen-free product	References
Metathebainone	NaOH	Des-*N*-methylmetathebainone	..	37
Methyl ether	NaOH	Metathebainonemethine methyl ether	..	37, 122
α-Methyldihydrothebaine	NaOH	α-Methyldihydrothebaineisomethine	..	309
δ-Methyldihydrothebaine	NaOH	δ-Methyldihydrothebaineisomethine	..	309
Methyl ether	NaOH	δ-Methyldihydrothebaineisomethine methyl ether	..	309
η-Methyldihydrothebaine	NaOH	η-Methyldihydrothebaineisomethine	..	309
Methyl ether	NaOH	(+)Methyldihydrothebainemethine methyl ether	..	309
ω-Methyldihydrothebaine	NaOH	ω-Methyldihydrothebaineisomethine	..	309
α-Methyldihydrothebaineisomethine	TlOH + NaOH	Trimethylamine	rac.-Vinyldihydro-X-methylthebaol	309
δ-Methyldihydrothebaineisomethine	TlOH + NaOH	..	rac.-Vinyldihydro-X-methylthebaol	309
(−)Methyldihydrothebainemethine	NaOH	..	(+)Vinyldihydro-X-methylthebaol	309
α-Methyl-9-dimethylamino-6-methoxythebendiene	NaOH	..	(+)6-Methoxy-X-methylthebentriene	309
δ-Methyl-9-dimethylamino-6-methoxythebendiene	NaOH	..	(+)6-Methoxy-X-methylthebentriene	309
η-Methyl-9-dimethylamino-6-methoxythebendiene	NaOH	..	(−)6-Methoxy-X-methylthebentriene	309
Phenyldihydrothebaine	KOH or $NaOC_2H_5$	Des-*N*-methylphenyldihydrothebaine	..	125
Ethyl ether	$NaOC_2H_5$	Des-*N*-methylphenyldihydrothebaine ethyl ether	..	125
Methyl ether	$NaOC_2H_5$	Des-*N*-methylphenyldihydrothebaine methyl ether	..	125
Thebaine	AgOH or KOH or $NaOCH_3$	Tetramethylethylenediamine + some dimethylamine	Thebaol	73, 84, 116
α-Thebaizone	TlOH	Des-*N*-methylthebaizonic acid	Methanol	38

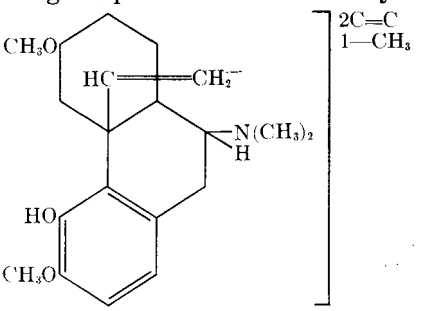
acetylethanoldimethylamine are the products of acetolysis of the latter base (124).

There are but few anomalies in the first phase of the elimination of the nitrogen atom by the Hofmann method. Thebaine methiodide exhibits a sensitivity towards alkali comparable with that of codeinone towards acetic anhydride; when it is warmed with moist silver oxide, potassium hydroxide, or alcoholic sodium methylate, thebaol is formed by loss of the complete nitrogen bridge (isolated as tetramethylethylenediamine). A similar reaction results when the methiodide is heated with ethanol at 160–165°, except that the basic product is now dimethylaminoethyl–ethyl ether (picrate, aurichloride) (116). Phenolic dihydrothebaine stands in direct antithesis to this. Alkali on the methiodide does not effect a ring fission, probably due to phenol betaine formation. Also, in those cases where carbomethoxy groups are present (α-thebaizone and dihydrodesoxythebaizone), it hardly need be pointed out that, under the conditions of the reaction, saponification of these groups accompanies the Hofmann transformation.

Application of the Hofmann reaction to the methiodides of the diastereomeric (about C_9) pair, α- and δ-methyldihydrothebaine (CLXI; assuming the carbon end of the nitrogen bridge has not suffered a change of position), causes fission at N–C_{16} yielding the phenolic α- and δ-methyl-



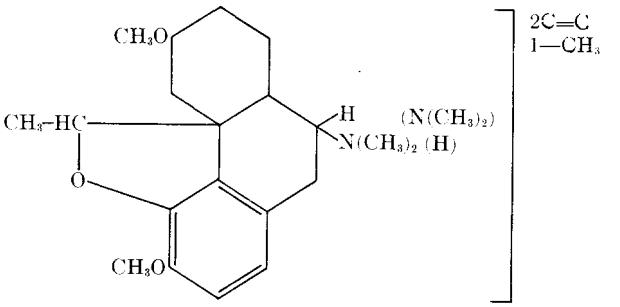
CLXI



CLXII

dihydrothebaineisomethines (CLXII) (309). The newly generated ethylenic double bond, in contrast to those assumed to be present in the parent bases, is reducible in the presence of platinum oxide (309). These phenolic isomethines (but not their dihydro derivatives) have been isomerized to the nonphenolic and nonreducible α- and δ-methyldimethylamino-6-methoxythebendienes (CLXIII) by partially hydrolyzed acetyl chloride (309). This reagent apparently catalyzes the addition of a molecule of water to the vinyl group (isolated in the case of δ-methyldihydrothebaineisomethine), followed by a cyclodehydration involving the C_4 hydroxyl group.

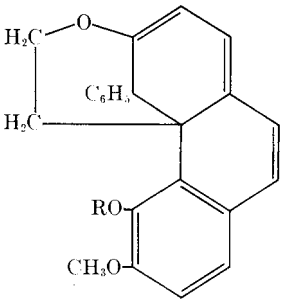
When the methohydroxides of the acetyl derivatives of α- and δ-methyldihydrothebaine are subjected to dry distillation, the decomposition follows a different course. Now both methohydroxides yield the same methine base contaminated, however, with some of the respective isomethines.



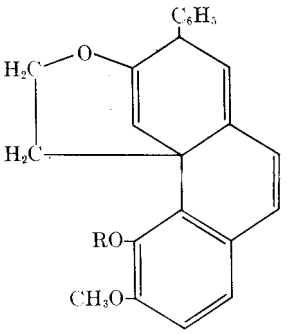
CLXIII

The methine, unlike the isomethines, is stable to partially hydrolyzed acetyl chloride. From the conversion of α- and δ-methyldihydrothebaine to the same methine, while the isomerism is maintained in the derived isomethines, it is to be inferred that the isomerism in the parent bases stems from a steric difference about C_9 and that fission of type M occurs in methine formation (thus destroying the steric difference in the two series). Fission of type V permits the retention of the steric difference in the two isomethines.

The normal course of the degradation of the des-bases in some cases (des-*N*-methyldihydrothebaine) is accompanied by the loss of methanol, and in other cases (des-*N*-methylthebaizonic acid and des-*N*-methyldi-



R = H, CH_3, C_2H_5
CLXIV

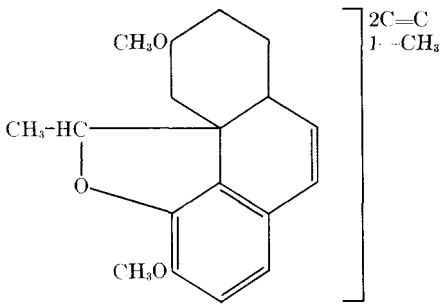


R = H, CH_3, C_2H_5
CLXV

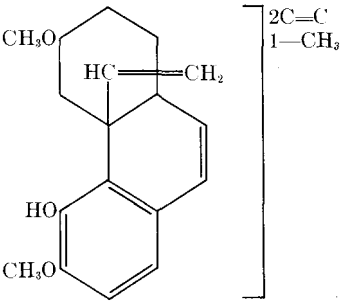
hydrodesoxythebaizonic acid) this becomes the predominant reaction. The methiodide of metathebainonemethine, on the other hand, is not degraded by alkali (37). Secondary reactions involving the loss of the

elements of CH_2 accompany the normal decomposition of the methiodides of des-*N*-methylphenyldihydrothebaine and its C_4 methyl and ethyl ethers. A cyclization involving the vinyl group and the C_4 hydroxyl group, combined with demethylation of the C_6 methoxyl, would yield a product conforming with the analytical requirements (a Zeisel determination indicates the presence of only one methoxyl group (125)). That such a transformation does not occur in this instance is demonstrated by ethylation of the C_4 hydroxyl and its degradation to phenyldihydrothebenol ethyl ether (CLXIV or CLXV, R = C_2H_5).

Elimination of the dimethylamino grouping from α- and δ-methyldihydrothebaineisomethine by the Hofmann degradation removes the center of steric difference in the two isomers and both yield (+6-methoxy-X-methylthebentriene) (CLXVI). Compound CLXVI may be obtained in a similar manner from α-methyl-9-dimethylamino-6-methoxythebendiene (CLXVII), or in a stepwise fashion from (−)-methyldihydrothebainemethine. This methine has been degraded to trimethylamine and a separable mixture of (+)- and racemic-vinyldihydro-X-methylthebaol (CLXVII). Hot hydrochloric acid (or acetic anhydride) completes the conversion to CLXVI.



CLXVI



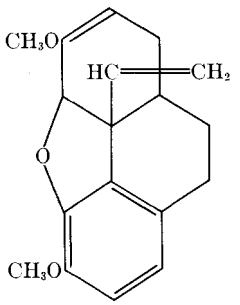
CLXVII

The des-base of phenolic dihydrothebaine methyl ether possesses the same degree of unsaturation as α-methylmorphimethine and, like the latter base, when subjected to the Hofmann degradation, loses the complete ethanamine chain ($CH_2{=}CH_2$ + $(CH_3)_3N$) with the formation of thebaol methyl ether.

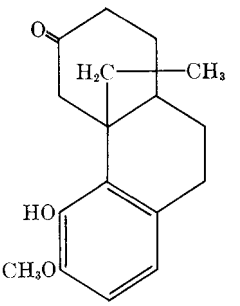
The newly generated center of unsaturation in a number of the above des-bases has been reduced catalytically and of these dihydro-des-N-methyldihydrothebaine,[2] dihydro-des-*N*-methyldihydrothebainone, dihydro-des-*N*-methyl-β-dihydrothebainone, dihydro-des-*N*-methyldi-

[2] Hydrolysis (HCl) of the enol methyl ether of dihydro-des-*N*-methyldihydrothebaine (34) yields the same keto des-base as obtained by oxidation (CrO_3) of dihydro-des-*N*-methyldihydrocodeine (34).

hydrohydroxycodeinone, dihydro-des-*N*-methyldihydrohydroxythebainone and its methyl ether have been degraded further. Trimethylamine is lost in the normal fashion from dihydro-des-*N*-methyldihydrothebaine (some starting material is regenerated by loss of methanol from the methohydroxide) (34), and the resulting vinyl compound, CLXVIII, may be reduced ($2H_2$ + palladium black + bicarbonate → abnormal reduction) in the absence of mineral acid to the C_{15}–C_{16} dihydro derivative and then hydrolyzed (2 *N* HCl) to CLXIX (206). These two steps may be achieved simultaneously if the reduction is carried out in the absence of sodium bicarbonate (34).

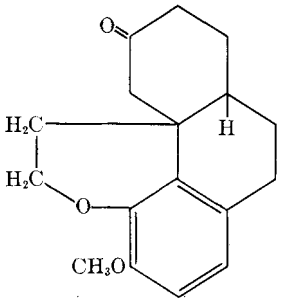


CLXVIII

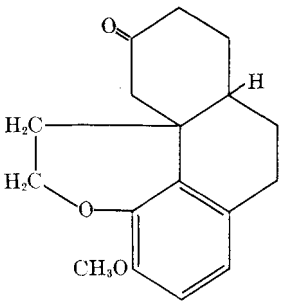


CLXIX

Dihydro-des-*N*-methyldihydrothebainone and the respective isomer from β-dihydrothebainone act in an analogous fashion upon removal of the nitrogen as trimethylamine. Cyclization occurs in each case by addition of the C_4 hydroxyl to the primarily formed vinyl group, yielding respectively thebenone (CLXX) and β-thebenone (CLXXI) (310).



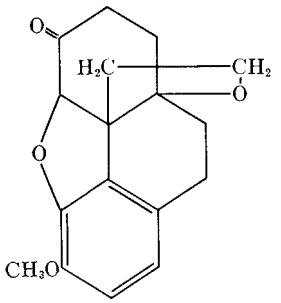
CLXX



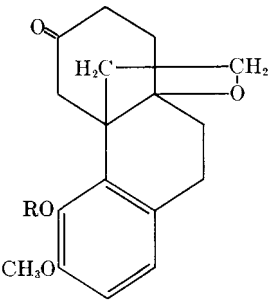
CLXXI

Dihydro-des-*N*-methyldihydrohydroxycodeinone, dihydro-des-*N*-methyldihydrothebainone and its methyl ether are degraded quite normally to tetrahydrohydroxycodeone (CLXXII), tetrahydrohydroxythebaone (CLXXIII) and its methyl ether. An alternative route to these last two

products lies in the degradation of des-*N*-methyldihydrohydroxycodeinone and des-*N*-methyldihydrohydroxythebainone methyl ether to dihydrohydroxycodeone and dihydrohydroxythebaon methyl ether followed by catalytic reduction (H_2 + Pd) (36).



CLXXII



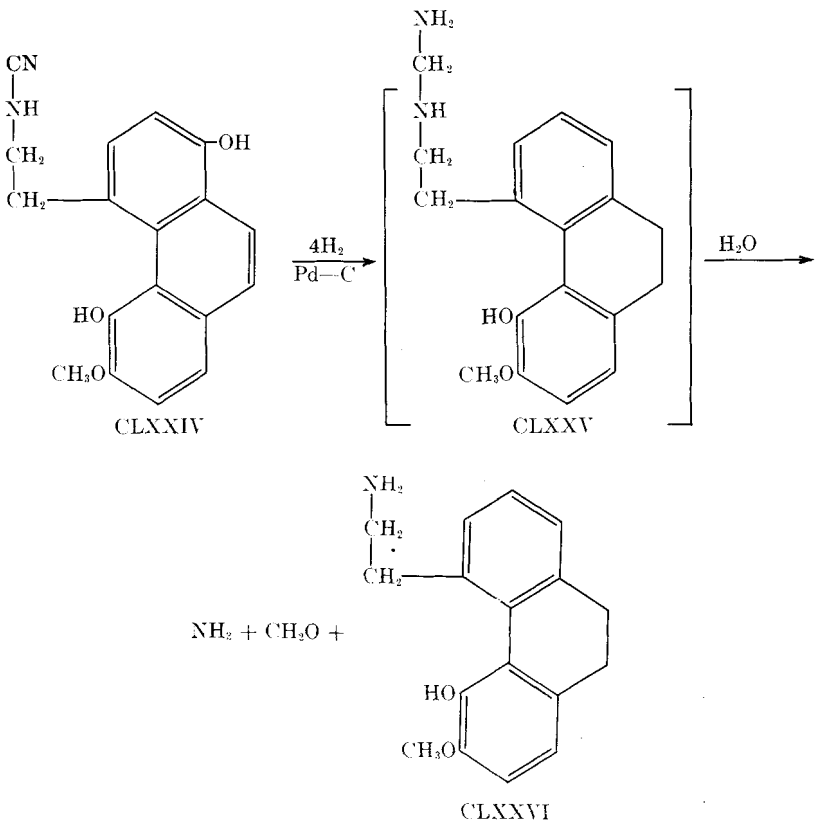
R = H, CH_3
CLXXIII

b. Cyanogen Bromide Method. The course of the reaction of cyanogen bromide upon dihydrothebaine (CXXXIII, R = R′ = CH_3) (189), acetylhydroxycodeinone (CXLVIII; X = $OCOCH_3$, R = CH_3) (319) and acetyldihydrohydroxycodeinone (200) appears to be quite normal. The cyano group of the primary cyanonor derivatives from the last two products has been hydrolyzed (25% H_2SO_4) yielding respectively norhydroxycodeinone (200) (CXLVIII; X = OH, R = H) and nordihydrohydroxycodeinone (200).

In the case of thebaine ($C_{19}H_{21}O_3N$), the course of the reaction appears to be dependent to a large extent upon the solvent. In chloroform (179, 205), the reaction seems to proceed quite normally for a substituted allylamine system, although difficulty was experienced in isolating the oily product in a pure state (some thebaine hydrobromide was also isolated from this reaction). The presence of some bromine-free contaminant in the primary product was evident from the analysis for this element (bromine analysis was 14% instead of a calculated 19%). A crystalline sample of this contaminant was eventually isolated (m.p. 147°) by digestion with ether.

When acetic acid is the solvent, this bromine-free compound now becomes the main product ($C_{18}H_{16}O_3N_2$; m.p. 146–147°) (205). It is phenolic and represents a loss of C_2H_5 and the gain of CN. The acid conditions obtaining in this reaction may be sufficient to cause a primary thebenine rearrangement followed by *N*-demethylation to the phenolic cyanonorthebenine ($C_{18}H_{16}O_3N_2$) (CLXXIV) (a Zeisel determination shows the presence of one methoxyl group as required by this hypothesis) (205). Hydrolysis of the cyano group under various conditions led only to oily and ill-defined

products. This C_{18}-compound rapidly absorbed four mole equivalents of hydrogen in the presence of palladized charcoal, which was considered to involve reduction of the Δ^{9-10} double bond, the cyano group (two moles of H_2), and hydrogenolysis of the C_8 hydroxyl group. Water hydrolyzed this reduction product (CLXXV) to the primary amine, CLXXVI (three carbon atoms were introduced in converting CLXXVI to its methiodide (205)).



5. Rearrangements

Thebaine is very susceptible to rearrangement in acid media. This has already been clearly manifest through its conversion to metathebainone and cyanonorthebenine. Another rearrangement product, thebenine, materially held up the morphine structural problem and progress was not made along this line again until it was recognized that thebenine is an acid (dilute HCl) rearrangement product of thebaine. Concentrated hydrochloric acid, on the other hand, leads to morphothebaine, a second rearrangement product.

a. Thebenine ($C_{18}H_{19}O_3N$) (79). This is a phenolic base resulting from thebaine ($C_{19}H_{21}O_3N$) and boiling, dilute hydrochloric acid.

Thebenine (84, 113). Ten grams of pure thebaine is introduced into 100 cc. of boiling hydrochloric acid (sp.g. 1.07) and the solution maintained at the boiling point for not more than 2 minutes. The flask is then chilled in an ice-bath and upon addition of ice to the reaction mixture a viscous, yellow mass settles out, which is recovered by decantation of the hydrochloric acid. Thebenine hydrochloride is recovered from the sirupy mass by crystallization from water. The hydrochloride (6.0 g.) melts at 235° with previous sintering. (Thebenine hydrochloride results when the same reagent is applied to codeinone (113).)

The hydrochloride, when decomposed with alkali, yields the amorphous base, thebenine,[3] which is soluble in alkali.

Loss of one carbon and the generation of phenolic properties in the formation of thebenine might suggest that the primary phase in this acid medium is the hydrolysis of the enol methyl ether. This conjecture has been demonstrated to be correct by the formation of thebenine from codeinone under similar conditions (113) (pseudocodeinone shows a marked stability to 14% hydrochloric acid, but is degraded to the triacetyl derivative of thebenine by acetic anhydride (145)). One of the phenolic hydroxyls of thebenine, like that of α-naphthol, is readily alkylated with alcoholic (CH_3OH, C_2H_5OH, and C_3H_7OH) hydrogen chloride. This alkylation accompanies rearrangement when thebaine is warmed with any one of the above reagents (89). For example, when methanol, ethanol, or propanol are the solvents for the hydrogen chloride, the rearrangement products are methebenine (thebenine methyl ether), ethebenine and prothebenine, respectively (when stannous chloride in acetic acid is the reagent, hydrolysis of the methoxyl group of thebaine is circumvented and methebenine results directly (42)). Methebenine is still phenolic because it is soluble in aqueous alkali, and methylation of its quaternary salt with methyl sulfate (diazomethane and methyl iodide failed to methylate this phenolic hydroxyl group of thebenine) yielded (with KI) methebenine methyl ether methiodide. Methebenine (89, 113, 114), in contrast to thebenine (145), yields a diacetyl and a dibenzoyl derivative. Since two of the three oxygens of methebenine occur in methoxyl groups (89), then one of the acyl groups of the diacyl derivatives must be associated with the nitrogen atom. Hence, thebenine must be either a primary or secondary amine (a thiourea derivative is formed when thebenine hydrochloride reacts with phenylisothiocyanate (84)). The introduction of but two carbon atoms into thebenine in methiodide formation (84) and elimination of the nitrogen as methyldiethylamine after exhaustive ethylation (79)

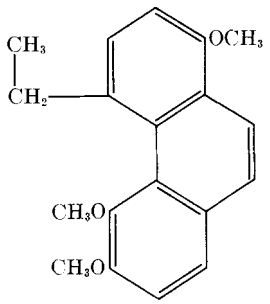
[3] Brief treatment of thebenine with concentrated hydrochloric acid promotes a further change (probably demethylation) to thebaicine (6), a phenolic product which is very sensitive to oxygen.

and one Hofmann degradation suffice to characterize this base as a secondary amine in which the nitrogen atom is not a component of a ring but does bear one methyl group.

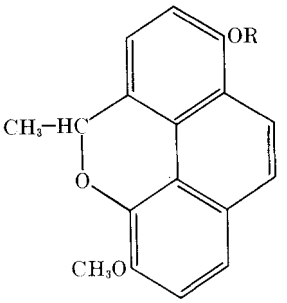
The oxygen-bearing groups of thebenine were assigned to C_3, C_4, and C_8 of the phenanthrene nucleus after identification of the products of exhaustive methylation and Hofmann degradation. The product from addition of two moles of methyl iodide to thebenine is *N*-methylthebenine methiodide (also called thebeninemethine methiodide) (84). This methiodide, as well as that of methebenine (89) and ethebenine (89), is degraded by alkali to trimethylamine (aurichloride) and a nitrogen-free product, thebenol ($C_{17}H_{14}O_3$) (79, 84) (methebenol and ethebenol, identical with the etherification products of thebenol (84), are the corresponding products from methebenine and ethebenine). Methebenol appears to be abnormal in certain respects. It exhibits properties neither of a phenol nor of an ethylene (114). If, however, the phenolic hydroxyl of methebenine is methylated prior to degradation of the amine, then the resulting nitrogen-free product ($C_{19}H_{18}O_3$) (23, 114, 294) does decolorize bromine instantly and is converted to a dihydro derivative by absorption of one mole equivalent (palladized charcoal) of hydrogen (294). Crystallization of this vinyltrimethoxyphenanthrene (it forms a picrate, and a Zeisel determination establishes the presence of three methoxyl groups) (114) from acetic acid or alcohol containing a little hydrogen chloride converts it to methebenol (two methoxyl groups; Zeisel determination) which no longer decolorizes bromine. The most obvious conclusion is that a cyclization involving the interaction of the phenol with the vinyl group has occurred.

Oxidation ($KMnO_4$ + HOAc) of the unsaturated group of $C_{19}H_{18}O_3$ to a trimethoxyphenanthrenecarboxylic acid ($C_{18}H_{16}O_5$) (the corresponding aldehyde is the main product from this oxidation (23, 294)) establishes the presence of a vinyl group in the molecule (114), while decarboxylation of the acid to 3,4,8-trimethoxyphenanthrene (143) located the three oxygen atoms of thebenol and thebenine but gave no clue as to which one was involved in thebenol formation. Since thebenine has been derived from codeinone, the methoxyl group of thebenine must be at C_3; hence, thebenol formation must involve the phenolic hydroxyl at either C_4 or C_8. The ethoxyl group of ethebenine is not lost in its conversion to ethebenol. This combined with the degradation of ethebenine methiodide to a vinyldimethoxyethoxyphenanthrene and removal of the vinyl group by its oxidation ($KMnO_4$ + acetone) and decarboxylation of the resulting acid gave 3,4-dimethoxy-8-ethoxyphenanthrene (23) (compared with that prepared by a Pschorr synthesis from 2-nitro-3,4-dimethoxybenzaldehyde + sodium *o*-ethoxyphenylacetate) (24), thus locating the ethoxyl group at C_8. Hence, the C_4 hydroxyl group is involved, along with the vinyl group, in thebenol

formation (84) (HI cleaves the methoxyl and the ether ring of thebenol; $C_{17}H_{14}O_3 \rightarrow C_{16}H_{13}O_3I$ (84)). Furthermore, the vinyl group of thebenol must be in close proximity to the C_4 hydroxyl group and may, on speculative grounds, be tentatively assigned to C_5. This conclusion is based on the conversion (zinc dust distillation (79, 84, 166) or phosphorus and hydriodic acid (79, 84, 166)) of thebenine, if at high temperature and in poor yield, to pyrene (picrate). The validity of this conjecture was confirmed by reduction of the above vinyltrimethoxyphenanthrene to 5-ethyl-3,4,8-trimethoxyphenanthrene (CLXXVII) (compared with that prepared by a Pschorr synthesis from 2-nitro-3,4-dimethoxybenzaldehyde + sodium 2-methoxy-5-ethylphenylacetate) (294). (Prior to the location of the vinyl group through its conversion to, and the synthesis of, the respective ethyl

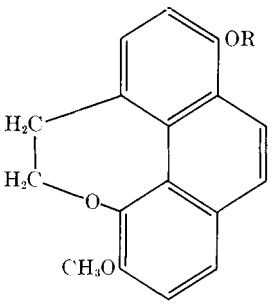


CLXXVII



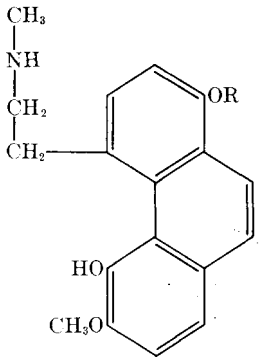
R = H, CH_3, C_2H_5, C_3H_7

CLXXVIII



R = H, CH_3, C_2H_5, C_3H_7

CLXXIX



R = H, CH_3, C_2H_5, C_3H_7

CLXXX

derivative, the unsaturated side chain was oxidized to a carboxyl. The stock method for the location of the carboxyl in this trimethoxyphenanthrene-carboxylic acid failed since demethylation of the sensitive C_4–methoxyl occurred during the conversion of the acid azide to the amine. Intra-

molecular dehydration to the lactone followed (294).) Hence thebenol, methebenol, ethebenol, and prothebenol must be either CLXXVIII (294) or CLXXIX (23) (CLXXVIII contains one center of asymmetry and should be resolvable, thebenol, however, has resisted all attempts at resolution (315)), while thebenine, methebenine, ethebenine, and prothebenine must be CLXXX.

Catalytic hydrogenation (Pd on $BaSO_4$ (44a), but not electrolytic reduction or sodium and alcohol, reduced the Δ^{9-10} double bond of thebenine. It has been reported also, that sodium hydrosulfite yields a dihydrothebenine (204) which is very similar in properties to thebenine itself. It is readily acetylated and benzoylated, while methyl sulfate transforms an alkaline solution of the base into dimethyldihydrothebeninemethine methohydroxide. This methohydroxide is degraded by thermal decomposition to trimethylamine and dihydromethebenol (demethylation of the C_4 methoxyl group has also occurred). The conditions for the conversion of thebenol to pyrene have been applied to dihydromethebenol, but the results are not as clearly defined.

This interesting rearrangement, involving as it does the migration of the C_6 oxygen to C_8 and the simultaneous fission of the C_9—N bond and migration of the carbon end of the nitrogen chain from C_{13} to C_5 with accompanied aromatization of the nucleus, has given rise to a number of speculations concerning the mechanism of this reaction.

b. Morphothebaine ($C_{18}H_{19}O_3N$) (89). This base is readily prepared in good yield by heating thebaine ($C_{19}H_{21}O_3N$) or codeinone ($C_{18}H_{19}O_3N$) with concentrated hydrochloric or hydrobromic acid.

Morphothebaine (37, 70, 121). A solution of 10.0 g. of thebaine in 50 cc. of 38% hydrochloric acid is heated on the steam bath for not more than 3 hours. On cooling, the so-called "acid hydrochloride" (37), which separates, is collected and washed with concentrated hydrochloric acid and then converted to the "neutral hydrochloride" by boiling in ethanol; yield 80–85%.

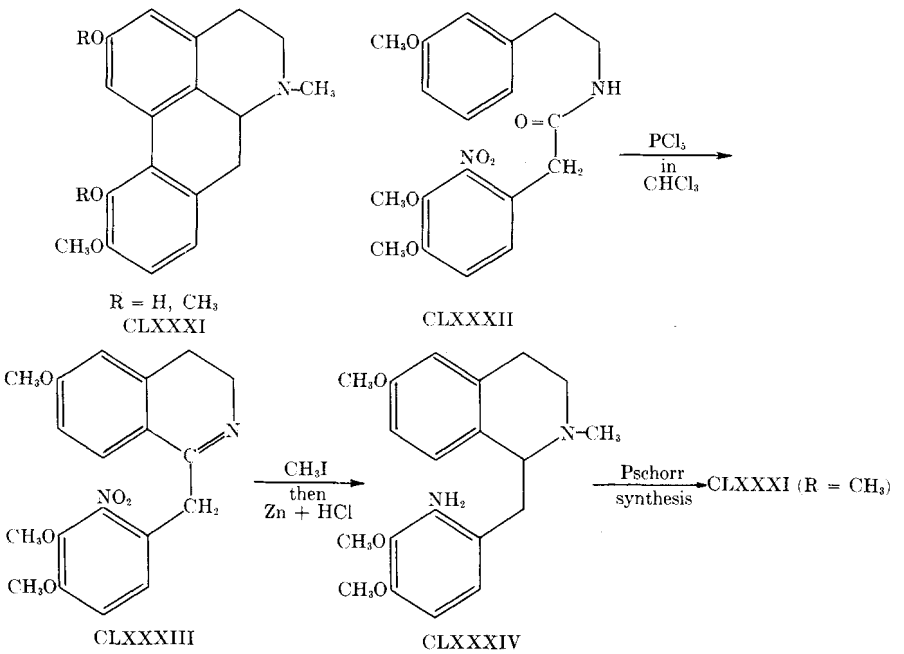
Morphothebaine is liberated from its hydrochloride by the addition of sodium carbonate solution, collected on a funnel and washed with water. The base, after crystallization from methanol, melts at 197°. Yields of the pure base as high as 68% have been reported (58). (Codeinone is transformed into morphothebaine under similar conditions, but the conversion is somewhat slower (112).)

Morphothebaine was originally assigned the formula, $C_{17}H_{17}O_3N$ (70), but this has since been revised to $C_{18}H_{19}O_3N$ (89, 113). This transformation of thebaine to morphothebaine, involving the loss of CH_2 (appearing as a combustible gas, probably methyl chloride (70)), must include a rearrangement as well as a demethylation because thebaine (as its methiodide) is not regenerated when morphothebaine is methylated with methyl iodide (89). Furthermore, it differs from the isomeric thebenine in that the nitrogen is a tertiary amine (73) and is still a component of a ring (two

exhaustive methylations and two Hofmann degradations are required to eliminate the nitrogen of morphothebaine dimethyl ether as trimethylamine (23)). In contrast to thebaine, this C_{18}-base contains but one methoxyl group (Zeisel (89): demethylation of morphothebaine in an atmosphere of carbon dioxide with 1 *N* hydrobromic acid yields a base ($C_{17}H_{17}O_3N$) which is very sensitive to air (32)). The remaining two oxygens are present in phenolic hydroxyl groups (ferric chloride test, solubility in alkali (23), failure to react with phosphorus pentachloride (70) and its methylation with diazomethane (58, 295) or methyl sulfate (23) to morphothebaine dimethyl ether ($[\alpha]_D^{20} = -172.7°$) containing three methoxyl groups (121)).

Morphothebaine exhibits none of the color reactions of thebaine or thebenine (70) nor can it be converted into the latter by hydrochloric acid or alcoholic hydrogen chloride (hence, it is not an intermediate in the formation of thebenine) (89). Unlike thebaine, the nitrogen ring of morphothebaine shows a marked stability towards acetic anhydride, while its methiodide does not suffer degradation in alkaline medium (89). On the other hand, many of the reactions of morphothebaine are so remarkably similar to those of apomorphine (23) that this base might well be just a hydroxyapomorphine. With either benzoyl chloride (121) or acetic anhydride (89) a triacyl derivative is formed by esterification of the two phenolic hydroxyls and rupture at the nitrogen of the tetrahydroisoquinoline nucleus (a monoacetyl derivative is also described in the literature (70)). This tribenzoylmorphothebaine ($C_{39}H_{31}O_6N$) has been oxidized (CrO_3+HOAc) to the phenanthrenequinone, tribenzoylmorphothebainequinone ($C_{39}H_{29}O_8N$) (it yields a phenazine with *o*-phenylenediamine), which was subsequently saponified (alcoholic solution of sodium ethylate) (144) to *N*-benzoylmorphothebainequinone. Then, too, the degradation of morphothebaine dimethyl ether mirrors the conversion of apomorphine dimethyl ether to 3,4,8-trimethoxyphenanthrene. A sequence of two Hofmann degradations was required to liberate trimethylamine (aurichloride (121); hence, there is an N–CH_3 grouping in morphothebaine) from morphothebaine dimethyl ether with the formation of a vinyltrimethoxyphenanthrene (23, 121) (no reaction analogous to thebenol formation was observed when this vinyl compound was warmed in acetic acid (121)). Potassium permanganate (121) oxidized the vinyl group of the above phenanthrene to a carboxyl group. The results of the decarboxylation of this trimethoxyphenanthroic acid (different to that from thebenine were far from satisfactory; for decarboxylation of the acid itself failed, whereas a similar reaction on its silver salt afforded only a minute amount of a neutral oil whose picrate, although not well characterized, behaved very much like that of 3,4,6-trimethoxyphenanthrene. If the analogy of morphothebaine with apomorphine

is valid, then the position of the methoxyls of the tetramethoxyphenanthrene resulting from the degradation of this trimethoxyphenanthroic acid would be expected to be C_3, C_4, C_6 and C_8. The validity of this conjecture was confirmed by synthesis of this tetramethoxyphenanthrene (a Pschorr synthesis from 2-nitro-3,4-dimethoxybenzaldehyde + sodium 2,4-dimethoxyphenylacetate) (26). Thence, from the above two observations it would appear safe to conclude that the carboxyl of the above trimethoxyphenanthroic acid is at C_8 and that morphothebaine dimethyl ether is CLXXXI(R = CH_3). This structure for morphothebaine dimethyl ether was then confirmed by synthesis (the major steps of which are outlined below (CLXXXII–CLXXXI)) and resolution of the *dl*-base with *d*-tartaric acid (rotation of the *l*-form is $[\alpha]_D^{20} = -173.5°$).

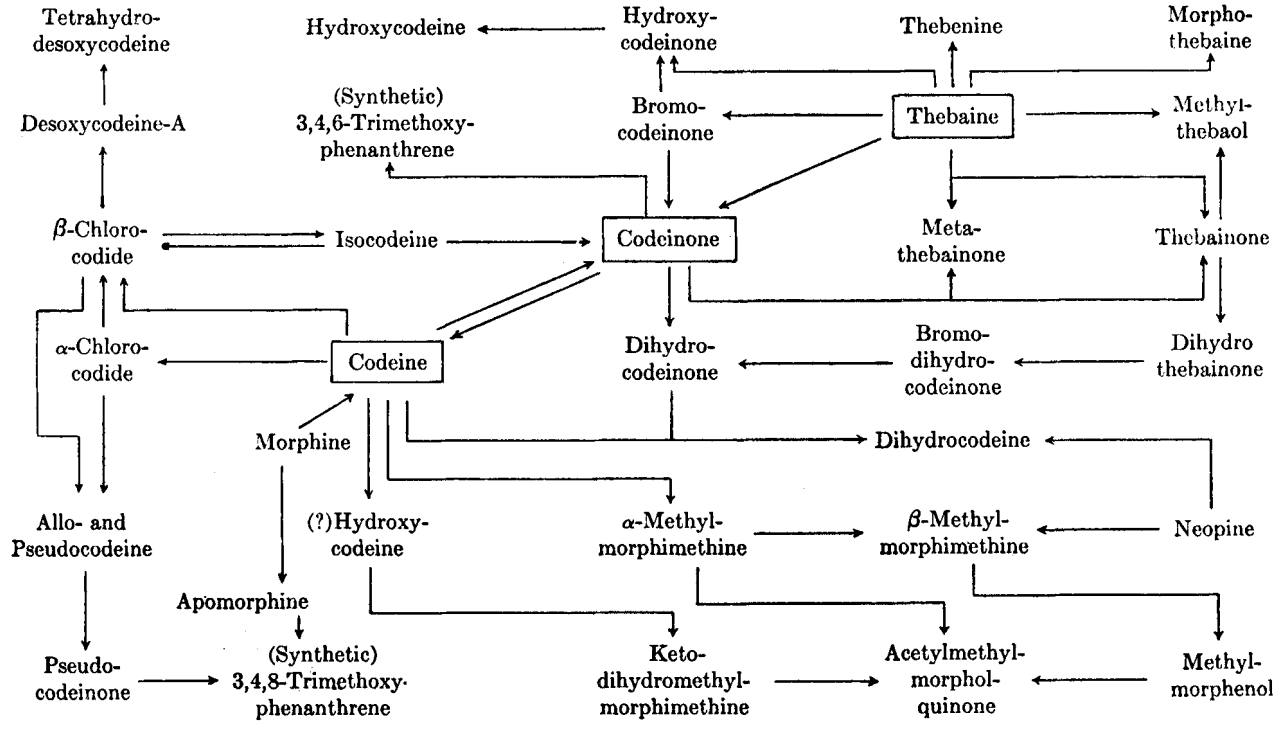


Then, when its formation from codeinone is considered, morphothebaine must be CLXXXI (R = H), a structure which obviously must involve a rearrangement in its formation from thebaine.

The early mechanisms (34, 183) put forth to account for this transformation were based on a bridge formula for morphine and hardly need be considered today. Robinson (321) considered that a hydrolytic cleavage of the oxide bridge and of the C_{12}–C_{13} bond of codeinone followed by rotation of ring III about an axis through C_6 and C_{14} and subsequent dehydra-

CHART I

CODEINE AND THEBAINE AND THEIR PRODUCTS OF TRANSFORMATION AND DEGRADATION

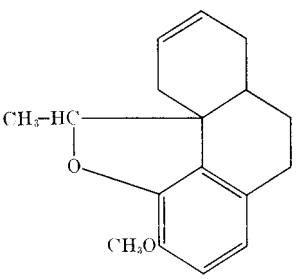


tion adequately accounted for the formation of morphothebaine. Schöpf and Borkowsky (37) in their extensive study on the action of hydrochloric acid on thebaine consider that a number (CXLII–CXLIV) of intermediates are common to the formation of both morphothebaine and metathebainone. The tendency towards aromatization of ring III in CXLIV is the driving force for the elimination of the elements of hydrogen chloride and for the migration of the ethanamine bridge from C_{14} to C_8.

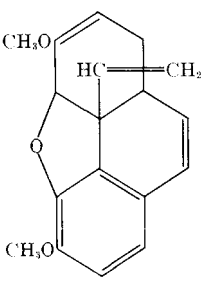
The interrelationship of thebaine, codeinone and codeine as well as the relation of their more important products of transformation and degradation is graphically illustrated in Chart I.

V. Synthetic Hydrophenanthrenes Related to The Morphine Alkaloids

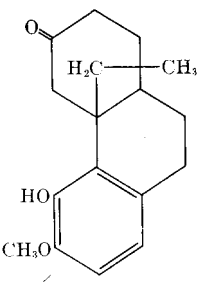
The elucidation of the structure of the morphine alkaloids by their conversion to, and the synthesis of, simpler hydroaromatic structures possessing the same degree of saturation as the parent bases has not kept pace with the work on their fully aromatic counterparts. The ease of conversion of the methine bases as well as codeinone and thebaine to fully aromatic phenanthrenes combined with the great flexibility of the Pschorr synthesis is only partly responsible for this. The primary reasons for the paucity of work in this synthetic field have been (1) the lack of an objective for such syntheses since all attempted conversions of this nature have fallen short of their goal due to anomalous reactions; and (2) because there has been no method available, until just recently, for introducing functional groups into the angular positions (C_{13} or C_{14}) of the hydrophenanthrene system as found in these alkaloids. Certain degradation products, however, have been anticipated and the synthesis of some of these has been realized, while other attempts have fallen short of the mark.



CLXXXV



CLXXXVI



CLXXXVII

The attempts to convert codeine and thebaine to 3,4-dimethoxy-13-ethyl-5,6,7,8,9,10,13,14-octahydrophenanthrene have been the only serious degradative effort in this field. The first attempt (33) to prepare this

hydrophenanthrene involved tetrahydromethylmorphimethine as the starting material. The alcoholic hydroxyl was replaced by chlorine (PCl_5) and the halogen, in turn, reductively eliminated ($Na + C_2H_5OH$) with simultaneous rupture of the oxide bridge. The methiodide of this desoxytetrahydro-α-methylmorphimethine readily lost trimethylamine when boiled with alkali (the methyl ether under similar conditions lost methanol with regeneration of the starting material (292, 309)). The nonbasic moiety, however, was not phenolic (insoluble in alkali and it could be neither methylated nor acetylated). Cyclization must have occurred during the process yielding CLXXXV. Desoxytetrahydro-α-methylmorphimethine absorbed one mole equivalent of hydrogen and this saturated, phenolic base, when treated with methyl sulfate, yielded the methyl ether methomethyl sulfate of the dihydro base. Methyl alcohol, and not trimethylamine, was lost in the Hofmann degradation of this quaternary salt with generation of dihydrodesoxytetrahydro-α-methylmorphimethine methyl ether (292).

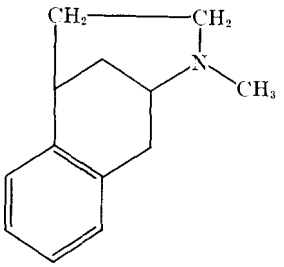
An alternative approach (297) to the desired dimethoxyethyloctahydrophenanthrene employed dihydrothebaine as the starting material. Conversion of this base to the corresponding methine and treatment of its methiodide with amyl alcoholic potassium hydroxide yielded the expected vinyl compound, CLXXXVI (189). Conversion of this to 6-keto-13-ethyloctahydromorphol-3-methyl ether (34) (CLXXXVII) was obtained in small yield by hydrolysis of the enol ether of CLXXXVI (HCl), catalytic hydrogenation of the two double bonds ($2H_2$ + Pt on C) and reductive fission of the oxide bridge (aluminum amalgam). Attempts to methylate ($(CH_3)_2SO_4 + K_2CO_3$) the C_4 phenolic hydroxyl or to eliminate the carbonyl group (ZnHg + HCl) failed.

The oxidative degradation (O_3) of dihydrocodeine and chlorocodide to dihydrocodinal and chlorodihydrocodinal does lead to simpler products; however, the nature of their complexity does not lend itself to synthesis.

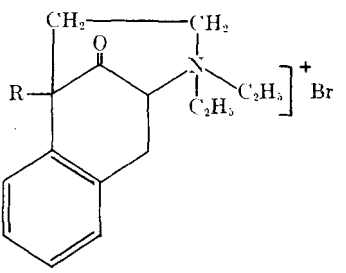
For convenience, the syntheses of possible degradation products of the morphine alkaloids may be divided into two groups: (1) those involving the synthesis of the azocyclic system with reactive groups suitably located for the subsequent elaboration of the hydrophenanthrene nucleus; and (2) those having the synthesis of the hydrophenanthrene nucleus with a reactive group or a chain at C_{13} as their primary objective. The more ambitious program of the synthesis of the alkaloids themselves has also been initiated.

Type 1. At the outset of this work it was considered (240) that the crux of the synthesis of various degradation products of these alkaloids lay in the fabrication of the piperidine ring. With this in view the synthesis of CLXXXVIII was undertaken but had to be dropped at an intermediate

stage because of discouragingly poor yields and the difficulty encountered in the purification of the intermediates.



CLXXXVIII



R = CH_3, $-CH(CH_3)-CH_2-CO_2C_2H_5$

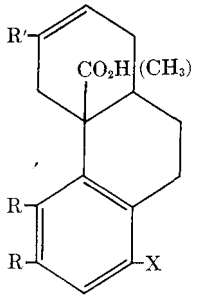
CLXXXIX

The synthesis of CLXXXIX (R = CH_3) proved to be more feasible (303). This was achieved by alkylation (sodamide) of 1-methyl-2-keto-1,2,3,4-tetrahydronaphthalene with diethyl-β-chloroethylamine followed by bromination of the methylene group alpha to the ketone carbonyl (bromine on a chloroform solution of the hydrobromide). When the brominated base was liberated by bicarbonate, cyclization to CLXXXIX (R = CH_3) occurred. The analogous series of reactions designed to lead to CLXXXIX (R = $-CH(CH_3)-CH_2-CO_2C_2H_5$) failed due to aromatization of the hydrogenated naphthalene ring and the extrusion of the ethanamine chain as diethylvinylamine hydrobromide.

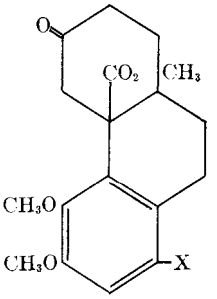
Type 2. The synthesis of 3,4-dimethoxy-13-ethyloctahydrophenanthrene has been realized (302). The series of reactions leading to this key compound involved the addition of ethyl magnesium bromide (4–5 moles) to 1-keto-5-chloro-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene and dehydration of the resulting tertiary carbinol. Oxidation of the derived ethylene with hydrogen peroxide afforded 1-ethyl-2-keto-5-chloro-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene from which the halogen was reductively eliminated (Pd on $SrCO_3$). Condensation (sodamide) of this ketone with the methiodide of 4-diethylaminobutanone-2 followed by reduction of the resulting 3,4-dimethoxy-7-keto-13-ethyl-5,6,7,9,10,13-hexahydrophenanthrene (first by hydrogen and platinum oxide catalyst and then by the Clemmensen method) yielded the desired product. The 1-chloro analog was prepared in the same way; however, the hydrogenolysis of this halogen atom could not be realized.

Failure to degrade these alkaloids to 3,4-dimethoxy-13-ethyloctahydrophenanthrene necessitated the synthesis of degradation products less

remote from these bases. The addition of dienes (butadiene and 2-ethoxybutadiene) to suitably substituted 3,4-dihydro-1-naphthoic acids or their methyl esters (264, 266, 272) appeared at the outset to fulfill the requirements (similar additions to substituted 3,4-dihydro-2-naphthoic acids and their esters have been described (229)). It is to be seen that addition of 2-ethoxybutadiene to methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoate followed by hydrolysis of the resulting enol ethyl ether of CXC (R = OCH_3, R′ = OC_2H_5, X = Br) is an avenue of approach to methyl 1-bromo-3,4-dimethoxy-6-ketooctahydrophenanthrene-13-carboxylate, CXCI (X = Br) (230, 272). The salient features of this method are that it offers a novel means of introducing a functional group at C_{13} by which the chain may be lengthened (Arndt-Eistert method or reduction of the ester to an alcohol and subsequent extension of the chain through the derived cyanide) as well as a double bond or ketone in ring III. The obvious weakness of this method is that it provides no reactive group at C_9 by which the extended side chain may be cyclized into this position. The acids, CXC (where X = R = R′ = H and where X = Br, R = OCH_3,



X = H, Cl, Br
R = H, OCH_3
R′ = H, OC_2H_5
CXC



X = Cl, Br
CXCI

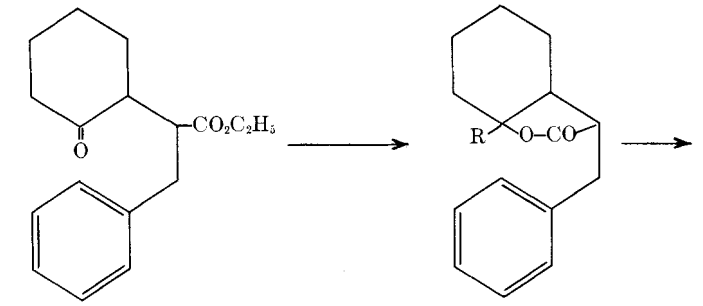
R′ = H), have been prepared (264, 266) and converted to their acid chlorides and the angular chain of the former extended by the use of diazomethane.[4] This method for the preparation of the homo acid failed in the case of the more highly substituted product. Efforts to extend the chain by the alternate method proved equally unsuccessful (266).

The addition product from 2-ethoxybutadiene-1,3 and methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoate has been prepared in 13% yield; however, it has been demonstrated that the addition proceeds in the opposite direction to that desired and that the acid hydrolysate is not CXCI but the 7-keto isomer (272). Hence, it is to be expected that addition of the same diene to methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-2-

[4] L. F. Fieser and R. C. Clapp, private communication.

naphthoate (230, 272) would lead to the C_{14} analog of CXCI (X = Br), a possible degradation product of metathebainone.

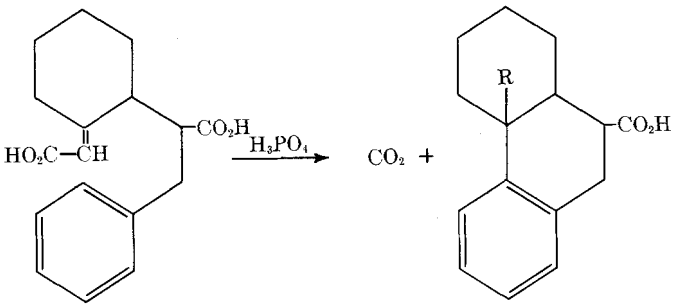
The syntheses of octahydrophenanthrenes with substituents at C_{13} and a functional group at C_9 or C_{10} have been developed and applied to the synthesis of model compounds. In one instance the ethanamine bridge has been introduced at C_{13} and C_{10}. After a Reformatsky reaction on CXCII and saponification of the reaction product to the lactone, CXCIII, it was then possible to cyclize the acid with phosphoric acid (the reaction proceeds through the unsaturated product, CXCIV, followed by decarboxylation (223)). The acid, CXCV (R = CH_3), has been esterified and converted to the corresponding amine by the Curtius reaction (225). This reaction does not appear to be of general applicability for, when the carboxyl group of CXCIV was retained as the ester, cyclization failed (225).



CXCII

R = CH_3, CH_2—$CO_2C_2H_5$

CXCIII



CXCIV

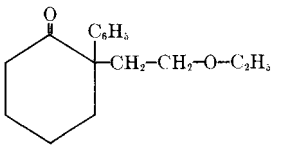
R = CH_3

CXCV

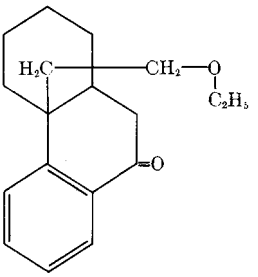
The 13-allyloctahydrophenanthrene has been prepared by a slight modification of this method and the side chain degraded to the corresponding C_{13}–acetaldehyde (225). This would serve admirably as the precursor for the elaboration of the ethanamine chain.

The synthesis of an octahydrophenanthrene with a C_{13}–C_{10} ethanamine

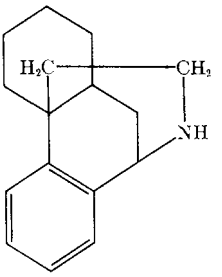
bridge (CXCVIII) has recently been described (269), but unfortunately the product, as yet, has not been fully characterized. The series of reactions leading from CXCVI to CXCVIII involves a Reformatsky reaction ($Br–CH_2–CO_2C_2H_5 + Zn$), a dehydration and hydrolysis to the acid, reduction of the double bond, conversion to the acid chloride (PCl_5) and cyclization by stannic chloride to CXCVII. Reduction of the oxime of



CXCVI



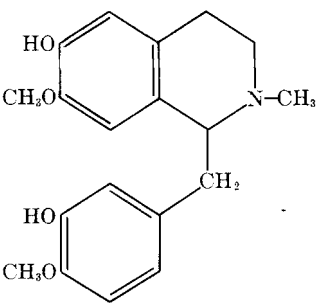
CXCVII



CXCVIII

CXCVII and substitution of a bromine for the ethoxyl group gave a mixture, on intramolecular alkylation, which undoubtedly contained some CXCVIII.

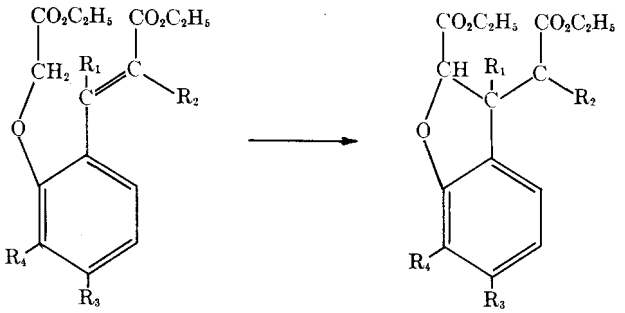
Experiments directed towards the synthesis of the alkaloids themselves have followed two avenues of approach. Robinson (298, 299, 300) attempted to reproduce experimentally his proposed mechanism for the biogenesis of these alkaloids. Though the synthetic experiments in the preparation of protosinomenine (CXCIX) were successful, his efforts to induce ring closure of this alkaloid precursor were of no avail. The cycliza-



CXCIX

tion of the unsubstituted tetrahydro derivative of CXCIX has recently been achieved by Grewe (326a). The yield in each step leading to the final product, morphinane, as outlined below is surprisingly good.

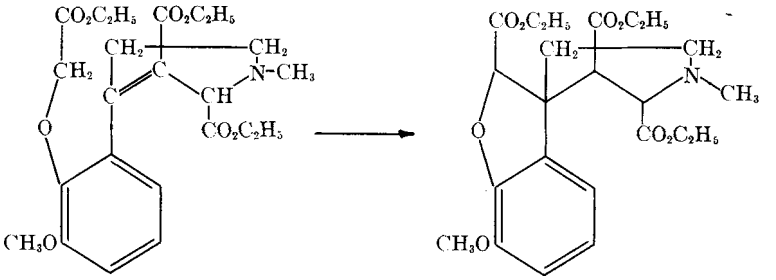
The recent synthetic approach, although as yet it has been applied only to the preparation of the model CCI, does offer some promise of success (268). The salient feature of this method is the intramolecular Michael condensation of compounds of type CC. Good yields in the syn-



CC

R_1 = H, H, H, C_2H_5
R_2 = H, H, CH_3, CH_3
R_3 = H, H, CH_3, CH_3
R_4 = H, OCH_3, H, H

CCI

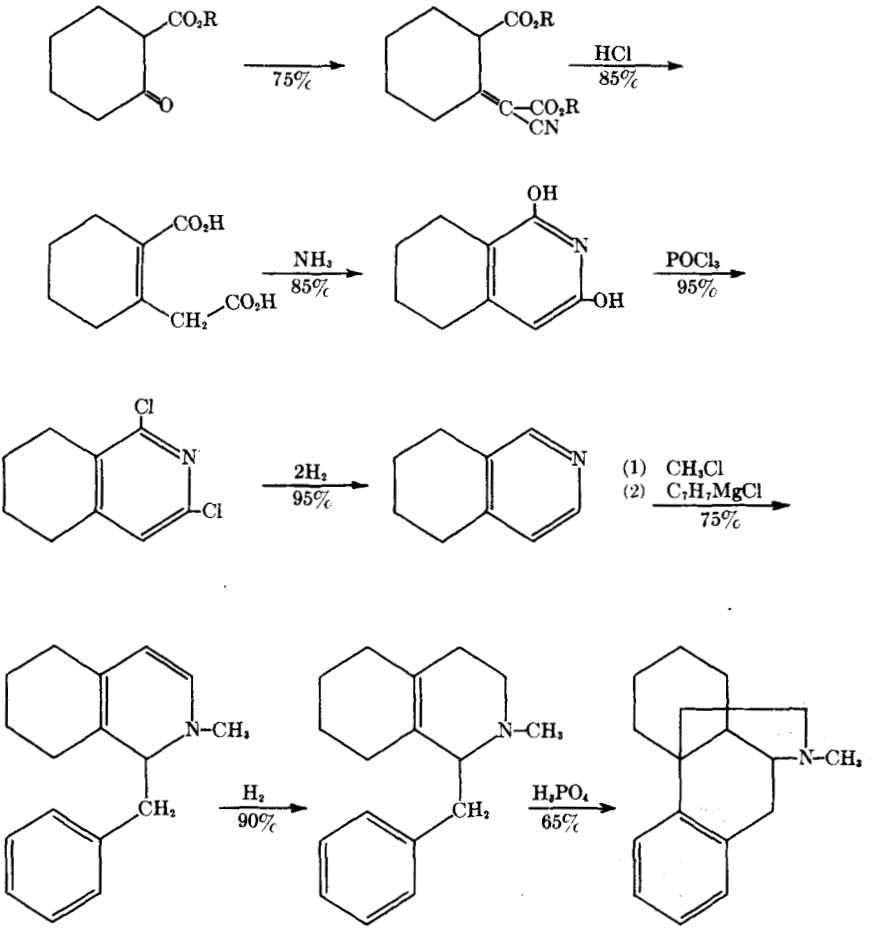


CCII CCIII

thesis of CC gave a ready source of material incorporating the dihydrocoumarone ring of the morphine alkaloids with substituents suitably located for completion of ring III and the ethanamine chain. A similar condensation when applied to CCII should lead to the morphine model, CCIII.

No discussion of this nature would be complete without mentioning Schöpf's classical conversion of dihydrothebainone into dihydrocodeinone, a partial synthesis which firmly established the presence of the hydro-

phenanthrylene oxide structure in the morphine alkaloids and which, at the same time, threw some light on the center of attack of the halogens on the codeine molecule.



Morphinane

VI. Table of Physical Constants

The data presented in this table list only the physical constants of those compounds appearing in the literature after 1930. It is intended that this table should only supplement that appearing in Small and Lutz, *The Chemistry of the Opium Alkaloids* (331). The conventions adopted here are those used in Chapters 6 and 7.

TABLE 7

THE MORPHINE ALKALOIDS AND THEIR PRODUCTS OF TRANSFORMATION AND DEGRADATION

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		A		
1-Aceto-6-acetylcodeine	146–147	. .	. .	312
Oxime	. .	. .	. .	312
Hydrochloride	240 (dec)	. .	Silky needles	312
Allopseudocodeine	. .	. .	. .	255
Hydrochloride	*256–258 (dec)	−202° (H_2O)	Crystals (C_2H_5OH)	255
Salicylate	*202	−145° (H_2O)	. .	255
1-Aminocodeine	226–228 (V)	−178.7° (H_2O)	Leaflets (acetone)	312, 222
Diacetyl- (trihydrate)	112–115	−220.8° (C_2H_5OH)	Plates (C_2H_5OH–H_2O)	312
2-Aminocodeine	95–96.5	. .	Prisms (acetone)	222
Hydroperchlorate	170 (dec)	. .	Needles (acetone)	222
8-Aminocodide	128.5–129	−79.2° (C_2H_5OH)	Crystals (ether)	267
Dihydrochloride	*300–305 (V)	−40.7° (H_2O)	Crystals (C_2H_5OH)	267
Diacetyl-	218–220 (dec)	−83.1° (C_2H_5OH)	Crystals	267
7-Aminodihydrothebainone	235–245 (dec)	. .	White powder	218
4-Benzyl-	183–185 (dec)	. .	Yellow-white powder	218
Amyldihydrocodeinone	153–155	−9.3° (C_2H_5OH)	Crystals (ligroin–ethyl acetate)	308
Picrate	174–177	−52.8° (acetone)	Yellow plates (C_2H_5OH)	308
Salicylate	. .	. .	Needles (C_2H_5OH)	308
Styphnate	142–145 (gas)	−45.5° (acetone)	Yellow plates (C_2H_5OH)	308
Amyldihydromorphinone (hemihydrate)	113–116 (gas)	−97.3° (C_2H_5OH)	Rods (ethyl acetate)	308
Hydriodide (monohydrate)	182–184 (V)	−59.8° (C_2H_5OH)	Needles (C_2H_5OH)	308
Hydrobromide (hydrate)	189–190 (V)	−66° (C_2H_5OH)	Prisms (C_2H_5OH)	308
Hydrochloride	322–325 (V)	−63.9° (H_2O)	Plates (H_2O)	308

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Amyldihydrothebainone	153–155	−12.8° (C_2H_5OH)	Needles (acetone)	308
Hydriodide	238–239 (V)	−1.4° (C_2H_5OH)	Plates (C_2H_5OH–H_2O)	308
Hydrobromide	223–224.5°(V)	+1.5° (C_2H_5OH)	Six-sided plates (H_2O)	308
Hydrochloride	203–205	+2.8 (C_2H_5OH)	Plates (C_2H_5OH–ether)	308
Hydroperchlorate	235–236 (V)	−2.13° (C_2H_5OH)	Plates (C_2H_5OH–H_2O)	308
Sulfate (hydrate)	95–105	0° (C_2H_5OH)	Short rods (H_2O)	308
Oxime	113–115	+18.6° (C_2H_5OH)	Rectangular plates (C_2H_5OH)	308
Anhydrometathebainol	106–107 (dec) 130/0.001 mm.	−201° (C_2H_5OH)	Crystals (C_2H_5OH)	249
Acetyl-	166	..	Crystals (CH_3OH)	249
Apocodeine	122.5–124.5	−97.0° (C_2H_5OH)	Prisms (CH_3OH)	313, 263
Hydrochloride	260–263 (dec)	−41.3°	White crystals (HCl–H_2O)	263, 313
Apomorphine				
Hydrochloride	..	−47.8° (H_2O)	..	313
Diacetyl-	127–128	−87.5°(HCl–H_2O)	..	313
		B		
Benzyldihydrocodeinone	160/0.01 mm.	−114.3° ($CHCl_3$)	Oil	308
Benzyldihydrodesoxycodeine-D	..	..	Oil	307
Hydrobromide	226–227 (V)	−29.8° (C_2H_5OH)	Crystals (C_2H_5OH)	307
Hydrochloride	249 (V. gas)	−34.4° (C_2H_5OH)	Crystals (C_2H_5OH)	307
Hydroperchlorate	223–224 (V. gas)	−51.5° (C_2H_5OH)	Flaky crystals (C_2H_5OH)	307
Methiodide	70 (dec)	−25.8° (CH_3OH)	Crystals (CH_3OH)	307
Benzyldihydromorphine monohydrate	95–97	−88.1° (C_2H_5OH)	Crystals (ethyl acetate)	307
Hydriodide	215–217 (V. gas)	−45.3° (H_2O)	Crystals (H_2O)	307
Hydrobromide (monohydrate)	193–195 (V)	−44° (H_2O)	Crystals (H_2O)	307
Hydrochloride (monohydrate)	233–235 (V)	−52.1° (H_2O)	Crystals (H_2O)	307
Hydroperchlorate	188–192	−59.5° (C_2H_5OH)	Crystals (H_2O)	307
Methiodide	242–244 (V. gas)	−43.2° (CH_3OH)	Flaky crystals (CH_3OH)	307
Methyl ether (alc.)	..	−89.1° (C_2H_5OH)	Oil	307
Methiodide	155–157 (V)	−54.6° (H_2O)	Crystals (C_2H_5OH)	307

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Benzyldihydromorphinone	..	..	..	308
Hydrochloride (hydrate)	241–242 (V)	−100.6° (H_2O)	Prisms (C_2H_5OH)	308
Benzyldihydrothebainone	227–229	−51.6° ($CHCl_3$)	Needles (C_2H_5OH)	308
Hydrochloride	243–244 (V. gas)	−29° (H_2O)	Crystals (C_2H_5OH)	308
Oxime	135–142	+5.5° ($CHCl_3$)	Crystals (C_6H_6)	308
Benzylmorphine(alc.) methyl ether				
Acid sulfate	247–249 (V)	−90.1° (H_2O)	Crystals (H_2O)	307
Hydrochloride	233–236 (V)	−88.9° (H_2O)	Crystals (H_2O)	307
Methiodide	155–157 (V)	−75.8° (C_2H_5OH–H_2O)	Crystals (C_2H_5OH–H_2O)	307
Benzylmorphine-*N*-oxide	236–238 (V. dec)	−53.2° (C_2H_5OH)	Crystals (C_2H_5OH)	307
Bis-dihydrodesoxycodeine	..	−113.3° (C_2H_5OH)	Yellow glassy solid	243
Dimethiodide	230–250	−71.5° (C_6H_5–CH_2OH)	Amorphous powder	243
Monomethiodide	246–250 (dec)	−8.6° (C_2H_5OH)	Needles (C_2H_5OH–acetone)	243
Monomethochloride	..	..	Yellow glassy solid	243
1-Bromoamyldihydrocodeinone	143–145	−76.7° (C_2H_5OH)	Crystals (C_2H_5OH)	308
Oxime (hydrate)	170–174	−29.7° (C_2H_5OH)	Needles (CH_3OH)	308
1-Bromoamyldihydrothebainone	241–242 (V)	−30.6° (C_2H_5OH)	Rods (C_2H_5OH)	308
1-Bromobenzyldihydrocodeinone	167–168	−101.4° (C_2H_5OH)	Needles (C_2H_5OH)	308
1-Bromobenzyldihydrothebainone	230–232 (V)	−59.4° (C_2H_5OH)	Needles (C_2H_5OH)	308
Bromochlorocodide	131–133.5	−288.5° (C_2H_5OH)	Crystals (CH_3OH)	265
1-Bromocodeine	159.5–160.5	..	Prisms (acetone)	222
2-Bromocodeine	160–161	..	Needles	222
Bromodesoxycodeine-C	210–212.5 (V)	+65.9° (C_2H_5OH)	Crystals (acetone)	265
Bromodesoxycodeine-D	125–126	..	Six-sided plates (C_2H_5OH–H_2O)	314
8-Bromodihydrocodide (?)	230–232	..	Crystals	313
Bromodihydrodesoxycodeine-D	156–157	−37.6° (C_2H_5OH)	Crystals (CH_3OH)	265
Bromodimethyldihydrothebainone	218–221	..	Crystals (acetone)	308

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
1-Bromoethyldihydrothebainone	201.5–202.5 (V)	−6.8° (C_2H_5OH)	Crystals (C_2H_5OH)	308
1-Bromoisomethyldihydrothebainone	237–239 (V)	−66.2° (C_2H_5OH)	Crystals (C_2H_5OH)	308
1-Bromoisopropyldihydrocodeinone	164–167	−79.4° (acetone)	Crystals (acetone)	308
1-Bromo-6-methyldihydrocodeine	60–70	..	Amorphous	316
Hydriodide	248–249	−64.6° (C_2H_5OH)	Crystals (H_2O)	316
Methiodide	235–237	−73.1° (C_2H_5OH)	..	316
Bromomethyldihydrocodeinone	143.5–145	−109.4° (C_2H_5OH)	Crystals (ethyl acetate)	262
Bromomethyldihydrothebainone	207–208 (V. dec)	−33.2° (C_2H_5OH)	Crystals (acetone)	262
Bromotetrahydrodesoxycodeine	156–157.5	−28.2° (C_2H_5OH)	Crystals (CH_3OH)	265
Hydrate	119–128	−3.3° (C_2H_5OH)	Crystals (ethyl acetate)	265
		C		
α-Chlorocodide	145–147	..	..	241
Acid sulfate (dihydrate)	192–193 (dec)	+101.1° (H_2O)	Crystals (H_2O)	241
Acid tartrate	..	−219.3° (H_2O)	..	241
β-Chlorocodide	..	..	..	241
Acid tartrate	..	+8.3° (H_2O)	Glassy crystals(H_2O)	241
Hydrochloride	168–171 (dec)	−3.85° (H_2O)	Crystals (H_2O)	241
Chlorodihydroallopseudocodeine	189–191	..	..	313
Chlorodihydrocodide	173–175	−177.8° ($CHCl_3$)	Crystals (C_2H_5OH)	313, 247
Hydrochloride	226 (V)	−129.5° (H_2O)	..	313
Tartrate	191–192(froth)	..	..	313
β-Chlorodihydrocodide	145	+37.5° (C_2H_5OH)	Crystals (C_2H_5OH)	313
8-Chlorodihydrocodide	123–124	−42.7° (C_2H_5OH)	Crystals (acetone–H_2O)	313
Tartrate	230–232 (V)	..	..	313
Chlorodihydrohydroxychlorocodide	163.5	−141° (HOAc–H_2O)	Prisms (C_2H_5OH)	311
Chlorodihydrohydroxycodeine-B	..	..	..	311
Hydrochloride	238–239	−106° (H_2O)	Crystals (C_2H_5OH)	311
Chlorodihydromorphide	228–229	−145° (C_2H_5OH)	..	247
Hydrochloride	323–326	−131.0° (H_2O)	Crystals (H_2O)	247
8-Chlorodihydromorphide	257–258 (V. dec)	..	Crystals (acetone)	313

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
1-Chloro-6-methyl-desoxycodeine-C	171–172	−226° (C_2H_5OH)	Crystals (C_2H_5OH)	316
1-Chloro-6-methyl-dihydrocodeine	..	..	Oil	316
Hydriodide	260–262	−73.6° (C_2H_5OH)	Crystals (C_2H_5OH)	316
Hydroperchlorate	238–239	−81.4° (C_2H_5OH)	Crystals (C_2H_5OH)	316
α-Chloromorphide	..	−372.4° (CH_3OH)	..	247, 248
β-Chloromorphide	..	..	..	247
Hydriodide	..	0° (H_2O)	White needles (H_2O)	313
Hydrochloride	..	0°	..	313
Cyanonordesoxy-codeine-C	159.5–161	..	Crystals (C_2H_5OH)	314
Cyclohexyldihydro-desoxycodeine	131.5–132.5°	−51.0° ($CHCl_3$)	Sublimed	261
Hydroperchlorate	250–251	−26.3° ($CHCl_3$)	Crystals (C_2H_5OH–H_2O)	261
Cyclohexyltetrahydro-desoxycodeine	193–193.5	−14.2° ($CHCl_3$)	Crystals (C_2H_5OH)	261
Hydriodide	235–236	+14.8° ($CHCl_3$)	Crystals (C_2H_5OH–H_2O)	261
D				
Dehydrotetrahydrocodeine (see β-Tetrahydrodesoxycodeine)				247
Des-*N*-acetyldihydro-pseudocodeinone enol acetate	*191.5–192	..	Six-sided scales (C_2H_5OH)	259
Des-*N*-methyldihydro-desoxycodeine-B	144.5–145.5	+7.4° ($CHCl_3$)	Yellow crystals (acetone)	250
Hydrochloride	..	..	Crystals	250
Des-*N*-methyldihydro-desoxycodeine-C	175–176	−13.8° ($CHCl_3$)	Crystals	250
Des-*N*-methylflavothebaon trimethyl ether	160–161	..	Crystals (C_2H_5OH–H_2O)	46
Methiodide	295 (dec)	..	Crystals (H_2O)	46
Des-*N*-methyltetra-hydrodesoxycodeine	152–154	+66.2° (CH_3OH)	Flaky crystals (C_2H_5OH–H_2O)	244
Desoxycodeine-A	159–161	−118.8° (C_2H_5OH)	Sublimes 135° (0.001 mm.)	247, 241
Hemihydrate	122–126	..	Crystals (CH_3OH–H_2O)	241
Hydriodide	255–260	..	..	241
Hydrochloride	265–270	..	..	241
Methiodide	219–221	+95.7°	Crystals (C_2H_5OH–ether)	247
Salicylate	220.5–221	+104.4°	..	247
Desoxycodeine-B (is a mixture)				

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Desoxycodeine-C	105–106	−199.4° (C_2H_5OH)	Crystals (ethyl acetate)	241, 247
Hydriodide	272–275	..	..	247
Monohydrate	160–165	−131.6° (C_2H_5OH)	Yellow prisms(H_2O)	241
Hydrochloride	114	−132.7° (H_2O)	Crystals (C_2H_5OH)	241
Methiodide	236–240	..	Crystals (H_2O)	241
Salicylate	195–196	−112.2° (C_2H_5OH)	Crystals (C_2H_5OH)	261
Tartrate	161–165	..	..	247
Desoxycodeine-D	..	..	Oil	314
Acid oxalate	220–221 (V. dec)	..	Crystals (C_2H_5OH)	314
Acid tartrate	204–206 (V. froth)	0° (H_2O)	Crystals (H_2O)	314
Hydrochloride	234–235 (V)	−12.1° (H_2O)	Crystals (butanone)	314
Methiodide	204–206 (V)	..	Crystals (C_2H_5OH)	314
Desoxycodeine-D-methine	76–77	..	Six-sided plates (C_2H_5OH–H_2O)	314
Desoxymorphine-A	260–262	+106.1° (HOAc–H_2O)	Crystals	247, 248
Benzoate	240–245 (dec)	+81.9° (C_2H_5OH)	..	247
Salicylate	248–251 (dec)	+93.6° (CH_3OH)	Crystals (C_2H_5OH)	248, 247
Sulfate	145–151	+61.6° (H_2O)	..	247
Desoxymorphine-C	189–190	−155.7° (C_2H_5OH)	Crystals (ethyl acetate)	247
Hydriodide	292–294	−111° (H_2O)	Crystals (H_2O)	247
Hydrochloride	291–294 (dec)	−147° (H_2O)	Needles (H_2O)	247
Desoxymorphine-D	254–255 (V. dec)	..	Crystals (C_2H_5OH)	314
Dibromodihydrodesoxy-codeine-A	189–189.5	+10.2° (C_6H_6)	Crystals	265
Hydrobromide	..	..	Crystals	265
1,5-Dibromoisopropyl-dihydrothebainone	..	..	..	308
Hydrobromide	230–232 (V)	−2.7° (C_2H_5OH)	Crystals (H_2O)	308
1,8-Dichlorodihydro-codide	190.5–191.5	..	Crystals (C_2H_5OH)	313
Dichlorodihydrodesoxy-morphine	..	+276°	..	313
Hydrochloride	230–235	+272° (C_2H_5OH–H_2O)	Crystals (C_2H_5OH–H_2O)	313
Diacetyl	..	..	..	313
8-Diethylaminocodide	101–103	+42.6° (CH_3OH)	Sublimed (V)	267
Dihydriodide	179–182	+22.9° (C_2H_5OH)	Crystals (H_2O)	267
Dihydroperchlorate	180.5–183	+3.3° (H_2O)	Crystals (H_2O)	267
8-Diethylaminomor-phide	201–204 (V)	+49.1° (CH_3OH)	Sublimed	267

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Dihydriodide	87–93 (V)	+2.6° (H_2O)	Crystals (H_2O)	267
Dihydroperchlorate	114–116 (V)	+4.4° (H_2O)	Crystals (H_2O)	267
Dihydroallopseudo-codeine	78–79	−105° (C_2H_5OH)	Crystals (ethyl acetate–ligroin)	255, 258
Acid tartrate	*124–125	−50° (H_2O)	Crystals (H_2O)	255, 258
Hydriodide	*255 (dec)	−70° (H_2O)	Crystals (C_2H_5OH)	255
Hydroperchlorate	*265–270	−83° (H_2O)	Crystals (H_2O)	255
Dihydroallopseudocodeine (Phenolic)	..	..	Oil	255
Hydroperchlorate	*145–147	−16° (H_2O)	Crystals (H_2O)	255
Methiodide	*247–248 (dec)	−5.5° (H_2O)	Crystals (C_2H_5OH)	255
Dihydro-8-aminocodide	170 (V)	−28.7° (C_2H_5OH)	Glassy solid	267
Dihydrochloride	274–277	−14.7° (H_2O)	Crystals (C_2H_5OH)	267
Dihydroanhydrometa-thebainol	130/0.001 mm.	..	Colorless resin	249
Dihydrocodeine	85–87	..	..	313
Dihydrocodeinone-7-isonitroso	230–240 (dec)	..	Yellow powder	218
Dihydrodes-*N*-methyl-*β*-dihydrothebainone	177–178 (V)	+63.8° ($CHCl_3$)	Crystals (C_2H_5OH)	310
Hydrobromide	260–260.5 (V)	+24.0° (H_2O)	Needles (C_2H_5OH)	310
Hydroperchlorate	232.5–233.5(V)	+23.8° (CH_3OH)	Rods (H_2O)	310
Picrate	203–207 (V)	+18.2° (acetone)	Yellow needles (C_2H_5OH)	310
Dihydrodes-*N*-methyl-*β*-tetrahydrodesoxy-codeine	148–150	−14.5° (C_2H_5OH)	Needles (C_2H_5OH–acetone)	244
Hydrochloride	251–252	−82.1° (C_2H_5OH)	Needles (HCl–H_2O)	244
Dihydrodesoxycodeine-A	(is a mixture)			250, 254
Dihydrodesoxy-codeine-B	173–173.5	..	..	250
Hydrate	131–133	−106.9° (C_2H_5OH)	Flaky crystals (C_2H_5OH–H_2O)	242, 250
Hydriodide	255–256	−79.3° (C_2H_5OH)	Needles (H_2O)	242
Hydrochloride	154–156 (dec)	−76.4° (H_2O)	Crystals (C_2H_5OH)	242
Methiodide	175	..	Needles (H_2O)	242
Dihydrodesoxy-codeine-C	109–111	+5.6° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	242, 250
Hydriodide	242–243	+8.2° (H_2O)	Prisms (H_2O)	242, 250
Hydrochloride	241–242	+11.2° (H_2O)	Crystals (C_2H_5OH)	242, 250
Methiodide	245–246	+15.4° (C_2H_5OH)	Needles (H_2O)	242, 250
Dihydrodesoxy-codeine-D	106–107	−82.5° (C_2H_5OH)	..	242,247, 314
Acid tartrate	154–155	−29.9° (H_2O)	White crystals	247, 314
Hydrate	124–125	−39.6° (H_2O)	Needles (H_2O)	242,247, 313

TABLE 7 *(Continued)*

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydriodide	250–251 (dec)	..	Yellow needles (H_2O)	242
Methiodide	256	..	..	242
Dihydrodesoxy-codeine-E	139	..	..	242
Dihydrodesoxy-hydroxycodeine	137–138	−19°(HOAc–H_2O)	Crystals (pet.ether)	311
Dihydrodesoxymeta-codeine	135/0.001 mm.	−93.8° (C_2H_5OH)	..	249
Methanol of crystallization	72	..	..	249
Dihydrodesoxymorphine-D	188–189	−76.8° (CH_3OH)	Plates (acetone–H_2O)	248,247, 253
Acid oxalate	..	−57.9°	Crystals (C_2H_5OH–H_2O)	248
Hydriodide	..	−48.4° (H_2O)	Crystals (H_2O)	248
Hydrochloride	..	−66.8° (H_2O)	Crystals (C_2H_5OH)	248,253
Methiodide	..	−46.6° (H_2O)	Crystals (C_2H_5OH)	248
Salicylate	..	−42.8° (C_2H_5OH)	Crystals (C_2H_5OH)	248
Sulfate	..	−57.9° (H_2O)	Crystals (H_2O)	248
Dihydro-δ-diethyl-dithiocodide	125–126	−100° (ethyl acetate)	Crystals (ethyl acetate)	254
Dihydro-δ-ethylthio-codide-A	156–157	+167.6° (C_2H_5OH)	Needles (ethyl acetate)	254
Benzoate	151–154 (gas)	+119.8° (CH_3OH)	Crystals (C_2H_5OH)	254
Dihydro-δ-ethylthio-codide-B	..	..	oil	254
Malonate	170.5–171.5	+91.1° (CH_3OH)	Crystals (H_2O)	254
Dihydroflavothebaon	..	..	Unstable	46
Hydrochloride	365 (dec)	..	Crystals (H_2O)	46
Trimethyl ether	219–220	+213° ($CHCl_3$)	Needles (CH_3OH)	46
Dihydrohydroxychloro-codide	213.5–214	−151° (HOAc–H_2O)	Crystals (ethyl acetate)	311
Dihydrohydroxy-codeine-A	301–302 (V)	−64° (HOAc–H_2O)	Rect'g scales $CHCl_3$–C_2H_5OH)	311
Dihydrohydroxy-codeine-B	145–145.5	−136° (HOAc–H_2O)	Rect'g plates (ethyl acetate)	311
Methiodide	223–224 (dec)	−87° (H_2O)	Crystals (C_2H_5OH)	311
Diacetyl-	181–182	−127° (HOAc–H_2O)	Crystals (C_2H_5OH–H_2O)	311
Acid tartrate	181–182 (dec)	−82° (H_2O)	Fine needles (H_2O)	311
Dihydrohydroxy-codeine-B-dihydro-methine	168	−44° (HOAc–H_2O)	Crystals (ethyl acetate)	311
Dihydrohydroxy-codeine-B-methine	103	−70° (HOAc–H_2O)	Crystals (ether)	311

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Acid tartrate	190–191 (gas)	−25° (H_2O)	Crystals (H_2O)	311
Dihydrohydroxy-codeine-C	166–167	−152° (HOAc–H_2O)	Thin scales (C_2H_5OH–H_2O)	311
Diacetyl-	203	−107° (HOAc–H_2O)	Needles (C_2H_5OH–H_2O)	311
Acid tartrate	209–210	−67° (H_2O)	Six-sided scales (H_2O)	311
Dihydrohydroxy-codeinone	218	−97° (HOAc–H_2O)	Crystals (C_2H_5OH)	311
Dihydro-7-hydroxy-codeinone	195–197 (dec)	..	Yellow-white powder	218
Oxime	178–181 (dec)	..	Yellow-white powder	218
Dihydrohydroxycodeinone enol acetate				
Acetyl-	207.5	−167° (C_2H_5OH)	Crystals (C_2H_5OH)	311
Dihydrohydroxy-δ-methyldihydrothebaineisomethine	163–165	+25° (C_2H_5OH)	Crystals	309
Dihydrohydroxy-η-methyldihydrothebaineisomethine	163.5–165.5	−23° (C_2H_5OH)	..	309
Dihydrohydroxythebainone	143	..	..	311
Hydrochloride	270–272 (dec)	−123° (H_2O)	Crystals (C_2H_5OH)	311
Dihydroisocodeine	198–199	..	..	258, 313
Acid tartrate	180	−62.4° (H_2O)	Crystals (H_2O)	246
Dihydro-α-isomorphine	224–226	−125.8° (CH_3OH)	Needles (C_2H_5OH)	258
Binoxalate	..	−91.9° (H_2O)	Crystals (C_2H_5OH)	258
Hydrobromide	..	−97.9° (H_2O)	Crystals (H_2O)	258
Hydrochloride	..	−112° (H_2O)	Needles (C_2H_5OH)	258
Methiodide	..	−80.4° (H_2O)	Crystals	258
Ethyl ether	104	−110° (CH_3OH)	Crystals (ethyl acetate)	307
Acid tartrate	109–112 (gas)	−66° (H_2O)	Crystals (acetone)	307
Methiodide	277 (V. gas)	−76.2° (H_2O)	Crystals (C_2H_5OH–H_2O)	307
Methyl (alc.) ether	198–200	−118.1° (C_2H_5OH)	Crystals (C_2H_5OH)	307
Hydriodide	287–288 (V)	−85.2° (H_2O)	Crystals (H_2O)	307
Hydrochloride	273–275 (V)	−111.1° (H_2O)	Crystals (H_2O)	307
Methiodide	245–248 (V)	−77.9° (H_2O)	Crystals (C_2H_5OH)	307
Dihydro-β-isomorphine				
Monohydrate	202–203	−104[c] (CH_3OH)	Crystals (C_2H_5OH)	258
Acid fumarate	..	−81.3° (H_2O)	Crystals (H_2O)	258
Hydrobromide	..	−87°	Crystals (H_2O)	258
Hydrochloride	..	−98.7° (H_2O)	Crystals (C_2H_5OH)	258

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Ethyl ether	..	..	Glassy solid	307
Hydroperchlorate	231–234 (V)	−64.3° (H_2O)	Crystals (H_2O)	307
Picrate	187–189 (V)	−64.8° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	307
Dihydro-γ-isomorphine	222–223	−35°	White prisms	252
Hydriodide	*285–288	−21.7° (H_2O)	Colorless needles (H_2O)	252
Hydrochloride	*300–302	−27.4° (H_2O)	Diamond-shaped scales (C_2H_5OH)	252
Hydroperchlorate	..	−24.0° (H_2O)	Hairlike needles (H_2O)	252
Methiodide	*255–257	−21.0° (H_2O)	Flaky crystals (CH_3OH)	252
Salicylate	*131.5–132.5	−22.8° (H_2O)	Crystals (C_2H_5OH)	252
Ethyl ether	158–159	−36.2° (CH_3OH)	Crystals (ethyl acetate)	307
Fumarate	180–192 (V)	−23.7° (H_2O)	Crystals (C_2H_5OH)	307
Methiodide	252–253 (V. gas)	−40.8° (H_2O)	Crystals (C_2H_5OH–H_2O)	307
Ethyl (alc.) ether	220–223 (V)	−20.2° (C_2H_5OH)	Crystals (C_2H_5OH)	307
Hydriodide	277–281 (V)	−9.1° (H_2O)	Crystals (H_2O)	307
Hydrochloride	..	..	Noncrystalline	307
Methiodide	250–252 (V)	−7.2° (H_2O)	Crystals (C_2H_5OH–H_2O)	307
Methyl (alc.) ether	235–237 (V)	−83.4° (C_2H_5OH)	Crystals (C_2H_5OH)	307
Hydriodide	185–187 (V)	−52.8° (H_2O)	Crystals (H_2O)	307
Hydrobromide	256–258 (V)	−55.4° (H_2O)	Crystals (H_2O)	307
Dihydroisomorphinone	*198	+46° (C_2H_5OH)	Crystals (ethyl acetate)	259
Dihydrometathebainol	120	..	Crystals	249
Hydriodide	..	+16.4° (H_2O)	..	249
Dihydro-α-methyl dihydrothebaine-isomethine	..	..	Oil	309
Salicylate	165–167	−47.7° (C_2H_5OH)	Crystals (C_2H_5OH)	309
Dihydro-ε-methyl-morphimethine	..	..	Oil	246
Hydriodide	*232–235	+100° (H_2O)	Hexagonal prisms (H_2O)	246
Hydrochloride	*222–224	+123.0° (H_2O)	Rect'g prisms (C_2H_5OH)	246
Dihydro-ε-methyl-morphimethine-A				
Methyl ether	*102.5	+202° (C_2H_5OH)	Needles (C_2H_5OH–H_2O)	257
Hydrochloride	219–220	+157° (H_2O)	Crystals (C_2H_5OH)	257
Hydroperchlorate	*155–156	+136° (H_2O)	Crystals (H_2O)	257

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Dihydro-ϵ-methyl-morphimethine-B	*188.5–189.5	+28° ($CHCl_3$)	Crystals (ethyl acetate)	251
Dihydro-ϵ-methyl morphimethine-C	150	+62.5° ($CHCl_3$)	..	251
Methyl ether	*140–140.5	+138.5° (C_2H_5OH)	Crystals (acetone)	257
Dihydro-ζ-methyl-morphimethine	99	+117° (C_2H_5OH)	Pyramids (ethyl acetate–ligroin)	255
Salicylate	*175	+76° (H_2O)	Crystals (C_2H_5OH)	255
Dihydromorphine	..	..	..	
Benzyl ether (monohydrate)	95–97	−88.1° (C_2H_5OH)	Crystals (ethyl acetate)	307
Hydriodide	215–217 (V. gas)	−45.3° (H_2O)	Crystals (H_2O)	307
Hydrobromide (monohydrate)	193–195 (V)	−44° (H_2O)	Crystals (H_2O)	307
Hydrochloride (monohydrate)	233–235 (V)	−52.1° (H_2O)	Crystals (H_2O)	307
Hydroperchlorate	188–192	−59.5° (C_2H_5OH)	Crystals (H_2O)	307
Methiodide	242–244 (V. gas)	−43.2° (CH_3OH)	Flaky crystals (CH_3OH)	307
Methyl (alc.) ether	..	−89.1° (C_2H_5OH)	Oil	307
Methyl ether methiodide	155–157 (V)	−54.6° (H_2O)	Crystals (C_2H_5OH)	307
Ethyl ether	..	−135.9° (C_2H_5OH)	Oil	307
Acid tartrate	167	−59.4° (H_2O)	Crystals	307
Methiodide	260 (V)	−66.9° (H_2O)	Crystals (C_2H_5OH)	307
Ethyl (alc.) ether	189–190	−164.8° (C_2H_5OH)	Crystals (ethyl acetate)	307
Hydriodide	291–293 (V)	−110.6° (H_2O)	Crystals (H_2O)	307
Hydrobromide (dihydrate)	282–284	−125.1° (H_2O)	Crystals (H_2O)	307
Hydrochloride (trihydrate)	274–276 (V)	−121.7° (H_2O)	Crystals (H_2O)	307
Hydroperchlorate	234–235 (V)	−98° (C_2H_5OH)	Crystals (H_2O)	307
Methiodide	250–251 (V)	−79.4° (CH_3OH)	Crystals (CH_3OH–ether)	307
Methoxymethyl ether	99–101	−154° (C_2H_5OH)	Crystals (acetone)	307
Hydrochloride	124–126 (gas)	−71.8° (H_2O)	Crystals (C_2H_5OH–ether)	307
Methiodide	201–203 (V. gas)	−61.8° (H_2O)	Crystals (C_2H_5OH)	307
Sulfate	49 (gas)	−72.8° (H_2O)	Crystals (C_2H_5OH–ether)	307
Methyl (alc.) ether	216.5–217 (V)	−178.0° (C_2H_5OH)	Crystals (C_2H_5OH)	307
Acid fumarate	215–216 (V. gas)	−110° (H_2O)	Crystals (C_2H_5OH)	307

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydriodide	269 (V)	−98.9° (H_2O)	Crystals (H_2O)	307
Hydrochloride	299–299.5 (V. gas)	−136.5° (H_2O)	Crystals (C_2H_5OH)	307
Hydroperchlorate	258–260 (V. dec)	−110° (H_2O)	Crystals (H_2O)	307
Methiodide	260–261 (V. gas)	−91.4° (CH_3OH)	Crystals (CH_3OH)	307
Dihydromorphinone methyl enolate	233–235	−206.5° (C_2H_5OH)	Needles (C_2H_5OH)	308
Benzoate	229–230 (V)	−150.7° (C_2H_5OH)	Rods (C_2H_5OH)	308
Hydriodide	274–275 (V. dec)	−140.5° (H_2O)	Crystals (H_2O)	308
Hydrochloride	309–310 (V. dec)	−180.6° (H_2O)	Prisms (H_2O)	308
Methiodide monohydrate	259–261 (V)	−123.6° (acetone)	Small needles (CH_3OH)	308
Salicylate	268–270 (V)	−130.8° (acetone)	Needles (C_2H_5OH–H_2O)	308
Dihydro-8-piperidocodide	167–169	−1.2° (CH_3OH)	Sublimed (V)	267
Dihydro-6-piperidomorphide	215–217	−155.9° (CH_3OH)	Crystals (ethyl acetate)	267
Dihydropseudocodeine	*155	−41.4° (C_2H_5OH)	Plates (C_2H_5OH–H_2O)	246, 313
Hydriodide	*287	−22.5° (H_2O)	Crystals (H_2O)	246
Hydrochloride	*239–241	−24.0° (H_2O)	Rect'g scales (C_2H_5OH)	246
Methiodide	*241–243 (dec)	−22.1° (H_2O)	Octahedra (H_2O)	246
Dihydropseudocodeine-A methyl ether	*127	+35° (C_2H_5OH)	Square plates (C_2H_5OH–H_2O)	257
Hydroperchlorate	*243–244 (dec)	−6.5° (H_2O)	Plates or prisms (H_2O)	257
Dihydropseudocodeine-B	174.5–175.5 196–197	−14.1° (C_2H_5OH)	Truncated prisms (ethyl acetate)	251
Dihydropseudocodeine-C	100–116 *167.5–168	+13° (C_2H_5OH)	Prisms (C_2H_5OH)	251
Methyl (phenolic) ether	..	..	..	257
Hydriodide	*161–162 (dec)	+48° (H_2O)	Prisms (H_2O)	257
Hydroperchlorate	*252–255 (dec)	+38.7° (H_2O)	Plates (H_2O)	257
Methiodide	*230–232 (dec)	+43° (H_2O)	Rect'g scales (H_2O)	257
Dihydropseudocodeinone	*113	+37° (C_2H_5OH)	Rect'g prisms (ethyl acetate–ligroin)	259
Acid tartrate	199–200	+20° (H_2O)	Crystals (H_2O)	259
Hydriodide	*250–255 (dec)	+8.1° (H_2O)	Crystals (H_2O)	259

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride	*172–173	+13° (H_2O)	Crystals (acetone–C_2H_5OH)	259
Oxime	*244–245	..	Crystals (C_2H_5OH)	259
Dihydrothebaine	161–163	..	Crystals (C_2H_5OH)	262
Dihydrothebaine (Phenolic)	152–154	+25.5° (C_2H_5OH)	Prisms (methyl acetate)	310
Dihydrothebainehydroquinone	273 (dec)	..	Crystals (CH_3OH)	46
Dihydrothebainol	143	−49.9°	Six-sided plates (C_2H_5OH)	254
6-Methyl ether	140.5–142	−23.4° (C_2H_5OH)	Silky needles	310
Fumarate	198–201 (dec)	−28.1° (H_2O)	Crystals (C_2H_5OH)	310
Dihydrothebainone	139–143	..	Crystals (C_2H_5OH)	310
Fumarate	>220	..	..	310
Oxime	240–242 (dec)	..	..	310
β-Dihydrothebainone	..	−48.1° (C_2H_5OH)	Oil	310
Hydrobromide	255.5–257.5 (V)	−31.5° (H_2O)	Prisms (C_2H_5OH)	310
Hydrochloride	245–248 (V)	−34.4° (H_2O)	Rods (C_2H_5OH)	310
Hydroperchlorate	254–255 (V)	−32.5° (H_2O)	Prisms (C_2H_5OH)	310
Methiodide	149–154 (V)	..	Rect'g needles (C_2H_5OH)	310
Picrate	202–215 (V. dec)	−16.5° (acetone)	Yellow needles (C_2H_5OH–H_2O)	310
Oxime	225–226 (V)	−100.4° (C_2H_5OH)	Colorless needles (C_2H_5OH–H_2O)	310
β-Dihydrothebainone-methine	183–184	−257.9° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	310
Hydroperchlorate	225.5–226 (V)	..	Rosettes of crystals (C_2H_5OH)	310
Picrate	164–165 (V)	−181.1° (acetone)	Yellow needles (C_2H_5OH–H_2O)	310
Oxime	160–162 (V)	..	Rods(C_2H_5OH–H_2O)	310
Dihydrothebainone-$\Delta^{5,6}$ methyl enolate	165–166 (V)	−115.7° (C_2H_5OH)	Crystals (C_2H_5OH)	310
Fumarate	215–217 (dec)	−64.4° (H_2O)	..	310
Dihydrothebainone-$\Delta^{6,7}$ methyl enolate	127–128	−8.0° (C_2H_5OH)	Rect'g plates	310
9, 10-Dihydrothebenine	..	..	..	44a
Hydrochloride	261	..	Prisms (CH_3OH)	44a
Dimethyldihydrothebainone	199–202	+3.52° (C_2H_5OH)	Crystals (acetone)	308
Oxime	70–90	..	Crystals (ligroin–ethyl acetate)	308

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		E		
Ethyldihydrocodeine	120 (V)	−84.8° (C_2H_5OH)	Oil	308
Hydriodide	274–275 (V)	−50.6° (H_2O)	Crystals (C_2H_5OH)	308
Hydroperchlorate	275–276 (V. dec)	−60.5° (C_2H_5OH)	Crystals (C_2H_5OH)	308
6-Ethyldihydrocodeine	..	..	Oil	316
Methiodide	238–240	−82° (C_2H_5OH)	Crystals (CH_3OH–ether)	316
Picrate	217–219	−73° (C_2H_5OH–H_2O)	Crystals (C_2H_5OH–H_2O)	316
Ethyldihydrocodeinone	163–164	−100.9° (C_2H_5OH)	Needles (ethyl acetate)	308
Methiodide	255–257 (V. gas)	−48.8° (H_2O)	Crystals (C_2H_5OH)	308
Ethyldihydrocodeinone enol acetate	129–130	−124.1° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	308
α-Ethyldihydrodesoxycodeine	156–164	−148.2° ($CHCl_3$)	Crystals (acetone)	261
Hydriodide	205–210	−123.2° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	261
Hydroperchlorate	187–200	−134.7° (C_2H_5OH)	Prisms (C_2H_5OH–H_2O)	261
Methiodide	210–215	−111.4° (C_2H_5OH)	Crystals (H_2O)	261
Ethyldihydromorphinone	213–214	−103.5° (C_2H_5OH)	Crystals (C_2H_5OH)	308
Hydriodide	285–286 (V. gas)	−49.1° (H_2O)	Needles (C_2H_5OH)	308
Methiodide monohydrate	263–265 (V. gas)	−42.2° (H_2O)	Crystals (C_2H_5OH)	308
Ethyldihydrothebainone	190.5–191.5	+10.9° (C_2H_5OH)	Crystals (C_2H_5OH)	308
Hydriodide	253–255 (V. gas)	+14.0° (H_2O)	Crystals (C_2H_5OH)	308
Hydrochloride	280–282 (V. gas)	+17.8° (H_2O)	Needles (C_2H_5OH)	308
α-Ethyltetrahydrodesoxycodeine	168.5–169	−54.8° ($CHCl_3$)	Sublimed 125°/0.001 mm.	261
Hydriodide	234	−2.9° ($CHCl_3$)	Crystals (H_2O–CH_3OH)	261
β-Ethyltetrahydrodesoxycodeine	148–153	−37.6° ($CHCl_3$)	Crystals (acetone)	261
α-Ethylthiocodide				
Low melting form	77–79	−340.7° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	254
High melting form	86–87	−344.6° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	254
Sulfate	185–190	−276.6° (H_2O)	Needles (H_2O)	254

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
β-Ethylthiocodide	146–148	−49.8° (C_2H_5OH)	..	254
δ-Ethylthiocodide	..	+57.7° (C_2H_5OH)	Jelly	254
Hydroperchlorate	223–224	+40.5° (C_2H_5OH)	Crystals (C_2H_5OH)	254
Ethylthiodihydrodesoxycodeine	140/0.05 mm.	−59.8° (C_2H_5OH)	Oil	254
Ethylthiodihydrothebainone	181–182	+55.4° (acetone)	Crystals (acetone)	254
		F		
Flavothebaon monohydrate	255–257	..	Leaflets (H_2O)	46
Hydrochloride monohydrate	330 (dec)	..	Yellow crystals	46
Oxime	222 (dec)	..	Crystals	46
Hydrochloride	>350	..	Crystals (H_2O)	46
Dimethyl ether	257	..	Crystals (CH_3OH)	46
Monomethyl ether	276 (dec)	..	Crystals (CH_3OH)	46
Hydrochloride	308 (dec)	..	Yellow crystals (H_2O)	46
Triacetyl-	273	..	Crystals (C_6H_6)	46
Trimethyl ether	253	..	Crystals (CH_3OH)	46
Hydrochloride	188–190	..	Needles (H_2O)	46
Methiodide	251	..	..	46
		H		
Hexahydro-ε-methylmorphimethine	166.5–167.5	+28° (C_2H_5OH)	Fine needles (ethyl acetate)	246, 251
Acid tartrate	*114–115	+15.6° (H_2O)	Crystals (butanone)	246
Hydrochloride	*250–254 (dec)	+8.1° (H_2O)	Plates (C_2H_5OH)	246
Methyl ether	*138	+17.4° (C_2H_5OH)	Crystals (ethyl acetate)	257
Hexahydro-ζ-methylmorphimethine	..	..	..	255
Hydriodide	*279–281 (dec)	−39.8° (H_2O)	Crystals (H_2O)	255
Hexahydrophenyltetrahydrodesoxycodeine	132–134	−48.4° ($CHCl_3$)	Crystals (acetone–H_2O)	261
Hydroperchlorate	255–256	−16.7° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	261
Methiodide	250	−28.0° ($CHCl_3$)	Crystals (C_2H_5OH)	261
Hydroxycodeine	304–305 (V)	−143° (HOAc–H_2O)	Crystals ($CHCl_3$–C_2H_5OH)	311
Hydrochloride	269–275 (dec)	..	Crystals (HCl–H_2O)	311
Hydroxycodeinone	275–276 (V)	−111° (HOAc–H_2O)	Crystals ($CHCl_3$–C_2H_5OH)	311
Hydriodide	255–260 (V. dec)	−74° (H_2O)	Flat needles (H_2O)	311

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride dihydrate	272–274 (V)	−89° (H_2O)	Crystals (H_2O)	311
Hydroperchlorate	241–242 (dec)	−80° (H_2O)	Rect'g plates (H_2O)	311
Acetyl-	185	+21° (HOAc–H_2O)	Scales (C_2H_5OH–H_2O)	311
Hydrochloride	260–261 (V)	+15.7° (H_2O)	Scales (H_2O)	311
		I		
Iodocodide(orange form)	200 (dec)	+134.1° ($CHCl_3$)	..	241
Iodocodide(white form)	159–160	+136.5° ($CHCl_3$)	White crystals	241, 313
Hydrochloride	190–191	+126.9° (H_2O)	Crystals (CH_3OH)	241
Methiodide	187–188	..	Yellow needles (H_2O)	241
Iodomorphide	..	+123.2° (CH_3OH)	Vitreous solid	313
Acid tartrate	..	+120.3° (H_2O)	Crystals (C_2H_5OH–H_2O)	313
Benzoate	159–160	+115.5° (C_2H_5OH)	..	313
Hydriodide	..	+114.5° (H_2O)	White crystals(H_2O)	313
Methiodide	..	+90° (C_2H_5OH–H_2O)	..	313
Salicylate	161 (dec)	+113.4° (C_2H_5OH)	Crystals (C_2H_5OH)	313
Isocodeine	169–171	..	..	258
Acid tartrate	*185–186 (froth)	−99.4° (H_2O)	Plates (CH_3OH)	246
Methyl ether	80–82	..	..	310
Methiodide	196–198	−112.1°	..	310
Salicylate	158–159	−122.4° (H_2O)	Crystals (C_2H_5OH)	310
Isoethyldihydrothebainone	188–189°	−36.2°(C_2H_5OH)	Crystals (C_2H_5OH)	308
Hydriodide	191–193 (V)	−4.1° (H_2O)	Crystals (C_2H_5OH)	308
Methiodide hemihydrate	237–240 (V)	−5.8° (H_2O)	Crystals (C_2H_5OH)	308
Isomethyldihydrocodeine (monohydrate)	103–104	−126.9° (C_2H_5OH)	Crystals (H_2O)	308
Methiodide	252–254 (V. gas)	−56.8° (H_2O)	Crystals (C_2H_5OH–H_2O)	308
Salicylate	235–237 (V. gas)	−87.3° (C_2H_5OH)	Crystals (C_2H_5OH)	308
Isomethyldihydrocodeinone	144–145	−179.4° (C_2H_5OH)	Crystals (ethyl acetate)	262
Hydriodide (monohydrate)	209–210 (V. gas)	−102.1° (H_2O)	Needles (C_2H_5OH)	308
Hydrochloride	191–193 (V. gas)	−122.1° (H_2O)	Needles (C_2H_5OH)	308

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Isomethyldihydrocodeinone enol acetate	123–124	−250.3° (C_2H_5OH)	Crystals (ethyl acetate)	262
Isomethyldihydrothebainone	168–168.5	−57.0° (C_2H_5OH)	Needles (acetone)	262
Hydriodide	259–260 (V. gas)	−28.0° (H_2O)	Crystals (C_2H_5OH)	308
Methiodide (hydrate)	194–196 (V)	−18.6° (H_2O)	Needles (acetone)	308
Acetyl-	157–158	−9.9° (C_2H_5OH)	Crystals (acetone)	262
Oxime	191–192	−82.4° (C_2H_5OH)	Silky needles (C_2H_5OH)	262
Isomethyl-7-ketodihydrothebainone	258–259 (V)	−97.4° (C_2H_5OH)	Sublimed	308
Hydrate	172	−67.3° (C_2H_5OH)	Crystals (ethyl acetate)	308
α-Isomorphine	247–248	−168°	. .	253
Ethyl ether	128–130	−143.7° (C_2H_5OH)	. .	307
Methiodide	243 (V)	−91.6° (H_2O)	Crystals (C_2H_5OH)	307
Ethyl (alc.) ether	161–162 (V)	−205.1° (CH_3OH)	Distilled	307
Hydriodide	264 (V. dec)	−132.7° (H_2O)	Crystals (H_2O)	307
Hydrobromide	255–258 (V.dec)	−150.2° (H_2O)	Crystals (H_2O)	307
Hydrochloride	247–248 (V. dec)	−164.2° (H_2O)	. .	307
Methiodide	229–231 (V. gas)	−131.3° (H_2O)	Crystals (C_2H_5OH)	307
Methyl (alc.) ether	206.5–207 (V)	−185.5° (CH_3OH)	Crystals (C_2H_5OH)	307
Methiodide	227–228 (V. gas)	−105.4° (H_2O)	Crystals (C_2H_5OH)	307
β-Isomorphine	182	−216°	. .	258
Ethyl ether	. .	. .	Oil	307
Acid sulfate	195–198 (V)	−136.3° (H_2O)	Crystals (H_2O)	307
Fumarate	172–175 (V)	−100.3° (C_2H_5OH)	. .	307
Hydroperchlorate	264–266 (V. dec)	−113.2° (H_2O)	Crystals (H_2O)	307
γ-Isomorphine	278–279 (V)	−93.6° (CH_3OH)	. .	252
Hydrochloride	278	−74.8°	. .	252
Ethyl ether	183–184	−75° (CH_3OH)	Crystals (C_2H_5OH)	307
Hydrochloride	298–300 (V. dec)	−62.7° (H_2O)	. .	307
Methiodide	252–253 (V. gas)	−40.8° (H_2O)	Crystals (C_2H_5OH–H_2O)	307
Ethyl (alc.) ether	215–220 (V. dec)	−43.5° (CH_3OH)	Crystals (C_2H_5OH)	307
Hydriodide (monohydrate)	276–277 (V. dec)	−23.2° (H_2O)	Crystals (H_2O)	307

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride (dihydrate)	287–290 (V. dec)	−30.5° (H_2O)	Crystals (H_2O)	307
Methyl (alc.) ether	239–241 (V)	−79.5° (CH_3OH)	Crystals (C_2H_5OH)	307
Hydriodide	185–188 (dec)	−48.7° (H_2O)	Crystals (H_2O)	307
Hydrochloride	274–276 (V. dec)	−48.6° (H_2O)	Crystals (H_2O)	307
Isophenyldihydrothebainone	213–215	+34.8° ($CHCl_3$)	Needles (C_2H_5OH)	308
Methiodide	214–215 (V)	0° (C_2H_5OH)	Plates (ethyl acetate–CH_3OH)	308
Methyl ether	..	..	..	308
Methiodide	264–265	+49.3° (C_2H_5OH)	Crystals (CH_3OH–ethyl acetate)	308
Methochloride	239–243 (V)	..	Crystals (ethyl acetate–CH_3OH)	308
Oxime	230–232	−157° (C_2H_5OH)	Needles (ethyl acetate)	308
Isopropyldihydrocodeinone	175–177	−110.5° (C_2H_5OH)	Needles (C_2H_5OH)	308
Hydriodide (monohydrate)	196–198 (V)	−67.2° (C_2H_5OH)	Rods (H_2O)	308
Hydrobromide	202–203 (V)	−58.3° (H_2O)	Needles (H_2O)	308
Methiodide	274–275 (V. dec)	−66.0° (acetone)	Crystals (C_2H_5OH–H_2O)	308
Oxime	224–226 (V)	−25.0° (C_2H_5OH)	Crystals (ethyl acetate)	308
Isopropyldihydromorphinone	236–238	−107.5° (C_2H_5OH)	Crystals (C_2H_5OH)	308
Hydriodide (monohydrate)	199–201 (V)	−61.5° (acetone)	Crystals (H_2O)	308
Hydrobromide	215–220 (V)	−56.4° (H_2O)	Needles (H_2O)	308
Hydrochloride	340–341 (V. dec)	−64.2° (H_2O)	Prisms (acetone)	308
Hydroperchlorate	168–170 (V)	−69.9° (C_2H_5OH)	Plates (C_2H_5OH–H_2O)	308
Isopropyldihydrothebainone	217.5–219.5	−31° ($CHCl_3$)	Needles (C_2H_5OH)	308
Hydrobromide	277–277.5 (V)	−12.6° (H_2O)	Crystals (H_2O)	308
Hydrochloride	273–275 (V)	−18.3° (H_2O)	Rods (C_2H_5OH)	308
Hydroperchlorate	236–238 (V)	−16.0° (acetone)	Crystals (C_2H_5OH)	308
Salicylate	165–185 (V)	−8.9° (acetone)	Needles (C_2H_5OH)	308
Oxime (dihydrate)	199–201	..	Needles (C_2H_5OH)	308
Hydrochloride	213–215 (V)	+43.8° (H_2O)	Crystals	308

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		M		
Metathebainol (anhydrous)	..	−66.7° (C_2H_5OH)	Resin	249
$CHCl_3$ addition product	92–93	−45.3° (C_2H_5OH)	Crystals ($CHCl_3$)	249
Hydriodide	..	..	Crystals	249
Hydrochloride (ethyl acetate of crystallization)	220 (dec)	..	Crystals (ethyl acetate–C_2H_5OH)	249
Methiodide	225	..	Crystals (C_2H_5OH)	249
Diacetyl-	140	..	Crystals (C_2H_5OH–H_2O)	249
Monoacetyl-	150 (dec)	..	Crystals (ethyl acetate)	249
Semicarbazone	217–218	+88.4° (HOAc–H_2O)	..	249
Metathebainone(yellow)	..	−419° (C_6H_6)	..	249
White form	..	−417° (C_6H_6)	..	249
3-Methoxy-5-methyl-5-phenanthro-3[4,5bcd]-pyrane	118.5	0° (C_2H_5OH)	Acicular crystals	315
Picrate	107–108	..	Purple rods (C_2H_5OH)	315
(+)6-Methoxy-X-methylthebendiene	56–59.5	−5° (C_2H_5OH)	Crystals (C_2H_5OH)	309
(+)6-Methoxy-X-methylthebentriene	99–101	+9° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	309
(−)6-Methoxy-X-methylthebentriene	99–101.5	−7.2° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	309
(rac)6-Methoxy-X-methylthebentriene	91.5–93.5	0°	..	309
6-Methyldesoxy-codeine	173–174	−242° (C_2H_5OH)	Crystals (C_2H_5OH)	316
Hydrochloride	262–263	−192° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	316
Methiodide	280–281	−149° (C_2H_5OH)	Crystals (CH_3OH)	316
Methyldihydrocodeine	85–88	..	..	262
Monohydrate	98–102	−84.8° (C_2H_5OH)	Crystals (acetone)	262
Hydrochloride	286–287	−64.5° (H_2O)	Crystals (C_2H_5OH)	262
Methiodide	269–271 (V)	−47.9° (H_2O)	Crystals (C_2H_5OH)	262
6-Methyldihydro-codeine	116	−139° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	316
Hydrochloride	268–273	−112° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	316
Methiodide	251–252	−86.3° (C_2H_5OH)	Crystals (CH_3OH)	316

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Oxalate(hemihydrate)	240–241	−99.5° (C_2H_5OH)	Crystals (C_2H_5OH)	316
Acetyl	124.5–125.5	−85.1° (C_2H_5OH)	Crystals(pet.ether)	316
Methyldihydrocodeinone	144–144.5	−146.9° (C_2H_5OH)	Long needles (acetone)	262
Methiodide	246–248 (V)	−74.2° (H_2O)	Crystals (C_2H_5OH)	262
Methyldihydrocodeinone encl acetate	191.5–194.5	−142.9° (C_2H_5OH)	Crystals (ethyl acetate)	262
Methyldihydrodesoxycodeine	145–146	+69.7° (C_2H_5OH)	Crystals (CH_3OH)	261
Hydriodide	155–158	+51.9° ($CHCl_3$)	Crystals (H_2O)	261
Hydrobromide	245–246	+61.5° ($CHCl_3$)	Six-sided plates (H_2O)	261
Methiodide	239	+28.8° ($CHCl_3$)	Crystals (acetone)	261
6-Methyldihydromethylmorphimethine	..	..	Oil	316
Hydrochloride	241–243	−6.7° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	316
Methiodide	269–271	+8.1° (C_2H_5OH)	Crystals (CH_3OH)	316
Salicylate	198–200	−2.3° (C_2H_5OH)	Crystals (C_2H_5OH)	316
Methyldihydromorphine	206–207	−92.9° (C_2H_5OH)	Crystals (ethyl acetate)	262
Hydriodide	289–291 (V)	−50.5° (H_2O)	Crystals (C_2H_5OH)	262
Hydrochloride	316–317 (V. dec)	−65.7° (H_2O)	Crystals (C_2H_5OH)	262
6-Methyldihydromorphine	209–211	−147° (C_2H_5OH)	Crystals (acetone)	316
Hydrochloride	308–309	−121° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	316
Methiodide	277–278	−86.8° (C_2H_5OH)	Crystals (CH_3OH)	316
Methyldihydromorphinone	243–245 (V)	−140.7° (C_2H_5OH)	Long needles (C_2H_5OH)	262
Hydrochloride	315–318	−104.8° (H_2O)	Crystals (C_2H_5OH)	262
Methyldihydropseudocodeine methyl ether	182.5–183	+121.0° (C_2H_5OH)	Crystals (ethyl acetate)	308
Hydriodide	256–257 (V. gas)	+91.5° (C_2H_5OH)	Needles (C_2H_5OH)	308
Hydrochloride	247–251 (V. dec)	+125.9° (H_2O)	..	308
Hydroperchlorate	285–287 (V. dec)	+103.1° (C_2H_5OH)	Crystals (C_2H_5OH)	308
Methiodide	273–276 (V. gas)	+98.1° (C_2H_5OH)	Needles (C_2H_5OH)	308
α-Methyldihydrothebaine	87.5–89.5	+140° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	309
Hydroperchlorate	..	+84° (C_2H_5OH)	Crystals (C_2H_5OH)	309
Methiodide	219–221	+76° (C_2H_5OH)	Crystals (C_2H_5OH)	309

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methyl ether	..	..	..	309
Methiodide	177–178	+43.3° (C_2H_5OH)	Crystals (H_2O)	309
α-Methyldihydrothebaineisomethine	..		..	309
Methiodide	227–230	−80° (C_2H_5OH)	..	309
Salicylate	163–164.5	−90° (C_2H_5OH)	Crystals (C_2H_5OH)	309
Methyldihydropseudocodeinone	*213.5–214.5	..	Crystals(propanol-2)	259
δ-Methyldihydrothebaine	..	..	Noncrystalline	309
Hydroperchlorate	..	+50° (C_2H_5OH)	Crystals (C_2H_5OH)	309
Acetyl-	..	..	Oil	309
Hydroperchlorate	..	+67.5° (C_2H_5OH)	Crystals (C_2H_5OH)	309
Methiodide	198	+56° (C_2H_5OH)	Crystals (C_2H_5OH–ethyl acetate)	309
(−)Methyldihydrothebaine-9,10-dihydromethine methyl ether	..	..	Oil	309
Methiodide	182–183	+29.1° (C_2H_5OH)	Crystals (H_2O)	309
Tartrate	106–110	+32.3° (C_2H_5OH)	Crystals (H_2O)	309
δ-Methyldihydrothebaineisomethine	..	..	Noncrystalline	309
Methiodide monohydrate	233	−30° (C_2H_5OH)	Crystals (H_2O)	309
Salicylate	209–211	−16° (C_2H_5OH)	Crystals (C_2H_5OH)	309
Methyl ether	..	..	Oil	309
Methiodide	172.5–174	−25° (C_2H_5OH)	Crystals (H_2O)	309
Picrate	125–128	..	Crystals (C_2H_5OH)	309
(+)Methyldihydrothebainemethine				
Methyl ether	190.5–192	−20° (C_2H_5OH)	..	309
(−)Methyldihydrothebainemethine	106–108	−21.3° (C_2H_5OH)	..	309
Tartrate	135–140	−7° (C_2H_5OH)	Crystals (C_2H_5OH)	309
Methyl ether	..	..	..	309
Methiodide	190–192	+20° (C_2H_5OH)	Crystals (ethyl acetate–C_2H_5OH)	309
Tartrate	135–137	+23° (C_2H_5OH)	Crystals (H_2O)	309
(rac)Methyldihydrothebainemethine	139.5–141.5	0° (C_2H_5OH)	Crystals (C_2H_5OH)	309
η-Methyldihydrothebaine	..	..	Oil	309
Hydroperchlorate	..	−49° (C_2H_5OH)	Crystals (C_2H_5OH)	309
η-Methyldihydrothebaineisomethine	209–211	+14° (C_2H_5OH)	..	309
Methyl ether methiodide	172.5–174	+26.4° (C_2H_5OH)	..	309

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
ω-Methyldihydrothebaine	86.5–89.5	−140° (C_2H_5OH)	Crystals (C_2H_5OH)	309
Hydroperchlorate	..	−81° (C_2H_5OH)	Crystals (C_2H_5OH)	309
ω-Methyldihydrothebaineisomethine	161.5–165.5	+85° (C_2H_5OH)	..	309
α-Methyl-9-dimethylamino-6-methoxythebendiene	76.5–78	−82° (C_2H_5OH)	..	309
Methiodide	207	−51° (C_2H_5OH)	Crystals (C_2H_5OH–ethyl acetate)	309
δ-Methyl-9-dimethylamino-6-methoxythebendiene	101.5–103	+33° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	309
Methiodide hemihydrate	207–208	−13° (C_2H_5OH)	Crystals (H_2O)	309
η-Methyl-9-dimethylamino-6-methoxythebendiene	101–103	−34° (C_2H_5OH)	..	309
Methyldihydrothebainone	192–193	−20.5° (C_2H_5OH)	Plates (C_2H_5OH)	262
Hydrochloride	283–285 (V. dec)	−6.8° (H_2O)	Crystals (H_2O)	262
Methiodide	212–216 (V)	+3.9° (H_2O)	Crystals (acetone)	262
Acetyl-	179–179.5	+13.1° (C_2H_5OH)	Crystals (ethyl acetate)	262
Oxime	244 (V. gas)	+69.4° (C_2H_5OH)	Needles (C_2H_5OH–H_2O)	262
Hydrochloride	244 (V. gas)	+38.9° (H_2O)	Crystals (H_2O)	262
Methylmorphenol	64–65	..	Crystals (CH_3OH)	256
ε-Methylmorphimethine	..	..	Oil	246
Hydrochloride	*211–212	−154.5° (H_2O)	..	246
Hydrate	149–150	−151°	..	246
ζ-Methylmorphimethine	..	..	..	255
Acid tartrate	*99–101	−126° (H_2O)	Crystals (H_2O)	255
Hydroperchlorate	*117–118	−154° (H_2O)	Crystals (H_2O)	255
Salicylate	*118–120	−141° (H_2O)	Crystals (H_2O)	255
Methyltetrahydrodesoxycodeine	128–129	−47.8° (C_2H_5OH)	Crystals (CH_3OH–H_2O)	261
Hydrobromide	248–249	−21.9° ($CHCl_3$)	Crystals (H_2O)	261
Hydrochloride	240.5	−23.1° ($CHCl_3$)	Needles (acetone)	261
Methiodide	254–255	−34.9° ($CHCl_3$)	Crystals (C_2H_5OH)	261
6-Methyltetrahydrodesoxycodeine	157.5–158.5	−4.5° (C_2H_5OH)	Crystals (acetone)	316
Hydrochloride	254–255	+8.0° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	316

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methiodide	265–266	+6.4° (C_2H_5OH)	Crystals (CH_3OH–ether)	316
Oxalate	171–172	+4.8° (C_2H_5OH)	..	316
Methylthiodihydrothebainone	138–140 164–166	...	Crystals (C_6H_6)	254
Monohydrate	95–97	..	..	254
Morphenol	145	..	Crystals (C_6H_6)	256
Morphine				
Ethyl (alc.) ether monohydrate	110–112	−178.8° (C_2H_5OH)	Crystals (ethyl acetate)	307
Hydriodide dihydrate	282 (V. dec)	−115.8° (H_2O)	Crystals (H_2O)	307
Hydrobromide dihydrate	285–287 (V)	−119.2° (H_2O)	Crystals (H_2O)	307
Hydrochloride trihydrate	241–243 (V)	−134.9° (H_2O)	Crystals (H_2O)	307
Hydroperchlorate	249–250 (V. dec)	−126° (C_2H_5OH)	Crystals (H_2O)	307
Methiodide	255–265 (V. dec)	−104.6° (H_2O)	Crystals (H_2O)	307
Methyl ether	242	..	..	253
Morphine-γ-isomorphine	268–269 (V)	−26.4° (HCl)	Crystals (NH_4OH)	253
		N		
1-Nitrocodeine	220–221.5	..	..	222
2-Nitrocodeine	172	..	Yellow prisms(H_2O)	222
Hydrochloride	249 (dec)	..	..	222
		O		
Octahydro-γ-pseudomorphine	..	..	..	253
Dihydrobromide	..	+8.2° (H_2O)	Yellow crystals (H_2O)	253
Dihydroperchlorate	..	+6.3° (H_2O)	Yellow crystals (H_2O)	253
Hydrochloride	..	+8.9° (H_2O)	Crystals (H_2O)	253
		P		
Pentachloroxycodide	>200 (dec)	−298.8° (acetone)	Needles (acetone)	313
6-Phenyldihydrocodeine	130/0.1 mm.	−155° (C_2H_5OH)	Amorphous solid	316
Hydrochloride	190–191	−131° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	316
Hydroperchlorate	246–248	−126° (C_2H_5OH–H_2O)	..	316
Oxalate	126–127	−117° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	316

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Phenyldihydrocodeinone	149–151	−166.2° (C_2H_5OH)	Needles (ligroin–ethyl acetate)	308
Phenyldihydrodesoxycodeine	184.5–185.5	+129.3° ($CHCl_3$)	Sublimed (vac)	261
Benzoate	203–204	+82.1° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	261
Methiodide	257.5–258	+105° (C_2H_5OH)	Rect'g flakes (C_2H_5OH)	261
Picrate	129–132	+69.5° ($CHCl_3$)	Yellow rect'g crystals (C_2H_5OH)	261
Phenyldihydromorphinone	278–280 (V. dec)	−164.5° (acetone)	Prisms (C_2H_5OH)	308
Hydriodide	273–276 (V)	−95.1° (acetone)	Prisms (C_2H_5OH–H_2O)	308
Hydrobromide	281–284 (V)	−97.4° (acetone)	Rods(C_2H_5OH–H_2O)	308
Hydrochloride	334–337 (V. dec)	−126.9° (H_2O)	Needles (C_2H_5OH–H_2O)	308
Phenyldihydrothethebainone	230–232	−165.9° ($CHCl_3$)	Crystals (C_2H_5OH)	308
Hydroperchlorate	201 (V. gas)	−97.6° (acetone)	Crystals (C_2H_5OH)	308
Methiodide	245–248 (V. dec)	−96.5° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	308
Oxime	198–200	−106.7° (C_2H_5OH)	Crystals (C_2H_5OH)	308
Phenyltetrahydrodesoxycodeine	218–220	+16.1° ($CHCl_3$)	Crystals (C_2H_5OH–H_2O)	261
6-Piperidocodide	75–80	−233.9° (CH_3OH)	Sublimed (vac)	267
Dihydroperchlorate	172–175	−113.4° (H_2O)	Crystals (H_2O)	267
8-Piperidocodide	116–117	+25.8° (CH_3OH)	Crystals (CH_3OH)	267
Diacid sulfate dihydrate	161–163.5 (V)	+19.8° (H_2O)	Crystals (C_2H_5OH)	267
Dihydroperchlorate	181–183	+13.2° (C_2H_5OH–H_2O)	Crystals (H_2O)	267
Monohydriodide	*234–237 (V)	+13.3° (H_2O)	Crystals (H_2O)	267
Monomethiodide	..	+22.0° (H_2O)	..	267
6-Piperidomorphide	216–217 (V)	−234.8° (CH_3OH)	Crystals (ethyl acetate)	267
Methiodide	*236–241 (V)	−145.8°(C_2H_5OH–H_2O)	Needles (H_2O)	267
8-Piperidomorphide	222–224 (V)	+28.7° (CH_3OH)	Crystals (C_2H_5OH)	267
Dihydriodide	208–214	+14.9° (H_2O)	Crystals (H_2O)	267
Monomethiodide	243–245 (V)	+23.7° (C_2H_5OH–H_2O)	..	267
Pseudocodeinone	..	..	..	259
Hydrochloride	*201–203 (dec)	−24° (H_2O)	Crystals (C_2H_5OH)	259
Semicarbazinosemicarbazone	225–227 (dec)	..	Crystals (C_2H_5OH–H_2O)	259

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Pseudomorphine(alc.)-dimethyl ether	250–252 (V)	..	Crystals (NH_4OH)	253
Hydrochloride	..	−192° ($HOAc-H_2O$)	..	253
α-Pseudomorphine	276 (V)	+6.2° (HCl)	Crystals (H_2O)	253
β-Pseudomorphine	272 (V)	−77° (HCl)	Crystals	253
γ-Pseudomorphine	282–283 (V)	+44.8° (HCl)	Granular crystals (NH_4OH)	253
Dibenzoate	..	+42.5° (H_2O)	Amorphous	253
Dihydriodide	..	+35.3° (H_2O)	Crystals (H_2O)	253
Dihydrobromide	..	+39.0° (H_2O)	Crystals (H_2O)	253
Dihydrochloride	..	+46.6° (H_2O)	Crystals (H_2O)	253
Dihydroperchlorate	..	+49.4° (H_2O)	Crystals ($C_2H_5OH-H_2O$)	253
Dimethiodide	..	+31.1° (H_2O)	Crystals (H_2O)	253
Disalicylate	..	+40.4° ($C_2H_5OH-H_2O$)	Amorphous	253
Monosulfate	..	+29.6° (H_2O)	Crystals ($C_2H_5OH-H_2O$)	253
Monomethyl ether	..	..	..	253
Dioxalate	..	−5.6° (H_2O)	Crystals (C_2H_5OH–ether)	253
Hydrobromide	..	..	Needles	253
Monomethiodide	..	+13.1° (H_2O)	Crystals (H_2O)	253
Tetraacetyl-	189–191	+57.5° (C_2H_5OH)	Prisms (ether)	253
Dihydriodide	..	+62.4° (H_2O)	Yellow crystals (H_2O)	253
Dihydrobromide	..	+72.6° (H_2O)	Crystals (C_2H_5OH)	253
Dihydroperchlorate	..	+57.7° (H_2O)	Crystals (C_2H_5OH)	253
Dimethiodide	..	+61.0° (H_2O)	Crystals (C_2H_5OH)	253
		T		
Tetrahydroallopseudo-codeine	*145.5	−58° (C_2H_5OH)	Sublimed (vac)	255, 258
Hydrate	113–118	−52° (C_2H_5OH)	Scales (ethyl acetate)	255
Hydroperchlorate	*102–104	−35° (H_2O)	Crystals (H_2O)	255
Methiodide	*241–242 (dec)	−22° (H_2O)	Crystals (CH_3OH)	255
Tetrahydro-8-amino-codide	138.5–140	−9.7° (C_2H_5OH)	Sublimed (vac)	267
Dihydrochloride	..	+6.6° (H_2O)	Crystals (C_2H_5OH)	267
β-Tetrahydrodesoxy-codeine	124–125	−72.3° (C_6H_6)	Crystals (ligroin)	247, 244
	157–158	−70.2° (C_6H_6)	..	244, 250
Hydrate	143–145 (gas)	−33.3° (C_2H_5OH)	Crystals (acetone)	241,247, 250
Hydriodide	245–246	−24.3° (C_2H_5OH)	Yellow needles	244

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride	260–262	−23.5° (H_2O)	White prisms	244, 242
Methiodide	263	−33.3° (H_2O)	..	244, 242
Methyl ether	..	..	Colorless oil	244
Hydriodide	217–218	−21.8° (C_2H_5OH)	Yellow needles(H_2O)	244
Methiodide	256–257	−3.54°	Crystals (C_2H_5OH–ether)	244
Methochloride	255–256 (dec)	−9.5° (H_2O)	White crystals (acetone)	244
Tetrahydrodesoxy-hydroxycodeine	242–244	−28° (H_2O)	Crystals (H_2O)	311
Tetrahydrodesoxy-metacodeine	..	..	Oil	249
Hydriodide	..	−12.5° (H_2O)	Crystals (H_2O)	249
Tetrahydrodesoxy-morphine	228–230	−77° (methyl acetate)	Crystalline powder	247,248, 258
Hydriodide	268–271	−32.7° (H_2O)	Crystals (H_2O)	247
Hydrochloride	260–262	−47.1° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	247
Salicylate	238–240	−31° (CH_3OH)	Crystals (C_2H_5OH)	247, 258
Tetrahydrodidesoxy-pseudomorphine	318 (V. dec)	−13.4° (HCl)	White crystals (CH_3OH)	253
Tetrahydro-8-diethyl-aminocodide	154–157	+31.5° (CH_3OH)	Sublimed (vac)	267
Hydrate	116–119 (gas)	..	..	267
Monohydroperchlorate	234–238 (V)	+18.3° (H_2O)	Crystals (H_2O)	267
Tetrahydro-β-ethyl-thiocodide	..	+15.3° (C_2H_5OH)	Oil (distilled, vac)	254
Tetrahydro-β-isomorphine	245–247 (dec)	−60.4° (HOAc–H_2O)	Crystals	258
Hydroperchlorate	..	−76° (H_2O)	Crystals (H_2O)	258
Tetrahydro-γ-isomorphine	..	..	Noncrystalline	252
Hydriodide	*280–290	−1.8° (H_2O)	Crystals (H_2O)	252
Hydrochloride	*275–280	−3.5° (H_2O)	Needles(HOAc–HCl)	252
Hydroperchlorate	*215–220	0° (H_2O)	Crystals (H_2O)	252
Tetrahydro-ε-methyl morphimethine (nonphenolic)	..	..	Oil	246
Acid tartrate	*195.5° (froth)	+27° (H_2O)	Scales (H_2O)	246
Hydriodide	*225–226	+17.4° (H_2O)	Flat prisms (H_2O)	246
Hydrochloride	*187	+18.6° (H_2O)	Needles (ethyl acetate)	246
Salicylate	*198	−18.1° (H_2O)	Prismatic needles (H_2O)	246

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Tetrahydro-ϵ-methyl-morphimethine (phenolic)	*196–197 (dec)	+192° (C_2H_5OH)	Prisms (ethyl acetate)	246
Hydriodide	*123–124	...	Rect'g scales (acetone)	246
Methyl ether	*156.5–157	+199° (C_2H_5OH)	Rect'g scales (acetone)	257
Tetrahydro-ϵ-methyl-morphimethine-A				
Methyl ether	98.5	+54° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	257
Hydrochloride	*251–252 (dec)	+42° (H_2O)	Needles (C_2H_5OH)	257
Tetrahydro-ζ-methyl-morphimethine	110	−26° (C_2H_5OH)	Needles (ligroin–ethyl acetate)	255
Salicylate	175–175.5	..	Crystals (H_2O)	255
Tetrahydro-ζ-methyl-morphimethine (phenolic)	..	..	..	255
Hydriodide	*249	+47.6° (H_2O)	Crystals (acetone–H_2O)	255
Tetrahydro-8-piperido-codide	125	+36.7° (C_2H_5OH)	Sublimed (vac)	267
Tetrahydro-8-piperido-morphide	270–280 (V. dec)	+45.1° (HOAc–H_2O)	Sublimed (vac)	267
Tetrahydropseudo-codeine	179–180	..	..	251
Hydrate	*115–120	−9.9° (C_2H_5OH)	Prisms (C_2H_5OH)	246,251, 259
Hydrochloride	*263 (dec)	+1.9° (H_2O)	..	246
Methiodide	..	−0.9° (H_2O)	..	246
Salicylate monohydrate	165–166	−1.7° (C_2H_5OH)	..	246
Salicylate dihydrate	135–136	..	Hexagonal plates (C_2H_5OH)	246
Methyl ether	125–130	−5° (C_2H_5OH)	Thin scales (C_2H_5OH–H_2O)	257
Hydriodide	*251–252 (dec)	+6° (H_2O)	Needles (H_2O)	257
Methiodide	*250–255 (dec)	+25.5° (H_2O)	Crystals (H_2O)	257
Tetrahydropseudo-codeinone	*170–171	+8.0° (C_2H_5OH)	Sublimed (vac)	259
Hemihydrate	*137–138.5	..	Crystals (acetone)	259
Hydriodide hydrate	*154–155	−5.9° (H_2O)	Crystals (H_2O)	259
Hydrochloride hydrate	*165–166	−6.2° (H_2O)	Crystals (C_2H_5OH)	259
Oxime	*218–219	..	Crystals (C_2H_5OH)	259

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Tetrahydropseudomorphine	300–302 (V. dec)	−85.9° (HCl)	White crystals	253
Monotartrate pentahydrate	..	−54.4° (H_2O)	Crystals (H_2O–C_2H_5OH)	253
Tetrahydro-γ-pseudomorphine	254 (V.dec)	+34.3° (HCl)	Crystals (NH_4OH)	253
Monosulfate	..	+20.9° (H_2O)	Crystals (H_2O)	253
Thebaine				
p-Benzoquinone adduct	247–249	..	Yellow crystals (acetone)	220
Maleic acid adduct	..	..	..	46
Diethyl ester	152	..	Needles (ligroin)	46
Diethyl ester hydrochloride	248	..	..	46
Maleic anhydride adduct	270 (dec)	..	Dense crystals (C_6H_6)	46, 220
1,4-Naphthoquinone adduct	239–240	..	Needles (C_2H_5OH)	220
Thebainehydroquinone	270	..	Prismatic needles (CH_3OH)	46, 220
Hydrochloride	280 (dec)	..	..	46
Dimethyl ether	212	..	Crystals (C_2H_5OH)	46
Monoacetyl-	259	..	Crystals (CH_3OH)	46
Monomethyl ether	238	..	Crystals (CH_3OH)	46
Hydriodide	261 (dec)	..	Crystals (H_2O)	46
Acetyl derivative	259	..	Crystals (CH_3OH)	46
Thebainone	145–147	−46.9° (C_2H_5OH)	Crystals (ethyl acetate)	310,245, 254
Hydriodide	258–261 (dec)	..	Crystals (H_2O)	254,245, 310
Hydrochloride	254–256 (dec)	−24.6° (H_2O)	Crystals (C_2H_5OH)	254
Methiodide	250–251	..	..	245, 254
Oxime hydrochloride	285–287	..	..	310
α-Thebainone	184–185	+158.5° ($CHCl_3$)	Crystals (acetone)	310
β-Thebainone	98–99	+114.9° (C_2H_5OH)	Crystals (acetone–H_2O)	310
Hydriodide	150–155 (V. dec)	+55.3° (H_2O)	Rods (C_2H_5OH)	310
Hydrobromide	168–169 (V. dec)	+61.1° (H_2O)	Rods (C_2H_5OH)	310
Hydroperchlorate	149–157	+67.3° (CH_3OH)	Plates (C_2H_5OH–H_2O)	310
Picrate	172–183 (dec)	+43.8° (acetone)	Yellow needles (C_2H_5OH–H_2O)	310
Oxime fumarate	220.5 (V)	+46.0° (H_2O)	Fine needles (C_2H_5OH)	310

TABLE 7 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Semicarbazone picrate	203–204 (V. dec)	..	Yellow rods (C_2H_5OH)	310
Thebainone methyl enolate	154–156	+9.6° (C_2H_5OH)	Crystals (C_2H_5OH)	310
β-Thebenone	189–190	+113.6° (C_2H_5OH)	Rods (C_2H_5OH)	310
Oxime	176–177 (V)	+30.6° (C_2H_5OH)	Cubes (C_2H_5OH–H_2O)	310
Tribromodihydrodesoxycodeine	184.5–185.5 (dec)	−156.7° (C_6H_6)	Crystals	265
Trichlorocodide	143–143.5	−302° (ethyl acetate)	Crystals (C_2H_5OH)	313
Hydrochloride	..	−218° (H_2O)	Crystals (H_2O)	313
Trichloromorphide	195 (dec)	−285° (CH_3OH)	Crystals (ethyl acetate)	313
Hydrochloride	..	−245.6° (H_2O)	Crystals (H_2O)	313
		V		
(rac)Vinyldihydro-X-methylthebaol	..	0°	Oil	309
Acetyl-	103–105.5	0° (C_2H_5OH)	Crystals (C_2H_5OH)	309

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Chapter VIII

Part II

The Morphine Alkaloids. II

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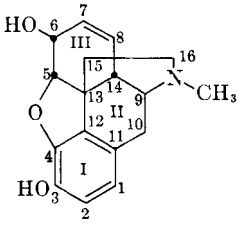
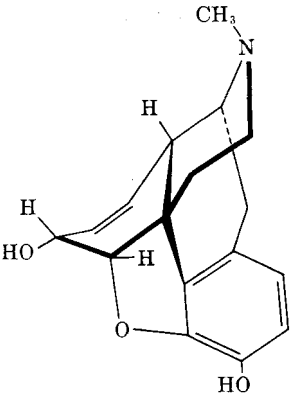
* Numbers in parentheses refer to pages of Part I of Chapter VIII, "The Morphine Alkaloids. I."

I. Introduction

The rapid developments since Part I of Chapter VIII was submitted for publication have prompted the compilation of this supplementary chapter on the morphine alkaloids. In this interval tetrahydrodesoxycodeine has been synthesized and oripavine, because of the identity of its C_3-methyl ether with thebaine, must now be classified as a member of this series of bases. The structure of phenyldihydrothebaine, the most refractory problem outstanding then, is resolved now that Robinson has so ingeniously interpreted Small's experimental results. The isomeric phenyldihydrothebaines, which are noncoplanar biphenyls with a five atom diethanamine chain fused to C_2 and $C_{2'}$, are unique structures in alkaloid chemistry, while the genesis of the optical activity by such a system inherent in certain of their degradation products is novel in the field of natural products. This insight into the deep-seated rearrangements leading to structures so radically different from the parent base necessitates a complete revision of the interpretation of the various reactions of methyldihydrothebaine as outlined in the first part of the chapter. Fortunately the reactions of the phenyldihydrothebaines are comparable with those of their methyl analogs, so the former will be used as the vehicle for the reinterpretation of these changes. Removal of the last of these structural problems has focused attention on the stereochemical problem and there is sufficient evidence upon which to assign configurations to the five asymmetric centers in morphine as succinctly expressed in formula CCIV. Finally only a consideration of the mechanisms of the various rearrangement and elimination reactions which lead to such a diversity of structure remains to complete the picture.



CCIVa



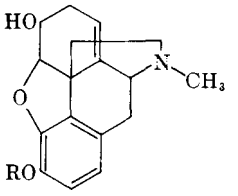
CCIVb

The general plan of organization of the previous part encompasses all phases of the recent work and so permits its adoption here. To avoid

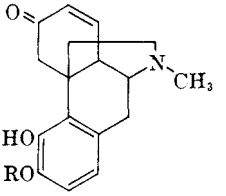
ambiguity and to facilitate cross reference, table, chart, formula and reference numbers will be carried over from Chapter VIII, Part I, and the page numbers of the previous Part will appear in parentheses alongside the section headings.

II. The Reactions of Morphine, Codeine and Neopine

Two new morphine isomers, neomorphine (CCV, R = H) and *O*-desmethylthebainone (CCVI) have been prepared and characterized. Neomorphine, the neopine (CCV, R = CH_3) analog of morphine, unlike the latter base can be prepared by demethylation of neopine with 48% hydrobromic acid or by hydrogen bromide in acetic acid followed by saponification ($NH_2OH \cdot HCl$) of the derived 6-acetylneomorphine (340). The



R=H, CH_3
CCV



R=H, CH_3
CCVI

reduction of neomorphine to dihydromorphine and its methylation (CH_2N_2) to neopine provides an alternate route for the relation of neopine to codeine and shows that no alteration of structure has accompanied the demethylation of neopine. The catalytic intramolecular disproportionation (p. 39) of morphine and codeine to dihydromorphinone and dihydrocodeinone may be induced to follow a different course by suitable choice of catalyst. Furthermore, increasing the relative amount of this catalyst with respect to that of morphine or codeine improves the yield of *O*-desmethylthebainone (CCVI, R = H) and thebainone (CCVI, R = CH_3).

An apparent anomaly in the course of the exhaustive methylation of 1-acetocodeine has now been removed while methylation (Rodionow) of the C_6 alcoholic hydroxyl occurs to a certain extent in the dry distillation of the methohydroxides of dihydro-α-methylmorphimethine and tetrahydro-α-methylmorphimethine.

1. Oxidation and Reduction (pp. 38–44)

By using a relatively large amount of 10% palladium-charcoal catalyst in the Knoll procedure for converting morphine to dihydromorphinone [codeine to dihydrocodeinone (p. 39)] a separable mixture of *O*-desmethylthebainone (60%) and dihydromorphinone is obtained (341). Diacetate

formation clearly demonstrates that the oxide bridge has been opened, while formation of an oxime and its reduction to dihydro-*O*-desmethylthebainone (p. 85) and the methylation (CH_2N_2) of the latter to dihydrothebainone is sufficient to characterize this base as an α,β-unsaturated C_6-ketone (the absorption spectrum of its thiosemicarbazone substantiates this conclusion, Table 8). The difference in molecular rotation of *O*-des-

TABLE 8

ULTRAVIOLET ABSORPTION MAXIMA (AND LOG ϵ VALUES) OF CERTAIN KEY COMPOUNDS

Compound					References
Apocodeine	280(4.16)	314(3.55)			350
Apomorphine hydrochloride	277(4.3)	303(3.52)	308(3.55)	317(3.6)	228
Codeine hydrochloride	242(3.62)	283(3.15)			228
O-Desmethylthebainone thiosemicarbazone	240(~4.0)	301.5(~4.3)			341
Diacetylmorphine hydrochloride	233(3.65)	278(3.2)			228
Dihydrothebaine (phenolic)	282(3.3)				350
β-Dihydrothebaine	283(4.1)				351
Metathebainone	212(4.18)	278(4.21)			350
α-Methyldihydrothebaine	282(3.7)				350
α-Methylmorphimethine	273(4.0)				350, 369
β-Methylmorphimethine	319(4.0)				350, 369
Morphine hydrochloride	285(3.2)				228
Oxoisomorphinane (desoxy compound)	264(3.3)	270(3.3)			367
α-Phenyldihydrothebaine	282(3.7)				350
(+)-Phenyldihydro-thebainemethine	319(4.3)				350
Tetrahydro-β-dihydro-thebaine	283(3.25)				351
Thebaine hydrochloride	283(3.8)				228

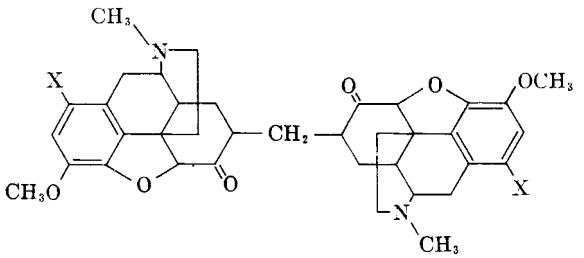
methylthebainone from its dihydro derivative (+96°) is in good accord (+91°) with that of thebainone and its dihydro derivative and supplies the necessary evidence to locate the double bond at Δ^{7-8}.

Application of the catalytic method or Woodward and Brehm's improved method for the preparation of pseudostrychnine to neopine might provide the necessary evidence to locate the hydroxyl of hydroxycodeine (p. 21). The dihydro derivative of the tertiary base resulting from *N*-methylation of the carbinolamine that would be expected from this allylamine would be either identical or isomeric with the dihydro

derivative of ketodihydromethylmorphimethine (LXXVIII). It is to be expected that the product from the successive action of CH_3MgI, acetic anhydride and methylation of the derived C_4-hydroxyl would be 3,4-dimethoxy-9-methylphenanthrene (271).

2. Substitution Reactions (p. 47)

The Mannich reaction when applied to dihydrocodeinone leads to anomalous results while sulfoacetic acid introduces an aceto group at C_1 in morphine, codeine and their dihydro derivatives (p. 50).



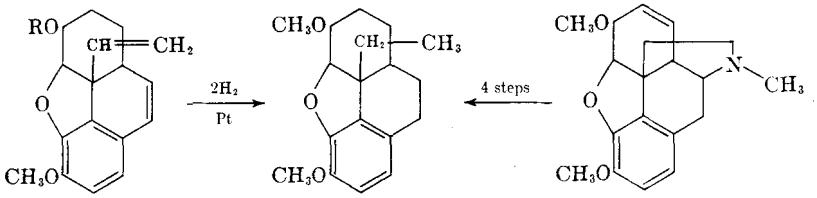
X=H, Br
CCVII

Dihydrocodeinone when condensed with formaldehyde in the presence of dimethylamine hydrochloride or diethylamine (but not trimethylamine hydrochloride) (342, 343) gives a 40% yield of a crystalline dimeric product ($C_{37}H_{42}O_6N_2$) (dimethiodide and dihydrochloride) (343). Condensation occurs at C_7 and the dimer must be 7,7′-methylenebisdihydrocodeinone (CCVII, X = H) since the same product is obtained from 1-bromodihydrocodeinone after hydrogenolysis of the bromine atoms from the derived 7,7′-methylenebis(1-bromodihydrocodeinone) (CCVII, X = Br) (343).

Sulfoacetic acid (heat 1 part H_2SO_4 and 3 parts of Ac_2O at 85° for 10 minutes) (340) introduces an aceto group at C_1 in morphine and dihydromorphine as in codeine and dihydrocodeine since methylation (CH_2N_2) of acetomorphine and 6-acetyldihydromorphine yields respectively 1-acetocodeine and 6-acetyl-1-acetodihydrocodeine (340). 1-Acetocodeine and its 6-acetyl derivative are catalytically hydrogenated to the respective dihydro derivatives in the presence of palladium but when platinum is used the aceto group is reduced as well leading to a mixture of the respective 1-ethyl- and the 1-(1′-hydroxyethyl)-derivatives.

3. Fission Around the Nitrogen (p. 51)

The conversion of 1-acetocodeine directly to 1-aceto-β-methylmorphimethine (164) under normal conditions for the Hofmann reaction is unique in this field. The driving force for the secondary shift of the codeine double bond to the beta position is ascribed to the lower energy content of the extended conjugated system which terminates in the ketone grouping of the C_1-aceto side chain. The inference that the alpha isomer is too unstable to isolate has been demonstrated to be erroneous. By reducing the time required for this reaction from 30 to 5 minutes it has been possible to isolate 1-aceto-α-methylmorphimethine in 70% yield (340). The ease with which it is isomerized (alcoholic potassium hydroxide) to the beta isomer accounts for the earlier observation. The dry distillation of 1-aceto-β-methylmorphimethine methohydroxide yields a small amount of a neutral product having the properties and formula required for 1-acetomethylmorphenol (340).



R=H, CH_3
CCVIII CCIX CCX

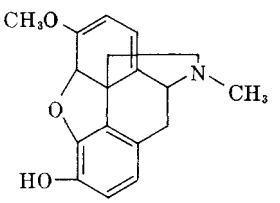
A second anomaly has been observed in the Hofmann degradation of both dihydro-α-methylmorphimethine (from dihydrocodeine) and tetrahydromethylmorphimethine. Dry distillation of the methohydroxide of the former base gives a separable mixture of 59% nonbasic and 34% basic material (344). Both fractions proved to be mixtures. By acylation of the neutral fraction it was possible to resolve it into CCVIII, R = H and its C_6-methyl ether. The position of the methyl ether grouping was established by the four step degradation of codeine-6-methyl ether (171) to CCIX. The wide range of melting point of the salts of the recovered methine indicates that a similar alkylation has occurred here as well. This clearly demonstrates that even a free alcoholic hydroxyl (p. 103) exerts a pronounced influence on the course of a Hofmann degradation since the amount of recovered methine base must bear a direct relationship to the extent of alkylation occurring. The recovery of 40–50% of basic material from the degradation of tetrahydro-α-methylmorphimethine and only 2–3% from its 6-methyl ether illustrates this point (344).

III. Reactions of Thebaine and Related Products

Oripavine, a phenolic alkaloid that has been known for some time, has now been structurally related to thebaine. The recent elucidation of the structure of the phenyldihydrothebaines and the marked parallelism in the reactions of Grignard reagents and lithium aluminum hydride has prompted a study of the reduction of thebaine by the latter reagent.

1. Oripavine (p. 80)

Oripavine, $C_{18}H_{21}O_3N$ (345) has been isolated along with thebaine and certain benzylisoquinoline alkaloids from *Papaver orientale* Linn. (345) and *Papaver bracteatum* Lindl. (346). Diagnostic tests show that it contains a methoxyl and a methylimino grouping as well as a phenolic hydroxyl group (345, 346). Methylation (CH_2N_2) of this phenol to thebaine was



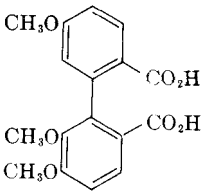
CCXI

sufficient to assign structure CCXI to the new base (347). Oripavine, like thebaine, is sensitive to mineral acid but attempts to isolate the C_3-hydroxy analog of thebenine or morphothebaine in crystalline form have failed (347).

2. The Phenyldihydrothebaines (pp. 97–98)

Acceptance of the inviting hypotheses that ring II of thebaine ($C_{19}H_{21}O_3N$) has been aromatized in the formation of the isomers + α- and + δ-phenyldihydrothebaine ($C_{25}H_{27}O_3N$) now seems justified and the perplexing problem of how to accommodate the extra two hydrogen atoms arising from such a premise has been disposed of most ingeniously by Robinson (348, 349). In order to retain the degree of unsaturation of the phenyldihydrothebaines obviously a ring must have been opened. This attack of phenylmagnesium bromide on thebaine leads to many deep-seated changes (see p. 197) and results in a substituted noncoplanar biphenyl system. The arguments leading to structures CCXII–CCXV for + α-, − α-, + δ- and − δ-phenyldihydrothebaine involve the optically active plus and minus vinylphenyldihydrothebaols ($C_{24}H_{22}O_3$, CCXVII) which

are derived from the parent bases by two successive Hofmann degradations. The three benzene nuclei of the latter substance account for eighteen of the twenty-four carbon atoms of these doubly unsaturated isomers (two mole equivalents of hydrogen are absorbed in the presence of platinum oxide and acetic acid (350)). Of the remaining six carbon atoms two are present in methoxyl groups, and only four carbon atoms are left to accommodate the two ethylenic double bonds. Consequently the optical activity of these products cannot be ascribed to an asymmetric carbon atom unless an allene is present, which at best seems highly doubtful. The asymmetry of these molecules must be due to the noncoplanarity of the biphenyl ring system. Oxidation ($KMnO_4$) of phenyldihydrothebaine to 4-methoxy-



CCXXV

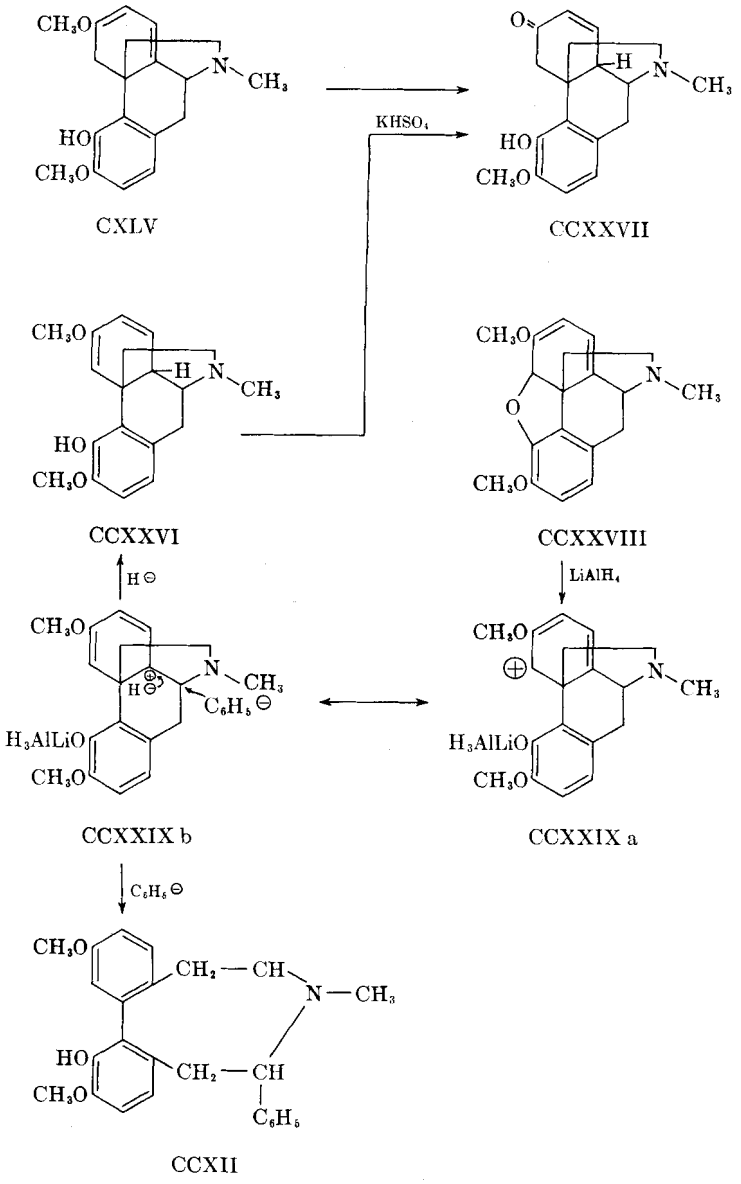
phthalic acid clearly demonstrates that one end of the diethanamine chain of the phenyldihydrothebaines must be fused to $C_{2'}$ while the location of the other end of the chain at C_2 is based on the optical activity of the vinylphenyldihydrothebaols and the oxidation of their *O*-methyl ether to CCXV (348, 349) (identical with that from the oxidation of dithebaol methyl ether (reference 62, p. 701)). Finally, examination of models clearly demonstrates that the five-atom side chain fused to the biphenyl system of the phenyl dihydrothebaines permits the strainless orientation of the two benzene rings at any angle up to and including a right angle (348, 349). The interference of the phenyl group with the biphenyl rings makes it quite apparent why generation of one of the phenyldihydrothebaines predominates over the other and why the thermal isomerization of that formed in lesser amount is the more favored of the two. The above argument for the structure of the phenyldihydrothebaines seems convincing and derives added support from the fact that such a structure is consistent with their varied reactions.

Since the transformation of (+) α-phenyldihydrothebaine to the − δ-isomer (200°C.) is reversible (the (+)δ-isomer likewise has been thermally isomerized to the (−) α-modification but because of limited quantities of the latter isomer the reverse change has not been realized)

(350) this must only involve the molecular asymmetry of the biphenyl ring system as indicated in formulas CCXII and CCXIII and the antipodes are represented respectively by CCXIV and CCXV. Since (+)α and (+)δ are diastereomers, the difference observed in the Hofmann degradation of the two is not surprising. The (+)δ-isomer affords only the isomethine (CCXVI) whereas with the (+)α- form a small amount of a so-called normal methine base (CCXXI) accompanies the α-isomethine (CCXVIII). If the four phenyldihydrothebaines are correctly represented in formulas CCXII to CCXV, elimination of the asymmetric carbon atom in the (+)α- and (+)δ-isomers should lead to a common product; forcing the benzene rings of the biphenyl of the resulting product into a plane by ring formation should lead to optical inactivity. Both expectations have been experimentally realized. Destruction of the asymmetric center of (+)α- and (+)δ-phenyldihydrothebaine has been achieved by hydrogenation. Both isomers, on absorption of one mole equivalent of hydrogen ($PdCl_2$ + HOAc + gum arabic) (350) yield (+)-phenyltetrahydrothebaimine, (CCXXIII). With this evidence it is now possible to assign structure CCXXI to the methine base and CCXVIII to the isomethine. By the steps outlined at the bottom of Chart II the (+)α-methine base can be converted to the methomethiodide of (+)-phenyltetrahydrothebaimine. Contrary to the methiodide of the (+)α-isomethine base the methine methiodide is resistant to degradation by the Hofmann method. More extensive reduction occurs if the acetic acid in the above hydrogenation is replaced by alcoholic HCl. Then (+)α-phenyldihydrothebaine absorbs four mole equivalents of hydrogen and (+)-phenyltetrahydrothebaimine three, yielding (+)-hexahydrophenyltetrahydrothebaimine ($C_{25}H_{35}O_3N$). In this instance hydrogenation of one of the benzene rings has accompanied hydrogenolysis of the C—N bond. The phenolic properties of the reduced base make it apparent that ring I has not been attacked but unfortunately the sensitivity of cyclohexyldihydrothebaine (thebaine + cyclohexylmagnesium bromide) (350) to aerial oxidation has prevented a direct comparison of cyclohexyltetrahydrothebaimine with this hydrogenated product.

The two benzene rings of *rac*-phenyl-6-methoxythebentriene (CCXX) are held in a plane by ring formation between the C_2-vinyl group and the C_2' phenolic hydroxyl. As expected, this product, prepared by alternate methods from (+)α- and (+)δ-phenyldihydrothebaines, is optically inactive. The (+)α-phenyldihydrothebaine isomethine (CCXVIII) may be cyclized (HCl) to (+)α-phenyl-9-dimethylamino-6-methoxythebendiene (CCXIX) and this in turn converted to CCXX by Hofmann degradation. The same optically inactive product is obtained from (+)δ-phenyldihydro-

thebaine isomethine by elimination of the dimethylamino group first (Hofmann) and cyclization (HCl) of the derived (+)-vinylphenyldihydrothebaol (CCXVII).



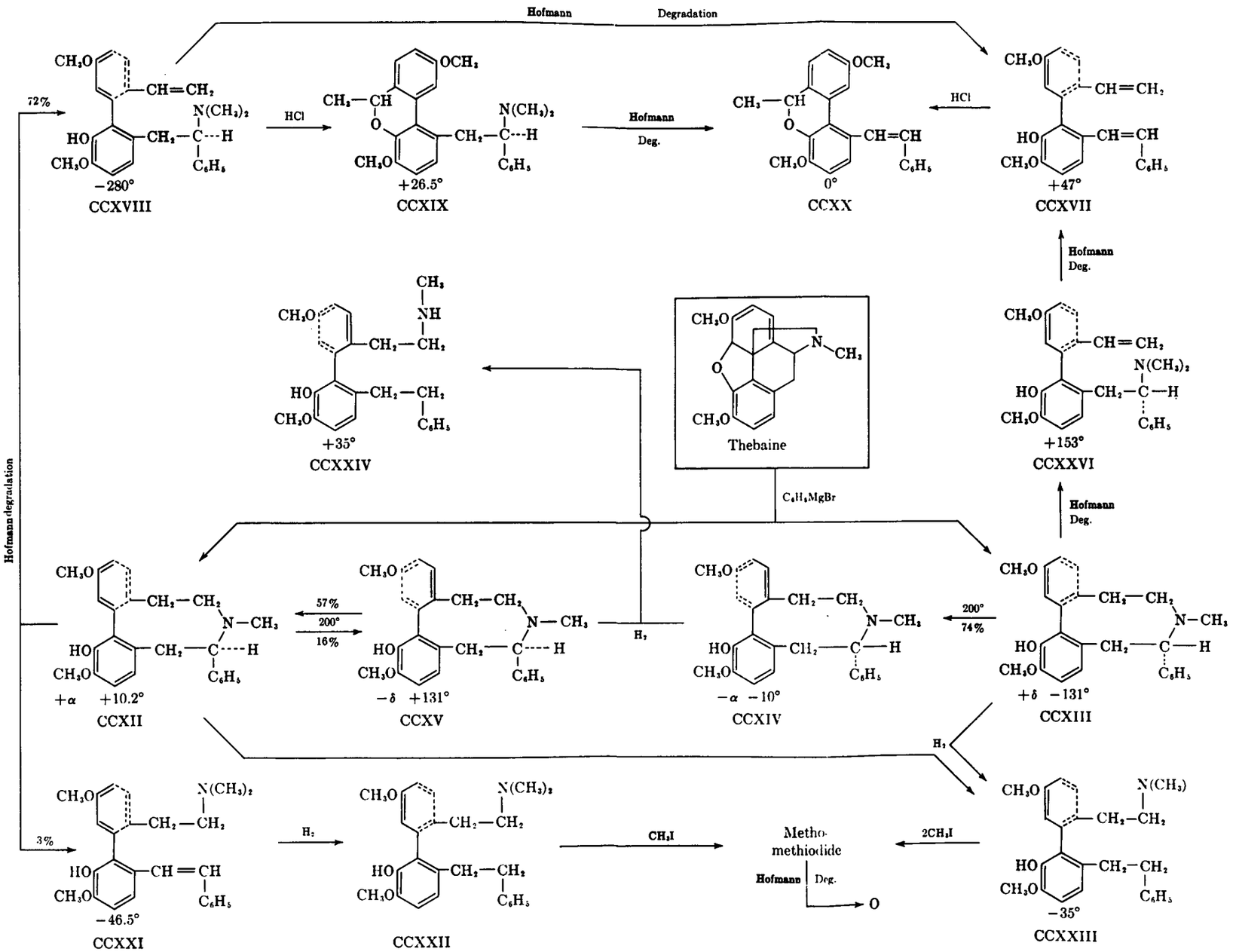


CHART II

THE PHENYLDIHYDROTHEBAINES AND THEIR PRODUCTS OF DEGRADATION

Examination of models makes it quite apparent that the interference of the phenyl and biphenyl systems is the reason for the predominant formation of one of the two phenyldihydrothebaines and why that formed in lesser amount is favored in the thermal equilibration of these two isomers.

3. Lithium Aluminum Hydride Reduction of Thebaine

The divergence in properties of phenyldihydrothebaine and β-dihydrothebaine make it evident that the parallelism so commonly exhibited by Grignard reagents and lithium aluminum hydride does not obtain in their reactions with thebaine. This difference has been attributed (351) to the small dimensions of the hydride ion which permits it to approach C_{14}, thus terminating at an intermediate stage the sequence of reactions that otherwise would lead to a structure analogous to that of the phenyldihydrothebaines.

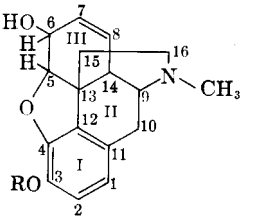
Reduction of a boiling benzene-ether solution of thebaine ($C_{19}H_{21}O_3N$) with lithium aluminum hydride affords a 30% yield of phenolic β-dihydrothebaine ($C_{19}H_{23}O_3N$) (351). In contrast to the phenyldihydrothebaines this new base is susceptible to catalytic hydrogenation (yielding a tetrahydro derivative which is now stable to 1 *N* hydrochloric acid) and acid hydrolysis. When aqueous potassium bisulfate is used to hydrolyze the enol methyl ether β-thebainone (CCXXVII) results. Obviously β-thebainone, which has the unnatural orientation of the hydrogen atom at C_{14}, can only arise from either CXLV or CCXXVI and as CXLV is phenolic dihydrothebaine, β-dihydrothebaine must be CCXXVI.

It is claimed that rupture of the allyl ether of thebaine may initiate this reaction, while approach of a hydride ion to C_{14} from the back side (see however p. 203) terminates the reaction and leads to the unnatural configuration at C_{14} (351).

IV. The Stereochemistry of Morphine and Sinomenine

(By Gilbert Stork) *

With the resolution of the last of the structural problems (p. 204) the stereochemistry of the morphine alkaloids can now be discussed in



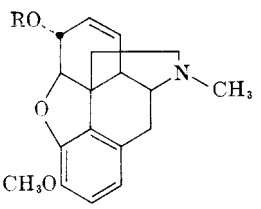
R=H,CH3
CCXXX

* The author thanks Dr. H. L. Holmes for his help in editing the manuscript of parts IV and V of this chapter.

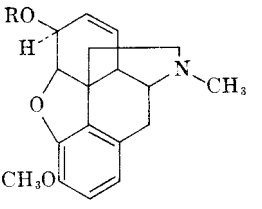
detail. Morphine and codeine have five asymmetric centers but the restriction imposed by the bridged ring system permits only sixteen (eight racemic pairs) of the thirty-two possible optical isomers demanded by the two-dimensional projection, CCXXX. By analysis of the known reactions of the morphine alkaloids it is now possible to decide which of these eight pairs represents *d*- and *l*-morphine. Such a derivation, based on a rational interpretation of the course of pertinent reactions has not previously been elaborated. Some workers have decided in favor of a specific three-dimensional representation of the morphine structure (40, 352, 352a) but their conclusions are based on incorrect premises and cannot be evaluated.

1. Relation of C_5-Oxygen to C_6-Hydrogen

We will assume that the C_6-hydrogen in codeine extends above the plane of the ring, as shown in CCXXXI, while isocodeine will be represented by CCXXXII. The respective methyl ethers (CCXXXI, and CCXXXII,

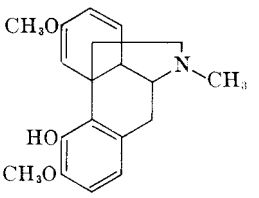


R=H,CH$_3$
CCXXXI

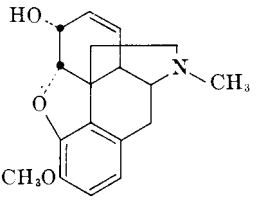


R=H,CH$_3$
CCXXXII

R = CH$_3$) of these two C_6-epimeric alcohols have been prepared and thoroughly characterized. One of these, codeine methyl ether, is isomerized by sodium methoxide to the phenolic enol methyl ether, CCXXXIII (310). It is evident that this β-elimination reaction requires the existence of a *trans* relationship between the oxygen at C_5 and the hydrogen at C_6. Recovery of isocodeine methyl ether from this reaction clearly demonstrates



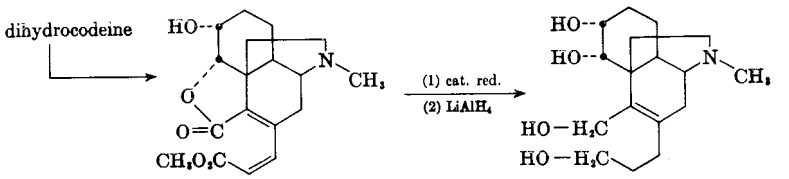
CCXXXIII



CCXXXIV

that epimerization does not occur in this base catalyzed isomerization, so the configuration of codeine may safely be expanded to CCXXXIV.

The above conclusion of a *cis* relationship at C_5 and C_6 is confirmed (352b) by the marked contrast in the rate of lead tetraacetate cleavage of tetrahydromorphitetrol (CCXXXIV B) and tetrahydro-α-isomorphitetrol.

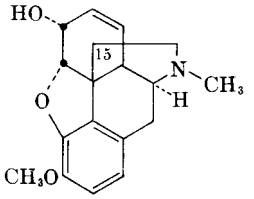


CCXXXIV A CCXXXIV B

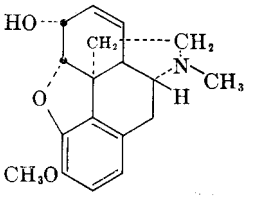
These two glycols are derived respectively from codeine and isocodeine by the same sequence of reactions and retain the configuration of the parent bases at C_5 and C_6. For example, tetrahydromorphitetrol results when the Δ′ double bond of ozodihydrocodeine (CCXXXIV A) is hydrogenated and the remaining functional groups are reduced to carbinols by lithium aluminum hydride. The comparative rate study of the lead tetraacetate cleavage indicates that the two hydrogen atoms are *cis* in tetrahydromorphitetrol and codeine and are *trans* in tetrahydro-α-isomorphitetrol and isocodeine.

2. The Relation of the C_9-C_{13} Side Chain to the C_5-Hydrogen

The two *a priori* possible orientations for the C_{13}-side chain with respect to C_5 are shown in CCXXXV and CCXXXVI. The distinctive features



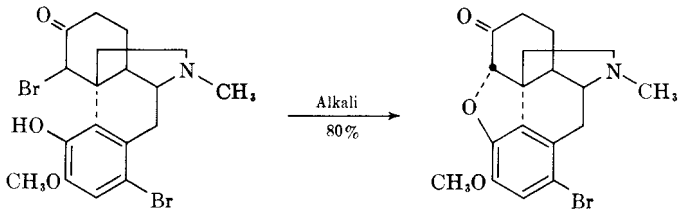
CCXXXV



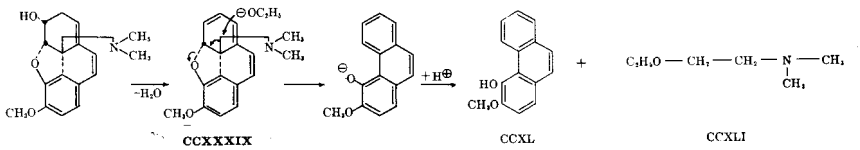
CCXXXVI

of these two structures are that in CCXXXV the five membered oxide ring and ring III have a *cis* junction and that of necessity C_{15} is *trans* to the bridge oxygen whereas in CCXXXVI the ring junction is *trans* and the relationship of C_{15} to the bridge oxygen is *cis*. The formula CCXXXV must truly represent the relationship existing in codeine, since if a *trans* 6-5 fused ring system of the α-hydrindanone type were present in dihydrocodeinone it would be epimerized by base to the more stable *cis*-system. Contrary to this, however, dihydrocodeinone is not affected by hot aqueous

alkali (353) and hence a *cis* relationship at C_5-C_{13} must exist in this dihydroketone. This last deduction applies equally well to cŏdeine and dihydrocodeine since the latter base is the sole product of catalytic hydrogenation of dihydrocodeinone (229). This conclusion that the oxide ring is fused *cis* to ring III is in accord with the observed ease of generation of 1-bromodihydrocodeinone (CCXXXVII) when 1,5-dibromodihydrothebainone (CCXXXVIII) is treated with alkali (40). Furthermore the corollary that C_{15} and the bridge oxygen are *trans* is amply substantiated by a number of concerted eliminations of the side chain and rupture of the oxide bridge by nucleophilic attack on C_{15}. For instance the ethanamine chain is eliminated as the ethyl ether (CCXLI) of β-hydroxyethyldimethylamine from β-methylmorphimethine (CCXXXIX) when this des base is heated with sodium ethoxide (19). Similarly, by an analogous path, acetolysis (Ac_2O

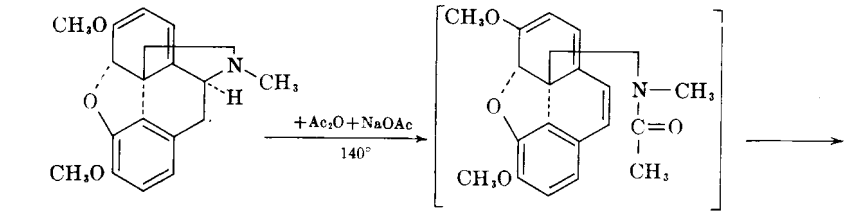


CCXXXVII CCXXXVIII

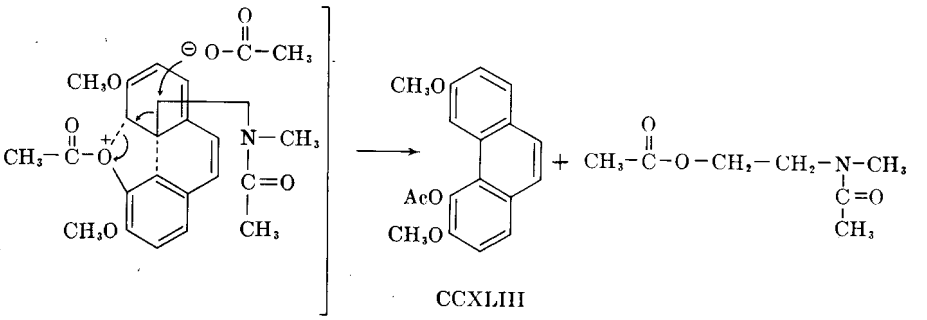


CCXXXIX CCXL CCXLI

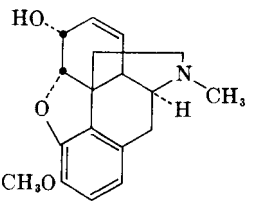
+ NaOAc at 140°) of thebaine (CCXLII) results in the formation of acetylthebaol (CCXLIII) and the diacetate of β-hydroxyethylmethylamine (80). The above two eliminations, as well as the primary step in the conversion of codeinone to 3,4,6-trimethoxyphenanthrene (p. 15) are most satisfactorily explained if C_{15} is *trans* to the bridge oxygen. On steric grounds this permits but one arrangement at C_9 as expressed in formula CCXLIV.



CCXLII



CCXLIII



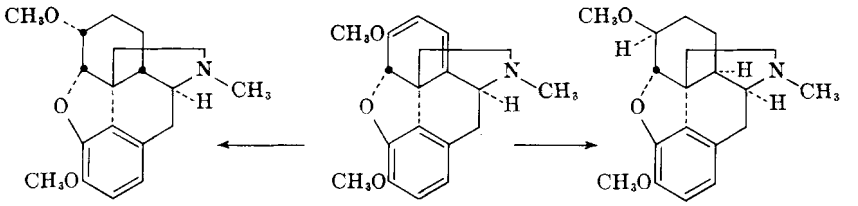
CCXLIV

3. The Configuration at C_{14}

The catalytic hydrogenation of thebaine to dihydrocodeine methyl ether (60) is sufficient to assign unambiguously a configuration to C_{14} of both codeine and dihydrocodeine. Hydrogen, adsorbed on the catalyst, may add to the conjugated system on the same side of the thebaine molecule as the C_5-hydrogen atom yielding CCXLV, or on the opposite side (CCXLVI). Since the product of the reaction, dihydrocodeine methyl ether, has the same configuration as codeine methyl ether (C_5 and C_6 hydrogens *cis*), this requires that the hydrogen atoms at C_5 and C_6, and hence at C_{14}, in dihydrocodeine methyl ether must be *cis* (CCXLV).

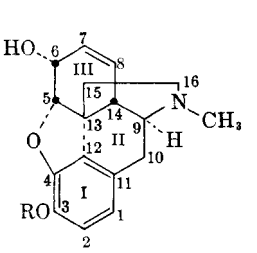
Thus the stereochemical relationships derived for morphine and codeine make it apparent that in these alkaloids rings II and III comprise

a *cis* octalin system while the piperidine ring is fused to ring III in the form of a *trans*-octahydroisoquinoline. Morphine (R = H) and codeine



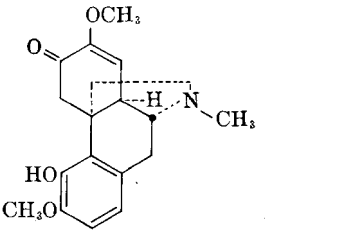
CCXLV CCXLVI

(R = CH_3) must then be represented by CCXLVII and sinomenine in which the configurations at C_9, C_{13} and C_{14} are known to be enantiomorphic



R=H,CH_3

CCXLVII



CCXLVIII

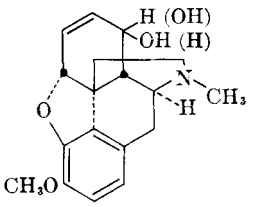
with the corresponding centers in the morphine alkaloids (see sinomenine, p. 228) must be CCXLVIII.

4. Codeine Isomers and the Halocodides

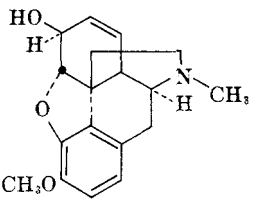
The oxidation of the four codeine isomers clearly shows that codeine and isocodeine are epimeric alcohols about C_6 while pseudocodeine and allopseudocodeine (CCXLIX) bear the same relationship at C_8 with the allylic double bond at $\Delta^{6(7)}$. This relationship of isocodeine to codeine requires that the iso base have the constitution CCL. There remains, therefore, only the problem of the configuration of pseudocodeine and allopseudocodeine.

To establish which of the constitutional formulas, CCLI or CCLII, represents psudocodeine and which represents allopseudocodeine it will be necessary to consider the constitution of α-chlorocodide, the chloride obtained from codeine and thionyl chloride (27). That this chloro base is represented by CCLIII is derived from the following facts. The chlorine was located at C_6 by catalytic reduction of α-chlorocodide to the product from the action of phosphorus pentachloride on dihydrocodeine (62).

This chlorodihydrocodide is one of two possible epimers about C_6 since electrolytic reduction affords dihydrodesoxycodeine-C (CCLIV) and sodium methoxide (140°) gives desoxycodeine-C (CCLV). Furthermore the

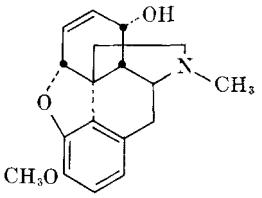


CCXLIX

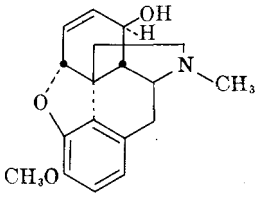


CCL

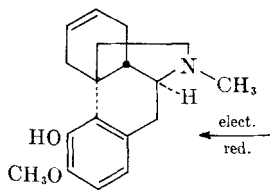
orientation of the C_6-chlorine with respect to the C_5-hydrogen must be *cis* as in CCLIII since neither thionyl chloride nor phosphorus pentachloride on dihydroisocodeine (CCLVIII) yield a stereoisomeric chloride but only phosphorus and sulfur containing compounds (313). The failure of this dihydroisocodeine to form a chloride must be ascribed to hindrance encountered in the backside approach of chloride ion. Such hindrance is not present in dihydrocodeine (CCLVI) which, then, must give CCLVII in which the C_6-chlorine is *cis* to the C_5 hydrogen atom, a relationship which must therefore also obtain in α-chlorocodide itself. This conclusion is in agreement with the observed absence of an SN_2 reaction when



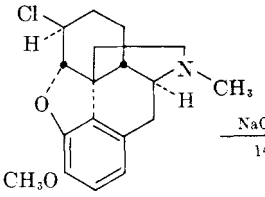
CCLI



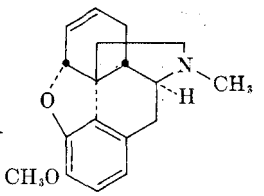
CCLII



elect. red.



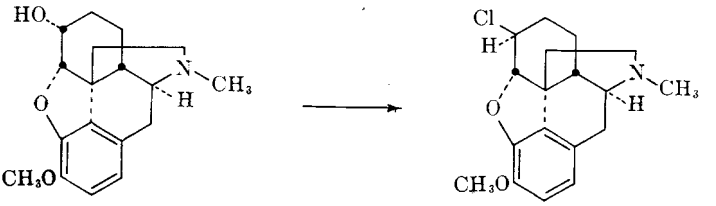
$NaOCH_3$ 140°



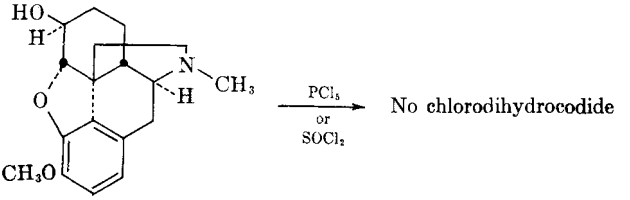
CCLIV CCLIII CCLV

α-chlorocodide is treated with methoxide ion (111) since backside approach of an anionoid fragment to CCLIII would be difficult. Under such circumstances an $SN_{2'}$ displacement might be expected to occur at the C_8 end

of the allylic system in α-chlorocodide. Were such a displacement to take place the anticipated product on mechanistic and steric grounds would be CCLIX. If substitution in a solvolytic reaction were to occur at C_8 then

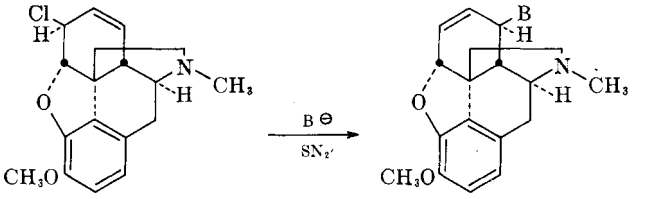


CCLVI CCLVII



CCLVIII

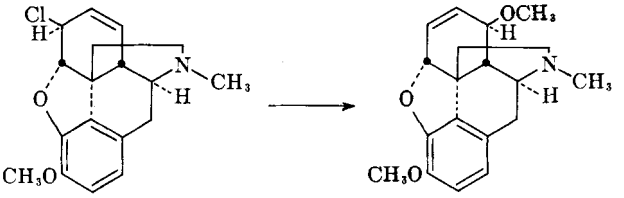
the major product from CCLIII again should be CCLIX. A number of reactions of α-chlorocodide are known in which substitution has occurred at C_8 and the considerations just outlined permit the assignment of definite



CCLIII CCLIX

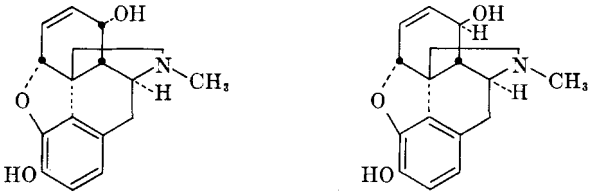
configurations to these products. The attack of methoxide ion (SN_2) at C_6 in α-chlorocodide cannot be detected but under forcing conditions an $SN_{2'}$ reaction does occur leading to pseudocodeine methyl ether (172, 172a, 175) which must then be assigned the constitution CCLX. Solvolysis of α-chlorocodide with alcohols or phenols, as might be expected, proceeds much more readily and again the products are the ethers of pseudocodeine (174). In fact pseudocodeine itself is the major product from the solvolysis of α-chlorocodide in aqueous acetic acid (136). From these facts it is evident that the configuration of pseudocodeine must be CCLII and that

of allopseudocodeine CCLI. Finally since β-isomorphine and γ-isomorphine can be methylated respectively to allopseudocodeine and pseudocodeine,



CCLIII CCLX

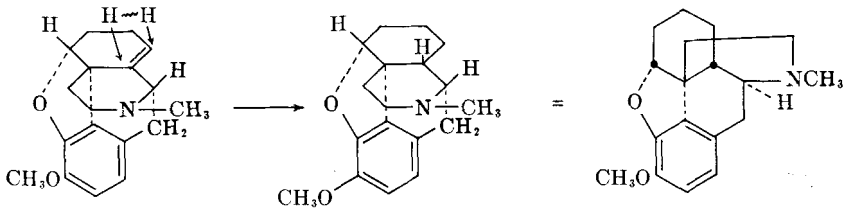
the configurations CCLXI and CCLXII may now be assigned to these morphine bases.



CCLXI CCLXII

5. The Reduction of $\Delta^{8(14)}$-Compounds

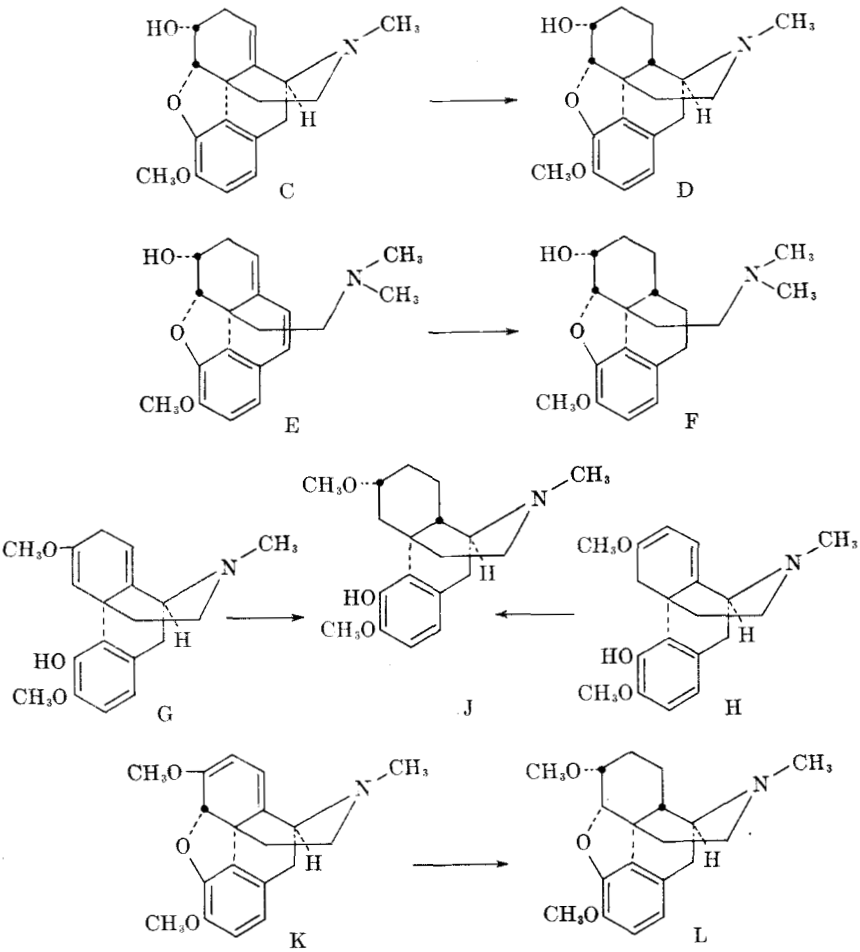
A consideration of the structure of substances with an 8,14-double bond suggests that adsorption on a catalyst surface will be capable of taking place only on the plane of the isoquinoline ring opposite to the phenyl group with consequent addition of hydrogen as shown. Catalytic



(A) (B) (B)

hydrogenation of compounds of this type will, therefore, always result in substances of the natural configuration at C_{14} as indicated in the illustration above, which represents the conversion of desoxycodeine D (A) to dihydrodesoxycodeine (B). Among the numerous other examples of this stereospecificity in the catalytic hydrogenation of an 8,14-double bond may be cited the reduction of neopine (C) to dihydrocodeine, (D) the hydrogenation of β-methylmorphimethine (E) to a compound identical with dihydrodes-*N*-methyldihydrocodeine (F), the hydrogenation of $\Delta^{5,8}$-

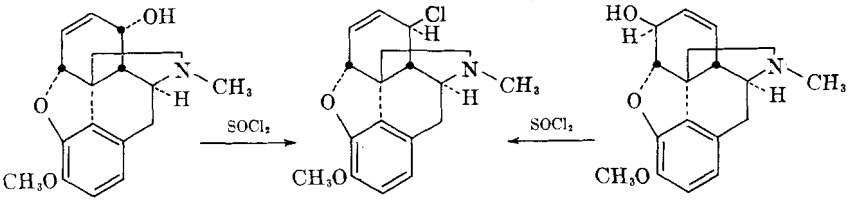
phenolic dihydrothebaine (G) and its $\Delta^{6,8}$-isomer (H) to dihydrothebainol-6-methyl ether (J), and finally the formation of dihydrocodeine methyl ether (L) among the products of the catalytic hydrogenation of thebaine (K):



6. The Halocodides

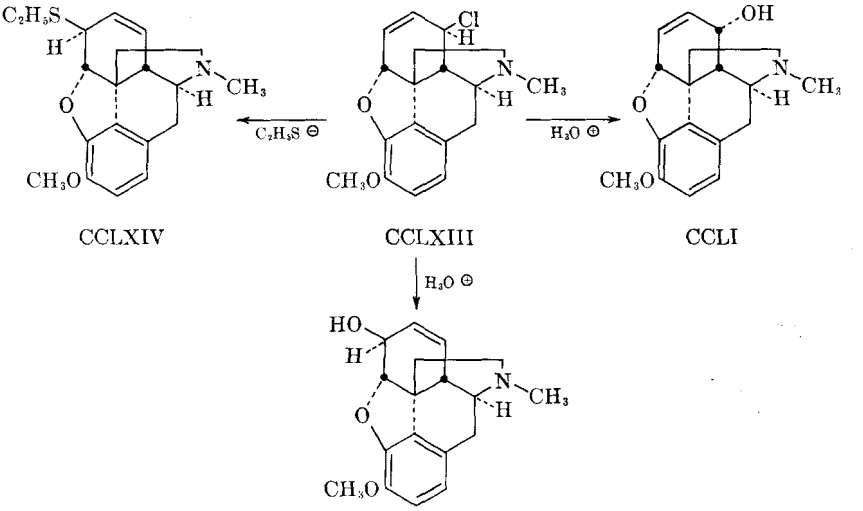
The structures just derived for the isomeric codeines permit the prediction that codeine and allopseudocodeine, in which back side approach is not hindered, will be capable of reacting by an SN_2 mechanism. Furthermore, in those cases where back side displacement is difficult or impossible, solvolysis or an $SN_{2'}$ type reaction might occur, accompanied by rearrangement. The products resulting from the action of thionyl chloride on

codeine, isocodeine and allopseudocodeine support the above hypothesis. Codeine, as has already been stated, yields α-chlorocodide. Both allopseudocodeine (CCLI) (SN_2) and isocodeine (CCXXXII) would be expected to give the same chloride CCLXIII, an expectation which is fully substantiated by the formation of β-chlorocodide from both isomers.



CCLI CCLXIII CCXXXII

A further consequence of formulating β-chlorocodide as CCLXIII with a hindered back side is that difficulty of an SN_2 reaction at C_8 might well be expected, and that if a reaction does occur the solvolysis or $SN_{2'}$ type reaction must proceed by attack at C_6. The failure of β-chlorocodide to react with methanolic potassium iodide and the formation of α-ethylthiocodide (C_6-thioether, p. 66) (CCLXIV) as the major product by ethyl mercaptide ion substantiate the validity of this argument. Also



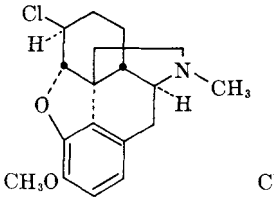
CCLXIV CCLXIII CCLI

CCXXXII

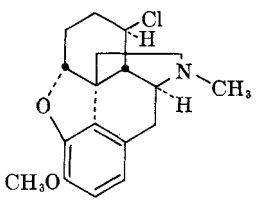
the solvolysis of β-chlorocodide in aqueous acetic acid, to the extent that it is concerted, would be expected to give principally isocodeine and possibly some allopseudocodeine. The formation of isocodeine (CCXXXII)

(55%) and allopseudocodeine (CCLI) (20%) as the main products (10% of pseudocodeine was also isolated) of this solvolysis reaction again accord with theory.

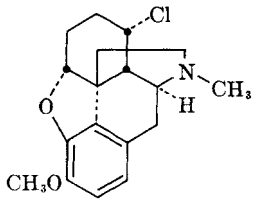
The three known dihydrochlorocodides, in which allylic rearrangement is not possible, will next be considered. Dihydro-α-chlorocodide is obtained either by catalytic hydrogenation of α-chlorocodide or by the action of phosphorus pentachloride on dihydrocodeine and has already been shown to be correctly represented by CCLXV. Dihydro-β-chlorocodide (CCLXVI) has been isolated despite experimental difficulties attendant upon the catalytic hydrogenation (hydrogenolysis of the allylic ether) of β-chloro-



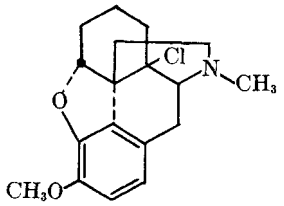
CCLXV



CCLXVI

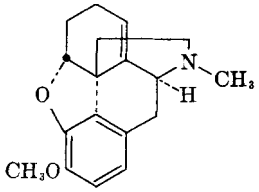


CCLXVII



CCLXVIIa

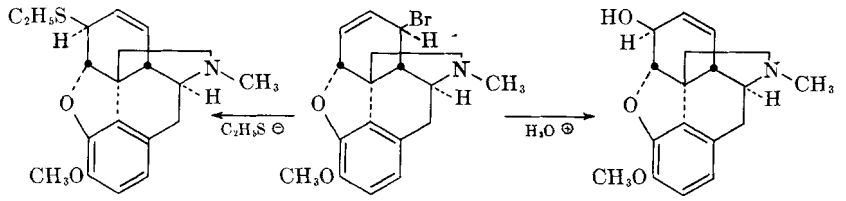
codide. The third dihydrochlorocodide is obtained from the action of phosphorus pentachloride on *either* dihydropseudocodeine or dihydroallopseudocodeine. This "8-chlorodihydrocodide" must then be CCLXVII or CCLXVIIa, on which formulations its conversion to desoxycodeine-D (CCLXVIII) by sodium and cyclohexanol (313) is understandable.



CCLXVIII

On similar grounds it is possible to assign constitutional formulas to the one bromocodide and iodocodide so far isolated. Bromocodide is

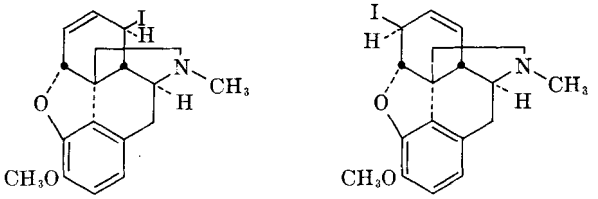
formed when codeine or pseudocodeine is treated with phosphorus tribromide (20, 281, 282). This formation of a single halocodide from codeine and pseudocodeine would be quite unexpected were it not for the fact that α-chlorocodide is unstable with respect to β-chlorocodide to which it can be isomerized under a variety of conditions (see table, p. 62). Since a bromide is always more susceptible to allylic rearrangement than the corresponding chloride, and since the known bromocodide is stable to all conditions for isomerizing the α-chlorocodide, it must be concluded that isomerization has accompanied the replacement of the hydroxyl of codeine by bromine. Thus, this bromocodide must be CCLXIX and its formation



CCLXIV CCLXIX CCLXXII

from pseudocodeine demonstrates the greater stability of the β-bromocodide over the hypothetical α-compound. Under reaction conditions comparable with those applied to β-chlorocodide, β-bromocodide yields α-ethylthiocodide (CCLXIV) and isocodeine (CCLXXII) as the major products.

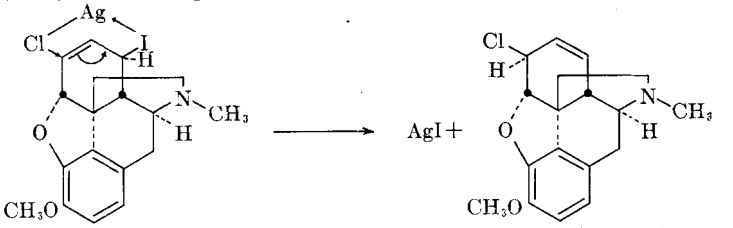
The available evidence also indicates that the only known iodocodide must be similarly constituted. This halocodide is formed by treatment of α-chlorocodide with methanolic potassium iodide (173a) and as a by-product when methylmagnesium iodide is the reagent (241). Since the same factors that make β-chlorocodide and bromocodide more stable than the respective α-halocodides would be expected to operate here, the logical constitutional formula for iodocodide would be CCLXX. A reaction



CCLXX CCLXXI

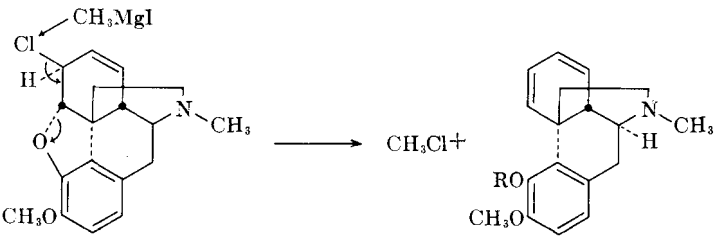
involving solvation of the chloride ion with the concerted displacement at C_8 by iodide ion, would indeed lead directly to CCLXX. In connection with its constitution, the action of aqueous methanolic silver chloride on iodocodide is very illuminating. The formation of α-chlorocodide, which

from a cursory examination might appear unexpected, provides strong support for CCLXX. Obviously it is an internal reaction, since if it were a concerted solvolysis the product would be a methyl ether and not α-chlorocodide. Since α-chlorocodide is readily isomerized to the more stable β-isomer, the isolation of α-chlorocodide in this case shows that it is the primary product of the reaction. This halogen exchange reaction must therefore involve an $SN_{i'}$ type reaction, limiting the constitution of iodocodide to either CCLXX or CCLXXI. Structure CCLXXI is precluded by the conversion (CH_3OH + KI) of β-chlorocodide to iodocodide since such a constitutional formula for iodocodide would imply that this anionic displacement reaction proceeds without inversion or rearrangement. On CCLXX a special sort of reaction ($SN_{i'}$), dependent upon the allylic system, may be envisaged as follows:



α-Chlorocodide

The reported result (173a) of the solvolysis of iodocodide seems to argue in favor of CCLXXI and to contradict the above argument. It is reported that pseudocodeine rather than isocodeine is the principal product. Small and his collaborators may have been misled by their conviction that iodocodide is the analog of α-chlorocodide, a conclusion prompted by the conversion of both halocodides by methylmagnesium iodide to desoxycodeine-A (CCLXXII) (241) and by the contrasting stability of β-chlorocodide to the same reagent. In fact the formation of some iodocodide



CCLIII

R=H, −MgI

CCLXXII

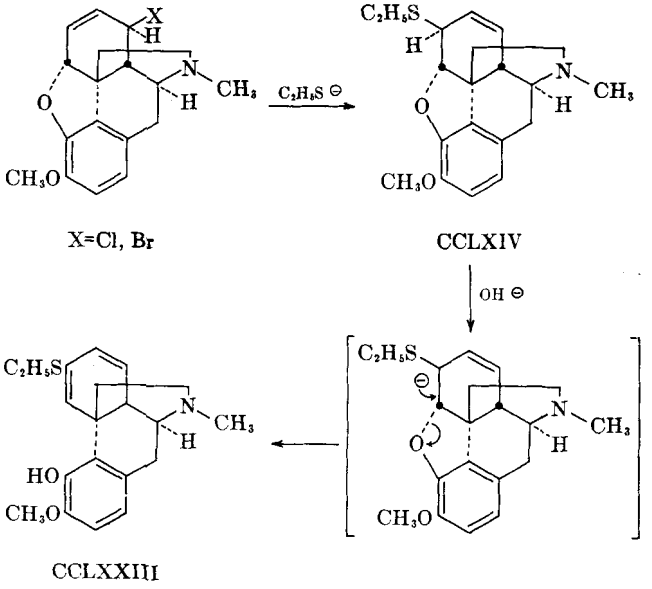
when α-chlorocodide is treated with methylmagnesium iodide has been taken by these workers as evidence that the iodo compound is an inter-

mediate in the formation of desoxycodeine-A. Their own results, when scrutinized more closely, argue against such a conclusion. If iodocodide were an intermediate in this reaction, its conversion to desoxycodeine-A should proceed with at least equal facility as that of α-chlorocodide. This, however, is not the case (241) and the only other possible conclusion is that the iodocodide is a byproduct resulting from the competing action of iodide ion (from MgI_2) on α-chlorocodide. Consequently, the facts which were intended to demonstrate the analogous constitution of iodocodide and α-chlorocodide actually support structure CCLXX for iodocodide. The validity of the characterization of the hydrolysis product of iodocodide as pseudocodeine is open to some question. The hydrolysis product was isolated as its hydrochloride but no data were reported that might serve to substantiate the claim that it was pseudocodeine. The foregoing considerations make it likely that the main solvolysis product is actually isocodeine hydrochloride.

It is a matter of interest that the optical rotations of β-chlorocodide, bromocodide and iodocodide are in agreement with the proposed structures since they show a continuous increase from β-chlorocodide (−10°) to bromocodide (+56.5°) and from the latter to iodocodide (+136.5°).

7. The Thiocodides

These substances, as already described, result from the attack of alkylmercaptide anions on the halocodides. While others have been prepared, the ethylthiocodides (ethyl mercaptan and sodium hydroxide)

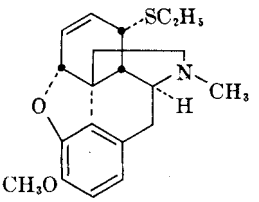


X=Cl, Br

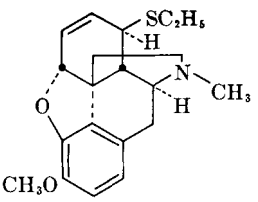
CCLXIV

CCLXXIII

have been most extensively studied. β-Chlorocodide and bromocodide yield α-ethylthiocodide, which then must be represented by CCLXIV. The thioether grouping was located at C_6 by relating the compound to thebainone. Heating with base isomerized CCLXIV to the phenolic β-ethylthiocodide CCLXXIII, and acid hydrolysis of the enol thioether of CCLXXIII completed the conversion to thebainone. Formation of the anion on C_6 is facilitated by the thioether grouping, which, because



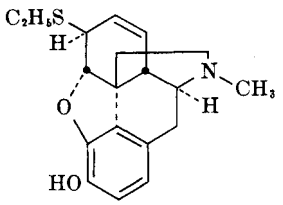
CCLXXIV



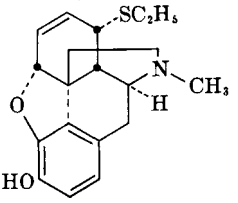
CCLXXV

of the possibility of expansion of the sulfur shell, leads to a nonstereospecific elimination of the oxide bridge (contrast isocodeine methyl ether).

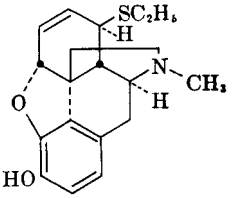
γ-Ethylthiocodide, a third isomer, occurs as a byproduct in the preparation of α-ethylthiocodide and must be CCLXXIV. When α-chlorocodide is treated with ethyl mercaptan and alkali δ-ethylthiocodide is



CCLXXVI



CCLXXVII

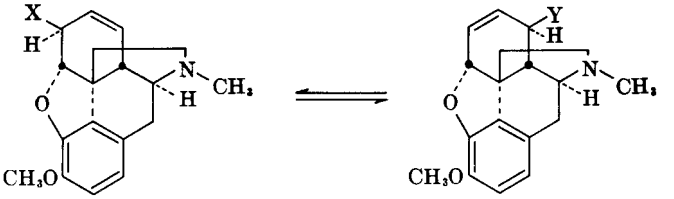


CCLXXVIII

formed by a reaction which is obviously analogous to the conversion of α-chlorocodide to pseudocodeine. Thus δ-ethylthiocodide is represented by CCLXXV. The corresponding α-, γ-, and δ-ethylthiomorphides are all known and may be represented respectively by CCLXXVI–CCLXXVIII.

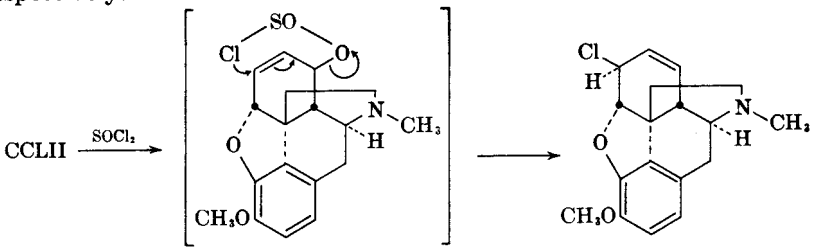
A correlation of the dependence of the types of substitution reactions with the stereochemistry of the various codeine isomers is appropriate here. In those cases where back side approach of anions is unhindered a normal SN_2 displacement is to be expected. The conversions of codeine and allopseudocodeine respectively to α- and β-chlorocodide clearly illustrate this point. When the configuration, as in isocodeine and pseudo-

codeine is not compatible with back side anion approach, displacement is accompanied by rearrangement in both solvolytic and SN_2' type reactions. It should be noted, however, that a special type of internal displacement reaction (SN_i') may operate in those cases (isocodeine, pseudocodeine and iodocodide) where back side approach is hindered and there is a suitably located double bond. Typical examples already cited which may fall into



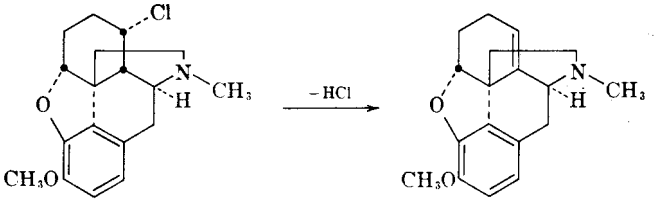
X=OH, Cl Y=OH, Cl, Br, I, SC_2H_5, OR

this category are the conversion of pseudocodeine (CCLII) and iodocodide to α-chlorocodide (CCLIII) by thionyl chloride and silver chloride respectively.



CCLIII

A significant reaction of the dihydrocodeine series of bases that should still be considered is the conversion of dihydropseudocodeine and dihydroallopseudocodeine to the same dihydrochlorocodide. If it is an 8-chloro compound it must be CCLXVII since elimination of the elements of



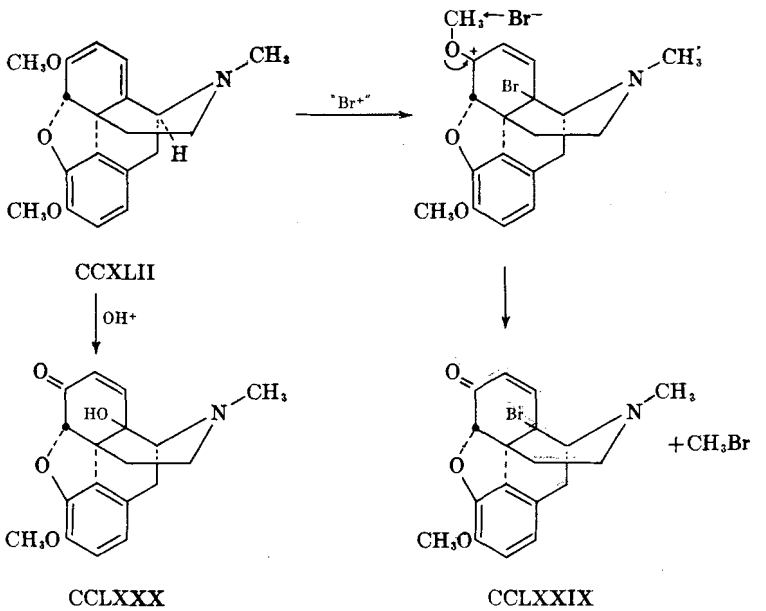
CCLXVII CCLXVIII

hydrogen chloride gives desoxycodeine-D (CCLXVIII). The fact that CCLXVII is the hindered chloride makes the result unexpected and worthy

of further investigation since a 14-chloro structure for the compound certainly cannot be excluded, and it is not easy to rationalize the retention of configuration which would have to be postulated in the case of dihydroallopseudocodeine. The formation of the less hindered of the two possible 14-chloro compounds from either of the two epimeric alcohols, via dehydration followed by addition of hydrogen chloride, would, however, be readily explicable.

These codeine derivatives, to which stereochemical formulas have now been assigned, would seem to be good objects of kinetic investigation: they are readily available, optically active crystalline solids that can be obtained in a high state of purity. Such investigations would prove most valuable in deciding between various possible mechanisms.

Two further substances, bromocodeinone and hydroxycodeinone, will now be considered. The formation of bromocodeinone (CCLXXIX), as shown below, must involve attack at C_{14} of the methoxydiene system of thebaine (CCXLII) by the equivalent of a bromine cation. In a similar manner attack at C_{14} by the equivalent of OH^+ (H_2O_2 in HOAc) would

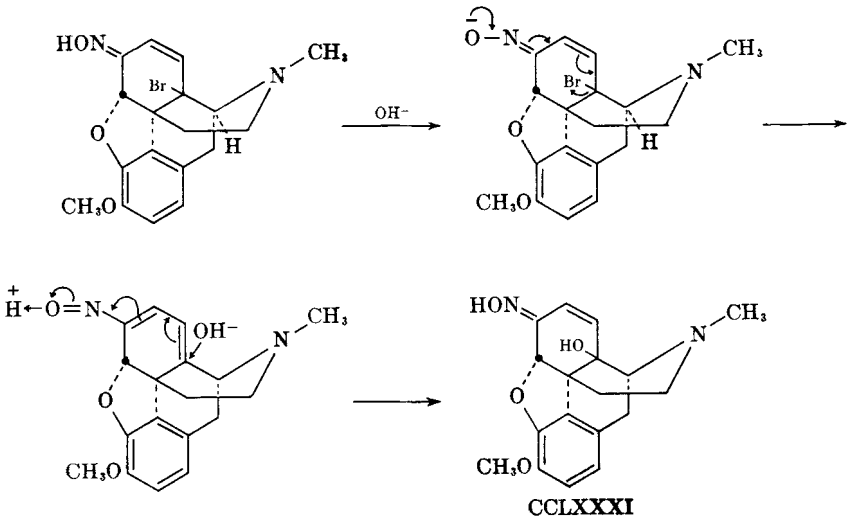


CCLXXX CCLXXIX

lead to hydroxycodeinone (CCLXXX). Since the attacking reagent must approach from the less hindered side, as shown, the bromine and the hydroxyl group must be *cis* to the ethanamine chain.

Bromocodeinone is unaffected by bases but with hydroxylamine it is converted to hydroxycodeinone oxime (CCLXXXI) (128, 319, 321). This

transformation is not surprising when formulated as shown below. If such a formulation is correct, the substitution of bromine by hydroxyl proceeds with overall retention of configuration.



CCLXXXI

V. Rearrangement and Elimination Reactions

(By Gilbert Stork)

Progress in the evolution of the constitution of morphine was frequently interrupted by the occurrence of complex rearrangements. The molecular cartwheels executed by this substance in its varied deep seated rearrangements have earned for it billing as "star performer among molecular acrobats" (349). A few typical examples are outlined briefly below illustrating the paths followed and the underlying similarity and *ex post facto* simplicity of the changes involved.

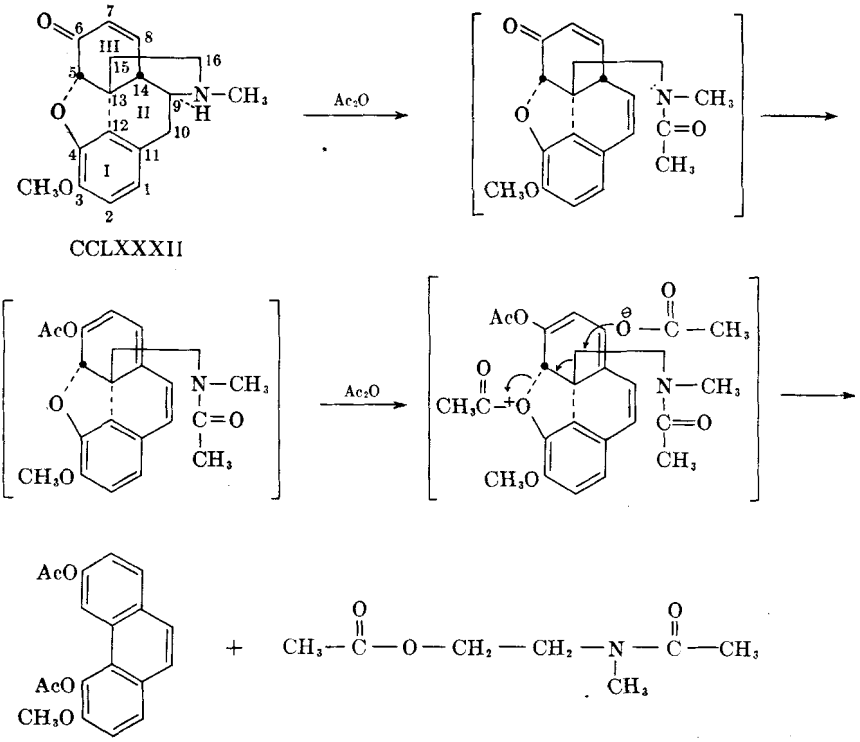
Only those reactions involving gross structural changes will be considered here. This excludes the rearrangements involved in the formation and reaction of the halocodides which were considered in the previous section. Those reactions in which the ethanamine chain is lost are considered first. Then, those rearrangements in which that structural element is retained will be examined. Finally, some reduction reactions involving the cleavage of the oxide bridge will be critically reviewed.

1. Rearrangements with Loss of the Side Chain

The compounds in which complete loss of the ethanamine chain is expected to occur most readily are those in which the nitrogen atom is detached from C_9. This is especially true in the case of acid catalyzed rearrangements when utilization of the bonding electrons between C_{13} and

C_{15} to meet a contiguous electron deficiency is facilitated by participation of the unshared electron pairs of the nitrogen atom, with the formation of a cyclic imonium structure.

Several examples of the elimination of the side chain in base catalyzed reactions have already been cited (*e.g.*, the formation of β-ethoxyethyldimethylamine and methylmorphol from β-methylmorphimethine and sodium ethoxide). Examples of elimination by acetolysis have already been given for which a push-pull mechanism is easily envisaged as in the formation of CCLXXXIII from codeinone (CCLXXXII).



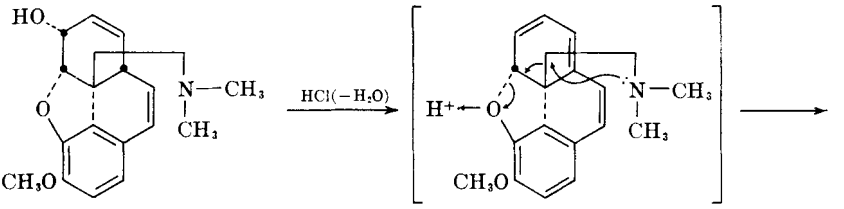
CCLXXXII

CCLXXXIII

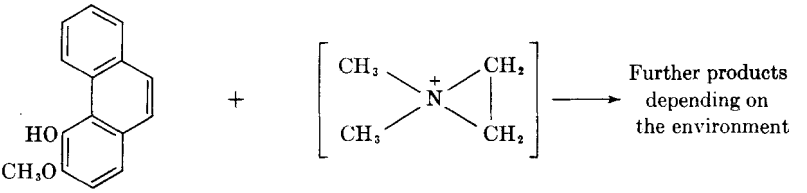
These reactions involving the concerted elimination of the side chain and rupture of the oxide bridge derive much of their driving force from the concomitant aromatization of the ring system. A good illustration of the required participation of the nitrogen atom in the acid catalyzed elimination of the side chain is the conversion of α-methylmorphimethine (CCLXXXIV) to methylmorphol by hydrochloric acid.

When the bond from C_9 to the nitrogen atom is still intact, as in codeine,

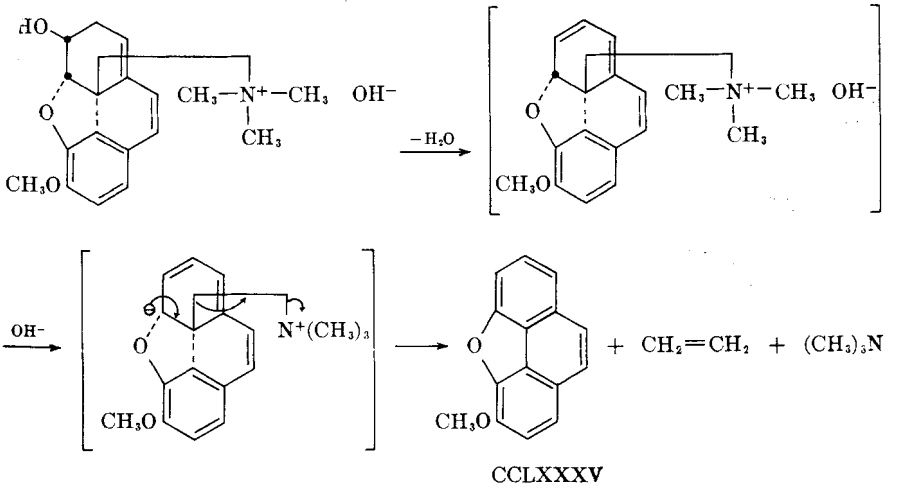
the rearrangement takes an altogether different course (formation of apocodeine) because of the inability of the nitrogen to participate in stabilizing the C_{15} cation which would be formed by utilization of the C_{13}-C_{15} bonding electrons.



CCLXXXIV



A different type of elimination of the side chain occurs in suitably constituted quaternary salts in which electron attraction is provided by the positive charge on the nitrogen atom. This is illustrated below in the formation of methylmorphenol (CCLXXXV) and ethylene from β-(or α-)-methylmorphimethine methohydroxide by strong bases (see page 58).

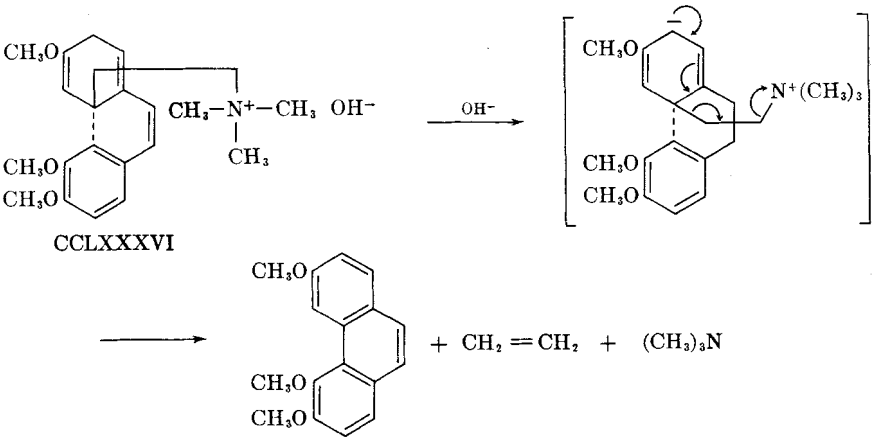


CCLXXXV

A mechanism such as that depicted above rules out one involving the

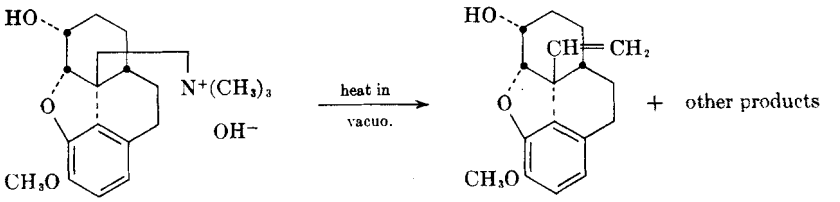
consecutive Hofmann degradation of the quaternary base and elimination of ethylene and water from the postulated vinyl intermediate.

Another example (see p. 105) of this type of elimination is the decomposition of the methohydroxide of the des base of phenolic dihydrothebaine methyl ether (CCLXXXVI) to thebaol methyl ether.

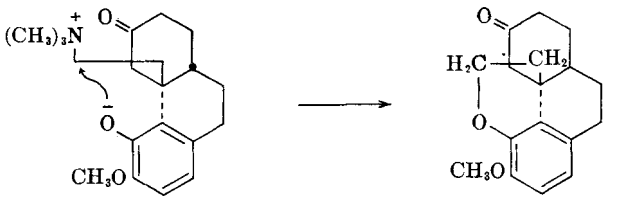


CCLXXXVI

This extrusion of the side chain from quaternary salts of methine bases, however, is observed only when ring III contains elements which permit



CCLXXXVII



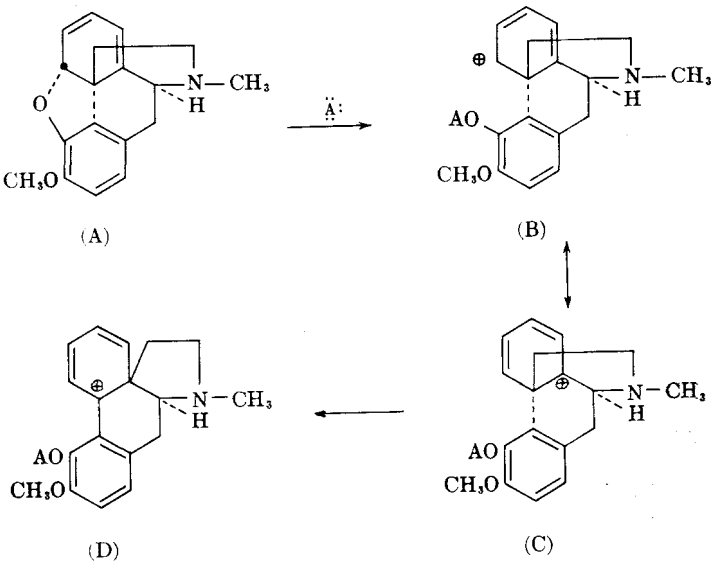
CCLXXXVIII CCLXXXIX

the ready formation of a carbanion that in turn can be stabilized by the path indicated in the foregoing examples. If this condition is not met, normal Hofmann elimination is observed as in the case of the metho-

hydroxide (CCLXXXVII) of the dihydro-des base from dihydrocodeine. A system may be envisaged, however, where an alternate mechanism competes with or even supplants the expected elimination reaction in the stabilization of the molecule as is illustrated by the degradation of the methohydroxide (CCLXXXVIII) of the dihydro derivative of des-*N*-methyldihydrothebainone to thebenone (CCLXXXIX).

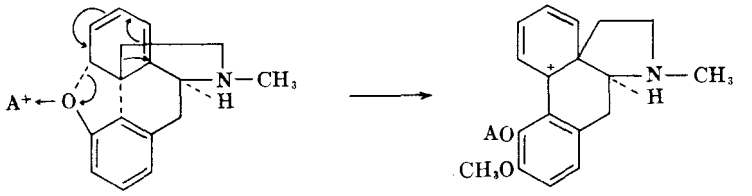
2. Rearrangements with Retention of the Side Chain

Some of the most interesting rearrangements of the morphine alkaloids fall into this category. The compounds which undergo such a change have two structural features in common: they all possess an allylic ether bridge system which is susceptible to cleavage by acid reagents and secondly the nitrogen atom is invariably linked to C_9 so that it is incapable of participating in a reaction parallel to those observed in the acid catalyzed elimination of the side chain. In all the rearrangements grouped under this



heading there is the possibility of distributing the charge created by rupture of the allylic oxide bridge in such a way that migration of the chain takes precedence over the elimination reaction. For clarity this is illustrated by generalized formulas in a stepwise fashion as shown above although the process by which (A) goes to (D) is undoubtedly a concerted

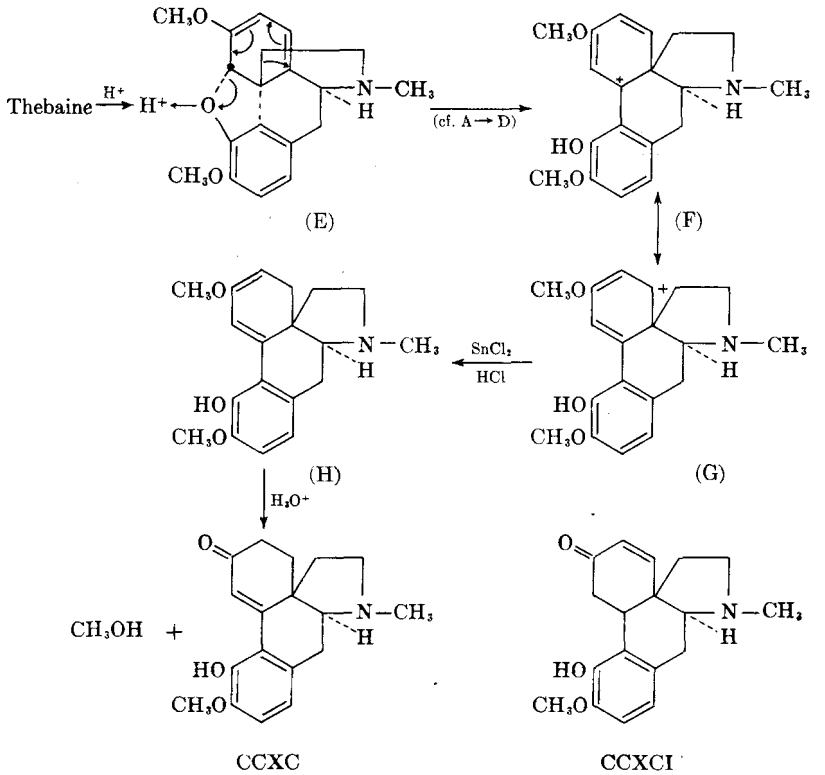
one which may be depicted as:



(A)

The subsequent fate of the intermediate (D) depends on the specific reaction conditions so that such diverse structures as metathebainone, apomorphine, morphothebaine, thebenine and the phenyldihydrothebaines may be formed.

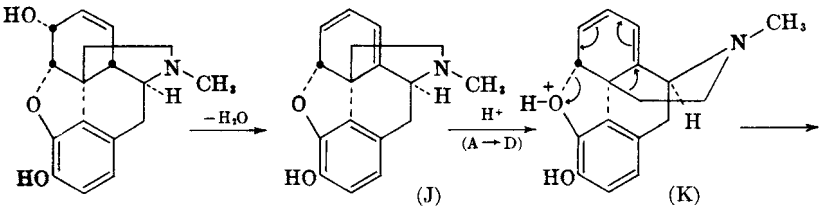
a. Metathebainone (CCXC). This isomer of thebainone is formed by the reduction of thebaine with a solution of stannous chloride in hot concentrated hydrochloric acid. This transformation is shown as follows:



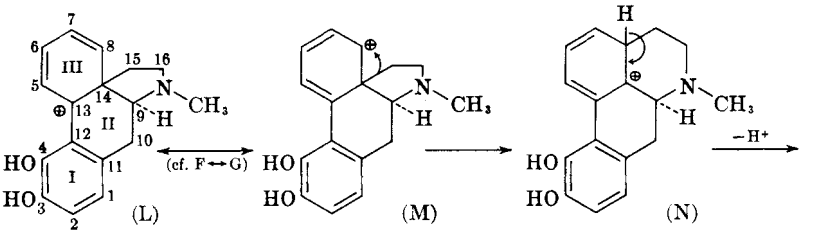
Reduction of the resonating cation (F⟷G) could have given the alternate product, CCXCI, but the formation of CCXC is not surprising as it involves the more stable transition state.

In the absence of some external electron donor (reducing agent) to supply electrons to a cation such as (G) they may be derived from some center within the molecule with further rearrangements as will be exemplified in the sequel.

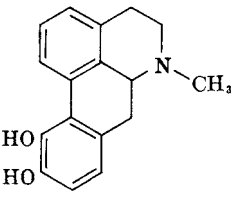
b. Apomorphine. The action of concentrated hydrochloric acid upon morphine (CCXCII) (or codeine) leads to rearrangement to apomorphine (CCXCIII) (or its methyl ether, apocodeine).



CCXCII (J) (K)



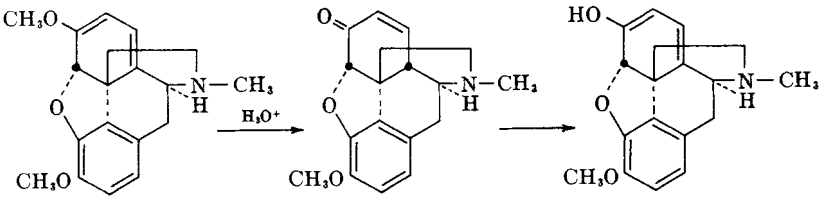
(L) (M) (N)



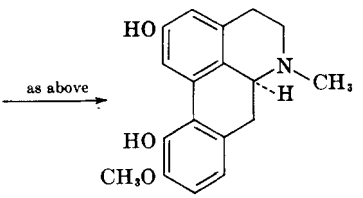
CCXCIII

This formation of apomorphine illustrates one possible way in which electron deficiency in (M) (cf. G above) can be made up by migration of the chain as shown in (M) → (N), which leads finally to aromatization of ring III. The identical process is involved in the formation of morphothebaine (CCXCIV) by the action of hot concentrated hydrochloric acid on thebaine or codeinone (CCLXXXII).

Another way in which electron deficiency in an intermediate of type (L←→M) could be accommodated is by the utilization of the C_9-C_{14} bond ing electrons and aromatization of ring III, a process which is favored by

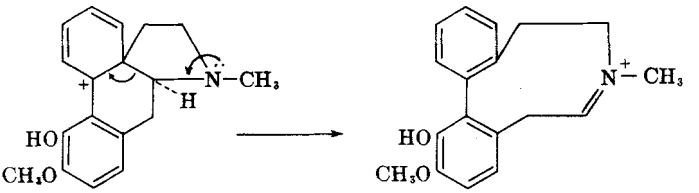


CCLXXXII



CCXCIV

dilute acid conditions since withdrawal of electrons from the vicinity of the nitrogen atom is unlikely in those molecules in which the nitrogen has a formal positive charge (the result in such a case as we have already seen is migration of the chain and formation of substances of the apomorphine type). If the acid is sufficiently dilute to enable enough molecules to be present as the free base structures of type (L) will be changed to (O):

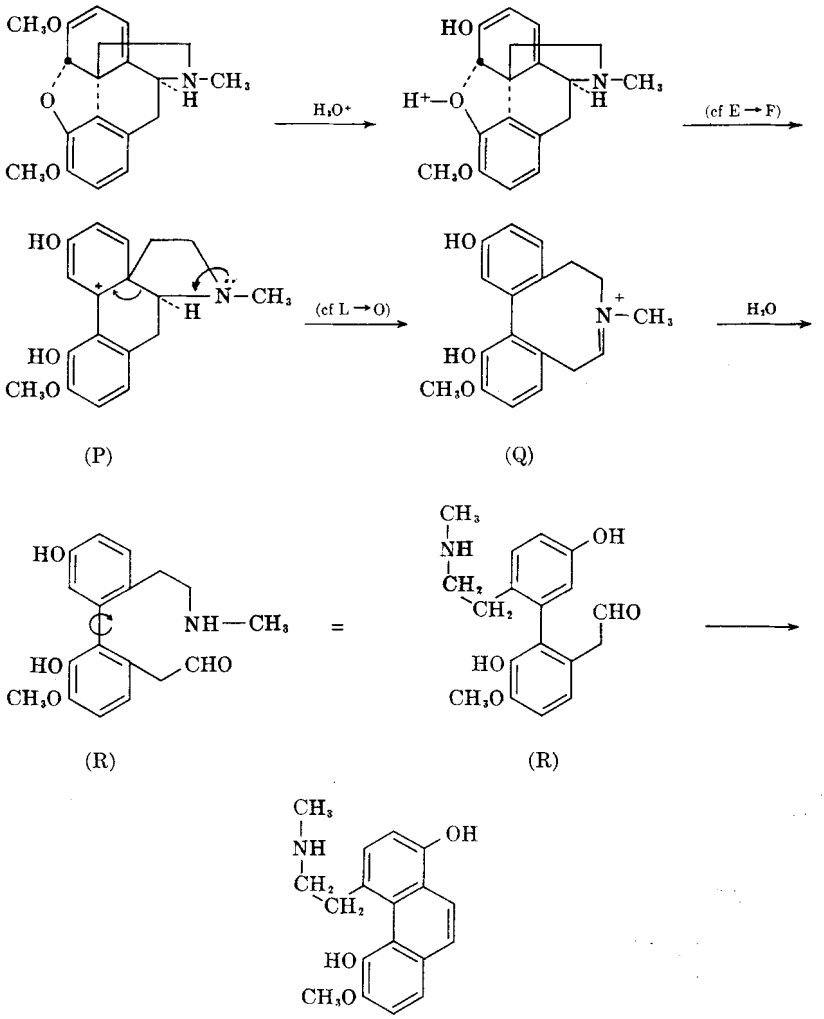


(L) (O)

The further fate of intermediate (O) will depend upon the environment. This is illustrated by the formation of thebenine and the phenyldihydrothebaines.

c. Thebenine. The reaction of thebaine or codeinone with dilute hydrochloric acid proceeds to an intermediate similar to (O) which in

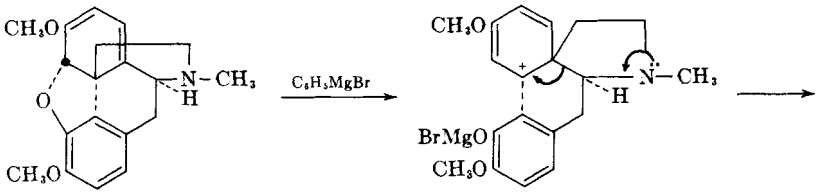
water will be solvated to form an amino aldehyde (R), which then undergoes intramolecular ring closure to thebenine (CCXCV).



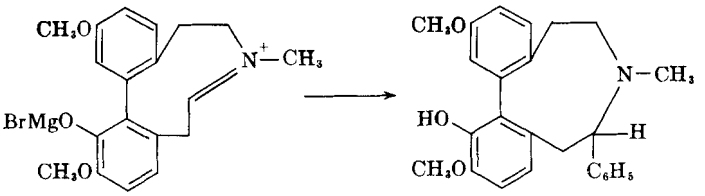
CCXCV

d. α- and δ-*Phenyldihydrothebaines* (*CCXCVI*). The fate of an intermediate of the type of (O), as mentioned above, depends on the medium. In the reaction of thebaine with phenylmagnesium bromide, the inter-

mediate (T) pictured below can add a phenyl anion as follows:



(S)



(T) CCXCVI

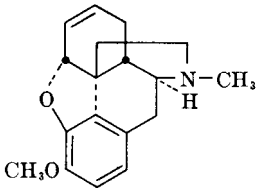
Since an asymmetric center is created by the fusion of a phenyl group in (T) to form CCXCVI, two optical isomers are to be expected in addition to those demanded by the noncoplanarity of the biphenyl system in CCXCVI. Four isomers are known and designated (see p. 97) as (+)α-, (+)δ-, (−)α-, and (−)δ-phenyldihydrothebaines.

The schematic picture presented here for the course of the reaction, although straightforward, does not do justice to the extensive and excellent experimental work done by Small on the constitution of the phenyldihydrothebaines, a problem which owes its final solution to the brilliant structural deductions of Sir Robert Robinson.

3. Reductive Cleavage of the Oxide Bridge

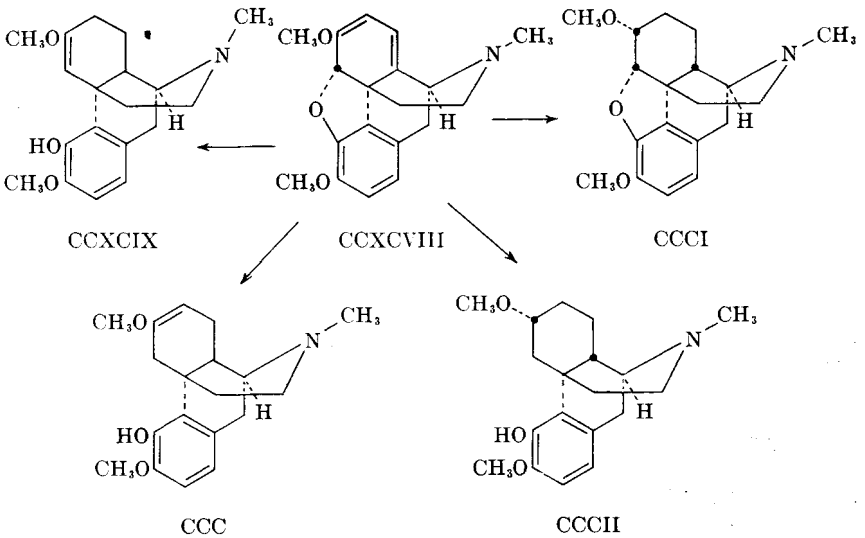
The susceptibility of allylic ethers to hydrogenolysis leads us to expect similar reactions on the oxide bridge of those morphine derivatives containing a Δ^6-double bond (*e.g.*, CCXCVII). The conversion of β-chlorocodide, pseudocodeine and allopseudocodeine to tetrahydrodesoxycodeine are examples illustrating this rupture of the oxide bridge. The results obtained in the reduction of thebaine deserve, however, closer scrutiny as they have in some instances been misinterpreted. Catalytic hydrogenation of thebaine not involving saturation of the enol ether double bond will be examined first and will be followed by a discussion of the

action on this base of such reducing agents as sodium and alcohol and lithium aluminum hydride.



CCXCVII

a. Catalytic Hydrogenation of Thebaine. Small and Browning (310) have reported that in neutral medium thebaine (CCXCVIII) is reduced to a separable mixture of 45% of dihydrothebainone-$\Delta^{5(6)}$-methyl enolate (CCXCIX), 31% of tetrahydrothebaine (dihydrocodeine methyl ether) (CCCI) and 18% of dihydrothebainol-6-methyl ether (CCCII). As will be indicated later, Small's characterization of the major product as CCXCIX is wrong and structure CCC is in better accord with the facts.

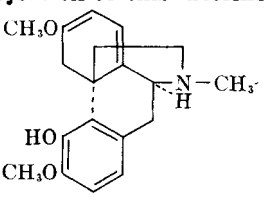


CCXCIX CCXCVIII CCCI

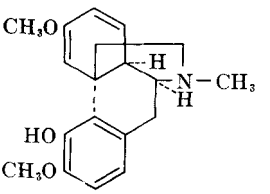
CCC CCCII

The isolation of these three products from the hydrogenation of thebaine is not surprising and might lead to the inference that CCC is an intermediate in the formation of CCCII. This enol ether is, however, resistant to further hydrogenation under these conditions so dihydrothebainol-6-methyl ether probably arises from some intermediate such as CCCIII. The possibility of CCCIII being the intermediate in the formation of CCCII was rejected by Small on the ground that this structure had

already been assigned to phenolic dihydrothebaine, a base which cannot be hydrogenated under these conditions to dihydrothebainol-6-methyl ether. Objection to this intermediate can now be ruled out since phenolic



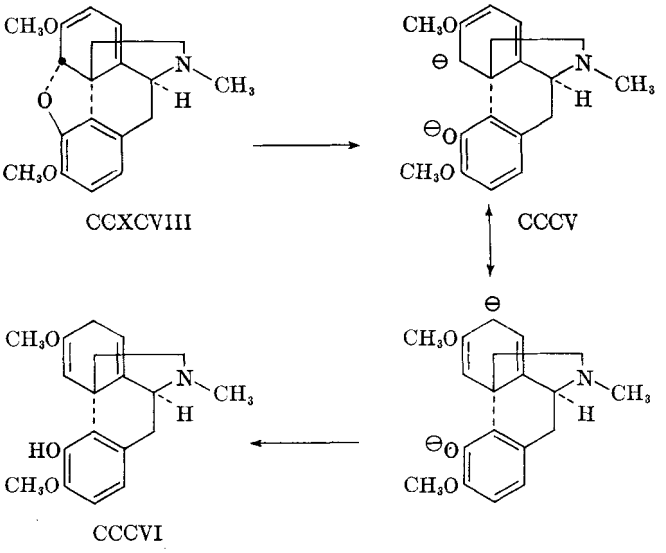
CCCIII



CCCIV

dihydrothebaine, as will be shown later, does not have the structure CCCIII. The experimental work of Schmid and Karrer further substantiates our hypothesis. They have prepared a "β-dihydrothebaine" (see p. 203) which can be hydrogenated to dihydrothebainol-6-methyl ether, and to which they assigned structure CCCIV (see p. 203), basing their argument on the assumption that phenolic dihydrothebaine is CCCIII. The following work will clearly show that the so-called β-dihydrothebaine is actually CCCIII.

b. Sodium and Alcohol Reduction of Thebaine. Phenolic dihydrothebaine was first prepared by Freund (89) by the action of sodium on an alcoholic solution of thebaine (a 95% yield is obtained when sodium and liquid ammonia are the reducing agents (354a)). The formulation by Small and Browning of phenolic dihydrothebaine as CCCIII is now known to be incorrect and the course of the reduction can be represented as shown below, resulting in structure CCCVI for phenolic dihydrothebaine (355).

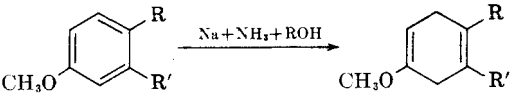


CCXCVIII

CCCV

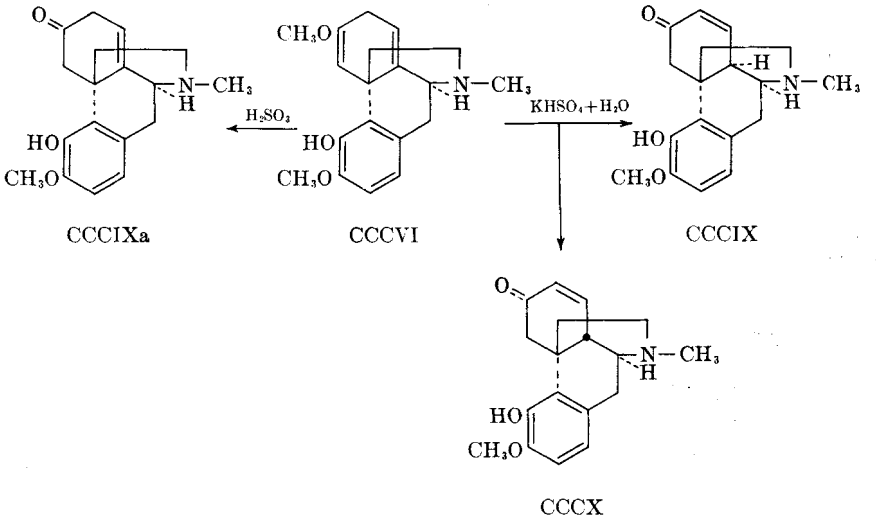
CCCVI

The addition of electrons to the bridge oxygen with the attendant formation of a stable phenoxide anion yields phenolic dihydrothebaine (CCCVI) which in contrast to CCCIII would be resistant to further reduction by sodium and alcohol. Ultraviolet and infrared absorption spectra are in keeping with this structure (355). Birch (356) has demonstrated that substituted dihydroanisoles of the type CCCVIII are readily prepared by reduction of CCCVII by sodium in liquid ammonia in the presence of a



CCCVII CCCVIII

proton donor. These nonconjugated dienol ethers are readily hydrolyzed under mild conditions to β,γ-unsaturated ketones, but if more vigorous conditions are employed the double bond usually migrates into a position of conjugation with the ketone carbonyl. The results of Small's and Browning's hydrolysis experiments are in accord with Birch's observations. Under mild conditions (warm sulfurous acid) they report that it is possible to obtain α-thebainone, which they formulated as a β,γ-unsaturated ketone (CCCIXa). Furthermore, Small's hydrolysis of phenolic dihydrothebaine with aqueous potassium acid sulfate to a mixture of α-thebainone (a trace),



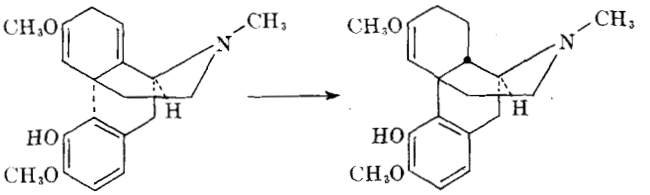
CCCIXa CCCVI CCCIX

CCCX

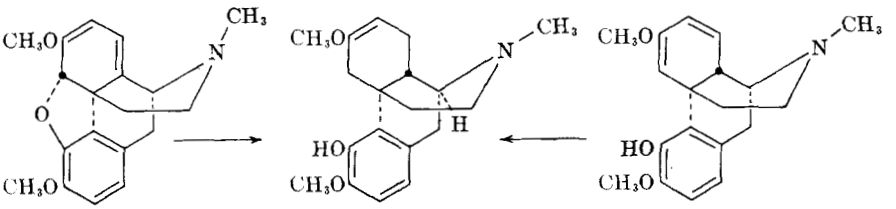
thebainone (5%) (CCCX) and β-thebainone (81%) (CCCIX) completes the analogy with Birch's hydrolysis experiments.

Small and Browning have catalytically hydrogenated phenolic dihydrothebaine (CCCVI) to an enol ether of dihydrothebainone presumed to

be $\Delta^{6(7)}$-dihydrothebainone methyl enolate (CCCXII) but which must now be assigned the $\Delta^{5(6)}$-structure (CCCXI). The $\Delta^{5(6)}$-structure postulated for the different enol ether formed by catalytic hydrogenation of thebaine



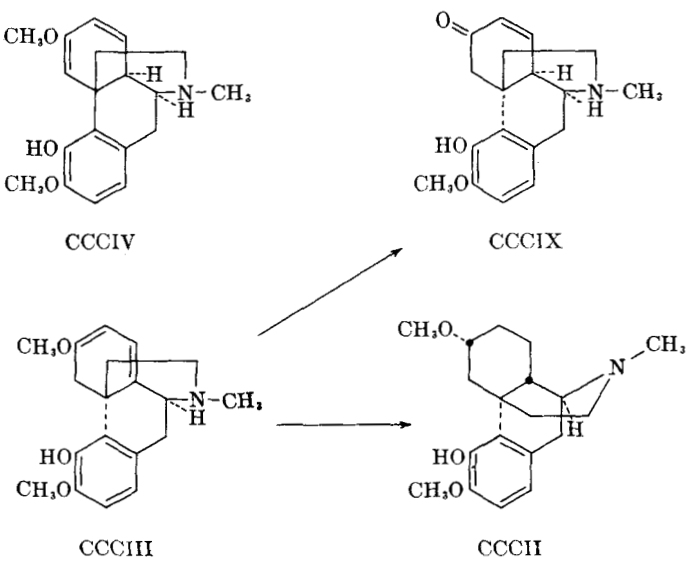
CCCVI CCCXI



CCXCVIII CCCXII CCCXIII

(CCXCVIII) in neutral medium and by the sodium and alcohol reduction of $\Delta^{5(7)}$-thebainone enol methyl ether (CCCXIII) must be replaced by the isomeric $\Delta^{6(7)}$-structure CCCXII.

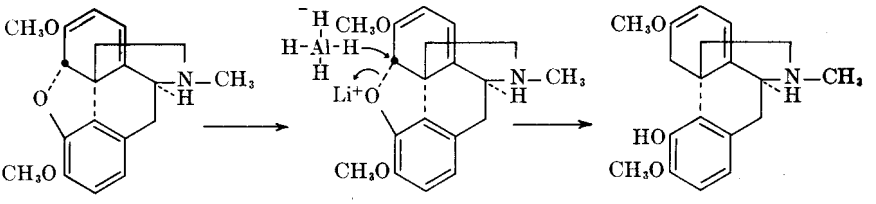
c. Lithium aluminum hydride reduction of thebaine. Recently Schmid



CCCIV CCCIX

CCCIII CCCII

and Karrer (351a) have described a β-dihydrothebaine obtained from the lithium aluminum hydride reduction of thebaine. The structure CCCIV which these workers have proposed for this compound is not correct, and must be replaced by CCCIII (355). The claim (351a) that the isolation of "β-dihydrothebaine" throws light on the mechanism of the formation of the phenyldihydrothebaines is therefore without foundation. The term "β-dihydrothebaine" is a misnomer, and the compound, which has the structure formerly assigned to phenolic dihydrothebaine, may be called $\Delta^{6,8}$-phenolic dihydrothebaine. In accordance with formula CCCIII the compound has ultraviolet and infrared spectra similar to those of thebaine, CCXCVIII, is reduced catalytically to dihydrothebainol-6-methyl ether, and is hydrolyzed by $KHSO_4$ solution to β-thebainone, CCCIX. The formation of $\Delta^{6,8}$-phenolic dihydrothebaine may be represented simply as the cleavage of an allylic phenol ether, a reaction which is related to the carbon oxygen cleavage observed with certain sulfonic esters:



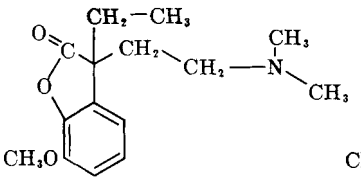
CCXCVIII CCCIV CCCIII

The fact that there is no rearrangement such as occurs in the formation of the phenyldihydrothebaines is simply a reflection of the fact that lithium aluminum hydride, although it is capable of functioning as an electron acceptor (either through Li^+ or AlH_3), is nevertheless much less active in that capacity than magnesium bromide (compare the lack of rearrangements in the reduction of epoxides with lithium aluminum hydride to their frequent occurrence with Grignard reagents).

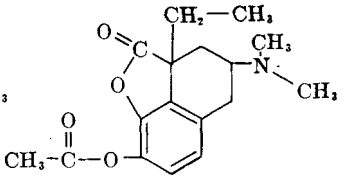
VI. The Synthesis of Related Products

A number of interesting model compounds such as CCCXV and CCCXVI have been synthesized (357–362), but this work has been overshadowed by the simplification and extension of Grewe's classical *N*-methylmorphinane synthesis (363) to tetrahydrodesoxycodeine and to 3-hydroxy-*N*-methylmorphinane whose analgesic activity is comparable with that of morphine (351b, 364). In analogy with similar polar additions to ethylenes, cyclization probably proceeds by a *trans* mechanism and leads to a *cis* juncture between rings II and III but this has not yet been proved. *N*-Methylisomorphinanes, the *N*-methylmorphinanes with a *trans* juncture (?) are byproducts of the above synthesis but are the main products from

a reaction sequence which involves the primary addition of butadiene to various cyanomethyl-1,2-naphthoquinones.



CCCXV



CCCXVI

Failure of 3,4-dimethoxybenzyl chloride to form a Grignard (354) has stimulated the development of two new preparations for the dimethoxybenzyltetrahydroisoquinoline, CCCXXIII (R = R′ = OCH_3), needed for the synthesis of tetrahydrodesoxycodeine. In both cases the optimum conditions for each step were determined on the unsubstituted member of the series and then applied to the 3-methoxy- and 3,4-dimethoxy-derivatives. The modified Grewe procedure (354) involved the reaction of the lithium tetrahydroisoquinoline, CCCXX, with various benzaldehydes (benzaldehyde, anisaldehyde and veratraldehyde). In the case of veratraldehyde, the respective carbinol was obtained in 54% yield. Reduction of this carbinol to the desired benzyl derivative CCCXXIII (R = R′ = OCH_3) has been achieved in a variety of ways (HBr + Zn, 83%; oxidation to and Clemmensen reduction of the respective ketone) but the most satisfactory method (85%) involved a disproportionation (Pd-C + tetralin) of the carbinol and Clemmensen reduction of the mixture of CCCXXIV (R = R′ = OCH_3) and CCCXXIII (R = R′ = OCH_3) (Chart III). Furthermore it was found possible to eliminate one step in the quantitative reduction of the methobromide of CCCXXIII (R = R′ = OCH_3) to CCCXXVI (R = R′ = OCH_3) if a trace of iodine was added with the Adams' catalyst. Partial demethylation of CCCXXVI (R = R′ = OCH_3) at C_3 and simultaneous ring closure at C_2 and C_6 by hydrochloric acid at 120° afforded a separable mixture of isomeric hydroxymethoxy-*N*-methylmorphinanes. The isomer with cryptophenolic properties (see p. 77) was assigned structure CCCXXVII (R = OCH_3, R′ = OH) and proved to be identical with *dl*-tetrahydrodesoxycodeine (Clemmensen reduction of sinomenine and dihydrothebainone (ref. 34, p. 228)). Resolution with *d*-tartaric acid completed the synthesis of natural tetrahydrodesoxycodeine.

The alternate synthesis (Chart III, method B) developed by Schnider and Hellerbach (351b) involves the synthesis of Δ^1-cyclohexenylethylamine (CCCXXVIII) and the cyclization of its phenylacetamide derivative by a Bischler-Napieralski type ring closure. The most satisfactory preparation

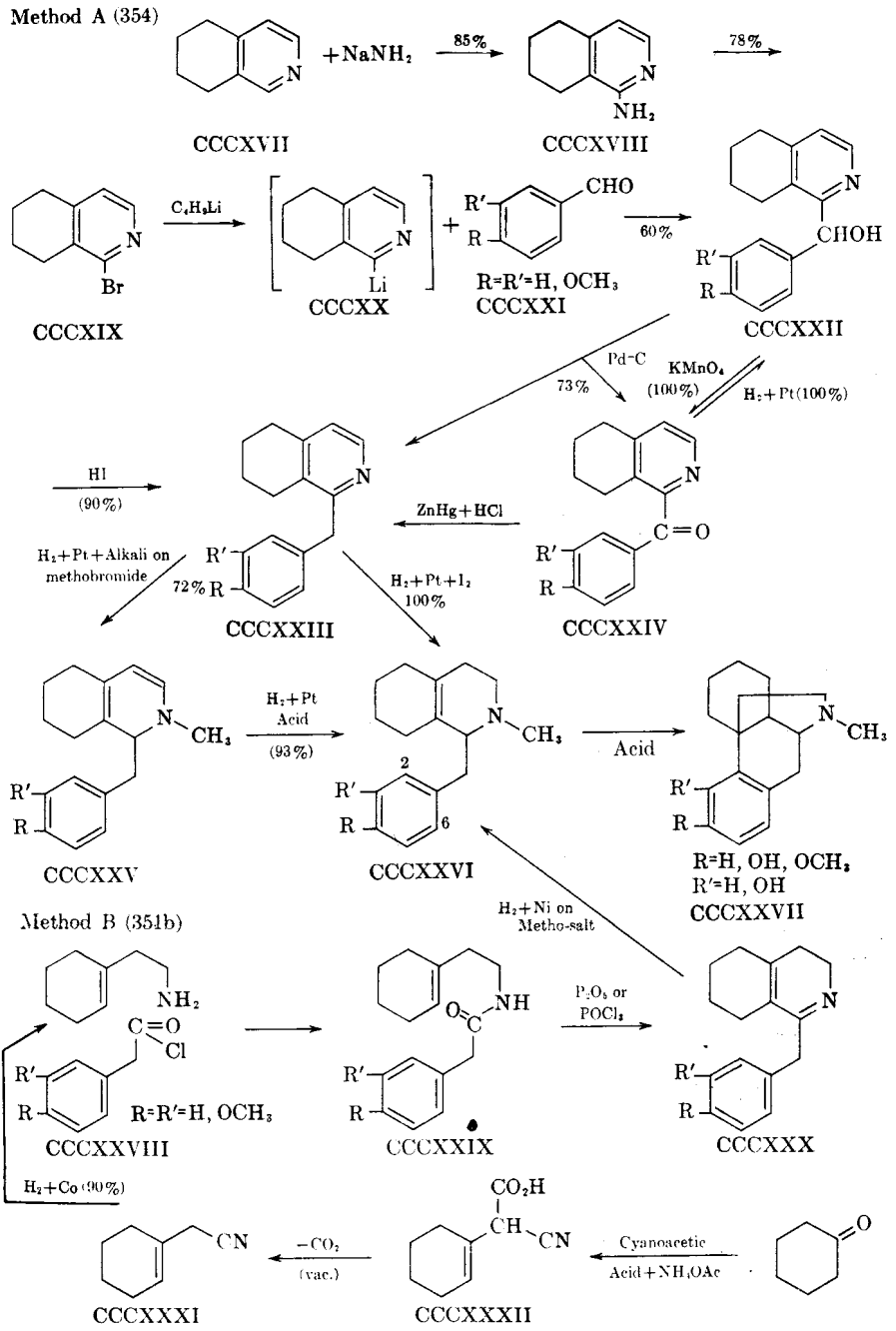


CHART III

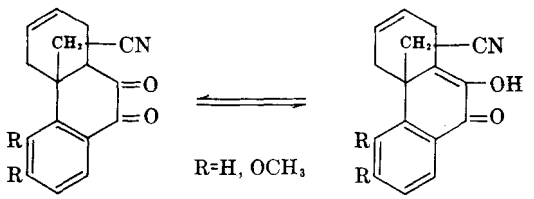
ALTERNATE MORPHINANE SYNTHESES*

*All yields refer to the synthesis of *N*-methyl-morphinane (R – R'=H).

of this amine is by the condensation (ammonium acetate) of cyanoacetic acid with cyclohexanone, decarboxylation of CCCXXXII in vacuum and reduction of the cyanide CCCXXXI with Raney cobalt. Cyclization of its homoveratric amide, CCCXXIX, either with phosphorus oxychloride or phosphorus pentoxide provides a straightforward route to CCCXXX (R = R′ = OCH_3) while methylation (CH_2O + HCO_2H) and reduction in the presence of Raney nickel led to the penultimate product of the Grewe synthesis. The method may be applicable to the preparation of compounds with a suitable substitution at C_6.

3-Hydroxy-*N*-methylmorphinane has also been obtained by a series of standard reactions (nitration, reduction and diazotization and cyclization where appropriate) on *N*-methylmorphinane and CCCXXVI (R = R′ = H) (354, 364). Iodination (I_2 + NaOH) of this 3-hydroxy derivative must occur at C_2 since replacement of the halogen of the C_3-methyl ether by lithium (C_4H_9Li) and oxygenation of the derived product leads to a strongly phenolic base, identical to the companion substance of *dl*-tetrahydrodesoxycodeine.

The diastereomeric *N*-methylisomorphinane (rings II/III trans(?)) has been synthesized by Gates and his collaborators (365–367) and provides a route to products derivable from β-dihydrothebainone (368). This reaction sequence also demonstrates clearly the essential role absorption spectra now play in structural organic chemistry. Interpretation of the stepwise hydrogenation of the alkali soluble adduct CCCXXXIII (R = R′ = H) (83% yield) from butadiene and 4-cyanomethyl-1,2-naphthoquinone proved most baffling until ultraviolet and infrared absorption spectra were

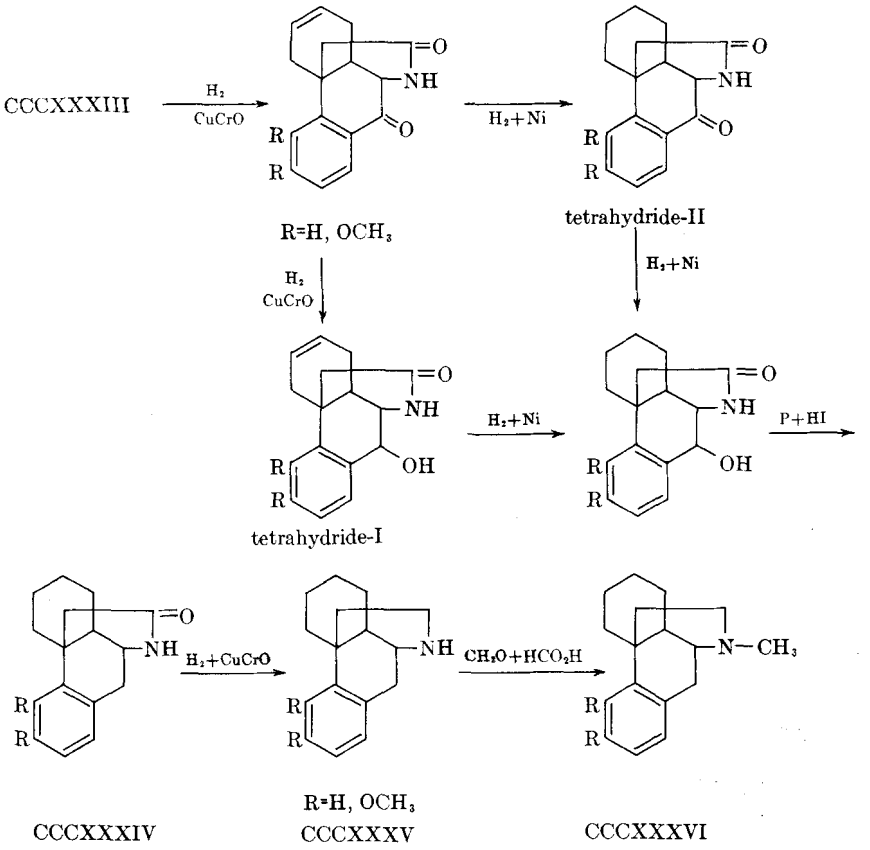


CCCXXXIII

available. Depending upon the experimental conditions CCCXXXIII absorbs one or two (tetrahydride-I) moles of hydrogen when copper-chromium oxide (135° + 80 atm.) is the catalyst. When Raney nickel is the catalyst absorption of one mole equivalent of hydrogen by the alkali insoluble dihydro derivative leads to an isomeric tetrahydride-II while absorption of a second yields the hexahydro derivative obtained from tetrahydride-I. Red phosphorus and hydriodic acid removed one of the two oxygen atoms in the hexahydro compound while catalytic hydro-

genation over copper-chromium oxide (200° + 150 atm.) removed the last oxygen from the so-called desoxy compound.

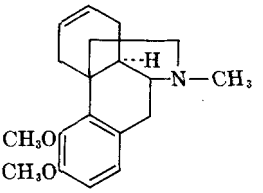
Infrared spectra showed that only the dihydride and the tetrahydride-II contained a ketone grouping but these did not contain a nitrile. Instead absorption at 6.01μ and 2.94μ showed the presence of a cyclic amide with a N—H grouping. In analogy with the reductive conversion of *o*-cyanoacetophenone to 3-methylphthalimidine these products of hydrogenation were eventually formulated as follows:



Reduction of the lactam of CCCXXXIV and methylation (CH_2O + HCO_2H) of the secondary amine of CCCXXXV gave *N*-methylisomorphinane (CCCXXXVI).

An alternate procedure leading to *N*-methylisomorphinane and its $\Delta^{6(7)}$-dehydro derivative has been perfected and successfully applied to the synthesis of the methyl ether of racemic β-Δ^6-dihydrodesoxycodeine

(368). The reaction sequence leading to the methyl ether of racemic β-Δ^6-dihydrodesoxycodeine (CCCXXXVII) involves the Wolff-Kischner reduction of the ketone group of the dihydride from CCCXXXIII (R = OCH_3)



CCCXXXVII

followed by lithium aluminum hydride reduction of the lactam carbonyl and subsequent methylation (CH_2O + HCO_2H) of the resulting secondary amine (368). The infrared spectrum of this racemic base (CCCLI) was identical with that of the optically active product derived from β-dihydrothebainone. The optically active β-Δ^6-dihydrodesoxycodeine methyl ether was obtained by hydrogenation (PtO_2) of the ketone of β-dihydrothebainone, methylation (CH_2N_2) of the phenol and elimination (collidine) of *p*-toluenesulfonic acid from the C_6-tosylate (368).

Although β-Δ^6-dihydrodesoxycodeine methyl ether does not possess the normal configuration at C_{14} this synthesis does provide the first unambiguous evidence that the ethanamine chain is linked to C_{13} in the morphine alkaloids.

VII. Tables of Physical Constants

The conventions used in Table 9 are those adopted for tabulating the properties of the various alkaloids in Chapters VI–IX.

TABLE 9

THE MORPHINE ALKALOIDS AND THEIR PRODUCTS OF TRANSFORMATION AND DEGRADATION

Compound	M.p. °C. or B.p.	$[\alpha]_D$		References
		A		
1-Acetocodeine	130 (gas)	..	..	340
(monohydrate)	149–150			
6-Acetyl-	125–126.5			
(dimorphous)	146–147	(−)208°($CHCl_3$)	..	340
1-Acetodihydrocodeine	138–140	−101°(C_2H_5OH)	Crystals (ethyl acetate)	340
6-Acetyl-	166–167	−105° (acetone)	Crystals (ethyl acetate)	340

TABLE 9 (*Continued*)

Compound	M.p. °C. or B.p.	$[\alpha]_D$		References
1-Acetodihydromorphine				
6-Acetyl-	242 (V. dec)	−97.2°	Crystals(CH_3OH)	340
3,6-Diacetyl	..	..	Oil	340
1-Acetomethyl-morphenol	273–276 (V. gas)	..	Crystals (CH_3OH)	340
1-Aceto-α-Methyl-morphimethine	188–188.5 (V)	+12.6° (2 *N*HOAc)	Glassy prisms (C_2H_5OH)	340
1-Aceto-β-methyl-morphimethine	149°	+151° ($CHCl_3$)	Crystals (ethyl acetate)	340
1-Acetomorphine	260–262.5 (V)	−156° (C_2H_5OH)	Crystals (C_2H_5OH—H_2O)	340
Hydrochloride	235–237 (V)	−121° (H_2O)	Crystals (C_2H_5OH)	340
Perchlorate	261–262.5 (V. dec)	−111° (C_2H_5OH)	Crystals (H_2O)	340
3,6-Diacetyl-	..	−207° ($CHCl_3$)	Crystals (C_2H_5OH)	340
		C		
Codeinone	*181.5–182.5	(−)205° (C_2H_5OH)	Crystals (ethyl acetate)	370
Hydrochloride	*180–181	..	Crystals (H_2O)	370
Methiodide	*175	..	Crystals (H_2O)	370
Picrate	*208.5	..	Yellow prisms (C_2H_5OH—H_2O)	370
Sulfate	*176–177	..	Crystals (H_2O)	370
2,4-Dinitrophenyl-hydrazone	..	..	Orange tablets ($CHCl_3$—C_2H_5OH)	370
Oxime	*209–210 (dec)	..	Needles (C_2H_5OH)	370
Hydrochloride	*258° (dec)	..	Prisms (C_2H_5OH)	370
		D		
O-Desmethyldihydro-thebainone	274 ..	−68° (10% HOAc)	Crystals (pyridine)	341
Oxime hydrochloride	318–320	..	Crystals (CH_3OH)	341
Thiosemicarbazone	260–280 (dec)	..	Short needles	341
Hydrochloride	250 (dec)	..	Microcrystals (H_2O)	341
O-Desmethylthebainone	220–221 (V)	−34.3° (10% HOAc)	Crystals (pyridine)	341
Diacetyl-	183–184	..	Needles ($CHCl_3$—ether)	341
Oxime	274–279	..	..	341
Thiosemicarbazone hydrochloride	219–220 ..	.. ..	Yellow platelets (H_2O)	341
Dihydrocodeine	112–113	..	Crystals (pet. ether)	370
Dihydromorphine	207	..	..	370
6-Acetyl-	246 (V)	−117° (C_2H_5OH)	Glassy needles (C_2H_5OH)	370

TABLE 9 (*Continued*)

Compound	M.p. °C or B.p.	$[\alpha]_D$		References
β-Dihydrothebaine	171–173	+307° (C_2H_5OH)	Crystals (C_2H_5OH—H_2O)	351
Methiodide (pyridine of crystallization)	120 (dec)	..	Crystals (pyridine—ether)	351
Picrate	173 (dec)	..	Crystals (acetone—C_2H_5OH)	351
Dihydrothebainol	*168–169	−28° (C_2H_5OH)	Prisms (ethylacetate)	370
Methiodide	*276° (V)	..	..	370
Picrate	*202–203	..	..	370
Dihydrothebainone	144–146	..	Crystals (acetone)	341
Oxime	245	..	..	341
hydrochloride	311	..	..	341
α-Dimethylmorphimethine. See α-Methylmorphimethine.				
		E		
1-Ethyldihydrocodeine	..	..	Oil	340
6-Acetyl-	104.5–105.5	−126°(C_2H_5OH)	Crystals (C_2H_5OH—H_2O)	340
Tartrate monohydrate	160–170°	..	Crystals (H_2O)	340
(+)-Ethylphenyldihydrothebaol	118 ..	−74.4° (ethyl acetate)	Crystals (C_2H_5OH)	350
Acetyl-	122.5–123	−77.0° (ethyl acetate)	Rectg. plates (C_2H_5OH)	350
(+)-Ethylphenylhexahydrothebaol	..	..	Oil	350
Acetyl-	82.5–83	−23.4° (ethyl acetate)	Crystals (C_2H_5OH—H_2O)	350
		H		
(+)-Hexahydrophenyldihydrothebaine-isomethine	108–108.5 ..	−24.2° (C_2H_5OH)	Needles (C_2H_5OH—H_2O)	350
Methiodide	207–208	−14.7°(C_2H_5OH)		350
(−)-Hexahydrophenyltetrahydrothebaimine	128–129.5	+10.0°(C_2H_5OH)	..	350
N-Methomethiodide	231–232	+6.6°(C_2H_5OH)	..	350
(+)-Hexahydrophenyltetrahydrothebaimine	129–130.5 ..	−8.5°(C_2H_5OH) ..	Crystals (ethyl acetate)	350
Hydrochloride	253–255 (gas)	−17.6° (C_2H_5OH)	Crystals (C_2H_5OH—ether)	350
N-Methomethiodide	231–232.5	−4.8°(C_2H_5OH)	Crystals (C_6H_6)	350

TABLE 9 (*Continued*)

Compound	M.p. °C. or B.p.	$[\alpha]_D$		References
5-Hydroxydihydro-thebainone	*207	−115° (C_2H_5OH)	Crystals (ethyl acetate)	353
Hydrochloride	*238.5–240	..	Crystals (C_2H_5OH)	353
Methiodide	*250	..	Fine needles (CH_3OH—ethyl acetate)	353
Acetyl-	*149.5–150.5	..	Tabular crystals (ethyl acetate)	353
Methiodide	188–203	..	Rhombohedra (CH_3OH—ethyl acetate)	353
5-Hydroxydihydro-thebainonemethine	..	..	..	353
1-(1′-Hydroxyethyl-codeine	222–224	−101° (C_2H_5OH)	Crystals (C_2H_5OH)	340
6-Acetyl-	185–187	−212°($CHCl_3$)	Crystals (C_2H_5OH—H_2O)	340
Tartrate monohydrate	165–170	−115(H_2O)	Crystals(H_2O)	340
1(1′-Hydroxyethyl)-dihydrocodeine	225–227 (V)	−82° (10% HOAc)	Rods (C_2H_5OH—H_2O)	340
6-Acetyl-	251–252 (V. dec)	−91.2°($CHCl_3$)	Crystals (C_2H_5OH)	340
5-Hydroxythebainone	*201	−136°(C_2H_5OH)	Crystals (ethyl acetate)	353
Hydrochloride	*186–189	..	Prisms(H_2O)	353
2,4-Dinitrophenyl-hydrazone	*220–230	..	Red prisms (C_2H_5OH)	350
Oxime	*274° (V)	..	Prisms(C_2H_5OH)	350
Hydrochloride	*261.2–261.9	..	Prisms(C_2H_5OH)	350
		I		
Isomethyldehydro-thebenone	116.5–117	+252° (C_2H_5OH)	Crystals (C_2H_5OH)	350
Isomethyldihydro-thebainonemethine	193	+231° (C_2H_5OH)	Crystals (ethyl acetate)	350
		M		
6-Methylchlorocodide	*163.5–164	..	Crystals (ligroin)	373
6-Methylcodeine	*114.5–116.5	−163° (C_2H_5OH)	Crystals (ligroin)	373
Methiodide	*232–233	..	Crystals (CH_3OH)	373
Perchlorate	*139–144	..	Crystals (C_2H_5OH)	373
Salicylate	*167–169	..	Prisms (ethyl acetate)	373
Methyldehydro-thebenone	183–184	+262° (acetone)	Crystals (C_2H_5OH)	350

TABLE 9 (*Continued*)

Compound	M.p. °C. or B.p.	$[\alpha]_D$		References
Methyldihydrotheba-inonemethine	164–165 (darkens)	+163° (C_2H_5OH)	Needles (ethyl acetate)	350
Methiodide	246–249 (V)	+117° (C_2H_5OH)	Crystals (CH_3OH)	350
7,7′-Methylenebis-(1-bromodihydro-codeinone)	274–275	−287° (dioxane)	Crystals (acetone)	343
Dihydrochloride	271–273	−243° (C_2H_5OH)	Crystals	343
7,7′-Methylenebis-dihydrocodeinone	174–175	−314° (dioxane)	Crystals (acetone)	340
Dimorphic form	247–248	−318° (dioxane)	Crystals (acetone)	340
Dihydrochloride pentahydrate	278–280 (dec)	−252° (C_2H_5OH)	..	340
Dimethiodide dihydrate	270–272 ..	−177° (C_2H_5OH—H_2O)	Crystals (CH_3OH)	340
Monosemicarbazone	218–220	−383° (C_2H_5OH)	Crystals (C_2H_5OH—H_2O)	340
6-Methylmethyl-morphenol	*89–90	..	Prisms (CH_3OH)	373
Picrate	*138.5–139.5	..	Red Prisms (CH_3OH)	373
6-Methyl-α-methyl-morphimethine	*106.5–107.5 ..	−222° (C_2H_5OH) ..	Prisms (ethyl acetate)	373
Methiodide	*203.5–205.5 (dec)	..	Amorphous	373
6-Methyl-β-methyl-morphimethine	*95.5–97	+357° (C_2H_5OH)	Crystals (sublimed)	373
Methiodide	*283–284	..	Prisms (CH_3OH)	373
O-Methyl-*N*-Methylthebenine.	See Thebenine			
α-Methylmorphimethine				
Methyl ether	92–94	..	..	344
β-Methylmorphimethine	136	+414° (C_2H_5OH)	..	372
		N		
Neomorphine	240–241 (V. dec)	..	..	372
$CHCl_3$ of crystallization	107 (froth)	−18.2° ($CHCl_3$)	..	372
Hydrochloride	295–298 (V. dec)	+22.6° (H_2O) ..	Glassy crystals (C_2H_5OH)	372
6-Acetyl-Sesquihydrate	243–251 (V. dec)	+27.6° (C_2H_5OH)	Crystals (C_2H_5OH)	372
Hydrochloride	238–245 (V. dec)	+8.8°	Crystals (C_2H_5OH)	372
3,6-Diacetyl-	127–127.5	+17.5° (C_2H_5OH)	Crystals (ligroin)	372
Neopine	127.5–128.5	−28.13° ($CHCl_3$) / −30.5° ($CHCl_3$)	Needles (cyclohexane)	371, 372
Hydrobromide	280–285 (dec)	+16.99° (H_2O)	Crystals (H_2O)	371, 372
Hydrochloride	..	+18.2° (H_2O)	..	372

TABLE 9 (*Continued*)

Compound	M.p. °C. or B.p.	$[\alpha]_D$		References
Methiodide	..	+23.5° (C_2H_5OH)	..	372
Sulfate	166–167	+16.38° (H_2O)	Fine needles	371
Norphenyldihydrothebaine hemihydrate	130–136	+12.3° (C_2H_5OH)	Crystals (C_2H_5OH—H_2O)	350
Hydrochloride Trihydrate	200–210	+31.4° (C_2H_5OH)	Crystals (C_2H_5OH—ether)	350
O				
Oripavine	201–202	−211.8° ($CHCl_3$)	Needles (C_2H_5OH)	345, 346, 347
Hydrochloride	258–259 (dec)	..	Plates (C_2H_5OH)	346, 345
Methiodide	207–208	..	Glistening needles (CH_3OH)	345
Methyl ether is thebaine. See Thebaine				347
P				
(−)α-Phenyldihydrothebaine	..	−10° (C_2H_5OH)	..	350
Methiodide	216	−43.6° (C_2H_5OH)	Crystals (CH_3OH)	350
(+)α-Phenyldihydrothebaine	150/0.1 mm.	+25.3° (C_2H_5OH)	Glassy solid	350
Alcoholate	40–70	+10.2° (C_2H_5OH)	Prisms (C_2H_5OH)	350
Methiodide	216.5–218	+42.7° (C_2H_5OH)	Crystals (CH_3OH)	350
Perchlorate	248 (V. dec)	+35° (C_2H_5OH) +8° (acetone)	Crystals (C_2H_5OH)	350
Methyl ether	..	..	Sirup	350
Hydrobromide	86–88° (gas)	+21.9° (C_2H_5OH)	..	350
Methiodide	196–197.5	+20.7° (C_2H_5OH)	..	350
(+)α-Phenyldihydrothebainedihydroisomethine	70–72 ..	−175° (C_2H_5OH) ..	Crystals (C_2H_5OH—H_2O)	350
Methiodide	212–213	−121° (C_2H_5OH)	Crystals (ethyl acetate)	350
Perchlorate Dihydrate	85–87 (froth)	−104° (C_2H_5OH)	Crystals (H_2O—C_2H_5OH)	350
(−)α-Phenyldihydrothebaineisomethine	101 ..	+281° (C_2H_5OH) ..	Crystals (C_2H_5OH—H_2O)	350
Perchlorate	111–116	+197° (C_2H_5OH)	Crystals (C_2H_5OH)	350
(+)α-Phenyldihydrothebaineisomethine	120/0.1 mm. 101	−280° (C_2H_5OH) ..	Crystals (C_2H_5OH—H_2O)	350
Methiodide	159–160	..	..	350
Dihydrate	100–110	−207° (C_2H_5OH)	Needles (H_2O—C_2H_5OH)	350

TABLE 9 (*Continued*)

Compound	M.p. °C. or B.p.	$[\alpha]_D$		References
Perchlorate	111–117 (gas)	−197° (C_2H_5OH)	Needles (C_2H_5OH—H_2O)	350
(+)α-Phenyldihydrothebainemethine	126–127	−46.5° (C_2H_5OH)	Crystals (CH_3OH)	350
Methiodide	244 (V)	−51.5° (C_2H_5OH)	Crystals (CH_3OH)	350
Perchlorate				
Alcoholate	106–120 (gas)	−34° (acetone) −60.3° (C_2H_5OH)	Crystals (C_2H_5OH)	350
(−)δ-Phenyldihydrothebaine	143.5	+110° ($CHCl_3$) +131° (acetone)	Crystals (CH_3OH)	350
Methiodide				
Dihydrate	206–208	+44° (C_2H_5OH)	Crystals (CH_3OH)	350
Perchlorate	209–213	+42.8° (C_2H_5OH)	Crystals (C_2H_5OH)	350
(+)δ-Phenyldihydrothebaine	143.5	−110° ($CHCl_3$) −131° (acetone)	Needles (C_2H_5OH)	350
Methiodide				
Dihydrate	206–208	−43° (C_2H_5OH)	Crystals (CH_3OH)	350
Perchlorate	209–213	−44.5° (C_2H_5OH)	Crystals (C_2H_5OH—ether)	350
(+)δ-Phenyldihydrothebainedihydroisomethine	217–219	+145° (C_2H_5OH)	Crystals (C_2H_5OH—ether)	350
(−)δ-Phenyldihydrothebaineisomethine	117–119	−154° (C_2H_5OH)	Crystals (C_2H_5OH—H_2O)	350
Methiodide	202–203	−105° (C_2H_5OH)	Crystals (C_2H_5OH—ether)	350
Perchlorate				
Alcoholate	114–116	−90° (C_2H_5OH)	Crystals (C_2H_5OH)	350
(+)δ-Phenyldihydrothebaineisomethine	117–119	+153° (C_2H_5OH)	Long prisms (C_2H_5OH—H_2O)	350
Methiodide	202–203	+108° (C_2H_5OH)	Crystals (C_2H_5OH—ether)	350
Perchlorate				
Dialcoholate	114–116	+89.6° (C_2H_5OH)	Crystals (C_2H_5OH)	350
(+)α-Phenyl-9-dimethylamino-6-methoxythebendiene			Oil	350
Methiodide	212–213	+0.6° (C_2H_5OH)	Square-ended prisms	350
Perchlorate	168	+26.5° (C_2H_5OH)	Crystals (C_2H_5OH—H_2O)	350
rac-Phenyl-6-methoxythebenane	80–83.5	0° (ethyl acetate)	Prisms (acetone)	350
rac-Phenyl-6-methoxythebendiene	119–120.5	0° (ethyl acetate)	Leaflets (CH_3OH)	350
rac-Phenyl-6-methoxythebentriene	162.5–163	0° (acetone)	Crystals (ethyl acetate)	350

TABLE 9 (*Continued*)

Compound	M.p. °C. or B.p.	$[\alpha]_D$		References
(−)-Phenyltetrahydrothebaimine	121	+35.4° (acetone)	Pentagonal plates (C_2H_5OH—H_2O)	350
N-Methomethiodide	235 (V)	+5.3° (CH_3OH)	..	350
(+)-Phenyltetrahydrothebaimine	120–121	−35.0° (acetone)	Pentagonal plates (C_2H_5OH—H_2O)	350
N-Methomethiodide	235° (V)	−5.2° (CH_3OH)	Crystals (C_6H_6)	350
Dimorphic form	250–253	..	..	350
rac-Phenyltetrahydrothebaimine	105–108	0° (acetone)	Crystals (hot C_2H_5OH)	350
T				
l-Tetrahydrodesoxycodeine				
Tartrate	110 (froth)	..	Crystals (dioxane)	354
dl-Tetrahydrodesoxycodeine	135 (gas)	..	Six-sided plates (acetone)	354
Picrate	211	..	Crystals (C_2H_5OH)	354
Tetrahydro-β-dihydrothebaine	143.5–144.5	−17.5° (C_2H_5OH)	Needles (ether—C_2H_5OH—H_2O)	351
Acetyl-Tetrahydro-α-methylmorphimethine Methyl ether Methiodide	110–111	..	Crystals (pe . ether)	351
	246–248			344
Thebaine	192–193	−217°	Platelets(C_2H_5OH)	354, 347
Picrate	214–215		Crystals (C_2H_5OH—H_2O)	362
Thebaine-Acrolein Adduct	105	..	Crystals (ether)	374
Oxime	180 (dec)	..	Crystals (C_2H_5OH—H_2O)	374
Thebainone	..	..	..	341
β-Thebainone	97–99	+114.3° (C_2H_5OH)	Needles (ethyl acetate—ether-water)	351
Thebenine				
O, *N*-Dimethyl-Methiodide	243–244	..	Crystals (C_2H_5OH)	347
Metho methylsulfate	265–266	..	Crystals (C_2H_5OH)	347
V				
Vinylhexahydrophenyltetrahydrothebaol	70–72	+35.4°	..	350

TABLE 9 (*Continued*)

Compound	M.p. °C. or B.p.	$[\alpha]_D$		References
(+)-Vinylhexahydrophenyltetrahydrothebaol	75.5–77	−22.7° (ethyl acetate)	Needles (C_2H_5OH—H_2O)	350
(−)-Vinylphenyldihydrothebaol	149.5–150	−47.4° (ethyl acetate)	Needles (C_2H_5OH)	350
(+)-Vinylphenyldihydrothebaol	149	47.1° (ethyl acetate)	Crystals (C_2H_5OH)	350
dl-Vinylphenyldihydrothebaol	146–147	0°	Crystals (C_2H_5OH)	350
(+)-Vinylphenyltetrahydrothebaol	85.5–87	−58.7° (C_2H_5OH)	Crystals (C_2H_5OH—H_2O)	350
Acetyl-	102–104	−48.5° (ethyl acetate)	Rect'g. prisms (CH_3OH)	350

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CHAPTER IX

Sinomenine

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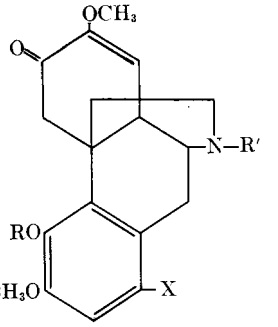
I. Physiological Action, Isolation and Color Reactions

Sinomenine, I (X = R = H, R′ = CH_3), containing as it does, a hydrophenanthrene nucleus and an ethanamine bridge is structurally very similar to morphine and codeine but there the similarity ends. The configuration at the asymmetric centers, C_9, C_{13}, and C_{14} (also C_5 when generated), is the mirror image of those in morphine and therein lies the interest in this alkaloid; it affords a route to the interesting enantiomorphs of dihydromorphine, dihydrocodeine, and a number of other morphine transformation products (chlorodihydrocodide, desoxycodeine-C, dihydrothebainone, dihydrothebainol-A, β-tetrahydrodesoxycodeine and thebenone). The enantiomorph of dihydromorphine has proved to be equally as strong a narcotic as morphine (18), but the physiological activity of the antipodes of the other morphine transformation products reflects to a greater or lesser extent the steric difference in these two alkaloid series (92). These bases do not possess the analgesic properties of morphine, but on the contrary their effect on the respiratory and nervous system is antagonistic to that

of their morphine counterparts. Hence, the physiological action characteristic of the morphine derivatives is dependent not only upon chemical constitution but also upon configuration (91, 92, 101).



X = H, Br, N = N—C_6H_5
R = H, CH_3, C_2H_5, $COCH_3$, COC_6H_5
R′ = CH_3, CN

I

Sinomenine possesses no therapeutic action against avian malaria, but, like quinine, small amounts of this alkaloid stimulate the pregnant and nonpregnant uterus of the rabbit, strengthening its rhythmic contraction as well as lengthening the period that this organ remains in this contracted state. Larger doses throw this organ in convulsions (69), thus terminating pregnancy (70). When injected into rabbits subcutaneously sinomenine exerts an antiphlogistic action (65, 66, 67): it decreases the liver and muscle glycogen (73) and the adrenalin content of the suprarenals and at the same time increases the amount of sugar (73) and adrenalin (74) in the blood stream. This base has found some use as a therapeutic agent in the treatment of rheumatism (1).

Sinomenine (cucoline (78)) is the main alkaloid (0.45%) (78) occurring in the roots and stems of the climbing plants, *Sinomenium acutum* Rehder and Wilson (1) and *Sinomenium diversifolius* Diels (*Cocculus diversifolius* D.C.) (64, 91), which are indigenous to the woods of southern Japan and from which it has been isolated as follows:

The ground roots and stems are heated with twice their weight of 95% ethyl alcohol for several days. After recovery of the alcoholic extract the solvent is removed and the residue treated with lead acetate and finally a hydrochloric acid solution of the basic material is extracted with ether. The hydrochloride salt crystallizes from its aqueous solution in white prisms (m.p. 224°). The base is liberated from an aqueous solution of its hydrochloride by the addition of sodium carbonate and recovered by extraction with ether. It crystallizes from benzene in radiating clusters of needles and melts at 161–162°, then crystallizes in a different crystal system, remelting at 182°.

Other minor alkaloids that have been isolated from the same source are acutumine[1] (33), disinomenine (2, 93) (dehydrosinomenine (1, 93) or

dehydrocucoline (78, 91)), diversine[1] (81, 83, 91) (cocculinum (81, 99)), sinactine[1] (33) and tuduranine[1] (15, 16, 17, 33). Disinomenine may be present in the stems and roots of these plants, yet the marked ease with which sinomenine is oxidized to this dimeric base suggests that the relatively small amount (0.02% or 5% of the total alkaloid content) (78) of disinomenine may result from aerial oxidation of sinomenine during the process of isolation.

The color reactions of these bases have not been extensively investigated and are limited, for the most part, to their reaction with such reagents as formaldehyde-sulfuric acid and alkaline potassium ferricyanide (Table 1). The diazo reaction has been used in many instances to demonstrate the absence of substituents at C_1 (the reaction is not negative for bases with C_1-substituents but its intensity is greatly reduced). The color display (yellow → green → blue with a red fluorescence) exhibited by sinomenine with formaldehyde-sulfuric acid reagent is very similar to that of the aporphine bases and was one of the factors which prompted Goto to advance a provisional aporphine formula for this alkaloid. The color developed with alkaline potassium ferricyanide is usually a purple and the derived tinctorial compound may be extracted into chloroform. The minimum concentration of these bases required for detection in this and the diazo reaction is listed in Table 1.

TABLE 1

COLOR REACTIONS OF SINOMENINE AND ITS TRANSFORMATION PRODUCTS

Compound	Formalin-sulfuric acid	Alkaline $K_3Fe(CN)_6$ (1 part in)	Diazo reaction (1 part in)
Benzoylsinomenine	Yellow (39)	Negative (39)	Negative (39)
Bis-8,8'-demethoxydihydrosinomenine	Pure blue (34)	Purple (34)	2,500,000 (34)
Bis-demethylsinomenylidene	Yellow → green → bordeaux red (34)	Transitory (34)	2,000,000 (34)
1-Bromodemethoxydesoxodihydrosinomenine	Yellowish brown (37)	Negative (37)	50,000 (37)
1-Bromodemethoxydihydrosinomenine	Greenish blue (37)	1,000 (37)	200,000 (37)
1-Bromodihydrosinomenilone	Green (red fluorescence) (10)	..	..
1-Bromosinomeneine	Reddish violet (32)	Negative (32)	800 (32)
1-Bromosinomenilic acid	Negative (8)	..	..
1-Bromosinomenilone	Red (8)	..	Negative (8)

[1] Since diversine and tuduranine are aporphine bases, while acutumine and sinactine are isoquinolines, these alkaloids will not be discussed in this chapter.

TABLE 1 (*Continued*)

Compound	Formalin-sulfuric acid	Alkaline $K_4Fe(CN)_6$ (1 part in)	Diazo reaction (1 part in)
1-Bromosinomenine	Yellow → green → blue (red fluorescence) (32)	100,000 (32)	5,000 (32)
1-Bromosinomeninone	Yellowish brown (36)	Negative (36)	1,000,000 (36)
1-Bromosinomeninone imine	Yellowish brown (36)	Negative (36)	50,000 (36)
Demethoxydesoxodihydrosinomenine	Yellow → purple (34)	500,000 (34)	2,000,000 (34)
Demethoxydihydrosinomenine	Yellow → green (34)	500,000 (34)	2,500,000 (34)
Demethoxydihydrosinomeninol	Yellow → green → violet (40)	500,000 (40)	2,000,000 (40)
1,1¹-Dibromo-bis-8,8¹-demethoxydihydrosinomenine	Greenish blue (37)	Negative (37)	400,000 (37)
Dihydro-5-hydroxymethylsinomenine	Bluish violet (42)	Just positive (42)	2,000,000 (42)
Dihydromethylsinomeninone	Yellow (39)	Negative (39)	Negative (39)
Dihydrosinomenilone	Yellow → green → violet (10)	..	2,000,000 (10)
Dihydrosinomenine	Negative (30)	..	..
Dihydrosinomeninol	Yellow → green → blue (40)	500,000 (40)	2,000,000 (40)
α-Dihydrosinomeninone	Green → blue (35)	500,000 (35)	2,000,000 (35)
β-Dihydrosinomeninone	Green → blue (35)	500,000 (35)	2,000,000 (35)
1,5-Dihydroxymethylsinomenine	Green (42)	Negative	20,000 (42)
Disinomenine	Pink (29)	..	50,000 (29)
5-Hydroxymethylsinomenine	Green → brown (42)	Just positive (42)	2,000,000 (42)
Methylsinomenine	Yellow → green (39)	Negative (39)	20,000 (39)
Methylsinomeninone	Green → bordeaux red (39)	Negative (39)	10,000 (39)
Pseudodisinomenine	Yellow (29)	..	50,000 (29)
Sinomenine	Yellow → green → blue (red fluorescence) (30, 35)	500,000 (28, 35)	2,000,000 (28, 35)
Sinomeninol	Yellow → green → blue (40)	500,000 (40)	2,000,000 (40)
Sinomeninone	Yellow → bordeaux red (35)	500,000 (35)	2,000,000 (35)
Tetrahydrodisinomenine	Weakly pink (30)	500,000 (30)	50,000 (30)
Tetrahydropseudodisinomenine	Faintly yellow (30)	500,000 (30)	25,000 (30)
1,5,8-Tribromosinomeninone hydrobromide	Brownish red (8)	..	..

II. Elucidation of the Constitution of Sinomenine

Sinomenine was first isolated in crystalline form in 1920 (64) and later (1, 81) it was demonstrated that it is dimorphous (m.p. 161–162° and 182°) (81). The higher melting form may be converted to the lower melting one by solution in hydrochloric acid and reprecipitation of the base with ammonia (81). At various times the formulas $C_{16}H_{20}O_3N \cdot 3H_2O$ (91), $C_{16}H_{19}O_3N \cdot H_2O$ (64), and $C_{19}H_{21}O_4N$ (81) have been assigned to sinomenine but its composition has since been shown to be correctly represented by $C_{19}H_{23}O_4N$ (1, 78, 82).

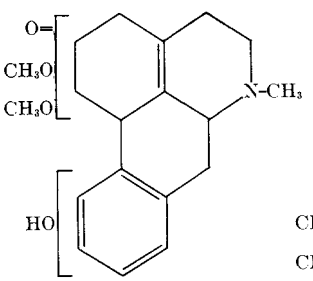
1. Functional Groups

The formation of a monoxime (1, 39, 82, 97) and a monosemicarbazone (1, 82) by sinomenine and its reduction to a carbinol reveal that one of the four oxygen atoms of this base is present in a carbonyl group. The marked susceptibility of this base to oxidation is evident in its positive reaction with Fehling's and Tollen's reagents, a property which, in this instance, might erroneously be construed as evidence for the presence of an aldehyde or an α-hydroxy ketone. Then the marked ease of hydrolysis (2 *N* HCl at 100°) (9, 35, 38) of one of the two methoxyl groups (Zeisel) (1) characterized this grouping as either an enol methyl ether (see thebaine) or the methyl ether of a carbinolamine (see pseudostrychnine methyl ether). Formation of a dioxime by the hydrolyzate (sinomeninone) (35, 38), however, favors the former, while anhydride formation by the dioxime (sinomenininonefurazane) and oxidation (H_2O_2) of sinomeninone methyl ether to a dicarboxylic acid (7, 56) with the same number of carbon atoms characterize the hydrolyzate as an α-diketone (hence locates the enol methyl ether with respect to the ketone group of sinomenine). Finally, *O*-benzoate formation (1, 39) and a Zerewitinoff determination (1) would suggest that the fourth oxygen atom and the active hydrogen of sinomenine are the elements of a hydroxyl group. Furthermore, the phenolic nature of this hydroxyl group is clearly manifest by the solubility of sinomenine in aqueous alkali (81) and its precipitation by carbon dioxide (64), the formation of a methyl ether with diazomethane (39) (methylsinomenine is insoluble in aqueous alkali (81)) and its very pronounced ferric chloride reaction (green to blue) (1, 81). Its positive diazo reaction (31, 41) requires that there be an unsubstituted position in this base ortho or para to this phenolic hydroxyl.

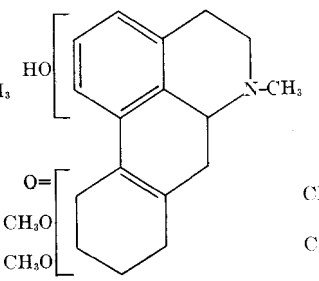
Sinomenine, containing as it does one ethylenic double bond, decolorizes aqueous potassium permanganate (78, 85) and is catalytically reduced (Skita's colloidal platinum (1, 82) or palladous chloride (78)) to a dihydro derivative ($C_{19}H_{25}O_4N$) that still yields a monoxime and a monosemicarbazone (1) (the iodine number, 53.89, of benzoylsinomenine is added

support for one ethylenic double bond in sinomenine) (1, 82). Then, from the observed difficulty of hydrolysis of the methoxyl groups (25% HBr) (12) of dihydrosinomenine it is evident that it was the enol ether double bond that underwent hydrogenation. This enol ether double bond could hardly be classified as a reactive ethylene since sinomenine, when treated with bromine, is more susceptible to substitution at C_1 (the intensity of the diazo reaction of 1-bromosinomenine (I, R = H, R′ = CH_3, X = Br) is but one-fortieth that of sinomenine) than to addition at the double bond, and even substitution alpha to the ketone group (C_5) takes precedence over the addition reaction (9).

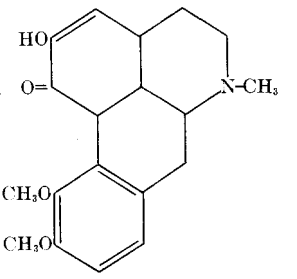
Sinomenine, although it is a weaker base than ammonia (81), is readily soluble in dilute mineral acids and forms a crystalline aurichloride, hydriodide, hydrobromide, methiodide, and picrate (Table 4). The tertiary nature of this amine is revealed by its failure to react with nitrous acid (no Liebermann test) (78), while the generation of methylamine by this base (soda lime) (78) as well as a positive Herzig-Meyer test (agreement with theory was not all that might be desired: theory, 4.56%; found, 6.66%) (1) attest the presence of a methylamino grouping in this alkaloid. Furthermore, this nitrogen must be a component of a ring since two Hofmann degradations are required to eliminate it as trimethylamine from a number of products derived from sinomenine (1, 4, 46, 48, 94). Its reaction with ethyl chloroformate was deceptive. This reagent, which up to this time was considered diagnostic for tetrahydroisoquinolines (21), pointed to a close structural relationship between sinomenine and the aporphine bases. The introduction of six carbon atoms as well as the insolubility of the derived product ($C_{25}H_{32}O_8NCl$) (1, 82) in acid and alkali would suggest that a tetrahydroisoquinoline system (93) had been ruptured and the phenolic hydroxyl esterified by the reagent.



II



III



IV

On this meager evidence Kondo (82) (1924) advanced a provisional aporphine formula (II or III) for sinomenine, but other than arbitrarily assigning the double bond to $\Delta^{8\text{-}14}$ no attempt was made to assign positions to the other functional groups. Goto (93) sought to relate sinomenine to

apomorphine dimethyl ether and suggested IV as a tentative formula for this base, but later (28) pointed out the inadequacy of such a formula. Such a structure would not account for the phenolic and ketonic properties of dihydrosinomenine (solubility in alkali, ferric chloride test, positive diazo reaction and formation of an oxime).

2. Nuclear Structure — Products of Degradation

The marked similarity in chemical behavior between sinomenine ($C_{19}H_{23}O_4N$) and the morphine alkaloids (codeinone, $C_{18}H_{21}O_3N$) would suggest that this base is a hydrophenanthrene with an ethanamine bridge, a conclusion which has since been confirmed in a number of ways. Sinomenine (1, 82), like morphine, yields a small amount of phenanthrene when distilled with zinc dust, but in view of the pyrolytic conditions this can hardly be construed as evidence for such a system in these bases. The desired result, however, can be achieved in other ways when but slight chemical stimulus (potassium hydroxide, acetic anhydride, or benzoic acid anhydride) is required to eliminate the nitrogen complex of sinomenine (1, 28, 31, 82, 93) and a number of related products (sinomenineachromethine (44), sinomenineviolomethine (44), methylsinomenineviolomethine (45), 1-bromoethylsinomenine ethiodide (61), 1-bromomethylsinomenine methiodide (60), 5-hydroxymethylsinomenine (42) and disinomenine (29)) as methylethylamine (sinomenine would appear to have the same degree of saturation as codeinone because the latter base is aromatized in the same way with acetic anhydride; the basic moiety being ethanolmethylamine in this instance). The nonbasic fragment, sinomenol ($C_{16}H_{14}O_4$) (diacetylsinomenol or dibenzoylsinomenol when acetic anhydride or benzoic acid anhydride is used), accounts for the rest of the carbon atoms of sinomenine.

$$C_{19}H_{23}O_4N + \xrightarrow{KOH} C_3H_9N + C_{16}H_{14}O_4$$

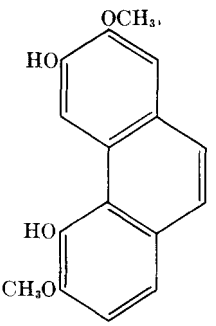
$$C_{19}H_{23}O_4N + 2C_4H_6O_3 \longrightarrow C_3H_9N + (C_{16}H_{12}O_2)(OCOCH_3)_2 + 2CH_3CO_2H$$

$$C_{19}H_{23}O_4N + 2C_{14}H_{10}O_3 \longrightarrow C_3H_9N + (C_{16}H_{12}O_2)(OCOC_6H_5)_2 + 2C_6H_5CO_2H$$

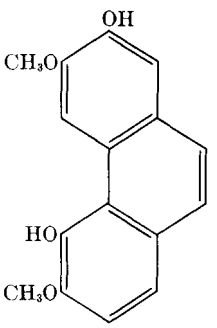
Sinomenol has been degraded (zinc dust distillation) (1, 93) to phenanthrene, and by protecting its two phenolic hydroxyls by methylation, acetylation, or benzoylation it was possible to oxidize (CrO_3 + HOAc) (31) it to an orthoquinone (phenazine). The dibenzoylsinomenolquinone was further degraded to a tetramethoxybiphenyl (53) by oxidation of the *o*-quinone with hydrogen peroxide, replacement of the benzoyl residues by methyl groups and decarboxylation (Cu + quinoline) of the derived tetramethoxydiphenic acid. The striking similarity of properties and color reactions of sinomenol and 3-methoxy-4,6-dihydroxyphenanthrene (from codeinone (28)) prompted the conclusion that sinomenol is similarly constituted with a second methoxyl at C_5 or C_7 (31). The validity of this conjecture was

established by the synthesis of 3,4,6,7-tetramethoxyphenanthrene by the Pschorr method (2-nitro-3,4-dimethoxybenzaldehyde + sodium 2-bromo-3,4-dimethoxyphenylacetate) (1, 31, 84), which proved to be identical with sinomenol dimethyl ether (93). This definitely located the four oxygen atoms in sinomenol and sinomenine. Furthermore, the acetolytic degradation of sinomeninone (the α-diketone from the hydrolysis of the enol methyl ether of sinomenine: the 1-bromo derivative acts similarly) (9) to 3-methoxy-4,6-diacetoxyphenanthrene (24) (this is accompanied by a rearrangement product, triacetylisothebenine (9)) narrowed the possibility for sinomenol to V or VI. By considering the formation of the nonphenolic 1-bromosinomeneine from sinomenine a choice between these two may be made in favor of V. In order to close the hydrophenanthrylene oxide bridge, bromination must occur at C_5 (as well as C_1), and, hence, the ketone of sinomenine and the phenolic hydroxyl of sinomenol must be at C_6.

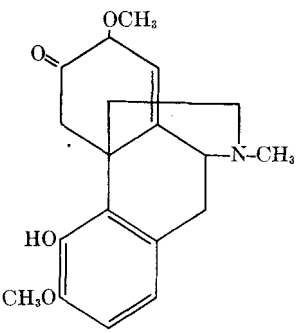
To account for the ease of extrusion of the side chain upon aromatization of the nucleus, Kondo (83a) revised his earlier formula (II) to VII but retained the arbitrarily assigned position of the double bond. This structure, however, fails on a number of counts. For instance, structure VII fails to account for the yellow color (4, 31) developed by sinomenine in alkaline solution and for its absence when the corresponding alcohol, sinomeninol (40), is treated similarly. This and a number of other properties diagnostic for α,β-unsaturated ketones prompted Goto (31, 76) to alter



V



VI



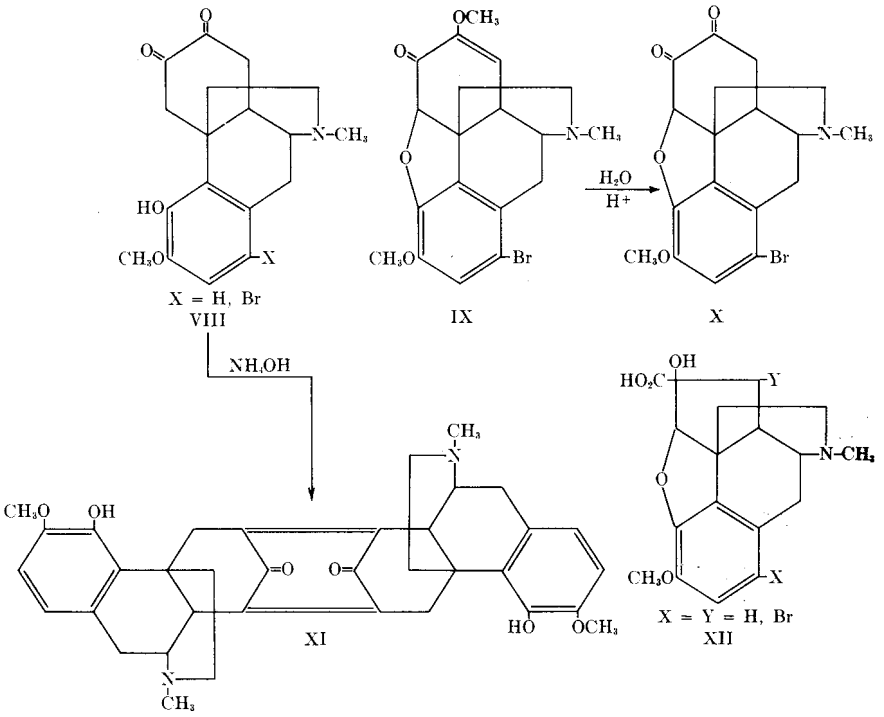
VII

Kondo's formula to I (R = X = H, R′ = CH_3). This revised formula adequately accounts now for the observed dimolecular reduction of sinomenine by sodium amalgam, for the facile hydrolysis of sinomenine to an α-diketone and for the reduction of sinomenine to dihydrosinomenine by zinc amalgam (or zinc dust) and hydrochloric acid. Also, the action of cyanogen bromide upon benzoylsinomenine and methylsinomenine affords a clear-cut argument against a $\Delta^{8\text{-}14}$ double bond in sinomenine. Finally, the formation of monopiperonylidene (31) and 5-hydroxymethyl (42)

derivatives by sinomenine may be readily accommodated on I (R = X = H, R′ = CH_3).

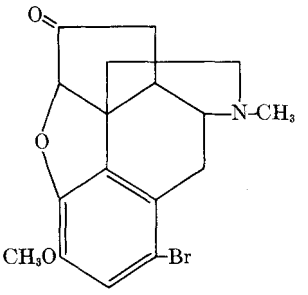
The problems of locating the ends of the ethanamine bridge and the center of attack by bromine resolve themselves into the solution of similar problems for morphine, since sinomenine and bromosinomenine have been transformed into a number of products enantiomorphic with those from codeine and thebaine. Thus 1-bromosinomenine has been related, by an unbroken sequence of reactions, to 1-bromocodeine which in turn was degraded to 1-bromo-3,4-dimethoxyphenanthrene. Hence, the bromination of sinomenine must have occurred at C_1. The problem of the position of the nitrogen bridge in sinomenine, like that of morphine, still awaits solution.

If, however, the nitrogen bridge is assigned, with reservations, to C_9–C_{13}, then 1-bromosinomeninone, 1-bromosinomeneine and 1-bromosinomeneine ketone would be VIII (X = Br), IX and X respectively. If,

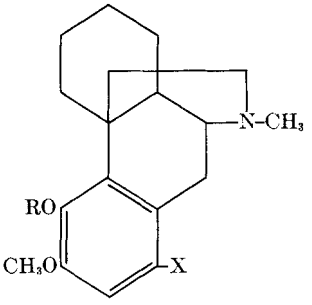


after the acid hydrolysis of sinomenine, the reaction mixture is treated with ammonia, a 10–40% yield of bisdemethylsinomenylidene ($C_{36}H_{38}O_6N_2$) (34, 35) is obtained. This quinonelike dimer, XI, however, is colorless and forms only a monoxime (34).

The bromination of 1-bromosinomeninone and 1-bromosinomeneine ketone provided additional evidence that these bases are α-diketones. 1-Bromosinomeninone brominates in a stepwise fashion, first at C_5 and then at C_8, yielding a crystalline hydrobromide salt of 1,5,8-tribromosinomeninone (8, 9). Upon liberating the base from its hydrobromide salt with either sodium carbonate or sodium hydroxide (70% yield) the hydrophenanthrylene oxide bridge is formed and the benzilic acid rearrangement of the α-diketone grouping yields the α-hydroxy acid, 1,7-dibromosinomenilic acid (XII, X = Y = Br) (the same result is achieved by bromination of 1-bromosinomeneine ketone at C_8 and liberating the base from its hydrobromide salt with alkali (8)). Reductive elimination of one of the bromine atoms by sodium amalgam afforded an acid identical with that from the action of alkali upon 1-bromosinomeneine ketone (8, 10). Hence, the bromine in the derived bromosinomenilic acid must be at C_1. That 1-bromosinomenilic acid (XII, X = Br, Y = H) is an α-hydroxy acid (monobenzoyl derivative (8) and monoethyl ester (8)) is clearly illustrated by its oxidation with fuming sulfuric acid to the cyclic ketone (oxime), 1-bromosinomenilone (XIII) (8). By the proper choice of reducing agents it is possible to remove the halogen atom in this ketone, and then cleave the oxide bridge and finally to reduce the ketone to a methylene group.



XIII



X = H, Br
R = H, CH_3

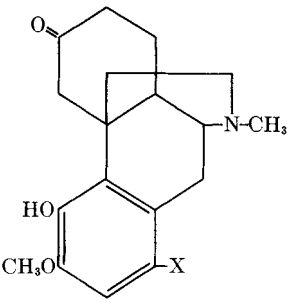
XIV

3. Relation of Sinomenine to Morphine

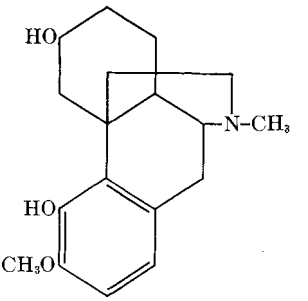
The most direct route for equating these two series of bases lies in the Clemmensen reduction of sinomenine ($C_{19}H_{23}O_4N$), (1, 26, 34, 83a) its dihydro derivative (34) and 1-bromosinomenine (37) to demethoxydesoxodihydrosinomenine (XIV, R = X = H) and its 1-bromo derivative. These bases have the same physical and chemical properties as β-tetrahydrodesoxycodeine (26, 90) (dihydrothebacodine (25), dehydrotetrahydrocodeine (20) or dihydrothebainane (89)) and its 1-bromo derivative, except that their specific rotations are equal and opposite in sign. On admixture

of equal amounts of the respective bases in acetone complete racemization is reported to have ensued[2] (34).

An alternate route to antipodes of the morphine bases lies in reduction of dihydrosinomenine (1, 14, 34, 40, 89) and 1-bromodihydrosinomenine (37) with sodium amalgam. This reagent leads to a difficultly separable mixture (separated through their hydrobromides) (52) of demethoxydihydrosinomenine (XV) and demethoxydihydrosinomeninol (XVI) (in the case of 1-bromodihydrosinomenine, 1-bromodemethoxydihydrosinomenine was the main product and proved to be identical with that from the bromination of demethoxydihydrosinomenine (37)). Demethoxy-



X = H, Br
XV



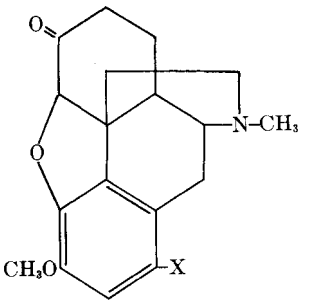
XVI

dihydrosinomenine proved to be the antipode of dihydrothebainone, while demethoxydihydrosinomeninol completely racemized dihydrothebainol-A on admixture of equal amounts of their methiodides (40).

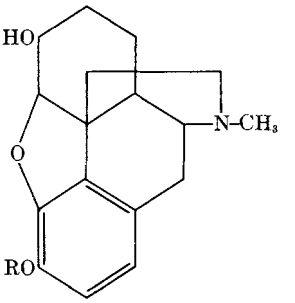
The transformation of sinomenine to the antipode of dihydromorphine provides a third and more circuitous route to the same conclusion. The first phase of this conversion involves the bromination of demethoxydihydrosinomenine. Like dihydrothebainone (3), this base brominates first at C_1 and then at C_5 (5) and the resulting 1,5-dibromodemethoxydihydrosinomenine readily loses the elements of hydrogen bromide, thus generating the oxide bridge of the nonphenolic (no ferric chloride test and insoluble in aqueous alkali) (5) 1-bromodemethoxydihydrosinomeneine ($C_{18}H_{20}O_3NBr$) (XVII, X = Br). This antipode of 1-bromodihydrocodeinone (5) has been catalytically debrominated (H_2 + $PdCl_2$) (5) and the ketone group of the derived demethoxydihydrosinomeneine (XVII, X = H: the antipode of dihydrocodeinone) (5) quantitatively reduced (H_2 + PtO_2 in pyridine solution) (18, 96) to a carbinol (XVIII, R = CH_3). This carbinol is the antipode of dihydrocodeine and its demethylation (XVIII, R = H) com-

[2] It is difficult for the author to understand how demethoxydesoxodihydrosinomenine, with a specific rotation of +43.22°, could be completely racemized by a sample of β-tetrahydrodesoxycodeine with a very weak negative rotation (34).

pletes the conversion of sinomenine to the interesting enantiomorph of dihydromorphine (18, 96). The analogy between the two series of bases has been carried two stages further. Substitution (PCl_5) of a chlorine



X = H, Br
XVII



R = H, CH_3
XVIII

atom for the hydroxyl group of XVIII (R = CH_3) and the elimination of the elements of hydrogen chloride by methanolic sodium methylate afforded the respective antipodes of chlorodihydrocodide and desoxycodeine-C (18).

III. Reactions of Sinomenine and Related Products

The reactions of sinomenine closely mirror those of the morphine alkaloids and where divergencies do occur these may be attributed to the distinctive structural features present in ring III of sinomenine and related products. The most noteworthy differences are to be found in the reduction of these bases with metal combinations and in their reaction toward hydrogen peroxide. On aromatization of the nucleus of codeinone and thebaine the ethanamine bridge is extruded as ethanolmethylamine, whereas methylethylamine results when similar reactions are applied to sinomenine.

1. Substitution

Substitution reactions have not been applied to sinomenine and related products to the same extent as they have to codeine, probably because of the marked susceptibility of these bases to oxidation and acid hydrolysis. So far there is no record of the action of sulfuric acid-acetic anhydride or of nitric acid upon sinomenine. 1-Aminodihydrosinomenine, however, has been prepared by reduction of benzeneazodihydrosinomenine with sodium hydrosulfite (41). It is possible to sulfonate sinomenine (and sinomeninone) without affecting the enol methyl ether by using concentrated sulfuric acid and operating at a low temperature (80). Speculations are that sulfonation occurred at C_1 but, as yet, no experimental evidence has been set forth to confirm this. The two substitution reactions that have been studied most extensively are bromination and hydroxymethylation.

Bromination of the hydrohalide salts of sinomenine (1, 5, 7, 38, 78, 93) and a number of related bases (bis-8,8¹-demethoxydihydrosinomenine (37), demethoxydesoxodihydrosinomenine (37), demethoxydihydrosinomenine (5, 37), dihydrodes-*N*-methyldemethoxydihydrosinomenine (51), dihydrosinomenine (32), and sinomeninonefurazane (48)) yield the respective 1-bromc derivatives. This position has been assigned with certainty to the halogen atom through the relation of bromosinomenine to 1-bromocodeine which in turn has been degraded to 1-bromo-3,4-dimethoxyphenanthrene (the diminished diazo reaction of bromosinomenine (29, 41) and its failure to give a brominated disinomenine on gentle oxidation (29, 32) are in accord with this conclusion). This relationship to 1-bromocodeine was established by comparison of 1-bromodemethoxydesoxodihydrosinomenine (37) with β-1-bromotetrahydrodesoxycodeine (37) (the reaction sequence leading to the latter base was: bromocodeine, bromochlorocodide, bromodesoxycodeine-C and β-1-bromotetrahydrodesoxycodeine[3]).

The yield of monobromosinomenine seldom exceeds 80% (38) because under these conditions bromination proceeds through a second stage to a labile dibromosinomenine (isolated as its hydrobromide) (9) which spontaneously loses the elements of hydrogen bromide yielding (2–20%) the nonphenolic (insoluble in aqueous alkali and negative ferric chloride test) (93) 1-bromosinomeneine ($C_{19}H_{21}O_4N$) (1, 38, 78, 93) (known at various times as isobromosinomenine (38), isobromocucoline (78) and bromosinomenine-B (1)). The disappearance of phenolic properties leaves little doubt that the second bromine atom entered the molecule at C_5 and was subsequently lost in oxide bridge formation (this conclusion has been confirmed by degradation of 1-bromosinomeneine to a derivative of morphenol (5). Bromination alpha to the ketone (as well as at C_1) has also been observed for bromodihydrosinomenine (5), demethoxydihydrosinomenine (5), α-dihydrosinomeninone (12) and sinomeninone (8, 9).

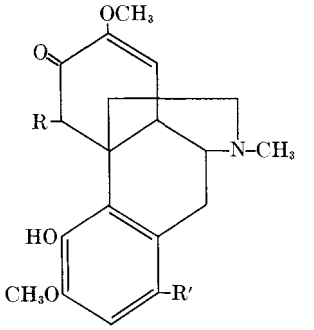
With three moles of bromine the hydrohalide salts of the labile tribromo derivatives of dihydrosinomenine and sinomeninone result (tribromosinomeninone reacts acid because of the ease with which hydrogen bromide is evolved (8, 9)). On liberating the base from 1,5,7-tribromodihydrosinomenine hydrobromide with alkali the C_5 halogen is involved in hydrophenanthrylene oxide formation, while the introduction of the Δ^{7-8} double bond by loss of a second mole of hydrogen bromide completes the conversion to 1-bromosinomeneine (this gives an insight into the location of the double bond in sinomenine) (5). Halogenation of sinomeninone occurs at C_1, C_5 and C_8.

Bromine oxidizes the secondary carbinol to a ketone group in the

[3] This relationship supplies the necessary evidence to assign the bromine atom of bromodihydrocodeinone and bromodihydrothebainone to C_1.

halogenation of α-dihydrosinomeninone and, depending upon the amount of bromine used, 1-bromosinomeninone, 1-bromosinomenilic acid, and 1,7-dibromosinomenilic acid are formed (12).

Boiling formaldehyde, on the other hand, reacts with sinomenine first at C_5 and then at C_1, yielding a separable mixture of 5-hydroxymethylsinomenine ($C_{20}H_{25}O_5N$) (very soluble in methanol-water mixture) and 1,5-dihydroxymethylsinomenine ($C_{21}H_{27}O_6N$) (difficultly soluble in methanol-water mixture) (42). While structure XIX (R = CH_2OH, R′ = H) for hydroxymethylsinomenine has been derived by elimination of other possibilities and still lacks experimental confirmation, yet such a structure does seem to accommodate the requirements of this base quite satisfactorily. This *levo*-rotatory base gives positive ferric chloride and diazo reactions,



R = R′ = H, $-CH_2OH$

XIX

quantitatively absorbs one mole of hydrogen (the hydroxymethyldihydrosinomenine is dextrorotatory and is not available from formalin and dihydrosinomenine), and on acetolysis yields methylethylamine and the triacetyl derivative of a hydroxymethylsinomenol (hence the hydroxymethyl group of hydroxymethylsinomenine cannot be located at C_{13} or C_{14}, or on the ethanamine bridge).

$$C_{20}H_{25}O_5N + 3C_4H_6O_3 \rightarrow (CH_3{-}CO)_3(C_{17}H_{13}O_5) + CH_3{-}NH{-}C_2H_5 + 3CH_3{-}CO_2H$$

5-Hydroxymethylsinomenine, when boiled with formalin, yields 1,5-dihydroxymethylsinomenine (XIX, R = R′ = CH_2OH) which does not give a positive diazo reaction (42) and is stable in hot acetic anhydride (42).

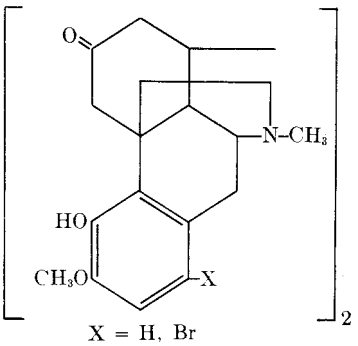
2. Reduction

Metal combinations and catalytic hydrogenation have found the most widespread application in the reduction of sinomenine and related bases, although other reducing agents have been used in a few instances. For example, zinc and hydrochloric acid was one of the first reagents used for reducing sinomenine to dihydrosinomenine (15%) (34, 37). The same

reagent converts 1-bromosinomeneine into 1-bromodihydrosinomenine (5). Sodium hydrosulfite has been used in the reduction of benzeneazodihydrosinomenine to 1-aminodihydrosinomenine (41) and of sinomenine to dihydrosinomenine (20%) (41).

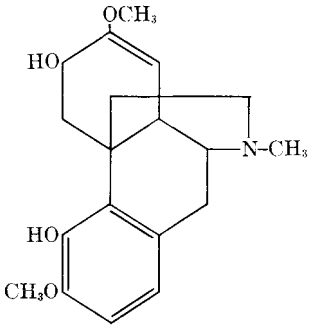
a. Chemical Methods. Reduction of sinomenine to dihydrosinomenine by metal combinations provided the early evidence for the presence of an α,β-unsaturated ketone grouping in this base. Subsequently these reagents proved peculiarly advantageous for demethoxylation, reduction of ketones to carbinols and methylene groups as well as for the dehalogenation of dichlorodihydrosinomenilane.

Reduction of the ethylenic double bond of sinomenine in the cold with zinc amalgam and hydrochloric acid (yield 60%) (34) clearly demonstrates that this cannot be an isolated ethylenic double bond but one in conjugation with some other center of unsaturation, probably the ketone carbonyl. This found added support in the sodium amalgam reduction of sinomenine



X = H, Br

XX



XXI

in alkaline medium. In a fashion diagnostic for α,β-unsaturated ketones (23) sinomenine (but not dihydrosinomenine (34)) underwent dimolecular reduction yielding a separable mixture of bis-8,8¹-demethoxydihydrosinomenine ($C_{36}H_{44}O_6N_2$) (XX, X = H) (1, 34, 89) and bis-8,8¹-demethoxydihydrosinomeninol(?) (89) (a Zeisel determination demonstrated that demethoxylation accompanied dimolecular reduction (34)). From the strong diazo reaction exhibited by bis-8,8¹-demethoxydihydrosinomenine and the reduction of 1-bromosinomenine to the respective dimer without the loss of the halogen atom (the same product is available from the bromination of bis-8,8¹-demethoxydihydrosinomenine) (37), it is inescapable that dimerization did not occur at C_1. Finally, disemicarbazone formation by the dimer (34) effectively disposes of any dimolecular reduction at this point, thus eliminating from consideration all reactive centers except C_8 of the α,β-unsaturated ketone grouping.

It is not to be construed that this reductive demethoxylation is a

reaction diagnostic only for enol ethers of α-diketones because dihydrosinomenine (1, 34, 40, 52, 89) and bromodihydrosinomenine (37) are reductively demethoxylated by the same reagent respectively to the antipodes (XV) of dihydrothebainone (52) and its 1-bromo derivative (52). Reduction of the ketone carbonyl to a secondary carbinol accompanies reductive demethoxylation so that a considerable amount of demethoxydihydrosinomeninol (XVI) can be isolated from the reaction mixture (40, 52, 89). This competing reaction becomes more apparent in the reduction of sinomenine and dihydrosinomenine in acid medium. When these two bases are reduced by sodium amalgam in dilute acetic acid solution, sinomeninol (XXI) and dihydrosinomeninol result respectively in yields of 30% and 50% (40).

When sinomenine (1, 34) and 1-bromosinomenine (37) are reduced in hydrochloric acid solution with zinc amalgam, the reduction products are demethoxydesoxodihydrosinomenine and its 1-bromo derivative (XIV) (dihydrosinomenine (34) and methyldihydrosinomenine (26) under similar conditions yield demethoxydesoxodihydrosinomenine and its methyl ether). The first phase in this transformation undoubtedly is the hydrolysis of the enol ether grouping, followed by the Clemmensen reduction of the derived α-diketone.

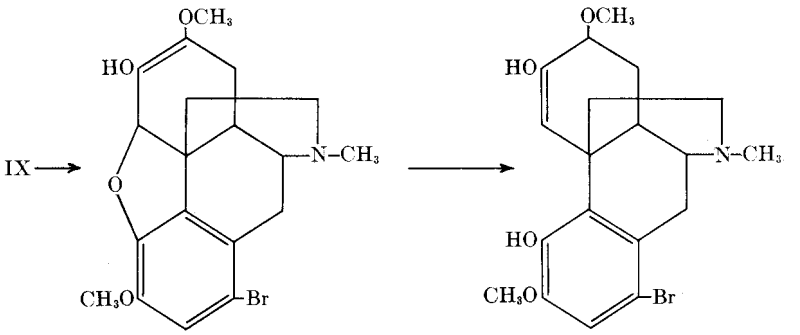
Hydrogenolysis of the oxide bridge of sinomenilone and 1-bromosinomenilone (XIII) has been achieved with sodium amalgam (10). The properties and reactions of the resulting phenolic dihydrosinomenilone are very similar to those of demethoxydihydrosinomenine and dihydrothebainone (10). The Clemmensen reduction of this ketone failed but dihydrosinomenilane was obtained indirectly by conversion of dihydrosinomenilone to the ketodichloride (PCl_5), followed by catalytic dehalogenation (13).

Sodium amalgam will reduce 1,7-dibromosinomenilic acid (XII, X = Y = Br) to 1-bromosinomenilic acid (XII, Y = H, X = Br) (8).

b. Catalytic Hydrogenation. A variety of catalysts have been employed in saturation of the ethylenic double bond, in dehalogenation and in the reduction of ketone carbonyl groups of a number of bases related to sinomenine. In a single instance hydrogenolysis of the oxide bridge has been recorded. Attempts to reduce the benzene nucleus of sinomenine, however, have not been described.

The hydrogenation of the enol ether double bond of sinomenine (1, 40, 78, 82), methylsinomenine (26), 1-bromosinomenine (37), 5-hydroxymethylsinomenine (42) (the hydrogenation of 1,5-dihydroxymethylsinomenine failed under similar conditions) (42) disinomenine (1, 30, 78, 86), pseudodisinomenine (30) (due to the dimeric nature of disinomenine and pseudodisinomenine two moles of hydrogen were absorbed and the respective

tetrahydro derivatives obtained) and sinomeninol (40) has been achieved in the presence of such catalysts as colloidal platinum, colloidal palladium, and palladium on charcoal (for the hydrogenation of the Δ^{9-10} double bond of various des-bases see p. 244). In the case of 1-bromosinomeneine two moles of hydrogen are absorbed over colloidal palladium yielding, amongst other products, the phenolic 1-bromodihydrosinomenine (a more uniform product is obtained by reduction with zinc and hydrochloric acid) (5). This abnormal type of reduction (see pseudocodeine) would suggest that the first mole of hydrogen adds 1,4 to the α,β-unsaturated ketone, followed by a similar addition to the derived allyl ether (XXII) and ketonization of the resulting enol (XXIII).



XXII XXIII

The marked influence on the optical rotation of an ethylene alpha-beta to a center of asymmetry (77) is again apparent in this series of bases. When the double bond alpha-beta to C_{14} (at Δ^{7-8} or, in the case of the des-*N*-methyldihydro bases, at Δ^{9-10}) is reduced, there is an accompanied inversion of the sign of rotation (Table 2).

Two supported catalysts (Pd on $BaSO_4$ and Pd on C) and palladous chloride have been successfully used in the catalytic dehalogenation of bromodemethoxydihydrosinomeneine (5), bromodihydrosinomenine (32), bromosinomenilone (10) and bromotetrahydrosinomeninone (XXIV) (55). In the case of bromosinomenine, hydrogenation of the double bond accompanies dehalogenation (32). Palladium on barium sulfate proved to be an effective catalyst for the reduction of dichlorodihydrosinomenilane (PCl_5 on dihydrosinomenilone) to dihydrosinomenilane (13).

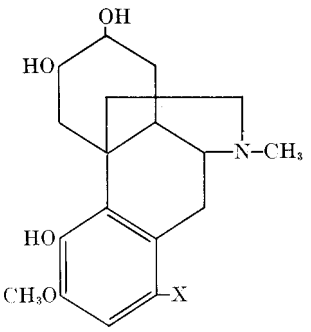
The crux in the conversion of sinomenine to the antipode of dihydromorphine proved to be the reduction of the ketone group of demethoxydihydrosinomeneine to a carbinol. After reduction by sodium amalgam in both acid and alkaline medium and the Clemmensen method failed, it was found that it could be quantitatively reduced in pyridine solution over platinum oxide catalyst (18, 96). Then by proper choice of the catalyst

TABLE 2

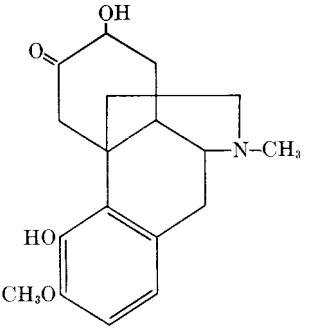
SPECIFIC ROTATION OF THE SINOMENINE BASES AND THEIR HYDRO DERIVATIVES

Product	$[\alpha]_D$	$[\alpha]_D$ of the hydro derivative	References
Bromosinomenine	−8.87°	+102.4°	38, 32
Des-*N*-methyl-1-bromodemethoxydihydrosinomenine	−8.67°	+61.60°	51, 51
Des-*N*-methyldemethoxydihydrosinomeneine	+4.00°	+50.00°	52, 52
Des-*N*-methyldemethoxydihydrosinomenine	−54.94°	+67.82°	4, 4
Des-*N*-methyldihydrosinomenilane	−98.22°	+45.48°	13, 13
Des-*N*-methyldihydrosinomenilone	+18.55°	−24.56°	10, 10
Disinomenine	−149.97°	+264.41°	93, 29, 30
5-Hydroxymethylsinomenine	−40.71°	+73.03°	42, 42
Pseudodisinomenine	−127.03°	+167.00°	29, 30
Sinomenine	−73.92°	+193.58°	78, 93
Sinomeninol	−23.70°	+1.93°	40, 40

it has been found possible to reduce one or both of the carbonyl groups of various sinomeninones to hydroxyl groups. With palladium, sinomeninone (12, 35) absorbs one mole of hydrogen yielding a separable mixture (only one product has been isolated from the analogous reduction of methylsinomeninone (39)) of the isomeric α- and β-dihydrosinomeninones (the same pair of isomers result when 1-bromosinomeninone reacts with two moles of hydrogen in the presence of a supported palladium catalyst (12)). When,



X = H, Br
XXIV



XXV

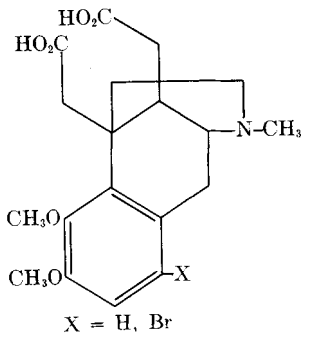
however, a pyridine solution of 1-bromosinomeninone is hydrogenated over Adams' catalyst, two moles of hydrogen are absorbed transforming it into the glycol, 1-bromotetrahydrosinomeninone (XXIV) (triacetyl derivative) (55).

The nature of the isomerism of α- and β-dihydrosinomeninone is still obscure. At first it was considered to be a structural isomerism at C_6 and C_7 (–CO–CHOH– and –CHOH–CO–), but the ease with which alpha isomerized into beta dihydrosinomeninone (heating above its melting point or with 5% NaOH solution or 25% HBr) made it highly probable that only an epimerization had occurred (12). Selective demethylation (25% HBr) of dihydrosinomenine to α-dihydrosinomeninone (the reagent in turn isomerized part of it to the β-form) argues strongly in favor of XXV for the structure of the α- form (12).

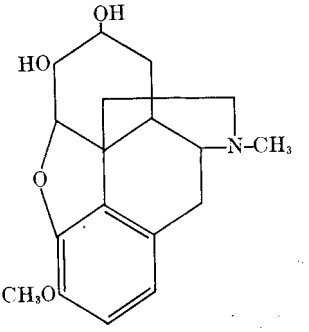
3. Oxidation

As was true for the morphine alkaloids, oxidative degradation has contributed nothing significant with regard to the constitution of sinomenine. The oxidation of methylsinomeninone and its 1-bromo derivative to dicarboxylic acids with hydrogen peroxide characterized these bases as α-diketones. Also, a new hydroxycodeine and its antipode have been prepared by the gentle oxidation of the enantiomorphic desoxycodeines-C with aqueous potassium permanganate. In general, gentle oxidizing agents only lead to dimeric products.

Acetic acid solutions of methylsinomeninone ($C_{19}H_{23}O_4N$) (7) and its 1-bromo derivative (56) (1-bromosinomeneine ketone, X, acts similarly (7)) are oxidized by hydrogen peroxide to the dicarboxylic acids, methylsinomeninic acid ($C_{19}H_{23}O_6N$) and its 1-bromo derivative (XXVA) containg the same number of carbon atoms as their progenitors (hence, methyl-



XXVA



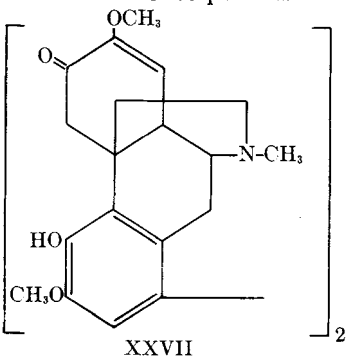
XXVI

sinomeninone is an α-diketone). Sinomeninone and 1-bromosinomeninone have been oxidized in a similar manner but, because of the lactonization of the C_5 carboxyl group with the C_4 hydroxyl, the derived sinomeninic acids were monobasic (7). Methylsinomeninic acid, when heated with acetic anhydride, lost carbon dioxide to form a cyclic ketone, methyldihydrosinomenilone (63) (a more circuitous route to the same type of compound has already been described). The conversion of this dicarboxylic acid to

a cyclic ketone imposes the limitation that ring III of sinomenine must be either a six ring or a seven ring.

Enantiomorphic 7-hydroxydihydrocodeine and 7-hydroxydemethoxydihydrosinomeneinol (XXVI) have been prepared by the mild oxidation of the double bond of desoxycodeine-C and its antipode with aqueous potassium permanganate (55). The nonconformity of physical constants of this 7-hydroxydihydrocodeine with those of the dihydrohydroxycodeines derived from hydroxycodeinone (thebaine + H_2O_2) unequivocally establishes that the hydroxyl group of hydroxycodeinone is not at C_7. 1-Bromosinemeneine has been regenerated from 1-bromosinomeneine alcohol by oxidation with chromic anhydride or potassium permanganate in acetone but not by hydrogen peroxide or sodium hypobromite (63b).

Sinomenine (1, 29, 93), dihydrosinomenine (30), and demethoxydihydrosinomenine (14) (but not 1-bromosinomenine (29, 32)), like morphine and the associated bases with a C_4 hydroxyl group and an unsubstituted C_1 position, undergo oxidative dimerization with such mild oxidizing agents as ferric chloride (78, 93), aurichloride (29, 93), hydrogen peroxide (29), potassium ferricyanide (30, 32, 78), potassium permanganate (78, 93), and silver nitrate (30, 32, 50, 78). Sinomenine yields a mixture of two isomers (29), disinomenine ($C_{38}H_{44}O_8N_2$) (1, 29, 78, 93) (23–50% yield) (78) and pseudodisinomenine (it is reported that disinomenine, but not pseudodisinomenine, occurs to a limited extent in Sinomenium plants (29, 78, 93)). The forty fold decrease in the intensity of the diazo reaction (Table 1) of disinomenine and pseudodisinomenine combined with the failure of 1-bromosinomenine to yield an analogously constituted dimer (29) has prompted the inference that disinomenine is XXVII. The nature of this isomerism is still obscure. It is hardly likely that the difference is in the position of the double bond because this difference persists in the derived tetrahydro



XXVII

derivatives (30). It has been suggested that the ethanamine bridge may not occupy the same position in the two bases, but there is, as yet, no experimental evidence to substantiate this (30). Disinomenine and pseudo-

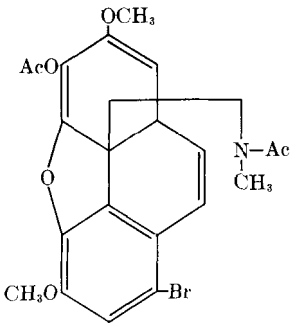
disinomenine, like sinomenine, are aromatized by acetolysis and the derived tetraacetyldisinomenol is identical with that obtained from the air oxidation of sinomenol in the presence of 66% potassium hydroxide solution (29).

4. Fission Around the Nitrogen Atom

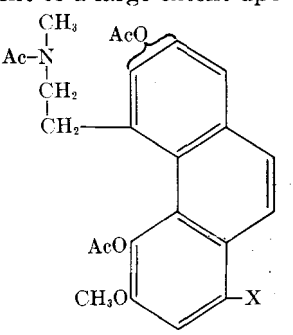
A number of reagents causing fission around the nitrogen atom have been applied to sinomenine and the derived bases and, while fission of type D has been achieved in one instance, rupture of the heteroazo ring is somewhat more common. In some instances these fissions are accompanied by migration of the ethanamine bridge, with attendant aromatization of the nucleus in some cases and not in others. On the whole sinomenine and sinomeninone are very similar to thebaine and codeinone, requiring, as they do, but slight chemical stimulus for the extrusion of the nitrogen complex. While the Hofmann method has found more widespread application than any of the other methods, nevertheless, several anomalies have been observed to occur.

Of the many reagents that normally effect fissions of type D only cyanogen bromide has been applied to benzoylsinomenine and methylsinomenine (89). In both instances the respective halogenfree cyanonor derivatives were isolated but no attempt was made to isolate the nor bases themselves or to replace the methyl group of sinomenine by alkyl groups of larger dimensions. The formation of these halogen-free products rather than brominated cyanamides implies that the double bond in ring III is not beta-gamma to the nitrogen atom in these bases and may be used as evidence to refute Kondo's second formula (IV) for sinomenine.

The effect of acetic anhydride (benzoic anhydride has been used in some instances) upon these bases is dependent to a large extent upon their



XXVIII



X = H, Br

XXIX

structure. Two acetyl residues (micro acetyl determinations) are introduced by this reagent into 1-bromosinomeneine ($C_{19}H_{20}O_4NBr$) with the formation of the nonbasic bromodiacetylsinomenenine ($C_{23}H_{24}O_6NBr$) (49) (1-bromosinomeneine methiodide is converted, by the same reagent, into

(30%) 1-bromodiacetylsinomenol (49)). The non-basic character of the reaction product reveals that one acetyl residue has been introduced by acetylytic cleavage of a C–N bond (probably of type M), while enolization of the ketone and its reaction with the reagent probably accounts for the second acetyl residue. If this is correct, then bromodiacetylsinomenenine is probably XXVIII.

Under the same conditions of acetolysis the C_9–N bond of sinomeninone and 1-bromosinomeninone is broken and ring III is aromatized by loss of the ethanamine chain or by its migration to C_5. Migration of the nitrogen complex to C_5 seems to be favored in this case because the yield of triacetylisothebenine and 1-bromotriacetylisothebenine (XXIX) is many fold greater than that of 3-methoxy-4,6-diacetoxyphenanthrene and its 1-bromo derivative (6, 9). It is still uncertain whether the C_6 or C_7 ketone carbonyl of these α-diketones is the precursor for the acetoxyl group in ring III of the derived triacetylisothebenines. Extrusion of the ethanamine bridge becomes the predominant reaction in the acetolysis of 1-bromosinomeneine ketone (49). Failure to replace the acetyl residues in the resulting 1-bromotriacetyl-3-methoxyphenanthrene by methyl groups has, so far, prevented comparison of this phenanthrene with 1-bromosinomenol dimethyl ether (49). Complete aromatization of the nucleus by this reagent accompanies extrusion of the ethanamine bridge from sinomenine (31), disinomenine (29), pseudodisinomenine (29), and 5-hydroxymethylsinomenine (42) (1,5-dihydroxymethylsinomenine, on the other hand, is not affected (42)).

Potassium hydroxide was the first reagent used in the aromatization of the nucleus of sinomenine (93). If a good yield of sinomenol (V) is to be obtained, conditions must be carefully controlled to minimize its aerial oxidation to disinomenol (29, 94a) (if the C_4 hydroxyl of sinomenol is methylated, oxidative dimerization occurs instead at C_5 (45)).

While these reagents provide a number of interesting transformation products, nevertheless ring fission by the Hofmann method has been the one most extensively studied (Table 3). The product, resulting from sinomenine methiodide, depends largely upon the concentration of the alkali used. With 2% sodium hydroxide solution a phenol betaine(?) is formed (44, 94), which, in turn, has been transformed by more concentrated alkali (5%) into a series of isomeric sinomeninemethines (94). These methines are also available from the action of alkali upon sinomenine methiodide (44) (methylsinomenine also yields a pair of isomeric methines (94)).When sinomenine methiodide is boiled for one minute with two mole equivalents of 2% sodium hydroxide solution a good yield of sinomenineachromethine is obtained (a very weak halochromy is developed by this methine in concentrated sulfuric acid). This primary methine may be transformed into sinomenineviolomethine (dark blue halochromy with

TABLE 3

SOME PRODUCTS OF HOFMANN DEGRADATION

Methiodide of	Reagent	Basic fragment	Nonbasic fragment	Reference
Bis-(8,8′)-demethoxydihydrosinomenine	25% KOH	Bis-des-*N*-methyl demethoxydihydrosinomenine	..	14
Bis-des-*N*-methyldemethoxydihydrosinomenine	25% KOH	..	(−)Bis-dehydrothebenone	14
Bis-dihydro-des-*N*-methyldemethoxydihydrosinomenine	25% KOH	..	(−)Bis-(1,1[1])-thebenone	14
1-Bromodemethoxydihydrosinomeneine	2% NaOH	Des-*N*-methyl-1-bromodemethoxydihydrosinomeneine	..	52
1-Bromodemethoxydihydrosinomenine	15% NaOH	Des-*N*-methyl-1-bromodemethoxydihydrosinomenine	..	51
1-Bromoethylsinomenine[a]	Dilute alkali	..	1-Bromo-3,7-dimethoxy-4-ethoxyphenanthrene	61
1-Bromomethylsinomenine	1% NaOH	Des-*N*-methyl-1-bromomethylsinomenine	..	56
1-Bromosinomeneine	10% NaOH	Des-*N*-methyl-1-bromodehydrometasinomenine	..	57
1-Bromosinomeneine	5% NaOH	Des-*N*-methyl-1-bromosinomeneine	..	5
1-Bromosinomenine	2% NaOH	Des-*N*-methyl-1-bromosinomenine	..	5
1-Bromosinomeninone dioxime	16.5% KOH	Des-*N*-methyl-1-bromosinomeninone furazane	..	48
Demethoxydesoxodihydrosinomenine	16.5% KOH	Des-*N*-methyldemethoxydesoxodihydrosinomenine	..	46
Demethoxydihydrosinomeneine	10% NaOH	Des-*N*-methyldemethoxydihydrosinomeneine	..	52
Demethoxydihydrosinomenine	25% KOH	Des-*N*-methyldemethoxydihydrosinomenine	..	4
Des-*N*-methyl-1-bromodemethoxydihydrosinomenine	11% NaOH	..	(−)1-Bromodehydrothebenone	51

[a] The ethiodide was employed in this instance.

TABLE 3 (*Continued*)

Methiodide of	Reagent	Basic fragment	Nonbasic fragment	Reference
Des-*N*-methyl-1-bromomethylsinomenine	5% NaOH	..	1-Bromomethylsinomenol	56
Des-*N*-methyl-1-bromosinomeneine	10% NaOH	..	1-Bromo-3-methyl-6,7-dimethoxymorphenol	5
Des-*N*-methyl-1-bromosinomenine	10% NaOH	..	1-Bromodimethylsinomenol	5
Des-*N*-methyl-1-bromosinomeninone furazane	16.5% KOH	Trimethylamine	1-Bromodihydro-*l*-thebenone-7-Ketone furazane	48
Des-*N*-methyldemethoxydesoxodihydrosinomenine	..	Trimethylamine	Dehydrothebenane	46
Des-*N*-methyldemethoxydihydrosinomenine	25% KOH	Trimethylamine	Dehydrothebenone	4
Des-*N*-methyldihydrosinomenilane	16.6% KOH	Trimethylamine	Sinomelane	13
Des-*N*-methyldihydrosinomenilone	16.6% KOH	..	Anhydro-bis-sinomelone	10
Des-*N*-methyldihydrosinomenine	16.5% KOH	Trimethylamine	7-Methoxydehydro-*l*-thebenone	47
α-Des-*N*-methylmethylsinomenine[b]	2% NaOH	Trimethylamine	Trimethoxyvinylketotetrahydrophenanthrene	94
Des-*N*-methylsinomeninone furazane	16.5% KOH	Trimethylamine	Dehydro-*l*-thebenone-7-ketone furazane	46
Dihydrodes-*N*-methyl-1-bromodemethoxydihydrosinomenine	25% KOH	Trimethylamine	(−)1-Bromo thebenone	51
Dihydrodes-*N*-methyldibromosinomeninone furazane	16.5% KOH	..	Dibromodehydrothebenone-7-ketone ketone furazane	48
Dihydrodes-*N*-methyldemethoxydesoxodihydrosinomenine	16.5% KOH	Trimethylamine	Thebenane	46
Dihydrodes-*N*-methyldemethoxydihydrosinomenine	11% NaOH	Trimethylamine	*l*-Thebenone	4
Dihydrodes-*N*-methyldihydrosinomenilane	16.5% KOH	Trimethylamine	Dihydrosinomelane	13
Dihydrodes-*N*-methyldihydrosinomenilone	16.6% KOH	..	Anhydro-bis-dihydrosinomelone	10

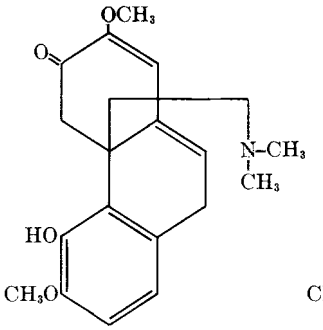
[b] The methylmetho sulfate was employed in this instance.

TABLE 3 (*Continued*)

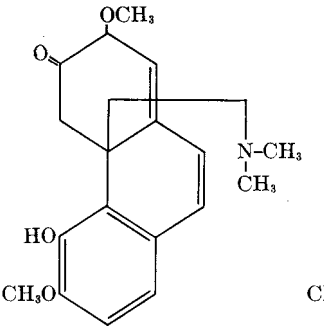
Methiodide of	Reagent	Basic fragment	Nonbasic fragment	Reference
Dihydro-des-*N*-methyldihydrosinomenine	16.5% KOH	Trimethylamine	7-Methoxy-*l*-thebenone	47
Dihydro-des-*N*-methylsinomeninone furazane	16.5% KOH	..	*l*-Thebenone-7-ketone furazane	46
Dihydrosinomenilane	16.5% KOH	Des-*N*-methyldihydrosinomenilane	..	13
Dihydrosinomenilone	16.6% KOH	Des-*N*-methyldihydrosinomenilone	..	10
Dihydrosinomenine	16.5% KOH	Des-*N*-methyldihydrosinomenine	..	47
Methylsinomenineviolomethine[b]	2–25% NaOH	Trimethylamine	4,4[1]-Dimethyl-bis(5,5[1])-sinomenol	45
Sinomenine	5% NaOH	α-Methylsinomenine-methine β-Methylsinomenine-methine	..	94
Sinomenine	2% NaOH	Sinomenine achromethine	..	44
Sinomenine	5% NaOH	Sinomenine violomethine Sinomenine roseomethine	..	44
Sinomenine[b]	33% NaOH	Methylsinomenine violomethine Methylsinomenine roseomethine	..	45
Sinomenine achromethine	3.3% NaOH	..	Sinomenol	44
Sinomenine violomethine	3.3% NaOH	..	Sinomenol	44
Sinomeninone furazane	16.5% KOH	Des-*N*-methylsinomeninone furazane	..	46

sulfuric acid) by boiling its methiodide with 10% sodium hydroxide solution. The two steps are achieved simultaneously when sinomenine methiodide is boiled with 5% sodium hydroxide but now the violomethine has to be separated from 7% of sinomenineroseomethine (red halochromy with sulfuric acid). The achromethine is converted to the roseomethine on long standing or by boiling a methanolic solution of the methine for a short time with a trace of sodium bicarbonate. The isomerization of the roseomethine methiodide to the violomethine by 10% sodium hydroxide completes the interrelationship of these methine bases (44). Fission of type M (the influence exerted by the free C_4 hydroxyl of α- and δ-methyldihydrothebaine on isomethine formation does not seem to operate in the case of

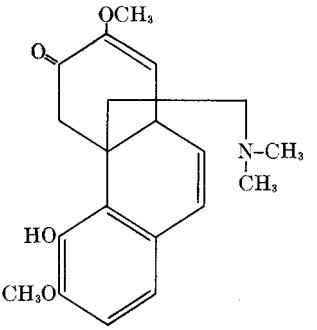
sinomenine) would appear to have occurred and migration of the ethanamine chain to other than an angular position seems to be excluded by conversion of these methines (KOH) to sinomenol (44). While no experimental substantiation is yet at hand, it is considered that the isomerism of these methines, as in the case of α- and β-methylmorphimethine, is due to positional differences of the double bonds (44). Because of the close analogy (high rotatory power and intense halochromy) with β-methylmorphimethine, sinomenineviolomethine has been tentatively assigned structure XXXI (this should no longer exhibit properties of an enol methyl ether). The weak halochromy of sinomenineachromethine has been attrib-



XXX



XXXI



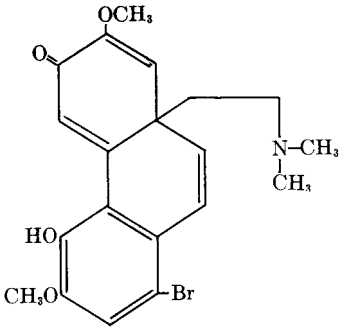
XXXII

uted to the absence of a Δ^{9-10} double bond so structure XXX has been assigned provisionally to this methine. Color reactions would suggest structure XXXII for the roseomethine.

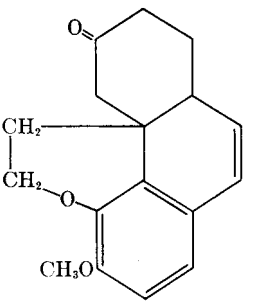
While demethoxydihydrosinomenine and 1-bromosinomeneine, amongst others, yield only one des-base, nevertheless the course of the Hofmann reaction upon the latter base is largely dependent upon the experimental conditions. If 5% sodium hydroxide solution is used, the normal des-base results (5), but with more concentrated solutions (10%) deep-seated changes occur yielding des-*N*-methyl-1-bromodehydrometasinomenine (57). This des-base, like metathebainone, is yellow and gives a red sodium salt. The ethanamine chain must be located at an angular position since it is lost in boiling acetic anhydride to give a quantitative yield of 1-bromodiacetylsinomenol. The oxide bridge must have been cleaved in the process because this des-base is now soluble in alkali and yields a monomethyl ether (a green color is developed with ferric chloride solution). On this circumstantial evidence, structure XXXIII has been tentatively assigned to this des-base. This migration (in alkaline medium) of the ethanamine chain to C_{14}, if correct, is very unusual because mineral acid usually promotes such a change.

A number of these des-bases and their 9,10-dihydro derivatives have

been exhaustively methylated and subjected to a Hofmann degradation (Table 3). When the phenolic hydroxyl, as in methylsinomeninemethine (94), is protected as its methyl ether, it is sometimes possible to isolate the primary vinyl compound but this residue of the original side chain is usually lost simultaneously with aromatization of the nucleus. When,



XXXIII



XXXIV

however, the C_4 hydroxyl in these methines is not protected, then the primary vinyl group, resulting from the second Hofmann degradation, usually interacts with the phenolic hydroxyl yielding cyclic ethers. When des-*N*-methyldemethoxydihydrosinomenine methiodide (the same holds true for its 1-bromo derivative (51)) was degraded in such a manner, *l*-dehydrothebenone (XXXIV) results, which in turn may be converted to the antipode of thebenone by hydrogenation of the Δ^{9-10} double bond (4). This *l*-thebenone is also available from the Hofmann degradation of dihydro-des-*N*-methyldemethoxydihydrosinomenine (4).

Secondary reactions occur in the Hofmann degradation of the methiodides of des-*N*-methyldihydrosinomenilone and dihydro-des-*N*-methyldihydrosinomenilone. The respective nitrogen-free products, anhydro-bis-sinomelone and anhydro-bis-dihydrosinomelone (10), are dimeric and will not form an oxime. Des-*N*-methyldihydrosinomenilane and its 9,10-dihydro derivative, on the other hand, behave quite normally (13).

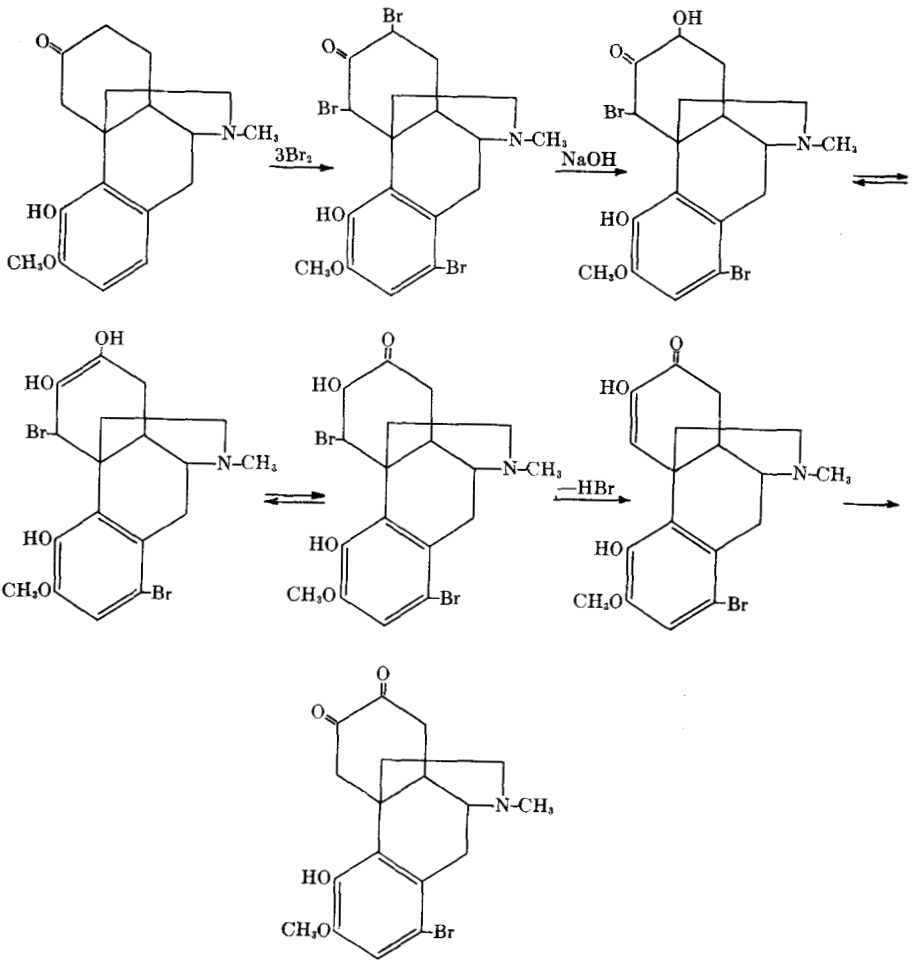
The Hofmann degradation of des-*N*-methyl-1-bromosinomeneine (like β-methylmorphimethine) yields, after methylation ($(CH_3)_2SO_4$ + NaOH), 1-bromo-5,6-dimethoxy-3-methylmorphenol (5).

IV. Partial Synthesis of the Antipode of 1-Bromosinomeninone

Dihydrothebainone brominates progressively at C_1, C_5, and C_7. If the product resulting from treatment of this base with three mole equivalents of bromine, without isolating it, is digested with dilute aqueous alkali, a diketone (dioxime) results ($C_{18}H_{20}O_4NBr$) whose properties and reactions

are those required for the antipode of 1-bromosinomeninone (6). The mechanism for this transformation, as proposed by Schöpf, may be depicted as shown below.

This product, like 1-bromosinomeninone, gave a mixture of 1-bromotriacetylisothebenine and 1-bromo-3-methoxy-4,6-diacetoxyphenanthrene (6) when heated with acetic anhydride. With bromine the antipode of 1-bromosinomenilic acid was formed (11).



V. Table of Physical Constants

The conventions used in Table 4 are those adopted for tabulating the properties of the various alkaloids in Chapters 6, 7, and 8.

TABLE 4

SINOMENINE AND RELATED PRODUCTS

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		A		
1-Aminodihydrosinomenine				
Dihydrochloride (monohydrate)	>300	..	Stout prisms (C_2H_5OH–$CHCl_3$)	41
Anhydro-bis-dihydrosinomelone	246–247	..	Prisms (C_2H_5OH)	10
Anhydro-bis-sinomelone	266	−522.7° ($CHCl_3$)	Prisms (C_2H_5OH)	10
		B		
Benzeneazodihydrosinomenine	231 (dec)	..	Red prisms (CH_3OH)	41
Benzeneazosinomenine	253	..	Red hexagonal plates (nitrobenzene)	41
(−)Bis-(1,1¹)-dehydrothebenone	208–212	−201.9° ($CHCl_3$–CH_3OH)	Prisms (HOAc)	14
Bis-demethoxydihydrosinomenine	305 (dec)	..	..	89
Bis-(8,8¹)-demethoxydihydrosinomenine	304	−24.5°(H_2O–HCl)	Stout prisms	34, 1
Methiodide	>300	..	Needles	34, 1
Semicarbazone	>300	..	..	34, 1
Bis-demethoxydihydrosinomeninol	180–220 (dec)	..	..	89
Bis-(demethyl)-sinomenilydene	>312	..	Prisms	34, 35
Hydrochloride	..	+335.5° (H_2O–HCl)	..	34
Methiodide	>300	..	Needles (H_2O)	34
Dioxime	>315	..	..	34
Monosemicarbazone	>300	..	Crystals ($CHCl_3$)	34
Bis-(1,1¹)-des-*N*-methyldemethoxydihydrosinomenine	252	+45.1° ($CHCl_3$)	Prisms	14
Bis-(1,1¹)-dihydrodes-*N*-methyldemethoxydihydrosinomenine	248–249 (dec)	+33.16° ($CHCl_3$)	Fine prisms	14
(−)Bis-(1,1¹)-thebenone	230–233	−163.3° ($CHCl_3$–CH_3OH)	..	14

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
1-Bromodehydrosinomenine				
Diacetyl-	203	..	..	58
Methiodide	204	..	..	58
(−)1-Bromodehydrothebenone	145	−186.8° ($CHCl_3$)	Prisms ($CHCl_3$)	51
(−)1-Bromodehydrothebenone-7-ketofurazane	191	..	Crystals (HOAc–H_2O)	48
9(?)-Bromo-	152–153	..	Plates (acetone)	48
1-Bromodemethoxy desoxodihydrosinomenine	127	+40.44° (C_2H_5OH)	Prisms (acetone)	37, 8
Methiodide	253–255	..	..	37
1-Bromodemethoxydihydrosinomeneine	206	+161.02° ($CHCl_3$)	Prisms (CH_3OH)	5
Hydrobromide	217	..	..	5
1-Bromodemethoxydihydrosinomenine	127 167	+78.67° (CH_3OH–$CHCl_3$)	Prisms (acetone)	52, 37
Methiodide	127 (dec)	..	Prisms (H_2O)	37
Oxime	263 (dec)	..	Prisms	37
1-Bromodiacetylsinomenenine	135	+8.84° ($CHCl_3$)	Yellow prisms (CH_3OH)	49
1-Bromodihydrosinomenilone	224	..	Prisms (C_2H_5OH)	10
Methiodide	220 (dec)	..	Crystals (H_2O)	10
Benzoyl-	180	..	Prisms (C_2H_5OH)	10
Oxime	222 (dec)	..	Crystals (C_2H_5OH)	10
Hydrochloride	280	..	..	10
1-Bromodihydrosinomenine	236–237	+102.4° ($CHCl_3$)	Long prisms ($CHCl_3$)	32,5,37,63b
Hydrobromide	229–232 (dec)	..	..	32
Methiodide	225 (dec)	..	Prisms	32
Semicarbazone	250 (dec)	..	Flat prisms (CH_3OH–H_2O)	32, 63b
1-Bromodihydrosinomeninone	231	..	Long prisms (C_2H_5OH)	39
Oxime	147	..	..	39
1-Bromoisothebenine				
Triacetyl-	191	..	Dense prisms	9, 6
1-Bromosinomeneine	217	−83.03° ($CHCl_3$)	Prisms (C_2H_5OH)	38, 1, 3, 5, 9, 78, 93, 63b
Hydrobromide	229	..	..	38, 78
Hydrochloride	231 (dec)	+51.8°	..	38, 78
Methiodide	211–212	..	..	38, 78

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Oxime	162	..	..	38
Hydrochloride	>280	..	..	38
1-Bromosinomeneine alcohol	171	+53.5° (CH_3OH)	Crystals (CH_3OH)	63b
Methiodide	232–233	..	Crystals (H_2O)	63b
Monobenzoate	194.5	..	Crystals (C_2H_5OH–acetone)	63b
1-Bromosinomeneine ketone	198	+119.9°	Crystals ($CHCl_3$)	38
Methiodide	195 (dec)	..	..	38
Dioxime	173.5 (dec)	..	..	38
Hydrochloride	212	..	..	38
1-Bromosinomeneinic acid	261–262 (dec)	+34.6° (H_2O)	Prisms	7
Methiodide	249 (dec)	+45.77° (H_2O)	Prisms (H_2O)	7
1-Bromosinomenilic acid	290–293	+91.58° (NaOH)	Dense prisms (CH_3OH)	11,8
Methiodide	180 (dec)	..	Prisms (H_2O)	8
Acetyl-	265 (dec)	..	Prisms (C_2H_5OH)	8
Benzoyl-	267	..	Prisms ($CHCl_3$–CH_3OH)	8
Ethyl ester	62	..	Dense prisms (C_2H_5OH)	8
1-Bromosinomenilone	179	+243.4° (C_2H_5OH)	Needles (C_2H_5OH)	8
Methiodide	220 (dec)	..	Needles (H_2O)	8
Oxime	270 (dec)	..	Prisms (ether)	8
1-Bromosinomenine	153	−8.87° ($CHCl_3$)	Needles (C_2H_5OH–H_2O)	38,1,3, 5, 7, 78, 93
Hydrobromide	232	..	..	38,7,78
Hydrochloride trihydrate	116	−30.19°	..	38, 78
Methiodide	80	..	..	38,78
Oxime	215 (dec)	..	..	7, 38
Ethyl ether ethiodide	234	..	..	61
Methyl ether methiodide	257	..	..	56, 60
1-Bromosinomeninic acid	251	+70.25° (H_2O)	Colorless prisms	7
Hydrobromide	306 (dec)	+54.82° (H_2O)	Plates (H_2O–HBr)	7
Hydrochloride	292 (dec)	..	Plates	7
Methiodide	276 (dec)	+49.7° (H_2O)	Colorless prisms	7
Methyl ether	271	..	..	56
1-Bromosinomeninone	227–228	+54.52° (C_2H_5OH)	Prisms (CH_3OH)	36,5,6, 7,8,9, 38

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methiodide	244–246	..	Crystals (H_2O)	36,5,6,38
Dioxime	189 (dec)	..	..	36,5,6,38
Methiodide	254 (dec)	..	..	48
Furazane	262 (dec)	..	Dense prisms	48
Disemicarbazone	118 (dec)	..	Crystals (acetone)	36
Imine	233	+110.9° ($CHCl_3$)	Prisms ($CHCl_3$–CH_3OH)	36
Oxime	300 (dec)	..	Colorless prisms	36
Methyl ether	110	..	..	56
1-Bromotetrahydrosinomeninone	136	..	..	55
Triacetyl	184	..	..	63b
(−)1-Bromothebenone	70	−22.67° ($CHCl_3$)	Crystals (CH_3OH)	51
(−)1-Bromothebenone-7-keto furazane	202–203	..	Prisms(HOAc–H_2O)	48
		C		
(+)Chlorodihydrocodide	173	+177.2° ($CHCl_3$)	..	18
Methiodide	248	+114.8° (C_2H_5OH)	Crystals (CH_3OH)	18
Cyanonorsinomenine				
Benzoyl-	257	−14.42° ($CHCl_3$)	..	89
Methyl ether	245–246	+39.31°	..	89
		D		
Dehydrothebenane	..	−175.7° (CH_3OH)	..	46
l-Dehydrothebenone	113	−206.87° ($CHCl_3$)	Prisms (ether)	4
l-Dehydrothebenone-7-keto furazane	200	−485.2° ($CHCl_3$)	Prisms (CH_3OH)	46
Demethoxydesoxodihydrosinomenine	150–151	+48.2° (C_2H_5OH)	Hexagonal plates (acetone)	1, 34
Hydriodide	250–251	..	Long needles (H_2O)	1, 34
Methiodide	265	..	Needles (H_2O)	1, 34
Methyl ether Hydriodide	104–106	+20.53° (H_2O)	Needles	26
Methiodide	257–258(froth)	..	..	26
Demethoxydihydrosinomeneine	193	+207.42° ($CHCl_3$)	Long prisms	5
Methiodide	259–260	+99.26° (H_2O)	Leaflets (H_2O)	5
Demethoxydihydrosinomenine	152–153	+59.17° (C_2H_5OH)	*Prisms*	52, 1, 34, 40, 89
Hydrobromide	291 (dec)	..	Dense prisms (HBr)	52
Hydrochloride	293 (dec)	+48.88° (H_2O–HCl)	Slender prisms	52, 34
Methiodide	268–272	+23.9° (CH_3OH)	Prisms	1, 34
Oxime hydrochloride	317	..	..	52
Semicarbazone	235	..	Crystals (acetone)	34

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Demethoxydihydrosinomeninol	143 (dec)	+46.8° (CH_3OH)	Rhombic plates (acetone)	40, 1, 89
Des-*N*-methyl-1-bromodehydrometasinomenine	199–201	..	..	57
Des-*N*-methyl-1-bromodemethoxydihydrosinomeneine	130	+7.0° (CH_3OH)	Crystals (C_2H_5OH)	52
Methiodide	278–279	..	Crystals	52
Des-*N*-methyl-1-bromodemethoxydihydrosinomenine	200–201	−8.67° ($CHCl_3$)	Prisms (CH_3OH–H_2O)	51
Methiodide	243 (dec)	..	..	51
Des-*N*-methyl-1-bromosinomeneine	187	+112.3° ($CHCl_3$)	Prisms (CH_3OH)	5
Methiodide	213–214	..	..	5
Des-*N*-methyl-1-bromosinomenine	185 (dec)	+15.92° ($CHCl_3$)	Yellow prisms (CH_3OH)	5
Methyl ether	143	..	..	56
Methiodide	228	..	..	56
Des-*N*-methyl-1-bromosinomeninone furazane	225 (dec)	..	Prisms	48
Des-*N*-methyldemethoxydesoxodihydrosinomenine	140	−65.2° (CH_3OH)	Colorless needles	1, 46
$C_{17}H_{20}O$ (Hofmann degrad.)	93	−181.6° (C_2H_5OH)	Yellow needles (pet. ether)	1
Des-*N*-methyldemethoxydihydrosinomeneine	120	+4.0° (CH_3OH)	..	52
Des-*N*-methyldemethoxydihydrosinomenine	182	−54.94° ($CHCl_3$)	Prisms (CH_3OH–H_2O)	4
Des-*N*-methyl-1,9-dibromodemethoxydesoxodihydrosinomenine	205 (dec)	..	Crystals (CH_3OH)	48
Perbromide	112–113	..	Golden-yellow prisms (HOAc)	48
Des-*N*-methyl-1,9-dibromosinomeninone furazane	212 (dec)	..	Prisms (CH_3OH)	48
Des-*N*-methyldihydrosinomenilane	183–185	−98.2° (C_2H_5OH)	Prisms (C_2H_5OH)	13
Methiodide	225–227	..	Prisms (H_2O)	13

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Des-*N*-methyldihydro-sinomenilone	220 (dec)	+18.55° ($CHCl_3$)	Crystals (C_2H_5OH)	10
Des-*N*-methyldihydro-sinomenine	173	−84.32° ($CHCl_3$)	Prisms (ether)	47
Des-*N*-methylsino-meninone furazane				
Methiodide	226–227 (dec)	+49.9° ($CHCl_3$)	Prisms (CH_3OH)	46
(+)Desoxycodeine-C	103	+179.6° (C_2H_5OH)	Rhombic crystals	18
Methiodide	238	+102.4° (CH_3OH–H_2O)	Crystals (H_2O)	18
l-1,9-Dibromodehydro-thebenone-7-ketofurazane	210–211	..	Prisms (HOAc–H_2O)	48
1,1¹-Dibromo-bis-8,8¹-demethoxydihydro-sinomenine	227	+19.02° (C_2H_5OH)	Granules (acetone)	37
Methiodide	253–255	..	Stout prisms (H_2O)	37
Dioxime	237 (dec)	..	..	37
1,7-Dibromosinomenilic acid	235	+80.33° (H_2O–NaOH)	Four-sided prisms	11, 8
Methiodide	213 (dec)	..	Long prisms (H_2O)	8
Acetyl-	202	..	Prisms	8
Benzoyl-	216	..	Prisms	8
Ethyl ester	80	..	Prisms (C_2H_5OH–H_2O)	8
Hydrochloride	234–236	..	Prisms (C_2H_5OH)	8
Methyl ester hydro-chloride	209–210	..	Long prisms	8
1,5-Dibromosinomenine hydrobromide	197 (dec)	..	Crystals (C_2H_5OH–ether)	9
6,6-Dichlorodihydro-sinomenilane	110–116	..	Prisms (CH_3OH)	13
(+)Dihydrocodeine	110	+146.4° (C_2H_5OH)	Crystals (CH_3OH–H_2O)	18, 96
Dihydrate	87–88	..	..	18
Methiodide	257	+80.1° (H_2O)	Crystals (C_2H_5OH)	18, 96
Dihydro-des-*N*-methyl-1-bromodemethoxy-dihydrosinomenine	192	+61.6° ($CHCl_3$)	Prisms (CH_3OH)	51
Hydrobromide	257 (dec)	..	Crystals (HOAc)	51
Methiodide	273	..	..	51
Dihydro-des-*N*-methyl-1-bromosino-meninone furazane	221–223 (dec)	..	Prisms (acetone)	48
Hydrobromide	259 (dec)	..	Long needles (H_2O)	48

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Dihydro-des-*N*-methyl-demethoxydesoxo-dihydrosinomenine	161	+77.9° ($CHCl_3$–CH_3OH)	Prisms (ether)	46
Dihydro-des-*N*-methyl-demethoxydihydro-sinomeneine	93–97	+50.0° (C_2H_5OH)	Prisms (C_2H_5OH–ether)	52
Dihydro-des-*N*-methyl-demethoxydihydro-sinomenine	156.5	+67.82° ($CHCl_3$)	Prisms (ether)	4
Methiodide	226–229	..	Prisms (CH_3OH)	4
Dihydro-des-*N*-methyl-dihydrosinomenilane	143–146	+45.48° (C_2H_5OH)	Prisms (acetone)	13
Methiodide	..	..	Amorphous	13
Dihydro-des-*N*-methyl-dihydrosino-menilone	175	−24.56° ($CHCl_3$)	Leaflets (acetone)	10
Dihydro-des-*N*-methyl-dihydrosinomenine	133	+2.09° ($CHCl_3$)	Prisms	47
Dihydro-des-*N*-methyl-sinomeninone furazane	205–207	+21.9° ($CHCl_3$)	Prisms (CH_3OH)	46
9,10-Dihydroisothebenine				
Triacetyl	181–182	..	Crystals (C_2H_5OH)	9
(+)Dihydromorphine	158–159	+151.5° (C_2H_5OH)	..	18, 96
Hydriodide	285	+87.9 (H_2O)	Golden prisms(H_2O)	18, 96
Methiodide	245	+74.9° (H_2O)	..	18
Dihydrosinomelane	50–55	−104.63° (C_2H_5OH)	Prisms	13
Dihydrosinomenilane	145–150	+34.15° (C_2H_5OH)	Plates (acetone)	13
Methiodide	85–87	..	Crystals (H_2O)	13
Dihydrosinomenilone	132	+207.75° ($CHCl_3$)	Leaflets (C_6H_6)	10
Methiodide	220–240 (dec)	..	Prisms	10
Oxime	155–156 (dec)	..	..	10
Methyl ether	99–104	..	..	63
Dihydrosinomenine	198–201	+193.58° ($CHCl_3$)	Crystals (CH_3OH)	40, 1, 32, 34, 41, 78, 82, 93, 63b
Hydrochloride	..	+33.06° (H_2O–HCl)	..	40
Methiodide	268 (dec)	..	..	40, 78, 93
Benzoyl-	..	..	Iodine No. = 53.89	82
Methyl ether	..	..	Amorphous	26
Hydrochloride	150 (froth)	+35.05° (H_2O)	..	26
Semicarbazone	220 (froth)	..	Needles	26

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Oxime	211 (dec)	..	..	40,78,93,63b
Semicarbazone	209 (dec)	..	Needles (C_2H_5OH–H_2O)	40, 1, 93
Dihydrosinomeninol	162	+1.93° (CH_3OH)	Crystals (CH_3OH)	40, 63b
Methiodide	249 (dec)	−6.28° (H_2O)	Oblong plates (CH_3OH)	40
α-Dihydrosinomeninone				
A-Isomer	128–129	+64.65° ($CHCl_3$)	Dense prisms ($CHCl_3$–CH_3OH)	12, 35
Methiodide	284 (dec)	..	Thin plates	12, 35
Dibenzoyl-	141	..	Long prisms (CH_3OH)	12
Methyl ether	128	+71.05° ($CHCl_3$)	Prisms (H_2O–CH_3OH)	39
Methyl ether methiodide	248 (dec)	..	Long needles (CH_3OH)	39
Methyl ether oxime	177	..	Crystals (CH_3OH)	39
Oxime	170	..	Short prisms	12, 35
Oxime hydrochloride	..	..	Large prisms	12
Phenylhydrazone	140	..	(Hygroscopic)	35
Semicarbazone	191 (dec)	..	..	35
B-Isomer	202	+64.65° ($CHCl_3$)	Dense prisms	12
Oxime	170	..	..	12
β-Dihydrosinomeninone	104	+95.2° ($CHCl_3$)	Needles (CH_3OH)	35, 12
Methiodide	281 (dec)	..	Long prisms	12, 35
Oxime	145–150	..	Long prisms	12, 35
Semicarbazone	206 (dec)	..	..	35
1,5-Dihydroxymethyl-sinomenine	242 (252)	−74.39° (CH_3OH–H_2O)	Crystals	42
Methiodide	210	..	Crystals (CH_3OH)	42
Oxime	200–215	..	Amorphous	42
Disinomenine	218–220	+97.38° (CH_3OH)	Needles (C_6H_6)	1, 29, 93
Hydrochloride	>290	..	..	29, 93
Methiodide	263 (dec)	..	Long prisms (H_2O)	29, 93
Nitrate	280	..	Colorless needles (H_2O)	1
Oxime	265 (dec)	..	..	29, 93
Semicarbazone	>290	..	..	29, 93
		E		
(+)-Epidihydro-thebainol	154	+48.6 ($CHCl_3$)	Prisms (CH_3OH)	63a
Methiodide	282	..	Crystals (C_2H_5OH)	63a
dibenzoyl-	273	..	Crystals (C_2H_5OH)	63a
(+)-Epidihydro-thebainone	130	+37° ($CHCl_3$)	Prisms (acetone)	63a
Methiodide	253	..	Crystals (C_2H_5OH)	63a
Semicarbazone	205	..	Crystals (acetone)	63a

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		H		
(+)7-Hydroxydihydrocodeine	225	..	.	55
Dibenzoyl-	..	..	..	55
(+)7-Hydroxydihydrothebainol	..	..	..	55
5-Hydroxymethyldihydrosinomenine	244	+73.03° (CH_3OH–$CHCl_3$)	Short prisms (CH_3OH)	42
Methiodide	205–220 (dec)	..	Crystals (CH_3OH)	42
Oxime	215–225 (dec)	..	Amorphous	42
5-Hydroxymethylsinomenine	260 (dec)	−40.71° ($CHCl_3$)	Stout prisms (CH_3OH)	42
Methiodide	223 (dec)	..	Long needles (CH_3OH)	42
Oxime	240–245 (dec)	..	Amorphous	42
		I		
(−)Isobromodehydrothebenone	125–133	−113.33° ($CHCl_3$)	Crystals (acetone)	51
Isothebenine				
Triacetyl-	182–183	..	Colorless prisms	6, 9
		M		
l-7-Methoxydehydrothebenone	118	−286° ($CHCl_3$)	Colorless prisms (ether)	47
Oxime	180 (dec)	..	Prism (C_2H_5OH)	47
l-7-Methoxythebenone	128	−147.66° ($CHCl_3$)	Long prisms	47
Isonitroso-	..	..	Resinous ppct.	47
Oxime	168	..	Tetragonal plates (ethyl acetate)	47
N-Methylanhydrosinomenine (see sinomenineachromethine (44))	183	+31°	..	94
Methylsinomenine	179	−29.61° ($CHCl_3$)	Crystals (H_2O)	39, 1, 26
Hydrochloride	252	..	Short prisms	1
Methiodide	151 (dec)	..	Crystals (H_2O)	39
Methylmetho sulfate	265	..	..	94, 45
Oxime	139 (dec)	..	Stout prisms	39
Semicarbazone	250–252	..	Prisms (C_2H_5OH)	1, 82
Methylsinomenine methine methylmetho sulfate				
α-Form	213	+478°	..	94
β-Form	178	..	..	94

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		P		
Pseudodisinomenine	228	−127.03°	. .	29
Methiodide	267–268 (dec)	. .	Polyhedra (H_2O)	29
Oxime	>280	. .	. .	29
Semicarbazone	290 (ca)	. .	. .	29
		S		
Sinomelane	85–90	−178.03° (C_2H_5OH)	Prisms (ether)	13
Sinomenilone	176	+442.14° ($CHCl_3$)	Prisms (C_2H_5OH)	10
Oxime	238	. .	Polygons	10
Sinomenine	161 182	−70.76° (C_2H_5OH)	Radiating crystals (C_6H_6)	1, 64, 78, 81, 91, 93 94, 97
$C_{25}H_{32}O_8NCl$ ($Cl-CO_2C_2H_5$)	183	−108.4° ($CHCl_3$)	Yellow powder	1, 82
Aurichloride	. .	. .	Amorphous	1
Hydriodide	233	. .	. .	78
Hydrobromide	231	. .	. .	78, 32
Hydrochloride dihydrate	231	−82.4° (H_2O)	Prisms (H_2O)	1, 64, 78, 81
Methiodide	251	. .	Colorless prisms	1, 78, 94
Methylmetho sulfate	265 (dec)	. .	Crystals (H_2O)	45, 94
Nitrate	215 (dec)	. .	. .	78
Picrate	140 (ca)	. .	Yellow plates	64
Benzoyl-	225	−109.6° (C_2H_5OH)	Crystals (C_6H_6–pet. ether)	1, 39
Aurichloride	. .	. .	Crystalline	1
Methiodide	237 (dec)	. .	Hairy crystals(H_2O)	39
Oxime	249 (dec)	. .	Prisms (CH_3OH)	39
Oxime	254 (dec)	. .	Crystals (C_2H_5OH)	1, 82, 97
Semicarbazone	264 (dec)	. .	Prisms (C_2H_5OH)	1, 82
Sinomenineachromethine	179	+72.58° ($CHCl_3$)	Prisms (ether)	44, 94
Hydriodide	115–118	. .	Hygroscopic crystals	44
Methiodide	212 (dec)	. .	Crystals (CH_3OH)	44, 94
Oxime	204–205 (dec)	. .	Prisms (CH_3OH–ether)	44
Sinomenineroseo methine	163	+135.7° ($CHCl_3$)	. .	44, 94
Methiodide	276 (dec)	−48.26° (H_2O)	Yellow prisms (CH_3OH)	44, 94
Methyl ether methylmetho sulfate	. .	. .	. .	45
Sinomeninesulfonic acid	265	. .	Colorless prisms	80
Sinomenineviolomethine	172–173	+434.78° ($CHCl_3$)	Flat prisms	44
Methiodide	209 (dec)	+373.36° (H_2O)	Prisms (H_2O)	44
Methyl ether methylmetho sulfate	204 (dec)	+478° (H_2O)	Long prisms (C_2H_5OH)	45

TABLE 4 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Sinomeninic acid	291 (dec)	+88.9° (H_2O)	Dense prisms	7
Hydrochloride	278–280 (dec)	+81° (H_2O)	Colorless plates	7
Methiodide	239	+18.11° (H_2O)	Prisms (CH_3OH)	7
Methyl ether	295 (dec)	+12.38° (H_2O)	Prisms	7, 63
Barium salt	>300	..	White prisms	7
Imide	239–241	..	Crystals (acetone)	63
Sinomeninol	127	−23.7° ($CHCl_3$)	Crystals (CH_3OH)	40
Methiodide	272 (dec)	..	Prisms (H_2O)	40
Sinomeninone (Methyl)	139	+40.8° ($CHCl_3$)	Prisms (CH_3OH)	35, 38, 9, 46
Alcholate	157–160			
Methiodide	264 (dec)	..	..	35, 38
Dioxime	231 (dec)	..	Crystals (acetone–CH_3OH)	35, 38
Disemicarbazone	191 (dec)	..	Amorphous	35
Furazane	223–225	+136.2° ($CHCl_3$)	Prisms (CH_3OH)	46
Methiodide	218–220 (dec)	..	Colorless prisms (CH_3OH)	46
Methyl ether	188	+18.65° ($CHCl_3$)	Prisms (CH_3OH)	39
Methiodide	225–227 (dec)	..	Stout prisms	39
Oxime	170–213 (dec)	..	Crystals	39
Sinomeninonesulfonic acid	275–280	..	Colorless prisms	80
Dioxime	>300	..	Colorless prisms	80
		T		
Tetrahydrodisinomenine	252	+264.41°	Crystals (C_2H_5OH)	30, 1, 78, 86
Hydrochloride	>295	+141.24°	..	30, 78
Methiodide	>275	..	..	30, 1, 78, 86
Oxime	245–250 (dec)	..	..	30, 1, 86,
Semicarbazone	>290	..	..	30
Tetrahydropseudodisinomenine	271 (dec)	+167°	Long needles	30
Hydrochloride	..	..	Amorphous	30
Methiodide	285 (dec)	..	..	30
Oxime	242 (dec)	..	..	30
Tetrahydrosinomeninone	157	..	..	55
Thebenane	..	−3.14° (CH_3OH)	..	46
l-Thebenone	134	−78.6° ($CHCl_3$)	Prisms (CH_3OH)	4
Oxime	204.5	..	Prisms (CH_3OH)	4
l-Thebenoneketone	187	..	Prisms (CH_3OH)	46
Dioxime	255–260 (dec)	..	..	46
Furazane	148	−120.4° ($CHCl_3$)	Crystals (CH_3OH)	46
1,5,8-Tribromosinomeninone hydrobromide	235 (dec)	..	Dense prisms (CH_3OH–ether)	8

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CHAPTER X

Colchicine

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I. Chemistry of Colchicine

1. INTRODUCTION

Colchicine occurs in the corm, seeds, flowers and other tissues of the meadow saffron, *Colchicum autumnale* L. (family Liliaceae), crude extracts of which have long been used in medicine for the treatment of gout.

According to Goodman and Gilman (1), the highly toxic nature of colchicum was known to Dioscorides, who in A.D. 78 first described colchicum proper; its use in the therapy of gout dates at least from the sixteenth century, and it is said to have been used by the Byzantines. Although colchicum extracts may afford dramatic relief in acute gout, it does not relieve pain or inflammation due to other causes. Colchicine has no effect on uric acid metabolism, and the mechanism of its action in gout is quite unknown.

Colchicum autumnale is a perennial plant common in England and is also found in Central and Southern Europe. Its name is stated to be derived from Colchis, the former name of a district of Transcaucasia where several species of the plant grew (2). This district on the eastern shore of the Black Sea was the legendary home of the Golden Fleece, symbolical of wealth and fertility, and to the Greek mind, a region associated with sorcery.

The toxic principle of colchicum was first isolated in a relatively pure state in 1820. Crystalline preparations were described in 1884, and important contributions to the chemistry of colchicine were made by Zeisel, and especially by Windaus, who in 1924 proposed a structural formula for the alkaloid. The investigations which have established the main structural features are outlined in a later section. Some details still require elucidation, so that synthesis of the alkaloid has not yet been attempted. From the standpoint of molecular structure it is possible that colchicine may represent a unique type of plant product.

In recent years intense interest has been aroused by the remarkable biological properties of colchicine, which were first revealed by the work of Dustin and Lits, at the University of Brussels. Colchicine has the specific characteristic, also shown to some degree by other substances, of bringing cell-division to an abrupt halt at a particular stage. This behavior has led to the unravelling of many interesting aspects of cytology, and has also resulted in the elaboration of valuable and sensitive methods of assay of natural hormones and some of their synthetic counterparts. Above all, the action of colchicine on cell division has led to the discovery of methods for the artificial production of polyploid varieties of many plants. These new varieties have many attributes which are superior to those of the forms from which they are derived, and the artificial production of polyploids has considerable economic importance as well as scientific interest. That this is widely recognized is testified by the very extensive literature published during the past decade, from many different countries, on the artificial production of polyploid forms of plants by treatment with colchicine and other compounds. This literature is reviewed in a later section. Yet another facet of the cytological action of colchicine is reflected in the

numerous studies of its effect on tumor growth. Although the promise of a therapeutic agent against cancer indicated by some of the earlier reports has not been sustained by more extensive investigation, it is probable that the last word on this subject has not yet been written. In a recent review, Levine (3) has suggested that more extensive studies should be made of the action of colchicine, combined with X-rays, on animal tumors. The very high toxicity of the alkaloid prevents its use for this purpose in any but the smallest doses, but when its structure is completely elucidated it may be hoped that the way will open for the synthesis of analogous compounds, less toxic than colchicine, but with similar action on the cell nucleus.

2. Occurrence and Estimation

Although colchicine is usually extracted from the meadow saffron this is by no means the only natural source of the alkaloid. Albo (4) listed a dozen species of *Colchicum* in which colchicine was detected, and found it also in *Merendera caucasia* Bieb. and *Merendera sobolifera* Fisch. and Mey. with a localization almost identical with that in *Colchicum*. He extracted the colchicine from the whole plant of *Colchicum Cupani* Guss. and found the amount to be 0.464%, which is of the same order as the content of *Colchicum autumnale*. From histochemical studies of its distribution Albo concluded that colchicine is present mainly in cells in full activity, and plays an essential part in the nutrition and growth of the plant. According to Klein and Pollauf (5), colchicine also occurs in large quantities in the following Liliaceae: *Bulbocodium*, *Tofieldia*, *Veratrum anthenicum*, *Hemerocallis*, *Ornithogalum*, and *Tulipa;* and in traces in *Asphodelus*, *Fritillaria*, *Lloydia*, and *Muscari*. It is reported by Perrot (6) that *Androcymbium gramineum* MacBr., a plant from the central Sahara, contains colchicine distributed throughout its parts, and in a quantity comparable with *Colchicum autumnale*. Clewer, Green, and Tutin (7) extracted from the dried tubers of *Gloriosa superba* L. a mixture of alkaloids consisting chiefly of colchicine (assay showed the presence of 0.3% of colchicine in the dried tubers) together with small amounts of two other crystalline nitrogenous materials. One of these crystallized from ethyl acetate in pale yellow leaflets, m.p. 177–178°; the composition corresponded with $C_{33}H_{38}O_9N_2$ or $C_{15}H_{17}O_4N$. The other also crystallized from ethyl acetate and formed colorless needles, m.p. 267°; its carbon and hydrogen content corresponded with the formula $C_{23}H_{27}O_6N$, which is that of a methylcolchicine. The chemistry of these minor products does not appear to have been studied. Incidentally, Clewer, Green, and Tutin, by using ethyl acetate as the solvent, seem to have been the first workers to obtain colchicine in a pure crystalline form, free from solvent of crystallization. By this means they obtained crystalline colchicine, not only from *Gloriosa superba*, but also

from *Colchicum autumnale*. This was achieved in 1915, nearly a century after the earliest report of the isolation of colchicine. (For minor alkaloids of *Colchicum autumnale*, see Addendum.)

The distribution of colchicine in *Colchicum autumnale* has been studied by several workers, and there is general agreement that it occurs most abundantly in the seeds. According to Chemnitius (8), the ripe seeds contain from 0.4 to 0.9% of colchicine, whereas the content of the bulbs, sap, and leaves is essentially lower. Grier (9) found from 0.38 to 0.4% of colchicine in the corms, and 0.72 to 0.75% in the seeds (see also Niemann (10)). Lipták (11) states that the alkaloid is located chiefly in the endosperm and the third layer of the seed coat.

For the study of the distribution of colchicine in plants use has been made of microchemical methods of detection and estimation. Albo (4) utilized the yellow color which colchicine gives with dilute mineral acids; color reactions also formed the basis of the work of Lipták (11), whereas Klein and Pollauf (5) used a microchemical reaction with platinum thiocyanate, which is stated to be sensitive to 2×10^{-7} g. of colchicine. The methods for the estimation of this alkaloid are reviewed by Grier (9), who found that the most reliable values were given by precipitation with phosphotungstic acid, according to the procedure of E. C. Davies. Other methods of estimation in pharmaceutical preparations and in *Colchicum* seeds have been described (12). By mild acid hydrolysis colchicine is converted into colchiceine, which gives an intense green color with ferric chloride. This also has been employed as the basis for methods of detection and estimation of colchicine. Fühner (13) recommended the use of dilute hydrochloric acid, instead of the concentrated acid used by earlier workers, for the preliminary hydrolysis to colchiceine, and the method was adapted to the colorimetric estimation of colchicine by Boyland and Mawson (14). Colchicine withstands putrefaction for 3 to 6 months (15), and the alkaloid, or an analogous substance, was detected in a corpse as long as 22 months after death (16). The subject appeared to have taken "coffee" prepared from autumn crocus.

3. Extraction and Isolation

The toxic principle of *Colchicum autumnale* was first isolated by Pelletier and Caventou (17), who believed it to be veratrine. Geiger (18) extracted a crystalline alkaloid which he recognized as a distinct substance and named it colchicine. Oberlin (19), using the same method of extraction, was unable to obtain a crystalline product, but showed that his preparation was converted by boiling dilute hydrochloric or sulfuric acid into a crystalline material with the properties described by Geiger. Oberlin designated the amorphous initial material as colchicine, and named the

crystalline product colchiceine. Colchicine is easily soluble in water, whereas colchiceine is sparingly so. Other workers have obtained alkaloidal preparations from autumn crocus by extraction with alcohol containing sulfuric acid; these must be regarded as mixtures (20). The presence of colchiceine in the plant cannot be regarded as established, in fact, the balance of evidence is against its occurrence in the free state. Aschoff (21) was the first to extract the alkaloid without the use of a mineral acid. He precipitated the colchicine with tannic acid, and decomposed the salt (or complex) with lead oxide.

Crystalline colchicine was first obtained by Zeisel (22) and by Houdès (23). This, however, was not solvent-free, but contained firmly bound chloroform of crystallization which was not lost after standing in the air for a month, and was only incompletely expelled by heating for several hours at 100°. Pure crystalline colchicine, free from solvent, was first described in 1915 by Clewer, Green, and Tutin (7), who used ethyl acetate as the medium for recrystallization and obtained pale yellow needles, m.p. 155–157°. Completely pure colchicine is colorless. With water it forms a sesquihydrate ($B_2 \cdot 3H_2O$), yellow rhombic crystals, and with chloroform it forms two crystalline compounds, containing respectively one and two molecules of colchicine combined with one molecule of chloroform of crystallization (24).

Both Zeisel (20) and Houdès (23) obtained their colchicine preparations from alcoholic extracts of *Colchicum* seeds. Zeisel distilled the alcohol from the extract, dissolved the residue in water, and separated the aqueous colchicine solution from undissolved resin and fat. By repeated fractional extraction with chloroform he obtained a chloroform solution of colchicine that was concentrated to a viscous oil. Rosettes of crystals of the chloroform complex were obtained from the oil by standing below 0°. Houdès, after distillation of the alcoholic extract of *Colchicum* seeds, treated the residue with aqueous tartaric acid. The colchicine passed into the acid solution and this, freed from fat and resin, was extracted with chloroform, from which crystals were obtained after concentration by spontaneous evaporation of a solution in chloroform, alcohol, and petroleum ether. Zeisel noted that the crystals of the chloroform complex emitted a bluish-white light when rubbed in the dark. This behavior was not shown by pure (amorphous) colchicine. The chloroform is removed by evaporation with water, and Zeisel recovered the colchicine from the crystalline complex by treating with water and blowing in steam, followed by evaporation of the clear solution to dryness. This gave scales of analytically pure material, after drying in a vacuum at 100° and then 130°.

The fractional chloroform extraction procedure used by Zeisel seems somewhat cumbersome and wasteful, and the simplified procedure used by

Chemnitius (8) for the isolation of colchicine, combined with the chromatographic purification of Ashley and Harris (25), has been used successfully by Mr. T. Y. Johnston, in the University of Glasgow laboratories, for the isolation of pure colchicine from an alcoholic extract of *Colchicum* prepared by Wm. Ransom & Sons Ltd. Ashley and Harris describe their purified colchicine as pale yellow needles, m.p. 155°, $[\alpha]_D^{17}$, −120.7° (compare Clewer, Green, and Tutin (7).) They state that it crystallizes from benzene in pale yellow prisms, m.p. 140°, containing one molecule of benzene of crystallization. The following is a description of an isolation experiment carried out by Johnston:

The dark brown gum (330 g.) from an alcoholic extract of *Colchicum* seeds is diluted with 450 cc. of water and the solution, which contains undissolved solid and resinous material, is heated with 75 g. of paraffin wax until the wax is molten. The mixture is stirred vigorously and then allowed to cool. The solid wax, which dissolves the resin, is lifted from the surface, and the process twice repeated with fresh wax. The combined wax layers are thrice extracted with 100 cc. of boiling water, and the aqueous extracts added to the solution of the alkaloid.

A paste of filter paper pulp (50 g.) is then added to the aqueous colchicine solution. (This is prepared by boiling filter paper with concentrated hydrochloric acid in order to effect complete disintegration, the mass is then washed with water until neutral.) The mixture is filtered on a filter bed, to which some paper pulp has already been added, and yields a clear brown solution. The filter bed is boiled with a little water and then refiltered. The combined filtrates are extracted with 12 portions of 200 cc. of chloroform, care being taken to insure that the chloroform is free from hydrochloric acid (compare Zeisel (20)). Addition of potassium carbonate to the yellow extract causes precipitation of some brown flocculent material, which is filtered from the dried solution. The latter is evaporated, leaving a golden brown sirup.

The sirup is redissolved in chloroform (150 cc.) and the solution passed through a column of alumina (B.D.H. chromatographic alumina), 25 cm. long and 3.5 cm. in diameter, which has been saturated previously with benzene. Three bands are formed, an upper reddish-brown band, a larger bright yellow band, and a lower almost colorless band that contains the colchicine. The column is washed with chloroform until the yellowish eluate becomes colorless and yields no residue on evaporation. Distillation of the chloroform from the total eluate gives a golden-yellow sirup which is distilled thrice with an equal volume of absolute alcohol to remove the residual chloroform. The residue is finally crystallized from ethyl acetate, and yields 10 g. of colchicine as fine colorless needles, m.p. 148–150°. A further 1.75 g. of slightly less pure material (m.p. 147–150°) is obtained from the liquors. A second chromatographic purification, followed by crystallization from ethyl acetate, raises the m.p. to 155°; $[\alpha]_D^{13}$, −119. 9° (in chloroform).

4. Chemical Characteristics: Simple Derivatives

The most extensive description of the chemical characterization of colchicine is that of Zeisel. Although he did not succeed in obtaining crystalline colchicine free from solvent, there is little reason to doubt that he was dealing with substantially pure material, which he obtained by evaporating the crystalline chloroform complex with water. The substance

so formed had m.p. 143–147°, after being dried at 110°. Analysis corresponded with the formula $C_{22}H_{25}O_6N$, which has been confirmed by all subsequent work with colchicine derivatives. In one important respect the description alkaloid is a misnomer, as colchicine is not a base but a neutral substance. It does not contain a free amino group nor does it form a well-defined series of salts as other alkaloids do. It is true that Zeisel noted the formation of a saltlike compound with tannic acid, but it now seems more probable that this is a molecular complex. Colchicine solutions are colored intensely yellow by strong mineral acids. Similar behavior is shown by colchiceine, and here also molecular complex formation is probably involved; the implied latent basicity appears to reside in an oxygen-containing group rather than in nitrogen. Although a neutral substance, colchicine is a highly toxic nitrogenous plant product, and gives characteristic alkaloidal reactions with many of the usual alkaloid precipitants. Its dissociation constant has been measured by Weisse and Lévy (26) and by Kolthoff (27). The latter investigator gives the value, $K = 4.5 \times 10^{-13}$ ($pK = 12.35$), which is in keeping with the lack of pronounced basicity. According to Schuhler (28), who made potentiometric measurements at the antimony electrode, colchicine has three dissociation constants, namely, pK, 1.8, 7.2, and 10.3.

A remarkable physical attribute of colchicine is its high solubility in water, in spite of the absence of any of the groups usually associated with a high degree of water solubility. Zeisel (20) states that the substance is miscible with water in all proportions in the cold, but is less soluble in hot water. A saturated solution at 82° contains about 12% of colchicine. Furthermore, if colchicine is hydrolyzed to colchiceine, liberating a hydroxyl group, the water-solubility decreases substantially. This high solubility of colchicine in water has not been satisfactorily explained, although Dewar (29) has recently suggested that it is due to ionic resonance. Zeisel (35) refers to the increase in solubility which attends the esterification of aceturic acid, $CH_3CONH \cdot CH_2 \cdot CO_2H$, as a possible analogy to the behavior of colchicine and colchiceine.

Zeisel and Stockert (30) drew attention to the parallelism in properties between colchicine and water-soluble gums. They examined the possibility that colchicine might owe its amorphous character (it had not then been obtained crystalline) and water solubility to its existence in the form of a high-molecular colloid. They found, however, that it would diffuse through membranes, and it shows no Tyndall cone. Moreover, molecular weight determinations by cryoscopic and ebullioscopic methods gave little evidence of a high degree of association. In boiling ethylene dibromide it is monomolecular, although in aqueous solution and in ethylene dibromide at lower temperatures it appeared to be bimolecular and probably also trimolecular.

Zeisel (20) describes a number of color tests and precipitation reactions with colchicine. Thus, it dissolves in concentrated nitric acid to a violet solution, which gradually becomes yellow; excess sodium hydroxide then transforms the solution to reddish yellow. Colchicine dissolves in concontrated sulfuric acid containing a trace of nitric acid to give first a yellow-green color, which becomes green, then blue and violet, and finally red and yellow. Dilution, followed by addition of excess alkali, then gives a fine red color. Bromine water, and iodine in potassium iodide (the latter only in acid solution) both give colored precipitates. Ferric chloride gives no color in neutral or acid solution, but if the acidified solution is boiled for a few minutes after addition of ferric chloride an intense green color is formed. This is due to hydrolysis to colchiceine (see below). Mercuric chloride gives a citron-yellow precipitate with solutions of colchicine in dilute hydrochloric acid. Cadmium iodide also gives a precipitate — white in neutral solution, citron yellow in acid solution. Colchicine gives two complexes with auric chloride. The composition of one of these corresponds with that of the chloroaurate, $C_{22}H_{25}O_6N \cdot HCl \cdot AuCl_3$. (This compound, m.p. 209°, was also described by Clewer, Green, and Tutin (7)). The other, obtained by using excess colchicine, appears to have the formula $(C_{22}H_{25}O_6N \cdot HCl)_2AuCl_3$. Precipitates are obtained with salts of many complex acids. Mention has been made of the use of phosphotungstic acid in the estimation of colchicine.

The action of bromine on colchicine was further investigated by Zeisel and Stockert (31), who isolated mono-, di- and tribromo derivatives. Bromine water gave a crystalline monobromo compound and an amorphous dibromo compound, whereas a tribromo derivative was formed by the action of excess bromine in methanol. The tribromo compound contained one labile bromine atom which was displaced from the molecule when the compound was treated with methyl alcoholic potash. Two hydrolysis products of colchicine, namely, colchiceine and trimethylcolchicinic acid, also gave tribromo derivatives with bromine in acetic acid. Evidently colchicine and its two hydrolysis products all contain three hydrogen atoms readily replaceable by bromine.

Colchicine solutions undergo autoxidation in the presence of light. By fractional precipitation of a chloroform solution of the oxidized material by petroleum ether Jacobj (32) separated a brown resinous oxidation product, less soluble than colchicine, which he denoted as "oxydicolchicine." Analysis corresponded with the formula $(C_{22}H_{25}O_6N)_2O$, indicating the uptake of one atom of oxygen by two molecules of colchicine. In view of the intractible nature of the oxidation product this conclusion must be accepted with reserve, and further investigation is desirable. It is of interest, however, that in its toxicity and pharmacology "oxydicolchicine"

showed significant differences from colchicine. It has been stated that "oxydicolchicine" is formed from colchicine by electrolytic oxidation, and also in the body. In fact, the pharmacological effects of colchicine in warm-blooded animals were believed to involve preliminary oxidation to "oxydicolchicine." In this connection interest attaches to the oxycolchicine described by Zeisel and Friedrich (33). Friedrich prepared this in 1890 by oxidation of colchicine with chromic acid in aqueous solution; the purified oxycolchicine was isolated as yellowish microscopic prisms, m.p. 266–268°. Analyses indicated the formula $C_{22}H_{23}O_7N$, and the formation of this compound appears to involve the oxidation of a reactive methylene group to a carbonyl. Zeisel and Friedrich stated that there was evidence that oxycolchicine reacted with hydroxylamine, although an oxime was not isolated. According to Windaus (34), however, the compound gives a semicarbazone, m.p. 220–223°. This oxidation is of importance in indicating the presence of a reactive methylene group in the colchicine molecule and in view of Jacobj's work on "oxydicolchicine" the effect of oxycolchicine on animal organisms is of interest.

5. Hydrolysis Products of Colchicine

Colchicine, $C_{22}H_{25}O_6N$, is susceptible to acid hydrolysis and contains no less than five molecular groupings which can undergo hydrolysis under conditions of varying stringency. The nomenclature of these hydrolysis products is somewhat confused and misleading, due largely to Zeisel's mistaken conclusion that colchicine is the methyl ester of a carboxylic acid. The first product of acid hydrolysis, formed under very mild conditions, is colchiceine. Methanol is formed concurrently, and it is now known that colchiceine contains an enolic type of hydroxyl group and that colchicine is its methyl ether.

The further action of hydrochloric acid on colchiceine was studied by Zeisel (35). By heating with hydrochloric acid (*d*, 1.15) at 150° for 6 hours and then estimating the acetic acid produced it was shown that one molecule of acetic acid is formed for each molecule of colchiceine that undergoes hydrolysis. The other product of hydrolysis, termed trimethylcolchicinic acid contains a free amino group in addition to the enolic hydroxyl group of colchiceine.

Trimethylcolchicinic acid. A solution of colchiceine (6.6 g.) in hydrochloric acid (*d*, 1.15; 25 cc.) is heated on the water bath until a sample no longer gives a precipitate of colchiceine on dilution with water (about an hour). The orange-yellow solution is diluted somewhat and extracted with chloroform. This removes the dihydrochloride of trimethylcolchicinic acid and some unchanged colchiceine, leaving in aqueous solution the hydrochlorides of dimethylcolchicinic and colchicinic acids. The golden-yellow chloroform extract is evaporated and the residue warmed with water. Unchanged colchiceine crystallizes and is filtered off, the remainder being removed by extraction

with a little chloroform. The aqueous solution is concentrated until it deposits crystals of the monohydrochloride of trimethylcolchicinic acid. This, after recrystallization from water, yields almost colorless glistening plates, m.p. 191° (yield 50%, after allowing for recovered colchiceine).

Addition of caustic potash to the aqueous solution precipitates the free trimethylcolchicinic acid, which is soluble in excess alkali. The free base, m.p. 159° (sinters 156°), is obtained as a dihydrate which incompletely loses its water of hydratation when heated at 135°, and partially decomposes when heated at 150°.

Trimethylcolchicinic acid is an amphoteric substance, giving salts with both acids and alkalies. Its chloroplatinate is readily obtained pure. Zeisel (35) also gives details of procedures for converting colchiceine into dimethylcolchicinic acid (obtained in 60% yield by heating with 30% hydrochloric acid at 100°, in a sealed tube), a crystalline compound, m.p. 141–142°, and colchicinic acid, an amorphous material obtained by completing the hydrolysis with hydrochloric acid at 150°.

Colchicine thus contains in its molecule four methoxyl groups, one of which is extremely readily hydrolyzed, and an acetylated amino group. The presence of the four methoxyl groups was demonstrated by the well-known estimation method of Zeisel (36), which may well have been devised specifically for the study of colchicine. By exhaustive methylation of trimethylcolchicinic acid Johanny and Zeisel (37) obtained evidence that this substance is a primary amine, a conclusion fully substantiated by the more detailed investigation of Windaus and Schiele (38) on colchinol methyl ether. As will be shown later, the three methoxyl groups of colchicine hydrolyzed with difficulty are attached to an aromatic ring. The relationship between colchicine and its hydrolysis products are summarized in Table 1.

TABLE 1

RELATIONSHIP BETWEEN COLCHICINE AND ITS HYDROLYSIS PRODUCTS

Name	Formula	Functional groups
Colchicine	$C_{22}H_{25}O_6N$	$=C \cdot OMe$, $(OMe)_3$, $NHCOCH_3$
Colchiceine	$C_{21}H_{23}O_6N$	$=C \cdot OH$, $(OMe)_3$, $NHCOCH_3$
Trimethylcolchicinic acid	$C_{19}H_{21}O_5N$	$=C \cdot OH$, $(OMe)_3$, NH_2
Dimethylcolchicinic acid	$C_{18}H_{19}O_5N$	$=C \cdot OH$, OH, $(OMe)_2$, NH_2
Colchicinic acid	$C_{16}H_{15}O_5N$	$=C \cdot OH$, $(OH)_3$, NH_2

It is necessary now to consider the important initial product of hydrolysis, colchiceine, in greater detail.

6. Colchiceine and Isocolchicine

The preparation of colchiceine from colchicine may be effected as follows:

A solution of colchicine (1 g.) in water (60 cc.) containing concentrated hydrochloric acid (0.6 cc.) is gently boiled under reflux for 2 hours. Occasionally the product crystal-

lizes in the process but should be redissolved by the addition of boiling water; the resulting solution is filtered hot through a pad of cotton wool to remove suspended tarry matter, of which the quantity varies with the quality of the colchicine used. Colchiceine crystallizes from the filtrate and the yield may be augmented slightly by extracting the mother liquor with chloroform. (Traces of trimethylcolchicinic acid remain in the acid liquors.)

Colchiceine, dried under high vacuum, may be recrystallized from a mixture of dioxane and ether in pale yellow needles, m.p. 178–179°. It has $[\alpha]_D^{14} = -252.5°$ (c = 1.192 in chloroform) (43).

Colchiceine, crystallized from water and dried at 100°, is a monohydrate; it loses its water at 140–150°. Colchiceine is sparingly soluble in water, and crystallization may be more satisfactorily effected from a mixture of dioxane and ether (39). Colchiceine is readily soluble in sodium carbonate solution, and is reprecipitated by acid. It was this fact which led Zeisel to the erroneous conclusion that it is a carboxylic acid. In conformity with its true character as an enol it gives an intense green color with ferric chloride (20). The presence of a hydroxyl group rather than a carboxyl group is also supported by the finding of Windaus (40) that trimethylcolchicinic acid undergoes acylation (with benzoyl chloride or benzene sulfochloride) not only of the primary amino group but also of the acidic hydroxyl group, so that diacyl derivatives are formed in which the *O*-acyl group is easily removed by hydrolysis. Pure colchiceine crystallizes in colorless plates. It was pointed out by Zeisel (20) that if its solutions are filtered through unwashed paper the crystals subsequently obtained have a yellowish tinge on account of the presence of traces of iron in the filter paper. For the same reason it is obviously desirable to use pure iron-free water and hydrochloric acid for the hydrolysis of colchicine.

As first noted by Hübler (41), colchiceine forms a crystalline copper salt. This was obtained pure by Zeisel (20) in the form of microscopic quadratic crystals that had the composition required for the formula $(C_{21}H_{22}O_6N)_2Cu$. It is doubtless a doubly chelated compound involving tetracovalent copper and two co-ordinate linkages with carbonyl oxygens in the vicinity of the enolic groupings of the two colchiceine residues. Colchiceine dissolves in strong mineral acids with rise in temperature, to give intensely yellow solutions. Here also molecular compound formation is the probable interpretation of the phenomenon. Such compounds, which have not been isolated, are not stable, for colchiceine is reprecipitated on dilution with water. As with colchicine itself, it is probable that the capacity to form such complexes resides in the carbonyl oxygen atom of the molecule.

Zeisel argued that if colchicine were an ester of a carboxylic acid, as he supposed, then it might undergo conversion into the corresponding

amide by treatment with ammonia. He found (35) that colchicine did indeed react with replacement of a methoxyl group by an amino group, when heated in a sealed tube with 5% alcoholic ammonia at 100°. The resulting colchicamide had the character of an amide because it was hydrolyzed by alkali to ammonia and colchiceine. Colchicamide has basic properties being insoluble in cold water but soluble in cold dilute hydrochloric acid. A crystalline hydrochloride could not be isolated. Although colchicamide behaved like an acid amide it is clear from what is now known of the chemistry of colchicine that it cannot be such a compound. If, as is possible, colchicine is an α-methoxymethylene ketone then the reaction is easily explicable as it is well known that methoxymethylene ketones react with ammonia to give readily hydrolyzable aminomethylene ketones.

The conversion of colchicine to colchiceine involves the hydrolysis of a methoxy compound to methyl alcohol and a hydroxy compound. If no secondary transformations occur it should be possible to reverse this process and obtain colchicine by methylation of colchiceine. This was accomplished by Johanny and Zeisel (37) who obtained colchicine and also a methylcolchicine (apparently by *N*-methylation) when the sodium salt of colchiceine was treated with methyl iodide. The yield of colchicine was not good. It was obtained also, in still smaller yield, by the action of gaseous hydrogen chloride on colchiceine in methanolic solution. A similar transformation of colchiceine to colchicine was attempted by Lettré and Fernholz (42) by means of ethereal diazomethane. They obtained an amorphous material which did not give a color with ferric chloride, and they regarded this as a stereoisomeride of colchicine. The reaction was reinvestigated by Meyer and Reichstein (39) who showed that the product was a mixture from which they were able to isolate pure crystalline colchicine. Finally, Sorkin (43) subjected the reaction product to chromatographic separation on alkali-free alumina and isolated, not only pure colchicine, m.p. 152°, but also a pure isomeride which he termed isocolchicine. This crystallized in colorless rectangular or six-sided plates, m.p. 225–226°, $[\alpha]_D^{12} = -307°$ (c = 1.063 in chloroform); it was hydrolyzed to colchiceine by the usual treatment with hot dilute mineral acid.

The relationship of isocolchicine to colchicine is of great importance in connection with some details of molecular structure not yet completely elucidated. The isomerism is clearly analogous to that of the isomeric dibenzenesulfonyl derivatives of trimethylcolchicinic acid which Windaus (40) prepared. He showed that both were hydrolyzed to the same monobenzenesulfonyl compound. If, as Windaus believed, colchiceine is a hydroxymethylene ketone, then we must be dealing with examples of geometrical isomerism, analogous to the stereoisomerism of the *p*-nitrobenzoates of ethyl formylacetate (44). There is, however, considerable

doubt as to the correctness of this conception of the structure of colchiceine, and the isomerism of these derivatives may be structural rather than spatial. A decision on this question is therefore of major importance in connection with the principal unsolved problem in connection with the structure of colchicine.

A new isomeride of colchicine has recently been reported by Grewe (44a) who noted that in aqueous solution colchicine is rapidly destroyed by ultraviolet light with a radical change in the absorption spectrum. New bands appeared which were attributed to an unstable intermediate product, and Grewe was able to isolate this product as colorless needles, which on heating decomposed above 220°. This "lumicolchicine" was shown by analysis to be isomeric with colchicine and Grewe suggested that its formation was due to rearrangement of the double bonds under the influence of light. Lumicolchicine showed an intense absorption band at 2700 A., and a weaker band at about 2900 A.

7. Structural Chemistry of Colchicine

a. General. The molecular formula of colchicine is $C_{22}H_{25}O_6N$. The investigations of Zeisel, summarized in Sections 4 and 5, established the presence in the molecule of one readily hydrolyzable and three more difficultly hydrolyzable methoxyl groups, and also an acetylated primary amino group. These substituents account for the nitrogen atom and five of the six oxygen atoms. The remaining oxygen atom, as will be shown later, is present in a non-reactive carbonyl group. This has been established indirectly (see below), as colchicine and colchiceine are inert towards the usual carbonyl reagents (45). The following partial formula may therefore be ascribed to the alkaloid:

$$C_{16}H_9 \left\{ \begin{array}{l} (OCH_3)_4 \\ NH \cdot CO \cdot CH_3 \\ =O \end{array} \right.$$

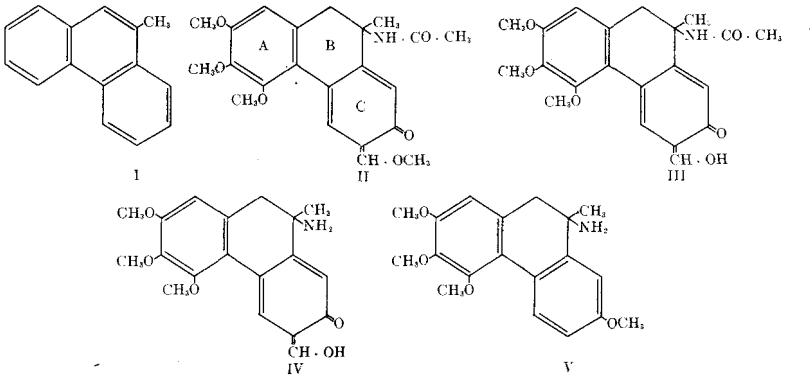
The essential structural problem was, therefore, to determine the nature of the carbon skeleton of 16 atoms, and the positions of the substituents within this framework. This problem has not been completely solved, although the main features have been elucidated, and the structure of a closely related degradation product, deaminocolchinol methyl ether, which contains all but one of the carbon atoms of the $C_{16}H_9$ residue, has been unequivocally established. The most important evidence bearing on the structure of colchicine has been derived from an elegant series of investigations carried out by Windaus, and reviewed by him in two publications (34, 45). A structural formula was advanced by Windaus that was recognized to be in doubt in certain minor respects, but these points of doubt have been clarified by later workers. Recent interest in the biological

properties of colchicine has stimulated renewed chemical investigation, with the result that it has been necessary to revise Windaus' structure in some important respects. It will be convenient, however, to summarize the evidence in favor of Windaus' structure, and then to discuss in turn what modifications have later been made, and what further modification or substantiation appears to be necessary.

b. The Nature of the Ring System. The parent hydrocarbon corresponding to the partial formula already given would be $C_{16}H_{16}$. This contains eighteen hydrogen atoms less than the related paraffin, $C_{16}H_{34}$. Windaus showed (34) (with Schiele and Bredenbeck) that both colchicine and colchiceine could be hydrogenated over a platinum catalyst. The reactions were studied in much greater detail by Bursian (46), who characterized the products as hexahydro derivatives. Hexahydrocolchicine, $C_{22}H_{31}O_6N$, obtained in 75–80% yield by hydrogenation of colchicine with Adams's platinum oxide catalyst, still contained an ethylenic bond, as shown by titration with perbenzoic acid and the isolation of a crystalline oxide, $C_{22}H_{31}O_7N$. Moreover, hexahydrocolchicine, unlike colchicine, contains a hydroxyl group, shown by the formation of crystalline acetyl and benzoyl derivatives. This evidence indicates, therefore, the presence in colchicine of three ethylenic bonds. Furthermore, it may be inferred from other evidence that an aromatic ring is present in hexahydrocolchicine. The corresponding completely reduced hydrocarbon would therefore have the formula $C_{16}H_{28}$, which is still 6 hydrogen atoms short of the paraffin ($C_{16}H_{34}$). Hence we may conclude that colchicine contains three rings. Bursian also studied the hydrogenation product of colchiceine and showed it to be a hexahydride containing one ethylenic linkage and two hydroxyl groups. Clearly one of these hydroxyl groups is the one originally present in colchiceine, and the other is evidently formed by the reduction of a carbonyl group. This argument is of course not completely infallible, as it is conceivable, although unlikely, (a) that the new hydroxyl group may arise by hydrogenation of an oxide ring rather than a carbonyl group, and (b) that one of the "ethylenic bonds" revealed by hydrogenation is in reality a cyclopropane ring. In any final assessment of the structure of colchicine regard must be paid to the further observations of Bursian that neither colchicine nor colchiceine took up oxygen when titrated with perbenzoic acid (in which respect they resemble α,β-unsaturated carbonyl compounds), nor did they undergo Diels-Alder addition with maleic anhydride.

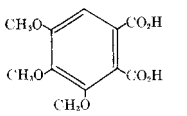
Windaus reached the conclusion that the colchicine molecule contains three rings, not from argument on the lines given above, but from the isolation of various oxidation products which, from their nature, must clearly have arisen from three distinct rings. However, some of the

reactions involved rather drastic conditions and may have been accompanied by modification of the ring system. By a series of reactions outlined below Windaus converted colchicine into a compound, colchinol methyl ether (a tetramethoxy compound containing two benzene rings and an aliphatic primary amino group) which, after Hofmann deamination and demethylation with hydriodic acid, followed by distillation with zinc dust, yielded a very small amount of 9-methylphenanthrene (I) (34). This hydrocarbon was not then known, but was synthesized by Windaus, Jensen, and Schramme (47) by a modified Pschorr reaction and found to be identical with the hydrocarbon from colchinol methyl ether. Windaus accordingly regarded colchicine as a hydrophenanthrene derivative and assigned to it the structure II, with the reservation that the positions of the substituents in ring C had not been determined. On this basis, colchiceine and trimethyl colchicinic acid would have the structure III and IV, respectively, and colchinol methyl ether would be V.

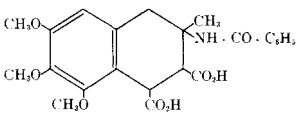


c. The Structure of Ring A. In colchicine and its simple derivatives one ring is aromatic and resistant to oxidation. Accordingly, Windaus (48) was able to oxidize colchicine with warm alkaline permanganate to a trimethoxyphthalic acid (it gave an anhydride on heating) which was later (49) converted into gallic acid by heating with hydriodic acid. The orientation of the oxidation product was determined beyond doubt by the agreement of its properties with those of a sample of 3 : 4 : 5-trimethoxyphthalic acid (VI), synthesized by Bargellini and Molina (50) by treatment of the ester of trimethylgallic acid with chloral and sulfuric acid. In colchicine the ring which gives this trimethoxyphthalic acid (ring A) is unsymmetrically substituted; it is therefore necessary to distinguish between two alternative orientations for the methoxyl groups, namely that shown in formula II (the 2:3:4-structure), and the other possible 1:2:3-structure. A decision in favor of the former was made by Windaus and has been confirmed by more recent synthetic studies.

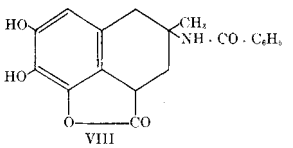
Windaus (40) obtained as one of the oxidation products of *N*-benzoyltrimethylcolchicinic acid (derived from IV) a dicarboxylic anhydride which was reduced by zinc and acetic acid to a dicarboxylic acid, and which he considered (34) to be a tetrahydronaphthalene derivative (VII). This, when heated with hydriodic acid, was demethylated and also lost carbon dioxide to give a substance which was formulated as a lactone (VIII). In conformity with the considerations advanced by Sachs (51), this can only arise if there is a hydroxyl group in ring A in the *peri* position to the carboxyl group remaining from the degradation of ring C. A hydroxyl group is thus placed in position 4 of formula II, so that the orientation of the three methoxyl groups in ring A must be as shown.



VI



VII



VIII

d. The Evidence for Ring B. By fusion of colchicine with potash and subsequent oxidation of the extracted melt with potassium permanganate there was obtained (49) a mixture of terephthalic and trimellitic (benzene-1 : 2 : 4-tricarboxylic) acids. The same products were formed by similar treatment of colchicinic acid. These acids must be derived from ring B or ring C of colchicine. In view of the ease with which the latter ring in *N*-benzoyltrimethylcolchicinic acid and analogous compounds is oxidized (with permanganate), they are most simply regarded as derived from ring B. This evidence, together with the degradation to 9-methylphenanthrene, led Windaus to conclude that ring B is six-membered. It should be noted, however, that the oxidation is preceded by the rather drastic treatment with fused potash at 245.°* (See Addendum.)

In the hydrolysis of *N*-acetylcolchinol methyl ether to colchinol methyl ether (V) some demethylation occurs as a side reaction. The alkali-soluble products so formed were oxidized by Windaus (52) with chromic acid and gave a crystalline product which he identified as 4-methoxyphthalimide. The benzene nucleus in this compound clearly arises from ring C, and Windaus regarded the production of 4-methoxyphthalimide as evidence for the attachment of the nitrogen atom of colchicine to a carbon atom which is directly linked to ring C. This places the

* It is evident from recently-published articles that the trimellitic acid originates from ring C (259). H. Lettré reported that H. Fernholz found that colchicine is transformed into a carboxylic acid by alcoholic alkali or (better) by sodium ethoxide. This change clearly involves a modification of ring C. Moreover, J. Ch. Salfeld found that the resulting acid could be oxidized to trimellitic acid (compare Dewar, 29).

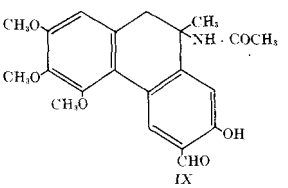
amino group of colchinol methyl ether in the position shown in formula V.

The formation of 9-methylphenanthrene by degradation of colchinol methyl ether suggests that the latter compound is a derivative of 9 : 10-dihydrophenanthrene with a methyl group at position 9 or 10. The choice between these two alternatives was made by Windaus in favor of that shown in formulas II and V in order to interpret the oxidation of colchicine to the ketonic derivative, oxycolchicine. This requires the presence of a reactive methylene group in colchicine, and the methylene group of ring B, adjacent to an aromatic nucleus, would clearly be expected to show such reactivity. It is difficult to accommodate a reactive methylene group in any other position of the colchicine molecule.

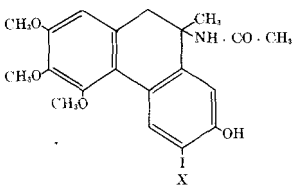
Thus, the evidence in favor of the nature and orientation of ring B is suggestive, but somewhat indirect and inconclusive.

e. Transformations in Ring C. The least satisfactory feature of the Windaus structure for colchicine is the evidence in support of ring C. The degradation of colchinol methyl ether (V) to 4-methoxyphthalimide leads to a clear presumption that ring C of (V) is benzenoid, but this is certainly not true of colchicine itself, and the reactions by which ring C of colchicine become aromatic have not yet been satisfactorily explained. (See Addendum.)

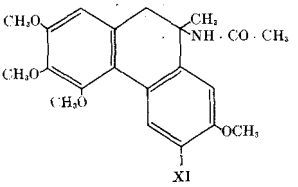
If colchicine were correctly represented by formula II, then the structure of colchiceine must be that of a hydroxymethylene ketone (III) and this would be expected to isomerize to an *o*-hydroxy aromatic aldehyde (IX). In fact, however, colchiceine shows no tendency to react in this form. It is strongly acidic, it shows no carbonyl reactivity, and its absorption spectrum (28, 46) closely resembles that of colchicine and is distinct from that of *N*-acetylcolchinol methyl ether in which ring C is undoubtedly aromatic. Moreover, methylation of colchiceine gives colchicine and isocolchicine, and the facile hydrolysis of the latter to colchiceine precludes any possibility that it is a methoxy aldehyde derived from IX. These difficulties were clearly appreciated by Windaus (34), and have further been emphasized by Horning (53) and by Dewar (29). It is uncertain, however, to what extent the equilibrium between III and IX would be



IX



X



XI

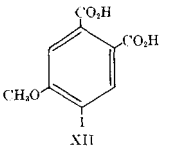
influenced by the dicyclic system attached to ring C, and Windaus was able to show that in one important respect a close analogy does indeed exist between colchiceine and salicylic aldehyde. This was the action of

alkaline hypoiodite. He found (49, 52) that this leads, in the case of colchiceine, to iodination and oxidation, with elimination of a carbon atom, and the formation of an iodophenol, *N*-acetyliodocolchinol (X). Reduction of X with zinc dust and alkali gave *N*-acetylcolchinol, and these two compounds were methylated to give, respectively, *N*-acetyliodocolchinol methyl ether (XI) and *N*-acetylcolchinol methyl ether (XIII, p. 280).

N-Acetyliodocolchinol and its methyl ether. To a solution of colchiceine (1 g.) in 1 *N* sodium hydroxide (200 cc.), cooled in ice and vigorously stirred, there is slowly added about 70 cc. of a solution made from iodine (2 g.) potassium iodide (10 g.) and water (100 cc.). The addition is stopped when an acidified test portion, treated with a drop of aqueous ferric chloride, no longer gives a green color. The resulting mixture is acidified with dilute sulfuric acid and decolorized by passing a stream of sulfur dioxide. The collected precipitate is washed with water, rubbed with small quantities of ice-cold methanol to remove adhering colored impurities, and crystallized from ethanol. *N*-Acetyl iodocolchinol forms pale yellow pointed prisms, m.p. 229–230°. From it the methyl ether, needles, m.p. 123°, from benzene then from aqueous methanol, is prepared (a) quantitatively, by means of diazomethane in acetone or (b) by shaking (1 g.) in 10% sodium hydroxide (50 cc.) with methyl sulfate (5 cc.) for 4 hours.

N-Acetylcolchinol and its methyl ether. *N*-Acetyliodocolchinol (1 g.; unrecrystallized material is satisfactory), 1 *N* sodium hydroxide (10 cc.) and zinc dust (3 g.) are heated at 100° for 1 hour. The cooled (0°), filtered, and acidified solution slowly deposits *N*-acetylcolchinol, which forms colorless needles containing water of crystallization, m.p. 150° from methanol; anhydrous, m.p. over 200°. A further quantity may be obtained from the acid mother liquor by extraction with chloroform. *N*-Acetylcolchinol methyl ether, colorless needles, m.p. 199° from methanol, may be prepared (a) by the methods described above for its iodo-derivative, (b) by reduction of the iodo-derivative with zinc and acetic acid, and also (c) by adding methyl *p*-toluenesulfonate (1.5 g.) to a solution of the parent phenol (1 g.; unrecrystallized) in 1 *N* sodium hydroxide (30 cc.) and heating the mixture at 100° for 1 hour.

The transformations described above do not, of course, determine the positions of the two substituents in ring C of the compounds III, X, and XI, beyond showing that they are contiguous. The exact location of the substituents depends upon other evidence. Thus, Windaus (52) oxidized *N*-acetyliodocolchinol (X) to trimethoxyphthalic acid (VI) but showed that methylation of the phenolic hydroxyl group rendered ring C more stable than ring A, so that oxidation of *N*-acetyliodocolchinol methyl ether (XI) using first nitric acid and then alkaline permanganate, gave an



XII

iodomethoxyphthalic acid (XII) which could be reduced to 4-methoxyphthalic acid. The structure of XII was proved by its subsequent synthesis by Grewe (54). Even this evidence does not completely elucidate the

orientation of the substituents in ring C, and if they were interchanged the same 5-iodo-4-methoxyphthalic acid would still arise by oxidation. That they are correctly placed in formula XI was finally shown, however, by synthetic experiments outlined below.

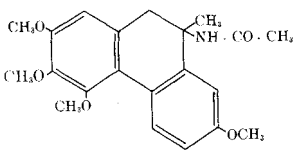
f. Deaminocolchinol Methyl Ether and Its Structure: Isodeaminocolchinol Methyl Ether. Hydrolysis of *N*-acetylcolchinol methyl ether to the hydrochloride of colchinol methyl ether (V) is effected by the prolonged action of a boiling mixture of concentrated hydrochloric acid and methanol (52). The primary character of the amino group in the resulting base was shown by Windaus and Schiele (38) by the standard procedure of exhaustive methylation which led successively to a secondary amine, a tertiary amine, and then a quaternary ammonium salt. The quaternary ammonium hydroxide formed from the latter by treatment with silver hydroxide readily lost trimethylamine on heating and gave a nitrogen-free crystalline product, deaminocolchinol methyl ether, which if structure (V) were correct for colchinol methyl ether, should be 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene (XIV).

The same deaminocolchinol methyl ether was obtained more simply by Cook and Graham (55), who found that *N*-acetylcolchinol methyl ether (XIII), when heated with phosphoric oxide in xylene, eliminated acetamide and gave the product obtained by Windaus and Schiele from the Hofmann degradation.

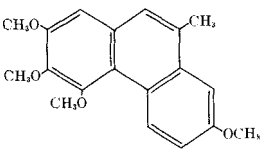
The first direct evidence that the structure V for colchinol methyl ether is erroneous came from the synthesis of 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene by Buchanan, Cook, and Loudon (56). At that time the position of the methoxyl group in ring C of V had not been settled, and there was an alternative possibility, therefore, that deaminocolchinol methyl ether might be 2 : 3 : 4 : 6-tetramethoxy-9-methylphenanthrene (XV). This, too, was synthesized (56), and both were found to be different from the Hofmann degradation product.

In the meantime, other facts had come to light which had served to cast doubt on the validity of structure V for colchinol methyl ether. It was pointed out by Cohen, Cook, and Roe (57) that a compound of this structure should be unstable and readily lose ammonia to form a completely aromatic structure. This type of behavior had already been observed (47, 58) in simpler derivatives of 9-amino-9 : 10-dihydrophenanthrene. Such a difficulty would be removed if the amino group were present in the side chain and not directly attached to the nucleus. On this basis colchinol methyl ether would have the structure XVI. This, however, was rendered unlikely by the observation (57) that *N*-acetylcolchinol methyl ether did not undergo the facile dehydrogenation which would be expected of such a derivative of 9 : 10-dihydrophenanthrene. On the other hand,

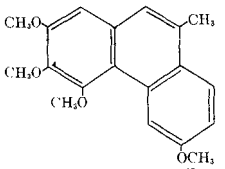
treatment of colchinol methyl ether with nitrous acid led (57) to a carbinol which, if V were correct, should be a tertiary carbinol (XVII). This carbinol showed a degree of resistance to dehydration incompatible with such a structure and seemed, in fact, to be a secondary carbinol. That no profound molecular rearrangement had occurred in the replacement of the amino group by a hydroxyl (nitrous acid) was shown (59) by the dehydration of the carbinol to deaminocolchinol methyl ether together with an isomeric compound, isodeaminocolchinol methyl ether. (See Addendum).



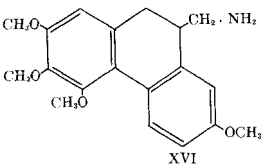
XIII



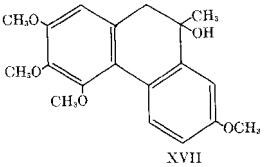
XIV



XV



XVI



XVII

Colchinol methyl ether. A solution of *N*-acetylcolchinol methyl ether (1 g.) in methanol (10 cc.) is heated under reflux with concentrated hydrochloric acid (10 cc.) for 16 hours. The methanol is distilled off, water is added and, after extraction with chloroform to remove unchanged material, the aqueous solution is concentrated under reduced pressure until the hydrochloride (m.p. with decomposition 255°) crystallizes. This is assisted by the addition of concentrated hydrochloric acid and the free base, liberated from the hydrochloride by aqueous sodium hydroxide, is recovered in chloroform and crystallizes from ether–ligroin as tiny needles, m.p. 94°. The acid mother liquor contains partially demethylated material.

Action of nitrous acid on colchinol methyl ether. A 10% solution of sodium nitrite (2.8 g.) is added during 1 hour to a stirred ice-cooled solution of colchinol methyl ether hydrochloride (13.2 g.) in 10% acetic acid (150 cc.). After being kept at room temperature for 2 hours, the product is extracted with ether, and the extract washed with dilute sodium carbonate solution, dried, and distilled. The resinous distillate (5.1 g.), b.p. 230°/3 mm., is dissolved in benzene, and light petroleum is added until a slight turbidity is produced. The solution slowly crystallizes at 0° yielding a carbinol of m.p. 115.5–116.5°.

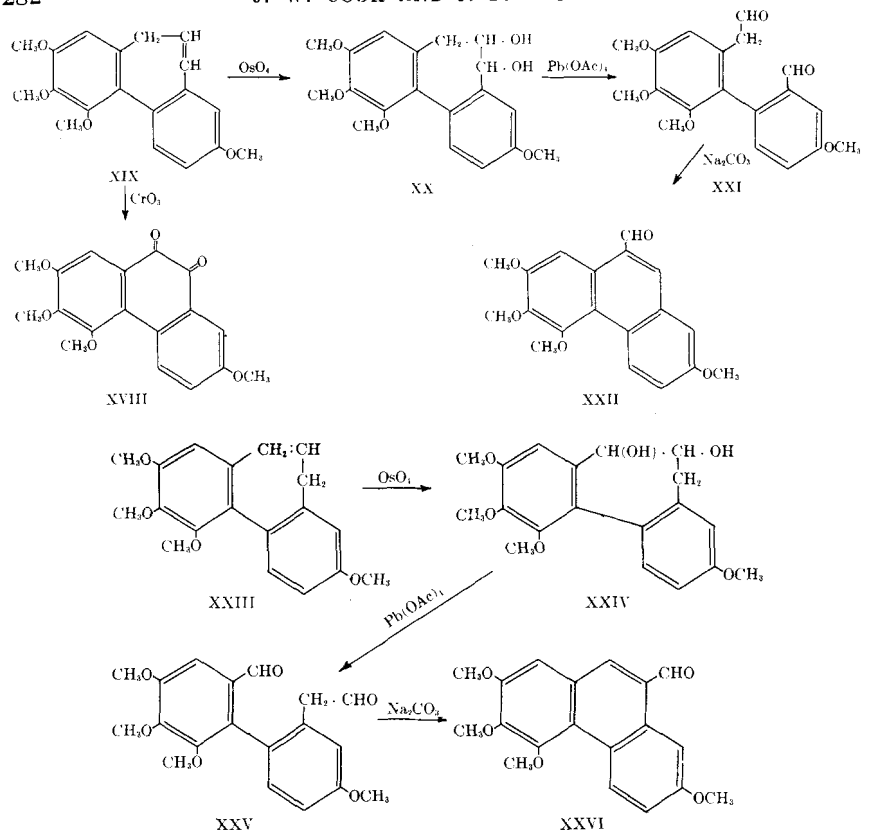
Deamino- and isodeaminocolchinol methyl ether. (a) Phosphoric oxide (0.8 g.) is added to a solution of *N*-acetylcolchinol methyl ether (0.4 g.) in pure dry xylene (20 cc.) and the mixture is boiled for 15 minutes. The hot xylene solution is decanted from insoluble material which is well washed with more boiling xylene. The gum, obtained by evaporating the combined solution and washings under reduced pressure, crystallizes from methanol, yielding deaminocolchinol methyl ether as colorless plates which finally melt within the range 111–113° and usually sinter, or even melt and resolidify, within the range 98–105°. The solid obtained from the concentrated methanol mother-liquor

yields a little isodeaminocolchinol methyl ether, m.p. 99–100° (depressed to ca. 84° by admixture with the preceding isomer), on fractionation from methanol.

(b) The carbinol (0.6 g.), obtained as already described from colchinol methyl ether, is dissolved in xylene (30 cc.) and the solution refluxed with phosphoric oxide (1.5 g.) for 15 minutes. After decanting the solution from insoluble material the xylene is removed and the resulting gum yields a viscous distillate (0.23 g.), b.p. 145° (air bath), 0.2 mm., which solidifies when rubbed with cold methanol. Fractional crystallization from methanol gives the two isomers, isodeaminocolchinol methyl ether preponderating.

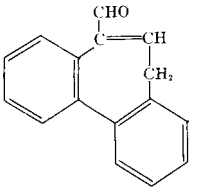
It was increasingly clear, therefore, that deaminocolchinol methyl ether was a key compound in the solution of the problem of the structure of colchicine, and it became imperative to determine its constitution and to elucidate the mechanism of the reactions by which it had been converted by Windaus into 9-methylphenanthrene. Fortunately, a link-up with the synthetic compounds was soon achieved, for oxidation of deaminocolchinol methyl ether by sodium dichromate in acetic acid (59) yielded 2 : 3 : 4 : 7-tetramethoxyphenanthrenequinone (XVIII), identical with the product of oxidation of 2 : 3 : 4 : 7-tetramethoxyphenanthrene-9-carboxylic acid, an intermediate in the synthesis of XIV. As the structure of XVIII was established beyond doubt by the synthetic methods employed this result confirmed the positions assigned by Windaus to the three methoxyl groups of ring A of colchicine, and also settled for the first time the position of the methoxyl group in ring C of colchinol methyl ether, and related compounds.

There remained, therefore, the determination of the structure of the central ring of deaminocolchinol methyl ether. Barton, Cook, and Loudon (59) showed that this is an unsaturated compound which contains one ethylenic bond. Hydrogenation gave a dihydride which was also formed by hydrogenation of isodeaminocolchinol methyl ether. Consequently deaminocolchinol methyl ether and its isomeride differ only in the position of the ethylenic double bond. Both unsaturated compounds were oxidized by osmium tetroxide to isomeric diols (XX and XXIV), which by further oxidation with lead tetraacetate gave resinous products, believed to be dialdehydes (XXI and XXV); these with a trace of alkali passed into crystalline mono-aldehydes. By these reactions deaminocolchinol methyl ether was converted into 2 : 3 : 4 : 7-tetramethoxy-10-phenanthraldehyde (XXII) and its isomeride into 2 : 3 : 4 : 7-tetramethoxy-9-phenanthraldehyde (XXVI). The 10-aldehyde was identified by oxidation with permanganate to the 10-carboxylic acid, identical with a synthetic specimen, and the 9-aldehyde by direct comparison with a synthetic specimen (59). These results were interpreted as providing unambiguous proof that deaminocolchinol methyl ether and its isomeride have the structures XIX and XXIII, respectively, and the reactions, by which they were converted into the substituted phenanthrenes were formulated as follows:

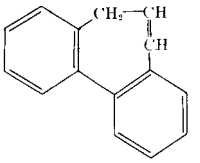


At first glance, the direct oxidation of deaminocolchinol methyl ether (XIX) to the tetramethoxyphenanthrenequinone (XVIII) seemed a somewhat curious reaction. However, a counterpart was already present in the literature, for Weitzenböck (60) had oxidized the aldehyde (XXVII) to phenanthrenequinone with chromic acid in acetic acid. Moreover, Cook, Dickson, and Loudon (61) have shown that synthetic 3 : 4 : 5 : 6-dibenz-$\Delta^{1:3:5}$-cycloheptatriene (XXVIII), which they prepared by adapting the earlier work of Kenner (62), undergoes a series of reactions exactly comparable with those described for deaminocolchinol methyl ether and its isomeride. The hydrocarbon (XXVIII) is oxidized to phenanthrenequinone by sodium dichromate in acetic acid, and is converted by osmium tetroxide into a diol which undergoes fission with lead tetraacetate to a dialdehyde (not isolated), and this readily passes into 9-phenanthraldehyde. Furthermore, by analogy with Windaus' transformation of deaminocolchinol methyl ether into 9-methylphenanthrene, it was found that the model hydrocarbon (XXVIII), if heated with hydriodic acid and the

product distilled with zinc, gives appreciable amounts of 9-methylphenanthrene.



XXVII



XXVIII

The structure assigned to deaminocolchinol methyl ether has been confirmed also by subsequent work of Tarbell, Frank, and Fanta (63), who prepared deaminoiodocolchinol methyl ether from iodocolchinol methyl ether (compare XI), and oxidized it to a derivative of homodiphenic acid.

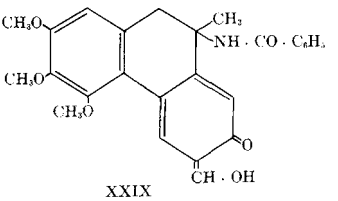
The deaminocolchinol methyl ether structure (XIX) may, therefore, be regarded as resting on a completely sure foundation.

g. Products of Oxidative Degradation of Ring C. Before discussing, with regard to the general problem of the constitution of colchicine, the implications of these investigations of deaminocolchinol methyl ether, reference may be made to an interesting series of degradation products obtained by Windaus (40). In these compounds ring C is degraded, whereas rings A and B are preserved apparently unchanged. Any final assessment of the structure of colchicine must clearly be one which is capable of providing a rational explanation of these degradations. To facilitate illustration, Windaus' colchicine structure showing ring B as six-membered will be used.

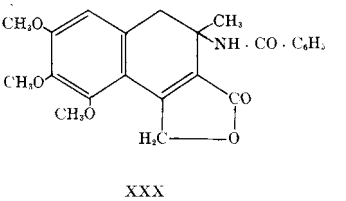
By treatment of trimethylcolchicinic acid (IV) with benzoyl chloride in pyridine there is formed a dibenzoyl derivative from which one benzoyl group may be removed by brief boiling with alcoholic potash. The monobenzoyl derivative, unlike the dibenzoyl derivative, gives a dark green color with ferric chloride, and must be regarded as *N*-benzoyltrimethylcolchicinic acid (XXIX). It was on the basis of these reactions that Windaus concluded that colchiceine is an enol and not a carboxylic acid, as Zeisel originally supposed. Similar treatment of trimethylcolchicinic acid with benzenesulfonyl chloride gave the isomeric dibenzenesulfonyl derivatives to which reference has already been made.

Oxidation of *N*-benzoyltrimethylcolchicinic acid (XXIX) by cold alkaline permanganate gave not only the dicarboxylic anhydride mentioned, but also, in substantially larger yield, a compound, *N*-benzoylcolchide, which gave no color with ferric chloride and had the properties of a lactone. This was formulated (45) as XXX, and the free aminolactone, colchide, was obtained by hydrolysis with alcoholic hydrogen chloride. Colchide, however, was not the main product of hydrolysis. The reaction was accom-

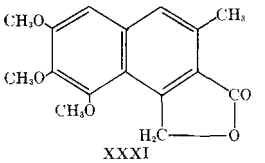
panied by the formation of ammonium chloride, and a nitrogen-free lactone, trimethoxyhomonaphthide. This latter product was also obtained, together with benzamide, when *N*-benzoylcolchide was slowly sublimed at 250°. It was formulated as a naphthalene derivative (XXXI), and if formula XXX is correct for *N*-benzoylcolchide then the tendency for aromatization of ring B provides a ready explanation for the facility with which the



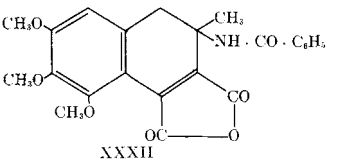
XXIX



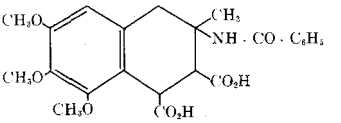
XXX



XXXI



XXXII

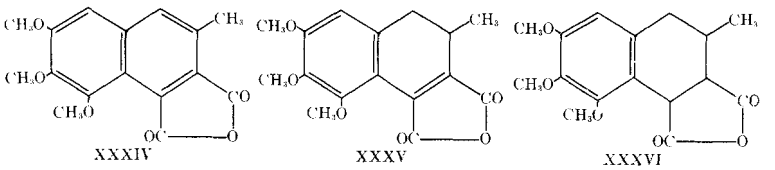


XXXIII

nitrogen is eliminated from the molecule. *N*-Benzoylcolchide (XXX) is strongly *levo*rotatory ($[\alpha]_D^{17} = -275°$), but trimethoxyhomonaphthide is optically inactive, as is required by formula XXXI. Colchicine itself was similarly oxidized to *N*-acetylcolchide, regarded as analogous to (XXX).

The second product of permanganate oxidation of *N*-benzoyltrimethylcolchicinic acid (XXIX) was a yellow dicarboxylic anhydride. This was termed *N*-benzoylcolchinic acid anhydride and formulated as XXXII. It dissolved in alkali to give a colorless solution. Acidification gave a colorless solution which became yellow and deposited the yellow anhydride. The amine obtained by hydrolysis of this anhydride with alcoholic hydrochloric acid apparently showed no tendency to lose ammonia, and was acylated by benzenesulfonyl chloride to give a *N*-benzenesulfonylcolchinic acid anhydride which was also formed by oxidation of *N*-benzenesulfonyltrimethylcolchicinic acid. Reduction of *N*-benzoylcolchinic acid anhydride (XXXII) with zinc dust and acetic acid led to the addition of two atoms of hydrogen with the formation of a dicarboxylic acid (not an anhydride) which was regarded as a tetrahydronaphthalene derivative (XXXIII). This was stable to potassium permanganate.

The formulation of these degradation products as naphthalene and hydronaphthalene derivatives is entirely consistent with their chemical behavior, but in view of the demonstration that deaminocolchinol methyl ether contains a seven-membered ring B it would obviously be desirable to have confirmation of these structures. This question is being approached from the synthetic side in The University of Glasgow laboratories, and Mr. T. Y. Johnston has prepared the three anhydrides, XXXIV, XXXV, and XXXVI by synthetic reactions which establish their structures. It is hoped to compare these compounds with appropriate degradation products of colchicine. (See Addendum.)



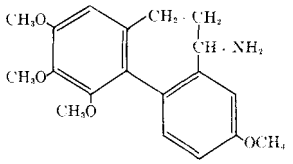
XXXIV XXXV XXXVI

It has been pointed out that colchiceine shows some behavior which is difficult to reconcile with Windaus' structure for ring C. In this connection, it would be of interest to study the products which might arise by less extensive degradation of ring C than is involved in the permanganate oxidations. A step in this direction has been taken by Meyer and Reichstein (39) who have shown that oxidation of colchiceine with periodic acid (colchicine is unaffected by this reagent) leads to the addition of two atoms of oxygen with the formation of a monocarboxylic acid, $C_{21}H_{23}O_8N$, which failed to react with semicarbazide. If ring C were opened a dicarboxylic acid would be expected. Such an acid might be formed as an intermediate with subsequent lactonization involving a suitably placed ethylenic double bond. The compound merits, and will doubtless receive, further attention.

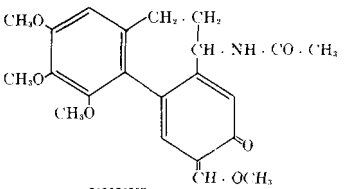
Another reaction which appears to involve mild oxidation in ring C was found by Windaus (52) who re-investigated the action of bromine in acetic acid on colchiceine (31). This leads to a tribromomonocarboxylic acid, $C_{21}H_{20}O_7NBr_3$. The acid appears to be somewhat easily decarboxylated as it loses carbon dioxide when heated to 230–240° (45). As colchiceine is $C_{21}H_{23}O_6N$ the process is equivalent to addition of one atom of oxygen, with replacement of three atoms of hydrogen by bromine. This product also merits further study.

h. Some Problems Still Outstanding. The clearest picture of the molecular structure of colchicine as a whole is given by the complete elucidation of the structure of its transformation product, deaminocolchinol methyl ether. If it were possible to trace back with complete certainty the reactions by which this is formed from colchicine, then the structural

problem would be finally solved. It is, however, premature to attempt this. Nevertheless, some general observations may be made in regard to the present state of the problem. Ring B in deaminocolchinol methyl ether has been shown to be seven-membered. If this be true also of colchinol methyl ether and colchicine itself, then these two compounds would be represented by the structures XXXVII and XXXVIII, respectively, assuming for the moment the correctness of Windaus' formulation of



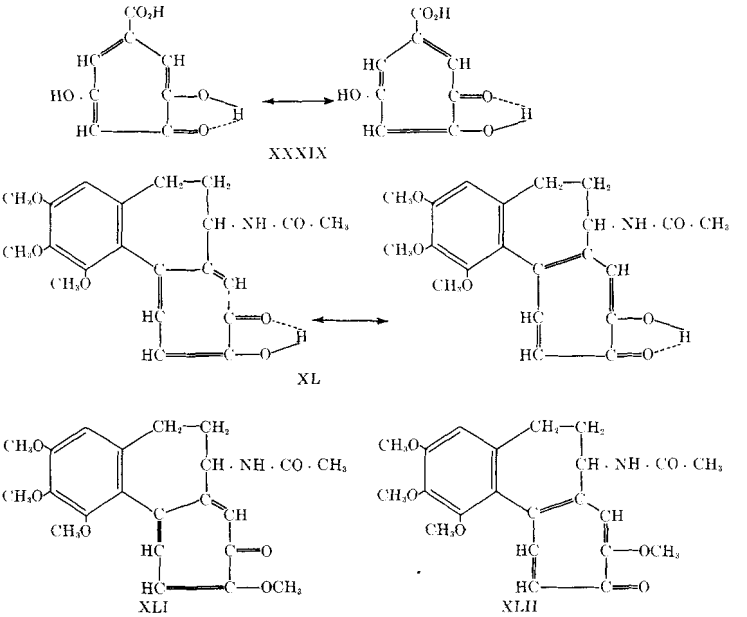
XXXVII



XXXVIII

ring C of colchicine. The structure XXXVIII provides a ready explanation for the formation of succinic acid by the oxidation of colchicinic acid with potassium permanganate (49). This is difficult to interpret in terms of Windaus' colchicine structure, which does not contain a linked pair of methylene groups. On the other hand, if the "naphthalene" degradation products described in Section 7, *g*, are correctly formulated, then their formation from a structure such as XXXVIII would involve an unusual type of ring contraction which requires elucidation.

It is by no means certain that Windaus' colchicine formula is correct with respect to ring C. As already pointed out, it is difficult to account for the failure of colchiceine to undergo isomerization to an aromatic *o*-hydroxy aldehyde, if colchiceine contains the postulated type of hydroxymethylene-ketone structure. An alternative "tropolone" structure for ring C has been advanced by Dewar (29). He had already proposed (64) a resonance structure of this type (XXXIX) for stipitatic acid, a metabolite of *Penicillium stipitatum* Thom, isolated by Birkinshaw, Chambers, and Raistrick (65). The essential feature of this is a seven-membered ring containing three double bonds, with an enolic hydroxyl group adjacent to a carbonyl group. It was suggested by Dewar that ring C of colchiceine is also seven-membered, with a similar disposition of double bonds and functional groups. The name "tropolone" was suggested for the parent cycloheptatrienolone, and this system is regarded as a novel type of aromatic structure without carbonyl reactivity or unsaturated character. If it is assumed that the seven-membered ring B of deaminocolchinol methyl ether is also present in colchicine, then, on Dewar's hypothesis, colchiceine and colchicine would be represented by the structures XL and XLI or XLII, respectively (but compare Dewar (66)).



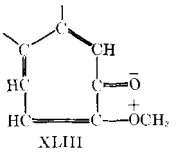
XXXIX

XL

XLI

XLII

If XLI represents colchicine, then XLII would represent Sorkin's isocolchicine (43), and a similar relationship would exist between the isomeric dibenzenesulphonyl derivatives of trimethylcolchicinic acid. Dewar claims that aromatization of ring C of colchiceine by treatment with alkaline hypoiodite is due to a benzilic acid type of rearrangement, and he suggested (66) that the enhanced solubility in water of colchicine as compared with colchiceine is due to an ionic resonance, involving a form such as XLIII.



XLIII

These speculations are of considerable interest, but lack experimental support, and are not free from objection. Dewar claimed (66) confirmation of the tropolone structure by an oxidation of crude hexahydrocolchiceine with lead tetraacetate. This gave a product from which was obtained an amorphous (apparently inseparable) mixture of dinitrophenylhydrazones. If Dewar's structure were correct then hexahydrocolchiceine would be a 1 : 2-diol and should undergo fission to a dialdehyde with lead tetraacetate. On the basis of Windaus' structure for ring C, hexahydrocolchiceine would be a 1 : 3-diol, with one primary and one secondary hydroxyl

group. It is not inconceivable that such a structure could be oxidized by lead tetraacetate to a product showing carbonyl reactivity.

A renewed investigation of the structure of ring C is clearly to be desired. (See Addendum.)

Reference has been made to the fact that colchiceine shows evidence of compound formation with mineral acids. In the case of trimethylcolchicinic acid a compound of this type has been isolated in a crystalline state. Windaus found (40) that this compound gives an almost colorless monohydrochloride, which is in keeping with its character as a monoamine. When, however, an alcoholic solution of this monohydrochloride was saturated with hydrogen chloride at 0–4°, then a dark yellow dihydrochloride separated. The second molecule of hydrogen chloride is presumably associated with a basic oxygen, and the dihydrochloride may be regarded as an example of a halochromic salt. Such salts are formed by many α,β-unsaturated ketones, and such a molecular grouping is present in ring C in the structures of both Windaus and Dewar. It should be noted, however, that these two structures are not necessarily the only alternatives between which a choice has to be made.

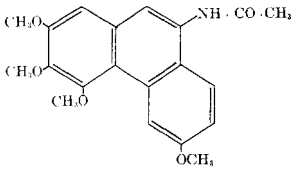
To sum up: uncertainty remains regarding the structure of ring C of colchicine — it is not aromatic but can readily become so although the mechanism of the process is not clear. Consequently, despite precise knowledge of the structure of deaminocolchinol methyl ether and the narrow limits thereby set to possible structures for colchinol derivatives, the true relationship of these more highly aromatic types to the parent alkaloid itself is still to be determined. Whatever the final solution may prove to be, it is apparent that this alkaloid is a natural product of quite unusual chemical interest.

8. Synthetic Approaches to the Colchicine Molecule

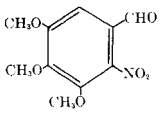
Until the constitution of colchicine is finally settled it is obviously impractical to attempt a complete synthesis. There are, however, many structural features which are known with a fair degree of certainty, and in view of the important biological properties of colchicine some attempt has been made already to prepare synthetic analogs which might reproduce some or all of the biological activity of the alkaloid.

The earliest experiments in this direction were by Sharp (67), who in 1936 synthesized 9-acetamido-2 : 3 : 4 : 6-tetramethoxyphenanthrene (XLIV), a structure closely related to that then considered to represent *N*-acetylcolchinol methyl ether. As an intermediate in his synthesis, Sharp prepared 2 : 3 : 4 : 6-tetramethoxyphenanthrene-9-carboxylic acid, using as one component in a Pschorr reaction the difficultly accessible 2-nitro-3 : 4 : 5-

trimethoxybenzaldehyde (XLV). The same method was adopted for the synthesis of some of the tetramethoxymethylphenanthrenes prepared more recently, but the nitroaldehyde was more satisfactorily obtained by an alternative method, involving reduction of the corresponding nitro acid (56).



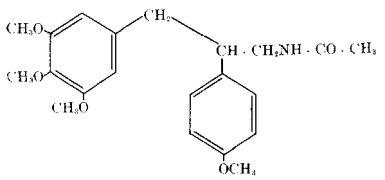
XLIV



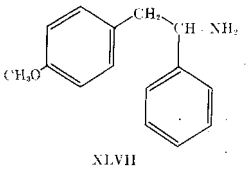
XLV

The synthetic procedures developed in Glasgow have been found adaptable to the preparation of a variety of 9- and 10-substituted 2 : 3 : 4 : 6- and 2 : 3 : 4 : 7-tetramethoxyphenanthrene derivatives, as well as some compounds of the 2 : 3 : 4 : 5-tetramethoxy series (56, 59).

In another method of approach, Cook and Engel (68) synthesized a derivative of β,γ-diphenylpropylamine (XLVI), which contained some of the structural features then under consideration for *N*-acetylcolchinol methyl ether, without the intact phenanthrene ring system. This compound (XLVI) was found by Brues to give, in large dosage, an effect analogous to that of colchicine on the regenerating liver of the rat. This line of attack was developed further by Lettré and Fernholz (42), who synthesized for biological test a number of substituted α,γ-diphenylpropylamines and α,β-diphenylethylamines. The former were obtained by reduction of the oximes of dihydrochalkones; the latter by stepwise reduction of the ω-nitrostyrenes resulting from condensation of aromatic aldehydes with arylnitromethanes. One of the synthetic compounds of the latter series (XLVII) showed something of the biological activity of colchicine (69). This is discussed in a later section.



XLVI



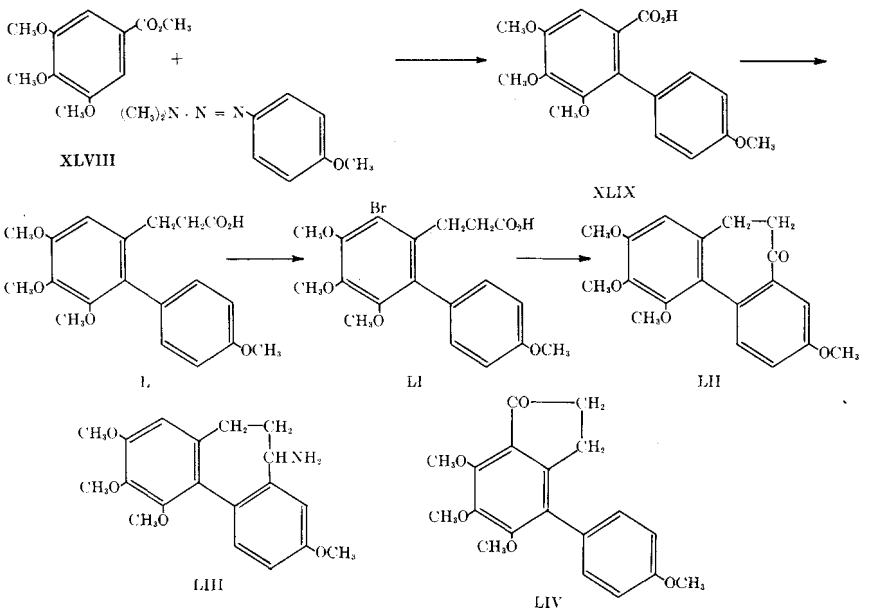
XLVII

With the recognition that deaminocolchinol methyl ether is a derivative of dibenzcycloheptatriene (Section 7, f), and that a seven-membered ring is probably present also in colchinol methyl ether and possibly in colchicine itself, it became desirable to devise methods for the synthesis of unsymmetrically substituted dibenzcycloheptatrienes. Work on this project is still at a comparatively early stage of development, but mention

may be made of a series of reactions which illustrates the nature of the problem and emphasizes its difficulties.

Barton *et al.* (70), making use of the ingenious device of Elks and Hey (71) for the stabilization of diazo compounds reacted methyl trimethylgallate (XLVIII), with 1-(*p*-methoxyphenyl)-3 : 3-dimethyltriazen and obtained the tetramethoxydiphenylcarboxylic acid (XLIX) which, by standard reactions (indirect reduction to aldehyde; condensation with malonic ester; reduction) was converted into the propionic acid (L).* This acid was brominated to (LI) and it was expected that the bromine substituent would block cyclization to an indanone and enable a seven-membered ring ketone to be obtained. From this, by reduction, it was hoped to prepare the ketone (LII) and thence, through the oxime, the amine (LIII). The product of this series of reactions might well have been the *dl*-form of colchinol methyl ether.

The various stages in this process were completed, but it was subsequently found that the final base had not the structure (LIII). A rearrangement with bromine migration had occurred in the cylization of (LI) so that the product, after debromination, was the indanone (LIV), which was obtained much more simply by direct cyclization of (L). Other synthetic routes to (LIII) are being explored.



* This acid has also been prepared by an alternative method by Frank, Fanta, and Tarbell (*J. Am. Chem. Soc.*, **70**, 2314, 1948) who likewise brominated the acid and cyclized the product to a bromo ketone.

II. Biological Effects of Colchicine

1. Toxicity and Pharmacology

Mention has been made in an earlier section of the use of colchicine in the treatment of gout. This remains the only therapeutic application of the alkaloid which has, however, attained in recent years a degree of importance in biological studies that far transcends that of all but a few of the other active principles of plants. The newer biological studies of colchicine largely had their origin in the work of Dustin on the mitosis-poisoning effect of chemical substances, in which respect colchicine is pre-eminent, and have given rise to an exceedingly extensive literature which cannot be reviewed adequately within the compass of this chapter. An outline of these investigations is given in the sections which follow, and attention is directed also to the excellent reviews of Levine (3, 72, 73) and of Ludford (74).

Colchicine is an intensely poisonous substance and its toxic symptoms have been described by Houdès (23), Dixon (75), Dixon and Malden (76), and Autenrieth (15). Houdès found the lethal dose for guinea pigs weighing 450 g. to be 30 mg., and described the principal general effects as a state of collapse, with stupor, but without analgesia. According to Autenrieth, however, colchicine is one of the most powerful poisons, and has caused death in a human adult in a single dose of only 3 mg. It is a slow poison, even in very large doses, and requires from three to six hours to cause death in carnivora. In this respect it resembles the bacterial toxins. This delayed action is due to slow absorption into the central nervous tissues and death is caused by vasomotor paralysis (76). Colchicine affects the gastrointestinal membrane and may cause vomiting, diarrhea, and pain in the bowels. It may also produce a lowering of the body temperature so that the skin feels cool.

As early as 1890 Jacobj (32) studied the pharmacological action of purified colchicine. He summarized and extended previous work on the action of the drug in frogs, rabbits, dogs, and cats and compared it with its oxidation product, "oxydicolchicine." The two drugs showed qualitative differences in their action on frogs, for whereas pure colchicine had very little effect, "oxydicolchicine" showed a veratrinelike action in doses of 10 mg. In warm-blooded animals both substances had the same action, qualitatively and quantitatively, which Jacobj described. He suggested that in these warm-blooded species the action of colchicine involves a preliminary biochemical oxidation to "oxydicolchicine." Hausmann (77) found that hibernating bats were resistant to the toxic action of colchicine. He noted, however, that hibernating bats which had been given colchicine and had lived in the cold, succumbed to colchicine poisoning when brought

into the warm. The action of colchicine on frogs was re-examined by Fühner (78), who also reported on its toxicity in cats and rabbits, and in addition investigated the effects of some of the transformation products prepared by Windaus, namely, colchiceine, trimethylcolchicinic acid and its methyl ether, *N*-benzoyltrimethylcolchicinic acid methyl ether, *N*-benzoylcolchinic acid anhydride, and oxycolchicine. Fühner showed that the resistance of frogs to the action of colchicine is only relative and depends on the temperature of their surroundings. Injection of doses of 50 mg. had normally very little action, but if the frogs were placed in a thermostat at about 30° they became so sensitive to the poison that doses of a fraction of a milligram were fatal in a few days. Pure colchicine did not produce in frogs the convulsions or veratrinelike action on muscle which had been reported by earlier workers and attributed by Jacobj to "oxydicolchicine" present as impurity. Fühner found, moreover, that oxycolchicine, formed from colchicine by oxidation with chromic acid, was toxic to frogs in small doses, and produced effects similar to those attributed to Jacobj's "oxydicolchicine." These results appear at first sight to be consistent with the view that the toxic effects of colchicine are the result of biochemical oxidation to "oxydicolchicine" and that the active component of this is the ketonic oxidation product, oxycolchicine. According to Lettré and Fernholz (42), on the other hand, the subdued activity of colchicine in hibernating animals is to be attributed to cessation of cell division during hibernation. Yet another explanation has been advanced by Ludford (74), who suggested that the reduced susceptibility of hibernating and cold-blooded animals is a consequence of their lowered metabolism.

None of these explanations can be complete, however, for Fühner found that oxycolchicine, which showed highly toxic effects in frogs in doses of 2–5 mg., proved to be the least toxic towards mammals of all the colchicine derivatives which he examined. Doses of 20–50 mg., given by various routes, showed no toxic effects in cats or rabbits, and Fühner administered to himself doses of 1 and 3 mg. and found them inactive (78). With regard to the other colchicine derivatives examined by Fühner, it is noteworthy that colchiceine was inactive in the doses given (10 mg. in frogs; 10–25 mg. in cats), that *N*-benzoyltrimethylcolchicinic acid methyl ether was ten times less toxic than colchicine, and that *N*-benzoylcolchinic acid anhydride still showed, albeit in large doses, the same effect on the stomach and intestines as does colchicine, from which it differs extensively in molecular structure.

In a further comparison of the pharmacological action of colchicine with that of a series of derivatives prepared by Windaus, Lipps (79) studied the effects produced in frogs and cats, and showed by histological examination of the stomach and intestines that colchicine acts as a capillary

poison. The other compounds investigated were colchiceine, trimethylcolchicinic acid and its methyl ether, colchicamide, *N*-acetyliodocolchinol, *N*-acetylcolchinol and its methyl ether, and colchinol and its methyl ether. Although the activity of colchicamide (formed by the action of ammonia on colchicine) was about 10–20 times weaker than that of colchicine, *N*-acetylcolchinol and its methyl ether were not essentially less active than colchicamide. The colchicinelike action of *N*-acetylcolchinol methyl ether was, however, completely lost if the acetyl group was removed by hydrolysis. It is apparent from the results reported by Lipps that considerable modification may be made in the structure of ring C without appreciable qualitative effect on the capillary-poisoning action of colchicine.

The pharmacology of colchicine, in respect to its action on the frog's heart, and the uterus and intestine of the rabbit, has also been studied by Jacobson (80), who described the effects on isolated organs of varying doses of colchicine, alone or in presence of other substances such as ergotamine, acetylcholine, adrenaline, etc. In suitable doses colchicine was found to produce an inhibition of the action of each of the organs.

In the first edition of his well-known *Manual of Pharmacology*, published in 1906, Dixon (75) referred in the following terms to the effect of colchicine on the white blood cells:

"Colchicine has a very decided action on leucocytosis. At first, for a period lasting about an hour, it expels the leucocytes from the circulation, hypoleucocytosis. During this period the corpuscles collect in various tissues of the body, especially in the bone-marrow and lungs. The leucocytes soon begin to increase again in the peripheral circulation until there is a very decided augmentation in their number (hyperleucocytosis). The alterations in the number occur almost entirely in the polymorphonuclear variety, the lymphocytes undergoing little or no alteration in number. In consequence, when the circulation contains an excess of the polynuclear corpuscles the bone-marrow shows a diminution in their number. A further effect of this drug is to excite karyokinesis. The exact significance of this action on the marrow cannot be adequately determined at present; but it should not be regarded as specific to the leucocytes, but rather a type of the action which goes on to a greater or less degree in other tissues of the body, but it is necessarily more easily investigated in the wandering cells of the blood."

This action of colchicine on the blood cells in rabbits and dogs, later described in detail by Dixon and Malden (76), was destined to lead to very important developments when it was reinvestigated nearly 30 years afterwards (see following section). In the meantime, Beck (81), in 1932, summarized briefly the earlier literature on the pharmacology of colchicine and examined in some detail its effect on the blood-picture when injected subcutaneously into rabbits. Dixon and Malden had found that the maximum leucocytosis, which follows the initial leucopenia, was reached after 10 to 24 hours, the blood becoming normal again after 36 to 48 hours. Beck found that the action of colchicine is not cumulative, but that the

effect of a single dose could be observed to persist in the blood picture for about 8 days.

Arloing and Langeron (82) examined the effect of colchicine on anaphylactic shock in guinea pigs and found that if it was given in small doses 3 days before administration of egg albumin then the colchicine prevented the onset of protein shock. There was no action if the colchicine was injected into the animals immediately before producing shock, and these workers found their results consistent with clinical experience that one should not give colchicine immediately before the onset of acute gout. Incidentally, they were unable to confirm the earlier statement of Houdès as to the magnitude of the toxic dose of colchicine in guinea pigs. They found that 0.1 mg. of colchicine per 100 g. of body weight was fatal in 24 to 48 hours, and the animals survived only when the dose per 100 g. of body weight was reduced to 0.05 or 0.025 mg.

2. General Cytological Effects

In their important paper on the pharmacology of colchicine, Dixon and Malden (76) gave a clear description of its immediate and remote effects. The former resemble those of pilocarpine and are exerted on plain muscle; the latter are manifested only after the drug has been in the circulation for some hours, and there is a close resemblance to the action of snake venom and the bacterial toxins, delay in poisoning being due to slow absorption into the central nervous tissues. Dixon and Malden were more concerned, however, with the effect of colchicine on the blood and bone marrow, which they examined in some detail in rabbits, rats, and dogs. Injections of colchicine caused a transient fall in the white blood cells, followed by a very great increase, and after a large dose of colchicine all the normal elements of the bone marrow were found in the general circulation. The effect of small repeated doses of colchicine in rabbits was studied, and abnormal cells were occasionally observed in the blood.

In 1934, Lits (83), wishing to confirm the effect of colchicine in producing leucocytosis, and to study the mechanism of this action, examined the effect of colchicine injections in mice. He observed not only the general effects on the blood described by Dixon and Malden, but also an effect on mitosis of cells in various organs. These mitosis effects were obtained with doses of colchicine varying from 0.5 to 0.005 mg. per 20 g. mouse, and the effects were similar to those which Dustin and Gregoire (84) had already observed with sodium cacodylate. The doses of colchicine required to produce these effects were some 1000 to 2000 times smaller than the requisite doses of sodium cacodylate. The cellular changes evoked by colchicine in the organs and tissues of mice were described in detail by Lits in two later papers (85), the second of which also refers to the action

of colchiceine, and should be consulted for the detailed description which it gives of the colchicine effect.

According to Dustin (86), colchicine induces a "choc caryoclasique," a property which it shares with sodium cacodylate; cellular necrosis follows a phase of vigorous mitotic stimulation. The action of colchicine on cell division has been re-examined by many workers and the findings of Lits and Dustin have been subjected to critical investigation. Colchicine is a "mitotic poison" and brings the process of cell division to an abrupt halt at the early metaphase. This is the most characteristic biological effect of colchicine and is the basis of the secondary effects to be described later. Dustin (87) believed that colchicine produced an initial stimulation of cell division before arresting it at metaphase, but the existence of this transient stimulation has been disputed by Ludford (74). The action of colchicine on cell division has been described and discussed in further papers by Dustin (88) and also by Chodkowski (89), who reviewed the effect on various organs, discussed the mechanism of its action, and indicated its importance in pathology.

New techniques in the study of the effects of colchicine on cell division were devised by Brues (90) and by Ludford (91). Brues examined the effect of colchicine on the cells of the regenerating liver of the rat, and found, with Cohen (92), that abnormal mitotic figures were produced not only by colchicine itself but also by some of its transformation products. These, as indicated in Table 2, proved to be less active.

TABLE 2

COLCHICINE DERIVATIVES PRODUCING ABNORMAL MITOSIS

Compound	Minimum effective dose (mg./100 g.)
Colchicine	0.02
Colchicine salicylate	0.05
Colchiceine	0.8
Hexahydrocolchicine	3.0
N-Acetylcolchinol	0.9
N-Acetylcolchinol methyl ether	8.0
Colchinol methyl ether hydrochloride	6.0
Carbinol obtained from colchinol methyl ether and nitrous acid	7.5
N-Acetyliodocolchinol	10.0
Dimethylcolchicinic acid	Ineffective in any sublethal dose
Trimethylcolchicinic acid	

In a subsequent paper Brues and Jackson (93) gave a fuller description of the abnormal mitotic figures produced by colchicine by injection of rats following partial hepatectomy. With doses of 0.01 to 0.2 mg. per 100 g.

of body weight large numbers of abnormal figures were seen, showing arrest of cell division at about the beginning of the metaphase. With larger doses (0.2 to 10 mg.) mitosis appeared not to begin at all. Observations were also made on a section of a mouse sarcoma from an animal injected 10 hours previously with 0.025 mg. of colchicine. About 12% of the cells were seen to be in mitosis in contrast with the normal 1 or 2%. In the majority of these there was no vestige of a spindle mechanism and this is in agreement with the conclusions of other cytologists that colchicine arrests mitosis by preventing formation of the spindle.

Ludford (91) introduced the use of tissue cultures for investigating the mitotic poisoning activity of colchicine. He described the action of a number of substances, including sodium cacodylate, colchicine, colchiceine, trimethylcolchicinic acid, and urethane, using as biological material both normal and malignant cells, *in vitro* and *in vivo*. Colchicine is by far the most potent mitotic poison, and arrests cell division *in vitro* in a dilution of one part in a hundred millions. Colchicine had the same action on cell division in tissue cultures as in the animal body, which shows that the action is a direct one on the cells. Dividing embryonic cells and malignant cells were equally sensitive to mitotic poisoning. Ludford states (74) that "colchicine is unique in that it does not arrest the initial phase of division but brings the process to a standstill at the metaphase, in a remarkably wide range of concentrations." Dustin (88) regarded the action of sodium cacodylate as being similar, although the dosage required was much higher, and Bucher (94) reached the same conclusion. Trypaflavine, which also arrests mitosis, acts differently.

As early as 1930 Ludford (95) described chromosome formation without spindle development in cancer cells, and found abortive mitoses of this type in Jensen Rat Sarcoma, mouse sarcoma S37, and mammary carcinoma 63. He was, however, unsuccessful in his attempts to produce such abortive mitoses by artificial means. Ludford pointed out that if the split chromosomes of these abortive mitoses were to assemble and form new nuclei, then cells with double or tetraploid chromosome number would result. This result is actually produced by colchicine. For instance, Tennant and Liebow (96) reported that in the cells derived from the heart of a new-born mouse, under the influence of colchicine, the chromosomes split longitudinally during prophase or metaphase may be dispersed throughout the cytoplasm. Afterwards, a single nucleus or group of small nuclei may be reconstituted. This may result in cells whose chromosome number exceeds the diploid, i.e., polyploidy. These workers also suggested that the effect of ethylcarbylamine on mitosis is similar to that of colchicine.

The action of colchicine on dividing epidermal cells of newt larvae was investigated by Barber and Callan (97). They observed complete sup-

pression or abnormal development of the spindle, and arrest of mitosis at the metaphase. In some cases tetraploid cells were formed. Similar effects were produced by the application of cold. Untreated epidermal cells swell during anaphase, and the swelling was found to be much exaggerated in cells held at metaphase by the action of colchicine. This condition was described as a state of "intracellular dropsy." Barber and Callan give some striking illustrations of the abnormal mitotic figures produced by colchicine.

The typical action of colchicine on cell division is, then, to arrest the process at the stage of early metaphase. With larger doses the toxic action may be so great as to suppress mitosis completely. When the effect of the drug wears off, then according to the extent of the toxic action the cells either become necrotic or recover and resume division, either in a normal or modified manner. The production of polyploidy is of rare occurrence in animals, but is of greater frequence in plants, in which connection it has assumed considerable importance. Peters (97a) has recently described the types of chromosomal arrangement in the cornea of *Triturus viridescens* during recovery from the mitotic arrest due to colchicine.

Other effects of colchicine in animal organisms have also been reported. Pincus and Waddington (98) treated fertilized ova *in vitro* with colchicine and other substances, and found that colchicine is especially effective, not only in preventing spindle formation, but also in inhibiting the normal movements of the pronuclei. Foster (99), in a study of the effect of injection of colchicine in adult mice found that the effect on the parathyroid was to cause a reduction in the degree of dispersion of the Golgi bodies, similar to that produced by parathormone. Polyploidy has been produced artificially in insects and amphibian larvae, but not in mammalian embryos. In an attempt to achieve this, Chang (100) inseminated four doe rabbits with spermatozoa of one male rabbit suspended in a dilute solution of colchicine. There were 29 normal young and two monstrosities, which are described and illustrated. Without colchicine no abnormalities were found in 425 young. Auerbach and Robson (101) were able to produce mutations in *Drosophila melanogaster* with allyl isothiocyanate and with a series of substances related to mustard gas. In order to ascertain whether colchicine had this property, Hadorn and Niggli (102) dissected the gonads of larval *Drosophila melanogaster*, transferred them to isotonic sodium chloride solution containing colchicine, and then implanted them in host larvae of the same age. Colchicine had a sex-reversal effect, but mutations were not observed. This is in agreement with Law (103), who found that colchicine was ineffective in altering the lethal mutation rate in these insects.

There is a considerable measure of agreement among cytologists that the action of colchicine on mitosis is brought about with extremely small

amounts, is highly specific, and operates essentially by preventing spindle formation. Östergren (104), although agreeing that colchicine causes an arrest of mitosis at metaphase on account of the absence of the mitotic spindle, states that similar effects are produced by many organic substances and are associated with their narcotic action and insolubility in water. Colchicine is exceptional in that it is very soluble in water. Östergren suggests that the active, lipoid-soluble molecules are inactivated by the introduction of typically hydrophilic radicals which increase solubility in water and decrease lipoid solubility. Levan and Östergren (105) had found in a series of naphthalene derivatives a correlation between the mitotic-activity threshold and the water solubility of the substances. It was supposed that the decisive concentration might be, not that in the aqueous phase of the cell, but that in its lipoids, and it was suggested that there is a close relation between mitosis-poisoning activity and narcosis. This is, of course, an extension of the Meyer and Overton theory of narcosis, as restated by Meyer and Hemmi. Whether Östergren was truly dealing with the colchicine effects described by Dustin, Brues, Ludford, and others is not clear, but it is of interest that Politzer (106) had already shown that narcotics prevent resting cells from entering mitosis, and also arrest dividing cells at metaphase.

The view that there is a close parallel between mitosis arrest and narcosis is also held by Gavaudan (107), who gives a description of the action of mitotic poisons on rabbit intestine and other tissues. The mitosis-arresting power of colchicine and other narcotics is correlated with the thermodynamic activity of their solutions. Gavaudan, however, disputes the generally accepted conclusion that spindle formation is suppressed by colchicine and regards the spindle as being formed, but no longer functional. The view is also expressed that there are two groups of mitosis inhibitors, namely, those whose action is physical in character and those whose action is of a chemical type. The former are regarded as acting on lipoids by virtue of their lipoid solubility. The latter group, which includes colchicine, phenol, chloral hydrate, and sodium cacodylate, are water-soluble and act on constituents of the cells. They are held to be capable of modifying the metabolism of cell constituents; in the case of colchicine these are the lipoids. Obviously these views require to be substantiated by further experimental evidence.

In discussing the mechanism of mitotic poisoning by colchicine, Ludford (91) attributed the failure to form a spindle to a lowering of the cytoplasmic viscosity which prevented coagulation of the spindle substance. Kartaschova (108), on the other hand, treated the stems and leaves of certain plants with a 0.1% solution of colchicine and observed an increase in the viscosity of the cytoplasm.

The importance of specific mitosis poisons in connection with general biological problems has been discussed by Ries (109).

The production of polyploidy in plants by means of colchicine is dealt with in a later section, but at this stage brief mention may be made of some of the investigations concerning the general cytological effects of colchicine in plants. For details, reference should be made to the original memoirs. The mechanism of the effect of colchicine on cell division in plants has been studied by Blakeslee and Avery (188) and by Gavaudan and his collaborators (110), who described the chromosome modifications and compared the mode of action of colchicine with that of other substances, including acenaphthene, naphthalene, and biphenyl. Naphthalene vapors show some of the same effects as acenaphthene, but the effective dose is close to the toxic dose. Biphenyl vapors are feebly toxic, and also produce anomalous mitosis. The effects of acenaphthene are similar to those of colchicine. In some of their experiments these workers used onion root tips (*Allium cepa* Tourn.) which have also been extensively used by other workers in similar studies. Levan (111) described the effect of colchicine on mitosis and meiosis in *Allium*. He noted not only the characteristic effect on the spindle mechanism but also an effect on chiasma formation and on spiralization. Acenaphthene was found to produce the same effect on mitosis, but more slowly and less completely. *Colchicum* was also highly susceptible to acenaphthene, but entirely immune to colchicine. Levan (112) described a root swelling caused by plant hormones of the type of 3-indolylacetic acid and found that the mechanism of the observed chromosome doubling was different from that produced by colchicine; with the plant hormones doubling occurs in the resting stage. Hawkes (113) also discusses the cause of root swelling. Smith (114) found that pollen germination and tube elongation in *Antirrhinum majus* L. and *Bryophyllum daegremontianum* was stimulated by plant growth hormones, but depressed by colchicine. Cytological effects of colchicine in plants were also described by Mangenot (115) who found them to be quite different from X-ray effects, and by Eigsti (116), who observed, in generative cells of *Polygonatum*, *Tradescantia*, and *Lilium*, that colchicine inhibits the movement of chromosomes during division in a manner similar to the inhibition of mitosis in other tissues. The biological effects were enlargement of the pollen tube, increase in the size of the tube wall, decrease in the percentage of bursting of pollen tubes, and branching of the tubes. Garrigues (117) examined in detail the action of colchicine and chloral on roots of *Vicia faba*, and found profound differences. Effects comparable with those of colchicine were found by Simonet and Guinochet (118) in *Triticum vulgare* L. with α-chloro- and α-bromonaphthalene. These gave figures blocked in metaphase, absence of anaphase, and an abnormal number of chromosomes

in mutliple variations, but difficult to evaluate with precision. Other colchicine effects in plants were described by Piettre (119). In an examination of colchinized onion root tips Levine and Gelber (120) found that as a result of exposure to 0.1% colchicine solution the proportion of cells in metaphase increased up to 24 hours and thereafter the number of mitotic figures gradually fell to a point slightly below that observed in untreated root tips. A detailed study of the effect of colchicine and acenaphthene in combination with X-rays was also made by Levine (3, 73).

3. Colchicine as an aid to the Biological Assay of Hormones

When colchicine acts on animal cells, if the dose is not too large there is no effect on the resting cells that come normally into mitosis. But during division there is an arrest of mitosis at the metaphase, and this effect may last for many hours. Consequently, after a time there is an accumulation of cells in metaphase, and the largest accumulation of arrested mitosis will be in tissues in which cell division is normally of frequent occurrence. This, in fact, was found to be the case (91). Consequently, the extent of the colchicine effect on tissues may be used as an index of rate of growth. It was so used by Oughterson, Tennant, and Hirshfeld (121) to measure the rate of growth of cancer tissue. These workers examined the rate of growth of a carcinoma of the human colon by means of the colchicine technique. Twelve hours after injecting the drug they found an increase of 700% in the number of mitotic figures in metaphase.

Clearly, this procedure is also of service in evaluating the action of substances which stimulate growth of specific tissues; such substances are found among the hormones. Normally, the majority of the cells are in the resting state at any given moment, and any increase in the rate of cell division is difficult to detect by histological examination. Under the influence of colchicine, however, all of the cells which have come into mitosis during a given limited time will be arrested at metaphase, and may thereby be identified and counted. If, therefore, the experimental animals are divided into two groups and one group is treated with colchicine alone while the other group is treated with colchicine and the growth-stimulating substance, then the sections of tissue from the second group will show a large accumulation of arrested mitoses due to greater frequency of cell division, and the differences in numbers of these in the two groups will give an index of the growth-stimulating influence of the substance under examination.

When the effect of colchicine on mitosis became known the possibility of such an application was rapidly appreciated, and in 1937 several workers reported the use of colchicine for the biological assay of hormones, by means of this apparent accentuation of the influence of the hormone on

the susceptible tissues. Voss and Loewe (122), in 1930, had already used the effect of androgenic substances on the mitotic activity of the seminal vesicles of castrated rats and mice as a method of assay of androgens, and Fleischmann (123) found that by injecting colchicine this stimulating effect of androgens on the seminal vesicle of the castrate rat became sharply defined. Several groups of workers had independently described the use of colchicine in the study of the growth response to androgens of the male accessory sex organs (124), including the seminal vesicles and the prostate. The effect on seminal vesicles was shown in either castrated or immature rats.

Allen, Smith, and Gardner (125) made similar use of colchicine in the assay of estrogenic hormones. By the application of both colchicine and estrogen to ovariectomized mice they found that growth of genital tissue could be more effectively delineated. Rapid growth was taking place after 9½ hours, and examination of a section of the vagina showed about half the cells to be in mitosis. The accumulated dividing cells showed clearly that the growth response to the hormone was restricted almost entirely to the epithelial tissues of the genital organs (vagina, uterus, and mammary glands). Muscular, vascular, and connective tissue, and sympathic ganglion cells did not show enhanced cell division under the influence of estrogen. The method, although rapid, is not quite so simple to carry out as the vaginal smear test of Allen and Doisy for estrogenic stimulation.

Similar use has been made of colchicine in the assay of other hormones. Leblond and Allen (126), using pigeons, found it possible to assay preparations of prolactin by observing the mitotic figures 10 hours after injection of the hormone, whereas the classic method of assay takes 96 hours. The detection of stimulation of the thyroid by extract of anterior pituitary, using the colchicine technique, has also been reported (127). This was likewise studied by Fleischmann and Kann (124), who also applied the method to the study of the action of adrenal cortical hormones.

4. Action on Tumors and Tumor Growth

Much attention has been devoted to the possibility of using colchicine to arrest the growth of malignant tumors in the hope that this drug might find a place in the chemotherapy of cancer. This hope has been stimulated by a number of factors, one of which naturally was the recognition of the nature of the action of colchicine in arresting cell division. Another factor which has focused attention on colchicine as a possible chemotherapeutic agent against cancer was the apparent high promise of some of the earlier investigations in this field. More detailed study has, however, made it fairly clear that colchicine itself is unlikely to be of much value in cancer therapy. The published work is summarized by Stern and Willheim (128)

and is critically discussed in a recent authoritative review by Ludford (74) (see also Levine (73)).

According to Lits (85) and to Hirshfeld, Tennant, and Oughterson (129), the first observations that colchicine affected malignant growth were reported in 1932 by Dominici (130). This was before the influence of colchicine on cell division was known. Widespread interest in this subject was first aroused by some observations published in 1935 by Amoroso (131). He injected small doses of colchicine on alternate days for two weeks into a group of twelve tumor-bearing mice. A second group of twelve was used as controls. At the end of the second week the tumors had completely regressed in two-thirds of the injected animals and only small nodules remained in the others. These finally regressed completely, and no tumor tissue could be recognized 8 weeks later. The control animals showed normal tumor development. In another series of colchicine-injected mice there was no recognizable tumor tissue in any of them after 2 weeks. Injection of colchicine into a dog bearing a malignant tumor also brought about rapid regression of the tumor.

A similarly impressive result was obtained by Williamson (132), who gave intramuscular injections of colchicine to a 7-year old mare that had several tumors, one of which was diagnosed by histological examination as a spindle-celled sarcoma. After 7 weeks of treatment terminating in a final dose of 10 mg. which produced transient toxic symptoms of considerable severity, the tumors had largely regressed. The ultimate result of the treatment is not reported.

At the other end of the scale was the result of the treatment of four advanced cases of human carcinoma by Seed, Slaughter, and Limarzi (133). Two of the patients died of colchicine poisoning within a few days (one received 12 mg. and the other 22 mg., in all). In the other two cases the tumors initially regressed but afterwards grew at an accelerated rate. These authors concluded: "Although the rapidly growing cancer cells are much more susceptible to the poison, the concomitant general toxic effect is much too great to expect any curative effect." In one of these cases colchicine-therapy was supplemented by irradiation. Local injections of colchicine combined with irradiation were used by Brücke and Hueber (134). Two patients had superficial metastases treated; these became necrotic.

The effect of colchicine on the growth of mouse tumors has been studied by several workers. Dustin (86, 87, 88) found that colchicine has the same effect of mitosis in cells of tumor tissue (grafted tumors, adenocarcinoma, and tar-induced epithelioma in mice) as in normal tissues. Poulsson (135) gave daily subcutaneous injections of 1/80 mg. of colchicine to fifteen mice with malignant tumors (five spontaneous mammary carci-

nomas; ten tar cancers). This treatment did not in any way influence the development of the tumors. Failure to retard the growth of mouse sarcoma 37S was reported by Clearkin (136). Nicod and Regamey (137), using both induced and spontaneous mouse tumors, found that the development of tumors was favorably modified, but that the survival time of the animals was not affected. Dittmar (138) found that grafted tumors were appreciably inhibited by colchicine, but not by larger doses of colchiceine or oxycolchicine. By injection of colchicine into mice bearing transplanted malignant lymphoid tumors, Lits, Kirschbaum, and Strong (139) found that the time of survival was lengthened in a large proportion of the mice, but tumor growth was not permanently suppressed. The malignant lymphocytes were extremely susceptible to colchicine. An inhibitory action of colchicine on ascites tumor of the mouse was reported by Lettré (140) who also found (141) that strong inhibition of growth of this tumor was caused by doses of 0.1 to 0.15 mg. of trypaflavine per 20 g. of body weight. In doses of this order, trypaflavine was rather more effective than 0.01 mg. doses of colchicine. The length of life of the mice was doubled by this treatment. The effect of colchicine on experimental rat tumors was examined by Ten Seldam and Soetarso (142) and by Guyer and Claus (143). The latter workers used rats bearing the Flexner-Jobling carcinoma, 0.1 mg. per 100 g. of body weight being injected into each rat; 15 hours later distilled water was injected directly into each tumor in as great a quantity as it would hold. Complete healing took place in 59 of 103 cancer-bearing animals.

The effect of colchicine on the mitotic activity of the Brown-Pearce epithelioma of the rabbit was studied by Du Bilier and Warren (144). They found the greatest increase in the metaphase count with a dose of 0.1 mg. per 100 g. of body weight, but stated that the results were unpredictable and that a trial of the combined effect of colchicine and X-rays did not seem feasible. Complete regression of a non-malignant rabbit tumor, namely the Shope papilloma, was brought about by colchicine treatment (145).

The ineffectiveness of colchicine in arresting tumor growth has been reported by Passey (153) and by Carr (154). For the influence of urethane on animal tumors, and its comparison with that of colchicine, see Haddow and Sexton (155).

Other workers have attempted to combine colchicine with X-rays in tumor therapy. Since dividing cells are reputed to be more vulnerable to X-rays, Guyer and Claus (146) irradiated tumor-bearing rats (Flexner-Jobling carcinoma) some hours after the injection of colchicine. In all, 672 cancerous rats, including controls, were used. The results indicated that the tumors treated with both colchicine and X-rays grew less than

those in the other groups. On the other hand, Brues, Marble, and Jackson (147) found that colchicine did not influence the effects of irradiation. These workers point out that although relatively large doses of colchicine may initiate tumor regression, these doses are close to the lethal dose and cannot be repeated with impunity. They cause hemorrhage and metabolic changes in the tumors. Smaller doses, sufficient to produce profound mitotic changes, may be repeated over long periods, but have consistently failed to alter the growth rate. The combined action of colchicine and X-rays on transplantable mammary carcinomas in mice (Yale carcinoma No. 1 in strain A mice) was described by Hirshfeld, Tennant, and Oughterson (129). With doses of 0.0009, 0.0010 and 0.0012 mg. of colchicine per gram of body weight there was a progressive increase in the number of cells blocked in metaphase, beginning 1 hour after injection and reaching a maximum in 9½ hours. Doses of 0.0020 mg. per gram produced extensive necrosis and hemorrhage in the tumor. Smaller doses led to moderate prolongation of life but all the animals eventually succumbed. The dose of colchicine which produced a maximum accumulation of mitoses, together with a single dose of X-rays of 2,500 r. gave a slightly higher rate of curability than X-rays alone.

The hemorrhagic-effect of colchicine has been noted by a number of investigators and is obviously a result of the capillary action to which reference has already been made. Boyland and Boyland (148) noted that in doses approaching the toxic dose colchicine produces hemorrhage in grafted tumors of rats and mice, and also a reduction in their ascorbic acid content and a modification of metabolism. Similar effects were produced by a filtrate of *B. typhosus*. This action was confirmed by Andervont (149) who had earlier (150) shown that injection of a *B. Coli* filtrate produces hemorrhage in tumors produced in mice by injection of 1 : 2 : 5 : 6-dibenzanthracene. In some instances the bacterial filtrates brought about complete regression of transplants of these tumors. Similar effects of bacterial products on mouse tumors were observed by Fogg (151), and concentration of the hemorrhage-producing fractions of *B. prodigiosus* was achieved by Shear and Turner (152), who found that the active fractions were rich in polysaccharide.

It is evident from the above summary of the action of colchicine on tumor growth that there is ample justification for Ludford's conclusion (74) that in order to effect regression of tumors it is necessary to employ doses of colchicine far in excess of those required to arrest mitosis, and just short of the minimum lethal dose, and that when regression of tumor growth does occur it is primarily the result of vascular damage.

To conclude this section, reference may be made to the action of colchicine on plant tumors, a phenomenon which, unlike the effect on

animal tumors, appears to be related to the mitotic-poisoning action. These plant overgrowths are usually of bacterial origin, and it is unlikely that they have any close relationship to animal tumors. They have been induced by inoculation of plants, especially tomato, with *B. tumefaciens*, an organism which induces crown gall. Havas (156), working in Dustin's laboratory, found that administration of colchicine considerably inhibits development of plant tumors produced in this way, and discussed the mechanism of inhibition. Solacolu, Constantinesco, and Constantinesco (157) also found that colchicine arrested the growth of these tumors, as did Dermen and Brown (158), who suggested that the effect was associated with excessive polyploidy. Brown (159) found that tumor formation was prevented in only a few cases, but brushing the surface of the bacterial tumors with colchicine effectively inhibited growth and ultimately killed the tumor. Indoleacetic acid tumors were inhibited in growth but not killed. Acenaphthene, and other substances which have been reported to produce polyploidy, did not act on bacterial plant tumors in the same way as colchicine (160). Destruction of the tumors by colchicine was thought to be due to an effect on the growth substances in the plant, rather than to a direct action on the bacterial organism.

5. Other Compounds Showing Colchicine-like Effects on Mitosis

The action of colchicine in arresting cell-division has many interesting applications, and it is scarcely surprising that attempts should have been made to find other substances with similar action, especially in view of the highly toxic nature of colchicine. Such substances were, of course, known before colchicine was shown to be a mitotic poison, and it was, in fact, in the course of a systematic examination in Dustin's laboratory of the effect of various substances on mitosis that this action of colchicine was revealed. Very similar effects on mitosis had already been found with sodium cacodylate, except that the dose required was very much greater than in the case of colchicine. Trypaflavine also arrests cell division, but does so in a different manner from that of colchicine and sodium cacodylate. Ludford (91) investigated the action of a number of toxic substances on the division of normal and malignant cells, both *in vivo* and *in vitro*. He described the action not only of colchicine and sodium cacodylate, but also of urethane, auramine, colchiceine, trimethylcolchicinic acid, cyclohexylamine, atropine, and aconitine. Bucher (94) found nicotine and coramine (nicotinic acid diethylamide) to have no characteristic action on cell division. Reference has been made already to the colchicinelike action of some derivatives of the alkaloid (92), and also to the similar action of some synthetic compounds that have some of its structural

features. Other compounds having colchicinelike action will be discussed in the present section. With the possible exception of sodium cacodylate no other compound has been shown to reproduce exactly the effects of colchicine on cell division, and no other compound has been found to approach the high potency of colchicine as a mitotic poison. Although sodium cacodylate arrests cell division at the metaphase, the dose required is very much greater than with colchicine. Blakeslee (189) has reported the use of sodium cacodylate to induce plants with doubled chromosome number in *Portulaca*, but no systematic attempts seem to have been made to induce polyploidy with this compound.

The polyploidogenic action of colchicine was shown by Shmuck (161) and Kostoff (162) to be reproducible by acenaphthene. Shmuck found that treatment of wheat seeds with acenaphthene produced an effect quite analogous to that of colchicine, and the cytological studies of Kostoff with germinating seeds of cereals and grasses showed irregular mitosis and meiosis, with acenaphthene as with colchicine. Nebel (163) suggested that the action of acenaphthene as a polyploidogenic agent was not at all comparable with that of colchicine, but as he used solutions of acenaphthene, whereas Kostoff in most of his experiments exposed the seedlings to crystalline material, it is uncertain what degree of importance attaches to this criticism. The effect of acenaphthene and X-rays on the growth of onion root tips was studied in considerable detail by Levine (3). Anomalous cell division similar to that produced by colchicine was reported by Simonet (164) with 1 : 3 : 5-trinitro-*m*-xylene. As stated above Östergren (104) believes that colchicinelike effects on mitosis are shown by a large number of substances, mostly insoluble in water, and that there is a close relationship between narcotic action, mitotic-poisoning activity, and solubility in water and lipoids. Whether the many compounds mentioned by Östergren as "efficient" in influencing mitosis really show the characteristic colchicine effect requires confirmation. They include such widely different chemical substances as nitrous oxide, haloforms, nitromethane, aliphatic alcohols, acetone, ether, chloral, paraldehyde, urea, urethane, benzophenone, anisole, benzenoid hydrocarbons, aniline, nitrobenzene, benzoic acid, indole, and others.

Möllendorff (165) investigated the action on cultures of rabbit fibrocytes of alcohol, acetone, chloral hydrate, sex hormones (estrone, testosterone) and carcinogenic hydrocarbons (3 : 4-benzpyrene, methylcholanthrene), and described the abnormal mitosis forms to which they gave rise.

In a very interesting series of investigations Lettré and his collaborators have attempted to correlate mitotic poisoning activity with chemical constitution. The biological findings of these workers have not, however,

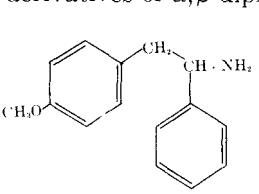
been generally accepted, partly on account of the unsatisfactory nature of the published illustrations (compare Knake (166)), and it is difficult to assess the precise significance of the results obtained by Lettré, although they nevertheless merit description and further study.

For purposes of biological test, Lettré used the action on mitosis in tissue cultures of fibroblasts from embryonic chick heart (167, 168, 42) and also the inhibitory action on the growth of the ascites tumor of the mouse (140, 42). Schairer (169) had shown that mitosis is arrested in the cells of this tumor by colchicine, and using the same test object Brodersen (170) found that trypaflavine inhibits mitosis at its start, whereas colchicine influences the later stages. In discussing the nature of mitosis poisons, Lettré and Fernholz (42) mentioned that Brock, Druckrey, and Herken (171) had elaborated a method to determine whether a toxic substance acts on the cell nucleus or the cytoplasm and had found that colchicine acts purely on the nucleus and has scarcely any action on the growth processes located in the cytoplasm. The alkaloid veratrine has just the reverse effect. There are other substances which lie between these extremes and affect both nucleus and cytoplasm. Lettré and Albrecht (167) studied the action of a number of sympathomimetic amines of the type of β-phenylethylamine, and found that several of these, including tyramine, hordenine, and ephedrine, had an effect on the cell plasma, but none of them acted as a mitosis poison. Reference has already been made to the mitotic poisoning effect of α-phenyl-β-(p-methoxyphenyl)-ethylamine (69). Lettré and Albrecht (167) found similar activity with adrenaline, but concluded that this was due not to the base itself but to a colored oxidation product (see also Lettré (168, 172), and Lettré and Fernholz (42)).

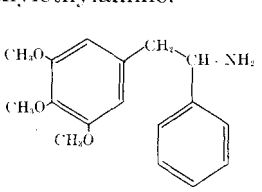
Lettré (42, 168) also examined the action of some colchicine derivatives on the growth of ascites tumor and the activities were in agreement with those observed by Brues and Cohen (92) using regenerating rat liver as the biological test material. He noted that removal of the acetyl group of colchiceine with the formation of trimethylcolchicinic acid was accompanied by loss of activity, and found that the activity was restored by methylating the active hydroxyl group of trimethylcolchicinic acid. Lettré suggested that the inactivity of trimethylcolchicinic acid is associated with internal salt formation. The mitotic poisoning activity of colchicamide was also confirmed by Lettré and Fernholz (42), but they were unable to detect any activity, using the tissue culture method, in the *N*-acetyl-β-(*p*-methoxyphenyl)-γ-(3 : 4 : 5-trimethoxyphenyl)-propylamine of Cook and Engel (68). A series of methoxylated α,γ-diphenylpropylamine derivatives of the following type were also prepared by Lettré and Fernholz and found inactive.

R^1	R^2	R^3	R^4
OCH_3	OCH_3	OCH_3	OCH_3
H	OCH_3	OCH_3	OCH_3
H	OCH_3	H	OCH_3
H	H	H	OCH_3
OCH_3	OCH_3	OCH_3	H
H	OCH_3	OCH_3	H
H	OCH_3	H	H
H	H	H	H

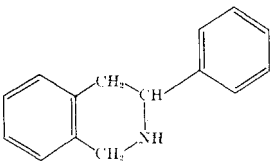
On the other hand, although α,β-diphenylethylamine was inactive, some of its methoxylated derivatives showed marked activity. This was the case with α-phenyl-β-(*p*-methoxyphenyl)-ethylamine (LV) (69) (see above), α-phenyl-β-(3 : 4 : 5-trimethoxyphenyl)-ethylamine (α-phenylmescaline; LVI) (168), and derivatives of 3-phenyltetrahydro-isoquinoline (LVII) (173). Compounds of this type were termed "stilbylamines," i.e., derivatives of α,β-diphenylethylamine.



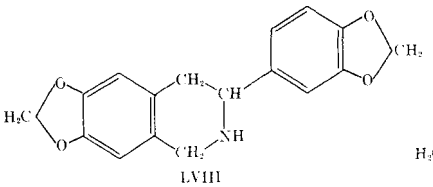
LV



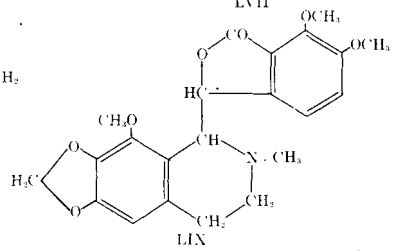
LVI



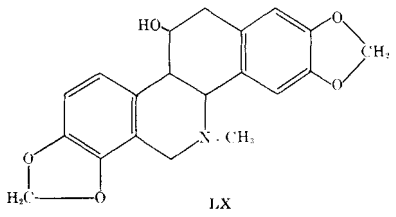
LVII



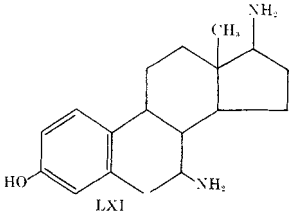
LVIII



LIX



LX



LXI

This work was extended to other compounds of similar type by Lettré and Delitzsch (174), who found the compound (LVIII) to be an active mitotic poison, and by Lettré and Albrecht (175), who examined a series of alkaloids for activity as mitosis poisons. All of twenty-five alkaloids having no structural relationship to the stilbylamine group were found to be without mitotic poisoning activity. By contrast, out of thirty alkaloids

and their derivatives having such a relationship four are mitosis poisons. These are colchicine, narcotine (LIX) (176), chelidonine (LX), and homochelidonine. The two last-named alkaloids occur in *Chelidonium majus* L., and attention was drawn to them by the circumstance that a decoction of the plant had been used as a traditional remedy for warts and tumors. Chelidonine was found to be active as a mitosis poison in cultures of chick fibroblasts in doses of 1×10^{-6} g./cc. and was 100 times feebler than colchicine, but 25 times more potent than narcotine. Homochelidonine showed activity of a similar order of magnitude, as did the related synthetic compound LVIII.

Also of interest in this connection is the recent report of King and Sullivan (177) that the drug podophyllin shows a colchicinelike action on mitosis. This drug has been used recently in dermatology, and produces a favorable response in condylomata acuminata. When applied to normal human and rabbit skin it was found by King and Sullivan to produce distorted mitotic figures in the epidermal and other cells, and exactly similar changes were produced by application of suspensions of colchicine in oil to the skin. Moreover, colchicine gave results superior to those of podophyllin in the treatment of condylomata acuminata. Application of both agents to the unbroken skin gave immediate degenerative action with resultant death of the cells, and King and Sullivan suggest that this action is different from the arrest of mitosis caused by injection of colchicine. It seems likely, however, that their method of application would result in a very high concentration locally in the superficial tissues, and this may well account for the apparent difference in effect on the cells.

The conception of the active bases discovered by Lettré as ammonia addition products of stilbene (stilbylamines), led him to examine stilbestrol and other estrogenic compounds (178). Stilbestrol, in doses of 100×10^{-6} g./cc. showed an appreciable mitotic poisoning action resembling that of colchicine.* The natural hormones were stated to be insufficiently soluble to permit the attainment of the requisite concentration, but amounts in excess of 100×10^{-6} g./cc. of disodium estradiol diphosphate inhibited the growth of cultures considerably. Mitosis disturbances by sex hormones and carcinogenic hydrocarbons had already been reported (165). Lettré's hypothesis that mitosis poisoning activity is associated with the presence in the molecule of a benzene nucleus linked through two carbon atoms to nitrogen led him to examine 7-amino derivatives of the estrane series, in which such an arrangement is present. Using equilin as starting material he prepared (179) the diaminophenol (LXI) and its methyl ether. The latter showed distinct mitosis poisoning action in doses of

* Ludford and Dmochowski (*Lancet*, 718, 1947) were unable to confirm this claim that stilbestrol has mitotic poisoning activity.

1×10^{-6} g. cc. No activity was shown by 7-aminocholesterol or by the amine resulting from reduction of the oxime of equilin.

Lettré suggests (178) that mitosis poisons may arise naturally in the body by transformation of hormones, and act physiologically as regulators of mitosis. He believed that a similar function was exercised by an oxidation product of adrenaline (168), and that normal growth is determined by a balance between inhibition due to natural products of this type and stimulation due to vitamins, hormones, etc. This view is not accepted by Knake (166), who not only found the published photomicrographs of Lettré insufficient to support his claim regarding the mitosis poisoning action of his active compounds, but also questioned the validity of the view that a somatic cell is prevented from division through the agency of a mitotic poison. The condition of an adult body cell is one of non-dividing as distinct from arrested division. The indifference of tumor cells to oxidized adrenaline was attributed by Lettré to the high content and reducing action of sulfydryl compounds, but Knake suggested that these characteristics are not restricted to malignant cells when tissue cultures are involved.

6. Effect on Plant Growth

The principal effects of colchicine on plants are concerned with the production of polyploidy, but before dealing with this question, in the next section, reference may be made to some of the more general effects. The earliest publication appears to be that of Havas (180) whose purpose was to ascertain how far the reactions observed in animals treated with colchicine could be reproduced in plants. He studied the effect on the germination of seeds of Wilhelmina wheat, and on the growth of the seedlings, and found that colchicine had a definite stimulating action on the rate of development of the roots and root hairs. In 5 to 8 days this effect was followed by a marked depression in the growth rate of the roots, followed soon after by complete arrest of growth. The growth-inhibitory influence on the growth rate of the shoots began even earlier. The most specific effects were a bulbous hypertrophy of the root cap, and a bulbous hypertrophy of the coleoptile with thickening of its walls thus causing a resistance to the elongation and breaking through of the shoot. In a later paper, Havas (181) discusses the question of whether colchicine may act as a plant growth hormone, and concludes that of six effects which are shown by colchicine, four suggest that it functions as a growth hormone, whereas two suggest that it does not. Effects on root growth quite parallel to those described by Havas for wheat were noted for *Allium cepa* by Gavaudan, Gavaudan, and Pomriaskinsky-Kobozieff (110), who also described cytological changes, including an increase in the number of chromosomes.

The effects of colchicine on root growth have also been studied by other workers. Mangenot (115) described in detail the cytological changes in tissues of *Allium cepa* and *Hyacinthus orientalis* L. and also the root hypertrophy produced by colchicine in these plants and in *Lupinus albus* L. Duhamet (182) likewise examined the effect of colchicine on the growth of root meristems of *Lupinus albus* and found that in a molecular concentration as low as 10^{-4} moles per liter colchicine completely inhibits the growth of isolated roots in 10 to 12 days, but that growth is not blocked if there is also added heteroauxin (3-indolylacetic acid) in a concentration of 10^{-12} moles per liter. This plant growth hormone thus appeared to inhibit the action of colchicine and to restore normal cell division.

In a study of the effect of various substances on root growth in *Allium cepa*, Levine and Lein (183) found that whereas 3-indolylacetic acid accelerates root growth, both vitamin B_1 and colchicine inhibit it, but the results did not appear to be invariable. Onion bulbs, exposed to a $10^{-3}\%$ solution of colchicine, following exposure to a $10^{-8}\%$ solution of heteroauxin, were stimulated both in regard to formation of new primary roots and in linear growth of roots. Loo and Tang (184), who studied the effects of manganese sulfate, 3-indolylacetic acid and colchicine in seed germination and early growth, found that low concentrations of colchicine stimulated germination and higher concentrations restricted growth.

Villars (185) investigated the combined effects of colchicine and X-rays on meristem cells of the roots of *Allium cepa* and *Pisum sativum* L. and found that the effect produced by X-rays on colchinized roots is completely superposable on the modifications produced by the radiations on normal roots. For a more detailed description of the effects of colchicine and X-rays on roots of *Allium cepa*, see Levine (3).

7. Production of Polyploidy in Plants

This effect of colchicine on plants does not seem to have been observed to any appreciable extent in animals. The effect is one in which the number of chromosomes is converted into a multiple of the normal (diploid) number. Thus there arise plants in which the cells contain double (tetraploid), quadruple (octaploid), and other multiples (polyploid) of the normal number of chromosomes. This multiplication of chromosomes occasionally occurs spontaneously, but by treatment of the seeds with colchicine it can be made of very frequent occurrence. As the polyploid plants sometimes show improved characteristics the effect is of considerable practical importance. The phenomenon is a direct consequence of the action of colchicine in arresting cell division. If the dose of colchicine is not so high as to kill the cell, but is large enough to arrest mitosis at the metaphase, then

after a time cell division is resumed. In the cells which have been under the influence of colchicine splitting of the chromosomes will have taken place, but in the absence of a spindle the daughter chromosomes cannot travel to opposite poles and therefore form two separate nuclei; thus the net effect in a proportion of cases is a doubling of the number of chromosomes. New treatment of the tetraploid cell with colchicine may give octaploid and higher forms. In the case of sugar beet, Levan (186) has observed the production of a haploid form after colchicine treatment.

A chronological survey of the effect of colchicine on plants is given by Havas (187). Mention has been made of the observations of Gavaudan and his collaborators, in 1937, that the cytological changes effected by colchicine in *Allium cepa* include an increase in the number of chromosomes. In the United States, in the same year, Blakeslee and Avery (188) described methods of inducing doubling of chromosomes in plants by treatment with colchicine. These authors pointed out that doubling of the number of chromosomes in the cells of roots is a relatively common phenomenon. Indeed, as early as 1904 Němec had reported that doubling was induced by chloral hydrate and other narcotics. In many cases roots with tetraploid tissue had appeared without known stimuli. The effect was confined to root cells, however, and Blakeslee and Avery confirmed that both chloral hydrate and nicotine were ineffective in inducing chromosome doubling in stems, which alone bear seeds, and might thus lead to production of $4n$ races. Blakeslee and Avery, following a suggestion of O. J. Eigsti who had observed polyploid cells in roots treated with colchicine, investigated the action of colchicine on plants and found that the alkaloid would induce the formation of branches with doubled chromosome number. Seeds of *Datura* were treated with colchicine and then germinated, with abundant production of tetraploids. These showed retarded growth, but gave larger flowers. Demonstration of the production of polyploid plants was provided by determination of the size of pollen grains and chromosome counts, and by the recovery of tetraploids in the second generations. Many excellent illustrations are given of the effect of colchicine on plants. Of several chemical substances tested colchicine was the only one which induced polyploidy in the plants. Double diploids were also obtained by the action of colchicine on sterile hybrids between *Nicotiana tabacum* L. and *N. glutinosa* L. In a later paper, Blakeslee (189) gave a list of sixty-five different species or varieties of plants in which chromosome doubling had been effected by colchicine. In *Datura*, normal chromosome doubling ($4n$) is accompanied also by chromosomal deficient types (e.g., $2n-1$; $4n-1$). Blakeslee states that algae may be susceptible to the polyploidogenic action of colchicine, but fungi are immune, like meadow saffron.

He failed to find any chemical "anti-colchicine factor" in meadow saffron.[1] Simonet and Chopinet (190) listed twenty new tetraploid modifications obtained by colchicine, and polyploid production was also described by Gavaudan (191), Levan (111), and Krythe and Wellensiek (192). The last-named authors give a literature review of the subject. The action of colchicine in inducing polyploidy, especially in wheat, was described in detail by Kostoff (162), who also obtained precisely similar effects by means of acenaphthene. Kostoff (193) suggested that as the pulp and disintegrating tissues of *Colchicum* are effective in the laboratory they should also produce polyploidy in plants growing near *Colchicum*. This was found not to be the case by Bates (194), probably on account of suppression of the polyploid individuals through delayed germination and stunting of growth, with delayed establishment of a root system.

The technique for producing polyploidy, the mechanism of this action of colchicine, and the characteristics of the polyploid plants have been discussed by a number of authors. Warmke and Blakeslee (195) described the induction of simple and multiple polyploidy in *Nicotiana Sanderae* Hort. ($n = 9$) and various hybrids. They found that treatment of the seeds gave 100% tetraploid plants in this variety. For the spraying of shoots an emulsion containing colchicine was found more effective than an aqueous solution. Of thirty-nine plants so sprayed, more than 12% gave branches with doubled chromosome numbers. A means of increasing the effectiveness of colchicine for producing tetraploid forms of camphor-yielding basil was found by Glotov (196). He noted that whereas treatment with colchicine alone caused most of the plants to die, if the seeds were germinated in colchicine solution and the seedlings then treated with heteroauxin, then about 85% of the plants survived. Eigsti and Schnell (197) found that a 1% solution of colchicine in glycerol is more effective than an aqueous solution of the same concentration, in inducing tetraploidy in *Vinca rosea* L., and Eigsti and Tenney (198) found that five applications of the glycerol solution produced more polyploids than fewer treatments and/or more dilute solutions. Yeager and Haubrich (199) examined various unsuccessful methods of applying colchicine to plants, including the application of 1% pastes in lanolin. They were successful in producing polyploidy in some species (including lilac, blueberry, and pepper) but

[1] The action of colchicine on roots of *Colchicum byzantinum* Tenore and *Colchicum autumnale* was studied by I. Cornman (*Botan. Gazz.*, **104**, 50 (1942)) who found that although *Colchicum* is resistant to concentrations of colchicine 100 times those which completely block mitosis in other angiosperms, it responds to very high concentrations (e.g., 10%) with a typical colchicine effect. Cornman concluded that the immunity of *Colchicum* is due to some extramitotic protection of unknown nature and not to any difference in the mitotic mechanism.

not in others by soaking the seeds in dilute colchicine solution for periods varying from 8 to 72 hours. For discussion of the technique, see also Dermen (200), and for discussion of the mechanism of polyploidy by means of colchicine see Nebel (201), and Györffy (202).

It has long been known that polyploid forms may give larger and often improved fruits, and the artificial production of polyploidy by means of colchicine has removed the haphazard character of the phenomenon and has rendered possible scientific programs of fruit breeding (203). Noguti, Okuma, and Oka (204) found a large increase in the nicotine content of *Nicotiana rustica* L. and *N. tabacum* in the tetraploids as compared with the diploids. Rowson (205) likewise found an increased alkaloidal content in induced polyploids of *Datura*, *Atropa*, and *Hyocyamus*. Boas and Gistl (206) give a detailed description of the effects of colchicine in barley (enlargement of cells and nucleoli, production of abnormal mitoses, formation of tetraploid, octaploid, and higher forms). The effect on cereals was also studied by Fetissov (207) who used *Avena brevis* Roth, *Hordeum disticon* L., and *Triticum durum* L. Treatment of the seeds with 0.1 to 0.2% aqueous solutions of colchicine caused delay in growth and decrease in the numbers germinating. Chromosome doubling occurred in 46% of the oat, 9% of the barley, and 5% of the wheat seedlings. In no case were the chromosomes more than doubled. Chen, Shen, and Tang (208) also described colchicine-induced autotetraploid barley plants, and Simonet (209) reported that tetraploids were produced in *Petunia* by colchicine treatment.

The action of colchicine on germinating seeds and young seedlings of cotton plants was studied by Amin (210) who observed retardation of growth, broader leaf lobes, larger flowers, larger seeds, etc. The mass production of polyploids in cotton was reported by Zhebrak and Rzaev (211), and Zhurbin (212) found that fertility was restored in sterile cotton hybrids by treatment with colchicine. This restoration of fertility in sterile hybrids has been noted also by other workers (213). Polyploidy has been induced in cranberries (214) and peaches (215), and Sinnott, Blakeslee, and Franklin (216) have reported that colchicine-induced tetraploids of *Cucurbita* and *Lagenaria* show, in the young fruit, larger cells than in the corresponding diploids, and that this larger cell size is maintained. As the number of cells is correspondingly reduced the fruit volume is about the same in both diploids and tetraploids. Tetraploids obtained by germinating seeds of *Delphinium cardinale* Hook. after colchicine treatment were later in flowering than diploids, were fertile, and yielded larger seeds (217). Nebel and Ruttle (218) described colchicine-induced polyploidy in marigold, petunia, antirrhinum, pink, *Tradescantia reflexa* Rafin. and tomato. The tetraploids of the tomato gave no fruit. For the effect on

tomato, see also Shimamura (219) and Havas (219a). Shalygin (220) noted in the tetraploid plants of perennial ryegrass (*Lolium perenne* L. and *Lolium multiflorum* Lam.) (a) a more compact habit of growth, (b) a darker green coloration of leaves and stem, (c) delay in germination of the seeds, and (d) later crops. A large proportion of the plants contained tissue having both diploid and tetraploid cells.

The induction of polyploidy by colchicine in the green alga, *Oedogonium*, was observed by Tschermak (221).

Shmuck and Gusseva (222) found that hydrogenation of colchicine destroyed its polyploidogenic effect.

8. Polyploidy in Plants Due to Compounds Other than Colchicine

Since the discovery that colchicine is an extremely effective agent in the production of polyploidy in plants, attempts have been made to find other chemical substances having the same action. In 1938, Shmuck (161) reported that treatment of wheat grain with the aromatic hydrocarbon, acenaphthene, produces an effect quite analogous to that of colchicine, but that fluorene was wholly inactive. Naphthalene suppressed germination, but gave an effect different from that of acenaphthene. The action of acenaphthene was studied in detail by Kostoff (162) who, in his earliest paper, described experiments in which seeds of *Triticum vulgare*, *Tr. monococcum* L. and *Secale cereale* L. were soaked in saturated aqueous solutions of acenaphthene before germination, and in all three cases polyploidy was produced. The solubility of acenaphthene in water was stated to be 0.0028%, and it is clear that very low concentrations must be effective. This substance has the advantage over colchicine that lethal concentrations cannot be attained. Kostoff subsequently modified his manner of procedure and covered the seeds with crystals of the hydrocarbon for a few days before germination. He extended his observations to other species. The polyploidogenic action of acenaphthene has been well authenticated. With it, Fatalizade (223) produced polyploidy in *Nicotiana*. Arenkova (224) induced tetraploidy in muskmelons, and described phenomena exactly comparable with those induced by colchicine. The plants gave some large seeds, and these produced seedlings of which the root tips showed chromosome doubling. Fukusima (225) treated young inflorescences of *Brassica alboglabra* L. H. Bailey with acenaphthene with results suggesting the formation of haploid, diploid, tetraploid, and octaploid nuclei in the pollen grains.

Shmuck and Gusseva (226) extended the study to a large number of naphthalene derivatives, and using wheat seeds as test objects, they reported that the following were active in producing polyploidy: acenaph-

thene, acenaphthylene, α-chloronaphthalene, α-bromonaphthalene, α-iodonaphthalene, 3-chloroacenaphthene, 3-bromoacenaphthene, ethyl α-naphthoate, α-methoxynaphthalene, α-cyanonaphthalene, α-nitronaphthalene, α-methylnaphthalene, and also quinoline and 3 : 5-dibromopyridine. Many inactive compounds are also listed. In a later paper (227) the same workers described tests with a number of methoxy derivatives of benzene, naphthalene, and anthracene, and reported that of the substances tested only 1-methoxynaphthalene and 1 : 8-dimethoxynaphthalene produced polyploids in wheat. Favorski (228) tested twelve substances on barley. Three of these (diphenylamine, a related dye, aurantia, and tribromoaniline) produced a profuse formation of polyploid cells in the roots of the plant. Tribromophenol and trinitrophenol did not give this effect.

Gavaudan and Gavaudan (229) made the interesting observation that parsley apiole is capable of modifying mitoses and ultimately producing polyploidy. After colchicine, this was the first naturally occurring compound found to have this effect. The same action was claimed for anethole by Lefèvre (230). Simonet and Guinochet (118) confirmed the action of α-chloronaphthalene and α-bromonaphthalene on *Triticum vulgare*. These compounds gave mitotic figures blocked in metaphase, absence of anaphase, and an abnormal number of chromosomes in multiple variations. These effects were stated to be comparable with those of colchicine, but of a different type from those of *p*-dichlorobenzene vapors, which the same workers (231) found capable of producing polyploidy. Carey and McDonough (232) found that the roots of 4-day-old *Allium* seedlings, after exposure to vapors of *p*-dichlorobenzene, were stunted and polyploid. Colchicinelike effects were obtained by Simonet and Igolen (233) when germinating seeds were exposed to vapors of an essential oil extracted from leaves of *Citrus nobilis* Lour. The principal component of this oil is methyl methanthranilate, which in a pure state was more active and also less toxic than the essential oil.

In view of the similarity in pharmacological action between impure or oxidized colchicine and veratrine it is interesting that Witkus and Berger (234) found veratrine to give tetraploids when a 1% solution of the sulfate was applied to the root tips of the onion, *Allium cepa*. The material employed was stated to contain not only veratrine, but also cevadine and small amounts of two other alkaloids. Modifications of cell division in plants, although polyploidy does not appear to be claimed, has also been reported with vapors of benzene and its homologs (235) and a number of derivatives with substituents such as OH, OCH_3, $COCH_3$, NO_2, NH_2, CHO, COOR, and halogen (236). Benzoic, *p*-aminobenzoic and naphthoic acids were stated to be practically inactive, but their esters were active. Lefèvre (237) described effects on wheat seedlings of phenylurethane (ethylphenyl-

carbamate) and considered these effects to resemble those described for colchicine. This work has recently been extended by Templeman and Sexton (238) who found phenylurethane to be extremely active towards cereal seeds and seedlings. The most active of a series of related compounds was isopropyl phenylcarbamate, which when applied at the rate of 1 lb. per acre completely inhibited the growth of cereal seeds or seedlings.

9. Action on Lower Organisms

To complete this survey, reference may be made to attempts to extend the action of colchicine to microfungi, yeasts, and bacteria. Jennison (239) grew cultures of *Escherichia coli* in media to which colchicine was added, but found no significant change in the rates of reproduction or in the size of the cells. Walker and Youmans (240) pointed out that true bacterial cells do not contain chromosomes or well-defined nuclei. They examined a number of organisms grown in the presence of colchicine and found with most of them no variation from the normal. Colchicine did not affect the metabolism of bacteria. Growth of *Streptococcus haemolyticus* and *M. catarrhalis* was inhibited; with *Staphylococcus aureus H.* there was a change in the type of growth. Colchicine-treated paramecia did not differ from untreated organisms in their sensitivity to the lethal action of X-rays (241).

In the case of yeast, Richards (242) found that addition of colchicine to the medium produced no difference in cytological structure, and there was no evidence of other than amitotic division. A concentration of 1% of colchicine gave the maximum stimulation of yeast growth. Levan and Sandwall (243) likewise found that colchicine, and also acenaphthene, even in high concentration, had no effect on cell propagation. On the other hand, Bauch (244) reported that although colchicine did not influence growth of yeast, acenaphthene had some effect and gave mutants with larger cells. Camphor was even more effective, and in a later paper, Bauch (245) suggested, apparently on the basis of an increase in the volume of the cells, that camphor vapor gives tetraploid and octaploid mutants of yeast.

Blakeslee stated in 1939 (189) that fungi are immune to the action of colchicine. In 1945, however, Gordon and McKechnie (246) claimed to have produced polyploidy in *Penicillium notatum* by adding 0.2% of colchicine to a modified Czapek-Dox medium. In such species the chromosomes are very small and therefore they were not counted, so that there was no absolute proof of polyploidy. But the resultant strains showed the characteristics quoted by Huxley (247) for polyploids and the yield of penicillin was increased six to eight times. In regard to this claim our colleague, Dr. G. Pontecorvo, writes:

"Although there is no reason to doubt the claim of Gordon and McKechnie to have increased the yields of penicillin by successive treatments with colchicine, there

is not the slightest cytological or genetical evidence, in their published account, for the actual production of polyploidy. Indeed, the very kind of change obtained — a mass change in a culture — is not what usually follows colchicine treatment, which induces polyploidy in only a fraction of the cells treated. As the strain used by the authors was probably a very heterogeneous one, a more likely explanation of their results is that colchicine treatment killed selectively the weaker components. In *Penicillium notatum* the mycelium is made of multinucleate cells whilst the spores are uninucleate. Thus the gigantism often associated with polyploidy in higher plants would be expected to occur in polyploid spores, but probably not in the mycelium. In fact, Sansome (248) has produced, by camphor treatment of *P. notatum*, what is more likely to be real polyploidy; in her 'polyploid' strain the spores are considerably larger than in the original strain."

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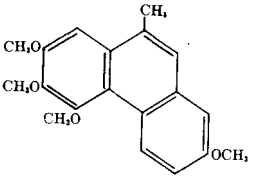
Addendum

Since the time when the foregoing account of the chemistry of colchicine was written the problem of the alkaloid's structure has been brought close to its final solution. Synthetic work has confirmed completely the structures assigned by Barton, Cook, and Loudon (59) to colchinol derivatives. The seven-membered ring B, which is a feature of these derivatives, is now also a recognized feature of the products formed from colchicine by oxidative degradation of ring C. Its presence in both series of degradation products is accordingly strong presumptive evidence of its presence in the alkaloid itself. There is direct evidence in support of the tropolone methyl ether structure for ring C of colchicine, as well as indirect evidence which derives from experimental proof of the aromatic properties predicted by Dewar for tropolone and its derivatives. These developments all point to (XLI) or (XLII) as the probable structure of colchicine and they are here briefly discussed. Moreover, in another direction, events have shown that *Colchicum autumnale* contains a number of minor alkaloids and that most or all of these are constructed on the colchicine pattern.

Barton, Cook, and Loudon (59) noted that an unsaturated ketone, which they formulated as (LXV), was formed as a by-product during the oxidation of deaminocolchinol methyl ether to 2 : 3 : 4 : 7-tetramethoxyphenanthrenequinone. The compound of structure (LXV) was synthesized by Buchanan, Cook, Loudon and MacMillan (249) and its identity with the oxidation product was established. The synthetic method con-

sisted in expansion of the central ring of 2 : 3 : 4 : 7-tetramethoxy-10-methylphenanthrene (LXII). The latter was hydroxylated by means of osmium tetroxide in benzene-pyridine affording the diol (LXIII) and hence, by scission with lead tetraacetate and cyclization of the intermediate ketonic aldehyde (LXIV), the required compound (LXV) was produced. Cook, Jack, and Loudon (250) applied the same procedure to 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene (XIV) and obtained an isomer of (LXV), which on reduction afforded the saturated ketone (LII). This was converted, *via* the oxime, into the *dl*-amine of structure (LIII). Resolution of the amine, effected by *d*-6 : 6′-dinitrodiphenic acid, showed that the *l*-base and its *N*-acetyl derivative were respectively identical with colchinol methyl ether and *N*-acetylcolchinol methyl ether as prepared from colchicine. Rapoport, Williams, and Cisney (251) synthesized the same ketone (LII) and *dl*-amine (LIII) by another route and identified the base with the product obtained by racemizing colchinol methyl ether. In their synthesis the 9-monoxime of 2 : 3 : 4 : 7-tetramethoxyphenanthrenequinone was converted by Beckmann change into 2 : 3 : 4 : 4′-tetramethoxy-6′-cyanobiphenyl-6-carboxylic acid and in this, by standard methods, the carboxyl group was transformed into a β-cyanoethyl side chain for cyclization to (LII).

These results settle the structural question for one series of degradation products, and their implications with respect to the structure of the alkaloid itself have been strengthened by renewed investigation and consequent reassessment of the supposed naphthalene-type of degradation product (p. 283). Here the key compound was *N*-benzoylcolchinic acid anhydride. By analogy with the deamination of *N*-acetylcolchinol methyl ether (p. 279) and also with other cases subsequently examined (252), this anhydride may be expected to eliminate the elements of benzamide when heated with phosphoric oxide in boiling xylene. This expectation was realized by Cook, Johnston, and Loudon (253), who showed that deaminocolchinic acid anhydride, so produced, was isomeric and not identical with the naphthalene derivative (XXXIV) which they synthesized by an unambiguous route (cf. also ref. 254). Moreover the properties of this new degradation product were quite inconsistent with a fully aromatic structure and, taken in conjunction with the known structure of deaminocolchinol methyl ether, this strongly suggested formula (LXVI) for deaminocolchinic acid anhydride. Horning, Ullyot, and their colleagues (255) showed that on hydrogenation the latter compound yielded a dihydride and they synthesized this dihydride by cyclization of the ketonic dibasic acid (LXVII), thereby placing beyond dispute the presence of the seven-membered ring in this second series of colchicine degradation products.



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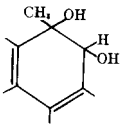

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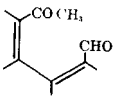

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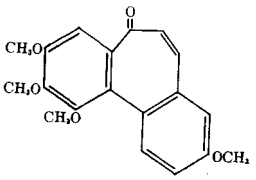
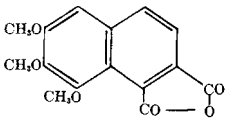
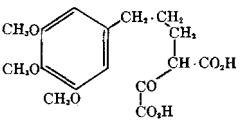


LXV



LXVI



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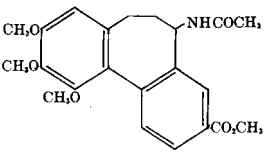

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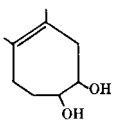

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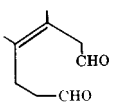
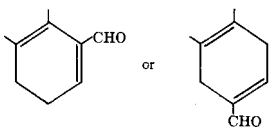


LXX



LXXI

Many of the difficulties and seeming inconsistencies met with in degradative studies of colchicine originate in molecular rearrangement. In a field which bristles with this insidious complication it is perhaps only of incidental interest that the carbinol derived from colchinol methyl ether (p. 280) appears on the basis of its ultraviolet absorption spectrum (256) to be more closely allied to derivatives of fluorene than to those of dibenz*cyclo*heptadiene. The incidence of rearrangement here would not affect the main structural issue whereas this is intimately concerned in the changes by which ring C is converted from the non-benzenoid form in colchicine into the benzenoid form in *N*-acetylcolchinol. The formation of this phenol, through its iodo derivative, by the action of alkaline hypoiodite on colchiceine was referred to on p. 278. The direct conversion was effected by Čech and Šantavý (257) by means of alkaline hydrogen peroxide. Another type of change was independently observed by Šantavý (258) and by Fernholz (259), who found that colchicine or isocolchicine, but not colchiceine, was isomerized when heated with sodium methoxide in methanol. The product of isomerization was the methyl ester, allocolchicine (LXVIII), of which the structure follows from its relationship to *N*-acetylcolchinol as established by Fernholz through the reaction sequence: $RCO_2Me \longrightarrow RNH_2 \longrightarrow ROH$. Incidentally, the observed oxidation of the corresponding acid, namely allocolchiceine, to trimellitic acid indicates the probable origin of the latter as a degradation product of colchicine (Section 7, *d*). It is consequently a prerequisite of any formula for colchicine that it be capable of interpreting these changes and, on the plausible assumption that rings A and B of colchinol and of colchinic acid anhydride are also present in the alkaloid, this requirement must be met in terms of the structure assigned to ring C.

The rapidly developing chemistry of tropolones (260) provides numerous examples of isomerization from a tropolone to a benzoic acid. The change, although not invariably found, occurs in presence of alkali and with varying ease in individual cases. In a general sense it provides analogy for the ether-ester change found in the colchicine-allocolchicine conversion and more specifically, Doering and Knox (261) have shown that tropolone methyl ether may likewise be rearranged to methyl benzoate. Although failure attended the first attempts (262, 263) to find in the tropolone series an analogy for the transformation of colchiceine to the phenol, *N*-acetylcolchinol, Doering and Knox also reported the successful conversion of tropolone ultimately into triiodophenol by means of alkaline hypoiodite. These results go far to confirm the tropolone nature of ring C and they are supported by other evidence. Hydrogenation of tropolones commonly results either in the formation of a 1 : 2-diol or, where the carbonyl group survives, in the unmasking of ketonic reactivity. Both

features are found in the case of colchiceine as Tarbell and his colleagues showed. Hexahydrocolchiceine is cleaved by reaction with periodic acid (264, 265). This indicates that the compound is a 1 : 2-diol (p. 287) and, although the product isolated (as an amorphous 2 : 4-dinitrophenylhydrazone) was a monoaldehyde instead of a dialdehyde, a plausible reaction course is illustrated by (LXIX) → (LXX) → (LXXI). Hydrogenation of colchiceine with palladized charcoal as catalyst afforded a gum which apparently contained a ketonic tetrahydride since it yielded a 2 : 4-dinitrophenylhydrazone (amorphous) consistently with this view (265). The infrared absorption spectrum of colchiceine was examined by Scott and Tarbell (266) and was found to contain bands which are considered to be characteristic of tropolones (261, 266, 267). Brdička (268) and Šantavy (269) likewise concluded from their independent polarographic measurements that colchiceine closely resembles γ-thujaplicin, a fully authenticated tropolone.

The accumulated evidence therefore indicates formula (XL) (but without the resonance implications) for colchiceine and formula (XLI) or (XLII) for colchicine. The isomerism of colchicine and isocolchicine is a further point of resemblance to (unsymmetrical) tropolones in which similar pairs of methyl ethers are known and are still not differentiated individually. Colchicine and tropolone methyl ether both form hydrates which are less soluble in water than the anhydrous forms, as also are the respective hydrolysis products, namely colchiceine and tropolone (263). The formation of colchicamide (p. 272) and its derivatives (270) from colchicine finds its parallel in the production of 2-amino*cyclo*heptatrienone from ammonia and tropolone methyl ether (261).

The X-ray powder photograph of colchicine, used to distinguish the compound from its hydrate (271), serves as another means of characterizing the alkaloid.

Colchicine may be regarded as the prototype of a group of alkaloids which are now known to occur with it in *Colchicum autumnale*. Seven new crystalline alkaloids have been isolated from this source (272, 273) and there are indications that the group is still incomplete. At least five of these alkaloids are akin to colchicine in absorption spectra. Of these, one has been identified by partial synthesis from colchicine and contains an *N*-formyl group in place of the *N*-acetyl group. Two others have a hydroxyl group instead of a methoxyl group in ring A and yield colchicine on methylation. A fourth is possibly a homologue of colchicine since it is hydrolyzed to colchiceine and is convertible into allocolchiceine. Two of the remaining alkaloids are mutually related but, from their absorption spectra, appear to be less closely allied to colchicine.

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CHAPTER XI

Alkaloids of the Amaryllidaceae

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I. Occurrence and General History

As is so frequently the case in the history of alkaloids, attention was first attracted to the present group by the poisonous or medicinal properties associated with certain species of the plant family. Among the earliest investigators, and in centers as far apart as Britain and Japan, it was the knowledge of these properties which first led Gerrard and later Morishima to seek for active principles in the more accessible species of their respective localities. Subsequent development ran a natural course: inadequate characterization and multiplicity of compounds, initially named according to source, gave place to more accurate identification and recognition of a limited number of individuals whereas again, at the present stage, the group has been expanded by the discovery of minor alkaloids and by the investigation of less accessible sources. From the chemical as distinct from the botanical point of view, the treatment of these alkaloids as a single group is still largely a matter of convenience but it also expresses the conjecture, already realized in part, that extensive structural relationships will ultimately be found among the individual members.

In 1877 Gerrard (1) isolated from the bulbs of *Narcissus pseudo-narcissus* L. an alkaloid which he named "narcissia" but which he did not characterize in any definite fashion. For physiological tests with this alkaloid Ringer and Morshead (2) used two extracts which were chemically indistinguishable but had been obtained by Gerrard from flowering and resting bulbs, respectively. From their results, they concluded that the extract from the resting bulbs produced an effect similar to the effect of pilocarpine, whereas the extract from the flowering bulbs resembled atropine in its action: an accompanying emetic action was attributed to impurities in the extracts.

Fragner (3) obtained a substance which he named "amarylline" from *Amaryllis formosissima* L. (*Sprekelia formosissima* Herb.) and another, "belamarine," from *Amaryllis belladonna* L., but he characterized neither beyond recording melting points and giving a few precipitation and color reactions.

Morishima (4) isolated and chemically analyzed two alkaloids, which he named lycorine and sekisanine, from *Lycoris radiata* Herb. He attributed the poisonous nature of the plant to the more abundant lycorine, which he found to be a powerful emetic, moderately toxic, and to cause death in dogs and cats through paralysis and general collapse.

Ewins (5) in 1910 repeated Gerrard's work and showed that both the resting and flowering bulbs gave the same crystalline alkaloid of which he established the correct molecular formula and which he re-named narcissine. He noted that the yield from the flowering bulbs was about half that from the resting bulbs whereas the bulbs of a cultivated variety (*N. princeps* Hort.) yielded only traces. Laidlaw (cf. 5) who examined the physiological action of narcissine failed to find the resemblances to pilocarpine or atropine noted by Ringer and Morshead. Oral administration to a cat caused nausea, vomiting, salivation, and purgation but the salivation could not be produced in the anaesthetized animal as is the case with pilocarpine.

Tutin (6) examined *Buphane disticha* Herb. (*Haemanthus toxicarius* Herb.), a plant native to South Africa where it had earned the Dutch name "gift bol" or "poison bulb" and had a reputation as an arrow poison as well as some medicinal uses. From the inner portion of the bulbs he isolated buphanine, an amorphous alkaloid, and detected the presence of three other alkaloids one of which was identified with narcissine. Previous conjectures, attributing the toxicity of the plant to the presence of brucine or aconitine, were definitely refuted. According to Laidlaw's findings, buphanine exerts a physiological action similar to, but weaker than those of hyoscine and hyoscyamine. From the same source Lewin also isolated an amorphous base, haemanthine, and described its toxic action on animals.

In 1913 Asahina and Sugii (7) repeated Morishima's work and revised

the molecular formula given by him for lycorine. Since the new values and also the general properties corresponded with those of narcissine, they suggested that the two alkaloids were identical. This was confirmed by Gorter (8) and the name lycorine has become established by subsequent usage. Gorter (9) showed that lycorine occurred in many species of Amaryllidaceae and regarded buphanine, and an alkaloid isolated by Yamanouchi (10) from *Narcissus tazetta* L., as identical with it. Later (11), having found lycorine in both of the sources from which Fragner had prepared amarylline and belamarine, and also in *Clivia miniata* Benth. from which Molle (12) had isolated "cliviin," he concluded that all three of these earlier extracts had consisted essentially of lycorine. While Gorter's results properly emphasize the widespread occurrence which makes lycorine the principal alkaloid of the group, care must be taken to avoid any oversimplification of the facts. For instance it may be urged that Tutin is not likely to have confused buphanine with lycorine since he isolated each of these compounds and describes their very different properties; again, subsequent work (cf. below) suggests that tazettine and not lycorine is the main, though not the only alkaloid of *Narcissus tazetta*.

Kondo and his school (13–19) have developed the work of Morishima on the alkaloids of *Lycoris radiata*. In all, nine alkaloids have been described from this source (cf. Table 1) one of which (base VIII) has been identified with the tazettine isolated by Späth and Kahovec (20, 21) from *Narcissus tazetta*, and by Norkina and Orechoff (22, 23) from *Ungernia sewerzowii* (Rgl.) Fedtsch. Another, homolycorine, is possibly identical with narcipoetine, isolated by Kolle and Gloppe (24) from *Narcissus poëticus* L., while a third, ψ-lycorine, may also accompany lycorine in *Cooperia pedunculata* Herb., according to Greathouse and Rigler (25). Two new alkaloids have also been reported by other investigators in recent years: suisenine, isolated by Kihara (26) from *Narcissus tazetta* appears to be distinct from tazettine while Tanaka (27) isolated crinamine together with lycorine from a species of *Crinum*. It may here be pointed out that, in so far as the scanty available data permit of comparison, a marked superficial resemblance exists between crinamine and Fragner's amarylline.

Table 1 summarizes the present state of knowledge regarding the distribution of alkaloids in Amaryllidaceae. It is sufficiently impressive to warrant the expectation that this family of monocotyledons will repay further and more detailed study. Ruthruff (28), in a survey of the occurrence of these alkaloids, concludes with a reference to the economic value of the amaryllis bulbs which are said to contain 15–20% sugar, although their toxicity makes them dangerous to man and cattle alike. Greathouse and Rigler (25) found the presence of alkaloids denoted by histochemical

tests in every species of Amaryllidaceae examined by them. From the demonstrated fungicidal action of lycorine, considered together with the quantity and localization of the alkaloids in the plants, they concluded that the alkaloid content contributes to the immunity displayed by this plant family towards *Phymatotrichum* root rot.

TABLE 1

BOTANICAL DISTRIBUTION

Plant	Source	Alkaloid	Per Cent	References
Amaryllis belladonna	Bulbs	Lycorine	0.9	11
		Belamarine[a]	..	3
Buphane disticha (*Haemanthus toxicarius*)	Bulbs	Lycorine; Buphanine; Amorphous bases;	..	6
		Haemanthine	..	29
Clivia miniata	Roots	Lycorine	0.3	11; 12
Cooperia drummondii Herb.	..	Lycorine	..	11
C. pedunculata	Bulbs	Lycorine	0.04–0.05[b]	25
		ψ-Lycorine	..	25
Crinum asiaticum	Roots	Lycorine	1–1.8	9
var. *japonicum*	Bulbs	Lycorine;	0.018	27
		Crinamine	Trace	27
Cr. giganteum Andr. (= *asiaticum*)	Seeds	Lycorine	1–1.5	9
Cr. pratense Herb.	Roots	Lycorine	0.9	9
Cr. scabrum Herb.	..	Lycorine	..	30
Cyrtanthus pallidus Sims.	Root nodules	Lycorine	Small	11
Eucharis grandiflora Planch. and Linden	Roots	Lycorine	0.45–0.75	9
Eurycles sylvestris Salisb.	Roots	Lycorine	Trace	9
(*E. amboinensis*)	Bulbs	Lycorine	..	31
Galanthus woronowii Losinsk	Bulbs	..	1.03	32
	Leaves	..	0.60	32

TABLE 1 (*Continued*)

Plant	Source	Alkaloid	Per Cent	References
Hymenocallis littoralis Salisb.	Roots	Lycorine	0.015	9
Lycoris radiata	Bulbs	Lycorine	..	4; 14
		ψ-Lycorine	..	16
		Sekisanine	..	4; 13
		Base IX	..	17
		Lycoramine	..	16
		Lycorenine	..	16
		Tazettine (base VIII)	..	16; 21
		Sekisanoline	..	15
		Homolycorine	..	15
Narcissus orientalis[c]	..	(?)	..	33
N. poëticus	Bulbs	Narcipoetine (= Homolycorine ?)	..	24
N. princeps (cultivated)	Bulbs	Lycorine (?)	Trace	5
N. pseudo narcissus	Bulbs	Lycorine	0.2[d]	1; 5
N. tazetta[c]	Bulbs	Lycorine	..	10; 9
		Tazettine	..	20
		Suisenine	..	26
Sprekelia formosissima	..	Lycorine	0.9	11
Amaryllis formosissima	Bulbs	Amarylline[a]	..	3
Ungernia sewerzowii	Bulbs	Tazettine	0.067–0.11	22; 23
U. tadshikorum Vved.	Bulbs	Lycorine	0.28	34
		Other bases	0.03	34
Zephyranthes rosea Lindl.	Roots	Lycorine	Trace	9
Z. texana Herb.	Bulbs	Lycorine	0.02[b]	25

[a] Belamarine, long colorless needles, m.p. *ca.* 181°, and amarylline, needle clusters from ethanol, m.p. *ca.* 196°, were both considered by Gorter (11) to be impure lycorine.

[b] Based on fresh bulb weight.

[c] Identical (Index Kew.).

[d] Refers to resting bulbs; flowering bulbs, 0.1%.

ADDENDUM TO TABLE

By histochemical tests on bulb and root sections Greathouse and Rigler (25) also showed the presence of unspecified alkaloids in the following species: — *Cooperia traubii* Hayward; *Hymenocallis galvestonensis* Baker; *Zephyranthes Andersoniana* Benth. and Hook (*Habranthus andersonii* Herb.); *Z. ajax* Spreng (*Z. citrinia candida*); *Z. atamasco* (L). Herb.; *Z. candida* Herb. *var. major* Hort.; *Z. longifolia* Hemsl.; *Z. robusta* (Herb.) Baker (*Habranthus robustus* Herb.); *Z. simpsonii* Chapm. and *Z. treatiae* Wats.

Gorter (9) states that lycorine is absent from *Hippeastrum reginae* Herb.; *Pancratium zeylanicum* Linn. and *Polianthes tuberosa* L.

Most of the experimental work bearing on the chemical structure of the alkaloids is due to Kondo and his school but, although Gorter (8) had early suggested the presence of an isoquinoline residue in lycorine, the most penetrating contribution was made by Späth and Kahovec in 1934 (20) who interpreted the course of Hofmann degradation in the case of tazettine and showed that this alkaloid yields phenanthridine when distilled with zinc dust. Subsequently Kondo and his coworkers obtained phenanthridine or its derivatives from lycorine (35) and lycoramine (36) and suggested that lycorenine (37) also contains a similar arrangement of atoms. These results definitely portend a close structural relationship in the alkaloids mentioned and afford the prospect of an alkaloidal group related to phenanthridine in much the same way as the chelidonium alkaloids (38) are related to 1:2-benzphenanthridine (naphthaphenanthridine). At the same time it is well to add that in no case has the structure of an alkaloid of the present group been rigidly established and that it is therefore for future research to determine whether, and to what extent there is general conformity to a fixed structural pattern among these alkaloids.

II. Chemistry of Individual Alkaloids

1. Lycorine

Lycorine, $C_{16}H_{17}O_4N$, forms colorless prisms, m.p. 276–280° (dec) from ethanol; $[\alpha]_D^{25}$ −120° (ethanol).

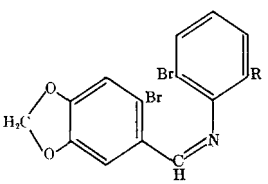
Bulbs (5) of the common daffodil (*Narcissus pseudonarcissus*) are dried at 40° (1400 g. from 4 kg. or 2500 bulbs) and the finely ground material is extracted for 6 hours with boiling ethanol. The resulting solution is concentrated to 200 cc. and the dark, sirupy acid liquid is treated with an equal volume of water. A very dark resinous precipitate is collected, resuspended in a little very dilute acid and again collected after thorough shaking. The combined filtrate and washings are extracted twice with about one third of their volume of ether. The aqueous solution is then made alkaline by the addition of sodium carbonate and the crystalline precipitate, which slowly separates, is recrystallized from 90% ethanol — m.p. 266–267° (*cf. also extraction given by* Morishima (4)).

It is best purified by crystallizing the hydrochloride which forms a monohydrate, dec 206° (217°); $[\alpha]_D$ + 43.0°. The picrate forms yellow needles, dec 196°, and the perchlorate plates, dec 230°. An intense blue color is produced when aqueous solutions of the sulfate and potassium permanganate are mixed (8). The base, probably lycorine, obtained (12) from *Clivia miniata* yields a blue color with potassium dichromate in sulfuric acid. Lycorine is a tertiary base that contains one ethylenic bond, two nonphenolic hydroxyl groups, and a methylenedioxy group but no methoxyl group; the formation of methyl iodide in Herzig-Meyer estimations, considered by Gorter to indicate the presence of an *N*-methyl group,

was subsequently regarded by Kondo as the result of side reactions (14). Diacetyllycorine, $C_{20}H_{21}O_6N$, has a melting point of 215–216°; $[\alpha]_D^{19}$ + 31.5° (14). Dihydrolycorine, $C_{16}H_{19}O_4N$, obtained by catalytic reduction of the alkaloid, forms small prisms, dec 247°, and yields a diacetyl derivative, m.p. 175° (14, 39).

When heated with methyl iodide at 100°, or under reflux, lycorine forms a mixture of α- and β- methiodides. These may be separated (a) by crystallization of the mixture from water, from which the β-form crystallizes as a monohydrate whereas the α-form is recovered from the mother liquor by concentration, or (b) by preferential extraction of the β-form with ethanol. The ratio of α- to β-forms is about 4:3. The α-form decomposes at 247° and has $[\alpha]_D^{20}$ −46.11° (water); the β-form decomposes at 281° (anhydrous, from ethanol), monohydrate dec 198°, $[\alpha]_D^{20}$ + 122.9° or, calculated as anhydrous, +128.1° (water). Since both forms of the methiodide give identical products on degradation, they are regarded as stereoisomers resulting from the 4-covalent nitrogen atom (40).

Neither the Hofmann nor the Emde reactions yields a normal product: in each case the reaction is complicated by dehydration which removes the two nonphenolic hydroxyl functions. The Hofmann transformation yields lycorine-anhydromethine, $C_{17}H_{15}O_2N$, m.p. 98.5° (40). This is an optically inactive compound and the main features of its structure are revealed in its oxidation products. With cold permanganate (35) it affords a mixture of acids — $C_{17}H_{11}O_6N$, m.p. 250°, and $C_{16}H_{11}O_5N$, dec 288°, of which the former yields the latter on further oxidation with alkaline hydrogen peroxide and is, therefore, likely to be an α-keto acid, produced as the result of oxidizing a vinyl group. Fusion of the C_{16}-acid causes elimination of carbon dioxide yielding 6:7-methylenedioxy-*N*-methylphenanthridone (III), identified by synthesis from the anil (I) (R=H) which is cyclized to the phenanthridine (II) (R=H), followed by formation and oxidation



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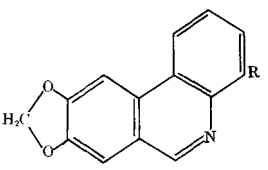
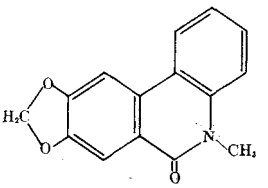


II

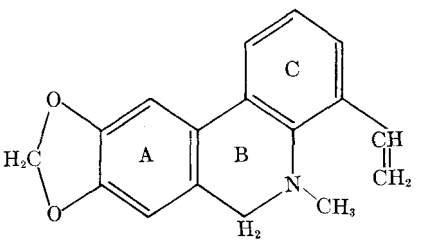


III

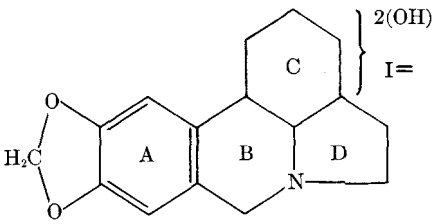
of the methiodide. In the degradation product (III), the carbonyl group is clearly introduced during oxidation of the anhydromethine which, accordingly, contains the corresponding dihydrophenanthridine structure with an additional vinyl substituent.

The location of the vinyl substituent is deduced from other evidence (41). Lycorine itself yields phenanthridine when distilled from zinc dust.

Hydrogenation (Pd-C) of the anhydromethine affords a dihydride, $C_{17}H_{17}O_2N$, m.p. 87.5°, and when this is similarly distilled from zinc dust it yields a mixture of phenanthridine, 1-methylphenanthridine and 1-ethyl-6:7-methylene-dioxyphenanthridine (II; R = C_2H_5) of which the two latter were also synthesized from the appropriate anils (cf. I→ II). From the position of the alkyl substituents Kondo and Uyeo inferred (41) that the original vinyl group is located at position 1 and accordingly they formulated lycorine anhydromethine as (IV). At first sight the remarkable assortment of pyrogenic products is perplexing, but it may be recalled that among pyrolytic reactions of polycyclic aromatic hydrocarbons, both elimination and degradation of substituents have been observed (42). Nevertheless it is unfortunate in the present connection that an attempt to synthesize the 1-carboxylic acid derivative of (III) proved unsuccessful (41), through failure of the corresponding phenanthridine carboxylic ester (II; R = CO_2CH_3) to react with methyl iodide. Had this objective been achieved, direct comparison with the C_{16}-acid would have avoided any possible misinterpretation arising from rearrangement during pyrolysis of the anhydromethine dihydride.



IV



V

Of the two aromatic nuclei present in the anhydromethine (IV) it may be concluded that ring A is also present in lycorine, since oxidation of the latter yields hydrastic acid (4:5-methylenedioxy-*o*-phthalic acid) (8). Consequently the second aromatic nucleus, ring C, cannot exist as such in the alkaloid and must be formed in the concurrent processes of dehydration and Hofmann degradation. The simplest view is to represent the precursor of ring C as a hydroaromatic diol, and the inclusion of the double bond of lycorine in the same ring further expresses ease of convertibility into the aromatic form. Accordingly (41), lycorine is given the partial structure (V) in which ring D is considered to be opened by Hofmann degradation while, at the same time, dehydration occurs in ring C.

Undoubtedly in formulating lycorine as (V) Kondo and Uyeo were influenced by the conclusions previously reached by Späth and Kahovec (20) regarding the course of Hofmann degradation in the case of tazettine.

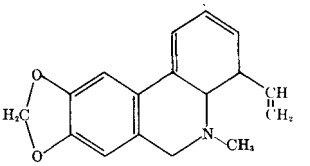
Comparison of the respective proposals, however, will show an important point of difference between the two cases. In the case of tazettine (XXI) the Hofmann degradation is depicted as an essential step in the process by which ring C becomes aromatic — it contributes a necessary double bond. On the other hand, in formula (V) for lycorine all the potentialities for an aromatic ring C are already present.

It would follow from this that ring C of lycorine should readily become aromatic quite independently of Hofmann degradation. Consequently there is an apparent anomaly in the previously reported formation of an isolycorine, $C_{16}H_{17}O_4N$, m.p. 201–202° (amorphous, yielding a crystalline hydrochloride, m.p. 266°, and catalytically reduced to dihydroisolycorine, $C_{16}H_{19}O_4N$, dec 103°; hydrochloride, dec 118°), by the action of phosphorus oxychloride or pentachloride on the alkaloid. The need for clarification is all the more necessary since it is also reported (14) that dihydrolycorine, which lacks the double bond for aromatization, is converted by phosphorus oxychloride into anhydrodihydrolycorine, $C_{16}H_{15}O_2N$, m.p. 102°.

It is unfortunately not clear from the available literature to what extent the earlier work of Kondo and his coworkers has been discounted in their more recent views on the structure of lycorine and on the stereoisomeric nature of the two lycorine methiodides. For instance (14, 18), lycorine β-methiodide ("ψ-methiodide") of m.p. 281° was reported to form a "ψ-methohydroxide" (dec 219°) which, when heated in a vacuum, gave "neutral methyl lycorine isomethine," $C_{16}H_{16}O_4NCH_3$ (dec 234°). Lycorine α-methiodide, on the other hand, when boiled with 20% potassium hydroxide, was said to give "basic methyl lycorine methine," $C_{16}H_{16}O_4NCH_3$. By heating with methyl iodide at 100° both the neutral isomethine and the basic methine yielded "methyl anhydrolycorine methiodide," $C_{16}H_{12}O_2NCH_3I$ (dec 235°). This last compound was stated to be *interconvertible* with the neutral isomethine, $C_{16}H_{16}O_4NCH_3$. Clearly such a process of reversible hydration is not to be reconciled with the ring C structure of (V).

Dehydration also accompanies Emde reduction (sodium amalgam) of lycorine methochloride, $C_{17}H_{20}O_4NCl$ (either α- or β-form, obtained by shaking an aqueous solution of the corresponding iodide with silver chloride). The product, $C_{17}H_{17}O_2N$, m.p. 71–71.5°, is isomeric and not identical with the dihydride of m.p. 87.5° obtained from lycorine anhydromethine (p. 338) (40). It yields hydrastic acid on vigorous oxidation, and formaldehyde but no acetaldehyde on ozonolysis. Hydrogenation, using platinic oxide as catalyst, yields a hexahydride, $C_{17}H_{23}O_2N$, m.p. 70–72°. It is concluded that Emde reduction, like Hofmann degradation, opens ring D thus generating the vinyl group which is responsible for the production of formaldehyde on ozonolysis. Since, however, the Emde reduction product contains one molecule of hydrogen more than the Hofmann product, it is assumed that ring C is not aromatic, one double bond having been reduced. From spectrographic evidence discussed below, Kondo and Katsura (43) place the remaining two double bonds as shown in (VI), which they propose as the structure of the Emde reduction product. This same product is also said to be formed when the metho-

chloride of lycorine anhydromethine (methochloride of IV) is reduced with sodium amalgam. Renewed and exhaustive Emde treatment gives the successive oily products, $C_{18}H_{21}O_2N$ (isolated as picrate, m.p. 147–148°, from which the regenerated base has b.p. 165° bath temp./0.01 mm.; methiodide, m.p. 186–187°) and $C_{16}H_{16}O_2$, neither of which has yet been extensively examined.

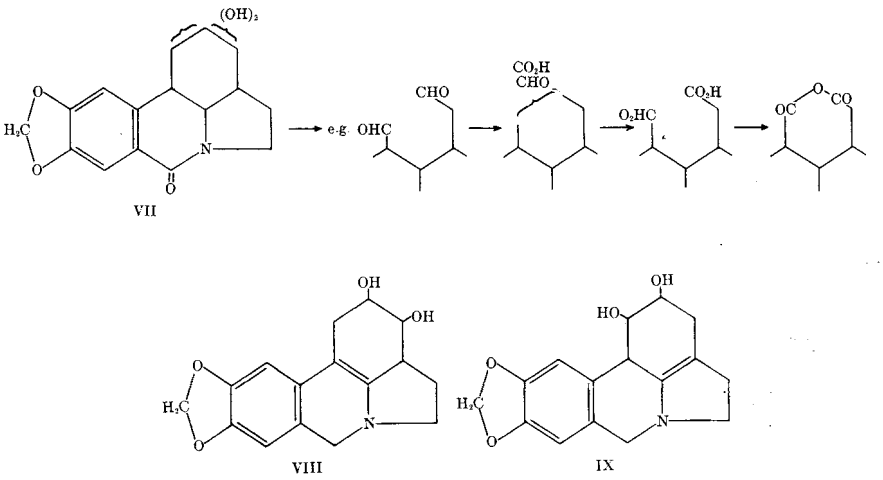


VI

This interpretation does not carry conviction. The hydrogenation results, obtained with a platinum catalyst, might be explained by the reduction of an aromatic ring, but on this basis the vinyl group could not be present. Clemo and Macdonald (44) have shown that the diagnosis of a vinyl substituent by means of ozonolysis requires the production of formaldehyde in significantly high yield and, in the present case, the experimental finding of an 86% yield of formaldehyde (isolated as the dimedon derivative) justifies the conclusion of Kondo and Katsura that a vinyl group is present. On the other hand, the alleged conversion of the methochloride of (IV) into (VI) under Emde conditions is so unusual as to require the fullest substantiation in order to make it acceptable. Straus (45) has shown that vinyl groups are not reduced by means of sodium amalgam, although 1-arylbutadienes (cf. VI) are decidedly less resistant. The main point at issue, however, is not the survival of these unsaturated centers, but the partial reduction alleged to occur in the aromatic ring C when the methochloride of (IV) is treated with this reagent. Kondo and Katsura state that this reduction is encountered only in conjunction with the change from quaternary to tertiary nitrogen and that the anhydromethine itself, namely (IV), reacts with sodium amalgam in a different, but unspecified fashion. While it may be conceded that sodium amalgam effects the partial reduction of the aromatic nucleus of benzoic acid (46) and of terephthalic acid (47), yet such reductions are rare. Quantitative studies on the Emde reduction of aryltrimethylammonium salts (48) afford no evidence of products analogous to (VI) and if, as is possible, the nucleus is less stable in polycyclic structures the point is sufficiently important to merit experimental proof.

Although in this group of alkaloids there is evidence that two diols, namely lycorine (cf. below) and lycoramine (p. 345), are α-glycols yet

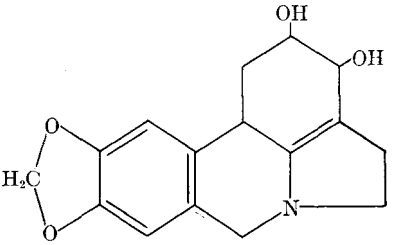
anomalous or negative results are obtained with lead tetraacetate and periodic acid oxidations. Titration of lycorine itself is stated to require 2 moles of lead tetraacetate but the available experimental work (49) refers to a lycorine derivative, namely dihydrolycorinone, for which the same titer was found. Dihydrolycorinone, $C_{16}H_{17}O_5N$, m.p. 246°, is a diol obtained by mild permanganate oxidation of dihydrolycorine or, better, of its diacetyl derivative followed by hydrolysis. The compound is neutral, shows no carbonyl properties and is considered to be the lactam (VII) (cf. lycoramine, p. 346). In view of this preliminary oxidation and of the absence of the double bond which in lycorine itself is a possible cause of interference, it is surprising that the lead tetraacetate titer remains twice that expected of an α-glycol. Nevertheless evidence of normal glycol scission has been obtained from the crude, noncrystalline, titration products. These, on the one hand, by reaction with hydroxylamine have yielded a dialdoxime, $C_{16}H_{17}O_5N_3$, dec 233°, and, on the other hand, after further oxidation with peracetic acid have furnished a crystalline monobasic acid, $C_{16}H_{15}O_6N$[= $C_{14}H_{13}O_3(CHO)CO_2H$] dec 245°, together with an ill-defined amorphous product, tentatively regarded as an acid anhydride. In consequence Kondo and Katsura conclude (49) that the two hydroxyl groups of lycorine are vicinally placed and the above reaction course is represented as follows:



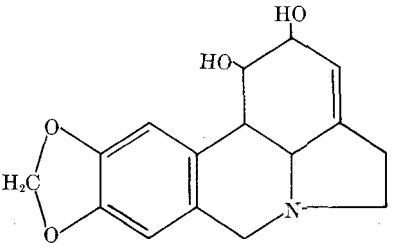
A decision between the alternative arrangements (VIII and IX) now envisaged for lycorine is reached from spectrographic considerations (43). This is based on the fact that lycorine, dihydrolycorine and their respective diacetyl derivatives resemble safrole, allyl benzene and ethyl benzene in showing similar absorption curves with a single maximum (ca. 295 mμ)

whereas isosafrole, propenyl benzene and other compounds, in which an external double bond is conjugated with the nucleus, exhibit a second maximum. Accordingly Kondo and Katsura assign to lycorine the structure (IX) (43). By similar reasoning the Emde-reduction product is represented by (VI) since its absorption spectrum shows a closer resemblance to those of the second group.

Even on the basis of these facts it may be objected that the structure (IX) for lycorine is not uniquely determined. The spectrographic evidence requires only that the double bond of ring C be placed out of conjugation with the aromatic ring A. The absence of enolic properties in the hydroxyl group imposes a further restriction, but both of these requirements are fulfilled by the arrangements of formulas (VIIIa) and (IXa), which could also afford easy transitions of ring C to the aromatic form.



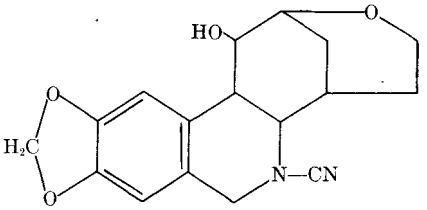
VIIIa



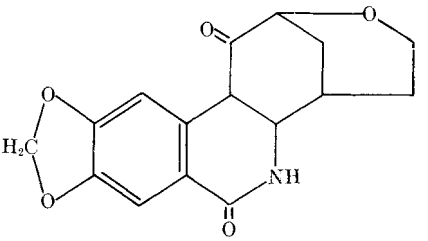
IXa

A further series of degradation products has been obtained by Kondo and Katsura starting from dihydrolycorine (39). This compound is unresponsive to treatment along Hofmann or Emde lines, but its diacetyl derivative, when heated with cyanogen bromide in benzene, yields a cyanobromide, $C_{16}H_{17}O_2(OCOCH_3)_2NCNBr$, m.p. 176°, from which by boiling with *N*-alcoholic potassium hydroxide a bromine-free cyanamide (neutral), $C_{16}H_{18}O_4NCN$, m.p. 217°, and a basic sirup were obtained. The cyanamide yields a monoacetyl derivative, $C_{16}H_{17}O_3N(CN)OCOCH_3$, m.p. 236°, and like the basic sirup, on further hydrolysis with acid or alkali gives a secondary base (Liebermann test), $C_{16}H_{18}O_4NH$, m.p. 198° (anhydrous, from ethanol), or m.p. 204° (monohydrate, from acetone or ethanol-water). This also gives a monoacetyl derivative, $C_{16}H_{18}O_4NCOCH_3$, m.p. 198°. Since the cyanamide showed no sign of unsaturation to tests with permanganate and tetranitromethane, and since it lacks one of the original hydroxyl functions of dihydrolycorine, it is considered to be the dihydrocyanolycorine anhydride (X), in which the oxide ring has been formed through the opening of ring D and elimination of water between the resulting hydroxyethyl side chain and one of the original hydroxyl groups. Evidence in support of this view is adduced from oxidation of the cyanamide

with chromic acid in acetic acid at room temperature. The product $C_{16}H_{15}O_5N$, dec 341°, is described as a ketone (monoxime dec 293–295°) which is soluble in dilute sodium hydroxide solution, contains no reactive methylene group and yields, with methyl sulfate in alkali, an *N*-methyl (not an *O*-methyl) derivative, $C_{16}H_{14}O_5NCH_3$, m.p. 258° (insoluble in alkali; monoxime dec 266–268°). On the basis of these results the ketone was represented by formula (XI), its solubility in alkali and its *N*-methylation being interpreted by reference to the behavior of carbostyril (50). Structure (XI), however, is not transparently the structure of a carbostyril nor yet of an isocarbostyril, being in fact a dihydro derivative of the latter compound. Reference to the properties of 3:4-dihydroisocarbostyril (51) will show that this latter analogy affords little warrant for the solubility in alkali attributed to (XI) and, accordingly, these conclusions of Kondo and Katsura must be treated with reserve.



X



XI

To sum up: the experimental work of Kondo and his collaborators furnishes strong evidence that lycorine contains a partially reduced phenanthridine, or closely related structure, although in respect to structural detail uncertainty remains. The precise location of the double bond and of the hydroxyl groups remains to be settled while interesting problems, germane to the structural issue, are raised by the results of degradation and, in our opinion, are not completely resolved in the available published work. Unfortunately the facts themselves, frequently accessible only in abstract form, are not always clear and appear at times to be definitely contradictory. In these circumstances it seems idle to speculate further, the paramount need being for clarification and supplementary experiment.

2. Pseudolycorine

Pseudolycorine, $C_{16}H_{17}O_4N + 4H_2O$, silky scales m.p. 245° (from ethanol or acetone), $[\alpha]_D^{21} - 41.53°$ (ethanol), was isolated from *Lycoris radiata* by Kondo, Tomimura and Ishiwata (16). It is a phenolic tertiary base which contains one methoxyl and three hydroxyl groups but no methylimino group. It dissolves in alkali, gives a red-brown coloration

with ferric chloride and yields a hydrochloride, needles dec 261°; a methiodide, m.p. 150° and a triacetyl derivative, m.p. 98–100°.

Pseudolycorine probably also accompanies lycorine in *Cooperia pedunculata* according to Greathouse and Rigler (25), who extracted the ground, dried, bulb tissue with 95% ethanol, removed the solvent at 45° under reduced pressure, acidified the residual dark yellow sirup, extracted fatty material with ether and liberated the bases with ammonia. After two days in the refrigerator the crystalline precipitate (lycorine, m.p. 277°, from pyridine) was filtered off and the filtrate was repeatedly extracted first with ether and then with chloroform. The chloroform extract yielded a base, m.p. 246° (hydrochloride, m.p. 260°) which was not completely characterized owing to lack of material (no analyses given).

3. Sekisanine

Sekisanine, $C_{16}H_{19}O_4N$, prisms m.p. 207–209°, $[\alpha]_D$ + 114.6°, was isolated by Morishima (4) from the bulbs of *Lycoris radiata*, and was examined and given the present molecular formula by Kondo and Tomimura (13). They obtained it by crystallizing, from ethanol, the ether-soluble basic component of the bulbs. It contains a methylenedioxy group, two nonphenolic hydroxyl groups and possibly one methylimino group. It forms a hydrochloride, dec 211°, $[\alpha]_D$ + 106.4°; a chloroplatinate, m.p. 194°; a methiodide, m.p. 237° and a diacetyl derivative, m.p. 72°. When reduced it yields a dihydride, m.p. 250°, $[\alpha]_D^{16}$ −57.14°, from which a hydrochloride, m.p. 261° $[\alpha]_D^{16}$ −16.4° and a nitrate, m.p. 250°, have been obtained.

4. Base IX

Base IX, $C_{16}H_{19}O_3N$, colorless scales m.p. 190° (from benzene), $[\alpha]_D^{20.5}$ −222.4° (methanol), was isolated by Kondo, Ishiwata and Okayama (17) from *Lycoris radiata*. It contains one methoxyl, one methylimino and two hydroxyl groups, and forms a hydrochloride, m.p. 234°; a picrate, m.p. 146°; a perchlorate, m.p. 237°; a methiodide, m.p. 275°; a methosulfate, m.p. 175°; a diacetyl derivative, m.p. 275° and (with phenyl isocyanate) a bis-phenylurethane, m.p. 192–193°. Heating the methiodide of base IX with 30% potassium hydroxide yields a mixture of an ether-soluble α-methine base, $C_{17}H_{21}O_3N$, m.p. 270°, $[\alpha]_D^{20}$ −184.8° (methanol) (picrate, m.p. 211°) and a β-methine base (? isomeric) m.p. 275° (picrate, m.p. 100°) which is only sparingly soluble in ether. The α-methine base, treated with methyl sulfate and then with potassium iodide, yields a methiodide, $C_{14}H_{10}(OH)(OCH_3)_2N(CH_3)_2I$, m.p. 207°, in which one of the original hydroxyl groups has been methylated. The same methiodide is also obtained by Hofmann degradation of a compound, $C_{15}H_{15}O(OCH_3)_2$ NI, m.p. 245°, which is produced when base IX is treated with methyl sulfate and alkali followed by addition of potassium iodide. Removal of nitrogen and formation of a neutral crystalline compound (no analyses

or molecular formula given in abstracts) of m.p. 100–105° results from heating the methiodide of m.p. 207° with 30% potassium hydroxide.

5. Crinamine

Crinamine, $C_{17}H_{19}O_4N$, needles m.p. 193–194°, was obtained together with lycorine from an aqueous extract of *Crinum asiaticum* L. *var. japonicum* Bak. by Tanaka (27). It is soluble in chloroform, contains one methoxyl group, and is shown by mixed melting point behavior to be distinct from lycorine and from Base IX.

6. Suisenine

Suisenine, $C_{17}H_{19}O_5N$, light yellow needles m.p. 229°, was isolated by Kihara from *Narcissus tazetta* (26).

The bulbs are extracted with hot 95% ethanol and the solution, which has a violet fluorescence, is treated with water. The base is purified by precipitation with phosphotungstic acid and is recovered as a sirup which changes to a crystalline mass when rubbed with a drop of water.

It contains a methylenedioxy group and one hydroxyl group but no methylimino grouping. The function of the remaining oxygen atoms appears to be undetermined. The presence of an isoquinoline nucleus (and probably therefore of a phenanthridine nucleus as in tazettine) is said to be indicated by the absorption spectrum. It forms a hydrochloride, m.p. 180°; a picrate, m.p. 189°; a monomethyl ether, m.p. 188° and a benzoate, m.p. 196°. Oxidation with alkaline permanganate affords a compound, $C_{12}H_{15}O_4N$, colorless needles m.p. 244°.

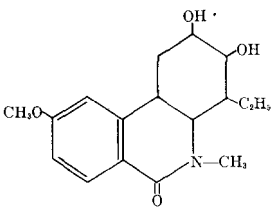
7. Lycoramine

Lycoramine, $C_{17}H_{25}O_3N$, m.p. 120° $[\alpha]_D^{27}$ −98.2° (ethanol) was isolated from *Lycoris radiata* by Kondo, Tomimura and Ishiwata (16) and was originally named ψ-homolycorine. It is readily soluble in cold water from which it separates as an oil on addition of neutral salts or alkali. It contains (36) one methylimino, one methoxyl and two nonphenolic hydroxyl groups and yields a diacetyl derivative, m.p. 95°; a picrate, m.p. 108–109°; a chloroplatinate, $B_2 \cdot H_2PtCl_6 \cdot H_2O$ dec 245°; a perchlorate, m.p. 138–139° and a methiodide, m.p. 220° (with solvent from methanol) or dec 308° (from water).

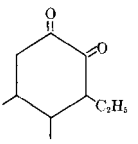
Lycoramine resists Hofmann degradation yielding only traces of a methine base, $C_{18}H_{27}O_3N$ [isolated as its picrate (m.p. 148°) or its methiodide (dec 213–214°)]. Emde reduction of lycoramine methochloride yields two hydromethines, $C_{18}H_{29}O_3N$, distinguished as A and B and separated by fractional crystallization of their hydrochlorides from ethanol. The more abundant hydromethine base A, m.p. 95°, $[\alpha]_D^{18}$ −54.2° (c=2.14 in ethanol), forms the much more soluble hydrochloride, m.p. 210–211°, and

yields a bis-phenylurethane, m.p. 150–151°, and a methiodide, dec 152–153°; attempted deamination by further Emde treatment was ineffective. The hydromethine base B, m.p. 145°, $[\alpha]_D^{18}$ + 43.6° (c = 2.522 in ethanol), yields a less soluble hydrochloride, m.p. 210°, and a methiodide, dec 105–106°.

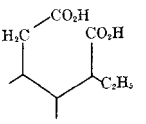
When oxidized with cold permanganate lycoramine yields 4-methoxyphthalic anhydride and a neutral compound, $C_{17}H_{23}O_4N$, m.p. 253° $[\alpha]_D^{18.5}$ + 73.65° (c = 0.964 in chloroform). The latter retains the two hydroxyl functions (analysis, but no m.p. given for a diacetyl derivative), is indifferent to carbonyl reagents, Clemmensen reduction and treatment with methyl iodide, but regenerates lycoramine on electrolytic reduction and, when distilled with zinc dust, yields 1-methylphenanthridine (identified by mixed m.p. with an authentic specimen). It is considered to be a lactam (e.g. XII; but cf. below regarding the 1-alkyl group) formed by oxidation of a methylene group at position 9. Despite the resistance shown by this lactam to oxidation with periodic acid or lead tetraacetate it is oxidized by chromic acid in acetic acid to an α-diketone (no analysis given), yellow prisms m.p. 220°, $[\alpha]_D^{17}$ + 275.5°; phenazine derivative dec 175–178°; *p*-nitrophenylosazone dec 267–268°; dioxime m.p. 257°; triazine derivative (from semicarbazide) dec 238° (all of which analyzed correctly). The presence of a reactive methylene group in the diketone is shown by the formation of an isonitroso derivative, dec 189–190°, from reaction with amyl nitrite and concentrated hydrochloric acid in chloroform. Oxidation of the diketone with permanganate in presence of sodium carbonate yields, in addition to 4-methoxyphthalic anhydride, three crystalline acids: Acid A, $C_{17}H_{21}O_6N$, m.p. 222–223°, is dibasic and probably results from oxidative rupture of the bond uniting the α-carbonyl groups. Acid B, $C_{13}H_{13}O_6N$, m.p. 261–262°, is an *o*-dicarboxylic acid (fluorescein test) and



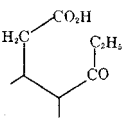
XII



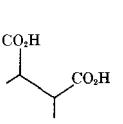
XIII



XIV



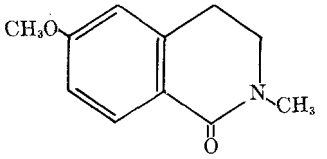
XV



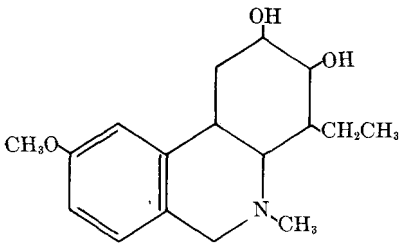
XVI

affords the known 6-methoxy-2-methyldihydroisocarbostyril (XVII) on decarboxylation. This fixes the position of the methoxyl group in lycoramine and suggests structure (XVI) for acid B. Acid C, $C_{16}H_{19}O_5N$, m.p. 119–120°, is a ketonic monobasic acid (*p*-nitrophenylhydrazone, dec 125–127°) which gives a positive iodoform reaction. It is concluded that either the group $COCH_3$ or $COCH_2CH_3$ is present.

Interpretation of these results meets with some difficulty. If lycoramine contains the 1-alkylhydrophenanthridine skeleton, the likeliest arrangement of substituents is shown for the lactam in (XII). This would accommodate successive oxidation of the corresponding α-diketone (XIII) first to the dibasic acid (XIV) and thence to the ketonic acid (XV). It would also accommodate a probably independent course of oxidation leading to acid B, which is satisfactorily represented by (XVI) although no mention has been made of its optical activity. On the other hand, the positive iodoform test given by acid C would seem to suggest a *methyl* rather than an *ethyl* ketone (XV) and the former would be in better accord



XVII



XVIII

with the production of 1-methyl, and not 1-ethylphenanthridine by zinc dust distillation of the lactam. Nevertheless in support of the presence of the ethyl group it is found that propionic acid is produced by alkaline permanganate oxidation of the methohydroxide derived from the hydromethine base A.

In proposing formula (XVIII) for lycoramine Kondo and Ishiwata do not attempt to resolve these difficulties. Nor do they discuss the striking contrast in behavior presented by the hydroxylated rings of lycorine and lycoramine respectively under the conditions of Hofmann degradation. Apparently lycoramine undergoes reaction without dehydration although, on the basis of formula (XVIII), the resulting methine base would presumably have just those features which in ring C of lycorine, and under similar conditions, were held to be responsible for aromatization.

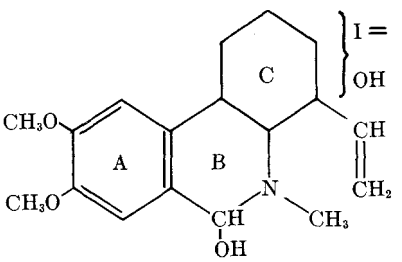
8. Lycorenine

Lycorenine, $C_{18}H_{23}O_4N$, m.p. 200–202° from acetone, $[\alpha]_D^{22}$ + 149.3° (methanol), was isolated from *Lycoris radiata* by Kondo, Tomimura and Ishiwata (16, 19). It is a tertiary base (37) which contains one methylimino-, two methoxyl and two nonphenolic hydroxyl groups. (For oxime formation cf. below.) It forms a picrate (dec 162°) and yields both a monoacetyl (m.p. 185–187°) and, with greater difficulty, a diacetyl (m.p. 175–176°)

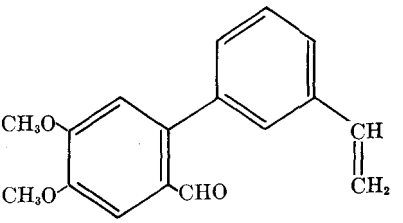
derivative. Catalytic reduction in acetic acid with palladium-charcoal as catalyst yields first a dihydride, $C_{18}H_{25}O_4N$, m.p. 175–177°, and then a desoxy-compound, $C_{18}H_{25}O_3N$, m.p. 165–168°, while with platinic oxide as catalyst crystalline products of m.p. 120–130° and m.p. 165–167° have been obtained but have not been fully examined.

Hofmann degradation of lycorenine methiodide (dec 260°) yields (37) two methine bases (α and β) separable by extraction with ether in which only the preponderating α-methine is soluble. Neither of the bases has been obtained crystalline and the β-methine has not been examined to any extent. The α-methine forms a crystalline methiodide, $C_{18}H_{20}O_3N(CH_3)_2I$ (dec 223°), from which it appears that at this stage loss of one molecule of water accompanies the normal degradation. Renewed Hofmann treatment affords des-*N*-lycorenine, $C_{15}H_{16}O(OCH_3)_2$ needles, m.p. 114–115°, in which the oxygen atom not involved in the methoxyl groups is present as a carbonyl function as is manifest by oxime formation, $C_{17}H_{16}O_2{:}NOH$, m.p. 147–150°.

In interpreting these results Kondo and Ikeda (37) assume that lycorenine, like lycorine and lycoramine, is a hydrophenanthridine derivative (XIX) in which ring C becomes aromatic in the course of Hofmann degradation. Accordingly, to accommodate this aromatization, one double bond and one hydroxyl group have been assigned to ring C. Location of the second hydroxyl group at C_9 has been adopted to explain the formation of the carbonyl (aldehyde) function found in the des-*N*-lycorenine. This is supported by the fact that lycorenine, like cotarnine (52), yields an oxime hydrochloride, $C_{18}H_{24}O_4N_2 \cdot HCl$ (dec 258°) in reaction with



XIX



XX

hydroxylamine hydrochloride. There remains the allocation of two methoxyl groups and a C_2H_3 residue. The latter is considered to be probably a vinyl group since formaldehyde is produced in unspecified amount when the alkaloid is ozonized. Its position and those of the methoxyl groups are fixed by ozonization of des-*N*-lycorenine to a dialdehyde $C_{16}H_{14}O_4$, m.p. 155–157° (bis-semicarbazone dec 238°), which is further oxidized by permanganate, either directly or by way of an alde-

hydic acid, $C_{16}H_{14}O_5$, m.p. 228–230°(*p*-nitrophenylhydrazone dec 276–278°) to 3:4-dimethoxydiphenyl-6:3′-dicarboxylic acid, m.p. 256–257°. The dimethyl ester of this acid was synthesized by Ullmann condensation between the methyl esters of 6-bromoveratric acid and *m*-iodobenzoic acid.

Formula (XX) is therefore indicated for des-*N*-lycorenine and accordingly Kondo and Ikeda assign to lycorenine the structure (XIX) in which the positions of the double bond and the hydroxyl group in ring C remain to be fixed. They omit, however, to discuss in any detail the individual stages of the Hofmann degradation although the considerations involved appear to be of some importance.

9. Tazettine

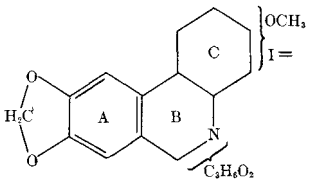
Tazettine, $C_{18}H_{21}O_5N$, was isolated by Späth and Kahovec (20) from the bulbs of *Narcissus tazetta* and was subsequently identified (21) with "Base VIII," earlier obtained by Kondo, Tomimura and Ishiwata (16) from *Lycoris radiata*, and also (23) with "ungernine," obtained by Norkina and Orechoff (22) from the bulbs of *Ungernia sewerzowii* (Rgl.).

The extract (20), obtained from boiling the dried and crushed bulbs of *Narcissus tazetta* with ethanol and removing the solvent in a vacuum, was dissolved in dilute hydrochloric acid and, after removal of nonbasic material in ether, the base was liberated with alkali and recovered from chloroform as a colorless residue which slowly crystallized. It was purified by recrystallization from methanol and by sublimation at 190–200° (air bath) in a high vacuum.

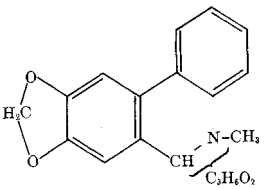
Tazettine has m.p. 212–213°, b.p. 200–210° (air bath)/0.03 mm., $[\alpha]_D^{18}$ + 165.8° (c = 1.46 in chloroform). In concentrated sulfuric acid it gives a brown red solution which changes to dirty green and brownish violet on warming. It is a tertiary base which contains one methoxyl and one methylenedioxy group. It is also stated to yield an *O*-acetyl derivative, m.p. 125–126.5°, but the absence of analytical data renders it uncertain whether a mono- or diacetate is implied. The methiodide decomposes at 222°, while from "ungernine" a picrate m.p. 205–208° and a perchlorate m.p. 105–108° have been described. Oxidation of tazettine with potassium permanganate yields hydrastic acid while distillation with zinc dust yields phenanthridine.

Hofmann degradation (20) of tazettine methiodide yields an oily methine base, b.p. 190–200° (air bath)/0.01 m.m., $[\alpha_D^{15}$ −40.6° (picrate dec 171°), in the formation of which the methoxyl group of the alkaloid has been eliminated as methanol while the simultaneous production of a new aromatic ring is shown by oxidation of the methine base to benzoic acid. The methiodide of the methine base underwent further degradation to 6-phenylpiperonyl alcohol (XXIII) which was synthesized from 6-bromopiperonal and iodobenzene followed by application of the Cannizzaro

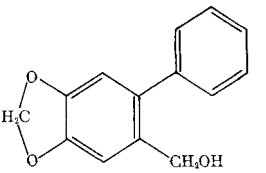
reaction. These results have been interpreted (20) in the partial structure (XXI), for tazettine. This incorporates the phenanthridine skeleton, accounts for hydrastic acid as an oxidation product and affords a plausible route for the production of (XXIII) by exhaustive methylation. Fission of ring B between the nitrogen atom and the hydroaromatic nucleus, thereby forming the methine (XXII), is in harmony with the behavior of chelidonine. The complication in the present case, namely elimination of methanol to make ring C aromatic, suggests that this ring, besides carrying the methoxyl group, already contains one double bond but the presence of a double bond has not yet been established independently.



XXI



XXII



XXIII

It has not been settled definitely whether or not the nitrogen atom carries a methyl group and the nature and mode of attachment of the $C_3H_6O_2$ residue shown in (XXI) await elucidation.

10. Sekisanoline

Sekisanoline, $C_{18}H_{23}O_5N$, dec 152°, $[\alpha]_D^{17}$ −60.72° (chloroform), was isolated from *Lycoris radiata* by Kondo and Tomimura (15). It is a tertiary base which contains a methylenedioxy group and two hydroxyl groups, of which one at least is phenolic, but no methylimino group. The base does not react with carbonyl reagents and the function of the fifth oxygen atom remains undetermined. It forms an amorphous hydrochloride, dec 152°; a perchlorate, dec 211°; a picrate, dec 127–133°; a methiodide, dec 117–122° and a diacetyl derivative, dec 155°.

11. Homolycorine

Homolycorine, $C_{19}H_{23}O_4N$, m.p. 175°, $[\alpha]_D^{19}$ + 65.1° (ethanol), was isolated from *Lycoris radiata* by Kondo and Tomimura (15). It is a tertiary base which contains two methoxyl and two nonphenolic hydroxyl groups, while the presence of a methylimino group is doubtful. It forms a hydrochloride, ($+2H_2O$) dec 285°, $[\alpha]_D^{30}$ + 86.2° (water); an aurichloride, m.p. 137°; a picrate, dec 268°; a methiodide, dec 256° and a diacetyl derivative, dec 173°.

According to Kolle and Gloppe (24) extraction of the dried bulbs of *Narcissus poëticus* yields a base very similar to homolycorine but they reserve the name "narcipoetine" in the event of non-identity with homo-

lycorine. This base, $C_{18}(H_{21}$ or $H_{23})O_4N$, was obtained as needles m.p. 172°, $[\alpha]_D$ + 84.4° (ethanol) and contains two methoxyl groups and possibly one *N*-methyl group, but no methylenedioxy group. It forms a hydrochloride (+ $1H_2O$), m.p. 271°, $[\alpha]_D$ + 111.2° (ethanol), an aurichloride, m.p. 131–132° and a picrate, dec 261°.

12. Alkaloids from Buphane disticha

Buphanine was isolated by Tutin (6) as an amorphous solid which formed the more strongly basic, ether-soluble fraction of an ethanol extract obtained from the bulbs of *Buphane disticha*. When hydrolyzed with potassium hydroxide in ethanol, it yielded buphanitine, $C_{23}H_{24}O_6N_2$, m.p. 240°, crystallizing from ethanol with one molecule of solvent which is lost at 130°. Buphanitine forms a hydrochloride, $C_{23}H_{24}O_6N_2 \cdot HCl$, m.p. 265–268° and a methiodide, $C_{23}H_{24}O_6N_2CH_3I$, dec 278°.

Lycorine (narcissine) and two other amorphous bases were also found by Tutin (6).

"Haemanthine," an amorphous base obtained by Lewin (29) from the same source, was given the molecular formula $C_{18}H_{23}O_7N$. No crystalline derivatives were obtained. A drop of a 2% aqueous solution of the base, mixed with a drop of concentrated sulfuric acid, slowly developed a violet coloration, which changed to yellow and then to green when a drop of concentrated nitric acid was added.

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CHAPTER XII

Acridine Alkaloids

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I. Introduction

1. OCCURRENCE

In certain botanical families a close structural relationship exists between the alkaloids found in the different species and genera of which the family is composed, while in other families a variety of heterocyclic structures is encountered. In the Rutaceae, for example, quinoline, furanoquinoline, isoquinoline, carboline and imidazole derivatives are to be found as well as amides of the fagaramide type. In view of this biogenetic versatility it seems appropriate that the recently discovered group of acridine alkaloids (1) should also occur in the Rutaceae. Members of this group have been found in five species, belonging to three genera, indigenous to the tropical rain forests of Northern Australia.

The group comprises ten alkaloids, seven of which are listed in Table 1. Two are not included in this table and will not be referred to by trivial names because there is some doubt as to whether they occur as such in the plant or arise by demethylation during the isolation process. They are identified in Table 2 by their melting points. The remaining alkaloid, which likewise has not been given a trivial name, is 1,3-dimethoxy-10-methylacridone (II) colorless needles, m.p.163–164°. The first five alka-

loids listed are all *N*-methylacridones, *melicopine*, *melicopidine* and *melicopicine* being derivatives of a tetrahydroxy-*N*-methylacridone, while *evoxanthine* is derived from a trihydroxy-*N*-methylacridone. *Acronycine* is

TABLE 1

ACRIDINE ALKALOIDS

Name	Molecular formula	Methoxyl groups	Methylenedioxy groups	Melting point, °C.
Melicopicine	$C_{18}H_{19}O_5N$	4	..	133–134
Melicopine	$C_{17}H_{15}O_5N$	2	1	178.5–179.5
Melicopidine	$C_{17}H_{15}O_5N$	2	1	121–122
Evoxanthine	$C_{16}H_{13}O_4N$	1	1	217–218
Acronycine	$C_{20}H_{19}O_3N$	1	..	175–176
Xanthevodine	$C_{16}H_{13}O_5N$	2	1	213–214
Evoxanthidine	$C_{15}H_{11}O_4N$	1	1	312–313

a derivative of a dihydroxy-*N*-methylacridone, one of the hydroxyl groups being methylated and the other involved in a *gem*-dimethylpyran ring. *Xanthevodine* and *evoxanthidine* are acridones, that is, the nitrogen atom is not methylated. The first is a derivative of a tetrahydroxyacridone, the second of a trihydroxyacridone. All are nicely crystalline pale yellow to yellow solids whose solutions in chloroform or alcohols are strongly fluorescent. They are optically inactive.

TABLE 2

DISTRIBUTION OF THE ACRIDINE ALKALOIDS

Species	Source	Alkaloids	Amount, %	Author(s)
Melicope fareana Engl. (syn. *Evodia fareana* F. Muell.)	Bark	Melicopine	*Ca.* 1	Price (2)
		Melicopidine	1	
		Melicopicine	1	
	Leaves	Melicopine	*Ca.* 0.2	
		Melicopidine	0.8	
		Melicopicine	0.03	
Acronychia Baueri Schott.	Bark	Acronycine	1.0–1.2	Lahey and Thomas (3)
		Melicopine	1.3	
		Melicopidine	0.2–0.3	
	Leaves	Melicopicine	*Ca.* 0.26	Lamberton and Price (19)
		Melicopidine	0.14	
		Melicopine	0.01	
		1,3-Dimethoxy-10-Methyl-acridone	0.05	

TABLE 2 (*Continued*)

Species	Source	Alkaloids	Amount, %	Author(s)
A. acidula F. Muell.	Bark	Melicopine	*Ca.* 0.02	Lahey and Lamberton (4)
Evodia xanthoxyloides F. Muell.	Bark	Evoxanthine	*Ca.* 1.0	Hughes and Neill (5)
		Melicopidine	0.8	
	Leaves	Evoxanthine	*Ca.* 0.6	
		Melicopidine	0.1	Hughes,
		Xanthevodine	0.2	Neill and
		Evoxanthidine	0.03	Ritchie (20)
		Base m.p. 176–177°		
		Base m.p. 265–267°	0.1	
E. alata F. Muell.	Bark	Evoxanthine	*Ca.* 1	Neill (6)
		Melicopidine	2	

The distribution of the alkaloids is shown in Table 2. They are accompanied in most instances by small amounts of furanoquinoline bases. Leaves of *Melicope fareana* Engl. contain about 0.3% *skimmianine* in addition to the acridine alkaloids, while the bark of this tree and of *Acronychia Daueri* Schott. contains 0.1–0.2% *acronycidine*, which has been shown to be a tetramethoxyfuranoquinoline (7). Similarly the bark of *Evodia xanthoxyloides* F. Muell. contains *kokusaginine* (5). Four furanoquinolines have been isolated from the leaves of *A. aueri*, skimmianine, kokusaginine, acronycidine and *acronidine*, a dimethylpyranofuranoquinoline (19), while from the leaves of *E. xanthoxyloides* Hughes, Neill, and Ritchie (20) have isolated four colorless bases in addition to the six acridine derivatives.

2. Behavior with Acids

As would be expected of acridones, all the alkaloids are very weak bases, melicopine and melicopicine being so weak that salt formation with such acids as picric or picrolonic does not take place. These two alkaloids are soluble in 10% hydrochloric acid but as the acid concentration is reduced to about 5% hydrolysis ensues and the free bases are liberated. Consequently, mineral acid salts of melicopine and melicopicine can only be isolated by precipitation from nonhydroxylic solvents. The hydrochlorides of evoxanthine and acronycine separate conveniently from 10% hydrochloric acid, whereas melicopidine is readily soluble in acid of this strength. Curiously enough, melicopidine hydrochloride is less soluble in weaker acid and separates on reduction of the acid concentration to 2–3%. This anomalous behavior is probably due to oxonium salt forma-

tion at low values of the pH. It is also encountered with 1,3-dimethoxy-10-methylacridone.

The following salts, which are hydrolyzed by water, have been described (2, 3): melicopidine hydrochloride, $C_{17}H_{15}O_5N \cdot HCl$, orange needles from dilute hydrochloric acid, m.p. 88–90° (dec), melicopidine picrate, $C_{17}H_{15}O_5N \cdot C_6H_3O_7N_3$, orange needles from methanol, m.p. 133–134°; melicopidine picrolonate, $C_{17}H_{15}O_5N \cdot C_{10}H_8O_5N_4$, orange needles from methanol, m.p. 153–154°; acronycine hydrochloride, bright red needles from 10% hydrochloric acid, m.p. 125–130° (dec); acronycine sulfate, long red needles from alcoholic sulfuric acid, m.p. 158–159° (dec); acronycine picrate, $C_{20}H_{19}O_3N \cdot C_6H_3O_7N_3$, orange crystals m.p. 150–154°; 1,3-dimethoxy-10-methylacridone hydrochloride, bright yellow needles from dilute hydrochloric acid, m.p. 135–136° (dec); 1,3-dimethoxy-10-methylacridone picrate, yellow needles from methanol, m.p. 203–205°.

The salts of mineral acids have one diagnostic feature in common; they are unstable and on heating demethylation of one methoxyl group occurs. The products, which revert to the parent bases upon methylation, have been designated as "noralkaloids."

Normelicopine ($C_{16}H_{13}O_5N$, red needles m.p. 235.5–236.5°) is obtained in 96% yield by refluxing melicopine (10 g.) with a mixture of ethanol (500 ml.) and concentrated hydrochloric acid (50 ml.) for one hour (8). *Normelicopidine* ($C_{16}H_{13}O_5N$, orange-red, m.p. 211–212°), *normelicopicine* ($C_{17}H_{17}O_5N$, orange, m.p. 129–129.5°) and *norevoxanthine* (5) ($C_{15}H_{11}O_4N$, orange, m.p. 274–275°) are prepared in the same manner. *Noracronycine* ($C_{19}H_{17}O_3N$, bright yellow, m.p. 200.5–201°) can only be obtained by heating the dry hydrochloride at 130° — treatment of the alkaloid with alcoholic acid gives an amorphous product (9). See also Addendum, p. 368.

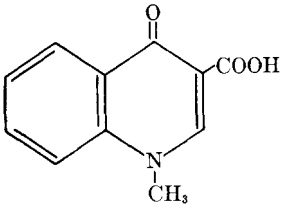
In addition to being more highly colored, the noralkaloids are even weaker bases than their progenitors and exhibit properties of a cryptophenol. They are insoluble in alkalis and the only indication of phenolic character (apart from methylation and acetylation) is that the color of their alcoholic solutions is enhanced by the addition of alcoholic alkali. The ease with which demethylation to the noralkaloids takes place may give rise to difficulties in isolation, which usually involves the use of acid solutions at some stage, and, as indicated previously, there is reason to suspect that due to this cause, at least one and possibly two acridine derivatives isolated from *Evodia xanthoxyloides* leaves may not occur as such in the plant.

II. Degradation

1. Establishment of the Acridone Structure

By oxidizing melicopine, melicopidine or melicopicine with nitric acid, Price (10) obtained *1-methyl-4-quinolone-3-carboxylic acid* (I), colorless needles from acetic acid, m.p. 294–296° which in turn has been decarboxylated to *1-methyl-4-quinolone*. The position of the carboxyl group was established by comparison of the acid with a specimen prepared by

methylating 4-hydroxyquinoline-3-carboxylic acid with dimethyl sulfate and caustic soda (11). This same acid (I) was also obtained by Hughes and Neill (5) by oxidation of evoxanthine. Drummond and Lahey (11) found that noracronycine and dihydroacronycine yielded (I), whereas

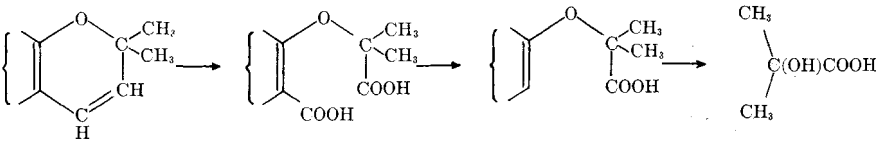


I

acronycine under the same conditions was first nitrated, and the resulting sparingly soluble yellow *trinitroacronycine*, $C_{20}H_{16}O_3N(NO_2)_3$ m.p. 289–290.5°, in turn was slowly oxidized by boiling nitric acid to *6-nitro-1-methyl-4-quinolone-3-carboxylic acid*, cream plates, m.p. 259–261°.

The degradation of melicopicine to 1-methyl-4-quinolone by way of the acid (I), involves the loss of a fragment $C_8H_{10}O_4$ containing the four methoxyl groups. Crow and Price (12) concluded that this moiety must represent a tetramethoxybenzenoid ring fused to the quinolone nucleus in the 2,3 positions. In fact, the formation of (I) from the above alkaloids, taken in conjunction with their molecular formulas and the nature and number of substituent groups, implies that all five are *N*-methylacridone derivatives.

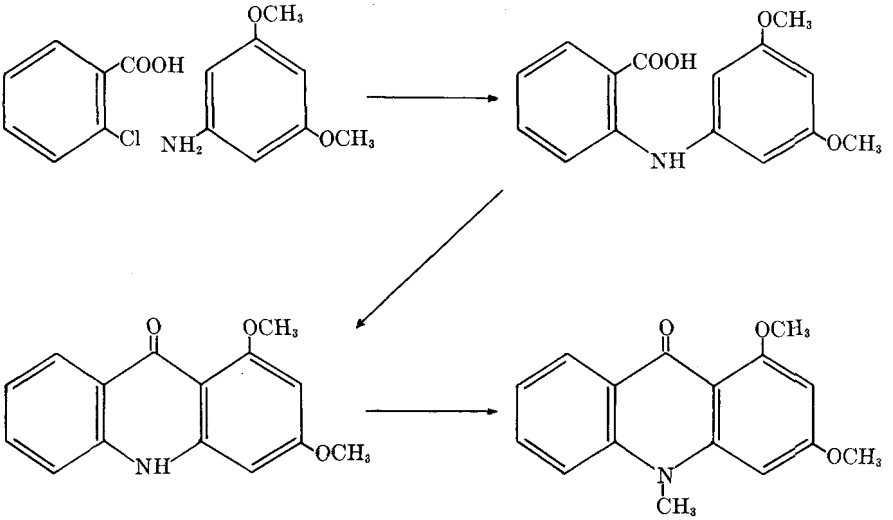
Experimental confirmation followed shortly in the case of acronycine. Brown, Drummond, Lahey, and Thomas (9), by oxidizing acronycine with permanganate in acetone, obtained an acid $C_{20}H_{19}O_7N$, m.p. 215–217°, which lost carbon dioxide readily giving the monobasic *acronycinic acid*, $C_{19}H_{19}O_5N$, m.p. 227°.



Identification of α-hydroxyisobutyric acid as the volatile pyrolysis product of acronycinic acid led to the recognition of the dimethylpyran ring as a component part of the nuclear structure of this base. From the nonvolatile material Drummond and Lahey (11) isolated 1,3-dihydroxy-10-methylacridone,* the identity of which was settled by synthesis of its dimethyl ether (II) from phloramine dimethyl ether and *o*-chlorobenzoic

* The numbering of the acridine nucleus in the original papers differs from that used in this article, which follows current *Chemical Abstracts* usage.

acid. The primary condensation product was cyclized by means of phosphorus oxychloride and the derived 1,3-dimethoxy-9-acridone methylated by heating its potassium salt with dimethyl sulfate. Oxidation of xanthevodine and evoxanthidine with nitric acid did not give rise to (I), but instead, *4-quinolone-3-carboxylic acid* was produced (21). This is in agreement with the observed absence of a methylimino group in these alkaloids.



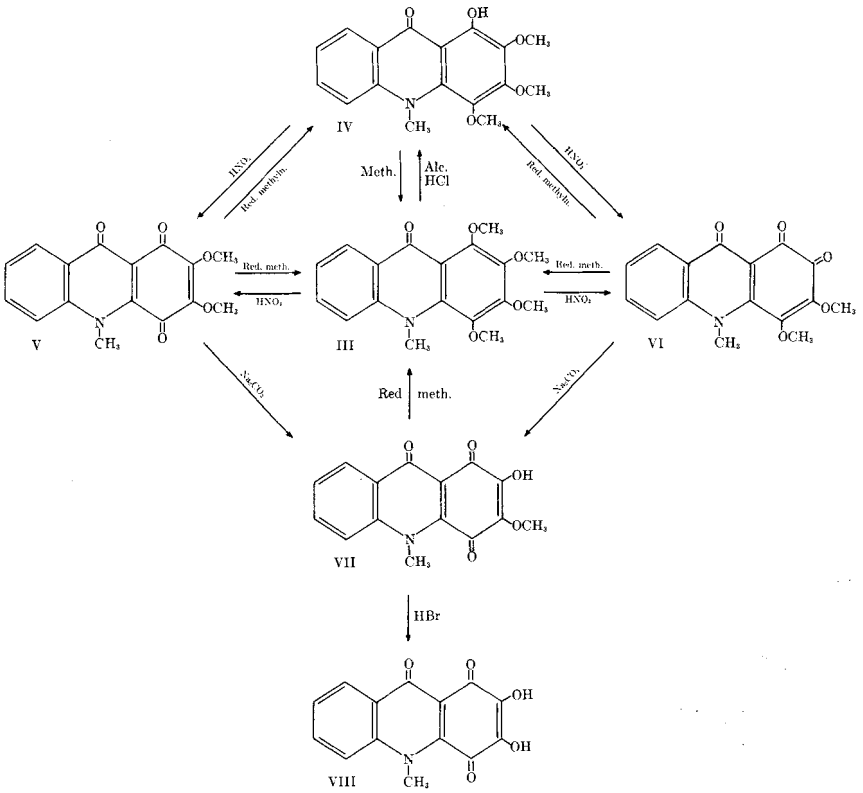
II

The ultraviolet absorption spectra of the alkaloids (13) provide additional evidence for the acridone structure. From the spectra of melicopine, melicopidine and melicopicine a relationship can be traced through those of evoxanthine, dihydroacronycine, 1,3-dihydroxy-10-methylacridone and the monomethoxy-10-methylacridones to the spectra of 10-methylacridone, acridone and acridine itself. Because of the conjugation of the double bond of the pyran ring with the acridone system, the maxima of the acronycine spectrum are shifted to longer wavelengths than those of its dihydro derivative. Similar shifts are also observed, especially in the bands of longer wavelength, when the C_1 methoxyl of these bases is replaced by the hydroxyl in their nor analogs.

2. The Structure and Reactions of Melicopicine

The formation of 1-methyl-4-quinolone-3-carboxylic acid from five of the alkaloids not only leads to the conclusion that they are *N*-methylacridones, but also reveals that in each of these alkaloids the alkoxyl substituents are all in the same ring. Melicopicine, then, is 1,2,3,4-tetramethoxy-10-methylacridone (III), a structure which is in accord with its

behavior towards nitric acid. Melicopicine is oxidized by this reagent (14) to a mixture of two quinones, one being a dimethoxy-*p*-quinone $C_{16}H_{13}O_5N$ (V), bright red needles, m.p. 200.5-201.5° and the other (in smaller amount) an isomeric dimethoxy-*o*-quinone (VI), dark red needles, m.p. 233–235°. The same mixture of quinones was obtained from normelicopicine (IV). Mild conditions are required for the above reactions and the quinones are presumably intermediates in the oxidation of melicopicine to (I). The formation of quinones by oxidative demethylation with nitric acid is characteristic of such polymethoxy compounds and finds a parallel in the recent work of Seshadri and his collaborators on pedicellin (15).



The dimethoxy-*o*- and *p*-quinones (V) and (VI) are both hydrolyzed by sodium carbonate to the same hydroxymethoxyquinone, $C_{15}H_{11}O_5N$ (VII), red needles m.p. 247–248° (dec) which can be further demethylated by hydrobromic acid to a dark red dihydroxyquinone $C_{14}H_9O_5N$ (VIII; no definite m.p., decomposes above 250°). Each of these quinones and hydroxyquinones can be reductively methylated to melicopicine. Their

interrelations are shown in Chart I. The formation of the dimethoxy-*p*-quinone (V) from normelicopicine (IV) establishes that the methoxyl group demethylated in the formation of normelicopicine must be at position 1 or 4. Its allocation to position 1 in Chart I anticipates information supplied in a later section.

1,2,3,4-Tetramethoxy-10-methylacridone has been synthesized by Hughes, Neill, and Ritchie (18) by condensing 2,3,4,5-tetramethoxyiodobenzene with anthranilic acid to give 2,3,4,5-tetramethoxydiphenylamine-2′-carboxylic acid which was cyclized by means of phosphorus oxychloride to 1,2,3,4-tetramethoxy-9-chloroacridine. Sodium methoxide in dry methanol gave 1,2,3,4,9-pentamethoxyacridine, and this when heated with methyl iodide in a sealed tube was converted to 1,2,3,4-tetramethoxy-10-methylacridone identical with melicopicine from natural sources.

3. The Structures of Melicopidine and Xanthevodine

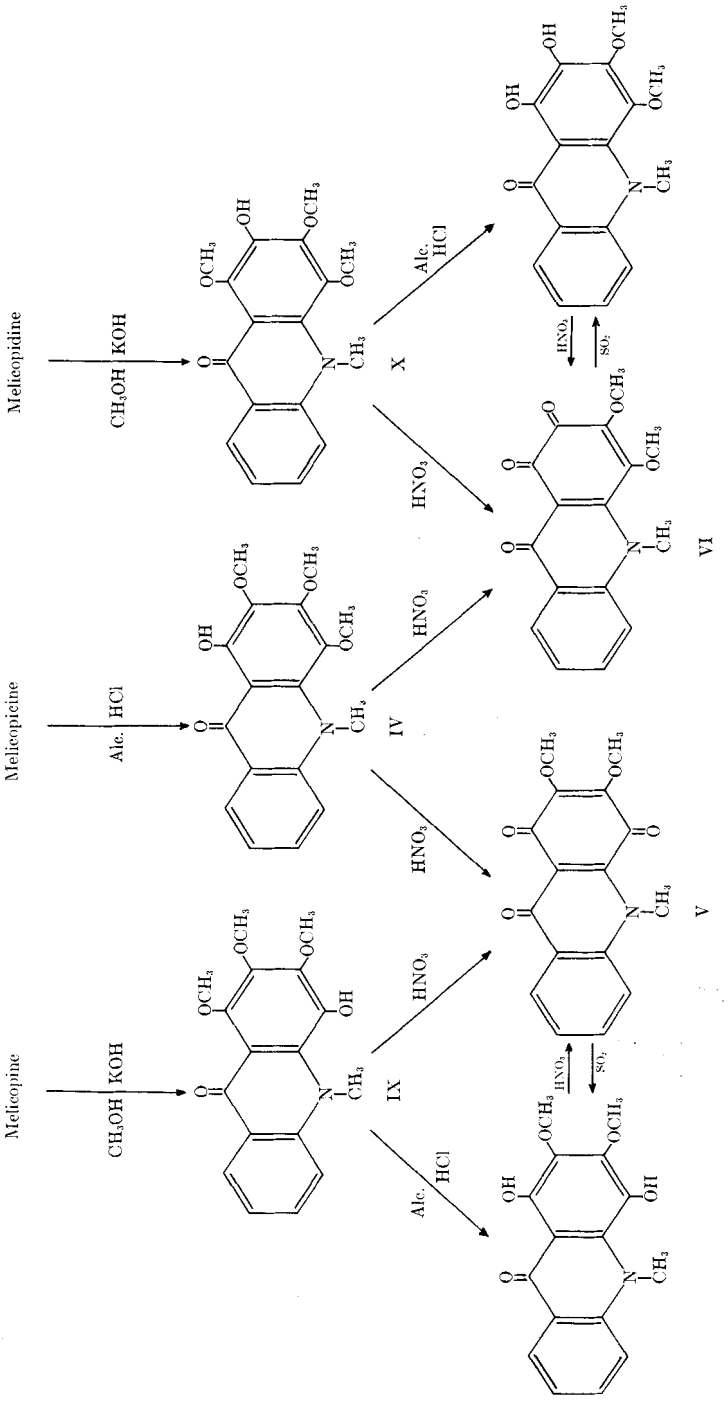
When three of the alkaloids that contain a methylenedioxy group — evoxanthine (5), melicopine, and melicopidine (8) — are refluxed with alcoholic potash, an alkoxylative fission of the methylenedioxy group occurs and each is converted to a yellow monohydric phenol. As would be expected the alkoxyphenol so obtained depends on the alcohol employed as solvent.

Melicopine, $C_{17}H_{15}O_5N$, with methanolic potash, gives a trimethoxyphenol $C_{17}H_{17}O_5N$ (IX) m.p. 190.5–191.5° and with ethanolic potash an ethoxydimethoxyphenol, $C_{18}H_{19}O_5N$ (XI) m.p. 147–149°. Likewise, melicopidine gives a trimethoxyphenol (X) m.p. 165–166° and an ethoxydimethoxyphenol (XII) m.p. 181.5–182.5°, while evoxanthine, $C_{16}H_{13}O_4N$ gives with methanolic potash a dimethoxyphenol $C_{16}H_{15}O_4N$ m.p. 226–227° and with ethanolic potash an ethoxymethoxyphenol $C_{17}H_{17}O_4N$, m.p. 199–201°.

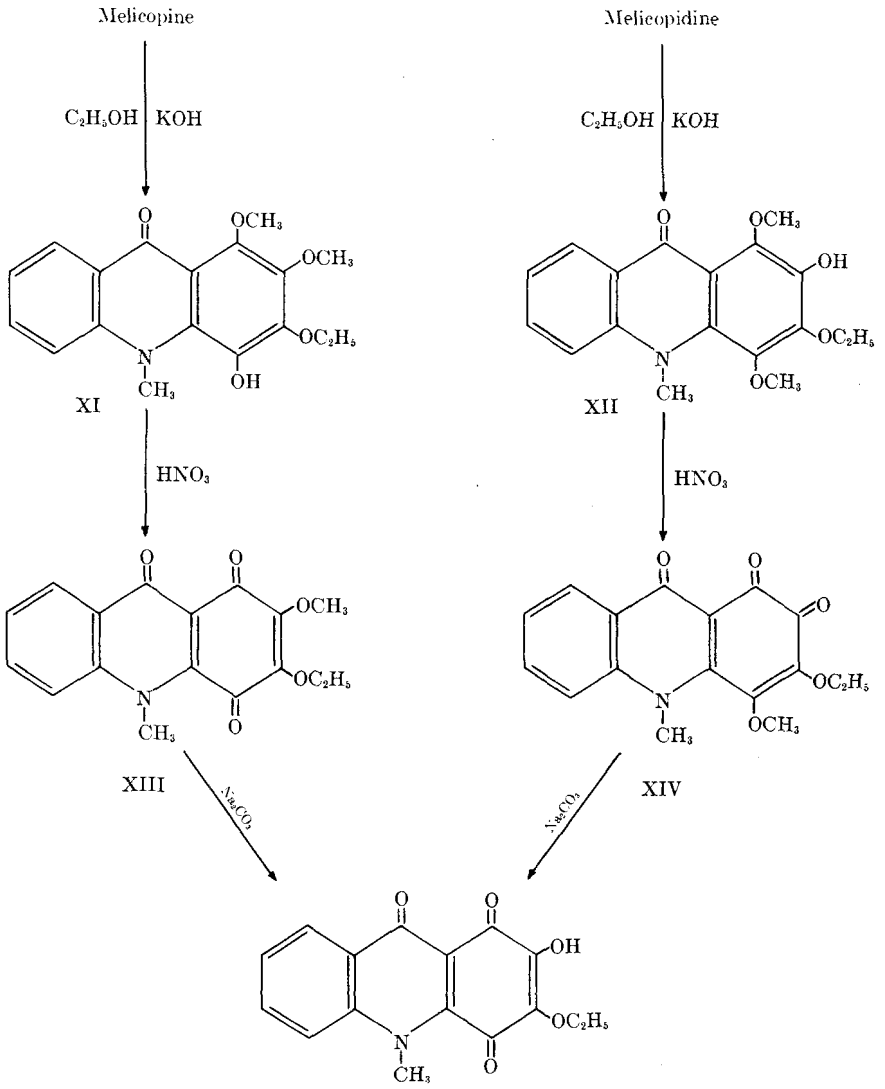
This is analogous to the conversion of 4-nitro-1,2-methylenedioxybenzene (XVI) to 2-alkoxy-5-nitrophenol by sodium alkoxides (16).

XVI R = CH_3,C_2H_5

The monohydric phenols arising from the three alkaloids by fission of the methylenedioxy ring can be demethylated to dihydroxy compounds by alcoholic acid (the same procedure as that employed in the preparation of the noralkaloids). These dihydroxy compounds are quinols, oxidizable to quinones which are also available from the phenols directly by treatment with nitric acid. In this way the trimethoxyphenol (X) from melicopidine and methanolic potash gives rise to a dimethoxy-*o*-quinone identical with


Melicopine
CH3OH | KOH
Melicopicine
Alc. | HCl
Melicopidine
CH3OH | KOH
IX
IV
X
Alc. | HCl
HNO3
HNO3
HNO3
HNO3
Alc. | HCl
HNO2
SO2
HNO2
SO2
V
VI

(VI) obtained from melicopicine, while the trimethoxyphenol (IX) from melicopine and methanolic potash gives the corresponding dimethoxy-*p*-



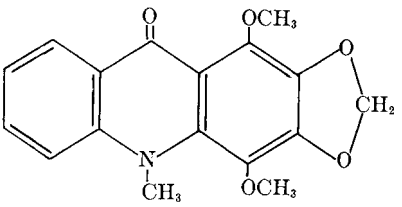
quinone (V); (see Chart 2). It follows that the phenolic hydroxyl group resulting from fission of the methylenedioxy ring of melicopine must occupy position 4 or 1 according as the hydroxyl group in normelicopicine is located at position 1 or 4. In other words the methylenedioxy group in

melicopine must be situated either 1, 2 or 3, 4. It can also be deduced that the hydroxyl group resulting from fission of the methylenedioxy ring of melicopidine must occupy position 2 or 3.

The ethoxydimethoxyphenols resulting from the action of ethanolic potash on melicopine and melicopidine are converted by nitric acid to an ethoxymethoxy-*p*-quinone, $C_{17}H_{15}O_5N$ (XIII; bright red needles, m.p. 195–196°) and the isomeric ethoxymethoxy-*o*-quinone (XIV; dark red, m.p. 225–226°) respectively.

As shown in Chart 3, warm sodium carbonate demethylates these two quinones to the same red hydroxyethoxyquinone $C_{16}H_{13}O_5N$ (XV; m.p. 197–198°). Consequently, the ethoxyl group must be in the same position in the two ethoxydimethoxyphenols (XI and XII) from which it follows that the methylenedioxy groups in melicopine and melicopidine have one position in common. Melicopidine is, therefore, 1,4-dimethoxy-2,3-methylenedioxy-10-methylacridone (XVII), this conclusion being independent of which of the alternative structures for melicopine is the correct one.

The structure of melicopidine leads to that of xanthevodine (21). Xanthevodine is not oxidized to I, but instead gives 4-quinolone-3-carboxylic acid, implying that it is an acridone, not *N*-methylated. It is converted to melicopidine in good yield by methylation with methyl



XVII

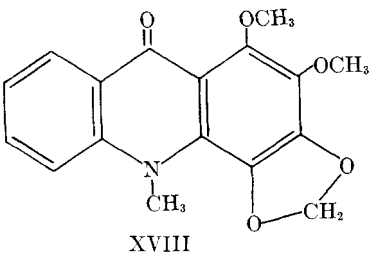
iodide in acetone solution in the presence of anhydrous potassium carbonate. Consequently xanthevodine is 1,4-dimethoxy-2,3-methylenedioxy-9-acridone.

4. The Structures of Melicopine, Evoxanthine, and Evoxanthidine

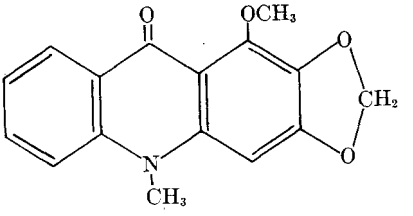
Because of the remarkable facility with which the alkaloids are demethylated to their respective nor compounds it is probable that the methoxyl group which undergoes demethylation occupies the same position in each molecule. This, in fact, has been established by Crow and Price (12) for melicopine, melicopidine and melicopicine, but the argument need not be reproduced here. The properties of the noralkaloids, such as their color, low basicity, solubility in organic solvents, and insolubility in alkali all point to hydrogen bonding between the hydroxyl and carbonyl groups.

This locates the hydroxyl peri (at C_1) to the acridone oxygen atom. This is supported by the results of wet melting point determinations and by measurements of the infrared absorption spectra of the four isomeric monohydroxytrimethoxy-10-methylacridones derived from the *Melicope* alkaloids. The characteristic O-H band, present in the spectra of the trimethoxyphenols (IX and X) and of the 3-hydroxy compound (3254–3279 $cm.^{-1}$) is absent from the spectrum of normelicopicine. Further support is found in the mechanism of fission of the methylenedioxy ring by alcoholic alkali. Robinson and Robinson (16) regard the reaction of 4-nitro-1,2-methylenedioxybenzene with sodium alkoxides as proceeding by means of ether interchange analogous to that encountered with 2,4-dinitroanisole. That the behavior with alcoholic potash of those acridine alkaloids containing a methylenedioxy group is due to ether interchange in which the methylenedioxy grouping plays only a secondary role is shown by the fact that melicopicine reacts* with ethanolic potash giving 3-ethoxy-1,2,4-trimethoxy-10-methylacridone. Accordingly, Crow and Price (12) formulate the reactions of melicopine and melicopidine as ether interchange involving nucleophilic attack by the alkoxyl ion, and from electronic considerations this attack can take place only at positions 1 or 3. Of these two, position 1 is excluded, first because it is not involved in the methylenedioxy ring in melicopidine but carries a methoxyl group, and secondly because the ethoxydimethoxyphenol (XI) from melicopine can be converted to a *p*-quinone (XIII) still containing the ethoxyl group. Knowing then, that an entering group takes up the 3 position, it may safely be concluded that the nor position is C_1. Finally, Hughes (17) reports that of the 1-,2-,3- and 4-methoxy-10-methylacridones only the 1-methoxy compound is easily demethylated.

With the nor position definitely located, then melicopine must be



XVIII



XIX

1,2-dimethoxy-3,4-methylenedioxy-10-methylacridone (XVIII). Similarly, evoxanthine is 1-methoxy-2,3-methylenedioxy-10-methylacridone (XIX)

* However, the reaction with melicopicine is considerably slower than with melicopine and *ca.* 30% 3-hydroxy-1,2,4-trimethoxy-10-methylacridone is formed as well as the 3-ethoxy compound.

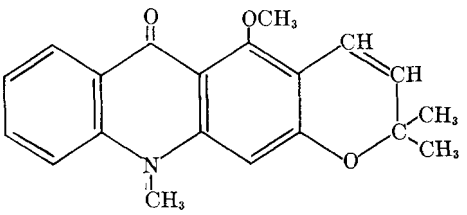
since the phenols obtained by Hughes and Neill (5) by the action of alcoholic potash are converted by alcoholic acid to *o*-quinols and by nitric acid to *o*-quinones. By methylation of these phenols Hughes and Neill obtained 1,2-dimethoxy-3-ethoxy-10-methylacridone, yellow needles m.p. 141–142°, and 1,2,3-trimethoxy-10-methylacridone, pale yellow plates, m.p. 168.5–170°. The identity of the latter compound was confirmed by its synthesis from the appropriate trimethoxydiphenylamine carboxylic acid (18). Evoxanthidine, like xanthevodine, gives 4-quinolone-3-carboxylic acid on oxidation. On methylation it is converted to evoxanthine and consequently must be formulated as 1-methoxy-2,3-methylenedioxy-9-acridone (21).

The two remaining acridine derivatives ("Base m.p. 176–177°" and "Base m.p. 265–267°") isolated from the leaves of *Evodia xanthoxyloides* are best dealt with here because of their relation to evoxanthine. Both carry a hydroxyl substituent at C_1 and this may have arisen by demethylation brought about by the hot aqueous hydrochloric acid employed in the isolation. The first of these substances, $C_{16}H_{15}O_4N$ (m.p. 176–177°), containing two methoxyl groups and a methylimino group, is identical with 1-hydroxy-2,3-dimethoxy-10-methylacridone prepared by demethylating 1,2,3-trimethoxy-10-methylacridone. Further proof was afforded by its oxidation to 3-methoxy-10-methylacridone-1,2-quinone (20). The second, $C_{15}H_{13}O_4N$ (m.p. 265–267°) contains two methoxyl groups but no methylimino group and methylation in acetone solution with methyl iodide and anhydrous potassium carbonate resulted in a mixture of 1,2,3-trimethoxy-10-methylacridone and 1-hydroxy-2,3-dimethoxy-10-methylacridone. The substance is evidently 1-hydroxy-2,3-dimethoxy-9-acridone and this structure was confirmed by synthesis. 3,4,5-Trimethoxydiphenylamine-2′-carboxylic acid was cyclized to 1,2,3-trimethoxy-9-chloroacridine by means of phosphorus oxychloride. Hydrolysis with hydrochloric acid yielded 1,2,3-trimethoxyacridone whose hydrochloride, heated in the dry state at 150–160° for a short time, underwent demethylation to 1-hydroxy-2,3-dimethoxyacridone identical with that isolated from the plant extract (20). The relationship of this substance and 1-hydroxy-2,3-dimethoxy-10-methylacridone to evoxanthine is obvious and of some interest in view of their co-occurrence.

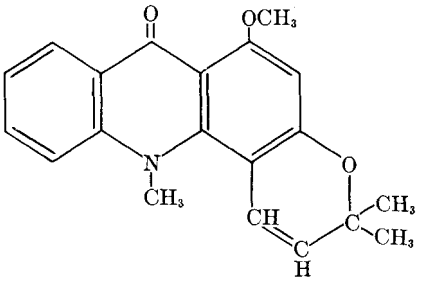
5. The Structure of Acronycine

The formation of 1,3-dihydroxy-10-methylacridone from acronycine shows that the isoprene chain is attached either at C_2 or C_4. With the methoxyl group evidently located at position 1, there remains a choice between structures (XX) and (XXI) for this alkaloid. The data now available do not enable us to distinguish between these alternatives.

A number of other reactions of acronycine have been reported (9, 11), but as these are essentially due to the pyran ring, only a brief description

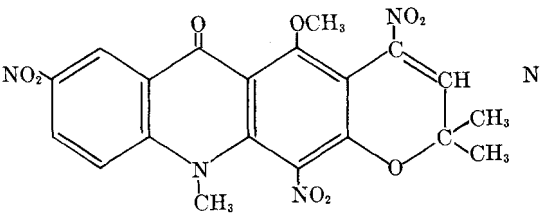


XX

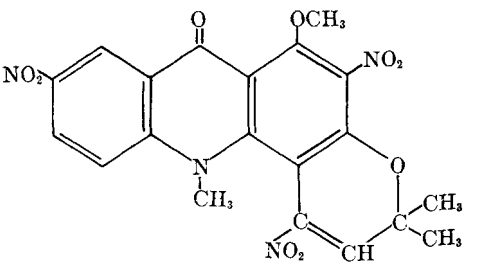


XXI

is necessary. On ozonolysis acronycine gives a phenolic aldehyde, *2- or 4-formyl-1-methoxy-3-hydroxy-10-methylacridone*, pale yellow needles, m.p. 235° (dec), which is readily converted to the dimethoxy compound (II). Acronycine is brominated in chloroform solution giving the hydrobromide of a *monobromoacronycine* (base, golden yellow needles, m.p. 195° solidifying and remelting at 203°). The bromine is attached to one of the unsaturated carbon atoms of the pyran ring, since the bromine-free, acronycinic acid results on oxidation. Ozonolysis of bromoacronycine does not give the phenolic aldehyde but an acid $C_{16}H_{13}O_3N$, m.p. 210–210.5°, presumably *1-methoxy-3-hydroxy-10-methylacridone-2- or 4-carboxylic acid.* The formation of an acid rather than an aldehyde shows that the bromine atom in bromoacronycine is substituted at the α carbon atom. Nitration of acronycine in alcohol gives *mononitroacronycine*, deep yellow prisms m.p. 218°, in which by analogy the nitro group has been assigned to the α position of the pyran ring. Further nitration gives the previously described trinitroacronycine (XXII) or (XXIII).



XXII



XXIII

Dihydroacronycine, $C_{20}H_{21}O_3N$ yellow needles, m.p. 140–141.5°, is obtained when acronycine is hydrogenated over Raney nickel.

III. Conclusion

Because their weakly basic character prevents the use of aqueous solutions except of very low pH, the pharmacological properties of the acridine alkaloids have not been investigated. Their main biological interest will probably lie in the mode of formation in the plant. Since their structure presents yet another instance of the recurrent anthranilic acid pattern, there is presumably a biogenetic relation with evodiamine and rutaecarpine and the quinoline alkaloids of the angostura group as well as with the co-occurring furanoquinolines. The taxonomic significance of this grouping within the Rutaceae is by no means clear, but it is evident that the family is one which should amply repay further study. In that event it is to be expected that additional examples of acridine alkaloids will be found in related species or genera from other parts of the world.

Hughes and Ritchie (22) have pointed out that in all the acridine alkaloids discovered up to date, alkoxyl substituents are present in only one of the two benzene nuclei and that the 1 and 3 positions are always substituted. On the basis of these facts they suggest a scheme for the biogenesis involving the following steps:

(a) Condensation of *o*-aminobenzaldehyde (or a precursor) with phloroglucinol (or a precursor) to form 1,3-dihydroxyacridine,
(b) Oxidation of the acridine to an acridone,
(c) Nuclear oxidation to 1,2,3-trihydroxy- and 1,2,3,4-tetrahydroxyacridone,
(d) Methylation and/or methylenation.

These reactions need not necessarily occur in the order cited, for instance, a hydroxy derivative of phloroglucinol might be involved in the biosynthesis of evoxanthine or melicopicine. The reaction between phloroglucinol and *o*-aminobenzaldehyde, first investigated by Eliasberg and Friedländer (23) proceeds smoothly in dilute aqueous solution at room temperature to give 1,3-dihydroxyacridine. Hughes and Ritchie found that the yield varied with the pH as follows:

pH	4	5	6	7	8	9	10	11	12	13
Yield %	0	0	5	28	90	87	87	83	81	43

Attempts to effect nuclear oxidation of 1,3-dihydroxyacridine, 1-hydroxy-3-methoxy- or 1,3-dihydroxy-10-methylacridone were unsuccessful but methylation of the first named with diazomethane gave a nearly quantitative yield of 1,3-dimethoxyacridine, the methosulfate of which was oxidized by hot alkaline ferricyanide, also in nearly quantitative yield, to 1,3-dimethoxy-10-methylacridone. 1,2,3,5-Tetrahydroxybenzene condensed with *o*-aminobenzaldehyde in hot alkaline solution in the absence of air (under milder conditions much amorphous material resulted) and the crude

product, after methylation gave only 1,2,3-trimethoxyacridine in 40% yield. Oxidation of the methosulphate with alkaline ferricyanide gave 1,2,3-trimethoxy-10-methylacridone identical with that obtained from evoxanthine. The ability of phenols to condense with *o*-aminobenzaldehyde to an acridine derivative is evidently limited to those with three hydroxyl groups in the 1,3 and 5 positions since pyrogallol and a number of mono- and dihydric phenols failed to react.

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21. J. R. Cannon, G. K. Hughes, K. G. Neill, and E. Ritchie, *Australian J. Sci. Research*, **A** (in the press).
22. G. K. Hughes and E. Ritchie, *Australian J. Sci. Research*, **A** (in the press).
23. J. Eliasberg and P. Friedländer, *Ber.* **25**, 1752 (1892).

Addendum.

In addition to the noralkaloids listed on p. 356, the following have been described. *Norxanthevodine* ($C_{15}H_{11}O_5N$, orange, m. p. 272-273°), *norevoxanthidine* ($C_{14}H_9O_4N$, golden, m. p. 327°) and *1-hydroxy-3-methoxy-10-methylacridone* ($C_{15}H_{13}O_3N$, yellow, m. p. 175-176°). They were prepared by heating the hydrochlorides of the alkaloids at 170-180°.

CHAPTER XIII

The Indole Alkaloids

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I. Introduction

This group of alkaloids includes some which are widely used, such as the ergot bases and strychnine. However, the latter together with the remaining *Strychnos* alkaloids are described in a separate chapter because of the voluminous literature concerning them. The group also includes gramine, which affords an example of an alkaloid that is easily synthesized and can be used in synthetic organic chemistry as a starting material for the preparation of compounds otherwise accessible only with difficulty. A further point of interest is that the indole alkaloids lend themselves remarkably well to the interpretation of their formation in the plant by biosynthesis from the amino acid tryptophan.

Indole, the index compound of the group occurs in plants, probably as a breakdown product from tryptophan. It occurs in the distilled oil obtained from jasmine flowers by enfleurage (1) and, together with skatole in the decaying wood of *Celtis reticulosa* Miq (2). Numerous other occurrences of indole have been reported but since indole is not an alkaloid, these are not given here in detail. A few of the alkaloids to be described are simple derivatives of indole, but most are much more complex and the latter are more widely distributed than the former.

In this chapter the various groups of alkaloids will be classified according to the position of the substituents and the degree of substitution in the pyrrole part of the indole nucleus. The index compounds with substituents at position 3 will be in group I, those with substituents at positions 2 and 3 will be in group II, those with substituents at positions 1, 2 and 3 will be in group III, while those alkaloids the structure of which has not been fully determined will constitute group IV. The groups will be further extended to accommodate alkaloids carrying substituents in the benzene ring as well as those already specified for each group. Thus the order of presentation will be: (1) abrine, (2) hypaphorine, (3) gramine, (4) the ergot alkaloids, (5) the alkaloids of *Peganum harmala*, (6) those of *Evodia rutaecarpa*, (7) the yohimbe alkaloids, (8) the quebracho alkaloids, (9) the alkaloids of *Rauwolfia* species, (10) the alkaloids of *Gelsemium* species, (11) the alkaloids of *Calycanthaceae*, (12) those of the Calabar bean, (13) the iboga alkaloids, (14) the *Alstonia* alkaloids, (15) those of *Geissospermum vellosii*, (16) quinamine and cinchonamine, and finally, (17) C-dihydrotoxiferine-I.

II. The Simple Bases

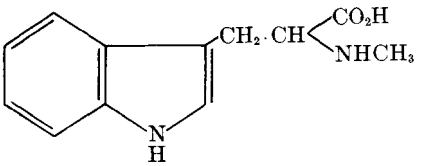
The simpler alkaloids contain one substituent only and this is located in the 3-position of the indole nucleus. They include abrine, hypaphorine and the alkaloids of barley and *Arundo donax* L., i.e., gramine and donax-

arine. Of these, however, knowledge of the constitution of donaxarine is still wanting.

1. Abrine

The name abrine was first applied to the impure substance isolated from the seeds of *Abrus precatorius* L. (3). Later, the same name was used to designate a pure crystalline base also isolated from the seeds (4, 5). The alkaloid is accompanied in the plant by a toxic protein (6).

Abrine, $C_{12}H_{14}O_2N_2$ (4), is an amino acid which is decarboxylated on heating and gives rise to β-3-methylaminoethylindole. Since abrine is optically active and forms nitroso and acetyl derivatives, indicating the presence of a secondary nitrogen atom, it has been assumed to be methyltryptophan (I). This structure has been confirmed by the results of the



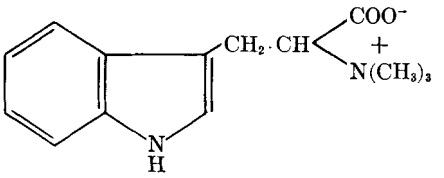
I

methylation of *l*-tryptophan and of abrine with methyl iodide and methanolic sodium hydroxide. In each case, the same ester methiodide is obtained (7, 8). The racemic form of abrine (α-methylamino- β-3-indolylpropionic acid) has been synthesized by condensation of indole-3-aldehyde with 1-methylhydantoin, reduction of the product and hydrolysis of the reduced substance (9, 10).

2. Hypaphorine

The alkaloid hypaphorine was first isolated from the seeds of *Erythrina subumbrans* (Hassk.) Merrill (*Erythrina hypaphorus* Boerl.) (11). It occurs also in numerous other species of *Erythrina* and it has been obtained from *E. variegata* var. *orientalis* (L) Merrill (*E. indica* Lam.) (12, 13), where it is present as the nitrate (14), *E. crista-galli* L. (15), *E. sandwicensis* Degener (16), *E. glauca* Willd., *E. folkersii* Krukoff and Moldenke, *E. velutina* Willd., *E. macrophylla* DC., *E. velutina* forma *aurantiaca* (Ridl.) Krukoff, *E. grisebachii* Urb., *E. fusca* Lour. (17), *E. americana* Mill. (18), *E. costaricensis* M. Micheli, *E. dominguezii* Hassler, *E. acanthocarpa* E. Mey. and *E. rubrinervia* HBK (18a). It is also possible, although not definite, that hypaphorine may occur in beetroot shoots (19). Numerous species of Erythrina contain alkaloids, beside hypaphorine, which possess a physiological action similar to that of curare. Because of their importance and the uncertainty of their structure these alkaloids will be dealt with in a separate chapter.

Hypaphorine, $C_{14}H_{18}O_2N_2$ (20), forms crystalline salts and is readily isolated by crystallization of its hydrochloride or its nitrate. It is an optically active substance which, on heating with potassium hydroxide, is split into indole and trimethylamine. Hypaphorine, therefore, was assigned the structure II (20) (α-trimethyl- β-indolylpropiobetaine), which has been confirmed by synthesis.



II

l-Tryptophan by treatment with methyl iodide and methanolic sodium hydroxide is converted to the iodide of methyl α-trimethylamino-β-indolepropionate and this is hydrolyzed to the corresponding betaine identical with hypaphorine (II) which is thus the methylbetaine of methyl abrine (21).

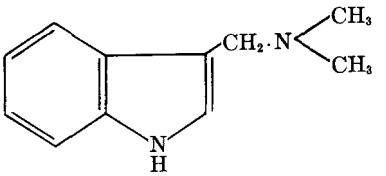
3. Gramine

The alcoholic extract of chlorophyll-deficient barley mutants contains a basic substance which has been designated gramine (22). The concentration of this base in barley leaves increases from the base to the tip of the leaf and the quantity which remains constant for the first ten days of germination disappears after one month (23). It was originally believed that barley mutants that are not deficient in chlorophyll did not contain this substance (24, 25) and consequently that gramine was a genetic substance which could be related to the chlorophyll factor (25). However, it is now known that gramine occurs in normal sprouting barley (23, 26) so that the original interpretation of the role of gramine no longer holds.

Gramine is not specific to barley and the alkaloid donaxine, which has been isolated from *Arundo donax* (Gramineae) (27) has been found to be identical with it (28, 29). Besides gramine, *Arundo donax* contains another crystalline base, donaxarine and perhaps a third which, however, has not been sufficiently characterized (30, 31).

Gramine, $C_{11}H_{14}N_2$ (32), is a monoacidic base containing two methyl groups attached to nitrogen and giving an ultraviolet absorption spectrum indicative of the indole nucleus (32). It is optically inactive and contains one active hydrogen (Zerewitinow) (27). Distillation of the base with zinc dust gives rise to skatole (28), thus confirming the presence of the indole nucleus. Because of the possibility of substituents wandering between the α- and β-positions of a substituted indole, the isolation of skatole under drastic conditions was not considered as definite evidence

of substitution in the 3-position and gramine was first assumed to be a 2-substituted indole (28), and later 3-methyl-2-dimethylaminoindole (33). However, no acetic acid is produced when gramine is oxidized by the Kuhn-Roth method (28), so that no *C*-methyl group can be present and therefore, the substituent on the indole nucleus must be $-CH_2NMe_2$. This substituent is not located in position 2 of the indole nucleus since synthetic 2-dimethylaminomethylindole is different from gramine although it has the same ultraviolet absorption spectrum (34). The base must, therefore, be 3-dimethylaminomethylindole (III) and this conclusion is supported by the degradation of gramine methiodide to 3-methoxymethylindole with methanolic sodium hydroxide and to 3-ethoxymethylindole with ethanolic sodium hydroxide (31). The structure of gramine was established by a fortuitous synthesis. The interaction of 3-indolemagnesium iodide and dimethylaminoacetonitrile gives rise to an oxygen-free base identical with gramine (35), thus confirming formula III. Gramine has also been synthe-

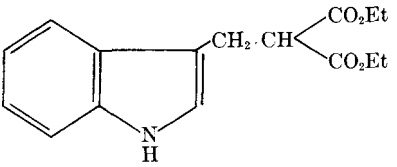


III

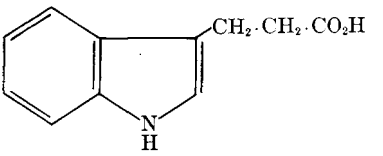
sized in almost quantitative yield by an application of the Mannich reaction, i.e., the interaction of indole, formaldehyde and dimethylamine in acetic acid at room temperature (36).

Chemical Reactions of Gramine. The alkaloid is of interest chemically because of the relative lability of its dimethylamino group which makes possible its use in alkylation reactions. As already mentioned the methiodide of the base can be converted into 3-methoxymethylindole (31). On the other hand if the methiodide is treated with ethyl sodiomalonate, it gives rise to ethyl β-3-indolyl-α-carbethoxypropionate (IV) which by hydrolysis and decarboxylation is converted to β-3-indolylpropionic acid (V). This reaction is general with compounds containing an active methylene group (37). The condensation of gramine methiodide with sodioacetaminomalonic ester gives rise to a 63% yield of ethyl-α-acetamino-α-carbethoxy-β-(3-indolyl)-propionate (VI), which by saponification and subsequent decarboxylation and hydrolysis can be converted into *dl*-tryptophan in 81% yield (38, 39). This last synthesis has been improved by the discovery that gramine itself, when heated in toluene with acetaminomalonic ester in the presence of a small amount of powdered sodium hydroxide, produces a 90% yield of the ester VI (40). Tryptophan can also be obtained more directly by heating gramine with ethyl nitroacetate

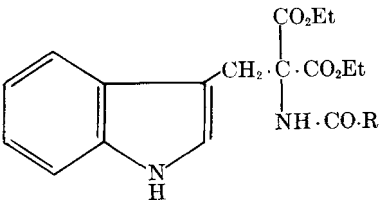
in xylene solution. The resulting ethyl α-nitro-β-(3-indolyl)-propionate is reduced catalytically to the corresponding amino compound which on



IV



V



VI

saponification yields *dl*-tryptophan (41). Gramine can also be converted to α-ethyltryptamine by condensation with nitropropane and catalytic hydrogenation of the product (42).

4. Donaxarine

Donaxarine, $C_{13}H_{16}O_2N_2$ (31), is a minor alkaloid accompanying gramine in the leaves of *Arundo donax*. It is a nonphenolic base which contains a methylimino group and one active hydrogen (Zerewitinow) but no *O*-methyl group. It produces no color with Ehrlich's reagent or in the Hopkins-Cole test (glyoxylic acid reagent) whereas gramine gives positive reactions in both cases. Donaxarine, however, shows the pine wood reaction (31).

III. The Ergot Alkaloids

Ergot is a drug consisting of the sclerotium of a fungus, *Claviceps purpurea*, which grows parasitically on the pistils of many grasses, but is obtained almost exclusively from rye. It has long been used in medicine because of its action on the uterus and on the vasomotor center and, on that account has been, in the course of the nineteenth and early twentieth centuries, the subject of a considerable number of investigations. In these investigations, which are mostly of no consequence today except from an historical point of view, the pharmacological action of ergot was attributed by some to acidic substances, by others to alkaloids. However, all the so-called alkaloids reported during that period such as ecboline, ergotine (43, 44) and cornutine (45) were amorphous, nonhomogeneous substances.

An historical account of this older work has been given by Barger (46, 47). The first real progress in this problem is due to Tanret (48, 49, 50) who isolated a crystalline alkaloid which he named ergotinine. The names picrosclerotine (51), sclerocrystalline (52), and secaline (53) that appeared in the subsequent literature are synonyms of ergotinine.

Eventually, ergotinine was shown to have but slight, if any, physiological activity, whereas the mother liquor from its crystallization yielded a highly active, amorphous, basic substance (45, 54–57) which was purified by the preparation of crystalline salts and named ergotoxine by Barger and Carr (58, 59) and hydroergotinine by Kraft (60). Ergotoxine is closely related to ergotinine, since the two bases could be interconverted (58, 60). Ergotoxine itself was finally crystallized (61) and a third alkaloid, ψ-ergotinine was isolated which could be converted both into ergotinine and into ergotoxine (62). A new pair of alkaloids, ergotamine and ergotaminine, was reported in 1920 (63, 64, 65) and found also to be interconvertible. Ergotamine has the same physiological activity, not only qualitatively but quantitatively, as ergotoxine. It acts paralytically on the sympathetic system, causing contraction of plain muscular tissue and a slight decrease in blood pressure, and its action on the uterus is exerted even at greater dilutions (66, 67, 68). Ergotamine and ergotaminine do not seem to occur in rye ergot, but are found in other ergots such as that growing on tall fescue (Fescuta) (61, 69) and on marrom grass (69).

The fact that the characteristic physiological effect of ergot extracts is not the same as that caused by ergotoxine and ergotamine (70) led to the discovery of a water-soluble alkaloid. This alkaloid, due to its almost simultaneous discovery in several laboratories, has been designated by numerous names, i.e., ergometrine (70, 71, 72), ergobasine (73, 74, 75), ergostetrine (76), ergotocine (78–84) and ergonovine which is the name used in *Chemical Abstracts*. The first of these names will be adhered to here. Like ergotoxine and ergotamine, this alkaloid can be transformed into a dextrorotatory isomer, ergometrinine (85). Another alkaloid, first described under the name ergoclavine (86, 87, 88), has been shown to consist of a crystalline complex of two interconvertible alkaloids, ergosine and ergosinine (89, 90). The dextrorotatory isomer, ergosinine, possesses the marked property of forming crystalline compounds similar to ergoclavine with other ergot alkaloids and this led to the discovery of the base ergocristine, which is isomeric with ergotinine. Ergocristine is levorotatory and can be converted into the isomeric dextrorotatory ergocristinine (91, 92). From the foregoing account, it is obvious that the ergot alkaloids occur in pairs, each comprising a levorotatory base and its dextrorotatory isomer. There was an exception offered by ergotoxine, the empirical formula of which appeared to differ from that of ergotinine, and by ψ-ergotinine which could be converted into both ergotinine and ergotoxine.

This anomaly which was further complicated by the fact that ergocristine and ergocristinine are isomeric with ergotinine, has recently been explained away by the discovery that ergotoxine is not homogeneous, but a complex mixture consisting not only of the known ergocristine but also of two new alkaloids, ergocryptine and ergocornine (93). Both ergocryptine and ergocornine can be converted to their respective dextrorotatory isomers, ergocryptinine and ergocorninine by the action either of boiling methanol or of alcoholic alkalies (93). Thus, so far six pairs of interconvertible alkaloids have been isolated from ergot. These are: ergotamine — ergotaminine, ergosine — ergosinine, ergometrine — ergometrinine, ergocristine — ergocristinine, ergocryptine — ergocryptinine, and ergocornine — ergocorninine.

The foregoing alkaloids are accompanied in ergot by a number of simple bases and amino acids, some of the latter being probably derived from the enzymatic hydrolysis of the major alkaloids. These substances include tyramine (*p*-hydroxy-β-phenylethylamine) (94, 95), leucine and aspartic acid (46, 96, 97), betaine (46), tyrosine, histidine and tryptophan (98), as well as histamine (4-β-aminoethylglyoxaline) (99–102). Putrescine, cadaverine, isoamylamine (103) have also been reported together with trimethylamine, choline, acetylcholine (104), secaleaminosulphonic acid (ergotic acid), $NH_2 \cdot C_{15}H_{26}O_{15} \cdot SO_3H$ (45, 60, 97), agmatine (δ-guanidylbutylamine) (105, 106, 107) and ergothioneine (thiolhistidinebetaine) (108-113). It is of interest to note that ergothioneine also occurs in pig's blood (114–117).

Although the ergot of commerce was formerly collected from rye crops, attempts to cultivate it have proved successful (118, 119) and the alkaloids are now largely prepared from material obtained by cultivation. The alkaloid content in the individual sclerotia is not constant and many have been found, in the course of numerous analyses, to be entirely devoid of alkaloid while others contained quantities which in some instances exceeded 1% (120). The average content varies from 0.025 to 0.4% (121).

The ergot alkaloids give characteristic color reactions apparently due to their common component, lysergic acid. With dimethylaminobenzaldehyde, they produce a deep blue color (122a–132). A solution of the base in acetic acid containing a trace of ferric chloride shows a cornflower blue coloration (Keller test). A violet-blue color is obtained when the ether-soluble portion of an ergot extract is dissolved in acetic acid and 4 cc. of the solution is added to 4 cc. of 50% sulfuric acid. A comparison of the color developed, with a standard, enables one to use this test quantitatively (122). Galenical preparations and extracts of ergot are unstable and deteriorate on standing (133–138) and numerous stabilization and assay methods have been described. The assay methods are based either on color (122, 132, 139, 140, 140a and b), or biological tests. The latter are based either

upon the reversal by ergot preparations of the action of adrenaline on strips of the isolated rabbit uterus (141, 142), or upon the modification of the cockscomb caused by injection of liquid preparations of ergot (143). Some of the tests can be used for the determination of specific alkaloids (144–148). More recently, the ethanesulfonates of the alkaloids have been used in both colorimetric and biological assays (149).

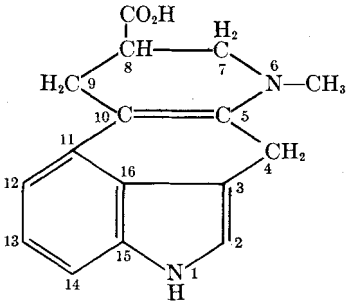
The six pairs of ergot alkaloids are all similar in this respect that each comprises a levorotatory, physiologically active component while the other member of the pair is dextrorotatory and physiologically almost inert. Furthermore, the two components of each pair are interconvertible. The dextrorotatory component is converted into its levorotatory isomer by the action of acetic acid or alcoholic phosphoric acid (150), whereas the transformation is reversed by the action of boiling methanol or of alcoholic alkalies on the levorotatory base (93). There is still another property shared by all the ergot alkaloids: on alkaline hydrolysis, each base gives rise to the same scission product, i.e., lysergic acid (151). These bases also exhibit the remarkable property of forming complexes with each other. Such complexes always consist of an *l*-base and a *d*-base and never occur between two *l*-bases or two *d*-bases (152).

1. Lysergic Acid

Lysergic acid, $C_{16}H_{16}O_2N_2$ (151), was first obtained as one of the products of the action of methanolic potassium hydroxide on ergocristine (ergotinine) (151). It is a dextrorotatory substance which still gives the characteristic blue Keller test of the ergot alkaloids. It is only slightly soluble in the usual neutral organic solvents, but quite soluble in pyridine. When reduced with sodium in amyl alcohol (153), lysergic acid is converted to dihydrolysergic acid ($C_{16}H_{18}O_2N_2$) and both acids can be esterified. Reduction of the methyl ester of lysergic acid with sodium in butyl alcohol produces a mixture of two forms of the corresponding reduced alcohol, i.e., α-dihydrolysergol and β-dihydrolysergol ($C_{16}H_{20}ON_2$) (154). Furthermore, lysergic acid contains one methylimino group and forms salts with only one equivalent of acid. Although no evidence could be obtained for the presence of a secondary amino group, yet the Zerewitinow test shows the presence of an active hydrogen (153). Hence, lysergic acid is an amino acid containing one readily reducible double bond and a tertiary nitrogen atom carrying a methyl group, while its second nitrogen is present in a pyrrole or indole group. The acid, when heated to 210–230°, decomposes with the copious evolution of CO_2 and methylamine, so that it is unlikely that the methyl group could be situated on the pyrrole nitrogen and this is confirmed by the fusion of dihydrolysergic acid with potassium hydroxide at 300° in an atmosphere of nitrogen which produces an indole (154) eventually shown to be 3 :4-dimethylindole (155). Before the indole was

definitely identified and on the basis of the facts already established, lysergic acid was assumed to be a carboline derivative. Synthetic experiments, however, soon proved this to be erroneous (154, 156, 157). Ultraviolet absorption spectra of lysergic acid and its derivatives support the conclusion that the indole nucleus is present in the molecule and also indicate that the readily reducible double bond is conjugated with one of those of the indole nucleus (158, 159).

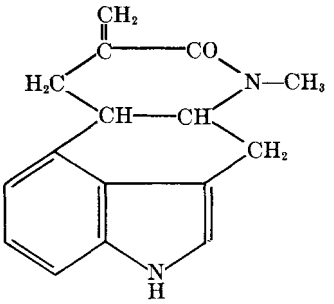
Since catalytic hydrogenation reveals no other double bond than the easily reducible one and those present in the indole nucleus, lysergic acid must consist of a tetracyclic structure. The fusion of dihydrolysergic acid with potassium hydroxide gives rise not only to 3:4-dimethylindole, but also to 1-methyl-5-aminonaphthalene and methylamine (154, 160). Since methylamine is obtained almost quantitatively, the amino group of the α-naphthylamine must be derived from the indole nitrogen and this restricts the position which can be assigned to the fused pyrrole ring in



VII

relation to the two rings liberated as the naphthalene nucleus. Furthermore, the oxidation of lysergic acid with nitric acid produces a tricarboxylic acid, $C_{14}H_9O_8N$, containing an *N*-methyl group (161) and this acid on distillation with soda lime, yields quinoline. The ring containing this basic nitrogen must, therefore, be the fourth ring of the molecule which can then be represented by structure VII (160, 162). The carboxylic group was first assigned to position 4, then to 7 (162) and subsequently to 8. Position 8 was finally accepted on account of the behavior of dihydrolysergic acid on pyrolysis. When this last acid is heated to 350° it undergoes a chemical change giving rise to a neutral, unsaturated substance, $C_{16}H_{16}ON_2$, m.p. 305 −7°, $[\alpha]_D^{25}$ −219° (in pyridine) which, on hydrogenation, is converted to a neutral dihydro derivative, $C_{16}H_{18}ON_2$, m.p. 336° (dec). It is well known that β-amino acids differ from the α-amino acids in decomposing readily when heated, into unsaturated acids and ammonia. If the carboxylic group occupies position 8, then lysergic acid is a β-amino acid and this is in agreement with the formation of the above neutral com-

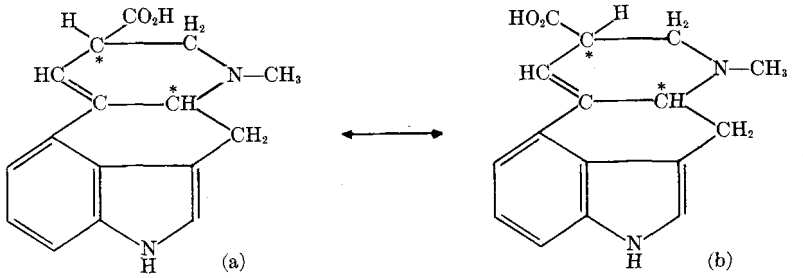
pound which must be interpreted as an unsaturated cyclic amide represented by formula VIII (163) or one in which the $-CH_2C(=CH_2)CO-$ group is present as $-CH=C(CH_3)CO-$.



VIII

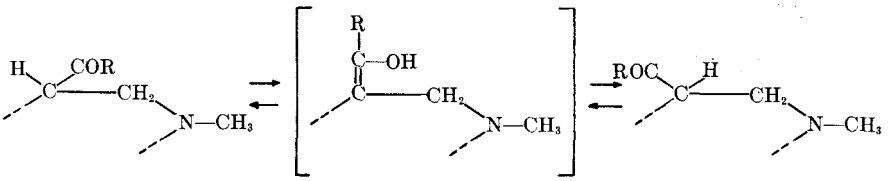
There are five positions in the structure assigned to lysergic acid (VII) in which a double bond could be located (Δ^{7-8}, Δ^{8-9} Δ^{4-5}, Δ^{5-10} and Δ^{9-10}), but positions Δ^{7-8} and Δ^{8-9} are incompatible with the ultraviolet absorption spectrum of the acid which indicates that the double bond is conjugated with the indole nucleus (164). The interconversion of ergot alkaloids from levorotatory to strongly dextrorotatory bases is due to a change taking place in the lysergic acid part of the molecule since no such interconversion is possible in the dihydro alkaloids (162) and since it has been shown that lysergic acid (dextrorotatory) can be isomerized to a more strongly dextrorotatory acid, isolysergic acid (165). Methanolic solutions of the alkaloids mutarotate (166), becoming dextrorotatory or more so. Furthermore, if the levorotatory alkaloids (ergotamine, ergometrine, etc.) are first hydrogenated and then hydrolyzed, dihydrolysergic acid (α-dihydrolysergic acid) is produced, whereas the similar treatment of a base of the dextro series yields dihydroisolysergic acid (I) (γ-dihydrolysergic acid (162) and/or an isomer, dihydroisolysergic acid (II) depending on the catalyst used in the hydrogenation (162a). Whereas the reduction with sodium in butyl alcohol of the methyl ester of lysergic acid produces α- and β-dihydrolysergols, the similar reduction of the methyl ester of isolysergic acid gives rise to dihydroisolysergol (γ-dihydrolysergol). These facts were interpreted as indicating that the reducible double bond in lysergic acid occupied a different position than in isolysergic acid and that the isomerization of the acids was due to a wandering of the double bond. Since the basicity of the $N-CH_3$ group is equally strong in isolysergic acid and dihydrolysergic acid, but stronger than in lysergic acid, it was assumed that the double bond was further removed from the basic group in isolysergic acid than in its isomer (167). The two positions consistent with

this are Δ^{5-10} in lysergic acid and Δ^{9-10} in isolysergic acid (see formula VII) (164). However, this formula for lysergic acid with the double bond at Δ^{5-10} contains one asymmetric C atom only. It has recently been pointed out that the lactam VIII obtained from dihydrolysergic acid (163) and the similar lactam formed from lysergic and isolysergic acids by the action of acetic anhydride (163a) are both optically active and consequently that lysergic and isolysergic acids each contain two asymmetric C-atoms (163a). The formula with the double bond at Δ^{5-10} is therefore untenable. The ultraviolet absorption spectrum of the lactam obtained from both lysergic and isolysergic acids shows that the new double bond created in its formation is conjugated with that originally present in the acids (163a), and therefore position Δ^{4-5} can be eliminated, thus leaving Δ^{9-10} as the only possible location for the double bond. It is concluded that the isomerization does not involve a shift of the reducible double bond, which retains position Δ^{9-10} in both acids, but a reorientation of the carboxylic group so that lysergic acid (a) and isolysergic acid (b) are represented by IX (163a), in which C5 and C8, marked with an asterisk, are the opti-



IX

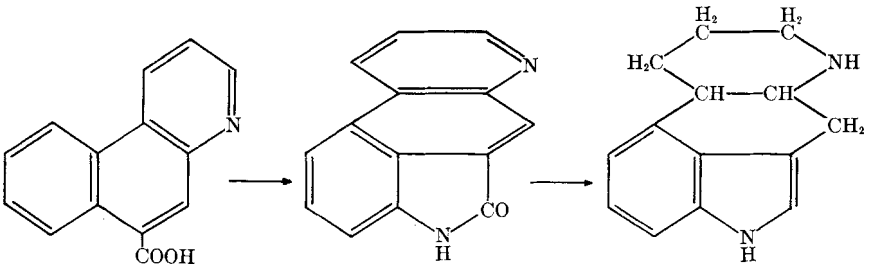
cally active centers. All derivatives of the acids in which the carboxylic group is replaced by another substituent can no longer isomerize and it is assumed that the isomerization of the alkaloids takes place thus (163a):



Because of the two asymmetric C-atoms in the acids two pairs of optically active isomers are possible and these are in fact known in the two optically active lysergic acids and the two optically active isolysergic acids (163a, 168). The C5 location of one of the two optically active centers finds some confirmation in the results of the Hofmann degradation of 6-*N*-methyl-

8-acetylaminoergolene and 6-*N*-methyl-8-acetyl-aminoisoergolene (168a). Hence, of the two series of ergot alkaloids, the one (ergocristine, ergotamine, etc.) consists of derivatives of *d*-lysergic acid while the other (ergocristinine, ergotaminine, etc.) consists of derivatives of *d*-isolysergic acid (164, 168, 169).

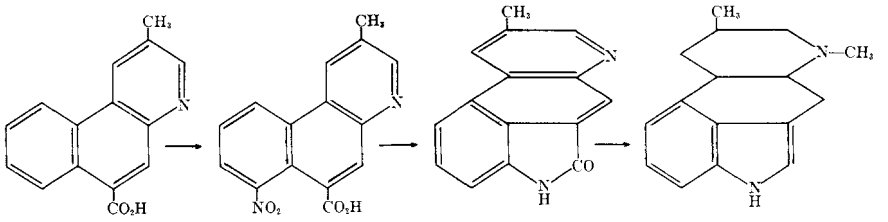
The structure (IX) assigned to lysergic acid, with reservations as to the position of the double bond, has been confirmed by synthesis. The nuclear structure assumed to be present in lysergic acid was synthesized as follows: 1,8-naphthalic acid is converted by nitration into 3-nitro-1-naphthoic acid which after reduction to 3-amino-1-naphthoic acid is converted by means of the Skraup synthesis into 5,6-benzoquinoline-7-carboxylic acid X. This acid on nitration gives mainly 3′-nitro-5,6-benzoquinoline-7-carboxylic acid which is reduced to 3′-amino-5,6-benzoquinoline-7-carboxylic acid and this, on treatment with hydrochloric acid, readily



X XI XII

forms the benzoquinoline lactam XI. Reduction with sodium in butyl alcohol converts the lactam into the desired product XII which it has been suggested to designate by the trivial name "ergoline." The color reactions of ergoline are very similar to those of lysergic acid although the color produced in the Keller test is more of a violet-blue than a deep pure blue (170–172). The color reactions of 6-methylergoline (*N*-methylergoline are even closer to those of lysergic acid. The former is obtained when the lactam XI is converted to the quinolinium methiodide and this salt is first hydrogenated catalytically and subsequently reduced with sodium in butyl alcohol (173, 174). A direct comparison of 6-methylergoline with a degradation product of lysergic acid could not be made since dihydrolysergic acid does not decarboxylate on pyrolysis, but loses water, giving rise to the unsaturated lactam (VIII). However, this lactam when hydrogenated catalytically produces a saturated lactam which is converted by further reduction with sodium in butyl alcohol to 6,8-dimethylergoline XVI (175, 168a). The synthesis of this compound is carried out by a modification of the method already described for the preparation of 6-methylergoline. 3-Amino-1-naphthoic acid and the $\alpha\gamma$-diethyl ether

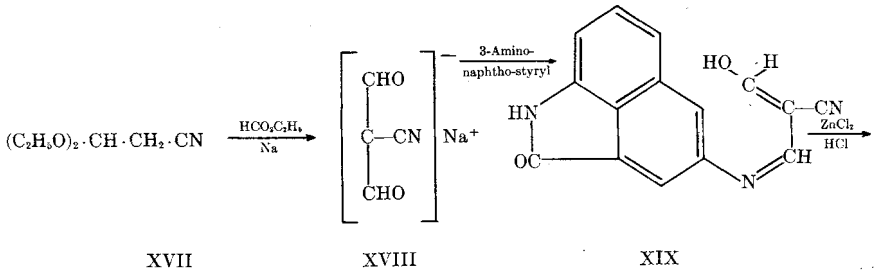
of β-methylglycerol in the Skraup reaction give rise to 3-methyl-5,6-benzoquinoline-7-carboxylic acid XIII which can be nitrated to the 3′-nitro derivative XIV. Reduction of the nitro group followed by lactamization



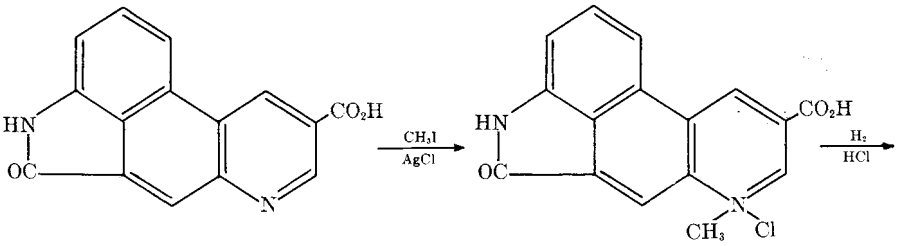
XIII XIV XV XVI

yields the lactam of 3′-amino-3-methyl-5,6-benzoquinoline-7-carboxylic acid XV, and this is converted to the methochloride via the methiodide. The methochloride on successive catalytic hydrogenation and reduction with sodium in butyl alcohol produces 6,8-dimethylergoline XVI (176), identical in every respect with the 6,8-dimethylergoline produced from *dl*-dihydrolysergic acid (168).

Synthesis of Dihydrolysergic Acid. Finally, dihydrolysergic acid itself was synthesized (177). Cyanoacetal (XVII), when allowed to react with



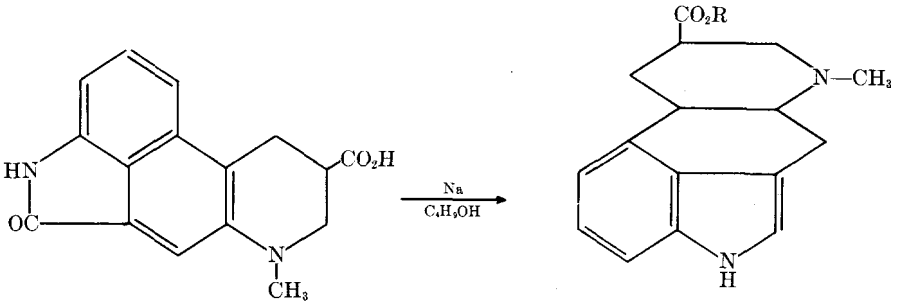
XVII XVIII XIX



XX XXI

ethyl formate and sodium in ether, gives rise to the sodium derivative of cyanomalonic dialdehyde (XVIII) which condenses with 3-aminonaphtho-

styril to form 2-cyano-2-formylethyliden-3-aminonaphthostyril (XIX). This last compound is converted to 3′-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam (XX) by fusion with zinc chloride and hydrolysis of the mixture of basic products with hydrochloric acid. The methochloride



XXII XXIII

(XXI) of the lactam is hydrogenated in hydrochloric acid solution to 3′-amino-*N*-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic acid lactam (XXII) and this on reduction with sodium in butyl alcohol is converted to dihydro-*dl*-lysergic acid (XXIII, R = H).

Hydrolysis of the ergot alkaloids with hydrazine splits off the lysergic acid but leaves the polypeptide chain intact, although hydrazine reduces to a fatty acid the third structural unit which, by acid hydrolysis, is obtained as an α-keto-acid. Thus, hydrolysis of ergotamine yields propionyl-*l*-phenylalanyl-*l*-proline while ergocristine, ergocryptine, and ergocornine yield respectively isovaleryl-*l*-phenylalanyl-*l*-proline, isovaleryl-*l*-leucyl-*l*-proline and isovaleryl-*l*-valyl-*l*-proline (177a). It is, however, possible by careful partial hydrolysis with one equivalent of aqueous-alcoholic potassium hydroxide to split the molecule so that the peptide part contains the keto acid. Under these conditions ergotamine, ergocristine and ergocornine yield respectively pyruvoyl-*l*-phenylalanyl-*l*-proline, dimethyl-pyruvoyl-*l*-phenylalanyl-*l*-proline and dimethylpyruvoyl-*l*-valyl-*l*-proline (177b). It is curious and noteworthy that while thermal splitting and acid hydrolysis of the alkaloids produce *d*-proline, hydrolysis with hydrazine gives rise to *l*-proline. These polypeptides have been prepared synthetically (177a) as well as a number of peptides of both lysergic and dihydrolysergic acids (177c).

A second synthesis of dihydrolysergic acid has been reported recently. Condensation of 4-amino-benz [c,d] oxindole with ethoxymethylenemalonic ester followed by cyclization and a two-step reduction yielded dihydro-nor-lysergic acid. Since the product contains three asymmetric carbon atoms there are three stereoisomers possible and all three have been iso-

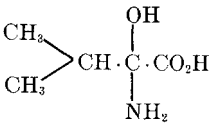
lated. The synthesis, therefore, produced *dl*-dihydro-nor-isolysergic acid-I, *dl*-dihydro-nor-lysergic acid and *dl*-dihydro-nor-isolysergic acid-II (177d). The first two have been converted to the corresponding *N*-methyl acids by the action of heat on their methyl esters. The resulting racemic acids were resolved into their optical isomers through their norephedrides (177e).

Possible starting materials for the synthesis of lysergic acid have been prepared (177f, 177g), although that synthesis has not yet been achieved. In the course of preliminary studies directed towards that synthesis, it has been shown that the lactamic carbonyl in the intermediate naphthostyril can be reduced with lithium aluminum hydride without simultaneous reduction of the double bonds (177h).

2. Ergocristine–Ergocristinine

Ergocristine–ergocristinine, $C_{35}H_{39}O_5N_5$ (91). These alkaloids have been shown (93) to be the main constituents of the impure bases formerly known as ergotoxine (58), ergotinine (48) and ψ-ergotinine (62). The relevant investigations carried out before 1943 (93) with this alkaloid involved the use of ergotinine, but since this base consisted predominantly of ergocristinine, the conclusions hold, especially as pure ergocristinine yields the same degradation products (178). When the alkaloid fraction formerly known as ergotoxine is dissolved in absolute ethanol and the solution added to absolute ethanol containing two equivalents of di(*p*-toluyl)-*l*-tartaric acid per equivalent of base, the ergocristine salt, which is almost insoluble, crystallizes out. Ergocristine dissolves in 40 parts of boiling benzene, but is only very sparingly soluble in ethanol and methanol (93). Ergocristinine (ergotinine) contains no methoxyl group but contains one methylimino group (179, 180). Oxidation with nitric acid yields *p*-nitrobenzoic and benzoic acids (180), while the action of potassium permanganate produces benzoic acid as well as the tricarboxylic acid ($C_{14}H_9O_8N$) originating from the lysergic acid part of the molecule (161). Ergocristinine, therefore, contains a benzene ring attached to the molecule through one carbon atom only. Furthermore, heating the base with aqueous sodium hydroxide liberates one mole of ammonia (180), while the action of heat yields dimethylpyruvic acid amide (181). The presence of the amide grouping thus revealed is confirmed by hydrolysis of the alkaloid with alcoholic potassium hydroxide, which gives rise to the monoacidic base ergine, $C_{16}H_{17}ON_3$, shown to be the amide of lysergic acid (151, 182, 183). Besides lysergic acid, hydrolysis of ergocristinine with aqueous alkali gives rise to dimethylpyruvic acid (151, 184). On the other hand, reductive cleavage of the base with sodium and butyl alcohol yields besides dihydrolysergol, α-hydroxyisovaleric acid (185), *d*-proline, ammonia and a dipeptide ($C_{14}H_{18}O_3N_2$) which on further hydrolysis with acid yields

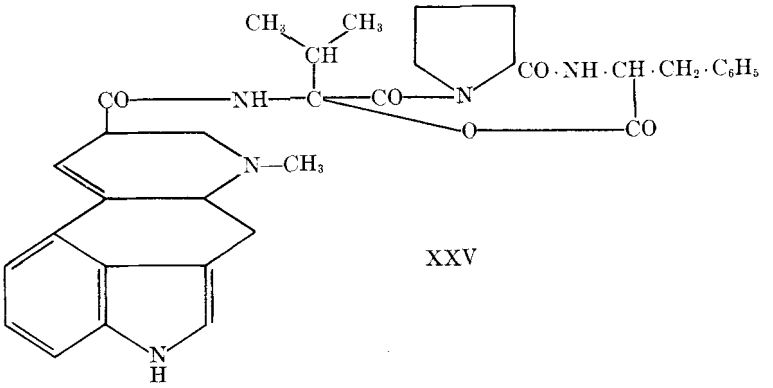
proline and phenylalanine (151, 186, 187). The amino acids thus obtained are partly racemized, but direct hydrolysis of the base with hydrochloric acid destroys the lysergic acid and yields *l*-phenylalanine and *d*-proline (187, 188). Hence, *d*-proline must be combined directly with *l*-phenylalanine in amide linkage. If the five components obtained by the degradation of ergocristinine, i.e., lysergic acid (isolysergic acid), ammonia, dimethylpyruvic acid, *d*-proline and *l*-phenylalanine are added with cleavage of four moles of water, the empirical formula of the base is obtained (178). Since hydrolysis of ergocristinine with alcoholic alkali gives rise to lysergamide (ergine) (182, 189) which readily loses ammonia with aqueous alkali, it is obvious that the ammonia constituent of the alkaloid must be that obtained as lysergamide. Furthermore, the base forms monoacid salts only, due to the basic group of lysergic acid, thus excluding the possibility of a terminal phenylalanyl or prolyl residue with unacylated amino or pyrrolidyl groups, a conclusion confirmed by the absence of amino nitrogen determined in the Van Slyke apparatus (190). However, when dihydroergocristinine (191) is hydrolyzed by alkali, dimethylpyruvic acid is isolated in approximately the same yield as in the similar hydrolysis of ergocristinine and no α-hydroxyisovaleric acid can be detected, whereas dimethylpyruvic acid itself when hydrogenated under similar conditions is reduced quantitatively to α-hydroxyisovaleric acid. Jacobs and Craig (190) concluded from this fact that dimethylpyruvic acid must be formed from a precursor during hydrolysis, a conclusion for which they found support in the similar behavior of ergotamine (which see) under the same conditions. They assume the precursor of dimethylpyruvic acid to be α-hydroxyvaline (XXIV) which in the free



XXIV

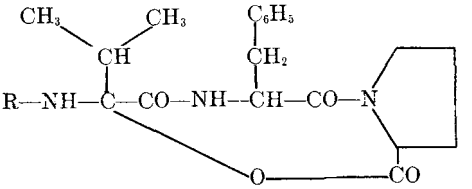
state should be unstable and decompose readily into ammonia and the keto acid. Since lysergamide is produced by hydrolysis of the alkaloid with alcoholic alkali, lysergic acid must be directly attached to the amino group of α-hydroxyvaline which is in turn joined in peptide linkage with either proline or phenylalanine. The alkaloid does not contain an acid group and, therefore, the carboxylic group of the terminal amino acid is represented as forming a lactone with the hydroxyl group of hydroxyvaline. Jacobs and Craig (190) prefer the structure in which phenylalanine is the terminal amino acid and represent ergocristinine by formula XXV.

However, Stoll has announced (191), the isolation of the complete polypeptide part of the molecule. By synthesis of the reduced polypep-



XXV

tide, it has been shown that proline occupies the terminal position. Accordingly, ergocristinine should be represented by XXVI where R is the isolysergyl radical.



XXVI

Ergocristine is represented similarly except that the isolysergic acid in XXV or XXVI is replaced by lysergic acid (IX) (164).

3. Ergotamine — Ergotaminine

Ergotamine — ergotaminine, $C_{33}H_{35}O_5N_5$ (65), form a pair of alkaloids first obtained as a complex named sensibamine (192). Ergotamine is converted into ergotaminine on standing in alcoholic solution or faster by refluxing in an atmosphere of nitrogen a methanolic solution of the base containing 0.1 cc. of glacial acetic acid. Ergotaminine has weaker basic properties than ergotamine and can be converted back into the latter by allowing to stand in the dark in presence of glacial acetic acid, methanol, and sulfuric acid. Ergotamine crystallizes from aqueous acetone with both acetone and water of crystallization while ergotaminine separates from alcohol free from solvent. Ergotamine forms crystalline salts (61, 193). This pair of alkaloids is similar to the other pairs in the ergot group,

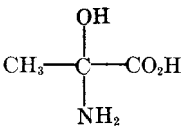
in that ergotamine is much more active physiologically than ergotaminine (66).

a. Isolation of Ergotamine.

Pure ergotamine is prepared from coarsely ground ergot which is mixed with aluminum sulfate and 300 cc. of water, whipped to a finely divided state with cooling and extracted continuously with hot benzene (1.5 liter). The residue obtained upon evaporation of the extract is stirred with 4 liters of benzene and made slightly alkaline with gaseous ammonia. After several hours of stirring, the material is filtered and washed with benzene until a 5 cc. portion of the washings fails to give the Keller reaction. The filtrate is then concentrated under reduced pressure to 75 cc., when practically colorless ergotamine crystallizes. More product is precipitated from the mother liquor by the addition of petroleum ether. The alkaloid is re-crystallized from aqueous acetone (194).

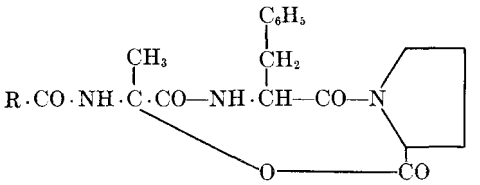
b. Structure. Ergotamine is converted by catalytic hydrogenation over palladium black to dihydroergotamine, $C_{33}H_{37}O_5N_5$, and the double bond thus hydrogenated is that of lysergic acid since hydrolysis of dihydroergotamine gives rise to dihydrolysergic acid (195). On the other hand, hydrolysis of the alkaloid with alcoholic alkali gives rise to lysergamide (ergine) (183, 189), while hydrolysis in aqueous alkali degrades it into lysergic acid, ammonia, phenylalanine, the piperazide, $C_{14}H_{20}N_2$, and pyruvic acid (187, 188). The amino acids thus obtained are partially racemized, but hydrolysis with hydrochloric acid although it destroys the lysergic acid, liberates the optically active acids, *l*-phenylalanine and *d*-proline. Furthermore, pyrolysis of the base in a high vacuum gives rise to pyruvic acid amide and to *l*-phenylalanine-*d*-proline lactam (194). Hence, both *l*-phenylalanine and *d*-proline are present in ergotamine as in ergocristine and as in the latter are directly linked together. Since the formula of ergotamine differs from that of ergocristine by C_2H_4 and since no dimethylpyruvic acid appears to occur amongst the degradation products of the former, it is evident that the difference is due to the replacement of that acid by pyruvic acid. Thus, it can be concluded that ergotamine consists of lysergic acid, ammonia, *d*-proline, *l*-phenylalanine and pyruvic acid combined in amide linkage; the addition of these five components with cleavage of four molecules of water gives the empirical formula of the base. Ergotaminine differs only in that it contains isolysergic acid instead of lysergic acid (196). However, although ergotamine or its isomer when hydrolyzed by alkali produce a mixture giving a strong positive test for pyruvic acid, neither of the alkaloids gives such a test before hydrolysis. Similarly, dihydroergotamine fails to give a test for pyruvic acid whereas after hydrolysis a strong positive test develops. The most satisfactory explanation for these observations is that pyruvic acid arises during hydrolysis from a precursor, α-hydroxyalanine (XXVII). Such a substance in the free state would decompose readily into ammonia and pyruvic acid although

when the amino group is acylated as in the alkaloid it is more stable. Further proof that pyruvic acid amide is immediately linked in amide



XXVII

linkage with lysergic acid is found in the isolation from ergotamine by pyrolysis of a substance representing the whole polypeptide part of the base (194). This substance on mild hydrolysis yields pyruvic acid and *l*-phenylalanyl-*d*-proline lactam. Thus, by the same reasoning which leads



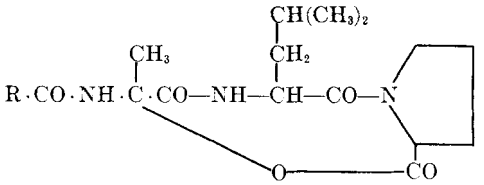
XXVIII

to the derivation of structure of ergocristine and assuming that proline again occupies a terminal position, ergotamine can be represented by XXVIII (R = lysergyl) while ergotaminine is XXVIII (R = isolysergyl) (190, 194).

4. Ergosine — Ergosinine

Ergosine — ergosinine, $C_{30}H_{37}O_5N_5$ (89, 197, 198), are the main components of Küssner's ergoclavine (89, 90, 152). On alkaline hydrolysis, ergosine gives rise to ammonia, lysergic and pyruvic acids (188, 196), and a dipeptide, $C_{11}H_{18}O_2N_2$, hydrolyzed by acid into *l*-leucine and *d*-proline (89). The dipeptide is also obtained as a product of the pyrolysis of the alkaloid (89). Like ergocristine and ergotamine, ergosine on catalytic hydrogenation takes up two atoms of hydrogen, forming dihydroergosine and, hence, contains only the double bond present in the lysergic acid part of the molecule. The combination of the five components (lysergic acid, ammonia, pyruvic acid, *d*-proline and *l*-leucine) of ergosine in amide linkage with cleavage of four moles of water, adds up to $C_{30}H_{37}O_5N_5$, the empirical formula of the alkaloid. Ergosine can be hydrolyzed to lysergamide and, therefore, the ammonia must be combined directly with the acid. Also, the isolation of the dipeptide, *l*-leucyl-*d*-proline lactam, indicates that *l*-leucine and *d*-proline must also be combined together in the

molecule. By analogy with ergocristine and ergotamine, ergosine can be represented by the probable formula XXIX (R = lysergic acid radical):



XXIX

5. ERGOCRYPTINE — ERGOCRYPTININE

Ergocryptine — ergocryptinine, $C_{32}H_{41}O_5N_5$ (93). The former of these two bases was separated from the mixture hitherto known as ergotoxine by fractional crystallization of the di-(*p*-toluyl)-*l*-tartrates. Ergocryptine di-(*p*-toluyl)-*l*-tartrate is sparingly soluble in both absolute methanol and absolute ethanol and it crystallizes from these solvents. The free base is readily obtained by liberation from its salt and crystallization from alcohol or acetone. It readily forms crystalline salts. Like the other levorotatory ergot alkaloids, ergocryptine is converted to the strongly dextrorotatory isomer ergocryptinine either by boiling its methanolic solution or by the action of alcoholic alkalis.

Boiling ergocryptine with hydrazine causes hydrolysis of the base, racemization and isomerization of the lysergic acid and gives rise to *rac*-isolysergic acid hydrazide (168, 178). Alkaline hydrolysis of the alkaloid produces lysergic acid, dimethylpyruvic acid and ammonia, whereas acid hydrolysis gives *l*-leucine and *d*-proline. Pyrolysis of the alkaloid *in vacuo* gives rise to *l*-leucyl-*d*-proline lactam, hydrolyzable by acids into its two constituents. Only one double bond is present in the molecule since the only product of the catalytic hydrogenation of ergocryptine is dihydroergocryptine, $C_{32}H_{43}O_5N_5$ (195). Addition of the five degradation products with cleavage of four moles of water produces a formula identical with that of ergocryptine. Ergocryptinine differs from ergocryptine in that isolysergic acid replaces the lysergic acid of the latter (178). Hence, the degradation products of ergocryptine are the same as those of ergocristine with the exception that *l*-phenylalanine of the latter is replaced by *l*-leucine.

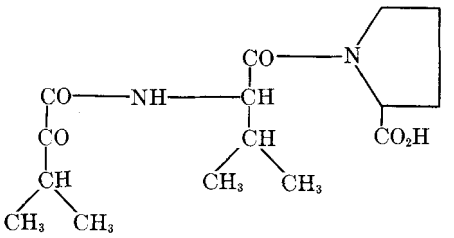
6. ERGOCORNINE — ERGOCORNININE

Ergocornine — ergocorninine, $C_{31}H_{39}O_5N_5$ (93). Like ergocryptine, ergocornine was also isolated from the mixture hitherto known as ergotoxine by fractional crystallization of the di-(*p*-toluyl)-*l*-tartrates. Ergocornine di-(*p*-toluyl)-*l*-tartrate is obtained from the methanolic mother

liquor from which the di-(*p*-toluyl)-*l*-tartrates of ergocristine and ergocryptine have crystallized, by diluting with water until the methanol content is about 80%. The pure base crystallizes from methanol in which it is sparingly soluble. It forms crystalline salts and it can be transformed into the dextrorotatory ergocorninine by the usual methods.

Catalytic hydrogenation of ergocornine causes the absorption of two atoms of hydrogen and gives rise to dihydroergocornine (195). The degradation of the alkaloid by the methods already described causes scission into lysergic acid, ammonia, dimethylpyruvic acid, *l*-valine and *d*-proline. The combination of these products in amide linkage with cleavage of four moles of water adds up to $C_{31}H_{39}O_5N_5$ which is the formula of the alkaloid obtained by analysis. Hence, the degradation products obtained from ergocornine differ from those of ergocristine only in that *l*-valine replaces the *l*-phenylalanine of the latter.

Pyrolysis of ergocornine *in vacuo* yields a small quantity of a substance consisting of the whole polypeptide part of the molecule and containing the keto acid as well as the two amino acids. The synthesis of the reduction product obtained from this substance establishes that the latter is dimethylpyruvylvalylproline (XXX) (191, 177a). The work concerning this polypeptide affords the first complete experimental proof of the order in which the amino-acids are linked in the ergot alkaloids.



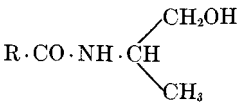
XXX

7. Ergometrine — Ergometrinine

Ergometrine — ergometrinine, $C_{19}H_{23}O_2N_3$ (73). The levorotatory alkaloid ergometrine was discovered almost simultaneously in several laboratories (70–84), while the dextrorotatory isomer was obtained later (85). The two bases can be separated by distribution between water and ether (199). Ergometrine does not occur in all types of ergot and its occurrence in New Zealand Festuca ergot has been reported as the first in which the base accompanies ergotamine and ergotaminine (200).

Ergometrine forms crystalline salts, but it is distinct from the other

ergot alkaloids in its solubility in water and its much smaller empirical formula which reflects its simpler structure. Like all other ergot alkaloids, ergometrine gives rise to lysergic acid on hydrolysis (201) and when hydrogenated, it takes up two atoms of hydrogen and forms dihydroergometrine, $C_{19}H_{25}O_2N_3$. The double bond thus reduced is that present in lysergic acid since hydrolysis of the dihydro alkaloid produces dihydrolysergic acid. Ergometrine is easily converted into ergometrinine as indicated by the fact that its solution mutarotates (202). Besides lysergic acid, the only other product of hydrolysis of ergometrine is *d*-2-aminopropanol-1 (83). Since ergometrine does not contain a primary amino group, it must consist of *d*-lysergic acid-*d*-isopropanolamide XXXI (R = lysergyl):



XXXI

Since both 2-aminopropanol-1 and lysergic acid contain a center of asymmetry and further, since lysergic acid can isomerize to isolysergic acid, there are eight possible amides of the formula $C_{19}H_{23}O_2N_3$. However, the structure of ergometrine has received confirmation by the partial synthesis not only of the base and its isomer ergometrinine (169), but also of the remaining six possible amides (203). The starting material for the synthesis, i.e., *rac*-isolysergic acid hydrazide (168) is resolved with the aid of di-(*p*-toluyl)-*l*-tartaric acid into *d*-isolysergic acid hydrazide and *l*-isolysergic acid hydrazide (204) which are converted by the method of Curtius (205) into their respective azides. The reaction of *d*-isolysergic acid azide with *d*-2-aminopropanol-1 (206) produces *d*-ergometrinine (natural ergometrinine) while reaction with *l*-2-aminopropanol-1 gives rise to the optical isomer *d*-isolysergic acid-*l*-propanolamide-(2). If, on the other hand, *l*-isolysergic acid azide reacts with *d*-2-aminopropanol-1 and with *l*-2-aminopropanol-1, *l*-isolysergic acid-*d*-propanolamide-(2) and *l*-isolysergic acid-*l*-propanolamide-(2) (*l*-ergometrinine) are obtained. Transformation of these four products by boiling with alcoholic potassium hydroxide gives rise to the corresponding lysergic acid derivatives, including *d*-lysergic acid-*d*-propanolamide-(2) (natural ergometrine) (203). Hence, of all the ergot alkaloids, the structures of ergometrine and ergometrinine are known with most certainty. The six known pairs of ergot alkaloids have been classified into three groups, i.e., group I includes those bases in which the keto acid obtained on hydrolysis is dimethylpyruvic acid (ergocristine, ergocryptine, ergocornine and their isomers); group II contains the bases which yield pyruvic acid on hydrolysis (ergotamine — ergot-

aminine and ergosine — ergosinine) and finally group III for bases such as ergometrine and ergometrinine in which the component common to all ergot alkaloids (lysergic acid, isolysergic acid) is combined in amide linkage with an amino alochol. *d*-Lysergic acid azide has also been caused to react with a variety of substituted amino alcohols and many homologues of ergometrine and ergometrinine thus prepared (203).

IV. The Alkaloids of *Peganum harmala* L.

The seeds of *Peganum harmala* L. contain the alkaloid vasicine (peganine) the main occurrence of which, however, is in the leaves of *Adhatoda vasica* Nees (Acanthaceae) (209). Although vasicine does not belong to the indole group, the seeds contain three other alkaloids which all contain the indole nucleus. These are harmaline (210), harmine (211), and harmalol, the last of which was first discovered in the plant (210, 212) and, later, prepared from harmaline by hydrolysis (213, 214). Harmine is found not only in the seeds, but also in the root of *P. harmala* (3% yield) (215). An extract from the South American liana known as Yage, Ayahuasca or Caapi and identified as *anisteria caapi* Spruce (Malpighiaceae) has long been prepared locally and used medicinally (216). The extract yields an alkaloid variously named telepathine (216), yageine (217), banisterine (218, 219), but shown eventually to be identical with harmine (220–222).

1. Isolation of Harmine and Harmaline

The crushed seeds are covered with three times their weight of water containing 30 g. of acetic acid per liter of water. The seeds swell as they absorb the liquid and form a thick dough which is pressed after 2 or 3 days. The pressed seeds are once more treated as above with twice their weight of dilute acetic acid and, after maceration, the liquid is again pressed out. To the combined liquors, sodium chloride (100 g./liter of liquid) is added to transform the acetates of harmine and harmaline into the hydrochlorides which are insoluble in cold sodium chloride solutions and are precipitated during cooling. The supernatant liquid is siphoned off, the crystalline residue filtered with suction and redissolved in hot water. Addition of sodium chloride to the filtered solution causes the precipitation of the hydrochlorides as a crystalline mush and this process is repeated until the hydrochlorides have acquired a yellow color. The separation of harmaline from harmine is based on the fact that when a warm aqueous solution of the hydrochlorides is alkalinized with ammonia, harmaline is liberated only after the decomposition of harmine hydrochloride is complete. The appearance of harmaline is readily detected under the microscope since it consists of plates while harmine forms long needles. The addition of ammonia, therefore, is stopped as soon as crystals of harmaline are detected, the harmine is filtered off and the harmaline recovered from the filtrate by the addition of ammonia. The bases are then further purified by recrystallization of their hydrochlorides (223).

Numerous methods of assay of the harmala alkaloids have been described. These are either gravimetric (212, 224), or volumetric, involving

titration of the extracted alkaloid with 0.1 *N* sulfuric acid (225), or with 0.05 *N* *p*-toluenesulfonic acid (226). With the latter acid, it is advisable to carry out the titration in chloroform (227). A microchemical test has also been described involving the use of 5-nitrobarbituric acid (dilituric acid) which is a specific reagent for harmine and a few other alkaloids (228). Harmine and harmaline yield fluorescence spectra (229) and the fluorescence of solutions of harmine at pH 3 permits the determination of the base to within 2% (230). In acid solution harmine hydrochloride shows an indigo-blue fluorescence which becomes a yellow-green in alkaline solution and this transition occurs within the pH interval 7.2–8.9 (231). This property makes it possible to use harmine as a fluorescent indicator in iodimetry of sodium thiosulfate, in halogenimetry of arsenious oxide and in the chloramine titration of arsenious oxide and stannous chloride (232). Determined by a gravimetric assay, the seeds of *P. harmala* contain 2.09% harmaline and 1.60% harmine (212).

2. Harmaline and Harmine

Harmaline, $C_{13}H_{14}ON_2$ (210, 233) and harmine, $C_{13}H_{12}ON_2$ (211), are both crystalline and form crystalline salts with one equivalent of acid. Both bases, which are optically inactive, are closely related in structure since harmine on reduction with sodium in ethanol is converted to tetrahydroharmine while the similar reduction of harmaline gives rise to dihydroharmaline, identical with tetrahydroharmine (214). Moreover, a solution of harmaline in ethanol and fuming hydrochloric acid is oxidized by nitric acid to harmine (214). The same oxidation is also brought about by the action of ammonium nitrate and hydrochloric acid (234), of chromic acid in hydrochloric acid (235), or finally by potassium permanganate (236). Hence, harmine contains two double bonds and harmaline is dihydroharmine. The presence of two double bonds in harmine is confirmed by the formation of tetrabromoharmine on treatment of the base in dilute sulfuric acid with bromine water (214). Tetrabromoharmine is converted back to harmine by boiling with alcohol, or to dibromoharmine by boiling with dilute alcohol. Bromination of the bases in acetic acid, however, gives rise to bromoharmaline and to two isomeric bromoharmines (237).

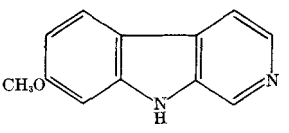
Harmine when heated with fuming hydrochloric acid at 140° gives rise to methyl chloride and a phenolic base, harmol, $C_{12}H_{10}ON_2$, and when similarly treated harmaline produces the corresponding harmalol identical with that found in the seeds of *P. harmala*. Both harmol and harmalol can be acetylated (213). The oxygen in each of the parent bases, therefore, is present in a methoxyl group. The action of zinc chloride, ammonia, and ammonium chloride converts harmol into aminoharman which is trans-

formed by diazotization into a base, $C_{12}H_{10}N_2$, named harman (238). The oxidation of harmine with chromic and sulfuric acids or better with chromic and acetic acids (214) gives rise to harminic acid, $C_{10}H_8O_4N_2$ which, on heating with concentrated hydrochloric acid at 190–200°, or on pyrolysis at 250–280° (239) loses carbon dioxide and forms apoharmine-carboxylic acid (240). Pyrolysis of harminic acid at higher temperature (above 330°) causes complete decarboxylation and conversion to the base apoharmine, $C_8H_8N_2$ (213). Harminic acid yields a phthalein when heated with resorcinol and sulfuric acid, and therefore, must be an *o*-dicarboxylic acid (241). Since apoharmine can be reduced both to dihydro- and tetrahydroapoharmine (242), it still contains the unsaturated nucleus present in harmine. From these facts it can be concluded that both harmine and harmaline contain a benzene nucleus fused in two ortho-positions to the rest of the molecule and carrying a methoxyl group. This conclusion is supported by the fact that both bases can be nitrated (243) and confirmed by the oxidation of harmaline with fuming nitric acid to *m*-nitroanisic acid (238).

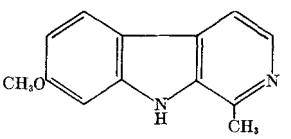
Of the two nitrogen atoms present in harmine and harmaline, one is neutral since the bases form salts with only one equivalent of acid. Dihydroharmaline forms a nitroso compound (214); it can also be acetylated and benzoylated (236) and, therefore, contains a secondary nitrogen. Harmaline can also be acetylated (238) and on treatment with methyl iodide gives rise to the hydriodide of an *N*-methyl base. Both harmine and apoharmine behave similarly (236). However, although these facts appear to indicate the presence of a secondary nitrogen in both harmine and harmaline, the peculiar stability of these hydriodides which are decomposed only by hot concentrated potassium hydroxide militates against such a conclusion. Furthermore, methylharmaline reacts with methyl iodide and produces a dimethylharmaline iodide which loses trimethylamine in contact with cold aqueous potassium hydroxide. On the other hand the action of methyl iodide on dihydroharmaline gives rise to dimethyldihydroharmaline iodide ($C_{15}H_{21}ON_2I$) converted by methanolic potassium hydroxide to a substance ($C_{15}H_{22}O_2N_2$) which, although it has the composition of a quaternary ammonium hydroxide, must be a pseudo base since it is soluble in ether and does not give off trimethylamine under the action of alkalis (244). Likewise, the Hofmann degradation of apoharmine does not follow a normal course, but yields a complex base ($C_{19}H_{22}N_4$) (245).

Both harmine and harmaline condense with aldehydes: with benzaldehyde harmaline forms benzylidenediharmaline whereas harmine gives rise to benzylideneharmine and this condensation is indicative of a methyl group on a pyridine ring in a position ortho to the nitrogen (241, 246). The presence of the methyl group in the bases is further confirmed by the following reaction: benzylideneharmine hydrochloride in pyridine solution

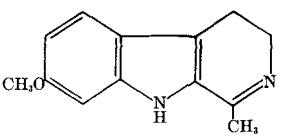
is oxidized by potassium permanganate to norharminecarboxylic acid which, on heating in glycerol is decarboxylated to norharmine (241). Since the sum of the carbon atoms of the methyl and the methoxyl groups together with those of the benzene and pyridine rings of harmine represents the total number of carbon atoms in the base, it is probable that the second nitrogen atom which is neutral must be located in a pyrrole ring. Hence, the formula of harmine must comprise a benzene, a pyrrole and a pyridine ring fused together (247). Various tentative formulae that subsequently proved untenable were suggested to represent the structure of harmine (241, 244, 247). Positive proof of the presence of the pyridine nucleus in harmine was obtained in the isolation of isonicotinic acid (γ-pyridinecarboxylic acid) as a product of the oxidation of harminic acid with nitric acid at 180–200° (244), and this also shows that the pyridine ring must be substituted in the gamma position. Harmine contains both one *C*-methyl and one *O*-methyl group and is, therefore, a derivative of a substance $C_{11}H_8N_2$ which has been designated norharman. The relation of harminic acid to harmine is such that the benzene ring must occupy a terminal position and Perkin and Robinson (248) have advanced the following group of formulae to represent norharmine (XXXII), harmine (XXXIII), harmaline (XXXIV), harminic acid (XXXV) and apoharmine (XXXVI). The structure of harmaline is based on the facts that the base is optically



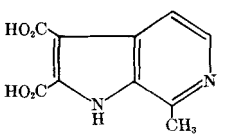
XXXII



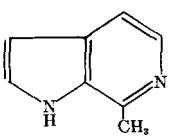
XXXIII



XXXIV



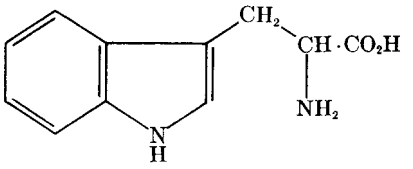
XXXV



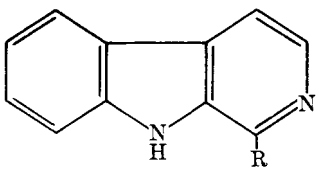
XXXVI

inactive, it forms addition products with hydroxylamine (244) and with hydrogen cyanide (249, 250) and its metho salts are quaternary. The order of fusion of the benzene, pyrrole and pyridine rings in these formulae was confirmed by the discovery that the base obtained by Hopkins and Cole (251), by the oxidation of tryptophan (XXXVII) with ferric chloride in the presence of ether, is identical with harman XXXVIII, R = Me (252). In this reaction, the actual oxidation was preceded by condensation with

acetaldehyde arising from the ether present. Harman has since been synthesized by oxidation with potassium dichromate of the condensation product of tryptophan with acetaldehyde in the presence of sulfuric acid

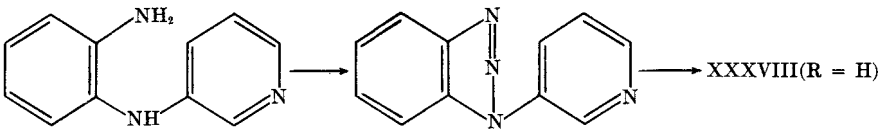


XXXVII



XXXVIII

(253), thus definitely establishing its structure (XXXVIII, R = Me). The unsubstituted harman, i.e., norharman (XXXVIII, R = H), can be synthesized similarly from tryptophan by condensation with formaldehyde and oxidation of the product with chromic acid (253). Norharman has also been synthesized from *o*-phenylenediamine which is condensed with 3-bromopyridine to *N*-3-pyridyl-*o*-phenylenediamine (XXXIX) and this is almost quantitatively converted by the action of sodium nitrite and

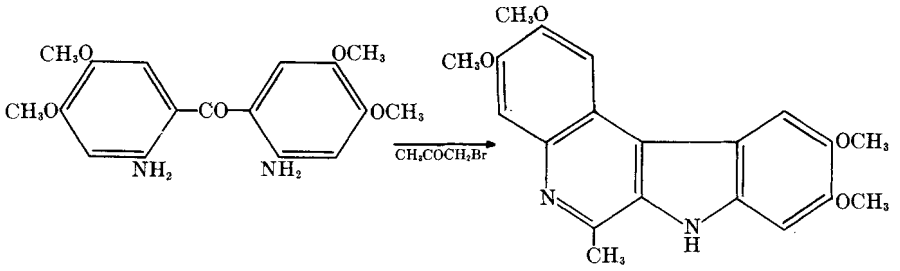


XXXIX XL

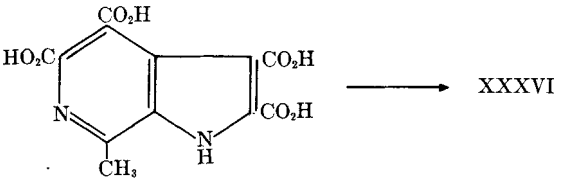
hydrochloric acid into 1-(3-pyridyl) benzotriazole (XL). On heating the triazole in an evacuated tube at 350°, a small yield of norharman (3-carboline) (XXXVIII, R = H) is obtained (254). It is obtained also from the condensation product of tryptamine with formaldehyde by dehydrogenation (255).

The validity of the structure assigned to harmine (XXXIII) has been confirmed by the synthesis of its various degradation products and of the base itself. Apoharmine, the most important degradation product of harmine since it contains both the pyridine and pyrrole rings, has been synthesized from 3, 4, 3′, 4′-tetramethoxybenzophenone which is nitrated and reduced to the diaminoveratrone (XLI). The amino compound (XLI) thus obtained is condensed with bromoacetone, the product (XLII) subsequently demethylated with hydriodic acid and oxidized with chromic acid to 8-methyl-7-pyrindole-2, 3, 5, 6-tetracarboxylic acid (XLIII). This acid when heated with soda lime in a stream of hydrogen produces a small yield of 8-methyl-7-pyrindole, identical with apoharmine (XXXVI) (256).

Since the product of the action of methyl iodide on harmine is not decomposed by ammonia or dilute alkali in the cold, but by hot concentrated alkalis only, it is not a simple salt and the formation of methyl-

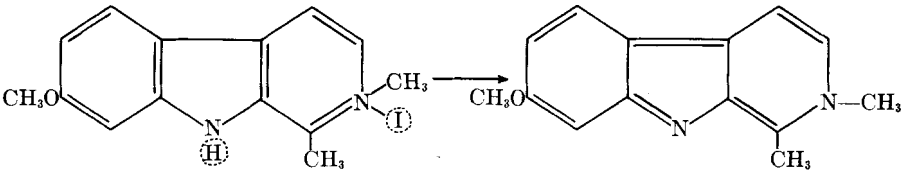


XLI XLII



XLIII

harmine is represented by formulae XLIV and XLV (248). Thus py-methylharmine (XLV) is an anhydronium compound and further methyl-

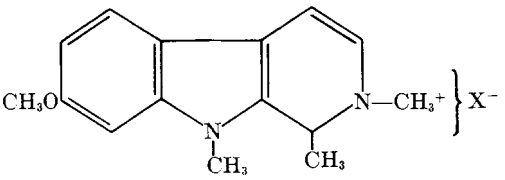


XLIV XLV

ation should convert it to a salt in which the indole nitrogen is alkylated (XLVI) (257).

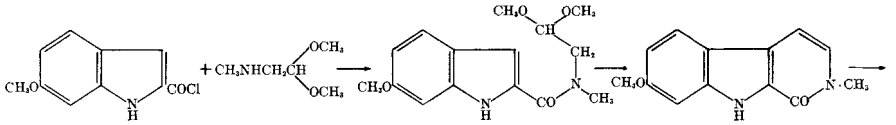
In the thermal decomposition of such a salt with elimination of methyl halide, it is the methyl group on the pyridine nitrogen which carries the cationic charge and should be eliminated. The decomposition of dimethylharmine chloride does, in fact, follow precisely this course and the product obtained is ind-*N*-methylharmine (258). This interpretation is further

confirmed by the fact that the use of two different alkyl halides brought to react with harmine in different order yields two different compounds (259). With harmaline, however, the products of alkylation with two

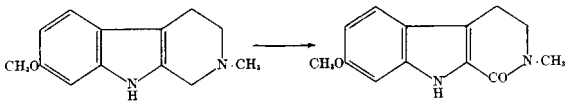


XLVI

different alkyl halides used in different order are identical (259). Moreover, harmaline methosulfate is oxidized by potassium permanganate to a keto compound (260) first assumed and later shown by synthesis to be 2-keto-3-methyl-8-methoxy-2, 3, 4, 5-tetrahydro-3-carboline (LII). This synthesis is carried out from 6-methoxyindolyl-2-carboxylic acid, the acid chloride (XLVII) of which by reaction with methylaminodimethylacetal (XLVIII)



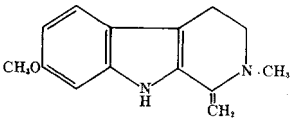
XLVII XLVIII XLIX L



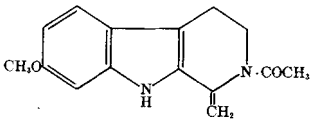
LI LII

is converted into the indolyl amide (XLIX). Cyclization of the amide by the action of ethanolic hydrogen chloride gives rise to 2-keto-3-methyl-8-methoxy-2, 3-dihydro-3-carboline (L) which is reduced by sodium in *n*-butyl alcohol to *N*-methyltetrahydronorharmine (LI). Oxidation of the reduced product (LI) with potassium permanganate yields 2-keto-3-methyl-8-methoxy-2, 3, 4, 5-tetrahydro-3-carboline (LII) identical with the product of the oxidation of harmaline methosulfate (257). Since methylharmaline also is oxidized to the keto compound (LII) and since it is converted by dilute hydrochloric acid to harmaline methochloride, it must be represented by formula LIII (261). Acetylharmaline possesses an analogous constitution since it is converted by reduction to *N*-acetyldihydroharmaline, while on oxidation with potassium permanganate it gives rise to a compound, $C_{14}H_{14}O_3N_2$, which on the basis of formula LIV for acetylharmaline must have the structure LV. This assumed structure

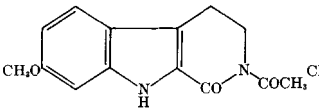
is supported by the fact that on hydrolysis the substance yields two products, one of which ($C_{12}H_{12}O_2N_2$) is neutral, while the other ($C_{12}H_{14}O_3N_2$) is an amino acid and the two products are undoubtedly represented by



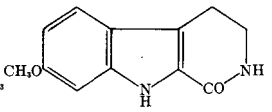
LIII



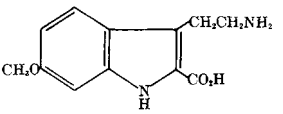
LIV



LV

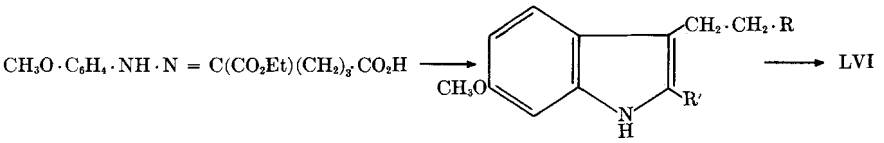


LVI



LVII

formulae LVI and LVII (261). The formula LIV assigned to acetylharmaline finds confirmation in the following synthesis of the neutral product (LVI) derived from it by stepwise oxidation and hydrolysis. The *m*-methoxyphenylhydrazone of ethyl hydrogen α-ketoadipate (LVIII) obtained by coupling ethyl cyclopentanonecarboxylate with *m*-methoxybenzenediazonium chloride in alkaline solution, is transformed by the action of boiling alcoholic sulfuric acid into ethyl-β-2-carbethoxy-6-

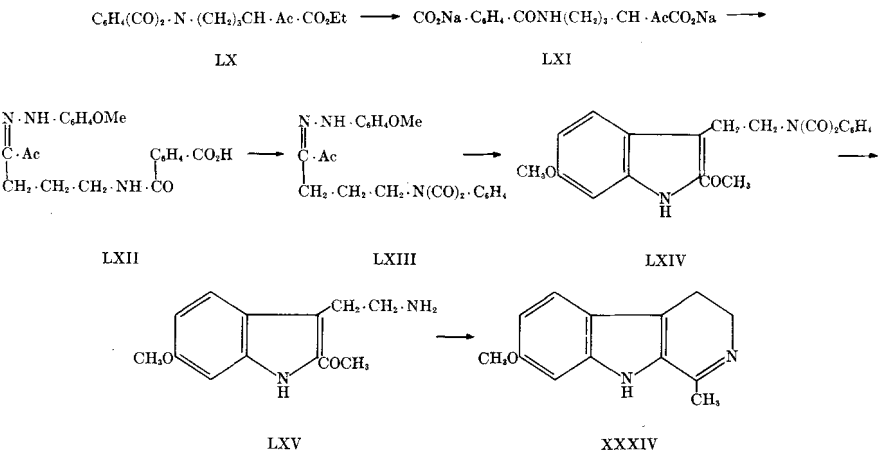


LVIII LIX

methoxyindolyl-3-propionate (LIX, R = R′ = CO_2Et). Hydrolysis of this ester yields the corresponding acid (LIX, R = R′ = CO_2H) which on heating loses carbon dioxide and produces β-6-methoxyindolyl-3-propionic acid (LIX, R′ = H, R = CO_2H). The hydrazide of this acid is converted to the azide (LIX, R′ = H, R = CON_3) which, by heating in chloroform-toluene and treatment with hydrogen chloride, is transformed into the ketotetrahydrocarboline (LVI) identical with that derived from acetylharmine (262).

Finally harmaline itself was synthesized. Ethyl δ-phthalimido-α-acetylvalerate (LX) obtained by the interaction of ethylacetoacetate with γ-bromopropylphthalimide in presence of sodium ethylate, is hydrolyzed with sodium hydroxide to the salt (LXI) of the diacid which is converted by the action of *m*-methoxybenzenediazonium chloride to ζ-*o*-carboxylbenzamidohexane-β, γ-dione β-*m*-methoxyphenylhydrazone (LXII). This

product is dehydrated with acetic anhydride to the corresponding phthalimide (LXIII) which is cyclized in *n*-butyl alcohol by hydrogen chloride into 6-methoxy-2-acetyl-3-β-phthalimidoethylindole (LXIV). Hydrolysis of the phthalimide with hydrazine yields 6-methoxy-2-acetyl-3-β-amino-

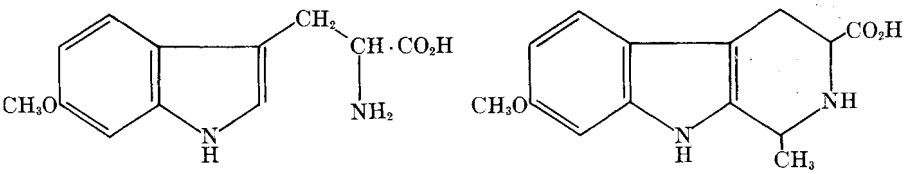


LX LXI

LXII LXIII LXIV

LXV XXXIV

ethylindole (LXV) and this is transformed into harmaline (XXXIV) by dehydration (263). Since harmaline is readily oxidized to harmine (214, 234–236) the foregoing synthesis constitutes a total synthesis of both alkaloids: Harmaline, however, can be synthesized by a much simpler method: the condensation of *m*-methoxyphenylhydrazine and γ-aminobutyraldehyde diethylacetal in the presence of zinc chloride gives rise to a mixture of 4-methoxy- and 6-methoxy-3-β-aminoethylindoles. The latter of the two products is converted with acetic anhydride to the acetyl derivative which is cyclized by phosphoric anhydride in boiling xylene to harmaline (264). A further synthetic route consists in allowing 6-methoxytryptophan (LXVI) in saturated aqueous solution (pH 6.7) to react with



LXVI LXVII

acetaldehyde. The resulting 2-methyl-2,3,4,5-tetrahydro-3-carboline-4-carboxylic acid (LXVII) yields harmine when oxidized with chromic acid in acetic acid (265). Finally, harmine is also prepared from 6-methoxy-

tryptamine obtained by reduction of the reaction product of 6-methoxyindole, methylmagnesium iodide and chloracetonitrile. Methoxytryptamine is condensed with acetaldehyde and the tetrahydroharmine thus produced is dehydrogenated to harmine in presence of maleic acid with palladium black (266).

3. Harman

Harman, $C_{12}H_{10}N_2$ (238), first prepared as a degradation product of harmine (238), also occurs in nature. Loturine, the alkaloid isolated from the bark of *Symplocos racemosa* Roxb. (Lotur bark) (267) has been shown to be identical with harman (268). Similarly the alkaloid aribine reported as occurring in the bark of *Arariba rubra* Mart., (269), is now known to be harman (270). Besides the synthesis of the base from tryptophan already mentioned (251, 253), various methods have been described for the preparation of dihydro- and tetrahydroharman both of which can be converted to harman by mild oxidation. Ring closure of various acid amides of tryptophan with the aid of phosphorus pentoxide in boiling xylene gives rise to dihydroharman or derivatives of it (271, 272) and these are dehydrogenated with palladium black (264). On the other hand, the condensation of tryptamine with paraldehyde gives rise to tetrahydroharman (273). This product, however, can be formed under very mild conditions, such as adding tryptamine hydrochloride in a 0.5 molar acetaldehyde solution buffered with acetate at pH 5.2 or with phosphate at pH 6.2 and keeping the solution for 3 days at 25° (274). The use of methylglyoxal (275), or of pyruvic acid, instead of acetaldehyde in the above buffered solution gives rise in each case to 2-methyl-2-carboxy-2,3,4,5-tetrahydro-3-carboline, which can be decarboxylated to tetrahydroharman (276).

The alkaloid eleagnine (276a) has recently been shown to be the racemic form of tetrahydroharman (276b).

V. Alkaloids of *Evodia rutaecarpa*

The Chinese drug Wü Chü Yü consists of the dried fruit of *Evodia rutaecarpa* Hook. f. & Thoms. Extracts of the drug contain the alkaloids evodiamine and rutaecarpine (282), the constitution of which has been determined and wuchuyine, which has not been further studied (283). Another species of *Evodia* (*E. danielli* Hemsl.) has been found to contain no alkaloids (284).

1. Isolation of the Alkaloids

The plant material is extracted with acetone and the extract evaporated. The residual sirupy liquid is treated with 2.5% aqueous sodium hydroxide and ether which removes most of the oil and leaves a yellow powder. This is washed repeatedly with ethanol and finally dissolved in hot acetone. On cooling the solution deposits a mass of

crystals which are filtered and digested with hot benzene. Part of the crystals dissolve and the separated benzene solution deposits rutaecarpine which is purified by recrystallization from acetone. The benzene-insoluble material is dissolved in acetone and the filtered solution on slow evaporation deposits a crop of crystals which is filtered and washed with chloroform in which evodiamine is soluble. The chloroform-insoluble crystalline residue is wuchuyine, while the base recovered from the chloroform washings is evodiamine. Both these alkaloids are purified by recrystallization from acetone (283).

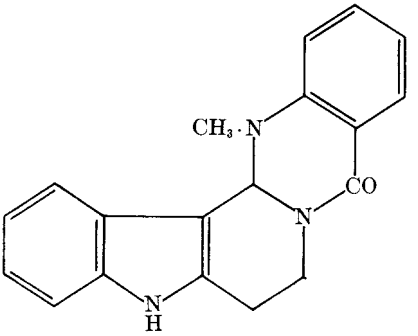
2. Evodiamine and Rutaecarpine

Evodiamine, $C_{19}H_{17}ON_3$ (282), and rutaecarpine, $C_{18}H_{13}ON_3$ (282), the two main alkaloids of the plant, are closely related structurally. Both alkaloids react very similarly towards reagents. However, evodiamine in concentrated sulfuric acid, or in hydrochloric acid, shows an orange color changing to a red brown on standing and to blue when the solution is diluted with water. The blue color is destroyed by alkalis with formation of a dirty blue precipitate. Rutaecarpine, on the other hand, shows a yellow color with concentrated sulfuric or hydrochloric acids (282).

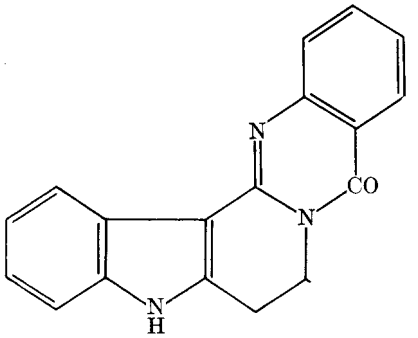
Evodiamine is transformed by boiling alcoholic hydrogen chloride into isoevodiamine (evodiamine hydrate) (282) which is converted to optically inactive evodiamine by the action of acetic anhydride (285), or of oxalic acid (286). The transformation, therefore, involves the asymmetric center in the base. Evodiamine is degraded by boiling concentrated alcoholic potassium hydroxide to *N*-methylanthranilic acid and a crystalline base, $C_{11}H_{10}N_2$. Under the same conditions, isoevodiamine gives rise to *N*-methylanthranilic acid and a base, $C_{11}H_{12}N_2$, forming crystalline salts and an acetyl derivative (285). The action of amyl alcoholic potassium hydroxide, on the other hand, decomposes rutaecarpine into anthranilic acid and a base, $C_{11}H_{12}O_2N_2$, which loses carbon dioxide when boiled with dilute hydrochloric acid and gives rise to the same base, $C_{10}H_{12}N_2$, obtainable from isoevodiamine (285, 287). Fusion of rutaecarpine with potassium hydroxide causes scission into aniline, carbon dioxide and indolyl-α-carboxylic acid (287). On the assumption that the base $C_{10}H_{12}N_2$ was indolyl-α-ethylamine and that the substance, $C_{11}H_{12}O_2N_2$, which gives rise to it was indole-α-ethylamine-β-carboxylic acid, Asahina and Mayeda (285) assigned formulae LXVIII and LXIX to evodiamine and rutaecarpine respectively. According to these formulae evodiamine contains two hydrogen atoms and an imino methyl group more than rutaecarpine. This difference between the two compounds finds confirmation in the fusion of isoevodiamine hydrochloride which results in the loss of methyl chloride and the formation of rutaecarpine (286). The transformation of evodiamine into rutaecarpine is also effected by carefully heating the base either in air or in carbon dioxide (288).

The structures LXVIII and LXIX are quite different from those of

the other indole alkaloids which are mostly all derivatives of tryptamine. The formulae were questioned by Kermack, Perkin and Robinson (253) on this ground, especially as the isolation of α-indolylcarboxylic acid is questionable evidence of α-substitution since the same acid is obtained

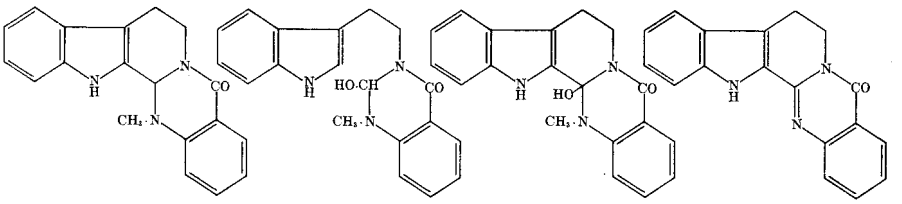


LXVIII



LXIX

from various β-substituted indoles (289). A re-examination by Asahina (290) of his earlier evidence led him to conclude that the base $C_{10}H_{12}N_2$ is 3-β-indolylethylamine and not the α-substituted indole as he had assumed. Moreover, the base $C_{11}H_{10}N_2$ obtained from evodiamine by the action of alcoholic potassium hydroxide yields norharman (XXXVIII, R = H) on mild oxidation. Hence, formulae LXVIII and LXIX for evodiamine and

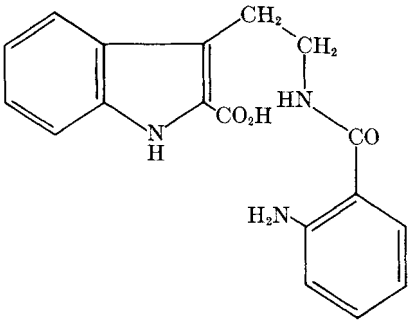


LXX LXXI LXXII LXXIII

rutaecarpine were no longer tenable and the bases are more correctly represented by structures LXX and LXXIII. Since the double transformation of evodiamine to isoevodiamine and back to the original base is accompanied by loss of optical activity, the mechanism of the reaction must involve first, addition of the elements of water with opening of the tetrahydropyridine ring and in the second step, loss of water and closure of the ring. Hence, isoevodiamine must be represented by formula LXXI. When evodiamine is oxidized with potassium permanganate in acetone, hydroxyevodiamine, $C_{19}H_{17}O_2N_3$, is produced and this compound, when boiled with alcoholic potassium hydroxide, is hydrolyzed to 3-β-ethylamino-

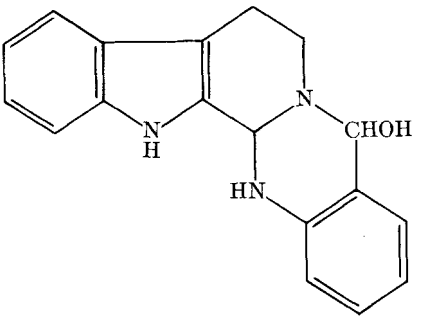
indolyl-2-carboxylic acid and *N*-methylanthranilic acid (286). Hydroxyevodiamine is, therefore, most probably represented by LXXII.

The validity of the structures assigned to evodiamine and to rutaecarpine has been confirmed by synthesis. Although attempts to synthesize rutaecarpine from norharman (291) and from 3-β-indolylethylamine failed (292), the synthesis proved successful when 3-β-indolylethylamine-2-carboxylic acid was used as starting material. Condensation of this acid with *o*-nitrobenzoylchloride gives rise to *o*-nitrobenzoyl 3-β-indolylethyl-



LXXIV

amine-2-carboxylic acid; this is reduced by ferrous sulfate and ammonium hydroxide to the corresponding amino compound LXXIV which is converted to rutaecarpine by heating in carbon tetrachloride with phosphorus oxychloride (293). The indolyl acid necessary for this synthesis is obtained by the action of alcoholic potassium hydroxide on 2-keto-2,3,4,5-tetrahydro-3-carboline (294, 295). Rutaecarpine can be obtained more directly,



LXXV

however, by condensing 2-keto-2,3,4,5-tetrahydro-3-carboline (295) with methyl anthranilate with the aid of phosphorus trichloride (296). The alkaloid is also obtained by heating to 195° for 20 minutes an intimate mixture of 2-keto-2,3,4,5-tetrahydro-3-carboline and isatinic anhydride (297, 298), or by treating *N*-*o*-nitrobenzoyl-2-keto-2,3,4,5-tetrahydro-3-

carboline with glacial acetic acid and zinc dust (294). A further synthesis of rutaecarpine consists in condensing *o*-aminobenzaldehyde with the perchlorate of 4,5-dihydro-3-carboline obtained from *N*-formyltryptamine by cyclization. The product of the condensation is the perchlorate of compound LXXV and this on oxidation in acetone solution with chromic acid in dilute acetic acid at 80–90° in the presence of sodium acetate, gives a 12% yield of rutaecarpine. However, a 70% yield of rutaecarpine is obtained by allowing an aqueous solution of the hydrochloride of 4,5-dihydro-3-carboline and *o*-aminobenzaldehyde to stand 10 hours at 25° and then treating with potassium ferricyanide in a phosphate-buffered solution, pH 6.9, for 17 days at 25° (299).

Evodiamine has also been synthesized. Heating *N*-methylisatoic acid anhydride (prepared by the action of ethyl chloroformate on methylanthranilic acid) with tryptamine produces 3-[β-*N*-methylanthranoylaminoethyl]-indole which is converted to evodiamine by heating with ethyl ortho-formate (300, 301).

VI. The Alkaloids of Yohimbe

The literature concerning this group of alkaloids is somewhat confused because of the existence of many isomers and the uncertain homogeneity of a number of the bases reported. Yohimbehe bark, the main source of yohimbine, is obtained from a tree (*Pausinystalia yohimba* Pierre, syn., *Corynanthe yohimbe* K. Schum.; Rubiaceae) indigenous to the Cameroons and the French Congo and further confusion is due to the fact that the genera *Pausinystalia*, *Corynanthe*, and *Pseudocinchona* have at one time been considered identical. Separation of the last two genera has been suggested on the basis that species containing no yohimbine should belong to *Pseudocinchona* whereas those containing this alkaloid should be included under the genus *Corynanthe* (302, 303).

The alkaloid yohimbine has also been reported in *Corynanthe paniculata* Welw., in which it occurs together with paniculatine (302), in *C. macroceras* (K. Schum.) Brant (304), and *Pausinystalia trillesii* Beille (305). The mother liquors from the commercial preparation of yohimbine contain several isomeric alkaloids, i.e., isoyohimbine (mesoyohimbine) (306–311), alloyohimbine (307, 310, 312), corynanthidine (α-yohimbine) (313, 314), β-yohimbine (311, 315, 316), γ-yohimbine (315), δ-yohimbine (316), pseudoyohimbine (317) and corynantheine (317, 318). However, the fact that corynantheine is not always found in commercial yohimbe bark together with its definite isolation from *Pseudocinchona africana* A. Chev. (318), may be taken as an indication that commercial yohimbe bark

does not always consist exclusively of *Pausinystalia yohimba* Pierre. The same conclusion can be drawn from the occurrence of corynanthidine (α-yohimbine). Besides the alkaloids enumerated, yohimbenine (319, 320) and yohimbene (321) have also been reported, but the former is still of doubtful identity. *Pseudocinchona africana* A. Chev., from which corynanthidine (322) and corynantheine (318) have been isolated, also contains corynanthine (318, 324, 325) and corynantheidine (322).

Quebrachine (326), the main alkaloid of *Aspidosperma quebracho-blanco* Schlecht., has been definitely shown to be identical with yohimbine (327–330), although the identity has repeatedly been questioned (306, 331, 332). Mitraphylline, an isomer of yohimbine, is obtainable from the bark of *Mitragyna stipulosa* Kuntze (333, 334), in which it is accompanied by mitrivermine which appears to be a methoxymitraphylline (335). The alkaloid rauwolscine which will be described with the alkaloids of rauwolfia, is also an isomer of yohimbine.

Numerous methods for the quantitative determination of yohimbine have been described. These mostly consist in isolating the crude base and determining the quantity of alkaloid either gravimetrically as one of its salts (336–341), or volumetrically (342). The alkaloid can also be determined by precipitation of a complex formed with salts of heavy metals (343–345). A number of color tests have been described (346–349): yohimbine in contact with concentrated sulfuric acid and potassium dichromate develops a violet streak which changes to blue and then green (343); a mixture of concentrated sulfuric acid, an aqueous solution of chloral and a solution of yohimbine hydrochloride on warming shows a blue color (350–352a). Both yohimbine and corynanthine when mixed with vanillin or piperonal and sulfuric acid develop a violet color and both bases when heated with epichlorohydrin develop a brown color which is changed to a cherry red by the addition of a few drops of concentrated nitrous acid (353). If in the test with vanillin, hydrochloric acid be used instead of sulfuric acid, a rose-violet color is produced (354). Yohimbine yields catalytic and reduction waves at the dropping mercury electrode and can be determined polarographically in the absence of other alkaloids (355).

The alkaloid content of commercial yohimbe bark is not constant: it is on an average 3.2–1.6%, but it can be as low as 0.5% and as high as 6.1% (356). It may be added, however, that methods of determination are not all equal in value and whereas 1 kg. of a given sample of bark yields 1.6 g. of yohimbine hydrochloride by one method of extraction, it yields 8.4 g. by another (302).

1. Isolation of Yohimbine

Several methods have been described for the isolation of yohimbine (357–359). That of Chemnitius is as follows (358):

The powdered bark (1.5 kg.) is sifted and moistened with 20% sodium carbonate solution in such a manner that the mass adheres together when pressed with the fingers. The mass is allowed to stand for 1 day with occasional stirring and subsequently extracted with ether in a Soxhlet apparatus for 4–5 hours, the extract being allowed to collect over a cold saturated solution of oxalic acid. The ether is distilled off and the cooled aqueous solution filtered into a separatory funnel, the filter being washed with a little water. The filtrate is covered with ether, carefully saturated with powdered sodium carbonate and shaken vigorously. After separation of the ether layer the aqueous solution is extracted again with several decreasing volumes of ether. The combined ether extract is concentrated, dried over fused calcium chloride, filtered and exactly neutralized with anhydrous alcoholic hydrogen chloride. The brown precipitate which separates is treated with anhydrous acetone for 24 hours with occasional stirring. The acetone dissolves the resinous components, leaving the bright yellow yohimbine hydrochloride which is filtered, washed with acetone, and dried.

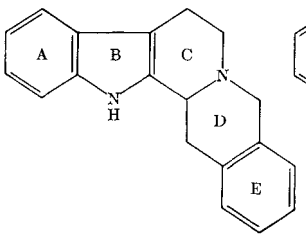
2. Yohimbine

Yohimbine, $C_{21}H_{26}O_3N_2$ (325, 360), the major alkaloid of yohimbe bark is a monoacidic base forming salts with only one equivalent of acid. It forms an acetyl derivative (319) and under certain conditions, a diacetyl derivative (361). On hydrolysis with alkalis, yohimbine loses a methyl group and gives rise to yohimbic acid, $C_{20}H_{24}O_3N_2$ (362, 363). Hence, the base contains both a hydroxyl group and a carbomethoxy group and it is probable that the second acetyl group in the diacetyl derivative is attached to the nonbasic nitrogen which must, therefore, be secondary (364). The basic nitrogen is tertiary and the base gives rise to a methiodide (361). The presence of the carbomethoxy group is confirmed by the reconversion of yohimbic acid to yohimbine on treatment with methanol and hydrogen chloride (360, 365). Numerous homologues of yohimbine have also been prepared by treatment of the acid with the required alcohol and hydrogen chloride (360, 365–368). The carbomethoxy group is reduced to a primary alcohol by sodium in ethanol with the formation of yohimbyl alcohol (361). On the other hand, the presence of an alcoholic group is confirmed by the formation between yohimbine and sulfuric acid of an ester decomposed by alkali to apoyohimbine, $C_{21}H_{24}O_2N_2$, which differs from yohimbine by the elements of water. Apoyohimbine contains a double bond which can be hydrogenated with the formation of dihydroapoyohimbine (deoxyyohimbine). The same reactions take place with yohimbic acid (369, 370). Furthermore, when yohimbic acid is decarboxylated it gives rise to the alcohol yohimbol, $C_{19}H_{24}ON_2$ (371), which is also accompanied by a small quantity of yohimbone, $C_{19}H_{22}ON_2$, if the decarboxylation takes place in the presence of soda lime. Yohimbone is also obtained from yohimbine

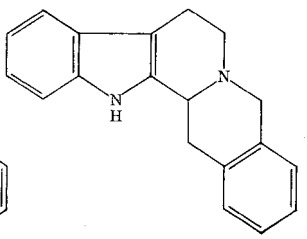
by the Oppenauer reaction (372). If, however, yohimbic acid is heated with thallium hydroxide desoxyyohimbol, $C_{19}H_{24}N_2$, is obtained (372). Although yohimbol is isomeric with the alkaloid cinchonamine, it differs from it pharmacologically (373).

The first insight into the structure of yohimbine came through the degradation of the base to substituted indoles. A mixture of indoles is obtained on heating yohimbine either with soda lime (369, 374), zinc dust, or superheated steam (374), or by dry distillation of yohimbic acid (312); it was eventually found to consist of 3-ethylindole and skatole (375). 3-Ethylindole is also obtained as a product of the potash fusion of the alkaloid (376). Cold potassium permanganate oxidizes yohimbine to *o*-oxycarbanil, $C_7H_5O_2N$, whereas the hot reagent produces an acid (307), shown to be identical with oxalylanthranilic acid (377). On the other hand diacetylyohimbine, when gently warmed with 1 :1 nitric acid, is oxidized to a mixture of succinic acid and an acid $C_8H_5O_4N_3$, which on heating loses carbon dioxide and gives rise to 6-nitroindazole so that it is a 6-nitroindazolecarboxylic acid (378) probably formed from the indole part of the molecule. However, the destructive distillation of yohimbine proved more important than its oxidation, giving rise as it does to indolyl-2-carboxylic and the monoacidic base harman, thus revealing the nuclear structure of the top moiety of the molecule.

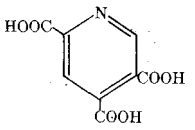
The first indication of the nature of the remainder of the molecule was obtained in the isolation of isoquinoline as a result of heating yohimbine with zinc dust or with superheated steam (374). Dehydrogenation of yohimbine, however, with selenium yields yobyrine, $C_{19}H_{16}N_2$, the ill-named tetrahydroyobyrine (tetrabyrine), $C_{19}H_{20}N_2$, and ketoyobyrine (379–382); it is from the further degradation of these substances that the structure of yohimbine was finally elucidated. Potassium permanganate oxidizes



LXXVI



LXXVII

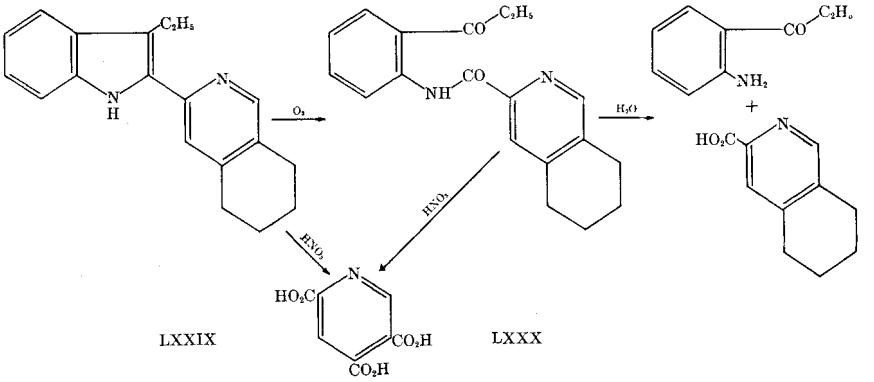


LXXVIII

yobyrine to phthalic anhydride, whereas nitric acid oxidizes tetrahydroisoyobyrine to pyridine, 2,4,5-tricarboxylic acid (LXXVIII). On the other hand, ketoyobyrine when boiled with potassium hydroxide in amyl alcohol yields norharman and 2,3-dimethylbenzoic acid (382). On the basis of the foregoing results formulae LXXVI and LXXVII were suggested to

represent yobyrine and tetrahydroisoyobyrine, respectively. In these, rings A, B and C are accounted for by the formation of norharman and rings D and E by the formation of isoquinoline (374) and of pyridine-2,4,5-tricarboxylic acid (LXXVIII).

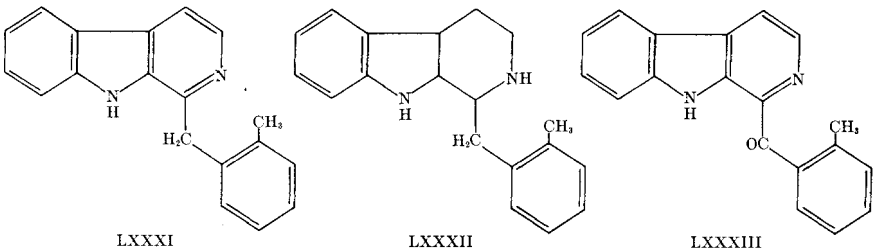
However, the catalytic hydrogenation of yobyrine yields hexahydroyobyrine (372, 383), whereas the catalytic hydrogenation of tetrahydroisoyobyrine yields octahydroisoyobyrine (383). Furthermore, the ozonization of tetrahydroisoyobyrine gives rise to a substance, $C_{19}H_{20}O_2N_2$, oxidized by nitric acid to pyridine-2,4,5-tricarboxylic acid, while on hydrolysis it is split into *o*-aminopropiophenone and 5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid (384). This series of reactions can be represented thus:



LXXIX LXXX

LXXVIII

and, therefore, tetrahydroisoyobyrine is not LXXVII, but 2-[3-(5,6,7,8-tetrahydroisoquinolyl)]-3-ethylindole (LXXIX) while the ozonization product is represented by LXXX (384). Whereas yobyrine is oxidized by potassium permanganate to phthalic anhydride (382), chromic acid oxidizes it to phthalic acid and *o*-toluic acid. The latter could scarcely

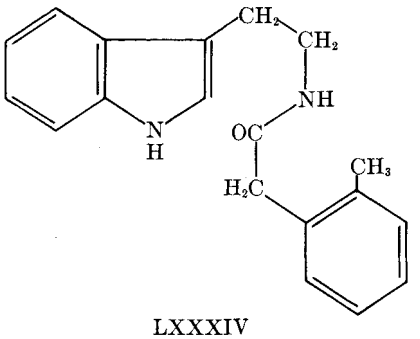


LXXXI LXXXII LXXXIII

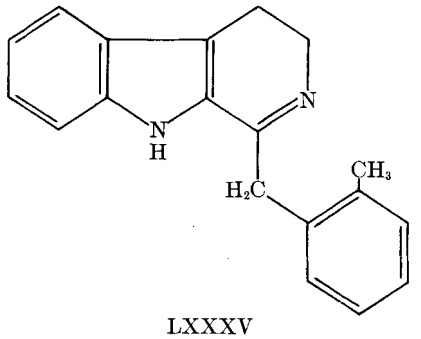
be an oxidation product of the substance LXXVI and formula LXXXI was suggested to represent yobyrine (372). Hexahydroyobyrine is formed by the complete hydrogenation of the pyridine ring in LXXXI as shown

by a comparison of ultraviolet absorption spectra (385) and must have formula LXXXII. According to structure LXXXI, yobyrine contains a CH_2 group attached to an α-position of a pyridine ring and, therefore, condensation with aldehydes should take place just as with α- and γ-picolines. This is indeed the case and condensation products of yobyrine can be prepared with acetaldehyde and *p*-nitrobenzaldehyde (372). Furthermore, the mild oxidation of yobyrine with selenium dioxide (372) replaces two hydrogens with an oxygen atom and forms yobyrone which must be represented by LXXXIII. Structures LXXXI and LXXIX assigned to yobyrine and tetrahydroisoyobyrine respectively have both been confirmed by synthesis.

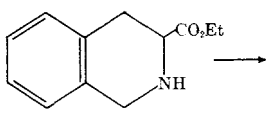
a. Synthesis of Yobyrine. 3-β-*o*-Tolylacetamidoethyl indole (LXXXIV), the condensation product of *o*-tolylacetic acid and tryptamine, undergoes



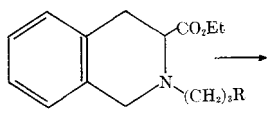
LXXXIV



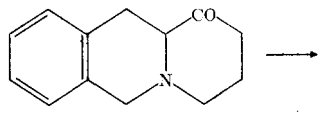
LXXXV



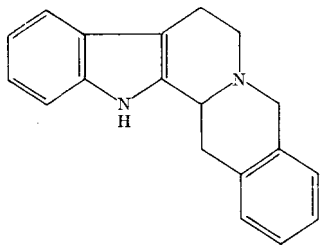
LXXXVI



LXXXVII



LXXXVIII

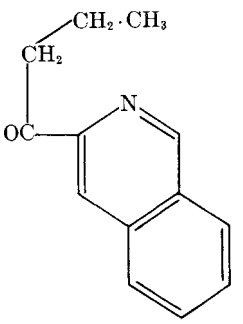


LXXXIX

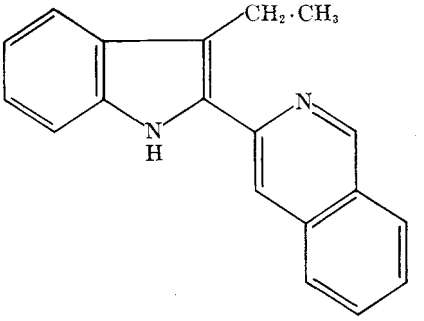
ring closure in the presence of phosphoryl chloride with the formation of dihydroyobyrine (LXXXV) which on dehydrogenation with palladium black is transformed to yobyrine (LXXXI) (386, 387). The atmospheric

oxidation of dihydroyobyrine (LXXXV) yields yobyrone (387) identical with the product of oxidation of yobyrine with selenium dioxide (372). A second synthesis of yobyrine is interesting because it produces an intermediate which on dehydrogenation, exhibits the same type of ring scission as yohimbine. Ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (LXXXVI) when condensed with γ-bromopropylcyanide, gives ethyl 2-γ-cyanopropyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (LXXXVII; R = CN), which is alcoholyzed to the corresponding diester (LXXXVII, R = CO_2Et). The diester is converted by means of the Dieckmann reaction to 1-keto-7 :8-benzo-1,2,3,4,6,9-hexahydropyridocoline (LXXXVIII), the phenylhydrazone of which is transformed by the Fischer indole reaction to 7,8-benzo-1,2-(2′,3′-indolo)-3,4,6,9-tetrahydropyridocoline (LXXXIX). However, all attempts to dehydrogenate this product to obtain substance LXXVI caused ring scission and the formation of yobyrine (386).

b. Synthesis of Tetrahydroisoyobyrine. The reaction between 3-carboxy-1,2,3,4-tetrahydroisoquinoline and *n*-propyllithium yields a mixture of 3-butyryl-1,2,3,4-tetrahydroisoquinoline and its dehydrogenation product, 3-butyrylisoquinoline (XC). Dehydrogenation of the mixture with palladium black gives pure (XC) which forms a phenylhydrazone converted by the Fischer indole reaction to 2-(3-isoquinolyl)-3-ethylindole (XCI)



XC

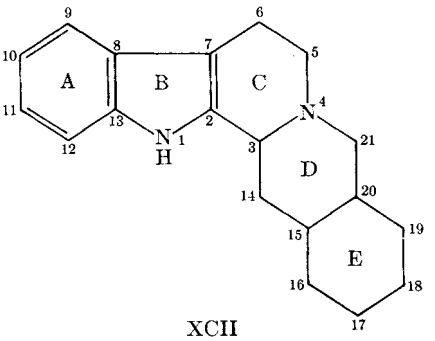


XCI

identical with the product of the dehydrogenation of tetrahydroisoyobyrine with palladium black (387). The same series of reactions applied to 3-carboxy-5,6,7,8-tetrahydroisoquinoline gives rise to tetrahydroisoyobyrine (tetrabyrine) (387).

Except for the indole nucleus, yohimbine is fully hydrogenated and on the basis of the evidence so far accumulated formula XCII has been advanced to represent the nuclear structure of the alkaloid (384). The structure of the two main products formed simultaneously in the course of the dehydrogenation of yohimbine with selenium is firmly established

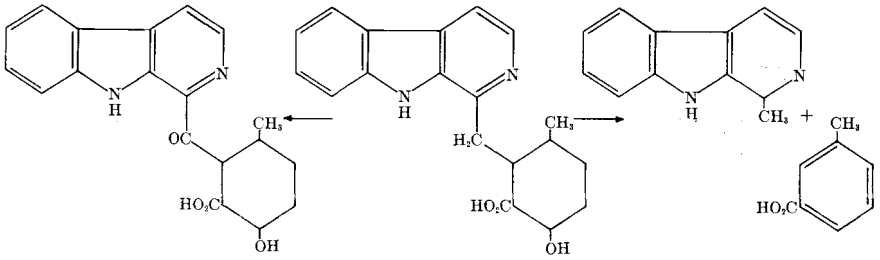
and it is obvious that their formation is due to cleavage of the molecule at the basic nitrogen atom of the carboline nucleus, between positions 4–5



XCII

and 4–21. It has been shown by model experiments that such are the weak points in a molecule of type XCII (388). To complete the formula of yohimbine, it is necessary to add a hydroxyl group and a carbomethoxy group to XCII.

The position of the carbomethoxy group was determined by a study of the reaction of lead tetraacetate with yohimbine (389). With lead tetraacetate, yohimbic acid is oxidized to tetradehydroyohimbic acid while apoyohimbic acid is oxidized to tetradehydroapoyohimbic acid. Both these oxidation products show absorption spectra very similar to that of yobyrine. Hence lead tetraacetate attacks both molecules in the same position and it is again ring C which becomes aromatized at the expense of ring D (389). Similarly, the dehydrogenation of yohimbine with palladium black in the presence of maleic acid yields tetradehydroyohimbine (390). When tetradehydroyohimbine hydrochloride is boiled with amyl alcoholic potassium hydroxide, it is split into harman and *m*-toluic acid

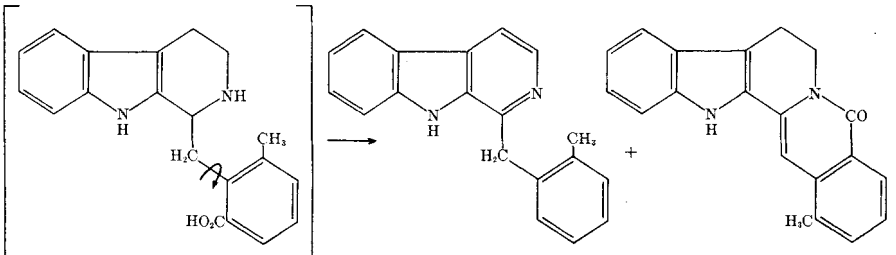


XCIV XCIII

(389). Tetradehydroyohimbic acid was, therefore, represented by formula XCIII which is related to that of yobyrine and this assumption is supported by the fact that, like yobyrine, tetradehydroyohimbic acid is oxidized by

selenium dioxide to a ketone which would then be represented by formula XCIV. Recently, however, it has been shown by a study of absorption spectra that tetradehydroyohimbine contains five rings and that the top three possess the same structure as sempervirine and serpentine (390a). The formation of *m*-toluic acid and of harman points to position 16 (XCII) as that occupied by the carbomethoxy group since C-14 must be the methyl group of harman and C-21 the methyl group of *m*-toluic acid (391). On the basis of color tests it has been suggested that the carbomethoxy group occupied position C-5 (392), but the foregoing experimental evidence disposes of that suggestion (393). Carbon atom 14 seems precluded as the position of the hydroxyl group which was assigned position 17 (391), although 18 and 19 were also possible.

The position of the carbomethoxy group received confirmation in the eventual elucidation of the structure of ketoyobyrine, the third of the three main products of the dehydrogenation of yohimbine with selenium. This work was carried out independently in five different laboratories and published almost simultaneously (394–398). Ketoyobyrine differs from both yobyrine and tetrahydroisoyobyrine in being nonbasic. It contains the norharman nucleus since on heating with potassium hydroxide in amyl alcohol it gives rise to norharman and hemellitylic acid (2,3-dimethylbenzoic acid). The first indication of the true structure of ketoyobyrine came through a comparison of its ultraviolet absorption spectra with that of rutaecarpine. The two were found to be remarkably similar (394, 399).

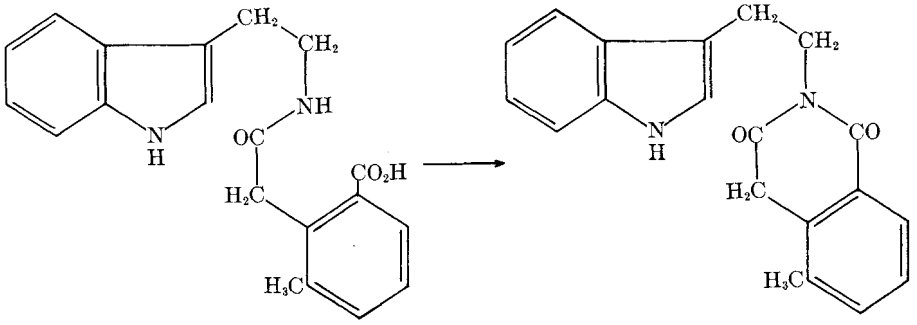


XCV XCVI XCVII

It is assumed that the first step in the dehydrogenation of yohimbine with selenium aromatizes ring E with elimination of the hydroxyl group at the expense of ring D which breaks open between N-4 and C-21, giving rise to an hypothetical intermediate (XCV). This intermediate in part becomes dehydrogenated and decarboxylated to yobyrine (XCVI) and in part by rotation of the aromatized ring E through 180° about C.14–C.15, followed by dehydrogenation at C.3–C.14 and lactamization, gives rise to ketoyobyrine (XCVII) (394a, 395, 396). Formula XCVII shows that ketoyobyrine is not fully aromatized and indeed, heating with palladium

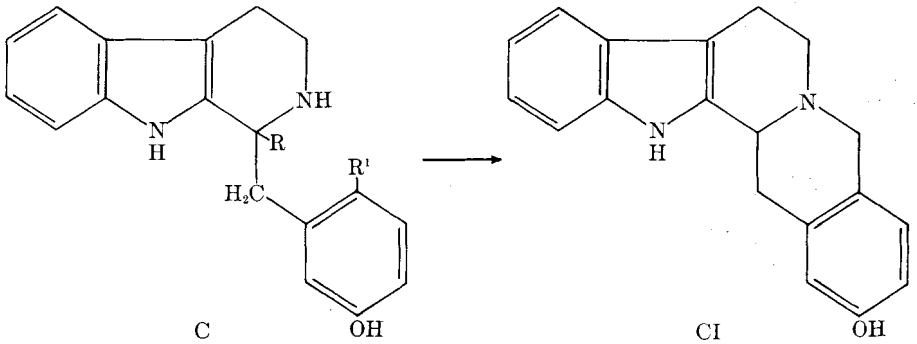
releases exactly one mole of hydrogen and yields dehydroketoyobyrine. In contrast with ketoyobyrine, its dehydrogenated product, on heating with amyl alcoholic potassium hydroxide, is converted to an amino acid, $C_{20}H_{16}O_2N_2$, which readily reverts to its precursor even on attempted recrystallization from alcohol (395).

c. Synthesis of Ketoyobyrine. The condensation of tryptamine with 6-methylhomophthalic acid anhydride produces the amide XCVIII, which



XCVIII XCIX

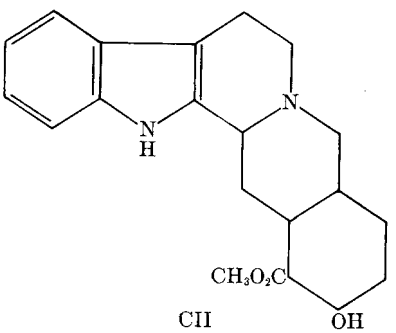
on attempted esterification with diazomethane is converted to the imide (XCIX). Under the action of phosphoryl chloride the imide undergoes cyclization and yields a compound identical with ketoyobyrine (XCVII) (396, 397, 398). This confirmation by synthesis of the structure assigned to ketoyobyrine definitely establishes position C-16 as that occupied by the carbomethoxy group; it further lends support to the structure (XCIII) assigned to tetradehydroyohimbic acid.



C CI

There remains to determine the position occupied by the hydroxylic group. By the cautious decarboxylation of yohimbic acid a hydroxylic compound named yohimbol is obtained (371). The condensation of tryptamine hydrochloride with *m*-hydroxyphenylpyruvic acid in water at pH 4.2 and 25° in sunlight yields 2-(*m*-hydroxybenzyl)-2,3,4,5-tetrahydro-

3-carboline-2-carboxylic acid (C, R = COOH, R′ = H) which is decarboxylated to 2-(*m*-hydroxybenzyl)-2,3,4,5-tetrahydro-3-carboline (C, R = R′ = H). The hydrochloride of this base is converted by formaldehyde in a buffered solution (pH 4.4) to 2-(3-hydroxy-6-hydroxymethylbenzyl)-2,3,4,5-tetrahydro-3-carboline (C,R = H,R′ = CH_2OH) which undergoes ring closure when a hot solution of its hydrochloride is alkalized with hot sodium carbonate solution, yielding a hexadehydroyohimbol (CI). When in this series of reactions *p*-hydroxyphenylpyruvic acid was substituted for its *m*-isomer, it was claimed that the reaction with formaldehyde did not take place. Since this synthesis was carried out under so-called physiological conditions, it was argued that failure of the *p*-isomer to condense militates in favor of the hydroxyl group of yohimbine occupying position 17 (formula XCII) (391). It was found later, however, that the product of the reaction with CH_2O is not C(R = H,R′ = CH_2OH) but CI. Furthermore, *p*-substitution does not prevent condensation with formaldehyde even if the substituent is a hydroxyl group since 2-(3-methoxy-4-hydroxybenzyl)-2,3,4,5-tetrahydro-3-carboline condenses, although there must be a substituent in the metaposition (400, 401). A more convincing proof of the position of the hydroxyl group is obtained by the Oppenauer oxidation of yohimbine (372). This oxidation converts the secondary hydroxyl group to a keto group, but the product (yohimbone) no longer contains the carbomethoxy group. The ready scission of the carbomethoxy group indicates that the oxidation gives rise to a β-keto acid and, therefore that the hydroxyl group in yohimbine must be attached to C-17. Moreover, the production of a small yield of *p*-cresol in the distillation of yohimbine hydrochloride with zinc dust (372) leads to the same conclusion. The



CII

structure of yohimbine is, therefore, completely established and is represented by CII. Although some attempts have been made to synthesize the nuclear structure of yohimbine (386, 400, 402), the synthesis of the alkaloid itself is rendered quite difficult owing to the presence in the

molecule of five asymmetric centers. In connection with the synthesis of a degradation product of yohimbine it has recently been shown that rings D and E (XCII) of the base are *trans* fused (402a).

3. Yohimbene

Yohimbene, $C_{21}H_{26}O_3N_2$ (321, 403), was isolated from the mother liquors of the industrial preparation of yohimbine. It is a methyl ester of yohimbenic acid and the acid is produced on saponification of the base. The acid is converted by the action of dimethylsulfate to a methyl betaine, $C_{21}H_{26}O_3N_2$. On decarboxylation with soda-lime, yohimbenic acid yields the same yohimbol ($C_{19}H_{24}ON_2$) as yohimbic acid (371). It has since been shown, however, that most of the product of the decarboxylation is yohimbone and further that the Oppenauer oxidation of yohimbenic acid produces not yohimbone, but yohimbenone (372). It is, therefore, assumed that the steric difference is destroyed at the high temperature of the decarboxylation, but retained under the mild conditions of the oxidation (372).

4. Isoyohimbine

Isoyohimbine, $C_{21}H_{26}O_3N_2$ (307, 403), obtained from the mother liquors from the large-scale preparation of yohimbine, is also isomeric with the latter (315). Spiegel's mesoyohimbine (306) was probably impure isoyohimbine (307–311, 404, 405). The latter is saponified by alkalis to isoyohimbic acid ($C_{20}H_{24}O_3N_2$), which is converted back to isoyohimbine by the action of methanolic hydrogen chloride, or esterified to isoyohimbethyline with ethanolic hydrogen chloride (310). Just like yohimbine, isoyohimbine when dehydrogenated by heating with selenium yields yobyrine, tetrahydroisoyobyrine and ketoyobyrine (380, 383). Moreover, the decarboxylation of isoyohimbic acid produces yohimbol (371). It is probable, therefore, that isoyohimbine is a stereoisomer of yohimbine. The alkaloid yields a diacetyl derivative which is quantitatively converted by alcoholic potassium hydroxide to isoyohimbic acid, but is hydrolyzed by hydrochloric acid to an *O*-acetylisoyohimbine containing a secondary nitrogen atom (364). This conversion of an initially tertiary nitrogen into a secondary nitrogen involves the rupture of a ring and the formation of a double bond. This is confirmed by the catalytic hydrogenation of the product which results in the absorption of one mole of hydrogen. In the diacetyl derivative one acetyl group is linked to oxygen while the other is linked to the nonbasic nitrogen since the compound can still form with methyl iodide a quaternary salt.

5. Alloyohimbine

Alloyohimbine, $C_{21}H_{26}O_3N_2$ (307, 310, 312), is isomeric with yohimbine and is the methyl ester of alloyohimbic acid, liberated when the base is

saponified. The distillation of alloyohimbine with soda lime gives a better yield of harman and β-ethylindole than does yohimbine under the same conditions (312). However, alloyohimbic acid when decarboxylated produces an amino alcohol ($C_{19}H_{24}ON_2$) isomeric with, but different from yohimbol similarly obtained from yohimbic acid (371) together with alloyohimbone (372).

6. β-Yohimbine

β-Yohimbine, $C_{21}H_{26}O_3N_2$ (316) is characterized by its unusually low solubility in methanol. It is precipitated from acidic solutions by alkalis as a hydrated gel which turns into a crystalline monohydrate on heating. β-Yohimbine is isomorphous with yohimbine and an equimolecular mixture of the two bases has the same melting point as yohimbine although it depresses the melting point of alloyohimbine. It is separated from yohimbine by crystallization from methanol. Saponification of β-yohimbine with alkali converts it to β-yohimbic acid of which it is the methyl ester. The alkaloid has the same effects on arterial pressure and the negative nervous system in dogs as yohimbine (406).

7. γ-Yohimbine

γ-Yohimbine, $C_{21}H_{26}O_3N_2$ (315), occurs in very small quantity in the liquors from the technical preparation of yohimbine. On saponification it yields γ-yohimbic acid, which, on decarboxylation produces yohimbol. Hence γ-yohimbine differs from yohimbine either in that its carbomethoxy group occupies a different position than it does in the latter, or in that the two are stereoisomers.

8. δ-Yohimbine

δ-Yohimbine, $C_{21}H_{26}O_3N_2$ (316), occurs only in very small amount in the bark. On saponification it yields δ-yohimbic acid, which is precipitated from solutions of its salts in highly hydrated form, but separates from methanol as anhydrous crystals. Just as β-yohimbine, δ-yohimbine has the same effects on arterial pressure and the negative nervous system in dogs as yohimbine (406). When rings D and E are *trans* as in yohimbine, four stereoisomers are possible. On decarboxylation two of these, yohimbine and corynanthine, yield yohimbol while δ-yohimbine and ε-yohimbine, produced along with yohimbine by the esterification with methanol of the sulfuric ester of yohimbic acid (372), give rise to epiyohimbol (406a).

9. Pseudoyohimbine

Pseudoyohimbine, $C_{21}H_{26}O_3N_2$ (317, 406a), has been isolated from the mother liquors of the technical preparation of yohimbine. The dehydrogenation of the base with selenium gives rise to yobyrine, tetraisoyobyrine and

ketoyobyrine. Hydrolysis of the alkaloid with potassium hydroxide produces pseudoyohimbic acid which can be re-esterified with methanol to pseudoyohimbine. Whereas decarboxylation of the acid affords yohimbone, the Oppenauer oxidation of the base gives pseudoyohimbone. However, the Wolff-Kishner reduction of the latter does not produce pseudoyohimbane, but yohimbane identical with that obtained from yohimbine and corynanthine (406b). A comparison of these results with those obtained from yohimbene show a striking similarity between the two alkaloids. Further, both bases are dextrorotatory whereas their hydrochlorides are levorotatory. Since rings D and E in yohimbine are *trans*, it is assumed that in pseudoyohimbine and yohimbane these rings are *cis*.

10. Corynanthine

Corynanthine, $C_{21}H_{26}O_3N_2$ (324, 407, 408), discovered in the bark of *Pseudocinchona africana*, is isomeric with yohimbine, but levorotatory (325). It also occurs in the bark of *Corynanthe yohimbe* (409). When boiled with acetic anhydride and sodium acetate, the base forms both a diacetyl- and a monoacetylcorynanthine (410). The Oppenauer oxidation converts corynanthine to yohimbone, the product of the similar oxidation of yohimbine (372). Dehydrogenation of the base with selenium produces yobyrine and tetrahydroisoyobyrine, just like yohimbine (322). When the base is hydrolyzed with 2.2 *N* hydrochloric acid, the product is corynanthic acid which can be re-esterified with methanol and hydrogen chloride to corynanthine (411). If, on the other hand, hydrolysis is effected by alcoholic potassium hydroxide, an acid ($C_{20}H_{24}O_3N_2$) is obtained which when re-esterified with methanol and hydrogen chloride, gives rise to a dextrorotatory base (412), identical with yohimbine (413). It is, therefore, concluded that the action of alkali brings about the isomerization of corynanthic acid to yohimbic acid. Furthermore, the decarboxylation of corynanthic acid affords apocorynanthol which on catalytic hydrogenation gives rise to desoxycorynanthol, $C_{19}H_{24}N_2$ also obtainable from the sulfuric ester of corynanthine (406c, 413a). Although apocorynanthol is different from yohimbol, desoxycorynanthol is identical with yohimbane obtained by the Wolff-Kishner reduction of yohimbone (406c, 413b). Hence, yohimbine and corynanthine only differ in the spatial position of their functional groups (carbomethoxy and hydroxyl) which are *cis* in corynanthine and *trans* in yohimbine (406c, 413, 413c).

11. Corynanthidine

Corynanthidine (α-yohimbine), $C_{21}H_{26}O_3N_2$ (309, 315, 322, 323, 404), discovered in *Pseudocinchona africana* (322), where it occurs with corynanthine, is an isomer of the latter. It had previously been found in the

mother liquors from the preparation of yohimbine (313, 314). Its isolation and purification is facilitated by the almost total insolubility of its hydrochloride in alcohol. It is a levorotatory base converted on saponification to corynanthidinic acid, $C_{20}H_{24}O_3N_2$ (315), which when esterified with methanol and hydrogen chloride, gives back corynanthidine. The dehydrogenation of corynanthidine with selenium produces yobyrine and tetrahydroisoyobyrine, just as yohimbine and corynanthine (322) and the ultraviolet absorption spectra of the last two alkaloids are superposable on that of corynanthidine (414). In contrast, however, the Oppenauer oxidation of corynanthidine does not give rise to yohimbone, which is obtained by the similar oxidation of both yohimbine (372) and corynanthine, but to the isomeric corynanthidone (314). Hence, the skeletal structure of corynanthidine is probably the same as that of yohimbine, but the hydroxyl group (and perhaps also the carbomethoxy group) in the former occupies a different position than it does in the latter.

12. Corynantheine

Corynantheine, $C_{22}H_{26}O_3N_2$ (406a, 415), was first reported as an amorphous base forming a crystalline hydrochloride (302, 317, 318, 359, 416). It occurs in *Pseudocinchona africana*, together with corynanthine, corynanthidine and corynantheidine and pseudoyohimbine. Eventually, however, this amorphous base was separated into a crystalline, dextrorotatory base (corynantheine) and an amorphous base which seemed to be isomeric (314, 415a, 417). Corynantheine has an ultraviolet absorption spectrum which differs from those of corynanthine and yohimbine, but is very similar to those of the diacetyl derivatives of these two bases (414). Besides a carbomethoxy group, corynantheine contains a methoxyl group. Saponification with potassium hydroxide gives rise to methanol and corynantheic acid (415).

The dehydrogenation of corynantheine with selenium gives rise to a base $C_{19}H_{22}N_2$, first named corynanthyrine (415a) and later found to be identical with alstyrine, the product of the selenium degradation of alstonine (417a). Whereas tetrabyrine (one of the products of the degradation of yohimbine), when ozonized and the oxidation product hydrolyzed, yields *o*-aminopropiophenone and 5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid (384) (*cf.* p. 410), alstyrine under the same treatment gives rise to *o*-aminopropiophenone and 3,4-diethylpyridine-6-carboxylic acid. Consequently, alstyrine is α-(α-diethyl-3,4-pyridine)-β-ethyl indole (415a). The action of lithium aluminum hydride on corynantheine not only reduces the carbomethoxy group to a primary alcohol, but hydrolyzes the methyl ether group or substitutes hydrogen for the methoxyl giving rise to desmethylcorynantheine alcohol and desmethoxycorynantheine alcohol,

the latter still containing a reducible double bond. The former, desmethylcorynantheine alcohol, no longer contains a double bond but contains a carbonyl group since it forms a *p*-nitrophenylhydrazone. Lithium aluminum hydride is known to hydrolyze enol ethers readily (417b) and therefore, corynantheine must contain a methyl group attached in ether linkage to an enol. This conclusion is supported by the fact that ethereal hydrogen chloride transforms corynantheine into a base still having the carbomethoxy group of the parent alkaloid, but having lost a methyl group, and this new base gives rise to a *p*-nitrophenylhydrazone, thus indicating the presence of a carbonyl group. The substance, desmethylcorynantheine shows the reactions of a β-keto ester and consequently the relative positions of the carbomethoxy and methoxy groups in corynantheine are known to be *ortho*. This is supported by the ultraviolet absorption spectrum of corynantheine, which indicates that the carbomethoxy group is conjugated with the double bond (417c). Desmethylcorynantheine undergoes decarboxylation readily and on heating with 3% aqueous hydrochloric acid gives rise to descarboxycorynantheone (417b). From these facts it has been concluded that corynantheine contains the five rings present in yohimbine, that ring E carries the carbomethoxy and methoxy substituents in vicinal positions and contains the enolic double bond (417b). It has recently been argued, however, that since corynantheone (descarboxydesmethylcorynantheine alcohol) and corynantheane, the Wolff-Kishner reduction product of corynantheone, when dehydrogenated with selenium do not give rise to yobyrine and tetrabyrine, they cannot contain the five rings of yohimbine and consequently that they cannot be stereoisomers of yohimbone and yohimbane (417d). It appears from these experiments that the formation of alstyrine from corynantheine is independent of the double bond and that the three ethyl groups present in the degradation base, if they do not pre-exist, may arise from the rupture of C—N bond as in the production of 3,4-diethylpyridine from ethyl quinuclidine (417d).

13. Corynantheidine

Corynantheidine, $C_{22}H_{28}O_3N_2$ (418), is the fourth crystalline alkaloid isolated from *Pseudocinchona africana*.

The crude alkaloid obtained from the plant is dissolved in benzene from which the corynanthine crystallizes. The sirupy residue left after evaporation of the benzene mother liquor is dissolved in 2% formic acid, the solution alkalized with ammonia and the precipitated base dissolved in ethanol. Corynantheine is precipitated from this solution as the *d*-tartrate and filtered. The base recovered from the ethanol mother liquor is dissolved in boiling ethanol, the solution filtered hot and added to a solution of picric acid. On cooling, the picrate of corynantheidine separates.

Corynantheidine crystallizes from acetone with one molecule of solvent, readily forms crystalline salts and is isomeric with corynantheine.

VII. The Quebracho Alkaloids

The alkaloids described in this section are obtained from species of *Aspidosperma* and of *Vellesia*. Quebracho colorado (*Quebrachia Lorentzii* Griseb), the source of the tanning extract, in which the presence of loxopterygine, an ill-defined, ill-characterized alkaloid has been reported (419), is not included. Quebracho blanco, the bark of *Aspidosperma quebracho-blanco* Schlecht., which contains aspidospermine (420, 421), and quebrachine (yohimbine) (422), has also been claimed to contain two more crystalline bases, i.e., quebrachamine and aspidospermatine, and two amorphous bases, i.e., hypoquebrachine and aspidosamine (422). These findings have been confirmed by a later investigator (423), although in a more recent investigation of quebracho blanco, only five of these bases were reported and aspidosamine was not found (424). Two other alkaloids have been isolated from quebracho blanco although they were not named (425), but one of these is probably identical with quebrachamine (426), while the other which crystallizes from ethyl acetate as octahedra, m.p. 176–7°, is probably new. A further alkaloid, aspidospermicine, whose solutions show a blue fluorescence, occurs in *Aspidosperma polyneuron* Müell which contains 2–4% total alkaloids (423, 427). The alkaloid aspidospermine has also been found in *Aspidosperma quirandy* Hassler in which it is accompanied by aspidosamine, haslerine and quirandine (428); in *Vallesia glabra* Link and *Vallesia dichotoma* Ruiz & Pav. where it occurs with vallesine (429, 340, 431). The leaves of *Vallesia glabra* contain 4% while the stem contains 2% of aspidospermine (432). Quebracho blanco from Paraguay is said to be the richest in alkaloid content (433). It has been suggested that aspidosamine and hypoquebrachine are mixtures of decomposition products probably originating from aspidospermine which is known to undergo hydrolysis (425).

Paytine and paytamine are two bases which have been isolated from Payta bark (*Aspidosperma* spp.). The former is precipitated from solution by potassium iodide while the latter is not. The two bases are isomeric but paytamine is amorphous while paytine is crystalline. The latter when heated with alkalis gives rise to the crystalline paytone which is not formed by the former (434, 435, 436). Both alkaloids when boiled with perchloric acid show a fuchsin red color (436, 437).

1. Aspidospermine

Aspidospermine, $C_{22}H_{30}O_2N_2$ (420, 421), has been considered a weak base because it does not form crystalline salts. However, it is a relatively strong base having a pK = 8 (425a). It sublimes at 180° under diminished

pressure and distils at 220°/1–2 mm. When a crystal of potassium dichromate is added to a solution of the base in concentrated sulfuric acid, a brown coloration develops which becomes olive green after some time. A rose-red color is produced when the base is warmed with perchloric acid (425). Aspidospermine contains both an *O*-methyl and an *N*-acetyl, but no *N*-methyl group. The presence of an *N*-acetyl group is confirmed by the hydrolysis of aspidospermine with dilute hydrochloric acid to desacetylaspidospermine, a diacidic base which forms a dihydriodide and an *N*-benzoyl derivative, and is readily converted to the original base by acetylation. Furthermore, whereas aspidospermine reacts with methyl iodide only on prolonged heating to produce a mixture, desacetylaspidospermine reacts readily to form a dimethiodide. Both aspidospermine and the desacetyl base are converted by boiling hydriodic acid to a new base, desacetyldesmethylaspidospermine, termed aspidosine ($C_{19}H_{26}ON_2$) (425) which is phenolic and shows very intense color reactions with sulfuric acid (rose-red), sulfuric acid and either potassium dichromate, lead oxide or nitrous acid (reddish violet), with nitric acid-sulfuric acid mixture (orange-red) and with ferric chloride (greenish blue gradually changing to reddish brown). Desacetylaspidospermine reacts with nitrous acid to form what appears to be a nitro-nitroso derivative converted by the action of hydriodic acid to aspidosine.

In dilute sulfuric acid solution aspidospermine is oxidized by chromic acid to a crystalline acid ($C_{15}H_{24}O_2N_2$). From the foregoing data it is possible to conclude that desacetylaspidospermine is a secondary-tertiary base, containing a methoxyl group attached to an aromatic ring. The ultraviolet absorption spectrum of aspidospermine indicates the presence of a dihydroindole structure (438) and this evidence is supported by the action of ozone which results only in the formation of an amine oxide which is converted by thermal decomposition to aspidospermine and by hydrolysis to desacetylaspidospermine *N*-oxide (438a). Further evidence is found in the fact that desacetylaspidospermine has a basic nitrogen of approximately the same pK value as that of the alkaloid, and also a weakly basic one (pK = *ca.* 3) which is of the order to be expected for a secondary nitrogen linked to an aromatic ring, but too strong for one included in an indole system (425a). The isolation among the products of the dehydrogenation of aspidospermine with zinc dust and palladium of an isomorphous mixture of indole homologs affords further evidence of the presence of an indole nucleus in the base. The dehydrogenation also yielded a base which is presumably 3,5-diethylpyridine (438a).

2. Quebrachamine

Quebrachamine, $C_{19}H_{26}N_2$ (422, 426), is feebly basic and forms well-defined crystalline salts only with dibasic acids. It shows a positive test

with Ehrlich's reagent on warming, with vanillin and hydrochloric acid (violet) and with the Hopkins-Adamkiewicz reagent (blue), although it is unaffected by concentrated sulfuric acid. The addition of an oxidizing agent to a sulfuric acid solution of the base produces a blue color. These color reactions indicate the presence in quebrachamine of an indole nucleus and this indication is supported by the formation of a scarlet picrate and the presence in the base of an indifferent nitrogen atom. Quebrachamine forms a monomethiodide and a methosulfate and appears to be a monoacidic tertiary base. Oxidation of the base with concentrated nitric acid gives rise to picric acid, thus indicating the presence of a benzene ring (426).

3. Vallesine

Vallesine, $C_{20}H_{26}O_2N_2$ (439), is a crystalline base yielding crystalline salts with one equivalent of acid. It contains a methoxyl group and a *C*-methyl, but no iminomethyl nor active hydrogen. On hydrolysis with 2 *N* hydrochloric acid at room temperature it gives rise to formic acid and desformylvallesine, $C_{19}H_{26}ON_2$. By treatment with formic acid desformylvallesine can be reconverted to vallesine. Desformylvallesine on benzoylation gives rise to two products, one basic and one neutral. The basic product, $C_{26}H_{30}O_2N_2$, is the normal *N*-benzoyl derivative whereas the neutral product, $C_{26}H_{34}O_4N_2$, results from the addition of one benzoyl group and two moles of water and its formation obviously involves the opening of a ring. Desformylvallesine on acetylation gives a compound differing analytically from aspidospermine by containing CH_2 less, but not otherwise distinguishable from that base since it has the same melting point, same rotation and identical x-ray powder diagrams and infrared spectra. Similarly formyldesacetylaspidospermine differs from vallesine by containing CH_2 more, on the basis of analytical figures, but is undistinguishable from it by the above physical criteria (439). Furthermore, although desformylvallesine can be reconverted to vallesine by the action of formic acid, the mother liquor from which the product is crystallized also yields a quantity of a second formyl derivative which contains CH_2 more than vallesine and is identical with formyldesacetylaspidospermiue (439). No explanation has yet been offered for this anomaly.

VIII. Alkaloids of *Rauwolfia* Species

Several species of *Rauwolfia* (Apocynaceae) contain alkaloids, although *R. natalensis* Sond. has been reported to be devoid of them (440). Although the presence of alkaloids in these plants has been observed long ago (441), the actual isolation of definite bases has been carried out only recently. The root of *R. serpentina* Benth. contains the following five alkaloids:

ajmaline (rauwolfine (442)), ajmalinine, ajmalicine,* serpentine (isorauwolfine (442)) and serpentinine (443). The foregoing alkaloids are found in the plant originating from the hot, swampy Behar district of India. However, *R. serpentina* collected in the climatically milder Dehra Dun Valley contains no ajmaline and traces only of ajmalinine and ajmalicine, but yields isoajmaline and neoajmaline, which are isomers of ajmaline, together with two other, not well characterized alkaloids melting at 220 and 234° respectively (444). It is noteworthy that the physiological action of isoajmaline and neoajmaline differs markedly from that of ajmaline (445). Five of the alkaloids of *R. serpentina*, i.e., ajmaline, isoajmaline, ajmalicine, ajmalinine and serpentinine, also occur in *R. vomitoria* Afzel (446). The pinique-pinique of Colombia and the chalchupa of Guatemala are both identical with *R. heterophylla* Roem. and Schult (447), and the plant contains two alkaloids, chalchupine A and chalchupine B (448, 449). The bark of the South African "Quinine tree" of the Transkei or "Umjela" (*R. caffra* Sond. formerly *Tabernaemontana ventricosa* Hochst.) contains rauwolfine and two uncharacterized bases (450). Finally, *R. canescens* L., yields the alkaloid rauwolscine (451), isomeric with yohimbine and closely related to it in structure. Methods of assay of the alkaloids of *R. serpentina* involve extraction of the alkaloid and its subsequent gravimetric determination (452, 453).

1. Ajmaline

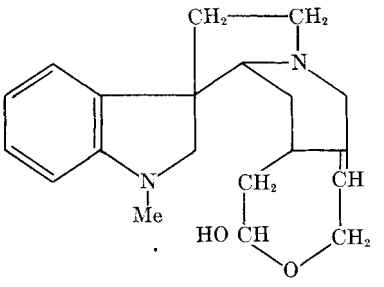
Ajmaline, $C_{20}H_{26}O_2N_2$ (443, 454), is an optically active base forming both a nitroso and a benzoyl derivative. These were first claimed to be nonbasic and, therefore, *N*-derivatives (454), although it has recently been shown that the latter is an *O*-benzoyl derivative giving rise to a crystalline hydrochloride and claimed that the former is probably a nitrite or an *O*-nitroso derivative (454a). Ajmaline contains one active hydrogen (Zerewitinow) and a methylimino group. It can be nitrated to trinitroajmaline and sulfonated to ajmalinesulfonic acid (454) and, therefore, must contain a benzene ring. The base is similar to strychnidine in its reactions. A methyl orange is produced on coupling with diazobenzenesulfonic acid and the reduction product obtained from the azo derivative is a *p*-aminodialkylaniline derivative. Furthermore, the action of nitrous acid on ajmaline in dilute hydrochloric acid produces an orange yellow *p*-nitrosoajmaline hydrochloride. Hence, of the two N atoms N(a) is tertiary and linked directly to a benzene ring. Since the methochloride of ajmaline couples normally with diazobenzenesulfonic acid it is possible

* Ajmalicine has not been analyzed although it is crystalline and two of its salts have been prepared.

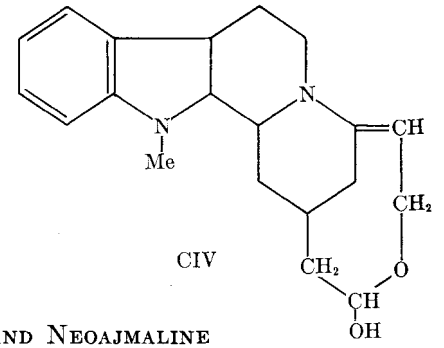
to conclude that N(b) is the basic center and also that ajmaline is a ditertiary base (454a).

Besides the *O*-benzoyl and the nitroso derivatives that indicate the hydroxylic function of one of the O-atoms, ajmaline forms a basic diacetyl derivative that is probably an enol-acetate plus alcohol acetate. Although the infrared absorption spectrum of ajmaline reveals no carbonyl group, the base gives rise to an oxime so that it must contain an aldehyde or a potential aldehyde such as a cyclic acetal group. This conclusion is supported by the fact that ajmaline combines with sulfur dioxide to a sulfonic acid betaine just like oxodihydroallostrychnine which is considered to be a basic aldehyde. Ajmaline forms a dibromo derivative (454), but on catalytic hydrogenation affords a hexahydro derivative ($C_{20}H_{32}O_2N_2$). The reduction product still couples with diazotized sulfanilic acid to a methyl orange and hence still contains the benzene ring. Ajmaline therefore contains at least one double bond (454a).

Distillation of ajmaline over zinc dust gives rise to two products in approximately equal amounts, identified as ind-*N*-methylharman and carbazole. From a consideration of the chemistry of yohimbine and strychnine and on the basis of the evidence described, two possible constitutions, CIII and CIV, have been suggested to represent ajmaline:



CIII



CIV

2. Isoajmaline and Neoajmaline

Isoajmaline and neoajmaline, $C_{20}H_{26}O_2N_2$ (444), both occur in *R. serpentina* originating from the Dehra Dun Valley. Isoajmaline can also be obtained from ajmaline by heating or treatment with alcoholic potassium hydroxide. Neoajmaline by the same treatment is also converted into isoajmaline which is a diacidic base containing one active hydrogen atom (Zerewitinow) and a methylimino group (454).

3. Ajmalinine

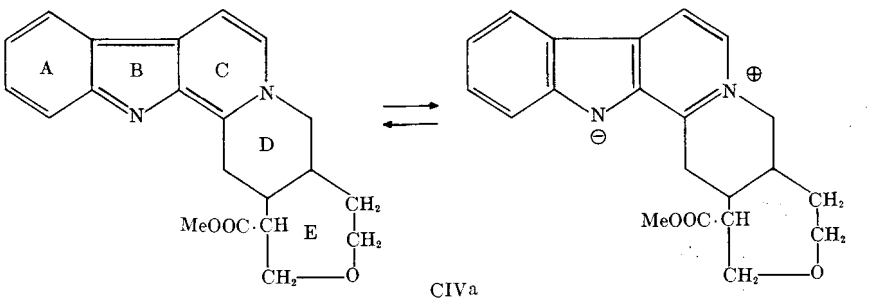
Ajmalinine, $C_{20}H_{26}O_3N_2$ (443, 454), is a tertiary base which forms a crystalline methiodide (454). It contains both a methoxyl and an hydroxyl

group, but no methylimino group. The presence of the hydroxyl is confirmed by the formation of a benzoyl derivative (454). When ajmalinine is heated in an atmosphere of hydrogen to 200° it is degraded to apoajmalinine, $C_{13}H_{17}O_3N$, a new, optically inactive base (454).

4. Serpentine

Serpentine, $C_{21}H_{22}O_3N_2$ (443, 454, 454b) is a bright yellow crystalline tertiary base containing solvent of crystallization that it loses *in vacuo* at 120°. It forms a methiodide and salts containing one equivalent of acid. The base contains one *O*-methyl group but contrary to earlier statements (454) contains no hydroxyl group (454a). It is hydrolyzed by 20% potassium hydroxide to serpentinic acid which on treatment with methanol and hydrogen chloride yields an ester which cannot yet be said with certainty to be serpentine (454b). Hence two oxygen atoms are involved in a carbomethoxy group while the third is inert and likely present in an ether bridge (454b).

The selenium dehydrogenation of serpentine gives rise to alstyrine ($C_{19}H_{22}N_2$) which represents the bulk of the molecule since the additional two carbon atoms must be those present in the carbomethoxy group. In analogy with ajmaline it is assumed that the third oxygen is an ether bridge completing ring E (formula CIVa). Hydrogenation of serpentine seems to result in the absorption of four moles of hydrogen, but the analytical results obtained for the product indicate more and there may be six double bonds in the molecule.



CIVa

The ultraviolet absorption spectra of serpentine and of its salts indicate that the structure of rings A, B and C must be the same as in sempervirine and tetradehydroyohimbine (454c). Tetradehydroyohimbine and serpentine on the one hand and tetradehydroyohimbine nitrate and serpentine nitrate on the other hand have almost identical spectra. Also the infrared absorption spectrum of serpentine shows the absence of an

imino group. Hence rings A, B and C in serpentine (formula CIVa) have the same structure as the corresponding rings in tetradehydroyohimbine and sempervirine. The structure of rings D and E is still hypothetical but in analogy to ajmaline it is assumed that E is seven-membered (454b).

5. Serpentinine

Serpentinine, $C_{20}H_{20}O_5N_2$ (443, 454), crystallizes from dilute alcohol with 1.5 moles of water of which it loses 0.5 mole at 100° and the remainder at 150°. It is a secondary base which readily forms a nitroso derivative. Serpentinine contains one methoxyl but no methylimino group.

6. Rauwolfine

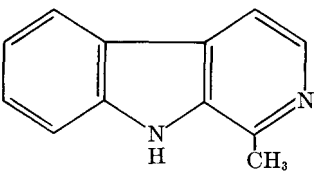
Rauwolfine, $C_{20}H_{26}O_3N_2$ or $C_{20}H_{24}O_2N_2$ (450), was isolated from *R. caffra* and should be distinguished from the rauwolfine of van Itallie and Steenhauer (442), which is identical with ajmaline. In concentrated sulfuric acid rauwolfine gives a brilliant yellow solution which is gradually discharged; the addition of concentrated nitric acid to the colorless solution develops a brilliant indigo blue rapidly passing through purple to a golden brown. Rauwolfine is crystalline and yields crystalline hydrogen halides although all the other salts prepared are amorphous. The base is soluble in hot water and insoluble in all organic solvents except methanol. It is soluble in aqueous sodium hydroxide but not in aqueous sodium carbonate and it is presumably phenolic.

7. Rauwolscine

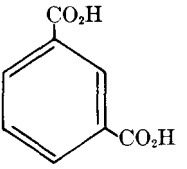
Rauwolscine, $C_{21}H_{26}O_3N_2$ (451), is an isomer of yohimbine which shows the same characteristic color reactions. With concentrated sulfuric acid it shows a blue color with a violet tinge changing to red; with concentrated sulfuric acid and potassium dichromate, a deep blue changing to green; with Fröhde's reagent, a navy blue, then purple and finally yellow; with Erdmann's reagent a bluish green gradually changing to yellow and with Mandelin's reagent blue changing to yellow. Rauwolscine is a monoacidic tertiary base containing one methoxyl group and two active hydrogen atoms (Zerewitinow). It does not condense with acetone or aromatic aldehydes and therefore contains no active methylene group. One of the active hydrogen atoms is contained in a hydroxyl group the presence of which is confirmed by the formation of an acetyl derivative (455). The base is easily hydrolyzed by aqueous alkalis or even by prolonged contact with ammonia to rauwolscinic acid, $C_{20}H_{24}O_3N_2$, and this on esterification with hydrogen chloride and methanol is converted back to rauwolscine. Hence the methoxyl group in the base is present in a carbomethoxy group. The

color reactions of rauwolscinic acid are very similar to those of the parent base and yohimbine. Moreover, the ultraviolet absorption spectrum of rauwolscine hydrochloride shows a well-defined absorption band with a maxima at 2750A. and a minima at 2450A. whereas the corresponding points for the similar salt of yohimbine are 2740 and 2430A (456). Therefore, although the two alkaloids are not identical they must be closely related structurally.

This conclusion is borne out by the results of the degradation of the base. Dry distillation of rauwolscinic acid at 300°/4–5 mm., gives rise to harman (CV) and 3-ethylindole, while fusion with potassium hydroxide at 300° produces harman, indole-2-carboxylic acid and isophthalic acid

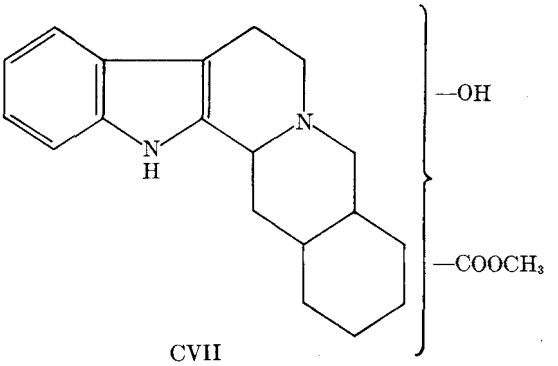


CV



CVI

(CVI) plus an unidentified indole (455). Under the same conditions yohimbine yields harman, 3-ethylindole, indole-2-carboxylic acid, tetrahydroisoyobyrine and *m*-toluic acid. It is therefore assumed that the struc-



CVII

tural skeleton of rauwolscine (CVII) is identical with that present in yohimbine, but that the substituents (OH, CO_2CH_3) occupy different, and as yet undetermined positions (455). This partial structure of the base has received further support from the results of the distillation of rauwolscine with zinc dust which yields isoquinoline besides harman and skatole (457).

IX. Alkaloids of *Gelsemium* Species

Species of the genus *Gelsemium* have yielded a number of alkaloids. However, the structure of only one, is definitely known although one other has been shown to belong to the indole group. From the rhizome and roots of *Gelsemium sempervirens* Ait. (Loganiaceae) an amorphous alkaloid was isolated in 1870 (459) which was later obtained in crystalline form and named gelsemine (460). In the older literature (461–471) which is now of historical interest only, a number of amorphous basic constituents of doubtful individuality have been reported from time to time. However, a second crystalline base, gelsemicine, was eventually isolated from the plant (472), together with a third, sempervirine (473). Finally, two amorphous bases have been reported, one of which yields a crystalline methiodide, $C_{20}H_{22(24)}O_3N_2 \cdot CH_3I$, while the other forms a crystalline picrate, $C_{20}H_{24}O_4N_2 \cdot C_6H_3O_7N_3$, m.p. 152° (474). The Chinese drug Kou Wen, identified as *Gelsemium elegans* Benth., contains four different alkaloids, koumine, kouminine, koumininine and kouminidine, although koumininine, the most physiologically active of the four, may not have been homogeneous (475). However, the Chinese gelsemium Ta-chá-yeh, *Gelsemium elegans* (Gardn.) Benth., which is thought to be the same plant as Kou Wen, has yielded only two of these four alkaloids, i.e., koumine and kouminine, together with gelsemine and a new base, kounidine (476). This difference in alkaloidal content suggests that the botanical identity of Kou Wen and Ta-chá-yeh should probably be re-examined. The Chinese plant Twan Chan Tsao has been reported to contain alkaloids, but these have been isolated only in the crude condition. The plant is presumed to be a species of *Gelsemium* (477). Recently sempervirine has been found to occur in *Mostuea buchholzii* Engl. (477a).

A number of methods for the chemical assay of Gelsemium extracts have been described. These involve the isolation of the crude alkaloid and its titration with standard acid (478–480). Since there seems to be no constant parallelism between chemical and biological assays (481, 482) the latter have been favored (483–485). A review of the methods used in the biological assay of gelsemium has recently been published (486).

1. Gelsemine

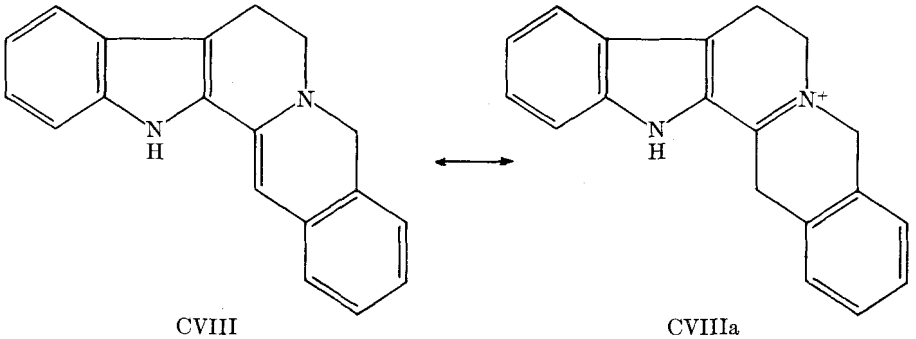
Gelsemine, $C_{20}H_{22}O_2N_2$ (487), crystallizes from acetone with one mole of solvent that it loses at 120°. The color reactions of gelsemine are reminiscent of those shown by strychnine (488, 489) and the ultraviolet absorption spectra of these two alkaloids are remarkably similar (490). Of the two nitrogen atoms present in the molecule, one is inert since the base forms salts with only one equivalent of acid, while the other, which

is basic, carries a methyl group (491). Gelsemine forms a methiodide, but this under the action of alkali regenerates the base. The base contains a double bond since it can be hydrogenated over palladium sponge to dihydrogelsemine (488, 492) and it also gives rise on bromination to dibromogelsemine (493). However, catalytic hydrogenation over Adams' catalyst results in the formation of hexahydrogelsemine (474). Gelsemine is isomerized by the action of zinc and hydrochloric acid to isogelsemine and this isomerization probably involves a shift of the double bond since the catalytic hydrogenation of isogelsemine gives rise to dihydrogelsemine (488). Boiling concentrated hydrochloric acid converts the alkaloid into a mixture of three new bases, apogelsemine ($C_{20}H_{24}O_3N_2$), chloroisoapogelsemine ($C_{20}H_{23}O_2N_2Cl$) and isoapogelsemine ($C_{20}H_{24}O_3N_2$) (494). The first of these differs from gelsemine by the elements of water which have been added and the second by the elements of hydrogen chloride. Chloroisoapogelsemine, also obtained by the action of hydrochloric acid on apogelsemine, is converted by hydrolysis to isoapogelsemine and by boiling diethylaniline to an isomeride of gelsemine melting at 140–145°. Iodoisoapogelsemine behaves similarly and, further, on reduction with zinc dust and acetic acid it yields dihydrogelsemine (474). Both apogelsemine and isoapogelsemine give rise to diacetyl derivatives whereas chloroisoapogelsemine forms a monoacetyl derivative (494). The formation of the products of the action of hydrochloric acid on the base would be explicable by the addition of the elements of water or hydrogen chloride either across the double bond, or possibly to a cyclic ether after scission of the ring. Although it has been claimed once that gelsemine can be acetylated to a crystalline *O*-acetyl derivative (494) other investigators have been unable to repeat this reaction (474). Gelsemine does not react with the usual reagents for aldehydes or ketones (474) and dihydrogelsemine forms neither acetyl nor benzoyl derivatives (488), nor does it react with methylmagnesium iodide (474).

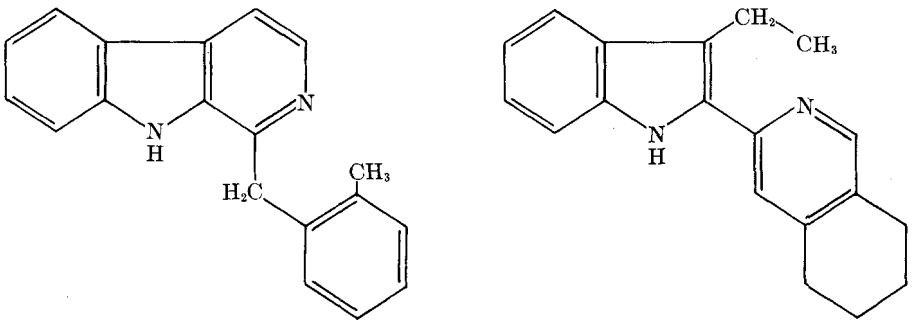
The only insight so far into the nature of the structure of gelsemine was obtained by degradation experiments and also by reduction. The action of selenium or soda lime on the base gives rise to an indole first reported as 2,3-dimethylindole (491), but since shown to be 3-ethylindole (495). Although the degradation of the alkaloid also yields basic scission products, none of these have been identified (491, 495). Recently, the nature of one of the oxygen atoms of gelsemine has been elucidated and it has been shown that the base is a 3,3-disubstituted oxindole (495a, 495b). On biogenetical grounds a structure of gelsemine has been developed ingeniously (495c), but the basic moiety of the molecule lacks chemical confirmation.

2. Sempervirine

Sempervirine, $C_{19}H_{16}N_2$ (473, 496, 497), is a colored (orange) crystalline alkaloid, which in dilute ethanolic solution is intensely fluorescent. It forms crystalline salts with only one equivalent of acid, among which is a remarkably insoluble nitrate. It also forms a monomethiodide and, consequently, only one of its two nitrogen atoms is basic. When hydrogenated catalytically it absorbs three moles of hydrogen over palladium and five over Adams' catalyst. Whereas hexahydrosempervirine is amorphous and resinifies immediately, the decahydro derivative is crystalline, but contains oxygen ($C_{19}H_{24}ON_2$) (474). Sempervirine, which is optically inactive, contains one active hydrogen (Zerewitinow) but no methylimino group (498, 499). When heated with selenium (or with palladium) it gives rise to yobyrine (CIX) together with a little yobyrone and, when boiled in



CVIII CVIIIa

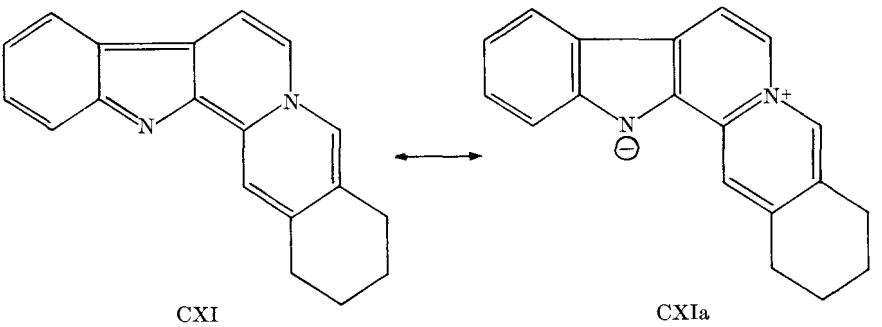


CIX CX

xylene with Raney nickel, to the so-called "tetrahydroyobyrine" (CX) (498, 499), three of the products obtained from the degradation of yohimbine. These products seemed to indicate that the nuclear structure of yohimbine was present in sempervirine and the latter was represented by structure CVIII⟷ CVIIIa, which takes into account the optical inactivity

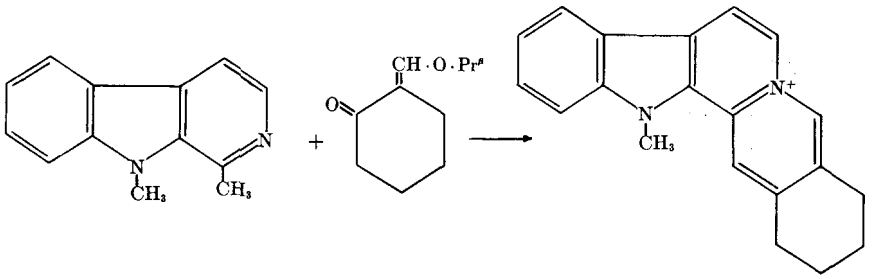
of the base (498, 499). Since the ultraviolet absorption spectra of sempervirine in acid and in neutral solutions are identical, whereas that in basic solution is markedly different (490, 499), it was assumed that the molecule rearranges to form a sempervirinium ion (CVIIIa) (499).

The compound of structure CVIII, however, has been synthesized and found to be quite different from sempervirine (500). Independently and simultaneously, it had been suggested that structure CVIII⟷CVIIIa did not account for the color of sempervirine and formula CXI⟷CXIa was proposed for the alkaloid (500a). The new formulation is supported



CXI CXIa

by the following facts: (a) the infrared absorption spectrum of sempervirine contains no band in the NH region whereas all *N*-unsubstituted indoles are characterized by an intense sharp band at 2.9 μ, and (b) sempervirine methochloride is converted on heating with selenium to ind-*N*-methylyobyrine (500a). Proof of this structure (CXI ⟷ CXIa) is afforded by the synthesis of sempervirine methochloride by the condensation of the lithium derivative of *N*-methylharman with 2-isopropoxymethylene cyclohexanone. Treatment of the reaction mixture with an acid gives rise to a salt of the methylsempervirinium ion (500b), thus:



The presence of an active hydrogen (Zerewitinow) in sempervirine is attributed to the presence in CXI ⟷ CXIa of a virtual substituted-γ-picolinium system (500a).

3. Gelsemicine

Gelsemicine (472), $C_{20}H_{24}O_4N_2$ (474), is a crystalline, optically active base forming salts with one equivalent of acid. It contains three active hydrogen atoms (Zerewitinow), but is insoluble in alkali. Gelsemicine gives rise to a nonbasic monobenzoyl derivative so that its basic nitrogen is secondary. This is confirmed by treatment of the base with methyl iodide which gives rise to methylgelsemicine hydriodide. Gelsemicine is unreactive towards reagents for the carbonyl group. On hydrogenation over Adams' catalyst, it absorbs three moles of hydrogen (474).

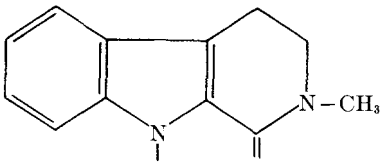
X. The Alkaloids of Calycanthaceae

Several species belonging to the order Calycanthaceae contain the alkaloid calycanthine which, in some plants, is accompanied by minor alkaloids. Calycanthine was first discovered in the seeds of *Calycanthus glaucus* Willd. (502, 503) and has since been found in *C. floridus* L. (1.2%) (504), in *C. occidentalis* Hook. and Arn. (0.8%) (505) and in *Meratia praecox* Rehder and Wilson (504). Isocalycanthine, an isomeric base, has also been reported as occurring in *C. glaucus* (506), but it is probably only a low-melting form of calycanthine (505). However, *C. glaucus* contains another well-characterized alkaloid, calycanthidine (507). *Meratia praecox* also seems to contain two minor alkaloids besides calycanthine, but these have not been characterized (504).

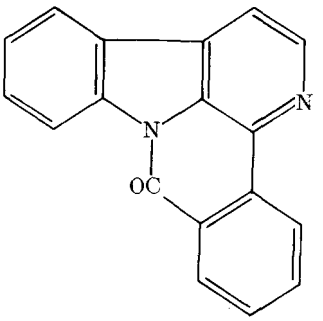
1. Calycanthine

Calycanthine, $C_{22}H_{26}N_4$ (505, 508), forms readily crystallizable salts with two equivalents of acid and shows a number of color tests (509). The first formula, $C_{11}H_{14}N_2$, assigned to calycanthine (509) was later doubled following the determination of the molecular weight of the base (508), although it appears more likely that it contains two hydrogen atoms less (505). Of the four nitrogen atoms of the base, two are secondary since calycanthine gives rise to a dinitrosoderivative (510) and shows the presence of two active hydrogen atoms (Zerewitinow) (508). The first clue to the constitution was afforded by the benzoylation of calycanthine and oxidation of the product with potassium permanganate. There is thus obtained a neutral crystalline substance, $C_{18}H_{18}ON_2$, giving a brilliant red color with Ehrlich's reagent and shown to be identical with synthetic *N*-benzoyl-*N*-methyltryptamine (511). The use of *m*-chloro- and *p*-nitrobenzoyl chloride in the same reaction gives rise to the corresponding chloro and nitro derivatives (511). The formation of this degradation product indicates the probable presence in the molecule of grouping CXII, a conclusion confirmed by, (a) the production of 3-carboline when the alkaloid is

dehydrogenated with selenium and (b) the isolation, when calycanthine is heated with phthalic anhydride of a substance, identical with the product of the condensation of tryptamine with phthalic anhydride and most probably represented by formula CXIII (512).



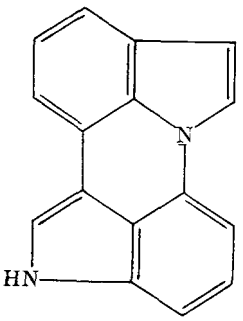
CXII



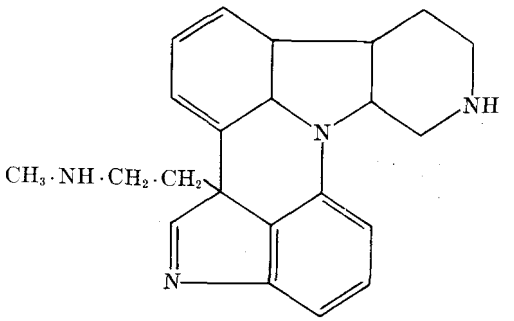
CXIII

Whereas the action of soda lime on benzoylcalycanthine produces 2-phenylindole and quinoline, calycanthine when treated similarly does not give rise to 2-phenylindole, but to *N*-methyltryptamine together with a small quantity of a base, $C_{12}H_{10}N_2$, assumed to be a methyl-3-carboline (513). On the other hand, calycanthine when pyrolyzed or heated with lead oxide, copper oxide, sulfur (513), or selenium (512) produces a weak base designated calycanine and originally assigned the empirical formula $C_{16}H_{10}N_2$. Besides calycanine, also obtainable by degradation of the base with zinc dust (505, 513), the action of selenium also gives rise to 3-carboline (512), skatole, 3-ethylindole and lepidine (505).

Calycanine was assumed by Barger, Madinaveitia and Streuli (513) to be a di-indolylene (CXIV) containing a quinoline nucleus; they added



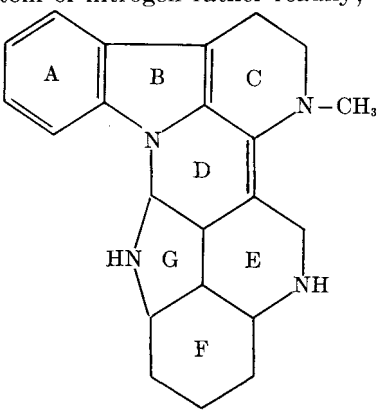
CXIV



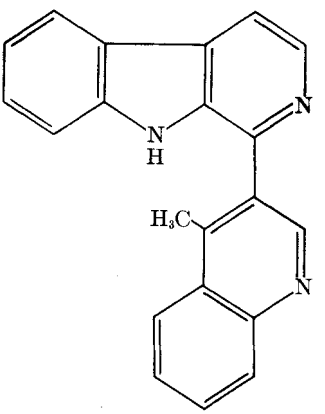
CXV

to this structure a methylaminoethyl side chain and a fused piperidine ring as in formula CXV, which was tentatively advanced to represent

calycanthine. However, calycanthine with Ehrlich's reagent exhibits a color change only on heating, and this is reversed on cooling. Therefore, it cannot contain an indole nucleus unsubstituted at the α- and β-positions. Furthermore, calycanine is basic and it is highly probable that the compound CXIV would be neutral. Finally, a compound such as CXV should react with phenylisocyanate and give rise to a neutral diphenylcarbamyl derivative, whereas the diphenylcarbamyl derivative obtained from calycanthine is basic (512). Hence, it is obvious that formulae CXIV and CXV are untenable. The source of the substituted indoles and of 3-carboline can be regarded as the carboline half of the molecule, but lepidine and quinoline must originate from the second moiety. Since no *C*-methyl group is present in calycanthine, the methyl group of lepidine must arise in the course of the degradation. Manske and Marion (505), therefore, expanded the partial formula CXII to CXVI in which the methyl group of the reduced lepidine is linked to the indole nitrogen, thus accounting for rings A, B, C, D, E and F (CXVI). Furthermore, calycanthine loses one atom of nitrogen rather readily;



CXVI

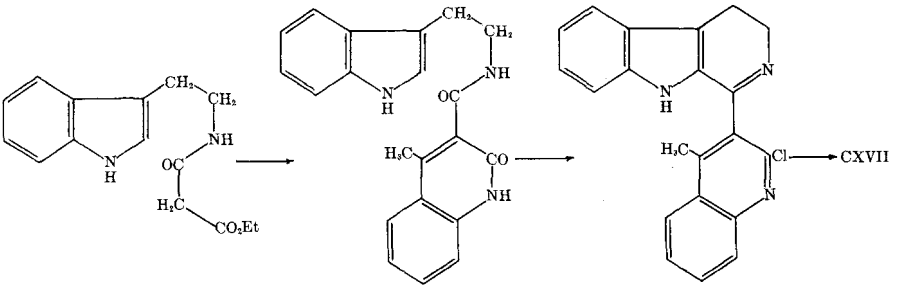


CXVII

when heated with palladium this nitrogen is liberated as ammonia (505), whereas on methylation it is eliminated as methylamine (508, 512). To account for the ease with which ammonia is eliminated, the fourth nitrogen atom was included in a reduced pyrrole ring G, thus completing the formula of calycanthine (CXVI) (505). In this structure rings A, B and C are formed of a tryptamine molecule while rings F, G and E arise from a fully reduced tryptamine molecule in which the nitrogen atom is linked to a C-atom of the cyclohexane ring and these two systems of rings are fused together through ring D.

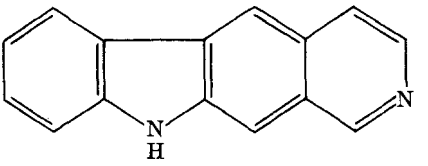
Although Manske and Marion (512) had first accepted the empirical

formula $C_{16}H_{10}N_2$ for calycanine, they later proposed $C_{21}H_{15}N_3$, and on the basis of structure CXVI for calycanthine, expanded it to CXVII (505). However, this formulation which seemed to agree with the known properties of the product was questioned on the basis of an x-ray investigation (514). Eventually it was found that the compound of structure CXVII is obtainable from *N*-carbethoxyacetyl tryptamine (CXVIII) by condensation with *o*-aminoacetophenone to (CXIX), which is cyclyzed with phosphorus oxychloride to a-(2′-chloro-3′-lepidyl)-4,5-dihydro-3-carboline (CXX). On heating with palladium black in tetraline CXX loses chlorine together with two hydrogen atoms and is converted to CXVII (515). The



CXVIII CXIX CXX

synthetic compound CXVII is quite different from calycanine and whereas the former is intensely fluorescent in neutral or acid solutions, the latter is not or only slightly so. It is, therefore, unlikely that calycanine is a carboline derivative. Since the analytical figures of the degradation base agree better with the formula $C_{15}H_{10}N_2$ and since a carboline nucleus seems to be excluded, it is now assumed that calycanine is CXXI consisting of a pyridine ring fused to carbazole through reorientation and ring closure between rings A, B and E of calycanthine (CXVI) (518).



CXXI

Calycanthine in 1% acetic acid solution is oxidized by silver acetate to a base ($C_{12}H_{10}N_2$), m.p. 115–6° (516, 517), which however, is further oxidized by alkaline potassium permanganate to *N*-oxalylanthranilic acid and ammonia (518). Recently, this degradation base has been shown by synthesis to be identical with 3-(*N*-methyl)-4-pyrroquinoline (518a) and this is inconsistent with either formulae CXV or CXVI for calycanthine.

2. Calycanthidine

Calycanthidine, $C_{13}H_{16}N_2$ (507), is isolated from the seeds of *Calycanthus glaucus* in which it is present in small quantities (0.026%). It is less soluble in acetone and in light petroleum than calycanthine. In the cold, with Ehrlich's reagent, the alkaloid shows a pale yellowish color only; on heating a claret color is produced which fades on cooling. This reversibility in color change is also shown by calycanthine (511), tetrahydroharman, and tetrahydroharmine (519). Calycanthidine contains one methylimino group and one active hydrogen (Zerewitinow). The direct addition of methyl iodide leads to an ill-defined product, but the action of methyl iodide in methanol containing potassium carbonate converts calycanthidine into a methiodide, $C_{16}H_{25}ON_2I$, in which a methoxyl group has been introduced together with a methyl group and a molecule of methyl iodide. This product of methylation when treated with silver oxide is converted to the corresponding ammonium base which, on distillation *in vacuo*, gives rise to trimethylamine and a neutral oil that polymerizes and can neither be redistilled, crystallized, nor hydrogenated. Because of the apparent similarity in behavior between calycanthidine and methyltetrahydroharmine (520), the base was assumed to be *N*-methyltetrahydroharman, but a synthetic specimen of this compound proved to be different (507).

XI. Alkaloids of Calabar Bean

The main alkaloid, physostigmine, present in the seeds of the Calabar bean (*Physostigma venenosum* Balf.) was first isolated in 1864 (521, 522). It was later obtained crystalline and named eserine (523); both names are still used to designate the base. Other alkaloids have been reported as occurring in the seeds, such as calabarine (524), later claimed to have been a mixture of decomposition products (525), eseridine (526, 527), eseramine (525), isophysostigmine (528), physovenine (529) and geneserine (530). However, the existence of isophysostigmine has never been confirmed (531) and it is probable that eseridine is identical with geneserine (532).

1. Isolation of Physostigmine

Methods have been described for the preparation of physostigmine in the laboratory (529) and on an industrial scale (533).

The ground seeds are extracted by continuous percolation with hot alcohol and the solvent largely distilled from the extract. Water is added to the residue and the floating layer of fat separated and washed with water. The washings are added to the main portion of the aqueous liquid which is then alkalinized with an excess of sodium carbonate and repeatedly extracted with ether. After concentration to a convenient volume the combined ether extract is washed with successive portions of 5% sulfuric

acid until the washings become just acid. To the aqueous solution of the sulfate thus obtained, an excess of a saturated solution of sodium salicylate is added which causes the precipitation of physostigmine salicylate as an almost colorless, crystalline powder which is filtered, washed well with water, and dried in a vacuum desiccator over sulfuric acid. The weight of salicylate represents a yield of ca. 0.18% of physostigmine. From the ether solution previously extracted with dilute sulfuric acid, the minor bases are obtained (529).

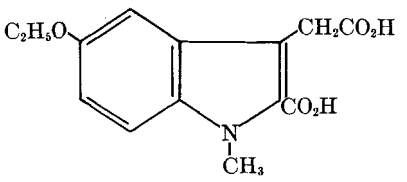
Physostigmine can be detected by a number of color reactions. The alkaloid added to a solution of phosphomolybdic acid and ammonium metavanadate in concentrated sulfuric acid produces an emerald green color (534). A solution of vanadic oxide in dilute sulfuric acid also produces a color with physostigmine (535). The base shows a blue color with potassium ferricyanide and ferric chloride (536), while the sulfate of the base shows a similar color when heated with potassium dichromate and molybdic acid (537). A solution of benzidine in dilute acetic acid containing hydrogen peroxide produces a violet color with the base (538, 539, 540) and the reaction can be used colorimetrically (541, 542). When 15–20 drops of 1*N* sodium hydroxide is added to 5 cc. of a 1% solution of the salicylate of the base and the solution shaken violently 1 minute, a purple color develops which gentle warming changes to a reddish brown and finally emerald green. Acidification of the cooled solution with dilute hydrochloric acid produces a wine color which is changed by the addition of a few drops of 0.1*N* sodium thiosulfate to a carmine red (543). When glyoxylic acid reagent (544) is added to a solution of the base in concentrated sulfuric acid color changes from rose to deep red to green are produced on heating, but the addition of water changes the color to greenish blue and finally deep blue (545). Several microchemical tests for physostigmine have also been described (546–549). Physostigmine can further be detected by the sparingly soluble salt that solutions of its sulfate form with *o*-hydroxyphenyl arsenate (550); by the precipitate given with potassium ferrocyanide and hydrochloric acid (551). It is also possible to determine the quantity of physostigmine physically by measuring the surface tension of its aqueous solution (552), or biometrically by measuring its inhibition of cholinesterase (553, 554, 555).

2. Physostigmine

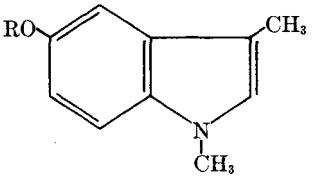
Physostigmine (eserine), $C_{15}H_{21}O_2N_3$ (522, 523), is a monoacidic, tertiary base, readily oxidized by oxygen in the presence of aqueous potassium hydroxide, giving rise to the red compound rubreserine (527, 556). It is easily hydrolyzed by the action of alkalis to methylamine, carbon dioxide, and a new base, eseroline ($C_{13}H_{18}ON_2$) (525, 557). The methylamine and carbon dioxide are present in the molecule as the carbamate group -OCONHCH$_3$ since physostigmine when heated with sodium

ethylate in the absence of air yields methyl urethane ($CH_3NHCO_2C_2H_5$) and eseroline, while its oxidation with potassium permanganate yields methyl isocyanate (558). The carbamate group is linked in the base to a phenolic hydroxyl group which is liberated in the formation of eseroline. Eseroline can be benzoylated (559), or it can be *O*-ethylated by treatment with ethyl *p*-toluenesulfonate in ethanol to eserethol ($C_{15}H_{17}N_2 \cdot OC_2H_5$) (558); it can also be converted to pheneserine by treatment with phenylisocyanate (560), or reconverted to physostigmine by the action of methyl isocyanate in the presence of a trace of sodium (561). Eseroline undergoes atmospheric oxidation, giving rise to rubreserine (556). Whereas physostigmine contains three methylimino groups, its hydrolytic product eseroline contains but two (562, 563, 564).

a. Structure. Eseroline gives rise to both a methiodide and a dimethiodide (565) and an attempt to convert the methiodide into the corresponding methyl ether by heating with methyl iodide and sodium ethoxide resulted in the formation of a complex compound, $C_{19}H_{34}O_2N_2I_2$, m.p. 235° (566, 567). The formation of such a compound requires the addition of several methyl groups and is interpreted as having involved the opening of a ring containing a nitrogen atom. Eseroline methiodide when pyrolyzed produces physostigmol, $C_{10}H_{11}ON$, first assumed to be a hydroxy-1,3-dimethylindole (563, 568), and subsequently characterized as 5-hydroxy-1, 3-dimethylindole (CXXIII, R = H) by synthesis of its ethyl ether. This synthesis (569) was achieved by the condensation of *p*-ethoxyphenylmethylhydrazine with α-ketoglutaric acid and subsequent decarboxylation of the derived 5-ethoxy-2-carboxy-1-methylindole-3-acetic acid (CXXII).



CXXII

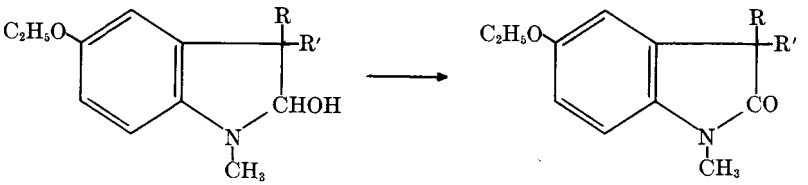


CXXIII

The synthetic product is identical with that obtained in 66% yield by heating eserethole methiodide at 180° in a high vacuum (569). A later synthesis was achieved from ethyl β-methylpyruvate-*p*-ethoxyphenylhydrazone obtained by pouring diazotized *p*-ethoxyaniline into a solution of ethyl α-ethyl-acetoacetate in alcoholic sodium hydroxide. On boiling with 10% alcoholic sulfuric acid, the substituted phenylhydrazone undergoes ring closure to 2-carbethoxy-3-methyl-5-ethoxyindole which on saponification and decarboxylation gives rise to norphysostigmol ethyl ether. This, when methylated at the indole nitrogen with methyl iodide and sodium,

yields physostigmol ethyl ether (CXXIII, R = C_2H_5) (570). The methyl ether of physostigmol (CXXIII, R = CH_3) has also been synthesized by the Fischer indole reaction from the *as*-*p*-methoxyphenylmethylhydrazone of propionaldehyde (571).

The synthesis of physostigmol ethyl ether establishes the position of the hydroxyl group in eseroline and also the presence of an indole nucleus. The presence of an indole nucleus is also indicated by the feeble basicity of one of the nitrogen atoms in physostigmine (563), by the properties of etheserolene, a compound obtained by the exhaustive methylation of eserethole (572–575), by the ultraviolet absorption spectrum of physostigmine which corresponds with that of indole (576), and is confirmed by the degradation of eseroline with zinc dust to 2-methylindole (556, 577). Eserethole methiodide is converted by the action of potassium hydroxide to eseretholemethine, the methiodide of which, in turn, is decomposed by potassium hydroxide to etheserolene, $C_{12}H_{12}N(OEt)$ (572). Eseretholemethine, one of the intermediate compounds in the foregoing degradation, is in reality a pseudo base (CXXIV) since it is reconverted by treatment with hydriodic acid into eserethole methiodide (567) and it forms a salt with sodium in dry ether, which is converted either to the original methine

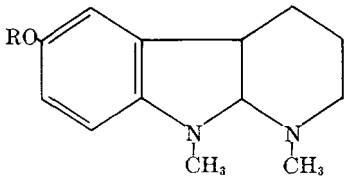


CXXIV CXXV

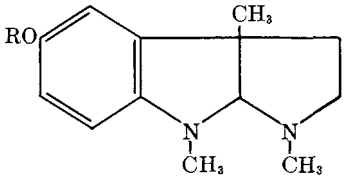
by the action of acids (578) or to an alcoholate by treatment with ethanol (579, 580). It is known that 1,3,3-trimethyl-2-indolinol is oxidized by ammoniacal silver nitrate in alcoholic solution to 1,3,3-trimethyl-2-indolinone (581) and since eserethole-methine is oxidized either by the same method, or with the aid of potassium ferricyanide, to dehydroeserethole-methine, the latter must be represented by structure CXXV (582). Hence, eseretholemethine is produced from methyleseretholinium hydroxide by a tautomeric change and not by loss of water.

In order to expand the formula of physostigmol (CXXIII, R = H) into that of eseroline, it is necessary to add the residue C_3H_7N and this residue must form a ring containing a tertiary nitrogen carrying a methyl group (563). The residue can, therefore, be added as in formula CXXVI (583, 584) or better as in CXXVII, since the high yield (66%) of physostigmol obtained by the pyrolysis of eseroline methiodide makes the preexistence of the angular methyl group in physostigmine highly probable

(582, 585, 586). Hence, eseroline is represented by CXXVII (R = H) and physostigmine by CXXVII (R = CH_3NHCO) while in formula

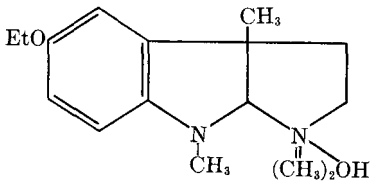


CXXVI



CXXVII

CXXIV and CXXV for eserethole-methine and dehydroeseretholemethine R = CH_3 and R′ = $CH_2CH_2N(CH_3)_2$, so that methyleseretholinium hydroxide from which the former arises by tautomeric changes has structure CXXVIII. The Hofmann degradation of dehydroeseretholemethine gives

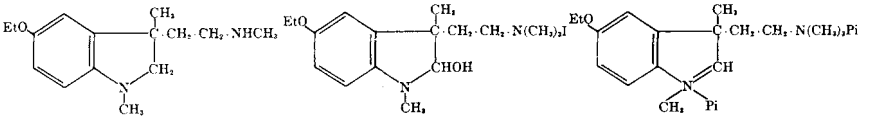


CXXVIII

rise to an unsaturated compound which must be represented by formula CXXV (R = CH_3; R′ = CH = CH_2) since it is converted by reduction to a substance considered to be 1,3-dimethyl-3-ethyl-5-ethoxy-2-indolinone, CXXV, (R = CH_3; R′ = C_2H_5) (582). That eseretholemethine (CXXIV, R = CH_3; R′ = $CH_2CH_2NMe_2$) is an indolinol is confirmed by the fact that its methiodide (CXXX) when treated with picric acid loses a hydroxyl group and produces a diquaternary picrate CXXXI.

Eserethole when reduced with zinc dust and hydrochloric acid (587, 588) or catalytically (582), takes up two atoms of hydrogen. Dihydroeserethole yields a dimethiodide almost quantitatively whereas eseroline and eserethole yield mixtures of mono- and dimethiodides (565, 589). This reduction, at first erroneously assumed to indicate the presence of a double bond (590), is due to the scission of a ring followed by hydrogenation since dihydroeserethole is a secondary base whereas eserethole is tertiary (583). The facile scission of a ring also accounts for the fact that physostigmine, eseroline and eserethole all behave as both tertiary and secondary nitrogen compounds; for instance, benzoyleserethole can be prepared by the Schotten-Baumann reaction (584, 591). Hence, dihydroeserethole possesses structure CXXIX. The ring opening is thus accompanied by the appearance of a double bond which is reduced more readily than the

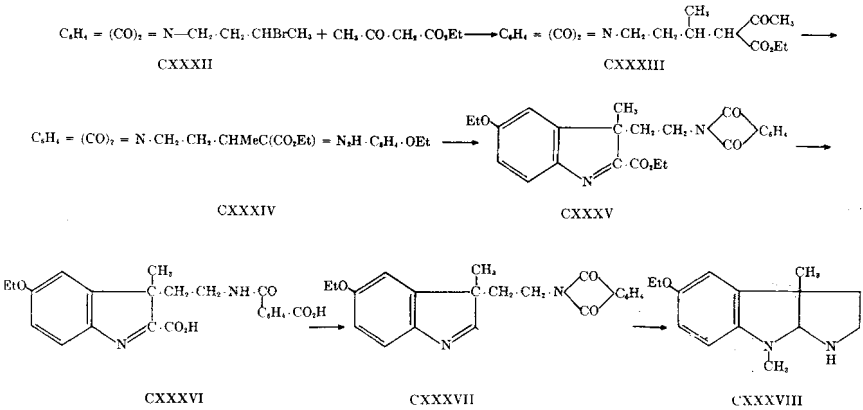
ethylenic linkage in etheserolene, ($C_{12}H_{12}N \cdot OEt$), the product obtained by the elimination of trimethylamine in the last step of the Hofmann degradation of eserethole. The reduction of etheserolene gives rise to dihydro-



CXXIX CXXX CXXXI

etheserolene which is identical with the final product of the Hofmann degradation of dihydroeserethole.

b. Synthesis. Structure CXXVII assigned to physostigmine (582) has been confirmed by numerous synthetical experiments and, finally, by the synthesis of the base itself. After preliminary model experiments (592), Robinson and his coworkers undertook a series of studies in the course of which the complete ring system of physostigmine was obtained by the synthesis of *dl*-noreserethole. This synthesis is achieved from γ-hydroxy-*n*-butylamine, the reduction product of acetaldoxime, which is heated with phthalic anhydride and the resulting phthalo-γ-hydroxybutylimide is converted to phthalo-γ-bromobutylimide (CXXXII) by the action of hydrogen bromide in ethanol. The bromo derivative (CXXXII) is condensed with ethyl sodioacetoacetate to δ-phthalimido-α-acetyl-β-methyl-



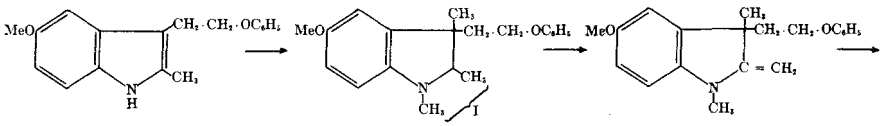
CXXXII CXXXIII CXXXIV CXXXV CXXXVI CXXXVII CXXXVIII

valerate (CXXXIII) which, when coupled with *p*-ethoxybenzenediazonium chloride in alkaline solution loses an acetyl group and is converted to ethyl δ-phthalimido-α-keto-β-methylvalerate-*p*-ethoxyphenylhydrazone (CXXXIV). The hydrazone under the influence of hydrogen chloride in ethanol, undergoes cyclization to ethyl 5-ethoxy-3-methyl-3-β-phthaliminoethylindolenine-2-carboxylate (CXXXV) and this is hydrolyzed with

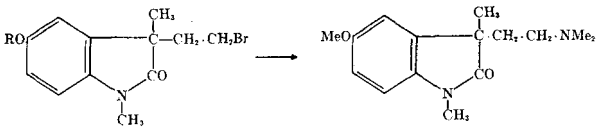
ethanolic potassium hydroxide to CXXXVI, which on decarboxylation by heating in boiling xylene gives rise to a low yield of 5-ethoxy-3-methyl-3-β-phthalimidoethylindolenine (CXXXVII). The methosulfate of CXXVII is converted to *dl*-noreserethole (CXXVIII) (593) by heating with hydrazine in ethanol and then with hydrochloric acid. *dl*-Noreserethole is methylated to *dl*-eserethole by the action of methyl *p*-toluenesulphonate (594).

This synthesis of *dl*-eserethole is not too satisfactory because of the low yield obtained on converting CXXXV to CXXXVII. This difficulty, however, is successfully overcome by the preparation of γ-phthalimido-α-methyl-butyraldehyde from the corresponding acid via the acid chloride, amide, and nitrile. The aldehyde is condensed with *p*-ethoxyphenylhydrazine and the product on cyclization affords 5-ethoxy-3-methyl-3-β-phthalimidoethylindolenine (CXXXVII) in good yield (595). The *dl*-eserethole synthesized by the second route crystallizes readily (596). Eserethole can be de-ethylated by the action of hydrobromic acid with formation of eseroline so that the foregoing can be considered as a synthesis of *dl*-eseroline (597).

By an application of the Plancher rearrangement to the proper indole derivatives (598) it is possible to achieve the synthesis of desethoxydehydroeseretholemethine (599) and also that of dehydroesermetholemethine, the methyl homolog of dehydroeseretholemethine. The latter is obtained from the *p*-methoxyphenylhydrazone of γ-phenoxypropylacetone, which is cyclized by ethanolic sulfuric acid to 5-methoxy-2-methyl-3-β-phenoxyethylindole (CXXXIX). Heating CXXXIX under pressure with methyl iodide in methanol produces 5-methoxy-1,2,3-trimethyl-3-β-



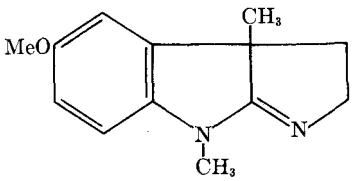
CXXXIX CXL CXLI



CXLII CXLIII

phenoxyethylindoleninium iodide (CXL) which is converted by sodium hydroxide to 5-methoxy-1,3-dimethyl-3-β-phenoxyethyl-2-methyleneindoline (CXLI) and this, on oxidation with potassium permanganate, gives rise to 5-methoxy-1,3-dimethyl-3-β-phenoxyethyl-2-indolinone. Hydrolysis

of the oxidation product with hydrobromic acid produces 5-hydroxy-1,3-dimethyl-3-β-bromoethyl-2-indolinone (CXLII; R = H) and this after methylation with dimethyl sulfate followed by heating under pressure with dimethylamine is converted to dehydroesermetholemethine (CXLIII). The methiodide of this base is resolved into its *d*- and *l*- antipodes with the aid of *d*- and *l*-bromocamphorsulfonic acid. The *l*-base-*d*-bromocamphorsulfonate thus obtained is converted by treatment with picric acid to the methopicrate, which is identical with the methopicrate derived from dehydroesermetholemethine obtained from the alkaloid (600). If 5-methoxy-1,3-dimethyl-3-β-bromoethyl-2-iddolinone (CXLII; R = Me) is heated with potassium phthalimide and the product treated with hydrazine hydrate and hydrolyzed, 5-methoxy-1,3-dimethyl-3-β-aminoethyl-2-indolinone is obtained. Dehydration of this product with phosphoric anhydride in boiling xylene gives rise to dehydronoresermethole (CXLIV) which, by successive treatment with methyl iodide and picric acid, is converted to *dl*-esermethole methopicrate (601), but this could not be resolved (602).

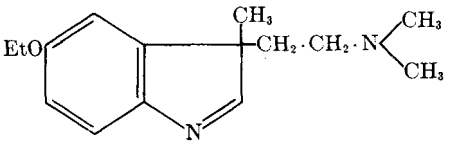


CXLIV

The tricyclic structure of physostigmine has also been synthesized by other methods. Ethylmagnesium iodide reacts with 3-β-indolylethylamine (tryptamine) to form a Grignard compound which, when treated with methyl iodide in benzene gives rise to dinordeoxyeseroline (603–605). The application of the same reactions to 5-methoxytryptamine and to 5-ethoxytryptamine produces dinoresermethole and dinoreserethole, respectively; the former can be resolved into its optical isomers with the aid of either *d*-bromocamphorsulfonic acid or *d*-tartaric acid (606). It is possible to obtain *dl*-noreserethole (CXXXVIII) in good yield by heating the hydriodide or hydrochloride of *dl*-dinoreserethole with methyl iodide. The isomers *l*- and *d*- obtained by resolution of dinoreserethole are converted by heating the hydrochlorides with methyl iodide to *l*- and *d*- noreserethole and these, in turn, are methylated to *l*- and *d*-eserethole.

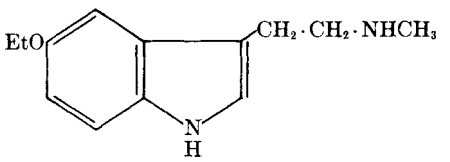
Either by the direct treatment of *dl*-noreserethole with methyl iodide, or by refluxing dinoreserethole benzoate with sodium benzoate and methyl iodide in ethanol, there is produced a substance first thought to have the empirical formula $C_{16}H_{24}ON_2$ and, therefore, designated methyleserethole (607). If, however, in this reaction sodium carbonate be substituted for

the sodium benzoate, some *dl*-eserethole can be isolated as the methopicrate. The empirical formula of "methyleserethole" was later corrected to $C_{15}H_{22}ON_2$ (597, 608) and the substance eventually shown by synthesis (609) to be the compound represented by formula CXLV (610).

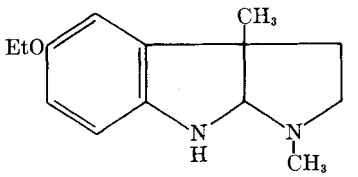


CXLV

The method used for the synthesis of *dl*-dinoreserethole can be modified to produce a compound carrying one iminomethyl group. 5-Ethoxy-*N*-methyltryptamine (CXLVI) is added in small portions to an ether solution



CXLVI

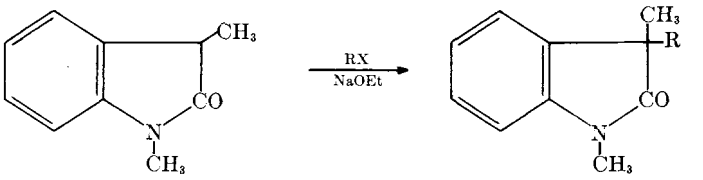


CXLVII

of ethylmagnesium iodide, the mixture stirred and heated on the steam bath until no more ethane is evolved and most of the ether has evaporated. The residue is heated 3 hours longer with methyl iodide. The product of this reaction is isonoreserethole (CXLVII), the hydrochloride of which, when heated with methyl iodide, is converted to *dl*-eserethole (611, 612).

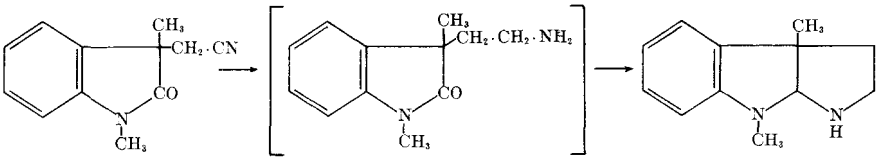
The various synthetic reactions already outlined are arduous and produce either noreserethole or dinoreserethole, which must then be converted to eserethole by methylation. Such a methylation is unsatisfactory as it leads to low yields of the desired product. A much simpler route to eserethole has now made this substance readily accessible. This new synthesis has the further advantage over those already described in that it gives rise to the same isomer as the natural base. It proceeds from the observation that 1,3-dimethyloxindole (CXLVIII) condenses with organic halides in the presence of sodium ethoxide to give excellent yields of 3,3-disubstituted oxindoles (CXLIX) (613). The condensation of 1,3-dimethyloxindole (CXLVIII) with chloroacetonitrile in the presence of sodium ethoxide gives rise to 1,3-dimethyloxindolyl-3-acetonitrile (CL) which on reduction with sodium in ethanol is converted to desoxynoreseroline (CLII) (613). The yields obtained in this synthesis are considerably improved if the reduction of the nitrile and the ring closure are carried out

separately. Catalytic reduction of the nitrile gives a good yield of the amine (CLI), which is then cyclized to CLII by the action of sodium in



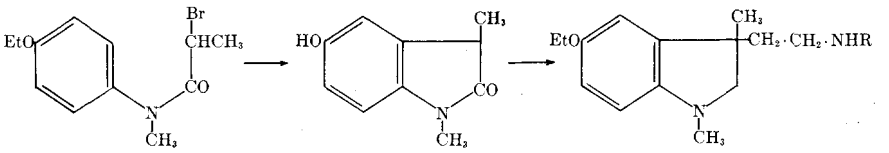
CXLVIII CXLIX

ethanol. The amine CLI is also accessible through the Gabriel synthesis in which the sodium salt of 1,3-dimethylindole is treated with β-bromo-



CL CLI CLII

ethylphthalimide and the resulting product cleaved to the amine (614). This method makes it possible to effect a direct synthesis of *dl*-eserethole. Methylphenetidine treated with α-bromopropionyl bromide yields the amide (CLIII), which, by the action of aluminum chloride, loses its ethyl group and is cyclized to 1,3-dimethyl-5-hydroxyoxindole (CLIV). The hydroxyl group is re-ethylated with ethyl sulfate and the product converted

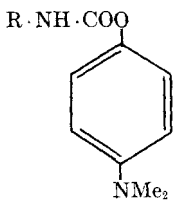


CLIII CLIV CLV

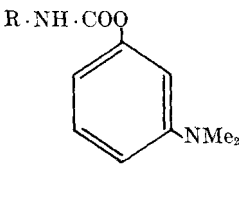
by condensation with chloroacetonitrile and catalytic reduction to 5-ethoxy-1,3-dimethyl-3-β-aminoethyloxindole (CLV; R = H). Condensation of this compound with benzaldehyde, followed by treatment with methyl iodide and hydrolysis, converts it to 5-ethoxy-1, 3-dimethyl-3-β-methylaminoethyloxindole (CLV; R = CH_3) which, by the action of sodium in ethanol, is smoothly converted to *dl*-eserethole, m.p. 38° (615). The synthetic *dl*-eserethole (m.p. 38°) so obtained, is different from the *dl*-eserethole (m.p. 80°) prepared by the other methods already described. While the former is designated *dl*-eserethole-a, the latter is named *dl*-eserethole-b, and it has been further suggested that they might be cis-cis

and cis-trans isomerides (597). The amine (CLV; R = CH_3) is easily resolved into its optical antipodes with *d*-camphorsulfonic acid, which yields *d*-amino-*d*-camphorsulfonate whereas the *l*-amine is crystallized as the *d*-hydrogen tartrate. Reduction of the *d*- and *l*-amines yields *d*-eserethole and *l*-eserethole respectively. This synthetic *l*-eserethole is crystalline and identical in every respect with that obtained from the alkaloid (616). *dl*-Eserethole can also be resolved directly by means of *d*-tartaric acid into its optical antipodes (610). Since eseroline can be reconverted to physostigmine by treatment with methyl isocyanate, all that remains to effect a complete synthesis of the alkaloid is to convert *l*-eserethole into *l*-eseroline. This conversion takes place smoothly by gentle boiling of a solution of *l*-eserethole in petroleum ether in which anhydrous aluminum chloride is suspended (616).

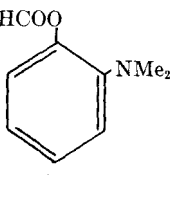
c. Physiologically Related Compounds. One of the properties of physostigmine is to produce miosis when instilled into the eye and that property is attributable to the urethane group since it is absent in the hydrolytic base eseroline. This observation has prompted the preparation of a number of substituted urethanes of relatively simple aminophenols which have been found to exhibit miotic properties. In the series of *o*-,*m*- and *p*-isomerides (CLVI–CLVIII) where R = Me, all three compounds



CLVI



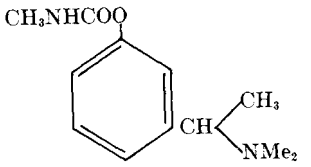
CLVII



CLVIII

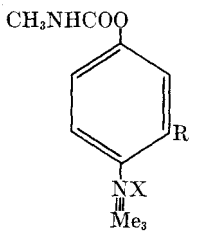
possess an action resembling that of physostigmine, but the position of the dimethylamino group modifies the activity so that *o*- > *m*-, *p*-. If R = H, Et, or C_6H_5, the activity is decreased or disappears. However, when the tertiary basic group is converted to a quaternary ammonium salt, the activity of the meta-isomeride is increased remarkably while that of the ortho and para is abolished (617). With the three isomerides of dimethylaminomethylphenyl *N*-methyl carbamates, the order of activity is *o*- > *p*- > *m*-, (618) whereas in the series of α-dimethylaminoethylphenyl *N*-methyl carbamates it is *m*- > *o*- > *p*- (619). The activity of meta-α-dimethylaminoethylphenyl *N*-methyl carbamate (CLIX) is increased appreciably when transformed into a quaternary salt. This *m*-isomeride has been named miotine. Numerous homologs of these substances and their isomerides have been prepared in an attempt to

correlate chemical structure with physiological activity (620–622). Miotine, a meta-substituted compound, shows a much greater activity than its

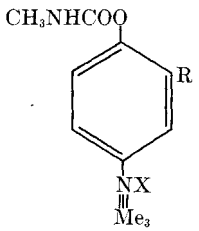


CLIX

o- or *p*-isomers and yet in physostigmine the methyl carbamate grouping is para to the nitrogen. This anomaly has been attributed to the activation caused by the alkyl residue ortho to the amino group attached to the



CLX



CLXI

benzene ring in the alkaloid, and this view is supported by the results of the comparison of the activities of a large number of derivatives of the types CLX and CLXI (623, 624, 624a).

3. Geneserine

Geneserine, $C_{15}H_{21}O_3N_3$ (530), forms crystalline salts and, like physostigmine, gives rise to methylisocyanate when heated to 160° or oxidized with potassium permanganate. On heating with aqueous barium hydroxide it produces one mole of carbon dioxide and one of methylamine. When heated with sodium ethoxide it produces ethyl methyl carbamate and geneseroline ($C_{13}H_{18}O_2N_2$). Geneserine in ethanol is converted by the action of ethyl *p*-toluenesulfonate in the presence of sodium ethoxide to geneserethole. Like physostigmine, geneserine has an ultraviolet absorption spectrum showing the absorption typical of indole groupings (576). Reduction of geneserine by zinc in acetic acid or by sulfur dioxide gives rise to physostigmine while geneseroline is converted similarly to eseroline (530, 625). Moreover, when physostigmine in acetone is treated with

hydrogen peroxide, it is converted into geneserine, while eserethole can be converted similarly to geneserethole (626). Consequently, geneserine, which differs from physostigmine by one atom of oxygen, is the *N*-oxide of the latter. This is confirmed by the methylation of the base. On heating with methyl iodide and methanol in a sealed tube, geneserine yields a mixture of physostigmine hydriodide and the hydriodide of ψ-geneserinemethine (586), which can be further degraded to derivatives analogous to those obtained from physostigmine. Furthermore, eserine methiodide is converted by the action of hydrogen peroxide to ψ-geneserinemethine (627–629). Finally, on reduction with zinc and hydrochloric acid geneserine first takes up two atoms of hydrogen and is converted to physostigmine which then takes up two more atoms of hydrogen to form dihydrophysostigmine (588).

XII. The Iboga Alkaloids

Tabernanthe iboga Baill. (Acanthaceae) is a shrub indigenous to the Gabon where it is designated "iboga"; it has long been used by the natives because extracts of its root bark increase resistance to fatigue. The root bark contains the alkaloid ibogaine (630), also called ibogine (631). The total alkaloid content of the whole root (1.0–2.6%) is much lower than that of the root bark (5–6%) (632). The stalks, leaves, pericarps and seeds also contain alkaloids, but the crude bases isolated from the seeds show sharp color reactions different from those of the crude root bases (632). Quite recently a second alkaloid, tabernanthine, has been found to accompany ibogaine (632).

With most alkaloidal reagents ibogaine shows color reactions quite similar to those of yohimbine. Ibogaine can be distinguished from the latter by no single test, but by a combination of tests (633).

1. Ibogaine

Ibogaine, $C_{20}H_{26}ON_2$ (632), or $C_{19}H_{24}ON_2$ (634), is an optically active, crystalline base forming crystalline salts. It contains one methoxyl group and is unsaturated. The color reactions of the base indicate the presence of an indole nucleus (634), while the ultraviolet absorption spectrum (max. at 2950A. and min. at 2575A.) indicates an indole nucleus and either a quinoline or isoquinoline nucleus (635). However, neither the presence of the indole nucleus nor that of the quinoline nucleus has been confirmed by chemical degradations. The pharmacological study of the alkaloid is far more advanced than its chemical investigation (636–643).

2. Tabernanthine

Tabernanthine, $C_{21}H_{28}ON_2$ (632), is an optically active crystalline base producing local anesthesia when placed on the tongue. It is unsatu-

rated and contains one methoxyl group. Its ultraviolet absorption spectrum (maxima at 2700 to 3000A. and minima at 2575 and 2800A.). The color reactions of tabernanthine with glyoxylic acid and phosphovanillic acid reagents indicate the presence of an indole nucleus, but the base has not been further investigated (632).

XIII. Alkaloids of *Alstonia* Species

The barks of *Alstonia* species were widely reputed in China and the Pacific Islands as febrifuges and antimalarials and the intense search initiated during the second world war for substitutes for quinine again turned the attention of chemists towards the Alstonia alkaloids. However, the total extract of *Alstonia scholaris* R. Br., seems to have no demonstrable effect in malaria (644).

The older literature dealing with these alkaloids is misleading because names were assigned to ill-defined bases such as alstonidine, porphyrine and porphyrosine in *A. constricta* F. Muell. (645), ditamine and echitenine in *A. scholaris* (646–648) and in *A. spectabilis* R. Br. (649). The last species also contains alstonamine which, like alstonidine, is crystalline, but of unknown constitution (649, 650). The two well-characterized alkaloids isolated in the course of the older work are alstonine (chlorogenine) in *A. constricta* (645) and echitamine (ditaine (651, 652)) in *A. scholaris* (648, 652) and in *A. spectabilis* (649). The presence of alstonine in *A. constricta* has been confirmed (653, 654) and the plant has further been shown to contain three other bases, which, being amorphous and not well characterized, were designated as A, B, and C (654), together with a crystalline base, alstoniline (0.02–0.05%) (655). The presence of echitamine in *A. scholaris* (0.2–0.3%) has also been confirmed (656) and shown to be the main alkaloid in *A. congensis* Engl. (0.18–0.34%), in *A. gilletii* De Wild. (0.21%), *A. angustiloba* Miq., *A. spatulata* Blume (656) and *A. verticillosa* F. Muell. (657). Both *A. scholaris* and *A. congensis* contain echitamidine as well (656). Finally, *A. macrophylla* Wall. yields the alkaloids villalstonine, macralstonine, macralstonidine and the uncharacterized base M (657, 658), while *A. somersetensis* F. M. Bailey contains villalstonine and macralstonidine (657) and *A. villosa* Blume contains villalstonine and the insufficiently characterized base V (657).

The yield of alkaloid varies with the location of the plant. The yields of total alkaloid and of echitamine hydrochloride in *A. congensis* collected in the Gold Coast are 0.38–0.56, 0.18–0.34%, in Nigeria, 0.11–0.12, 0.03–0.04%, in the Cameroons, 0.18, 0.09% (660).

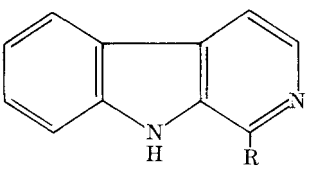
1. Alstonine

Alstonine, $C_{21}H_{20}O_3N_2$ (654), crystallizes only in the form of hydrates either with $4H_2O$ or $1\frac{1}{4}H_2O$ and it forms crystalline salts that, like the

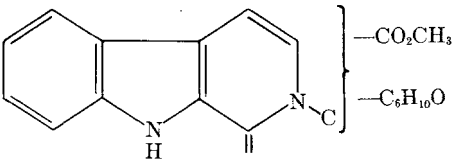
base, are colored. It is a monoacidic tertiary base containing one methoxyl group, but no methylimino or hydroxyl groups (654). Although its salts are inert to catalytic hydrogenation, the base itself can be hydrogenated to tetrahydroalstonine. This reduced base is hydrolyzed by alcoholic potassium hydroxide to tetrahydroalstoninic acid, $C_{20}H_{22}O_3N_2$, which, by the action of methanolic hydrogen chloride, is converted back to tetrahydroalstonine. Hence, the methoxyl group previously detected in alstonine is present in a carbomethoxy group. Tetrahydroalstonine can be reduced further by sodium in butyl alcohol to hexahydroalstonol, $C_{20}H_{26}O_2N_2$, in which the carbomethoxy group has been converted to a primary alcohol and an additional mole of hydrogen introduced. The ultraviolet absorption spectrum of hexahydroalstonol indicates that it is an α, β-disubstituted indole (659). The methyl ester in alstonine is very resistant to hydrolysis, thus suggesting a quaternary carbomethoxy group. Although the formation of tetrahydroalstonine indicates the presence of two double bonds, the action of bromine water on the base is peculiar. When an aqueous solution of alstonine sulfate is treated with bromine it gives rise to an unstable product converted by boiling ethanol to a stable hydrobromide, $C_{21}H_{18}O_4N_2Br_2 \cdot HBr$, containing two bromine atoms and an additional oxygen. On catalytic hydrogenation the stable bromo derivative produces two compounds, $C_{21}H_{21}O_4N_2Br$ and $C_{21}H_{22}O_3N_2$ formed presumably by replacement of one bromine by hydrogen in one case and in the other by replacement of both bromine atoms by hydrogen and removal of one oxygen atom (660).

Degradative experiments were more successful than the foregoing in revealing at least part of the structure of alstonine. The base is oxidized by potassium permanganate to a mixture of oxalic and oxalylanthranilic acids, thus indicating the presence either of a quinoline or an indole nucleus (660). While degradation of the base with selenium gives rise to alstyrine, $C_{19}H_{22}N_2$ (660, 660a), thermal decomposition of alstonine produces two isomeric bases which are also isomeric with, but different from alstyrine (659). The fusion of alstonine with potassium hydroxide gives rise to harman (CLXII; R = CH_3) while the similar fusion of tetrahydroalstonine produces besides harman and norharman (CLXII; R = H) three other, as yet unidentified, bases and indolyl-α-carboxylic acid (659). Alstonine contains an active hydrogen (Zerewitinow) obviously attached to the indole nitrogen since no hydroxyl group is present in the base and the second nitrogen is tertiary. Alstonine hydrochloride absorbs ultraviolet light of longer wavelength than 2-ethyl-β-carboline hydrochloride, lysergic acid or harmol and, therefore, possesses greater conjugation than any of these compounds. Partial structure CLXIII has been suggested to represent alstonine since it accounts for all the facts known so far (659). It has been shown recently that alstyrine is identical with corynanthyrine,

$C_{19}H_{22}N_2$, obtained from the selenium dehydrogenation of corynantheine (660a) and that it is identical with α-(α-diethyl-3,4-pyridine)-β-ethyl indole (660b). Alstonine, therefore, must be closely related to corynantheine.



CLXII



CLXIII

2. Alstoniline

Alstoniline, $C_{22}H_{18}O_3N_2$ (655), is an optically active minor base which is crystalline and also forms a crystalline monohydrate. When an alcoholic solution of alstoniline monohydrate is aerated for several hours a crystalline alstoniline oxide hydrate is formed. If, on the other hand, alstoniline monohydrate is hydrogenated catalytically over platinum oxide, two moles of hydrogen are absorbed, but in the course of isolation of the product the hydrogen previously taken up is lost, an atom of oxygen is absorbed, and alstoniline oxide monohydrate is the product. In contrast to this behavior, however, alstoniline hydrochloride absorbs two moles of hydrogen while alstoniline sulfate absorbs four when hydrogenated catalytically and the products are stable. Alstoniline monohydrate does not show the Ehrlich test, but tetrahydroalstoniline sulfate gives a color change from blue to olive-green in the modified Adamkiewicz reaction (661) usually considered indicative of a tetrahydro-β-carboline ring system.

3. Echitamine

Echitamine, $C_{22}H_{28}O_4N_2$ (646), first obtained from the bark of *A. scholaris* (662), was the subject of much controversy (646–648, 651–652, 664–666), probably owing to the subsequently established ease with which the alkaloid hydrolyzes. Echitamine is a strong base which cannot be liberated from its salts by ammonia and its mode of separation is based on this property. It forms crystalline salts readily. The hydrochloride separates from water either in the anhydrous form or hydrated, depending on the speed of separation (666). This salt shows a magenta color with hydrochloric acid in the presence of vanillin and a bright red coloration with strong nitric acid. Echitamine forms a complex with methanol (656). The base is readily hydrolyzed by sodium hydroxide to an amino acid, "demethylechitamine," $C_{21}H_{26}O_4N_2$, which no longer contains a methoxyl group and, like echitamine, shows an intense blue coloration with Hopkins

and Cole's glyoxylic acid reagent for tryptophan. Echitamine, therefore, contains a carbomethoxy group. Hydrolysis of the base takes place so readily that it has not yet been possible to prepare the free base and all attempts to do so have given rise to demethylechitamine. The base also contains a methyl group attached to nitrogen, but whether this nitrogen is secondary or tertiary is uncertain since the reaction of echitamine with nitrous acid is not definite (666). Furthermore, the base forms a diacetyl derivative, but because of the uncertainty of the nature of the basic nitrogen it cannot yet be concluded whether this indicates the presence of one or two hydroxyl groups in the base. Distillation with potassium hydroxide gives methylamine and a compound resembling an indole, but not identified nor fully characterized.

4. Echitamidine

Echitamidine, $C_{20}H_{26}O_3N_2$ (656) has been obtained from *A. congensis* and from *A. scholaris*. It is crystalline and forms crystalline salts. It behaves like a monoacidic base and probably contains a methylimino group, but no methoxyl.

5. Villalstonine

Villalstonine, $C_{40}H_{50}O_4N_4$ (657) gives various color reactions. With vanillin and alcoholic hydrochloric acid it shows an immediate pink color gradually turning to blue-violet; with Goebel's reagent a reddish brown; with concentrated nitric acid a greenish yellow and with concentrated sulfuric acid a brown color changing through purple to blue. The alkaloid contains two basic and two nonbasic nitrogen atoms and forms salts with two equivalents of acid. It contains one methoxyl group and two methylimino groups. The methoxyl is present in a carbomethoxy group and is eliminated by hydrolysis with alkali which gives rise to the acid $C_{38}H_{47}O_2N_4 \cdot CO_2H$, isolated as its dihydrochloride. Villalstonine yields a dimethiodide and a mono-*N*-benzyl derivative (657).

6. Macralstonine

Macralstonine, $C_{44}H_{54}O_5N_4$ (657, 658), gives the following color reactions: with vanillin and alcoholic hydrochloric acid it produces a pale yellow color which changes to yellow and then brownish pink. With Goebel's reagent it shows a brown color, with concentrated nitric acid yellow and with concentrated sulfuric acid yellowish green becoming yellow. The base has not been otherwise investigated.

7. Macralstonidine

Macralstonidine, $C_{41}H_{50}O_3N_4$ (657), gives no color for some time with vanillin and alcoholic hydrochloric acid, but gradually becomes pink.

With Goebel's reagent it shows a red color, with concentrated nitric acid yellow and with concentrated sulfuric acid no color at first, but then becomes blue and finally pink. This base has not been further investigated nor have been alkaloids A, B, C (654), M (657, 658), V (657), and alstonamine (649, 650).

XIV. Alkaloids of *Geissospermum vellosii* Allem. Diss.

The bark of *Geissospermum vellosii* Allem. Diss. (*Tabernaemontana laevis* Vell.) known as "pereiro bark," used in Brazil as a febrifuge, has long been known to contain the crystalline alkaloid geissospermine and the amorphous pereirine together with small quantities of a third, crystalline, base (667–670). The third base was later isolated again and characterized fully; it was named vellosine (671, 672). The bark contains 0.1–0.2% of geissospermine (673, 674).

1. Geissospermine

Geissospermine, $C_{40}H_{48}O_3N_4 \cdot 2H_2O$ (673), crystallizes either as a dihydrate or a sesquihydrate depending on the solvent and forms crystalline salts. It can neither be benzoylated nor acetylated, and it is indifferent towards reagents that condense with a carbonyl group (673). The base which is diacidic, forms a dimethiodide so that it contains two basic, tertiary nitrogen atoms and two that are neutral. Geissospermine further contains one methoxyl and one iminomethyl group. It gives most of the color reactions of yohimbine, but whereas the latter with concentrated nitric acid develops a yellow color, geissospermine under the same conditions shows a purple red (675).

The action of boiling hydrochloric acid causes a scission of the molecule and gives rise to the hydrochloride of a phenolbetaine, $C_{13}H_{20}O_2NCl$, which does not show a red color with nitric acid and contains no methoxyl group (674). On the other hand, hydrolysis of the alkaloid with alcoholic hydrogen chloride produces a base B, $C_{20}H_{26}O_2N_2$, which contains a methoxyl group and gives the red color with nitric acid, together with an isomeric base A which neither contains a methoxyl group nor shows the color test (676). Besides a methoxyl, the hydrolytic base B also carries a hydroxyl group since the methiodide of the base gives rise to an acetyl derivative (676). Hence, hydrolysis breaks open an ether link with addition of water and gives rise to two fragments each of the empirical formula $C_{20}H_{26}O_2N_2$. The function of the third oxygen, however, has not been determined. While base B carries a methoxyl but no iminomethyl, base A contains the latter but not the former group. Each of the fragments A and B yields a monomethiodide and therefore, each contains a tertiary nitrogen and an inert nitrogen (676).

The degradation of geissospermine with zinc dust yields an alkylated pyridine, probably 3-ethylpyridine, and indole derivatives detected by color tests (676). Fusion of the base with potassium hydroxide yields an indole derivative isolated as the picrate, but not definitely identified (674). On the basis of these rather incomplete degradation experiments, of the color reactions generally and of the brucinol reaction which is considered as due to the presence of a hydroxyl or methoxyl group on the benzene ring of an indole nucleus, one of the hydrolytic fragments of geissospermine has been assigned a skeletal structure similar to that of yohimbine (676).

2. Pereirine

Pereirine, $C_{20}H_{26}ON_2 \cdot \frac{1}{2}H_2O$ (674), is an amorphous base forming amorphous salts with one equivalent of acid and giving rise to a monomethiodide. In contrast to geissospermine, it is intensely bitter. It contains neither methoxyl nor iminomethyl, can neither be acetylated nor benzoylated, but is phenolic and is converted by diazomethane to a methyl ether. Both the methyl ether and pereirine show the purple red color with nitric acid (brucinol reaction, but only the latter gives a red color with ferric chloride (674).

3. Vellosine

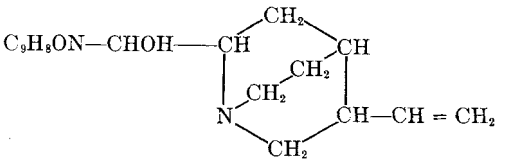
Vellosine, $C_{23}H_{28}O_4N_2$ (672), is a minor, crystalline base which accompanies geissospermine and pereirine. It forms crystalline salts with one equivalent of acid and a monomethiodide and is therefore a monoacidic, tertiary base. It contains two methoxyl groups thus accounting for two of its four oxygen atoms. Boiling mineral acids cause the condensation of two moles of the base with elimination of water and formation of apovellosine, $C_{46}H_{54}O_7N_4$. Apovellosine is amorphous but forms crystalline salts with, however, four equivalents of acid although it reacts with two moles only of methyl iodide, yielding a dimethiodide. Apovellosine contains four methoxyl groups which are split off by the action of concentrated hydrobromic acid with formation of apovellosol which, like its parent base, is amorphous but forms crystalline salts. When apovellosine is heated with concentrated alkali it does not revert to vellosine, but yields apovellosidine, $C_{42}H_{54}O_6N_4$.

XV. Quinamine and Cinchonamine

All the cinchona alkaloids of known structure are represented by the general formula Q—CH(OH)—Q′ where Q is quinolyl or 6-methoxyquinolyl and Q′ is 3-vinyl- or 3-ethylquinuclidyl, except two of the minor alkaloids, quinamine and cinchonamine which are indole bases. Quinamine was discovered in 1872 (677–684). It has been isolated from *Cinchona*

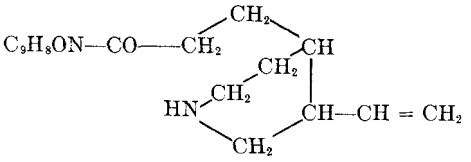
succirubra Pav. *C. nitida* Ruiz and Pav., *C. erythrantha* Pav., *C. erythroderma* Wedd, *C. rosulenta* Howard and *C. calisaya* Wedd (678), *C. officinalis* L. and *C. ledgeriana* Moens (681).

Quinamine, $C_{19}H_{24}O_2N_2$ (678), is a crystalline base forming crystalline salts (681–685). Oxidation of quinamine with chromic acid in the presence of sulfuric acid yields an acid, $C_{10}H_{15}O_2N$, that contains an ethylene linkage. The sodium salt of this acid when heated with soda lime gives rise to 3-ethyl pyridine. Decarboxylation of the acid yields a base, $C_9H_{15}N$, which absorbs one mole of hydrogen when hydrogenated catalytically and gives rise to 3-ethylquinuclidine, $C_9H_{17}N$. If it be assumed that the point of attachment of the quinuclidine nucleus to the rest of the molecule is position 8 as in the other cinchona alkaloids, then the acid $C_{10}H_{15}O_2N$ must be 3-vinylquinuclidine-6-carboxylic acid and quinamine can be represented by the partial formula CLXIV. The presence of the vinyl group in quinamine was confirmed by the catalytic hydrogenation of the



CLXIV

base which yielded dihydroquinamine, while the presence of the secondary alcoholic group between the 3-vinylquinuclidine nucleus and the rest of the molecule was assumed to be indicated by the resemblance in the behavior of the base to that of the other cinchona alkaloids. For instance,

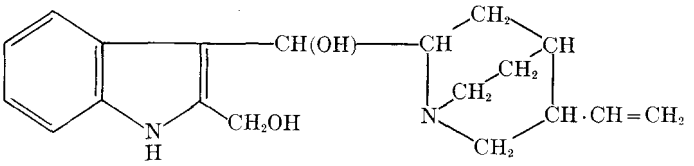


CLXV

prolonged boiling with dilute acetic acid converted quinamine into an isomeric quinicine (quinatoxine) which yielded an oxime and other well-crystallized derivatives and it was suggested that it be represented by formula CLXV (685).

Acetic anhydride converts quinamine into the amorphous acetyl apoquinamine which, on hydrolysis, yields the crystalline apoquinamine ($C_{19}H_{22}ON_2$) differing from the original base by the elements of water. This transformation is also brought about by the action of dilute acids

(681). In this reaction, it is assumed that the central carbinol group (CLXIV) is acetylated and that it is a hydroxyl in the C_9H_8ON residue which is eliminated as water. Furthermore, quinamine yields a nitroso derivative and hence must contain an imino group in the C_9H_8ON residue (685). Whereas the quinuclidine part survives, the rest of the molecule is destroyed by chromic acid oxidation. However, oxidation with nitric acid gives rise to picric acid which must indicate the presence either of a quinoline or an indole nucleus in the uncharacterized moiety, together with a compound ($C_9H_4O_7N_4$) the structure of which seems to be closely related to that of trinitrostrychol (686). The production of 2,3-dimethylindole when the base is distilled with zinc dust was assumed to indicate the presence of an indole. Vinylquinuclidine carboxylic acid and 2,3-dimethylindole each contain ten C-atoms and, hence, since quinamine contains nineteen C-atoms it is obvious that the carbon atom present in the carboxylic group of the acid must be the same as one of those which appear as methyl groups in the indole. On phytogenetic grounds this methyl is more likely to be that attached to position 3 of the indole. Consequently, the most probable structure for quinamine was considered to be CLXVI, since the base is neither phenolic nor ketonic and therefore the two oxygen atoms must be present in carbinol groups attached to the 2- and the 3-positions of the indole nucleus (686). Formula CLXVI errs, however, in



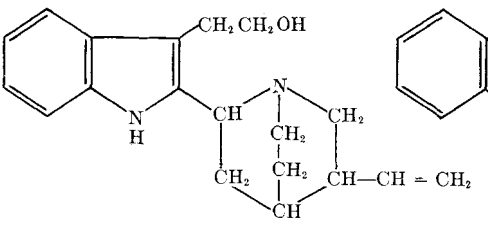
CLXVI

that it contains an indole nucleus whereas the ultraviolet absorption spectrum of the alkaloid does not show the usual absorption due to the indole structure. Further knowledge concerning the structure of quinamine was afforded through the elucidation of the structure of the related alkaloid cinchonamine.

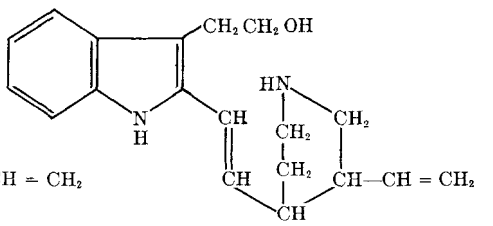
Cinchonamine, $C_{19}H_{24}ON_2$ (687–691) is a triboluminescent (692) base isolated from *Remijia purdieana* Wedd. (689), crystallizing as colorless prisms, m.p. 186°, α_D + 123° (693) and forming crystalline salts (690, 694–696). It shows the color reactions of yohimbine (697) and has the ultraviolet absorption spectrum typical of indoles (698, 699). The infrared absorption spectrum of the base reveals the characteristic bands of the hydroxy, imino and $CH_2 = C<$ groups (693). Cinchonamine contains a basic nitrogen (pK = 8.28) comparable in strength to those found in the

other Cinchona alkaloids, whereas the second nitrogen is nonbasic. Catalytic hydrogenation (Pd—$BaCO_3$) affords a dihydro derivative, $C_{19}H_{26}ON_2$, the infrared absorption spectrum of which no longer shows the band characteristic of the $CH_2 = C<$ group (693). Cinchonamine contains no methoxy, *N*-methyl or *C*-methyl groups, but does contain two active hydrogen atoms (Zerewitinow) attributable to the hydroxy group and the indole nucleus. Acetylation gives rise to a nonbasic diacetyl derivative so that the basic nitrogen must have become secondary and undergone acetylation. Hydrolysis of the diacetyl derivative indeed gives rise to a new base, allocinchonamine, the ultra violet absorption spectrum of which shows the presence of a double bond conjugated with the indole nucleus. The presence of this additional double bond is confirmed by the catalytic reduction of diacetylallocinchonamine, which absorbs two moles of hydrogen (693).

The oxidation of cinchonamine with chromic acid in sulfuric acid gives rise to 3-vinylquinuclidine-6-carboxylic acid and a second acid $C_{16}H_{22}O_7N_2$ that no longer shows the indole absorption in the ultraviolet and appears to be an *N*-acylanthranilic acid, indicating that the quinuclidine part of the cinchonamine molecule must be attached to the α-position of the indole nucleus. On the other hand, the oxidation of diacetyl-



CLXVII

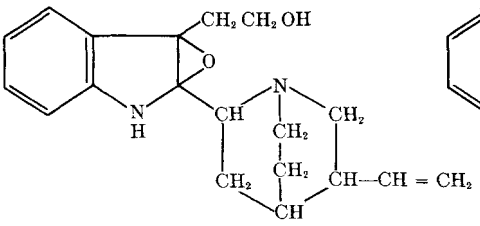


CLXVIII

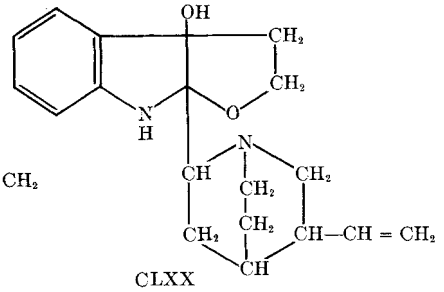
allocinchonamine with potassium permanganate affords β-(2-acetoxyethyl)-indole-α-aldehyde. The isolation of this aldehyde and the 3-vinylquinuclidine-6-carboxylic acid elucidate the structure of cinchonamine which must be represented by CLXVII while allocinchonamine is CLXVIII.

Formula CLXVI for quinamine is untenable because this alkaloid shows neither the color reactions nor the ultraviolet absorption spectrum of an indole base and also because it couples with diazobenzenesulfonic acid to give a methyl orange type compound (700, 701). Quinamine is transformed by amyl alcoholic potash into three isomeric substances, one of which, isoquinamine, like the parent base forms a monohydrochloride and a monomethochloride and absorbs one mole of hydrogen when reduced (702, 702a). On the basis of the similarity between the color and fluorescent properties of isoquinamine and the keto compound (CLXVI in

which the α-hydroxymethylindole is replaced by 4-ketotetrahydroquinoline), a formula was suggested for quinamine consisting of CLXVI with the α-hydroxymethylindole replaced by a 4-substituted-3,4-epoxy-1,2,3,4-tetrahydroquinoline (700). However, it has recently been found that the reduction of quinamine with lithium aluminum hydride gave rise to cinchonamine and this led to the proposal of structure CLXIX to represent



CLXIX



CLXX

quinamine (693). On the other hand, it has since been observed (703) that the reverse transformation of cinchonamine into quinamine can be effected with the aid of dilute peracetic acid. In accordance with the general course of oxidation in the indole series (704) this reaction was interpreted as probably first involving the formation of a β-hydroxyindolenine, followed by internal addition of the β-hydroxyethyl chain to the reactive $-C = N -$ double bond of the indolenine thus resulting in quinamine which should then be represented by CLXX. The removal of the hydroxyl group in quinamine by lithium aluminum hydride finds an analogy in the similar conversion of 11-hydroxytetrahydrocarbazolenine to tetrahydrocarbazole (705); this is accompanied by the opening of the oxide ring and loss of water in the transformation of quinamine (CLXX) into cinchonamine (703).

The action of amyl alcoholic potassium hydroxide on quinamine causes rapid epimerization and three products are obtained, i.e., epiquinamine, isoquinamine and epi-isoquinamine. The last compound is a diastereoisomeride of isoquinamine; it contains a double bond and can be hydrogenated to dihydroepi-isoquinamine. The rearrangement of quinamine to isoquinamine has been explained as involving the formation of an anion at the NH or OH group under the influence of the basic catalyst. The charge may then be transferred to the cyclic ether oxygen which is thus enabled to break away from C_2 and take the covalency electrons with it, the rearrangement following automatically (706).

Epiquinamine is assumed to be identical with conquinamine, a congener of quinamine, although no direct comparison has been made. It is reduced by lithium aluminum hydride to epicinchonamine and therefore

the epimerization takes place in the quinuclidine part of the molecule (702a). The action of acetyl chloride on quinamine transforms it to acetylapoquinamine which can be hydrolyzed to apoquinamine. Epiquinamine can also be transformed to apoquinamine which, on reduction with sodium in alcohol, gives rise to cinchonamine and epicinchonamine (702a).

XVI. *C*-Dihydrotoxiferine-I

Two of the numerous bases isolated from Calebasse curare, i.e., *C*-dihydrotoxiferine-I and the isomeric *C*-isodihydrotoxiferine-I (707) seem to belong to the indole group. These two bases form salts having no definite melting point. They have extremely similar ultraviolet absorption spectra and these are also similar to the spectrum of toxiferine-I obtained from *Strychnos toxifera* Schomb. (708). *C*-Dihydrotoxiferine-I, $C_{20}H_{22}N_2$ (707), absorbs three moles of hydrogen when hydrogenated catalytically. On the other hand, dehydrogenation of the alkaloid with sulfur yields isoquinoline, while heating with zinc dust gives rise to isoquinoline and a mixture of β-ethylindole and skatole (708). Since both isoquinoline and β-ethylindole are also obtainable from yohimbine by a similar degradation (709), it has been suggested that the ring skeleton of yohimbine is present in *C*-dihydrotoxiferine-I (708).

XVII. Table of Physical Constants

The alkaloids and their transformation products are listed in alphabetical order in Table 1 while their derivatives have been listed in the following order: ammonium salts of acids followed by C, O and N-substitution and addition products, the latter being arranged in alphabetical order. The physical data quoted have been taken from the first or at most the first two references cited, the remaining references having been arranged in numerical order. The abbreviation "dec" after the melting point indicates that decomposition accompanies melting and where two values are listed for the optical rotation the first quoted refers to $[\alpha]_D$, the second to $[\alpha]_{5461}$.

TABLE 1

THE PHYSICAL CONSTANTS OF THE INDOLE ALKALOIDS AND THEIR PRODUCTS OF TRANSFORMATION AND DEGRADATION

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
		A			
Abrine	$C_{12}H_{14}O_2N_2$	295	44.4°	Prisms	7,8
Hydrochloride	B·HCl	221.5			5
Nitrate	B·HNO_3	143 (dec)			5
Picrate	B·$C_6H_3O_7N_3$	194		Red prisms	5
Acetyl	$C_{14}H_{16}O_3N_2$	286–7 (dec)			5
N-Methyl methyl ester	$C_{13}H_{21}O_2N_2I$	197 (dec)			7, 8
Picrate	$C_{21}H_{23}O_9N_5$	163–164		Yellow rods	7, 8
Dipicrate	$C_{27}H_{26}O_{16}N_8$	155–6		Red plates	7, 8
N-Nitroso	$C_{12}H_{13}O_3N_3$	121			5
Phenylurethane	$C_{19}H_{19}O_3N_3$	271			5
Ajmalicine		250–2 (dec)		Long prismatic plates	443
Hydrochloride		260–3 (dec)		White powder	443
Picrate		212–5 (dec)		Yellow powder	443
Ajmaline	$C_{20}H_{26}O_2N_2$	158–160	128°	Large rect'g. plates	443
Chloroplatinate	$B_2·H_2PtCl_6$	217–8			443
Hydrochloride	B·HCl	253–5			443
Hydrochloride-hydrate	B·HCl·$2H_2O$	133–4			443
Picrate	B·$C_6H_3O_7N_3$	223		Yellow	443
Benzoyl-	$C_{28}H_{30}O_3N_2$	214–6		Broad needles	458
Dibromo-	$C_2H_{26}O_2N_2Br_2$	230 (dec)		Prismatic rods	454
N-Methyl	$C_{21}H_{28}O_2N_2$	130–1		Clusters of needles	458
Chloroplatinate	$B_2·H_2PtCl_6$	215–20		Amber colored powder	458
Hydrochloride	B·HCl	272		White powder	458
Hydriodide	B·HI	230–1			458
Picrate	B·$C_6H_3O_7N_3$	186		Yellow powder	458
Nitroso-	$C_{20}H_{25}O_3N_3·\frac{1}{2}H_2O$	209		Pale yellow needles	458
Trinitro-	$C_{20}H_{26}O_8N_6$	238–58		Amorphous	454
Ajmalinesulfonic acid	$C_{20}H_{26}O_5N_2S$	319–20 (dec)		Prismatic rods	454
Ammonium salt	$C_{20}H_{29}O_5N_3S$	319–20 (dec)		Rods and plates	454
Barium salt	$C_{20}H_{25}O_5N_2SBa$	322–4 (dec)		Needles	454
Ajmalinine	$C_{20}H_{26}O_3N_2$	180–1	−97°	Hexagonal prisms	443 454
Hydrochloride	B·HCl	240–5 (dec)		Semicrystalline powder	443
Picrate	B·$C_6H_3O_7N_3$	200–205		Yellow powder	443
Benzoyl-	$C_{27}H_{30}O_4N_2$	140–150		Amorphous	454
Methiodide	B·CH_3I	233–4		Rods	454
Alloyohimbic acid	$C_{20}H_{24}O_3N_2·H_2O$	248–50	−79.5°	Thick prisms	307
Ethyl ester	$C_{22}H_{28}O_3N_2$	282–5		Rhombohedra	307
Alloyohimbine	$C_{21}H_{26}O_3N_2$	135–40	−72.7°	Long needles	[307, 315
Hydrochloride	B·HCl	275–8	30.3°	Needles	[307, 315
Acetyl	$C_{23}H_{28}O_4N_2$	175–6	−33.9°	Colorless	364
Alloyohimbone	$C_{19}H_{22}ON_2$	230	144.6°	Needles	371
2,4-Dinitrophenylhydrazone Hydrochloride	$C_{25}H_{27}O_4N_6Cl·H_2O$	264			371
Alstoniline	$C_{22}H_{18}O_3N_2$	372 (dec)		Yellow-brown needles	655
Hydrate	B·H_2O	356 (dec)		Yellow-brown needles	655
Hydrochloride	B·HCl·H_2O	dec		Red needles	655
Sulfate	$B_2H_2SO_4$	260–4 (dec)		Red needles	655

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Picrate	$B \cdot C_6H_3O_7N_3 \cdot H_2O$	294 (dec)		Red needles	655
Methiodide	$B \cdot CH_3I$	dec		Orange-red needles	655
Oxide	$C_{12}H_{18}O_4N_2$	219–21.5			655
Hydrate	$B \cdot H_2O$	212.5–13.5		Yellow rosettes	655
Alstonine	$C_{21}H_{29}O_3N_2 \cdot 1\frac{1}{4}H_2O$	254 (dec)		Canary yellow	654
Acid oxalate	$B \cdot C_2H_2O_4$	239 (dec)		Soft yellow needles	654
Hydrochloride	$B \cdot HCl$	286 (dec)	131.9°	Yellow plates	[654, 659
Hydriodide	$B \cdot HI$	291 (dec)		Triangular yellow leaflets	[654, 659
Nitrate	$B \cdot HNO_3$	262–3 (dec)		Orange needles	[654, 659
Picrate	$B \cdot C_6H_3O_7N_3$	194–5		Reddish orange needles	654
Sulfate	$B_2 \cdot H_2SO_4 \cdot 5H_2O$	209	118.6°	Orange stout rods	[654, 659
Sulfate (acid)	$B \cdot H_2SO_4$	246–8	113.1°	Yellow prismatic needles	[654, 659
Bromo-, sulfate	$(C_{21}H_{21}O_4N_2Br)_2H_2SO_4$	212 (dec)	−13.6°	Yellow needles	660
Dibromo-, hydrobromide	$C_{21}H_{19}O_4N_2Br_3$	276 (dec)		Yellow plates	660
Methiodide	$B \cdot CH_3I$	246 (dec)		Yellow needles	654
Chloroplatinate	$B_2 \cdot H_2PtCl_6 \cdot H_2O$	220–1 (dec.)		Orange yellow prisms	659
Perchlorate	$B_2 \cdot HClO_4$	239–40		Yellow prisms	659
Alstoninehydromethine	$C_{22}H_{26}O_3N_2$	182–3		Prismatic needles	660
Hydriodide	$B \cdot HI$	262 (dec)		Rectangular prisms	660
Methiodide	$B \cdot CH_3I$	276 (dec)		Rosettes of soft needles	660
Alstyrine	$C_{19}H_{22}N_2$	113		Pale yellow plates	660
Picrate	$B \cdot C_6H_3O_7N_3$	215–6		Yellow platelets	660
Methiodide	$B \cdot CH_3I$	221 (dec)		Yellow prismatic needles	660
Methochloride	$B \cdot CH_3Cl$	242 (dec)			660
Alstyrinehydromethine	$C_{18}H_{25}N_2(CH_3)$				
Methiodide	$B \cdot CH_3I$	227 (dec)		Soft needles	660
Methochloride	$B \cdot CH_3Cl$	196–7		Soft needles	660
Aminoharman	$C_{12}H_{11}N_3$	298		Flat needles	238
Aminoharmine	$C_{13}H_{13}ON_3$	231–2		Greyish yellow needles	243
Apoajmalinine	$C_{13}H_{17}O_3N$	270–2		Rectangular plates	454
Hydrochloride	$B \cdot HCl$	243–4			454
Picrate	$B \cdot C_6H_3O_7N_3$	231–2			445
Apocorynanthine	$C_{21}H_{24}O_2N_2$	169–170	−183°		413
Apoharmine	$C_8H_8N_2$	185		Prisms	[213, 256
Picrate	$B \cdot C_6H_3O_7N_3$	247		Yellow needles	236
Methyl-	$C_9H_{10}N_2$	77–8		Needles	[236, 245
Chloroplatinate	$C_9H_{10}N_2 \cdot H_2PtCl_6$	260 (dec)		Yellow prisms	236
Hydriodide	$C_9H_{10}N_2 \cdot HI \cdot H_2O$	220		Needles	[214, 236
Nitro	$C_8H_7O_2N_3$	270 (dec)		Needles	236
Nitro-methyl	$C_9H_9O_2N_3$	225 (dec)		Yellow leaflets	240
Chloroaurate	$C_9H_9O_2N_3 \cdot HAuCl_4$	174		Yellow needles	240
Chloroplatinate	$C_9H_9O_2N_3 \cdot H_2PtCl_6 \cdot 2H_2$	240–5 (dec)		Reddish yellow	240
Apoharminecarboxylic acid	$C_9H_8O_2N_2$	330 (dec)		Needles or leaflets	240
Methyl-Hydriodide	$C_{10}H_{11}O_2N_2I$			Needles	240
Nitro-	$C_9H_7O_4N_3$	250 (dec)		Small yellow needles	[240, 246
Apogelsemine	$C_{20}H_{24}O_4N_2$	..	..	Amorphous	494
Hydrochloride	$B \cdot HCl \cdot H_2O$	250–60	18.9°	Needles	494
Acetyl	$C_{22}H_{26}O_4N_2$	295–298	..	Small prisms	494

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Diacetyl-	$C_{24}H_{28}O_3N_2$	..	..	..	
Hydrochloride	$C_{24}H_{28}O_3N_2 \cdot HCl$	286	21.7°	Plates	494
Methiodide	$B \cdot CH_3I$	295 (dec)	12.4°	Prisms	494
Apoquinamine	$C_{19}H_{22}ON_2$	115–7	..	Cream colored plates	[681, 685
Hydriodide	$B \cdot HI$	207–9	..	..	685
Picrate	$B \cdot C_6H_3O_7N_3$	172–4	−0.93°	Orange needles	685
Acetyl picrate	$C_{27}H_{27}O_9N_5$	143–5	..	Yellow needles	685
Benzoyl picrate	$C_{32}H_{29}O_9N_5$	191–3	..	..	685
Methiodide	$B \cdot CH_3I$	219–20	..	..	685
Apovellosidine	$C_{42}H_{44}O_6N_4$	154	..	Needles	672
Chloroplatinate	$B \cdot 4HCl \cdot PtCl_4$	203 (dec)	..	Brownish red needles	672
Hydrobromide	$B \cdot 3HBr \cdot 6H_2O$	235	..	Platelets	672
Methiodide	$C_{42}H_{52}O_6N_4 \cdot 2CH_3I$	262	..	Needles	672
Apovellosine	$C_{46}H_{44}O_7N_4$	..	..	Amorphous	672
Hydriodide	$B \cdot 4HI$	253–4 (dec)	..	Prisms	672
Hydrobromide	$B \cdot 4HBr$	210 (dec)	..	Prisms	672
Methiodide	$B \cdot 2CH_3I$	265	..	Yellow platelets	672
Apovellosol	$C_{42}H_{46}O_7N_4$	..	..	..	672
Hydriodide	$B \cdot 4HI \cdot 5H_2O$	235 (dec)	..	Stout crystals	672
Hydrobromide	$B \cdot 4HBr \cdot 5H_2O$	245	..	Stout crystals	672
Apoyohimbic acid	$C_{20}H_{22}O_2N_2$	..	..	..	370
Hydrochloride	$B \cdot HCl$	301	..	Microcrystalline powder	370
α-Chloropropyl ester	$C_{23}H_{29}O_3N_2Cl$	105–6	..	Plates	367
α-Diethylaminoethyl ester	$C_{26}H_{35}O_3N_3$	80–2	..	Microscopic crystals	367
α-Diethylaminopropyl ester	$C_{27}H_{39}O_3N_3$	95–6	..	Plates	367
Hydroxyethyl ester	$C_{22}H_{28}O_4N_2$	117–8	..	Irregular plates	367
Hydrochloride	$B \cdot HCl$	292–4	..	Flat needles	367
Apoyohimbine	$C_{21}H_{24}O_2N_2$	252	40°	Stout prisms	370
Hydrochloride	$B \cdot HCl$	299–300	..	Rhombic plates	370
Aspidosine	$C_{19}H_{26}ON_2$	244–5	−16°	Prisms	425
Hydriodide	$B \cdot HI$	280	..	Octahedra and cubes	425
Aspidospermatine	$C_{22}H_{28}O_2N_2$	162	−72.3°	Needles	422
Aspidospermine	$C_{22}H_{30}O_2N_2$	205–206	−99°	Prisms	420
Oxid. product	$C_{15}H_{24}O_3N_2$	192–3	..	Stout prisms	425
Hydrochloride	$C_{15}H_{24}O_3N_2 \cdot HCl$	286–7	..	Plates	425
	B				
C-Benzylharmine	$C_{20}H_{18}ON_2$	138	..	Prisms	241
Benzylideneharmaline	$C_{32}H_{32}O_2N_4$	245 (dec)	..	Microcrystalline powder	241
Benzylideneharmine	$C_{20}H_{16}ON_2$	191–2	..	Needles or prisms	241
α-Bromo	$C_{20}H_{15}ON_2Br$	230	..	Plates	279
β-Bromo	$C_{20}H_{15}ON_2Br$	125 (dec)	..	..	279
N-Ethyl	$C_{22}H_{20}ON_2$	199–200	..	Red rhombic plates	259
Methiodide	$B \cdot CH_3I$	250–1	..	Yellow needles	259
N-Methyl	$C_{21}H_{18}ON_2$	192–3	..	Red needles	259
Ethiodide	$B \cdot C_2H_5I$	230–1	..	Yellow needles	259
p-Nitro	$C_{20}H_{15}O_3N_3$	266	..	Red needles	241
	C				
Calycanthidine	$C_{18}H_{16}N_2$	142	−285.1°	Needles	507
Hydriodide	$B \cdot HI$	182	..	Needles	507

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Perchlorate	B·$HClO_4$	158	..	..	507
Picrate	B·$C_6H_3O_7N_3$	192	..	..	507
Methyl derivative	$C_{16}H_{28}ON_2I$	221	..	Needles	507
Calycanthine	$C_{22}H_{26}N_2$	245	..	Pyramids	[505, 508
Hydriodide	B·2HI	221–2	..	Silky needles	509
Hydrobromide	B·2HBr·$2H_2O$	216–7	..	Rectangular plates	509
Hydrochloride	B·2HCl·$2H_2O$	216–7	..	Rectangular plates	509
Dibenzoyl-	$C_{36}H_{34}O_2N_4$	235	..	Prismatic needles	511
Carboxy-yobyrine	$C_{20}H_{16}O_2N_2·H_2O$	..	..	Fine needles	396
Chalchupine-A	$C_{14}H_{21}O_{12}N_3$(?)	168	..	..	[448, 449
Chloroplatinate	..	261–2	..	..	449
Hydriodide	..	240	..	..	449
Picrate	..	150–2	..	..	449
Chalchupine-B	$C_{16}H_{24}O_{11}N_6$(?)	240	..	..	449
Hydriodide	..	258–60	..	..	449
Picrate	..	154–6	..	..	449
Tartrate	..	250–6	..	..	449
Cinchonamine	$C_{19}H_{24}ON_2$	186	123°	Prisms	693
Corynantheic acid	$C_{21}H_{26}O_3N_2$	..	..	..	417
Corynantheidine	$C_{22}H_{28}O_2N_2·C_3H_6O$	117	−142°	..	418
Hydrochloride	B·HCl·$2H_2O$	213	−128°	..	418
Picrate	B·$C_6H_3O_7N_3$	252	−152°	..	418
Styphnate	B·$C_6H_3O_8N_3$	246	−138°	..	418
Corynantheine	$C_{22}H_{28}O_3N_2$	117 and 169	27.7°	Prismatic needles	[317,415,417a, 418
Hydrochloride	B·HCl	205	43.4°	..	[317, 415
Corynanthic acid	$C_{20}H_{24}O_3N_2$	284	−85.9°	Needles	[411, 324
Ethyl ester	$C_{22}H_{28}O_3N_2$	240–1	−112°	..	413
Corynanthidine (α-yohimbine)	$C_{21}H_{26}O_3N_2$	243–4	−11.5°	Needles	[314, 316, 322
Hydrochloride	B·HCl	288	57.4°	Needles	314
Picrate	B·$C_6H_3O_7N_3$	231–2	6°	Yellow crystals	314
Acetyl-	$C_{23}H_{28}O_4N_2$	230–1	−12.2°	..	314
Corynanthidinic acid	$C_{20}H_{24}O_3N_2$	320–2	48.3°	Prismatic needles	314
Ethyl ester	$C_{22}H_{28}O_3N_2$	244–5	−11.8°	Needles	314
Hydrochloride	$C_{22}H_{28}O_3N_2·HCl$	288–9	56.7°	Needles	314
Corynanthidone	$C_{19}H_{22}ON_2$	..	..	Amorphous	314
Hydrochloride	B·HCl	265–6	−50.2°	Crystals	314
2,4-Dinitrophenyl-hydrazone	$C_{25}H_{26}O_4N_6$	260	..	..	314
Corynanthine	$C_{21}H_{26}O_3N_2$	221–2	−145°	Elongated platelets or needles	[318, 325, 413
Hydrochloride	B·HCl	285–90	−61.15°	Needles	325
Acetyl-	$C_{23}H_{28}O_4N_2$	135 (dec)	−60.4°	Prismatic needles	410
Diacetyl-	$C_{25}H_{30}O_5N_2$	194–5	−105°	Large prisms	410
		D			
Deacetylaspidospermine	$C_{20}H_{28}ON_2$	110–1	2.8°	Prismatic needles	425
Dihydriodide	B·2HI	243	..	Stout prisms	425
Acetyl-	$C_{22}H_{30}O_2N_2$	208	−104°	..	439
Benzoyl-	$C_{27}H_{32}O_2N_2$	186–7	..	Stout rhombs	425
Dimethiodide	B·$2CH_3I$	176–7	..	Octahedra	425
Formyl-	$C_{21}H_{26}O_3N_2$	152–3	−90°	Long columns	439
Hydrochloride	$C_{21}H_{28}O_2N_2·HCl$	255–70	..	Glistening needles	439
Nitronitroso	$C_{20}H_{26}O_4N_4$	155–6	..	Yellow prisms	425
Debromohydroalstonine hydrobromide	$C_{21}H_{22}O_3N_2·HBr$	291 (dec)	162.8°	Rosettes of boat-shaped crystals	661

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Decahydrosempervirine	$C_{19}H_{24}ON_2$	205	..	Yellow needles	474
Deformylvallesine	$C_{19}H_{26}ON_2$	107–8	7°	Prisms	439
Dihydriodide	B·2HI	>280 (dec)	..	Glistening prisms	439
Acetyl-	$C_{21}H_{28}O_2N_2$	208–10	−107°	Prisms	439
Benzoyl- (basic)	$C_{26}H_{30}O_2N_2$	187–190	..	Plates	439
Benzoyl- (neutral)	$C_{26}H_{34}O_4N_2$	203–5	..	Small columns	439
Formyl-	$C_{20}H_{26}O_2N_2$	154–6	−91°	..	439
Dihydroapoharmine	$C_8H_{10}N_2$	48–9	..	Plates	[214, 242
Chloroaurate	B·$HAuCl_4$	149 (dec)	..	Reddish brown needles	214
Hydrochloride	B·HCl	246–7	..	Soft needles	214
Bromo-	$C_8H_7N_2Br$	229	..	Needles	237
Methyl-	$C_9H_9N_2Br$	196	..	Needles	237
Iodo-	$C_8H_7N_2I$	158	..	Long needles	239
Methyl	$C_9H_9N_2I$	155–6	..	Needles	239
Nitroso-	$C_8H_9ON_3$	134–5	..	Needles	214
Tetrabromo-	$C_8H_8N_2Br_4$	..	..	..	214
Dihydroapoquinamine	$C_{19}H_{24}ON_2$	124–6	..	..	685
Picrate	B·$C_6H_3O_7N_3$	179–81	..	Orange needles	685
Acetyl (picrate)	$C_{27}H_{29}O_9N_5$	148–50	..	..	685
Dihydroergocristinine	$C_{35}H_{41}O_5N_5$	180	−56° −68°	Six-sided plates	195
Dihydroergocornine	$C_{31}H_{41}O_5N_5$	185–7	−48°	Six-sided plates	195
Dihydroergocryptine	$C_{32}H_{43}O_5N_5$	235	−41° −52°	Polyhedra	195
Dihydroergotamine	$C_{33}H_{37}O_5N_5$	239	−64° −79°	Prisms	195
Dihydroeserethole	$C_{13}H_{24}ON_2$	..	..	..	588
Chlorozincate	B·2HCl·$ZnCl_2$	252	..	..	588
Dehydroeseretholemethine	$C_{16}H_{24}O_2N_2$	..	..	..	582
Picrate	B·$C_6H_3O_7N_3$	199	..	Plates	582
Methiodide	B·$CH_3I·H_2O$	131	..	Prisms	582
Dehydroesermethole-methine	$C_{15}H_{22}O_2N_2$	186–7	..	Rectangular prisms	600
d-Bromocamphor-sulfonate	$C_{26}H_{39}O_6N_2Br·S·H_2O$	245–8	27.8°	Rectangular plates	600
Methiodide	B·CH_3I	142	..	Rectangular prisms	600
Methopicrate	$C_{24}H_{27}O_9N_5$	132–3	..	Orange needles	600
Dehydroketoyobyrine	$C_{20}H_{18}ON_2$	345–50	..	Yellowish green needles	395
Demethylechitamine	$C_{21}H_{26}O_4N_2·2H_2O$	290 (dec)	−46.8°	Prisms	[656, 666
Hydrochloride	B·HCl	306 (dec)	..	Prisms	666
Demethylvillalstonine Hydrochloride	$C_{39}H_{48}O_4N_4·2HCl$	291–3 (dec)	..	..	657
Deoxy-yohimbine	$C_{21}H_{26}O_2N_2$	200–3	..	Slender needles	370
Deoxy-yohimbol	$C_{19}H_{24}N_2$	149	−24.8°	Spears	372
Hydrochloride	B·HCl	228	..	Columns	372
Picrate	B·$C_6H_3O_7N_3$	224	..	Red crystals	372
Methiodide	B·CH_3I	198	..	Large spears	372
Oxalate	B·$C_2H_2O_4$	204	..	Sheaves of fine needles	582
Dimethopicrate	$C_{29}H_{34}O_{15}N_8$	204	..	Prisms	582
dl-Dihydroeserethole Picrate	$C_{21}H_{27}O_8N_5$	140	..	Orange red	615
Dihydroeseretholemethine	$C_{18}H_{26}ON_2$	..	..	..	571
Chlorozincate	B·2HCl·$ZnCl_2$	242	..	..	571
Methiodide	B·CH_3I	125	..	..	571
Dihydroeserine methiodide	$C_{15}H_{23}O_2N_3·CH_3I$	125	..	..	571

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Dihydroesermethole-methine					
Dimethiodide	$C_{17}H_{30}O_4N_2I_2$	205	..	Needles	[573, 600
dl-Dihydroesermethole-methine	$C_{15}H_{24}ON_2$	..	..	..	600
Methiodide	B·CH_3I	157–8	..	Rectangular plates	600
Methopicrate	B·$C_6H_3O_7N_3$	193–5	..	Yellow leaflets	600
Dihydroeseroline	$C_{13}H_{20}ON_2$	140	−95°	..	588
Chlorozincate	B·2HCl·$ZnCl_2$	194	..	..	571
Methiodide	B·CH_3I	128–9	11°	Prisms	588
Dihydroetheserolene	$C_{14}H_{21}O_2N$	..	35°	..	568
Hydrochloride	B·HCl	177	..	..	568
Dihydrogelsemine	$C_{20}H_{24}O_2N_2$	224–5	78.5°	Needles	[474, 488
Hydriodide	B·HI	294	..	..	488
Hydrobromide	B·HBr	328–30	..	..	488
Hydrochloride	B·HCl	328	..	Needles	488
Nitrate	B·HNO_3	285 (dec)	..	..	488
Dinitro-	$C_{20}H_{22}O_6N_4$	257–8 (dec)	6.6°	Bright yellow	493
Nitrate	$C_{20}H_{22}O_6N_4·HNO_3$	219–21 (dec)	−61.7°	Yellow	493
Methiodide	$C_{20}H_{22}O_6N_4·CH_3I$	255–6	−68.5°	Yellow	493
Methiodide	B·CH_3I	301–2	..	..	488
d-Dihydroisolysergic acid	$C_{15}H_{18}O_2N_2$	330	+32°	..	162
Dihydrolysergic acid	$C_{16}H_{18}O_2N_2$	336	−88°	Leaflets	153
Methyl ester	$C_{17}H_{20}O_2N_2$	182	..	Broad leaves	153
Pyrolysis prod. from Dihydro-	$C_{16}H_{16}ON_2$	305–7	−219°	..	163
rac. Dihydrolysergic acid	$C_{16}H_{18}O_2N_2$	336	..	..	163
α-Dihydrolysergol	$C_{16}H_{18}O_2N_2$	290–300	..	Platelets	176
Acetyl-	$C_{16}H_{20}ON_2$	282	−92°	Stout prisms	[162, 185
Methiodide	$C_{18}H_{22}O_2N_2$	200	..	Irregular leaves	185
β-Dihydrolysergol	$C_{17}H_{23}ON_2I$	237	..	Broad plates	162
Acetyl-	$C_{16}H_{20}ON_2$	190	−64°	Leaflets	185
Methiodide	$C_{18}H_{22}O_2N_2$	129	..	Needles	185
γ-Dihydrolysergol	$C_{17}H_{23}ON_2I$	253–4	..	Rhombs	160
Dihydroquinamicine oxime	$C_{16}H_{20}ON_2$	255	+33°	Rhombs	162
Dihydroquinamine	$C_{19}H_{27}O_4N_3$	225–7	..	Needles	685
Picrate	$C_{19}H_{26}O_2N_2$	184–5	119.8°	Needles	685
Dinitro-	B·$C_6H_3O_7N_3$	176–8	..	Orange rods	685
	$C_{19}H_{24}O_6N_4$	146–8	..	Yellowish brown needles	686
Methiodide	B·CH_3I	219–25	..	Short rods	685
Nitronitroso-	$C_{19}H_{24}O_4N_4$	228–30	..	Yellow rods	686
Tetranitronitroso	$C_{19}H_{21}O_{11}N_7$	..	..	..	686
Hydrochloride	$C_{19}H_{21}O_{11}N_7·HCl$	227 (dec)	..	Yellow needles	686
C-Dihydrotoxiferine-I	$C_{20}H_{22}N_2$	..	..	..	687
Hydrobromide	B·HBr·1½H_2O	260	..	Long needles	687
Hydrochloride	B·HCl	..	−610.6°	Small prisms	687
Picrate	B·$C_6H_3O_7N_3$	183–5	..	Broad needles	687
Sulfate	$B_2·H_2SO_4·3H_2O$	..	..	Small rods	687
l-6,8-*Dimethylergoline*	$C_{16}H_{20}N_2$	246–8	−49°	Polyhedra	176
dl-6,8-Dimethylergoline	$C_{16}H_{20}N_2$	222–3	..	Cryst ds	163
Hydrochloride	$C_{16}H_{21}N_2Cl$	..	..	Leaflets	175
d-1,3-Dimethyl-5-ethoxy-oxindolylethyl-methylamine	$C_{15}H_{22}O_2N_2$	..	30.2°	..	616
d-Camphorsulfonate	$C_{25}H_{38}O_6N_2S$	160	..	Spherical aggregates	616

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
l-1,3-Dimethyl-5-ethoxy-oxindolylethyl-methylamine	$C_{15}H_{22}O_2N_2$	..	−30.1°	..	616
d-Hydrogentartrate	$C_{19}H_{28}O_8N_2$	175–6	..	..	616
Picrate	$C_{21}H_{25}O_9N_5$	175	..	..	616
dl-1,3-Dimethyl-5-ethoxy-oxindolylethyl-methylamine					
Picrate	$C_{21}H_{25}O_9N_5$	192	..	..	616
Dimethylpyruvic acid					
Phenylhydrazone	$C_{11}H_{14}O_2N_2$	152	..	..	184
d-Dinoreserethole-*d*-ditartrate	$C_{17}H_{24}O_7N_2$	164–5	235.1°	Plates	606
l-Dinoreserethole-*d*-ditartrate	$C_{17}H_{24}O_7N_2$	157–9	..	Needles	606
dl-Dinoreserethole	$C_{13}H_{18}ON_2$	35–9	..	..	606
Acetate	$B \cdot C_2H_4O_2$	119–20	..	..	606
Benzoate	$B \cdot C_7H_6O_2$	154–5	..	Needles	606
Picrate	$B \cdot C_6H_3O_7N_3$	170–1	..	Orange prisms	606
dl-Dinoresermethole	$C_{12}H_{16}ON_2$	51–7	..	..	606
Benzoate	$B \cdot C_7H_6O_2$	159–60	..	Needles	606
Picrate-	$B \cdot C_6H_3O_7N_3$	137–8	..	Red rhombs	606
Dipheneserine	$C_{27}H_{28}O_3N_4$	184	−244°	Microneedles	560
Donaxarine	$C_{13}H_{16}O_2N_2$	217	0°	..	31
		E			
Echitamidine	$C_{20}H_{26}O_3N_2$	244	−515°	..	656
Hydriodide	$B \cdot HI \cdot 3H_2O$	182 (dec)	−389°	..	656
Hydrobromide	$B \cdot HBr \cdot 2H_2O$	181 (dec)	−422°	..	656
Hydrochloride	$B \cdot HCl \cdot 4H_2O$	179 (dec)	−473°	..	656
Nitrate	$B \cdot HNO_3 \cdot 2H_2O$	170 (dec)	−403°	..	656
Picrate	$B \cdot C_6H_3O_7N_3$	226–7 (dec)	..	..	656
Sulfate	$B_2 \cdot H_2SO_4 \cdot 11H_2O$	169 (dec)	−362°	..	656
Echitamine	$C_{22}H_{28}O_4N_2$	..	..	..	666
Hydriodide	$B \cdot HI$	267 (dec)	..	Prisms	[656, 666
Hydrobromide	$B \cdot HBr$	268 (dec)	−43.5°	Prisms	666
Hydrochloride	$B \cdot HCl$	295 (dec)	−58°	Needles	[648, 666
Hydrate	$B \cdot HCl \cdot H_2O$	292 (dec)	−54.3°	Stumpy prisms	666
Hydrogen oxalate	$B \cdot C_2H_2O_4 \cdot 2H_2O$	238 (dec)	..	..	666
Nitrate	$B \cdot HNO_3 \cdot 2H_2O$	176 (dec)	−51.4°	Pyramids	666
Picrate	$B \cdot C_6H_3O_7N_3 \cdot 2H_2O$	98 (dec)	..	..	666
Sulfate	$B_2 \cdot H_2SO_4 \cdot H_2O$	ca. 275 (dec)	−51.6°	Needles	666
Diacetyl-	$C_{26}H_{32}O_6N_2$	..	..	..	666
Hydrochloride	$B \cdot HCl$	271 (dec)		Silky needles	666
Methyl sulfate	$B \cdot CH_3 \cdot HSO_4$	253 (dec)	..	Plates	656
Dinitro	$C_{22}H_{26}O_4N_2(NO_2)_2$	184 (dec)	..	Red needles	666
Epiyohimbol	$C_{19}H_{24}ON_2$	258	−80.1°	Large prisms	372
Methiodide	$B \cdot CH_3I$	300	..	Needles	372
Methochloride	$B \cdot CH_3Cl$	298	..	Warts	372
Ergocornine	$C_{31}H_{39}O_5N_5$	182–4	−188° −226°	Polyhedra	93
Di-(*p*-toluyi)-*l*-tartrate	$B \cdot C_{20}H_{18}O_8$	180–1	+103°	Plates	93
Ethanesulfonate	$B \cdot C_2H_5SO_3H$	209	..	Thin prisms	93
Hydrobromide	$B \cdot HBr$	225	..	Prisms	93
Hydrochloride	$B \cdot HCl$	223	..	Prisms	93
Phosphate	$B \cdot H_3PO_4$	190–5	..	Prisms	93

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Ergocorninine	$C_{31}H_{39}O_5N_5$	228	+409° +512°	Massive prisms	93
Ergocristine	$C_{35}H_{39}O_5N_5$	160–75	−183° −217°	Flat prisms (acetone)	93
Di-(*p*-toluyl)-*l*-tartrate	$B_2 \cdot C_{20}H_{18}O_8$	191–2	+58°	Thin prisms	93
Ethanesulfonate	$B \cdot C_2H_6SO_3H$	207	..	Six-sided plates	93
Hydrochloride	B·HCl	205	+105.7° +126.5°	Elongated plates	91
Phosphate	$B \cdot H_3PO_4$	195	..	..	93
d-Tartrate	$B \cdot C_4H_6O_6$	185–90	..	Warts	93
Ergocristinine	$C_{35}H_{39}O_5N_5$	226	+366° +460°	Needles	[91, 93
Ergocryptine	$C_{32}H_{41}O_5N_5$	212	−187° −226°	Long prisms	93
Di-(*p*-toluyl)-*l*-tartrate	$B \cdot C_{20}H_{18}O_8$	186	+103°	Long needles	93
Ethanesulfonate	$B \cdot C_2H_6SO_3H$	204	..	Prisms	93
Hydrochloride	B·HCl	208	..	Clusters of needles	93
Phosphate	$B \cdot H_3PO_4$	198–200	..	Hexagonal plates	93
d-Tartrate	$B \cdot C_4H_6O_6$	209	..	Rectangular plates	93
Ergocryptinine	$C_{32}H_{41}O_5N_5$	240–2	+408° +508°	Needles	93
Ergoline	$C_{14}H_{16}N_2$	175–83	..	Powder	171
Ergometrine (*d*-lysergic acid-*d*-propanol-amide-(2))	$C_{19}H_{23}O_2N_3$	162	+90°	Tetrahedra	[150, 203
Ergometrinine (*d*-isolysergic acid-*d*-propanol-amide-(2))	$C_{19}H_{23}O_2N_3$	196°	+416°	Prisms	[150, 203
Ergosine	$C_{30}H_{37}O_5N_5$	228	−161° −194°	Prisms	[89, 198
Hydrobromide	B·HBr	230	..	Needles	[89, 198
Hydrochloride	B·HCl	235	..	Rhombic plates	[89, 198
Ergosinine	$C_{30}H_{37}O_5N_5$	228	+420° +522°	Prisms	[89, 198
Ergotamine	$C_{33}H_{35}O_5N_5$	212–4	−160° −192°	Flat prisms	194
Di-(*p*-toluyl)-*l*-tartrate	$B_2 \cdot C_{20}H_{18}O_8$	190	+79°	Rectangular plates	194
Ethanesulfonate	$B \cdot C_2H_6SO_3H$	207	..	Platelets	194
Hydrobromide	B·HBr	213	..	Plates and prisms	194
Hydrochloride	B·HCl	212	..	Plates and prisms	194
Methanesulfonate	$B \cdot CH_3SO_3H$	210	..	Platelets	194
Phosphate	$B \cdot H_3PO_4$	200	..	Plates	194
Sulfate	$B_2 \cdot H_2SO_4$	205	..	Plates	194
d-Tartrate	$B_2 \cdot C_4H_6O_6$	203	..	Rhombic plates	194
Ergotaminine	$C_{33}H_{35}O_5N_5$	241–3	+369° +462°	Plates	194
Eseramine	$C_{16}H_{23}O_2N_4$	245	..	Small needles	[525, 529
d-Eserethole-*d*-ditartrate	$C_{15}H_{22}ON_2 \cdot C_4H_6O_6$	173	115.5°	Needles	610
l-Eserethole	$C_{15}H_{22}ON_2$	b.p. 308–10	−81°	Oil	558
d-Ditartrate	$C_{19}H_{26}O_7N_2$	168	..	..	616
l-Ditartrate	$C_{15}H_{22}ON_2 \cdot C_4H_6O_6$	173–4	−115°	Needles	[594, 610
Hydrobromide	B·HBr	178	..	Prisms	558
Picrate	$B \cdot C_6H_3O_7N_3$	133	..	Yellow	616
Methiodide	$B \cdot CH_3I$	170–1	..	..	[558, 574
Nitropicrate	$C_{16}H_{23}O_2N_3C_6H_3O_7N_3$	133–4	..	Yellow	591
Trinitro	$C_{16}H_{19}O_7N_5$	152	..	Orange rectangular plates	582

TABLE I (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
dl-Eserethole-a	$C_{13}H_{22}ON_2$	38	..	Long needles	615
Dimethopicrate	$C_{29}H_{32}O_{15}N_8$	169–71	..	Yellow	615
Methylmethopicrate	$C_{22}H_{29}O_8N_5$	194	..	Red	615
dl-Eserethole-b	$C_{13}H_{22}ON_2$	80	..	..	611
Picrate	$B{\cdot}C_6H_3O_7N_3$	150–1	..	Orange prisms	611
Methopicrate	$B{\cdot}CH_3{\cdot}C_6H_2O_7N_3$	191–2	..	..	611
Eserethelemethine	$C_{16}H_{26}O_2N_2$	89	10°	Prismatic needles	574
Dipicrate	$B{\cdot}(C_6H_3O_7N_3)_2$	170	..	Yellow prisms	582
Hydriodide	B·HI	170	..	..	[558, 574
Picrate	$B{\cdot}C_6H_3O_7N_3$	196	..	Orange	574
Dimethiodide	$C_{20}H_{36}O_2N_2I_2$	208	..	Short prisms	[567, 589
Dimethoperchlorate	$C_{20}H_{36}O_2N_2(ClO_4)_2$	272–3	..	Prisms	567
Methiodide	$B{\cdot}CH_3I$	140–1	+2°	..	574
Eseridine	$C_{15}H_{23}O_3N_3$	132	..	..	[526, 527, 532
Esermethole	$C_{14}H_{20}ON_2$	b.p. 164–7/12 mm.	..	..	600
Methiodide	$C_{15}H_{23}ON_2I$	169–70	..	Rectangular prisms	600
Methopicrate	$C_{21}H_{25}O_8N_5$	194	..	Rhombic plates	600
Esermetholemethine	$C_{15}H_{24}O_2N_2$	..	..	..	589
Dimethiodide	$C_{19}H_{34}O_2N_2I_2$	235	..	..	[567, 589
Dimethoperchlorate	$C_{19}H_{34}O_2N_2(ClO_4)_2$	294	..	Prisms	567
Eseroline	$C_{13}H_{18}ON_2$	129	−107°	Needles	[558, 616
Benzoate	$B{\cdot}C_7H_6O_2$	155–6	−108.7°	Thick leaves	[559, 616
Hydrobromide	$B{\cdot}HBr{\cdot}H_2O$	208	..	..	558
Hydrochloride	B·HCl	212–3	..	..	558
Picrate	$B{\cdot}C_6H_3O_7N_3$	167–8	..	Rosettes of yellow needles	[558, 559
Sulfate	$B{\cdot}H_2SO_4$	202–3	−164°	..	558
Ethiodide	$B{\cdot}C_2H_5I$	172	..	Needles	567
Methiodide	$B{\cdot}CH_3I$	187–8	..	Prisms	[559, 556
Methopicrate	$B{\cdot}CH_3{\cdot}C_6H_2O_7N_3$	194.5	..	Yellow needles	[558, 597, 556
Etheserolene	$C_{14}H_{19}O_2N$	48	−98°	Large prisms	[573, 574
Picrate	$B{\cdot}C_6H_3O_7N_3$	98	..	Stout prisms	582
Isonitroso-	$C_{14}H_{18}O_3N_2{\cdot}H_2O$	97	..	Red prisms	574
Methiodide	$B{\cdot}CH_3I$	179	−40°	Prisms	574
5-Ethoxy-1,3-dimethyl-3-ethyl-2-indolinone	$C_{14}H_{19}O_2N$	68	..	Cubes	582
5-Ethoxy-1,3-dimethyl-3-vinyl-2-indolinone	$C_{14}H_{17}O_2N$	62	..	Prisms	582
Picrate	$B{\cdot}C_6H_3O_7N_3$	103	..	Crimson	582
3-Ethylquinuclidine picrate	$C_{13}H_{20}O_7N_4$	151–3	..	..	685
Evodiamine	$C_{19}H_{17}ON_3$	278	251°	Needles	282
Geissospermine	$C_{40}H_{46}O_4N_4{\cdot}2H_2O$	210–2 (dec)	−108.2°	Prisms	673
Oxalate	$B{\cdot}C_2H_2O_4{\cdot}5H_2O$	193 (dec)	..	Needles	673
Sulfate	$B{\cdot}H_2SO_4{\cdot}6H_2O$	226	−84.2°	Plates	673
Dimethiodide	$B{\cdot}(CH_3I)_2 4H_2O$	261–2 (dec)	−61.5°	Platelets	673
Hydrolytic base A	$C_{20}H_{28}O_2N_2$	ca. 205	..	..	676
Hydrolytic base B	$C_{20}H_{26}O_2N_2{\cdot}\frac{1}{2}H_2O$	115	−57.4°	Amorphous powder	674
Hydrochloride	$C_{20}H_{26}O_2N_2{\cdot}HCl{\cdot}\frac{1}{2}H_2O$	159–60	..	Prisms	676
Methicdide	$C_{70}H_{26}O_2N_2{\cdot}CH_3I{\cdot}\frac{1}{2}H_2O$	230–1 (dec)	..	Needles	[673, 674
Methoxyhydrolytic base B	$C_{21}H_{28}O_2N_2$	..	..	..	676
Methiodide	$C_{21}H_{28}O_2N_2{\cdot}CH_3I$	265–6	..	Fine needles	676
Phenolbetaine Hydrochloride	..	..	..	..	674
Gelsemicine	$C_{20}H_{24}O_4N_2$	171	−141°	Prisms	[472, 474
Hydrochloride	B·HCl	140–2	..	Rosettes of microprisms	[472, 474

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Picrate	$B \cdot C_6H_3O_7N_3$	203	..	Yellow plates	[474, 501
Benzoyl-	$C_{27}H_{28}O_6N_2$	262	..	Needles	474
Methyl-hydriodide	$C_{21}H_{27}O_6N_2I$	227	..	Plates	474
Gelsemine	$C_{20}H_{22}O_2N_2$	178	15.9°	Flat needles	[472, 487
Hydrochloride	$B \cdot HCl$	303	2.6°	Small prisms	[487, 489
Nitrate	$B \cdot HNO_3$	288	..	Prisms	[487, 489
Acetyl-	$C_{22}H_{24}O_3N_2$	106–8	23.9°	Prisms	494
Bromo-	..	>320	..	..	493
Dibromo-	$C_{20}H_{22}O_2N_2Br_2$	309 (dec)	..	..	493
Methiodide	$B \cdot CH_3I$	284	..	Prisms	[489, 494
Gelsemine (isomer)	$C_{20}H_{22}O_2N_2$	140–5	25.2°	Prisms	[474, 494
Geneseretholе	$C_{15}H_{22}O_2N_2$	83	−182°	Leaflets	530
Hydriodide	$B \cdot HI \cdot H_2O$	108	..	Silky needles	530
Hydrochloride	$B \cdot HCl$	120–4	..	..	530
l-Geneseretholemethine	$C_{14}H_{18}O_2N_2(CH_3)_2$	..	..	..	572
Hydriodide	$B \cdot HI$	214	..	..	572
Hydrochloride	$B \cdot HCl$	222	..	..	572
Methiodide	$B \cdot CH_3I$	140	..	..	572
Geneserine	$C_{15}H_{21}O_3N_3$	128–9	−17.5°	Orthogonal crystals	530
Picrate	$B \cdot C_6H_3O_7N_3$	175	..	Straw colored needles	530
Salicylate	$B \cdot C_7H_6O_3$	89–90	..	..	530
ψ-Geneserinemethine	$C_{14}H_{17}O_3N_3(CH_3)_2$	160	−17°	..	573
Hydriodide	$B \cdot HI$	214	..	Fine needles	573
ψ-Geneserolene	$C_{12}H_{13}O_2N$	215	−85°	Small needles	585
Ethyl-	$C_{14}H_{17}O_2N$	60	..	..	573
Geneseroline	$C_{13}H_{18}O_2N_2$	150	−176°	..	530
Hydrobromide	$B \cdot HBr$	208	..	..	530
Hydrochloride	$B \cdot HCl$	154	..	..	530
Picrate	$B \cdot C_6H_3O_7N_3$	175	..	Orange red	530
ψ-Geneserolinemethine	$C_{12}H_{14}O_2N_2(CH_3)_2$	171	−46°	Prisms	[573, 585
Hydriodide	$B \cdot HI$	234	..	..	573
Methiodide	$B \cdot CH_3I$	275	..	..	[572, 585
Acetyl-	$C_{14}H_{16}O_3N_2(CH_3)_2I$	175	..	..	573
Gramine	$C_{11}H_{14}N_2$	134	0°	Small plates	32
Chloroplatinate	$B_2 \cdot H_2PtCl_6$	180–1 (dec)	..	..	27
Perchlorate	$B \cdot HClO_4$	150–1	..	..	[27, 36
Picrate	$B \cdot C_6H_3O_7N_3$	144–5	..	..	[27, 33
Ethiodide	$C_{13}H_{19}N_2I$	176	..	Prisms	31
Methiodide	$C_{12}H_{17}N_2I$	175–6 (dec)	..	..	[33, 36
		H			
Harmalan	$C_{12}H_{13}N_3$	182–3	..	Yellow needles	263
Harmaline	$C_{13}H_{14}ON_2$	238	..	Platelets	[210, 213
Acetyl-	$C_{15}H_{16}O_2N_2$	204–5	..	Small needles	236
Bis-azobenzene-	$C_{25}H_{22}ON_6$	180 (dec)	..	Carmine needles	246
Bis-azo-*p*-bromobenzene	$C_{25}H_{20}ON_6Br_2$	200–3 (dec)	..	Small red needles	246
Bis-azo-*p*-chlorobenzene	$C_{25}H_{20}ON_6Cl_2$	185 (dec)	..	Red prisms	246
Bis-azo-*p*-toluene	$C_{27}H_{26}ON_6$	182–3 (dec)	..	Reddish brown needles	246
Bromo	$C_{13}H_{13}ON_2Br$	195	..	Needles	237
Methosulfate	$C_{15}H_{20}O_5N_2S$	170–2	..	..	248
Methyl-	$C_{14}H_{16}ON_2$	162	..	Small crystals	236
Chloroaurate	$C_{14}H_{16}ON_2 \cdot HAuCl_4$	153 (dec)	..	Violet needles	244
Chloroplatinate	$(C_{14}H_{16}ON_2)_2H_2PtCl_6$	220 (dec)	..	Orange leaflets	244
Hydrochloride	$C_{14}H_{16}ON_2 \cdot HCl \cdot 4H_2O$	265 (dec)	..	Glistening crystals	244
Nitrate	$C_{14}H_{15}ON_3 \cdot HNO_3$	230 (dec)	..	Yellow prisms	244
Picrate	$C_{14}H_{16}ON_2 \cdot C_6H_3O_7N_3$	216	....	Yellow needles	244

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Nitro-	$C_{13}H_{13}O_3N_3$	122 (dec)	..	Orange prisms	246
Acetyl-	$C_{15}H_{15}O_4N_3$	181 (dec)	..	Yellow leaflets	246
Harmalol	$C_{12}H_{12}ON_2$	212 (dec)	..	Orange crystalline powder	213
Acetyl	$C_{14}H_{14}O_2N_2$	..	..	Yellow warts	214
Harman	$C_{12}H_{10}N_2$	238	..	Glistening plates	[251, 252
Harmine	$C_{13}H_{12}ON_2$	256–7	..	Needles	211
Hydrochloride	B·HCl	262	..	..	215
Amino-	$C_{13}H_{13}ON_3$	231–2	..	Greyish yellow needles	243
Bromo-	$C_{13}H_{11}ON_2Br$	275	..	Prisms	237
Dibromo-	$C_{13}H_{10}ON_2Br_2$	209	..	Needles	[214, 237
9-(2-Diethylaminoethyl)-hydrochloride	$C_{19}H_{27}ON_3Cl_2·H_2O$	275 (dec)	..	Needles	281
Methosulphate	$B·(CH_3)_2SO_4$	220	..	Needles	248
Ind.-N-methyl	$C_{14}H_{14}ON_2·2H_2O$	124–5	..	Flat needles	258
Hydrobromide	$C_{14}H_{14}O_2N_2·HBr·2H_2O$	280	..	Needles	281
Hydrochloride	$C_{14}H_{14}O_2N_2·HCl·2H_2O$	280	..	Slender needles	258
Nitrate	$C_{14}H_{14}ON_2·HNO_3·H_2O$	280	..	Slender needles	258
Picrate	$B·C_6H_3O_7N_3$	249–50	..	Prisms	258
Py-N-methyl-	$C_{14}H_{14}ON_2$	209	..	Yellow needles	236
Hydriodide	$C_{14}H_{14}ON_2·HI$	305–7	..	Long needles	[213, 248
Hydrochloride	$C_{14}H_{14}ON_2·HCl$	305 (dec)	..	Yellow needles	248
Methiodide	$C_{14}H_{14}ON_2·CH_3I$	..	..	Needles	236
Methochloride	$C_{14}H_{14}ON_2·CH_3Cl$	280–5 (dec)	..	Needles	237
Nitro-	$C_{13}H_{11}O_3N_3$	204–5	..	Orange needles	[243, 246
Tetrabromo-	$C_{13}H_{12}ON_2Br_4$	..	..	*Amorphous*	[214, 237
Harminethiosulfuric acid	$C_{13}H_{13}O_4N_2S_2$	190	19.5°	..	280
Harminic acid	$C_{10}H_8O_4N_2$	345 (dec)	..	Silky needles	213
Ethyl-	$C_{12}H_{12}O_4N_2$	280 (dec)	..	Needles	236
Methyl-	$C_{11}H_{10}O_4N_2$	280 (dec)	..	Prisms	236
Harmol	$C_{12}H_{10}ON_2$	321	..	Small needles	213
O-Allyl-	$C_{15}H_{14}ON_2$	166–7	..	Needles	278
Hydrochloride	B·HCl	233	..	Small needles	278
O-*n*-Amyl-	$C_{17}H_{20}ON_2$	204–6	..	Needles	278
Hydrochloride	B·HCl	192–4	..	Long, silky needles	278
O-Benzyl-	$C_{19}H_{16}ON_2$	213	..	Minute needles	278
Hydrochloride	$C_{19}H_{16}ON_2·HCl$	256–7	..	Needles	278
O-*n*-Butyl-	$C_{16}H_{18}ON_2$	218–20	..	Thick rhombs	[243, 278
Hydrochloride	$C_{16}H_{18}ON_2·HCl$	232–40	..	Rhombs	278
Methochloride	$C_{17}H_{21}ON_2Cl$	279	..	Needles	278
O-*n*-Decyl-	$C_{22}H_{30}ON_2$	105–7	..	Needles	278
Hydrochloride	B·HCl	208	..	Leaflets	278
O-*N*-Di-n-butyl-	$C_{20}H_{26}ON_2$	113	..	Yellow needles	278
λ-Di-*n*-butylaminodecyl-	$C_{31}H_{54}ON_2·3H_2O$	65–7	..	..	278
Dihydrochloride	$C_{31}H_{54}ON_2·2HCl·3H_2O$	138–9	..	Needles	278
O-κ-Di-*n*-butylamino-decyl-	$C_{30}H_{47}ON_3·2H_2O$	59–60	..	..	278
Dihydrochloride	$C_{30}H_{47}ON_3·2HCl·1.5H_2O$	98–99	..	Needles	278
O-κ-Diethylaminodecyl-	$C_{26}H_{39}ON_3·2H_2O$	137	..	..	278
Dihydrochloride	$C_{26}H_{39}ON_3·2HCl·H_2O$	149–50	..	..	278
O-β-Diethylaminoethyl-	$C_{18}H_{23}ON_2$	167–8	..	..	278
Dihydrochloride	$C_{18}H_{23}ON_2·2HCl·3H_2O$	295	..	..	278
O-*n*-Diethylaminoheptyl	$C_{23}H_{33}ON_3$	109–111	..	..	278
Dihydrochloride	$C_{23}H_{33}ON_3·2HCl·3H_2O$	144–6	..	Thick needles	278

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
O-*i*-Diethylaminononyl	$C_{25}H_{37}ON_3$	92	..	..	278
Dihydrochloride	$C_{25}H_{37}ON_3 \cdot 2HCl \cdot 3H_2O$	168	..	..	278
O-*o*-Diethylaminooctyl	$C_{24}H_{35}ON_3$	98–9	..	..	278
Dihydrochloride	$B \cdot 2HCl \cdot 1 \cdot 5H_2O$	97–100	..	..	278
O-λ-Diethylaminoundecyl	$C_{27}H_{41}ON_3 \cdot 2H_2O$	82–4	..	..	278
Dihydrochloride	$C_{27}H_{41}ON_3 \cdot 2HCl \cdot H_2O$	99–101	..	..	278
O-κ-Dimethylaminodecyl	$C_{24}H_{35}ON_3$	91–4	..	..	278
Dihydrochloride	$C_{24}H_{35}ON_3 \cdot 2HCl \cdot 2 \cdot 5H_2O$	180–2	..	Needles	278
O-*n*-Dodecyl	$C_{24}H_{34}ON_2$	119–20	..	Needles	278
Hydrochloride	$C_{24}H_{34}ON_2 \cdot HCl$	208.5	..	Nacreous leaflets	278
O-Ethyl	$C_{14}H_{14}ON_2$	193	..	Long needles	[243, 278
Hydrochloride	$C_{14}H_{14}ON_2 \cdot HCl$	313	..	Needles	278
O-*n*-Heptyl	$C_{19}H_{24}ON_2$	131–2	..	Leaflets	278
Hydrochloride	$C_{19}H_{24}ON_2 \cdot HCl$	228–9	..	Needles	278
O-*n*-Hexyl-	$C_{18}H_{22}ON_2$	143–4	..	Needles	278
Hydrochloride	$C_{18}H_{22}ON_2 \cdot HCl$	212–3	..	Felted needles	278
O-ω-Hydroxy-*n*-decyl-	$C_{22}H_{30}O_2N_2$	174–5	..	Needles	278
Hydrochloride	$C_{22}H_{30}O_2N_2 \cdot HCl$	180	..	Needles	278
O-Isoamyl-	$C_{17}H_{20}ON_2$	237–8	..	Rhombs	[243, 278
Hydrochloride	$C_{17}H_{20}ON_2 \cdot HCl$	206–8	..	Needles	278
O-Isodecyl-	$C_{22}H_{30}ON_2$	101–4	..	Needles	278
Hydrochloride	$C_{22}H_{30}ON_2 \cdot HCl \cdot 2H_2O$	210–2	..	Needles	278
O-Isopropyl-	$C_{15}H_{16}ON_2$	181	..	Feathery needles	278
Hydrochloride	$C_{15}H_{16}ON_2 \cdot HCl$	277–8	..	Fine needles	278
N-Methyl-*O*-*n*-butyl-	$C_{17}H_{20}ON_2$	144	..	Dark green needles	278
O-*n*-Nonyl	$C_{21}H_{28}ON_2$	115	..	Long needles	278
Hydrochloride	$C_{21}H_{28}ON_2 \cdot HCl$	205–7	..	Leaflets	278
O-*n*-Octyl-	$C_{20}H_{26}ON_2$	98–100	..	Needles	278
Hydrochloride	$C_{20}H_{26}ON_2 \cdot HCl$	217–8	..	Thick needles	278
O-*sec* Octyl-hydrochloride	$C_{20}H_{27}ON_2Cl \cdot 2 \cdot 5H_2O$	254–5	..	Short prisms	278
O-κ-Piperidyldecyl	$C_{27}H_{39}ON_3$	109–11	..	..	278
Dihydrochloride	$C_{27}H_{39}ON_3 \cdot 2HCl \cdot 4H_2O$	117–8	..	..	278
O-Propyl-	$C_{15}H_{16}ON_2$	203–4	..	Small crystals	[243, 278
Hydrochloride	$C_{15}H_{16}ON_2 \cdot HCl$	259–61	..	Needles	278
Harmolic acid	$C_{12}H_{10}O_3N_2$	246–7 (dec)	..	Needles	214
Haslerine		237	..	..	428
Hexahydroalstonol	$C_{20}H_{26}O_2N_2$	282–4 (dec)	−78°	Small prisms	659
Hexahydrogelsemine	$C_{20}H_{28}O_2N_2$	170	..	Needles	474
Methiodide	$B \cdot CH_3I$	296	..	..	474
Hexahydroyobyrine	$C_{19}H_{32}N_2$	197	..	Fine needles	372
Hypaphorine	$C_{14}H_{18}O_2N_2$	255 (dec)	94.7°	..	[20, 21
Flavianate	$B \cdot C_{10}H_8O_8N_2S$	235 (dec)	..	..	15
Hydrochloride	$B \cdot HCl$	234–5	89.2°	..	15
Nitrate	$B \cdot HNO_3$	222–4	..	..	13
	I				
Ibogaine	$C_{20}H_{26}ON_2$ or $C_{19}H_{24}ON_2$	152	−53°	Orthorhombic prisms	[630, 632, 634
Hydrochloride	$B \cdot HCl$	..	−37.3°	..	634
Isoajmaline	$C_{20}H_{26}O_2N_2$	265–6	72.8°	Slender needles	[458, 454
Hydrochloride	$B \cdot HCl$	230–40 (dec)	98.7°	Amorphous powder	[458, 454
Picrate	$B \cdot C_6H_3O_7N_3$	180–200	..	Yellow powder	454
Isoapogelsemine	$C_{20}H_{24}O_3N_2$	290–300	16.6°	Prisms	494
Hydrochloride	$B \cdot HCl \cdot H_2O$	..	27.1°	..	494

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Bromo-	$C_{20}H_{23}O_2N_2Br$	ca. 220	..	Plates	494
Chloro-	$C_{20}H_{23}O_2N_2Cl$	220 ?	..	Prisms	494
Chloroaurate	$C_{20}H_{23}O_2N_2Cl \cdot HAuCl_4 \cdot H_2O$	160 (dec)	..	Orange prisms	494
Methiodide	$C_{20}H_{23}O_2N_2Cl \cdot CH_3I$	265	..	Prisms	494
Chloroacetyl-	$C_{22}H_{25}O_3N_2Cl$	180	..	Prisms	494
Diacetyl-hydrochloride	$C_{24}H_{29}O_4N_2Cl$	305	..	Plates	494
Iodo-hydriodide	$C_{20}H_{24}O_2N_2I_2$	298 (dec)	..	Needles	474
Methiodide	$B \cdot CH_3I$	266 (dec)	28.1°	Plates	494
Isobromoharmine	$C_{13}H_{11}ON_2Br$	203	..	Needles	237
dl-Isodesoxynoreseroline	$C_{12}H_{16}N_2$	111–2	..	*Prisms*	611
C-Isodihydrotoxiferine-I	$C_{20}H_{22}N_2$	..	..	..	..
Hydrochloride	$B \cdot HCl \cdot 3H_2O$	..	−566°	Needles	687
Perchlorate	$B \cdot HAuCl_4$	..	..	*Small rods*	687
Picrate	$B \cdot C_6H_3O_7N_3$	242 (dec)	..	Prisms	687
Isoevodiamine	$C_{19}H_{19}O_2N_3$	155–6	..	..	282
Hydrochloride	$B \cdot HCl$	265–7	..	*Rhombic plates*	282
Isogelsemine	$C_{20}H_{22}O_2N_2$	200–2	38.8°	..	488
Methiodide	$B \cdot CH_3I$	279–80 (dec)	..	..	488
d-Isolysergic acid	$C_{16}H_{16}O_2N_2$	..	+282°	..	..
d-Butanolamide-(2)	$C_{20}H_{25}O_2N_3$	192–4	+386°	Polyhedra	203
Diethylamide	$C_{20}H_{25}ON_3$	182	+217°	Prisms	203
2-Diethylaminoethyl-amide	$C_{22}H_{30}ON_4$	163	+396°	Plates	203
1,3-Dioxypropanamide-(2)	$C_{19}H_{23}O_4N_3$	231	+445°	Prisms	203
Ethanolamide	$C_{18}H_{21}O_2N_3$	204–6	+448°	Polyhedra	203
Hydrazide	$C_{16}H_{18}ON_4$	204	+452°	Thin prisms	204
Di-(*p*-toluyl)-tartrate	$C_{16}H_{18}ON_4 \cdot C_{20}H_{18}O_8$	..	+238°	Small needles	204
d-Methylpentanolamide-(2)	$C_{22}H_{29}O_2N_3$	160	+330°	Stout prisms	203
d-Norephedride	$C_{25}H_{27}O_2N_3$	125–130	+237°	Prisms	203
d-Nor-ψ-ephedride	$C_{25}H_{27}O_2N_3$	..	+370°	..	203
l-Propanolamide-(2)	$C_{19}H_{23}O_2N_3$	195	+355°	Massive prisms	203
l-Isolysergic acid					
l-Norephedride	$C_{25}H_{27}O_2N_3(Et_2O)$	125–30	−267°	Prisms	168
d-Propanolamide-(2)	$C_{19}H_{23}O_2N_3$	195	−351°	Massive prisms	203
l-Propanolamide-(2)	$C_{19}H_{23}O_2N_3$	196	−415°	Prisms	203
rac. Isolysergic acid	$C_{16}H_{16}O_2N_2$	240–5	..	..	168
Hydrazide	$C_{16}H_{18}ON_4$	240 (dec)	..	Six-sided plates	204
dl-Isonoreserethole	$C_{14}H_{20}ON_2$	71–2	..	Prisms	611
Oxalate	$B \cdot C_2H_2O_4$	152–3	..	..	611
Isophysostigmine	$C_{15}H_{21}O_2N_3$	197–8	..	..	561
Picrate	$B \cdot C_6H_3O_7N_3$	170	..	..	561
Sulfate	$B \cdot H_2SO_4$	200–2	..	..	528
α-(β'-Isoquinolyl)-β-ethylindole	$C_{19}H_{18}N_2$	128	..	Needles	[372, 387
Hydrochloride	$B \cdot HCl$	212	..	Needles	372
Picrate	$B \cdot C_6H_3O_7N_3$	208 (dec)	..	..	387
Methiodide	$B \cdot CH_3I$	192	..	Yellow crystals	372
Isoserpentine	$C_{70}H_{90}O_3N_2 \cdot 2 \cdot 5H_2O$	230–2 (dec)	..	Prismatic rods	454
Chloroplatinate	$B_2 \cdot H_2PtCl_6$	248–9 (dec)	..	Slender needles	454
Hydrochloride	$B \cdot HCl$	271–2	168°	Needles	454
Picrate	$B \cdot C_6H_3O_7N_3$	263–4 (dec)	..	Yellow needles	454
Isoyohimbic acid	$C_{20}H_{24}O_3N_2$	284	146.5°	Thick needles	307
N-Acetyl-betaine	$C_{23}H_{28}O_4N_2$	205–6	..	Needles	364
Methiodide	$C_{24}H_{29}O_4N_2 \cdot CH_3I$	248	..	Needles	364

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Ethyl ester	$C_{22}H_{28}O_3N_2$	238–9	..	Needles	307
Hydrochloride	$C_{22}H_{28}O_3N_2 \cdot HCl$	295	..	..	307
Isoyohimbine	$C_{21}H_{26}O_3N_2$	240–3	57.1°	Needles	307
Hydrochloride	$B \cdot HCl$	280–3	103.8°	Needles	307
Tartrate	$B \cdot C_4H_6O_6$	252–3	..	Warts	383
Diacetyl-	$C_{26}H_{30}O_5N_2$	185 (dec)	−20.8°	Crystalline powder	364
Methochloride	$B \cdot CH_3Cl$	272	114.1°	Clusters of needles	364
		K			
2-Ketotetrahydronorharmine	$C_{12}H_{12}O_2N_2$	198	..	Rhombs	261
N-Acetyl-	$C_{14}H_{14}O_3N_2$	207–8	..	Prisms	261
N-Methyl	$C_{13}H_{14}O_2N_2$	228	..	Yellow needles	248
Ketoyobyrine	$C_{20}H_{18}ON_2$	328–30	..	Yellow rectangular prisms	[383, 396
Kounidine	$C_{21}H_{24}O_5N_2$	315	..	..	476
Koumine	$C_{20}H_{22}ON_2$	170	−265°	..	[475, 489
Chloroplatinate	$B_2 \cdot H_2PtCl_6$	>310	..	Brown	489
Hydrobromide	$B \cdot HBr$	268–9	..	Cubes	489
Hydrochloride	$B \cdot HCl$	258	..	Cubes	489
Nitrate	$B \cdot HNO_3$	248–50	..	..	489
Sulfate	$B \cdot H_2SO_4$	261–2	..	..	489
Methiodide	$B \cdot CH_3I$	230 (dec)	..	Needles	489
Kouminidine	$C_{19}H_{25}O_4N_2$ (?)	299 (dec)	..	..	489
		L			
d-Lysergic acid	$C_{16}H_{16}O_2N_2$	235–40	+40°	..	151
Amide	$C_{16}H_{17}ON_3$	135	5461 = +514°	Prisms	[182, 183
Hydrobromide	$C_{16}H_{17}ON_3 \cdot HBr$	260	5461 = +349°	Prisms	[182, 183
Hydrochloride	$C_{16}H_{17}ON_3 \cdot HCl$	255–260	..	Colorless plates	[182, 183
Nitrate	$C_{16}H_{17}ON_3 \cdot HNO_3$	225–30	..	Plates	[182, 183
Perchlorate	$C_{16}H_{17}ON_3 \cdot HClO_4$	225	..	Needles	[182, 183
Picrolonate	$C_{16}H_{17}ON_3 \cdot C_{10}H_8O_5N_4$	215	..	Yellow plates	182
1-*N*-Benzylpropanolamide-(2)	$C_{26}H_{29}O_2N_3$	230	−17°	Aggregates	203
d-Butanolamide-(2)	$C_{20}H_{25}O_2N_3$	172	−45°	Prisms	203
Diethylamide	$C_{20}H_{18}ON_3$	80–95	+30°	Prisms	203
2-Diethylaminoethyl-amide	$C_{22}H_{30}O_4N_4$		−16°	..	203
Oxalate	$B \cdot (COOH)_2$	200	+79°	Needles	203
1,3-Dioxypropanamide-(2)	$C_{19}H_{23}O_3N_3$	..	55°	Clusters of needles	203
Oxalate	$B \cdot (COOH)_2$	..	..	..	203
l-Ephedride	$C_{26}H_{29}O_2N_3$	258	−21°	Polyhedra	203
Ethanolamide	$C_{18}H_{21}O_2N_3$	95	−10°	Plates	203
Hydrazide	$C_{16}H_{18}ON_4$	218	+11°	Clusters of needles	204
Hydrochloride	$C_{16}H_{18}ON_4 \cdot HCl$	208–10	..	..	153
Sulfate	$(C_{16}H_{18}ON_4)_2 \cdot H_2SO_4$	220	..	Leaflets	153
Methyl ester	$C_{17}H_{18}O_2N_2$	168	..	Leaflets	151
d-Methylpentanol-amide-(2)	$C_{22}H_{29}O_2N_3$	120–30	−38°	Flat prisms	203
d-Norephedride-HCl	$C_{25}H_{26}O_2N_3Cl$	230	+14°	Stout prisms	203
l-Norephedride	$C_{25}H_{27}O_2N_3$	130	−17°	Plates	203
Tartrate	$B_2 \cdot C_4H_6O_6$	185–200	+39°	Needles	203
d-Nor-ψ-ephedride	$C_{25}H_{27}O_2N_3$	131	+27°	Long needles	203

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
l-Propanolamide-(2)	$C_{19}H_{22}O_2N_2$	220	−11°	Flat prisms	203
1-Lysergic acid	$C_{16}H_{16}O_2N_2$	235–240 (dec)	−40°	Leaflets	168
Hydrazide	$C_{16}H_{18}ON_4$	218	−11°	Clusters of needles	204
l-Norephedride	$C_{26}H_{27}O_2N_3$	..	−40°	..	203
Hydrochloride	$C_{26}H_{27}O_2N_3 \cdot HCl$	230	−16°	Stout prisms	203
d-Propanolamide-(2)	$C_{19}H_{22}O_2N_2$	220	+10°	Flat prisms	203
l-Propanolamide-(2)	$C_{19}H_{22}O_2N_2$	162	−89°	Tetrahedra	203
rac. Lysergic acid	$C_{16}H_{16}O_2N_2$	240–50 (dec)	..	Rectangular plates	[165, 168
Hydrazide	$C_{16}H_{18}ON_4$	220	..	..	204
		M			
Macralstonidine	$C_{41}H_{50}O_3N_4$	270 (dec)	174.5°	Platelets	657
Dihydrochloride	B·2HCl	326 (dec)	136.5°	Soft needles	657
Macralstonine	$C_{41}H_{54}O_5N_4$	293 (dec)	427.5°	Rectangular rods	657
Sulfate	$B \cdot H_2SO_4$	ca. 263 (dec)	−36.8°	Prismatic rods	657
6-Methoxy-3,β-amino-ethylindole-2 carboxylic acid	$C_{12}H_{14}O_3N_2$	220–50 (dec)	..	Leaflets	261
r-α-Methylamino-β-(3-indolyl)-propionic acid	$C_{12}H_{14}O_2N_2$	297 (dec)	..	Needles	9, 10
Hydrochloride	B·HCl	192–3	..	..	10
Picrate	$B \cdot C_6H_3O_7N_3$	186 (dec)	..	Red platelets	9, 10
Methyleserolinium picrate	$C_{20}H_{23}O_8N_5$	184–5	..	Thick prisms	559
Methyleserethole	$C_{15}H_{22}ON_2$	80–1	..	Rods	608
Picrate	$B \cdot C_6H_3O_7N_3$	150–1	..	Orange	608
Methopicrate	$C_{28}H_{30}O_{15}N_8$	190–1	..	Red prisms	[608, 609, 610
N-Methyltryptamine					
Benzoyl-	$C_{18}H_{18}ON_2$	199–200	..	Elongated plates	511
m-Chlorobenzoyl-	$C_{18}H_{17}ON_2Cl$	153	..	Stout prisms	511
p-Nitrobenzoyl-	$C_{18}H_{17}O_3N_3$	134	..	Yellow rectangular plates	511
		N			
Neoajmaline	$C_{20}H_{26}O_2N_2$	205–7	..	..	444
d-Noreserethole-*d*-ditartrate	$C_{18}H_{26}O_7N_2$	188–9	202.1°	Platelets	606
l-Noreserethole-*d*-ditartrate	$C_{18}H_{26}O_7N_2$	190–1	−53.3°	..	606
dl-Noreserethole	$C_{14}H_{20}ON_2$	..	..	..	
Hydrochloride	B·HCl	191–2	..	Grey needles	593
Picrate	$B \cdot C_6H_3O_7N_3$	180–1	..	Orange prisms	[593, 615
Picrolonate	$B \cdot C_{10}H_8O_5N_4$	221	..	..	606
Norharman	$C_{11}H_8N_2$	198.5	..	Slender needles	253
		O			
Octahydroyobyrine	$C_{19}H_{24}N_2$	177–8	..	..	383
Picrate	$B \cdot C_6H_3O_7N_3$	220–1	..	..	383
		P			
Paytine	$C_{21}H_{20}ON_2 \cdot H_2O$	..	..	Prisms	437
Pereirine	$C_{20}H_{26}ON_2 \cdot 1\frac{1}{2}H_2O$	..	..	Amorphous	674
Methiodide	$B \cdot CH_3I$	233–5	..	Yellow powder	674
Pheneserine	$C_{20}H_{23}O_2N_3$	150	−80°	Prisms	560
Methiodide	$B \cdot CH_3I$	198	−92.8°	Needles	560
Phenogeneserine	$C_{20}H_{23}O_3N_3$	164	−125.5°	..	560
Physostigmine	$C_{15}H_{21}O_2N_3$	105–6	−75.8°	..	[521, 523
Benzoate	$B \cdot C_7H_6O_2$	115–6	−98.1°	Prisms	557
Chloroaurate	$B \cdot 2HAuCl_4$	163–5 (dec)	..	Yellow leaflets	559

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Chloroplatinate	B·H_2PtCl_6	180	..	Orange needles	559
Picrate	B·$C_6H_3O_7N_3$	114	..	Yellow needles	529
Salicylate	B·$C_7H_6O_3$	186–7	..	Needles	529
Physostigminesulfonic acid	$C_{15}H_{27}O_5N_3S$	174	−426°	Micro prisms	625
Physostigmol	$C_{10}H_{11}N$	103	..	Fine needles	[559, 563
O-Ethyl-	$C_{12}H_{15}ON$	86	..	Lustrous plates	[568, 569
Picrate	B·$C_6H_3O_7N_3$	95	..	Dark red brown	[568, 569
O-Methyl-	$C_{11}H_{13}ON$	60–1	..	Leaflets	570
Picrate	B·$C_6H_3O_7N_3$	116–7	..	Red	570
Physovenine	$C_{14}H_{18}O_3N_2$	123	..	Prisms	529
d-Proline lactam					
l-Leucyl-	$C_{11}H_{18}O_2N_2$	148–50	+92° +109°	Rods	89
l-Phenylalanyl-	$C_{14}H_{16}O_2N_2$	252	+92° +110°	Right angled prisms	193
l-Valyl-	$C_{10}H_{18}O_2N_2$	147–9	+88° +107°	Thick plates	178
Pseudoyohimbine	$C_{21}H_{26}O_3N_2$	264–5	26.6°	Rhombic plates	317
Hydrochloride	B·HCl	258	−10°	Needles	[317, 406b
Pseudoyohimbone	$C_{19}H_{22}ON_2$	287	−23.9°	..	406b
		Q			
Quebrachamine	$C_{19}H_{26}N_2$	147	−109.5°	Rhombohedral leaflets	426
Oxalate	B·$C_2H_2O_4$	270	..	Clusters of prisms	426
Picrate	B·$C_6H_3O_7N_3$	195–6	..	Scarlet needles	426
Bromo derivative	$C_{19}H_{23(25)}ON_2Br_3$	>290		Needles	426
Methiodide	B·CH_3I	234	..	Cream colored prisms	426
Methosulfate	B·$(CH_3)_2SO_4$	235	..	Slender prisms	426
Perbromide	$C_{19}H_{24}N_2Br_6$	160	..	Orange prisms	426
Quinamicine	$C_{19}H_{24}O_2N_2$		..	..	681
Picrate	B·$C_6H_3O_7N_3$	203–5	−17.5°	Yellow platelets	[685, 681
2,4-Dinitrophenyl-hydrazone	$C_{25}H_{28}O_6N_4$	239–40	..	Dark red needles	685
Oxime	$C_{19}H_{25}O_2N_3$	217–20	82.2°	..	685
N-Methyl methiodide	$C_{20}H_{26}O_2N_2 \cdot CH_3I$	275–6	−39.8°	..	685
Quinamine	$C_{19}H_{24}O_2N_2$	185–6	104.5°	Needles	685
Hydriodide	B·HI	224	84.42°	..	685
Hydrochloride	B·HCl·$2H_2O$	166–7	102.8°	..	685
Nitrate	B·HNO_3	186–8	94.9°	..	[685, 684
Picrate	B·$C_6H_3O_7N_3$	175–6	90.0°	Yellow needles	685
Methiodide	B·CH_3I	250–1	114.2°	Short rods	685
Methochloride	B·CH_3Cl	237–40	111.9°	..	685
Nitro-	$C_{19}H_{23}O_4N_3$	284–8	79.1°	Pale yellow needles	686
Nitronitroso-	$C_{19}H_{22}O_6N_4$	185	..	Yellow rods	686
Nitroso-					
Picrate	$C_{25}H_{26}O_{10}N_6$	161	..	Yellow leaflets	685
Acetyl-	$C_{21}H_{26}O_4N_3$	140	..	Yellow cubes	685
Oxidation prod. (HNO_3)	$C_9H_4O_7N_4$	303–6 (dec)	..	Yellow needles	685
Quirandine	?	218	..	..	426
		R			
Rauwolfine	$C_{20}H_{28}O_3N_2 \cdot 2 \cdot 5H_2O$	235–8 (dec)	..	Buff rhombs	450
Hydriodide	B·HI·H_2O	220–5 (dec)	..	..	450
Hydrobromide	B·HBr·H_2O	250–3 (dec)	..	..	450
Hydrochloride	B·HCl	330–3 (dec)	29°	Pink plates	450

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Rauwolscine	$C_{21}H_{26}O_3N_2$	231–2 (dec)	−40°	Flat needles	451
Hydrochloride	B·HCl	270–80 (dec)	74°	Long needles	451
Nitrate	B·HNO_3	257–8 (dec)	..	Slender needles	451
Oxalate	B·$C_2H_2O_4$	245–6 (dec)	..	Needles	451
Picrate	B·$C_6H_3O_7N_3$·$2C_2H_6O$	208 (dec)	..	Orange plates	451
Sulfate	B·H_2SO_4	256–7 (dec)	..	Needles	451
Acetyl-	$C_{23}H_{28}O_4N_2$	216–8 (dec)	..	Warts	455
Rauwolscinic acid	$C_{20}H_{24}O_3N_2$	262–4 (dec)	136.8°	Yellow prisms	[451, 456
Hydrochloride	B·HCl	255.5–7.5(dec)	..	Star-shaped crystals	456
Picrate	B·$C_6H_3O_7N_3$	232–4 (dec)	..	Brick red plates	456
Butyl ester	$C_{24}H_{32}O_3N_2$	181–2.5 (dec)	..	..	456
Hydrochloride	B·HCl	251–3 (dec)	..	Yellow needles	456
Ethyl ester	$C_{22}H_{28}O_3N_2$	262–4 (dec)	..	Shining needles	456
Hydrochloride	$C_{22}H_{28}O_3N_2$·HCl	262–4 (dec)	..	Shining needles	456
Picrate	$C_{22}H_{28}O_3N_2$·$C_6H_3O_7N_3$	179.5–81.5(dec)	..	Orange plates	456
Propyl ester	$C_{23}H_{30}O_3N_2$	206–8 (dec)	..	Silky rods	456
Hydrochloride	$C_{23}H_{30}O_3N_2$·HCl	264–6 (dec)	..	Slender needles	456
Rubreserine	$C_{13}H_{16}O_2N_2$·H_2O	152	..	Red needles	556
Chloroaurate	B·$HAuCl_4$	190–5 (dec)	..	Red needles	556
Hydrochloride	B·HCl	185	..	Red crystals	556
Picrate	B·$C_6H_3O_7N_3$	198 (dec)	..	Brick red leaflets	556
Methyl hydrochloride	$C_{14}H_{19}O_2N_3Cl$	185	..	Colorless needles	556
Rutaecarpine	$C_{18}H_{12}ON_2$	261.5–2	..	Yellow needles	[282, 283
		S			
Sempervirine	$C_{19}H_{16}N_2$·H_2O	258–60	..	Orange needles	496
Hydriodide	B·HI	333–5 (dec)	..	Yellow needles	[474, 497
Hydrobromide	B·HBr·$2H_2O$	325 (dec)	..	..	[474, 497
Hydrochloride	B·HCl·$2H_2O$	352	..	Yellow needles	[474, 497
Nitrate	B·HNO_3·$2H_2O$	282 (dec)	..	..	[474, 497
Picrate	B·$C_6H_3O_7N_3$	268 (dec)	..	..	[474, 497
Methiodide	B·CH_3I	348 (dec)	..	Plates	[474, 497
Methochloride	B·CH_3Cl	330–332	..	..	500b
Methopicrate	B·CH_3·$C_6H_3O_7N_3$	239–40	..	..	500b
Serpentine	$C_{20}H_{20}O_3N_2$·1·$5H_2O$	153–4	..	Prismatic plates	[443, 454
Chloroplatinate	B_2·H_2PtCl_6	217–20	..	Long needles	443
Hydrochloride	B·HCl·H_2O	133–5	..	Tufts of needles	443
Nitrite	B·HNO_2	165–6 (dec)	..	Needles	454
Picrate	B·$C_6H_3O_7N_3$	261–2 (dec)	..	Yellow, amorphous	443
Bromo hydrobromide	$C_{20}H_{20}O_3N_2Br$	257–8	..	Yellow needles	454
Methiodide	B·CH_3I	271–2 (dec)	..	Slender needles	454
Serpentinine	$C_{20}H_{20}O_3N_2$	263–5	..	..	[443, 454
Hydriodide	B·HI	271–2	..	Crystalline powder	454
Hydrobromide	B·HBr	271–2	..	Needles	454
Hydrochloride	B·HCl	271–2	166.9°	Amber pear shaped rods	454
Picrate	B·$C_6H_3O_7N_3$	263–4 (dec)	..	Prismatic rods	454
Nitroso-	$C_{20}H_{19}O_3N_3$	159–60	..	Broad needles	454
		T			
Tabernanthine	$C_{21}H_{26}ON_2$	209	−40°	Orthorhombic plates	632
Tetradehydroyohimbic acid	$C_{20}H_{20}O_3N_2$	335	..	..	390
Ethyl ester	$C_{22}H_{24}O_3N_2$	281–2	245.2°	..	390
Tetradehydroyohimbine	$C_{21}H_{22}O_3N_2$	256–265.5	289.9°	Yellow crystals	390
Tetradehydroyobyrine-carboxylic acid	$C_{20}H_{20}O_2N_2$·H_2O	286 (dec)	217.6°	Colorless crystals	[389, 372

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Tetradehydroyobyrone-carboxylic acid	$C_{20}H_{18}O_3N_2$	..	..	..	
Hydrochloride	B·HCl·½H_2O	244	..	Needles	372
Tetrahydroalstonine	$C_{21}H_{24}O_3N_2$	230–1	−107°	Glistening rods	[659, 660
Hydrochloride	B·HCl	298	15.75°	Diamond shaped platelets	660
Methiodide	B·CH_3I	236	..	Rosettes	660
Tetrahydroalstoninic acid	$C_{20}H_{22}O_3N_2$	..	..	..	660
Hydrochloride	B·HCl	296 (dec)	−22.1°	Hygroscopic needles	660
Tetrahydroapoharmine	$C_8H_{12}N_2·H_2O$	96	..	Flat needles	242
Tetrahydroapoquinamine Picrate	$C_{25}H_{29}O_8N_5$	175–7	..	Yellow needles	685
Tetrahydroharmine	$C_{13}H_{16}ON_2$	199	..	Waxy needles	214
Acetyl-	$C_{15}H_{18}ON_2$	239	..	Needles	236
N-Benzoyl-	$C_{20}H_{20}O_2N_2$	158–9	..	Warts	236
N-Benzyl-	$C_{20}H_{22}ON_2$	109–10	..	..	277
Methyl-	$C_{14}H_{18}ON_2$	173–4	..	Leaflets	244
Hydrochloride	$C_{14}H_{18}ON_2·HCl$	142–6	..	Small flakes	244
Methiodide	$C_{14}H_{18}ON_2·CH_3I$	203	..	Warts	244
Methohydroxide	$C_{14}H_{18}ON_2·CH_3OH$	129	..	Needles	244
Tetrahydroyobyrine	$C_{19}H_{20}N_2$	168	..	Platelets	383
Hydrochloride	B·HCl	236	..	Long yellow needles	372
Ozonolysis prod.	$C_{19}H_{20}O_2N_2$	154.5	..	Fine needles	384
Trimethyldiapoharmine (?)	$C_{18}H_{22}N_4$	74.5	..	Leaflets	245
		V			
Vallesine	$C_{20}H_{28}O_2N_2$	154–6	−91°	Fine long needles	439
Hydrochloride	B·HCl	247–51	..	Needles	439
Oxalate	B·$C_2H_2O_4$	233–4 (dec)	..	Prisms	439
Vellosine	$C_{23}H_{28}O_4N_2$	189	22.8°	Rhombic crystals	672
Chloroplatinate	$B_2·H_2PtCl_6$	ca. 80	..	Yellowish brown powder	672
Hydriodide	B·HI·H_2O	217–8	..	..	672
Hydrobromide	B·HBr·H_2O	194–5	..	..	672
Hydrochloride	B·HCl·H_2O	240	..	..	672
Nitrate	B·HNO_3·H_2O	225	..	Rods	672
Sulfate	B·H_2SO_4·H_2O	210	..	..	672
Methiodide	B·CH_3I	264	..	..	672
Villalstonine	$C_{40}H_{50}O_4N_4$	218–60	..	Granular powder	657
Hydriodide	B·2HI	286 (dec)	..	Needles	657
Hydrobromide	B·2HBr·$4H_2O$	293 (dec)	..	Needles	657
Hydrochloride	B·2HCl·$4H_2O$	270 (dec)	56.3°	Needles	657
Oxalate	B·$C_2H_2O_4$	235 (dec)	55.6°	Leaflets	657
Sulfate	B·H_2SO_4·$6H_2O$	>310	52.9°	Prismatic rods	657
N-Benzyl hydrochloride	$C_{47}H_{50}O_4N_4Cl_2$	246 (dec)	..	Prisms	657
Dimethiodide	B·2CH_3I	287 (dec)	..	Stout needles	657
3-Vinylquinuclidine-carboxylic acid	$C_{10}H_{15}O_2N$	206–8	57.9°	Deliquescent needles	685
		W			
Wuchuyine	$C_{13}H_{15}O_2N$	237.5	..	Clusters	283
		Y			
Yohimbene	$C_{21}H_{26}O_3N_2$	276–7	43.7°	Rhombic plates	[321, 403
Hydrochloride	B·HCl·$3H_2O$	234	−8.8°	Needles	[321, 403
Methiodide	B·CH_3I	288	..	Yellow needles	371
Yohimbenic acid	$C_{20}H_{24}O_3N_2·2H_2O$	230	−17.1°	Rhombic plates	[321, 403

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C	$[\alpha]_D$	Crystalline form	Ref.
Hydrochloride	B·HCl	299–300	..	Platelets	[321, 403
Ethyl ester	$C_{22}H_{28}O_3N_2$	250–1		..	[321, 403
Hydrochloride	$C_{22}H_{28}O_3N_2 \cdot HCl$	223–5	..	..	[321, 403
Methiodide	$C_{22}H_{28}O_3N_2 \cdot CH_3I$	258	..	Yellow needles	371
Methochloride	$C_{22}H_{28}O_3N_2 \cdot CH_3Cl$	225–30	..	Prisms	371
Methyl betaine	$C_{21}H_{26}O_3N_2$	258	−29.6°	Needles	[321, 403
Yohimbenone	$C_{19}H_{22}ON_2$	268	..	Needles	372
2,4-Dinitrophenyl-hydrazone hydrochloride	$C_{25}H_{27}O_4N_6Cl \cdot H_2O$	280	..	Small columns	372
Yohimbic acid	$C_{20}H_{24}O_3N_2$	259	125.1°	Short, stout prisms	308
α-Allylaminoethyl ester	$C_{25}H_{33}O_3N_3$	124–6	..	..	367
Dihydrochloride	$C_{25}H_{33}O_3N_3 \cdot HCl$	212–4	..	..	367
Benzyl ester	$C_{27}H_{32}O_4N_2$	77–8	..	Amorphous	367
Hydrochloride	$C_{27}H_{32}O_4N_2 \cdot HCl$	253–4	..	Crystalline powder	367
Butyl ester	$C_{24}H_{32}O_3N_2$	127	..	..	360
Cetyl ester hydrochloride	$C_{36}H_{59}O_4N_5Cl$	238	..	Small crystals	367
α-Chloroethyl ester	$C_{22}H_{29}O_4N_2Cl$	119–20	..	Stout, flat needles	367
α-Chloropropyl ester	$C_{23}H_{31}O_4N_2Cl$	110–1	..	Prismatic plates	367
α-Diethylaminoethyl ester	$C_{26}H_{37}O_3N_3$	76–8	..	..	367
Dihydrochloride	$C_{26}H_{37}O_3N_3 \cdot 2HCl$	263–4	..	..	367
α-Diethylaminopropyl ester	$C_{27}H_{41}O_4N_3$	..	..	Amorphous	367
Dihydrochloride	$C_{27}H_{41}O_4N_3 \cdot 2HCl$	192–3	..	..	367
Methiodide	$C_{27}H_{41}O_4N_3 \cdot CH_3I$	195–6	..	..	367
α,β-Dihydroxypropyl ester	$C_{23}H_{32}O_5N_2$	111–12	..	Microscopic crystals	367
Ethyl ester	$C_{22}H_{28}O_3N_2$	190	..	..	360
Hydrochloride	$C_{22}H_{28}O_3N_2 \cdot HCl$	304–5	..	..	360
α-Hydroxyethyl ester	$C_{22}H_{30}O_5N_2$	132–5	..	Prismatic needles	367
Hydroxyethyl sulfuric diester	$C_{22}H_{30}O_8N_2S$	288–9		Microscopic crystals	367
α-Hydroxypropyl ester	$C_{23}H_{32}O_5N_2$	135–8	..	Flat needles	367
α-Piperidinoethyl ester	$C_{27}H_{39}O_4N_3$	129–131	..	..	367
Dihydrochloride	B·2HCl	198–200	..	..	367
α-Piperidinopropyl ester	$C_{28}H_{41}O_4N_3$	107–8	..	Crystalline powder	367
Propyl ester	$C_{23}H_{30}O_3N_2$	137	..	..	360
Sulfuric ester	$C_{20}H_{26}O_7N_2S$	308	..	Clusters of needles	[370, 372
Yohimbine	$C_{21}H_{26}O_3N_2$	234	107.2°	Needles	308
Hydrochloride	B·HCl	301	101.9°	Platelets	308
Acetyl-	$C_{23}H_{28}O_4N_2$	133	..	Amorphous	[319, 361
Bromo-	$C_{21}H_{24}O_3N_2Br_2$	183	..	Prismatic needles	361
Hydrobromide	B·HBr	276	..	Needles	361
Diacetyl-	$C_{25}H_{30}O_5N_2$	183	..	Needles	361
β-Yohimbic acid	$C_{20}H_{24}O_3N_2$	256	125.6°	Prisms	[315, 316
β-Yohimbine	$C_{21}H_{26}O_3N_2$	215–6	94.8°	Needles	[315, 316
Hydrochloride	B·HCl	295	104.9°	Platelets	[315, 316
γ-Yohimbic acid	$C_{20}H_{24}O_3N_2 \cdot H_2O$	252	89.5°	Prisms	315
γ-Yohimbine	$C_{21}H_{26}O_3N_2 \cdot 3H_2O$	240	−28.3°	Platelets	315
Hydrochloride	B·HCl	312	37.6°	Needles	315
δ-Yohimbic acid	$C_{20}H_{24}O_3N_2$	253	1.5°	..	316
δ-Yohimbine	$C_{21}H_{26}O_3N_2$	254	−50.0°	Prisms	316
Hydrochloride	B·HCl	288	−18.6°	Scales	316
Yohimbol	$C_{19}H_{24}ON_2$	243	−63.4°	Glistening needles	[371, 372
Hydrochloride	$B \cdot HCl \cdot \frac{1}{2}H_2O$	291	−51.6°	..	372

TABLE 1 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Methiodide	B·CH_3I	282	..	Needles	[371, 372
Methochloride	B·CH_3Cl	259	..	Clusters of needles	372
Yohimbone	$C_{19}H_{22}ON_2$	307	−103.9°	Needles	372
Hydrochloride	B·HCl	328	−51.5°	Needles	372
Picrate	B·$C_6H_3O_7N_3$	171	..	Clusters of short needles	372
2,4-Dinitrophenyl-hydrazone	$C_{25}H_{26}O_4N_4$	300	..	Needles	372
Hydrochloride	$C_{25}H_{26}O_4N_4$·HCl	286	..	Warts	372
Methiodide	B·CH_3I	290	..	Prisms	372
Methochloride	B·CH_3Cl	276	..	Small columns	372
Yohimbyl alcohol	$C_{20}H_{26}O_2N_2$	202	..	Needles	361
Hydrochloride	B·HCl	..	37.5°	Spears	361
Methiodide	B·CH_3I	215	..	Platelets	361
Yobyrine	$C_{19}H_{18}N_2$	218–9	..	Needles	[382, 383, 372
Hydrochloride	B·HCl	271	..	Prisms	372
Picrate	B·$C_6H_3O_7N_3$	239	..	Platelets	372
Ethylidene-Yobyrone	$C_{21}H_{18}N_2$	298	..	Needles	372
	$C_{19}H_{14}ON_2$	185	..	Glistening platelets	372

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CHAPTER XIV

The Erythrina Alkaloids

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I. Introduction

The alkaloids found in numerous species of the genus *Erythrina* are, with the exception of hypaphorine, of wide interest because of their remarkable physiological action. Although the investigation of the structure of these alkaloids shows that they probably include a partially reduced indole nucleus, their structure, as established at present, is not sufficiently definite to make it possible to classify them with certainty with any one group. They are, therefore, dealt with in a separate chapter.

The occurrence of hypaphorine in *Erythrina subumbrans* (Hassk.) Merr. (*Erythrina hypaphorus* Boerl.) has long been known (1). The presence in this plant of an uncharacterized alkaloid has been reported repeatedly (1, 2, 3), whereas the occurrence of amorphous alkaloids in other species of *Erythrina* has been recorded (1–6), but none has been satisfactorily characterized. However, an intense search for alkaloids in

plants belonging to this genus was initiated some ten years ago following the discovery of the curare-like action of extracts of various species of *Erythrina* (6–9), an action definitely not attributable to hypaphorine.

In a systematic investigation it has been shown that out of one hundred and five known species of *Erythrina*, the fifty which have been tested all contain alkaloids of paralyzing activity (10, 11, 12). Although the potency of this activity varies widely with different species, it is fairly uniform in closely related species (11). Alkaloids have now been isolated from the seeds of twenty-eight species of *Erythrina*. Besides hypaphorine, which occurs in a number of species (see hypaphorine, under Indole Alkaloids), the bases found in these plants fall into two groups. The bases of the first group or "free" alkaloids, are named from the prefix "erythr-," while those of the second group or "combined" alkaloids, which are esters of sulfoacetic acid, are named from the root "erysothio-" (13, 14). On hydrolysis the combined alkaloids yield the "liberated" alkaloids and these are designated by names including the stem "eryso-" (13, 14). The free alkaloids isolated so far are erythramine (15), erythraline (16), erythratine (16) and erythroidine (17), which occurs in two isomeric forms, α- and β-erythroidine (18). Only two "combined" alkaloids, erysothiovine (19) and erysothiopine (19), have been characterized, while the following "liberated" alkaloids have been described: erysopine (13), erysovine (13), erysodine (13) and erysonine (20). The alkaloid erysocine, described earlier (13), has since been found to consist of a mixture of erysodine and erysovine of which it may be a molecular complex (21). Recently, the presence of an alkaloid ($C_{16}H_{19}O_2N$) possessing curare-like activity has been reported in *Erythrina tholloniana* Hua. It has, however, not been named (21a).

II. Distribution

The distribution of these alkaloids, as established so far, is shown in Table 1.

The quantities of liberated alkaloids obtained from the seeds generally predominate and often greatly exceed those of the free alkaloidal fractions. Thus, in *E. sandwicensis*, the yield of the former is 2.12% while that of the latter is only 0.37% (13).

III. Isolation of the Alkaloids

Certain *Erythrina* alkaloids in the combined form are so readily hydrolyzed at 25–35° in an aqueous solution containing hydrochloric acid that a varying amount of liberated alkaloid is formed, depending on the length of time that the crude bases are kept under this condition. It is, therefore, necessary to clarify acidic aqueous extracts as quickly as possible

and immediately alkalinize them with sodium bicarbonate in order to remove the free alkaloids by chloroform extraction (13). The alkaloids

TABLE I

ALKALOIDS IN ERYTHRINA SPECIES

Plants	Erythroidine	Erythramine	Erythraline	Erythratine	Erysodine	Erysovine	Erysonine	Erysopine	Erysothiovine	Erysothiopine	Hypaphorine	References
E. abyssinica Lam.			+		+	+		+	+	+		13, 14, 22
E. acanthocarpa, E. Mey.						+					+	20
E. americana Mill.	+				+	+		+	+	+	+	23, 14, 17, 13
E. arborescens Roxb.					+	+		+				21
E. berteroana Urb.	+				+	+		+	+	+		13, 14, 24
E. costa-ricensis M. Micheli	+				+	+	+				+	
E. crista-galli L.		+	+	+	+	+		+			+	25, 26, 27
E. cubensis Wright					+	+		+				21
E. dominguezii Hassler					+	+		+			+	20, 26
E. excelsa Baker					+	+						21
E. falcata Benth.					+	+		+			+	28, 26
E. flabelliformis Kearn.					+	+		+	+	+		13, 14
E. folkersii Krukoff and Moldenke			+		+	+					+	16, 21
E. fusca Lour.			+		+	+					+	16, 20
E. glauca Willd.		+	+	+	+	+		+	+	+	+	16, 19, 13, 14
E. grisebachii Urb.			+								+	16
E. herbacea L.					+	+		+	+	+		13, 14
E. macrophylla DC.			+		+	+					+	16, 20
E. pallida Britton and Rose					+	+		+	+			19, 21
E. poeppigiana (Walp.) O. F. Cook					+	+		+	+			13, 14, 19
E. rubrinervia HBK.						+					+	20
E. sandwicensis Degener		+			+	+		+	+	+	+	15, 13, 14
E. senegalensis DC.											+	20
E. subumbrans (Hassk.) Merrill (*E. hypaphorus* Boerl)		+			+	+					+	1, 20, 15
E. variegata L. var. *orientalis* Merrill (*E. indica* Lam.)			+								+	29, 16, 30
E. velutina Willd.			+		+	+					+	16, 21
E. velutina forma *aurantiaca* (Ridl.) Krukoff			+								+	16

can be obtained from the seeds of *Erythrina* species by the following method of extraction:

The ground seeds are extracted first with petroleum ether and then with methanol. The methanol extract is concentrated at 30°/18 mm. to a gum and finally pumped out for three hours at 30°/2 mm., leaving a residue (16–19%) which is dissolved in water (15) and freed of residual fatty oil by centrifuging. This aqueous solution is covered with a thin layer of petroleum ether and allowed to stand at 25° for 4 months. Erysothiovine which gradually crystallizes out is filtered after this time and the filtrate is refrigerated for 40 days. During this second period of standing erysothiopine separates and is filtered (19). In order to isolate the free and the liberated alkaloids, the dried residue from the alcohol extract is dissolved in water containing hydrochloric acid, the solution extracted with petroleum ether, concentrated in vacuo and refrigerated. The hypaphorine hydrochloride which crystallizes is filtered, the filtrate is made alkaline with sodium bicarbonate and thoroughly extracted with chloroform. This extract yields the crude free alkaloids which are isolated and purified by fractional crystallization of their salts. The aqueous solution is made acid with hydrochloric acid, refluxed until hydrolysis is complete, cooled, again made alkaline with sodium bicarbonate and thoroughly extracted with chloroform. This second extract contains the liberated alkaloids (originating from combined alkaloids) which are purified by fractional crystallization (13) and by chromatography (21).

The action of concentrated sulfuric acid on β-erythroidine produces a degradation product which in solution shows an intense purple color when added to a ferric chloride solution. This reaction forms the basis of a colorimetric assay which gives duplicate results within 3%. Erythraline and erythratine, erysodine, erysopine and erysovine give only a faint color when assayed by this method (31).

IV. The Free Alkaloids

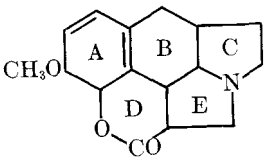
These alkaloids are isolated directly from extracts of the plant without the necessity of previous hydrolysis and are purified by fractional crystallization of their salts. With the possible exception of erythroidine they are closely related.

1. Erythroidine

Erythroidine, $C_{16}H_{19}O_3N$ (17, 23), is a mixture of two isomers, α- and β-erythroidine (18). β-Erythroidine which forms well-crystallized salts (32) is a lactone susceptible to destruction by strong alkali (24). The catalytic hydrogenation of β-erythroidine gives rise to a mixture of dihydro-β-erythroidine and two isomeric tetrahydro-β-erythroidines. Hydrogenation over a platinum oxide catalyst favors the formation of β-tetrahydro-β-erythroidine (33, 34). The course of the Hofmann degradation of β-erythroidine reveals that the nitrogen atom is common to two nuclei of the ring system (35). The base contains one methoxyl, a lactone ring, and two double bonds, and its nitrogen is tertiary so that it must be pentacyclic.

β-Erythroidine can be degraded to three different isomeric derivatives. The action of hydrofluoric acid at room temperature (35b), of syrupy phosphoric acid at 80° (35b) or of 35% sulfuric acid at 100° (35a) on the

base gives rise to desmethoxy-β-erythroidine ($C_{15}H_{15}O_2N$), while syrupy phosphoric acid at 120° converts either β-erythroidine or its desmethoxy derivative to a mixture of apo-β-erythroidine and isoapo-β-erythroidine (35b, 35c). The conversion of the alkaloid into desmethoxy-β-erythroidine involves the loss of the elements of methanol and the formation of a double bond since hydrogenation of the compound produces a hexahydro derivative whereas hydrogenation of the alkaloid results in the addition of two moles of hydrogen only. Methylation of desmethoxy-β-erythroidine in alkaline solution with dimethyl sulfate and subsequent oxidation of the product with potassium permanganate results in the formation of 3-methoxyphthalic acid. Dehydrogenation of β-erythroidine in dilute hydrochloric acid with palladium chloride followed by methylation of the product in alkaline solution with dimethyl sulfate gives rise to 3,4-dimethoxyphthalic anhydride. On the basis of these results formula I has been suggested to represent the base (35a).



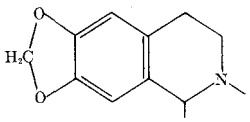
I

Desmethoxy-β-erythroidine obviously arises by loss of the methoxyl group and aromatization of ring A while the formation of apo-β-erythroidine involves the scission of a ring as well and the appearance of another double bond. Apo-β-erythroidine when oxidized gives rise to formic acid, and when reduced to an octahydro derivative (35d). Isoapo-β-erythroidine when reduced produces the same octahydro-derivative, but does not yield formic acid on oxidation (35d). It is therefore assumed that apo-β-erythroidine arises by scission of ring E at the nitrogen with the formation of an exocyclic methylene group, and that it is the migration of the exocyclic double bond that gives rise to isoapo-β-erythroidine (35d).

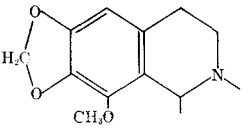
2. Erythraline

Erythraline, $C_{18}H_{19}O_3N$ (16), is a crystalline base which readily forms salts and is easily isolated owing to the relative insolubility of its hydriodide. It contains an aliphatic methoxyl and a methylenedioxy group so that all three oxygen atoms are present in the molecule in ether linkages (36). No iminomethyl is present, but the nitrogen atom is tertiary as the base gives rise to a methiodide. Erythraline when hydrogenated over palladium-

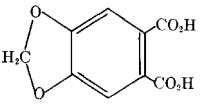
barium carbonate absorbs one mole of hydrogen and gives rise to a dihydro derivative identical with erythramine (22). If, however, erythraline is hydrogenated in acetic acid solution over platinum oxide the product is tetrahydroerythraline (22, 36), and hence the base contains two double bonds. The ultraviolet absorption spectrum of tetrahydroerythraline is very closely similar to that of 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, but different from that of hydrocotarnine. The fully reduced base, therefore, contains the partial nucleus Ia and not II. This conclusion finds confirmation in the oxidation of erythraline methohydroxide to



Ia

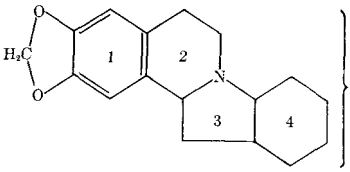


II

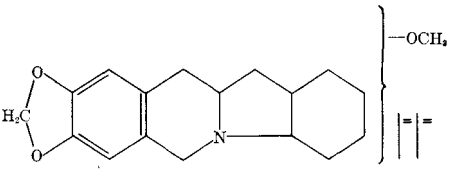


III

hydrastic acid (III) (36). Since all the functional groups in the alkaloid are known, it is possible to conclude that its structural formula must include four rings exclusive of that due to the methylenedioxy group. Furthermore, since the fusion of erythraline with potassium hydroxide gives rise to indole, the partial structure Ia can be expanded to either IV or V where the nuclear system represented contains a methoxyl group and two



IV



V

double bonds (37). Structure IV is favored on biogenetical grounds and it is likely that the double bonds are located in ring 4 since erythraline does not give the Ehrlich test as might be expected were the double bonds in ring 3.

When tetrahydroerythraline is first heated with concentrated hydriodic acid and red phosphorus, then reduced with zinc and subsequently methylated with diazomethane it gives rise to a crystalline base, $C_{18}H_{25}O_2N$, m.p. 114°, $[\alpha]_D^{20.5}$ −45°, which forms a crystalline picrate melting at 216–219°. This base contains two aromatic methoxyl groups instead of the methylenedioxy and has lost the aliphatic methoxyl originally present in the molecule (22). The new base is isomeric with a base similarly obtained from tetrahydroerysodine, but is not identical with it (22). Very recently a synthesis of a base of this structure has been described, but although the

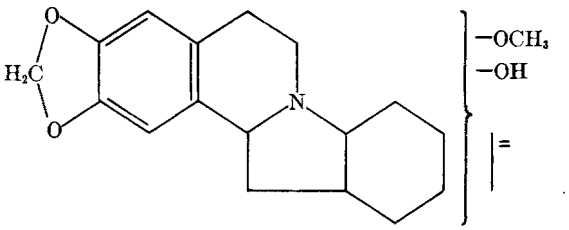
ultraviolet absorption spectra of the synthetic and degradation bases were identical the other properties were not (37a).

3. Erythramine

Erythramine, $C_{18}H_{21}O_3N$ (15), forms stable crystalline salts although the free base gradually decomposes on standing. Like erythraline, it contains a methoxyl and a methylenedioxy group (35). Furthermore, its nitrogen atom is tertiary since the base forms a methiodide. Catalytic hydrogenation converts erythramine into dihydroerythramine, a compound which is identical with tetrahydroerythraline (35). The ultraviolet absorption spectra of the reduction products obtained from the two alkaloids are exactly superposable. Hence, erythramine is a dihydroerythraline and the alkaloid must be represented by formula IV in which one double bond only is present instead of two (36). This conclusion finds confirmation in the fact that erythraline when partially hydrogenated in ethanol over palladium-barium carbonate is converted into erythramine (22).

4. Erythratine

Erythratine, $C_{18}H_{21}O_4N \cdot \frac{1}{2}H_2O$ (16), crystallizes with half a mole of water which it does not lose at 140°/0.01 mm. It forms salts crystallizing readily and it is separated from erythraline by fractional crystallization of the hydriodides. Erythratine contains one methoxyl and one methylenedioxy group, but no iminomethyl nor *C*-methyl. It also contains a nonphenolic hydroxyl, the presence of which is confirmed by the formation of an *O*-acetyl and an *O*-benzoyl derivative. The nitrogen atom is tertiary



VI

and the base forms a methiodide which is converted to the methohydroxide by moist silver oxide. This quaternary ammonium base on distillation gives rise to *N*-methylerythratine methine ($C_{19}H_{23}O_4N$), but the degradation was not pushed further. Erythratine contains one double bond, the catalytic hydrogenation of which results in the formation of dihydroerythratine. The hydrobromide of the reduced base has an ultraviolet

absorption spectrum which is almost superposable on the absorption spectra of the hydrobromides of tetrahydroerythraline and of 6,7-methylehedioxy-1,2,3,4-tetrahydroisoquinoline (37). Furthermore, fusion of erythratine with potassium hydroxide gives rise to indole. Hence, erythratine seems to possess the same ring structure as erythramine and erythraline and may partially be represented by formula VI in which the methoxyl, the hydroxyl and the double bond are assumed to be present in the hydroaromatic ring (37).

V. The Combined Alkaloids

Only two of the combined alkaloids have so far been isolated although it is probable that there are at least four in these plants. The physiological action of these bases is more pronounced than that of either the free or the liberated alkaloids (38).

1. Erysothiovine

Erysothiovine, $C_{20}H_{23}O_7NS$ (19), crystallizes from water as a dihydrate. It is readily hydrolyzed by dilute hydrochloric acid into erysovine and sulfoacetic acid ($HO_3S{\cdot}CH_2{\cdot}COOH$) so that the alkaloid is an ester of this acid and erysovine. Sulfoacetic acid is precipitated both by lead acetate and by barium chloride whereas erysothiovine is not and therefore the alkaloid is assumed to be a sulfonic ester involving a phenolic hydroxyl present in erysovine (19).

2. Erysothiopine

Erysothiopine, $C_{19}H_{21}O_7NS$ (19), crystallizes from 95% ethanol as a monohydrate. It is readily hydrolyzed by acid into sulfoacetic acid and erysopine. The alkaloid is therefore an ester of sulfoacetic acid and erysopine, probably also a sulfonic ester. Erysothiopine and erysothiovine possess a more potent curare-like action than the corresponding liberated alkaloids (19, 38).

VI. The Liberated Alkaloids

These bases, do not apparently occur as such in the plant but are liberated in the course of isolation by the hydrolytic action of dilute mineral acids, are purified first by fractional crystallization and finally by chromatography.

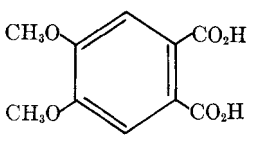
1. Erysovine, Erysodine and Erysopine

The three alkaloids, erysovine, $C_{18}H_{21}O_3N$ (13), erysodine, $C_{18}H_{21}O_3N$ (13) and erysopine, $C_{17}H_{19}O_3N$ (13), are weak bases which crystallize from dilute hydrochloric acid. Whereas the first two are isomeric, the last has an empirical formula containing CH_2 less than the others and it is much

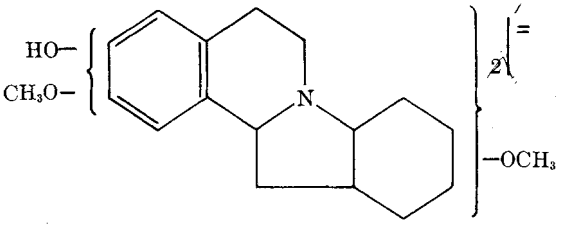
less soluble in water, chloroform and alcohols, a property which facilitates its isolation and purification. In all three alkaloids, iminomethyl and *C*-methyl groups are absent (13). Both erysovine and erysodine contain one aliphatic methoxyl and one aromatic methoxyl groups together with one phenolic hydroxyl. On the other hand, erysopine contains one methoxyl group only and two phenolic hydroxyls which are probably vicinal since the base shows a characteristic green color with ferric chloride in acid solution and since it is very unstable when dissolved in aqueous sodium hydroxide (13). Hence all three alkaloids must contain a benzenoid ring.

Erysodine readily forms a methiodide and, therefore, contains a tertiary nitrogen atom. Although it is hydrogenated in alcoholic solution over palladium-barium carbonate to dihydroerysodine (22), hydrogenation in acetic acid over platinum oxide converts it to tetrahydroerysodine (22, 39), which forms an *O*-acetyl derivative still containing a tertiary nitrogen atom (39). Consequently, the nitrogen atom of erysodine must be common to two rings and, since all the functional groups are characterized, it is possible to conclude that the base contains four rings (39).

Erysodine, treated with methyl sulfate and subsequently oxidized with potassium permanganate, yields *m*-hemipinic acid (VII). Because of the analogy of this acid with hydrastic acid obtained similarly from erythraline



VII



VIII

(36), erysodine has been assigned structure VIII (22) which has the same nuclear arrangement as that proposed for erythraline (VI). However, tetrahydroerysodine by boiling with concentrated hydriodic acid and red phosphorus followed by reduction with zinc and subsequent methylation with diazomethane is converted to a base $C_{18}H_{25}O_2N$ (picrate melting at 205–206° and having $[\alpha]_D^{20}$ −39°) which contains two aromatic methoxyl groups but has lost the aliphatic methoxyl present in the original base (22). This new base although isomeric with, is different from, the base obtained similarly from tetrahydroerythraline. It is, therefore, probable that formula VIII for erysodine will have to be revised.

Erysopine, on hydrogenation gives rise to tetrahydroerysopine which still contains a tertiary nitrogen atom (39). While erysodine reacts with

dimethylsulfate in alkaline solution to give erysotrine methomethylsulfate* ($C_{21}H_{29}O_7NS$), erysopine reacts similarly to give the methomethylsulfate of *O*-dimethylerysopine which is identical with erysotrine methomethylsulfate (39). Erysopine is, therefore, *O*-desmethylerysodine. Although neither erysodine, erysovine nor erysopine can be methylated directly by diazomethane, the corresponding *N*-oxides react smoothly with this reagent yielding in each case a product which is reduced with zinc and hydrochloric acid to the same erysotrine (39). Consequently, all three alkaloids possess the same four-ring structure and the same oxygen system and differ only in the position or number of *O*-methyl groups.

* The fully oxygen-methylated alkaloid has been designated "erysotrine" so that the methomethylsulfate of *O*-methylerysodine becomes erysotrine methomethylsulfate.

2. Erysonine

Erysonine, $C_{17}H_{19}O_3N$ (20), is isomeric with erysopine and, like it, contains neither iminomethyl nor *C*-methyl, but contains one methoxyl group and two hydroxyls. Erysonine does not give a green color with ferric chloride in aqueous solution as does erysopine and, therefore, does not apparently contain two vicinal phenolic hydroxyls. However, at least one of the hydroxyls is phenolic since the base is soluble in dilute sodium hydroxide (40). Erysonine differs from erysopine either in the location of its oxygen atoms or in having a different ring structure since the methylation of its *N*-oxide followed by reduction does not produce erysotrine (39).

TABLE 2

THE PHYSICAL CONSTANTS OF THE ERYTHRINA ALKALOIDS AND THEIR PRODUCTS OF TRANSFORMATION AND DEGRADATION

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Erysothiovine	$C_{20}H_{23}O_7NS \cdot 2H_2O$	187	208.5°	..	[14, 19
Erysothiopine	$C_{19}H_{21}O_7NS \cdot H_2O$	168–9	194°	..	19
Erysovine	$C_{18}H_{21}O_3N$	178–9.5	252°		13
Hydrochloride	B·HCl	237–8	233.8°	Needles	27
Hydrobromide hemihydrate	B·HBr·½H_2O	150–1 (dec)	..	..	14
Hydriodide hydrate	B·HI·H_2O	159–160	..	..	14
Erysopine	$C_{17}H_{19}O_3N$	241–2	265.2°		13
Hydrochloride	B·HCl	270	248°	Prisms	27
Tetrahydroerysopine hydrobromide	$C_{17}H_{23}O_3N \cdot HBr$	244–5	..	..	39
Erysodine	$C_{18}H_{21}O_3N$	204–5	248°		13
Methiodide	B·CH_3I	229–9.5	..	..	39
Tetrahydroerysodine	$C_{18}H_{23}O_3N$	158–9	−25°		[22, 39
Hydrobromide	B·HBr	251–1.5	..	..	39
O-Acetyl	$C_{20}H_{25}O_4N$	135–6	..	..	39
Erysotrine methomethylsulfate	$C_{21}H_{29}O_7NS$	61	..	..	39
Erysotrine	$C_{19}H_{23}O_3N$	..	..	..	39
Picrate	B·$C_6H_3O_7N_3$	160–1	138.1°	..	39
Dihydroerysodine	$C_{18}H_{23}O_3N$	212–214	239°	Needles	22
Erysonine	$C_{17}H_{19}O_3N$	238–9	285–8°	..	[20, 40
β-Erythroidine	$C_{16}H_{19}O_3N$	99.5–100	88.8°	..	[17, 32

TABLE 2 (*Continued*)

Compound	Formula	M.p. °C.	$[\alpha]_D$	Crystalline form	Ref.
Hydrochloride hemihydrate	B·HCl·½H_2O	229.5–30 (dec)	109.7°	Needles	17
Hydrochloride	B·HCl	232 (dec)	109°	..	32
Hydrobromide	B·HBr	222.5	111.2°	..	32
Hydriodide	B·HI	206	108.1°	..	32
Methiodide	B·CH_3I	211	..	Prisms	35c
Perchlorate	B·$HClO_4$	203–3.5	96.3°	..	32
Flavianate	B·$C_{10}H_6O_8N_2S$	216–6.5	..	..	32
Dihydro-β-erythroidine	$C_{16}H_{21}O_2N$	85–6	102.5°	..	33
Hydrochloride	B·HCl	238	124.7°	..	33
Hydrobromide	B·HBr	231 (dec)	106–7.5°	..	33
Hydriodide	B·HI	230	95.5°	..	33
Perchlorate	B·$HClO_4$	235–6 (dec)	102.5°	..	33
Salicylate	B·$C_7H_6O_3$	179–80	95.8°	..	33
Desmethoxy-β-erythroidine	$C_{15}H_{15}O_2N$	108–9	..	..	35c
Methiodide	B·CH_3I	165–7	..	..	35c
Hexahydrodesmethoxy-β-erythroidine					
Methiodide	$C_{15}H_{21}O_2N·CH_3I$	246	..	Prisms	35c
Apo-β-erythroidine	$C_{15}H_{13}O_2N$	144	26.6°	Prisms	35c, 35d
Hydrochloride	B·HCl	179	..	Needles	35c
Methiodide	B·CH_3I	189	..	Prisms	35c
Octahydro-apo-β-erythroidine	$C_{15}H_{23}O_2N$	134-6	..	..	35d
Hydrochloride	B·HCl	250–2.5	..	..	35d
Isoapo-β-erythroidine	$C_{15}H_{15}O_2N$	154–5	-7.1°	..	35d
Erythramine	$C_{18}H_{21}O_4N$	103–4	227.6°	Small crystals	[15, 35, 41
Hydrochloride	B·HCl	250 (dec)	..	..	15
Hydrobromide	B·HBr	228 (dec)	203.2°	Needles	[15, 41
Hydriodide	B·HI	249 (dec)	220°	Yellow-orange needles	[15, 41
Methiodide	B·CH_3I	96–8	176°	Yellowish white	15
Dihydroerythramine (tetrahydroerythraline)	$C_{18}H_{23}O_3N$	89–90	..	..	35
Hydrobromide	B·HBr	240	..	..	35
Hydriodide	B·HI	214–5 (dec)	−19°	..	[22, 35
Methiodide	B·CH_3I	160–1	..	..	35
Picrate	B·$C_6H_3O_7N_3$	221–2	..	..	22
Picrolonate	B·$C_{10}H_8O_5N_4$	170–2	..	..	22
Erythraline	$C_{18}H_{19}O_3N$	106–7	211.8°		[16, 42
Hydrobromide	B·HBr	243	216.6°	Granular	[16, 42
Hydriodide	B·HI	252–3 (dec)	177°	Yellow	16
Methiodide	B·CH_3I	185–7	..	Pale yellow	36
Erythratine	$C_{18}H_{21}O_4N·½H_2O$	170–70.5	145.5°	..	[16, 43
Hydrobromide	B·HBr	241	158.7°	..	[16, 43
Hydriodide	B·HI	242–2.5	113.3°	..	[16, 43
Methiodide	B·CH_3I	135–6	110.4°	Small crystals	37
O-Benzoyl-	$C_{25}H_{23}O_5N·2H_2O$	248–9	..	Needles	37
O-Acetyl-	$C_{20}H_{23}O_5N$	128–9	..	..	37
N-Methylerythratine methine	$C_{19}H_{23}O_4N$	Oil	..	..	37
Dihydroerythratine	$C_{18}H_{23}O_4N$	..	..	..	
Hydrobromide	B·HBr	249	..	Pinkish crystals	37

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CHAPTER XV

The Strychnos Alkaloids. Part II

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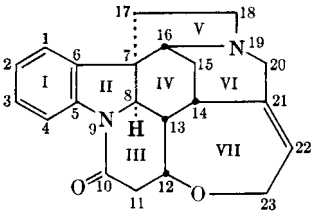
I. Introduction

The chemical evidence available in 1946 enabled Robinson (231, 232, 247)† to deduce correctly the structure (LXXXIX) of strychnine and in the following year the same structure was proposed independently by Wood-

* Numbers in parentheses refer to page numbers in Vol. I of "The Alkaloids."

† See footnote on page 904 of reference 231.

ward (261, 262)† in a very clear exposition of the problem. In the interval since the first chapter was sent to press sufficient experimental evidence has accumulated to permit speculation as to the stereochemistry of this base. The recent evidence upon which this argument rests is (1) the correct interpretation of the pseudostrychnine-strychnone transformation, (2) the conversion of isostrychnine to strychnine and (3) the lactonization of two 12-hydroxy-14-carboxylic acid derivatives. It is indeed gratifying that these deductions are in complete accord with the findings of X-ray analysis of the isomorphous bromide, sulfate and selenate salts of this base and which finds adequate expression in formula CXXXVIII.‡



The structure and configuration of vomicine has been related to that of *N*-methyl-*sec*-pseudostrychnine and *N*-methyl-*sec*-pseudobrucine through a common degradation product and vomipyrine has been synthesized. Also pseudostrychnine has been converted to neostrychnine and the presence of a vinylamine ($\Delta^{20(21)}$) in the latter has been demonstrated. It has been definitely established that rupture in alkoxylating fission occurs at N_b—C_{18} thus requiring some revision in the structure of methoxymethyldihydroneostrychnine and related products. Finally there has been some speculation regarding the mode of biogenesis of these alkaloids in the plant (247, 263).

Most of the work since 1947 has been but a logical extension of work presented in Chapter VII, Vol. I, so for convenience the same general plan of organization will be followed here and the corresponding page numbers from this chapter will appear in parentheses alongside the section headings. To avoid ambiguity and to facilitate cross reference, table, chart, formula and reference numbers will be carried over from Chapter VII, Vol. I.

II. Elucidation of the Structure of Strychnine and Brucine

1. Products of Oxidative Degradation (pp. 383–397)

At the beginning of the interval under consideration, the structure of strychnine in the environs of ring IV was based more upon speculation

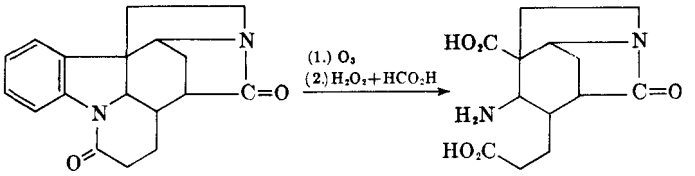
† See footnote 1 on page 2107 of reference 262.

‡ This numbering system (262) and the Linstead convention representing the stereochemistry (262a) have been adopted by Woodward and Prelog.

than upon experimental fact so an attempt was made to add definition to this blurred picture by degrading dihydrostrychninone in a stepwise fashion to a C_{13}-aminodicarboxylic acid. This acid contains the components of rings III, IV and V and provides a degradation product of strychnine of sufficient simplicity to be within the scope of synthesis.

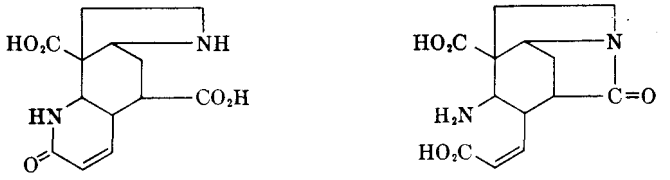
While two more by-products from the neutral permanganate oxidation of strychnine have been identified, attention has been focused for the first time on permanganate oxidation in weakly acidic medium and the derived products have been converted, in turn, into strychninonic acid by neutral permanganate oxidation. Ultraviolet absorption spectra demonstrate that *N*-bromosuccinimide dehydrogenates ring III of the strychninolones and strychninone to an α-pyridone. Finally, a mechanism has been advanced that adequately accounts for the extrusion of glycolic acid from strychninolic acid, dihydrostrychninonic acid and their brucine analogs and for the failure of brucinonic acid to undergo this elimination reaction.

a. C_{13}-Aminodicarboxylic Acid. The lactam of cuninecarboxylic acid, CXXXIX, has been obtained by oxidation (H_2O_2 + formic acid) of dihydrostrychninone followed by the facile lactamization of the derived acid (264). Energetic ozonolysis of the lactam, followed by oxidation with hydrogen peroxide in formic acid degraded the benzene ring of CXXXIX to the carboxyl group (no Otto test) of CXL. Compound XII, obtained in poor



CXXXIX CXL

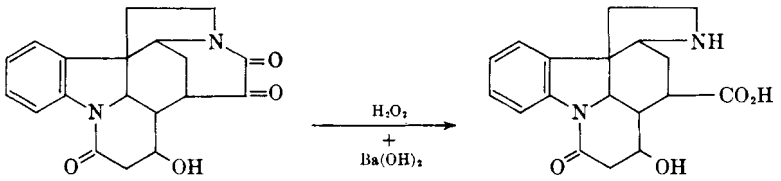
yield by the chromic acid oxidation of brucinonic acid (126, 60), differs from CXL by two hydrogen atoms and prompts the suggestion (265) that this acid may be more correctly represented by either CXLI or CXLII.



CXLI CXLII

b. Permanganate Oxidation (pp. 384–387). Isolation of the hydroxydihydrostrychninone, CXLIII, and the hydroxycuninecarboxylic acid,

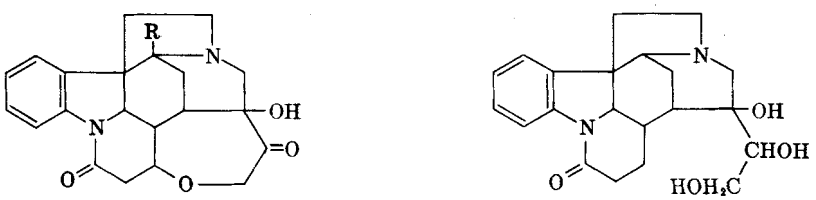
CXLIV, as by-products from the neutral (acetone) permanganate oxidation of strychnine has been reported (266).



CXLIII CXLIV

The α-keto amide of CXLIII has been degraded (H_2O_2 + $Ba(OH)_2$) to CXLIV and the latter characterized as the *N*-nitroso derivative which readily lactonized (266). If inversion at C_{14} has not occurred under these alkaline conditions then this lactonization is suggestive of a *cis* relationship of the hydrogen atoms at C_{12} and C_{14} in strychnine.

In weakly acidic medium, the permanganate oxidation of strychnine ($C_{21}H_{22}O_2N_2$) (pseudostrychnine methyl ether acts similarly) yields the hydroxyketone ($C_{21}H_{20}O_4N_2$), CXLV (R = H) (267). The ketone (semicarbazone and *p*-nitrophenylhydrazone) must be located as shown while

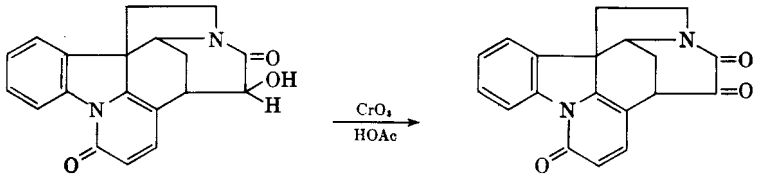


R=H, OCH_3
CXLV CXLVI

the hydroxyl cannot be at C_{20} since this compound exhibits none of the properties diagnostic of a carbinolamine but can be oxidized ($KMnO_4$ + acetone) further to strychninonic acid (267). Catalytic hydrogenation (PtO_2 + C_2H_5OH) reduces this hydroxy ketone (CXLV, R = H) to the glycol already isolated from the neutral oxidation of strychnine (268) while with zinc and hydrochloric acid, hydrogenolysis of the cyclic ether accompanies reduction of the ketone. In contrast to strychnine the ketol, CXLV, its dihydro derivative and CXLVI respectively react readily with three, three, and four-mole equivalents of lead tetraacetate (267), the former being oxidized to strychninonic acid (267).

c. N-Bromosuccinimide on the Strychninolones and Strychninone (pp. 387–391). Treatment of the acetyl derivative of all three strychninolones ($C_{19}H_{18}O_3N_2$) with *N*-bromosuccinimide and subsequent removal of the acetyl group led to one dehydrostrychninolone ($C_{19}H_{16}O_3N_2$)

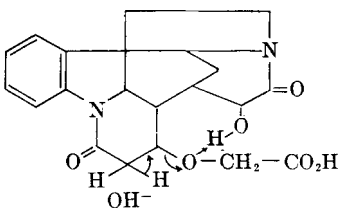
(CXLVII). No alteration in the nuclear skeleton has occurred since dehydrostrychninolone has been catalytically reduced to dihydrostrychninolone-c.



CXLVII CXLVIII

Dehydrostrychninone (CXLVIII) has been obtained in a similar manner from strychninone and by oxidation (CrO_3 + HOAc) of CXLVII (269). The similarity of the absorption spectra for dehydrostrychninolone and dehydrostrychninone with maxima at longer wavelengths than that of strychninolone-a (see Table 6) argues in favor of a $\Delta^{8(13)}$ — instead of a $\Delta^{13(14)}$ — position for the newly generated double bond (269). Dehydrostrychninolone and the colorless benzylidene derivative of strychnine, which is also considered by Robinson (231) to be an α-pyridone, have many properties in common. Their absorption spectra are similar and they both show an abnormally high levorotation and a negative Otto reaction.

d. The Strychninolic Acid Cleavage (pp. 387–391). The successful β-elimination of glycolic acid from strychninolic acid, dihydrostrychninonic acid and their brucine analogs by 1 *N* alkali at room temperature and the failure of brucinonic acid and brucidinolic acid to undergo the same reaction (61, 100) is understandable (270) on a push-pull mechanism. For alkali to promote the electron shift indicated in CXLIX a proton donor must approach the ether oxygen from the opposite side to stabilize the glycolate



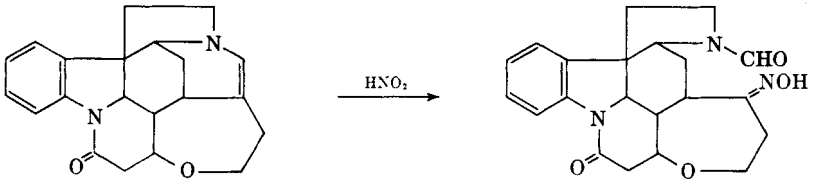
CXLIX

ion. From steric considerations such an approach of a solvent molecule into the strychnine cage (p. 536) seems highly improbable, so hydrogen bonding with the C_{21}—OH may effectively fulfill the role of the proton donor in this unusual β-elimination. This effectively accounts for the marked difference in the ease of formation of strychninolone-a and isostrychninolone-I and for the failure of brucinonic acid to undergo this

cleavage. The reported (95, 105) elimination of glycolic acid by the oxime of brucinonic acid, if true, on the other hand is strong evidence in support of this hypothesis. The extrusion of glycolic acid by *N*-acetyl-*sec*-pseudobrucinonic acid might, at first glance, appear to refute the above theory, but the rupture of the N_b—C_{16} bond destroys the rigidity of the molecule thus permitting the displacement of carbons C_{20} and C_{21} and the approach of a solvent molecule to the ether oxygen brings the observation into accord with theory. Moreover, the reason for the drastic conditions required for the alkaline isomerization of strychnine to isostrychnine is now apparent.

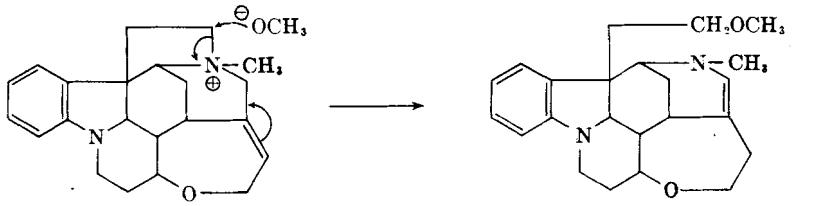
2. Fission Around N_b (pp. 397–401)

After examination (262) of the bridge structure LXXXIX for strychnine it will be evident on steric grounds that of all the positions suggested for the double bond in neostrychnine (CL) only $\Delta^{20(21)}$, as suggested on



CL CLI

page 420, Vol. I, is open for consideration. This conclusion has been amply verified by conversion of neostrychnine (CL) with nitrous acid to the oxime of the *N*-formyl derivative, CLI (271). Dilute hydrochloric acid hydrolyzed CLI to hydroxylamine, formic acid and the secondary base $C_{20}H_{22}O_3N_2$. In view of the conversion of the quaternary salts of both strychnidine and neostrychnidine to methoxymethyldihydroneostrychnidine (CLIII) and the difficulty attendant upon a similar conversion of their dihydro derivative would suggest that the migration of the strych-

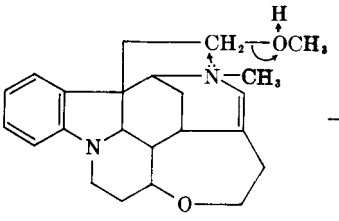


CLII CLIII

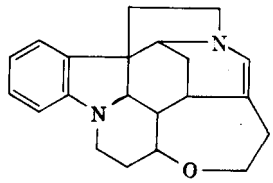
nidine double bond to the neo position is the prime factor promoting this reaction. The weaker basicity of a vinylamine (272) decreases the stability of the quaternary salt and favors the nucleophilic displacement on C_{18} as

formulated in CLII. Conversely the greater basicity of dihydromethoxymethyldihydroneostrychnidine as contrasted with methoxymethyldihydroneostrychnidine would favor salt formation in mineral acid and thus restrict the nucleophilic displacement on C_{18} which proceeds so smoothly in the formation of the quaternary salts of neostrychnidine CLIV from CLIII.

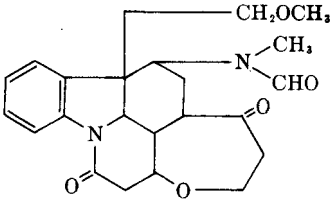
This formulation for neostrychnine (CL) requires that methoxymethylchanodihydrostrychnone be formulated as CLV while it would be anticipated that methoxymethylchanodihydrostrychnane (Clemmensen reduction of



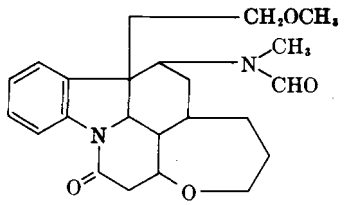
CLIII



CLIV



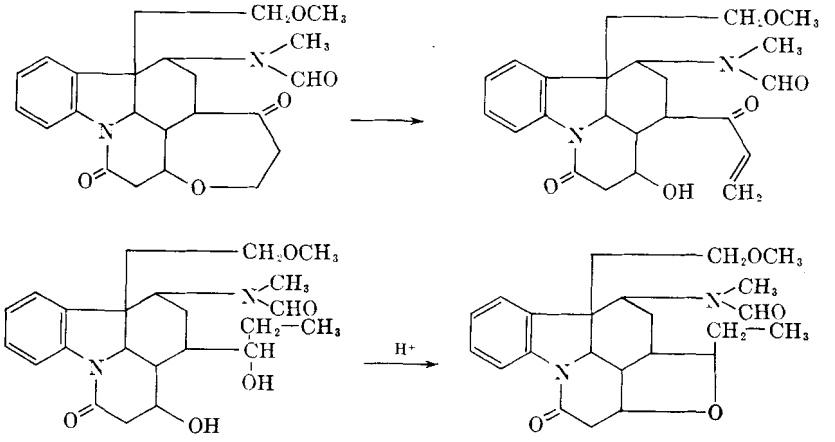
CLV



CLVI

CLV) would be CLVI. Two serious objections must be resolved, however, before such structures can be unreservedly accepted for these products. First the difficulty observed in the hydrolysis of the formamide in CLV, either by strong mineral acid or alcoholic barium hydroxide must be accounted for, and secondly the formation of one mole of acetic acid in the Kuhn-Roth oxidation of methoxymethylchanodihydrostrychnane must be explained. The deep-seated changes that occur when methoxymethylchanodihydrostrychnone is subjected to strongly acidic conditions and which probably involve the β-alkoxycarbonyl system prompted Woodward (262) to reduce the carbonyl group by other means. This was achieved by treatment of an alcoholic solution of the ethyl mercaptal of CLV with Raney nickel. The derived product desoxomethoxymethylchanodihydrostrychnone, CLVI, was isomeric with but not identical with methoxymethylchanodihydrostrychnane. Since conditions promoting isomerization were

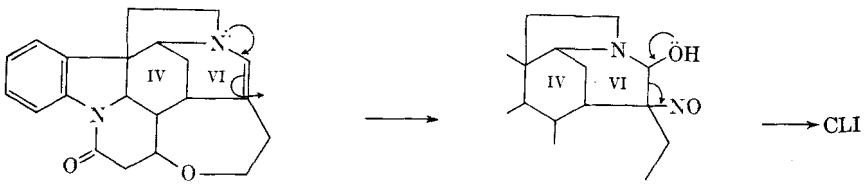
stringently avoided, it is inescapable that methoxymethylchanodihydrostrychnane formation must involve some rearrangement. The first step in such a rearrangement may be envisaged as a rupture of the β-alkoxycarbonyl system which in turn is followed by reduction of the α,β-unsaturated ketone and cyclization of the derived di-alcohol to the cyclic ether CLVII.



CLVII

Hence it is quite apparent why methoxymethylchanodihydrostrychnane yields a mole of acetic acid in the Kuhn-Roth oxidation while desoxomethoxymethylchanodihydrostrychnone does not (262).

The presence of a formamide grouping in methoxymethylchanodihydrostrychnone has now been demonstrated so that the last argument against structure CLV for this compound has been removed. Methoxy-



methylchanodihydrostrychnane (methoxymethylchanodihydrostrychnone and its dihydro derivative act similarly) yields a mole of formic acid and a base $C_{23}H_{30}O_3N_2$ when boiled with 2 *N* sulfuric acid. That this deformylation is not the result of an acid catalyzed rearrangement is manifest by regeneration of methoxymethylchanodihydrostrychnane by formylation ($HCO_2H + Ac_2O$) of the base $C_{23}H_{30}O_3N_2$ (262). Woodward (262) attributes the reluctance of methoxymethylchanodihydrostrychnone to deformylate under the conditions of the Clemmensen reaction to the reduced activity

of water in the concentrated hydrochloric acid containing zinc chloride while the stability towards alkali is ascribed to steric effects.

With the double bond of neostrychnine located, its reaction with nitrous acid or an acidic solution of diazotized *p*-nitraniline may be formulated as indicated on page 520.

3. Isostrychnine and Isobrucine (pp. 411–412)

In analogy with isovomicine and because it was resistant to reduction by sodium amalgam the newly generated double bond of isostrychnine-I has been located at $\Delta^{12(13)}$. Assignment of the double bond to this position finds added support in the similarity of its absorption spectrum with that of strychninolone-b (273). Furthermore the base catalyzed (methanolic KOH) isomerization of strychninolone-a in part to the sterically more stable strychninolone-c (through the b-isomeride) and the remainder to methoxydihydrostrychninolone finds its counterpart here. When isostrychnine-I is warmed with alcoholic potassium hydroxide the base-catalyzed isomerization of the double bond into a position of conjugation with the lactam provides an equilibrium mixture of two (about C_{13}) stereoisomers. The nucleophilic attack of the C_{23}-alkoxide ion on the carbon beta to the lactam of the base with the strychnine configuration resulted in a 20% conversion to strychnine. The preponderant amount of the equilibrium mixture which failed to cyclize was shown by ultraviolet spectra to have the sterically more stable configuration of strychninolone-c (273).

From an examination of the two models it is quite apparent why the strychninolone a-type isomer cyclizes whereas that with the c-configuration does not. The C_{23}-alkoxide ion is in close juxtaposition to the carbon beta to the lactam in the model of the a-compound and approaches from the back side of the molecule whereas the alkoxide ion is remote from the beta carbon in the model with the alternate configuration at C_{13}.

As might be expected from the above observation, the opening of the lactam of isostrychnine (274) and of isobrucine (275) by boiling amyl alcoholic sodium hydroxide is accompanied by isomerization of the iso-double bond. The imino group in the derived isostrychninic and isobrucinic acid has been characterized as its acetyl derivative and it has been observed that the protecting group alters the course of the catalytic reduction of these acids. *N*-Acetylisostrychninic acid can be reduced to a di- and a tetrahydro-derivative (275) but isostrychninic acid absorbs five moles of hydrogen leading directly to a decahydro acid in which the benzene ring and the two ethylenic double bonds have been reduced. Isodihydrobrucinic acid cannot be prepared in this way because of the ready lactamization of the acid in the presence of mineral acids (265). In fact isodihydrobrucine II is readily prepared by boiling dihydrobrucine with amyl alcoholic

sodium hydroxide or by dissolving the base in 13 *N* sulfuric acid. The former procedure proved to be the simpler of the two since purification of the product from the sulfuric acid method is complicated by the difficulty encountered in removing the demethylated product.

4. Pseudostrychnine and Pseudobrucine (pp. 412–418)

Preparation of an isomer of strychnone now brings this series into accord with that of brucine. The new dilactam was obtained by the modification of a procedure that has made the high- and low-melting forms of both pseudostrychnine and pseudobrucine readily available substances. In spite of the availability of these pseudo bases the nature of the isomerism, which is apparently real (different optical rotations and different rates of hydrogenation) is still obscure (276). Pseudostrychnine has been transformed into neostrychnine by boiling a xylene solution of dihydropseudostrychnine methyl ether ($H_2 + PtO_2$ or pseudostrychnine methyl ether (276)) with Raney nickel (276). The same result is achieved if the disproportionation (Raney nickel) of pseudostrychnine methyl ether to an *x*-hydroxyneostrychnine is followed by reduction of the double bond and then dehydration completes the alternate conversion to neostrychnine (276). The ketone carbonyl of the ketoimine tautomeride of these bases has now been experimentally recognized by formation of characteristic carbonyl derivatives (*p*-nitrophenylhydrazone and 2,4-dinitrophenylhydrazone (276) and the benzene ring of *N*-methyl-*sec*-pseudostrychnine and its brucine analog has been oxidatively degraded (chromic acid (277)) and the $C_{17}H_{22}O_5N_2$ acid from vomicine obtained. Finally the conversion of pseudostrychnine and pseudobrucine respectively to strychnone and bruzone has been demonstrated to involve the oxidation of the C_{16} ketone of the keto-imine tautomeride to a lactone and the elimination of the

elements of water yielding an indole derivative with a $-C_{16}-N_b-$lactam.

a. Preparation and By-products. A method that has been used so successfully in the preparation of norcodeine (p. 52) and a number of its analogs and which involves the chromic acid isomerization of the *N*-oxides to carbinolamines and subsequent elimination of formaldehyde has proved to be the most direct route to pseudostrychnine and pseudobrucine (278, 279).

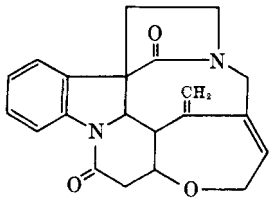
Pseudostrychnine and Oxostrychnine (278,279)

A suspension of 150 g. of strychnine in 1500 cc. of 3% hydrogen peroxide is warmed with stirring for 2½ hours or until a clear solution is obtained. The excess hydrogen peroxide is destroyed by the portionwise addition of freshly precipitated manganese dioxide (from $KMnO_4 + CH_3OH$) until frothing ceases. Decolorization with charcoal

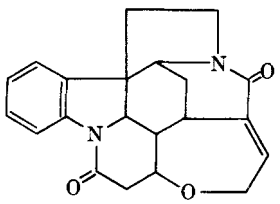
and cooling of the solution affords 110 g. of strychnine N-oxide, m.p. 205–206°. Isomerization is effected by dissolving the *N*-oxide in 500 cc. of hot water and cautiously adding 200 cc. of a 10% aqueous solution of potassium dichromate (it is reported (278) that potassium chromate or chromic acid is equally effective?). Care must be exercised at this point if loss by spattering is to be avoided. Addition of excess ammonium hydroxide precipitates 105 g. of a solid which is only partially soluble in 600 cc. of 1 *N*-hydrochloric acid. The nonbasic residue, A, weighs 23.5 g. Neutralization of the acidic solution gives solid B (79.4 g.) which when dry is extracted in a Soxhlet apparatus with ethanol when an insoluble residue of about 10 g. remains in the thimble. Decolorization and concentration of the ethanolic solution gives 62.7 g. of pseudostrychnine ethyl ether. Pseudostrychnine is regenerated from this ether by solution in 400 cc. of warm 1 *N* hydrochloric, decolorization and neutralization with ammonium hydroxide, weight 52.7 g.

The oxostrychnine can be recovered by extraction of residue A in a Soxhlet apparatus with benzene. On cooling usually about 20 g. of buff-colored crystals melting at 296–301° can be recovered. The melting point of this crude oxostrychnine may be raised to 332–334° by successive crystallization from acetic acid-water, then chloroform-ligroin, and finally *n*-propyl alcohol.

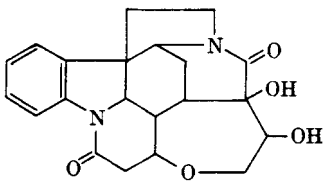
By increasing the amount of chromic acid in the isomerization reaction, a 33% yield of oxostrychnine ($C_{21}H_{20}O_3N_2$) (279, 280), the strychnine analog of the brucone isomer (152a, 171) can be obtained. The absence of basic properties in oxostrychnine requires that one or more methylene groups (C_{16}, C_{18}, or C_{20}) adjacent to N_b be oxidized to a lactam. Structure CLVIII can be discounted on the grounds that it absorbs only one mole



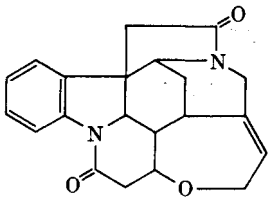
CXLVIII



CLIX



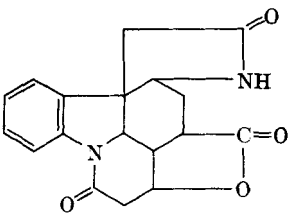
CLX



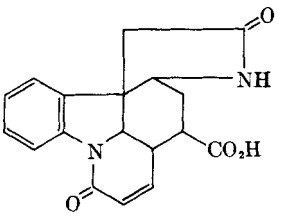
CLXI

of hydrogen (PtO_2 + C_2H_5OH) and that the derived dihydro derivative gave negative results in the Kuhn-Roth oxidation (280). Furthermore, on this formulation, the reduction of dihydrooxostrychnine to dihydrostrych-

nidine-A by lithium aluminum hydride (280) would involve a reductive cyclization. Oxidative attack on the reactive allylic carbon C_{20} (CLIX) would seem more reasonable but contrary to expectation, oxostrychnine could not be oxidized to strychninonic acid but instead only the oxostrychnine analog (CLX) of the dihydro derivative of CXLV was obtained. However, in contrast to the latter compound, CLX failed to yield crystalline products when treated with periodic acid, aqueous permanganate, sodium bismuthate and lead tetraacetate (280). The similarity of the absorption spectra of oxostrychnine and its dihydro derivative effectively exclude structure CLIX from further consideration, leaving only the other alternative CLXI. The presence of a five-ring lactam in oxostrychnine is clearly manifest in its infrared spectrum (see Table 7) and later confirmed by ozonolysis of oxostrychnine (280). Energetic ozonolysis (HOAc) of oxostrychnine followed by treatment with hydrogen peroxide afforded a lactonic dilactam ($C_{18}H_{16}O_4N_2$) (CLXII), a transformation involving the loss of C_3H_6 and the gain of the elements of water. Methanolic sodium methoxide opened the lactone ring affording the primary unsaturated acid-a (m.p. 299–302°) (CLXIII) which, like strychninolone-a, could be isomerized progressively by the same reagent to acid-b (m.p. 255-259°)



CLXII

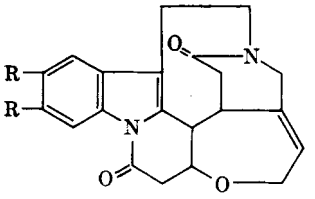


CLXIII

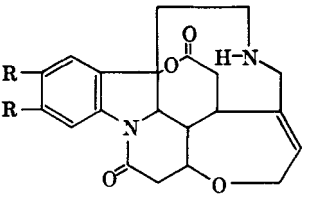
and acid-c (m.p. 285–292°). If the hydroxy acid is the precursor of the lactone CLXII and if, as in the case of CXLIV, inversion at C_{14} be excluded, then the hydrogen atoms at C_{12} and C_{14} of strychnine must be *cis* (280).

b. Strychnone and Bruzone. The correct diagnosis (261) of the changes occurring in the oxidation (H_2O_2 + HOAc) of pseudostrychnine and pseudobrucine to strychnone and bruzone has provided positive evidence regarding the architecture in the neighborhood of rings IV/V/VI and also permits some interesting speculation regarding the fusion of rings II/IV. The similarity of the ultraviolet absorption spectrum of the neutral strychnone with various *N*-acylindoles and the weak basicity of the N_a-strychnone hydrate finds adequate expression in CLXIV. The initial phase must be the peracid oxidation of the keto-imine tautomeride of pseudobrucine to a lactone CLXV (R = OCH_3) followed by generation (in dilute sulfuric acid)

of an indole nucleus and lactamization of the derived C_{16} carboxyl group with the secondary (N_b) amine. Considering the stereospecificity which obtains in the peracid oxidation of ketones to lactones and the conditions

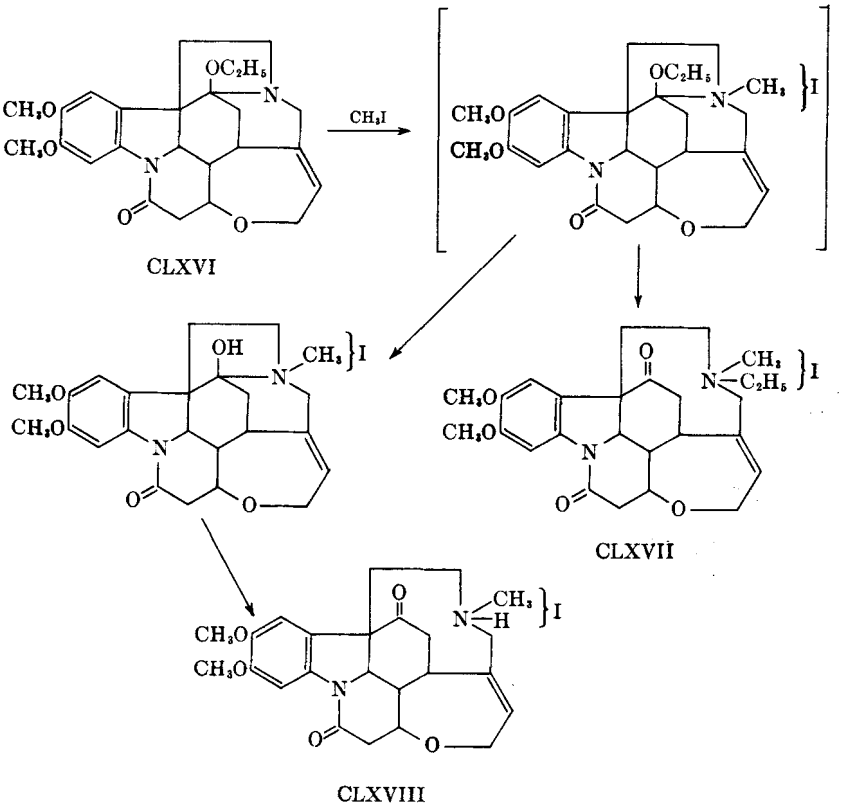


R=H, OCH_3
CLXIV



R=H, OCH_3
CLXV

of this reaction which appear to favor a *trans* elimination (although a *cis* elimination is not excluded), this transformation is consistent with a *trans* relationship between the hydrogen atom at C_8 and the lactone grouping at



CLXVI

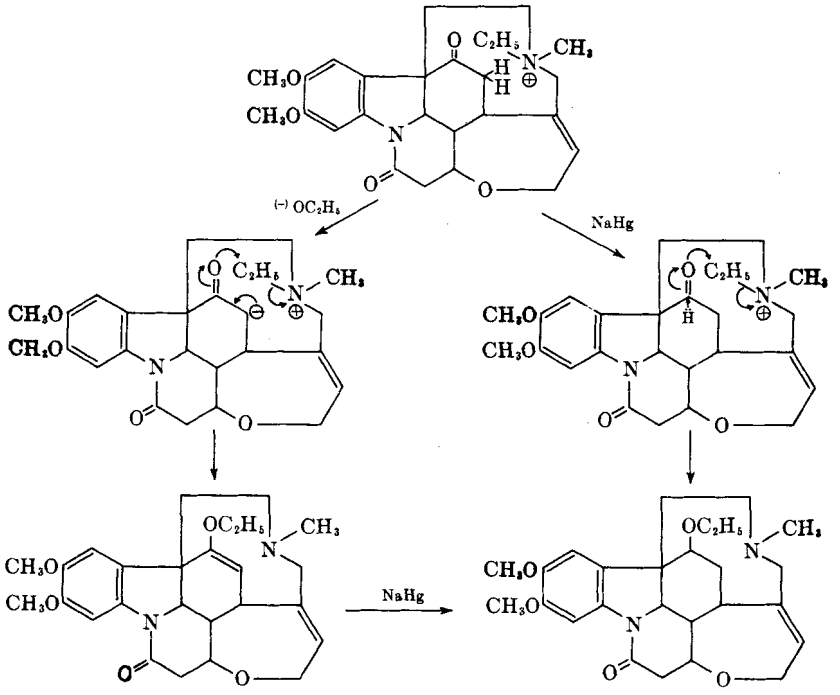
CLXVII

CLXVIII

C_7. This sequence of reactions definitely precludes Prelog's formula (XC) from further consideration.

c. Alkylation of Pseudobrucine. The alkylation of pseudostrychnine (152a, 212) and pseudobrucine (164, 267) and the transposition of alkyl groups from oxygen to nitrogen (dilute mineral acid) and its reverse (sodium alkoxides and sodium amalgam) has assumed a position of greater importance now that vomicine has been related to *N*-methyl-*sec*-pseudobrucine through the common degradation product, $C_{17}H_{22}O_5N_2$ (277). This study clarifies some of the unusual changes observed in the Emde reduction of the quaternary salts of vomicine (29, 35).

It might appear at first sight that the formation of a mixture of the hydriodide and methiodide of *N*-methyl-*sec*-pseudobrucine when methyl iodide is added to pseudobrucine methyl ether proceeds by hydrolysis of the ether and alkylation of the keto-imine tautomeride of the derived pseudobrucine. This however, is not the case since *N*-methyl-*sec*-pseudobrucine will not react with methyl iodide (like vomicine, it will combine



CLXIX CLXX

with dimethyl sulfate and the methomethylsulfate, so formed, may be transformed to the methiodide with potassium iodide (281). Also such a

mechanism would not account for the formation of *N*-ethyl-*sec*-pseudobrucine methiodide in both the methylation of pseudobrucine ethyl ether (CLXVI) and the ethylation of pseudobrucine methyl ether (281). It is inescapable that there is an attendant migration of an alkyl group from oxygen to nitrogen in the formation of CLXVIII and that hydrolysis of the carbinolamine ether must precede rearrangement in the formation of the hydriodide, CLXVIII (281).

Migration of an alkyl group in the reverse direction is achieved with sodium alkoxides. For example, *N*-ethyl-*sec*-pseudobrucine methiodide (CLXVII), yields the enol ethyl ether, CLXIX, when treated with sodium methoxide and its dihydro derivative (CLXX) when sodium amalgam is used. It has been suggested by Wieland (282) that these base-catalyzed migrations might be initiated by removal of a proton from C_{15} or in the amalgam reduction to the addition of a hydride ion to C_{16} as schematically indicated below. It is evident that this is in effect but a modification of Rodionow's process for the methylation of a phenol (see codeine). The enol ether, CLXIX, has been hydrolyzed to a ketone by hot concentrated hydrochloric acid and reduced to CLXX by sodium amalgam while cold dilute acid reverses the migratory process leading to the chloride derivable from CLXVII (281).

III. Vomicine and Vomipyrine (pp. 425-436)

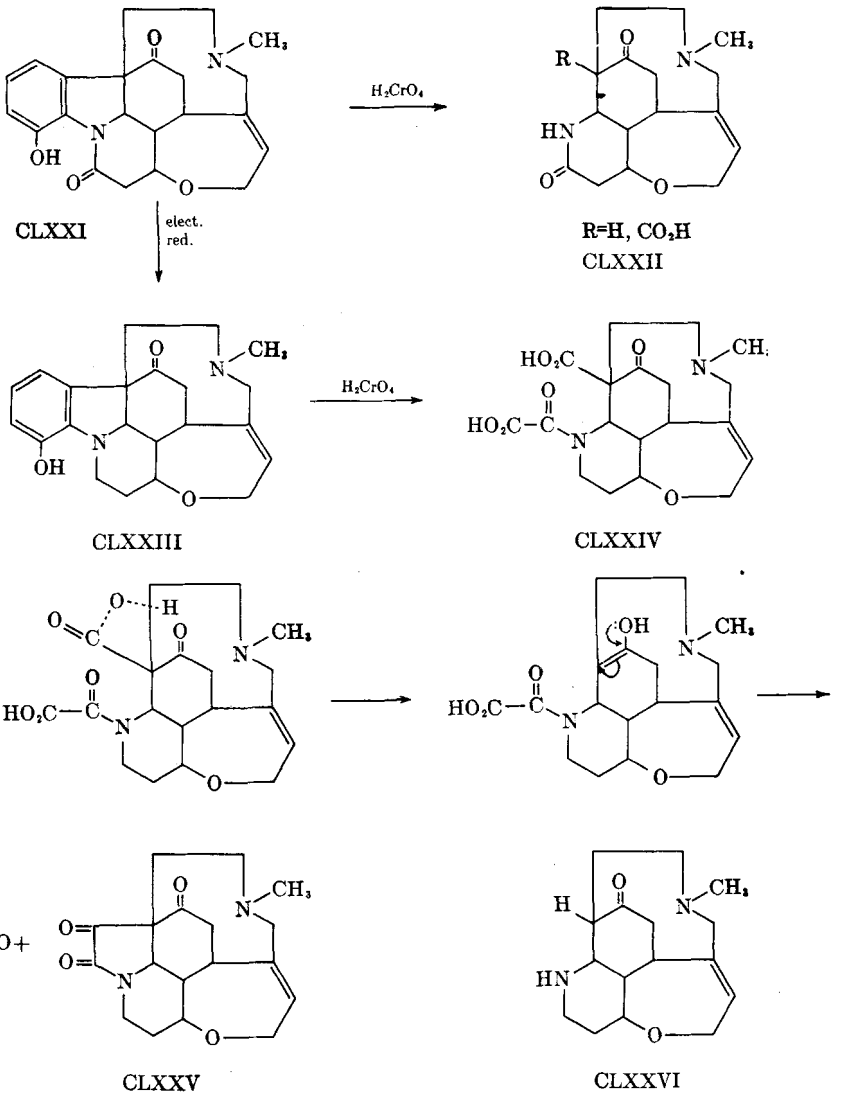
1. Structure of Vomicine and Vomipyrine

In the interval covered by this chapter the structure of vomicine has been established except for the location of the phenolic hydroxyl and the structure of vomipyrine deduced and the base synthesized. An isomeric desoxyvomicine has also been isolated and a combination of Emde and Hofmann degradations on vomicine and the desoxyvomicines has afforded desazadesoxyvomicine and its tetrahydro derivatives (282).

The chromic acid oxidation of *N*-methyl-*sec*-pseudostrychnine and *N*-methyl-*sec*-pseudobrucine to the $C_{17}H_{22}O_5N_2$ acid (CLXXII, R = CO_2H) and the decarboxylation product CLXXII (R = H) and their derivation from vomicine (CLXXI) in a similar manner clearly establishes the structure of the intricate part of the vomicine molecule (283, 277) and permits a complete assignment of structure except for the phenolic hydroxyl. While other positions cannot be definitely excluded, the hindered character of this phenol and the nature of the nitration product argue strongly in favor of its location at C_4. The similarity between the above compounds is also reflected in other properties, as for example their failure to react with methyl iodide whereas their dihydro derivatives react readily.

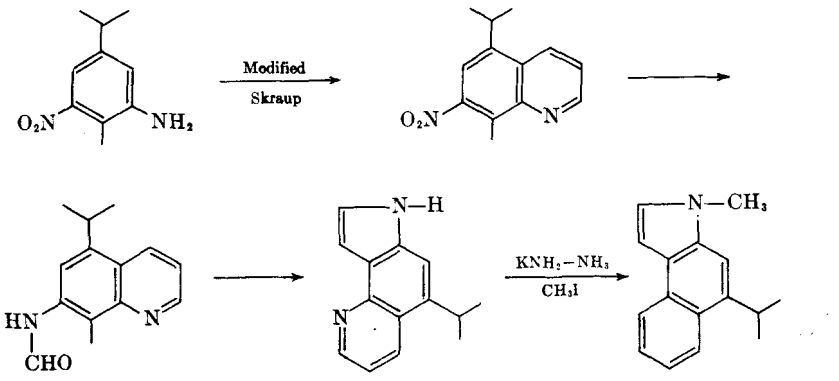
The carboxyl of CLXXII (R = CO_2H) is so readily lost that during hydrogenation to the dihydro derivative (15) a part of the material is simul-

taneously decarboxylated to the dihydro derivative of CLXXII (R = H). The contrasting stability of the carboxyl in the analogous oxidation product



CLXXIV from vomicidine (CLXXIII) has been attributed by Robinson (276) to betaine formation of the type $O_2C-\overset{OH}{\underset{|}{C}}-\overset{|}{C}-\overset{(+)}{N}-CH_3$. It seems

difficult to understand why stabilization through betaine formation should operate in CLXXIV and not in CLXXII (R = CO_2H). Considering the mechanism of decarboxylation of β-keto acids it would seem more likely that hydrogen bonding to the amide carbonyl is the stabilizing factor and it is not until temperatures of the order of 200° are attained that this bonding is overcome and decarboxylation and condensation at the potential anionid center ensues yielding CLXXV. Because of the size of the ring generated inversion at this center is hardly to be anticipated. It is not CLXXV that is the interesting and revealing compound, but its companion substance, CLXXVI which when catalytically dehydrogenated loses one carbon and eight hydrogens yielding vomipyrine, which has characteristic yellow salts and contains one methylimino grouping (284). The similarity of color reaction in the Hopkins-Cole Color test and ultraviolet spectrum (285) with various pyrroquinolines is more than coincidence and is strongly suggestive of such a structure for vomipyrine. A similar loss of one carbon has been observed in the pyrolysis of the reduction product of the methylstrychninium salts and has been considered to be C_{23} (286). Rupture of the C_{20}—N_b bond and loss of the C_{23} carbon atom would make *ind*-N-



CLXXVII

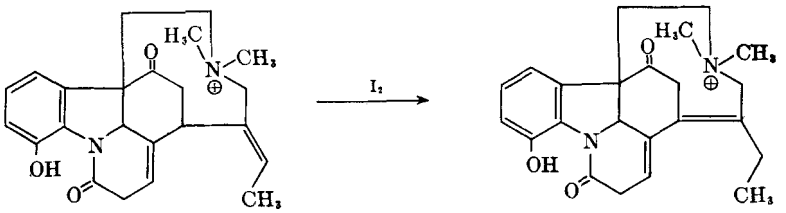
methyl-5-isopropyl-7,8-pyrroquinoline (CLXXVII) (270, 277) the logical structural choice for this base, a conjecture that has now been confirmed by the following synthesis (286).

2. Fission Around N_b

The effect of various alkylating agents on the products obtained from vomicine and desoxyvomicine have been examined and the resulting products subjected to the Emde reduction (282). The course of the reaction is markedly dependent upon whether catalytic reduction or sodium amal-

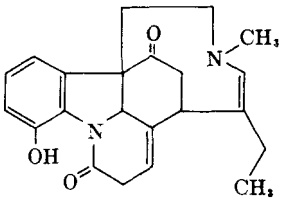
gam is the reducing agent (282). Neodesoxyvomicine has been obtained in an alternate way and by a series of two Emde reductions and one Hofmann degradation desazadesoxyvomicine has been obtained (282).

Vomicine, in contrast to its dihydro derivative and the desoxyvomicines, fails to react with methyl iodide but the methiodide has been prepared by successive treatment of the base with dimethyl sulfate and sodium iodide (29, 282). The methiodide, like the yellow desoxyvomicine itself, is readily isomerized in the presence of a little alkali into the corresponding isomer of the colorless base so that the products of Emde reduction from the two bases are identical. The quaternary salt obtained from the colorless isomer is dependent upon the reagent used. The methiodide derived from the methomethylsulfate is stable to acid but is isomerized to the methiodide obtained directly from methyl iodide by catalytic amounts of iodine. Since the possibility of a structural change in the nuclear skeleton has been excluded (36) and because the two methiodides, which both contain two methylimino groups, are reducible with sodium amalgam (hence an allylamine structure) have been assigned structures CLXXVIII and CLXXIX. The driving force for this isomerization may be ascribed to the



CLXXVIII CLXXIX

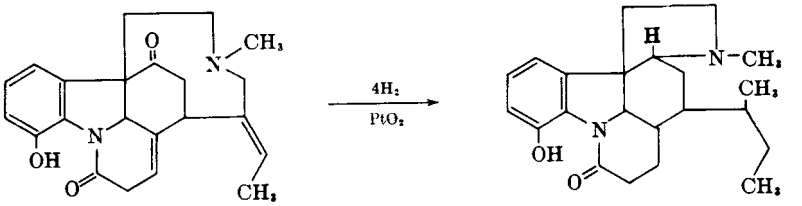
tendency of the vomicine double bond to assume a position of conjugation with the iso-double bond. The feebly basic neodesoxyvomicine (CLXXX) has been recovered from the mother liquors from the direct preparation



CLXXX

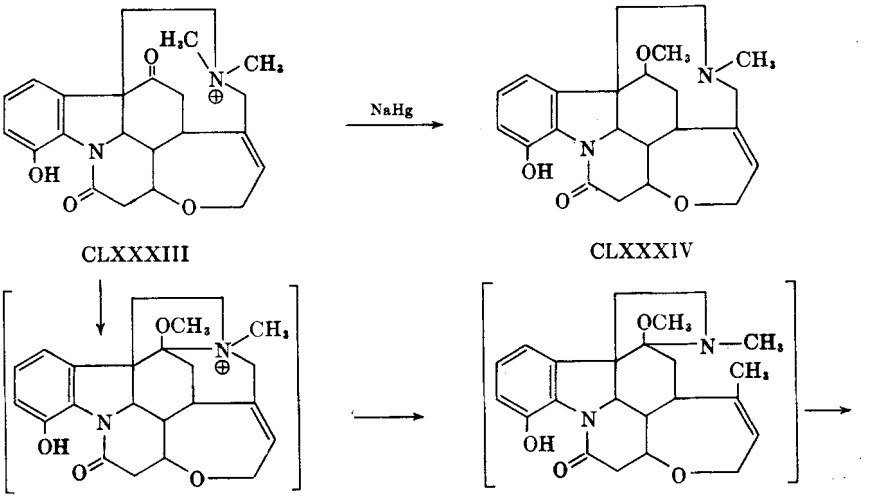
of the methiodide, CLXXIX. The insolubility of the base in $N/10$ acetic acid and its failure to react with methyl iodide or dimethyl sulfate (the methylneodesoxyvomicinium salts, however, have been prepared by iso-

merization of the quaternary salts of the colorless desoxyvomicine (282)) are in accord with this vinylamine structure (282).



CLXXXI CLXXXII

This neodesoxyvomicine is identical with the base previously obtained (34) from the action of potassium iodide and phosphoric acid on vomicine. Unlike the colorless desoxyvomicine (CLXXXI) → (CLXXXII) neode-



CLXXXIII CLXXXIV

CLXXXV CLXXXVI

soxyvomicine yields only a dihydro derivative but as yet there is no evidence indicating which of the two double bonds has been reduced (282).

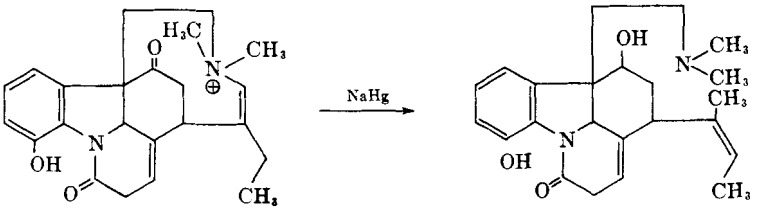
These quaternary salts have all been subjected to reduction by sodium amalgam and by catalytic means and in some instances the course of the

reaction is dependent upon the method used. Moreover since the quaternary salts of the yellow desoxyvomicine are isomerized into those of the colorless form by traces of alkali, the sodium amalgam reduction products of the yellow isomer are identical with those from the colorless form (282).

The sodium amalgam reduction of the quaternary salts of vomicine is quite comparable with that for the comparable salt of *N*-methyl-*sec*-pseudobrucine and involves the migration of a methyl group from nitrogen to oxygen. A shift of the double bond of CLXXXIV to the neo position accounts for the isomeric product (35) isolated from this reduction (282). By altering the previously described conditions (29) for the catalytic hydrogenation of methylvomicinium methylsulfate to its dihydro derivative, two isomeric $C_{22}H_{28}O_3N_2$ bases have been isolated in 75% yield (282). Both isomers contain one methylimino grouping but no methoxyl. Doubtless this can be ascribed to a transposition of one methyl group from nitrogen to oxygen, an Emde reduction and hydrogenolysis of the derived methoxyl (85% of the methanol recovered (282)) (CLXXXIII → CLXXXV). On steric grounds if the hydrogenolysis precedes the Emde fission of ring VI, then the isomerism must be attributed to a steric difference at C_{21}, otherwise the possibility of a similar isomerism at C_{16} must be entertained.

The course of the sodium amalgam reduction of the quaternary salts of the yellow and colorless forms of desoxyvomicine is quite analogous with that of vomicine. Catalytic hydrogenation, surprisingly enough, leads to the same product (CLXXXVI) as obtained in the catalytic hydrogenation of desoxyvomicine. Plainly, this must involve the migration of a methyl group to oxygen and a rupture of the N_b—C_{20} bond with attendant saturation of the double bonds and hydrogenolysis of the methoxyl group (the methanol has been recovered from the reaction). A small amount of an isomeric product was also isolated (282).

Sodium amalgam not only breaks the N_b—C_{20} bond in the quaternary salts of neodesoxyvomicine (CLXXXVII) in the formation of $C_{23}H_{30}O_3N_2$

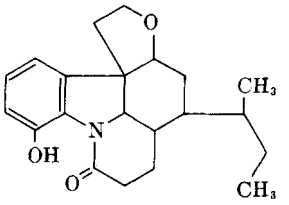


CLXXXVII CLXXXVIII

but also reduces the ketone (diacetate formation) and induces migration of the neo double bond to $\Delta^{21(22)}$ as in CLXXXVIII (formation of acetaldehyde on ozonolysis). The ease with which the ketone of CLXXXVII can

be reduced as soon as the rigid cage structure is destroyed is dramatic evidence of the steric hindrance about this center. The uptake of 2 mole equivalents of hydrogen on catalytic hydrogenation to two isomeric tetrahydro derivatives ($C_{23}H_{34}O_3N_2$) is evidence that the two ethylenic double bonds are still intact. Catalytic hydrogenation of the quaternary salts of neodesoxyvomicine yields a base ($C_{23}H_{32}O_3N_2$) containing two methylimino groups. Reduction of the ketone with sodium amalgam afforded a base $C_{23}H_{34}O_3N_2$ which was isomeric but different from the above tetrahydro derivatives of $C_{23}H_{30}O_3N_2$ (282).

In earlier experiments (29, 35) trimethylamine was isolated from vomicine by a series of two Emde and one Hofmann degradations but the isolation of desazavomicine was not realized. The analogous desazadesoxyvomicine and a pair of isomeric tetrahydro derivatives were obtained, however, by pyrolysis (270° and high vacuum) of the methiodides of CLXXXVIII and its tetrahydro derivatives. The resistance of these



CLXXXIX

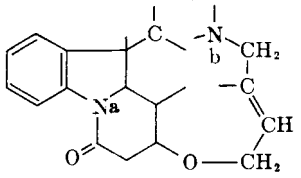
tetrahydrodesazadesoxyvomicines-A and -B to acetylation (Ac_2O at 100°) and catalytic hydrogenation ($PtO_2 + C_2H_5OH$) suggests that a nucleophilic attack of the C_{16} alkoxide ion on the primary vinyl amine has occurred (see thebenol) generating the tetrahydrofuran structure, CLXXXIX.

IV. The Structure and Stereochemistry of Strychnine

1. Structure

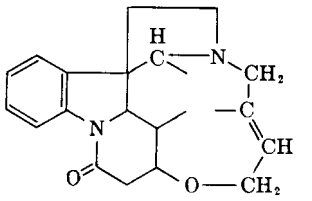
With the successful resolution of the last of the doubts in the structural problem it is now appropriate to recapitulate the highlights of the evidence that led to structure LXXXIX for strychnine (262). The evidence presented on page 379, Vol. I, clearly manifests the presence of an *o*-substituted *N*-acylaniline grouping in strychnine. Nitric acid oxidation of strychnine to strycholcarboxylic acid (I) next permits an expansion to an α,β-disubstituted-*N*-acylindole or its dihydro derivative (III). While such meager evidence as the strong basicity of XXIV and XXVI, and the similarity of the ultraviolet absorption spectra of strychnine and the lactam of hexahydrocarbazole-1,11-dipropionic acid (282, 287) is indicative of a dihydroindole system in strychnine, yet it was the elucidation of the changes leading to the formation of strychnone (261) which unequivocally established

this point. Next Robinson's interpretation of Leuch's oxidation of strychnine to strychninonic acid and its transformation to the strychninolones related N_a to N_b and permitted expansion of the part formula to CXC. These deductions were experimentally confirmed by the location of the double bond in neostrychnine (271) and by Woodward's interpretation (262) of the mechanism of methoxylating fission. Evidence is now avail-



CXC

able relating the terminal points of the other two chains emanating from N_b to some carbon atom in CXC. The nature of the changes involved in strychnone formation require that N_b be linked to the beta carbon of the dihydroindole nucleus through a methine bridge. Furthermore, the mode of formation of strychnone combined with the thermal stability of carboxyaponucidine and the resistance of methoxymethylchanodihydrostrychnanic acid to dehydrogenating conditions amply demonstrates the presence of a second chain attached to the beta carbon of the dihydroindole nucleus. If rearrangements in the alkaline degradation of various strychnine derivatives to tryptamine be excluded, then this last chain extending from C_7 to N_b must be a two-carbon chain. While the necessary evidence to

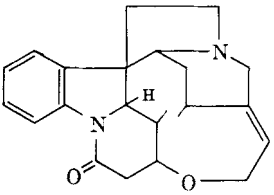


CXCI

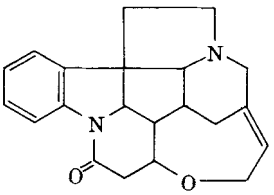
demonstrate the presence of four hydrogens on these two carbons is still lacking the presence of a methene group next to N_b is clearly manifest by the difference in hydrogen content of oxostrychnine ($C_{21}H_{20}O_3N_2$) (CXLI) and strychnine ($C_{21}H_{22}O_2N_2$). If two hydrogen atoms are not present on C_{17}, then it is conceivable that the methine bridge between the beta carbon of the dihydroindole nucleus and N_b may be identified with C_{17}. In that event pseudostrychnine must be a potential cyclopropanone and this possibility may safely be discarded. On this evidence it is possible to incorporate nineteen of the twenty-one carbon atoms in part formula CXCI.

From the observed ease of lactamization of cuninecarboxylic acid

(232, 264) and the formation of the carbinolamine ether, XCII (185, 190) it is mandatory that ring VI be a piperidine ring and hence the remaining two carbon atoms must be a chain linking C_{16} to C_{21} as in CXCII. Structure



CXCII

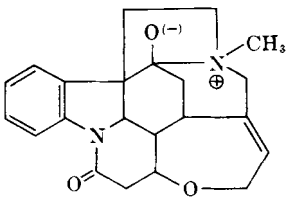


CXCIII

CXCII can be brought into accord with analytical figures by linking C_{13} to either C_{14} (LXXXIX) or to C_{15} (CXCIII). While structure LXXXIX is in accord with all the facts, the formation of a dibenzylidene derivative of *N*-methyl-*sec*-pseudostrychnine would be hard to accommodate on structure CXCIII and bromination of strychninonic acid would be expected to occur beta to the α-keto amide (262).

2. Relation of Basicity to Structure

The basicity of a number of strychnine and brucine derivatives has been measured (Table 5) and a hypothesis accounting for the observed change in pK_a values with structure has been advanced by Prelog (288). When the alteration in structure is remote from N_b as in isostrychnine and 21,22-dihydroisostrychnine the pK_a value is lowered by only about 0.3 units below that of strychnine (7.37) and brucine (7.45) (Table 5) but changes in the environs of N_b have a pronounced effect on the basicity of the amine. Isomerization of the strychnine double bond to the neo position, as has been observed in the case of other vinyl amines (272) reduces the basicity by 3.65 pK units and a similar effect is observed with the introduction of a hydroxyl at C_{16}. Also the similarity of values for vomicine, *N*-methyl-*sec*-pseudostrychnine and *N*-methyl-*sec*-pseudobrucine is in complete accord with chemical deduction. The weak basicity of these last three compounds has been attributed by Prelog to the unavailability of the electron pair on nitrogen due to the proximity of the strongly electronegative group to N_b and expressed by Wieland (282) as due to the large contribution of the following resonance form.



3. Stereochemistry

If the configuration of an asymmetric center adjacent to an alpha keto amide is retained it is possible, with certain reservations, to assign a configuration to strychnine. The same configuration at the various asymmetric centers may be assigned with equal certainty to brucine and vomicine in view of the conversion of strychnine and brucine to both dioxonucidine and octahydrostrychnidine and of *N*-methyl-*sec*-pseudostrychnine and its brucine analog to the $C_{17}H_{22}O_5N_2$ acid (CLXXII, R = CO_2H) from vomicine.

While any asymmetric center in the strychnine molecule might arbitrarily be selected as the reference point, in this argument the hydrogen at C_{14} in CXXXVIII will be considered to be above the plane of the paper. Taking cognizance of the bridge structure between rings IV and VI, this fusion cannot exist in other than the *cis* arrangement. Hence the C_{16}—N_b and, of necessity, the C_7—C_{17} bond must extend below while the C_7—C_{16} bond rises above the plane of the paper. While the relation of the above three centers is quite unambiguous the relation of the remaining centers is not without inherent ambiguities but it must be said that the available evidence at least is not contradictory. Since the peracid oxidation of cyclic ketones to lactones has been clearly demonstrated to proceed without inversion, a knowledge of the course of the elimination reaction leading to the indole nucleus in bruzone would clearly relate the configuration at C_8 to that at C_7. The polar nature of the environment in which this reaction occurs is suggestive of a *trans* elimination between the supraplanar oxygen function at C_7 and the infraplanar hydrogen at C_8, yet it does not preclude the formation of a planar carbonium ion at C_7 and the subsequent loss of a proton from C_8. Location of the C_8 hydrogen below the plane of the paper, however, is in accord with the ready lactamization of dioxonucidine hydrate (112). An alternate argument which relates C_7 through C_{12} to C_{13} and this in turn to C_{14} but which, like the first, involves one or more uncertainties, leads to the same conclusion. Being mindful of the strain inherent in a *trans* perhydroacenaphthene as well as cognizant of the direction of the isomerization of strychninolone-a to -c, one is prone to conclude that the hydrogen atoms at C_8 and C_{13} in strychnine are *trans*. This seems to be in accord with experimental fact since it has been reported that norstrychninic acid, in contrast to strychninic acid, cannot be induced to lactamize (266) and from an examination of models it is amply clear that if the C_{23}-alkoxide ion is to attack C_{12} then the hydrogen at C_{13} must be above the plane of the paper and of necessity the attack must be from the reverse side of the molecule. This argument which assigns the hydrogen atoms at C_{12} and C_{13} to the same side and that at C_7 to the opposite side

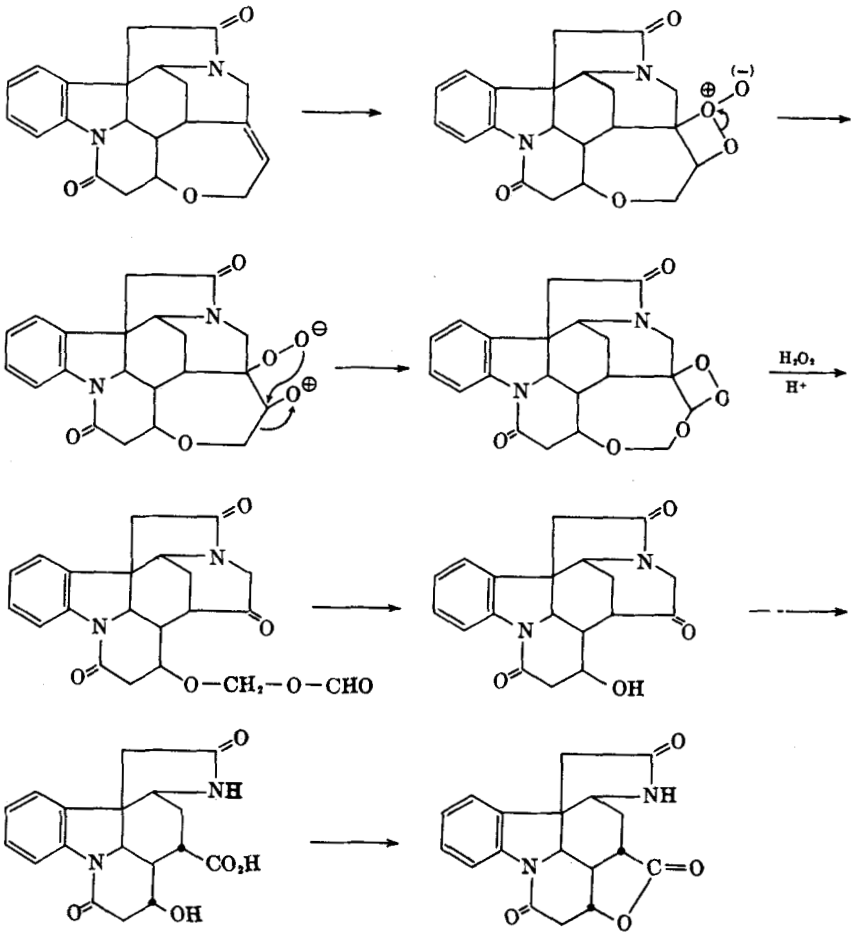
of the molecule is not free from criticism. Before such is the case the C_{12}-epimeric norstrychninic acid must be prepared and lactamized. Two pieces of evidence are available which complete the argument and which indicate a *cis* relationship of the hydrogen atoms at C_{12} and C_{14}. From the lactamization of cuninecarboxylic acid to the bridge structure CXXXIX it is apparent that no inversion has occurred in the alkaline hydrogen peroxide oxidation of dihydrostrychninone to the above acid. If the same is true in the comparable oxidation of hydroxydihydrostrychninone (CXLIII) to hydroxycuninecarboxylic acid (CXLIV), then the lactonization of the *N*-nitroso derivative demonstrates that a *cis* relationship exists at these two centers (289). This argument implies that the hydroxyl group of hydroxydihydrostrychninone is of primary origin and arises from the oxidation of the glycolic acid side chain of strychninonic acid to oxalic acid. The same relationship but involving similar reservations may be inferred from the lactone derived from the ozonolysis and hydrogen peroxide oxidation of oxostrychnine. In analogy with the ozonolysis of various allyl ethers this transformation may be represented schematically as indicated in formulas on page 538 (280). If the premise that the C_{12}-hydroxyl is of primary origin is accepted, then the hydrogen atoms at C_{12} and C_{14} in strychnine are *cis*.

These conclusions, as expressed in CXXXVIII, are in complete accord with the results of Fourier and Patterson syntheses from the |010| and |001| X-ray projections of the isomorphous bromide (290), sulfate (291, 292, 293) and selenate (291, 292, 293) salts of strychnine. Thus elimination of any one of the uncertainties from the above argument will spell finis to a long and interesting structural and stereochemical problem.

It is now possible to proceed to a consideration of the steric attack of hydrogen and permanganate on brucine whereby dihydrobrucine and dihydrobrucinonic acid are obtained. These two reagents must approach from above or from the least hindered side of the molecule so that dihydrobrucinonic acid should have the hydroxyl group above the plane of the paper and remote from the ether oxygen of the glycolic acid residue. On similar grounds the hydrogenation of brucinonic acid should lead to brucinolic acid with the hydroxyl behind the plane and sterically vicinal to the ether oxygen atom. The validity of these conclusions is reflected in the apparent lactonization of XXIV and the facile elimination of glycolic acid from brucinolic acid. Furthermore the failure of curbine to yield an α,β-unsaturated ketone is difficult to explain on Prelog's piperidine formula, XC, but is adequately accommodated on the bridge structure, LXXXIX.

When the dihydroindole system is removed from the molecule as in

carboxyaponucidine (122) or the rigid cage structure is destroyed by fission of rings V, VI, VII as in CLXXXIII (282) hydrogen can approach from

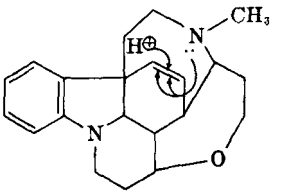


CXCIV CXCV

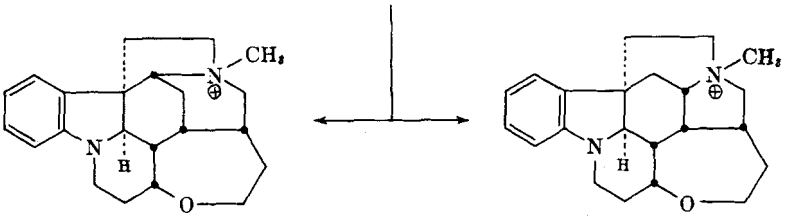
either side of the molecule yielding stereoisomeric mixtures of hydrogenation products.

Finally, the formation of a separable mixture of methyldihydrostrychnidinium-A acetate (CXCVI) and methyldihydrostrychnidinium-D acetate (CXCVII) when des-base-D is subjected to hydrogenating conditions in acetic acid is not an unique reaction, since apoconessine undergoes a similar reaction. This reverse Emde cyclization apparently is the result

of a concerted reaction initiated by the approach of a proton to the $\Delta^{15(16)}$-double bond from above as schematically depicted in CXCVIII. The



CXCVIII



CXCVI CXCVII

steric position of the nitrogen atom with respect to the double bond permits bond formation at either end of the double bond and thus accounts for the formation of the two methyldihydrostrychnidinium salts.

V. Tables of Physical Constants

The conventions used in Tables 8 to 10 are those adopted for tabulating the properties of the various alkaloids in Chapters 6 and 7.

TABLE 5

THE BASICITY OF STRYCHNINE, BRUCINE, AND VOMICINE AND THEIR TRANSFORMATION PRODUCTS (288)

	pK_a
Brucine	7.45
23-Desoxy-21,22-dihydroisostrychnine	7.05
Dihydroisostrychnine	7.10
21,22-Dihydrostrychnine	7.45
21,22-Dihydroxy-21,22-dihydrostrychnine	7.34
Isostrychnine	7.07
N-Methyl-*sec*-pseudobrucine	6.08
N-Methyl-*sec*-pseudostrychnine	6.07
Neostrychnine	3.8

TABLE 5 (*Continued*)

	pK_a
Pseudostrychnine	5.60
Pseudostrychnine methyl ether	5.58
Strychnidine	8.29
Strychnine	7.37
Strychnine-*N*-oxide	5.17
Strychninic acid-*N*-oxide	5.09; 6.65
Strychninolic acid	6.01
Strychninonic acid	5.45
Vomicine	5.88

TABLE 6

ULTRAVIOLET ABSORPTION MAXIMA (AND LOG ϵ VALUES)

Compound				References
N-Acetylhexahydrocarbazole	257 (4.2)	281 (3.57)	290 (3.53)	279
N-Acetyltetrahydrocarbazole	243 (4.23)	270 (4.02)	297 (3.70)	279
Dehydrostrychninolone	340 (3.94)			279
Dehydrostrychninone	Ca. 340 (3.94)			279
Dihydrooxostrychnine	255 (4.03)			280
Benzal —	292 (4.35)			280
Dihydrostrychnidine	240 (3.36)	255 (3.82)	305 (3.3)	
Hexahydrocarbazole-1,11-dipropionic acid	257 (4.25)	283 (3.7)	290 (3.65)	287
Lactam of	254 (4.08)	279 (3.60)	288 (3.50)	287
Hydroxymethyldihydroneostrychnine*	251 (4.25)			
Methoxymethyldihydroneostrychnine*	252 (4.24)			
Neostrychnidine*	254 (4.0)	306 (3.5)		
Neostrychnine *	252 (4.2)			
Oxostrychnine	255 (4.13)			287
Benzal —	292 (4.33)			287
Oxyvomipyrine	272 (4.3)	337 (3.9)		262
Strychnine	257 (4.2)	281 (3.62)	290 (3.53)	279
Benzal —	287 (4.28)			279
Strychninolone-a	282 (3.6)			269, 280
Strychninolone-b	257 (4.18)			269
Strychninolone-c	299 (3.8)			280
Strychnone	246 (4.15)	270 (3.92)	294 (3.72)	261
Vomipyrine	226 (4.17)	338 (3.75)		282, 286
Hydrochloride	284 (4.2)	356 (3.83)		282
Acid-a (m.p. 299–302°)	282 (3.6)			280
Acid-b (m.p. 255–259°)	253 (4.13)			280
Acid-c (m.p. 285–292°)	315 (3.75)			280

* Samples for these analyses were kindly provided by Dr. P. J. Scheuer and Dr. Richard Hall.

TABLE 7

CHARACTERISTIC INFRARED ABSORPTION BANDS (IN MICRONS)

N-Acetyl-*sec*-pseudostrychnine	2.93	5.86	6.0	6.23
Benzaldihydrooxostrychnine*	5.88	6.02	6.23	..
Dihydrostrychnidine	6.21	..	..	..
Hydroxymethyldihydroneostrychnine*	2.95	6.02	6.22	..
Neostrychnidine*	6.06	6.24	..	..
Neostrychnine	6.03	6.27	..	..
Benzal — *	6.0	6.21	..	..
N-Oxide	6.03	6.25	..	..
Oxostrychnine*	5.90	6.03	6.2	..
Oxostrychnine	5.83–6.0	6.22	..	..
Benzal —	5.85	6.0	6.21	..
Epoxide	5.85–6.0	6.21	..	..
Pseudostrychnine	2.84	6.0	6.23	..
Strychnidine*	6.20	..	..	..
Strychnine	6.03	6.27	..	..
Benzal — *	6.0	6.21	..	..
N-Oxide	6.02	6.25	..	..
Strychninonic acid*	5.8	5.92	6.06	6.21
Compound CLXII (m.p. 288–292°)	3.08	5.65	5.9–6.05	6.21

* The asterisk indicates the determination was made in mineral oil, in all other cases chloroform was the solvent.

TABLE 8

PHYSICAL CONSTANTS OF STRYCHNINE AND ITS DERIVATIVES

Compound	M.p. or b.p., °C.	$[\alpha]_D$		References
		A		
N-Acetyl-*sec*-pseudostrychnine	187 (dec)	..	Yellow needles (C_2H_5OH—H_2O)	276
p-Nitrophenylhydrazone	..	..		
Anhydrohydroxytetrahydrodichanostrychnidine	Ca. 280 (dec)	..	..	294
Anhydroneostrychnine phosphorous acid	316 (dec)	..	Prisms (H_2O)	276
Anhydropseudostrychninenitromethane	170 (froth)	..	Pale yellow needles (C_2H_5OH–H_2O)	276
	..	..		
Anhydropseudostrychninephosphorous acid	315 (dec)	..	Crystals (H_2O)	276
Perchlorate	266 (dec)	−21° (2*N* NH_4OH)	Needles (H_2O)	276
		B		

Base-E. See Hydroxytetrahydrodichanostrychnidine

Base-F. See Dehydrodihydrostrychnidine

TABLE 8 (*Continued*)

Compound	M.p. or b.p., °C.	$[\alpha]_D$		References
Bisanhydroneostrychninephosphoric acid	185 (dec)	..	Prisms (H_2O)	276
		C		
Cuninecarboxylic acid hydrate	*291–293°	+33° ($CHCl_3$–CH_3OH)	Crystals (CH_3OH—H_2O)	264
Hydrochloride	*288–289	..	Crystals (H_2O–acetone)	264
Lactone	*291–293	+110.5° ($CHCl_3$)	Crystals ($CHCl_3$–CH_3OH)	264
Aminodicarboxylic acid $C_{13}H_{18}O_5N_2$	*340	−106° (0.2 *N* HCl)	Prisms (pyridine–H_2O—CH_3OH)	264
		D		
Decahydrotetrachanostrychnidine	258–260	..	Needles (ethyl acetate)	294
Dehydroaponucidine	94	..	Crystals (ligroin)	284
Dihydrochloride	240 (dec)	..	Crystals (ether)	284
Dehydrodihydrostrychnidine	254	..	Crystals (ethyl acetate)	294
Dehydrostrychninolone	*233–234	−547° ($CHCl_3$)	Prisms (CH_3OH)	269
Acetyl-	*285–287	−508° ($CHCl_3$)	Platelets (CH_3OH)	269
Dehydrostrychninone	*260–262 (dec)	−512° ($CHCl_3$)	Prisms (CH_3OH)	269
Hydrate	*125	..	Prisms (H_2O)	269
Oxime	*299–300 (dec)	..	Needles (CH_3OH—H_2O)	269
Desformylmethoxymethylchanodihydrostrychnane	86.0–86.8	..	Needles (ligroin)	262
Perchlorate	244.5–245.5	..	Needles (abs. C_2H_5OH)	262
Picrate	176–178	..	Yellow wooly needles (C_2H_5OH)	262
Desoxomethoxymethylchanodihydrostrychnone	136–139	..	Prisms (C_6H_6–ligroin)	262
Dibromoisostrychninic acid	252	−102°/d (N/10 NaOH)	Prismatic needles (H_2O)	274
N-Nitrosohydrochloride	240 (dec)	..	Solid (dil. HCl)	274
Perchlorate	..	..	Needles (H_2O)	274
Sulfate	..	..	Prisms (dil. H_2SO_4)	274
Phenylisocyanate derivative	205	..	..	274
Phenylisothiocyanate derivative	170	..	Prisms	274
N-Acetyl perchlorate	258–260 (dec)	..	..	274

TABLE 8 (*Continued*)

Compound	M.p. or b.p., °C.	$[\alpha]_D$		References
Ethyl ester dipricate	..	..	..	274
Methyl ester dipricrate	..	..	..	274
Dihydroanhydroneostrychninephosphorous acid	312 (dec)	+67° (H_2O)	Needles (CH_3OH)	276
Dihydrobisanhydroneostrychninephosphoric acid hydrate	318–320 (dec)	..	Prisms (CH_3OH)	276
Dihydroisostrychninic acid				
Acetyl perchlorate	85–89	..	Prisms (H_2O)	274
picrate	249–251	..	Glistening leaflets (CH_3OH)	274
Dihydropseudostrychnine methyl ether	196–199	..	Crystals (CH_3OH)	276
Dihydrostrychnidine-A	216–219	..	Crystals (ethyl acetate)	280, 276, 294
Dihydrostrychnine	217–218	..	Needles (CH_3OH—H_2O)	276
Dihydrostrychninolone-c	*254–257	−131° (HOAc)	Crystals	269
Dihydrostrychninone	314	..	Crystals (ethyl acetate)	268
21,22-Dihydroxy-21,22-dihydrostrychnine	*243–245 ..	+22° ($CHCl_3$) ..	Crystals ($CHCl_3$—ethyl acetate)	267
Dihydroxystrychnine	240	..	Crystals (CH_3OH)	268
Hydrochloride	212 (dec)	..	Needles (H_2O)	268
Methiodide	322	..	Crystals (H_2O)	268
		H		
Hexahydrodichanostrychnidine	247 ..	.. ..	Prisms (ethyl acetate)	294
Hydroxycuninecarboxylic acid	..	..	..	266
N-Nitroso-	..	..	..	266
Lactone	..	..	..	266
x-Hydroxydihydrostrychnine sesquihydrate	114 ..	.. ..	Needles (C_2H_5OH–H_2O)	276
Hydroxydihydrostrychninone	..	..	..	266
21-Hydroxy-22-keto-21,22-dihydrostrychnine	*239–241	−33° ($CHCl_3$)	Needles (C_2H_5OH)	267
$C_{21}H_{20}O_6N_2$ ($Pb(OAc)_4$ oxid)	*247–248 (dec)	−47° (NaOH)	Crystals (dioxane)	267
Methiodide	*312–316	..	Crystals (CH_3OH—H_2O)	267

TABLE 8 (*Continued*)

Compound	M.p. or b.p., °C.	$[\alpha]_D$		References
p-Nitrophenylhydrazone	*220–225 (dec)	..	Powder (CH_2Cl_2—CH_3OH)	267
Semicarbazone	*251 (dec)	..	Rosettes of crystals (CH_3OH—H_2O)	267
β,β-N_b-Hydroxymethyldihydroneostrychnine	160 (dec) ..	..	Prismatic needles (C_6H_6—ligroin)	295
x-Hydroxyneostrychnine	116	..	Crystals (pet. ether)	276
Hydroxytetrahydrodichanostrychnidine	165 (efferv) ..	..	Needles (ethyl acetate)	294
Oxime	122	..	Microcrystals (C_6H_6—ligroin)	294
		I		
Isostrychnine	*226–227	..	Needles (ethyl acetate—ether)	273
Isostrychninic Acid				
Perchlorate	235–242 (dec)	..	Domatic crystals (H_2O)	274
Acetyl-				
Methoperchlorate	248–252	..	Plates or leaflets	274
Perchlorate	250–285 (dec)	..	Lancets	274
Ethyl ester methiodide	252–258 ..	..	Needles (C_2H_5OH–ether)	274
Ethyl ester perchlorate	210–220 (dec)	..	Prisms (C_2H_5OH)	274
Ethyl ester				
Dihydrochloride	..	..	Amorphous	274
Dipicrate	..	..	Amorphous	274
Methiodide	246	..	Crystals	274
Methyl ester				
Dihydrochloride	225–230	..	..	274
Methiodide	252–253	..	Domatic prisms (CH_3OH)	274
		M		
16-Methoxy-21,22-dihydroxy-21,22-dihydrostrychnine	*218 (dec) ..	+21° ($CHCl_3$) ..	Crystals (CH_3OH—$CHCl_3$)	267
16-Methoxy-21-hydroxy-22-keto-21,22-dihydrostrychnine	*340 ..	−20° ($CHCl_3$) ..	Crystals ($CHCl_3$—CH_3OH)	267
p-Nitrophenylhydrazone	*237 (V. dec) ..	..	Colored prisms (CH_2Cl_2–CH_3OH)	267
Methoxymethylchanodihydrostrychnane	163–164.5 ..	..	Rosettes of crystals (C_6H_6—ligroin)	262
Methoxymethylchanodihydrostrychnone	189–191 ..	..	Crystals (ethyl acetate—ether)	262

TABLE 8 (*Continued*)

Compound	M.p. or b.p., °C.	$[\alpha]_D$		References
Diethylmercaptal	183–184.5	..	Prisms (C_6H_6—ligroin)	262
Semicarbazone	242–244 (dec)	..	Needles (CH_3OH)	262
Methoxymethylchanostrychnol	225.5–226.5	..	Needles (C_2H_5OH—ether)	262
Methoxymethyldihydroneostrychnine	143	..	..	262
Methoxymethyltetrahydrostrychnidine	220–221	..	Crystals (C_6H_6)	296
N-Methyl-*sec*-pseudostrychnine				
Acid $C_{17}H_{22}O_5N_2 \cdot 3H_2O(H_2CrO_4)$	..	..	..	277
Base $C_{16}H_{22}O_3N_2$ (decarboxylation)	..	..	..	277
		N		
Neostrychnine	226–227	+215° ($CHCl_3$) +90° (HOAc)	Crystals (C_2H_5OH)	276
N-Oxide	179–180	..	Plates (H_2O)	208
		O		
Oxodihydromethoxymethyldihydroneostrychnidine				
A-Isomer	224	..	..	296
B-Isomer	285	..	..	296
p-Nitrophenylhydrazone	185–186 (dec)	..	Amorphous	296
Oxodihydromethoxymethyldihydroneostrychnine	225 275–277	..	Needles (C_2H_5OH)	296
p-Nitrophenylhydrazone	155–157	..	..	296
Oxodihydroneostrychnine	190	..	..	296
CH_3OH of crystallization	128 (dec)	..	Prisms (CH_3OH)	296
Hydrobromide-monohydrate	>170 (dec)	..		296
Oxostrychnine	325–330	..	Crystals ($CHCl_3$—ligroin)	280, 279
$C_{18}H_{16}O_4N_2$ (ozonolysis)	288–292	+139° (HOAc)	Crystals (CH_3OH)	280
Acid-a	299–302	..	Leafy crystals (CH_3OH)	280
Acid-b	255–259	..	Rect'g plates (CH_3OH)	280
Acid-c	285–292	..	Crystals (HOAc—H_2O)	280

TABLE 8 (*Continued*)

Compound	M.p. or b.p.,°C.	$[\alpha]_D$		References
Epoxide	313–316	..	Prisms ($CHCl_3$)	280
Glycol	300–305	..	Plates (H_2O)	280
Monoacetate	285–288	..	Needles or rods ($CHCl_3$—ligroin)	280
		P		
Pseudostrychnine				
Isomer-I	253–257	..	Crystals ($CHCl_3$—ether)	278
Isomer-II	235–237 (dec)	−63° ($CHCl_3$)	..	278, 276, 286
N-Nitroso	288–290	..	Prisms (C_2H_5OH—H_2O)	278
Perchlorate	235–240 >300	..	Stout needles (H_2O)	278
2,4-Dinitrophenylhydrazone	166 (dec)	..	Orange needles (C_2H_5OH—H_2O)	276
Ethyl ether	217–219 (dec)	..	Slender needles (C_2H_5OH)	278
Benzylidene	205–207 (dec)	..	Yellow needles (C_2H_5OH)	278
Methyl ether	196–198 (dec)	−64 ($CHCl_3$)	Needles (CH_3OH)	278
p-Nitrophenylhydrazone	235	..	Yellow needles (C_2H_5OH—H_2O)	276
		S		
Strychnine	*278–279.5	..	Needles ($CHCl_3$)	273, 278
N-Oxide hydrate	205–207	..	Crystals (H_2O)	278
Strychninone	273	..	Crystals (CH_3OH—ethyl acetate)	268
Strychninonic Acid Hydrate	*248–250 (dec)	−43 (NaOH)	Crystals (dioxane)	267
Dianisylidene-	203 (dec)	..	Yellow solid (CH_3OH—H_2O)	276
Dibenzylidene-	181–183 (dec)	..	Yellow needles (dioxane—H_2O)	276
Methyl ester	*244–245	−62° ($CHCl_3$)	Needles (CH_3OH)	267
		T		
Tetrahydroanhydropseudostrychnine phosphorous acid	302 (dec)	+67° (H_2O)	Prisms (H_2O)	276
Tetrahydrodichanostrychnidine	200/14 mm. 192	..	Rect'g tablets (C_6H_6)	294
Picrate monohydrate	127 (dec)	..	microcrystals (C_2H_5OH—H_2O)	294
Acetyl-	158–160	..	Needles	294

TABLE 9

PHYSICAL CONSTANTS OF BRUCINE AND ITS DERIVATIVES

Compound	M.p. or b.p., °C.	$[\alpha]_D$		References
		B		
Brucine	175–177	..	..	278
Ehiodide	292 (dec)	..	Rt. ⌊ 'd plates (ether—C_2H_5OH)	281
Ethoperchlorate	290 (dec)	..	Prisms	281
Bruzone	313–317 322–325	−20° ($CHCl_3$)	..	278
Isomer	180–186	−410° ($CHCl_3$)	Flat plates (CH_3OH)	278
		D		
Dihydrobrucine				
Tetrahydrate	..	−17.4°/d (C_2H_5OH)	..	265
Ethiodide	285 (dec)	..	Rt. ⌊ 'd plates (C_2H_5OH)	281
Ethoperchlorate	293 (dec)	..	Quadratic plates	281
Hydrobromide	115–135	..	Rhombic leaflets	265
N-Oxide	186–190	..	Six-sided plates (H_2O)	265
perchlorate	250–255	..	Quadratic plates (H_2O)	265
Perchlorate	205–210	..	Rhombic leaflets (H_2O)	265
Sulfate	203–205	..	Dense prisms (dil. H_2SO_4)	265
Dihydroisobrucinic acid				
Picrate	167–172	..	Prismatic needles (H_2O)	275
		E		
N-Ethyldihydro-*sec*-pseudobrucine	234–236 (froth)	..	Prisms (C_2H_5OH)	281
Methiodide	269–271	..	Prisms (C_2H_5OH)	281
Methoperchlorate	289–291	..	Rhombic leaflets	281
Perchlorate	210–220 (froth)	..	Domatic plates	281
N-Ethyl-*sec*-pseudobrucine	135–148 (V)	..	Platelets (C_2H_5OH—H_2O)	281
Ethiodide	221–225	..	Crystals (H_2O)	281
Methylate base ($C_{27}H_{34}O_5N_2$)	..	..	Microcrystals	281
Amalgam base ($C_{27}H_{36}O_5N_2$)	..	..	Microcrystals	281
Amalgam base perchlorate	287 (dec)	..	Plates (H_2O)	281
Ethoperchlorate	275–280 (dec)	..	Domatic prisms	281

TABLE 9 (*Continued*)

Compound	M.p. or b.p., °C.	$[\alpha]_D$		References
Hydriodide	195–215 (dec)	..	Rt. ⌊ 'd platelets (C_2H_5OH)	281
Methiodide	248 (dec)	..	Leaflets (H_2O)	281
Methylate base ($C_{26}H_{32}O_5N_2$)	..	..	Microcrystals	281
Methylate base methiodide	257 (dec)	..	Rt. ⌊ 'd plates (C_2H_5OH)	281
Methylate base methoperchlorate	275 (dec)	..	Plates (H_2O)	281
Amalgam base ($C_{26}H_{34}O_5N_2$)	70	..	Crystalline powder	281
Amalgam base perchlorate	270 (dec)	..	Needles (H_2O)	281
Methoperchlorate	280–285 (dec)	..	Domatic plates	281
Perchlorate	215 (froth)	..	Domatic plates (H_2O)	281
		I		
Isobrucinic acid	215–220	$-123.6°/d$ ($N/10$ NaOH)	Colorless prisms (H_2O)	275
Methiodide	..	..	Not crystalline	275
Methoperchlorate	260	..	Prisms	275
Perchlorate	>270	..	Needles (H_2O)	275
Phenylisocyanate deriv.	185–192	..	Leaflets ($CHCl_3$)	275
Perchlorate	221–226 (dec)	..	Prisms (H_2O)	275
Phenylisothiocyanate	145–153	..	Needles	275
Picrate	255–260 (dec)	..	Needles (HOAc—H_2O)	275
Acetyl-	185–200	..	Prisms (H_2O)	275
Methiodide	190–210	..	Needles	275
Methoperchlorate	264 (dec)	..	Quadratic plates (H_2O)	275
Picrate	142–153	..	Prisms	275
Ethyl ester	..	..	..	275
Hydrochloride	..	..	..	275
Methiodide	232–238 (dec)	..	Crystals (acetone)	275
Perchlorate	248–250	..	Prisms (C_2H_5OH)	275
Picrate	..	..	Needles (C_2H_5OH)	275
Isotetrahydrobrucine	245–250	$-70°/d$ ($CHCl_3$)	..	275
Perchlorate	198–205	..	Groups of needles (H_2O)	275
		M		
M-Methyldihydro-*sec*-pseudobrucine				
Perchlorate	215 (froth)	..	Leaflets (H_2O)	281
N-Methyl-*sec*-pseudobrucine	228–230	..	Prisms (CH_3OH)	281

TABLE 9 (*Continued*)

Compound	M.p. or b.p., °C.	$[\alpha]_D$		Reference
Acid $C_{17}H_{22}O_5N_2 \cdot 3\,H_2O(H_2CrO_4)$	..	..	..	277
Base $C_{16}H_{22}O_3N_2$ (decarboxylation)	..	..	..	277
Hydriodide	222	..	Plates	281
Methiodide	218	..	Needles	281
Methoperchlorate	280–285	..	Prisms (H_2O)	281
		P		
Pseudobrucine	255–258 (dec)	−64° ($CHCl_3$)	Crystals ($CHCl_3$—ether)	275, 281
N-Nitroso-	245–247 (dec)	..	Needles (C_2H_5OH—C_3H_7OH)	275
Ethyl ether	178–184	..	Prisms (C_2H_5OH)	281
		T		
Tetrahydrobrucine-II				
Tetrahydrate	110–120 (froth)	..	Prisms (acetone)	265
Hydrobromide	230–280	..	Needles	265
Methiodide	225	..	Dense prisms (CH_3OH)	265
Picrate	181–183 (dec)	..	Orange needles	265

TABLE 10

PHYSICAL CONSTANTS OF VOMICINE AND ITS DERIVATIVES

Compound	M.p. or b.p., °C.	$[\alpha]_D$		References
		D		
Desazadesoxyvomicine	186	..	Needles (C_2H_5OH)	282
Desoxyvomicine	206	..	Crystals (C_2H_5OH)	282
Methiodide	260 (dec)	..	Prisms (CH_3OH)	282
Methobromide	>300 (dec)	..	Leaflets (H_2O)	282
Methopicrate	170	..	Crystals (CH_3OH)	282
Methomethylsulfate	240 (froth)	..	Rods(H_2O—CH_3OH)	282
$C_{23}H_{28}O_3N_2$ (Emde, NaHg)	177–178	+190°($CHCl_3$)	Plates (CH_3OH)	282
$C_{23}H_{30}O_2N_2$ (Emde, PtO_2+H_2)	210–212	+74°($CHCl_3$)	Prisms (C_2H_5OH)	282
$C_{23}H_{30}O_2N_2$ Isomer	179–180	−101°($CHCl_3$)	Colorless polyhedra	282
Desoxyvomicine (yellow)				
Methomethylsulfate	249 (dec)	..	Needles (C_2H_5OH—acetone)	282
$C_{23}H_{28}O_3N_2$ (Emde, NaHg)	178	..	Plates (CH_3OH)	282
		N		
Neodesoxyvomicine	310 (dec) 327 (dec)	..	Needles (C_2H_5OH)	282

TABLE 10 (*Continued*)

Compound	M.p. or b.p., °C.	$[\alpha]_D$		References
Methiodide	270 (dec)	..	Crystals (CH_3OH)	282
Methochloride				
$C_{23}H_{32}O_3N_2$ (Emde H_2+PtO_2)	177 ..	..	Silky needles (CH_3OH)	282
Base-I, $C_{23}H_{30}O_3N_2$ (Emde, NaHg)	217	+99°	Pointed crystals	282
Base-I, methiodide	294	..	Prismatic rods (CH_3OH)	282
Base-I, acetyl derivative	137–138	..	Needles (ligroin)	282
Base-II, $C_{23}H_{30}O_3N_2$ (Emde, NaHg)	174–179 ..	+34° ..	Polyhedra (ethyl acetate)	282
Base-II, methiodide	280 (dec)	..	Crystals (CH_3OH)	282
		T		
Tetrahydrodesazadesoxyvomicine-A	246 ..	..	Quadratic prisms (C_2H_5OH)	282
Tetrahydrodesazadesoxyvomicine-B	182	..	Needles (acetone-water)	282
		V		
Vomicine				
Acid $C_{17}H_{22}O_5N_2 \cdot 3\,H_2O(H_2CrO_4)$	..	..	..	277
Base $C_{16}H_{22}O_3N_2$ (decarboxylation)	..	..	..	277
Methobromide	..	..	Crystals (CH_3OH)	282
Methomethylsulfate				
$C_{22}H_{28}O_3N_2$ (Emde, H_2+PtO_2)	204	+89° ($CHCl_3$)	Needles (C_2H_5OH)	282
↓				
$C_{22}H_{27}O_2N_2Br$	154–156	..	Crystals (C_2H_5OH)	282
↓				
$C_{22}H_{28}O_2N_2$	153	..	Crystals (CH_3OH)	282
Vomipyrine	108–108.5	..	Rect'g plates (hexane)	282

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Author Index*

* Numbers in parentheses are reference numbers and are included to assist in locating references where the author's name is not mentioned in the text. Numbers in italics refer to the page of the article on which the reference is listed.

D

G

H

N

O

P

Y

Z

Subject Index*

*(Botanical names are printed in italics. Prefixes such as *nor-*, *iso-*, *proto-*, *apo-*, are printed in italics and disregarded for indexing purposes.)

D

L

M