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The Alkaloids

VOLUME 9

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The Alkaloids

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The Alkaloids

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between July 1977 and June 1978

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Foreword

The policy adopted in this ninth volume of *The Alkaloids* is once again to furnish a comprehensive annual survey of the alkaloid literature. As a result of unavoidable omissions in the eighth volume, a two-year coverage is provided of tropane alkaloids and, within the isoquinoline group (Chapter 8), of the chemistry of emetine and related bases, dibenzopyrrocolines, benzophenanthridines, and colchicine. The chapter on Miscellaneous Alkaloids also surveys the literature of the period July 1976—June 1978; purines are no longer included.

Dr. V. A. Snieckus, one of our most regular authors, is not taking part this year, and I would like to draw particular attention to his substantial and invaluable contributions to the preceding eight volumes.

Dr. R. H. F. Manske, who died in late 1977 as a result of a motor car accident, was a life-long alkaloid chemist and founder editor of the review series 'The Alkaloids'; a tribute to Dr. Manske and his work is included in Volume XVII of the series.

July 1979

M. F. GRUNDON

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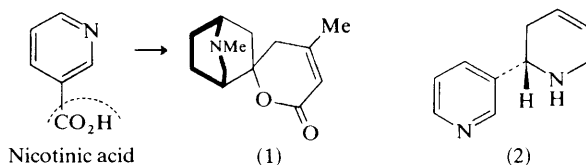
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1 Introduction

As before, previous Reports in this series appear as the first references,¹⁻⁸ and extensive reference is made to them in the text. A new review⁹ on alkaloid biosynthesis and a wide-ranging book¹⁰ on alkaloid biology and metabolism have been published.

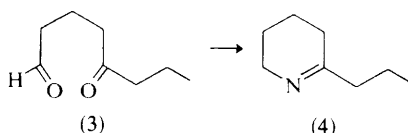
2 Piperidine, Pyridine, and Pyrrolidine Alkaloids

Dioscorine.—The most interesting observation, that the piperidine fragment (heavy bonding) of dioscorine (1) arises not from lysine (or acetate) but nicotinic acid, previously published in preliminary form,¹¹ is now available in full.¹² A similar finding¹³ for the piperidine ring of anatabine (2) is to be noted.



- ¹ R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1.
- ² J. Staunton, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1972, Vol. 2.
- ³ R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3.
- ⁴ R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4.
- ⁵ R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1975, Vol. 5.
- ⁶ R. B. Herbert, in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6.
- ⁷ R. B. Herbert, in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London, 1977, Vol. 7.
- ⁸ R. B. Herbert, in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London, 1978, Vol. 8.
- ⁹ R. B. Herbert, in 'Comprehensive Organic Chemistry', ed. D. H. R. Barton and W. D. Ollis, Pergamon, Oxford, 1978, Vol. 5, p. 1045.
- ¹⁰ G. R. Waller and E. K. Nowacki, 'Alkaloid Biology and Metabolism in Plants', Plenum, New York, 1978.
- ¹¹ E. Leete, *J. Amer. Chem. Soc.*, 1977, **99**, 648; R. B. Herbert, in ref. 8, p. 1.
- ¹² E. Leete, *Phytochemistry*, 1977, **16**, 1705.
- ¹³ E. Leete and S. A. Slattery, *J. Amer. Chem. Soc.*, 1976, **98**, 6326; R. B. Herbert, in ref. 8, p. 2.

Coniine.—Further experiments^{14,15} on the enzyme-catalysed conversion¹⁶ of 5-oxo-octanal (3) plus alanine into γ -coniine (4) plus pyruvate have led to the isolation, from *Conium maculatum*, of two enzymes which will carry out this reaction. Their properties have been explored and it is suggested, from their different rates of reaction with (3) and differing inhibitions by pyruvate and (3), that they act together in mediating this reaction in the plant.¹⁴

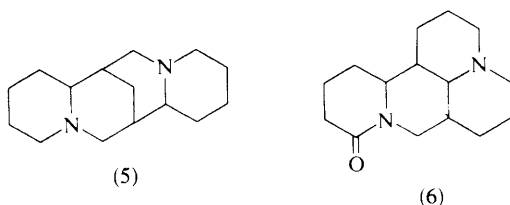


Quinolizidine Alkaloids.—Cadaverine is known to be a precursor for quinolizidine alkaloids.⁹ (For discussion of the biosynthesis of these alkaloids see also previous Reports). Recent experiments have shown that cadaverine is a precursor for alkaloids (anagryne, pachycarpine, ammodendrine, *N*-methylcytisine, and cytisine) in *Ammodendron karelinu* too. Metabolism of lupanine, anagryne, ammodendrine, and pachycarpine in the plant was also studied.¹⁷

It has been found that isophoridine and allomatrine are not biosynthetic intermediates in *Sophora alopecuroides*. Curiously, alkaloids of the sparteine (5) type were found to be precursors of those with the matrine (6) skeleton. Methylation of cytisine (7) was observed to be reversible.¹⁸

Matrine-type alkaloids [as (6)] were found to be labelled by radioactive lysine and cadaverine in *Goebelia pachycarpa* and to be interconvertible.¹⁹

Quinolizidine alkaloids of the sparteine type [as (5)] are known to arise from three molecules of lysine *via* a symmetrical intermediate (cadaverine).⁹ Aphylline (8) also arises from three molecules of lysine in *Anabasis aphylla*, but without the participation of a symmetrical intermediate.²⁰



¹⁴ M. F. Roberts, *Phytochemistry*, 1978, **17**, 107.

¹⁵ M. F. Roberts, *Phytochemistry*, 1977, **16**, 1381.

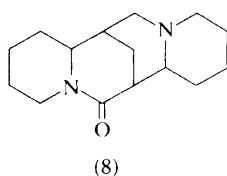
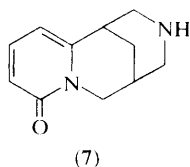
¹⁶ M. F. Roberts, *Phytochemistry*, 1971, **10**, 3057; R. B. Herbert, in ref. 4, p. 10.

¹⁷ Yu. K. Kushmuradov, H. R. Schütte, Kh. A. Aslanov, and S. Kuchkarov, *Khim. prirod. Soedinanii*, 1977, 247 (*Chem. Abs.*, 1977, **87**, 98 902).

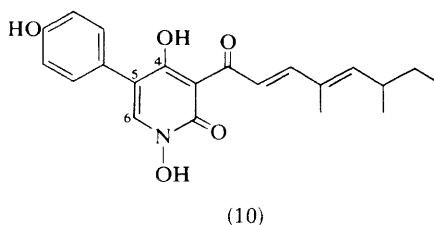
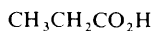
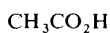
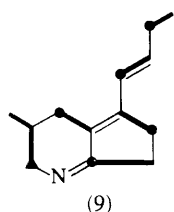
¹⁸ Yu. K. Kushmuradov, Kh. A. Aslanov, H. R. Schütte, and S. Kuchkarov, *Khim. prirod. Soedinanii*, 1977, 244 (*Chem. Abs.*, 1977, **87**, 98 901).

¹⁹ B. A. Abdusalomov, Kh. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinanii*, 1977, 549 (*Chem. Abs.*, 1977, **87**, 164 322).

²⁰ E. Nurimov, M. Ya. Loukova, and B. A. Abdusalomov, *Priklad. Biokhim. Mikrobiol.*, 1977, **13**, 628 (*Chem. Abs.*, 1977, **87**, 148 764).



Pyrindicin.—The pattern of ^{13}C n.m.r. signal enhancement observed on incorporation of $[1-^{13}\text{C}]$ - and $[2-^{13}\text{C}]$ -acetate and $[1-^{13}\text{C}]$ propionate into pyrindicin (9) in *Streptomyces griseoflavus* var. *pyrindicus* indicates that the metabolite is formed from five acetate units and one propionate unit, as shown in (9).²¹ Some labelling by acetate of the propionate unit was observed, which was interpreted as being the result of metabolism *via* both the tricarboxylic acid and glyoxalate cycles.



Tenellin.—Results of a study on the biosynthesis of tenellin (10), previously reported in a preliminary communication,²² are now available in a full paper.²³ New information is that tyrosine is a less efficient precursor than phenylalanine, which indicates that benzene-ring hydroxylation occurs after the phenylalanine has undergone further modification. It is to be noted that incorporation of phenylalanine into tenellin (10) (benzene ring plus carbons 4, 5, and 6) involves an intramolecular rearrangement of the phenylalanine skeleton.²⁴

Tropane Alkaloids.—Hygrine [as (11)] is a proven precursor for tropane alkaloids, *e.g.* hyoscyamine (12).²⁵ It has now been shown further that (+)-hygrine (11) is much preferred over its enantiomer as a substrate for elaboration of tropane alkaloids, *e.g.* (12), in *Datura innoxia*.²⁶ On the other hand (+)-hygrine was only slightly preferred for the formation of cuscohygrine (14).

Tiglic acid is found as the esterifying acid in a number of tropane alkaloids, *e.g.* 3α -tigloyloxytropane (13). It is known to be derived from L-isoleucine²⁷ *via*

²¹ Y. Iwai, K. Kumano, and S. Omura, *Chem. and Pharm. Bull. (Japan)*, 1978, **26**, 736.

²² A. G. McInnes, D. G. Smith, J. A. Walter, L. C. Vining, and J. L. C. Wright, *J. C. S. Chem. Comm.*, 1974, 282; R. B. Herbert, in ref. 5, p. 11.

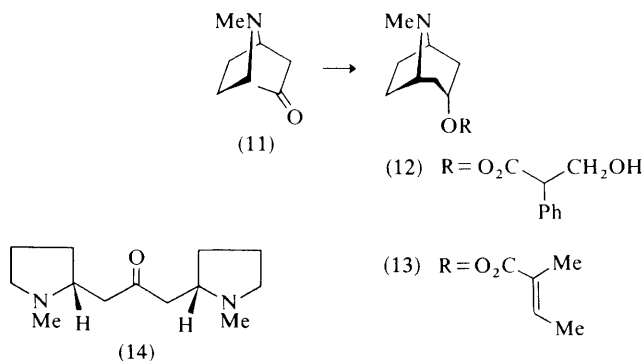
²³ J. L. C. Wright, L. C. Vining, A. G. McInnes, D. G. Smith, and J. A. Walter, *Canad. J. Biochem.*, 1977, **55**, 678.

²⁴ E. Leete, N. Kowanko, R. A. Newmark, L. C. Vining, A. G. McInnes, and J. L. C. Wright, *Tetrahedron Letters*, 1975, 4103; R. B. Herbert, in ref. 7, p. 9.

²⁵ D. G. O'Donovan and M. F. Keogh, *J. Chem. Soc. (C)*, 1969, 223; R. B. Herbert, in ref. 1, p. 9.

²⁶ B. A. McGaw and J. G. Woolley, *Phytochemistry*, 1978, **17**, 257; *J. Pharm. Pharmacol.*, 1977, **29**, 16P.

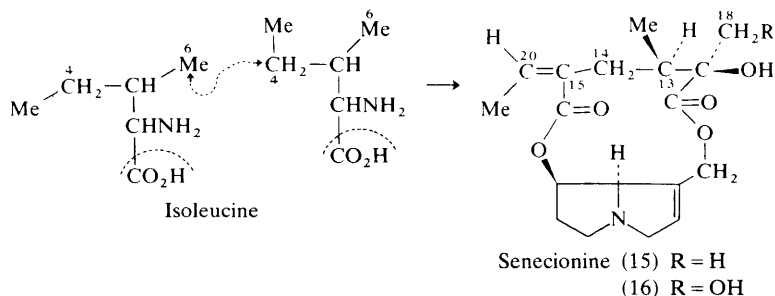
²⁷ P. J. Beresford and J. G. Woolley, *Phytochemistry*, 1974, **13**, 2143; and refs. cited; E. Leete and J. B. Murrill, *Tetrahedron Letters*, 1967, 1727.



2-methylbutanoic acid.²⁸ Alternative formation of tiglic acid in *D. meteloides* from C₁/C₂/C₃ sources, passing through 3-hydroxy-2-methylbutanoic acid, has been examined, with negative results. The hydroxy-acid was tested as an alkaloid precursor but was found not to be incorporated, whereas isoleucine was found to be incorporated in a parallel experiment.²⁹

Pyrrolizidine Alkaloids.—Two molecules of L-isoleucine are used for the biosynthesis of the senecic acid component of senecionine (15).³⁰ In order to understand how the two isoleucine fragments are linked together (C-6 of one joins to C-4 of the other), further work³¹ has been undertaken. First, 2-methyl-3-oxobutanoic acid and the five-carbon intermediates in isoleucine metabolism, *i.e.* 2-methylbutanoic acid and angelic acid (17), were examined as precursors for the senecic acid fragment of senecionine (15), with negative results [angelic acid rather than the isomeric tiglic acid, see (13), was examined since its stereochemistry is the same as that around C-15–C-20 in (15)].

Attention was then directed³¹ to determining changes in oxidation level at C-4 and C-6 of isoleucine on conversion into senecic acid. [6-³H, 6-¹⁴C]Isoleucine

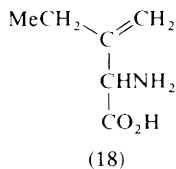
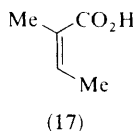


²⁸ K. Basey and J. G. Woolley, *Phytochemistry*, 1973, **12**, 2197; E. Leete, *ibid.*, p. 2203; R. B. Herbert, in ref. 5, p. 12.

²⁹ B. A. McGaw and J. G. Woolley, *Phytochemistry*, 1977, **16**, 1711.

³⁰ D. H. G. Crout, N. M. Davies, E. H. Smith, and D. Whitehouse, *J. C. S. Perkin I*, 1972, 671; R. B. Herbert, in ref. 3, p. 40.

³¹ N. M. Bale, R. Cahill, N. M. Davies, M. B. Mitchell, E. H. Smith, and D. H. G. Crout, *J. C. S. Perkin I*, 1978, 101.



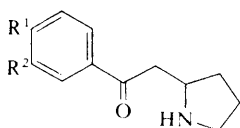
gave senecionine (15) in which the ^{14}C activity was expected to be confined to C-14 and C-18, and equally distributed between them (see ref. 30). Approximately five-sixths of the tritium label was retained, and, although the probable interference of a tritium isotope effect would distort the results, it is clear that one, probably two, hydrogen atoms from C-6 of isoleucine are retained at C-14 of (15).

Half the tritium label from L-[4- ^3H]isoleucine was retained in the formation of the necic acid fragment of retrorsine (16) (at C-13 and C-20). This limits the isoleucine C-4 oxidation level to that of a carbinol or vinylic methine group, and excludes carbonyl formation at this centre. Corroboration is thereby provided for the negative results referred to above with 2-methyl-3-oxobutanoic acid.

Following up the possibility that C-4 of isoleucine becomes part of a vinyl system, supported by mechanistic considerations, (18) was tested as a precursor. Preliminary results³¹ indicate that it is incorporated into the senecic acid fragment of senecionine (15). The significance of this, however, must await more detailed investigation.

Phenanthroindolizidine Alkaloids.—Previous results establish that the phenacylpyrrolidines (19), (20), and (21) are important precursors for phenanthroindolizidine alkaloids, e.g. tylophorinine (28), in *Tylophora asthmatica*.³² These results and a consideration of the oxygenation pattern of the *T. asthmatica* bases in relation to possible biosynthesis by phenol oxidative coupling, as well as the structure (22) for the alkaloid septicine, pointed to (26) as a key intermediate.

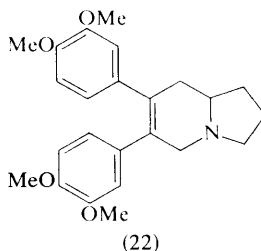
Samples of (26), (23), and (25), doubly labelled as shown (● = ^{14}C), were examined as precursors for tylophorine (30), tylophorinidine (29), and tylophorinine (28) and were found to be incorporated into each alkaloid at a similar level, indicating a close biosynthetic relationship.³³ The changes in isotope ratio were consistent with the necessary tritium loss from sites in (23) and (25) which became hydroxylated in the course of biosynthesis, and from C-6' in (26) during phenol coupling. It follows that (23), (25), and (26) are intact precursors for (28),



(19) $\text{R}^1 = \text{R}^2 = \text{H}$

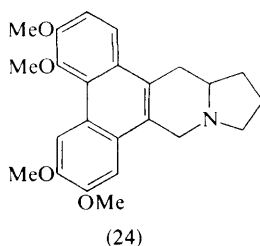
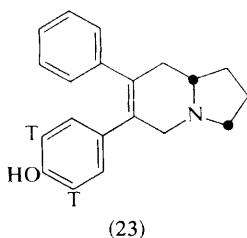
(20) $\text{R}^1 = \text{OH}, \text{R}^2 = \text{H}$

(21) $\text{R}^1 = \text{OH}, \text{R}^2 = \text{OMe}$

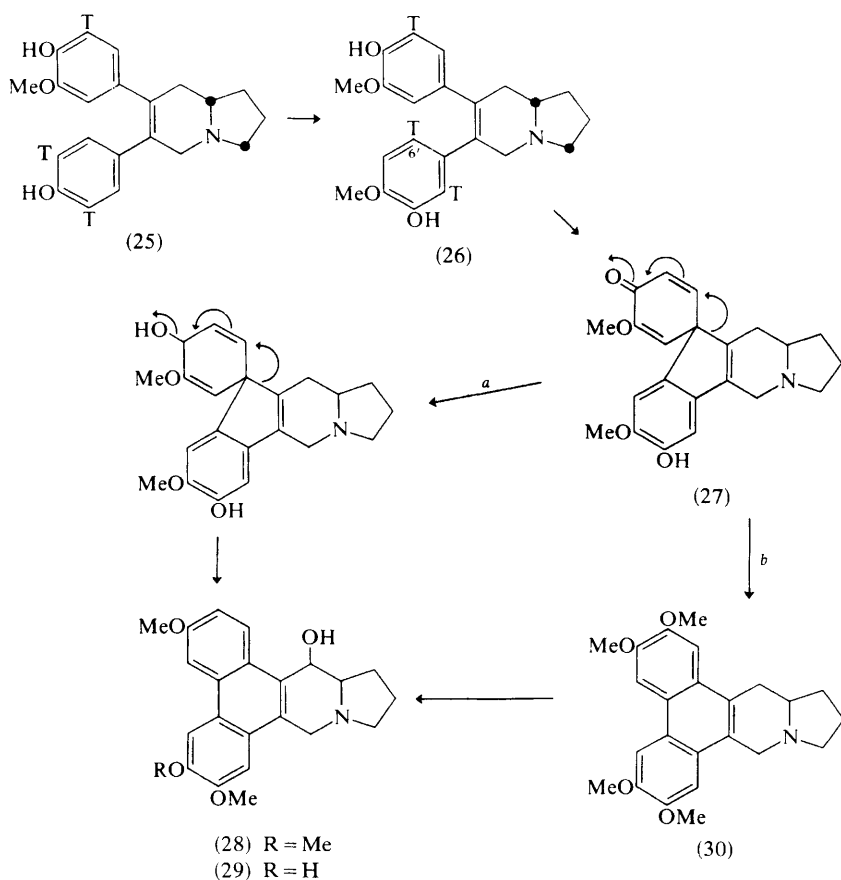


³² R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J. C. S. Chem. Comm.*, 1976, 865; R. B. Herbert, in ref. 8, p. 6.

³³ R. B. Herbert and F. B. Jackson, *J. C. S. Chem. Comm.*, 1977, 955.



(29), and (30), but the much lower incorporation observed for (23) compared to the other two compounds indicated that it was utilized along a minor pathway. The major route to (26) must be (19) → (20) → (21) → (25) → (26). The hexahydroindolizine (26) can only give (28), (29), and (30) *via* the dienone (27), alternative courses of rearrangement, *i.e.* path *b* in Scheme 1, and reduction and rearrangement (path *a*) affording the three alkaloids after further minor

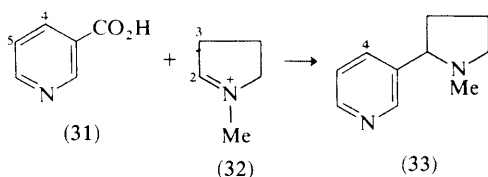


Scheme 1

modification. In the rearrangement of (27) (and the dienol derived from it), the unique opportunity, in alkaloid biosynthesis, of styryl (as against aryl) migration must be taken in affording (28) and (29), and it may well be taken in the formation of (30); isotylocrebrine (24), a minor base of *T. asthmatica*, may arise by alternative aryl shift within (27).

The base (26) can, on paper, give almost all the other known phenanthroindolizidine alkaloids. It will be of interest to see whether this is so or not.

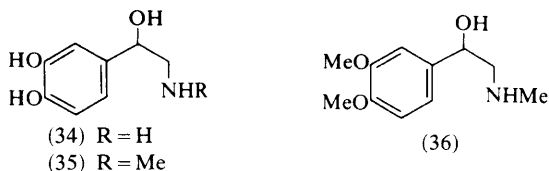
Nicotine.—Nicotine (33) is assembled in *Nicotiana* species from nicotinic acid (31) and *N*-methyl- Δ^1 -pyrroline (32).⁹ Administration to *Nicotiana* plants of 5-fluoronicotinic acid and derivatives of (32) methylated at C-2 and C-3 has resulted in the formation *in vivo* of unnatural nicotine analogues.³⁴ In contrast, 4-methylnicotinic acid has been found not to be transformed *in vivo* into 4-methylnicotine, presumably because this particular methyl group interferes sterically with the appropriate enzyme reactions involved in nicotine biosynthesis.³⁵



3 Phenethylamine and Isoquinoline Alkaloids

A stimulating review on unsolved problems in isoquinoline biosynthesis has been published.³⁶

Normacromerine.—The β -hydroxy-phenethylamines, *e.g.* normacromerine (36), are closely related biosynthetically to phenethylamines.^{37,38} Both tyrosine and tyramine serve as precursors for (36) in *Coryphantha macromeris* var. *runyonii*,³⁷ and so do norepinephrine (34)^{37,39} and epinephrine (35).³⁹ A role for these compounds as intermediates in normacromerine biosynthesis is supported by their detection as normal constituents of the plant.³⁹ A two-fold difference in the level of incorporation of (34) and (35) was interpreted as indicating separate pathways *via* these bases to (36), but firm conclusions must await further work.



³⁴ E. Leete, G. B. Bodem, and M. F. Manuel, *Phytochemistry*, 1971, **10**, 2687; M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, **93**, 7021; *ibid.*, 1970, **92**, 5528; R. B. Herbert, in ref. 3, p. 32.

³⁵ E. Leete and S. A. S. Leete, *J. Org. Chem.*, 1978, **43**, 2122.

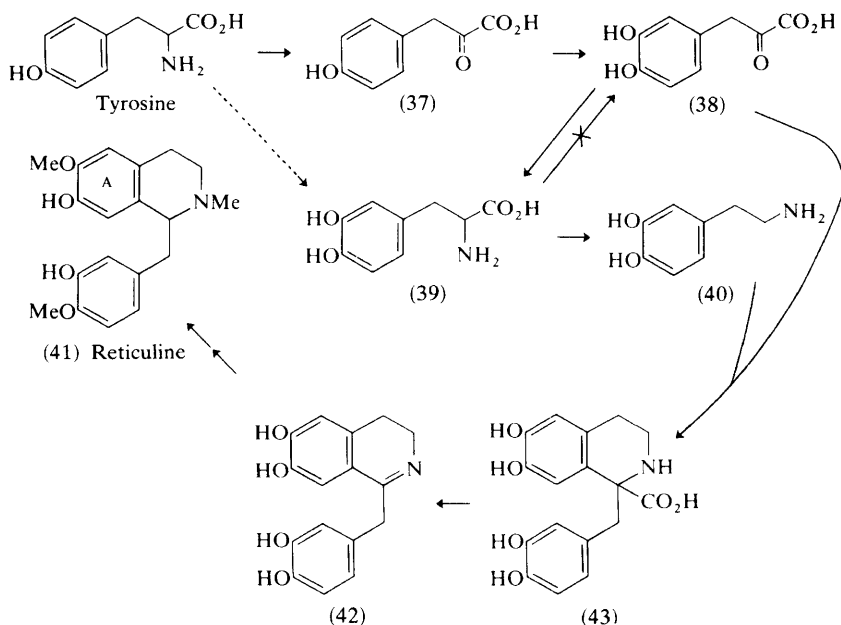
³⁶ S. F. Dyke, *Heterocycles*, 1977, **6**, 1441.

³⁷ W. J. Keller, L. A. Spitznagle, L. R. Brady, and J. L. McLaughlin, *Lloydia*, 1973, **36**, 397; R. B. Herbert, in ref. 5, p. 48.

³⁸ T. A. Wheaton and I. Stewart, *Phytochemistry*, 1969, **8**, 85.

³⁹ W. J. Keller, *Lloydia*, 1978, **41**, 37.

Reticuline.—A biosynthetic study of the important benzyloquinoline reticuline (41), published in preliminary form,⁴⁰ has appeared in full.⁴¹ Important new information is that 4-hydroxyphenylpyruvic acid (37) and 3,4-dihydroxyphenylpyruvic acid (38) are incorporated, like tyrosine, into both C₆–C₂ units of reticuline (41), in contrast to the transamination product of (38), *i.e.* dopa (39), which, curiously, is only used for the elaboration of one of these units (ring A and attached ethanamine residue), being incorporated *via* dopamine (40). Condensation of dopamine with (38) affords (43), which has been shown to be a benzyloquinoline precursor followed in sequence by (42).⁴² The new results⁴¹ confirm these findings by showing that (42) and (43) are reticuline precursors too.



Morphinan Alkaloids.—Extensive research on the biosynthesis of morphine (51) and related alkaloids in *Papaver somniferum* has allowed a detailed description of the pathway from the amino-acid tyrosine through reticuline (44), thebaine (46), and codeine (50) to morphine (51) (Scheme 2).^{9,43,44} The incorporation of (*R*)- and (*S*)-reticuline (44) occurs with extensive loss of tritium from C-1, consistent with equilibration of (44) and 1,2-dehydroreticuline (47) prior to their use in biosynthesis.⁴⁵ This is strongly supported by the observation that (47) is an

⁴⁰ S. Tewari, D. S. Bhakuni, and R. S. Kapil, *J. C. S. Chem. Comm.*, 1975, 554; R. B. Herbert, in ref. 7, p. 10.

⁴¹ D. S. Bhakuni, A. N. Singh, S. Tewari, and R. S. Kapil, *J. C. S. Perkin I*, 1977, 1662.

⁴² M. L. Wilson and C. J. Coscia, *J. Amer. Chem. Soc.*, 1975, **97**, 431; A. R. Battersby, R. C. F. Jones, and R. Kazlauskas, *Tetrahedron Letters*, 1975, 1873; R. B. Herbert, in ref. 6, p. 17.

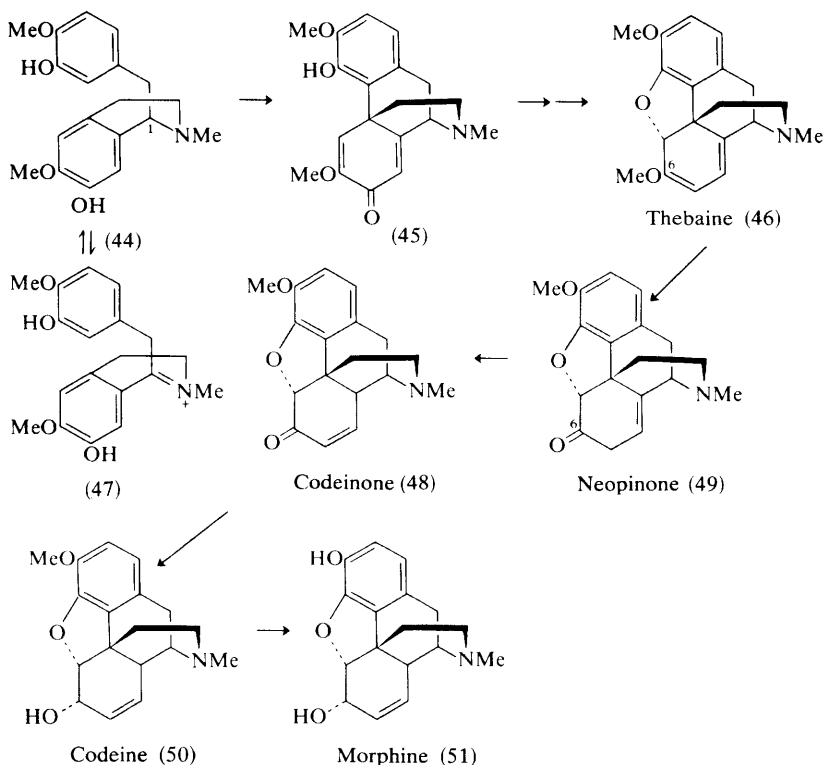
⁴³ R. B. Herbert, in ref. 3, p. 17.

⁴⁴ R. B. Herbert, in ref. 4, p. 15; in ref. 6, p. 17.

⁴⁵ A. R. Battersby, D. M. Foulkes, and R. Binks, *J. Chem. Soc.*, 1965, 3323.

alkaloid precursor,⁴⁵ a result which has been confirmed recently.⁴⁶ Further conviction that (47) must be a biosynthetic intermediate follows from its isolation by radio-isotope dilution from *P. somniferum* after assimilation of ¹⁴CO₂. The pool size of (47) appeared to be one-fifth of that of reticuline. (The use of a double-labelling technique to ensure the purity of material isolated is to be noted)⁴⁶

Biotransformation of thebaine (46) into codeine (50) (Scheme 2) occurs by way of neopinone (49) and codeinone (48),^{43,47} and involves 6-*O*-demethylation as a



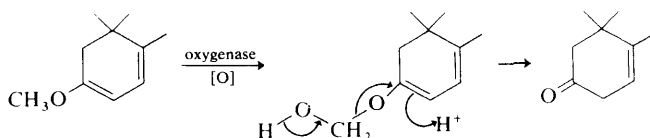
Scheme 2

first step. The mechanism of this reaction has been explored⁴⁸ with thebaine (46) labelled with an ¹⁸O-label at C-6. The codeine (50) and morphine (51) isolated in the experiment showed retention of one-third of the label. In a parallel experiment, however, codeinone (48) was shown to lose two-thirds of ¹⁸O-label from C-6 (by exchange). It follows that the conversion of thebaine (46) into neopinone occurs without loss of the oxygen at C-6. This means that a mechanism related to

⁴⁶ P. R. Borkowski, J. S. Horn, and H. Rapoport, *J. Amer. Chem. Soc.*, 1978, **100**, 276.

⁴⁷ H. I. Parker, G. Blaschke, and H. Rapoport, *J. Amer. Chem. Soc.*, 1972, **94**, 1276.

⁴⁸ J. S. Horn, A. G. Paul, and H. Rapoport, *J. Amer. Chem. Soc.*, 1978, **100**, 1895.



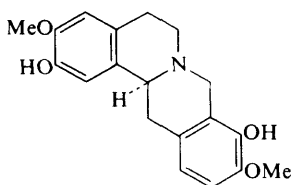
Scheme 3

the chemical hydrolysis of an enol ether does not operate, and an alternative has been tentatively suggested (Scheme 3).

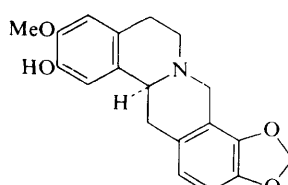
The conversion of reticuline (44) into morphinan alkaloids, which occurs with loss of tritium from C-1 in *P. somniferum* (see above),⁴⁵ has been observed also for the formation of thebaine (46) in *P. bracteatum*,⁴⁹ a plant which produces this alkaloid but not codeine or morphine. Radioactive 1,2-dehydroreticuline (47) labelled both reticuline (44) and thebaine (46), whilst radioactive reticuline again labelled thebaine (46).⁵⁰ Codeinone (48) and codeine (50) are biosynthetic intermediates between thebaine (46) and morphine (51) in *P. somniferum*,⁹ and it was shown that (48) was efficiently reduced to (50) in *P. bracteatum*.^{49,50} It is apparent that alkaloid biosynthesis in the two plants is similar, with the important difference that in *P. bracteatum* the enzymes which effect demethylation of (46) are missing, and so biosynthesis goes no further than thebaine (46).

Callus tissue of *P. somniferum* has been reported not to produce morphinan alkaloids but benzophenanthridine, protopine, and aporphine bases.⁵¹ Recent experiments⁵² have shown that (*S*)-reticuline from (*R,S*)-reticuline (41) administered to tissue cultures was transformed into (*S*)-scoulerine (52) and (*S*)-cheilanthifoline (53) [(*R*)-reticuline was recovered unchanged]. Morphine, codeine, and thebaine were not metabolized by the culture but (–)-codeinone (48) was converted stereospecifically and in high yield into (–)-codeine (50), both by the culture and by a crude enzyme preparation from it.

Other workers have obtained a callus tissue culture from the same plant which does produce morphinan alkaloids.⁵³ The production of alkaloids was found to be stimulated by tyrosine and ascorbic acid.⁵⁴



(52)



(53)

⁴⁹ E. Brochmann-Hanssen and S. W. Wunderly, *J. Pharm. Sci.*, 1978, **67**, 103.

⁵⁰ C. C. Hodges, J. S. Horn, and H. Rapoport, *Phytochemistry*, 1977, **16**, 1939.

⁵¹ T. Furuya, A. Ikuta, and K. Syono, *Phytochemistry*, 1972, **11**, 3041; A. Ikuta, K. Syono, and T. Furuya, *ibid.*, 1974, **13**, 2175.

⁵² T. Furuya, M. Nakano, and T. Yoshikawa, *Phytochemistry*, 1978, **17**, 891.

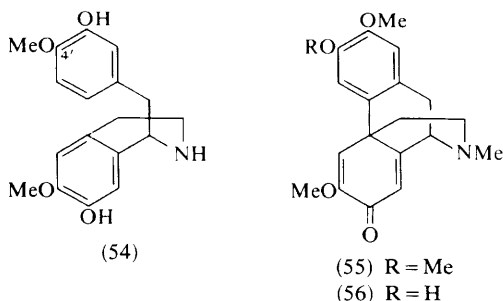
⁵³ P. Khanna and R. Khanna, *Indian J. Exp. Biol.*, 1976, **14**, 628.

⁵⁴ P. Khanna, R. Khanna, and M. Sharma, *Indian J. Exp. Biol.*, 1978, **16**, 110.

The latex of *P. somniferum* is known to metabolize morphine *in vivo*.⁵⁵ Incubation of morphine with latex *in vitro* also results in its metabolism.⁵⁶ One of the products was identified as morphine *N*-oxide, which also occurs naturally in the plant.⁵⁷

The efficient absorption through the surface of *P. bracteatum* and *P. somniferum* plants of radioactive glycine, phenylalanine, and urea, in the presence of detergent, and the appearance of radioactivity in morphine alkaloids, has been noted.⁵⁸

The morphinandienone alkaloid flavinantine (56) is biosynthesized *via* reticuline (44) in *Croton flavens*.⁵⁹ Its *O*-methyl ether, sebiferine (55), has now been shown also to arise from reticuline and nor-reticuline (54) (in *Cocculus laurifolius*);⁶⁰ two other possible isoquinoline precursors (nororientaline and laudanone) were excluded by experiment. As in the case of morphine biosynthesis (above), both (*R*)- and (*S*)-reticuline (44) were equally good precursors, suggesting that (47) is again involved in biosynthesis. It appears that the 4'-*O*-methyl group in nor-reticuline (54) is retained on formation of sebiferine, although the results are not unambiguous. A further finding is that flavinantine (56) is converted into sebiferine (55) in *C. laurifolius*.



Bisbenzylisoquinoline Alkaloids.—Until recently, the biosynthesis of only one of the many bisbenzylisoquinoline alkaloids had been studied. This was epistephanine (57), shown to derive from two units of coclaurine (59).⁶¹ New results establish that several other bisbenzylisoquinolines are variations on the coclaurine theme too.

The diastereoisomeric bases tiliacorine and tiliacorinine (61) have been found to incorporate radioactivity from tyrosine, norcoclaurine (58), coclaurine (59), and *N*-methylcoclaurine (60) in *Tiliacora racemosa*; the fully methylated isoquinoline, as to be expected, was not utilized for biosynthesis.⁶² Degradation of

⁵⁵ J. W. Fairbairn, F. Hakim, and Y. El-Kheir, *Phytochemistry*, 1974, **13**, 1133.

⁵⁶ J. W. Fairbairn, S. S. Handa, E. Gürkan, and J. D. Phillipson, *Phytochemistry*, 1978, **17**, 261.

⁵⁷ J. D. Phillipson, S. S. Handa, and S. W. El-Dabbas, *Phytochemistry*, 1976, **15**, 1297.

⁵⁸ J. K. Wold, B. S. Paulsen, and A. Nordal, *Acta Pharm. Suecica*, 1977, **14**, 403; A. Nordal, B. S. Paulsen, and J. K. Wold, *ibid.*, p. 37.

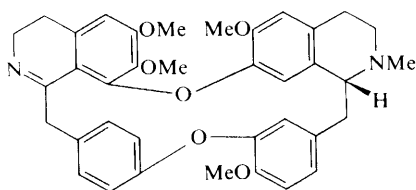
⁵⁹ K. L. Stuart and L. Graham, *Phytochemistry*, 1973, **12**, 1967; R. B. Herbert, in ref. 5, p. 17.

⁶⁰ D. S. Bhakuni, V. K. Mangla, A. N. Singh, and R. S. Kapil, *J. C. S. Perkin I*, 1978, 267.

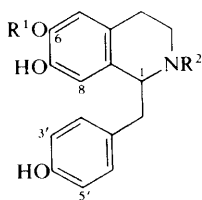
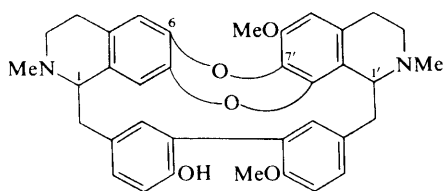
⁶¹ D. H. R. Barton, G. W. Kirby, and A. Wiechers, *J. Chem. Soc. (C)*, 1966, 2313.

⁶² D. S. Bhakuni, A. N. Singh, S. Jain, and R. S. Kapil, *J. C. S. Chem. Comm.*, 1978, 226.

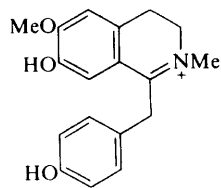
the alkaloids derived from *N*-methyl[3',5',8-³H₃]coclaurine [as (60)] established that they were formed from two units of the precursor (60). Further experiments demonstrated that this base was used with the expected loss of one of the methyl/methoxyl groups from C-6, but without loss of tritium from C-1. This latter observation has two consequences. First, the incorporation of (62) which was observed must occur through reduction to (60), and no equilibration occurs between (60) and (62) in the course of biosynthesis (*cf.*, by contrast, morphine biosynthesis above). Second, the stereochemistry at C-1 of a precursor [as (60)] will be retained on formation of tiliacrine and tiliacrinine. It was shown then that (+)-(*S*)-*N*-methylcoclaurine gave the 'left-hand' half of tiliacrine (61) whilst the (-)-(*R*)-isomer gave the 'right-hand' half. The previously unknown configurations at C-1 and C-1' of tiliacrine (61) follow as (*S*) and (*R*), respectively. A seventy-fold difference in the incorporation of the *N*-methylcoclaurine isomers into tiliacrinine (61) leads to the conclusion that both of its asymmetric centres are (*S*); and (*S*)-isomer was shown to label both halves of tiliacrinine.



(57)

(58) $R^1 = R^2 = H$ Coclaurine (59) $R^1 = Me, R^2 = H$ (60) $R^1 = R^2 = Me$ 

(61)



(62)

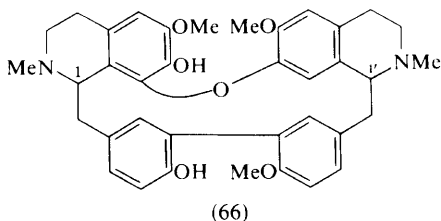
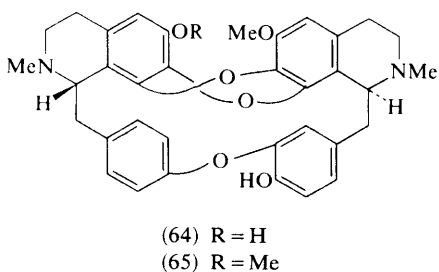
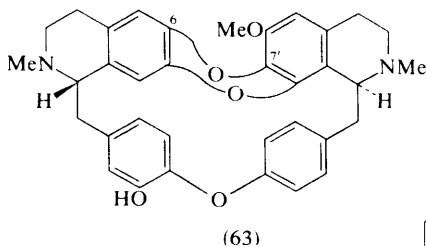
These results firmly point to the derivation of tiliacrine and tiliacrinine from *N*-methylcoclaurine (60), and it is clear that the coupling of the two units is stereospecific. A final piece of evidence confirms the biosynthetic role of (60); it was isolated in a trapping experiment after feeding radioactive tyrosine. It is thus a normal constituent of *T. racemosa*.

The biosynthesis of cocsuln (63)⁶³ and cocsulnin (64)⁶⁴ in *Cocculus laurifolius* has been found to parallel that of tiliacrine and tiliacrinine (above). Thus both are formed from two units of *N*-methylcoclaurine (60), without *N*-demethylation [coclaurine (59) and norcoclaurine (58) were also incorporated; an incorporation

⁶³ D. S. Bhakuni, V. M. Labroo, A. N. Singh, and R. S. Kapil, *J. C. S. Perkin I*, 1978, 121.

⁶⁴ D. S. Bhakuni, S. Jain, and A. N. Singh, *J. C. S. Perkin I*, 1978, 380.

of (62) and of tyrosine but not of *N*-methylnorcoclaurine into (63) was also observed]. Tritium at C-1 of (60) is retained on alkaloid formation, and both (63) and (64) derive specifically from (*S*)-*N*-methylcoclaurine [as (60)], which has also been found to occur naturally in *C. laurifolius*.⁶⁵ The incorporation of *O*-methylcocsulinin (65) into cocsulinin (64) established that 6-*O*-demethylation is probably the terminal step of biosynthesis.



Tiliagenine (66) has also been shown to derive from *N*-methylcoclaurine (60), the (+)-(*S*)-isomer providing one half of the molecule, with the other arising from (-)-(*R*)-*N*-methylcoclaurine; the configurations at C-1 and C-1' could be deduced as (*S*) and (*R*), respectively.⁶⁶

The formation of (57), (61), (63), (64), and (66) from the coclaurine (59) skeleton can be rationalized in terms of phenol oxidative coupling.⁶⁷ The coupling is seen at its simplest in (57) and (66), where two such reactions must occur. The formation of (64) is only slightly more complex, formally involving three such coupling steps. In the case of (61) and (63), coupling results in loss of an oxygen function from C-6 (or C-7'). These losses can be interpreted in terms of a radical^{67,68} or cationic mechanism.^{68,69} As a step towards understanding the

⁶⁵ J. Kunitomo, *J. Pharm. Soc. Japan*, 1961, **81**, 1261.

⁶⁶ D. S. Bhakuni and A. N. Singh, *Tetrahedron*, 1978, **34**, 1409.

⁶⁷ D. H. R. Barton, in 'Festschrift Dr. A. Stoll', Birkhäuser, Basel, 1957, p. 117.

⁶⁸ C. W. Thornber, *Phytochemistry*, 1970, **9**, 157.

⁶⁹ A. R. Battersby, in 'Oxidative Coupling of Phenols', ed. A. R. Battersby and W. I. Taylor, Dekker, New York, 1967, p. 119.

mechanism of coupling, as well as the late stages of bisbenzylisoquinoline biosynthesis, it will be of considerable interest to examine various bisbenzylisoquinolines with one link, rather than two or three, as precursors for compounds like (57), (61), (63), (64), and (66).

Protoberberine and Related Alkaloids.—Recent extensive work has allowed detailed description of the biosynthesis of protoberberine alkaloids, e.g. tetrahydrocoptisine (67), and bases derived from them.⁷⁰ Results of a study on the interrelationships of *Corydalis incisa* alkaloids provide supplementary information, particularly in regard to the intermediacy of compounds of type (69).⁷¹

Radioactive tetrahydrocorysamine (68) was found to label corynoline (71), acetylcorynoline (72), and corydalic acid methyl ester (74) specifically, and radioactive tetrahydrocoptisine (67) specifically labelled the same alkaloids plus corydamine (73); corynoline (71) was not incorporated into (74). These results are consistent with the pathway outlined in Scheme 4, in which (69) and (70) are logical intermediates. Their intermediacy is further supported by the observation that (75), labelled as shown, gave radioactive corynoline (71) in which the residual tritium label was located at C-6.

The conversion of reticuline (41) into protoberberine alkaloids (coreximine and scoulerine), a morphinandienone alkaloid (pallidine), and an aporphine alkaloid (isoboldine) by rat-liver enzyme has been reported.⁷²

Aporphine Alkaloids.—As discussed previously, the formation of the aporphine skeleton [as (76)] from that of a benzylisoquinoline [as (77)], although simple, may take one of a number of courses, and the methylation pattern of the aporphine does not provide a reliable guide to the particular phenol oxidative coupling reaction involved.^{9,73} Thus, a number of benzylisoquinolines may have to be tested as precursors for a particular aporphine. In the case of isocorydine (76), in *Annona squamosa*, nororientaline (77), norprotosinomenine (78), norlaudanidine (79), and reticuline (41) were tested.⁷⁴ Of these only reticuline was significantly utilized for biosynthesis. It could, moreover, be isolated by isotope dilution from the plant after feeding radioactive tyrosine. The evidence clearly points then to reticuline (41) being an intermediate in the biosynthesis of isocorydine (76), the conversion of (41) into (76) occurring by simple *ortho-ortho* phenol oxidative coupling followed by *O*-methylation.

The configuration of (76) at C-1 is (*S*), indicating its derivation from (*S*)-reticuline. This was confirmed in a feeding experiment with the enantiomers of nor-reticuline (80).

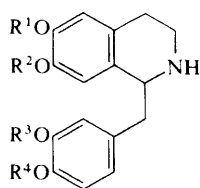
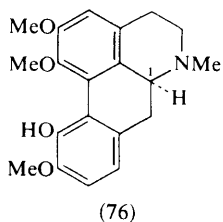
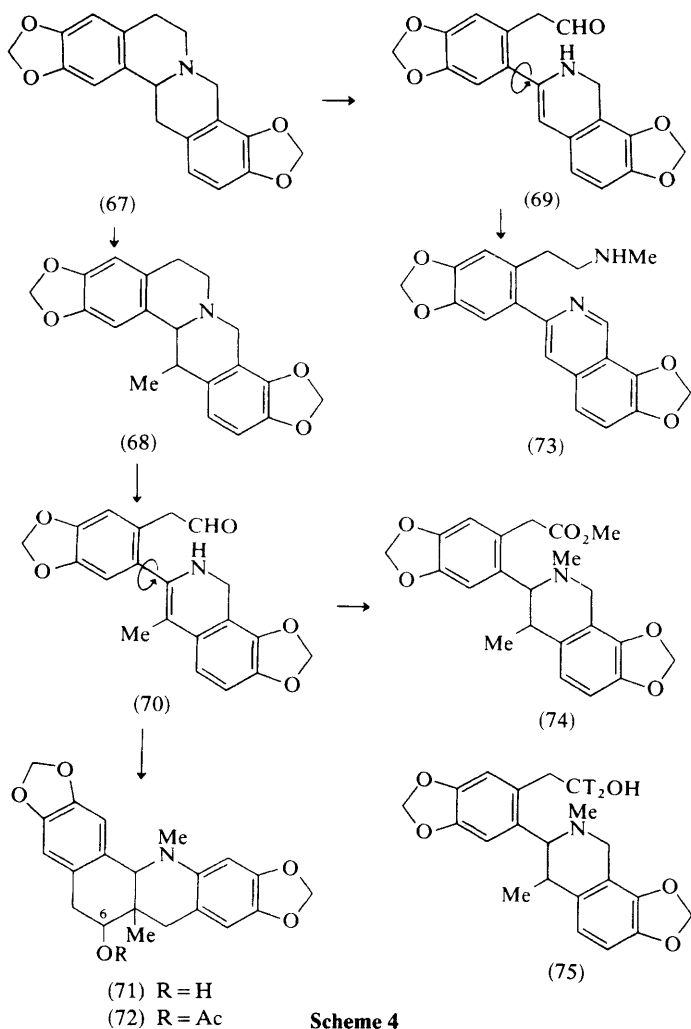
⁷⁰ A. R. Battersby, R. J. Francis, M. Hirst, E. A. Ruveda, and J. Staunton, *J. C. S. Perkin I*, 1975, 1140; A. R. Battersby, J. Staunton, H. R. Wiltshire, R. J. Francis, and R. Southgate, *ibid.*, p. 1147; A. R. Battersby, J. Staunton, H. R. Wiltshire, B. J. Bircher, and C. Fuganti, *J. C. S. Perkin I*, 1975, 1162; C. Tani and K. Tagahara, *Chem. and Pharm. Bull. (Japan)*, 1974, **22**, 2457; N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *ibid.*, 1976, **24**, 2859; G. Blaschke, *Arch. Pharm.*, 1970, **303**, 358; H. L. Holland, M. Castillo, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1974, **52**, 2818; R. B. Herbert, in ref. 6, pp. 22, 23; in ref. 7, p. 12; in ref. 8, p. 14.

⁷¹ A. Yagi, G. Nonaka, S. Nakayama, and I. Nishioka, *Phytochemistry*, 1977, **16**, 1197.

⁷² T. Kametani, Y. Ohta, M. Takemura, M. Ihara, and K. Fukumoto, *Bio-org. Chem.*, 1977, **6**, 249.

⁷³ R. B. Herbert, in ref. 6, p. 19; in ref. 5, p. 15; in ref. 4, p. 17; in ref. 1, p. 19; J. Staunton, in ref. 2, p. 10.

⁷⁴ O. Prakash, D. S. Bhakuni, and R. S. Kapil, *J. C. S. Perkin I*, 1978, 622.



- (77) $R^1 = R^3 = \text{Me}, R^2 = R^4 = \text{H}$
 (78) $R^1 = R^3 = \text{H}, R^2 = R^4 = \text{Me}$
 (79) $R^1 = R^2 = R^4 = \text{Me}, R^3 = \text{H}$
 (80) $R^2 = R^3 = \text{H}, R^1 = R^4 = \text{Me}$

Erythrina Alkaloids.—Isococculidine (88) is unusual among *Erythrina* alkaloids in lacking an oxygen function at C-16. Nonetheless, it is formed, like other *Erythrina* bases, from (*S*)-norprotosinomenine (81), and the pathway must parallel that of the normal bases (Scheme 5).^{75,76} (*S*)-Norprotosinomenine (81) again serves as an intact and efficient precursor for cocculidine (89) in the same plant [norlaudanosoline (92) was also incorporated, but not protosinomenine (91), nor-reticuline (80), nororientaline (77), or (93)].⁷⁷ It is to be noted that the bioconversion of (81) into cocculidine (89) involves retention of both methoxy-groups and the C-1 proton.

In the formulation of (88) and (89), the point at which loss occurs of the oxygen atom, expected to be at C-16, is of considerable interest and relevance to the biosynthesis of *Erythrina* alkaloids in general. Consideration of the pathway deduced for bases like erythraline (84), as shown in Scheme 5,^{76,78,79} indicates two points at which elimination of the oxygen atom could occur. First by reduction of (82) to (86) and elimination to give (87),⁷⁵ which could not, however, cyclize in a way similar to that proposed for (83) *via* (85) (Scheme 5).⁷⁶ Second, oxygen loss may occur by cyclization on (94), which is simply a lower oxidation-equivalent of (85).⁷⁶ Distinction between these possibilities can be made by feeding experiments with (83) and (87), and by noting whether label on either of the *O*-methyl groups of (81) becomes equally spread over the *O*-methyl groups of (88) and (89), as it does in the biosynthesis of erythraline because of passage *via* the symmetrical intermediate (83)⁷⁹ (there are no symmetrical intermediates in the other pathway).

The relationships of *C. laurifolius* alkaloids were studied, with the following results: (88) was reversibly converted into (89), and a similar relationship was found for (89) and (90);⁷⁷ the retention of label from the 7-methoxy-group of (81) in (89) indicates that (89) precedes (90) in biosynthesis.

4 Mesembrine Alkaloids

The octahydroindole moiety of these alkaloids, *e.g.* mesembrenol (101), is known to arise from tyrosine whereas the aryl residue has a separate genesis in phenylalanine.⁸⁰ Utilization of phenylalanine in alkaloid biosynthesis usually occurs *via* cinnamic acid and its derivatives. This has proved true for mesembrine bases too, efficient incorporations of cinnamic acid (95) and its 4'-hydroxy-derivative (96) being observed.⁸¹ A series of conventional feeding, as well as trapping and dilution, experiments established that alkaloid formation may occur *via* phloretic

⁷⁵ D. S. Bhakuni, A. N. Singh, and R. S. Kapil, *J. C. S. Chem. Comm.*, 1977, 211.

⁷⁶ R. B. Herbert, in ref. 8, p. 10.

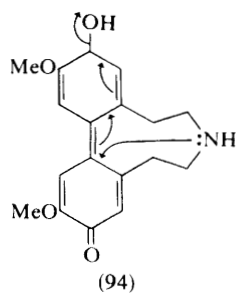
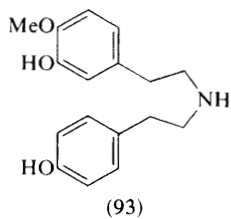
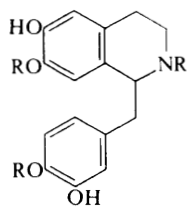
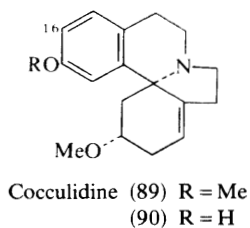
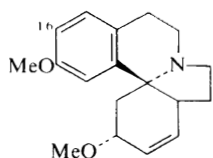
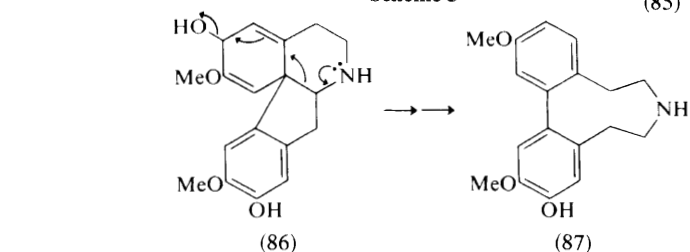
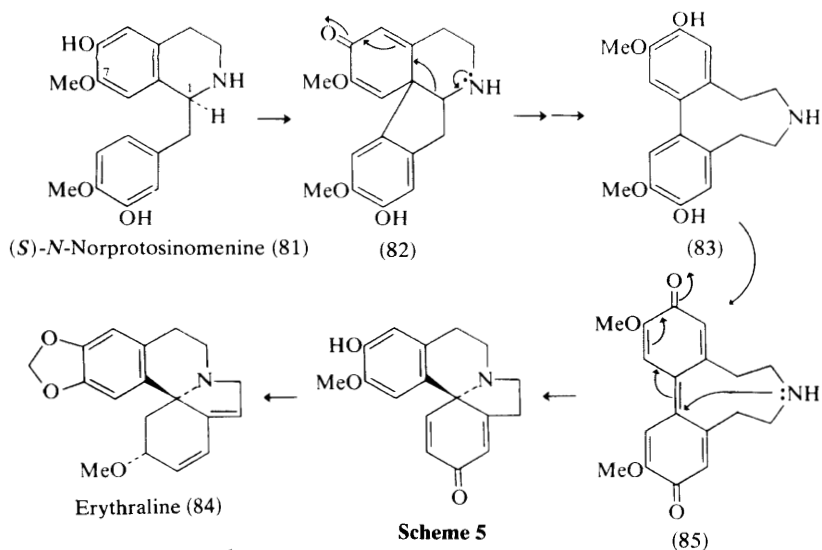
⁷⁷ D. S. Bhakuni and A. N. Singh, *J. C. S. Perkin I*, 1978, 618.

⁷⁸ D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *J. Chem. Soc. (C)*, 1968, 1529; D. H. R. Barton, R. D. Bracho, C. J. Potter, and D. A. Widdowson, *ibid.*, 1970, 2278; R. B. Herbert, in ref. 5, p. 24; in ref. 6, p. 25.

⁷⁹ D. H. R. Barton, B. B. Boar, and D. A. Widdowson, *J. Chem. Soc. (C)*, 1970, 1213; R. B. Herbert, in ref. 1, p. 22.

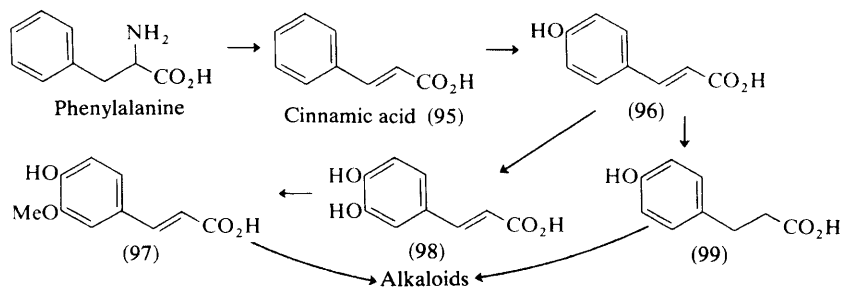
⁸⁰ P. W. Jeffs, W. C. Archie, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, 1971, **93**, 3752; P. W. Jeffs, H. F. Campbell, D. S. Farrier, G. Ganguli, N. H. Martin, and G. Molina, *Phytochemistry*, 1974, **13**, 933; P. W. Jeffs, D. B. Johnson, N. H. Martin, and B. S. Rauckman, *J. C. S. Chem. Comm.*, 1976, 82; R. B. Herbert, in ref. 3, p. 23; in ref. 5, p. 22; in ref. 7, p. 23.

⁸¹ P. W. Jeffs, J. M. Karle, and N. H. Martin, *Phytochemistry*, 1978, **17**, 719.



acid (99), and to lesser extent *via* (98) and ferulic acid (97) (see Scheme 6). It was observed additionally that 4'-hydroxycinnamyl alcohol was a good mesembrenol precursor, but 4'-hydroxycinnamaldehyde and 4'-hydroxydihydrocinnamyl alcohol were not.

A major pathway to mesembrenol (101) *via* (95), (96), and (99) with further hydroxylation at a late stage of biosynthesis is supported by the observation that sceletenone (100), which has a singly oxygenated aromatic ring, is an efficient precursor for mesembrenol (101). Details of this work, previously reported in preliminary form,⁸² are now available in full.⁸¹



5 Alkaloids Derived from Tryptophan

Terpenoid Indole Alkaloids.—Recent publication concerned with the incorporation of vincoside (109) and strictosidine (104) into terpenoid indole alkaloids is clearly most significant, although it is about but a small part of the biosynthesis of these alkaloids, and must be seen in this perspective.

Extensive research on the elaboration of terpenoid indole alkaloids in whole plants has allowed a fairly clear picture of their biosynthesis to be drawn.^{9,83-86} Results obtained using tissue cultures have provided useful supplementary

⁸² P. W. Jeffs and J. M. Karle, *J. C. S. Chem. Comm.*, 1977, 60; R. B. Herbert, in ref. 8, p. 21.

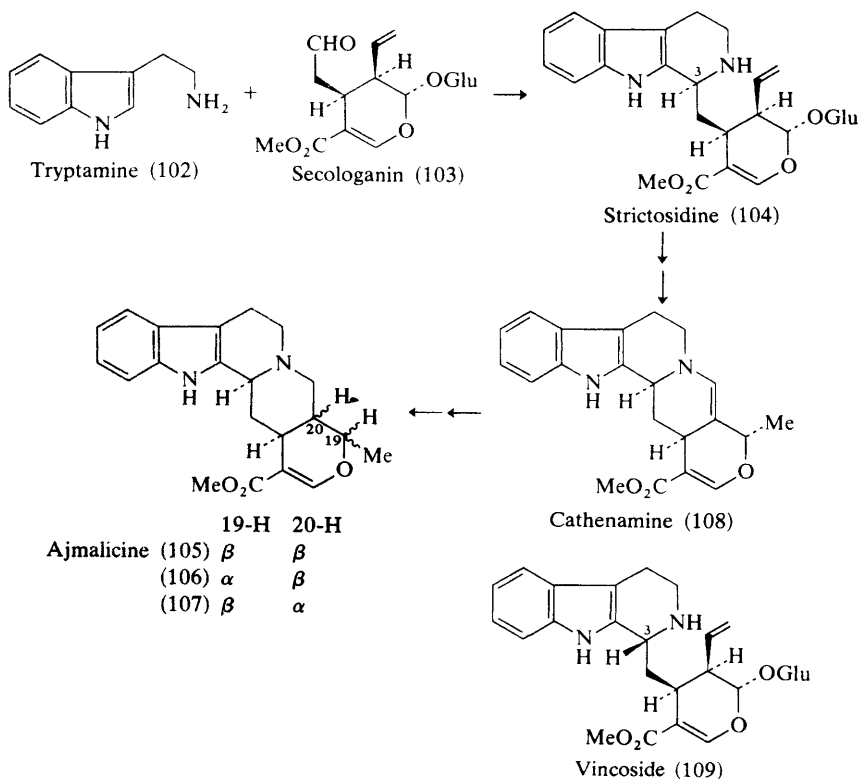
⁸³ G. A. Cordell, *Lloydia*, 1974, **37**, 219.

⁸⁴ A. R. Battersby, in ref. 1, p. 31.

⁸⁵ J. Staunton, in ref. 2, p. 1; R. B. Herbert, in ref. 3, p. 1; in ref. 4, p. 30; in ref. 5, p. 25; in ref. 6, p. 33; in ref. 7, p. 22.

⁸⁶ R. B. Herbert in ref. 8, p. 27.

evidence.⁸⁶⁻⁸⁸ In particular, it has been deduced, using a crude cell-free system from *Catharanthus roseus*, that cathenamine (108) is an important early intermediate in biosynthesis.^{86,88} Earlier intermediates are known^{9,83,84} to be secologanin (103) and tryptamine (102). Chemical condensation of these compounds affords vincoside (109) and strictosidine (isovincoside) (104), which are epimeric at C-3. It has been thought that vincoside (109) with the 3 β (*R*) stereochemistry is the precursor for indole alkaloids.⁸⁹ This has been puzzling because the first terpenoid indole bases to be formed have the 3 α configuration. The recent publications have been concerned with the solution of this puzzle.



When [2-¹⁴C]tryptamine and secologanin (103) were incubated with a crude enzyme preparation from a *Catharanthus* cell culture, in the presence of a β -glucosidase inhibitor or at low pH, strictosidine (104), and *not* vincoside (109), was formed; the reaction was clearly enzyme-dependent.^{90,91} This material was

⁸⁷ A. I. Scott and S.-L. Lee, *J. Amer. Chem. Soc.*, 1975, **97**, 6906; A. I. Scott, S.-L. Lee, and W. Wan, *Biochem. Biophys. Res. Comm.*, 1977, **75**, 1004.

⁸⁸ J. Stöckigt, J. Treimer, and M. H. Zenk, *F. E. B. S. Letters*, 1976, **70**, 267; J. Stöckigt, H. P. Husson, C. Kan-Fan, and M. H. Zenk, *J. C. S. Chem. Comm.*, 1977, 164.

⁸⁹ A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc. (C)*, 1969, 1193.

⁹⁰ J. Stöckigt and M. H. Zenk, *F. E. B. S. Letters*, 1977, **79**, 233.

⁹¹ J. Stöckigt and M. H. Zenk, *J. C. S. Chem. Comm.*, 1977, 646.

then converted enzymically into ajmalicine (105), 19-*epi*-ajmalicine (106), and tetrahydroalstonine (107), in the presence of NADPH. In the absence of NADPH, cathenamine (108) was formed as before.⁸⁸

Strictosidine (104) is produced by the plant *Rhazya stricta*.⁹² A crude enzyme preparation from the plant was used to produce labelled strictosidine; this, when incubated with *Catharanthus* enzyme, again gave the three alkaloids (105), (106), and (107).⁹⁰ Cell-free preparations of cell-suspension cultures of *Amsonia tabernaemontana*, *Rhazya orientalis*, and *Vinca minor* were also observed to convert (102) plus (103) into strictosidine (104) with fair efficiency; the formation of vincoside (109) was never observed.⁹¹

It is quite clear from this evidence that the previous observation about vincoside/strictosidine incorporation is wrong, and strictosidine (104) with the 3 α (*S*) configuration is the correct alkaloid precursor. This has been confirmed for whole-plant biosynthesis.⁹¹ Doubly labelled strictosidine (104) was incorporated in *C. roseus* into representatives of the three main groups of alkaloids, *i.e.* ajmalicine (105), serpentine (110), vindoline (111), and catharanthine (112), without significant change of isotope ratio, indicating that there is intact incorporation; vincoside (109) was not utilized for alkaloid biosynthesis. Further results^{93,94} demonstrate the universal intermediacy of strictosidine in the biosynthesis of terpenoid indole alkaloids with the 3 α -configuration and also those with the 3 β arrangement in taxonomically very different plant families. It was found to be a precursor for α -yohimbine (113) and reserpiline (114) in *Rauwolfia canescens* and for mitragynine (115) and speciociliatine (116) in *Mitragyna speciosa*; tritium at C-3 of (104) was retained on formation of the 3 α -alkaloids but lost on formation of those with the 3 β -configuration.⁹³ Again, vincoside was not used in biosynthesis, nor was it used in the formation of alkaloids in *Amsonia*, *Cinchona*, *Rhazya*, *Stemmadenia*, *Uncaria*, and *Vinca* species, where, as before, incorporation of strictosidine was observed.⁹⁴

Independent confirmation puts the above findings beyond doubt.⁹⁵⁻⁹⁷ Satisfying incorporations have been recorded of [*Ar*-³H]strictosidine into tetrahydroalstonine (107), ajmalicine (105), catharanthine (112), and vindoline (111) in *C. roseus* (syn. *Vinca rosea*).⁹⁶ Good, intact incorporations have been reported too of strictosidine (104), but not of vincoside (109), into ajmalicine (105), 19-*epi*-ajmalicine (106), and tetrahydroalstonine (107) in *C. roseus* callus cultures, and into ajmalicine (105), vindoline (111), and catharanthine (112) in *C. roseus* shoots.⁹⁷

Camptothecin (117) had previously been deduced to arise from strictosidine (104), not vincoside,⁹⁸ and this has been confirmed in feeding experiments with strictosidine and vincoside.⁹⁹ Thus, the relationship between camptothecin and terpenoid indole alkaloids is now one step closer than originally thought. Further

⁹² G. N. Smith, *Chem. Comm.*, 1968, 912.

⁹³ M. Rueffer, N. Nagakura, and M. H. Zenk, *Tetrahedron Letters*, 1978, 1593.

⁹⁴ N. Nagakura, M. Rueffer, and M. H. Zenk, manuscript in preparation; quoted in ref. 93.

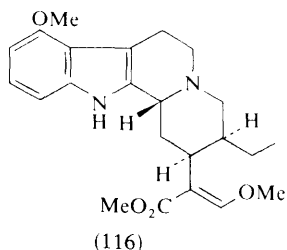
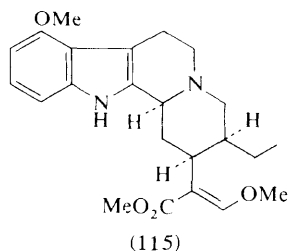
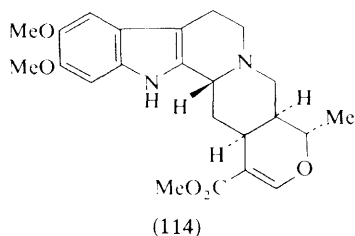
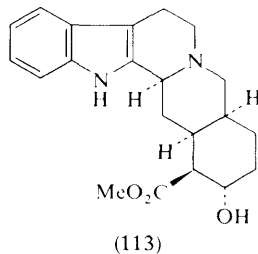
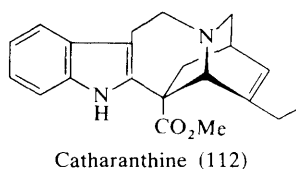
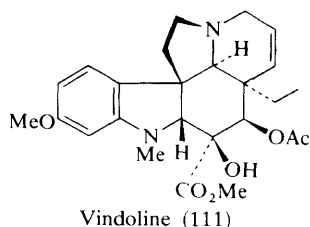
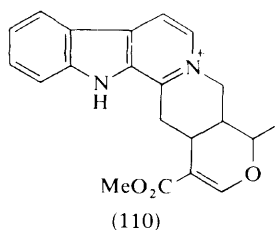
⁹⁵ A. R. Battersby, personal communication.

⁹⁶ R. T. Brown, J. Leonard, and S. K. Sleight, *Phytochemistry*, 1978, **17**, 899.

⁹⁷ A. I. Scott, S. L. Lee, P. de Capite, M. G. Culver, and C. R. Hutchinson, *Heterocycles*, 1977, **7**, 979.

⁹⁸ C. R. Hutchinson, A. H. Heckendorf, P. E. Daddona, E. Hagaman, and E. Wenkert, *J. Amer. Chem. Soc.*, 1974, **96**, 5609; R. B. Herbert, in ref. 6, p. 36; in ref. 7, p. 21.

⁹⁹ A. H. Heckendorf and C. R. Hutchinson, *Tetrahedron Letters*, 1977, 4153.

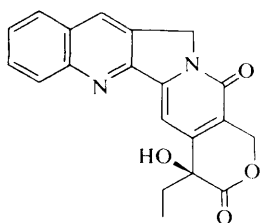


new detail is that the aglycone (119), derived from the lactam (118), which is a known precursor for camptothecin,⁹⁸ is not involved in biosynthesis.⁹⁹

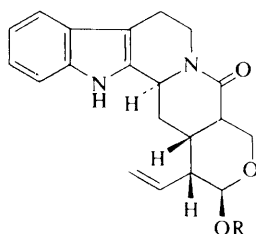
The *Ipecac* alkaloids, e.g. emetine (121), are reported to have their genesis through desacetylipecoside (120).¹⁰⁰ This biogenesis results in the inversion of configuration at C-5 of (120) and, in the light of the discussion above on terpenoid indole bases, is being re-examined.⁹⁵ [The stereochemistry of (120) follows unambiguously from an *X*-ray analysis of *OO*-dimethylipecoside.¹⁰¹]

¹⁰⁰ A. R. Battersby and R. J. Parry, *Chem. Comm.*, 1971, 901; J. Staunton, in ref. 2, p. 6.

¹⁰¹ O. Kennard, P. J. Roberts, N. W. Isaacs, F. H. Allen, W. D. S. Motherwell, K. H. Gibson, and A. R. Battersby, *Chem. Comm.*, 1971, 899.

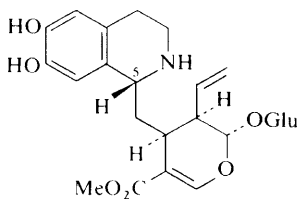


Camptothecin (117)

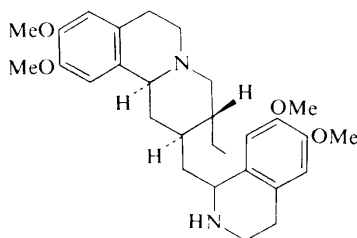


(118) R = Glu

(119) R = H



(120)



(121)

Further work with callus tissue and cell-suspension cultures has been reported. The soluble enzyme system from *C. roseus* cell-suspension cultures, referred to above,^{88,90,91} has been further characterized.¹⁰² The enzymic synthesis was found to proceed optimally at pH 6.5, and a β -glucosidase is involved in alkaloid formation (see above). The enzyme system catalysed the formation of unnatural ajmalicine analogues from ring-substituted tryptamines, and secologanic acid (but not loganin or loganic acid) could substitute for secologanin (103).¹⁰² Of wide interest, in this study, was the use of a radio-immunoassay method for following the enzymic formation of ajmalicine (105) and its isomers, sensitively and quantitatively.

Callus tissue cultures of *C. roseus* have been used to study the metabolism of three terpenoid indole bases.¹⁰³ Vindoline (111) gave desacetylvindoline and dihydrovindoline, catharanthine (112) was not metabolized, and vincal leukoblastine (122) gave three unidentified metabolites.

Leaves of mature *C. roseus* have been made to yield a cell-free system which catalyses the formation of vindoline (111).¹⁰⁴ Radioactivity was incorporated into this alkaloid from [2-¹⁴C]tryptamine and *S*-adenosyl[*Me*-¹⁴C]methionine.

Although stemmadenine (123) has been shown to be a precursor for vindoline (111), *inter alia*, in whole plants,¹⁰⁵ other evidence argues against its being an intermediate in biosynthesis.¹⁰⁶ The failure of [³H]stemmadenine to label vindoline (111) in the *C. roseus* cell-free system supports this argument.¹⁰⁴

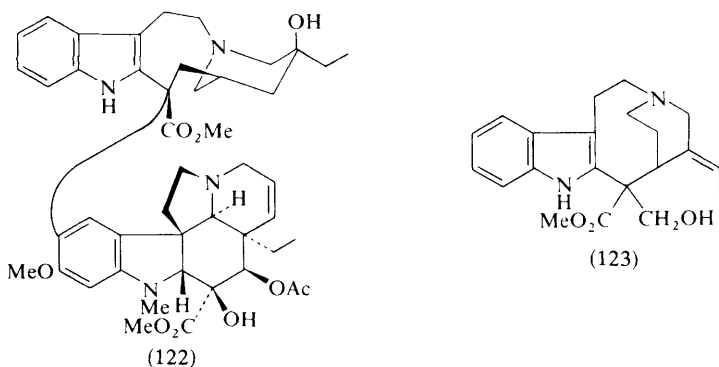
¹⁰² J. F. Treimer and M. H. Zenk, *Phytochemistry*, 1978, **17**, 227.

¹⁰³ D. P. Carew and R. J. Krueger, *Phytochemistry*, 1977, **16**, 1461.

¹⁰⁴ K. L. Stuart, J. P. Kutney, T. Honda, N. G. Lewis, and B. R. Worth, *Heterocycles*, 1978, **9**, 647.

¹⁰⁵ A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 948; A. R. Battersby in ref. 1, p. 43.

¹⁰⁶ A. I. Scott, P. B. Reichardt, M. B. Slaytor, and J. G. Sweeney, *Bio-org. Chem.*, 1971, **1**, 157; R. B. Herbert, in ref. 3, p. 1.



Earlier results¹⁰⁷ in a study of the clinically important dimeric alkaloid vincaleukoblastine (122) had provided some evidence on the course of biosynthesis. The obvious correlation of (122) with vindoline (111) and catharanthine (112) has not been supported, owing to insignificant incorporations into (122) of the two monomeric bases. Using apical cuttings of *C. roseus*, however, where catabolic turnover of (111) and (112) is lower than in intact plants, the specific incorporation of (111) and (112) was observed.¹⁰⁸ The level of incorporation was low, thus casting some doubt on whether vincaleukoblastine (122) is formed by dimerization of (111) and (112).

The terpenoid fragment of alkaloids like ajmalicine (105), which is represented by (103), have an orthodox genesis from mevalonate.^{9,84} Mevalonic acid is derived in living systems from acetate, but acetate has never been observed as a specific precursor for terpenoid indole alkaloids.^{109–111} Indeed, in *Rauwolfia serpentina*, β -sitosterol was specifically labelled by acetate but alkaloid was not.^{110,111} This has stimulated a search for mevalonate sources other than acetate, and some evidence has been obtained for these and for the *Ipecac* alkaloids that glycine can be such a source.^{111–113} Recent exploration of leucine as a possible source has given negative results,¹¹⁴ in agreement with earlier findings.^{111,112,115}

The alkaloids represented by ellipticine (124) and apparicine (125) are manifestly most interesting variations on the terpenoid indole theme. Regrettably little has been deduced about their biosynthesis, this being in part attributable to low incorporations of precursors.¹¹⁶ Low incorporation has also been found in a new study in *Ochrosia* species of tryptophan into ellipticine (124), although a

¹⁰⁷ P. E. Daddona and C. R. Hutchinson, *J. Amer. Chem. Soc.*, 1974, **96**, 6806; R. B. Herbert, in ref. 6, p. 35.

¹⁰⁸ S. B. Hassam and C. R. Hutchinson, *Tetrahedron Letters*, 1978, 1681.

¹⁰⁹ E. Leete, A. Ahmad, and I. Kompis, *J. Amer. Chem. Soc.*, 1965, **87**, 4168.

¹¹⁰ A. R. Battersby and G. V. Parry, *Tetrahedron Letters*, 1964, 787.

¹¹¹ A. K. Garg and J. R. Gear, *Phytochemistry*, 1972, **11**, 689; R. B. Herbert, in ref. 3, p. 4.

¹¹² D. Gröger, W. Maier, and P. Simchen, *Experientia*, 1970, **26**, 820.

¹¹³ J. P. Kutney, J. F. Beck, V. R. Nelson, K. L. Stuart, and A. K. Bose, *J. Amer. Chem. Soc.*, 1970, **92**, 2174; W. Maier and D. Gröger, *Arch. Pharm.*, 1971, **304**, 351.

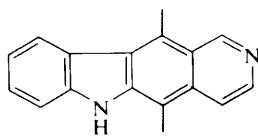
¹¹⁴ D. C. Wigfield and B. P. Wen, *Bio-org. Chem.*, 1977, **6**, 511.

¹¹⁵ D. C. Wigfield, B. Lem, and V. Srinivasen, *Tetrahedron Letters*, 1972, 2659.

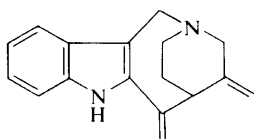
¹¹⁶ J. P. Kutney, *Heterocycles*, 1976, **4**, 169; *ibid.*, p. 429; *ibid.*, 1977, **7**, 593.

good incorporation was recorded into apparicine (125); no incorporation of mevalonate was observed into either alkaloid.¹¹⁷

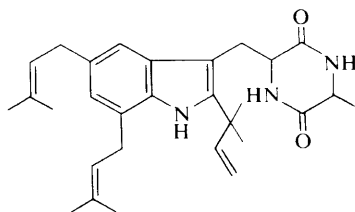
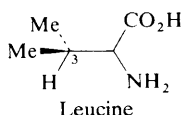
Echinulin.—The mould metabolite echinulin (126) and its relatives have been the subject of some elegant biosynthetic experiments leading to a clear picture of the way they are elaborated.¹¹⁸ Echinulin has recently been used as a monitor for the stereochemistry involved in the catabolism of leucine to mevalonic acid;¹¹⁹ label from the leucine was expected at specific sites in the mevalonate-derived isoprenoid units of (126). In the event, extensive scrambling of label was observed from the two enantiomers of leucine chirally labelled with ¹³C at C-3. Some selectivity in the labelling was detected, which was interpreted as indicating that carriage of label from leucine to mevalonate had occurred *via* acetoacetate.



(124)



(125)



(126)

Streptonigrin.—Streptonigrin, a metabolite of *Streptomyces flocculus*, with the unusual structure (128), has anti-cancer properties¹²⁰ and is the most potent bone-marrow-depressant drug known.¹²¹ It is established that the four methyl groups arise from methionine.¹²² The sequence of methylation and the origin of part of the ring system have been the subject of recent investigations.^{123,124} The clever use¹²⁴ of ¹³C-¹⁵N n.m.r. coupling deserves wider application in the study of nitrogen-containing metabolites.

[3-¹⁴C]Tryptophan [as (127)] was efficiently incorporated into streptonigrin, the location of all the activity at C-3¹ indicating that rings C and D, but not A and B, originate from this amino-acid¹²³ (the origin of rings A and B is not yet known).

¹¹⁷ G. Kunesch, C. Poupat, N. van Bac, G. Henry, T. Sévenet, and P. Potier, *Compt. rend.*, 1977, **285**, C, 89.

¹¹⁸ R. B. Herbert, in ref. 6, p. 29; in ref. 4, p. 29; in ref. 7, p. 19.

¹¹⁹ R. Cardillo, C. Fuganti, D. Ghiringhelli, and P. Grasselli, *J. C. S. Chem. Comm.*, 1977, 474.

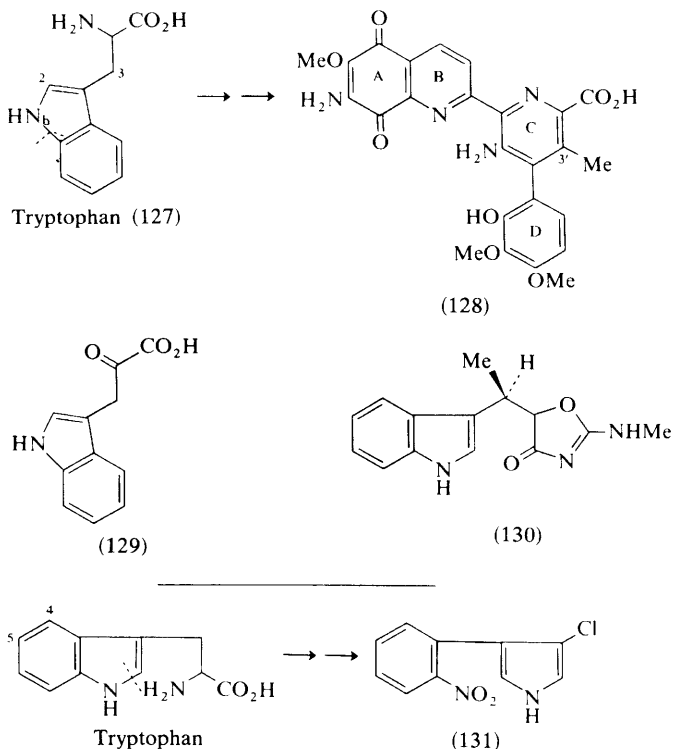
¹²⁰ J. J. Oleson, L. A. Calderella, K. J. Mjos, A. R. Reith, R. S. Thie, and I. Toplin, *Antibiotics and Chemother.*, 1961, **11**, 158; W. L. Wilson, C. Labra, and E. Barrist, *ibid.*, p. 147; T. J. McBride, J. J. Oleson, and D. Woolf, *Cancer Res.*, 1966, **26**, 727.

¹²¹ C. A. Hackethal, R. B. Golbey, C. T. C. Tan, D. A. Karnofsky, and J. H. Burchenal, *Antibiotics and Chemother.*, 1961, **11**, 178.

¹²² V. L. Karpov and L. G. Romanova, *Antibiotiki*, 1972, **17**, 419.

¹²³ S. J. Gould and C. C. Chang, *J. Amer. Chem. Soc.*, 1977, **99**, 5496.

Novel scission of the indole nucleus is clearly involved, and observation of ^{13}C - ^{15}N coupling in the ^{13}C n.m.r. spectrum of (128) derived from $[2\text{-}^{13}\text{C}\text{-}^{15}\text{N}_b]$ tryptophan establishes that both atoms are retained and that cleavage of tryptophan occurs along the dotted line in (127).¹²⁴ It is notable that this cleavage reaction differs from the equally unique one seen in the biosynthesis of pyrrolnitrin (131) (Scheme 7).¹²⁵



Scheme 7

Confirmation was obtained that the *C*-methyl group of (128) and the three methoxy-groups originate from methionine. In addition, label from serine, a major donor to the C_1 -pool, appeared to a greater extent in the methoxy-groups than in the methyl group, indicating that *C*-methylation occurs at an earlier stage of biosynthesis. This can be conceived of as occurring on tryptophan¹²³ or (129), which is mechanistically more attractive and has analogy¹²⁶ with indolmycin (130) biosynthesis.

¹²⁴ S. J. Gould and C. C. Chang, *J. Amer. Chem. Soc.*, 1978, **100**, 1624.

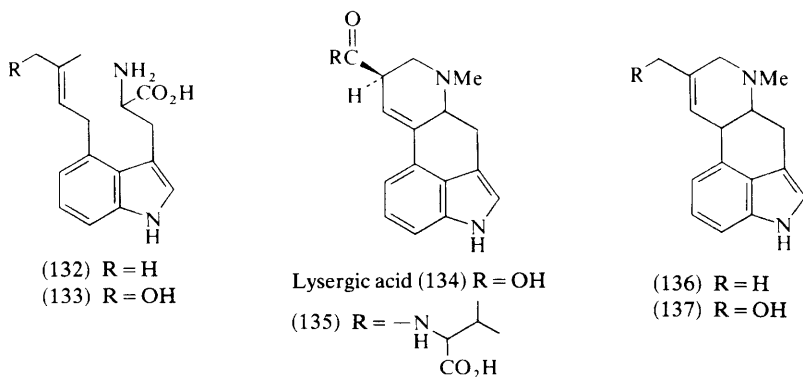
¹²⁵ H. G. Floss, P. E. Manni, R. L. Hamill, and J. A. Mabe, *Biochem. Biophys. Res. Comm.*, 1971, **45**, 781; R. B. Herbert, in ref. 3, p. 13; in ref. 4, p. 28, and refs. cited.

¹²⁶ U. Hornemann, L. H. Hurley, M. K. Speedie, and H. G. Floss, *J. Amer. Chem. Soc.*, 1971, **93**, 3028; M. K. Speedie, U. Hornemann, and H. G. Floss, *J. Biol. Chem.*, 1975, **250**, 7819; L. Mascaro, jun., R. Hörhammer, S. Eisenstein, L. K. Sellers, K. Mascaro, and H. G. Floss, *J. Amer. Chem. Soc.*, 1977, **99**, 273; R. B. Herbert, in ref. 8, p. 23; in ref. 7, p. 16; in ref. 3, p. 10; and refs. cited.

Actinomycin.—Further exploration of actinomycin biosynthesis has involved the preparation of protoplasts of *Streptomyces* species.¹²⁷

Ergot Alkaloids.—Ergot alkaloid biosynthesis begins with the isoprenylation of tryptophan to give (132).¹²⁸ Recent results¹²⁹ with tryptophan tritiated on the benzene ring established that, on formation of lysergic acid (134), a hydrogen atom is lost only from C-4, in agreement with earlier findings.¹³⁰

The synthesis of dimethylallyltryptophan (132) by a crude extract of *Claviceps purpurea* from tryptophan and dimethylallyl pyrophosphate recorded earlier¹³¹ has been reported again recently.¹³² In addition to (132), the formation of (133) was observed. (The latter compound, with unspecified stereochemistry around the double bond, has also been isolated from a *C. purpurea* culture¹³³). It was found further that both (132) and (133) could act as precursors for lysergic acid amides in *C. paspali* cultures. Both (133) and its (*Z*)-isomer have been found to act as precursors for elymoclavine (137) but not chanoclavine-I (138) or agroclavine (136), which are considered to be normal intermediates in elymoclavine biosynthesis.¹³⁴ It may be concluded, however, from the combined evidence, that elymoclavine, lysergic acid, and related compounds may normally be formed along an alternative pathway *via* these allylic hydroxy-compounds.



The peptidic ergot alkaloids, *e.g.* ergocornine (139), derive by combination of three appropriate α -amino-acids with lysergic acid (134).¹²⁸ The sequence by which the individual units become linked is, however, obscure. There is some evidence¹³⁵ for linkage between a cyclic dipeptide and a lysergyl amino-acid

¹²⁷ U. Keller and H. Kleinkauf, *Arch. Biochem. Biophys.*, 1977, **184**, 111; M. J. M. Hitchcock and E. Katz, *Antimicrobial Agents Chemotherapy*, 1978, **13**, 104.

¹²⁸ H. G. Floss, *Tetrahedron*, 1976, **32**, 873.

¹²⁹ M. Bellatti, G. Casnati, G. Palla, and A. Minghetti, *Tetrahedron*, 1977, **33**, 1821.

¹³⁰ H. Pleininger, R. Fischer, G. Keilich, and H. D. Orth, *Annalen*, 1961, **642**, 214.

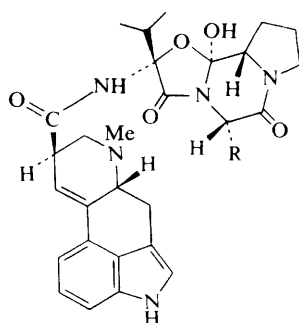
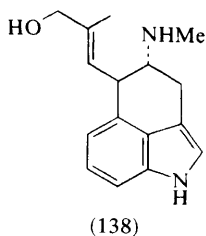
¹³¹ S.-L. Lee, H. G. Floss, and P. Heinsteinst, *Arch. Biochem. Biophys.*, 1976, **177**, 84.

¹³² R. J. Petroski and W. J. Kelleher, *F. E. B. S. Letters*, 1977, **82**, 55.

¹³³ J. A. Anderson and M. S. Saini, *Tetrahedron Letters*, 1974, 2107; R. B. Herbert, in ref. 5, p. 31.

¹³⁴ P. Pachlatko, C. Tobacik, W. Acklin, and D. Arigoni, *Chimia (Switz.)*, 1975, **29**, 526; R. B. Herbert, in ref. 7, p. 20.

¹³⁵ M. Abe, T. Ohashi, S. Ohmoto, and T. Tabuchi, *Agric. and Biol. Chem., (Japan)*, 1971, **35**, A1; T. Ohashi, H. Takahashi, and M. Abe, *Nippon Nogei Kagaku Kaishi*, 1972, **46**, 535; R. B. Herbert, in ref. 5, p. 34; in ref. 4, p. 33.

Ergocornine (139) R = PrⁱErgokryptine (140) R = Buⁱ

derivative [e.g. lysergyl-valine (135) in ergocornine (139) biosynthesis], but the weight of evidence^{136–138} is against such a biosynthetic reaction. An alternative is for lysergic acid to link to a tripeptide. However, L-valyl-L-valyl-L-proline and L-valyl-L-leucyl-L-proline were found to be incorporated into ergocornine (139) and ergokryptine (140), respectively, only after fragmentation into their constituent amino-acids.^{138,139}

The sum of negative evidence has led to the suggestion that assembly of the peptidic ergot alkaloids takes place within the confines of a multi-enzyme complex to give a lysergyl tripeptide which then undergoes cyclization to yield alkaloid.¹³⁹ Recently, the methyl esters of lysergyl-L-valyl-L-valine, lysergyl-L-valyl-L-leucine, and the lysergyl tripeptide lysergyl-L-valyl-L-valyl-L-proline (ready hydrolysis of such methyl esters by the organism used is known) have been examined as precursors for alkaloids (ergocornine and ergokryptine).¹⁴⁰ None of these precursors was used for biosynthesis without prior fragmentation, which indicates, in terms of the multi-enzyme-complex model, that exogenous lysergyl di- and tri-peptides do not reach the enzyme which carries out cyclization.

The utilization of various nitrogen sources in the production of ergot alkaloids in *C. purpurea* cultures has received detailed investigation.¹⁴¹ The relationship between the amount of cell-pool tryptophan, time, and the synthesis of ergot alkaloids in *Aspergillus fumigatus* has been noted.¹⁴²

6 Steroidal Alkaloids

Dormantinal (141) and dormantinone (142) have been isolated from *Veratrum grandiflorum*.¹⁴³ Their side-chain functionality indicates that they may be pre-

¹³⁶ H. G. Floss, G. P. Basmadjian, M. Tchong, C. Spalla, and A. Minghetti, *Lloydia*, 1971, **34**, 442; H. G. Floss, G. P. Basmadjian, M. Tchong, D. Gröger, and D. Erge, *ibid.*, p. 446; D. Gröger and S. Johné, *Experientia*, 1972, **28**, 241.

¹³⁷ W. Maier, D. Erge, and D. Gröger, *Biochem. Physiol. Pflanzen*, 1974, **165**, 479.

¹³⁸ D. Gröger, S. Johné, and S. Härtling, *Biochem. Physiol. Pflanzen*, 1974, **166**, 33.

¹³⁹ H. G. Floss, M. Tchong-Lin, H. Kobel, and P. Stadler, *Experientia*, 1974, **30**, 1369; R. B. Herbert, in ref. 6, p. 31.

¹⁴⁰ A. Baumert, D. Gröger and W. Maier, *Experientia*, 1977, **33**, 881.

¹⁴¹ Z. Řeháček, J. D. Desai, P. Sajdl, and S. Pažoutová, *Canad. J. Microbiol.*, 1977, **23**, 596.

¹⁴² K. K. Rao and A. R. Gupta, *Indian J. Exp. Biol.*, 1977, **15**, 588.

¹⁴³ K. Kaneko, M. W. Tanaka, and H. Mitsuhashi, *Phytochemistry*, 1977, **16**, 1247; K. Kaneko, M. Watanabe, and H. Mitsuhashi, *ibid.*, 1973, **12**, 1509.

cursors, in this plant, for alkaloids represented by verazine (143), an early intermediate.¹⁴⁴ Taken with other results¹⁴⁵⁻¹⁴⁷ on the formation of the nitrogen ring of different alkaloids, it appears that hydroxylation of one of the terminal methyl groups of cholesterol (144) is a first step in steroidal alkaloid biosynthesis, followed by functionalization of C-22 and formation of the nitrogen ring. The formation of the furan ring in alkaloids such as solasodine (145) and soladulcidine (146) may be deduced to be a last step. Substance is given to this deduction, and further biosynthetic detail provided, by the observation that (147) and (148) were substantially better incorporated into soladulcidine (146) than cholesterol; a similar observation was made with (149) and (150) as precursors for solasodine (145).¹⁴⁸ The incorporation of (150) with hydroxy-group at C-16 indicates that oxygenation of this site, rather than of one on the side-chain, occurs in the course of formation of the furan ring. This hydroxylation reaction is unusual in that it apparently occurs^{146,147} with inversion of configuration at C-16.

An alternative sequence of functionalization and ring-closure in steroidal alkaloid biosynthesis has been reported, proceeding *via* 26-amino-furostanols for, *e.g.*, the biosynthesis of solasodine.¹⁴⁹ In the light of the new evidence it has been concluded that such a pathway must be a minor one.¹⁴⁸

7 Miscellaneous

Phenazines.—Consideration of structural relationships between the various microbial phenazines, in association with evidence on the way in which these metabolites are formed from two molecules of shikimic acid (151),¹⁵⁰ leads to phenazine-1,6-dicarboxylic acid (152) as a likely common intermediate (Scheme 8), but it has not been found to act as a precursor for various phenazines,^{151,152} exemplified by phenazine-1-carboxylic acid (153). Although the dimethyl ester of (152) has been reported to be a precursor for (153) in *Pseudomonas aureofaciens*,¹⁵² it could not be confirmed as such under various conditions.¹⁵³ The dihydro-derivative (156) was likewise found not to be a precursor for (153) and (154) in *P. aureofaciens*.¹⁵³

¹⁴⁴ K. Kaneko, H. Seto, C. Motoki, and H. Mitsuhashi, *Phytochemistry*, 1975, **14**, 1295; R. B. Herbert, in ref. 6, p. 52.

¹⁴⁵ F. Ronchetti, G. Russo, G. Ferrara, and G. Vecchio, *Phytochemistry*, 1975, **14**, 2423; F. Ronchetti and G. Russo, *J. C. S. Chem. Comm.*, 1974, 785; A. R. Guseva and V. A. Paseshnichenko, *Biochemistry (U.S.S.R.)*, 1962, **27**, 721; R. Tschesche, E. Goossens, and A. Töpfer, *Phytochemistry*, 1976, **15**, 1387; R. B. Herbert, in ref. 7, p. 32.

¹⁴⁶ R. B. Herbert, in ref. 8, p. 28.

¹⁴⁷ L. Canonica, F. Ronchetti, G. Russo, and G. Sportoletti, *J. C. S. Chem. Comm.*, 1977, 286.

¹⁴⁸ R. Tschesche and M. Spindler, *Phytochemistry*, 1978, **17**, 251.

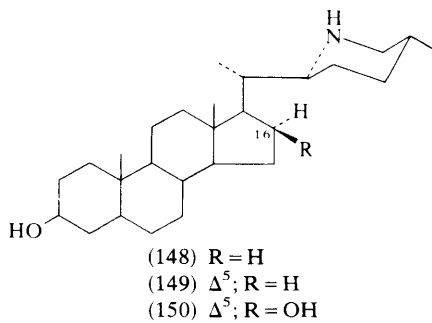
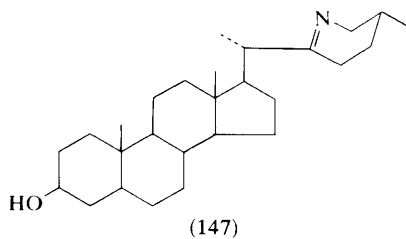
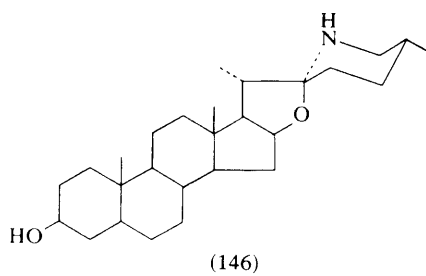
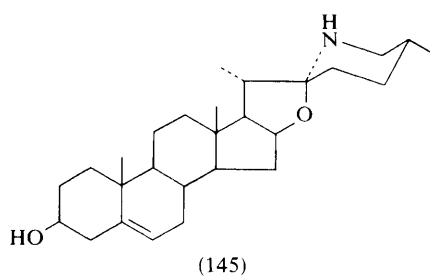
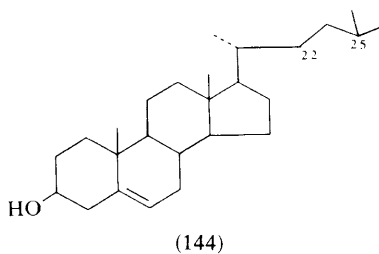
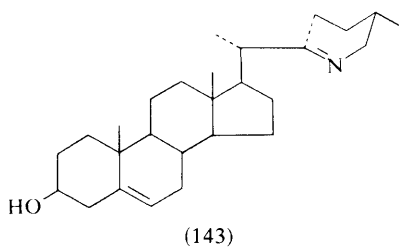
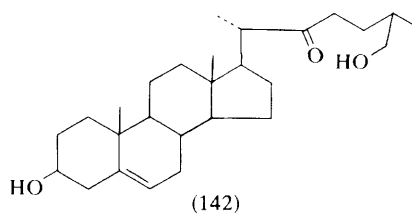
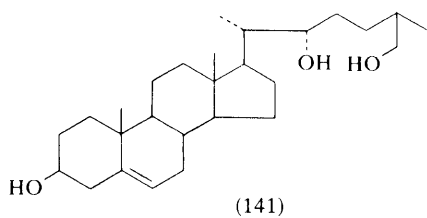
¹⁴⁹ R. Tschesche and G. Piestert, *Phytochemistry*, 1975, **14**, 435.

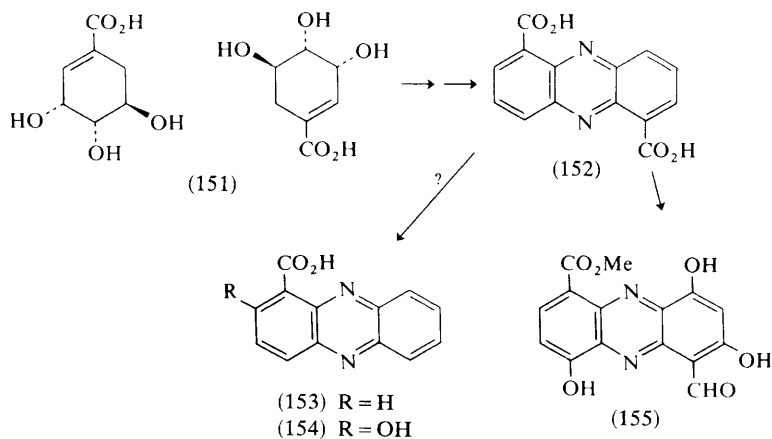
¹⁵⁰ R. B. Herbert, F. G. Holliman, and J. B. Sheridan, *Tetrahedron Letters*, 1976, 639; *ibid.*, 1974, 4201; U. Hollstein and D. A. McCamey, *J. Org. Chem.*, 1973, **38**, 3415; U. Hollstein and L. G. Marshall, *ibid.*, 1972, **37**, 3510; R. B. Herbert, in ref. 7, p. 27; in ref. 5, p. 44; in ref. 4, p. 46.

¹⁵¹ M. E. Flood, R. B. Herbert, and F. G. Holliman, *J. C. S. Perkin I*, 1972, 622; R. B. Herbert, F. G. Holliman, and P. N. Ibberson, *J. C. S. Chem. Comm.*, 1972, 355; R. B. Herbert, in ref. 3, p. 36.

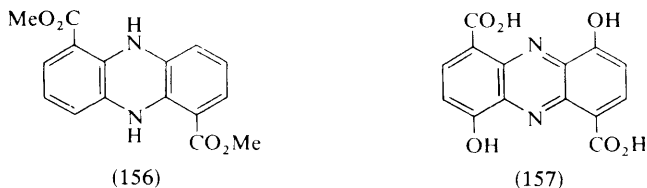
¹⁵² U. Hollstein, G. E. Krisov, and D. L. Mock, *Tetrahedron Letters*, 1976, 3267; R. B. Herbert, in ref. 8, p. 33.

¹⁵³ R. B. Herbert, F. G. Holliman, and S. P. Gulliford, *Tetrahedron Letters*, 1978, 195.





Scheme 8



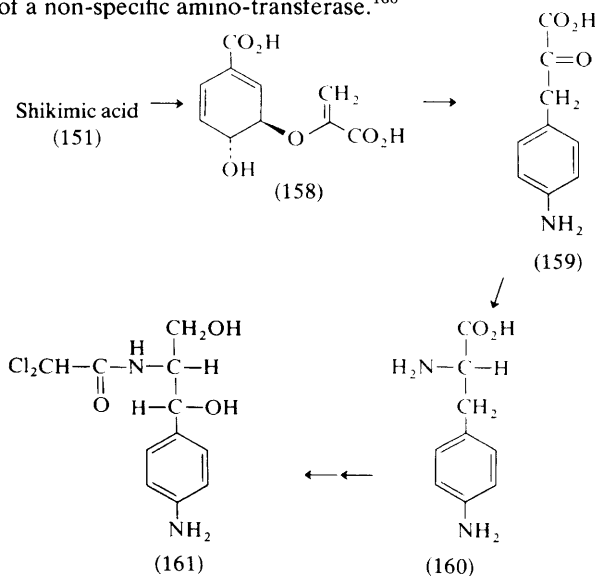
The above negative results with (152) and its dimethyl ester were obtained in *Pseudomonas* and closely related species for metabolites bearing a single aryl- C_1 substituent or none. It was still an attractive possibility that (152) could be a precursor for phenazines bearing two aryl- C_1 substituents, e.g. lomofungin (155), and indeed it was found to be incorporated into this metabolite in *Streptomyces lomodensis* with an efficiency which indicated that it is an intermediate in lomofungin biosynthesis.¹⁵³ It is not yet clear whether this positive result was obtained because (152) is transported across the cell walls of *Streptomyces* but not *Pseudomonas* species or because (152) is only a precursor for phenazines with two aryl- C_1 substituents. Experiments with another *Streptomyces* species (*S. luteoreticuli*) which produces the methyl ester of phenazine-1-carboxylic acid (153) should allow resolution of the problem.

4,9-Dihydroxyphenazine-1,6-dicarboxylic acid (157) has been isolated as its dimethyl ester from *Pseudomonas cepacia*.¹⁵⁴ Although the acid (157) has been proposed as an intermediate in phenazine biosynthesis before phenazine-1,6-dicarboxylic acid (152), the necessary loss *in vivo* of two phenolic hydroxy-groups in the formation of (152) or, e.g., (153), makes this highly unlikely, and preliminary testing¹⁵⁴ of the hypothesis supports this view. The dihydroxy-acid (157) could, however, be an intermediate, and more reasonably so, in the biosynthesis of compounds like lomofungin (155) at a stage *after* (152).

¹⁵⁴ H. Korth, A. Römer, H. Budzikiewicz, and G. Pulverer, *J. Gen. Microbiol.*, 1978, **104**, 299.

Chloramphenicol.—Like bacterial phenazines (above), chloramphenicol (161) is biosynthesized from shikimic acid (151) along the pathway to aromatic acids, branching from it at chorismic acid (158). The next detected intermediate in chloramphenicol biosynthesis is *p*-amino-L-phenylalanine, modification of which affords chloramphenicol (161) (Scheme 9).¹⁵⁵ The biosynthesis of the dichloroacetyl group has been studied¹⁵⁶ using [1,2-¹³C₂]acetate, which allowed more definitive conclusions to be reached than had been possible with ¹⁴C-labelled precursor.¹⁵⁷ It was found that, although label was incorporated into the dichloroacetyl function of (161), little, if any, acetate was used without prior fragmentation. The conclusion that incorporation and formation of this group was not occurring *via* the Krebs cycle follows from the incorporation of [2,3-¹³C₂]succinic acid into the carbonyl group only (heavy labelling of the dichloromethine group *via* the Krebs cycle was expected). Possible pathways to the dichloroacetyl group which may then be proposed are circumscribed by the observation that dichloroacetic acid was not incorporated into chloramphenicol (in agreement with some results,¹⁵⁸ but not others¹⁵⁹), indicating that dichloroacetic acid exists during biosynthesis only as a (co)enzyme derivative.

The pyruvate derivative (159) is a likely intermediate in the formation of the amino-acid (160) in chloramphenicol biosynthesis. A search for an enzyme in cultures of a *Streptomyces* species which produces (161) has led only to the isolation of a non-specific amino-transferase.¹⁶⁰



Scheme 9

¹⁵⁵ A. Jones and L. C. Vining, *Canad. J. Microbiol.*, 1976, **22**, 237; and refs. cited.

¹⁵⁶ J. N. Simonsen, K. Paramasigamani, L. C. Vining, A. C. McInnes, J. A. Walter, and J. L. C. Wright, *Canad. J. Microbiol.*, 1978, **24**, 136.

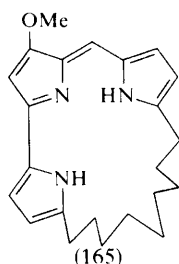
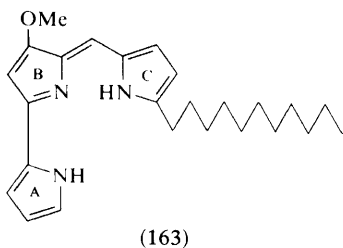
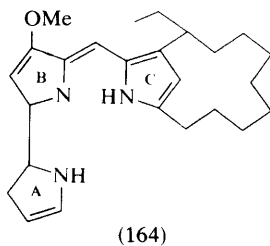
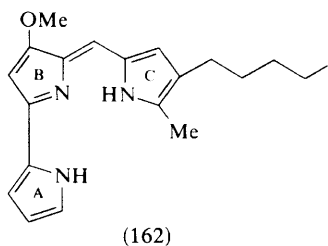
¹⁵⁷ D. Gottlieb, H. E. Carter, P. W. Robbins, and R. W. Burg, *J. Bacteriol.*, 1962, **84**, 888.

¹⁵⁸ D. Gottlieb, P. W. Robbins, and H. E. Carter, *J. Bacteriol.*, 1956, **72**, 153.

¹⁵⁹ E. Lin Wang, M. Izawa, T. Miura, and H. Umezawa, *J. Antibiotics*, 1959, **12A**, 81.

¹⁶⁰ A. Jones, M. M. Francis, L. C. Vining, and D. W. S. Westlake, *Canad. J. Microbiol.*, 1978, **24**, 238.

Prodiginines.—Rings A and B of prodigiosin (162) produced by *Serratia marescens* and of (163) and (164) produced by *Streptomyces longisporus ruber*, an actinomycete, have similar origins in proline, acetate, and serine.^{161,162} Ring C, where the structural differences lie, is formed differently in the two groups of metabolites: (162) from acetate and alanine,¹⁶¹ (163) and (164) from acetate and glycine.¹⁶² Other prodiginines, e.g. (165), produced by *Actinomadura* species, which are also actinomycetes, have been found to incorporate label from [1-¹³C]- and [1,2-¹³C]-acetate in a manner which parallels that for (163) and (164) in the other actinomycete.¹⁶³ It is apparent that ring C plus side-chain in each case is formed by condensation of glycine with a β -keto-acid or fatty acid of the appropriate chain length.



β -Lactam Antibiotics.—The biosynthesis of β -lactam antibiotics has been reviewed.¹⁶⁴

The assimilation of cysteine into the penicillin skeleton occurs with loss of the 3-*pro-S*-hydrogen atom.¹⁶⁵ Examination of the closely related cephalosporin skeleton [as (166)] has shown that it too is formed from cysteine with loss of the 3-*pro-S*-proton, and consequently retention of configuration at this centre, which

¹⁶¹ R. J. Cushley, D. R. Anderson, S. R. Lipsky, R. J. Sykes, and H. H. Wasserman, *J. Amer. Chem. Soc.*, 1971, **93**, 6284; H. H. Wasserman, R. J. Sykes, P. Peverada, C. K. Shaw, R. J. Cushley, and S. R. Lipsky, *ibid.*, 1973, **95**, 6874; R. B. Herbert, in ref. 5, p. 47.

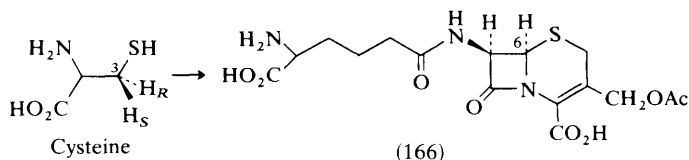
¹⁶² H. H. Wasserman, C. K. Shaw, R. J. Sykes, and R. J. Cushley, *Tetrahedron Letters*, 1974, 2787; R. B. Herbert, in ref. 6, p. 50.

¹⁶³ N. N. Gerber, A. G. McInnes, D. G. Smith, J. A. Walter, J. L. C. Wright, and L. C. Vining, *Canad. J. Chem.*, 1978, **56**, 1155.

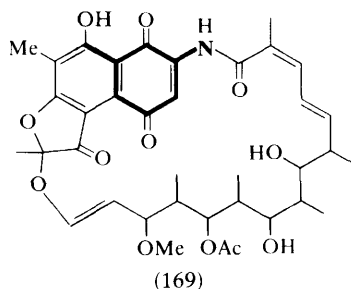
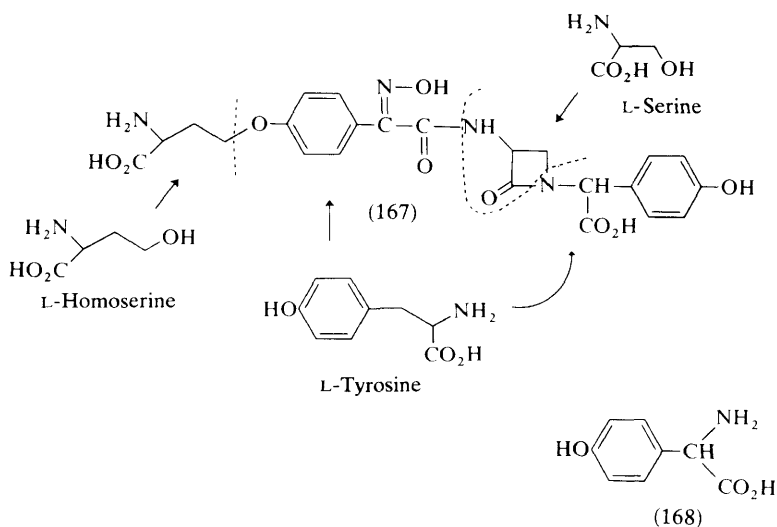
¹⁶⁴ D. J. Aberhart, *Tetrahedron*, 1977, **33**, 1545.

¹⁶⁵ D. J. Morecombe and D. W. Young, *J. C. S. Chem. Comm.*, 1975, 198; D. W. Young, D. J. Morecombe, and P. K. Sen, *European J. Biochem.*, 1977, **75**, 133; D. J. Aberhart, L. J. Lin, and J. Y.-R. Chu, *J. C. S. Perkin I*, 1975, 2517; R. B. Herbert, in ref. 6, p. 49; in ref. 7, p. 30.

becomes C-6 of cephalosporin C (166).¹⁶⁶ (Tritium label from C-2 of cysteine was also retained on formation of antibiotic, but, in addition, considerable loss was observed, attributable to transamination reactions).



Nocardicins.—Nocardicin A has the unusual structure (167), part of which is a β -lactam ring. Its biosynthesis has been studied¹⁶⁷ and it has been observed that two molecules of L-tyrosine (with proven loss of the carboxy-group), L-homoserine, and L-serine account for the carbon skeleton of (167). It has been suggested that the tyrosine is utilized by way of L-*p*-hydroxy-phenylglycine (168).



¹⁶⁶ J. A. Huddleston, E. P. Abraham, D. W. Young, D. J. Morecombe, and P. K. Sen, *Biochem. J.*, 1978, **169**, 705.

¹⁶⁷ J. Hosoda, N. Tani, T. Konomi, S. Ohsawa, H. Aoki, and H. Imanaka, *Agric. and Biol. Chem. (Japan)*, 1977, 2007.

Rifamycins.—Contained within the rifamycin skeleton, for example that of rifamycin S (169), is a C₇-N unit (heavy bonding) which has been deduced to arise from an intermediate of the shikimic acid pathway.¹⁶⁸ Fresh evidence arising from a study¹⁶⁹ using mutants of *Nocardia mediterranei* confirms this view, and it is apparent that divergence from the shikimate pathway to rifamycin synthesis occurs between sedoheptulose-7-phosphate and shikimic acid itself.

¹⁶⁸ A. Karlsson, G. Sartori, and R. J. White, *European J. Biochem.*, 1974, **47**, 251; R. J. White and E. Martinelli, *F. E. B. S. Letters*, 1974, **49**, 233; R. J. White, E. Martinelli, G. G. Gallo, G. Lancini, and P. Beynon, *Nature*, 1973, **243**, 273; R. B. Herbert, in ref. 5, p. 52; in ref. 6, p. 45; see also ref. 8, p. 30.

¹⁶⁹ O. Ghisalpa and J. Nüesch, *J. Antibiotics*, 1978, **31**, 202; *ibid.*, p. 215.

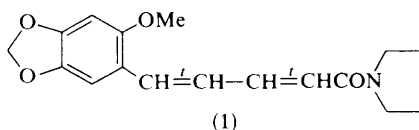
2

Pyrrolidine, Piperidine, and Pyridine Alkaloids

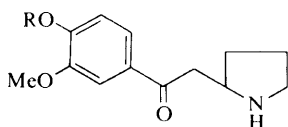
BY A. R. PINDER

1 Pyrrolidine Alkaloids

Cuscohygrine has been isolated for the first time from the roots of *Solanum carolinense*.¹ The guinea pepper alkaloid okolasine, which is the pyrrolidine amide (1) of 6-methoxypiperic acid, has been synthesized by the standard procedure of reaction of the acid chloride with pyrrolidine. The acid was reached by two routes from 2-methoxy-4,5-methylenedioxybenzaldehyde.²

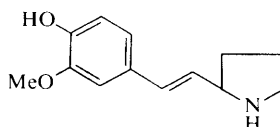


Three new pyrrolidine bases have been found in the roots of *Ruspolia hypercrateriformis* (Acanthaceae). Their structures have been established by spectroscopic measurements and by interconversions. Two of them, ruspolinone (2) and nor-ruspolinone (3), are ketones; the latter is phenolic and is converted into the former by methylation with diazomethane. The third, nor-ruspoline (4), forms an *N,O*-diacetyl derivative which on catalytic hydrogenation yields a dihydro-derivative identical with that obtained by similar treatment of *N,O*-diacetyl-nor-ruspolinone. Ozonolysis-oxidation of *N,O*-dimesylnor-ruspoline affords *O*-mesylvanillic acid (5), identified by its synthesis from vanillin.³

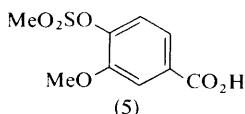


(2) R = Me

(3) R = H



(4)

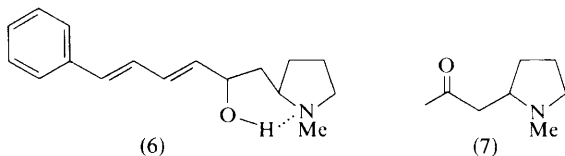


¹ W. C. Evans and A. Somanabandhu, *Phytochemistry*, 1977, **16**, 1859.

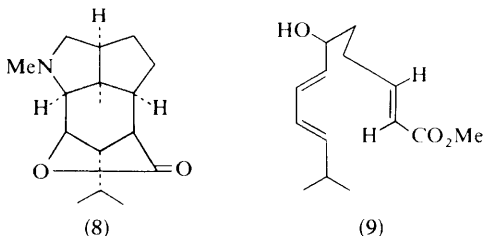
² H.-D. Scharf, J. Janus, F. Dallacker, and R. Morcinek, *Annalen*, 1978, 573.

³ F. Roessler, D. Ganzinger, S. Johnne, E. Schöpp, and M. Hesse, *Helv. Chim. Acta*, 1978, **61**, 1200.

Darlingianine is a new type of pyrrolidine base occurring in the stems and leaves of *Darlingia darlingiana* (Proteaceae), native to N. Queensland. Infrared spectroscopy reveals the presence of an intramolecularly hydrogen-bonded hydroxy-group, and the u.v. absorption is consistent with the presence of a 1-phenylbuta-1,3-diene chromophore, supported by the $^1\text{H.n.m.r.}$ spectrum. These observations, coupled with an analysis of its mass spectrum, point to structure (6), confirmed by an X-ray diffraction analysis of the alkaloid, and by synthesis of its racemate *via* condensation of (\pm)-hygrine (7) with cinnamaldehyde, followed by reduction of the carbonyl group with borohydride and preparative thin-layer chromatographic separation of the diastereomeric mixture of alcohols.⁴



Dendrobium Alkaloids.—A new total synthesis of (\pm)-dendrobine (8) has been described, by a highly stereoselective route using an intramolecular Diels–Alder reaction with the triene (9).⁵



Sceletium Alkaloids.—The total synthesis of (\pm)-sceletium alkaloid A₄ (10) has been described (Scheme 1). A parallel sequence afforded the 3'-demethoxy-alkaloid.⁶

2 Piperidine Alkaloids

Several reviews of subgroups of piperidine alkaloids have appeared. One on Lauraceae alkaloids includes a number of simple piperidine bases occurring therein.⁷ Another covers monoterpene alkaloids, some of which are piperidines;⁸ *Nuphar* alkaloids, which include some piperidine bases, have also been reviewed.⁹

⁴ B. F. Anderson, G. B. Robertson, I. R. C. Bick, J. W. Gillard, and H. M. Leow, *Chem. and Ind.*, 1977, 764.

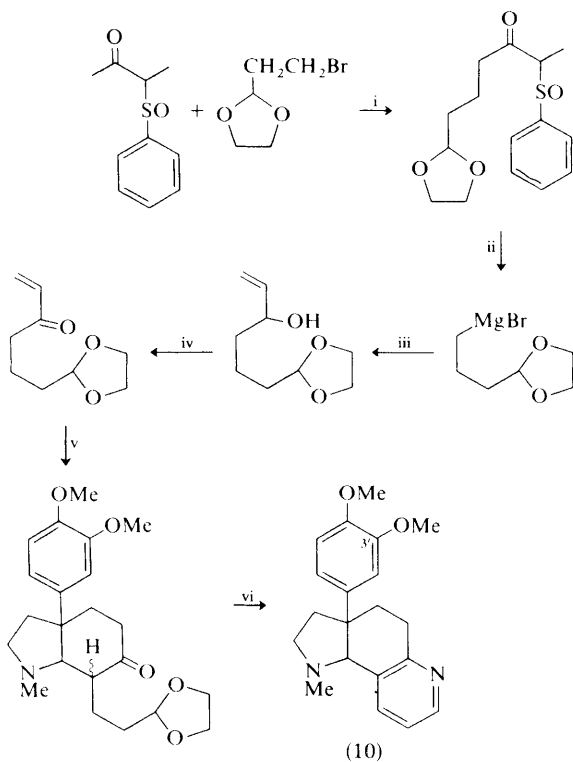
⁵ W. R. Rousch, *J. Amer. Chem. Soc.*, 1978, **100**, 3599.

⁶ C. P. Forbes, J. D. Michau, T. van Ree, A. Wiechers, and M. Woudenberg, *Tetrahedron Letters*, 1976, 935; C. P. Forbes, G. L. Wenteler, and A. Wiechers, *Tetrahedron*, 1978, **34**, 487.

⁷ I. R. C. Bick and W. Sinchai, *Heterocycles*, 1978, **9**, 903.

⁸ G. A. Cordell, in 'The Alkaloids, Chemistry and Physiology', ed. R. H. F. Manske, Vol. XVI, Chapter 8, Academic Press, New York, 1977.

⁹ J. T. Wrobel, in 'The Alkaloids, Chemistry and Physiology', ed. R. H. F. Manske, Vol. XVI, Chapter 13, Academic Press, New York, 1977.



Reagents: i, LiNPr_2 ; ii, CCl_4 , Δ ; iii, $\text{CH}_2=\text{CHCHO}$; iv, $\text{CrO}_3 \cdot 2\text{py}$; v, ; vi, $\text{NH}_2\text{OH} \cdot \text{HCl}$

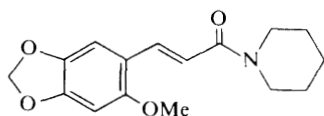
Scheme 1

A new pepper alkaloid, *N*-2-methoxy-4,5-methylenedioxcinnamylpiperidine (11), has been isolated from *Piper peepuloides*. Its structure was deduced mainly from spectral measurements; on oxidation it afforded 2-methoxy-4,5-methylenedioxybenzoic acid.¹⁰ Three new syntheses of wisanine have been published. In one, 2-methoxy-4,5-methylenedioxybenzaldehyde was subjected to a modified Wittig reaction with ethyl γ -diethylphosphonocrotonate (12), to give the *trans*, *trans*-dienoic ester (13; R = Et). Hydrolysis followed by conversion into the acid chloride and reaction with piperidine afforded wisanine (14).¹¹ A second route involved conversion of the same aldehyde into the phosphonium salt (15) by well-documented steps. Wittig reaction with ethyl *trans*-3-formylacrylate yielded the diene acid (13; R = H), convertible into wisanine.² In the third sequence the

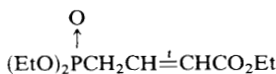
¹⁰ O. P. Gupta, S. C. Gupta, K. L. Dhar, and C. K. Atal, *Phytochemistry*, 1978, **17**, 601.

¹¹ O. P. Vig, M. Lal, I. R. Trehan, and S. Singh, *Indian J. Chem.*, 1977, **16**, 950; S. Linke, J. Kurz, and H.-J. Zeiler, *Tetrahedron*, 1978, **34**, 1979.

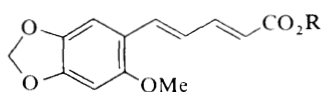
aldehyde was converted into its diethyl acetal, which with ethyl vinyl ether and a Lewis acid gave the triethoxypropane (16); this, on heating with phosphoric acid, yielded the phenylacrylaldehyde (17). This was condensed with monomethyl malonate to give ester (13; R = Me).²



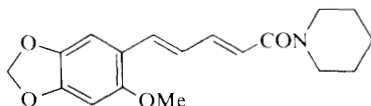
(11)



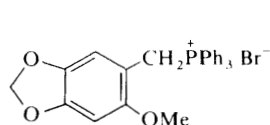
(12)



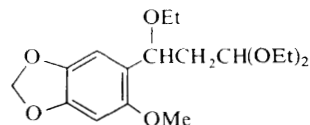
(13)



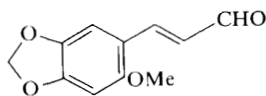
(14)



(15)

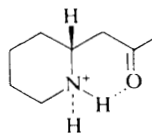


(16)

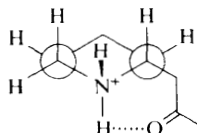


(17)

The chiroptical properties of pelletierine and anaferine have been studied. They reveal that both molecules are sensitive to conformational changes. The former apparently adopts the *trans*-pseudo-ring conformation (18) in acid solution and the *cis*-fused counterpart (19) in neutral solution. The latter, in acid solution, shows a positive ellipticity for the $n-\pi^*$ carbonyl transition, of about the same magnitude as for (-)-pelletierine sulphate but opposite in sign, suggesting major conformational changes of unknown character.¹²



(18)

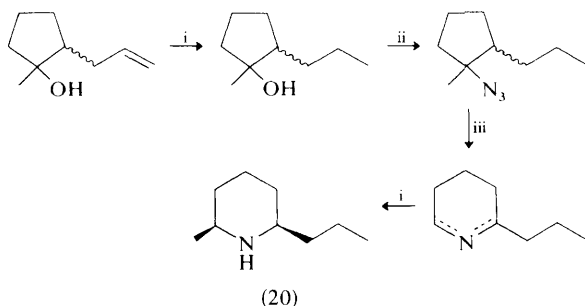


(19)

The acid-catalysed decomposition of tertiary azides derived from cyclopentane to give α -substituted piperideines has been applied to the synthesis of certain piperidine alkaloids such as γ -coniceine, (\pm)-coniine, and (\pm)-dihydropinidine.

¹² J. C. Craig, S.-Y. C. Lee, and S. K. Roy, *J. Org. Chem.*, 1978, **43**, 347.

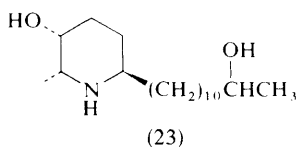
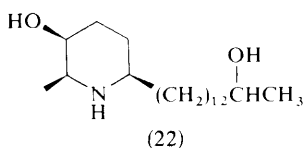
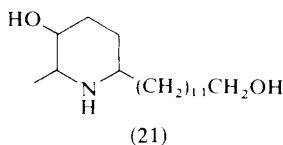
The route to the last base (20) is summarized in Scheme 2, the overall yield being about 60%.¹³



Reagents: i, catalytic hydrogenation; ii, HN_3 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$; iii, H_2SO_4

Scheme 2

Three new alkaloids have been isolated from the leaves of *Prosopis juliflora* DC. (mesquite). The minor base, julifloridine, has been examined spectroscopically, and structure (21), of unspecified relative and absolute configuration, has been advanced for it. The other two bases, juliflorine and julifloricine, are also 3-hydroxy-2-methyl-piperidines of apparently more complex structure.¹⁴ Spectalinine (22) and iso-6-carnavaline (23) are two new piperidine bases occurring in



the seeds of *Cassia spectabilis* DC. Their structures and stereochemistry have been established by mass and n.m.r. spectroscopy. The configuration of the side-chain secondary alcohol group in each remains to be settled.¹⁵ A synthetic approach to *Prosopis* alkaloids has been described; some refinements are necessary to induce a critical Bayer-Villiger oxidation to follow the desired course.¹⁶

The total syntheses of the racemic forms of the piperidine *Nuphar* alkaloids nupharamine (24) and 3-*epi*-nupharamine (25) have been reported, the route being as outlined in Scheme 3.¹⁷ The configuration (25) assigned to the *epi*-base

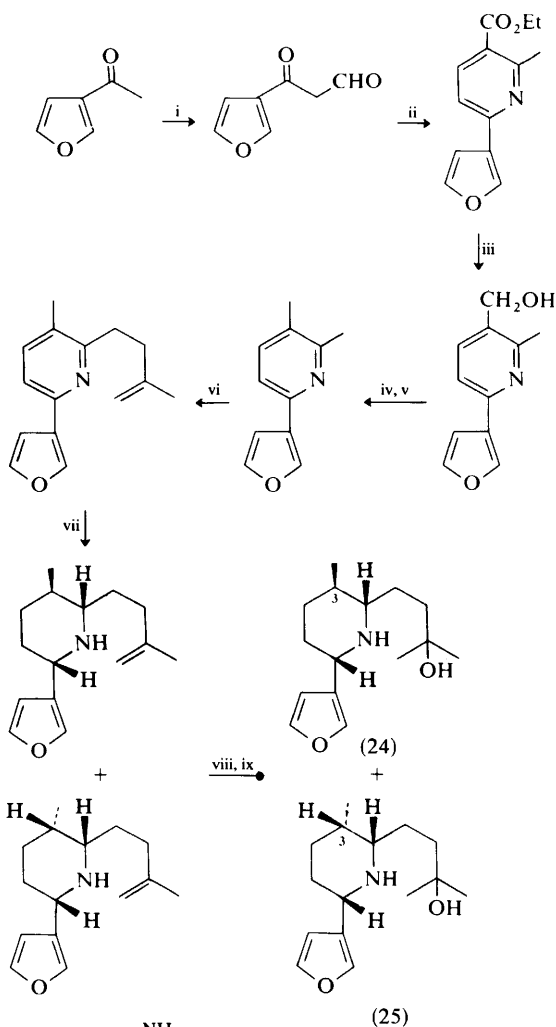
¹³ A. Astier and M. M. Plat, *Tetrahedron Letters*, 1978, 2051.

¹⁴ V. U. Ahmad, A. Basha, and W. Haque, *Z. Naturforsch.*, 1978, **33b**, 347.

¹⁵ I. Christofidis, A. Welter, and J. Jadot, *Tetrahedron*, 1977, **33**, 3005.

¹⁶ A. J. G. Baxter and A. B. Holmes, *J.C.S. Perkin I*, 1977, 2343.

¹⁷ J. Szychowski, J. T. Wrobel, and A. Leniewski, *Canad. J. Chem.*, 1977, **55**, 3105.



Reagents: i, HCO₂Et, Na; ii, MeC=CHCO₂Et; iii, LiAlH₄; iv, 60% HBr; v, Zn, HOAc; vi, NaNH₂, MeC(=CH₂)CH₂Cl; vii, Na, EtOH; viii, HCO₂H, HClO₄; ix, NaHCO₃, MeOH, H₂O, separation by column chromatography

Scheme 3

has been corroborated by an X-ray diffraction analysis of its hydrobromide.¹⁸

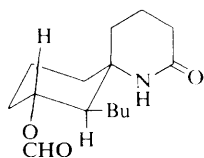
Spiropiperidine Alkaloids.—Full experimental details of a preliminary reported¹⁹ total synthesis of racemic perhydrohistrionicotoxin have been published.²⁰

¹⁸ M. Sabat, T. Glowiak, J. Szychowski, J. T. Wrobel, and A. Leniewski, *Canad. J. Chem.*, 1977, **55**, 3111.

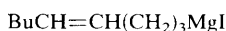
¹⁹ E. J. Corey, M. Petrzilka, and Y. Ueda, *Tetrahedron Letters*, 1975, 4343.

²⁰ E. J. Corey, M. Petrzilka, and Y. Ueda, *Helv. Chim. Acta*, 1977, **60**, 2294.

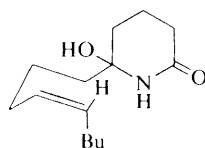
A synthesis of a precursor (26) of the same compound has been described, beginning with glutarimide, which was treated with the Grignard reagent (27) to yield (28), cyclized by formic acid to (26).²¹



(26)

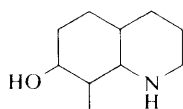


(27)



(28)

Decahydroquinoline Alkaloids.—A new decahydroquinoline alkaloid, isonitramine (29), has been isolated from *Nitrania sibirica*, its structure being inferred from spectral measurements.²²

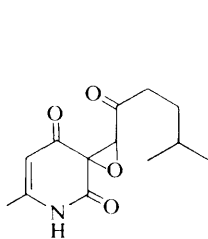


(29)

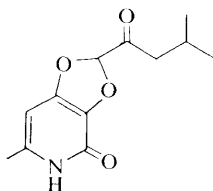
3 Pyridine Alkaloids

Anabasine has been isolated, for the first time, from the roots of *Solanum carolinense*.¹

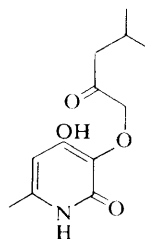
An *X*-ray diffraction analysis of (\pm)-flavipucine (30) has confirmed its structure and has revealed that the oxiran ring is *Z* in configuration.²³ Rearrangement of the compound may be effected in several ways, best by simply refluxing in xylene (80% yield). The structure (31) of the rearrangement product has been confirmed by spectral measurements and by its reduction with zinc–acetic acid to (32), the formation of which can be rationalized, and which has u.v. spectral characteristics of a 4-hydroxy-2-pyridone rather than a 3-hydroxy-2-pyridone. These and other observations tend to confirm (31) as the rearrangement product to the exclusion of (33).²⁴ An elimination–addition pathway has been established for the epoxidation reaction employed in the synthesis of flavipucine.²⁵



(30)



(31)



(32)

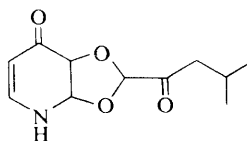
²¹ H. E. Schoemaker and W. N. Speckamp, *Tetrahedron Letters*, 1978, 1515.

²² Z. Osmanov, A. A. Ibragimov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 720.

²³ P. S. White, J. A. Findlay, and W. H. J. Tam, *Canad. J. Chem.*, 1978, **56**, 1904.

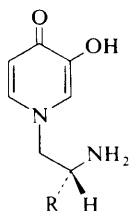
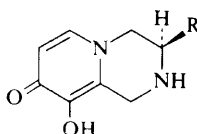
²⁴ N. N. Girotra, A. A. Patchett, and N. L. Wandler, *Heterocycles*, 1977, **6**, 1299.

²⁵ N. N. Girotra and N. L. Wandler, *Heterocycles*, 1978, **9**, 417.

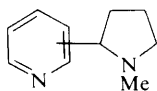


(33)

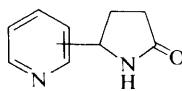
Mimosine (34) and mimosinamine (35) readily undergo Pictet–Spengler-type cyclizations to yield pyrido[1,2-*a*]pyrazines (36) and (37) respectively.²⁶

(34) R = CO₂H
(35) R = H(36) R = CO₂H
(37) R = H

Interest in nicotine alkaloids continues. The conformation of nicotine in solution has been investigated by ¹H and ²H n.m.r. measurements, employing selectively deuteriated nicotine analogues. The vicinal coupling constants for the pyrrolidine ring protons suggest that the ring adopts an envelope conformation, with the methyl and pyridine substituents equatorial, and the two rings in a perpendicular spatial orientation.²⁷ The ¹³C n.m.r. spectrum has also been measured in various solvents and assignments have been made.²⁸ Several compounds related structurally to nicotine, (38) and (39), have been synthesized



(38)



(39)

and their mass spectra measured and interpreted.²⁹ The radical methylation and hydroxymethylation of nicotine have been studied: the alkaloid is methylated at positions 4 and 6 (major), but hydroxymethylation occurs only at position 6, and less readily than methylation.³⁰ Nicotine reacts with sodium nitrite to give a variety of products, the nature of which depends on the conditions. At ambient temperature *N'*-nitrosornnicotine, 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-butan-1-one (40), and 4-(*N*-methyl-*N*-nitrosamino)-4-(3-pyridyl)-butanal (41) are formed in poor yield, most of the nicotine being unchanged. At 90°C nearly all the nicotine reacts, to give *N'*-nitrosornnicotine and (40), but (41) is not formed.

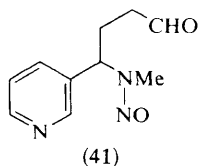
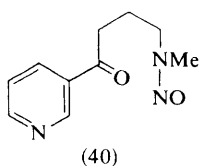
²⁶ C. M. Richards and A. Hofmann, *Austral. J. Chem.*, 1978, **31**, 187.

²⁷ T. P. Pitner, W. B. Edwards, R. L. Bassfield, and J. F. Whidby, *J. Amer. Chem. Soc.*, 1978, **100**, 246.

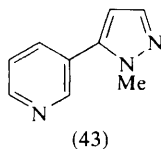
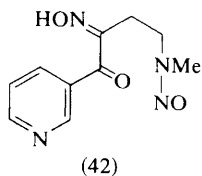
²⁸ T. P. Pitner, J. I. Seeman, and J. F. Whidby, *J. Heterocyclic Chem.*, 1978, **15**, 585.

²⁹ D. F. Glenn and W. B. Edwards, *J. Org. Chem.*, 1978, **43**, 2860.

³⁰ H. Itokawa, T. Inaba, R. Haruta, and S. Kameyama, *Chem. and Pharm. Bull. (Japan)*, 1978, **26**, 1295.

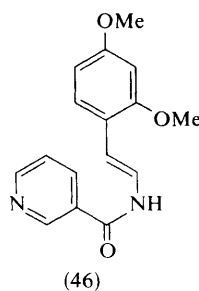
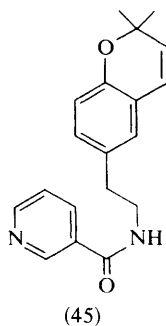
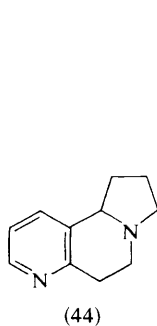


Fragmentation of the pyrrolidine ring gave *cis*- and *trans*-3-(3-pyridyl)acrylonitrile, *N*-methylnicotinamide, nicotinic acid, and products (42) and (43).³¹



Pyridine-substituted nicotines, nornicotines, and anabasines are available from α -cyano-amines by a new synthesis.³² The syntheses of (\pm)-[1'-¹⁵N]nornicotine and (\pm)-[1'-¹⁵N]nicotine have been described, from cyclopropyl 3-pyridyl ketone and [¹⁵N]formamide.³³ 4-Methylnicotine has been prepared; it shows no nicotine-like pharmacological activity.³⁴ An investigation into the stereochemical factors involved in the behaviour of nicotine and related compounds in the Menshutkin reaction has been conducted.³⁵ A 'bridged nicotine', 1,2,3,5,6,10b-hexahydropyrido[2,3-g]indolizine (44), has been synthesized by carboxylation of the dilithium derivative of 2-methylnornicotine followed by cyclisation and reduction with borane in tetrahydrofuran.³⁶ Several 5-halogeno-nicotines have been prepared and their *pK* values and biological activities measured.³⁷

Two nicotinamides, (45) and (46), have been isolated from *Amyris plumieri* of Jamaican origin, and have been assigned structures mainly on spectral evidence.³⁸



³¹ S. S. Hecht, C. B. Chen., R. M. Orna, E. Jacobs, J. D. Adams, and D. Hoffmann, *J. Org. Chem.*, 1978, **43**, 72.

³² E. B. Sanders, H. V. Secor, and J. I. Seeman, *J. Org. Chem.*, 1978, **43**, 324.

³³ W. B. Edwards, D. F. Glenn, F. Green, and R. H. Newman, *J. Labelled Compounds, Radiopharm.*, 1978, **14**, 255.

³⁴ E. Leete and S. A. S. Leete, *J. Org. Chem.*, 1978, **43**, 2122.

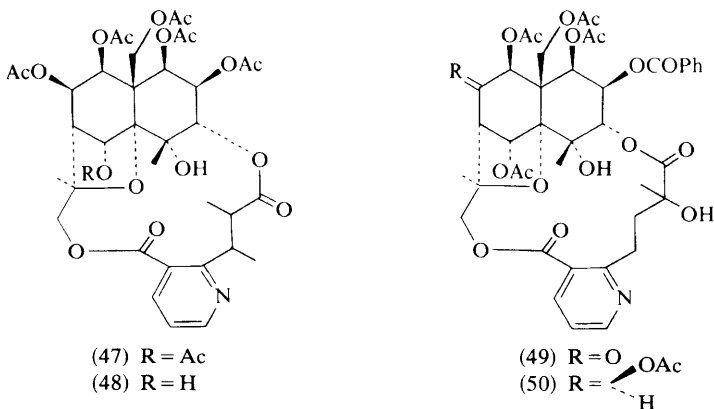
³⁵ J. I. Seeman, H. V. Secor, J. F. Whidby, and R. L. Bassfield, *Tetrahedron Letters*, 1978, 1901.

³⁶ T. E. Catka and E. Leete, *J. Org. Chem.*, 1978, **43**, 2125.

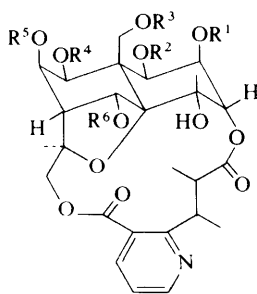
³⁷ L. Rondahl, *Acta Pharm. Suecica*, 1977, **14**, 113.

³⁸ B. A. Burke and H. Parkins, *Tetrahedron Letters*, 1978, 2723.

Celastraceae Alkaloids.—These alkaloids have been reviewed.³⁹ Two new bases, euonymine (47) and neo-euonymine (48), have been isolated from the seeds of *Euonymus sieboldiana* Blume. Their structures have been established by chemical transformations and spectral study. Neoeuonymine is converted into euonymine by *O*-acetylation.⁴⁰ Another new pair of members of this family has been isolated from *Euonymus alatus* forma *striatus* (Thunb.) Makino. These alkaloids, alatamine (49) and wilfordine (50), also had their structures elucidated by chemical



and spectroscopic investigation, and the former was converted into the latter by successive reduction with borohydride and *O*-acetylation. Wilfordine has insecticidal properties and is responsible for the earlier known insecticidal activity of *Tripergium wilfordii*.⁴¹ Chromatographic separation of extracts of khat (*Catha edulis*) of Kenyan origin has yielded five new weakly basic alkaloids.⁴² Structures for these, and for four bases encountered earlier⁴³ as components of the same plant of Ethiopian origin, have been advanced, largely as a result of mass and



(51)

³⁹ R. M. Smith, in 'The Alkaloids, Chemistry and Physiology', ed. R. H. F. Manske, Vol. XVI, Chapter 4, Academic Press, New York, 1977.

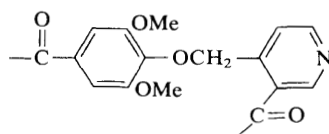
⁴⁰ K. Yamada, K. Sugiura, Y. Shizuri, H. Wada, and Y. Hirata, *Tetrahedron*, 1977, **33**, 1725.

⁴¹ K. Yamada, Y. Shizuri, and Y. Hirata, *Tetrahedron*, 1978, **34**, 1915.

⁴² L. Crombie, W. M. L. Crombie, D. A. Whiting, O. J. Braenden, and K. Szendrei, *J.C.S. Chem. Comm.*, 1978, 107.

⁴³ R. L. Baxter, L. Crombie, D. J. Simmonds, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1976, 463, 465.

n.m.r. spectral study, particularly on cathedulin K-2, the most abundant alkaloid of Kenyan khat. All have the atomic framework represented by (51), where most of the R's in each structure are acyl residues such as acetyl, 3,4,5-trimethoxybenzoyl, nicotinyl, $\text{AcOCMe}_2\text{CO-}$, benzoyl, and (52).⁴²



(52)

3

Tropane Alkaloids

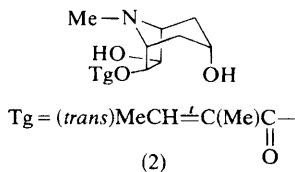
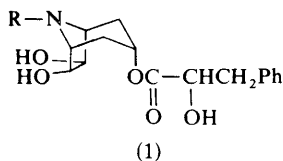
BY G. FODOR & J. BUTTERICK

This chapter was not published last year in view of an extremely detailed (almost 100 page) review on tropanes in the Manske series 'The Alkaloids'. Volume XVI, by R. L. Clarke. The present chapter is intended to avoid any overlap with Clarke's material.

1 Occurrence, and Structures of New Alkaloids

(-)-6 β ,7 β -Dihydroxylittorine, *i.e.* (-)-6 β ,7 β -dihydroxytropan-3 α -yl-3-phenyl-lactate (1), has been isolated¹ in 0.016% yield from the leaves of a peach-flowered form of *Datura candida sensu latu* in addition to hyoscyne (as a major component) and meteloidine, norhyoscyne, and norhyoscyamine as minor components. Hydrolysis gave (+)-3-phenyl-lactic acid and teloidine. Since H-6 and H-7 were equivalent in the ¹H n.m.r. spectrum and mass spectral analysis showed a relatively intense ion *M* - 60, indicative of an initial fission of the pyrrolidine ring, the ester group had to be located on C-3. A second new alkaloid, isolated as the hydrobromide in 0.11% yield, of formula C₁₃H₂₂BrNO₄, gave tiglic acid and teloidine when hydrolysed with barium hydroxide solution. The n.m.r. spectrum showed non-equivalence of the H-6 and H-7 protons; therefore the compound is the 6 β (or 7 β)-tigloyl-teloidine, an 'isometeloidine' (2). The same had already been isolated from aerial parts of another arborescent species of *Datura*, namely *D. suaveolens*.²

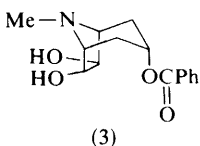
Teloidine-3-benzoate, *i.e.* 6 β ,7 β -dihydroxytropan-3 α -yl benzoate (3), was identified³ as a minor (0.001%) component of the alkaloids in the roots of



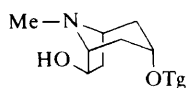
¹ W. J. Griffin, *Austral. J. Chem.*, 1976, **29**, 2329.

² W. C. Evans and J. E. Lampard, *Phytochemistry*, 1972, **11**, 3293.

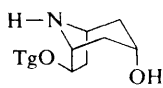
³ W. J. Griffin, *Austral. J. Chem.*, 1978, **31**, 1161.



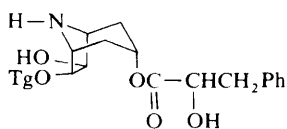
Erythroxylon australe; the aerial parts contain meteloidine (0.014%) (4), (+)-3 α -hydroxynor-tropan-6 β -yl tiglate (5) (0.002%), and another base to which the structure (+)-7 β -hydroxy-6 β -tigloyloxynortropan-3 α -yl 2-hydroxypropionate (6) has been assigned.³ All assignments were based on hydrolysis and on n.m.r. and mass spectral analyses. Alkaloid (4) was previously isolated² from *Datura* (*Brugmansia*⁴) *suaveolens* in both the (-) and (+)-forms, and is an intermediate in the metabolism of (-)-tropan-3 α ,6 β -yl ditiglate⁵ in *Brugmansia cornigera*. Furthermore, although (5) was not isolated from members of the Solanaceae, its isomer, nor-(4), has been found in low yield in *Brugmansia sanguinea*.⁶



(4)

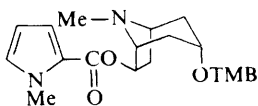


(5)

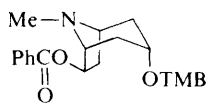


(6)

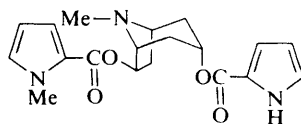
Catuabines A, B, and C [(7), (8), and (9)] are new diester alkaloids⁷ from *Erythroxylon vacciniifolium* Martius. The surprising feature of (8) is that 3,4,5-trimethoxybenzoic acid rather than pyrrole-2-carboxylic acid is the esterifying



(7)



(8)



(9)

TMB = 3,4,5-trimethoxybenzoyl

acid. The 3 α -configuration has been proven, as in other tropanes, by ¹H n.m.r. spectroscopy; the ¹³C n.m.r. spectra ascertained the β -configuration of the esterified hydroxyl function at C-6 (or -7). The ¹³C n.m.r. spectrum of catuabine B was most completely analysed.

Three-dimensional Structure.—X-Ray crystallography and n.m.r. spectroscopy have been used, as in several instances in the past, to deal with stereochemical fine-structural problems. The conformations and barriers to inversion of nitrogen

⁴ T. E. Lockwood, *Bot. Mus. Leaflet. Harv. University*, 1973, **23**, 273.

⁵ W. C. Evans and W. J. Griffin, *J. Pharm. Pharmacol.*, 1964, **16**, 337; *Phytochemistry*, 1964, **3**, 503.

⁶ W. C. Evans and V. A. Wooley, *Phytochemistry*, 1978, **17**, 171.

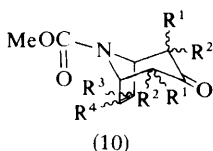
⁷ E. Graf and W. Lude, *Arch. Pharm.*, 1978, **311**, 139.

in tropanes that have been studied⁸ by ¹H n.m.r. spectroscopy and dipole-moment data were also investigated by ¹³C n.m.r.⁹ The contribution of flattened chair rather than boat conformers was corroborated.⁹ An independent ¹³C n.m.r. study was carried out mostly with non-natural tropanes, and gave preference to boat conformers in addition to other non-chair conformers.¹⁰ The conformations of atropine and scopolamine cations in aqueous solution were found by ¹H and ¹³C n.m.r. spectroscopy¹¹ to be similar to those in the crystalline state,¹² particularly as far as the positions of the phenyl nuclei are concerned. Also, non-equivalence of the pairs of protons at C-2 and C-4, and at C-2 and C-5, respectively, was observed, ultimately not altering the previous conclusions as to a somewhat flattened chair conformation of these alkaloids.¹³

An unusual magnetic equivalence in the ¹H n.m.r. spectrum of *N*-benzoylnorecgonine ester was observed, in contrast with cocaine.¹⁴ The crystal structure of *O*-benzoyltropine hydrochloride, determined by *X*-ray analysis, showed that the cation does not have the over-all shape and dimensions¹⁵ characteristic of potent anticholinergic agents. The 3β- and 3α-propanilido-tropanes have been synthesized and were studied by g.l.c. and n.m.r. analysis.¹⁶ The 3β-isomers exist in the chair form, whereas the 3α-isomers assume a flattened chair conformation, in agreement with a previous study.⁸

2 Synthesis

Two major new routes^{17,18} towards the synthesis of tropanes have appeared now as full papers. First, Noyori has given full details¹⁹ of his novel method of condensing pyrroles with tetrabromoacetone to produce 6-tropan-3-ones (10) in



the presence of di-iron enneacarbonyl, and this has now been done with a zinc-copper alloy. Also, the efficient removal of iron, with EDTA, is described. Secondly, Tufariello *et al.*²⁰ have described the nitron route (11)→(12)→(13)→(14)→(15) previously designed as a pseudotropine synthesis, leading to (±)-cocaine.

⁸ R. J. Bishop, G. Fodor, A. R. Katritzky, F. Soti, L. E. Sutton, and L. J. Swinbourne, *J. Chem. Soc. (C)*, 1966, 74.

⁹ H.-J. Schneider and L. Sturm, *Angew. Chem. Internat. Edn.*, 1976, **15**, 545.

¹⁰ P. Hanisch, A. J. Jones, A. F. Casey, and J. E. Coates, *J. C. S. Perkin II*, 1977, 1202.

¹¹ J. Feeney, R. Foster, and E. A. Piper, *J. C. S. Perkin II*, 1977, 2016.

¹² P. J. Pauling and T. J. Petcher, *Chem. Comm.*, 1969, 1001; *Nature*, 1970, **228**, 673.

¹³ N. Mandava and G. Fodor, *Canad. J. Chem.*, 1968, **46**, 2761.

¹⁴ V. I. Stenberg, S. P. Singh, and N. K. Narain, *J. Org. Chem.*, 1977, **42**, 2244.

¹⁵ Th. A. Hamor, *J. C. S. Perkin II*, 1977, 1359.

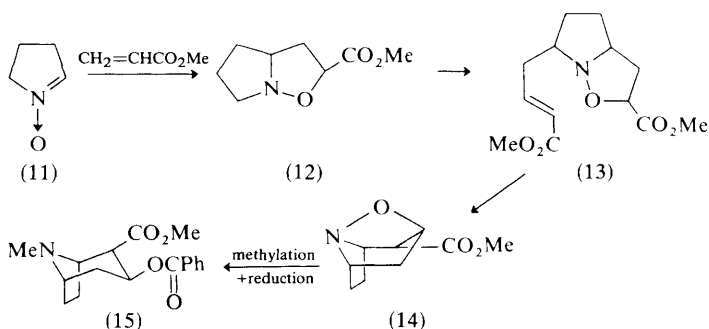
¹⁶ J. R. Bagley and Th. N. Riley, *J. Heterocyclic Chem.*, 1977, **14**, 599.

¹⁷ See 'Tropane Alkaloids', in these Reports, Vol. 5, p. 69; Vol. 6, p. 67.

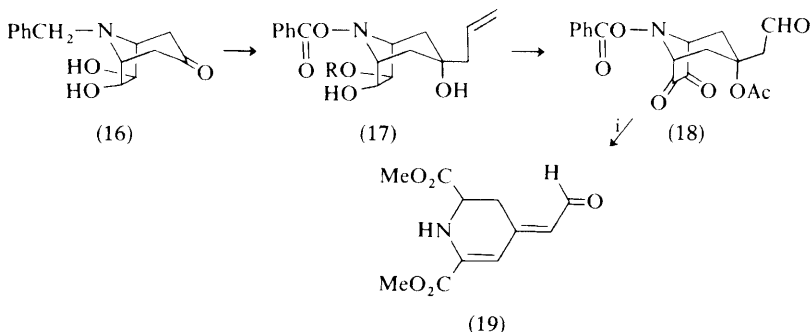
¹⁸ See 'Tropane Alkaloids', in these Reports, Vol. 7, p. 50.

¹⁹ Y. Hayakawa, Y. Baba, S. Makino, and R. Noyori, *J. Amer. Chem. Soc.*, 1978, **100**, 1786.

²⁰ J. J. Tufariello and G. B. Mullen, *J. Amer. Chem. Soc.*, 1978, **100**, 3638; *cf.* Tufariello *et al.*, *Tetrahedron Letters*, 1978, 1733.



In addition, the synthesis of nor-anatoxin- α and - α^1 from cocaine¹⁸ was published.²¹ As a new development, betalamic acid, the major building block of the betalaine pigments, was prepared as its dimethyl ester (19)²² from *N*-benzyl-norteloidinone (16) *via* the major intermediates (17) and (18), as shown in Scheme 1.



Reagents: i, $\text{Pb}(\text{OAc})_4$, PhH, MeOH

Scheme 1

Teloidinone was utilized²³ as a starting material for the synthesis of a showdomycin analogue (23), a *C*-nucleoside, in which the ribofuranosyl ring oxygen was replaced by a *N*-carbomethoxy-group. The main steps are (20) \rightarrow (21) \rightarrow (22) \rightarrow (23). Selective *N*-demethylation, *inter alia*, of tropanols²⁴ with vinyl chloroformate has been achieved without protecting the hydroxy-group.

Three recent papers deal with the improvement of the synthesis of norcocaine. First, oxidation of cocaine (24) with permanganate in acetonitrile,²⁵ acidified with acetic acid, gave 95% yield (about 50% conversion) of norcocaine (25a) with some *N*-benzoyllecgonine ester (25b); this, with dioxan and HCl, underwent *N*- \rightarrow *O*-acyl migration to form the same product, similarly to *N*-benzoyllecgonine itself.²⁶

²¹ H. F. Campbell, O. E. Edwards, and R. Kolt, *Canad. J. Chem.*, 1977, **55**, 1372.

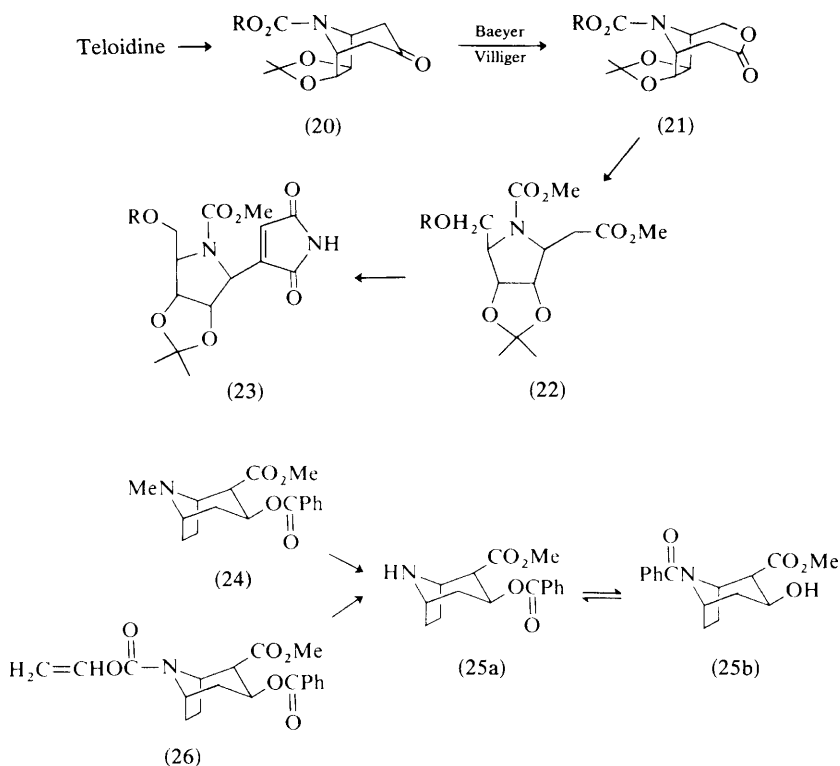
²² G. Büchi, H. Fliri, and R. Shapiro, *J. Org. Chem.*, 1977, **42**, 2192.

²³ G. Just and G. P. Donnini, *Canad. J. Chem.*, 1977, **55**, 2998.

²⁴ R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *Tetrahedron Letters*, 1977, 1567.

²⁵ V. I. Stenberg, N. K. Narain, S. P. Singh, and S. S. Parmar, *J. Heterocyclic Chem.*, 1976, **13**, 363.

²⁶ O. Kovacs, G. Fodor, and I. Weisz, *Helv. Chim. Acta*, 1954, **37**, 905.



Demethylation of cocaine was also achieved by 2,2,2-trichloroethyl chloroformate^{27,28} and reduction, or by using²⁷ Ollofson's reagent,²⁴ vinyl chloroformate, [via (26)] and subsequent cleavage²⁷ of the vinyloxycarbonyl group with mild acid. *N*-Allylnorcocaine [*N*-allyl-(22a)] has been synthesized,²⁹ for biological screening in monkeys. The cycloheptadienone route to tropanones and, in turn, to 3 α -tropanols was applied to alanine ester and other derivatives.³⁰

A large number of new tropanyl esters and other related compounds have been prepared, with the purpose of contributing further structure-pharmacological activity relationships. *Inter alia*, *para*-substituted tropanyl benzoates³¹ (for studies of the substrate specificity of atropine esterase), benzazocines (narcotic antagonists) from 6-hydroxytropanone,³² 5-aryl-furan-2-carboxylic esters³³ of pseudotropine (local anaesthetics), 2,4,5-trimethylpyrrole-3-carboxylic acid

²⁷ S. W. Baldwin, P. W. Jeffs, and S. Natarajan, *Synth. Commun.*, 1977, **7**, 79.

²⁸ R. F. Borne, J. A. Bedford, J. L. Buelke, D. C. Craig, Th. C. Hardin, A. H. Kribbe, and M. C. Wilson, *J. Pharmacol. Sci.*, 1977, **66**, 119.

²⁹ A. H. Kribbe, J. A. Bedford, R. F. Borne, and M. C. Wilson, *Pharmacol. Res. Commun.*, 1977, **9**, 367.

³⁰ Y. Cherkez and H. Yellin, *Israeli P.* 39 236, 1977 (*Chem. Abs.*, 1977, **87**, 84 847).

³¹ J. Wallace, M. S. Kidd, S. E. Canthen, and J. D. Woodyard, *J. Heterocyclic Chem.*, 1978, **15**, 317.

³² T. A. Montzka and J. D. Matiskella, *J. Med. Chem.*, 1977, **20**, 453.

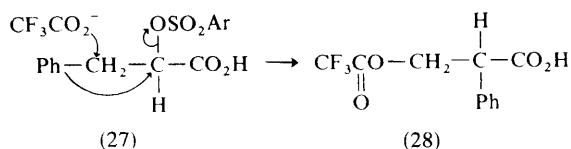
³³ T. I. Vozyakova, N. I. Koretskaya, M. D. Mashkovskii, K. Yu. Novitskii, A. F. Oleinik, and T. K. Trubitsnina, U.S.S.R. P. 508 057 (*Chem. Abs.*, 1977, **87**, 152 449) *cf.* N. I. Koretskaya *et al.*, *Khim-Farm. Zhur.*, 1977, **11**, 33.

esters of tropanols³⁴ (analgesics), polyethylene-glycol carbonates³⁵ of atropine (higher mydriatic *etc.* effects with higher molecular weight), tropinones that are *C*-substituted in the 6-position,³⁶ and derivatives obtained by replacing the hydroxymethyl group of atropine³⁷ (to study the 'third' binding site) have been synthesized. The participation of nitrogen in nucleophilic displacements of tropanes with an electronegative substituent³⁸ (*e.g.*, halogen) has now been amplified with tropanyl methanesulphonates and used in obtaining new tropeines with 'central' activities.³⁹

The epimers of 2-tropanol have been converted into parasymphatholytic esters.⁴⁰ Molecular complexes of cocaine with thiamine were prepared.⁴¹ ³H-labelled (–)-cocaine and -norcocaine were obtained with [³H]methanol.⁴² A synthesis⁴³ of *N*-C²H₃-labelled tropine and atropine from the *N*-ethoxycarbonyl derivatives was carried out by reduction with lithium aluminium deuteride.

A modified technical transesterification method has been elaborated⁴⁴ for 3-tropanyl and 3-granatanyl tropic acid esters, starting with methyl α -formyl-*p*-phenylacetate and tropine in toluene (66% yield) followed by reduction of the formyl group over Raney nickel.

Chemical simulation⁴⁵ of the formation of tropic acid (28) *in vivo* from optically active phenylalanine was achieved by trifluoroacetylation of *O*-*p*-nitrobenzenesulphonyl 3-phenyl-lactic acid (27).



Electrochemical oxidation of tropanes⁴⁶ in acetonitrile involves the formation of methylene-*NN*-bis-nortropanyl, of *NN*-bis-nortropanyl, of *N*-formyl-nortropine, and of *N*-cyanomethyl-nortropane. Dye-sensitized singlet oxygen, produced by laser excitation,⁴⁷ converts tropinone into *N*-formyl-nortropanone in moderate yields. Photochemical demethylation of cocaine to norcocaine has been carried out,⁴⁸ but the yields are less satisfactory than in the 'chemical'

³⁴ J. A. Waters, *J. Med. Chem.*, 1977, **20**, 1094.

³⁵ B. Z. Weiner, A. Zilkha, G. Parath, and Y. Grunfeld, *Eur. J. Med. Chem.-Chim. Ther.*, 1976, **11**, 525.

³⁶ W. Himmele, A. Friederany, H. Siegel, and D. Dieter, Ger. Offen. 2 645 781, 1978 (*Chem. Abs.*, 1978, **89**, 75 413).

³⁷ B.-H. Engel and O. Wassermann, *Arch. Pharm.*, 1976, **309**, 564.

³⁸ A. Archer *et al.*, *J. Amer. Chem. Soc.*, 1958, **80**, 4677.

³⁹ K. Nador, *Arzneim-Forsch. (Drug Res.)*, 1976, **26**, 1797.

⁴⁰ E. R. Atkinson, D. McRitchie, L. F. Shoer, L. S. Harris, S. Archer, M. D. Aceto, J. Pearl and F. P. Ludnena, *J. Med. Chem.*, 1977, **20**, 1612.

⁴¹ A. L. Misra and N. L. Vadlamani, *Res. Commun. Chem. Pathol. Pharmacol.*, 1976, **15**, 401.

⁴² W. J. Just and G. Werner, *J. Labelled Compd. Radiopharm.*, 1976, **12**, 281.

⁴³ V. A. Fung and J. I. DeGraw, *Synthesis*, 1976, 311.

⁴⁴ W. Schulz, R. Banholzer, and K.-H. Pook, *Arzneim-Forsch. (Drug Res.)* 1976, **26**, 960.

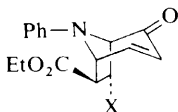
⁴⁵ S. Yamada, K. Koga, T. M. Juang, and K. Achiwa, *Chem. Lett.*, 1976, 927.

⁴⁶ B. L. Laube, M. R. Asirvatham, and C. K. Mann, *J. Org. Chem.*, 1977, **42**, 670.

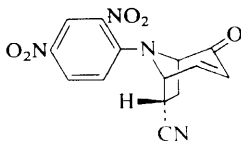
⁴⁷ D. F. Evans and J. N. Tucker, *J. C. S. Faraday II*, 1976, **72**, 1661.

⁴⁸ V. I. Stenberg, S. P. Singh, N. K. Narain, and S. S. Parmar, *J. C. S. Chem. Comm.*, 1976, 262.

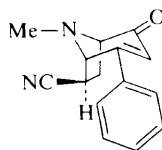
oxidative demethylation.²⁵ The novel route^{49–51} from *N*-substituted 3-oxido-pyridinium betaines by 1,3-dipolar addition has opened the way to a variety of 2-tropanones, *e.g.* (29), (30), and (31).



(29) X = Ph, 4-pyridyl, CO₂Me, or CN



(30)



(31)

3 Pharmacology

Presynaptic tryptamine receptors are selectively blocked⁵² by (–)-cocaine and (+)-cocaine. The tolerance and cross-tolerance to cocaine and *d*-amphetamine on milk intake of rats was determined.⁵³ Hydrolysis of [¹⁴C]cocaine in human serum has been monitored by t.l.c. and g.l.c.; after 1 hour (20% of the cocaine hydrolysed), ecgonine methyl ester was the major product; it had not hitherto been observed in humans. After 4 hours (67% hydrolysis), benzoylecgonine and ecgonine (1.6 to 1) were found; τ_1 was 2.5 hours in human serum.⁵⁴

The metabolism of cocaine was inhibited by SKF-525A, a microsomal enzyme inhibitor.⁵⁵ The relationship between the pharmacological activity of cocaine and its derivatives and the inhibitory action on uptake of dopamine into striatal synaptosomes has been studied.⁵⁶ [*N*-¹⁴CH₃]cocaine was metabolized in healthy humans; the production of labelled carbon dioxide provided a measure of *N*-demethylation, which proved to be greater with lower plasma cholinesterase activity.⁵⁷ Radioactivity excreted in the urine was 65–75% in 28 hours, and ecgonine methyl ester proved to be the major metabolite (32–49% of urinary metabolites).

Isomers of cocaine and tropacocaine affect the uptake of [³H]catecholamine by rat brain synaptosomes.⁵⁸

A series of papers^{59–61} deal with the pharmacology of the anti-asthmatic drug ipratropium bromide (32).

⁴⁹ N. Dennis, A. R. Katritzky, S. K. Parton, Y. Nomura, Y. Takahashi, and Y. Jakerichi, *J. C. S. Perkin I*, 1976, 2289.

⁵⁰ N. Dennis, A. R. Katritzky, and R. Rittner, *J. C. S. Perkin I*, 1976, 2329.

⁵¹ J. Banerji, N. Dennis, J. Frank, A. R. Katritzky, and T. Matsuo, *J. C. S. Perkin I*, 1976, 2334.

⁵² J. R. Fozard, A. T. M. Mobarok Ali, and G. Newgrosh, Proceedings of the B. P. S. 13–15th July 1977, p. 130.

⁵³ W. L. Woolverton, D. Kandel, and C. R. Schuster, *J. Pharmacol. Exp. Ther.*, 1978, **208**, 525.

⁵⁴ D. Taylor, V. S. Estevez, L. F. Englert, and B. T. Ho, *Res. Commun. Chem. Pathol. Pharmacol.*, 1976, **14**, 179.

⁵⁵ V. S. Estevez, B. T. Ho, and L. F. Englert, *Res. Commun. Chem. Pathol. Pharmacol.*, 1977, **17**, 179.

⁵⁶ N. Williams, D. H. Couet, A. L. Misra, and S. Mule, *Prog. Neuro-Psychopharmacol.*, 1977, **1**, 265.

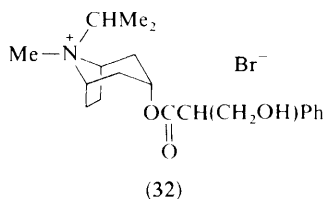
⁵⁷ T. Inaba, D. J. Stewart, and W. Kalow, *Clin. Pharmacol. Ther.*, 1978, **23**, 547.

⁵⁸ H. J. Komiskey, D. D. Miller, J. LaPidus, and P. N. Patil, *Life Sciences*, 1977, **21**, 1117.

⁵⁹ S. Yanaura, Y. Yamatake, and Y. Okamiya, *Oyo Yakuri*, 1978, **15**, 223 (*Chem. Abs.*, 1978, **89**, 33 466).

⁶⁰ Y. Savzo, Y. Yamatake, and Y. Okamiya, *Oyo Yakuri*, 1978, **15**, 31 (*Chem. Abs.*, 1978, **89**, 17 087).

⁶¹ H. J. Forester, I. Kramer, K.-H. Pook, and D. Wahl, *Arzneim.-Forsch. (Drug Res.)* 1976, **26**, 992.



4 Analytical Aspects

Carbon-13 n.m.r. and mass spectrometry have become essential methods in quantitative analysis of alkaloid mixtures extracted from plants, in addition to g.l.c. and photometry. Study of the mechanism of fragmentation⁶² of 3-substituted tropanes is a useful tool for analysis of mixtures of tropane alkaloids. A comprehensive study⁶³ on the ¹³C n.m.r. spectroscopy of tropane alkaloids included most major representatives of this class. Other papers^{64,77} deal with the ¹³C n.m.r. spectra of cocaine metabolites and derivatives. A radioimmunoassay of atropine and benzoylecgonine in urine was published.^{65,68} Photometric determination of tropane derivatives in chloroform extracts was done *via* colorimetry of the bromocresol purple complex.⁶⁶ Adsorption chromatography methods have been used with different resins.⁶⁷

Thin-layer chromatography, using π -acceptors for detecting alkaloids, has been developed.⁶⁹ The measurement of benzoylecgonine and cocaine in urine and the separation of various cocaine metabolites by reverse-phase high-performance liquid chromatography have recently been described.⁷⁰ Gas-liquid chromatography enabled the quantitative determination of cocaine in human urine, plasma, and blood cells, after extraction with cyclohexane.⁷¹ Thin-layer chromatography was used for the differentiation⁷² of the optical isomers of cocaine; also for the detection of benzoylecgonine in human urine.⁷³ The same compound and cocaine were quantitatively determined in human biofluids by g.l.c.^{74,76} The separation of a large number of tropane and of opium and other alkaloids on silica gel, by partition chromatography, and in methanol-chlorinated hydrocarbon mixtures has been studied.⁷⁵ A futile attempt was made⁷⁸ to convert

⁶² H. Gruetzmacher and G. Lange, *Chem. Ber.*, 1978, **111**, 1962.

⁶³ A. M. Taha and G. Rücker, *J. Pharmacol. Sci.*, 1978, **67**, 775.

⁶⁴ J. K. Bauer and R. F. Borne, *J. Heterocyclic Chem.*, 1978, **15**, 165.

⁶⁵ R. J. Wurzbürger, R. L. Miller, H. G. Boxenbaum, and S. Spector, *J. Pharmacol. Exp. Ther.*, 1977, **203**, 435.

⁶⁶ N. T. Bubon and P. L. Senov, *Farmatsiya*, 1977, **26**, 34.

⁶⁷ F. T. Dulbeke and M. Debackere, *J. Chromatog.*, 1977, **136**, 385.

⁶⁸ S. J. Mule, D. Jukofsky, M. Kogan, A. DePace, and K. Verebey, *Clin. Chem.*, 1977, **23**, 796.

⁶⁹ G. Rücker and A. Taha, *J. Chromatog.*, 1977 **132**, 165.

⁷⁰ P. I. Jatlow, C. van Dyke, P. Barash, and R. Bick, *J. Chromatog.*, 1978, **152**, 115.

⁷¹ J. I. Javaid, H. Dekirmeryian, J. M. Davis, and C. R. Schuster, *J. Chromatog.*, 1978, **152**, 105.

⁷² D. Erkes, *J. Chromatog.*, 1978, **152**, 589.

⁷³ M. A. Mueller, S. A. Adams, D. L. Lewand, and R. I. H. Wang, *J. Chromatog.*, 1977, **144**, 107.

⁷⁴ M. J. Kogan, K. G. Verebey, A. C. DePace, R. B. Resmick, and S. J. Mulé, *Anal. Chem.*, 1977, **49**, 1965.

⁷⁵ R. L. Munier and A.-M. Drapier, *Compt. rend.*, 1976, **283**, C, 719.

⁷⁶ D. L. V. Minden and N. A. D'Amato, *Anal. Chem.*, 1977, **49**, 1974.

⁷⁷ V. I. Stenberg, N. K. Narian, and S. P. Singh, *J. Heterocyclic Chem.*, 1977, **14**, 225.

⁷⁸ M. Wiechmann, *Z. Physiol. Chem.*, 1977, **358**, 967.

nor-amines into the sulphonamides with dansyl chloride (Hinsberg test) and then to subject these to thin-layer chromatography. Gas-liquid chromatography combined with mass spectrometry, using stable isotope-labelled analogues as internal standards, helped in the development of an ultra-micro-determination of cocaine, benzoylecgonine, and other metabolites in human urine.⁷⁹

⁷⁹ S. P. Jindal and P. Vestergaard, *J. Pharm. Sci.*, 1978, **67**, 811.

4

Pyrrolizidine Alkaloids

BY D. J. ROBINS

A useful summary of data on pyrrolizidine alkaloids has appeared,¹ although the presence of a number of mistakes was noted (*e.g.* necic acids are referred to as 'terpenoid carboxylic acids'). A review (in Japanese) on the chemistry of the pyrrolizidine alkaloids has been published.²

1 Syntheses of the Necine Bases

Danishefsky and co-workers have developed a novel route to saturated pyrrolizidine alcohols.³ Stereospecific syntheses of (\pm)-trachelanthamidine (7) and (\pm)-isoretronecanol (8) were achieved (Scheme 1). The (*Z*)-diazomalonate (2) was prepared in a number of steps from the lithium salt of propargyl alcohol tetrahydropyranyl ether (1). Cyclopropanation to give (3) was carried out by refluxing (2) with copper bronze for 22 h in toluene and utilized the *syn*-addition of carbenoids to double bonds. Treatment of the activated cyclopropane (3) with excess hydrazine released the free amine, which underwent intramolecular homoconjugate addition with complete inversion of stereochemistry to give the pyrrolizidine hydrazide (4). Removal of the hydrazide function of (4) produced a salt containing a γ -lactone function which was assigned the structure (5). The pyrrolizidine system (6) was regenerated using sodium methoxide, and a final reduction step yielded (\pm)-trachelanthamidine (7). Careful analysis of the pyrrolizidine derivative (6) by ¹H 250 MHz n.m.r. spectroscopy showed that there was no contamination with the C-1 epimeric compound. Analogous treatment of the (*E*)-isomer of (2) afforded (\pm)-isoretronecanol (8).

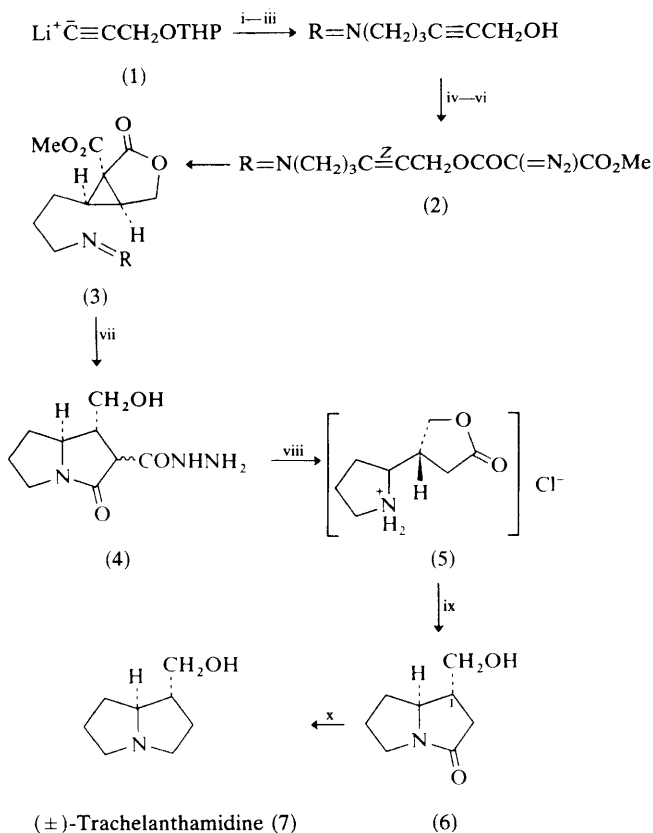
Danishefsky *et al.*⁴ have extended this strategy to synthesize necines with hydroxyl functions at C-7, namely (\pm)-hastanecine (12) and (\pm)-dihydroxy-heliotridane (13). This route is outlined in Scheme 2. Production of the diazomalonate (10) from the (*Z*)-olefin (9) was carried out in a manner related to their previous syntheses.³ Intramolecular insertion of the carbenoid derived from (10) was again highly stereospecific, yielding the bicyclo[3.1.0]oxohexanone system (11) with the phthalimidoethyl group in the *exo*-configuration. Ring

¹ H. C. S. Wood and R. Wigglesworth, in 'Rodd's Chemistry of Carbon Compounds,' ed. S. Coffey, Elsevier Scientific Publishing Company, Amsterdam, 1977, 2nd edn., vol. IVB, Ch. 8.

² T. Furuya and M. Hikichi, *Yuki Gosei Kagaku Kyokaiishi*, 1977, **35**, 653 (*Chem. Abs.*, 1977, **87**, 201 828).

³ S. Danishefsky, R. McKee, and R. K. Singh, *J. Amer. Chem. Soc.*, 1977, **99**, 4783.

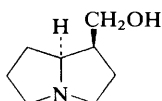
⁴ S. Danishefsky, R. McKee, and R. K. Singh, *J. Amer. Chem. Soc.*, 1977, **99**, 7711.



THP = tetrahydropyranyl; R = *o*-phthaloyl

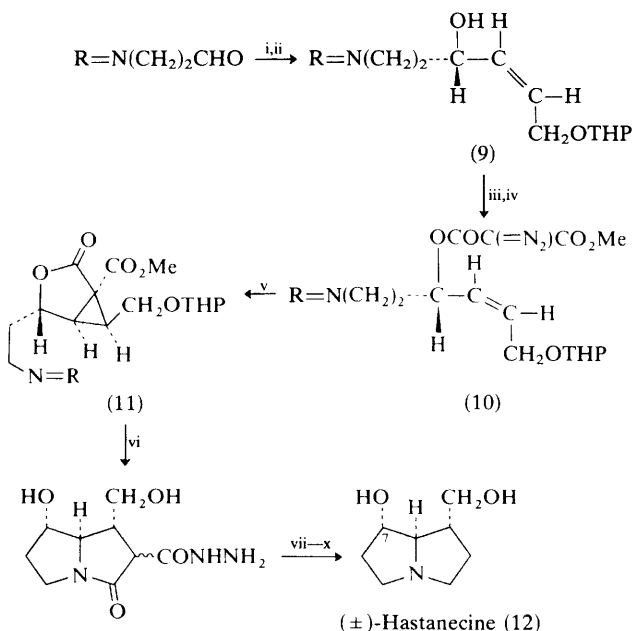
Reagents: i, $\text{Br}(\text{CH}_2)_3\text{Br}$; ii, K phthalimide; iii, H^+ ; iv, $\text{MeO}_2\text{CCH}_2\text{COCl}$; v, H_2 -5% Pd/BaSO₄, quinoline; vi, TsNHNH₂; vii, NH₂NH₂; viii, HCl; ix, NaOMe; x, LiAlH₄

Scheme 1



(±)-Isoretronecanol (8)

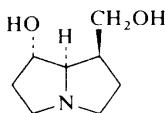
opening of the cyclopropane (11) again occurred with inversion of configuration, and (±)-hastanecine (12) was formed in a parallel fashion to (±)-trachelanthamide (7). In order to prepare the epimeric pyrrolizidine (13), the (*Z*)-olefin (9) was converted into the (*E*)-isomer *via* the (*E*)-enone (formed by Corey oxidation), followed by reduction with borohydride. Analogous treatment of this (*E*)-isomer (as in Scheme 2) eventually yielded dihydroxyheliotridane (13).



THP = tetrahydropyranyl; R = *o*-phthaloyl

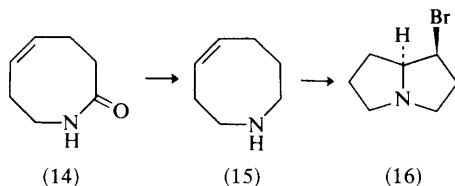
Reagents: i, $\text{Mg}^{2+}[\text{C}\equiv\text{CCH}_2\text{OTHP}]_2$; ii, H_2 -5% Pd/BaSO₄, quinoline; iii, $\text{MeO}_2\text{CCH}_2\text{COCl}$; iv, TsNHNH₂; v, Cu bronze; vi, NH_2NH_2 ; vii, HCl; viii, NaOMe; ix, pyridine, Ac₂O; x, LiAlH_4

Scheme 2



(±)-Dihydroxyheliotridane (13)

Wilson and Sawicki⁵ have developed a transannular route to the potentially useful intermediate 1-bromopyrrolizidine (16), from which some naturally occurring 1-substituted pyrrolizidines could be synthesized (Scheme 3). The

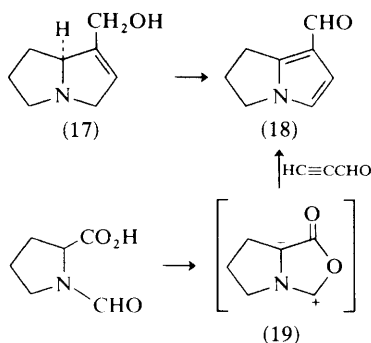


Scheme 3

⁵ S. R. Wilson and R. A. Sawicki, *J.C.S. Chem. Comm.*, 1977, 431.

lactam (14) was prepared by Beckmann rearrangement of the oxime toluene-*p*-sulphonate of cyclohept-4-enone. Reduction of (14) with lithium aluminium hydride gave the amine (15), which on transannular bromination yielded (\pm)-1-bromopyrrolizidine (16) stereospecifically. The authors suggest that formation of the *endo*-substituted pyrrolizidine (16) corresponds to a disfavoured *exo*-mode of cyclization⁶ by attack of the nitrogen on the bromonium ion.

The butterfly pheromone (18) was previously prepared by the oxidation of the necine base supinidine (17) (Scheme 4).⁷ A simple synthesis of this pheromone has now been reported by Pizzorno and Albonico.⁸ Regiospecific 1,3-cyclo-addition of propargylic aldehyde with the postulated⁹ azomethine ylide intermediate (19), formed by refluxing *N*-formylproline in acetic anhydride with 2,6-di-*t*-butyl-4-methylphenol as anti-oxidant, gave a 40% yield of the dihydropyrrolizine (18).



Scheme 4

2 Alkaloids of the Boraginaceae

Three new alkaloids which are esters of (-)-trachelanthamidine (7) have been isolated from *Heliotropium curassavicum* L. by Mohanraj *et al.*¹⁰ Alkaline hydrolysis of the major ester constituent, curassavine, gave an acid, C₈H₁₆O₄. The ¹H n.m.r. spectrum (taken in [2H₅]pyridine) showed the presence of an ethyl group (3H t at δ 0.96), MeCH-(3H d at δ 1.19), and MeCHOH-(3H d at δ 1.66). The rest of the signals were consistent with the structure (20). Oxidation of the methyl ester of (20) with periodate gave a ketone formulated as MeCH₂CHMe-COCO₂Me. (The mass spectrum lacked signals at *m/e* 71 and 43 which would have arisen from the presence of an isopropyl group in alternative formulations.) The configuration of the glycol group is presumed to be *erythro*, because of the similar electrophoretic mobility to another *erythro*-acid, viridifloric acid; hence the proposed name for the new acid is (\pm)-homoviridifloric acid (20). This

⁶ J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734.

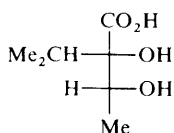
⁷ C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Austral. J. Chem.*, 1970, **23**, 1869.

⁸ M. T. Pizzorno and S. M. Albonico, *Chem. and Ind.*, 1978, 349.

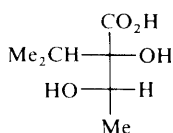
⁹ R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Chem. Ber.*, 1970, **103**, 2611.

¹⁰ S. Mohanraj, P. S. Subramanian, C. C. J. Culvenor, J. A. Edgar, J. L. Frahn, L. W. Smith, and P. A. Cockrum, *J.C.S. Chem. Comm.*, 1978, 423.

is the first example of a C₈ monocarboxylic necic acid. Biogenetically, it has a reasonable derivation from isoleucine by addition of a two-carbon fragment at the α -carbon of isoleucine, analogous to the formation of echimidinic acid [MeCH(OH)C(OH)(CO₂H)C(OH)Me₂] from valine and a two-carbon fragment.¹¹ The acid components of the two minor alkaloids are also interesting. Coromandalin contains another new acid, (+)-viridifloric acid (21); and heliovine is the ester of (-)-trachelanthamidine with (-)-trachelanthic acid (22). Both these acids have the unusual (2*R*) configuration.



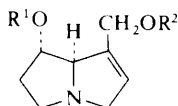
(+)-Viridifloric acid (21)



(-)-Trachelanthic acid (22)

The alkaloidal constituents of *Heliotropium curassavicum* have also been examined by Rajagopalan and Batra.¹² Surprisingly, they identified the known heliotridine esters heliotrine (23), lasiocarpine (24), and 7-angelylheliotridine (25). The differences between these two separate investigations may be due to this widespread species having developed markedly different populations.¹⁰

The *N*-oxide of europine (26) has been isolated from *Heliotropium marismortui* and *H. rotundifolium*.¹³ Echinatine (27) was present in *Lapulla glochidiata*.¹⁴



Heliotrine	(23) R ¹ = H, R ² = COC(CHMe ₂)(OH)CH(OMe)Me
Lasiocarpine	(24) R ¹ = (<i>Z</i>)-COCMe=CHMe, R ² = COC(CMe ₂ OH)(OH)CH(OMe)Me
7-Angelylheliotridine	(25) R ¹ = (<i>Z</i>)-COCMe=CHMe, R ² = H
Europine	(26) R ¹ = H, R ² = COC(CHMeOMe)(OH)C(OH)Me ₂
Echinatine	(27) R ¹ = H, R ² = COC(CHMe ₂)(OH)CH(OH)Me

3 Alkaloids of the Compositae

A new alkaloid, yamataimine (28), has been isolated from the roots of *Cacalia yatabei* Maxim. by Hikichi *et al.*¹⁵ The ¹H n.m.r. spectrum of (28) was typical of a twelve-membered macrocyclic diester of retronecine, particularly in the chemical

¹¹ D. H. G. Crout, *J. Chem. Soc. (C)*, 1966, 1968.

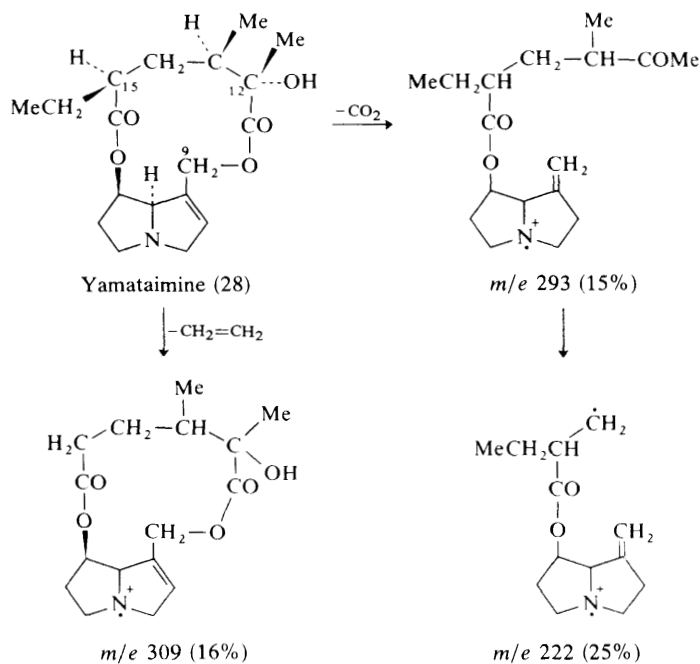
¹² T. R. Rajagopalan and V. Batra, *Indian J. Chem., Sect. B* 1977, **15**, 494.

¹³ L. H. Zalkow, L. Gelbaum, and E. Keinan, *Phytochemistry*, 1978, **17**, 172.

¹⁴ K. Suri, O. P. Suri, K. L. Dhar, and C. K. Atal, *Indian J. Chem., Sect. B*, 1978, **16**, 78.

¹⁵ M. Hikichi, T. Furuya, and Y. Iitaka, *Tetrahedron Letters*, 1978, 767.

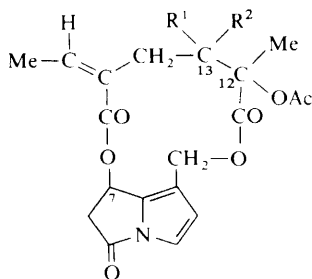
shift between the protons at C-9 of 1.22 p.p.m. High-resolution mass spectrometry established the presence of a C_{10} acid, and the fragment ions at m/e 309, 293, and 222 (Scheme 5), indicated that the ethyl group (n.m.r. data) was located at C-15, and one hydroxy-group was at C-12 in the necic acid. The structure (28) and the absolute configuration were established by X-ray analysis of the hydrobromide salt. The new necic acid is of a common C_{10} structural type, but the (12*S*)-configuration is less common.



Scheme 5

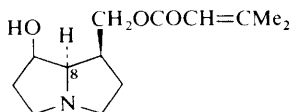
In last year's Report, reference was made to the discovery of three examples of a new type of pyrrolizidine alkaloid containing the dihydropyrrolizinone ring system. Two closely related acyl-pyrroles have now been detected in aerial parts of *Kleinia kleinoides* (Sch. Bip.) M. R. F. Taylor by Bohlmann and Knoll.¹⁶ Spectral data on the first pyrrole showed it to be an isomer of senaetnine (29), with different stereochemistry at C-7, C-12, or C-13. Lack of material prevented clarification of the stereochemistry of isosenaetnine (29). The second new compound differed from isosenaetnine in replacement of one methyl group by methylene, and it is therefore formulated as dehydroisosenaetnine (30). The stereochemistry is again uncertain.

¹⁶ F. Bohlmann and K.-H. Knoll, *Phytochemistry*, 1978, **17**, 599.



Senaetnine and Isosenaetnine (29) $R^1 = H$, $R^2 = Me$
 Dehydroisosenaetnine (30) $R^1 R^2 = CH_2$

Previous investigation of *Senecio fuchsii* C. C. Gmel. demonstrated the presence of an alkaloid, $C_{12}H_{21}NO_3$, named fuchsisenecionine.¹⁷ Re-examination of this species by Röder and Wiedenfeld¹⁸ has shown that fuchsisenecionine has the molecular formula $C_{13}H_{21}NO_3$, and structure (31) is put forward by the



(31)

authors on the basis of the following evidence. The alkaloid was isolated after g.l.c. separation of the basic extract. Hydrolysis of fuchsisenecionine gave senecioic acid and a saturated necine, $C_8H_{15}NO_2$, isolated as the gold chloride salt, which was probably platynecine or a stereoisomer (mass spectral data). The absence of a peak at m/e 140 in the mass spectrum of the necine indicated that the hydroxymethyl and H-8 are *trans*-disposed. In the i.r. spectrum of the necine, two peaks at 1070 and 1125 cm^{-1} are ascribed to the primary and secondary hydroxyl functions, respectively. The absence of absorption at 1070 cm^{-1} in the alkaloid spectrum is taken as evidence that the primary hydroxy-group is esterified with senecioic acid. Comparison of chemical and spectral data with known values for the necine bases and their derivatives would have been helpful in establishing the identity of this necine base.

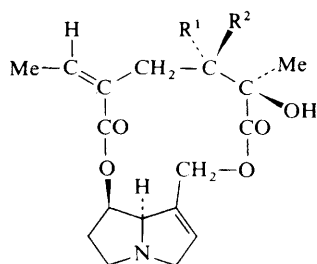
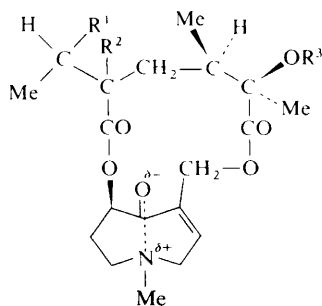
In an earlier study,¹⁹ the presence of otosenine (32), onetine (33), and seneciophylline (36) was established in *Senecio othonnae* Bieb. Russian workers²⁰ have now isolated doronine (34), otosenine (32), and floridanine (35) from the same species. Curiously, these are exactly the same constituents reported by the same workers from *Doronicum macrophyllum* (see last year's Report).

¹⁷ A. Müller, *Heil. Gewurzpflanzen*, 1924, 7, 1.

¹⁸ E. Röder and H. Wiedenfeld, *Phytochemistry*, 1977, 16, 1462.

¹⁹ A. V. Danilova, N. I. Koretskaya, and L. M. Utkin, *Zhur. obschchei Khim.*, 1962, 32, 647 (*Chem. Abs.*, 1963, 58, 2477).

²⁰ D. S. Khalilov, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 866 (*Chem. Abs.*, 1978, 88, 101 593).



Otosenine (32) $R^1R^2 = \alpha\text{-epoxide}$, $R^3 = \text{H}$

Onetine (33) $R^1 = R^2 = \text{OH}$, $R^3 = \text{H}$

Doronine (34) $R^1 = \text{Cl}$, $R^2 = \text{OH}$, $R^3 = \text{COMe}$

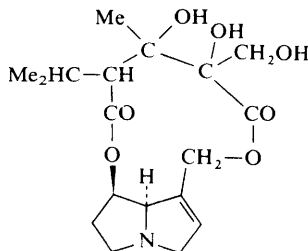
Floridanine (35) $R^1 = R^2 = \text{OH}$, $R^3 = \text{COMe}$

Seneciophylline (36) $R^1R^2 = \text{CH}_2$

Senecionine (37) $R^1 = \text{H}$, $R^2 = \text{Me}$

4 Alkaloids of the Leguminosae

Junceine (38) has been detected by Khanna and Manot²¹ in unorganized callus of *Crotalaria juncea* L. established from seedlings and grown on a standard medium. The maximum yield of junceine obtained was 0.6 mg per g of dried tissue. Previous investigation of seeds of *C. juncea* had shown the presence of five alkaloids, including junceine.²²



Junceine (38)

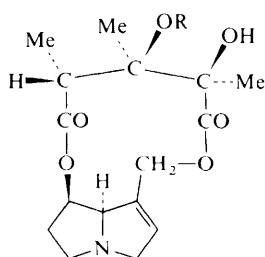
The seeds of *Crotalaria grahamiana* R. Wight et Walk.-Arn. have previously been shown²³ to contain grahamine (39) and monocrotaline (40). Rajagopalan and Batra²⁴ now report the occurrence of monocrotaline, together with a new alkaloid, monocrotalinine (41). The structure was confirmed by mild acid hydrolysis of (41) to give monocrotaline (40) and acetaldehyde, isolated as its 2,4-dinitrophenylhydrazone derivative. It should be pointed out that acetaldehyde is rare in biological systems, but not in refluxing ethanol (used for the extraction), and the possibility that this new alkaloid is an artefact has not been excluded by the authors.

²¹ P. Khanna and S. K. Manot, *Indian J. Exp. Biol.*, 1977, **15**, 807.

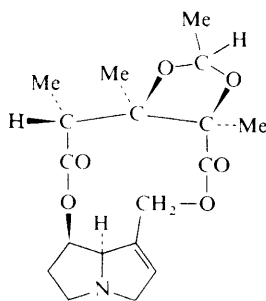
²² R. Adams and M. Gianturco, *J. Amer. Chem. Soc.*, 1956, **78**, 1919.

²³ C. K. Atal, C. C. J. Culvenor, R. S. Sawhney, and L. W. Smith, *Austral. J. Chem.*, 1969, **22**, 1773.

²⁴ T. R. Rajagopalan and V. Batra, *Indian J. Chem., Sect. B*, 1977, **15**, 455.

Grahamine (39) R = COCHMeCH₂Me

Monocrotaline (40) R = H



Monocrotaline (41)

5 Alkaloids of the Ranunculaceae

Senecionine (37) has been isolated by Stermitz and Adamovics²⁵ from the roots and aerial parts of *Caltha leptosepala* DC. and *C. biflora* DC. in very low yield (0.001—0.005% of dry weight), together with known aporphine alkaloids. This is the first report of pyrrolizidine alkaloids in the Ranunculaceae, and the first recorded co-occurrence of pyrrolizidine and aporphine alkaloids.

6 Alkaloids in Animals

Harborne²⁶ has reviewed the presence of secondary metabolites in animals from a taxonomic point of view. The occurrence of pyrrolizidine alkaloids of dietary origin in butterflies of the Danainae is discussed. The aposematic grasshopper *Zonocerus variegatus* has been shown by Bernays *et al.*²⁷ to sequester and store monocrotaline (40), obtained from its food plant, *Crotalaria retusa* L. No function for this stored pyrrolizidine alkaloid has yet been established.

7 General Studies

A large-scale extraction apparatus, employing ion-exchange resins, has been used for extracting pyrrolizidine alkaloids from *Senecio jacobaea*.²⁸ Isolation of platyphylline and seneciphylline (36) by electrodialysis of an extract from *S. platyphylloides* has been achieved by Russian workers.²⁹ Purification of the alkaloidal mixture was aided by electrochemical reduction of the extract.³⁰ H.p.l.c. has been used to separate alkaloidal extracts from *S. vulgaris*,³¹ *S. longilobus* (= *S. douglasii*),³² and *S. jacobaea*.³³ The major alkaloids were identified by mass

²⁵ F. R. Stermitz and J. A. Adamovics, *Phytochemistry*, 1977, **16**, 500.

²⁶ J. B. Harborne, *Pure Appl. Chem.*, 1977, **49**, 1403.

²⁷ E. Bernays, J. A. Edgar, and M. Rothschild, *J. Zool.*, (Lond.), 1977, **182**, 85.

²⁸ J. T. Deagen and M. L. Deinzer, *Lloydia*, 1977, **40**, 395.

²⁹ E. A. Vdoviko, S. A. Pokhmelkina, V. V. Petrenko, and N. I. Chernenko, *Khim. Prirod. Soedinenii*, 1977, 831 (*Chem. Abs.*, 1978, **88**, 126 258).

³⁰ E. A. Vdoviko, S. A. Pokhmelkina, and V. V. Petrenko, U.S.S.R. P. 556 138 (*Chem. Abs.*, 1977, **87**, 172 872).

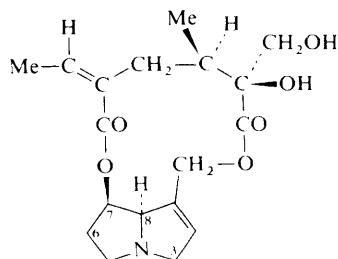
³¹ C. W. Qualls, and H. J. Segall, *J. Chromatog.*, 1978, **150**, 202.

³² H. J. Segall and R. J. Molyneux, *Res. Comm. Chem. Pathol. Pharmacol.* 1978, **19**, 545.

³³ H. J. Segall, *Toxicol. Letters*, 1978, **1**, 279.

spectrometry, and confirmed previous findings. Several minor components were detected, but not identified.

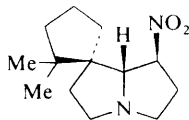
The mass spectra of pyrrolizidine alkaloids have been reviewed by Russian authors.³⁴ The ^{13}C n.m.r. spectrum of retrorsine (42), obtained from *Senecio selloi*



Retrorsine (42)

has been run and the ^{13}C chemical shifts have been assigned, mainly by analogy with other systems.³⁵ Doubts remain about the assignment of the two pairs of signals for C-3, C-6 and C-7, C-8, which have closely similar chemical shifts.

Nitropolyzonamine (43) is found in the defensive secretion of the millipede *Polyzonium rosalbum*. The single-crystal *X*-ray analysis of the perchlorate salt of (43) has established³⁶ the opposite absolute configuration to that previously



Nitropolyzonamine (43)

described.³⁷ Alkaloids with otonecine as base which have been subjected to *X*-ray analysis are retusamine,³⁸ clivorine,³⁹ and senkirkine.⁴⁰ Otosenine (32) has now been added to this list.⁴¹ Values for the transannular $\text{N}\cdots\text{C}=\text{O}$ distance obtained in these studies are 1.64 Å in retusamine (the least precise measurement), 2.0 Å in clivorine, 2.3 Å in senkirkine, and 2.18 Å in otosenine. These values suggest that there is a very weak interaction across the ring, although the carbonyl bond lengths are all close to the normal value for a ketone of 1.215 Å. The *X*-ray structure of jacobine has been refined.⁴²

³⁴ Ya. V. Rashkes, U. A. Abdullaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1978, 153.

³⁵ H. Casal, J. Altamirano, and P. Moyna, *Gazz. Chim. Ital.*, 1977, **107**, 361.

³⁶ R. W. Miller and A. T. McPhail, *J. Chem. Res. (S)*, 1978, 76.

³⁷ J. Meinwald, J. Smolanoft, A. T. McPhail, R. W. Miller, T. Eisner, and K. Hicks, *Tetrahedron Letters*, 1975, 2367.

³⁸ J. A. Wunderlich, *Acta Cryst.*, 1967, **23**, 846.

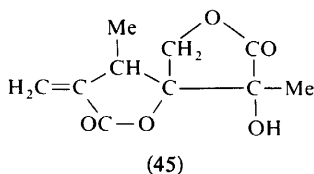
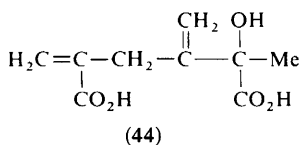
³⁹ K. B. Birnbaum, *Acta Cryst.*, 1972, **B28**, 2825.

⁴⁰ G. I. Birnbaum, *J. Amer. Chem. Soc.*, 1974, **96**, 6165.

⁴¹ A. Pérez-Salazar, F. H. Cano, J. Fayos, S. Martínez-Carrera, and S. García-Blanco, *Acta Cryst.*, 1977, **B33**, 3525.

⁴² A. Pérez-Salazar, *Anales de Quim.*, 1978, **74**, 196; A. Pérez-Salazar, F. H. Cano, S. García-Blanco, *Cryst. Struct. Comm.*, 1978, 105.

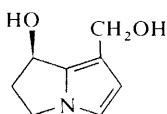
The dicarboxylic acid (44) has been synthesized by two separate routes by Gordon-Gray and Whiteley.⁴³ It is hoped that this acid will be a useful intermediate in the synthesis of swazinecic acid dilactone (45), the necic acid component of swazine.



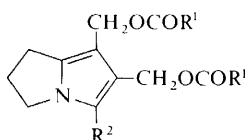
8 Pharmacological and Biological Studies

Ingestion of pyrrolizidine alkaloids is believed to be the cause of a number of cases of human veno-occlusive disease which have been reported in central India⁴⁴ and in Arizona, U.S.A.⁴⁵ In the latter study, consumption of herbal tea made from *Senecio longilobus* was shown to be the source of the disease.

The toxic metabolites of pyrrolizidine alkaloids are pyrrole derivatives, produced by the hepatic microsomal enzymes. The covalent interaction of one of these metabolites, dehydroretronecine (46), with cysteine and glutathione has been investigated.⁴⁶ Analysis of the reaction products suggested that alkylation of the sulphhydryl groups was occurring. The same research group⁴⁷ found that dehydroretronecine inhibited yeast alcohol dehydrogenase, and that the addition of excess cysteine to the assay system removed the inhibition. The role of cysteine and glutathione in the toxicity of pyrrolizidine alkaloids to rats has been studied previously (see last year's Report). The presence of selenium did not affect the metabolism of pyrrolizidine alkaloids by rat liver microsomes.⁴⁸ A number of synthetic dihydropyrrolizines (47) have been prepared.⁴⁹ Many of the diesters (47) showed significant antileukaemic activity, particularly when $\text{R}^1 = \text{NHMe}$.



Dehydroretronecine (46)



(47)

Atal⁵⁰ has reviewed the production of semi-synthetic derivatives of pyrrolizidine alkaloids, together with their pharmacological activities. Antimitotic activities have been observed in a number of semi-synthetic retronecine and

⁴³ C. G. Gordon-Gray, and C. G. Whiteley, *J.C.S. Perkin I*, 1977, 2040.

⁴⁴ H. D. Tandon, B. N. Tandon, R. Tandon, and N. C. Nayak, *Indian J. Med. Res.*, 1977, **65**, 679.

⁴⁵ A. E. Stillman, R. Huxtable, P. Consroe, P. Kohnen, and S. Smith, *Gastroenterology*, 1977, **73**, 349.

⁴⁶ K. A. Robertson, J. L. Seymour, M.-T. S. Hia, and J. R. Allen, *Cancer Res.*, 1977, **37**, 3141.

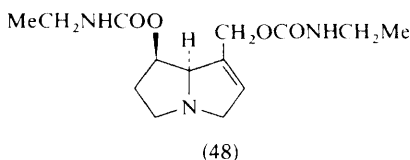
⁴⁷ P. S. Sun, M.-T. S. Hsia, F. S. Chu, and J. R. Allen, *Food Cosmet. Toxicol.*, 1977, **15**, 419.

⁴⁸ L. R. Shull, G. W. Buckmaster, and P. R. Cheeke, *Res. Comm. Chem. Pathol. Pharmacol.*, 1977, **17**, 337.

⁴⁹ W. K. Anderson and P. F. Corey, *J. Med. Chem.*, 1977, **20**, 812.

⁵⁰ C. K. Atal, *Lloydia*, 1978, **41**, 312.

platynecine derivatives.⁵¹ Chromosome-breaking activity (on onion roots) was noted for three retronecine diesters.⁵¹ The distribution of radioactivity in rats fed tritium-labelled diesters of retronecine or synthetic analogues (synthancines) has been described (see last year's Report). A similar distribution of radioactivity in rats has been observed with tritium-labelled retronecine 7,9-bis-*N*-ethylcarbamate (48).⁵² The neuromuscular blocking action of semi-synthetic quater-



nary pyrrrolizidines continues to receive attention. More syntheses⁵³ and pharmacological investigations⁵⁴ on salts based on 1-methylenepyrrrolizidine and fully saturated pyrrrolizidines have been reported. The blocking action of these derivatives has been compared with that of *d*-tubocurarine.⁵⁵ Bisquaternary salts of heliotridane⁵⁶ and loline⁵⁷ derivatives have been synthesized, but no biological activity has yet been reported.

The range of animals that have been subjected to the effects of pyrrrolizidine alkaloids continues to widen. Japanese quail were resistant to ragwort (*Senecio jacobaea*) in their diet, but were susceptible to injected alkaloids.⁵⁸ The effects of ragwort on the livers of young domestic fowls were also studied.⁵⁹ Concentrations of 0.01% of seeds of *Crotalaria retusa* L. in the diet of broiler chickens⁶⁰ and pigs⁶¹ were considered to be the maximum limit that could be tolerated by these animals. The cytotoxicity of fulvine from *C. fulva* to rat pancreatic cells has been investigated.⁶² In preparing silage from aerial parts of the prickly comfrey (*Symphytum asperum*), the alkaloid content was decreased by *ca.* 85%, and alkaloids were not detected in the cheese prepared from the milk of cows which had been fed on the silage.⁶³

⁵¹ B. L. Kaul and S. N. Kak, *Indian J. Exp. Biol.*, 1977, **15**, 397.

⁵² A. R. Mattocks, *Xenobiotica*, 1977, **7**, 665.

⁵³ K. A. Suri, O. P. Suri, R. S. Sawhney, O. P. Gupta, and C. K. Atal, *Indian J. Chem., Sect. B.*, 1977, **15**, 972.

⁵⁴ O. P. Gupta, M. M. Ali, B. J. R. Ghatak, and C. K. Atal, *Indian J. Med. Res.*, 1977, **65**, 436.

⁵⁵ O. P. Gupta, M. M. Ali, B. J. R. Ghatak, and C. K. Atal, *Indian J. Exp. Biol.*, 1977, **15**, 1001.

⁵⁶ N. P. Abdullaev, Kh. M. Shakhidoyatov, and Ch. Sh. Kadyrov, *Khim. prirod. Soedinenii*, 1977, 368 (*Chem. Abs.*, 1978, **88**, 23 216).

⁵⁷ N. P. Abdullaev, E. Kh. Batirov, V. M. Malikov, Kh. M. Shakhidoyatov, and Ch. Sh. Kadyrov, *Khim. prirod. Soedinenii*, 1977, 371 (*Chem. Abs.*, 1978, **88**, 23 216).

⁵⁸ G. W. Buckmaster, P. R. Cheeke, G. H. Arscott, E. O. Dickinson, M. L. Pierson, and L. R. Shull, *J. Anim. Sci.*, 1977, **45**, 1322.

⁵⁹ C. Gopinath and E. J. H. Ford, *Brit. Poultry Sci.*, 1977, **18**, 137.

⁶⁰ A. J. Ross and J. W. Tucker, *J. Agric. Sci.*, 1977, **89**, 95.

⁶¹ A. J. Ross, *J. Agric. Sci.*, 1977, **89**, 101.

⁶² H.-P. Putzke and T. V. N. Persaud, *Exp. Pathol. (Jena)*, 1976, **12**, 329 (*Biol. Abs.*, 1977, **64**, 5891).

⁶³ I. V. Man'ko and A. S. Shuvarikov, *Rastit. Resur.*, 1978, **14**, 121 (*Chem. Abs.*, 1978, **88**, 103 553).

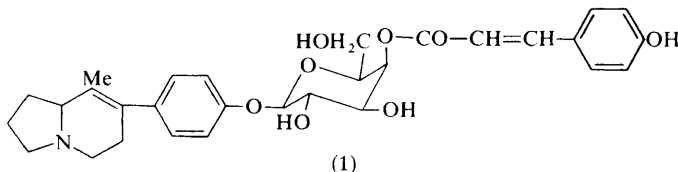
5

Indolizidine Alkaloids

BY J. A. LAMBERTON

1 *Ipomoea* Alkaloids

Seeds of *Ipomoea muricata* Jacq. from plants grown in Senegal afforded the known alkaloid ipalbidine in low yield (0.001%) and a new alkaloid ipomine (0.02%). Acid hydrolysis of ipomine gives ipalbidine, D-glucose, and *p*-coumaric acid, while enzymatic hydrolysis with emulsin yields ipalbidine. From a study of the hydrolysis products and spectroscopic data, ipomine has been shown to be 1- β -ipalbidinyl-4-*p*-coumaroyl-D-glucofuranoside (1).¹



2 *Tylophora* Alkaloids

A new synthesis of (\pm)-tylophorine (2) has been based on the discovery that vanadium trifluoride oxide (VOF_3) can be used to convert 1,2-diarylethylene derivatives into phenanthrenes in high yields. In the synthesis of (\pm)-tylophorine, as shown in Scheme 1, ring closure by VOF_3 is accompanied by dehydrogenation to give a phenanthrene.² Other syntheses of the phenanthroindolizidine ring system have been accomplished.^{3,4}

3 *Elaeocarpus* Alkaloids

In a survey of seven Indian *Elaeocarpus* species, only *E. ganitrus* was found to contain alkaloids.⁵

4 Slaframine

Slaframine (3) is photochemically converted into two products (4) and (5), which are also formed from slaframine by the action of rat or porcine liver microsomes.

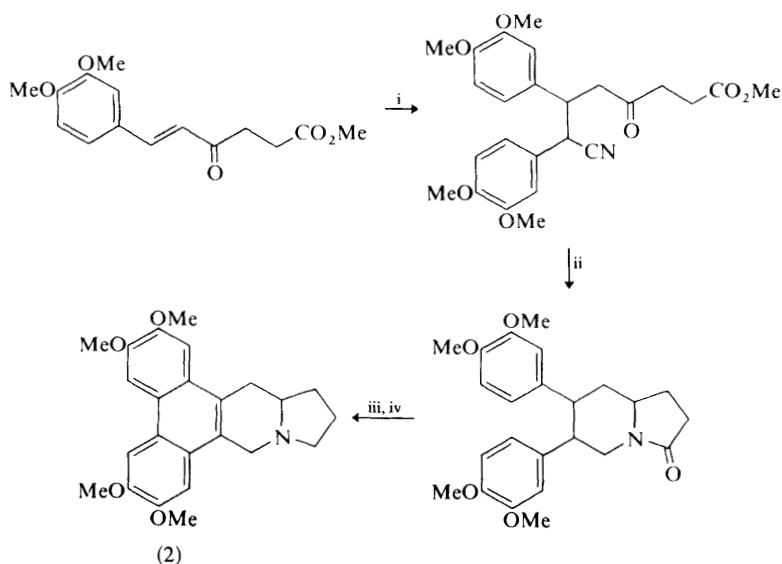
¹ A. M. Dawidar, F. Winternitz, and S. R. Johns, *Tetrahedron*, 1977, **33**, 1733.

² A. J. Liepa and R. E. Summons, *J. C. S. Chem. Comm.*, 1977, 826.

³ D. O. Shah and K. N. Trivedi, *Indian J. Chem., Sect. B*, 1977, **15**, 599.

⁴ G. Dannhardt and W. Wiegrebe, *Arch. Pharm.*, 1977, **310**, 802.

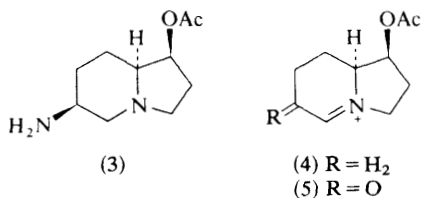
⁵ L. Chand, S. Dasgupta, S. K. Chattopadhyay, and A. B. Ray, *Planta Medica*, 1977, **32**, 197.



Reagents: i, 3,4-dimethoxybenzyl cyanide, K_2CO_3 (Michael addition); ii, H_2 -Pt/C in HOAc, EtOAc; iii, VOF_3 in TFA- CH_2Cl_2 at $0^\circ C$; iv, diborane in THF

Scheme 1

The keto-imine (5) has been shown to be active in stimulating exocrine glands. Because purified porcine hepatic microsomal flavoprotein oxidase has been shown to oxidize slaframine to (5), this enzyme is postulated to be primarily responsible for activation of slaframine *in vivo*.⁶



⁶ F. P. Guengerich and S. D. Aust, *Mol. Pharmacol.*, 1977, **13**, 185.

Valenta and Liu¹ have given an account of the structure and synthesis of *Ormosia* alkaloids, and a review of the *Nuphar* alkaloids has been published.² Carbon-13 n.m.r.³ and mass spectroscopy⁴ of quinolizidine alkaloids have been reviewed.

1 The Lupinine–Lupanine–Sparteine–Matrine Group

Occurrence.—Alkaloid isolation is recorded in Table 1.^{5–15} An extensive investigation of the alkaloid content of Bulgarian *Chamaecytisus* species resulted in the isolation of quinolizidines from ten members of the genus;^{8,9} the new alkaloid chamaetine (1) was obtained from six species, and another new alkaloid, of unknown constitution, has also been isolated. The Ethiopian shrub *Calpurnea aurea* contains a mixture of the angelic and tiglic acid esters of 13-hydroxy-lupanine.⁷ Two sub-species of *Genista hystrix* were studied and found to have the same alkaloidal constituents.¹⁰

Structural and Stereochemical Studies.—Lupinine *trans*-4-hydroxycinnamate was shown to be a constituent of seedlings of *Lupinus luteus* (cf. Vol. 7, p. 71), and the glycoside (3) has now been isolated from the same source.¹² The structure of the new compound was apparent from mass spectroscopy and from its hydrolysis (with acid) to rhamnose and the aglycone; the negative sign of the optical rotation indicated the presence of an α -glycosidic link. As in the case of the aglycone, the new alkaloid was shown by n.m.r. spectroscopy to be a mixture of *cis*- and *trans*-isomers (1 : 2); it was assumed that the *cis*-isomer was produced by irradiation during isolation.

The new alkaloid chamaetine (1), isolated from *Chamaecytisus* species, is an epimer of nuttaline (1; with β -OH group).⁹ The structure of chamaetine was established by n.m.r. and mass spectroscopy and by conversion of the alkaloid into sparteine and into lupanine. Reduction of chamaetine with lithium aluminium hydride gave an amorphous desoxy derivative, which was shown to be identical with 4- α -hydroxysparteine by a comparison of azo-esters.

¹ Z. Valenta and H. J. Liu, *Internat. Rev. Sci.: Org. Chem., Ser. Two*, 1976, **9**, 1.

² R. T. LaLonde and C. Wong, *Pure Appl. Chem.*, 1977, **49**, 169.

³ D. Turwe and G. Van Binst, *Heterocycles*, 1978, **9**, 507.

⁴ N. S. Vul'fson and V. G. Zaikin, *Uspekhi Khim.*, 1976, **45**, 1870.

Table 1 Isolation of quinolizidine alkaloids

Species	Alkaloid (Structure)	Ref.
<i>Ammodendron karelinii</i>	Ammodendrine	} 5
	Anagyryne	
	Cytisine	
	Lupanine	
	Methylcytisine	
	Pachycarpine	
	Pachycarpine <i>N</i> -16-oxide	
<i>Analoasis aphylla</i>	Aphylline <i>N</i> -oxide	6
<i>Calpurnea aurea</i>	Calpurnine	} 7
	13-Hydroxylupanine esters	
	Virgiline ester	
<i>Chamaecytisus</i> spp.	* Chamaetine (1)	} 8,9
	Lupanine	
	17-Oxosparteine	
	Sparteine	
<i>Genista hystrix</i>	Ammodendrine	} 10
	Anagyryne	
	Cytisine	
	Lupanine	
	Methylcytisine	
<i>Lupinus argenteus</i>	Anagyryne	} 11
	Δ^5 -Dehydrolupanine	
	α -Isolupanine	
	β -Isosparteine	
	Lupanine	
	Sparteine	
	Thermopsine	
<i>Lupinus luteus</i>	* Lupinine ester (3)	12
<i>Sophora alopecuroides</i>	Cytisine	13
	* 13,14-Dehydrosophoridine	13,14
	<i>N</i> -oxide (2)	
	Matrine <i>N</i> -oxide	13
	Neosophoramine	13
	Sophoridine	13
	Sophoridine <i>N</i> -oxide	14
<i>Vaccinium myrtillus</i>	* Myrtine (5)	15

* New alkaloids

⁵ Yu. K. Kushmuradov, Kh. A. Aslanov, and S. Kuchkarov, *Khim. prirod. Soedinenii*, 1977, 717 (*Chem. Abs.*, 1978, **88**, 71 429).

⁶ A. N. Nizamkhodzhaeva, A. I. Ishbaev, Kh. A. Aslanov and S. Z. Mukhamedzhanov, Deposited Document, 1975, VINITI 1368 (*Chem. Abs.*, 1978, **88**, 121 499).

⁷ J. L. Van Eijk and M. H. Radema, *Planta Med.*, 1977, **32**, 275.

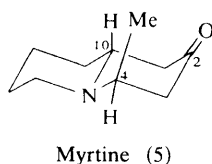
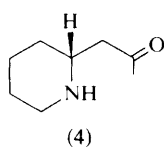
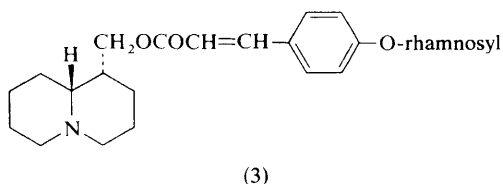
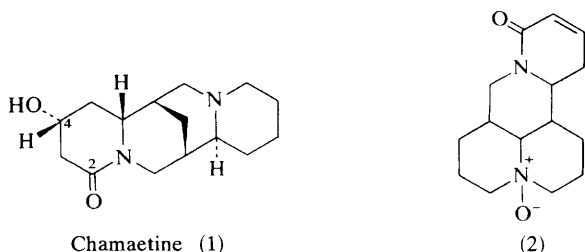
⁸ A. Daily, H. Dutschewska, and N. Mollov, *Planta Med.*, 1977, **32**, 380.

⁹ A. Daily, H. Dutschewska, N. Mollov, and S. Spassov, *Tetrahedron Letters*, 1978, 1453.

¹⁰ E. Steinegger and S. Scheurer, *Pharm. Acta Helv.*, 1976, **51**, 203.

¹¹ W. J. Keller and S. G. Zelenski, *J. Pharm. Sci.*, 1978, **67**, 430.

¹² I. Murakoshi, F. Kakegawa, K. Toriizuka, T. Haginiwa, S. Ohmiya, and H. Otomasu, *Phytochemistry*, 1977, **16**, 2046.



A re-investigation of *Sophora alopecuroides* resulted in the isolation of a new alkaloid of the matrine group, believed to be 13,14-dehydrosophoridine *N*-oxide (2) on the basis of spectroscopic and chemical studies.¹⁴

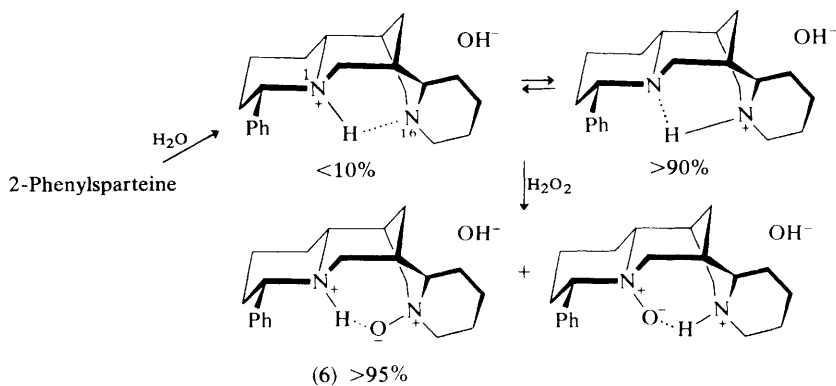
The quinolizidinone alkaloid myrtine (5) was isolated from *Vaccinium myrtillus* (Ericaceae) and its structure was established by spectroscopy and by synthesis.¹⁵ The presence of a ketonic carbonyl group was indicated by i.r. absorption at 1720 cm^{-1} . In the n.m.r. spectrum of myrtine, the doublet at τ 9.03 was shifted to 8.7 after addition to trifluoroacetic acid ($\text{>CH}-\text{CH}_3$, adjacent to N) and the quadruplet at τ 6.6 [$-\text{CH}(\text{Me})-$] in 1,1,3,3,3-tetradeuteriomyrtiline showed that the carbonyl group was at C-2; strong i.r. absorption at 2805 cm^{-1} was in accord with a *trans*-quinolizidine structure. The reaction of (\pm)-pelletierine [cf. (4)] with acetaldehyde afforded a mixture of (\pm)-myrtine and its 4-epimer; since treatment of either epimer with alkali gave an equilibrium mixture in which myrtine was the minor component, the methyl group of the alkaloid is apparently in the less stable axial position. ($-$)-(*R*)-pelletierine (4) afforded (+)-myrtine, thus showing that the alkaloid has the C-4(*R*)-C-10(*R*) configuration (5), but as natural myrtine has a lower specific optical rotation than the synthetic compound it appears that partial racemisation occurs during isolation.

¹³ S. Kuchkarov, Yu. K. Kushmuradov, and Kh. A. Aslanov, *Khim. prirod. Soedinenii*, 1977, 288 (*Chem. Abs.*, 1977, **87**, 114 623).

¹⁴ S. Kuchkarov, Yu. K. Kushmuradov, Kh. A. Aslanov, and S. A. Sadykov, *Khim. prirod. Soedinenii*, 1977, 581 (*Chem. Abs.*, 1977, **87**, 197 262).

¹⁵ P. Slosse and C. Hootelé, *Tetrahedron Letters*, 1978, 397.

In continuation of their stereochemical studies of sparteine *N*-oxides (*cf.* Vol. 6, p. 91), Wiewiórowski and co-workers¹⁶ prepared 2-phenylsparteine *N*-16-oxide and its perchlorate salt (6); X-ray analysis of the salt shows that there is a strong hydrogen bond between the *N*-16 oxygen function and the *N*-1 proton.¹⁷ Almost exclusive formation of the *N*-16-oxide in the reaction of 2-phenylsparteine with hydrogen peroxide is attributed to a greater accessibility of the *N*-16 atom to the reagent, although this site is protonated preferentially (Scheme 1). Previous views on the formation of *N*-oxides of sparteine and its derivatives have thus been revised; protonation affects the rate of reaction, but does not influence the site at which oxidation occurs.



Scheme 1

Thermolysis of sparteine *N*-oxides occurs readily when an aqueous acidic solution is heated in the presence of an excess of chloride ion.¹⁸ In the case of the *N*-16-oxide (7), alkaline work-up gives the carbinolamine (8); a study of the effect of the concentration of chloride ion and of the pH of the medium on the reaction rate led to the proposed mechanism (Scheme 2). Sparteine *N*-1-oxide and α -isosparteine *N*-1-oxide undergo similar β -elimination reactions, but the products are enamines. A preliminary investigation of the thermolysis of sparteine *epi-N*-16-oxide (9) showed that the carbinolamine (8) was the sole product, formed apparently by a *syn*-elimination.

Infrared studies of 13- α -hydroxylupanine indicated that the molecule exists in the all-chair conformation (10) in the solid state and in conformation (11) in chloroform solution.¹⁹ X-Ray analysis has now established conformation (10) for anhydrous 13- α -hydroxylupanine; the molecules are spirally linked into chains through intermolecular hydrogen bonds between the hydroxy-group at C-13 and the carbonyl group at C-2.²⁰

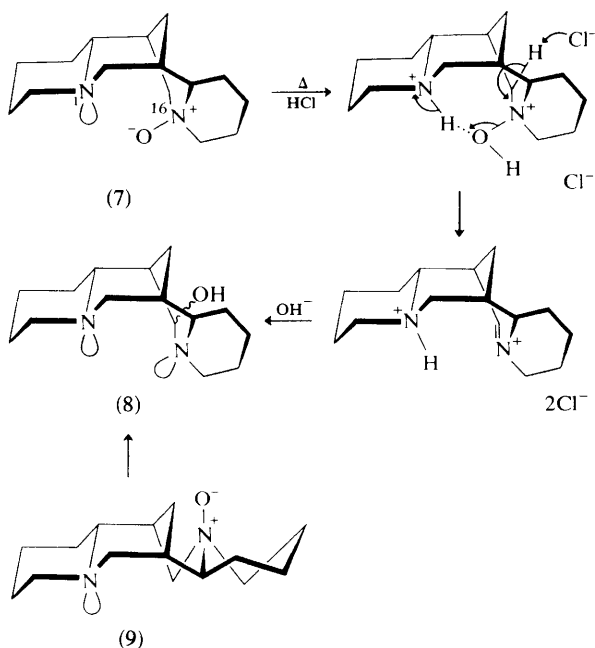
¹⁶ W. Boczon, G. Pieczouka, and M. Wiewiórowski, *Tetrahedron*, 1977, **33**, 2565.

¹⁷ H. Maluszynska and Y. Okaya, *Acta. Cryst.*, 1977, **B33**, 3889.

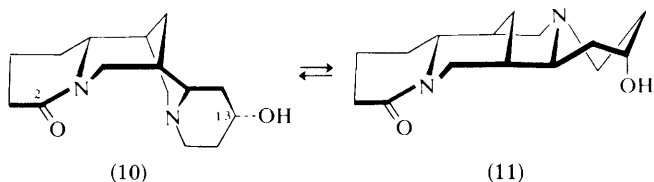
¹⁸ K. Langowska and M. Wiewiórowski, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1977, **25**, 757.

¹⁹ M. Wiewiórowski, O. E. Edwards, and M. D. Bratek-Wiewiórowska, *Canad. J. Chem.*, 1967, **45**, 1447.

²⁰ Z. Kaluski, J. Garbarczyk, A. I. Gusiev, Yu. T. Struchkov, J. Skolik, and M. Wiewiórowski, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1977, **25**, 347.



Scheme 2



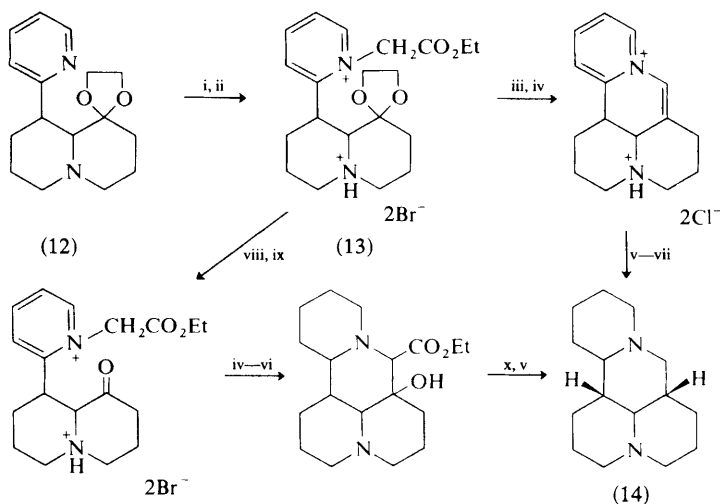
Synthesis.—Hamana and co-workers²¹ have described new syntheses of (±)-allomatridine (14) (Scheme 3). The protected pyridylquinolizidinone (12), prepared from *N*-benzoyloxypyridinium chloride and a quinolizidine enamine, was converted into the *N*-ethoxycarbonylmethyl derivative (13). The latter compound was then cyclized to tetracyclic intermediates by two routes.

2 Sesquiterpenoid Alkaloids

LaLonde and Wong²² have continued their studies of thiaspirane bis-amine sulphoxides. Oxidation of the *Nuphar* alkaloid thiobinupharidine (15) with hydrogen peroxide gave a mixture of the *syn*-sulphoxide (16) and the *anti*-sulphoxide (17); configurations of the sulphoxide groups were assigned by ¹³C

²¹ S. Saeki, A. Yamashita, Y. Morinaka, and M. Hamana, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 2509; 1977, **25**, 79.

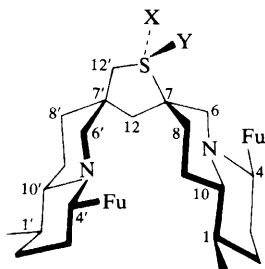
²² R. T. LaLonde and C. F. Wong, *Canad. J. Chem.*, 1978, **56**, 56.



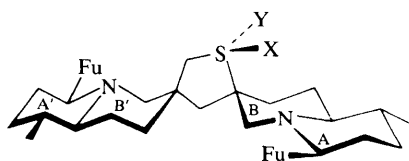
Reagents: i, NH_4Br , aq. EtOH, 60°C ; ii, $\text{BrCH}_2\text{CO}_2\text{Et}$, EtOH, reflux; iii, 20% HCl, reflux; iv, NEt_3 , EtOH, reflux; v, NaBH_4 ; vi, HCl; vii, H_2 -Pt; viii, 7% HCl, reflux; ix, dry HCl, EtOH; x, conc. HCl, 250 – 260°C

Scheme 3

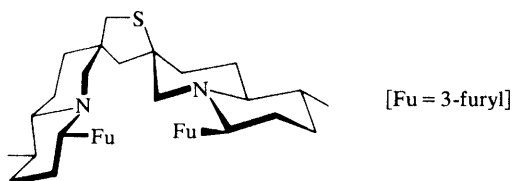
n.m.r. spectroscopy, as in the case of neothiobinupharidine sulphoxides (19) and (20) (*cf.* Vol. 8, p. 73). Thermolysis of the *syn*-sulphoxide (16), followed by reduction with borohydride, gave thiobinupharidine (15) and thionupharidine B (21), but sulphides were not formed by similar treatment of the *anti*-sulphoxide (17). Sulphoxides (19) and (20) behaved in the same way, the *syn*-isomer (19) yielding neothiobinupharidine (18) and a new thiaspirane, thionupharidine C (22); the structure of the latter compound was established by spectroscopic methods. It appears that only *syn*-sulphoxides are thermolysed to compounds reduced to thiaspirane bis-amines; the intermediates are probably immonium salts or hemiaminals, and as expected, the use of borodeuteride in the reduction step results in the formation of products in which deuterium is present only at C-6 and at C-6'.



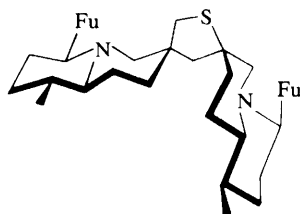
Thiobinupharidine (15) X = Y = electron pair
 (16) X = O, Y = electron pair
 (17) X = electron pair, Y = O



- Neothiobinupharidine (18) X = Y = electron pair
 (19) X = O, Y = electron pair
 (20) X = electron pair, Y = O

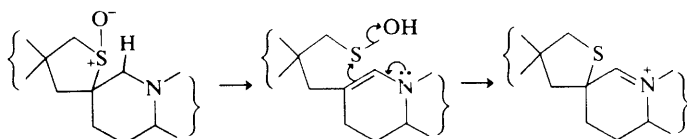


Thionuphlutine B (21)



Thionuphlutine C (22)

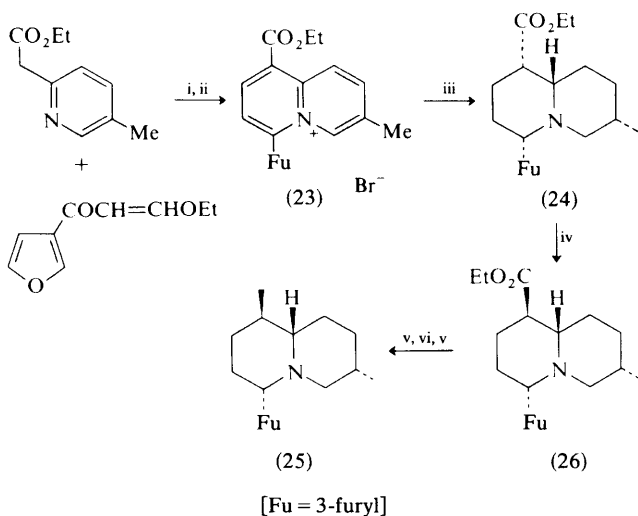
The proposed mechanism of thermolysis (Scheme 4) implies that rotation of the AB quinolizidine ring at the sulphenic-acid stage leads to the original sulphides (15) or (18) or to new products (21) or (22).



Scheme 4

A new synthesis of desoxynupharidine (25) has been reported (Scheme 5) by Wróbel and co-workers.²³ Although the quinolizidine (24) is not the major product of reduction of compound (23), the presence of an ethoxycarbonyl group ensures complete epimerization at C-1 to isomer (26), which possesses the correct stereochemistry for conversion into desoxynupharidine.

²³ J. Szychowski, A. Leniewski, and J. T. Wróbel, *Chem. and Ind.*, 1978, 273.

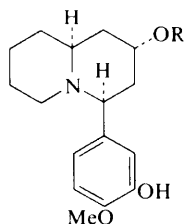


Reagents: i, F_3CCO_2H ; ii, 45% HBr, MeOH; iii, $NaBH_3CN$, EtOH; iv, NaOEt, EtOH; v, $LiAlH_4$; vi, $SOCl_2$, pyridine

Scheme 5

3 Alkaloids of the Lythraceae

After the recent considerable activity in the synthesis of macrocyclic Lythraceae alkaloids, published work this year has been confined to the isolation of the new aryl-quinolizidine alkaloids desmethoxyabresoline (28) and 10-*epi*-desmethoxyabresoline (29) from *Heimia salicifolia*.²⁴ The structure of alkaloid (28) was established by spectroscopy and by conversion into two known compounds, the alcohol (27) (*cf.* Vol. 6, p. 97) obtained by basic hydrolysis and

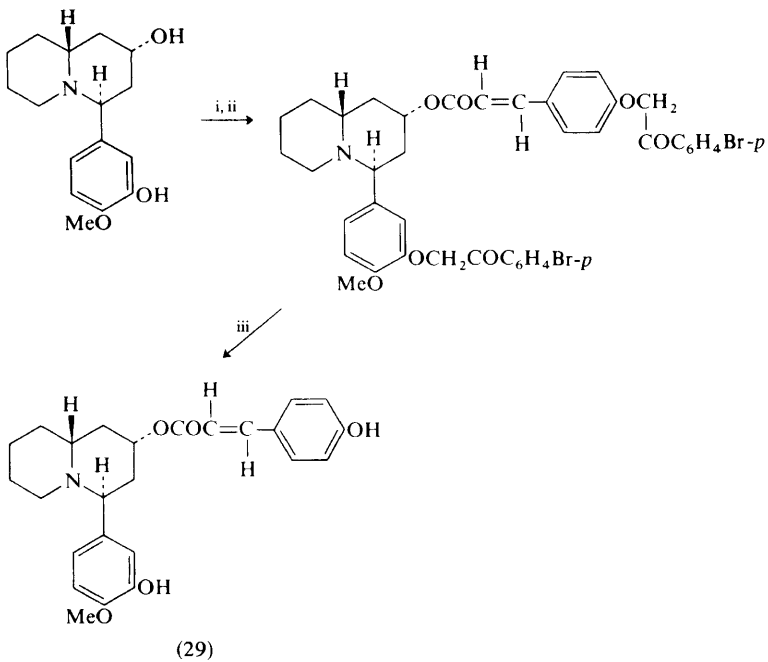


(27) R = H

(28) R = *trans*-*p*-hydroxycinnamoyl

the dihydro-derivative formed from the alkaloid by catalytic hydrogenation. The second alkaloid (29) was not readily isolated as the pure *trans*-4-hydroxycinnamate because of isomerisation to the *cis*-derivative during chromatography on silica, and it was identified by synthesis (Scheme 6).

²⁴ A Rother and A. E. Schwarting, *Phytochemistry*, 1978, **17**, 305.



Reagents: i, $p\text{-BrC}_6\text{H}_4\text{COCH}_2\text{Br}$, K_2CO_3 , Me_2CO , reflux; ii, $\text{HO}_2\text{CCH}=\text{CHC}_6\text{H}_4\text{OCH}_2\text{COC}_6\text{H}_4\text{Br}$, TsOH , PhH , reflux; iii, Zn , AcOH

Scheme 6

Quinoline, Quinazoline, and Acridone Alkaloids

BY M. F. GRUNDON

Reviews of quinoline¹ and acridine² alkaloids are now available in the second edition of 'Rodd'. The synthesis of quinazolones has been reviewed.³

1 Quinoline Alkaloids

New quinolone alkaloids and alkaloids of established constitution obtained from new sources are listed in Table 1.⁴⁻²⁰

Non-hemiterpenoid Quinolines.—The three non-hemiterpenoid quinoline alkaloids reported this year are all 3-methoxyquinoline derivatives. Furoquinoline alkaloids had been isolated previously from *Chloroxylon swietenia* (East Indian satin wood), but now two new alkaloids, swietenidins A and B, have been obtained from the bark.⁵ Spectroscopic studies of swietenidin A and its monomethyl ether, and comparison of the data with those of the known 8-methoxy-*N*-methyl-2-quinolone lunacridine, indicated that the alkaloid was the

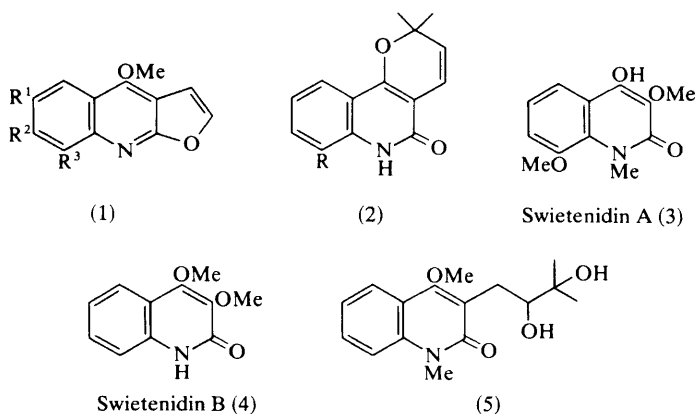
- ¹ M. Sainsbury in 'Rodd's Chemistry of Carbon Compounds', Elsevier, Amsterdam, 2nd edn., 1978 **4(G)**, p. 171.
- ² B. P. Swann and A. McKillop, 'Rodd's Chemistry of Carbon Compounds', Elsevier, Amsterdam, 2nd edn., 1978, **4(G)**, p. 257.
- ³ T. Kametani and K. Fukumoto, *Heterocycles*, 1977, **7**, 615.
- ⁴ I. H. Bowen and J. R. Lewis, *Lloydia*, 1978, **41**, 184.
- ⁵ K. S. Bhide, R. B. Mujumdar, and A. V. R. Rao, *Indian J. Chem., Sect. B*, 1977, **15**, 440.
- ⁶ A. G. Gonzalez, C. E. Diaz, H. D. Lopez, J. R. Luis, and L. F. Rodriguez, *Anales de Quim.*, 1977, **73**, 430 (*Chem. Abs.*, 1977, **87**, 148 668).
- ⁷ S. Johne and S. Haertling, *Pharmazie*, 1977, **32**, 415 (*Chem. Abs.*, 1977, **87**, 164 202).
- ⁸ R. Torres and B. K. Cassels, *Phytochemistry*, 1978, **17**, 838.
- ⁹ B. P. Das and D. N. Chowdhury, *Chem. and Ind.*, 1978, 272.
- ¹⁰ E. F. Nesmelova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 289 (*Chem. Abs.*, 1977, **87**, 81 276).
- ¹¹ Kh. A. Abdullaeva, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 425 (*Chem. Abs.*, 1977, **87**, 148 666).
- ¹² A. Ahond, F. Picot, P. Potier, C. Poupat, and T. Sévenet, *Phytochemistry*, 1978, **17**, 166.
- ¹³ G. J. Kapadia, Y. N. Shukla, and S. P. Basak, *Phytochemistry*, 1978, **17**, 1443.
- ¹⁴ J. Vaquette, R. Hocquemiller, J.-L. Poussset, and A. Cavé, *Planta Med.*, 1978, **33**, 78.
- ¹⁵ F. Fish, I. A. Meshal, and P. G. Waterman, *Fitoterapia*, 1977, **48**, 170 (*Chem. Abs.*, 1978, **88**, 166 747).
- ¹⁶ J. I. Okogun and J. F. Ayafor, *J. C. S. Chem. Comm.*, 1977, 652.
- ¹⁷ R. Hänsel and E.-M. Cybulski, *Arch. Pharm. (Weinheim)*, 1978, **311**, 135 (*Chem. Abs.*, 1978, **89**, 3140).
- ¹⁸ H. Ishii, T. Ishikawa, and J. Haginiwa, *Yakugaku Zasshi*, 1977, **97**, 890 (*Chem. Abs.*, 1977, **87**, 197 250).
- ¹⁹ F. R. Stermitz and I. A. Sharifi, *Phytochemistry*, 1977, **16**, 2003.
- ²⁰ N. Decandain, N. Kunesch and J. Poisson, *Ann. Pharm. Fr.*, 1977, **35**, 521 (*Chem. Abs.*, 1978, **89**, 43 872).

Table 1 Isolation of quinoline alkaloids

Species	Alkaloid (Structure)	Ref.	
<i>Atlantia roxburghiana</i>	Flindersine (2; R = H)	4	
<i>Chloroxylon swietenia</i>	* Swietenidin A (3) * Swietenidin B (4)	} 5	
<i>Dictamnus hispanicus</i>	Skimmianine (1; R ¹ = H, R ² = R ³ = OMe)		6
<i>Erythrochiton brasiliensis</i>	γ-Fagarine (1; R ¹ = R ² = H, R ³ = OMe)	7	
<i>Fagara mayu</i>	(-)-Edulinine (5) (±)-Ribalinine (6; R = H)	} 8	
<i>Glycosmis pentaphylla</i>	* Glycosolone (7)		9
<i>Haplophyllum latifolium</i>	7-Isopentenylxyloxy-γ-fagarine Haplopine (1; R ¹ = H, R ² = OH, R ³ = OMe)	} 10	
<i>H. perforatum</i>	* Triacetylglycerine (8)		11
<i>Melicope leratii</i>	Skimmianine	12	
<i>Melochia tomentosa</i>	* Melovinone (9)	13	
<i>Ruta chalepensis</i>	Graveolinine (12) Ribalinidine (6; R = OH)	} 6	
<i>Teclea boiviniana</i>	Evoxine [1; R ¹ = H, R ² = OCH ₂ CH(OH)- C(OH)Me ₂ , R ³ = OMe]		14
<i>T. sudanica</i> †	Flindersiamine (1; R ¹ R ² = OCH ₂ O, R ³ = OMe) Maculine (1; R ¹ R ² = OCH ₂ O, R ³ = H) Skimmianine	} 15	
<i>T. verdoorniana</i>	Flindersiamine Kokusaginine (1; R ¹ = R ² = OMe, R ³ = H)		} 16
	* Tecleaverdoornine (11)		
<i>Vepris pilosa</i>	Kokusaginine	17	
<i>Zanthoxylum arnotianum</i>	Skimmianine	18	
<i>Z. monophyllum</i>	* Desmethylzanthophylline (13; R = H) * Zanthophylline (13; R = Me)	} 19	
<i>Z. tsihanimposa</i>	Skimmianine		20

* New alkaloids

† Ghanaian species, provisionally identified

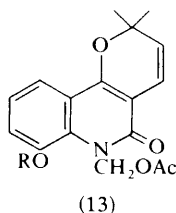
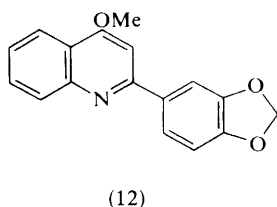
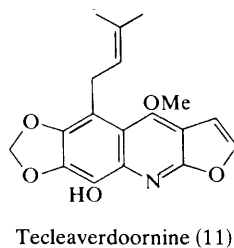
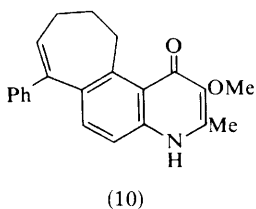
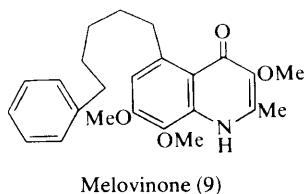
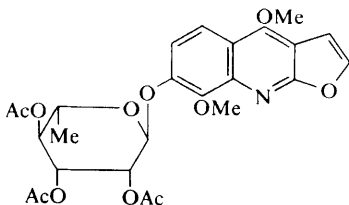
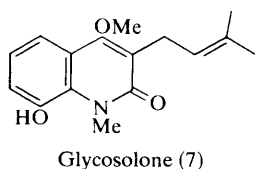
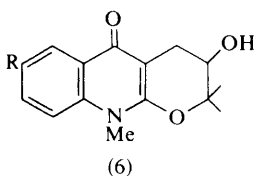


4-hydroxy-2-quinolone (3). Structure (4) for swietenidin B was assigned on the basis of the i.r. and n.m.r. spectra; it was known previously only as a synthetic compound. The two alkaloids are the first examples of naturally occurring 2-quinolones containing 3-methoxy-groups.

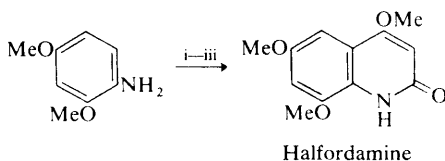
The unusual tricyclic 3-methoxy-4-quinolone (10) was obtained recently from *Melochia tomentosa* (cf. Vol. 7, p. 82) and a structurally related alkaloid, melovinine (9), has now been isolated from the same source.¹³ The constitution of melovinine was elucidated by spectroscopic studies.

A new high-yield synthesis of the simple 4-methoxy-2-quinolone halfordamine (cf. Vol. 6) has been described (see Scheme 1).²¹

Furoquinoline Alkaloids.—Furoquinoline alkaloids of established constitution have been isolated for the first time from ten species of the Rutaceae (see Table 1,



²¹ R. S. Mali, S. P. Bhagwat, and S. S. Kusurkar, *Indian J. Chem., Sect. B*, 1977, **15**, 856.



Reagents: i, $\text{CH}_2(\text{CO}_2\text{H})_2$, POCl_3 , reflux; ii, NaOMe , MeOH , reflux; iii, AcOH , reflux

Scheme 1

refs. 6, 7, 10, 12, 14—18, 20) and triacetylgycoepine (8) has been found, as well as glycoepine, in *Haplophyllum perforatum*.¹¹ 6,7,8-Trimethoxydictamnine (halfordinine) and skimmianine were shown previously to be constituents of *Teclea verdoorniana*, and extraction of the stem bark has now yielded koku-saginine, flindersiamine, and the most interesting new quinoline alkaloid of the year, tecleaverdoornine (11).¹⁶ The latter is the first tetrasubstituted dictamnine and the only *C*-prenylfuroquinoline alkaloid containing a fully aromatic homocyclic ring; a reasonable biosynthetic route to tecleaverdoornine involves *C*-prenylation of 8-hydroxy-6,7-methylenedioxy-dictamnine (desmethylflindersiamine), the absence of a 7-hydroxy-group precluding oxidative cyclization as occurs in the formation of choisyine (14). The presence of a phenolic hydroxy-group in tecleaverdoornine was indicated by i.r. absorption at 3410 cm^{-1} and by the formation of a monomethyl ether and a monoacetate. Other features of the molecule were apparent from the formation of a tetrahydro-derivative by catalytic hydrogenation and from the n.m.r. spectrum; the low-field chemical shift (τ 6.2) of the methylene group of the prenyl side-chain is apparently due to the neighbouring methoxy-group at C-4, an effect which is more pronounced in the 4-quinolone (15), obtained by the action of methyl iodide on tecleaverdoornine methyl ether. The failure of the alkaloid to form a chroman on treatment with acid eliminated an alternative structure in which the hydroxy-group is at C-7.

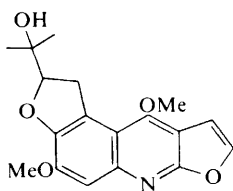
Structure (16) was proposed for the furoquinoline alkaloid perfamine (*cf.* Vol. 7, p. 83), and supporting evidence is now available.²² Thus, heating perfamine with acid yields 8-hydroxy-7-methoxydictamnine, and on hydrogenation the alkaloid is converted into the 2-quinolone (17).

Sekiba²³ has continued his study of the synthesis of phenolic furoquinolines and applied the procedure described earlier (*cf.* Vol. 8, p. 81) to the first synthesis of heliparvifoline (1; $\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{OH}$, $\text{R}^3 = \text{H}$) and to the preparation of *O*-desmethylpteleine (1; $\text{R}^1 = \text{OH}$, $\text{R}^2 = \text{R}^3 = \text{H}$); the latter compound has not yet been obtained from natural sources.

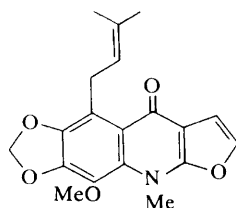
3-Prenylquinoline Alkaloids and Related Compounds.—Glycosolone (7), the first phenolic 3-prenyl-2-quinolone, has been isolated from the root-bark of *Glycosmis pentaphylla*.⁹ The structure of this base-soluble alkaloid was apparent from i.r. absorption at 3130 (hydrogen-bonded OH) and at 1640 cm^{-1} (2-quinolone carbonyl), and from the n.m.r. spectrum. Heating glycosolone with

²² D. M. Razakova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 791 (*Chem. Abs.*, 1977, **86**, 140 310).

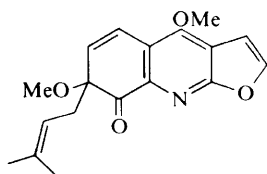
²³ T. Sekiba, *Bull. Chem. Soc. Japan*, 1978, **51**, 325.



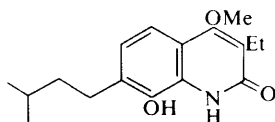
(14)



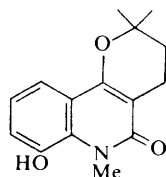
(15)



(16)



(17)



(18)

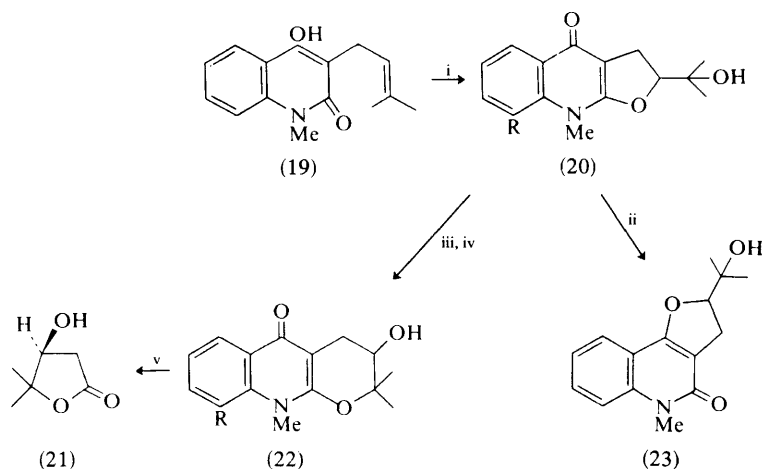
aqueous acid resulted in hydrolysis of the 4-methoxy-group and cyclization to the angular pyrano-2-quinolone (18).

Two new alkaloids of the flindersine group, zanthophylline (13; R = Me) and desmethylzanthophylline (13; R = H), were obtained from *Zanthoxylum mono-phyllum* by chromatography of the chloroform extract of the plant.¹⁹ The structure of zanthophylline was indicated by ¹H and ¹³C n.m.r. spectroscopy and by hydrolysis to 8-methoxyflindersine (2; R = OMe) and formaldehyde (identified as its 2,4-dinitrophenylhydrazone derivative). When aqueous acid was used in the isolation procedure, the only alkaloid obtained was 8-methoxyflindersine, and this is apparently an artefact formed by hydrolysis of zanthophylline. Desmethylzanthophylline is only a minor constituent of *Z. mono-phyllum*; although the alkaloid has not been fully investigated, its mass spectrum is in accord with structure (13; R = H), and the presence of *N*-acetoxymethyl and hydroxy-groups is confirmed by the appropriate i.r. absorptions.

The dihydrofuroquinolone alkaloids (+)-araliopsine (23) and (+)-isoplatydesmine (20; R = H) and the dihydropyranoquinolone (–)-ribalinine (22; R = H) are constituents of *Araliopsis soyauxii* (cf. Vol. 7, p. 88), and the objective of a synthetic study (Scheme 2) was to confirm the structure of araliopsine and to establish the absolute stereochemistry of the alkaloids.²⁴ The reaction of the 3-prenyl-2-quinolone (19) with (+)-(*S*)-peroxycamphoric acid gave isoplatydesmine containing an excess of the (+)-(*R*)-enantiomer. Treatment of (+)-isoplatydesmine with base afforded (+)-araliopsine, which thus has an (*R*)-configuration if isoplatydesmine rearranges by the same mechanism as established for the 8-methoxy analogue, balfouridine.²⁵ Rearrangement of (+)-isoplatydesmine with acetic anhydride and pyridine and hydrolysis of the

²² D. M. Razakova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 791 (*Chem.*

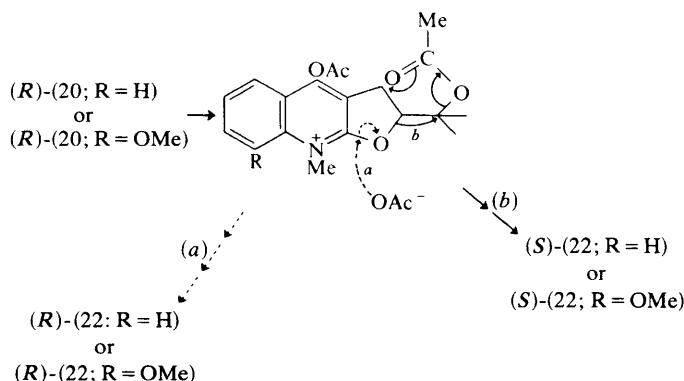
²⁵ M. F. Grundon and K. J. James, *Chem. Comm.*, 1970, 337.



Reagents: i, (+)-peroxycamphoric acid; ii, NaOMe, DMF, 20 °C; iii, Ac₂O, pyridine, reflux; iv, aq. NaOH, 20 °C; v, O₃

Scheme 2

product gave (–)-ribalinine (22; R = H), which was shown to have an (*S*)-configuration by ozonolysis to the (*S*)-hydroxy-lactone (21). This work revealed some interesting features of the well-known dihydrofuroquinolone–dihydro-pyranoquinolone acetate rearrangement. Thus, the conversion of balfourodine into isobalfourodine acetate occurs with retention of configuration at the chiral centre, and a mechanism involving nucleophilic attack at C-2 of the quinoline ring was suggested [Scheme 3, route (*a*)];²⁶ it appears, however, that rearrangement of isoplatydesmine, differing from balfourodine only in the absence of an aromatic methoxy-group, involves inversion [Scheme 3, route (*b*)]. Both reactions are

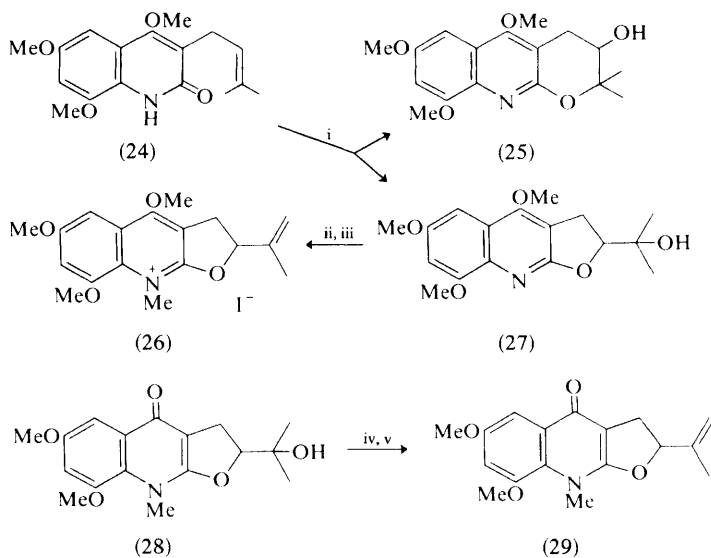


Scheme 3

²⁶ R. M. Bowman, J. F. Collins, and M. F. Grundon, *J. C. S. Perkin I*, 1973, 626.

accompanied by a reduction in optical purity, which is now attributed to finely balanced competing reactions in each case, rather than to 'racemisation', as had been supposed.^{26,27} (+)-Isoplatydesmine has been isolated from *Araliopsis tabouensis* (cf. Vol. 8, p. 82) as well as from *A. soyauxii*, but one species contains (+)-ribalinine and the other (-)-ribalinine; it is thus tempting to suggest that the dual mechanism for the rearrangement observed *in vitro* also might occur *in vivo*.

Ptelea trifoliata is the only known source of hemiterpenoid quinoline alkaloids containing terminal double bonds, and nine compounds of this type have been isolated (cf. Vols. 1—3, 5, and 7); the synthesis of two members of the group, *O*-methylptelefolonium iodide (26) and ptelefolone (29), has now been reported (Scheme 4).²⁸ The 3-prenyl-4-methoxy-2-quinolone (24) was prepared by standard procedures and was converted with a peroxy-acid into a mixture of the dihydropyrano-quinolone (25) and the dihydrofuro-quinolone (27). Treatment of the latter with thionyl chloride and pyridine resulted in regiospecific elimination to give a terminal olefin, which afforded *O*-methylptelefolonium iodide (26). Successive reaction of the *N*-methyl-4-quinolone (28) (cf. Vol. 7) with triphenyl phosphite dichloride and with pyridine resulted in an efficient synthesis of ptelefolone (29).



Reagents: i, *m*-ClC₆H₄CO₃H, CHCl₃; ii, SOCl₂, pyridine; iii, MeI, MeOH, 20 °C; iv, Ph₃POCl₂, Me₂CO; v, pyridine

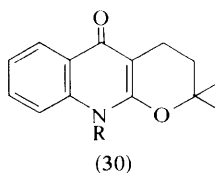
Scheme 4

Two research groups^{10,29} have independently synthesized haplobucharine (30; R = CH₂CH=CMe₂) by *N*-allylation of khaplofolone (30; R = H).

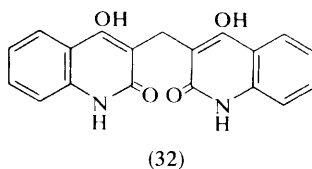
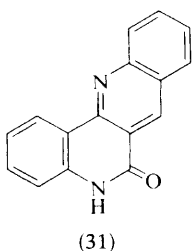
²⁷ H. Rapoport and K. G. Holden, *J. Amer. Chem. Soc.*, 1960, **82**, 4395.

²⁸ J. L. Gaston and M. F. Grundon, *Tetrahedron Letters*, 1978, 2629.

²⁹ P. Venturella and A. Bellino, *Heterocycles*, 1978, **9**, 193.



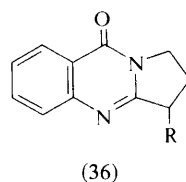
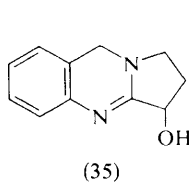
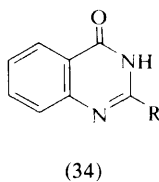
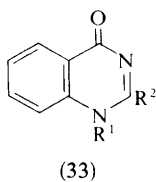
The traditional procedure for the preparation of 3-prenyl-2-quinolones involves refluxing a solution of an aromatic amine and diethyl prenylmalonate in diphenyl ether. An interesting study of other products of these reactions has led to the identification of tetracyclic compounds, *cf.* (31), and 3,3'-methylenebis-2-quinolones, *cf.* (32); mechanisms for the formation of these compounds were proposed.³⁰



2 Quinazoline Alkaloids

The new benzylquinazolone alkaloid glycophymine (33; $R^1 = H$, $R^2 = CH_2Ph$) has been isolated from the flower heads of *Glycosmis pentaphylla*.³¹ The structure was assigned on the basis of i.r. absorption at 3350 (NH) and 1700 cm^{-1} (C=O), and of the formation of glycofymimine by demethylation of arborine (33; $R^1 = Me$, $R^2 = CH_2Ph$); the alkaloid was synthesized from phenylacetanilide and ethyl carbamate. Glycophymine is not identical with the alkaloid glycosminine, which is reported to have the tautomeric structure (34; $R = CH_2Ph$).

A study of the ^{13}C n.m.r. spectra of peganine (35), vasicinone (36; $R = OH$), and related compounds has been reported,³² and the mass spectra of some alkaloids of this group have been discussed.³³



³⁰ R. Oels, R. Storer, and D. W. Young, *Chem. and Ind.*, 1974, 499; *J. C. S. Perkin I*, 1977, 2546.

³¹ M. Sarkar and D. P. Chakraborty, *Phytochemistry*, 1977, **16**, 2007.

³² S. Johne, B. Jung, D. Gröger, and R. Radeaglia, *J. Prakt. Chem.*, 1977, **319**, 919.

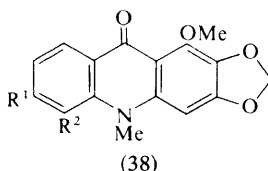
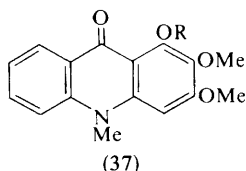
³³ Ya. V. Rashkes, M. V. Telezhenetskaya, V. N. Plugar, and S. Yu. Yunosov, *Khim. prirod. Soedinenii*, 1977, 378 (*Chem. Abs.*, 1978, **88**, 7152).

Kametani and co-workers³⁴ have applied their preparation of quinazolines from sulphinamide anhydrides (*cf.* Vol. 8, p. 83) to the synthesis of the alkaloids glycorine (33; R¹ = Me, R² = H), glomerine (33; R¹ = R² = Me), and homoglomerine (33; R¹ = Me, R² = Et). The reaction of the sulphinamide anhydride derived from anthranilic acid with *O*-benzyl-lactic acid amide furnished the quinazolinone [34; R = CH(OBz)Me], which was converted into the alkaloid crysogine [34; R = CH(OH)Me] by acid hydrolysis.

Russian workers have continued to explore the synthesis of quinazoline derivatives. Thus, desoxyvasicinone (36; R = H) has been condensed with a number of aromatic aldehydes,³⁵ and methylenebis-desoxyvasicinones have been prepared from methylenedianthranilic acids.³⁶

3 Acridone Alkaloids

Five acridone alkaloids were obtained previously from the bark of *Teclea boiviniana* (*cf.* Vol. 6, p. 108); a recent investigation¹⁴ showed that the constituents of the leaves are similar, and resulted in the isolation of arborinine (37; R = H), tecleanthine (38; R¹ = H, R² = OMe), evoxanthine (38; R¹ = R² = H), 6-methoxytecleanthine (38; R¹ = R² = OMe), and 1,3,4-trimethoxy-*N*-methylacridone (39; R¹ = Me, R² = OMe). The latter compound has not been obtained previously from a natural source. The n.m.r. and mass spectra indicated that the new alkaloid was a trimethoxy-*N*-methylacridone and that ring A was unsubstituted. The three possible acridones had been synthesized earlier,³⁷ and from melting-point data the alkaloid appeared to be the 1,3,4-trimethoxy-derivative; this was confirmed by synthesis using a modification of the published procedures. 1,2,3-Trimethoxy-*N*-methylacridone (37; R = Me), previously isolated from *Evodia alata*, has now been obtained from *Melicope leratii*.¹² The known alkaloids melicopidine (40; R¹ = Me, R² = OMe) and xanthovedine (40; R¹ = R² = H) were also shown to be constituents of *M. leratii*. Arborinine (37; R = H) has been obtained from *Vepris pilosa*¹⁷ and from *Ruta chalapensis*.⁶ Other known acridone alkaloids isolated from a new source include the 1-hydroxy-3-methoxy-derivative (39; R¹ = R² = H) and its methyl ether (39; R¹ = Me, R² = H), from *Vepris pilosa*.¹⁷

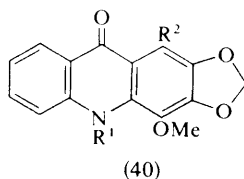
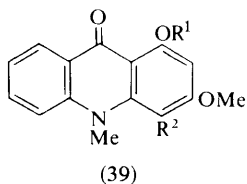


³⁴ T. Kametani, Chu Van Loc, T. Higa, M. Ihara, and K. Fukumoto, *J. C. S. Perkin I*, 1977, 2347.

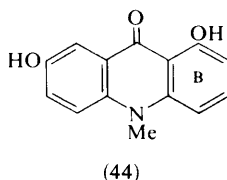
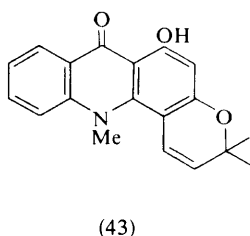
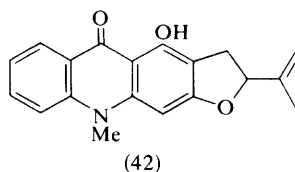
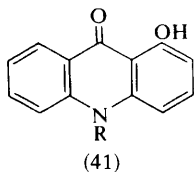
³⁵ Kh. M. Shakhidoyatov, Ya. M. Yamankulov, and Ch. Sh. Kadyrov, *Khim. prirod. Soedinenii*, 1977, 552 (*Chem. Abs.*, 1978, **88**, 7166).

³⁶ Kh. M. Shakhidoyatov and Ch. Sh. Kadyrov, *Khim. prirod. Soedinenii*, 1977, 544 (*Chem. Abs.*, 1978, **88**, 6830).

³⁷ G. K. Hughes, K. G. Neill, and E. Ritchie, *Austral. J. Sci. Res., Series A*, 1950, **3**, 497.



A preliminary study of the acridone alkaloids of the roots of *Boenninghausenia albiflora* resulted in the identification of 1-hydroxy-*N*-methylacridone (41; R = Me);³⁸ now the *Ruta* alkaloid rutacridone (42) (*cf.* Vol. 8, p. 84) and noracronycine (43) have been isolated from this species.³⁹ Of two new alkaloids obtained from *B. albiflora*, one was shown to be 1-hydroxyacridone (41; R = H) by methylation to (41; R = Me). The n.m.r. spectrum of the other new alkaloid suggested that it was a dihydroxy-*N*-methyl-acridone in which ring B contained a 1-hydroxy-group and three adjacent aromatic hydrogen atoms; structure (44) was proposed.



Full accounts are not available of the synthesis of acridones by the cyclisation, with sodium hydride in dimethyl sulphoxide, of 2-methoxy-benzophenones containing 2'-acetamido- or 2'-methylamino-groups (*cf.* Vol. 7, p. 90); the alkaloids (41; R = Me) and 1,3-dimethoxy-*N*-methylacridone have been prepared by this route.⁴⁰

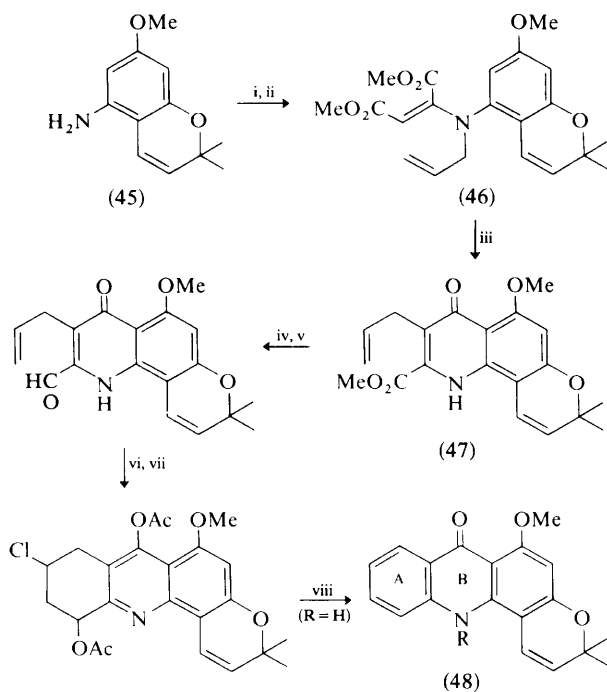
Winterfeldt and co-workers⁴¹ have described a novel regiospecific synthesis of acronycine (48; R = Me) which may be applicable to the preparation of metabol-

³⁸ Zs. Rózsa, K. Szendrei, I. Novák, J. Reisch, and E. Minker, *Pharmazie*, 1975, **30**, 753.

³⁹ Zs. Rózsa, K. Szendrei, Z. Kovacs, I. Novák, E. Minker, and J. Reisch, *Phytochemistry*, 1978, **17**, 169.

⁴⁰ J. H. Adams, P. Gupta, M. S. Khan, J. R. Lewis, and R. A. Watt, *J. C. S. Perkin I*, 1976, 2089; J. H. Adams, P. Gupta, M. S. Khan, and J. R. Lewis, *ibid*; 1977, 2173.

⁴¹ S. Blechert, K.-E. Fichter, and E. Winterfeldt, *Chem. Ber.*, 1978, **111**, 439.



Reagents: i, $\text{MeO}_2\text{CC}\equiv\text{CCO}_2\text{Me}$, HCl , MeOH , 20°C ; ii, $\text{BrCH}_2\text{CH}=\text{CH}_2$, KOBu^t , $(\text{MeOCH}_2)_2$, 0°C ; iii, Et_2O , 190°C ; iv, LiAlH_4 , $(\text{MeOCH}_2)_2$, 60°C ; v, MnO_2 , Me_2CO ; vi, TiCl_4 , CH_2Cl_2 ; vii, Ac_2O , pyridine, 50°C ; viii, KOBu^t , $(\text{MeOCH}_2)_2$

Scheme 5

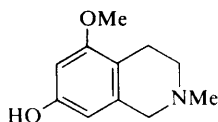
ites (Scheme 5). Addition of the amino-chromene (45) to acetylenedicarboxylic ester and subsequent allylation leads to the enamine (46). In a key step, Cope rearrangement and cyclization affords the 4-quinolone (47). The final stages of the synthesis involve elaboration of ring A to give des-*N*-methyl-acronycine (48; $\text{R} = \text{H}$), which has already been converted into acronycine.

1 β -Phenethylamines

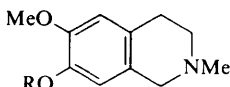
N-methyl- and *NN*-dimethyl- β -3,4-dimethoxyphenyl-ethylamine have been isolated from *Pilosocereus guerreronis*.¹ The Mexican cactus *Dolichothele uberiformis* has been shown to contain (–)-synephrine, *N*-methyltyramine, *ON*-dimethyltyramine, *N*-methyl- β -3,4-dimethoxyphenyl-ethylamine, hordenine, (–)-normacromerine, longimammatine, and ubine, which has been identified as (–)-*NN*-dimethyl- β -hydroxy- β -phenyl-ethylamine.² Several studies of the effects of mescaline have been reported, namely the regional localization of [¹⁴C]mescaline in rabbit brain and the effects of pretreatment with chlorpromazine and iproniazid,³ the actions of the alkaloid on isolated rat atria,⁴ interactions of mescaline with phenothiazines and the effects on behaviour, body temperature, and tissue levels in mice,⁵ amine-releasing action on the rat hypothalamus,⁶ and the effect of mescaline on rats.⁷

2 Simple Isoquinolines

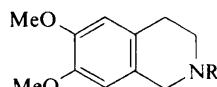
A new base, uberine, of structure (1), has been isolated from *Dolichothele uberiformis*.² *O*-Methyl-corypalline (2; R=Me) has been detected by mass spectrometry in *Pilosocereus guerreronis*,¹ and corypalline (2; R=H) has been synthesized by Pictet–Spengler cyclization of *N*-methyl- β -4-benzyloxy-3-methoxyphenyl-ethylamine, followed by debenzoylation.⁸ A number of *N*-substituted salsolidine derivatives (3), where R is PhCH₂, PhSO₂, Me₂CH, *p*-O₂NC₆H₄,



(1)



(2)



(3)

¹ J. E. Lindgren and J. G. Bruhn, *Lloydia*, 1976, **39**, 464.

² R. L. Ranieri and J. L. McLaughlin, *Lloydia*, 1977, **40**, 173.

³ N. S. Shah, O. D. Gulati, D. A. Powell, and V. Kleinburd, *Neurochem. Res.*, 1977, **2**, 265.

⁴ P. K. S. Siegl and R. F. Orzechowski, *J. Pharm. Sci.*, 1977, **66**, 938.

⁵ N. S. Shah, J. R. Jacobs, J. T. Jons, and M. P. Hedden, *Biol. Psychiatry*, 1975, **10**, 561.

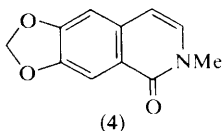
⁶ O. D. Gulati and N. S. Shah, *Eur. J. Pharmacol.*, 1977, **46**, 135.

⁷ M. W. Liefer and W. H. Bridges, *Biol. Psychiatry*, 1976, **11**, 457.

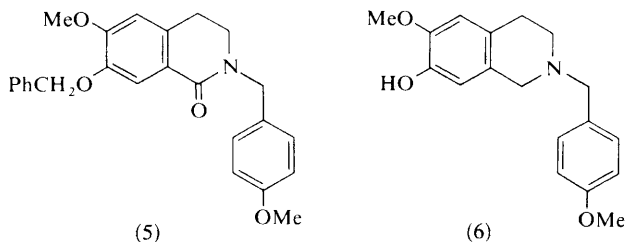
⁸ M. L. J. Fransisca, H. Suguna, S. Rajeswari, and B. R. Pai, *Indian. J. Chem., Sect. B*, 1977, **15**, 182.

or p -MeC₆H₄SO₂, have been prepared⁹ and examined for pharmacological action. Of these, the *N*-benzyl and *N*-phenylsulphonyl compounds showed spasmolytic activity.¹⁰

The isoquinolone doryanine (4) has been isolated from *Doryhora sassafras*, and its structure has been confirmed by synthesis from methylenedioxyhomophthalic anhydride.¹¹



The alkaloid sendaverine (6) has been prepared by reduction and debenzylation of the amide (5) obtained by the action of carbon monoxide and palladium(II) acetate on *N*-4-methoxybenzyl- β -2-bromo-4-benzyloxy-5-methoxyphenyl-ethylamine.¹² Sendaverine and its *N*-oxide have been isolated from *Corydalis gortschakovii*.¹³



A new synthesis of (\pm)-cherylline has been reported.¹⁴ The amine (7) was condensed with the *p*-quinone methide ketal (8) to give the amide (9), which was cyclized and reduced to (\pm)-cherylline (10). The methide (8) and its analogues are obtained from *p*-quinone dimethyl ketal (11) and α -trimethylsilyl amides.¹⁴

Two new alkaloids of the 7- α -naphthylisoquinoline series, *O*-methyl-triophylline (12) and *O*-methyl-1,2-dehydrotriophylline (13), have been isolated from *Triphophyllum peltatum*. The latter may be reduced to the former.¹⁵

The alkaloids nor-rufescine (14)¹⁶ and imerubine (15)¹⁷ are discussed in Chapter 9.

⁹ Yu. D. Sadykov, L. V. Yashchenkova, I. N. Grigina, A. E. Vezén, and K. Kh. Khaidarov, *Dokl. Akad. Nauk. Tadzh. S.S.R.*, 1977, **20**, 40.

¹⁰ A. E. Vezén, K. Kh. Khaidarov, and Yu. D. Sadykov, *Dokl. Akad. Nauk. Tadzh. S.S.R.*, 1977, **20**, 36.

¹¹ H. Iida, N. Katoh, M. Narimiya, and T. Kikuchi, *Heterocycles*, 1977, **6**, 2017.

¹² M. Mori, K. Chiba, and Y. Ban, *Heterocycles*, 1977, **6**, 1841.

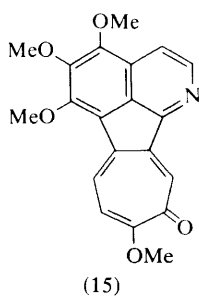
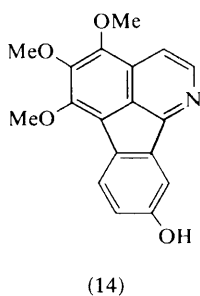
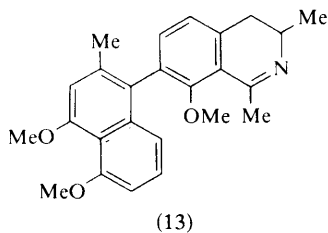
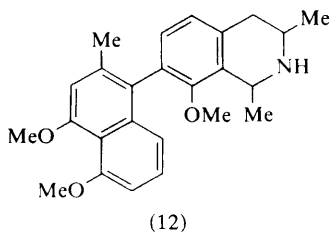
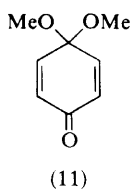
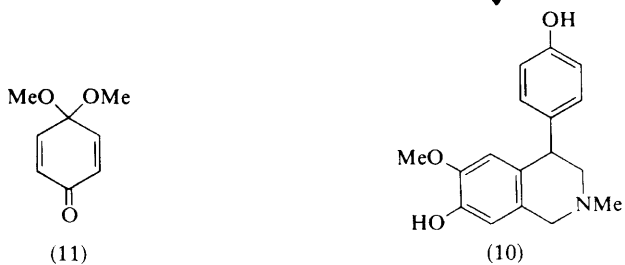
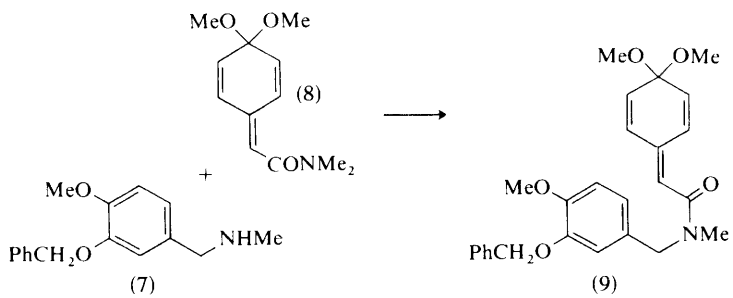
¹³ I. A. Israilov, T. Irgashev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 834.

¹⁴ D. J. Hart, P. A. Cain, and D. A. Evans, *J. Amer. Chem. Soc.*, 1978, **100**, 1548.

¹⁵ M. Lavault, M. Tehikouhon, and J. Bruneton, *C.R. Hebd. Seances Acad. Sci.*, 1977, **285**, C, 167.

¹⁶ M. D. Klein, K. T. Buck, M. P. Cava, and D. Voet, *J. Amer. Chem. Soc.*, 1978, **100**, 662.

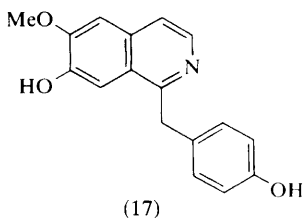
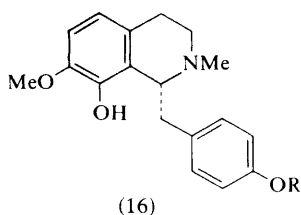
¹⁷ J. V. Silverton, C. Kabuto, K. T. Buck, and M. P. Cava, *J. Amer. Chem. Soc.*, 1977, **99**, 6708.



3 Benzylisoquinolines

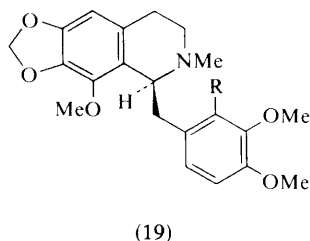
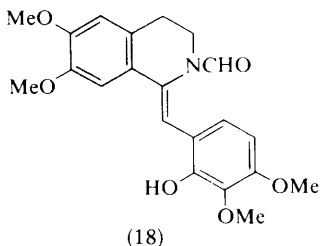
Laudanidine, reticuline, and *N*-methylcoclaurine have been isolated from *Thalictrum revolutum*.¹⁸ Two new bases, yuziphine (16; R = H) and yuzirine (17), have

¹⁸ J. Wu, J. L. Beal, W. -N. Wu, and R. W. Dorskotch, *Lloydia*, 1977, **40**, 593.



been isolated from *Ziziphus jujuba*,¹⁹ and the former, together with its *N*-oxide, has also been found in *Corydalis gortschakovii*.¹³ In the latter plant yuziphine is accompanied by its methyl ether, gorchacoin (16; R = Me), the structure of which was determined by spectroscopic methods and by its identity with an intermediate in the synthesis of petaline.²⁰

Another new benzylisoquinoline, polycarpine (18), has been isolated from the trunk bark of *Enantia polycarpa*; its structure has been determined by spectroscopic and *X*-ray crystallographic methods.²¹ Macrantoridine (19; R = CO₂H) and macrantaline (19; R = CH₂OH), both from *Papaver pseudo-orientale*, have been inter-related by the conversion of the former into the latter by reduction with lithium aluminium hydride, and since the latter can be further converted into the base (19; R = CH₃) obtainable from narcotine, the stereochemistry of these two alkaloids is as shown.²²



Novel benzylisoquinoline alkaloids bearing a reduced pyrrole unit at position 4 have been identified in macrostomine (20) and dehydronormmacrostomine (21), obtained from *Papaver macrostoma* (syn. *P. oligotrichum*; *Closteranda macrostoma*). Sevanine has also been found in the same plant.²³

The absolute configuration of (+)-6-hydroxymethyl-laundanosine has been determined by its conversion into norcoralydine by successive chlorination, cyclisation-quaternization, and dequaternization by *N*-demethylation.²⁴

¹⁹ R. Ziyayev, T. Irgashev, I. A. Israilov, N. D. Abdullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1977, 239.

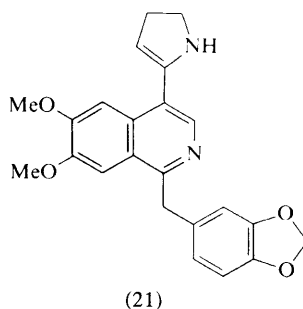
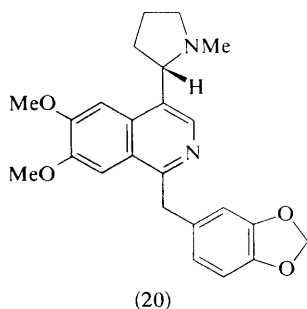
²⁰ T. Irgashev, I. A. Israilov, N. D. Abdullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1977, 127.

²¹ A. Jossang, M. Leboeuf, A. Cavé, M. Damak, and C. Riche, *C.R. Hebd. Seances Acad. Sci.*, 1977, 284, C, 467.

²² G. Sariyar and J. D. Phillipson, *Phytochemistry*, 1977, 16, 2009.

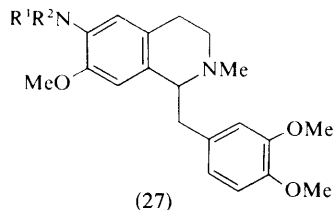
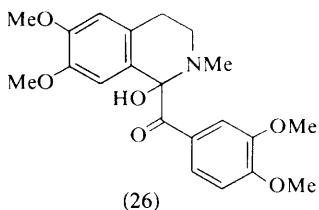
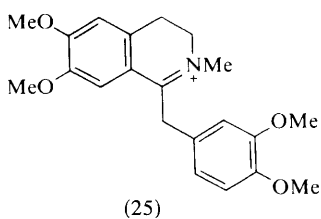
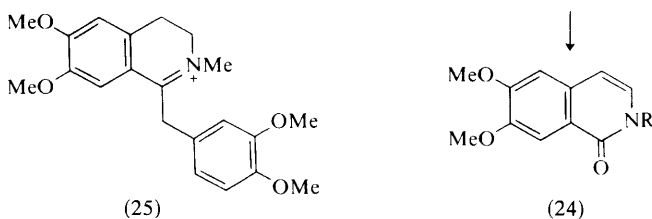
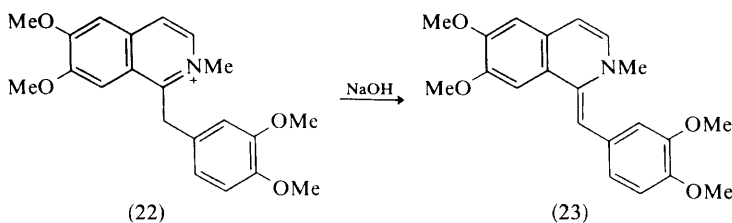
²³ V. A. Mnatsakanyan, V. Preininger, V. Simanek, J. Jurina, A. Klasek, L. Dolejs, and F. Santavy, *Coll. Czech. Chem. Commun.*, 1977, 42, 1421.

²⁴ H. M. Stephan, G. Langer, and W. Wiegrebe, *Pharm. Acta Helv.*, 1976, 51, 164.



Quaternary papaverinium salts (22) have been converted into enamines (23), which have been oxidised by singlet oxygen or by oxygen and cuprous chloride with fission to the quinolones (24). *N*-methyl-3,4-dihydropapaverinium salts (25), however, with oxygen and cuprous chloride, afford the α -hydroxy-ketone (26), though they are split by photosensitized oxygenation to the quinolone (24; R = Me).^{25,26}

A series of 6-amino-6-demethoxy-laundanosines (27) has been synthesized.²⁷



²⁵ S. Ruchirawat, *Heterocycles*, 1977, **6**, 1724.

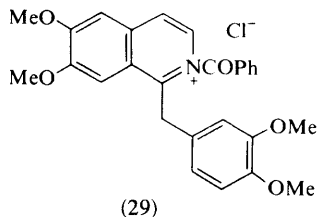
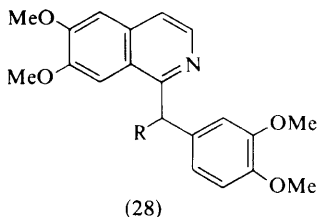
²⁶ S. Ruchirawat, U. Borvornvinyanant, K. Haintawong, and Y. Thebtaranonth, *Heterocycles*, 1977, **6**, 1119.

²⁷ H. Nishimura, S. Naruto, and Y. Mizuta, Japan. Kokai 77 95 676 (*Chem. Abs.*, 1978, **88**, 23 229).

Papaverine has been found to be converted into mixtures of 4'-desmethyl- and 6-desmethyl-papaverine by hepatic microsomes from phenobarbital-treated rats and by micro-organisms of *Aspergillus*, *Cunninghamella*, and *Streptomyces* species. Preparative amounts of the 4'-desmethyl compound can be obtained using *A. alliaceus* and of the 6-desmethyl isomer using *C. echinulata*.²⁸ The chemistry of the Calinberg-Husemann colour test for papaverine has been studied and shown to proceed through the 6'-sulphonic acid to 6'-nitropapaverine, which gives a red solution in concentrated sulphuric acid.²⁹

Reports on the pharmacological and biological effects of papaverine include the following: a review of the use of papaverine as an anti-arrhythmic agent,³⁰ the effect of the alkaloid on the malignancy of neuroblastoma cells,³¹ the inhibition by papaverine of spontaneous and ADP-induced platelet aggregation,³² the effect of the alkaloid on the oxygenation of cerebral blood following vasodilation,³³ the inhibition of the release of histamine from rat mast cells,³⁴ the effect of papaverine on levels of cyclic nucleotides in rat aorta,³⁵ effects on the contractile responses of guinea-pig ileum,³⁶ on guinea-pig *Taenia coli*,³⁷⁻³⁹ and on isolated DT diaphorase and mitochondrial respiration,³⁹ and the relationship between spasmolytic activity and dissociation constants of papaverine and its analogues.⁴⁰

Pharmacokinetic studies have been made of the tetra-ethoxy analogue of dihydropapaverine (drotaverine),⁴¹ and the pharmacological properties of the analogues (28; R = ClCH₂CO), (28; R = Cl₃CCO),⁴² and (29)⁴³ have been studied.



A structure-activity analysis has been made of tetrahydropapaveroline and its derivatives, certain tetrahydroberberines, and aporphines to determine whether

²⁸ J. P. Rosazza, M. Kammer, L. Youel, R. V. Smith, P. W. Erhardt, D. H. Truong, and S. W. Leslie, *Xenobiotica*, 1977, 7, 133.

²⁹ F. Klivenyi, E. Vinkler, and G. Simon-Talpas, *Pharmazie*, 1977, 32, 414.

³⁰ G. H. Whipple, *Angiology*, 1977, 28, 737.

³¹ J. S. Lazo and R. W. Ruddon, *J. Natl. Cancer Inst.*, 1977, 59, 137.

³² A. Favero and R. Zappoli, *Proc. Sero Sympos.*, 1974, 3, 235.

³³ J. Seylaz and E. Pinard, *Acta Neurol. Scand., Suppl.*, 1977, 104, 438.

³⁴ K. Sugiyama, *Arerugi*, 1977, 26, 490.

³⁵ F. Demesy-Waeldele and J. C. Stocklet, *Eur. J. Pharmacol.*, 1977, 46, 63.

³⁶ K. Kin, T. Uruno, and K. Kubota, *Nippon Yakurigaku Zasshi*, 1977, 73, 851.

³⁷ S. Tsuda, N. Urakawa, and Y. Saito, *Japan. J. Pharmacol.*, 1977, 27, 833.

³⁸ S. Tsuda, N. Urakawa, and J. Fukami, *Japan. J. Pharmacol.*, 1977, 27, 845.

³⁹ S. Tsuda, N. Urakawa, and J. Fukami, *Japan. J. Pharmacol.*, 1977, 27, 855.

⁴⁰ L. Simon, J. Poreszasy, P. K. Gibiszer, and S. G. Talpas, *Pharmazie*, 1977, 32, 720.

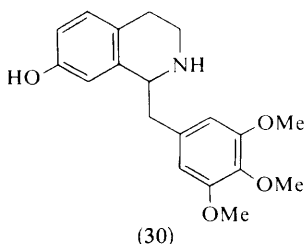
⁴¹ M. H. Rutz-Coudray, L. Balant, C. Revillard, P. Buri, and J. Guist, *Pharm. Acta Helv.*, 1976, 51, 258.

⁴² A. E. Vezén, K. Kh. Khaidarov, M. Kurbanov, and V. A. Degtyarev, *Dokl. Akad. Nauk Tadzh. S.S.R.*, 1977, 20, 33.

⁴³ F. Kh. Sharipov, V. Pol'skii, K. Kh. Khaidarov, and L. D. Lebedeva, *Izv. Akad. Nauk Tadzh. S.S.R.*, 1977, 105.

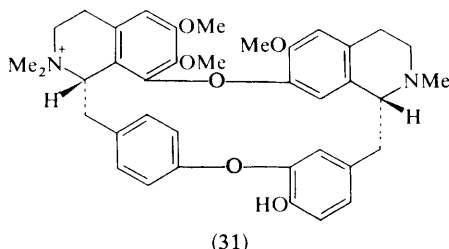
or not there is any preferred conformation of the 1-benzyl substituent in reactions with the β -adrenergic receptor. All compounds were found to be active, leading to the conclusion that a phenylalanine or tyrosine residue of the receptor is free to bind with bases with the benzyl group in either fixed position.⁴⁴

Synthetic analogues of tetrahydropapaverine of general structure (30) with a second hydroxy-group at position 5, 6, or 8 have been reported to have bronchodilating properties.⁴⁵



4 Bisbenzylisoquinolines

Berberamine, oxyacanthine, and magnoflorine have been isolated from *Berberis integerrima* and *B. oblongata*, and from the latter a new quaternary alkaloid, oblongamine (31), has been obtained.⁴⁶



Further investigation of *Thalictrum* species has resulted in the isolation of the following alkaloids:

<i>T. revolutum</i> ⁴⁷	thalidasine, <i>O</i> -methylthalmatine, thalphenine, <i>O</i> -methylthalicberine, thalrugosamine, thalicarpine
<i>T. podocarpum</i> ⁴⁸	hernandezine, thalidezine, isothalidezine, <i>N</i> -desmethylthalidezine, thalistryline, thalistryline methiodide, <i>N</i> -desmethylthalistryline
<i>T. rugosum</i> ⁴⁹	thaligosine, thaligosinine, thaligosidine, thalirugine, thaliruginine, thalirugidine

Of these bases, the six named from *T. rugosum* are new alkaloids and have been assigned the following structures on the basis of chemical and spectroscopic

⁴⁴ H. Sheppard, C. R. Burghardt, and S. Teitel, *Res. Commun. Chem. Pathol. Pharmacol.*, 1977, **17**, 53.

⁴⁵ K. Ikezawa, H. Takenaga, M. Sato, H. Nakajima, and A. Kiyomoto, *Japan. J. Pharmacol.*, 1977, **27**, 537.

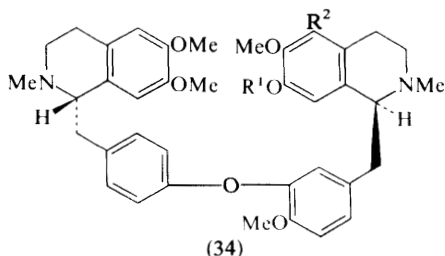
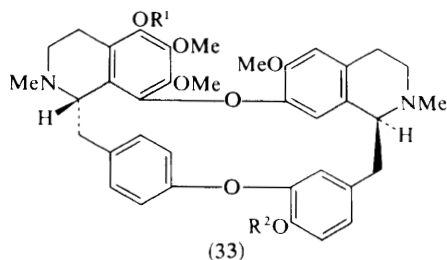
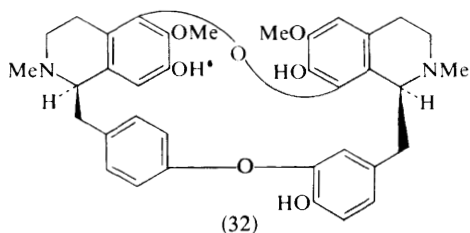
⁴⁶ A. Karimov, M. V. Telezhenetskaya, K. L. Lutufullin, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1977, **80**.

⁴⁷ W.-N. Wu, J. L. Beal, and R. W. Doskotch, *Lloydia*, 1977, **40**, 508.

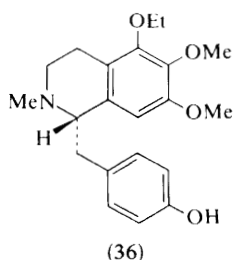
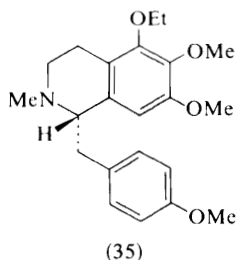
⁴⁸ W.-N. Wu, J. L. Beal, R.-P. Leu, and R. W. Doskotch, *Lloydia*, 1977, **40**, 384.

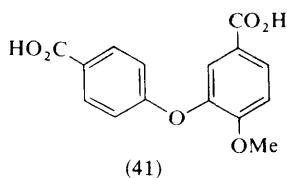
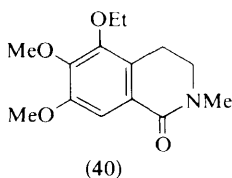
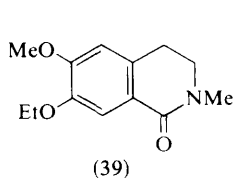
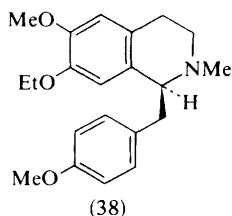
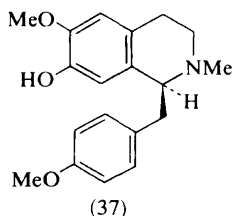
⁴⁹ W.-N. Wu, J. L. Beal, E. H. Fairchild, and R. W. Doskotch, *J. Org. Chem.*, 1978, **43**, 580.

evidence: thaligosidine (32), thaligosine (33; $R^1 = H, R^2 = Me$), thaligosinine (33; $R^1 = Me, R^2 = H$), thalirugine (34; $R^1 = R^2 = H$), thaliruginine (34; $R^1 = Me, R^2 = H$), thalirugidine (34; $R^1 = H, R^2 = OH$).⁴⁹

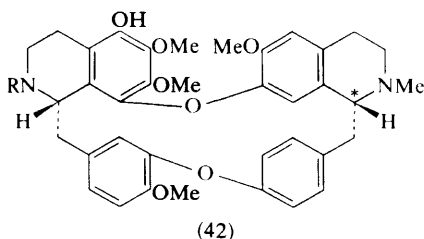


Fission of *OO*-diethylthalirugidine by sodium and liquid ammonia gives the bases (35) and (36), and *O*-ethylthaliruginine gives the bases (35) and (*S*)-*O*-methylarmepavine. The bases (36) and (37) are obtained in the same way from *O*-ethylthaligosine and (37) from thalrugosamine. Fission of *OO*-diethylthalirugine gives (37) and (38), and the latter is also obtained from *O*-ethylthalrugosidine. Oxidation of *OO*-diethylthalirugine affords the isoquinolone derivatives (39) and (40) and the dicarboxylic acid (41).



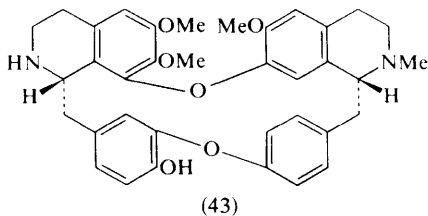


Thalrugosamine is the methyl ether of thaligosine and thaligosinine, (33; $R^1 = R^2 = \text{Me}$).⁴⁷ Thalidezine has the isomeric diphenyl ether structure (42; $R = \text{Me}$) and *N*-demethylthalidezine is the secondary base (42; $R = \text{H}$); iso-thalidezine is stereoisomeric with thalidezine at the carbon marked with an asterisk.⁴⁸



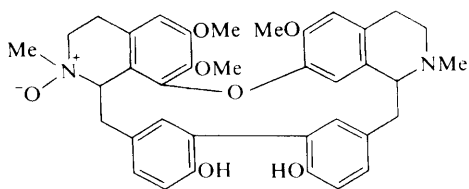
Thalidasine, *O*-methylthalmetine, thalphenine, and thalicarpine have been found to have some antihypertensive activity and *O*-methylthalmetine, thalphenine, and thalicarpine mild antifungal properties.⁴⁷

Other new bisbenzylisoquinolines reported are peinamine (43), from a specimen of curare from the upper Orinoco region, prepared from unknown plants, probably of the Menispermaceae,⁵⁰ and funiferine *N*-oxide (44), from *Tiliacora funifera*.⁵¹



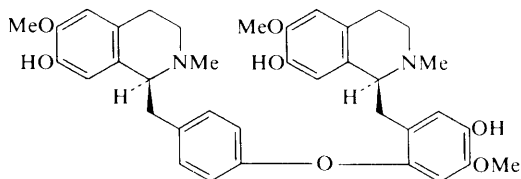
⁵⁰ C. Galeffi, R. Scarpetti, and G. Marini-Bettolo, *Farmaco, Ed. Sci.*, 1977, **32**, 665 (*Chem. Abs.*, 1977, **87**, 180 683).

⁵¹ D. Dwuma-Badu, T. U. Okarter, A. N. Tackie, J. A. Lopez, D. J. Slatkin, J. E. Knapp, and P. L. Schiff, *J. Pharm. Sci.*, 1977, **66**, 1242.

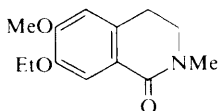


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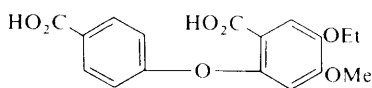
The structure of magnolamine has been revised to (45) following spectroscopic studies and the oxidation of magnolamine triethyl ether to the isoquinolone (46) and the dicarboxylic acid (47).⁵²



(45)



(46)

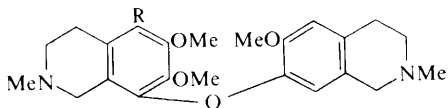


(47)

Chondrofoline has been isolated from *Uvaria ovata*.⁵³

Oxidation with ceric nitrate has been developed as a new degradative procedure in the study of bisbenzylisoquinoline alkaloids. This reagent splits laudanosine to veratric aldehyde and the *N*-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium ion, isolated as veratryl alcohol and *N*-methyl-3,4-dimethoxytetrahydroisoquinoline after reduction. In the same way, tetrandrine, hernandezine, and *O*-methylmicranthine have been degraded to the bis-tetrahydroisoquinolines (48; R = H), (48; R = OMe), and (49), the second product in each case being the diphenyl ether (50).⁵⁴

Further details of the total synthesis of trilobine, isotrilobine, and obaberine, reported in the previous Volume, have been published.⁵⁵



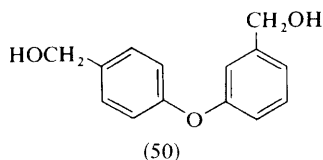
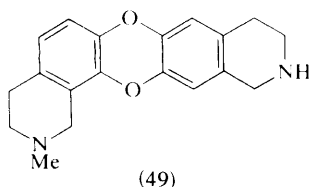
(48)

⁵² D. L. Yakhontova, O. N. Tolkachev, D. A. Fesenko, M. E. Perel'son, and N. F. Proskurnina, *Khim. Prir. Soedin.*, 1977, 234.

⁵³ K. Panchipol, R. D. Waigh, and P. G. Waterman, *Phytochemistry*, 1977, **16**, 621.

⁵⁴ I. R. C. Bick, J. B. Bremner, and M. P. Cava, *Aust. J. Chem.*, 1978, **31**, 321.

⁵⁵ Y. Inubushi, Y. Ito, Y. Masaki, and T. Ibuka, *Chem. Pharm. Bull.*, 1977, **25**, 1636.



A report of the stepwise demethylation of cycleanine to norcycleanine, isochondodendrine, and tetrademethylcycleanine with pyridine hydrobromide has been published.⁵⁶

The inhibitory action of cepharanthamine on the release of potassium ions following membrane injury has been studied.⁵⁷

The pharmacokinetics of (+)-tubocurarine in man with and without renal failure, and anaesthetized with halothane and nitrous oxide, have been studied.⁵⁸ Other studies with (+)-tubocurarine include investigations of its effects on neurally evoked compound electromyograms,⁵⁹ its actions at hyperbaric pressures,⁶⁰ the effects of circulating residue of the ED₅₀ dose five minutes after injection on unexposed neuromuscular junctions,⁶¹ the uptake of (+)-tubocurarine by liver lysosomes,⁶² the potentiation of (+)-tubocurarine neuromuscular blockade by lithium chloride in cats,⁶³ effects on the heart⁶⁴ and on ocular function,⁶⁵ and the distribution of the alkaloid in cerebrospinal fluid after intravenous injection.⁶⁶ The clinical pharmacology of dimethyl-(+)-tubocurarine (metocurine) has also been studied.⁶⁷

5 Pavines and Isopavines

The pavines platycerine and isonorargemonine have been isolated from *Thalictrum revolutum*.⁶⁸ (\pm)-Caryachine (51; R¹ = H, R² = Me) and the isomeric base (51; R¹ = Me, R² = H) have been synthesized by cyclization of the appropriate 1,2-dihydroisoquinolines.⁶⁹

(-)-Caryachine has been synthesized also by the action of ethanolic 6M hydrogen chloride on the (+)-(*S*)-isomer of the base (53), the reaction presumably proceeding *via* the cyclisation product, *i.e.* the 1,2-dihydroisoquinoline. The reaction also affords the isopavine alkaloid (-)-reframoline (52).⁷⁰ This synthesis confirms the absolute stereochemistry deduced from the aromatic chirality rule.

⁵⁶ O. P. Belichenko, O. N. Tolkachev, and D. A. Fesenko, *Khim. Prir. Soedin.*, 1977, 662.

⁵⁷ M. Miyahara, K. Utsumi, K. Sugiyama, and K. Aono, *Okayama Igakkai Zasshi*, 1977, **89**, 749.

⁵⁸ R. D. Miller, R. S. Matteo, L. Z. Benet, and Y. J. Sohn, *J. Pharmacol. Exp. Ther.*, 1977, **202**, 1.

⁵⁹ C. Lee and R. L. Katz, *Anaesthes. Analg. (Cleveland)*, 1977, **56**, 271.

⁶⁰ C. Gountis-Bonikos, J. J. Kendig, and E. N. Cohen, *Anaesthesiology*, 1977, **47**, 11.

⁶¹ E. Yang and C. Lee, *Can. Anaesthes. Soc. J.*, 1977, **24**, 468.

⁶² J. G. Weitering, W. Lammers, D. K. F. Meijer, and G. J. Mulder, *Nauyn-Schmiedeberg's Arch. Pharmacol.*, 1977, **299**, 277.

⁶³ B. N. Basuray and C. A. Harris, *Eur. J. Pharmacol.*, 1977, **45**, 79.

⁶⁴ P. Hommelgaard and S. Eriksen, *Acta Anaesthesiol. Scand.*, 1977, **21**, 430.

⁶⁵ S. Eriksen, T. Bramsen, and P. Hommelgaard, *Acta Anaesthesiol. Scand.*, 1977, **21**, 385.

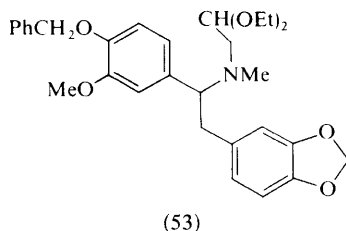
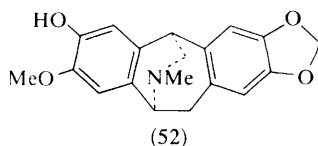
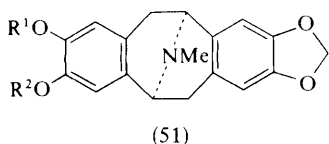
⁶⁶ R. S. Matteo, E. K. Pua, H. J. Khambarra, and S. Spector, *Anaesthesiology*, 1977, **46**, 396.

⁶⁷ J. Savarese, H. H. Ali, and R. P. Antonio, *Anaesthesiology*, 1977, **47**, 278.

⁶⁸ J. Wu, J. L. Beal, W.-N. Wu, and R. W. Doskotch, *Lloydia*, 1977, **40**, 593.

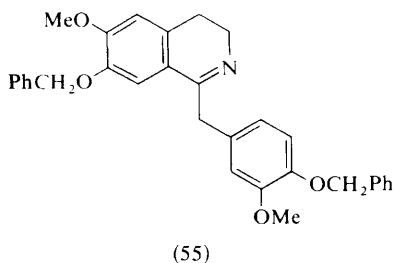
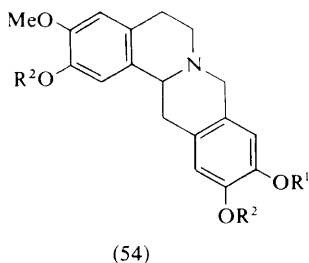
⁶⁹ C. H. Chen, J. Wu, N. A. Shaath, and T. O. Soine, *T'ai-wan Yao Hsueh Tsa Chih*, 1977, **28**, 43.

⁷⁰ S. F. Dyke, R. G. Kinsman, P. Warren, and A. W. C. White, *Tetrahedron*, 1978, **34**, 241.



6 Berberines

The occurrence of berberine and tetrahydroberberine alkaloids in *Thalictrum* species has been further studied, and the following have been isolated: from *T. revolutum*, berberine, palmatine, columbamine, jatrorrhizine, thalifendine and deoxythalidastine;⁴⁷ from *T. podocarpum*, berberine, palmatine, columbamine, jatrorrhizine, and thalifendine;⁴⁸ from *T. longistylum*, berberine, oxyberberine, palmatine, columbamine, jatrorrhizine, and thalifendine.⁴⁹ An investigation of *Corydalis govaniiana* has led to the isolation of the three related bases govanine (54; $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$), govadine (54; $R^1 = R^3 = \text{H}$, $R^2 = \text{Me}$), and corygovanine (54; $R^1R^2 = \text{CH}_2$, $R^3 = \text{Me}$).⁷¹ The assignment of structures is based on spectral studies and the synthesis of govadine from the benzylisoquinoline (55).

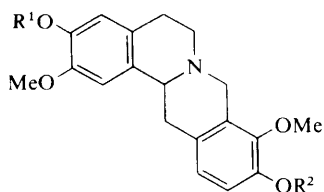


Structures assigned to certain tetrahydroberberine alkaloids have been shown to be incorrect, the bases being identified with known compounds by comparison with authentic specimens. The bases concerned are aequaline, coramine, schefferine, kikemanine, and discretinine, which have been shown to be identical with discretamine (56; $R^1 = R^2 = \text{H}$), coreximine (57), (-)-corydalmine (56; $R^1 = \text{Me}$, $R^2 = \text{H}$), (-)-corydalmine, and corypalmine (56; $R^1 = \text{H}$, $R^2 = \text{Me}$) respectively.⁷² The structure of discretamine has been confirmed by synthesis of the racemate from the tetrahydroisoquinoline (58; $R^1 = \text{PhCH}_2$, $R^2 = \text{Me}$) by its

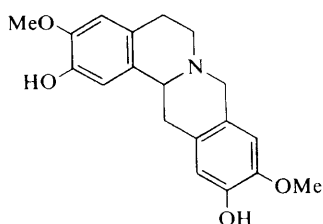
⁷¹ K. Mehra, H. S. Garg, D. S. Bhakuni, and N. M. Khanna, *Indian J. Chem., Sect. B*, 1976, **14**, 844.

⁷² E. Brochmann-Hanssen and H.-C. Chiang, *J. Org. Chem.*, 1977, **42**, 3588.

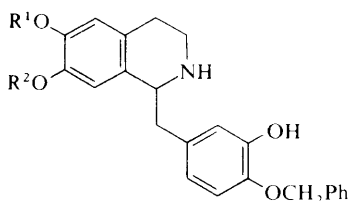
reaction with formaldehyde, *O*-methylation, and debenzoylation. Repetition of the sequence with the isomeric base (58; $R^1 = \text{Me}$, $R^2 = \text{PhCH}_2$) afforded the alkaloid (\pm)-stepholidine. In both of these reactions, cyclisation of the secondary base with formaldehyde also proceeded *para* to the hydroxy-group, giving coreximine (57) and the isomeric compound coramine from (58; $R^1 = \text{Me}$, $R^2 = \text{CH}_2\text{Ph}$) and (58; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Me}$) respectively; these were the sole products when the hydrochlorides of (58) were used in the cyclisation.⁷³ Other syntheses of stepholidine have also been recorded from the base (59; $R^1 = R^2 = R^3 = \text{H}$) and the *N*-formyl compound (59; $R^1 = \text{CHO}$, $R^2 = \text{Me}$, $R^3 = \text{Br}$),⁷⁴ and by the action of phosphorus oxychloride on the amine (60) followed by debenzoylation.⁷⁵ The amide (60) was prepared from the interaction of the appropriate β -phenethylamine with the lactone (61), itself obtained from 4-benzyloxy-3-hydroxyphenylacetic acid by hydroxymethylation and methylation.⁷⁵



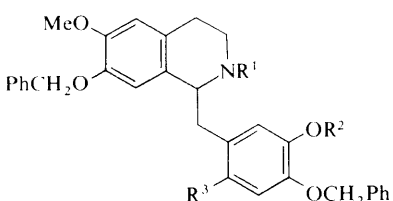
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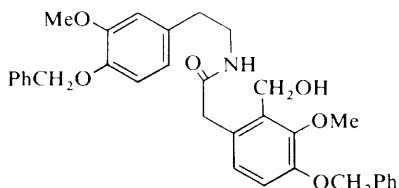
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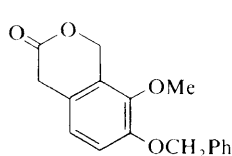
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(59)



(60)



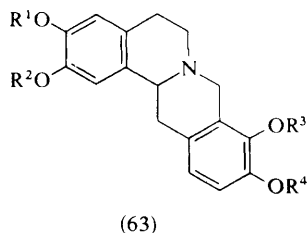
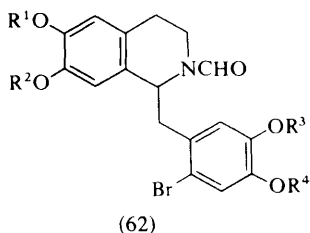
(61)

Other syntheses by cyclization of *N*-formyltetrahydroisoquinolines that have a blocking halogen atom on the receptor benzene ring have also been recorded. In this way the compound (62; $R^1R^2 = \text{CH}_2$, $R^3 = R^4 = \text{Me}$) yields 12-bromocanadife and tetrahydro- ψ -berberine (63; $R^1R^2 = \text{CH}_2$, $R^3 = R^4 = \text{Me}$) on successive treatment with phosphorus oxychloride and sodium borohydride with

⁷³ H.-C. Chiang and E. Brochmann-Hanssen, *J. Org. Chem.*, 1977, **42**, 3190.

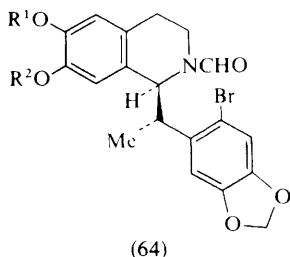
⁷⁴ S. Rajeswari, H. Suguna, and B. R. Pai, *Coll. Czech. Chem. Commun.*, 1977, **42**, 2207.

⁷⁵ H.-C. Chiang, *T'ai-wan Yao Hsueh Tsa Chih*, 1977, **28**, 111.

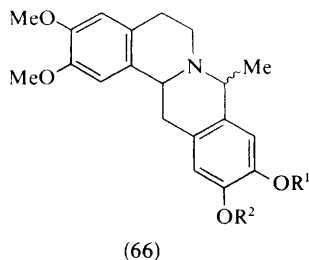
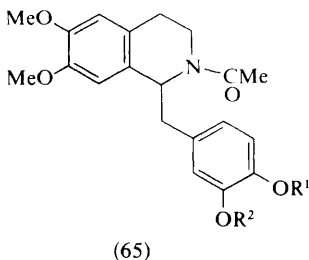


both retention and displacement of the halogen. Similarly, (62; $R^1 = R^2 = \text{Me}$, $R^3R^4 = \text{CH}_2$) yields 12-bromosinactine and tetrahydro- ψ -epiberberine (63; $R^1 = R^2 = \text{Me}$, $R^3R^4 = \text{CH}_2$), and (62; $R^1R^2 = R^3R^4 = \text{CH}_2$) yields 12-bromostylopine and tetrahydro- ψ -coptisine (63; $R^1R^2 = R^3R^4 = \text{CH}_2$).⁷⁶

A similar displacement of bromine in the cyclization of the *N*-formyl compounds (64; $R^1 = R^2 = \text{Me}$) and (64; $R^1R^2 = \text{CH}_2$) with the production of *C*-methylated tetrahydro- ψ -berberines and tetrahydro- ψ -coptisines has also been observed.⁷⁷



8-Methyltetrahydro- ψ -berberine derivatives (66; $R^1 = \text{H}$, $R^2 = \text{Me}$) and (66; $R^1 = \text{Me}$, $R^2 = \text{H}$) have been prepared by photocyclization of the *N*-acetylenamines (65; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Me}$) and (65; $R^1 = \text{Me}$, $R^2 = \text{CH}_2\text{Ph}$) followed by reduction and debenzylation.⁷⁸ A patent has been published covering the preparation of coralydine and *O*-methylcorytenchirine (67), by the thermolysis of benzocyclobutenes (68)⁷⁹ reported in the previous volume.

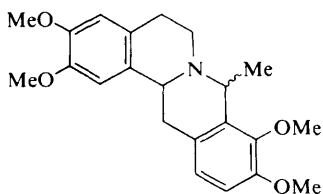


⁷⁶ R. Rajaraman, B. R. Pai, M. S. Premila, and H. Suguna, *Indian J. Chem., Sect. B*, 1977, **15**, 876.

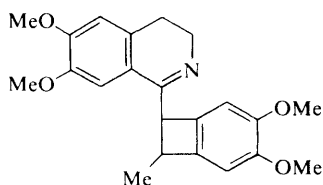
⁷⁷ B. R. Pai, S. Natarajan, G. Manikumar, R. Rajaraman, and H. Suguna, *J. Org. Chem.*, 1978, **43**, 1992.

⁷⁸ T. Kametani, Japan. Kokai 77 91 895 (*Chem. Abs.*, 1978, **88**, 7173).

⁷⁹ T. Kametani, Japan. Kokai 77 142 099 (*Chem. Abs.*, 1978, **88**, 136 833).

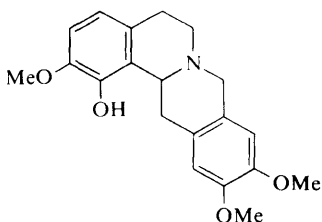


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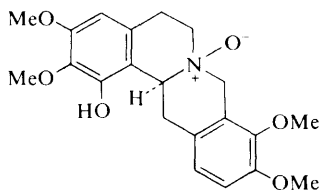


(68)

A synthesis of the base (69) has been reported, the product being apparently identical with caseadine.⁸⁰ The structure of nokoensine has been identified as (70) by X-ray crystallography.⁸¹

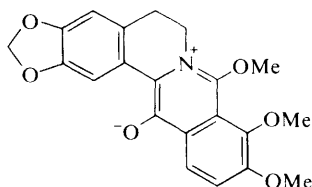


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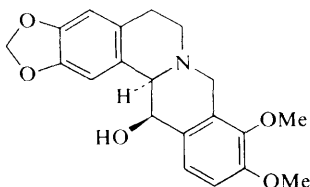


(70)

Photo-oxygenation of berberine chloride has been shown to afford the salt (71), which can be reduced with sodium borohydride to (\pm)-ophiocarpine (72) and (\pm)-epi-ophiocarpine.⁸²



(71)



(72)

The product of photo-oxidation of the betaine (73) has been shown to be dependent on the concentration. Below 0.1% the product is berberal (74), whereas above 0.1% the peroxide (75) is formed. The reaction of the betaine with singlet oxygen yields the peroxy-betaine (76), which can be converted into either (74) or (75) according to the conditions.⁸³

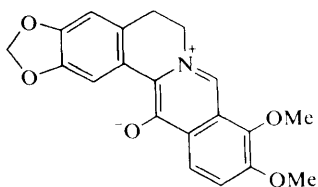
Photo-oxygenation of either dihydrocoralyne (77) or 13-hydroxy-coralyinium betaine (78) in sodium ethoxide solution has been found to give the dihydroisoquinolone (79) and the phthalide (80), and these two products and 13-hydroxycoralydine (81) are obtained if the reaction is carried out in the

⁸⁰ T. R. Govindachari, B. R. Pai, H. Suguna, and M. S. Premila, *Heterocycles*, 1977, **6**, 1811.

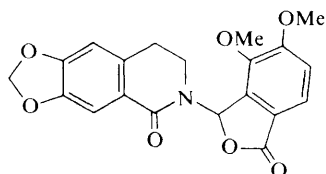
⁸¹ Z. Taira and W. H. Watson, *Cryst. Struct. Commun.*, 1977, **6**, 755.

⁸² M. Hanaoka, C. Mukai, and Y. Arata, *Heterocycles*, 1977, **6**, 895.

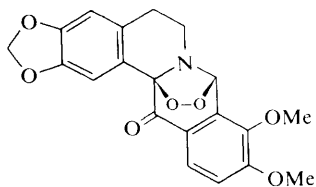
⁸³ Y. Kondo, H. Inoue, and J. Imai, *Heterocycles*, 1977, **6**, 953.



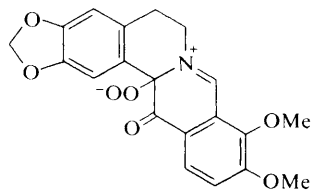
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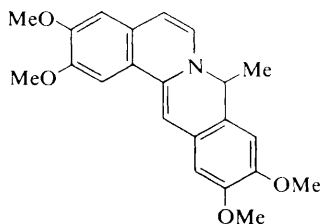
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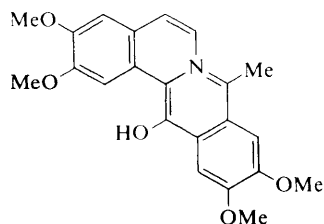
(75)



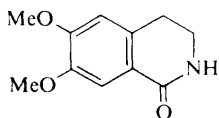
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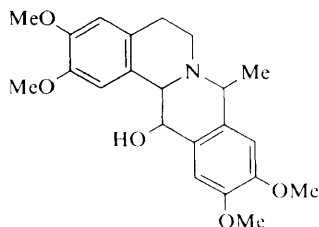
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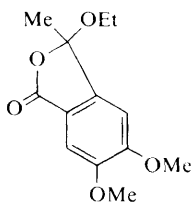
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(79)



(81)

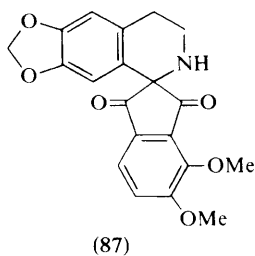
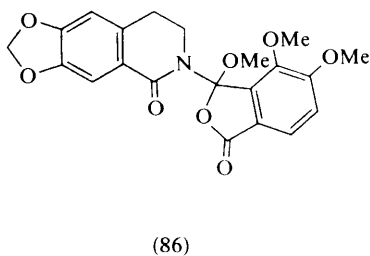
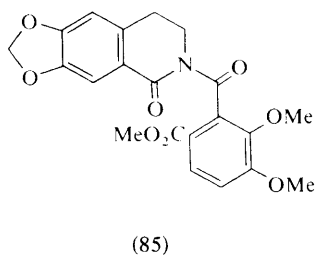
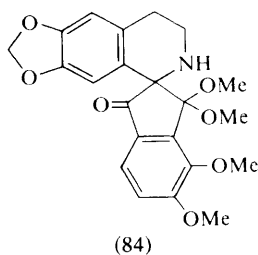
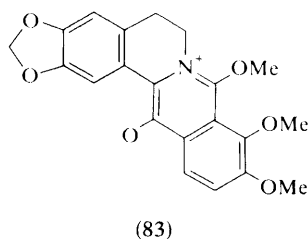
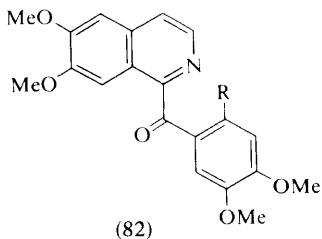


(80)

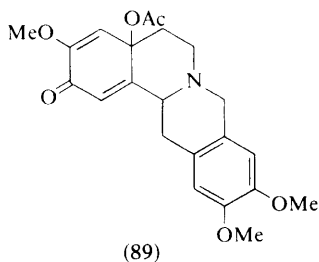
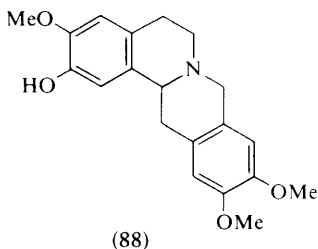
presence of sodium borohydride. Oxidation of the betaine (78) with oxygen and cuprous chloride gives 2'-acetyl-papaveraldine (82; R = COMe), and a 1:1 mixture of this ketone and the ester (82; R = CO₂Et) is obtained by irradiation of the betaine in methylene chloride in the presence of Rose Bengal.⁸⁴

⁸⁴ Y. Kondo, H. Inoue, and J. Imai, *Heterocycles*, 1977, 7, 45.

Photo-oxidation of the methoxyberberine betaine (83) in methanol has been shown to be a novel method of producing the spirobenzylisoquinoline (84) [which may be hydrolysed to the diketone (87)], though the keto-ester (85) and the hemiketal-lactone (86) are other products of the reaction.⁸⁵

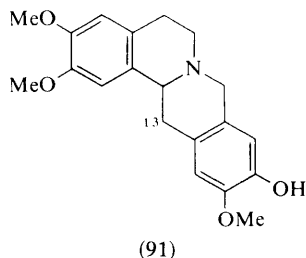
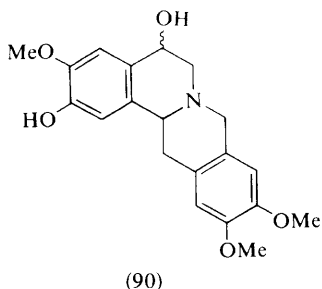


Oxidation of the base (88) with lead tetra-acetate yields the acetoxy-dienone (89), which can be aromatized in acids to the hydroxy-compounds (90) that are epimeric at the new asymmetric centre. Similar treatment of the isomeric phenol (91) affords epimeric 13-hydroxy-compounds.⁸⁶

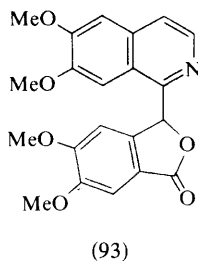
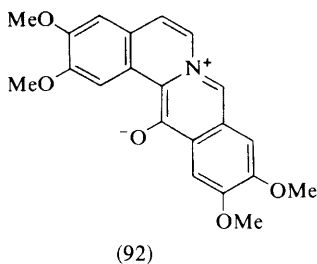


⁸⁵ M. Hanaoka and C. Mukai, *Heterocycles*, 1977, **6**, 1981.

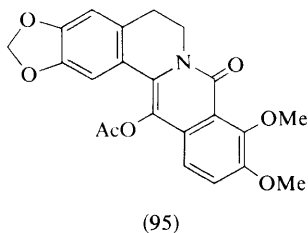
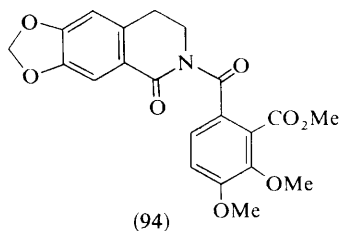
⁸⁶ H. Hara, M. Hosaka, O. Hoshino, and B. Umezawa, *Heterocycles*, 1977, **8**, 269.



Reduction of norcoralyne with zinc and acetic/hydrochloric acid yields dihydronorcoralyinium chloride, which can be oxidized by *m*-chloroperbenzoic acid to the betaine (92), photolysis of which (followed by reduction with sodium borohydride) yields the phthalide-isoquinoline (93), obtainable from 2'-acetyl-papaveraldine.⁸⁷

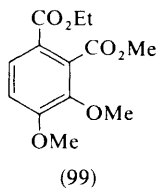
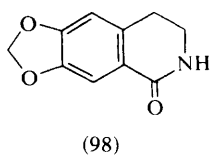
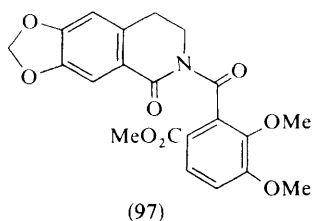
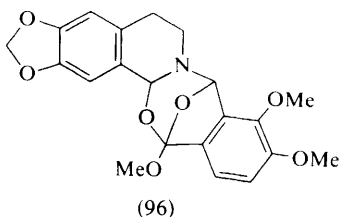


The methoxyberberine betaine (83) will undergo acyl migration in aqueous THF to give the imide methyl isoanhydroberberilate (94). That acyl migration had indeed occurred was shown by the conversion of the betaine (83) into the acetoxy-enamine (95) by acetic anhydride and pyridine, followed by hydrolysis of this by methanolic potassium hydroxide to the known methyl anhydroberberilate (97). The two isomeric compounds (94) and (97) react differently when treated with sodium borohydride in ethanol, the former suffering only solvolysis to noroxy-hydrastinine (98) and the diester (99) and the latter reduction to the ortho-ester (96). This ortho-ester, on *N*-methylation and further reduction with sodium borohydride, yields hydrohydrastinine and ψ -meconine.⁸⁸

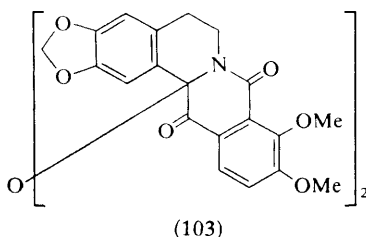
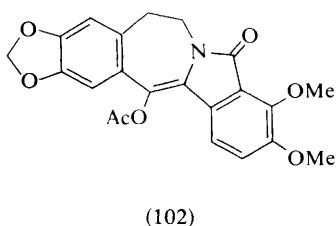
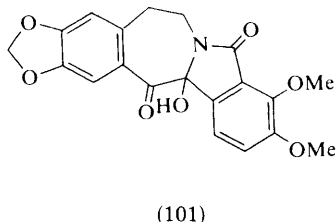
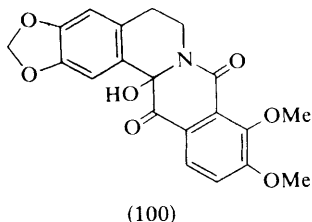


⁸⁷ J. Imai and Y. Kondo, *Heterocycles*, 1977, 6, 959.

⁸⁸ J. L. Moniot, Abd el Rahman H. Abd el Rahman, and M. Shamma, *Tetrahedron Letters*, 1977, 3787.

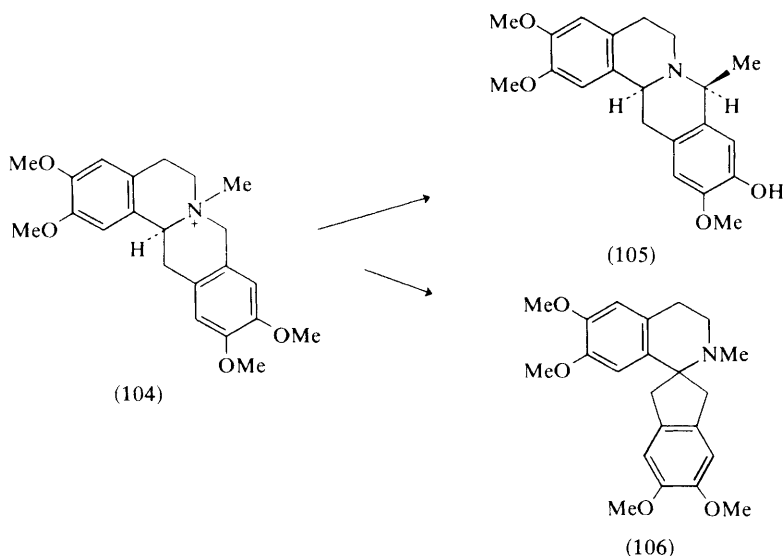


The methoxybetaine (83), on treatment with aqueous acid followed by aerial oxidation in pyridine solution, is converted into the dioxoberberine (100). This can be converted by ammonium hydroxide in chloroform into aporphoeadane (101), which can be reduced with sodium borohydride and then converted into the enol acetate (102). When the imonium salt from (100) is allowed to stand in concentrated hydrochloric acid it is converted into the ether (103).⁸⁹



When tetrahydroberberine methiodides are heated under reflux with sodium bis-(2-methoxyethoxy)borohydride in dioxan, Stevens rearrangement to spirobenzylisoquinolines and 8-methyltetrahydroberberines occurs. Thus xylopinine (104) gives the bases (105) and (106). Using deuterium-labelled material, it has been shown that the quasi-axially oriented hydrogens at C-8 and C-14 are independently extracted. In the B:C-*cis* salt series the products are spirocompounds with retention of configuration at C-8 and inversion at C-14 and

⁸⁹ M. Shamma, J. L. Moniot, and D. M. Hindenlang, *Tetrahedron Letters*, 1977, 4273.

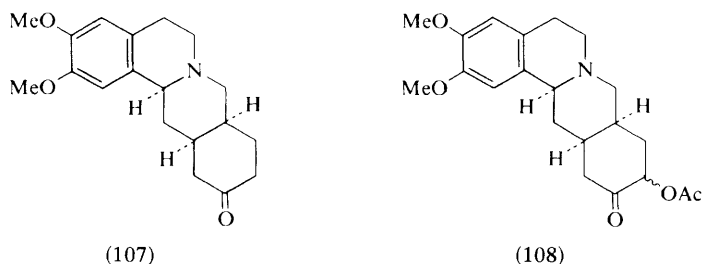


8-methyl compounds with inversion at C-8. The *trans*-series gives spiro-bases with retention at C-8 and C-14 and 8-methyl compounds with inversion at C-8.⁹⁰

The oxidation of the morpholine enamine of alloberbanone (107) with thallium(III) acetate has been shown to give the acetoxy-ketone (108) (both isomers), which can be converted into the β -keto-ester (109),⁹¹ and this in turn has been converted into the berban analogue of reserpine (110).⁹²

The mass spectra,⁹³ high-resolution n.m.r. spectra,⁹⁴ and fluorescence spectra⁹⁵ of tetrahydroberberines and some of their derivatives have been studied.

Biological and biochemical studies of tetrahydroberberine alkaloids cover a study of the pharmacology of scoulerine,⁹⁶ the mutagenicity of coraline,⁹⁷ and the



⁹⁰ T. Kametani, S.-P. Huang, C. Kosecki, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, 1977, **42**, 3140.

⁹¹ L. Szabo, I. Toth, L. Toke, and C. Szantay, *Justus Liebigs Ann. Chem.*, 1977, 634.

⁹² L. Szabo, I. Toth, L. Toke, C. Szantay, and J. Tamas, *Justus Liebigs Ann. Chem.*, 1977, 642.

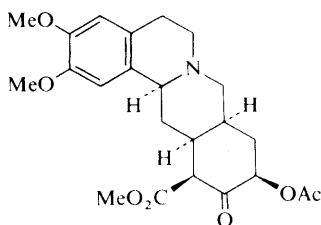
⁹³ C. Tani, Y. Suzuta, and K. Tagahara, *Yakugaku Zasshi*, 1977, **97**, 591.

⁹⁴ E. Smekal and S. Pavelka, *Stud. Biophys.*, 1977, **64**, 183.

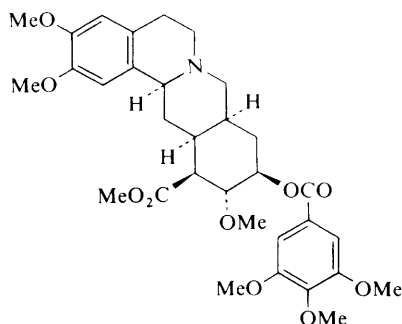
⁹⁵ D. Tourwe, G. Van Binst, and T. Kametani, *Org. Mag. Res.*, 1977, **9**, 341.

⁹⁶ F. S. Sadritdinov and I. Khamdamov, *Med. Zh. Uzb.*, 1977, 39.

⁹⁷ C. C. Cheng, R. R. Engle, J. R. Hodgson, R. B. Ing, H. B. Wood, S.-J. Yan, and K. Y. Zee-Cheng, *J. Pharm. Sci.*, 1977, **66**, 1781.



(109)



(110)

conversion of reticuline into coreximine and scoulerinine by rat liver enzymes without the incorporation of the *N*-methyl carbon.⁹⁸

7 Secoberberines

A group of alkaloids of modified tetrahydroberberine structure can now be separately identified. The group comprises aobamine (113; $R^1R^2 = CH_2$), canadaline (114; $R^1 = R^2 = OMe$), corydalisol (114; $R^1R^2 = CH_2$), macrantaline (19; $R = CH_2OH$), macrantoridine (19; $R = CO_2H$), peshawarine (116), and the racemic bases hycorine (121) and hycorinine (122).

Treatment of coptisine iodide with benzylmagnesium chloride followed by reduction affords the 8-benzyl compound (111), *N*-methylation and Hofmann degradation of which gives the olefin (112) (see Scheme 1). Oxidation of this with osmium tetroxide and acetic acid yields aobamine (113; $R^1R^2 = CH_2$), which can be reduced to corydalisol (114; $R^1R^2 = CH_2$) by sodium borohydride. Ring opening of the benzylamine system of (113) with ethyl chloroformate is accompanied by hemi-acetal formation, giving (115), which may be converted into (\pm) peshawarine by the sequence of processes shown.^{99,100} Hydrogenolytic cleavage of the benzylic ester system of peshawarine yields the corresponding acid (117), also obtainable by the hydrogenolysis of quaternary salts of bicuculline (118).¹⁰⁰ The absolute configuration of the natural ($-$)-peshawarine is shown by the identity of ($+$)-peshawarinediol (119) [obtained from ($+$)-peshawarine by reduction with lithium aluminium hydride] with the product of Emde degradation of rhoeagine methiodide (120),¹⁰⁰ and also by the Emde reduction of rhoeagine methiodide to a mixed acetal that on hydrolysis and oxidation gives ($+$)-peshawarine.¹⁰¹ ($+$)-Corydalisol (114; $R^1R^2 = CH_2$) and ($+$)-canadaline (114; $R^1 = R^2 = CH_2$) belong to the opposite absolute stereochemical series.^{99,100} ($+$)-Canadaline has been related to ($+$)-stylopine.⁹⁹

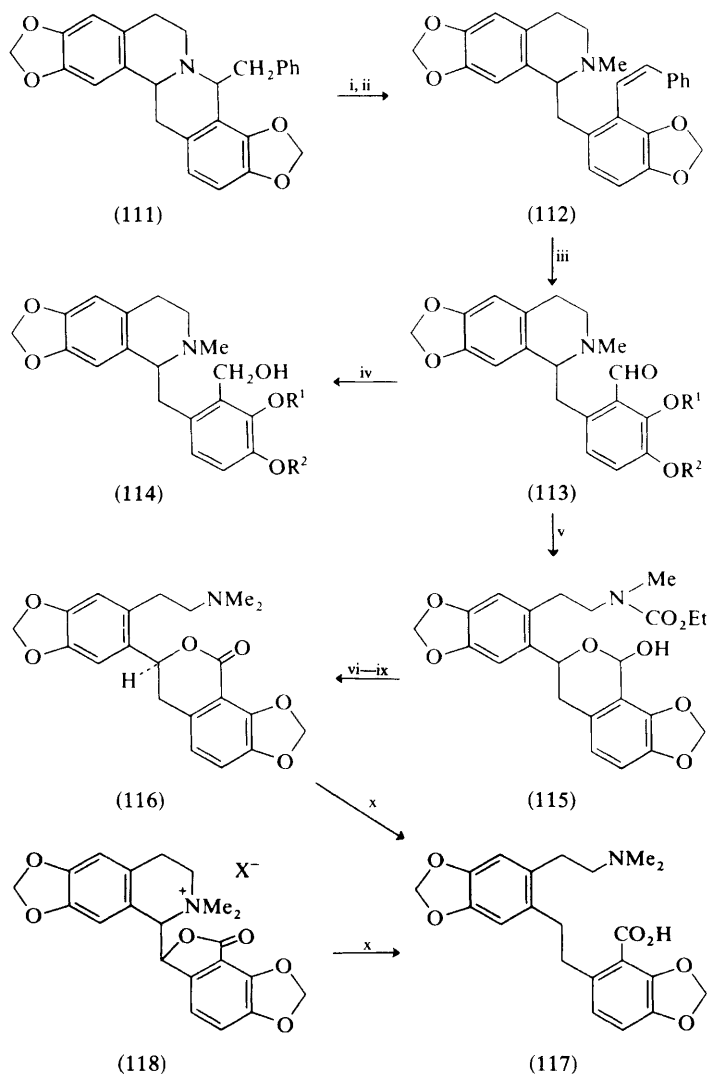
The relationship of macrantaline and macrantoridine to narcotine has been discussed above (p. 92).

⁹⁸ T. Kametani, Y. Ohta, M. Takemura, M. Ihara, and K. Fukumoto, *Bio-org. Chem.*, 1977, **6**, 249.

⁹⁹ M. Shamma, A. S. Rothenberg, and S. F. Hussain, *Heterocycles*, 1977, **6**, 707.

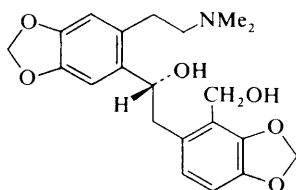
¹⁰⁰ M. Shamma, A. S. Rothenberg, G. S. Jayatilake, and S. F. Hussain, *Tetrahedron*, 1978, **34**, 635.

¹⁰¹ V. Simanek, V. Preininger, and F. Santavy, *Heterocycles*, 1977, **6**, 711.

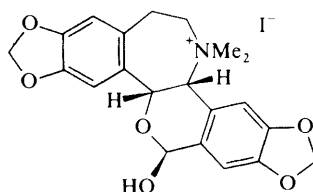


Reagents: i, MeI; ii, NaOH; iii, OsO_4 , HOAc; iv, NaBH_4 ; v, ClCO_2Et ; vi, $\text{HC}(\text{OEt})_3$; vii, LiAlH_4 ; viii, H^+ , H_2O ; ix, CrO_3 ; x, H_2 -Pd/C

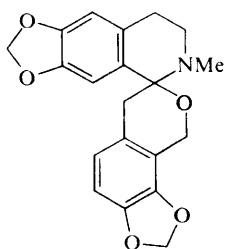
Scheme 1



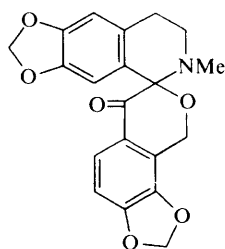
(119)



(120)



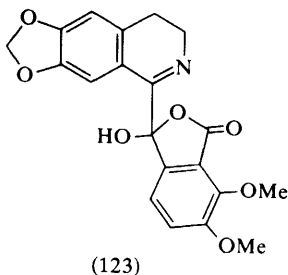
(121)



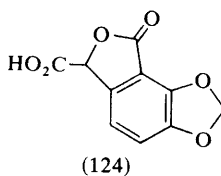
(122)

8 Phthalide-isoquinolines

A stereospecific conversion of berberine into (\pm)- β -hydrastine has been reported. Photolytic oxidation of oxyberberine yields the lactol (123), the *N*-methyl quaternary salt of which can be reduced with sodium borohydride to give racemic β -hydrastine in 95% yield.¹⁰² Both phthalide-isoquinolines (e.g. adlumine) and spirobenzylisoquinolines (e.g. corydaine) have been synthesized from β -phenethylamines and methylenedioxyphthalide carboxylic acid (124).¹⁰³ Several ethers of narcotine have been prepared and converted into derivatives of nornarceine.¹⁰⁴ The biotransformation of narcotine in rats has been examined and di-*O*-desmethylnarcotine, cotarnine, hydrocotarnine, oxocotarnine, and *O*-demethylmeconine have been isolated from urine.¹⁰⁵ Bicuculline, which has



(123)



(124)

¹⁰² M. Shamma, D. M. Hindenlang, T.-T. Wu, and J. L. Moniot, *Tetrahedron Letters*, 1977, 4285.

¹⁰³ S. McLean and D. Dime, *Can. J. Chem.*, 1977, 924.

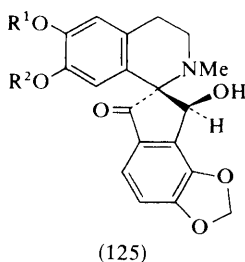
¹⁰⁴ P. Gorecki and M. Drodzdzynska, *Herba Pol.*, 1976, 22, 222, 228, 233.

¹⁰⁵ B. Goeber, K. P. Brandt, S. Pfeifer, and A. Otto, *Pharmazie*, 1977, 32, 543.

been isolated from *Corydalis govani*,⁷¹ has been further examined for pharmacological properties.¹⁰⁶

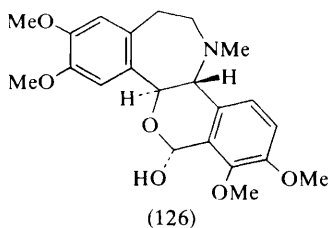
9 Spirobenzylisoquinolines

Carbon-13 n.m.r. spectroscopy has been shown to be a useful technique for distinguishing between stereoisomers of spirobenzylisoquinolines.¹⁰⁷ A review of the synthesis and biosynthesis of alkaloids of this group has been published.¹⁰⁸ Methods of synthesis from tetrahydroberberines have been described above. The dihydroxy-base (125; $R^1 = R^2 = H$) has been converted into yenusomidine (125; $R^1 = R^2 = Me$) and corydaine (125; $R^1R^2 = CH_2$).¹⁰⁹



10 Rhoeadines

The absolute configuration of (+)-alpinigene (126) has been confirmed by spectroscopic methods. The alkaloid is converted into (+)-*cis*-alpinigene by 1 M hydrochloric acid.¹¹⁰



11 Emetine and Related Bases

The structure of ankorine (130) has been revised following a successful total synthesis from the dihydroisoquinoline (127) as shown (Scheme 2). The previously assumed structure with the hydroxy-group in position 8 of the isoquinoline system was shown to be incorrect by synthesis of all four possible stereoisomers of the corresponding isomer of (130).¹¹¹

¹⁰⁶ E. D. Bigler, *Proc. West. Pharmacol. Soc.*, 1977, **20**, 191.

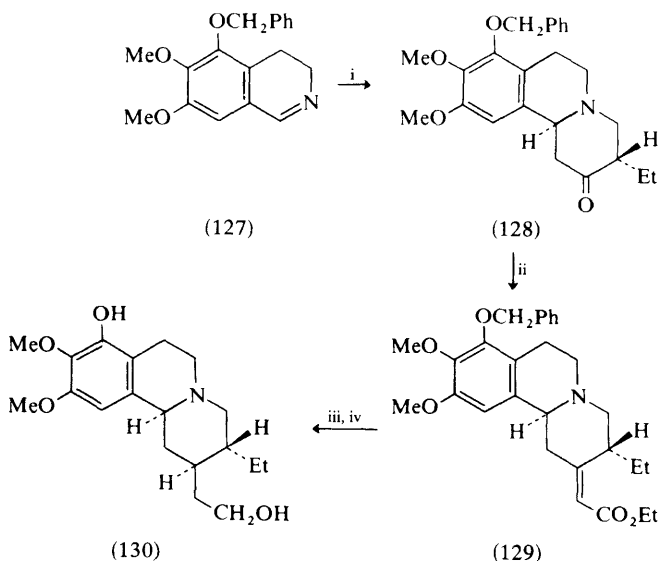
¹⁰⁷ D. W. Hughes, B. C. Nalliah, H. L. Holland, and D. B. Maclean, *Can. J. Chem.*, 1977, **55**, 3304.

¹⁰⁸ D. B. MacLean, *Isr. J. Chem.*, 1977, **16**, 68.

¹⁰⁹ S. McLean and D. Dime, *Can. J. Chem.*, 1977, **55**, 924.

¹¹⁰ A. Guggisberg, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1977, **60**, 2402.

¹¹¹ C. Szantay, E. Szentirmay, L. Szabo, and J. Tamas, *Ber.*, 1976, **109**, 2420.

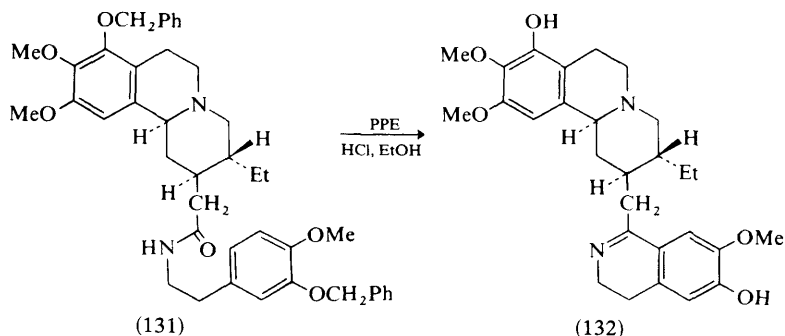


Reagents: i, $\text{CH}_2=\text{C}(\text{Et})\text{COMe}$; ii, Wittig + $(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}$; iii, H_2 -Pd; iv, LiAlH_4

Scheme 2

(±)-Alangicine (132) has been synthesized from the acid derived from (129) by reduction and hydrolysis. This, with the appropriate *β*-phenethylamine, gives the amide (131).¹¹² The absolute stereochemistry of alangicine has been confirmed by its synthesis from ethyl cincholoiponate *via* the lactam acid (133).¹¹³

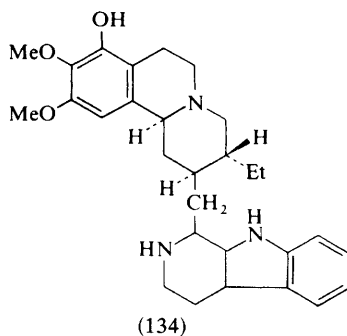
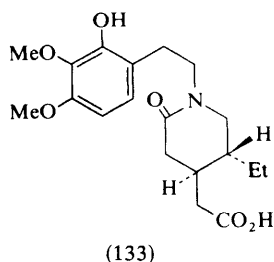
A similar synthesis of alangimarckine (134) has shown the structure to be isomeric with that previously suggested (with a 8-hydroxyisoquinoline system) and determined the absolute stereochemistry as shown.¹¹⁴



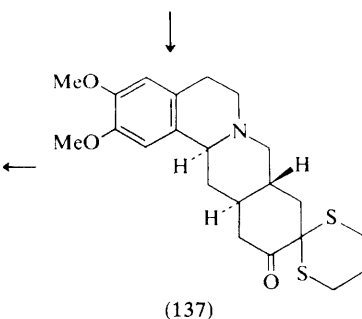
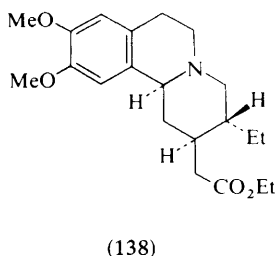
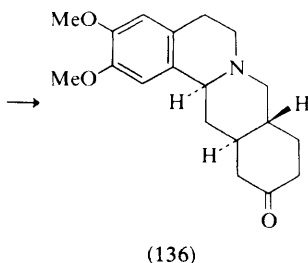
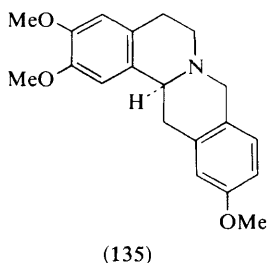
¹¹² T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, *Tetrahedron Letters*, 1976, 2553.

¹¹³ T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, C. Satyesh, and E. Ali, *Heterocycles*, 1977, **8**, 175.

¹¹⁴ T. Fujii, S. Yoshifuji, and H. Kogen, *Tetrahedron Letters*, 1977, 3477.



A new synthesis of (\pm)-emetine has been reported from the base (135) via the ketones (136) and (137) and the ester (138).¹¹⁵



An analogue of emetine, of structure (140), has been synthesized from the ketone (139) by established methods (Scheme 3).¹¹⁶

The effects of emetine on the synthesis of brain protein¹¹⁷ and on transplanted ascites tumour in mice¹¹⁸ and the effects of dehydroemetine on vascular tissue¹¹⁹ have been studied.

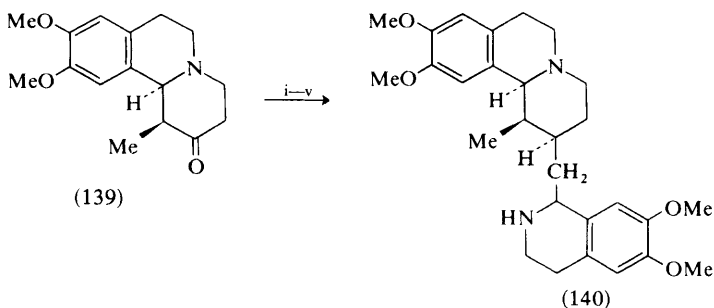
¹¹⁵ S. Takano, M. Sasaki, H. Kanno, K. Shishido, and K. Ogasawara, *Heterocycles*, 1977, 7, 143.

¹¹⁶ A. Buzas, R. Cavier, F. Cossair, J. P. Finet, J. P. Jacquet, G. Lavielle, and N. Platzer, *Helv. Chim. Acta*, 1977, 60, 2122.

¹¹⁷ S. Ohi, *Experientia*, 1977, 33, 1184.

¹¹⁸ E. Schwarz, M. Vincurova, and L. Badalik, *Bratisl. Lek. Listy*, 1977, 67, 583.

¹¹⁹ A. O. Durotoye, *West Afr. J. Pharmacol. Drug Res.*, 1976, 3, 119.



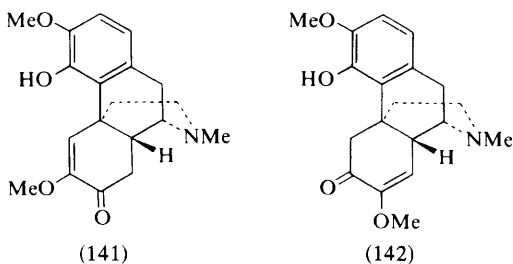
Reagents: i, Wittig+(EtO)₂POCO₂Et; ii, H₂-PtO₂; iii, homoveratrylamine; iv, POCl₃; v, H₂-PtO₂

Scheme 3

12 Morphine Alkaloids

A review of the cultivation of *Papaver somniferum*, and of its improvement and its utilization for medical purposes, has been published.¹²⁰ A method for the quantitative estimation of thebaine in *P. bracteatum* has been described and a study of the thebaine content of several strains of this poppy has been made.¹²¹ The occurrence of oripavine in *P. orientale*^{122,123} and of salutaridine in *P. bracteatum*^{122,124} and *P. lasiothrix*¹²² has been reported.

Nor-oripavine has been isolated as the new base oripavidine from *P. orientale*. Its structure has been confirmed by Eschweiler methylation to oripavine followed by *O*-methylation to thebaine with diazomethane.¹²⁵ Two other new bases, ocobotrine (141) and 14-*epi*-sinomenine (142), have been isolated, together with sinoacutine and pallidine, from *Ocotea brachybotra*.¹²⁶



The reduction of thebaine to mixtures of β -dihydrothebaine and dihydrothebaine- ϕ with potassium, calcium, and lithium in liquid ammonia has been studied.

¹²⁰ V. S. Ramanathan and C. Ramachandran, *Cultiv. Util. Med. Aromatic Plants*, 1977, 68.

¹²¹ P. C. Vincent, C. E. Bare, and W. A. Gentner, *J. Pharm. Sci.*, 1977, **66**, 1716.

¹²² T. Baytop and G. Sariyar, *Istanbul Univ. Eczacilik Fac. Mecm.*, 1977, **13**, 7.

¹²³ I. Lalezari and A. Shafiee, *Pazhoohandeh (Tehran)*, 1977, **13**, 50.

¹²⁴ G. Sariyar, *Istanbul Univ. Eczacilik Fac. Mecm.*, 1977, **13**, 171.

¹²⁵ I. A. Israilov, O. N. Denisenko, M. S. Yunusov, S. Yu. Yunusov, and D. A. Murav'eva, *Khim. Pri. Soedin.*, 1977, 714.

¹²⁶ V. Vecchietti, C. Casagrande, and G. Ferrari, *Farmaco, Ed. Sci.*, 1977, **32**, 767.

The best yield was 95% of a 1:1 mixture, and the unconjugated diene was obtained in 95% yield using potassium and ferric chloride.¹²⁷ Further patents for the conversion of thebaine into codeinone in high yield by methods previously described have been published.^{128,129} The conversion of thebaine into neopine in 72% yield *via* 14-chlorocodeinone followed by reduction with sodium borohydride to 14-chlorocodeine and then with sodium di-(2-methoxyethoxy)-aluminium hydride¹³⁰ or with the latter reagent alone¹³¹ has been reported. It has further been shown that the reduction of neopinone with bulky reducing agents such as lithium triethylborohydride yields mainly neopine, whereas isoneopine is the predominant product with 'small' reagents such as sodium borohydride.¹³²

Dihydrocodeinone has been converted into codeine by a novel process. Treatment with ethyl chloroformate gives the carbamate, and this with a phenylselenium chloride yields the 6-phenylseleno-compound, which, on treatment successively with periodic acid and lithium aluminium hydride, is converted into codeinone.¹³³ A previous report of the reduction of dihydrocodeinone to dihydroisocodeine by formamidine sulphuric acid has been corrected; the product is dihydrothebainone. Under the same conditions dihydro- ψ -codeinone yields dihydro- ψ -codeine.¹³⁴ Another study of the same reaction shows that dihydroisothebainol accompanies dihydrothebainone and that 14-hydroxy-dihydrocodeinone and 3-*O*-methylnaltrexone are reduced by the reagent predominantly to 6- β -alcohols under heterogeneous and to β -alcohols plus 14-hydroxy-dihydrothebainone derivatives under homogeneous conditions.¹³⁵ Dihydrocodeinone has been converted into 6-chloromethyl, 6-azidomethyl-, 6-aminomethyl-, and 6-hydroxymethyl-codeine and -isocodeine through the 6-spiro-oxirans.¹³⁶

Oxidation of thebaine with *m*-chloroperbenzoic acid has been shown to give a mixture of 14-hydroxycodeinone and 8-acetoxy-14-hydroxy-dihydrothebaine (143), which can be hydrolysed to 8,14-dihydroxy-dihydrocodeinone and hydrolysed and dehydrated to 14-hydroxy-dihydrocodeinone.¹³⁷

7,14-Cyclodihydrocodeinone, on catalytic reduction, yields 14-methyl-*C*-nordihydrocodeinone (144), which, on ring expansion with diazomethane, yields 14-methyldihydrocodeinone and the related 6-spiro-oxiran, together with the corresponding seven-membered ring products of further expansion.¹³⁸

¹²⁷ D. E. Portlock, Ger. Offen. 2 647 642 (*Chem. Abs.*, 1977, **87**, 102 508).

¹²⁸ F. Calvo, U.S. P. 4 052 402 (*Chem. Abs.*, 1978, **88**, 7172).

¹²⁹ Fabrica de Productos Quimicos y Farmaceuticos Abello S.A., Fr. Demande 2 342 288 (*Chem. Abs.*, 1978, **88**, 191 202).

¹³⁰ S. Makleit, S. Berenyi, and R. Bogнар, *Magy. Kem. Foly.*, 1977, **83**, 478.

¹³¹ S. Makleit, S. Berenyi, and R. Bogнар, *Acta Chim. Acad. Sci. Hung.*, 1977, **94**, 161.

¹³² S. W. Wunderly and E. Brockmann-Hanssen, *J. Org. Chem.*, 1977, **42**, 4277.

¹³³ I. Iijima, K. C. Rice, and J. V. Silverton, *Heterocycles*, 1977, **6**, 1157.

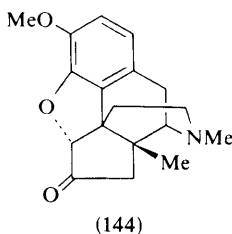
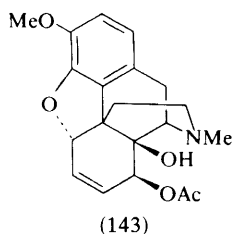
¹³⁴ N. Chatterjee, J. G. Umans, C. E. Inturrisi, W.-T. C. Chen, D. D. Clarke, S. P. Bhatnagar, and U. Weiss, *J. Org. Chem.*, 1978, **43**, 1003.

¹³⁵ G. A. Brine, K. G. Boldt, M. L. Coleman, D. J. Bradley, and F. I. Carrol, *J. Org. Chem.*, 1978, **43**, 1555.

¹³⁶ G. Horvath, G. Gaal, P. Kerekes, and R. Bogнар, *Acta Chim. Acad. Sci. Hung.*, 1977, **92**, 311.

¹³⁷ I. Iijima, K. C. Rice and A. Brossi, *Helv. Chim. Acta*, 1977, **60**, 2135.

¹³⁸ W. Fleischhacker and A. Klement, *Monatsh. Chem.*, 1977, **108**, 1441.



The analgesic properties of 6-azidodihydro-6-deoxymorphine have been examined.¹³⁹ The 3-ethyl and 3-morpholinoethyl ethers and the 3-deoxy-analogue of this base have also been prepared; the 3-ethyl ether has been found to be a potent antitussive agent.^{140,141} Similar preparations of the 14-hydroxy-compound¹⁴² and of the related nor-, *N*-allylnor- and *N*-cyclopropylmethyl-nor-compounds¹⁴³ have also been reported. The preparation of 6-mesyl esters of 3-*O*-acetylmorphine, dihydromorphine, and their 14-hydroxy-derivatives, all of which are usable in these reactions, has been described.¹⁴⁴

6- α - and 6- β -amino-6-deoxynaloxone and naltrexone have been prepared by reductive amination of the corresponding ketones. All are morphine antagonists, the 6- α -isomers being the more potent.¹⁴⁵

α -Fluoro-, α -chloro-, and bromo-dihydrocodides have been prepared from dihydrocodeine 6-mesyl ester and lithium halides; use of the iodide gives deoxycodeine.¹⁴⁶

An improved rapid procedure for the preparation of normorphine and norcodeine by *N*-demethylation with phenyl chloroformate followed by hydrazine has been reported.¹⁴⁷ An efficient synthesis of *N*-cyclobutylmethylnoroxymorphine (naltrexone) from thebaine, *via* 14-hydroxycodeinone, has been described,¹⁴⁸ as have preparations of *N*-tetrahydrofurfurylnoroxymorphine¹⁴⁹ and of *N*-*s*-alkyl- and *N*-*t*-alkyl-normorphines.¹⁵⁰ *N*-Demethylation and *O*-de-ethylation of 3-*O*-ethylmorphine by rat hepatic microsomes has been observed.^{151,152} A patent has been published covering the

¹³⁹ M. A. Levi, R. K. Rhines, and D. H. Ford, *Tissue Responses Addict. Drugs. (Proc. Workshop Session Int. Soc. Neuroendocrinol.)*, 1975, 471.

¹⁴⁰ S. Makleit, J. Knoll, R. Bogнар, S. Berenyi, G. Somogyi, and G. Kiss, *Acta Chim. Acad. Sci. Hung.*, 1977, **93**, 169.

¹⁴¹ J. Knoll, L. G. Harsing, and T. Friedmann, *Orvostudomány*, 1976, **27**, 263.

¹⁴² S. Makleit, J. Knoll, R. Bogнар, S. Berenyi, and G. Kiss, *Acta Chim. Acad. Sci. Hung.*, 1977, **93**, 165.

¹⁴³ S. Makleit, J. Knoll, R. Bogнар, S. Berenyi, G. Somogyi, and G. Kiss, *Acta Chim. Acad. Sci. Hung.*, 1977, **93**, 175.

¹⁴⁴ S. Makleit, S. Berenyi, R. Bogнар, and S. Elek, *Acta Chim. Acad. Sci. Hung.*, 1977, **94**, 161.

¹⁴⁵ J. B. Jiang, R. N. Hanson, P. S. Portoghese, and A. E. Takemori, *J. Med. Chem.*, 1977, **20**, 1100.

¹⁴⁶ G. Somogyi, S. Makleit, and R. Bogнар, *Magy. Kem. Foly.*, 1977, **83**, 327.

¹⁴⁷ K. C. Rice and E. L. May, *Heterocyclic Chem.*, 1977, **14**, 665.

¹⁴⁸ R. A. Olofson and J. P. Pepe, *Tetrahedron Letters*, 1977, 1575.

¹⁴⁹ H. Merz, G. Walther, A. Langbein, K. Stockhaus, and H. Wick, *Ger. Offen.* 2 538 075 (*Chem. Abs.*, 1977, **87**, 68 515).

¹⁵⁰ J. I. DeGraw, J. A. Lawson, J. L. Crace, H. L. Johnson, M. Ellis, E. T. Uyeno, G. H. Loew, and D. S. Berkowitz, *J. Med. Chem.*, 1978, **21**, 415.

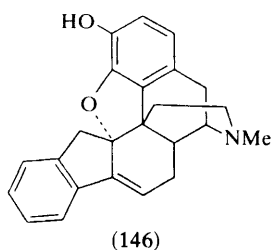
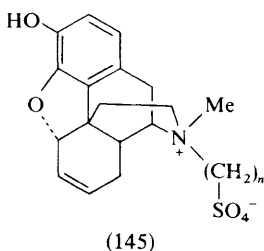
¹⁵¹ J. A. Thompson and J. L. Holtzman, *Drug Metab.*, 1977, **5**, 9.

¹⁵² A. P. Van den Berg, J. Noordhoek, E. M. Savenije-Chapel, and E. Koopman-Kool, *Chem. Biol. Interact.*, 1977, **19**, 185.

preparation of internal salts of *N*-sulphoalkyl-deoxymorphine (145); these are claimed to have analgesic and antitussive properties.¹⁵³

Iodination of codeine with sodium iodide and chloramine-T has been shown to proceed only at pH 1, the product being 1-iodocodeine, which is demethylated by boron tribromide to 1-iodomorphine.¹⁵⁴ An *X*-ray structure analysis of 6-acetyl-1-iodocodeine has been made.¹⁵⁴

The course of the closure of the 4,5-oxide bridge of dihydrothebainone by bromination and treatment with alkali has been studied. The sequence of products is 1-bromo-, 1,7 α -dibromo-, and 1,5 β ,7 α -tribromodihydrothebainone; the last of these, on boiling with ethanol, is converted into an equilibrium mixture of 1,7 α - and 1,7 β -dibromo-dihydrocodeinones.¹⁵⁵ Cyclodehydration of 5-benzylidihydromorphinone to the base (146) with hydrobromic acid has been achieved.¹⁵⁶



A greatly improved conversion of (-)-sinomenine into (+)-morphine with an overall yield of 28% has been recorded.¹⁵⁷ Reduction of sinomenine to sinomenol followed by treatment with polyphosphoric acid gives (+)-dihydrocodeinone, the dimethyl ketal of which suffers elimination of methanol to give dihydrothebaine, which can be converted by standard procedures¹⁵⁸ into (+)-codeinone, and hence into (+)-codeine and (+)-morphine.

Spin-labelled esters of morphine and codeine with 3-carboxy-2,2,5,5-tetramethylpyrrolin-1-oxyl have been prepared for e.s.r. studies of their interaction with receptors.¹⁵⁹ α -Chlorocodide, β -chlorocodide, and the corresponding morphides have been converted into spin-labelled products by reaction with the radical (147).¹⁶⁰

Anodic oxidation of 1-(3',4'-dimethoxybenzyl)-6,7-dimethoxy-isoquinolines at platinum anodes in acetonitrile affords morphinandienones with the flavinane orientation of substituents (148). Attempts to obtain the isomeric 3,4,6-substitution pattern of salutaridine by use of 6'-bromo-compounds failed, the bromine atom being removed, and 6'-chloro-compounds suffered cleavage.¹⁶¹

¹⁵³ A. Esteve, Fr. Demande 2 296 420 (*Chem. Abs.*, 1978, **88**, 7171).

¹⁵⁴ A. Lieberman, D. H. Malarek, J. F. Blount, N. R. Nelson, and C. M. Delaney, *J. Org. Chem.*, 1978, **43**, 737.

¹⁵⁵ C. Olieman, L. Maat, and H. C. Beyerman, *Rec. Trav. Chim.*, 1978, **97**, 31.

¹⁵⁶ S. P. Surenda and V. Weiss, *Heterocycles*, 1977, **6**, 1889.

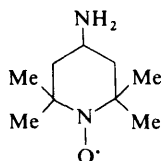
¹⁵⁷ I. Iijima, J. Minamikawa, A. E. Jacobson, and K. C. Rice, *J. Org. Chem.*, 1978, **43**, 1462.

¹⁵⁸ D. W. Weller and H. Rapoport, *J. Med. Chem.*, 1976, **19**, 1171.

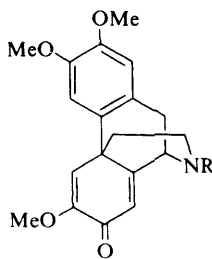
¹⁵⁹ W. Y. Wu, L. Abood, M. Gates, and R. W. Kreilick, *Mol. Pharmacol.*, 1977, **13**, 766.

¹⁶⁰ J. A. Cella and J. A. Kelley, *J. Pharm. Sci.*, 1977, **66**, 1054.

¹⁶¹ L. L. Miller, R. F. Stewart, J. P. Gillespie, V. Ramachandran, Y. H. So, and F. R. Stermitz, *J. Org. Chem.*, 1978, **43**, 1580.



(147)



(148)

Pharmacological and related studies of alkaloids of this group include comparisons of the analgesic activities of morphine and heroin¹⁶² and of the enkephalins,^{163,164} studies of ketocyclazocine,¹⁶⁴ of butorphanol,¹⁶⁵ of methoxycyclazocine,¹⁶⁶ and of buprenorphine,¹⁶⁷ a comparison of the analgesic properties of butorphanol and pentazocine,¹⁶⁸ and studies of the properties of buprenorphine,^{169–171} opiate effects at CNS sites of morphine and etorphine,¹⁷² the mechanism of action of naloxone and naltrexone,¹⁷³ the pharmacology of *N*-allyl- and *N*-cyclopropylmethyl-norazidodihydromorphinone and their 14-hydroxy-analogues,¹⁷⁴ and receptor-binding studies on morphine,^{175,176} dihydromorphine,^{177–181} etorphine,^{182,183} diprenorphine,¹⁸⁴ buprenorphine,¹⁸⁵ naloxone,^{179–181,184,186} and naltrexone.¹⁷⁷

¹⁶² R. G. Twycross, *Pain*, 1977, 3, 93.

¹⁶³ G. Urca, H. Frenk, J. C. Liegbeskind, and A. N. Taylor, *Science*, 1977, 197, 83.

¹⁶⁴ A. Cowan and G. Metcalf, *Opiates Endog. Opioid Pept. Proc. Int. Narc. Res. Club Meet.*, 1976, 95.

¹⁶⁵ F. F. Foldes, H. Nagashima, A. V. Karamanian, P. Radnay, R. Malovany, S. Koerner, and M. Ang, *Probl. Drug Depend.*, 1975, 373.

¹⁶⁶ W. T. Beaver and G. A. Feise, *J. Clin. Pharmacol.*, 1977, 17, 480.

¹⁶⁷ B. C. Hovell and A. E. Ward, *J. Int. Med. Res.*, 1977, 5, 417.

¹⁶⁸ R. E. S. Young, *J. Int. Med. Res.*, 1977, 5, 422.

¹⁶⁹ D. R. Jasinski, J. S. Pevnick, J. D. Griffith, C. W. Gorodetsky, and E. J. Cone, *Probl. Drug Depend.*, 1976, 112.

¹⁷⁰ A. Cowan, J. W. Lewis, and I. R. Macfarlane, *Br. J. Pharmacol.*, 1977, 60, 537.

¹⁷¹ K. Matsuki, A. Kato, H. Takei, E. Inomata, and T. Iwabuchi, *Oyo Yakuri*, 1977, 13, 259.

¹⁷² Y. F. Jacquet, *Tissue Responses Addict. Drugs (Proc. Workshop Sess. Int. Soc. Neuroendocrinol.)*, 1975, 89.

¹⁷³ B. A. Berkowitz, S. S. Spectro, and Ch.-H. Lee, *Tissue Responses Addict. Drugs (Proc. Workshop Sess. Int. Soc. Neuroendocrinol.)*, 1975, 139.

¹⁷⁴ J. Knoll, Z. Furst, and S. Makleit, *Arch. Int. Pharmacodyn. Ther.*, 1977, 228, 268.

¹⁷⁵ E. J. Simon, *Recherche*, 1977, 8, 416.

¹⁷⁶ Y. F. Jacquet, W. A. Klee, R. C. Rice, I. Iijima, and J. Minamikawa, *Science*, 1977, 198, 842.

¹⁷⁷ L. Terenius, *Psychoneuroendocrinology*, 1977, 2, 53.

¹⁷⁸ W. L. Dewey and T. T. Chau-Pham, *Opiates Endog. Opioid Pept. Proc. Int. Narc. Res. Club Meet.*, 1976, 403.

¹⁷⁹ D. T. Wong and J. S. Horng, *Tissue Responses Addict. Drugs (Proc. Workshop Sess. Int. Soc. Neuroendocrinol.)*, 1975, 391.

¹⁸⁰ C.-Y. Lee, T. Akera, and T. M. Brody, *J. Pharmacol. Exp. Ther.*, 1977, 202, 166.

¹⁸¹ R. Simantov, S. R. Childers, and S. H. Snyder, *Mol. Pharmacol.*, 1978, 14, 69.

¹⁸² S. J. Mule, G. Casella, and D. H. Clovet, *Tissue Responses Addict. Drugs (Proc. Workshop Sess. Int. Soc. Neuroendocrinol.)*, 1975, 409.

¹⁸³ H. North-Rott, D. W. Martin, and A. Toliver, *Physiol. Chem. Phys.*, 1976, 8, 437.

¹⁸⁴ C. B. Pert, S. H. Snyder, and M. J. Kuhar, *Tissue Responses Addict. Drugs (Proc. Workshop Sess. Int. Soc. Neuroendocrinol.)*, 1975, 89.

¹⁸⁵ J. M. Hanbrook and M. J. Rance, *Opiates Endog. Opioid Pept. Proc. Int. Narc. Res. Club Meet.*, 1976, 399.

¹⁸⁶ H. W. Kosterlitz and R. M. Leslie, *Br. J. Pharmacol.*, 1977, 59, 478P.

Other studies include the pharmacokinetics of codeine and metabolic morphine derived from it,¹⁸⁷ the inhibition of tolerance to morphine by naloxone,¹⁸⁸ a review of the tolerance and dependence mechanism for morphine,¹⁸⁹ studies of plasma^{190–198} and brain^{199–204} levels affected by the alkaloids, the teratogenic potency of codeine,²⁰⁵ and the metabolism of morphine.²⁰⁶

Analytical methods for the determination of morphine and related compounds in body fluids,^{207–215} for improved recovery from biological tissues,²¹⁶ and methods of radio-immunoassay^{217–220} have been described.

Attempts have been made to predict the agonist and antagonist potencies of different *N*-substituted normorphines on the basis of energy conformational studies,²²¹ and quantum-chemical calculations for a number of bases have been made in a study of receptor interactions.²²²

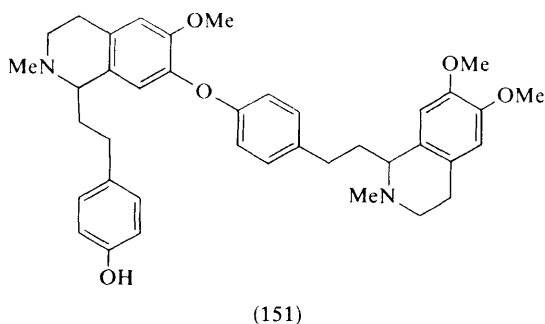
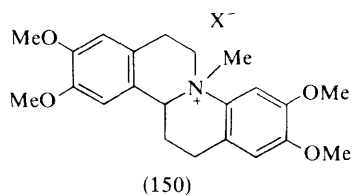
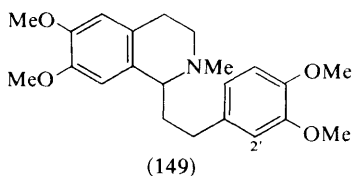
The biotransformation of morphine into dihydromorphinone and normorphine in several animal species has been studied.²²³

- ¹⁸⁷ P. Dahlstrom and L. Paalzow, *Opiates Endog. Opioid Pept. Proc. Int. Narc. Res. Club Meet.*, 1976, 395.
- ¹⁸⁸ I. Yano and A. E. Takemori, *Res. Commun. Chem. Pathol. Pharmacol.*, 1977, **16**, 721.
- ¹⁸⁹ W. E. Leong, *Psychopharmacol. Gener. Prog.*, 1978, 1535.
- ¹⁹⁰ H. Sagduyu and H. Koyuncuoglu, *Istanbul Univ. Tip Fak. Mecm.*, 1976, **39**, 315.
- ¹⁹¹ T. Muraki, Y. Tokunaga, and T. Makino, *Endocrinol. Jpn.*, 1977, **24**, 313.
- ¹⁹² K. D. Charampous and W. E. Askew, *Can. J. Physiol. Pharmacol.*, 1977, **55**, 117.
- ¹⁹³ J. H. Mendelson, R. E. Meyer, J. Ellingboe, S. M. Mirrin, and M. McDougale, *Probl. Drug Depend.*, 1975, 348.
- ¹⁹⁴ R. J. Capetola and A. Gero, *Arch. Int. Pharmacodyn. Ther.*, 1977, **225**, 208.
- ¹⁹⁵ J. F. Bruin, D. Van Vugt, S. Marshall, and J. Meites, *Life Sci.*, 1977, **21**, 461.
- ¹⁹⁶ S. Sanfacon and G. Labrecque, *Psychopharmacologia*, 1977, **55**, 151.
- ¹⁹⁷ C. N. Pang, E. Zimmermann and C. H. Sawyer, *Endocrinology*, 1975, **101**, 1726.
- ¹⁹⁸ W. Bechtel and K. Sinterhauf, *Arzneim.-Forsch.*, 1978, **28**, 308.
- ¹⁹⁹ H. Koyuncuoglu, E. Genc, A. Canberk, and H. Sagduyu, *Psychopharmacologia*, 1977, **52**, 181.
- ²⁰⁰ H. N. Bhargava and G. A. Maturyshyn, *Eur. J. Pharmacol.*, 1977, **44**, 25.
- ²⁰¹ R. J. Hitzemann and H. H. Loh, *Res. Commun. Chem. Pathol. Pharmacol.*, 1977, **17**, 15.
- ²⁰² K. Iwatsubo, *Jpn. J. Pharmacol.*, 1977, **27**, 903.
- ²⁰³ L. Branceo and A. J. Friedhoff, *Neuropsychobiology*, 1976, **2**, 307.
- ²⁰⁴ M. E. Davis, T. Akera, T. M. Brody, and L. Watson, *Proc., Natl. Acad. Sci. U.S.A.*, 1977, **74**, 5764.
- ²⁰⁵ J. E. Zellers and R. F. Gautieri, *J. Pharm. Sci.*, 1977, **66**, 1727.
- ²⁰⁶ E. F. Hahn, H. Roffwarg, and J. Fishman, *Res. Commun. Chem. Pathol. Pharmacol.*, 1977, **18**, 401.
- ²⁰⁷ T. Vu Cuc, A. Vernay, and C. Nicole, *Pharm. Acta Helv.*, 1976, **51**, 126.
- ²⁰⁸ E. J. Cone and C. W. Gorodetsky, *Probl. Drug Depend.*, 1975, 338.
- ²⁰⁹ M. Schneider, *Rocz. Akad. Roln. Poznaniu*, 1976, **90**, 127.
- ²¹⁰ G. Nicolau, G. Van Lear, B. Kaul, and B. Davidson, *Clin. Chem. (Winston-Salem, N.C.)*, 1977, **23**, 1640.
- ²¹¹ J. P. G. Thenot and K. D. Haegle, *Methods Biochem. Anal.*, 1977, **24**, 1.
- ²¹² S. Y. Yeh, C. W. Gorodetsky, and H. A. Krebs, *J. Pharm. Sci.*, 1977, **66**, 1288.
- ²¹³ R. L. Stiller and D. Pierson, *Neurotoxicology*, 1977, **1**, 81.
- ²¹⁴ E. J. Cone, B. A. Phelps, and C. W. Gorodetsky, *J. Pharm. Sci.*, 1977, **66**, 1709.
- ²¹⁵ S. P. Jindal and P. Vestergaard, *J. Pharm. Sci.*, 1978, **67**, 260.
- ²¹⁶ H. Bhargava, *J. Pharm. Sci.*, 1977, **66**, 1044.
- ²¹⁷ I. L. Honigberg, J. T. Stewart, W. J. Brown, H. W. Jun, T. E. Needham, and J. J. Vallner, *J. Anal. Toxicol.*, 1977, **1**, 70.
- ²¹⁸ J. W. A. Findlay, R. F. Butz, and R. M. Welch, *Clin. Pharmacol. Ther.*, 1977, **22**, 439.
- ²¹⁹ S. Lafissa, G. Bolelli, R. Mosca, and C. Zanon, *Ric. Clin. Lab.*, 1977, **2**, 179.
- ²²⁰ M. Steiner and J. L. Spratt, *Clin. Chem. (Winston-Salem, N.C.)*, 1978, **24**, 339.
- ²²¹ G. H. Loew, D. S. Berkowitz, J. I. DeGraw, H. L. Johnson, J. A. Lawson, and E. T. Uyeno, *Opiates Endog. Opioid Pept. Proc. Int. Narc. Res. Club Meet.*, 1976, 399.
- ²²² G. H. Loew and D. S. Berkowitz, *J. Med. Chem.*, 1978, **21**, 106.
- ²²³ S. Y. Yeh, R. L. McQuinn, and C. W. Gorodetsky, *Drug Metab. Dispos.*, 1977, **5**, 335.

(+)-Naloxone has been prepared from (+)-7-bromodihydrocodeinone dimethyl ketal and been shown to have 10^{-3} to 10^{-4} times the activity of the (-)-isomer in receptor binding and other assays.²²⁴

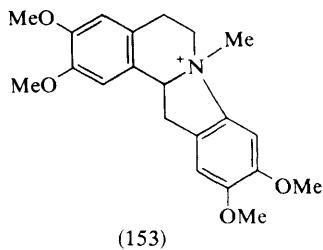
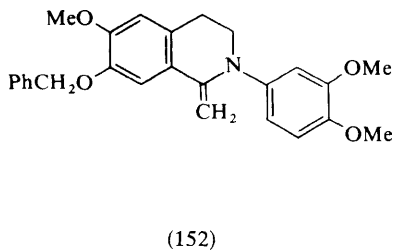
13 Phenethylisoquinolines

The base (149) has been oxidized by electrochemical methods to the dibenzoquinolinizinium salt (150); the methoperchlorate, under similar conditions, is oxidized to a 2':2' dimer.²²⁵ A bisphenethylisoquinoline, jolantine (151), has been isolated from *Merendera jolantae*; its structure has been assigned on the basis of spectroscopic evidence.²²⁶



14 Dibenzopyrrocolines

Cryptaustoline (153) has been synthesized by photolysis of the enamine (152), followed by reduction and *N*-methylation.²²⁷



²²⁴ I. Iijima, J. Minamikawa, A. E. Jacobson, A. Brossi, K. C. Rice, and W. A. Klee, *J. Med. Chem.*, 1978, **21**, 398.

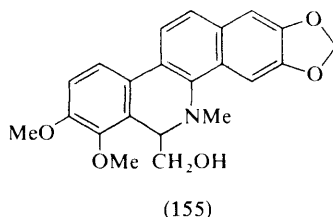
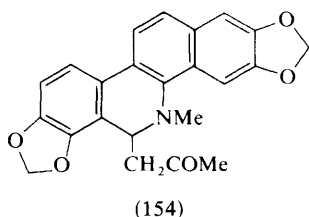
²²⁵ A. Najafi and M. Sainsbury, *Heterocycles*, 1977, **6**, 459.

²²⁶ A. M. Usmanov, M. K. Yusupov, and Kh. A. Aslanov, *Khim. Prir. Soedin.*, 1977, 422.

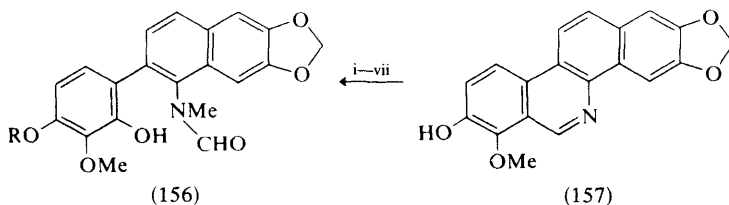
²²⁷ I. Ninomiya, J. Yasui, and T. Kiguchi, *Heterocycles*, 1977, **6**, 1855.

15 Benzophenanthridines

Sanguinarine, norsanguinarine, dihydrosanguinarine, chelerythrine, nor-chelerythrine, and the new base (154) have been isolated from *Argemone mexicana*.²²⁸ Dihydrosanguinarine, dihydrochelerythrine, dihydrochelilutine, dihydrochelirubine, chelidonine, sanguinarine, and *N*-demethyldihydrosanguinarine have been isolated from *Chelidonium majus*.²²⁹ Bocconoline (155) has been isolated from *Macleaya cordata* and synthesized by photolytic addition of methanol to chelerythrine.²³⁰



Iwamide (156; R = H), a new product from *Xanthoxylum arnottianum*, has been synthesized from decarine (157),²³¹ and similar syntheses of arnottianamide (156; R = Me) and isoarnottianamide have been achieved from chelerythrine and nitidine chlorides (Scheme 4).²³²



Reagents: i, PhCH₂Cl; ii, NaBH₄; iii, MeI; iv, Pd/C; v, *m*-ClC₆H₄CO₃H; vi, H⁺, H₂O; vii, H₂-Pd

Scheme 4

Corynoline (159; R = H) has been synthesized from the amide (158) by photolytic cyclisation and conversion into 12-hydroxycorynoline (159; R = OH) followed by hydrogenolysis (Scheme 5).^{233,234} Epicorynoline has been synthesized by an essentially similar process.²³⁵ An improved synthesis of a key intermediate in this synthesis has been reported.²³⁶ A related synthesis of homochelidonine has also been achieved.²³⁷

²²⁸ W. Doepke, V. Hess, and V. Jimenez, *Z. Chem.*, 1976, **16**, 54.

²²⁹ J. Slavik and L. Slavikova, *Coll. Czech. Chem. Commun.*, 1977, **42**, 2686.

²³⁰ H. Ishii, T. Ishikawa, K. Hosoya, and N. Takao, *Chem. Pharm. Bull.*, 1978, **26**, 166.

²³¹ T. Ishikawa and H. Ishii, *Heterocycles*, 1976, **5**, 275.

²³² H. Ishii, T. Ishikawa, and S.-T. Lu, *Tetrahedron Letters*, 1976, **15**, 1203.

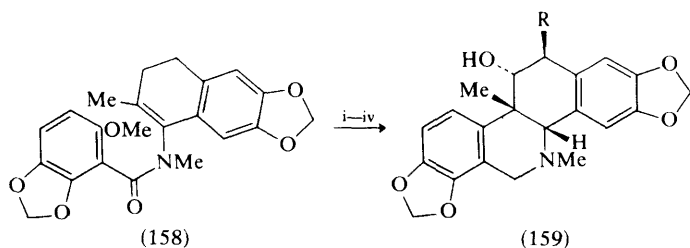
²³³ I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles*, 1976, **4**, 743.

²³⁴ I. Ninomiya, O. Yamamoto, and T. Naito, *J. Chem. Soc., Chem. Commun.*, 1976, 437.

²³⁵ I. Ninomiya and O. Yamamoto, *Heterocycles*, 1976, **5**, 67.

²³⁶ M. Onda, Y. Harigaya, and J. Horie, *Heterocycles*, 1977, **8**, 89.

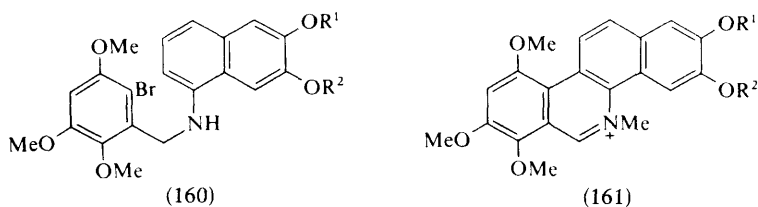
²³⁷ I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles*, 1977, **7**, 137.



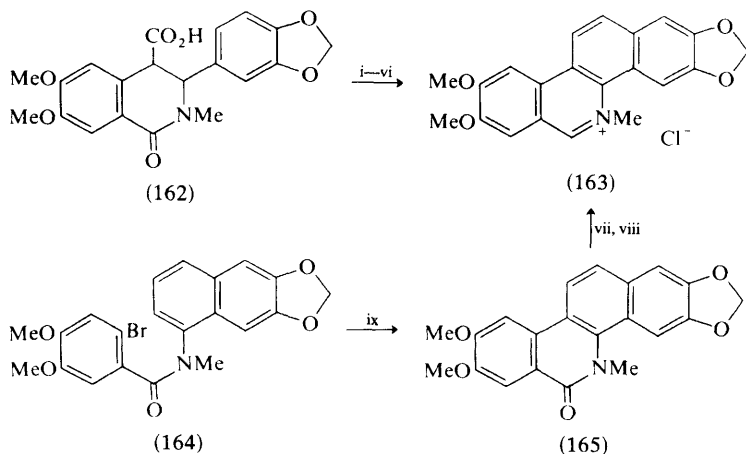
Reagents: i, $h\nu$; ii, H_2 -Pd/C; iii, $Cl_2(CN)_2C_6O_2$; iv, $LiAlH_4$

Scheme 5

Photochemical cyclizations of (160; $R^1 = R^2 = Me$) and (160; $R^1R^2 = CH_2$) have been used as the basis of syntheses of sangilitine (161; $R^1 = R^2 = Me$) and chelilutine ($R^1R^2 = CH_2$).²³⁸



Total syntheses of nitidine chloride (163) have been achieved from the acid amide (162)²³⁹ and the amide (164) as shown in Scheme 6.²⁴⁰ Oxidation of the



Reagents: i, Arndt-Eistert; ii, SO_2Cl_2 ; iii, $SnCl_4$; iv, $LiAlH_4$; v, $-H_2O$; vi, Pd/C; vii, $LiAlH_4$; viii, H_2O_2 , HBF_4 ; ix, $h\nu$

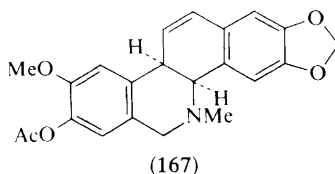
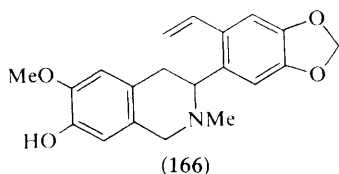
Scheme 6

²³⁸ S. V. Kessar, Y. P. Gupta, K. Dhinga, and S. Narula, *Tetrahedron Letters*, 1977, 1459.

²³⁹ M. Cushman and L. Cheng, *J. Org. Chem.*, 1978, **43**, 286.

²⁴⁰ W. J. Begley and J. Grimshaw, *J. Chem. Soc., Perkin Trans I*, 1977, 2324.

base (166) with lead tetra-acetate yields (167), which can be hydrolysed and methylated to dihydronitidine.²⁴¹



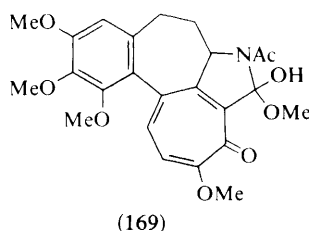
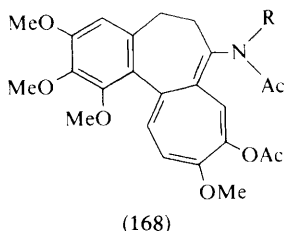
A patent has been published covering the synthesis of nitidine-like compounds.²⁴² Chelilutine has been correlated with nitidine and isoarnottianamide.²⁴³

The inhibition of mammalian virus nucleic acid polymerase by fagaronine chloride has been studied,²⁴⁴ as has the mutagenicity of nitidine and *O*-methyl-fagaronine.²⁴⁵ The basic optical electronic characteristics of sanguinarine sulphate have been discussed.²⁴⁶

16 Colchicine

10,11-Epoxycolchicine, colchicine, 2-demethylcolchicine, 2,3-demethylcolchicine, *N*-formyl-*N*-deacetylcolchicine, and 3-demethyl-*N*-formyl-*N*-deacetylcolchicine have been isolated from *Colchicum latifolium*.^{247,248}

Treatment of (–)-colchicine with acetic anhydride gives the enol acetate (168; R = Ac), which is hydrolysed to (±)-colchicine by acetic acid, and, on treatment with acid-washed alumina, yields the enol acetate (168; R = H). With aqueous base at room temperature (168; R = Ac) is converted into (±)-colchicine and the base (169).²⁴⁹ The *N*-mono-acetyl compound (168; R = H), on mild hydrolysis



with alkali, yields the ketone (170), which can be reduced with borohydrides to the secondary alcohol and which on more vigorous hydrolysis yields (±)-colchicine. Treatment of (168; R = H) with phenyltrimethylammonium bromide

²⁴¹ T. Kametani, M. Takemura, M. Ihara, K. Fukumoto, and K. Takahashi, *Isr. J. Chem.*, 1977, **16**, 4.

²⁴² K. Y. Zee-Cheng and C.-C. Cheng, U.S. P. Appl. 557 187 (*Chem. Abs.*, 1977, **86**, 171 705).

²⁴³ H. Ishii, T. Ishikawa, Y. Ichikawa, and M. Sakamoto, *Chem. Pharm. Bull.*, 1977, **25**, 3120.

²⁴⁴ V. S. Setti, *Cancer Res.*, 1976, **36**, 2390.

²⁴⁵ C. C. Cheng, R. R. Engle, J. R. Hodgson, R. B. Ing, H. B. Wood, S.-J. Yan, and R. K. Y. Zee-Cheng, *J. Pharm. Sci.*, 1977, **66**, 1781.

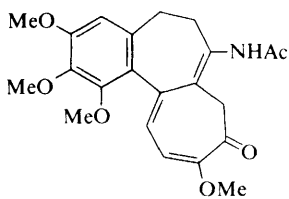
²⁴⁶ N. M. Turkevich and V. M. Musyanovich, *Farm. Zh. (Kiev)*, 1977, 40.

²⁴⁷ H. Potesilova, L. Doljes, P. Sedmera, and F. Santavy, *Coll. Czech. Chem. Commun.*, 1975, **42**, 1571.

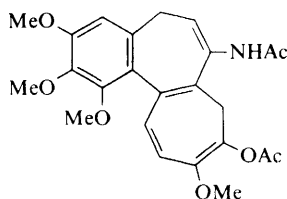
²⁴⁸ H. Potesilova, L. Hruban, and F. Santavy, *Coll. Czech. Chem. Commun.*, 1976, **41**, 3166.

²⁴⁹ A. Blade-Font, *Tetrahedron Letters*, 1977, 2977.

yields 6-dehydrocolchicine and with acetic anhydride gives the enol acetate (171).²⁵⁰

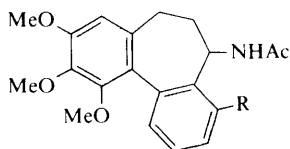


(170)



(171)

Refluxing colchicine in ethylene glycol leads to aromatisation, with the production of deoxycolchicine (172; R = H), *O*-hydroxyethyl-*N*-acetylcolchinol (172; R = OCH₂CH₂OH), and hydroxyethyl colchinoate (172; R = COOCH₂CH₂OH).²⁵¹ The crystal and molecular structures of deacetylthiocolchicine have been determined.²⁵²



(172)

The antileukaemic activity of colchicine derivatives²⁵³ and their effects on RNA synthesis,^{254–256} on intestinal disaccharidase activity,²⁵⁷ and on the secretion of parathyroid hormone²⁵⁸ have been studied.

²⁵⁰ A. Blade-Font, *Tetrahedron Letters*, 1977, 4097.

²⁵¹ V. V. Kiselev, M. E. Perel'son, B. S. Kikot, and O. S. Kostenko, *Zh. Org. Khim.*, 1977, **13**, 2337.

²⁵² C. Koerntgen and T. N. Margulis, *J. Pharm. Sci.*, 1977, **66**, 1127.

²⁵³ K. K. De and G. T. Shiau, *J. Prakt. Chem.*, 1976, **318**, 523.

²⁵⁴ J. D. Vassalli and S. S. Silverstein, *Exp. Cell Res.*, 1977, **106**, 94.

²⁵⁵ S. Imperato, F. Manca, L. Di Crescenzo, and D. Testa, *Boll. Soc. Ital. Biol. Sper.*, 1977, **53**, 317.

²⁵⁶ S. Imperato, F. Manca, S. Cantarella, and G. F. Margaroli, *Boll. Soc. Ital. Biol. Sper.*, 1977, **53**, 299.

²⁵⁷ G. Hartwich, R. Broll, and W. Domschke, *Exp. Pathol.*, 1977, **13**, 198.

²⁵⁸ J. Chanard, R. Black, M. Purkeson, J. Lewis, S. Klahr, and E. Slatopolsky, *Endocrinology*, 1977, **101**, 1792.

Aporphinoid Alkaloids

BY M. SHAMMA

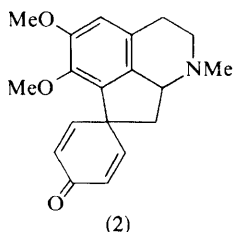
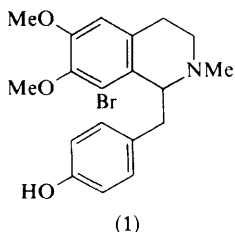
1 Introduction

Imerubrine has been shown to possess an unusual tropoloisoquinoline structure, which makes this alkaloid unique among all isoquinoline bases.¹

Reviews have appeared on the chemosystematics and chemotaxonomy of the alkaloids from the Lauraceae² and the Atherospermataceae,³ which include a large number of aporphinoids.

2 Proaporphines

The known base (\pm)-glaziovine has been found in the leaves of *Ocotea brachybotra*.⁴ Pronuciferine (2) has been synthesized from the tetrahydrobenzylisoquinoline (1) by photochemical cyclization in the presence of sodium borohydride and sodium hydroxide. The resulting dienol was oxidized to pronuciferine, using manganese dioxide.⁵



3 Aporphines

New aporphine alkaloids and their sources are shown in Table 1.⁶⁻¹² Of particular interest in this listing are leucoxylophine and ocoxylophine, which are the first aporphines with only one unsubstituted aromatic carbon atom.⁸

¹ J. V. Silverton, C. Kabuto, K. T. Buck, and M. P. Cava, *J. Amer. Chem. Soc.*, 1977, **99**, 6708.

² I. R. C. Bick and W. Sinchai, *Heterocycles*, 1978, **9**, 903.

³ A. Urzúa and B. K. Cassels, *Lloydia*, 1978, **41**, 98.

⁴ V. Vecchiotti, C. Casagrande, and G. Ferrari, *Farmaco, Ed. Sci.*, 1977, **32**, 767.

⁵ Z. Horii, C. Iwata, and Y. Nakashita, *Chem. and Pharm. Bull. (Japan)*, 1978, **26**, 481.

⁶ C. C. Hsu, R. H. Dobberstein, G. A. Cordell, and N. R. Farnsworth, *Lloydia*, 1977, **40**, 505.

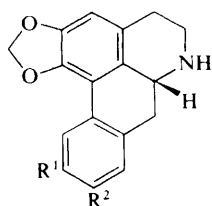
⁷ R. Hocquemiller, P. Cabalion, A. Bouquet, and A. Cavé, *Compt. rend.*, 1977, **285**, C, 447.

⁸ R. Ahmad and M. P. Cava, *Heterocycles*, 1977, **7**, 927.

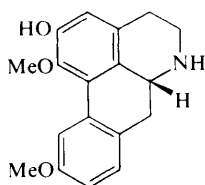
⁹ G. M. Brown, Chemical Division Annual Reports, Sept. 1966, ORNL-3994, p. 114.

Table 1 New aporphine alkaloids, and their sources

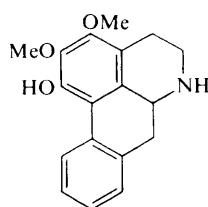
Alkaloid	Source	Ref.
(-)-Norlaureline (3)	<i>Guatteria elata</i> (Annonaceae)	6
(-)-Puterine (4)	<i>Guatteria elata</i>	6
(-)-Zenkerine (5)	<i>Isolona pilosa</i> (Annonaceae)	7
Isopiline (6)	<i>Isolona pilosa</i>	7
(+)-Leucoxylinine (7)	<i>Ocotea leucoxylin</i> (Lauraceae)	8
(+)-Ocoxylinine (8)	<i>Ocotea leucoxylin</i>	8
(+)-Leucoxine (9)	<i>Ocotea leucoxylin</i>	8, 9
(+)-Delporphine (10)	<i>Delphinium dictyocarpum</i> (Ranunculaceae)	10
Dehydroisolaureline (11)	<i>Liriodendron tulipifera</i> (Magnoliaceae)	11
O-Methylnorlirinine (12)	<i>Liriodendron tulipifera</i>	12



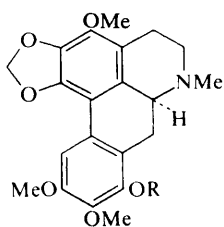
(3) $R^1 = \text{OMe}$, $R^2 = \text{H}$
 (4) $R^1 = \text{H}$, $R^2 = \text{OMe}$



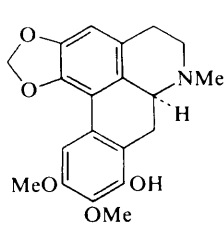
(5)



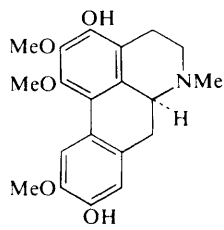
(6)



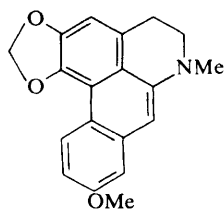
(7) $R = \text{Me}$
 (8) $R = \text{H}$



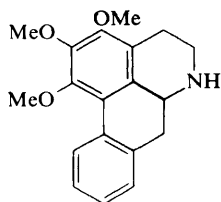
(9)



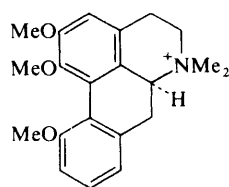
(10)



(11)



(12)



(13)

¹⁰ B. T. Salimov, N. D. Abdullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1978, 235.

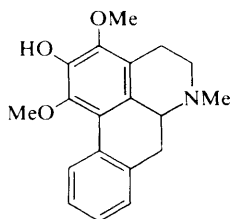
¹¹ R. Ziyaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 715; *Chem. Natural Compounds*, 1978, 602.

¹² C.-L. Chen and H.-M. Chang, *Phytochemistry*, 1978, **17**, 779.

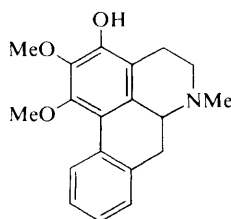
A new aporphine salt is zanthoxyphylline, found in *Zanthoxylum oxyphyllum* (Rutaceae), and tentatively assigned expression (13).¹³

Known aporphines re-isolated from natural sources include those shown in Table 2.^{14–22}

A reconsideration of the alkaloids in the bark of *Liriodendron tulipifera* has been carried out,² as a consequence of which the Yunusov structural assignments for lirinine, liridinine, lirinine *N*-oxide, and *O*-methyl-lirinine²³ have had to be corrected. Thus, lirinine and liridinine are now best represented by expressions (14) and (15), respectively, or *vice versa*. It follows that the alkaloid *O*-methyl-lirinine is 1,2,3-trimethoxyaporphine rather than 1,2,9-trimethoxyaporphine, as previously postulated, and that lirinine *N*-oxide is the *N*-oxide of (14) or (15).¹²



(14)



(15)

A review has appeared dealing in part with the synthesis of aporphines.²⁴ Oxidation of tetrahydropapavine with vanadium oxytrifluoride in trifluoroacetic acid (VOF₃ in TFA) gave norglaucine (30%) as well as the corresponding 4-hydroxylated aporphine norcataline (38%). Similar oxidation of (–)-tetrahydropapavine led to the dextrorotatory aporphines. Additionally, oxidation of (+)-glaucine (16) and of (–)-glaucine led to (+)-cataline (17) and to (–)-cataline, respectively. Minor quantities of the C-4 diastereomeric catalines were also obtained as side-products in each case.²⁵

Full details of the oxidation of phenolic tetrahydrobenzylisoquinolines using cuprous chloride and oxygen in pyridine have appeared. (+)-Reticuline led to (+)-corytuberine (28%), (+)-isoboldine (8%), and the morphinandienone pallidine (6%), so that *ortho–ortho* coupling is favoured.²⁶

¹³ K. P. Tiwari and M. Masood, *Phytochemistry*, 1978, **17**, 1068.

¹⁴ A. Urzúa and B. K. Cassels, *Rev. Latinoamer. Quim.*, 1977, **8**, 133.

¹⁵ A. Shafiee, I. Lalezari, and O. Rahimi, *Lloydia*, 1977, **40**, 352.

¹⁶ W.-N. Wu, J. L. Beal, and R. W. Doskotch, *Lloydia*, 1977, **40**, 508.

¹⁷ W.-N. Wu, J. L. Beal, R.-P. Lee, and R. W. Doskotch, *Lloydia*, 1977, **40**, 384.

¹⁸ J. Wu, J. L. Beal, W.-N. Wu, and R. W. Doskotch, *Lloydia*, 1977, **40**, 593.

¹⁹ M. Shamma and A. S. Rothenberg, *Lloydia*, 1978, **41**, 171.

²⁰ V. A. Mnatsakanyan, M. A. Manuschakyan, and N. E. Mesropyan, *Chem. Natural Compounds*, 1978, 361.

²¹ S.-L. Liu, *J. Chinese Chem. Soc. (Taipei)*, 1977, **24**, 209.

²² O. N. Denisenko, I. A. Israilov, D. A. Muraveva, and M. S. Yunusov, *Chem. Natural Compounds*, 1978, 456.

²³ R. A. Ziyayev, A. Abdusamatov and S. Yu. Yunusov, *Khim. prirod. Soeaininii*, 1973, **9**, 505.

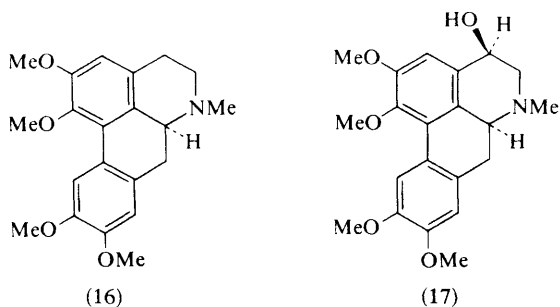
²⁴ T. Kametani and K. Fukumoto, *Heterocycles*, 1977, **8**, 465.

²⁵ J. Hartenstein and G. Satzinger, *Angew. Chem. Internat. Edn.* 1977, **16**, 730.

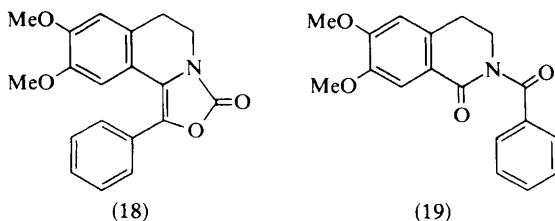
²⁶ T. Kametani, M. Ihara, M. Takemura, Y. Satoh, H. Terasawa, Y. Ohta, K. Fukumoto, and K. Takahashi, *J. Amer. Chem. Soc.*, 1977, **99**, 3805.

Table 2 Aporphines recently re-isolated from natural sources

Alkaloid	Source	Ref.
Dehydroroemerine	<i>Liriodendron tulipifera</i>	11
Roemerine	<i>Isolona pilosa</i>	7
Liriodenine	<i>Liriodendron tulipifera</i>	11
	<i>Annona cherimolia</i>	14
Glaucine	<i>Liriodendron tulipifera</i>	11
	<i>Glaucium vitellinum</i>	15
Caaverine	<i>Liriodendron tulipifera</i>	11
	<i>Isolona pilosa</i>	7
Asimilobine	<i>Liriodendron tulipifera</i>	11
Predicentrine	<i>Liriodendron tulipifera</i>	11
	<i>Ocotea brachybotra</i>	4
Dicentrine	<i>Glaucium vitellinum</i>	15
	<i>Ocotea brachybotra</i>	4
Ocoteine	<i>Ocotea leucoxydon</i>	8
Ocopodine	<i>Ocotea brachybotra</i>	4
Nornuciferine	<i>Isolona pilosa</i>	7
Anonaine	<i>Isolona pilosa</i>	7
	<i>Annona cherimolia</i>	14
Thalphenine	<i>Thalictrum revolutum</i>	16
Bulbocapnine	<i>Glaucium vitellinum</i>	15
	<i>Glaucium pulchrum</i>	15
Magnoflorine	<i>Thalictrum revolutum</i>	16
	<i>Thalictrum podocarpum</i>	17
<i>N</i> -Methyl-laurotetanine	<i>Thalictrum revolutum</i>	18
	<i>Thalictrum dioicum</i>	19
<i>N</i> -Methyl-lindcarpine	<i>Glaucium cherimolia</i>	15
Norushinsunine (michelalbine)	<i>Annona cherimolia</i>	14
Corydine	<i>Glaucium pulchrum</i>	15
	<i>Thalictrum dioicum</i>	19
	<i>Zanthoxylum oxyphyllum</i>	13
Isocorydine	<i>Papaver comutatum</i>	20
	<i>Glaucium vitellinum</i>	15
	<i>Glaucium pulchrum</i>	15
Launobine (norbulbocapnine)	<i>Illigera luzonensis</i>	21
Isothebaine	<i>Papaver bracteatum</i>	22
Bracteoline	<i>Papaver bracteatum</i>	22
Cassythicine	<i>Ocotea brachybotra</i>	4



Photolytic syntheses of cryptodrine,²⁷ 7-methylcryptodrine,²⁷ roemeroline,²⁸ cassythicine,²⁸ anolobine,²⁹ norranentine,³⁰ and a variety of other aporphines possessing a phenolic function at C-9³¹ have been carried out. An attempt to obtain an aporphine by photolysis of the 4-oxazolin-2-one (18) gave instead the imide (19).³²



Earlier studies on the electrochemical synthesis of aporphines have now been extended to the synthesis of glaucine (16) from 2'-iodopapaverine methiodide.³³

The rearrangement of thebaine and northebaine to morphothebaine and normorphothebaine, using concentrated hydrochloric acid under pressure, has been described.³⁴ Substitution of methanesulphonic acid at ambient pressure facilitated this rearrangement, with the generation of aporphines (20) and (21).³⁵

The synthesis of three new racemic aporphines (22)—(24), using either a Bischler–Napieralski–Pschorr sequence or a Reissert–Pschorr route, has been described.³⁶

Dehydronuciferine can be acylated by benzoyl chloride and TFA to give derivatives (25) and (26), respectively.³⁷ Dehydronuciferine and dehydro-

²⁷ B. R. Pai, S. Natarajan, H. Suguna, and G. Manikumar, *Indian J. Chem., Sect. B*, 1977, **15**, 1042.

²⁸ B. R. Pai, H. Suguna, S. Natarajan, and G. Manikumar, *Heterocycles*, 1977, **6**, 1993.

²⁹ H. Suguna and B. R. Pai, *Indian J. Chem., Sect. B*, 1977, **15**, 416.

³⁰ G. Manikumar, B. R. Pai, and H. Suguna, *Indian J. Chem., Sect. B*, 1977, **15**, 740.

³¹ T. R. Govindachari, K. Nagarajan, S. Rajeswari, H. Suguna, and B. R. Pai, *Helv. Chim. Acta*, 1977, **60**, 2138.

³² I. Ninomiya, I. Furutani, O. Yamamoto, T. Kiguchi, and T. Naito, *Heterocycles*, 1978, **9**, 853.

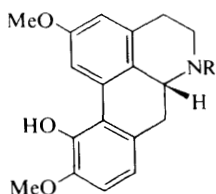
³³ R. Gottlieb, J. L. Neumayer, and D. Elmaleh, Proceedings of the 175th ACS National Meeting, Anaheim, CA; March 1978; item No. 111.

³⁴ F. E. Granchelli, A. H. Soloway, J. L. Neumeyer, and C. N. Filer, *J. Org. Chem.* 1977, **42**, 2014.

³⁵ F. E. Granchelli, A. H. Soloway, C. N. Filer, and J. L. Neumeyer, Proceedings of the 176th ACS National Meeting, Miami Beach, FL; Sept. 1978; item No. 51.

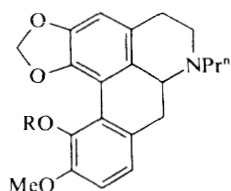
³⁶ D. R. Elmaleh, F. E. Granchelli, and J. L. Neumeyer, Proceedings of the 175th ACS National Meeting, Anaheim, CA; March 1978; item No. 55.

³⁷ J. M. Saá and M. P. Cava, *J. Org. Chem.*, 1978 **43**, 1096.



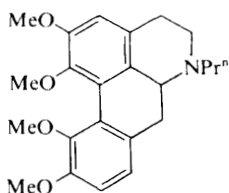
(20) R = Me

(21) R = H

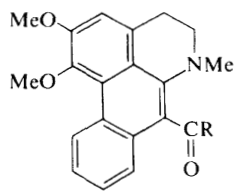


(22) R = Me

(23) R = H



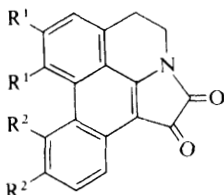
(24)



(25) R = Ph

(26) R = CF₃

aporphine dimethyl ether undergo direct acylative cyclization on treatment with oxalyl chloride to supply, in turn, isatins (27) and (28).³⁷

(27) R¹ = OMe, R² = H(28) R¹ = H, R² = OMe

The acid-catalysed reaction of glaucine (16) with *N*-(hydroxymethyl)acetamide furnished mostly 3-(acetamidomethyl)glaucine (29) (73%). Alternate treatment with formaldehyde under somewhat similar conditions led to 3-hydroxymethylglaucine. The latter aporphine can be converted into 3-formylglaucine, which through oxidation, hydrolysis, and *O*-methylation can be taken to thalicsimidine (purpureine) (30).³⁸ Attempted Vilsmeier reaction of glaucine (16) led to Hofmann elimination.³⁸

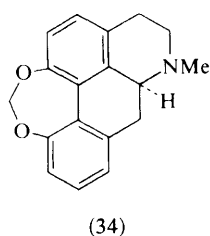
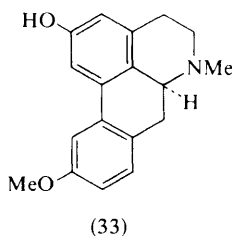
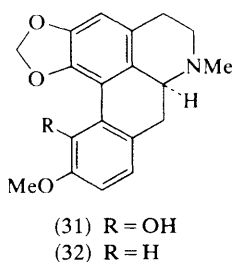
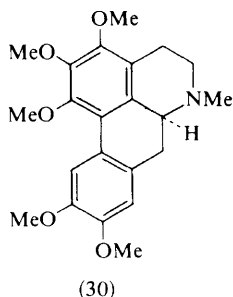
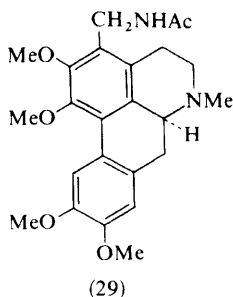
Hofmann-type elimination of aporphine salts such as glaucine methiodide, ethiodide, and benzyl bromide and hydrochloride was achieved in high yield through u.v. irradiation.³⁹

Musliner-Gates dehydroxylation of (+)-bulbocapnine (31) generated (+)-laureline (32). Also, reduction of the diethyl phosphate ester of (+)-bulbocapnine with lithium in liquid ammonia afforded the phenol (33).⁴⁰

³⁸ N. Mollov, S. Philipov, and H. Dutschewska, *Chem. Ber.*, 1978, **111**, 554.

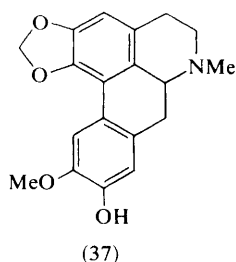
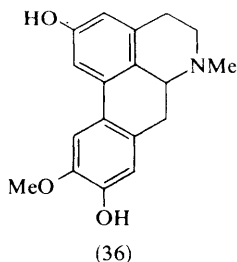
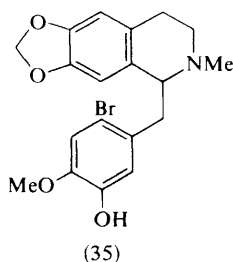
³⁹ J. B. Bremner and K. N. Winzenberg, *Austral. J. Chem.* 1978, **31**, 313

⁴⁰ A. Brossi, M. F. Rahman, and K. C. Rice, *Heterocycles*, 1977, **7**, 277.



Through the judicious use of such reagents as 48% HBr, boron tribromide, diazomethane, and Musliner–Gates conditions, the monophenol (33) was converted into (+)-aporphine, (+)-2,10-dimethoxyaporphine, and (+)-10-methoxyaporphine. Additionally, (+)-bulbocapnine (31) was transformed into mostly optically active 1,11-methylenedioxyaporphine (34). A similar sequence starting with (+)-boldine (1,10-dimethoxy-2,9-dihydroxyaporphine) generated (+)-1,10-dimethoxyaporphine and (+)-1,10-dihydroxyaporphine; while (–)-aporphine could be derived from (–)-apomorphine (10,11-dihydroxyaporphine). Both methods for the elimination of aromatic hydroxy-groups in the aporphine series have limitations. Reductive cleavage of phosphate esters by alkali metal in liquid ammonia suffers from side reactions involving the aromatic rings, while the elimination of tetrazolyl ether functions by hydrogenolysis is subject to steric requirements.⁴⁰

Another cleavage of the methylenedioxy-group was observed during a total synthesis of an aporphine. Irradiation of the brominated tetrahydrobenzylisoquinoline (35) in basic solution supplied aporphine (36) together with cassythicine (37).²⁸



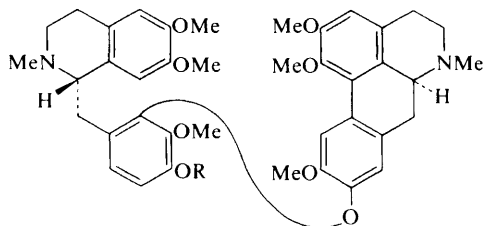
Eighteen chronic schizophrenic patients receiving subcutaneous doses of apomorphine (a dopamine receptor agonist) and of placebo, in separate trials, showed significant improvement in psychotic symptoms after apomorphine. The results were interpreted in terms of the activation of presynaptic dopamine receptors by apomorphine, with a subsequent decrease in dopamine-mediated neural transmission.⁴¹ The neuropsychotropic activity and toxicity of the oxidation products of apomorphine have been described.⁴²

Thalphenine shows hypotensive activity in rabbits, and is also active against *Mycobacterium smegmatis*.¹⁶ *N*-Demethylthalphenine and bisnortalphenine are effective against *M. smegmatis*, *Staphylococcus aureus*, and *Candida albicans*.¹⁸

4 Aporphine–Benzylisoquinoline Dimers

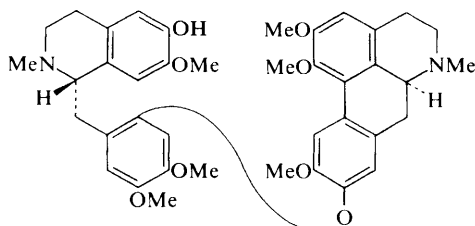
New aporphine–benzylisoquinoline dimers are (+)-thalirevolutine (38), (+)-thalirevoline (39), (+)-thalilutidine (40), and (+)-thalilutine (41), all present in *Thalictrum revolutum* (Ranunculaceae);^{18,43} while (+)-thaliadanine (42) is found in *Thalictrum minus* Race B.⁴⁴ Another new alkaloid is thaliadine (43), also located in *T. minus* Race B.⁴⁴ Thaliadine must be an oxidation product of an aporphine–benzylisoquinoline alkaloid.

Thalictrum dioicum produces the known (+)-thalicarpine and (+)-pennsylvanine, but not (+)-thalidoxine. The structure of (+)-pennsylvanine was further confirmed by its oxidation into *O*-desmethylnandaline by permanganate.¹⁹



(38) R = Me

(39) R = H



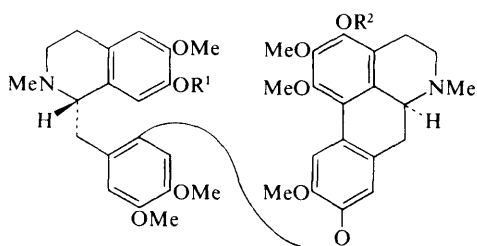
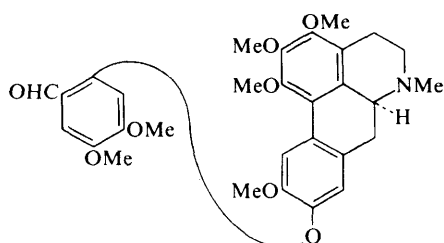
(40)

⁴¹ C. A. Tamminga, M. H. Schaffer, R. C. Smith, and J. M. Davis, *Science*, 1978, **200**, 567.

⁴² K. Rehse, G. Piesker, and R. Horowski, *Arch. Pharm.*, 1978, **311**, 360.

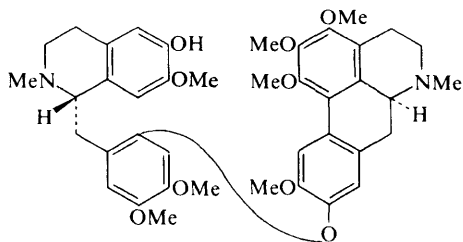
⁴³ W.-N. Wu, J. L. Beal, and R. W. Doskotch, *Tetrahedron*, 1977, **33**, 2919.

⁴⁴ W.-T. Liao, J. L. Beal, W.-N. Wu, and R. W. Doskotch, *Lloydia*, 1978, **41**, 271.

(41) $R^1 = \text{Me}, R^2 = \text{H}$ (42) $R^1 = \text{H}, R^2 = \text{Me}$ 

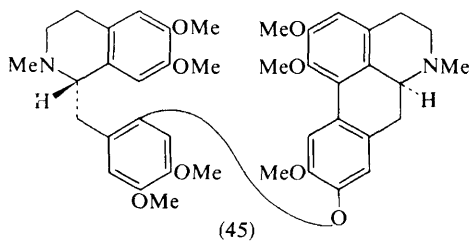
(43)

O-Desmethyladiantifoline should have structure (44) rather than (42), which is now assigned to (+)-thaliadanine.⁴⁴



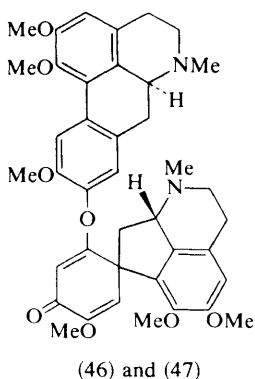
(44)

Oxidation of thalicarpine (45) with VOF_3 in TFA gave a mixture of dienones (46) and (47). The major isomer was converted into the corresponding epimeric dienols, which upon treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in methylene chloride produced the bisaporphine (48).⁴⁵

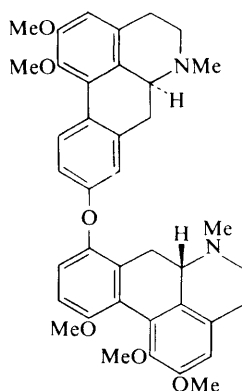


(45)

⁴⁵ S. M. Kupchan, O. P. Dhingra, V. Ramachandran, and C.-K. Kim, *J. Org. Chem.*, 1978, **43**, 105.



(46) and (47)

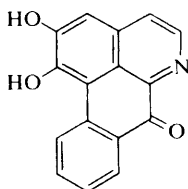


(48)

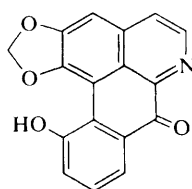
Thalicarpine (45), thaliadine (43), thalirevolutine (38), thalirevoline (39), and *O*-desmethylandiantifoline (44) show hypotensive activity in rabbits, while thaliadanine, thalirevoline, thalicarpine, thalmelatine, and pennsylvanine have antimicrobial activity against *Mycobacterium smegmatis*.^{16,43,44}

5 Oxoaporphines

A new violet oxoaporphine alkaloid, liriodendronine (49), has been isolated from the discolored sapwood of *Liriodendron tulipifera*. The compound exists primarily as a quinone methide in neutral medium, as a dianion in base, and as an isoquinolinium ion in weak acid.⁴⁶ Another new oxoaporphine is oxopukateine (50), present in *Duguetia eximia* (Annonaceae) together with the known *O*-methylmoschatoline (1,2,3-trimethoxyoxoaporphine) and oxoputerine (1,2-methylenedioxy-11-methoxyoxoaporphine).⁴⁷



(49)



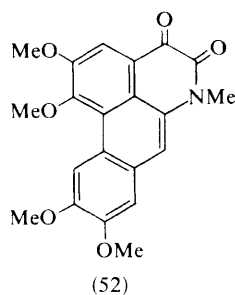
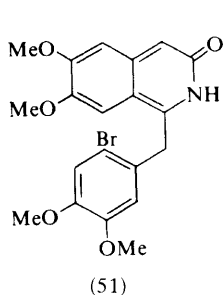
(50)

6 4,5-Dioxoaporphines

A synthesis of pontevedrine (52) has been accomplished. Irradiation of the bromo-pyridone (51) in the presence of oxygen and hydroxide ion generated

⁴⁶ P. D. Senter and C.-L. Chen, *Phytochemistry*, 1977, **16**, 2015.

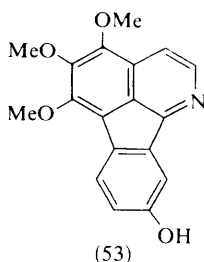
⁴⁷ O. R. Gottlieb, A. F. Magalhaes, E. G. Magalhaes, J. G. S. Maia, and A. J. Marsaioli, *Phytochemistry*, 1978, **17**, 837.



norponteveldrine. Ponteveldrine was then produced by *N*-methylation with methyl fluorosulphonate.⁴⁸

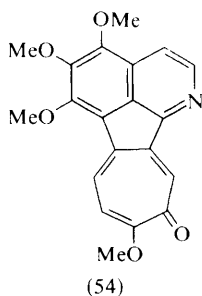
7 Azafluoranthenes

An *X*-ray crystal structure of nor-rufescine (53), which is present in the stems of the Amazonian vines *Abuta imene* and *A. rufescens*, has confirmed the previous structural assignment.⁴⁹



8 Imerubrine, a Tropoloisoquinoline

An *X*-ray study has shown that the orange-red base imerubrine, also present in *A. imene* and *A. rufescens*, possesses the remarkable tropolone ether structure (54). It is the first example of a new isoquinoline alkaloidal type for which the general term 'tropolisoquinoline' has been proposed.¹



⁴⁸ L. Castedo, R. Estévez, J. M. Saá, and R. Suau, *Tetrahedron Letters*, 1978, 2179.

⁴⁹ M. D. Klein, K. T. Buck, M. P. Cava, and D. Voet, *J. Amer. Chem. Soc.*, 1978, **100**, 662.

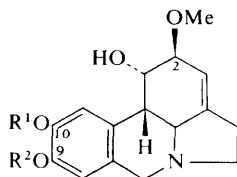
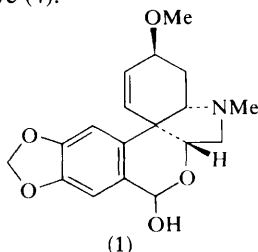
1 Introduction

Alkaloids of the group have been reviewed,¹ and an account of lactone alkaloids of the Amaryllidaceae has been published.² A concise account of recent developments in the synthesis of Amaryllidaceae alkaloids has appeared.³

Contrary to previous practice, *Sceletium* alkaloids and related compounds are classified as pyrrolidine derivatives and discussed in Chapter 2. The Amaryllidaceae alkaloid cherylline is included in the account of isoquinoline alkaloids (Chapter 8).

2 Isolation, and Structural Studies

A study of the bulbs of *Zephyranthes carinata* resulted in the isolation of pretazzettine (1), which had not been obtained previously from this species, and the new alkaloid carinatine (3).⁴ The n.m.r. and mass spectra of carinatine and its o.r.d. curve suggested that the alkaloid was an *O*-desmethylgalanthine, and this was confirmed by conversion of carinatine into galanthine (2). The phenolic hydroxy-group was assigned to C-10 as a result of nuclear Overhauser experiments which led to the identification of methoxy-groups at C-2 and at C-9; goleptine, which is another *O*-desmethylgalanthine, is apparently the 9-hydroxy-derivative (4).



- Galanthine (2) $R^1 = R^2 = \text{Me}$
 Carinatine (3) $R^1 = \text{H}, R^2 = \text{Me}$
 Goleptine (4) $R^1 = \text{Me}, R^2 = \text{H}$

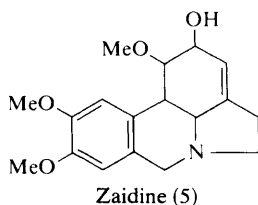
¹ M. Sainsbury in 'Rodd's Chemistry of Carbon Compounds', ed. S. Coffey and M. F. Ansell, Elsevier, Amsterdam, 2nd edn., 1977, **4B**, 165.

² W. Doepke, *Heterocycles*, 1977, **6**, 551.

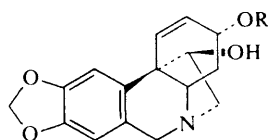
³ R. V. Stevens, *Accounts Chem. Res.*, 1977, **10**, 193.

⁴ S. Kobayashi, H. Ishikawa, M. Kihara, T. Shingu, and T. Hashimoto, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 2244.

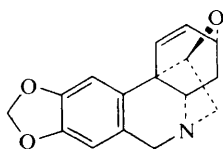
A new isomer of galanthine, zaidine (5), has been isolated from *Hymenocallis arenicola*.⁵ The structure of zaidine was determined by mass spectrometry, but its stereochemistry is unknown. *H. arenicola* also contains lycorine, tazettine, galanthamine, and haemanthamine.



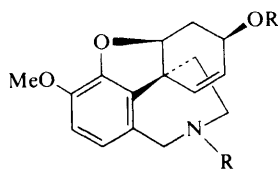
Crinamine (6) and the new alkaloid hamayne (7) have been obtained from *Crinum asiaticum* var. *japonicum*.⁶ Hamayne was shown to be *O*-desmethylcrinamine by a study of the n.m.r. spectrum of its diacetate and by the acid-catalysed conversion of crinamine and hamayne into the same apohaemanthamine (8). *O,N*-Diacetyl-*N*-desmethylgalanthamine (9; R = Ac) was also isolated from *C. asiaticum*, but since acetic anhydride was used in the isolation procedure, it was assumed that *N*-desmethylgalanthamine (9; R = H) rather than its diacetate is a constituent of the plant.



Crinamine (6) R = Me
Hamayne (7) R = H

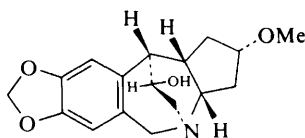


(8)



(9)

The crinine group of alkaloids was thought to be stable to light, but a phototransformation product of crinamine has now been prepared, and its structure (10) has been established by X-ray analysis.⁷



(10)

Russian chemists have continued their investigations of *Ungernia* species and other members of the Amaryllidaceae, particularly as sources of galanthamine.⁸ Dihydroepimacronine (11) was reported to be a constituent of *Ungernia spiralis*.⁹

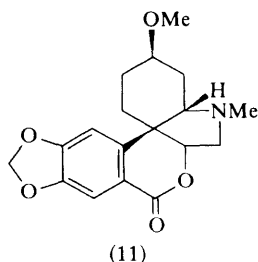
⁵ W. Doepke and Z. Trimino, *Z. Chem.*, 1977, **17**, 101.

⁶ M. Ochi, H. Otsuki, and K. Nagao, *Bull. Chem. Soc. Japan*, 1976, **49**, 3363.

⁷ Y. Tsuda, M. Kaneda, S. Takagi, M. Yamaki, and Y. Iitaka, *Tetrahedron Letters*, 1978, 1199.

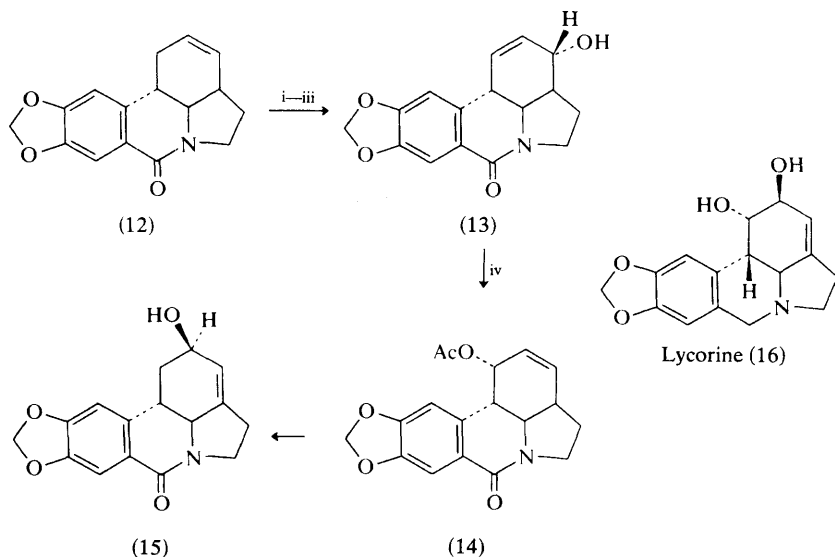
⁸ S. A. Khamidkhodzhaev and A. Abdusamatov, *Usb. Biol. Zh.*, 1978, **36** (*Chem. Abs.*, 1978, **88**, 148 987); O. A. Cherkasov, *Khim-Farm. Zhur.*, 1977, **11**, 84 (*Chem. Abs.*, 1977, **87**, 81 252).

⁹ Kh. A. Kadyrov and A. Abdusamatov, *Khim. prirod. Soedinenii*, 1977, 426 (*Chem. Abs.*, 1977, **87**, 130 468).



3 Synthesis

Full details are now available of Torssell's synthesis of 1-desoxylycorin-7-one (15) (cf. Vol. 5, p. 172).¹⁰ Application of the phenylselenium bromide procedure to the lactam (12) led to an improved synthesis of the enol (13), which by acid-catalysed allylic rearrangement was converted into the allylic acetate (14) (Scheme 1); lycorine (16) has already been prepared from the latter compound.



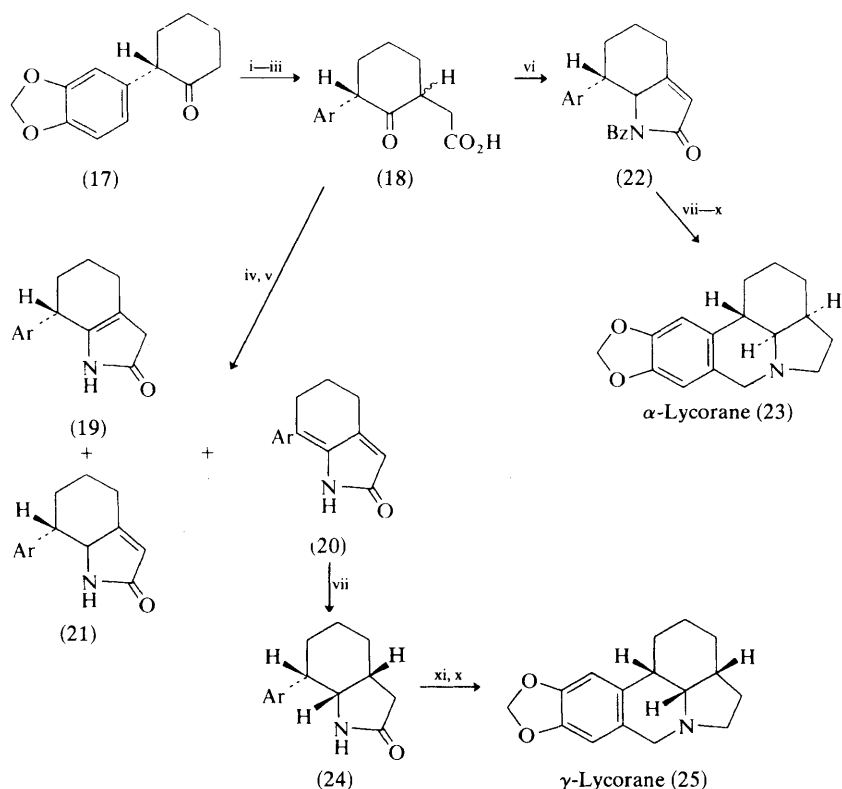
Reagents: i, Ph_2Se_2 , Br_2 , HOAc , KOAc ; ii, KOH , MeOH , CHCl_3 ; iii, H_2O_2 , pyridine, CH_2Cl_2 ; iv, H_2SO_4 , Ac_2O , AcOH , 50°C

Scheme 1

Alternative syntheses of α -lycorane (23) and γ -lycorane (25) depend on the preparation of unsaturated lactams (20) and (21) whereby ring C is derived from an aryl-cyclohexanone (17) (Scheme 2).¹¹ Reduction of the oxime of the 2-

¹⁰ O. Møller, E.-M. Steinberg, and K. Torssell, *Acta. Chem. Scand. (B)*, 1978, **32**, 98.

¹¹ B. Umezawa, O. Hoshino, S. Sawaki, S. Sato, and N. Numao, *J. Org. Chem.*, 1977, **42**, 4272.



Reagents: i, pyrrolidine, PhH, reflux; ii, $\text{BrCH}_2\text{CO}_2\text{Me}$; iii, aq. KOH, reflux; iv, NH_2OH ; v, Zn, AcOH, reflux; vi, PhCH_2NH_2 , *o*-xylene, reflux, then HCO_2H ; vii, H_2 -Pt, MeOH; viii, LiAlH_4 ; ix, H_2 -Pd; x, HCHO, HCl; xi, B_2H_6 , THF

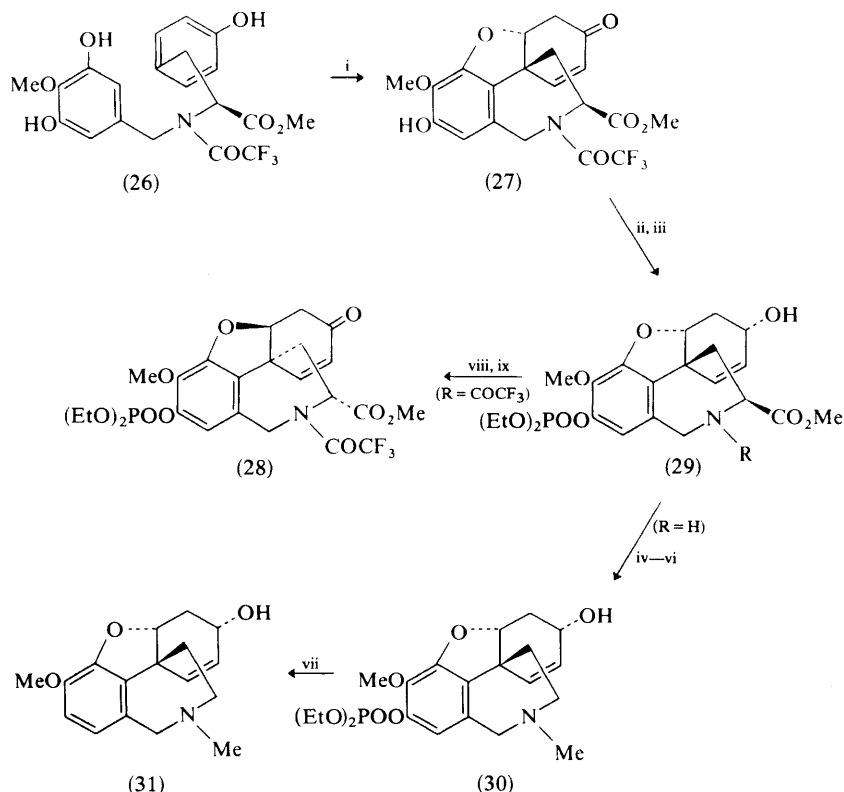
Scheme 2

oxocyclophenylacetic acid (18) with zinc and acetic acid gave a mixture of three unsaturated lactones (19), (20), and (21), instead of the expected cyclic hydroxamic acid. Catalytic reduction of the $\alpha\beta$ -unsaturated lactam (20) afforded the corresponding saturated lactam, which was prepared previously by the Diels-Alder route and had been converted into α -lycorane. Conversion of the keto-acid (18) into an *N*-benzyl-lactam (22) followed by reduction, debenylation, and Pictet-Spengler cyclisation constituted another synthesis of α -lycorane. Catalytic hydrogenation of the dieno-lactam (20) gave the all-*cis*-lactam (24), which was converted into γ -lycorane (25).

Yamada and co-workers have given a full account of their synthesis of (+)-maritidine (*cf.* Vol. 7, p. 169),¹² and have applied the methods to an asymmetric synthesis of (+)-galanthamine (31) from *L*-tyrosine (Scheme 3).¹³

¹² K. Tomioka, K. Koga, and S. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 2681.

¹³ K. Shimizu, K. Tomioka, S. Yamada, and K. Koga, *Heterocycles*, 1977, **8**, 277.



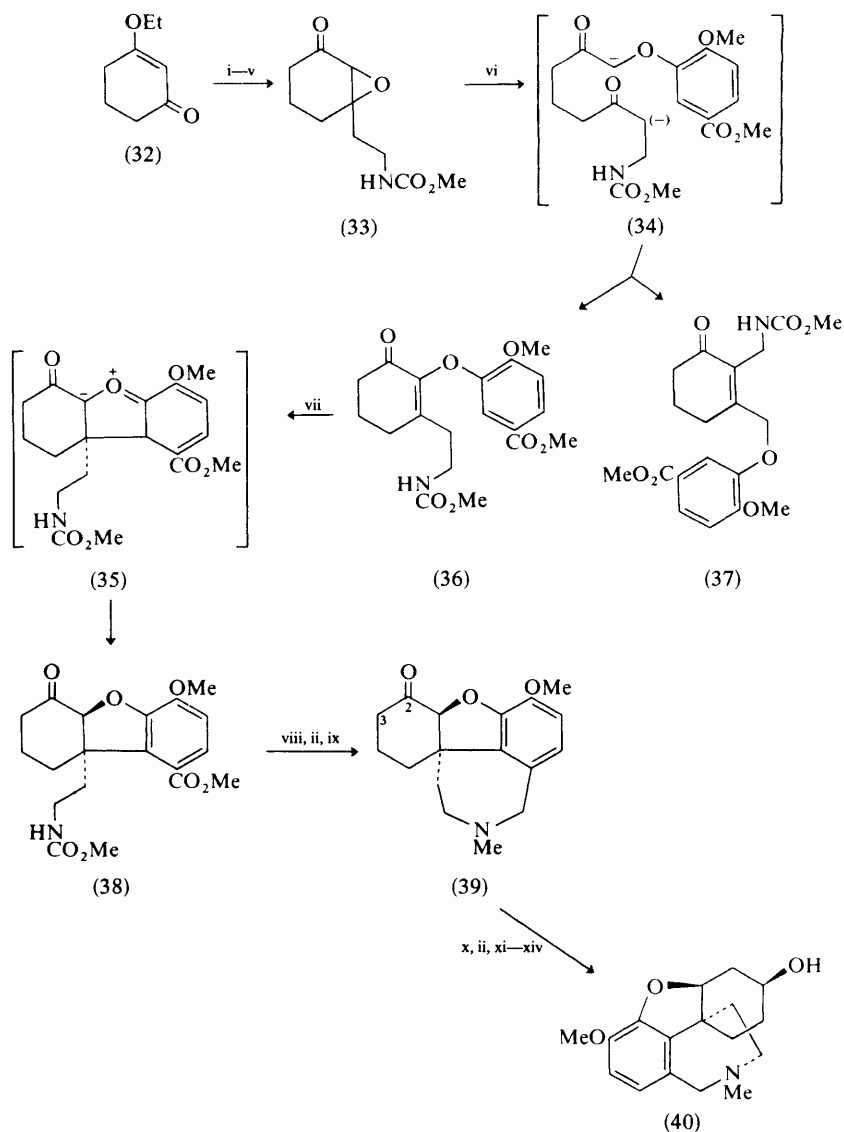
Reagents: i, Mn^{III} bis(acetylacetonate), MeCN; ii, $(EtO)_2POCl$, NEt_3 ; iii, $NaBH_4$; iv, HCHO, HCO_2H , then NH_3 ; v, Ac_2O , pyridine, then $POCl_3$; vi, $LiAlH_4$, THF, $0^\circ C$; vii, Na, liq. NH_3 ; viii, lithium di-isopropylamide, $(Me_2NCH_2)_2$, THF, at $-20^\circ C$; ix, pyridinium chlorochromate, CH_2Cl_2

Scheme 3

Oxidative coupling of the (-)-trifluoroacetyl derivative (26) was carried out with manganic tris(acetylacetonate) to give the (+)-enone (27) in 34% yield. The phenolic hydroxy-group required for coupling was later removed by reductive elimination of compound (30) to give (+)-galanthamine (31). The reaction of the trifluoroacetyl derivative (29; $R = COCF_3$) successively with lithium di-isopropylamide and with pyridinium chlorochromate gave the (-)-enone (28); this epimerization sequence constitutes a formal synthesis of (-)-galanthamine.

A new synthesis of (\pm)-lycoramine (40) (dihydrogalanthamine) has been reported by Schultz and co-workers¹⁴ (Scheme 4). The epoxide (33) was obtained from cyclohexane-1,3-dione enol ether (32) in five high-yield stages. The aryl ring was then introduced by base-catalysed reaction of the epoxide with 5-carbomethoxy-2-methoxyphenol; two isomeric enones (36) and (37) were formed,

¹⁴ A. G. Schultz, K. Y. Yee, and M. H. Berger, *J. Amer. Chem. Soc.*, 1977, **99**, 8065.



Reagents: i, $(EtO)_2POCH_2CN$, THF; ii, $LiAlH_4$, Et_2O ; iii, $ClCO_2Me$, PhH, aq. HCO_3^- ; iv, 10% aq. H_2SO_4 , THF, MeOH; v, H_2O_2 , OH^- , aq. MeOH; vi, 2-methoxy-5-methoxycarbonylphenol, KOH, 18-crown-6, THF, reflux; vii, PhH, MeOH, $h\nu$; viii, $HC(OMe)_3$, MeOH, H_2SO_4 ; ix, SO_2Cl_2 , Et_3N , CH_2Cl_2 , at $-20^\circ C$, then aq. H_2SO_4 ; x, lithium tetramethylpiperidine, THF, hexamethylphosphoramide, at $-78^\circ C$, then $PhSSO_2Ph$, THF; xi, MeCl; xii, $HgCl_2$, HgO aq. MeCN, at $50^\circ C$; xiii, $CrCl_2$, aq. Me_2CO ; xiv, $LiAlH_4$, THF, reflux

Scheme 4

apparently *via* alternative cyclization of an intermediate enolate (34), but the required compound (36) was the major product. The key step in the synthesis was heteroatom-directed photocyclization of (36) to give the *cis*-fused dihydrofuran (38); the photoreaction is believed to proceed through conrotatory cyclization to (35). Elaboration of the azaheptyl ring to give compound (39) was followed by introduction of a carbonyl group at C-3 *via* a thioketal and removal of the oxygen function at C-2.

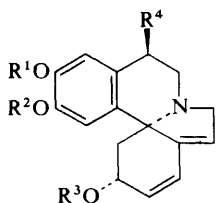
There is continuing interest in the synthesis and pharmacological properties of dibenzo[*c,e*]azocine derivatives related to apogalanthamine.¹⁵

The Japanese synthesis of (±)-lycoricidine (*cf.* Vol. 7, p. 172) has been published in full.¹⁶

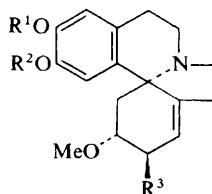
¹⁵ S. Kobayashi, M. Kihara, S. Shizu, S. Katayama, H. Ikeda, K. Kitahiro, and H. Matsumoto, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 3312; M. Kihara and S. Mineo, *ibid.*, 1978, **26**, 635; T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa, and T. Nakamura, *Yakugaku Zasshi*, 1977, **97**, 1353 (*Chem. Abs.*, 1978, **88**, 152 394).

¹⁶ S. Ohta and S. Kimoto, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 2977.

Recent reviews of methods of alkaloid synthesis have included brief sections concerned with applications in the *Erythrina* alkaloid series.¹ Preliminary studies² of the alkaloid content of the seeds of eight species of *Erythrina* (*E. resupinata*, *E. chiriquensis*, *E. eggersii*, *E. mildbraedii*, *E. decora*, *E. orophila*, *E. variegata*, and *E. merrilliana*), using gas chromatography-mass spectrometry, have shown that erysodine (1a), erysovine (1b), and erysopine (1c) were present in all species, and were the most abundant alkaloids. Erythratidine (2a) and erysotine (2b) were also widespread, but erythraline (1d) was only found in *E. mildbraedii* and erythravine (1e) in *E. eggersii*. In this study the alkaloid content of several samples of *E. lysistemon* seeds was found to differ quantitatively rather than qualitatively; similar results were obtained with *E. abyssinica*. The flowers of *E. variegata* (from Guyana) contained erysotrine (1f) and a new alkaloid, erythratine.³ This was shown to be 11- β -hydroxyerysotrine (1g) by spectroscopic studies and comparisons with other known alkaloids; the configuration of the hydroxy-group was assigned by correlations of optical rotations. The seeds of the same plants



- (1) a; R¹ = R⁴ = H, R² = R³ = Me
 b; R² = R⁴ = H, R¹ = R³ = Me
 c; R¹ = R² = R⁴ = H, R³ = Me
 d; R¹R² = -CH₂-, R³ = Me, R⁴ = H
 e; R¹ = R² = Me, R³ = R⁴ = H
 f; R¹ = R² = R³ = Me, R⁴ = H
 g; R¹ = R² = R³ = Me, R⁴ = OH
 h; R¹ = R² = R³ = Me, R⁴ = OMe



- (2) a; R¹ = R² = Me, R³ = OH
 b; R¹ = H, R² = Me, R³ = OH
 c; R¹ = Me, R² = R³ = H
 d; R¹R² = -CH₂-, R³ = OH

¹ T. Kametani in 'Total Synthesis of Natural Products', ed. J. Apsimon, Vol. 3, 1977, Wiley, New York, p. 1; R. V. Stevens, *Accounts Chem. Res.*, 1977, **10**, 193.

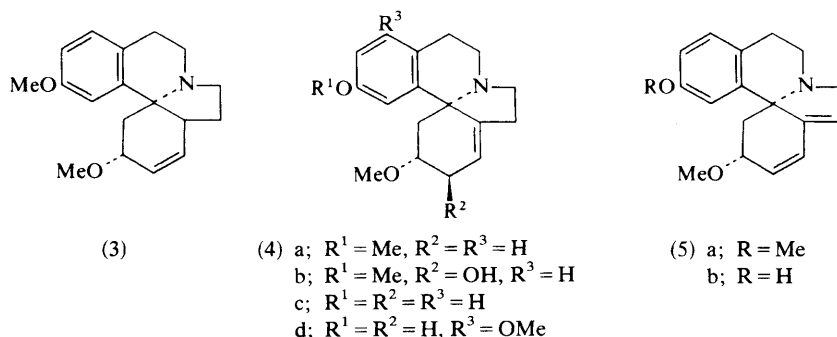
² I. Barakat, A. H. Jackson, and M. Abdullah, *Lloydia*, 1977, **40**, 471.

³ M. M. Olelemy, A. A. Ali, and M. A. Elmothal, *Lloydia*, 1978, **41**, 342.

contained erysotrine (1f) and erysodine (1a), and both seeds and flowers contained hypophorine, choline, and a glycoside of erysodine.³

A new alkaloid isolated from *Cocculus trilobus* has been assigned the structure dihydroerysovine (2c) based on chemical and spectroscopic studies;⁴ internuclear double resonance and nuclear Overhauser effects were used in this work, and the general utility of these methods in determining the substitution pattern of erythrinan alkaloids has been discussed.^{4,5} Isococculine (3), cocculidine (4a), and a new alkaloid coccupinine (5a) have also been isolated from the leaves of *Cocculus laurifolius* DC.⁶ The structure of the latter was deduced from spectroscopic evidence and chemical correlation, e.g. methylation of coccupinine (5b) with diazomethane gave coccupinine, whilst partial reduction of the latter gave cocculidine (4a). In another study,⁷ an abnormal alkaloid obtained from *C. trilobus*, coccutitine, was assigned the structure (4b) by n.m.r. spectral comparisons with erythratine (2d), and the stereochemistry was confirmed by double-resonance techniques and comparisons with erythistemine (1h).

X-Ray crystallographic studies⁸ of cocculine (4c) and coccutrine (4d) show that ring A is in the half-chair conformation, whilst ring C is intermediate between a half-chair and an envelope. In cocculine, ring B is in a half-chair conformation, whilst in coccutrine it is intermediate between a half-chair and an envelope, and the conformational difference is attributed to hydrogen-bonding in crystals of cocculine (4c) between the hydroxyl hydrogen and the nitrogen lone pair [which does not occur in coccutrine (4d)]. The crystal structure of the hydrobromide of (+)-cocculine has also been reported.⁹



In continuation of earlier work, a further series of mass spectra of eighteen erythrinan and erythrinan-8-one alkaloids and their 'homo'-analogues have been analysed.¹⁰ All the compounds exhibit similar fragmentations of ring A, but an

⁴ M. Juichi, Y. Ando, Y. Yoshida, J. Kunimoto, T. Shingo, and H. Furukawa, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 533.

⁵ M. Juichi, Y. Ando, A. Satoh, J. Kunimoto, T. Shingo, and H. Furukawa, *Chem. and Pharm. Bull. (Japan)*, 1978, **26**, 563.

⁶ A. N. Singh and D. S. Bhakuni, *Indian J. Chem., Sect. B.*, 1977, **15**, 388.

⁷ A. N. Singh, H. Pande, and D. S. Bhakuni, *Lloydia*, 1977, **40**, 322.

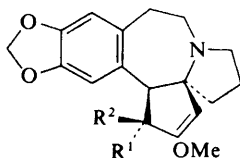
⁸ A. T. McPhail and K. D. Onan, *J.C.S. Perkin II*, 1977, 1156.

⁹ S. M. Nasirov, V. G. Adrianov, A. N. Chekhov, and Yu. T. Struchkov, *Tezisy Dokl. Vses. Soveshch. Org. Kristallochim. 1st (1974)*, 1975, 50.

¹⁰ Y. Migron and E. D. Bergmann, *Org. Mass Spectrometry*, 1977, **12**, 500.

aromatic ring D stabilises the C ring and secondary fragmentations of ring B occur, e.g. expulsion of CO , CH_2CO , C_2H_4 , or $\text{CH}_3\text{CH}=\text{CH}_2$; if ring D is not aromatic, parallel fragmentations of rings A and C occur.

Gas chromatography-mass spectrometry of the anti-tumour alkaloids of *Cephalotaxus harringtonia* callus¹¹ revealed the presence of cephalotaxine (6a) and the anti-tumour esters harringtonine (6c), isoharringtonine (6d), and homoharringtonine (6e) in both callus tissue and the medium; deoxyharringtonine (6f) was also found in relatively large amounts in the medium but not the callus. The variations of alkaloid content with time were studied, and a new alkaloid, homodeoxyharringtonine (6g), was also detected.¹¹ Chinese workers have continued their investigations of *Cephalotaxus* alkaloids and isolated deoxyharringtonine (6f), isoharringtonine (6d), harringtonine (6c), homoharringtonine (6e), cephalotaxine (6a), drupacine (7), desmethylcephalotaxinone (8), 3-*epi*-schelhammericine (9), and epicephalotaxine (6b) from *C. hainanensis*.¹² Compounds (6c), (6d), (6e), and (6f) prolonged the life-span of mice with lymphocyte leukaemia, whereas (6a), (7), (8), and (9) were ineffective; harringtonine was effective in treating both acute and chronic myelocytic leukaemia in human subjects.¹²



(6) a; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{OH}$

b; $\text{R}^1 = \text{OH}$, $\text{R}^2 = \text{H}$

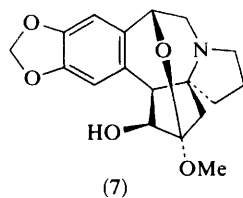
c; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}_2\text{C}(\text{OH})(\text{CH}_2)_2\text{C}(\text{OH})\text{CO}_2^-$
 $\text{CH}_2\text{CO}_2\text{Me}$

d; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}_2\text{CH}(\text{CH}_2)_2\text{C}(\text{OH})\text{CO}_2^-$
 $\text{CH}(\text{OH})\text{CO}_2\text{Me}$

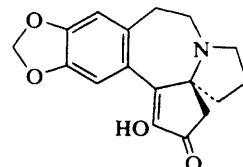
e; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}_2\text{C}(\text{OH})(\text{CH}_2)_3\text{C}(\text{OH})\text{CO}_2^-$
 $\text{CH}_2\text{CO}_2\text{Me}$

f; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}_2\text{CH}(\text{CH}_2)_2\text{C}(\text{OH})\text{CO}_2^-$
 $\text{CH}_2\text{CO}_2\text{Me}$

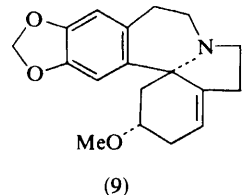
g; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}_2\text{CH}(\text{CH}_2)_3\text{C}(\text{OH})\text{CO}_2^-$
 $\text{CH}_2\text{CO}_2\text{Me}$



(7)



(8)



(9)

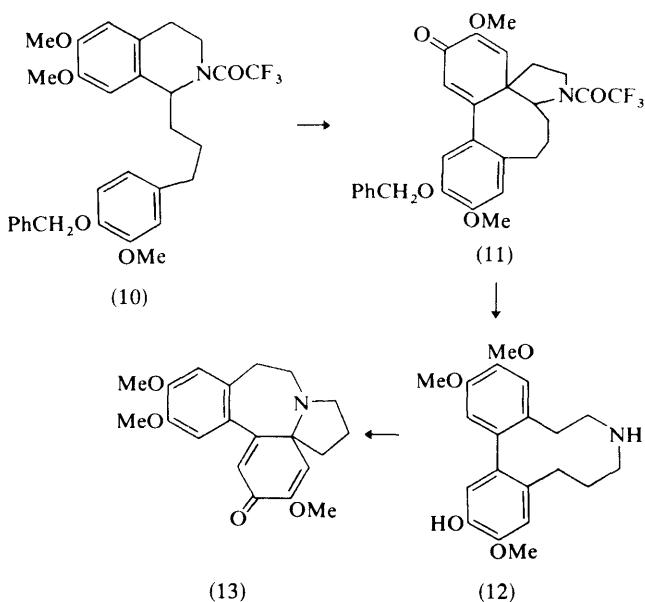
Synthetic work on *Erythrina* and related alkaloids has again moved at a rather slow pace during the past year. However, a new approach to *Cephalotaxus* alkaloids has been described,¹³ involving the oxidative coupling of a 1-phenethyl-

¹¹ N. E. Delfel and J. A. Rothfus, *Phytochemistry*, 1977, **16**, 1595.

¹² Chinese Academy of Medical Sciences, Chinese People's Liberation Army, 187th Hospital, *Hua Hsueh Hsueh Pao*, 1976, **34**, 283 (*Chem. Abs.* 1977, **88**, 126 256).

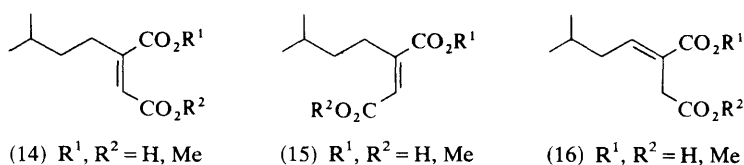
¹³ D. P. Ohingra, S. M. Kupchan, and C. K. Kim, *J.C.S. Chem. Comm.*, 1977, 847.

tetrahydroisoquinoline (10) to give a spirocyclic dienone (11), which was then transformed into a compound (13) containing a cephalotaxine-type skeleton, *via* the monophenolic dibenz[*d,f*]azocine (12) (Scheme 1). Attachment of side-chain



Scheme 1

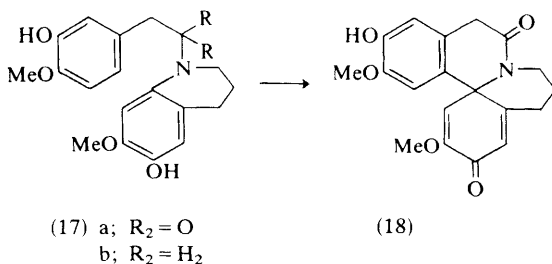
ester groups to cephalotaxine has proved a formidable problem, for steric reasons, but efficient new approaches to the synthesis of the unsaturated acids (14), (15), and (16) have been described, involving 1,4-addition of di-isomylcopper lithium to dimethyl acetylenedicarboxylate as the crucial stage.¹⁴



In the homoerythrina series, full details of work described earlier (Volume 8 of these Reports) have now appeared,¹⁵ and it was shown that intramolecular oxidative coupling of the phenolic 1-phenylacetamidoquinoline (17a) afforded a C-homo-erythrinandienone (18) in 67% yield, whereas the corresponding amine

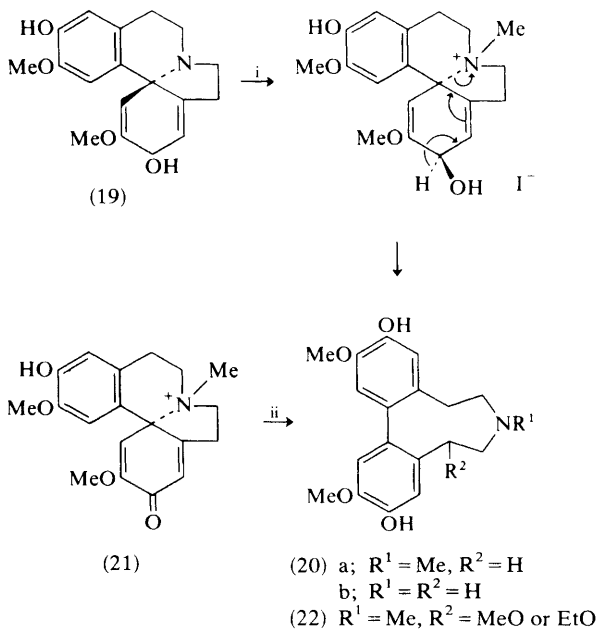
¹⁴ R. B. Bates, R. S. Cutler, and R. M. Freeman, *J. Org. Chem.*, 1977, **42**, 4162.

¹⁵ E. McDonald and A. Suksamrarn, *J.C.S. Perkin I*, 1978, 434, 440.



(17b) gave intractable mixtures.¹⁵ The high yield in the former case was attributed to removal of undesirable conformational interactions in the transition state for cyclisation of the amide.

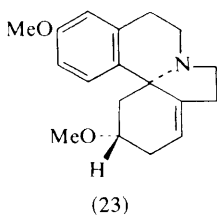
In the *Erythrina* series, the reaction of erysodienol (19) with methyl iodide resulted in ring opening (Scheme 2) to give the corresponding dibenzazepine (20a)¹⁶ whose structure was confirmed by comparison with an authentic specimen prepared by *N*-methylation of the known secondary amine (20b). Erysodienone methiodide (21), however, gave the methoxy- or ethoxy-dibenzazepines (22) on



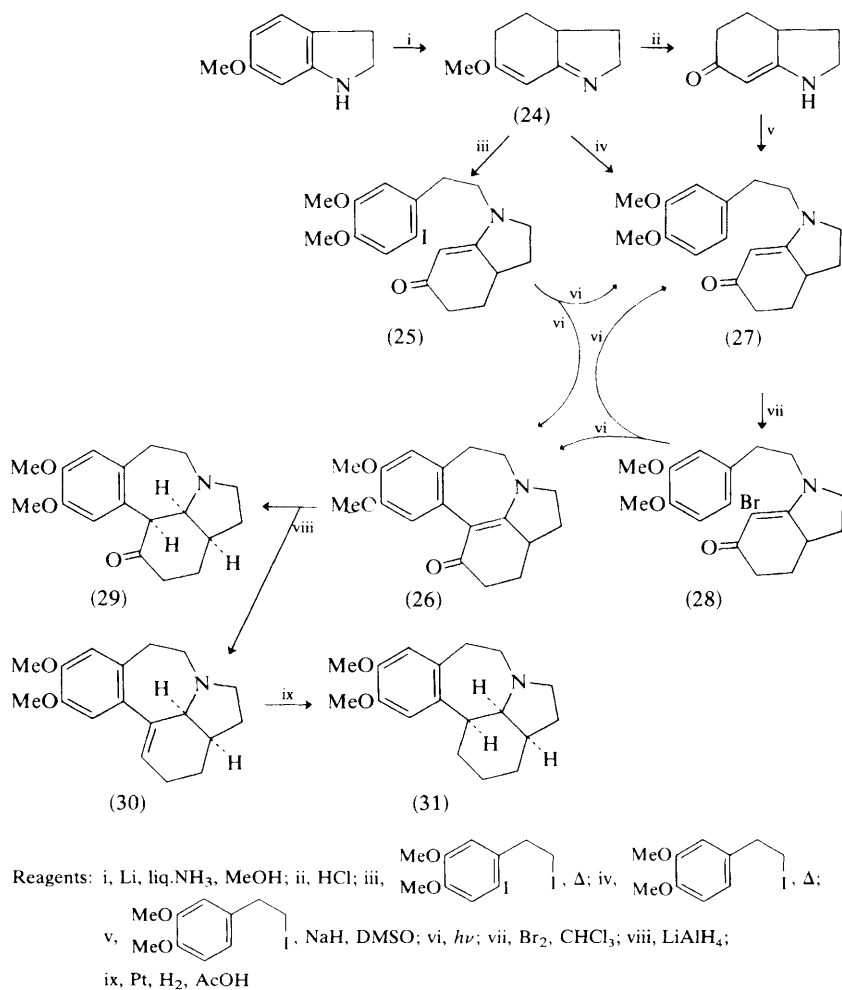
Reagents: i, MeI; ii, HO^- , MeOH or EtOH

Scheme 2

¹⁶ K. Ito and H. Tanaka, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 3301.

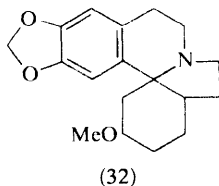


treatment with alkali in methanol or ethanol respectively. A synthesis of 3,2-(16)-dimethoxy-erythrinan-1-(6)-ene (23) has been reported,⁴ following an earlier route developed by Mondon.



Scheme 3

A novel synthesis of hexahydroapoerysopine dimethyl ether has been developed¹⁷ by intramolecular photo-arylation of an enamino-ketone. Following preliminary studies of suitable methods, the iodo-aryl enamino-ketone (25) was synthesised by the route shown in Scheme 3, and irradiated (using a high-pressure mercury lamp) in degassed dioxan containing triethylamine. The major product (50%) was the desired azepine (26), although competitive hydrogen transfer also afforded the photoreduction product (27) (30%). The latter was also prepared from the imino-enol ether (24), and bromination afforded the bromo-enamino-ketone (28); irradiation of this bromo-derivative in acetonitrile also afforded a mixture of the photocyclisation product (26) and the photoreduction product (27). The azepine (26) was reduced with lithium aluminium hydride to give the apoerysopinone (29) (10%) and tetrahydroapoerysopine (30) (63%); hydrogenation of the latter over Adams catalyst in acetic acid then afforded the hexahydroapoerysopine dimethyl ether (31). This material was spectroscopically very similar to the product obtained earlier by acid-catalysed rearrangement of tetrahydroerythraline (32) followed by methylation with diazomethane.



¹⁷ H. Iida, T. Takarai, and C. Kibayashi, *J. Org. Chem.*, 1978, **43**, 975.

1 Introduction

Of general interest to alkaloid chemists are the third volume¹ of the 'Encyclopedia of Alkaloids', and the third volume^{2a} in the series 'The Total Synthesis of Natural Products', which is entirely devoted to alkaloids. The surveys of general methods of alkaloid synthesis by Stevens in this latter volume^{2b} and elsewhere³ include reference to the indole alkaloids, and in particular to the synthetic utility of endocyclic enamines in the construction of the aspidospermine ring system. An account of indole alkaloid synthesis^{2c} is of considerable interest to the indole alkaloid specialist, while a concise survey of indole alkaloids, in the new edition of a standard, comprehensive text on organic chemistry, is useful for the non-specialist.⁴ Reviews of a more restricted scope include one on the use of β -keto-sulphoxides in the synthesis of pyranocarbazoles and pyridocarbazoles,^{5a} and two on the use of iminoketens in the synthesis of quinazolone alkaloids by retro-mass-spectral synthesis.^{5b,c} A thorough survey of the carbazole alkaloids has also appeared during the year under review.⁶

The published literature on antitumour agents from plants, for the period 1974-6, covers a very wide range of natural products, but necessarily includes reference to a number of indole alkaloids, particularly ellipticine, camptothecin, and bisindole alkaloids of the vinblastine group.⁷

2 Simple Alkaloids

Non-tryptamines.—Mukonine (1), from the stem bark of *Murraya koenigii* Spreng., is simply^{8a} the methyl ester of mukoeic acid (1-methoxycarbazole-3-carboxylic acid), isolated earlier from the same source. A pyranocarbazole

¹ J. S. Glasby, 'Encyclopedia of the Alkaloids', Vol. 3, Plenum Press, New York, 1977.

² (a) 'The Total Synthesis of Natural Products', Vol. 3, ed. J. ApSimon, Wiley-Interscience, New York, 1977; (b) R. V. Stevens, in ref. 2a, pp. 439-554; (c) J. P. Kutney, in ref. 2a, pp. 273-438.

³ R. V. Stevens, *Accounts Chem. Res.*, 1977, **10**, 193.

⁴ K. S. J. Stapleford, 'The Indole Alkaloids', Chap. 9, pp. 63-163, in Vol. IVB of 'Rodd's Chemistry of Carbon Compounds', ed. S. Coffey, Elsevier, Amsterdam, 2nd edn., 1977.

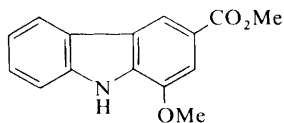
⁵ (a) Y. Oikawa and O. Yonemitsu, *Heterocycles*, 1977, **6**, 1693; (b) T. Kametani, K. Fukumoto, M. Ihara, and C. Van Loc, *Heterocycles*, 1977, **6**, 1741; (c) T. Kametani and K. Fukumoto, *ibid.*, 1977, **7**, 615.

⁶ D. P. Chakraborty, *Fortschr. Chem. Org. Naturstoffe*, 1977, **34**, 299.

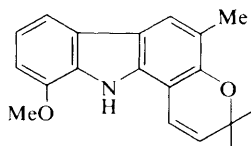
⁷ G. A. Cordell and N. R. Farnsworth, *Lloydia*, 1977, **40**, 1.

⁸ (a) D. P. Chakraborty, P. Bhattacharyya, S. Roy, S. P. Bhattacharyya, and A. K. Biswas, *Phytochemistry*, 1978, **17**, 834; (b) I. Mester, K. Szendrei, and J. Reisch, *Planta Med.*, 1977, **32**, 81; (c) I. Mester and J. Reisch, *Annalen*, 1977, 1725.

alkaloid, Ca 9, isolated^{8b} from *Clausena anisata* (Willd.) Oliv., has now been named mupamine, and has been shown^{8c} by spectroscopic methods to be a methoxygirinimbine of structure (2).

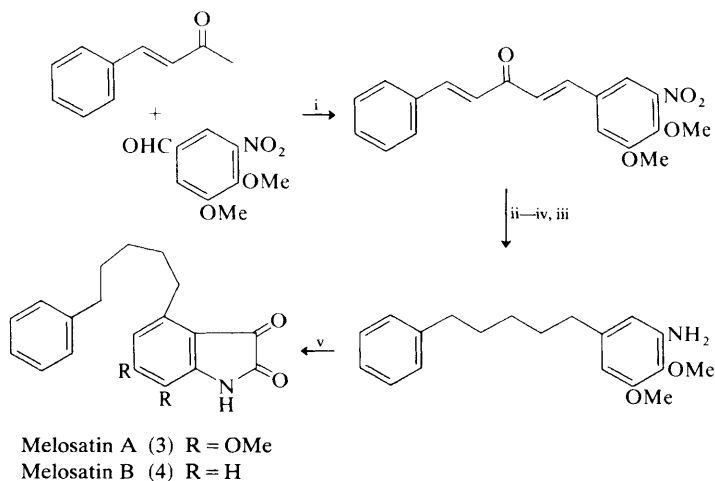


Mukonine (1)



Mupamine (2)

The constituents of the tumorigenic plant *Melochia tomentosa* include 6-methoxy-7,8-methylenedioxy coumarin, three cyclopeptide alkaloids, melochinone (a quinolinone derivative), and two novel phenylpentyl-isatins, melosatins A and B, for which the structures (3) and (4) have been deduced.⁹ The structure of melosatin A was confirmed by synthesis (Scheme 1).



Reagents: i, Base; ii, NaBH₄; iii, H₂, Pd/C; iv, P₂O₅; v, (COCl)₂.

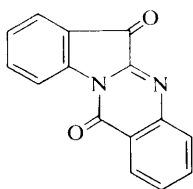
Scheme 1

The structure originally proposed for couroupite A has already been strongly criticised,¹⁰ and has now been proved¹¹ to be incorrect. Couroupite A is in fact 6,12-dihydro-6,12-dioxindolo[2,1,*b*]quinazoline (tryptanthrine) (5), a compound that has been known for some considerable time. Couroupite B, which accompanies couroupite A in *Couroupita guaianensis* Aubl., is simply indirubin.¹¹

⁹ G. J. Kapadia, Y. N. Shukla, B. K. Chowdhury, S. P. Basak, H. M. Fales, and E. A. Sokolski, *J.C.S. Chem. Comm.*, 1977, 535.

¹⁰ J. A. Joule, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1975, Vol. 5, p. 193.

¹¹ J. Bergman, B. Egestad, and J. O. Lindström, *Tetrahedron Letters*, 1977, 2625.



Courouputine A (5)

Non-isoprenoid Tryptamines.—An accidental case of mushroom poisoning led to the detection of the hallucinogenic tryptamine derivative psilocybin in *Gymnopilus validipes* (Pk.) Hesler (fam. Cortinariaceae).¹² Further examination of this genus revealed the presence of psilocybin in *G. luteus* (Pk.) Hesler, *G. spectabilis* (Fr.) A. H. Smith, *G. aeruginosus* (Pk.) Sing., and *G. viridans* Murr. Of these, *G. spectabilis* has previously been reported to be hallucinogenic. These are the first reports of psilocybin in *Gymnopilus* species, although its occurrence in this genus is not universal; in fourteen other *Gymnopilus* species psilocybin could not be detected.¹²

N-Acetyl-L-tryptophan has been found¹³ in *Claviceps purpurea* PRL 1980 cultures. *N*_b,*N*_b-Dimethyltryptophan is one of the constituent amino-acids in the peptide alkaloid nummularine-K (cf. Chapter 15).

The ¹³C n.m.r. spectrum of physostigmine (eserine) has again been discussed,¹⁴ but some of the assignments made differ from those reported earlier; some ¹⁵N n.m.r. data are also included. A new synthesis^{15a} of the eserine ring system takes advantage of the previously reported^{15b} photochemical isomerisation of Reissert compounds, e.g. (6a, b), to the cycloprop[*b*]indole derivatives (7a, b). Vigorous saponification of (7b), followed by methylation, gave the *N*-methyl-lactone (8), which was converted by a Rosenmund synthesis in two stages into (±)-esermethole (9) (Scheme 2).

The isolation of a new β-carboline alkaloid, 1-acetyl-3-methoxycarbonyl-β-carboline (10), from the leaves of *Vestia lycioides* Willd., constitutes the first reported occurrence of a β-carboline derivative in the family Solanaceae.¹⁶ Several simple β-carboline derivatives also occur in the bark and roots of *Ailanthus malabarica* DC. (fam. Simaroubaceae);¹⁷ these include 1-methoxycarbonyl-β-carboline, 4-methoxy-1-vinyl-β-carboline (dehydrocrenatine), crenatidine, crenatine, and four β-carboline derivatives not previously found in Nature, viz. 1-acetyl-β-carboline (11), 1-acetyl-4-methoxy-β-carboline (12), 4,8-dimethoxy-1-vinyl-β-carboline (dehydrocrenatidine) (13), and β-carboline-1-carboxamide (14). Canthine derivatives were not detected in this species. This contrasts with the alkaloid content of *A. altissima*,^{18a} and with that of *A. excelsa*

¹² G. M. Hatfield, L. J. Valdes, and A. H. Smith, *Lloydia*, 1978, **41**, 140.

¹³ H.-J. L. Liang and J. A. Anderson, *Phytochemistry*, 1978, **17**, 597.

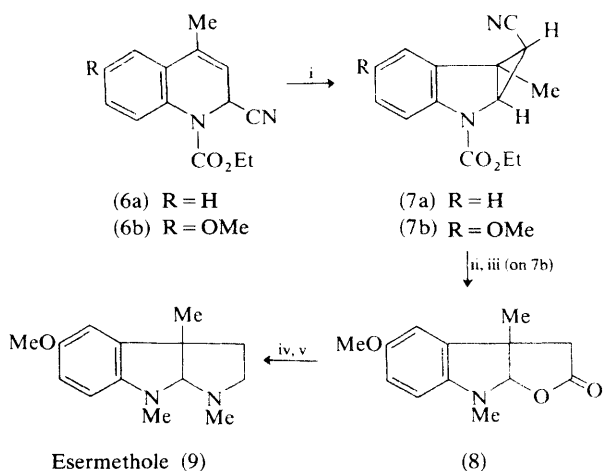
¹⁴ V. I. Stenberg, N. K. Narain, S. P. Singh, R. H. Obenauf, and M. J. Albright, *J. Heterocyclic Chem.*, 1977, **14**, 407.

¹⁵ (a) M. Ikeda, S. Matsugashita, and Y. Tamura, *J.C.S. Perkin I*, 1977, 1770; (b) M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi, and Y. Tamura, *J.C.S. Chem. Comm.*, 1974, 433.

¹⁶ F. Faini, M. Castillo, and R. Torres, *Phytochemistry*, 1978, **17**, 338.

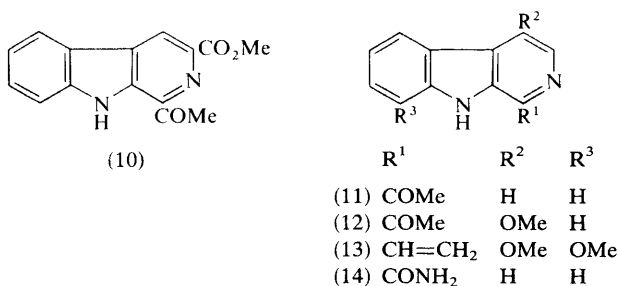
¹⁷ B. S. Joshi, V. N. Kamat, and D. H. Gawad, *Heterocycles*, 1977, **7**, 193.

¹⁸ J. E. Saxton, in 'The Alkaloids', ed. M. F. Grundon (Specialist Periodical Reports), The Chemical Society, London, 1978, Vol. 8; (a) p. 155; (b) p. 160; (c) p. 204; (d) p. 207.

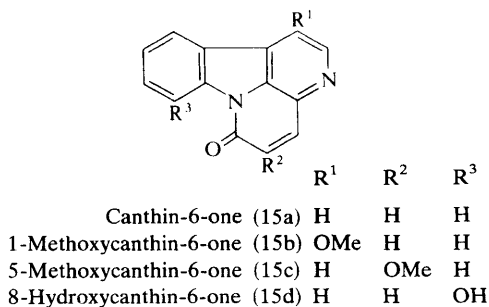


Reagents: i, $h\nu$; ii, 10% KOH, H₂O, EtOH, at 120–130 °C; iii, MeI, MeCOMe; iv, MeNH₂, EtOH, at 50 °C; v, LiAlH₄, THF.

Scheme 2

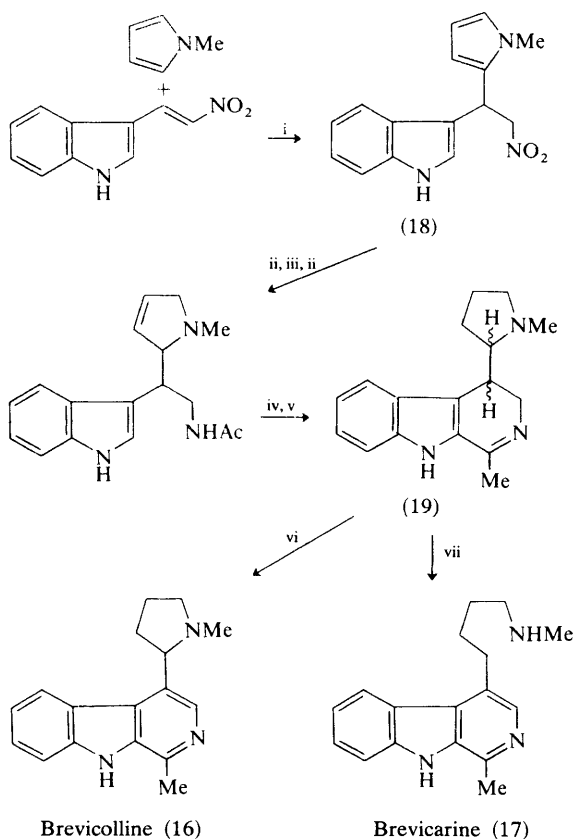


Roxb., the root bark of which contains¹⁹ several antileukaemic simaroubolides, together with four canthine derivatives: canthin-6-one (15a), 1-methoxycanthin-6-one (15b), 5-methoxycanthin-6-one (15c), and 8-hydroxycanthin-6-one (15d). Of these, the first three were already known, but the fourth is new.



¹⁹ G. A. Cordell, M. Ogura, and N. R. Farnsworth, *Lloydia*, 1978, **41**, 166.

The total synthesis of brevicolline (16) and brevicarine (17) by Winterfeldt and his collaborators²⁰ makes ingenious use of the addition of *N*-methylpyrrole to nitrovinylindole, which affords the intermediate (18). Reduction, acetylation, and cyclisation stages then yield the dihydro- β -carboline derivative (19), which on photochemical dehydrogenation gives brevicolline (16). Alternatively, acid-catalysed aromatization of (19) with concomitant opening of the pyrrolidine ring results in the formation of brevicarine (17) (Scheme 3), a stage which may well have its parallel *in vivo*.



Reagents: i, Heat for 48 h under N_2 ; ii, Zn, MeOH, HCl; iii, Ac_2O ; iv, H_2 , Pd/BaSO₄; v, POCl₃, CH₂Cl₂; vi, *hν*, O₂, Rose Bengal, AcOH, CF₃CO₂H; vii, Me₃CCO₂H, CF₃CO₂H, under N_2 for 6 h, at 120 °C.

Scheme 3

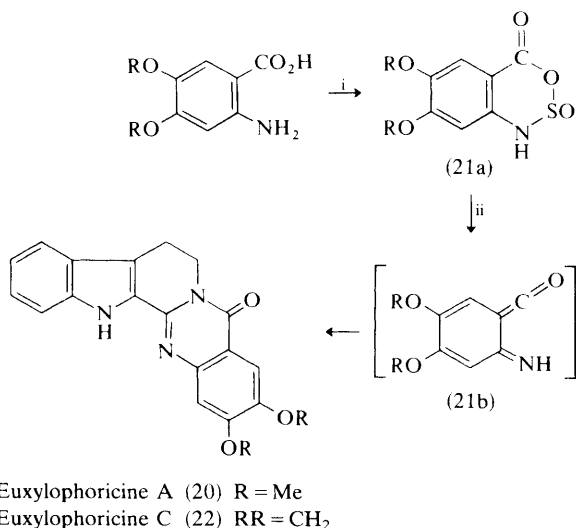
Cis- and *trans*-hexahydrorutaecarpine have been synthesised^{21a} by condensation of 1-oxo-1,2,3,4-tetrahydro- β -carboline with *cis*- and *trans*-hexahydro-

²⁰ W. H. Müller, R. Preuss, and E. Winterfeldt, *Chem. Ber.*, 1977, **110**, 2424.

²¹ (a) G. Tóth, K. Horváth-Dóra, and O. Clauder, *Annalen*, 1977, 529; (b) T. Kametani, C. Van Loc, T. Higa, M. Ihara, and K. Fukumoto, *J.C.S. Perkin I*, 1977, 2347.

anthranilic acid; the flexible conformation of ring C in these isomers explains the apparent anomalies in the proton n.m.r. spectra. Complete assignments of the signals in the ^{13}C n.m.r. spectra of these isomers, and of rutaecarpine, have also been made.

Kametani *et al.*^{21b} have achieved a very neat synthesis of euxylophoricine A (20) by application of their 'retro-mass-spectral' synthesis. Cycloaddition of 3,4-dihydro- β -carboline with the iminoketen (21b), prepared *in situ* by decomposition of the sulphinamide anhydride (21a), gave euxylophoricine A (20) directly. Euxylophoricine C (22) was prepared by an exactly analogous route (Scheme 4).



Reagents: i, SOCl₂, PhH, heat; ii, 3,4-dihydro- β -carboline, PhH, at r.t.

Scheme 4

The structures of the cytotoxic indol-3-yl[13]cytochalasans, chaetoglobosins A—D, were established earlier by X-ray crystal structure determination and chemical correlation,^{22a} and the structures of chaetoglobosins E and F were deduced principally from comparison of their ^1H n.m.r. spectra with those of A—D. Recently²³ a chemical proof of the structures has been provided. Thus, treatment of chaetoglobosin F (23) with hot acetic acid gives rise to chaetoglobosin E (24). Oxidation of F by means of bismuth(III) oxide in acetic acid gives the corresponding α -diketone (chaetoglobosin C) together with an isomer of chaetoglobosin B, now identified as a new constituent of *Chaetomium globosum* and named chaetoglobosin G (25). This structure is consistent with that deduced from the n.m.r. spectrum, which reveals the presence in chaetoglobosin G of

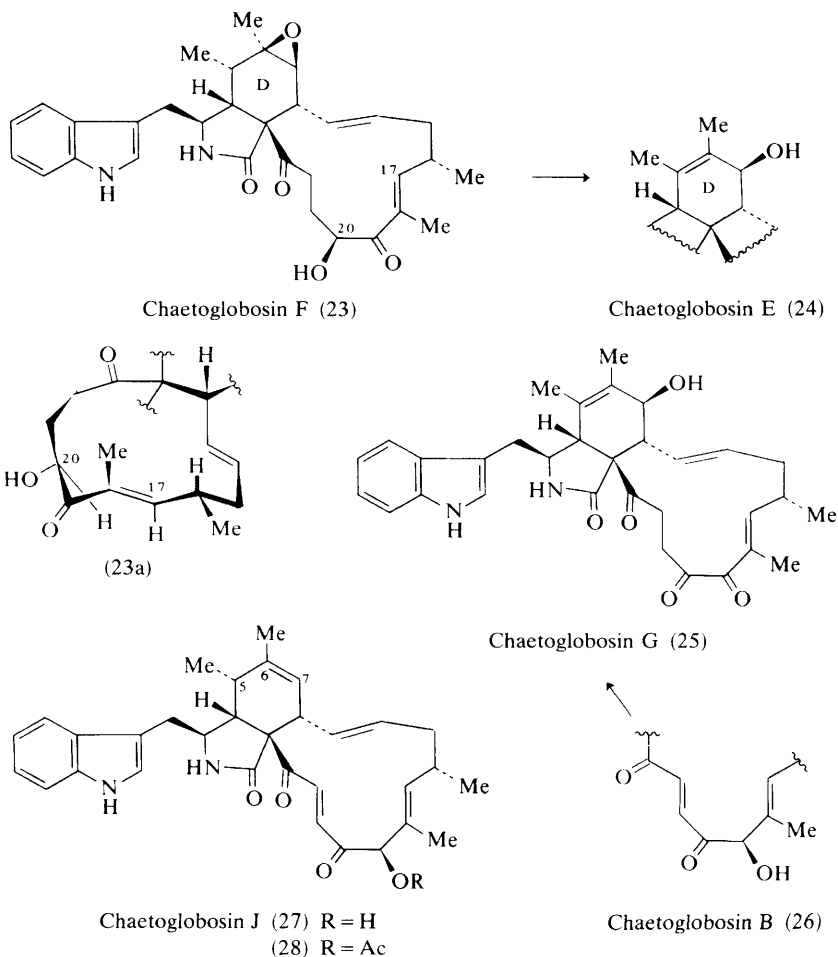
²² J. E. Saxton in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Chemical Society, London, 1977, Vol. 7; (a) p. 190; (b) pp. 195–6; (c) p. 194; (d) p. 209; (e) pp. 207–8; (f) p. 232; (g) p. 243; (h) p. 233; (i) pp. 237–8; (j) pp. 239–240; (k) pp. 243–4.

²³ S. Sekita, K. Yoshihira, S. Natori, and H. Kuwano, *Tetrahedron Letters*, 1977, 2771.

a perhydroisoindolone structural unit (as in B and E) and a substituted 13-membered ring (as in C); this was confirmed by the formation of G by acid-catalysed (AcOH) isomerisation of C, or alternatively by base-catalysed isomerisation of B (26).

The stereochemistry at C-20 in chaetoglobosins E and F becomes apparent from their n.m.r. spectra, which indicate that the conformation of the 13-membered ring is almost the same as in isomers A—D. A nuclear Overhauser effect observed between the olefinic proton at C-17 and the proton attached to C-20 in the spectra of both E and F suggests that C-20 must have the *S* configuration, as illustrated in (23a).

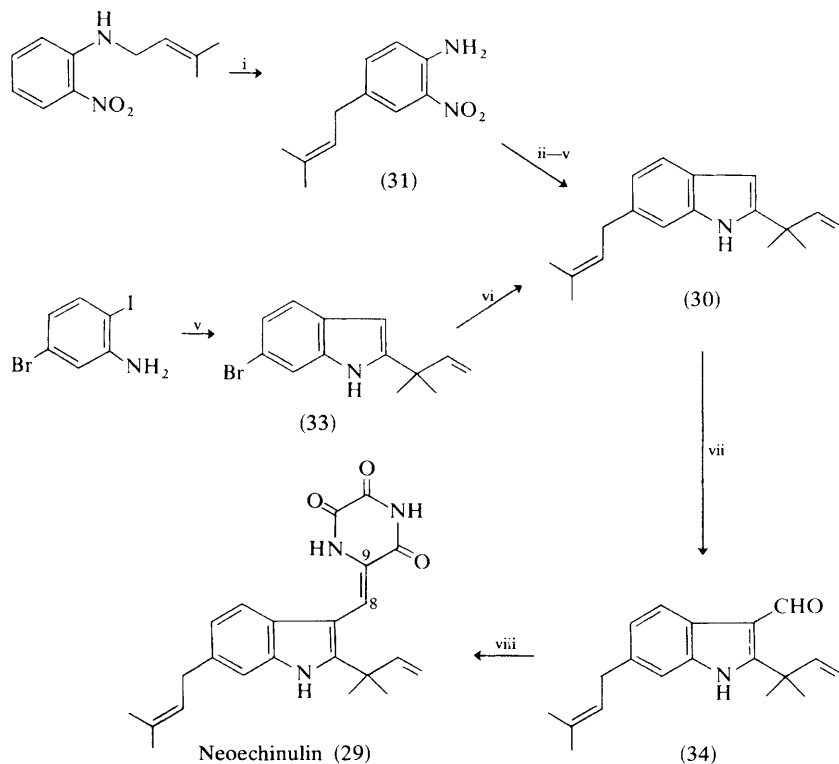
The second new metabolite from *C. globosum*, chaetoglobosin J, has the molecular formula of a deoxy-relative of A—D. Its n.m.r. spectrum indicates that its 13-membered ring is substituted as in chaetoglobosin A [*i.e.* as shown in part-structure (26)], but that it lacks the oxygen at position 7, and the double bond



is at position 6,7 rather than 5,6 (as it is in chaetoglobosins B, E, and G). The structure (27) thus deduced is confirmed²³ by the deoxygenation of chaetoglobosin A monoacetate [ring D as in (23)] with WCl_6 and BuLi , which affords the monoacetate (28) of chaetoglobosin J.

3 Isoprenoid Tryptamine and Tryptophan Alkaloids

Mould Metabolites.—The extensive work of Kishi and his collaborators on the metabolites of *Aspergillus amstelodami* has been published in detail,²⁴ regrettably in a Journal not readily intelligible to most Western readers. This work includes the total synthesis of echinulin,^{24a,b} previously reported in brief,²⁵ and a total synthesis of neocheinulin (29) (Scheme 5).^{24c} The crucial indole derivative



Reagents: i, ZnCl_2 , heat; ii, NaNO_2 , H^+ ; iii, KI ; iv, Fe , AcOH ; v, $\text{CH}_2=\text{CHCMe}_2\text{C}\equiv\text{CCu}$ (32), *N*-methylpiperidine, DMF; vi, $\text{Ni}(\text{CO})_4$, $\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}$, PhH , DMF; vii, POCl_3 , DMF; viii, piperazine-2,3,5-trione, piperidine.

Scheme 5

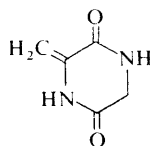
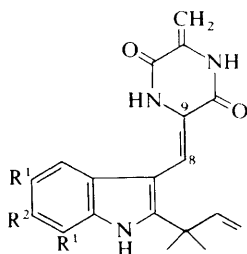
²⁴ (a) S. Inoue, N. Takamatsu, and Y. Kishi, *Yakugaku Zasshi*, 1977, **97**, 553; (b) *ibid.*, p. 558; (c) *ibid.*, p. 564; (d) S. Inoue, K. Hashizume, N. Takamatsu, H. Nagano, and Y. Kishi, *ibid.*, p. 569; (e) S. Inoue, J. Murata, N. Takamatsu, H. Nagano, and Y. Kishi, *ibid.*, p. 576; (f) S. Inoue, N. Takamatsu, K. Hashizume, and Y. Kishi, *ibid.*, p. 582.

²⁵ N. Takamatsu, S. Inoue, and Y. Kishi, *Tetrahedron Letters*, 1971, 4665.

(30) was prepared by two independent routes. The first of these involved the formation of 4-(3,3-dimethylallyl)-2-nitroaniline (31) by an acid-catalysed amino-Claisen rearrangement, followed by conversion into the corresponding iodide *via* the diazonium salt, then reduction, and condensation with the copper acetylide derivative (32). Alternatively, (30) could be obtained, and more efficiently, by the analogous reaction of 2-iodo-5-bromoaniline with (32), followed by direct replacement of bromine in the indole derivative (33) by reaction with the complex formed from nickel carbonyl and dimethylallyl bromide. Formylation of (30) by the Vilsmeier-Haack process, then base-catalysed condensation of the aldehyde (34) with piperazine-2,3,5-trione, completed the synthesis of neoechinulin (29).^{24c}

Of the six nitrogenous metabolites E-6 to E-11 isolated^{24e} by Kishi *et al.*, E-9 is neoechinulin and E-11 is echinulin; E-8 is identical with neoechinulin C (35), and E-10 is neoechinulin B (36). E-7 appears to be new, and is a tetrahydroechinulin of structure (37). These last three metabolites were synthesised by condensation of the appropriate indole-3-aldehyde derivative with methylenediketopiperazine (38) [*cf.* (34) \rightarrow (29)].

The sixth metabolite, aurechinulin (E-6) (39), is identical^{24f} with the cryptoechinulin B of Gatti *et al.*,²⁶ and was synthesised by the route earlier adopted by



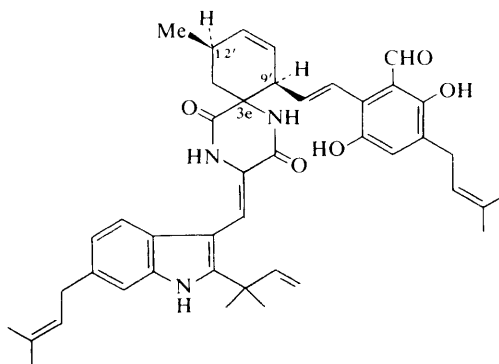
(38)

Neoechinulin C

(= Cryptoechinulin A = E-8) (35) $R^1 = H, R^2 = CH_2CH=CMe_2$

Neoechinulin B (= E-10) (36) $R^1 = R^2 = H$

Metabolite E-7 (37) $R^1 = CH_2CH=CMe_2, R^2 = H$

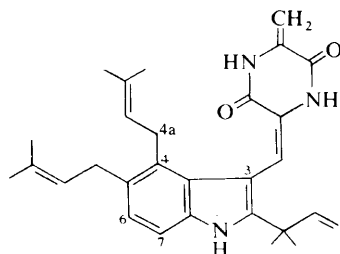


Aurechinulin (= Cryptoechinulin B) (39)

²⁶ G. Gatti, R. Cardillo, C. Fuganti, and D. Ghiringhelli, *J.C.S. Chem. Comm.*, 1976, 435.

the Italian group, *i.e.* by the condensation of auroglaucin with cryptoechinulin A (neoechinulin C). The structure (39) also incorporates the proposed stereochemistry at positions 9' and 12'; the configuration at position 3e is unknown.

The structure of cryptoechinulin G (40), a new metabolite isolated²⁷ from the fungal mat of *Aspergillus ruber* grown on sugar-beet molasses, represents a new departure among the *Aspergillus* metabolites in that the molecule contains two isopentenyl units attached to adjacent positions in the aromatic ring. That there are two adjacent aromatic hydrogen atoms in the molecule seems to be assured by the AB pattern of absorption in the n.m.r. spectrum at δ 7.05 and 7.15 ($J = 8.2$ Hz). Of the two possible structures, (40) is preferred for the following reasons: (a) in the ¹³C n.m.r. spectrum the chemical shift of C-6 and C-7 is characteristic of indoles without substituents at these positions; (b) C-3 absorbs at a slightly higher field than the corresponding atom in metabolites unsubstituted at C-4, presumably owing to shielding by C-4a; (c) the signal arising from the 4a-CH₂ group in the ¹H n.m.r. spectrum is split into two separated components below 15 °C, which indicates a restricted conformational mobility of this group; models indicate that this is only possible in the 4,5-disubstituted isomer (40), in which the methylene group at position 4a is in an extremely crowded position.



Cryptoechinulin G (40)

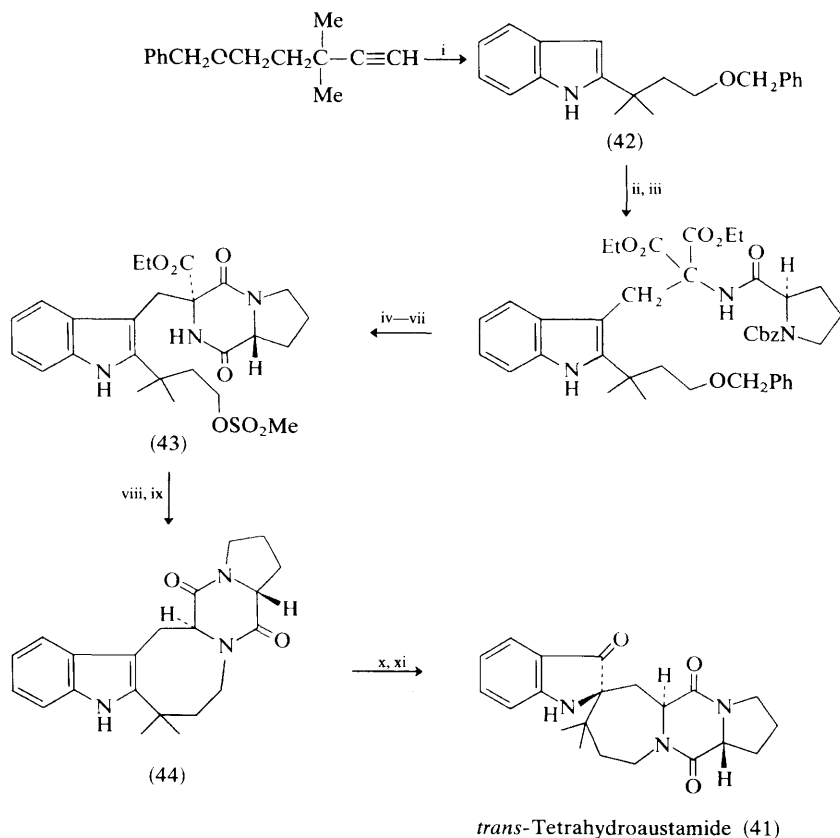
The mass spectra of neoechinulin and echinulin and their hydrogenated derivatives, and of cryptoechinulins A and C, have again been discussed;²⁸ not unexpectedly, the fragmentation patterns are strongly dependent on the nature (single or double) of the 8,9 bond.

The total synthesis²⁹ of *trans*-tetrahydroaustamide (41) (Scheme 6) follows conventional lines from the indole intermediate (42). In principle the dioxopiperazine (43) can cyclise either on the indole nitrogen atom or the dioxopiperazine nitrogen atom. In practice it was found that homogeneous conditions (KOBu^t in THF) favoured cyclisation on the indole nitrogen, but heterogeneous conditions (NaH in benzene) gave the desired product (44). Although L-proline was used in the synthesis, the final product (41) proved to be racemic, and it seems likely that this cyclisation stage [(43) → (44)] was the point at which racemisation occurred. The conversion of (44) into tetrahydroaustamide (41) proceeded with remarkable stereospecificity; since the pinacol-type rearrangement of the hydroxy-indolenine must be stereospecific, the overall stereochemistry of the process

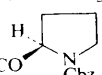
²⁷ G. Gatti, R. Cardillo, and C. Fuganti, *Tetrahedron Letters*, 1978, 2605.

²⁸ A. Selva and P. Traldi, *Biomed. Mass Spectrometry*, 1977, 4, 143.

²⁹ A. J. Hutchison and Y. Kishi, *Tetrahedron Letters*, 1978, 539.



Reagents: i, *o*-IC₆H₄NH₂, DMF, CuI, NEt₃, at 145 °C; ii, CH₂O, Me₂NH;

iii, (EtO₂C)₂CHNH CO , NaOH; iv, hydrogenolysis of *N*-benzyloxycarbonyl

group; v, PhMe, at 110 °C; vi, hydrogenolysis of benzyl ether; vii, MeSO₂Cl, base; viii, NaH, C₆H₆; ix, hydrolysis and decarboxylation; x, *m*-ClC₆H₄CO₃H, CH₂Cl₂ at r.t.; xi, 3M-HCl, EtOH, reflux.

Scheme 6

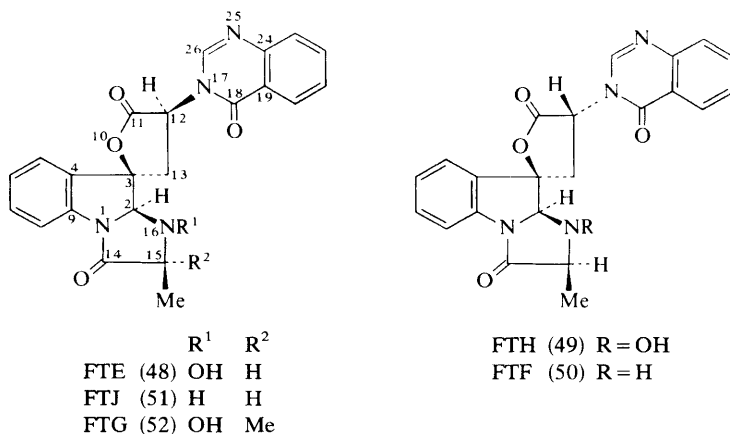
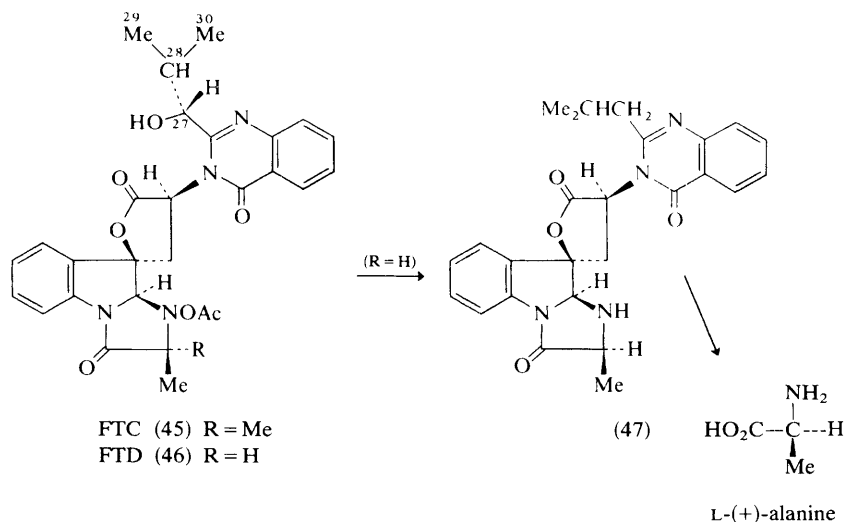
depends on the stereochemistry of the oxidation of (44) to the hydroxy-indolenine, a result which is best rationalised by postulating that (44) adopts a folded conformation in which approach to the β -position of the indole ring on one side is effectively blocked by the eight-membered ring and the dioxopiperazine unit.

The identity of Abe's roquefortine C^{30a} with Scott's roquefortine,^{30b} suggested earlier, has now been established.^{30c}

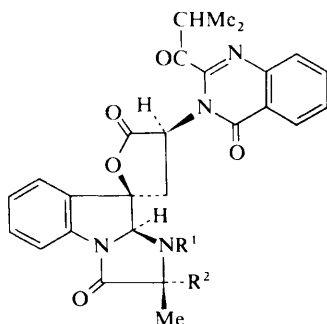
³⁰ (a) S. Ohmomo, T. Sato, T. Utagawa, and M. Abe, *Agric. Biol. Chem.*, 1975, **39**, 1333; (b) P. M. Scott, M. A. Merrien, and J. Polonsky, *Experientia*, 1976, **32**, 140; (c) S. Ohmomo, T. Utagawa, and M. Abe, *Agric. Biol. Chem.*, 1977, **41**, 2097.

Details of the elucidation of the structure and stereochemistry of tryptoquivalines C—H^{31a} have been published;^{31b,c} similar details are also included for two new metabolites of *Aspergillus fumigatus*, tryptoquivalines I and J.^{31c}

The *S* configuration at C-15 in isotryptoquivaline (FTC, now renamed tryptoquivaline C) (45) and norisotryptoquivaline (FTD, now renamed tryptoquivaline D) (46) was earlier assumed on the basis of the probable biogenetic derivation of this carbon atom from C-2 in L-alanine. This assumption has now^{31b} been proved to be correct by reduction of tryptoquivaline D (46) by means of zinc and acetic acid to the deacetoxy-deoxy-compound (47), which on hydrolysis with 6M hydrochloric acid released L-(+)-alanine.^{31b}



³¹ (a) M. Yamazaki, H. Fujimoto, and E. Okuyama, *Tetrahedron Letters*, 1976, 2861; (b) *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 2554; (c) *ibid.*, 1978, **26**, 111.



	R ¹	R ²
Nortryptoquivalone (53)	OH	H
FTI (54)	OH	Me
Deoxynortryptoquivalone (55)	H	H

Tryptoquivaline E (FTE), like tryptoquivalines C and D, is dextrorotatory and exhibits a positive Cotton effect in its o.r.d. spectrum. These observations, together with the similarity of the n.m.r. patterns owing to the three-proton systems at positions 12 and 13 in FTC, FTD, and FTE, strongly suggest that all three metabolites have the same stereochemistry. Hence the complete stereochemistry proposed for FTE is as shown in (48). FTH, the laevorotatory C-12 epimer of FTE, can be obtained by epimerization of FTE in the presence of dilute alkali, and thus has the stereochemistry shown in (49); this facile isomerization indicates that FTH may well be an artefact.^{31c}

Tryptoquivaline F (FTF) exhibits u.v. and i.r. spectra very similar to those of FTE and FTH, but lacks one oxygen atom in the molecule, and behaves as a secondary amine. Hence FTF is probably a 16-deoxy-FTE or (FTH); on the basis of its laevorotation it is concluded to be a deoxy-FTH, of structure (50). FTJ, a new metabolite, is readily converted into FTF by dilute alkali, and therefore has the stereochemistry shown in (51); again, the ease of this epimerization suggests that FTF is probably an artefact.

FTG exhibits very similar spectra to those of FTE, except that the n.m.r. signals owing to the $\text{Me}\underset{\text{C}}{\text{CH}}\text{Me}$ group are replaced by two singlets arising from a gem-dimethyl group. These facts, together with its strong dextrorotation, lead to the conclusion that FTG is (52).

The second new metabolite, tryptoquivaline I (FTI), exhibits similar i.r. and n.m.r. spectra to FTC, but its u.v. absorption is different, and shows a greater resemblance to that of the tryptoquivalones [*e.g.* nortryptoquivalone, (53)]. The presence of an isobutyryl group in FTI is also suggested by the absence of an absorption owing to a proton at C-27, and the downfield position of the multiplet owing to the proton at C-28 compared with the position of the analogous signal in the n.m.r. spectrum of FTC. FTI is thus regarded as (54), its strong dextrorotatory power indicating that it belongs to the same stereochemical series as FTC. In view of the constancy of the configuration at C-15 in this series [*i.e.* all the metabolites

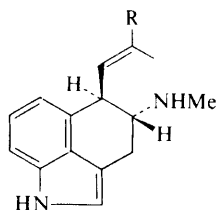
are presumed to arise from L-(+)-alanine] the complete stereochemistries of nortryptoqualone and deoxynortryptoqualone are as given in (53) and (55).^{31c}

Ergot Alkaloids.—A supplement to *Pharmacology* that is devoted to the ergot alkaloids is introduced by reviews on the history^{32a} and the general pharmacology^{32b} of this group of alkaloids. A third review^{32c} is concerned with the ergolines as potential inhibitors of prolactin and of mammary tumours.

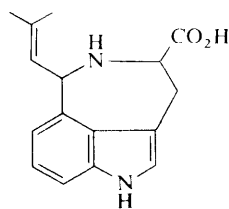
The seeds of *Ipomoea violacea*, variety 'Pearly gates', were earlier reported³³ to contain an ergoline acid of unknown constitution, which proves³⁴ to be chanoclavine-I acid (56), since reduction (LiAlH_4) gives rise to chanoclavine-I (57); conversely, oxidation of chanoclavine-I by means of manganese dioxide gives the related aldehyde, which, on further oxidation by manganese dioxide in methanol in the presence of cyanide ion, affords chanoclavine-I acid methyl ester directly.³⁴

It has again been demonstrated that the ergot fungus which grows parasitically on Bajra [pearl millet, *Pennisetum typhoides* (Burm.) Stapf and Hubbard] elaborates only clavine alkaloids; none of the therapeutically important peptide alkaloids appears to be present.³⁵ The ergot species involved was identified as *Claviceps microcephala* (Wallr.) Tul. (*C. fusiformis* Loveless), and was apparently responsible for epidemics of ergotism in Bajra-growing areas in 1964. The alkaloids identified following saprophytic culture of the sclerotia were elymoclavine (major alkaloid), chanoclavine, festuclavine, and agroclavine.

Details of the elucidation of the revised structure of clavicipitic acid, which exists as two diastereoisomers of structure (58), have now been published.³⁶



Chanoclavine-I acid (56) R = CO_2H
Chanoclavine-I (57) R = CH_2OH



Clavicipitic acid (58)

As suggested earlier,^{22b} roquefortines A and B, (59) and (60), are identical with isofumigaclavines A and B.^{37a} The structure of isofumigaclavine A (59) has been confirmed by X-ray crystal structure analysis,^{37b} and since isofumigaclavine B (60) is one of the products of hydroboration/oxidation of agroclavine (the other product is fumigaclavine B), the structures (59) and (60) must also represent the absolute configurations.

³² (a) A. Hofmann, *Pharmacology*, 1978, 16, Suppl. 1, p. 1; (b) J. R. Boissier, *ibid.*, p. 12; (c) J. M. Cassady and H. G. Floss, *Lloydia*, 1977, 40, 90.

³³ W. A. Taber, L. C. Vining, and R. A. Heacock, *Phytochemistry*, 1963, 2, 65.

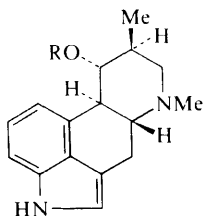
³⁴ T. C. Choong and H. R. Shough, *Tetrahedron Letters*, 1977, 3137.

³⁵ H. N. Singh and A. Husain, *Indian J. Exp. Biol.*, 1977, 15, 585.

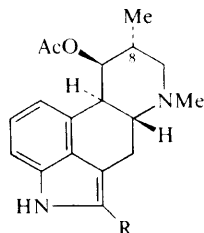
³⁶ G. S. King, E. S. Waight, P. G. Mantle, and C. A. Szczyrbak, *J.C.S. Perkin I*, 1977, 2099.

³⁷ (a) J. Clardy, personal communication to authors of ref. 30c; (b) B. Arnoux, M. A. Merrien, C. Pascard, J. Polonsky, and P. M. Scott, *J. Chem. Res. (S)*, 1978, 210; *J. Chem. Res. (M)*, 1978, 2829.

Aspergillus fumigatus is one of the predominant fungi found on moulded corn silage, and is responsible for acute toxic effects in cattle fed on it. Several toxic metabolites have now been isolated from the fungus extracted from this source; these include metabolite TR-2 and verruculogen,^{22c} and three other tremorgens of unknown constitution.^{38a} Two basic constituents also isolated are fumigaclavine A (61) and fumigaclavine C (62), the latter of which is probably identical with the metabolite of the same name and isolated from the same fungus in 1962 by Yamano *et al.*^{38b} The structure of fumigaclavine C (62) was established by single-crystal X-ray diffraction, and proves to be fumigaclavine A with an isopentenyl group attached to position 2 of the indole nucleus. The fact that the two alkaloids have identical stereochemical arrangements in ring D is clearly shown by their ¹³C n.m.r. spectra. Since fumigaclavine A is readily saponified to fumigaclavine B, which has been shown^{38c} to have axial groups at positions 8 and 9, the complete stereochemistries of fumigaclavines A and C are as shown in (61) and (62).

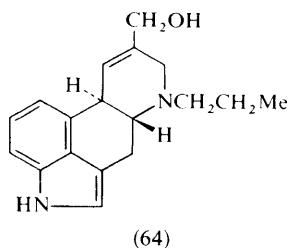
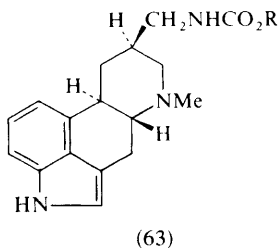


Roquefortine A (59) R = Ac
Roquefortine B (60) R = H



Fumigaclavine A (61) R = H
Fumigaclavine C (62) R = CMe₂CH=CH₂

New ergoline derivatives prepared for pharmacological evaluation include several urethanes of general formula (63),³⁹ several *N*-alkylated *N*-norelymoclavines,⁴⁰ of which the *N*-propyl derivative (64) proved to be as active as the most potent prolactin inhibitor reported to date, further examples of modified dihydrolysergic acid derivatives in which a substituent has been introduced into

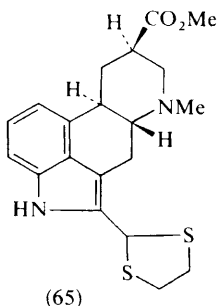


³⁸ (a) R. J. Cole, J. W. Kirksey, J. W. Dorner, D. M. Wilson, J. C. Johnson, A. N. Johnson, D. M. Bedell, J. P. Springer, K. K. Chexal, J. C. Clardy, and R. H. Cox, *J. Agric. Food Chem.*, 1977, **25**, 826; (b) T. Yamano, K. Kishino, S. Yamatodani, and M. Abe, *Takeda Kenkyusho Nempo*, 1962, **21**, 95 (*Chem. Abs.*, 1963, **59**, 3099); (c) N. J. Bach, H. E. Boaz, E. C. Kornfeld, C. J. Chang, H. G. Floss, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, 1974, **39**, 1272.

³⁹ J. Křepelka, M. Šeda, and M. Semonský, *Coll. Czech. Chem. Comm.*, 1977, **42**, 1886.

⁴⁰ A. M. Crider, J. M. Robinson, H. G. Floss, J. M. Cassidy, and J. A. Clemens, *J. Medicin. Chem.*, 1977, **20**, 1473.

position 2 of the indole ring,⁴¹ e.g. (65), and a series of *N*-alkyl derivatives of *N*-norlysergic acid diethylamide.^{42a} The preparation of this last group of compounds involved the initial removal of the *N*-methyl group by the von Braun reaction – a clear contravention of the general rule that in the von Braun degradation an *N*-allyl group is cleaved more readily than an *N*-methyl group.



Further studies of the von Braun reaction with 8-isoLSD and the dihydro-derivatives of LSD and 8-isoLSD^{42b} showed that the reaction was completely or almost completely inhibited in those isomers that possessed an axial substituent at C-8 in a 1,3-diaxial relationship with respect to the lone electrons on the basic nitrogen atom; otherwise the reaction with cyanogen bromide proceeded smoothly.

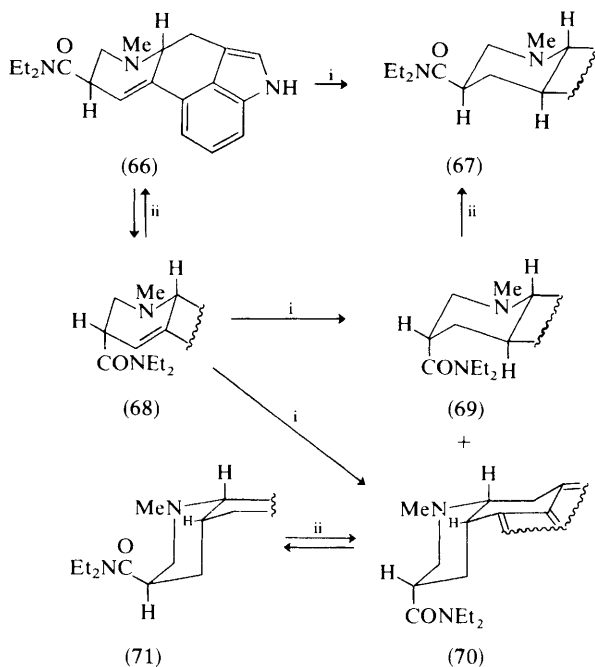
In connection with this investigation, the reduction of lysergic acid diethylamide, isolysergic acid diethylamide, and agroclavine was re-investigated.⁴³ Lysergic acid diethylamide (66), predictably, gives dihydrolysergic acid diethylamide-I (67) by addition of hydrogen at the unhindered face of the double bond. Isolysergic acid diethylamide (68), however, is hydrogenated much more slowly and gives some dihydroisolysergic acid diethylamide-I (69) by addition of hydrogen at the relatively hindered α -face, together with (mainly) dihydroisolysergic acid diethylamide-II (70). The fourth stereoisomer, dihydrolysergic acid diethylamide-II (71), is not obtainable by hydrogenation of LSD (66), but is formed as the minor component in the base-catalysed equilibration of dihydroisolysergic acid diethylamide-II (70) (Scheme 7).⁴³

The reduction of agroclavine (72) by means of sodium in butanol gives a mixture of lysergine (73), festuclavine (74), pyroclavine (75), and costaclavine (76). Hydrogenation of agroclavine (72) gives festuclavine (74) and pyroclavine (75) only; hence these products must have a *trans* C/D ring junction. Since hydrogenation of lysergine (73) gives festuclavine, the latter must have a β -methyl group at C-8, and consequently pyroclavine (75) must be the isomer with an α -methyl group. Costaclavine (76) must then have a *cis* C/D ring junction, and since reduction (with Na and BuOH) of lysergine (73) gives costaclavine as one product (the other is festuclavine), costaclavine (76) must have a β -methyl group at C-8 (Scheme 8).⁴³

⁴¹ J. Křepelka, M. Beran, and M. Semonský, *Coll. Czech. Chem. Comm.*, 1977, **42**, 2953.

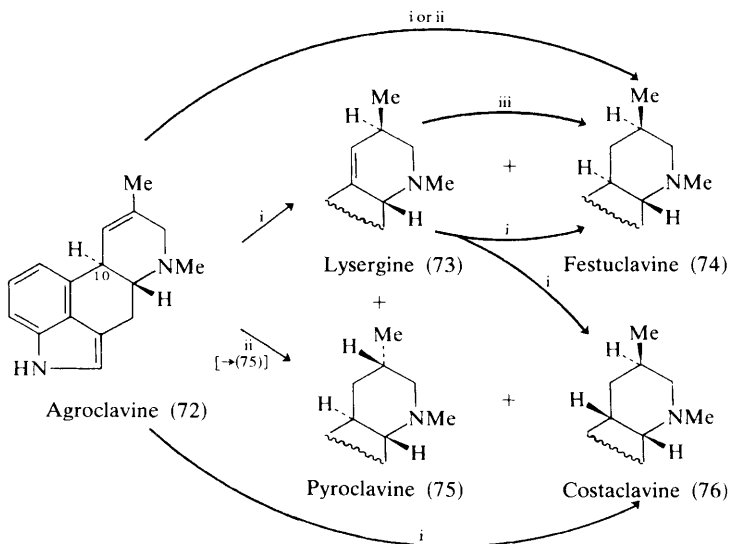
⁴² (a) T. Niwaguchi, Y. Nakahara, and H. Ishii, *Yakugaku Zasshi*, 1976, **96**, 673; (b) Y. Nakahara, T. Niwaguchi, and H. Ishii, *Tetrahedron*, 1977, **33**, 1591.

⁴³ Y. Nakahara, T. Niwaguchi, and H. Ishii, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 1756.



Reagents: i, H₂, 5% Pd/C, MeOH, 1 atm, at r.t.; ii, base.

Scheme 7



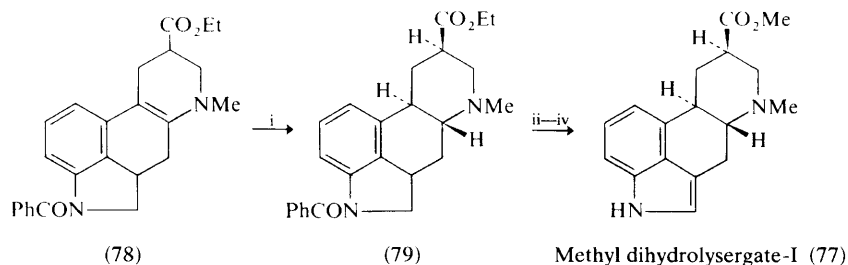
Reagents: i, Na, BuOH; ii, H₂, Pt; iii, H₂, Pd/C.

Scheme 8

The optical rotatory dispersion spectra of these alkaloids have also been discussed, from which it appears that the sign of the Cotton effect is dependent on the configuration at C-10. Those compounds that have α -hydrogen at this position, *i.e.* a *trans* C/D ring junction, [*e.g.* (67), (69), and (74)] exhibit a weak, negative Cotton effect, while those with β -hydrogen at C-10, *i.e.* a *cis* C/D ring junction, [*e.g.* (70), (71), and (76)] exhibit a strong, positive Cotton effect.⁴³

The conformations of the dihydrolysergic acid amides and their 10-methoxy-derivatives have been inferred from a study of the chemical shifts of the amide hydrogen atoms and their temperature dependence; complete ¹³C n.m.r. data for these compounds have also been given.⁴⁴

A new total synthesis⁴⁰ of (\pm)-methyl dihydrolysergate-I (77) makes use of the tetracyclic intermediate (78), prepared earlier.⁴⁵ Whereas platinum-catalysed hydrogenation of (78) results in a *cis* C/D product, and hence affords⁴⁵ a synthesis of (\pm)-methyl dihydroisolysergate-II, the reduction of (78) by sodium cyanoborohydride gives a product (79) containing a *trans* C/D ring junction, which therefore enables the synthesis of (\pm)-methyl dihydrolysergate-I to be completed (Scheme 9).⁴⁰



Reagents: i, NaBH₃CN; ii, KOH, MeOH; iii, MeOH, HCl; iv, MnO₂.

Scheme 9

In further investigations⁴⁶ into the alkaloids produced by Argentinian *Claviceps purpurea* growing parasitically on *Spartina alterniflora*^{18b} it has been demonstrated that α -ergocryptine constitutes 75% of the comparatively high total alkaloid content (0.95—1.15%); in consequence the Argentinian ergot is claimed to be the best natural source of this alkaloid reported to date.⁴⁶ A better pharmaceutical grade of ergot is also claimed⁴⁷ as the result of the cultivation of ergot on *Triticale* (wheat-rye hybrid) rather than on rye. A significantly higher total alkaloid content (0.69%) and higher ergotamine content (0.434%) were reported in the ergot thus cultivated.

The separation of ergot alkaloids by h.p.l.c. is recommended⁴⁸ as an analytical procedure, since it is rapid, accurate, and reproducible; the method was illus-

⁴⁴ L. Zetta and G. Gatti, *Org. Magn. Resonance*, 1977, **9**, 218.

⁴⁵ J. M. Cassady, G. S. Li, E. B. Spitzner, H. G. Floss, and J. A. Clemens, *J. Medicin. Chem.*, 1974, **17**, 300.

⁴⁶ G. E. Ferraro, S. L. Debenedetti, and J. D. Coussio, *Lloydia*, 1978, **41**, 179.

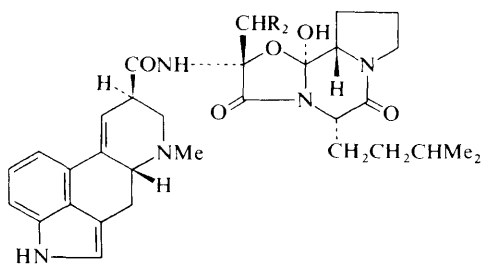
⁴⁷ K. K. Janardhanan and A. Husain, *Indian J. Exp. Biol.*, 1977, **15**, 501.

⁴⁸ (a) V. Hartmann, M. Rödiger, W. Ableidinger, and H. Bethke, *J. Pharm. Sci.*, 1978, **67**, 98; (b) L. Szepesy, I. Fehér, G. Szepesi, and M. Gazdag, *J. Chromatog.*, 1978, **149**, 271.

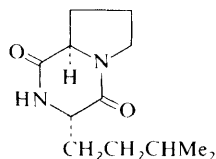
trated by the efficient separation of dihydroergocristine, dihydroergocornine, dihydro- α -ergocryptine, and dihydro- β -ergocryptine (the constituents of dihydroergotoxine).^{48a}

The preparation of bromocryptine (2-bromo- α -ergocryptine), by the bromination of pure α -ergocryptine by means of *N*-bromosuccinimide, has been described, together with details of 2-bromo- α -ergocryptine methanesulphonate, the clinically useful prolactin inhibitor.⁴⁹

Ergohexine (80) and ergoheptine (81) are two new ergot alkaloids which contain L-homoleucine in the peptide unit, an amino-acid not previously encountered in the natural alkaloids; the diketopiperazine derivative (82) containing the same amino-acid was also isolated from the fungus.⁵⁰

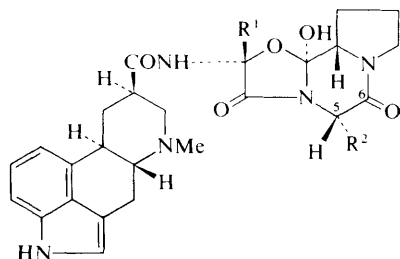


Ergohexine (80) R = H
Ergoheptine (81) R = Me



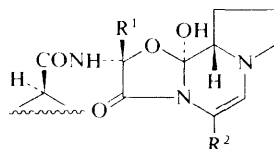
(82)

A group of products in which the cyclitol unit in the peptide alkaloids has been modified have been obtained⁵¹ by the reduction of the alkaloids by means of lithium in liquid ammonia at -35°C . The products were 6-dihydrodeoxy-5,6-dehydro-derivatives; e.g., dihydroergotamine (83) and its analogues (84) and (85) gave the enamines of structure (86)—(88); neither the indole ring nor the angular



R¹ R²

Dihydroergotamine (83) Me CH₂Ph
Dihydroergocryptine (84) CHMe₂ CH₂CHMe₂
Dihydroergocristine (85) CHMe₂ CH₂Ph



R¹ R²

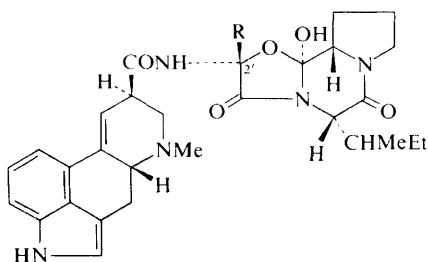
(86) Me CH₂Ph
(87) CHMe₂ CH₂CHMe₂
(88) CHMe₂ CH₂Ph

⁴⁹ H. R. Schneider, P. A. Stadler, P. Stuetz, F. Troxler, and J. Seres, *Experientia*, 1977, **33**, 1412.

⁵⁰ S. Ohmomo and M. Abe, *Nippon Nogei Kagaku Kaishi*, 1976, **50**, 543 (*Chem. Abs.*, 1977, **86**, 190 303).

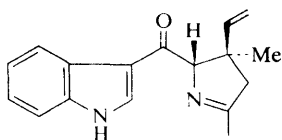
⁵¹ L. Bernardi and G. Bosisio, *Experientia*, 1977, **33**, 704.

cyclitol hydroxy-group was affected. β -Ergosine (89) and β -ergoptine (90), the methyl and ethyl analogues of the natural alkaloid β -ergocryptine (91), have been synthesised by methods previously used for the synthesis of the natural alkaloids; the pharmacological activities of (89) and (90) have also been reported.⁵²

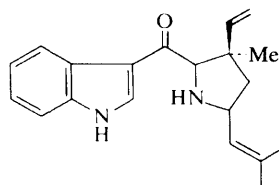


β -Ergosine (89) R = Me
 β -Ergoptine (90) R = Et
 β -Ergocryptine (91) R = CHMe₂

Monoterpenoid Alkaloids. — *Corynantheine* – *Heteroyohimbine* – *Yohimbine Group*, and *Related Oxindoles*. Details of the *X*-ray crystal structure determination of borreline (92) have now been published,⁵³ and the species from which it was isolated has been identified as *Borreria capitata* R. et P.⁵⁴ A second alkaloid from this species, borrecapine (93), has a similar structure but, in place of the second methyl group in borreline, borrecapine contains an isobutenyl group which completes the monoterpenoid unit of the non-tryptamine part of the molecule.



Borreline (92)



Borrecapine (93)

Two new alkaloids which contain a monoterpene unit that is not derived from loganin have been isolated in extremely small amounts from *Aristotelia chilensis* (Mol.) Stuntz.⁵⁵ The structures of both alkaloids were determined by the *X*-ray method; aristotelinine (94) has the constitution of the hydroxy-indolenine analogue of a hydroxy-aristoteline; in view of the comparative ease of oxidation of many indoles and the minute amount of alkaloid isolated it seems possible that aristoteline may be an artefact derived from a hydroxy-aristoteline that is as yet undetected in the plant. The second alkaloid, aristone (95), can be derived from

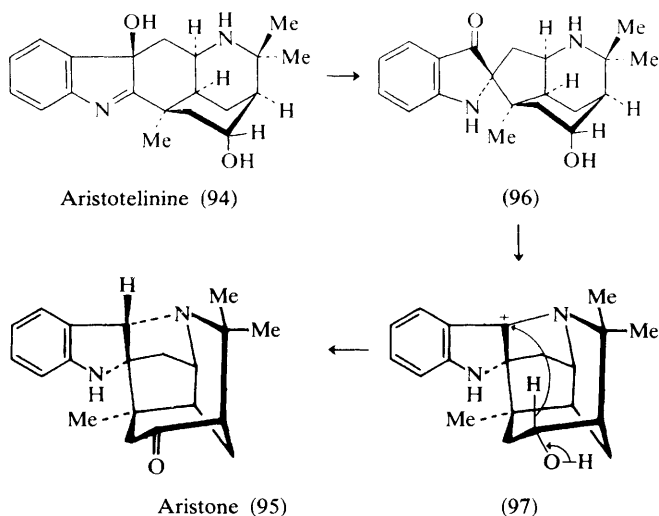
⁵² P. A. Stadler, P. Stuetz, and E. Stürmer, *Experientia*, 1977, **33**, 1552.

⁵³ M. Danak and C. Riche, *Acta Cryst.*, 1977, **B33**, 3415.

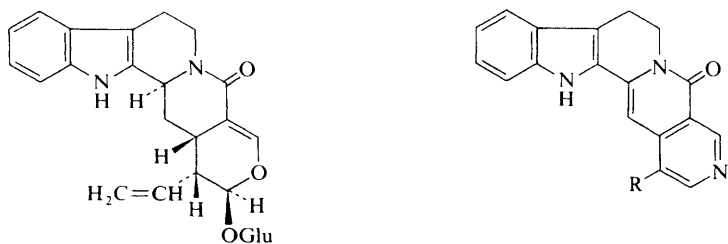
⁵⁴ A. Jössang, J. L. Pousset, H. Jacquemin, and A. Cavé, *Tetrahedron Letters*, 1977, 4317.

⁵⁵ M. Bittner, M. Silva, E. M. Gopalakrishna, W. H. Watson, V. Zabel, S. A. Matlin, and P. G. Sammes, *J.C.S. Chem. Comm.*, 1978, 79.

aristotelinine (94) by rearrangement to the related indoxyl derivative (96), which is a hydroxy-aristotelone, followed by interaction of N₆ with the indoxyl carbonyl group, and then intramolecular hydride transfer in the carbonium ion (97) thus generated.



Strictosidine (isovincoside) lactam (98) has been isolated from the root bark,^{56a} and the heartwood and bark,^{56b} of *Nauclea latifolia* Sm. In view of the ease with which derivatives of (98) can be converted into compounds containing a pyridinoid ring E [e.g. dihydrovincoside lactam → dihydroangustine (99a)], the opinion has again been expressed^{56b} that angustine (99b) and its congeners (99c)–(99e) isolated from *N. latifolia* may be artefacts, since ammonia was



Strictosidine (Isovincoside) lactam (98)

Dihydroangustine (99a) R = CH₂CH₃

Angustine (99b) R = CH=CH₂

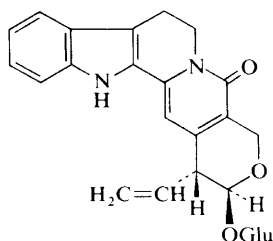
(99c) R = CH(OH)Me

(99d) R = H

(99e) R = Ac

employed in the extraction process. This view is reinforced by the isolation of the pyridone (100) from a solution of strictosidine lactam that had been allowed to

⁵⁶ (a) F. Hotellier, P. Delaveau, and J. L. Pouset, *Plant. Med. Phytother.*, 1977, **11**, 106; (b) R. T. Brown, C. L. Chapple, and A. G. Lashford, *Phytochemistry*, 1977, **16**, 1619.

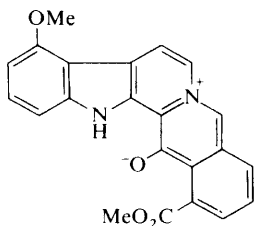


(100)

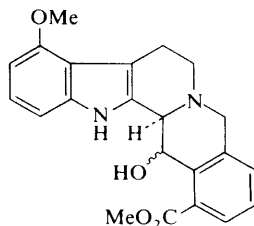
stand in air; obviously the oxidation stage required in the formation of (99b)—(99e) proceeds with considerable facility.

The occurrence of ajmalicine and lochnericine in the roots of *Catharanthus roseus* has again been noted;^{57a} the same two alkaloids are biosynthesised, together with catharanthine, vindoline, and vinblastine, in the callus tissue culture of the same species.^{57b} Ervine (raunicine) occurs in the aerial parts of *Vinca major*,^{57c} and tetrahydroalstonine in the seeds of *Amsonia elliptica*^{57d} and in the leaves of *Hunteria elliptica* (Stapf.) Pichon.⁵⁸

Anhydroalstonatine, a new alkaloid from the bark of *Alstonia venenata*,⁵⁹ is a bright red, zwitterionic indolic base which is tentatively formulated as (101), i.e. as a 9-methoxy-5,6-dehydro-neo-oxygambirtannine. In consonance with this structure, reduction of anhydroalstonatine by means of sodium borohydride gave a tetrahydro- β -carboline base, regarded as (102); the positions of the methoxy and methoxycarbonyl groups in (101) and (102) are based principally on the presence of two ABX systems of aromatic protons in the n.m.r. spectra of both compounds, and on the u.v. absorption of (102).



Anhydroalstonatine (101)



(102)

The constituents of *Uncaria orientalis* Guill., from the New Hebrides, have been investigated, apparently for the first time.⁶⁰ The aerial parts have so far yielded five oxindole alkaloids: (–)-mitraphylline, uncarine E (isopteropodine), isomitraphylline, isorhynchophylline, and rhynchophylline. Geissoschizine

⁵⁷ (a) A. Cuellar and H. O. Tejera, *Rev. Cubana Farm.*, 1976, **10**, 3 (*Chem. Abs.*, 1977, **86**, 185 876); (b) T. I. Andreeva and L. N. Bereznegovskaya, *Khim. prirod. Soedinenii*, 1977, 429 (*Chem. Abs.*, 1977, **87**, 130 470); (c) L. I. Il'yashenko, V. M. Malikov, M. R. Yagudaev, and S. Yu. Yunusov, *ibid.*, p. 382 (*Chem. Abs.*, 1978, **88**, 47 454); (d) N. Aimi, Y. Asada, S. Sakai, and J. Haginiwa, *Chem. and Pharm. Bull. (Japan)*, 1978, **26**, 1182.

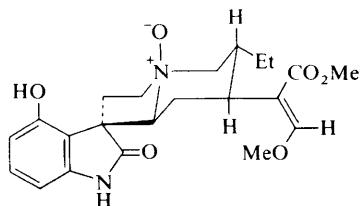
⁵⁸ A.-M. Morfaux, J. Vercauteren, J. Kerharo, L. Le Men-Olivier, and J. Le Men, *Phytochemistry*, 1978, **17**, 167.

⁵⁹ A. Chatterjee and S. Mukhopadhyay, *Indian J. Chem., Sect. B*, 1977, **15**, 183.

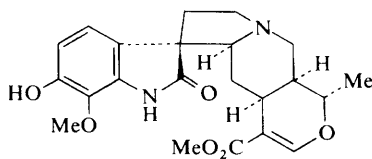
⁶⁰ G. Croquelois, C. Miet, J. Poisson, and T. Sévenet, *Ann. pharm. franc.*, 1977, **35**, 417.

methyl ether and akuammigine have been recognised⁶¹ among the minor alkaloids of *Uncaria rhynchophylla*.

Two *N*-oxides, one with a *trans* C/D ring junction and the other with a *cis* C/D ring junction, have been prepared from rotundifoline;⁶² previously it had been assumed that such *N*-oxides would be inaccessible by the simple oxidation of rotundifoline, since the non-phenolic behaviour of the alkaloid is indicative of a strong hydrogen bond between N_b and the phenolic hydroxy-group. One of these *N*-oxides, *anti*-rotundifoline *N*-oxide (103), is identical with a polar oxindole alkaloid of *Mitragyna rubrostipulata* (Schum.) Havil.



anti-Rotundifoline *N*-oxide (103)



Vinerinine (104)

The structure and stereochemistry of vinerinine have now been defined⁶³ as (104) by n.m.r. analysis of vinerinine and its 10-deuteriated derivative. The structure (104) is that of an *O*-demethylmajdine, but the preparation of majdine by methylation of vinerinine appears not to have been recorded. A complete listing of the *Vinca* alkaloids, together with a resumé of their structures, is given in a Russian review;^{64a} the influence of solvents on the n.m.r. spectra of majdine, isomajdine, *N*-acetylvinerine, vineridine, and reserpinine has been discussed in some detail, also in Russian.^{64b}

The structure and stereochemistry of the alkali-sensitive alkaloid powerine, which have previously eluded investigators, have now been established⁶⁵ by the *X*-ray crystal structure analysis of its methanol solvate; powerine proves to be 10-hydroxy-17-*epi*- α -yohimbine (105).

A second group of workers has concurred⁶⁶ that the preferred conformation of geissoschizine (106) in solution is one in which the C/D ring junction is *cis* and the substituent at C-15 is axially disposed to a boat-shaped ring D; in contrast, geissoschizine adopts a *trans* C/D quinolizidine conformation in the crystal.

The structure of the 18(17 \rightarrow 16)*abeo*-yohimbine derivative obtained^{22d} by the oxymercuration of demethylcorynantheine has now been confirmed⁶⁷ by the *X*-ray crystal structure determination of its *O*-acetate (107). The overall

⁶¹ N. Aimi, E. Yamanaka, N. Shinma, M. Fujii, J. Kurita, S. Sakai, and J. Haginiwa, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 2067.

⁶² E. J. Shellard, P. J. Houghton, and P. K. Lala, *Phytochemistry*, 1977, **16**, 1427.

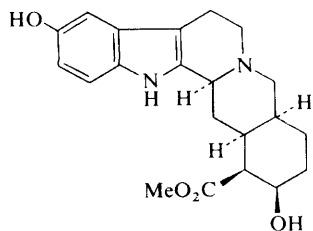
⁶³ M. M. Khalmirzaev, V. M. Malikov, K. L. Seitanidi, M. R. Yagudaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 718 (*Chem. Abs.*, 1978, **88**, 105 624).

⁶⁴ (a) V. M. Malikov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 597; (b) K. L. Seitanidi, M. R. Yagudaev, and V. M. Malikov, *ibid.*, p. 360.

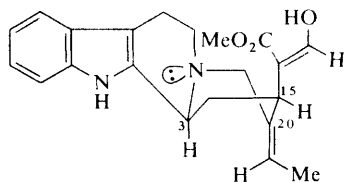
⁶⁵ C. Kowala, B. J. Poppleton, and J. A. Lambertson, *J. Cryst. Mol. Structure*, 1977, **7**, 1.

⁶⁶ R. Goutarel, M. Pais, H. E. Gottlieb, and E. Wenkert, *Tetrahedron Letters*, 1978, 1235.

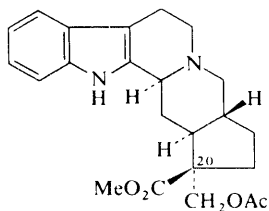
⁶⁷ H. Douceain and C. Riche, *Acta Cryst.*, 1977, **B33**, 1988.



Powerine (105)



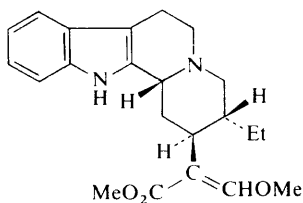
Geissoschizine (106)



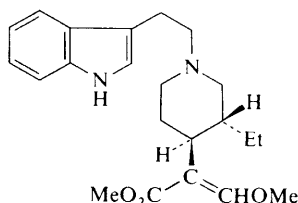
(107)

structure of this transformation product was not in doubt; this work serves mainly to establish the configuration at C-20.

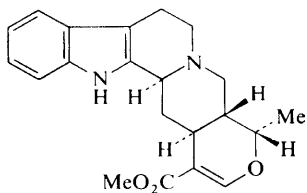
Two groups of investigators have reported⁶⁸ that the 2,3-bond in indole alkaloids can be cleaved by heating the alkaloid with anhydrous formic acid-formamide mixture. Thus, hirsutine (108) gives^{68b} 2,3-seco-2,3-dihydrohirsutine (109), and the ajmalicine group give rise to analogous 2,3-seco-derivatives;^{68a} e.g., ajmalicine (110) gives (111). Yohimbine and reserpine behave similarly.^{68b}



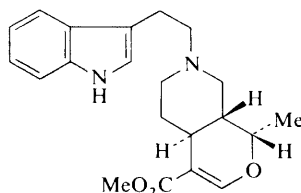
Hirsutine (108)



(109)



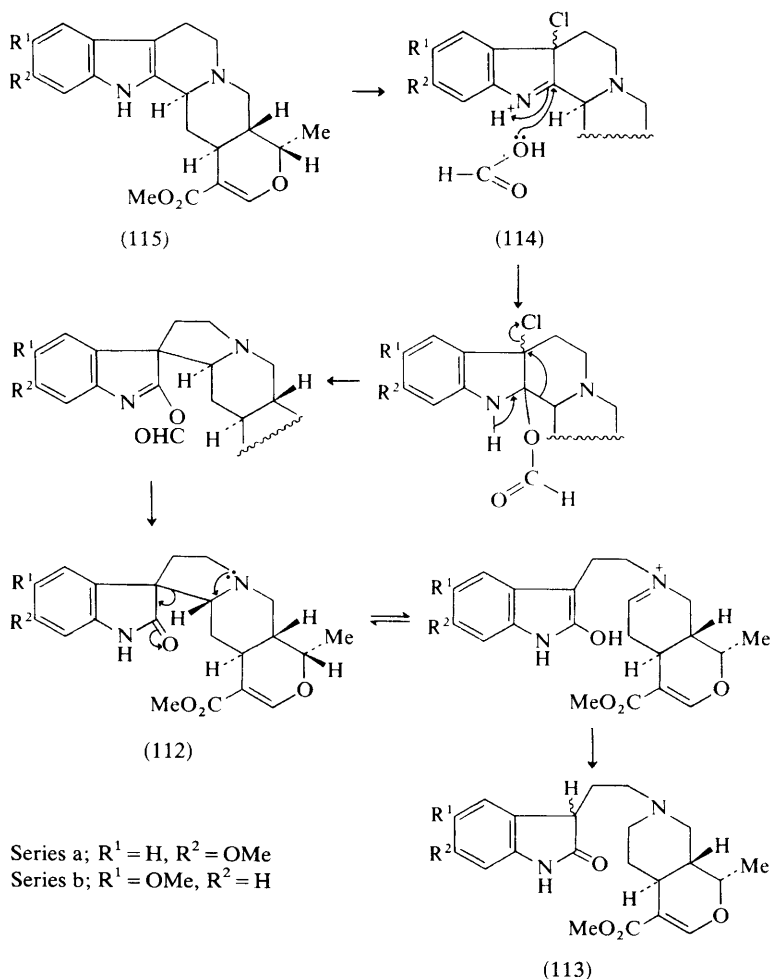
Ajmalicine (110)



(111)

⁶⁸ (a) F. Sigaut-Titeux, M. J. Hoizey, L. Le Men-Olivier, J. Lévy, and J. Le Men, *Tetrahedron Letters*, 1978, 2153; (b) S. Sakai and M. Ogawa, *Chem. and Pharm. Bull. (Japan)*, 1978, **26**, 678.

Presumably this reaction proceeds by reduction of the C-3, N_b -immonium ion formed by a reverse Mannich reaction on the starting alkaloid. This same reaction can be used to correlate alkaloids of the oxindole and heteroyohimbine groups.⁶⁹ For example, treatment of (112a) or (112b) with anhydrous formic acid-formamide gives the amorphous 2,3-seco products, (113a) and (113b), respectively; these same products can be obtained by the similar treatment of the 7-chloro-indolenine derivatives (114a) and (114b) derived, respectively, from the heteroyohimbine alkaloids tetraphylline (115a) and cabucine (115b) (Scheme 10). Presumably the oxindole analogues (112a) and (112b) are intermediates in this conversion.

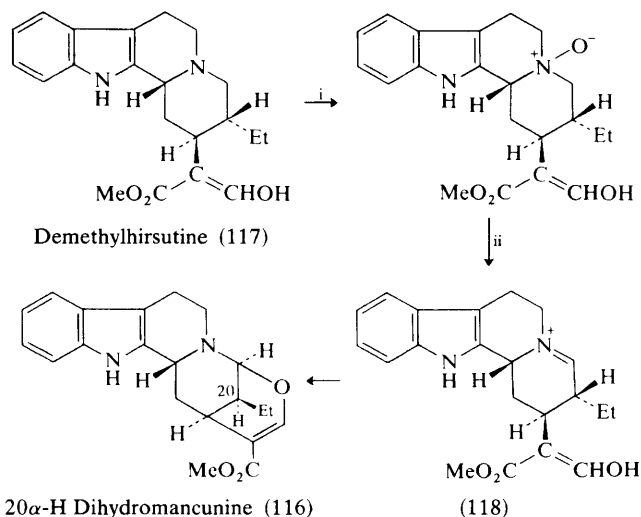


Scheme 10

⁶⁹ F. Sigaut-Titeux, L. Le Men-Olivier, J. Lévy, and J. Le Men, *Heterocycles*, 1977, **6**, 1129.

Other interesting transformations in the heteroyohimbine series include a partial synthesis of dihydromancunine from hirsutine⁷⁰ and the formation⁷¹ of eburnamonine analogues by the addition of a six-membered ring between C-14 and N_a.

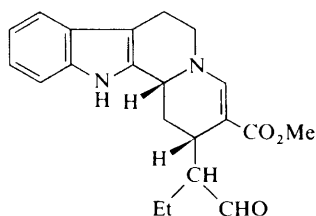
Sakai's synthesis of dihydromancunine (116) simply utilises the modified Polonovski reaction on the *N*-oxide of demethylhirsutine (117) (Scheme 11). The major product, dihydromancunine (116), must arise by epimerisation at C-20 during the reaction, presumably *via* reversible loss of a proton from the intermediate immonium ion (118). A very small amount of the 20 β -H epimer of (116)



Reagents: i, *m*-ClC₆H₄CO₃H; ii, (CF₃CO)₂O, CH₂Cl₂, 0 °C.

Scheme 11

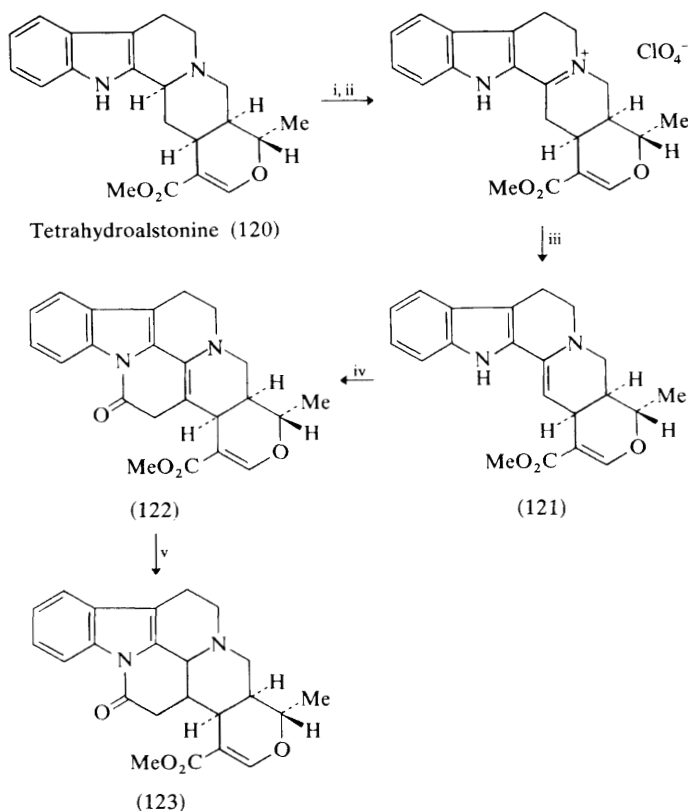
was also obtained, which was shown to equilibrate readily with (116) and to rearrange⁷⁰ to the thermodynamically more stable 19,20-dihydro-3-*epi*-vallesia-chotamine (119).



19,20-Dihydro-3-*epi*-vallesia-chotamine (119)

⁷⁰ S. Sakai and N. Shinma, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 842.

The addition of a six-membered ring between C-14 and N_a in tetrahydroalstonine (120) was achieved⁷¹ by oxidation with mercuric acetate, which gave the unstable 3,14-enamine (121) *via* the corresponding C-3, N_b-immonium salt. The reaction of (121) with methyl chloroacetate resulted in alkylation at C-14 and cyclisation, with formation of the crystalline hexacyclic enamine (122), reduction of which afforded the 3,14-dihydro-derivative (123) (Scheme 12).



Reagents: i, Hg(OAc)₂; ii, HClO₄; iii, OH⁻; iv, ClCH₂CO₂Me, under N₂, at 140 °C; v, NaBH₃CN, AcOH.

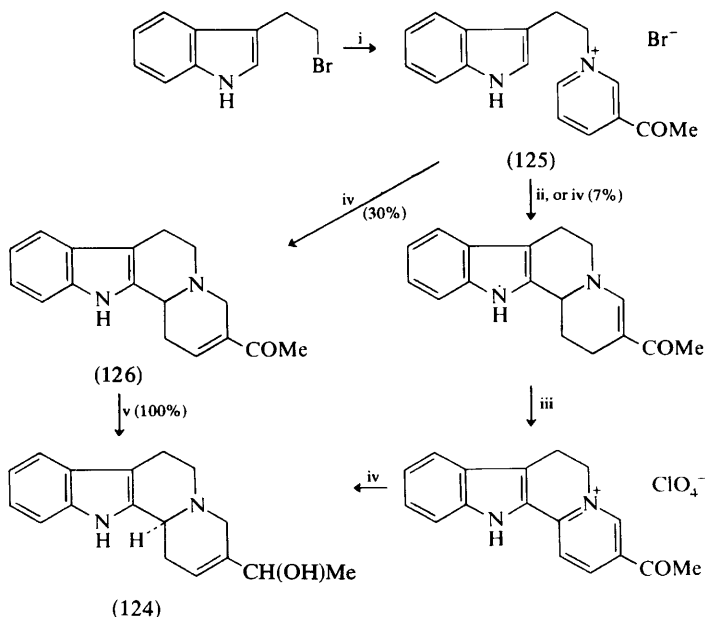
Scheme 12

The nitration of rescinnamine gives the 1- and 12-nitro-derivatives, together with a very small yield of an unidentified third product;^{72a} in contrast, ajmalicine and serpentine give only one nitration product, which in both cases proves to be the 10-nitro-derivative.^{72b}

⁷¹ Y. Rolland, J. Garnier, J. Mahuteau, and J. Poisson, *Compt. rend.*, 1977, **285**, C, 583.

⁷² (a) S. Siddiqui and S. I. Hameed, *Pakistan J. Sci. Ind. Res.*, 1975, **18**, 243; (b) *ibid.*, p. 247.

Synthetic work in this area includes a brief and efficient synthesis^{73a,b} of the indoloquinolizidine derivative (124), which has previously been employed in the synthesis of dihydrocorynantheol (Scheme 13).



Reagents: i, 3-Acetylpyridine; ii, $\text{Na}_2\text{S}_2\text{O}_4$; iii, Pd, H_2O , maleic acid; iv, NaBH_4 ; v, LiAlH_4 .

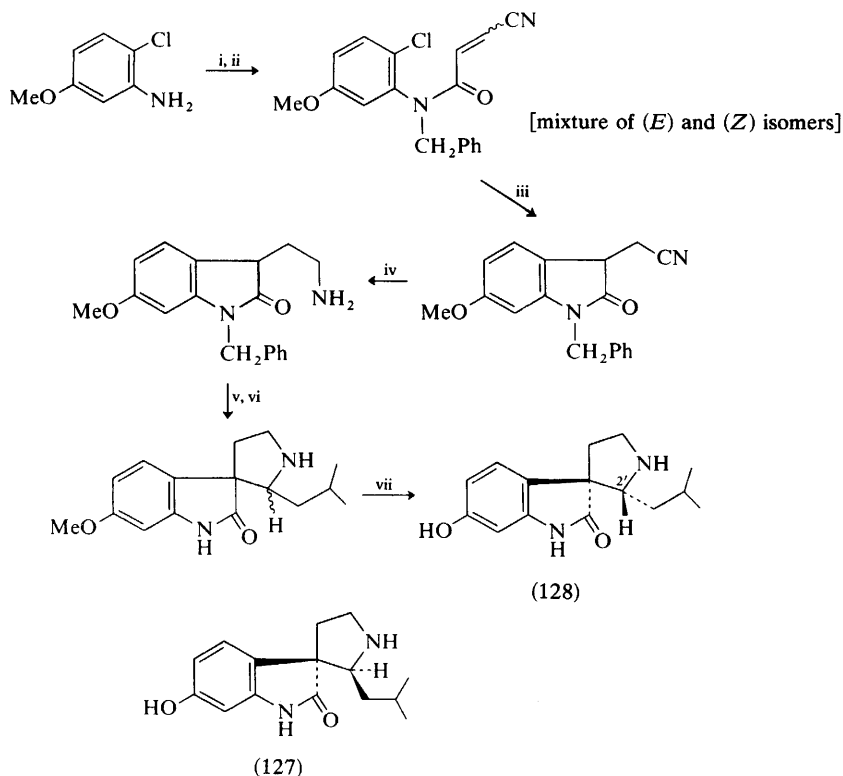
Scheme 13

Two routes to (124) were developed, the shorter of which simply involved^{73b} the reduction of the pyridinium salt (125) by means of sodium borohydride, followed by reduction of the tetrahydropyridine derivative (126) so obtained. The ^{13}C n.m.r. spectra of a number of indoloquinolizidine esters prepared earlier in this programme of research have been determined, and complete assignments made.^{73c}

The attempted total synthesis^{74a} of 6-hydroxy-2'-(2-methylpropyl)-3,3'-spiro(tetrahydropyrrolidino)-oxindole (127), an alkaloid of the dried root bark of *Eleagnus communis* (Wolf willow, or silverberry),^{74b} resulted in the formation of the epimer (128), or a mixture of (127) and (128) (Scheme 14). The final product showed great similarity to, but was not identical with, the alkaloid (127); however, (127) and the synthetic material gave the same product on acetylation, the reaction conditions for which presumably allowed epimerization at C-2'.

⁷³ (a) M. Lounasmaa and M. Puhakka, *Acta Chem. Scand. (B)*, 1978, **32**, 77; (b) *ibid.*, p. 216; (c) M. Lounasmaa and M. Hämeilä, *Tetrahedron*, 1978, **34**, 437.

⁷⁴ (a) M. Mori and Y. Ban, *Heterocycles*, 1978, **9**, 391; (b) M. N. G. James and G. J. B. Williams, *Canad. J. Chem.*, 1972, **50**, 2407.



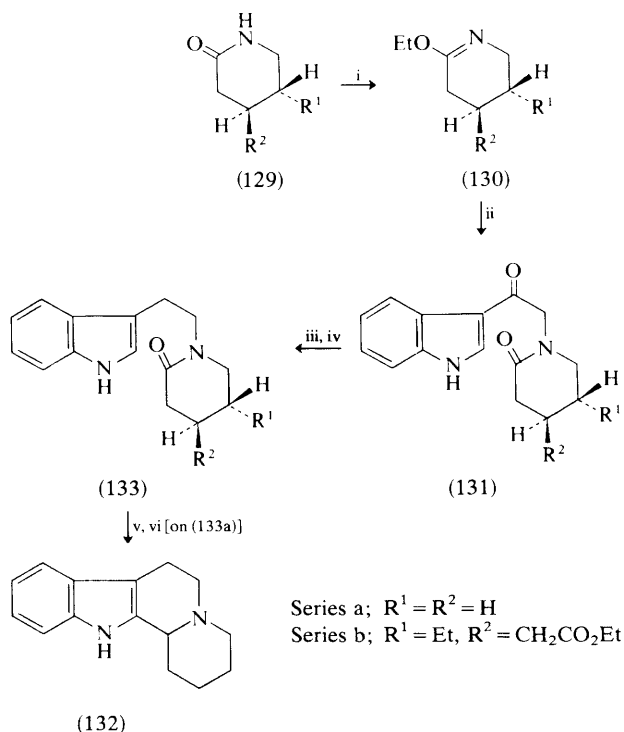
Reagents: i, $\text{NCCH}=\text{CHCO}_2\text{H}$, ClCO_2Et , NEt_3 ; ii, PhCH_2Br , NaH ; iii, $\text{Ni}(\text{PPh}_3)_n$, DMF, at 60°C for 2 h; iv, PtO_2 , H_2 , EtOH, HCl; v, $\text{Me}_2\text{CHCH}_2\text{CHO}$, NaOH, H_2O , EtOH; vi, Na, NH_3 ; vii, BBr_3 , CH_2Cl_2 .

Scheme 14

A new synthetic route^{75a} to indoloquinolizidine alkaloids, *via* the substituted 2-piperidones (129), employs the alkylation of the related lactim ether (130) for the purpose of introducing the indolyethyl group. Further modification of the product (131a) affords yet another synthesis of the simplest member (132) of this group, the (–)-enantiomer of which occurs in *Dracontomelum mangiferum* Bl. Application of this approach to the substituted piperidone (129b), synthesised earlier,^{75b} gives the intermediate (133b) (Scheme 15), which has already been converted^{75c} into (±)-dihydrocorynantheine; the formal synthesis of this alkaloid is therefore complete.

An account of Szántay's synthesis^{22e} of dihydrocorynantheine has been published, in Hungarian.^{75d,e}

⁷⁵ (a) T. Fujii, S. Yoshifuji, and H. Ito, *Heterocycles*, 1977, **7**, 149; (b) T. Fujii, S. Yoshifuji, and M. Tai, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2094; (c) E. E. van Tamelen and J. B. Hester, *J. Amer. Chem. Soc.*, 1959, **81**, 3805; 1969, **91**, 7342; (d) M. Bérczai-Beke, G. Dörnyei, M. Kajtar, and Cs. Szántay, *Magyar Kém. Folyoirat*, 1978, **84**, 26; M. Bérczai-Beke, G. Dörnyei, G. Tóth, J. Tamás, and Cs. Szántay, *ibid.*, p. 31.



Reagents: i, $Et_3O^+ BF_4^-$; ii, 3-chloroacetylindole, DMF, at 60 °C for 24 h; iii, $NaBH_4, H_2O, EtOH$; iv, $H_2, Pd/C, H_2O, EtOH, HClO_4$; v, $POCl_3, PhH$, at 80 °C; vi, $NaBH_4, MeOH$.

Scheme 15

The synthesis⁷⁶ of (\pm)-alangimarckine (134) (Scheme 16) corroborates the view, earlier expressed by the same workers, that the phenolic hydroxy-group is situated at position 8 of the benzoquinolizidine ring system, rather than position 11 as previously supposed. The spectroscopic (n.m.r.) properties and chromatographic behaviour of alangimarckine and its C-1' epimer, and the proportions of these epimers obtained in the reduction with $NaBH_4$ (the penultimate stage in the synthesis) indicate clearly that alangimarckine (134) is stereochemically analogous to tubulosine (its 8-deoxy derivative, which also occurs in *Alangium lamarckii* Thw.) and emetine.⁷⁶

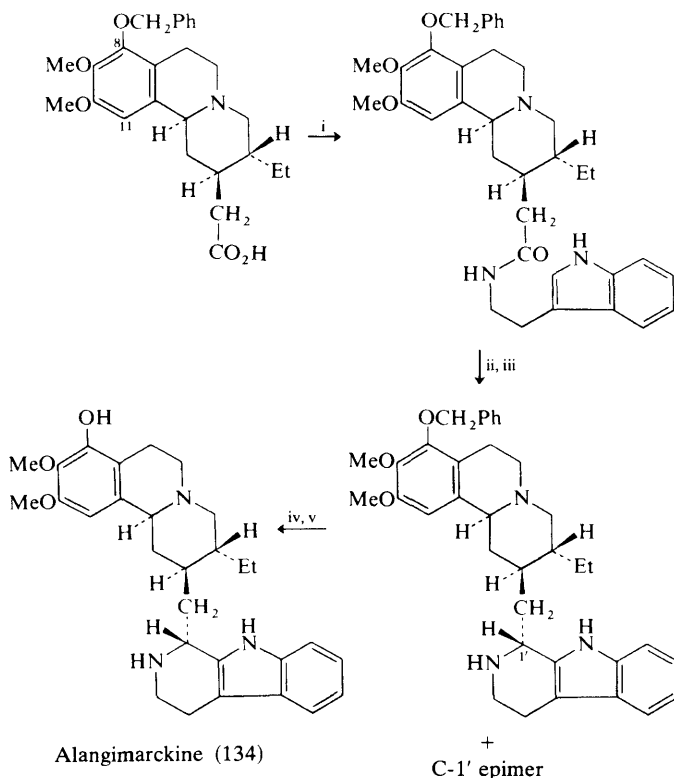
Full details of Sainsbury's synthesis of nauclefine^{77a} have now been published.^{77b}

Brown's biomimetic syntheses from secologanin have been further refined, and a 'one-pot' synthesis of heteroyohimbine alkaloids has been developed.⁷⁸

⁷⁶ T. Fujii, S. Yoshifuji, and H. Kogen, *Tetrahedron Letters*, 1977, 3477.

⁷⁷ (a) M. Sainsbury and N. L. Uttley, *J.C.S. Chem. Comm.*, 1977, 319; (b) *J.C.S. Perkin I*, 1977, 2109.

⁷⁸ R. T. Brown, J. Leonard, and S. K. Sleight, *J.C.S. Chem. Comm.*, 1977, 636.

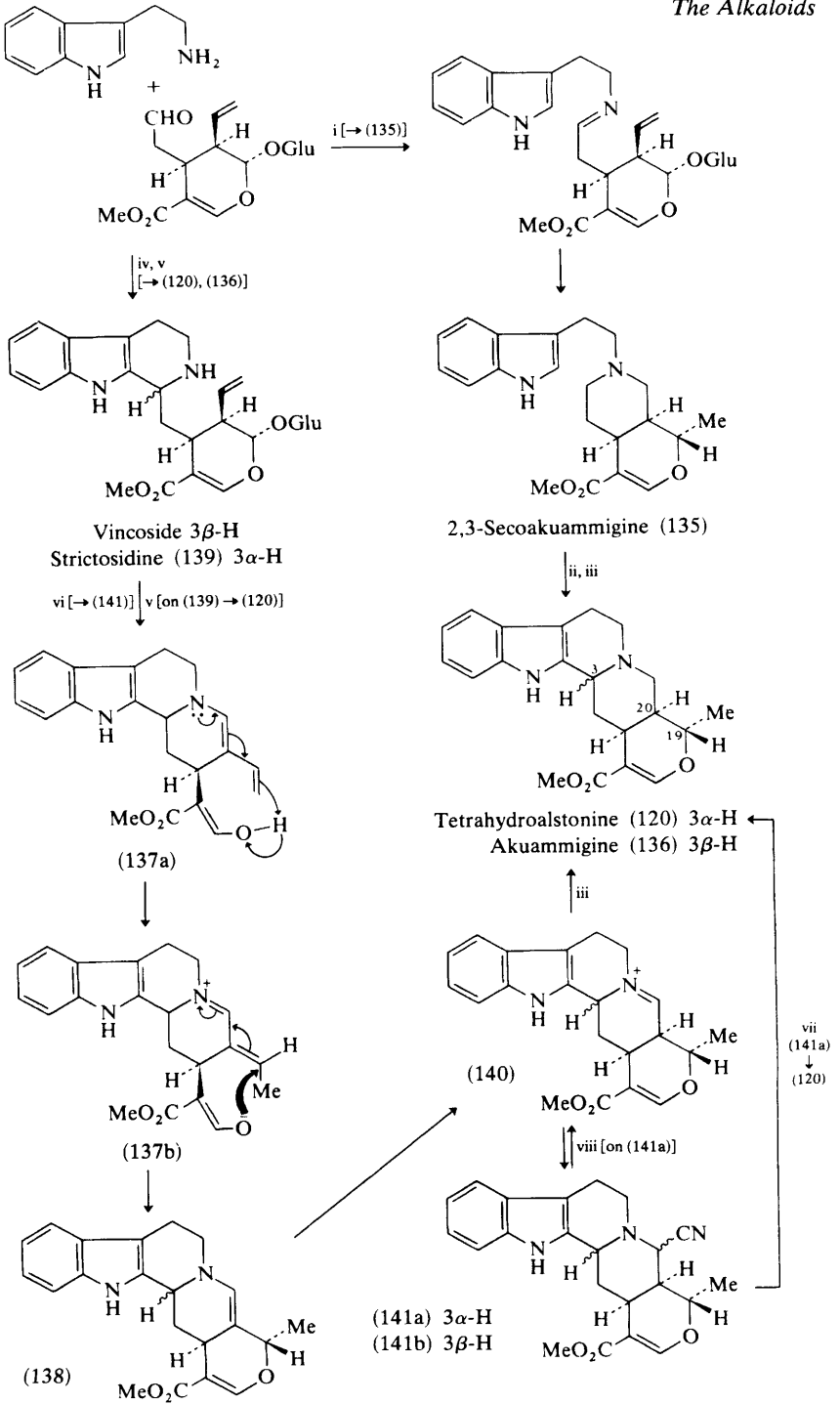


Reagents: i, Tryptamine, $\text{NCPO}(\text{OEt})_2$, NEt_3 , DMF; ii, POCl_3 , PhMe, at 110°C ; iii, NaBH_4 , MeOH; iv, separation of epimers; v, H_2 , Pd/C, MeOH, AcOH.

Scheme 16

Condensation of tryptamine with secologanin in the presence of β -glucosidase and sodium cyanoborohydride affords a tetracyclic product (Scheme 17), which is 2,3-secoakuammigine (135), since a mixture of tetrahydroalstonine (120) and akuammigine (136) is obtained on oxidation [$\text{Hg}(\text{OAc})_2$] followed by reduction; presumably no pentacyclic products are obtained in the initial condensation since the imine formed from tryptamine and secologanin suffers reduction before it can cyclise to a tetrahydro- β -carboline (*i.e.* vincoside or strictosidine).

When tryptamine and secologanin were allowed to condense, and then β -glucosidase and sodium cyanoborohydride were added, the products obtained were 2,3-secoakuammigine (135), akuammigine (136), and tetrahydroalstonine (120), together with a very small amount of ajmalicine (110); no other stereoisomers were detected. It is a notable fact that all these products have the same chirality (*S*) at position 19. This stereospecificity may be explained by postulating intramolecular proton transfer in a conjugated enamine intermediate such as (137a), which necessarily results in the formation of the universally



observed (*E*)-configuration of the ethylidene group; stereospecific β -attack by the enolate anion in (137b) at position 19 then gives a pentacyclic product (138) with 19*S* chirality (Scheme 17). The subsequent stage, which is protonation at C-20, must occur predominantly from the α -face, since very little ajmalicine is formed. This whole process occurs under mild conditions and with considerable regio- and stereo-selectivity, and would appear to duplicate the biosynthesis of these alkaloids in all essential details.

One further vital point emerges from this study. When strictosidine (139) was allowed to react with β -glucosidase and sodium cyanoborohydride, tetrahydroalstonine (120) was obtained, *but no akuammigine*. Hence no epimerization at C-3 is required, and it would seem that strictosidine acts as precursor for the 3 β -H alkaloids and vincoside for the 3 α -H series.⁷⁸

Evidence for the intermediacy of the enamine (138) and the immonium ion (140) derives from the condensation reaction in which potassium cyanide replaced sodium cyanoborohydride;⁷⁹ the immonium ion (140) was thus trapped by reaction with nucleophilic cyanide ion, with formation of 21-cyanotetrahydroalstonine (141a) and 21-cyanoakuammigine (141b). Both cyano-compounds suffered slow reduction to the parent alkaloid by sodium borohydride, and were re-converted (by silver acetate) into the precursor immonium ions (140), which could be rapidly reduced (NaBH_4) to the alkaloids.⁷⁹ Scheme 17 illustrates some, but not by any means all, of the numerous interconversions involved in these biomimetic experiments.

After an interval of more than twenty years, a second synthesis of the deserpidine/reserpine group of alkaloids has been achieved.⁸⁰ Details of this brief and ingenious route, one variant of which is outlined in Scheme 18, are not yet available. However, the critical stereochemistry at positions 3, 15, and 20 was obtained by Knoevenagel condensation of the ketone (142a) with malononitrile. Presumably the C-20 epimer of (142a), present in small amount in equilibrium with (142a), condenses preferentially with malononitrile anion (less crowded transition state) to give the unsaturated nitrile (142b), which can be reduced stereospecifically to the nitrile (142c) of *allo* stereochemistry. Elaboration of (142c) proceeded *via* the pentacyclic keto-ester (143a), which was converted into (\pm)-deserpidine (143b) as shown.⁸⁰

The pharmacological and biochemical properties of yohimbine and four of its stereoisomers have been examined and discussed.⁸¹

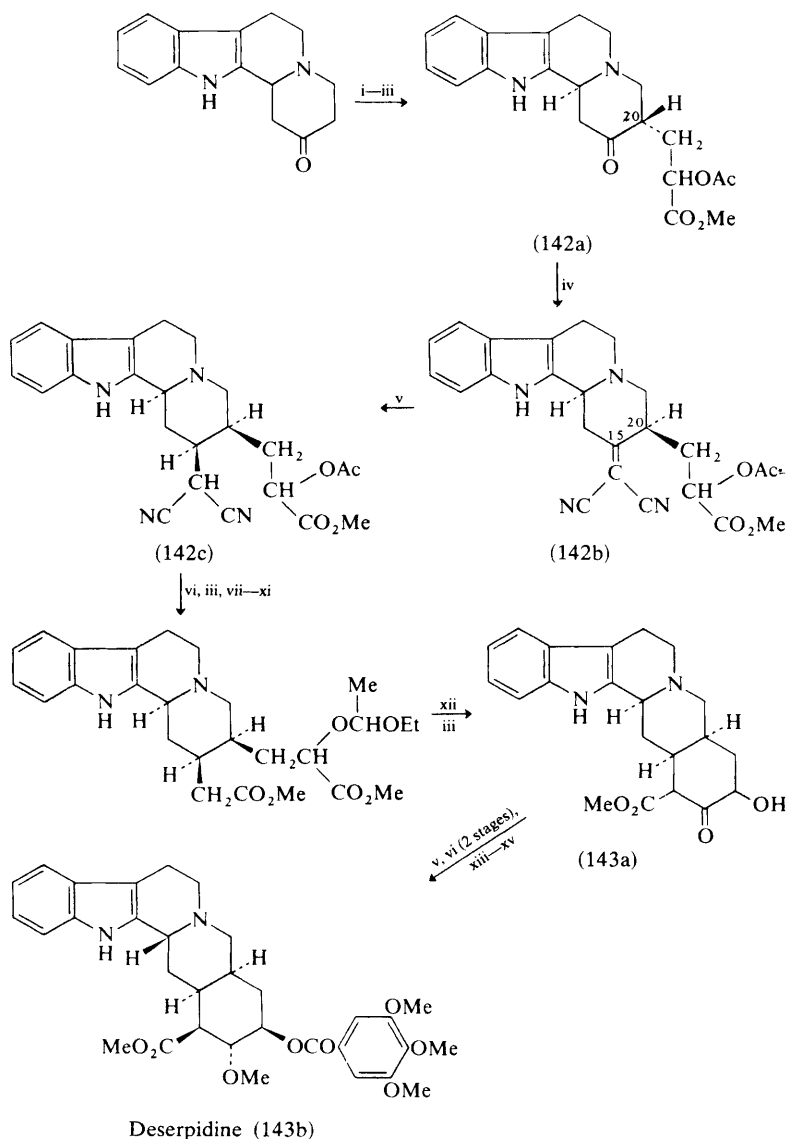
Sarpagine-Ajmaline-Picaline-Vobasine Group. The stem bark of *Rauwolfia cumminsii* Stapf. contains mitoridine and two new alkaloids, N_a -demethyl-

⁷⁹ R. T. Brown and J. Leonard, *Tetrahedron Letters*, 1977, 4251.

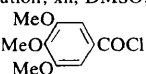
⁸⁰ (a) Cs. Szántay, G. Blaskó, K. Honty, L. Szabó, and L. Töke, *Heterocycles*, 1977, **7**, 155; (b) Cs. Szántay, L. Töke, G. Blaskó, K. Honty, and L. Szabó, *Lectures Heterocyclic Chem.*, 1978, **4**, 25.

⁸¹ G. A. Lambert, W. J. Lang, E. Friedman, E. Meller, and S. Gershon, *European J. Pharm.*, 1978, **49**, 39.

Reagents: i, β -Glucosidase, NaBH_3CN , at pH 5 and 37°C; ii, $\text{Hg}(\text{OAc})_2$; iii, NaBH_4 ; iv, pH 4, for 48 h; v, β -glucosidase, NaBH_3CN , at 37°C, for 18 h; vi, β -glucosidase, 2KCN; vii, NaBH_4 , EtOH, at 0°C, for 24 h; viii, AgOAc , EtOH.



Reagents: i, Pyrrolidine, PhH, heat; ii, $\text{CH}_2=\text{C}(\text{OAc})\text{CO}_2\text{Me}$, Bu^tOH , PhH, at r.t., for 3 days; iii, H^+ , H_2O ; iv, NCCH_2CN , P_2O_5 , $\text{Et}_3\text{NH}^+ \text{OAc}^-$; v, NaBH_4 ; vi, NaOMe , MeOH ; vii, 5% NaOH , H_2O , for 12 h, at r.t.; viii, DMF , NaCl , at 120°C , for 30 min; ix, 10% NaOH , H_2O , at 100°C , for 3 h; x, MeOH , H^+ ; xi, acetal formation; xii, DMSO ,

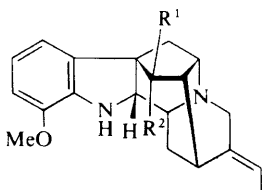
KOBU^t , for 4 days, at r.t.; xiii, $\text{Pb}(\text{OAc})_4$; xiv, Zn , HClO_4 ; xv, MeO  COCl

Scheme 18

purpeline (144) and N_a -demethyl Dihydropurpeline (145); this is the first report of the occurrence of dihydroindole alkaloids in this particular species.⁸² Perivine is reported^{57a} to occur in the roots of *Catharanthus roseus*, and (-)-vobasine in the leaves of *Pagiantha cerifera* Mgf.,^{83a} together with olivacine and apparicine; this contrasts with the alkaloids of *P. macrocarpa*,^{83b} which belong to the aspido-spermine and voacangine groups. Perivine, pericyclivine, and vobasine have been found in the roots of *Tabernaemontana holstii*;^{84a} the first two of these alkaloids also occur in the stem bark of *T. johnstonii* Pichon.^{84b} These are the first reports of the occurrence of these two alkaloids in the genus *Tabernaemontana*.

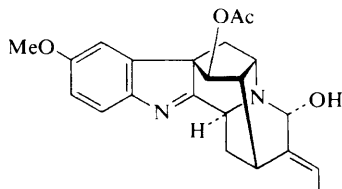
The comparatively rare alkaloid pseudoakuammigine has been isolated from the leaves of *Alstonia scholaris*;^{84c} this is only the second report of the isolation of this alkaloid from a natural source.

The presence of vincamajine and vincamajoreine in the aerial parts of *Vinca major* has again been noted,^{57c} and a new alkaloid, majorinine, has been isolated. Mainly on the basis of its spectroscopic properties, and particularly its 360 MHz n.m.r. spectra, majorinine is formulated as (146), i.e. as 10-methoxyvomilenine (10-methoxy-21-hydroxyvinorine).



N_a -Demethylpurpeline (144) $R^1R^2 = O$

N_a -Demethyl Dihydropurpeline (145) $R^1 = H, R^2 = OH$



Majorinine (146)

Further extractions of the roots of *Hazuntia modesta* have resulted in the isolation of six additional alkaloids, of which 16-demethoxycarbonyl-20-*epi*-ervatamine and 6-oxosilicine belong to this group.⁸⁵

The root bark of Madagascan *Pandaca boiteau* contains methuenine (147) and ervitsine (148), a 2-acyl-indole alkaloid of a new type.^{86a} The structure of ervitsine was established by X-ray crystal structure analysis, and corroborated by an interesting chemical sequence in which ervitsine was interrelated with methuenine. As a Mannich base, ervitsine fragments in acid solution to give an intermediate which can re-cyclise to a product (149) having the methuenine skeleton; hydrogenation of (149) then gives a mixture of epimers (150), one of which is identical with one of the products of the similar hydrogenation of methuenine (Scheme 19). Biogenetically, ervitsine could be generated by the

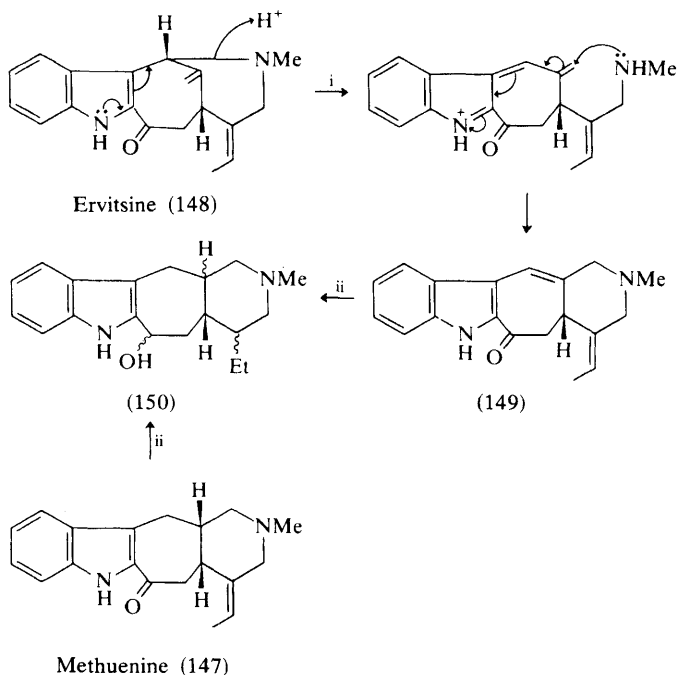
⁸² M. M. Iwu and W. E. Court, *Experientia*, 1977, **33**, 1268.

⁸³ (a) H. P. Ros, E. Schöpp, and M. Hesse, *Z. Naturforsch.*, 1978, **33c**, 290; (b) C. Miet and J. Poisson, *Phytochemistry*, 1977, **16**, 153.

⁸⁴ (a) D. G. I. Kingston, B. T. Li, and F. Ionescu, *J. Pharm. Sci.*, 1977, **66**, 1135; (b) D. G. I. Kingston, B. B. Gerhart, F. Ionescu, M. M. Mangino, and S. M. Sami, *ibid.*, 1978, **67**, 249; (c) A. Banerji and J. Banerji, *Indian J. Chem., Sect. B*, 1977, **15**, 390.

⁸⁵ V. Vecchiotti, G. Ferrari, F. Orsini, F. Pelizzoni, and A. Zajotti, *Phytochemistry*, 1978, **17**, 835.

⁸⁶ (a) M. Andriantsiferana, R. Besselièvre, C. Riche, and H. P. Husson, *Tetrahedron Letters*, 1977, 2587; (b) A. Husson, Y. Langlois, C. Riche, H. P. Husson, and P. Potier, *Tetrahedron*, 1973, **29**, 3095; (c) P. Mangeney, *ibid.*, 1978, **34**, 1359.



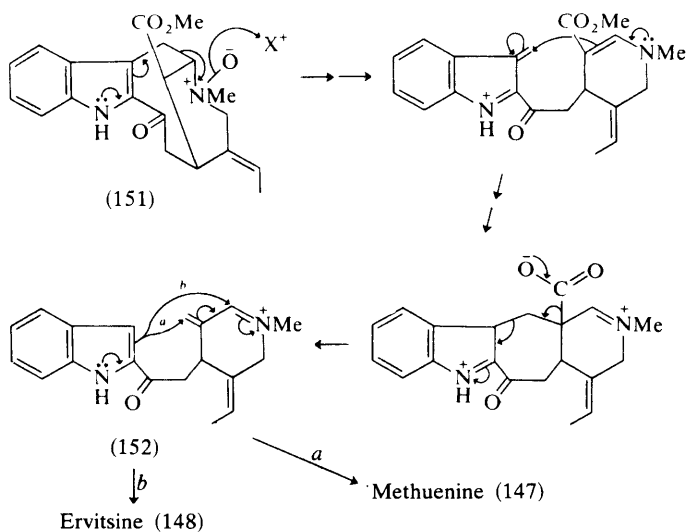
Reagents: i, AcOH, heat for 24 h; ii, H₂, PtO₂, MeOH.

Scheme 19

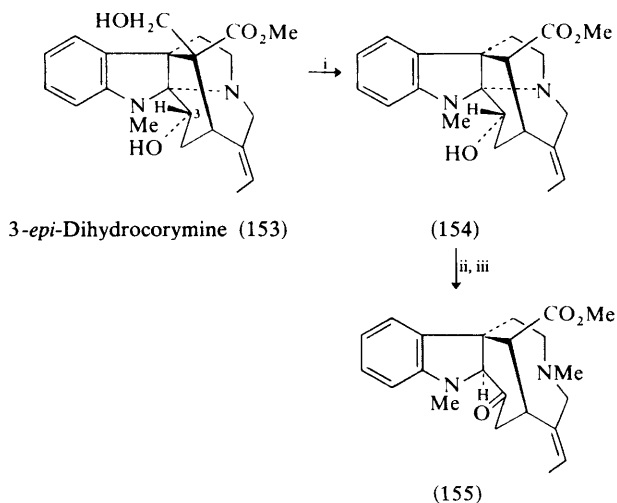
fragmentation of vobasine *N*_b-oxide (151), or its biochemical equivalent; re-cyclisation followed by appropriate trivial transformations then lead to an intermediate (152), which can cyclise either to methuenine (147) or to ervitsine (148) (Scheme 20).^{86a} The conversion of the *N*-oxides of vobasine, dregamine, and tabernaemontanine into alkaloids containing the methuenine (ervatamine) ring system has been achieved *in vitro*,^{86b,c} and is clearly feasible *in vivo*; the modification of this route to alkaloids such as ervitsine seems unexceptional.

Twelve of the thirteen alkaloids isolated⁵⁸ from the leaves of Senegalese *Hunteria elliptica* (Stapf.) Pichon are known, and include acetylcorymine and desformocorymine; the thirteenth, which proved to be 3-*epi*-dihydrocorymine (153), is new, and was correlated with dihydrocorymine [C-3 epimer of (153)] by retro-aldol loss of formaldehyde, which gave the ester (154), epimeric with the product of similar treatment of dihydrocorymine. However, methylation of (154) and formation of the methine base gave a product (155) identical with that obtained from dihydrocorymine (Scheme 21). A point of taxonomic interest is that the alkaloid content reported from this specimen of *H. elliptica* is quite different from that reported (eburnamine, pleiocarpamine, and yohimbol *N*_b-metho-salt) from a Ghanaian specimen.⁸⁷

⁸⁷ I. Sondergaard and F. Nartey, *Phytochemistry*, 1976, **15**, 1322.



Scheme 20



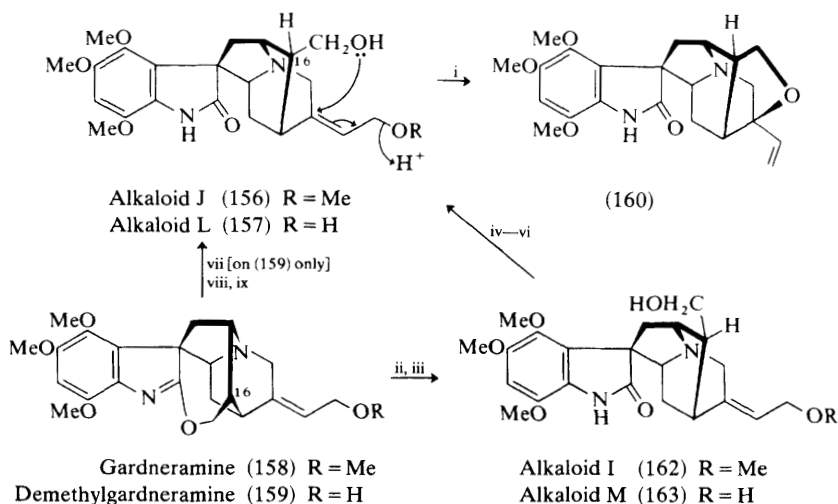
Reagents: i, KOMe, MeOH, heat; ii, MeI; iii, base.

Scheme 21

Several new alkaloids have been isolated from *Gardneria multiflora* Makino, and the structures of six of them, all closely related to gardneramine, have been elucidated.⁸⁸ Alkaloid J has the structure (156) and Alkaloid L is the corresponding allylic alcohol (157). Alkaloid J can be obtained by hydrolysis of the

⁸⁸ S. Sakai, N. Aimi, K. Yamaguchi, K. Hori, and J. Haginiwa, *Yakugaku Zasshi*, 1977, **97**, 399.

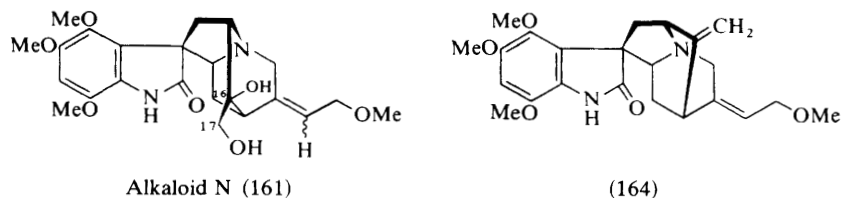
imino-ether function in gardneramine (158) followed by epimerisation at C-16 *via* the related aldehyde; two routes are available (Scheme 22). Alkaloid L can be obtained by one of these sequences of reactions on 18-demethylgardneramine (159), with prior protection of the allylic alcohol function by acetylation. The epimeric configuration at C-16 relative to that in gardneramine is confirmed by the formation of a cyclic ether (160) on treatment of Alkaloid J or Alkaloid L with hydrochloric acid (Scheme 22).



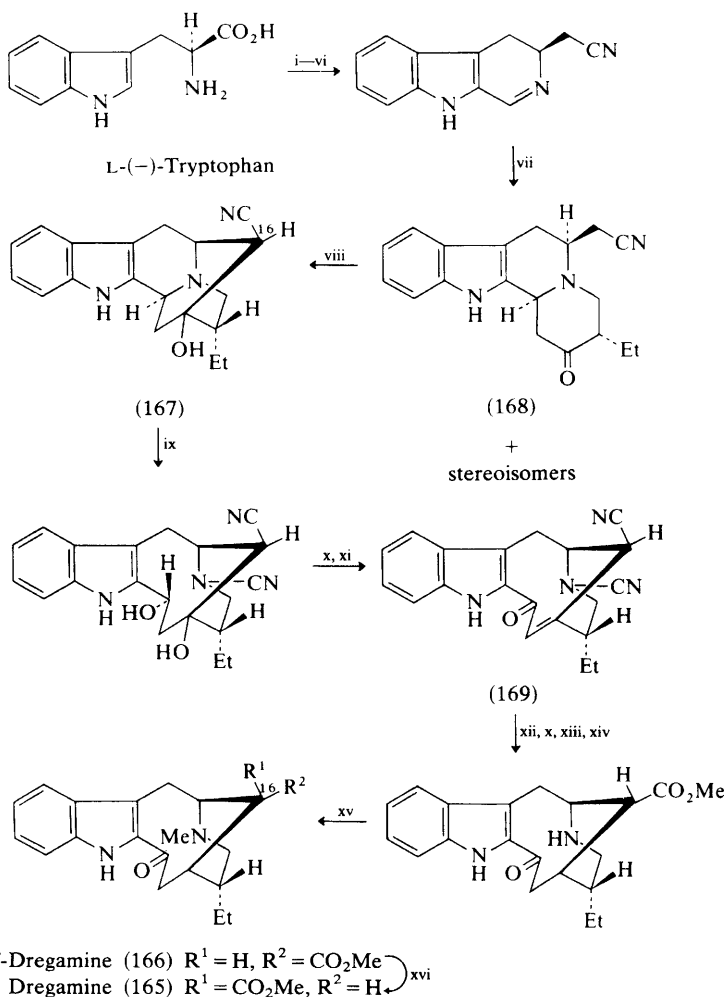
Scheme 22

Alkaloid N (161) is a vicinal glycol (since it gives an acetonide derivative) whose configuration at C-16 becomes clear from the formation of an imino-ether by internal displacement of a C-17 mesylate group by the oxindole function. The product is presumably a 16-hydroxy-gardneramine or a geometrical isomer, since the configuration about the double bond appears not to have been established. Other alkaloids isolated⁸⁸ are gardneramine *N*_b-oxide, Alkaloid I (162) (already known), Alkaloid M (163), and a base which is the anhydro-derivative (164) of Alkaloid I or Alkaloid J.

Extractions of *Gardneria liukiensis* Hatsushima showed that the alkaloid content is very similar to that of *G. multiflora*.⁸⁸



Kutney's synthesis^{89a,b} of dregamine (165) and 16-*epi*-dregamine (166) (Scheme 23) proceeds *via* an intermediate (167) having the sarpagine skeleton, and provides confirmation of the recently revised configuration of (165) and (166)



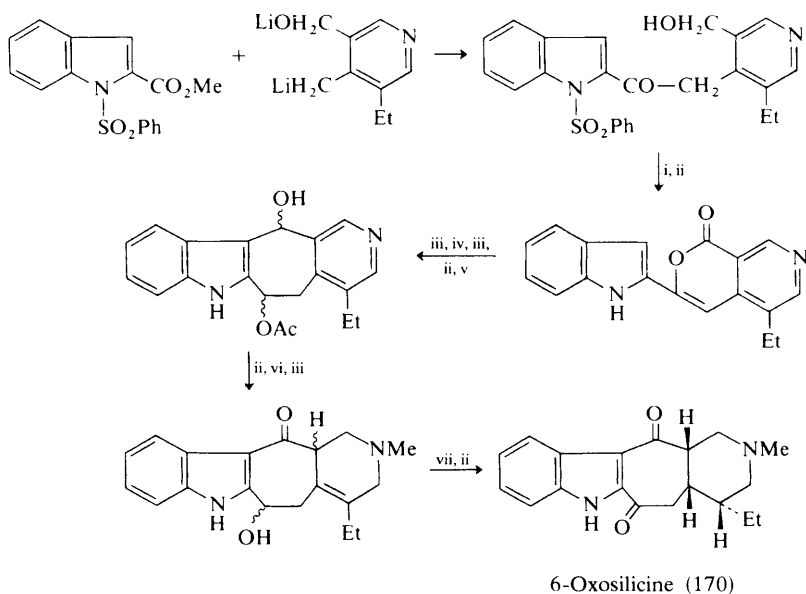
Reagents: i, LiAlH_4 , THF; ii, TsCl , pyridine; iii, KCN , MeOH , heat; iv, Na , NH_3 ; v, HCO_2Me , NaOMe , MeOH ; vi, PPE , CHCl_3 ; vii, $\text{MeCOCe}=\text{CH}_2$, MeOH , HCl , at 70°C ; viii, LiNEt_2 , THF, at 0°C ; ix, BrCN , MgO , THF, at 110°C , for 6 days; x, MnO_2 , THF; xi, SOCl_2 , pyridine; xii, NaBH_4 , pyridine, for 48 h; xiii, NaOH , H_2O , MeOH , heat; xiv, MeOH , HCl ; xv, CH_2O , HCO_2H , H_2 , Pd/C , dioxan; xvi, NaOMe .

Scheme 23

⁸⁹ (a) J. P. Kutney, G. K. Eigendorf, H. Matsue, A. Murai, K. Tanaka, W. L. Sung, K. Wada, and B. R. Worth, *J. Amer. Chem. Soc.*, 1978, **100**, 938; (b) J. P. Kutney, *Heterocycles*, 1977, **8**, 813; (c) H. P. Husson, K. Bannal, R. Freire, B. Mompon, and F. A. M. Reis, *Tetrahedron*, 1978, **34**, 1363.

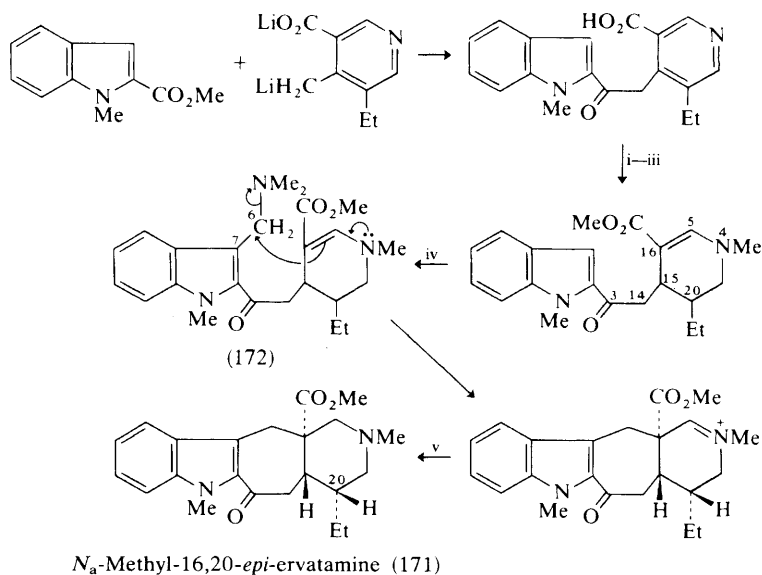
at position 20. The starting material, L-(-)-tryptophan, provided both the correct absolute stereochemistry at C-5 and an already formed 5,16 bond. The ketones, (168) and its three stereoisomers, were obtained by a seven-stage process which was non-stereospecific, but this proved not to be a serious disadvantage, since the stereoisomers could be converted into (168) by equilibration processes. The cyclisation of (168) gave (167) and its 16*R* epimer, and the synthesis was pursued with both epimers, a common product (16*S*)-(169) being obtained from both series at the dehydration stage; however, only the 16*S*-series is illustrated in Scheme 23.

In view of the conversion of dregamine into 20-*epi*-ervatamine mentioned above^{86b,c} this synthesis of dregamine also constitutes an indirect synthesis of the latter base. Almost simultaneously, however, the first direct total synthesis of the ervatamine ring system was reported by Husson and his collaborators,^{89c} who achieved the synthesis of 6-oxosilicine (170) and (\pm)-*N*_a-methyl-16,20-*epi*-ervatamine (171) (Schemes 24 and 25). The two routes to these bases are similar in concept, and rely for the formation of the required skeleton on the condensation of the lithium derivative of an appropriately substituted 4-methylpyridine with an indole-2-carboxylic ester. Aside from the ingenious and subtle use of certain reagents (the use of NaBH₄ to effect the preferential removal of one acetyl group in a diacetate, and the use of alumina to catalyse an electrophilic substitution at an indole β -position), the synthesis of 6-oxosilicine displays no special features. However, the introduction of the final, bridging methylene group (C-6) in the synthesis of (171) involves a skilful application of the Mannich reaction to



Reagents: i, OH⁻; ii, MnO₂; iii, NaBH₄; iv, Ac₂O, pyridine; v, Al₂O₃; vi, MeI; vii, H₂, PtO₂.

Scheme 24



Reagents: i, CH_2N_2 ; ii, MeI ; iii, H_2 , Pd/C , at pH 6.8; iv, $\text{Me}_2\text{N}=\text{CH}_2\text{CF}_3\text{CO}_2$; v, NaBH_3CN .

Scheme 25

yield a gramine derivative (172), which can cyclise by an enamine alkylation process with expulsion of dimethylamine; in the presence of NaBH_3CN the immonium ion produced is reduced to (171). This base is different from the C-20 epimers of *N_a*-methylervatamine and since, by reason of its mode of formation, the hydrogen atoms at positions 15 and 20 must be *cis*, it must differ from the natural ervatamine series in the configuration at C-16, and it must therefore be *N_a*-methyl-16,20-*epi*-ervatamine.^{89c}

The relative stereochemistry of ajmaline has been confirmed⁹⁰ by *X*-ray crystal structure analysis, but by the same method an effective anti-arrhythmic agent originally thought to be *N*-*n*-propylisoajmalinium bromide has been shown to be *N*-*n*-propyl-21-*epi*-isoajmalinium bromide.

Strychnine–Akuammicine–Ellipticine Group.—Very few new extractions have been recorded during the year under review. (–)-Akuammicine occurs⁵⁸ in the leaves of *Hunteria elliptica* and in the aerial parts of *V. major*.^{57c} A cytotoxic constituent of the roots of *Tabernaemontana holstii* K. Schum. proves to be tubotaiwine *N*-oxide.⁹¹ Olivacine and apparicine have been found in the leaves of *Paganthia cerifera*.^{83a}

The *X*-ray crystal structure determination of the BH_3 adduct of condylocarpine has been reported;⁹² this compound had been prepared by the oxidative

⁹⁰ R. Prewo and J. J. Stezowski, *Acta Cryst.*, 1978, **B34**, 454.

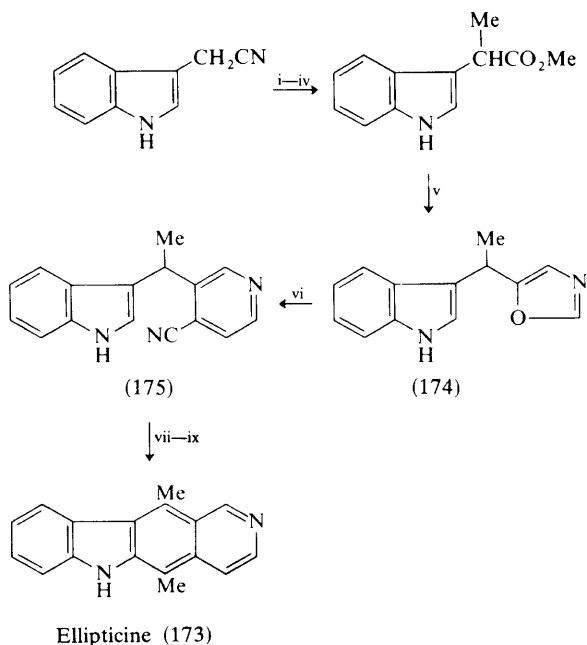
⁹¹ D. G. I. Kingston, F. Ionescu, and B. T. Li, *Lloydia*, 1977, **40**, 215.

⁹² A. H. J. Wang and I. C. Paul, *Acta Cryst.*, 1977, **B33**, 2977.

cyclisation (by mercuric acetate) of stemmadenine, followed by reduction with borohydride, and the presence of boron in the molecule had not been suspected.

The chiroptical properties of the strychnine group of alkaloids have been examined and discussed;⁹³ a considerable amount of attention has been paid to their ¹³C n.m.r. spectra,⁹⁴ and an impressive amount of data is now available.

The numerous existing syntheses of ellipticine (173) and olivacine have been discussed⁹⁵ in a general review devoted to the synthesis of 6*H*-pyrido[4,3-*b*]carbazoles. New routes to ellipticine continue to be reported. Kozikowski's oxazole approach (Scheme 26)⁹⁶ affords a low yield in the critical Diels–Alder stage [(174) → (175)] but is otherwise efficient and, it is claimed, should be sufficiently versatile to allow the introduction of substituents into ring D as desired.



Reagents: i, Me₂CO₃, NaOMe, PhH; ii, NaOMe, MeI; iii, KOH, HOCH₂CH₂OH, at 195 °C, for 13 h; iv, MeOH, AG 50W-X2, heat; v, LiCH₂NC, at –50 °C; vi, CH₂=CHCN, AcOH, at 145 °C, for 24 h; vii, MeLi; viii, hydrolysis; ix, 20% AcOH.

Scheme 26

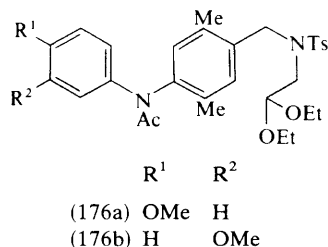
⁹³ J. W. Snow and T. M. Hooker, *Canad. J. Chem.*, 1978, **56**, 1222.

⁹⁴ (a) L. Leung and A. J. Jones, *Org. Magn. Resonance*, 1977, **9**, 333; (b) R. Verpoorte, P. J. Hylands, and N. G. Bisset, *ibid.*, p. 567; (c) E. Wenkert, H. T. A. Cheung, H. E. Gottlieb, M. C. Koch, A. Rabaron, and M. M. Plat, *J. Org. Chem.*, 1978, **43**, 1099.

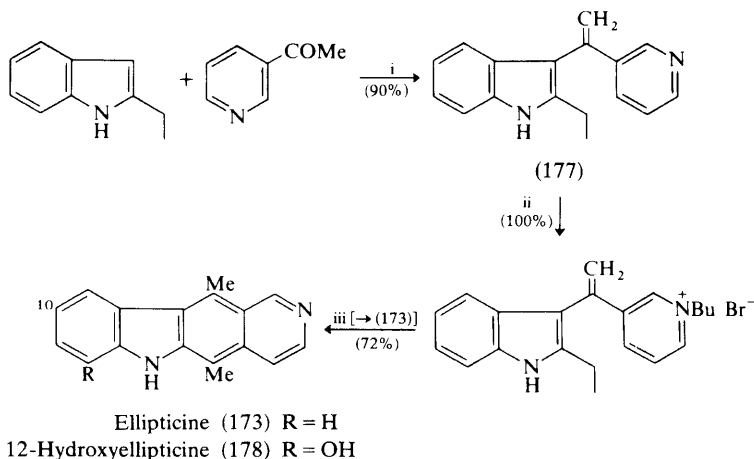
⁹⁵ M. Sainsbury, *Synthesis*, 1977, 437.

⁹⁶ A. P. Kozikowski and N. M. Hasan, *J. Org. Chem.*, 1977, **42**, 2039.

Jackson *et al.*⁹⁷ have reported yet another refinement of the Cranwell–Saxton synthesis of ellipticine, and have also investigated a new route, which has so far resulted in the preparation of the intermediates, (176a) and (176b). In principle, these diphenylamine derivatives should be convertible into *N*-acetyl-ellipticines by thermal cyclisation and dehydrogenation, or into ellipticine by photocyclisation of the free amines. Although a considerable amount of (176a) was prepared, its conversion into 9-methoxyellipticine has not yet been reported.



Perhaps the shortest synthesis⁹⁸ reported to date involves the acid-catalysed condensation of 2-ethylindole and 3-acetylpyridine to give the intermediate (177), which can be converted into ellipticine (173) by quaternization followed by pyrolysis (Scheme 27). Very high yields are quoted, although the final, pyrolysis stage is not completely regiospecific, and the yield obtained is clearly very sensitive to the experimental conditions.



Reagents: i, HBr, MeOH, reflux for 3 h; ii, BuBr; iii, >350 °C for 5 min.

Scheme 27

In the rat, ellipticine is hydroxylated⁹⁹ to give 10-hydroxyellipticine (major metabolite) and 12-hydroxyellipticine (178). The former was already known; the

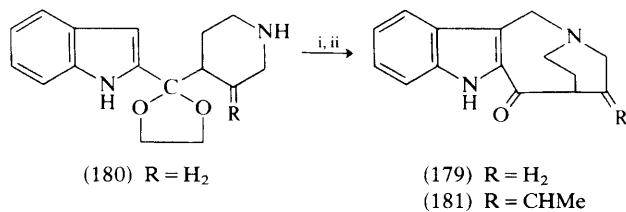
⁹⁷ A. H. Jackson, P. R. Jenkins, and P. V. R. Shannon, *J.C.S. Perkin I*, 1977, 1698.

⁹⁸ J. Bergman and R. Carlsson, *Tetrahedron Letters*, 1977, 4663.

⁹⁹ J. Y. Lallemand, P. Lemaitre, L. Beeley, P. Lesca, and D. Mansuy, *Tetrahedron Letters*, 1978, 1261.

latter was unequivocally identified, following a tentative structural assignment based on the n.m.r. spectrum, by synthesis from 7-methoxyindole, by the modified Cranwell–Saxton synthesis. The final product of the synthesis, 12-methoxyellipticine, was demethylated by means of pyridinium chloride.⁹⁹

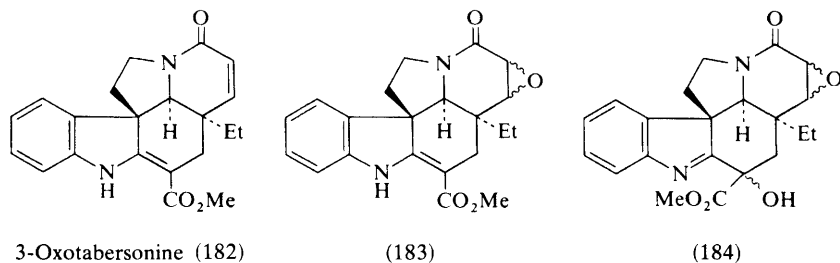
The first synthesis of the apparicine ring system has been reported by Joule and his collaborators.¹⁰⁰ The critical stage in the synthesis of the model compound (179) involved the closure of ring C by a Mannich reaction on the piperidine ketal (180) (Scheme 28); however, the extension of the route to the preparation of the desired apparicine precursor (181) has not yet proved possible.



Reagents: i, CH₂O, H₂O, AcOH, at r.t., for 4.5 h; ii, dilute HCl, at r.t., for 1 day.

Scheme 28

Aspidospermine–Aspidofractine–Eburnamine Group. New extractions of alkaloids of this group include the isolation of quebrachamine, (–)-vincadifformine, (–)-Δ¹-aspidospermidine, (–)-kopsinine, eburnamine, and (–)-12-methoxy-Δ¹⁴-vincamine from the leaves of *Hunteria elliptica*,⁵⁸ venalstonine and vindoline from the roots of *Catharanthus roseus*,^{57a} and voaphylline and its N_a-methyl derivative, hecubine, from the leaves of *Ervatamia coronaria* Stapf.¹⁰¹ Vindoline is also reported to be among the alkaloids obtained in the callus tissue culture of *C. roseus*.^{57b} Tabersonine, Δ¹⁴-vincamine, and 16-*epi*-Δ¹⁴-vincamine occur in the seeds of *Amsonia elliptica*,^{57d} together with four new alkaloids, 3-oxotabersonine (182), tabersonine N_b-oxide, 14,15-epoxy-3-oxovincadifformine (183), and 14,15-epoxy-16-hydroxy-16-methoxycarbonyl-3-oxo-1,2-dehydroaspidospermidine (184). This last compound may well be an artefact, derived by aerial oxidation of (183). The structures of Δ¹⁴-vincamine and



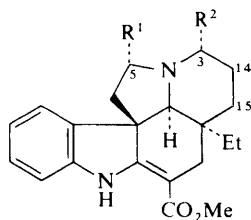
¹⁰⁰ D. I. C. Scopes, M. S. Allen, G. J. Hignett, N. D. V. Wilson, M. Harris, and J. A. Joule, *J.C.S. Perkin I*, 1977, 2376.

¹⁰¹ C. G. Gonzalez and J. Martinez, *Rev. Cubana Farm.*, 1976, **10**, 45 (*Chem. Abs.*, 1977, **87**, 2343).

its C-16 epimer were established by partial synthesis from tabersonine according to the Lévy-Le Men¹⁰² procedure; oxidation of tabersonine sulphate by means of *m*-chloroperbenzoic acid, followed by rearrangement in acetic acid, gave a mixture of Δ^{14} -vincamine and its 16-epimer.

Details of the X-ray crystal structure determination of meloscandonine¹⁰³ and *N*_a-methyl-19-*epi*-vindolinol^{104a} have been published. This latter derivative is obtained by the *N*_a-methylation of vindolinine, followed by reduction (LiAlH₄) and epimerization (CF₃CO₂H); this work also serves to confirm the structure of 19-*epi*-vindolinine, an alkaloid isolated earlier from *Melodinus balansae*.^{104b}

The photo-oxidation of vincadiformine (185) in the presence of Rose Bengal and potassium cyanide affords¹⁰⁵ the nitriles (186) and (187), presumably by nucleophilic attack by cyanide ion on the appropriate C-3 (or C-5), *N*_b-immonium ion; *N*-acetyl-2,16-dihydrovincadiformine gives mainly the 3 α -cyano-derivative. Tabersonine (188) and *N*-acetyl-2,16-dihydrotabersonine give exclusively 3 α -cyano-derivatives, owing to the superior stability of the conjugated 3, *N*_b-immonium ion; cyanide attack at C-15 in this ion was, however, not observed.



R ¹	R ²
(185) H	H
(186) H	CN
(187) CN	H
(188) H	H ; $\Delta^{14,15}$

A novel route to secodine derivatives (Scheme 29) involves the photo-induced addition of indoline-2-thiones, *e.g.* (189), to methyl acrylate.¹⁰⁶ The product (190) of this addition was converted by standard procedures into the close relative (191) of the unstable secodine. Attempts to introduce the desired 16,17 double bond *via* the sulphoxide gave a product which behaved as a mixture of dimers (192) of secodine. This is the closest approach that has yet been made to the synthesis of secodine; since distillation of the dimer is reported to give the fugitive monomer, this route may afford a preparation of the latter for cyclisation studies.

A new synthesis¹⁰⁷ of tabersonine uses as essential starting material (–)-3-oxovincadiformine (193), obtained by the oxidation of (–)-tabersonine with

¹⁰² G. Hugel, J. Lévy, and J. Le Men, *Compt. rend.*, 1972, **274**, C, 1350; (see also *Chem. Abs.*, 1975, **83**, 79 457).

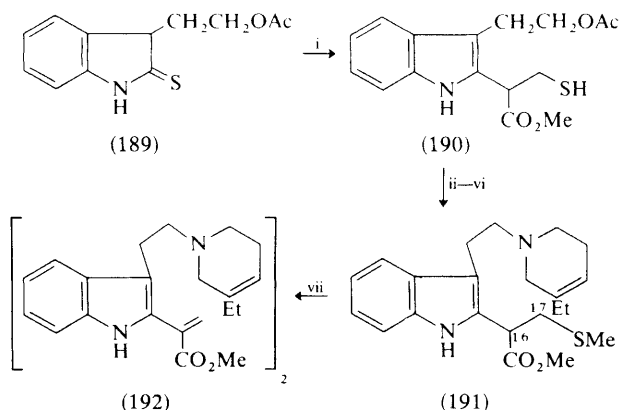
¹⁰³ N. Rodier, Y. Mauguen, M. Hachem-Mehri, and M. Plat, *Acta Cryst.*, 1978, **B34**, 232.

¹⁰⁴ (a) A. Chiaroni, N. Langlois, and C. Riche, *Acta Cryst.*, 1977, **B33**, 3410; (b) H. Mehri, M. Koch, M. Plat, and P. Potier, *Ann. pharm. franc.*, 1972, **30**, 643.

¹⁰⁵ J. Santamaria, D. Herlem, and F. Khuong-Huu, *Tetrahedron*, 1977, **33**, 2389.

¹⁰⁶ C. Marazono, J. L. Fourrey, and B. C. Das, *J.C.S. Chem. Comm.*, 1977, 742.

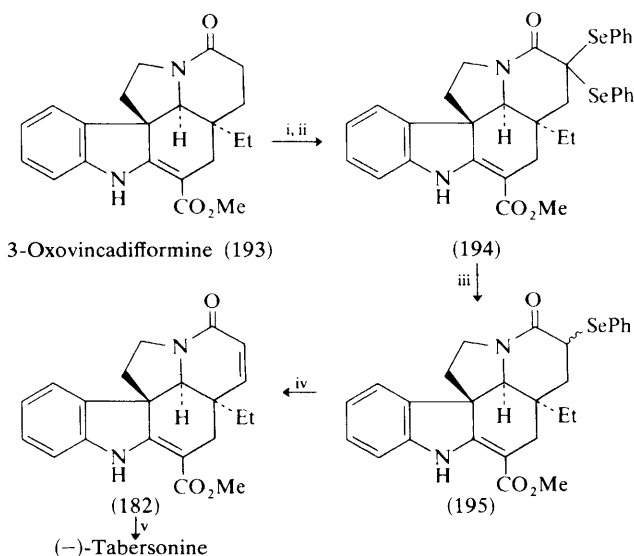
¹⁰⁷ J. Lévy, J. Y. Laronze, J. Laronze, and J. Le Men, *Tetrahedron Letters*, 1978, 1579.



Reagents: i, $h\nu$, $\text{CH}_2=\text{CHCO}_2\text{Me}$; ii, MeI, K_2CO_3 , acetone; iii, hydrolysis; iv, PBr_3 ; v, 3-ethylpyridine; vi, NaBH_4 ; vii, $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$, at -30°C .

Scheme 29

permanganate, followed by reduction of the 14,15 double-bond. The double bond was re-introduced into (193) by an ingenious process which involved the reaction of the dianion of (193) with phenylselenenyl chloride to give the disubstituted derivative (194). Reductive removal of one PhSe group gave a mixture of epimeric monophenylselenenyl derivatives (195), which on oxidation and spontaneous fragmentation gave 3-oxotabersonine (182). Carefully controlled



Reagents: i, LiNPr_2 , HMPA, THF, at -78°C ; ii, PhSeCl ; iii, PhS^- ; iv, $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$; v, LiAlH_4 , THF, at 0°C , for 4 h.

Scheme 30

reduction of (182) finally afforded (–)-tabersonine (Scheme 30). Since (±)-3-oxovincadifformine (193) is available by a three-stage synthesis from 2-hydroxytryptamine, the formal synthesis of tabersonine is complete.

Takano *et al.* have reported^{108a} two improved routes to the synthesis of the tetracyclic amino-ketone (196), a vital intermediate in Büchi's synthesis of vindoline. The first of these routes involved the construction of a diazo-ketone (197) which, in the presence of strong acid, behaves as the source of a highly electrophilic α -ketocarbenium ion. Electrophilic attack at the position α to the indole nitrogen followed by rearrangement gives a mixture of epimers (198), which was reduced to a single isomer (196) (Scheme 31). The second approach took advantage of the preferred electrophilic substitution at the 3-position in a 2,3-disubstituted indole. Thus, cyclisation of the indole ester (199), prepared from the appropriate tryptamine and ethoxymethylenemalonate ester, gave a tricyclic intermediate which could further cyclise, presumably *via* the Fischer base (200); the final product, following hydrolysis and decarboxylation, was again the unsaturated amino-ketone (198), which was reduced to (196). Both sequences were carried out on the un-methoxylated compounds (201) and (202), which gave the amino-ketone (203), the intermediate in Büchi's vindorosine synthesis (Scheme 31).^{108a}

Ban *et al.*^{108b} have reported yet another synthesis of (196) by appropriate modification of the route used by the same group for the synthesis of the aspidospermidine intermediate (204a). Construction of the methoxy-derivative (204b) by the same route from 2-hydroxy-6-methoxytryptamine resulted in the formation of a single isomer containing a *cis* C/D ring junction; methylation, which also gave a single isomer, followed by reduction, completed the synthesis (Scheme 31).

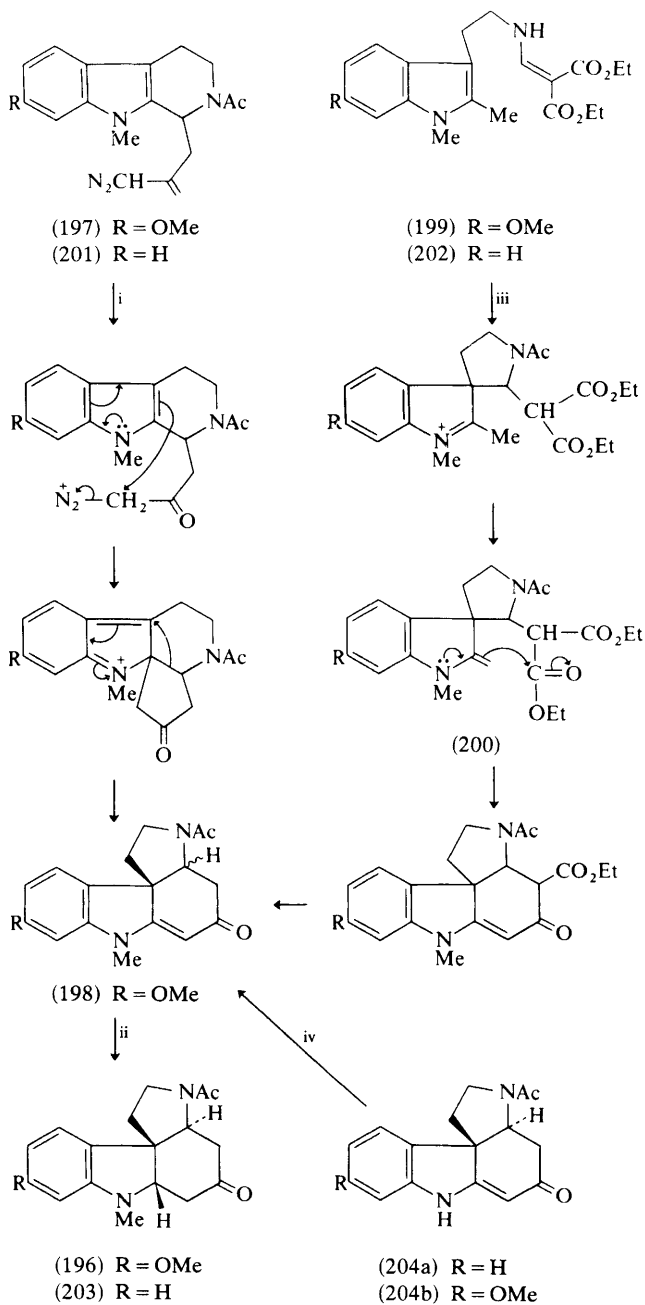
Kutney *et al.*¹⁰⁹ have investigated the general reactivity of the various positions in the vindoline (205) nucleus, and have prepared several new derivatives. Electrophilic substitution occurs with particular facility at position 10, as expected; N_b can be protected as the 3-lactam by oxidation with mercuric acetate, preferably on vindoline *O*-acetate. In contrast, dihydrovindoline derivatives are oxidised at position 5. Potassium permanganate was observed to attack both positions 3 and 5, with concomitant oxidation of the N_a-methyl group. Substitution reactions in ring C, particularly at C-17, depend critically on the existing substitution, and on the conformation of ring C.

Interest continues to be shown in the synthesis of eburnamonine and vincamine owing to their useful pharmacological properties. In their synthesis of eburnamonine, Szántay and his collaborators¹¹⁰ adopted the annelation reaction between 3,4-dihydro- β -carboline and an appropriate enone for the purpose of constructing the tetracyclic intermediate (207) (Scheme 32); both epimers of (207) were obtained. These were separated, and the synthesis was completed with both epimers. A synthesis of both eburnamonine and isoeburnamonine was thus reported; only that leading to eburnamonine is illustrated.

¹⁰⁸ (a) S. Takano, K. Shishido, M. Sato, and K. Ogasawara, *Heterocycles*, 1977, **6**, 1699; (b) Y. Ban, Y. Sekine, and T. Oishi, *Tetrahedron Letters*, 1978, 151.

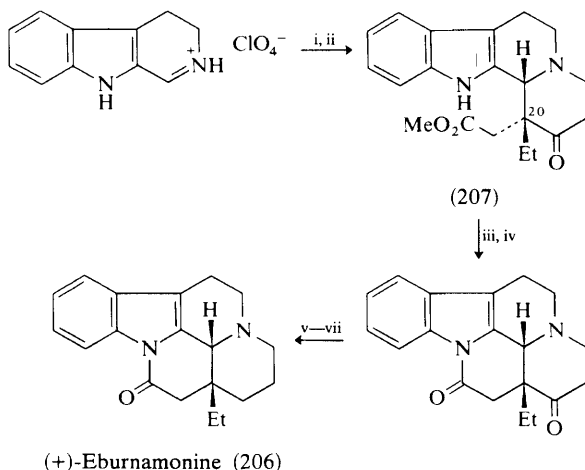
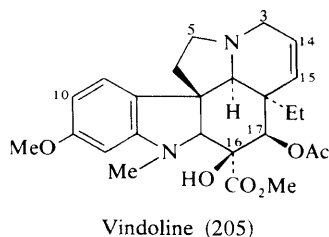
¹⁰⁹ J. P. Kutney, U. Bunzli-Trepp, T. Honda, J. Katsube, and B. R. Worth, *Helv. Chim. Acta*, 1978, **61**, 1554.

¹¹⁰ L. Novák, J. Rohály, and Cs. Szántay, *Heterocycles*, 1977, **6**, 1149.



Reagents: i, CF₃CO₂H; ii, Li, NH₃; iii, AcOH, Ac₂O, reflux, 72 h; iv, NaH, MeI, DMF.

Scheme 31



Reagents: i, $\text{MeO}_2\text{CCH}_2\text{CHEtCOCH}=\text{CH}_2$; ii, NEt_3 , MeOH , r.t., for 4 days; iii, NaOBU^1 , PhMe , at r.t., for 0.5 h; iv, separation of epimers; v, $p\text{-MeC}_6\text{H}_4\text{SO}_2\text{NHNH}_2$, HCl ; vi, NaBH_3CN , DMF , sulpholan, TsOH , at 110°C ; vii, (+)-*OO*-dibenzoyltartaric acid.

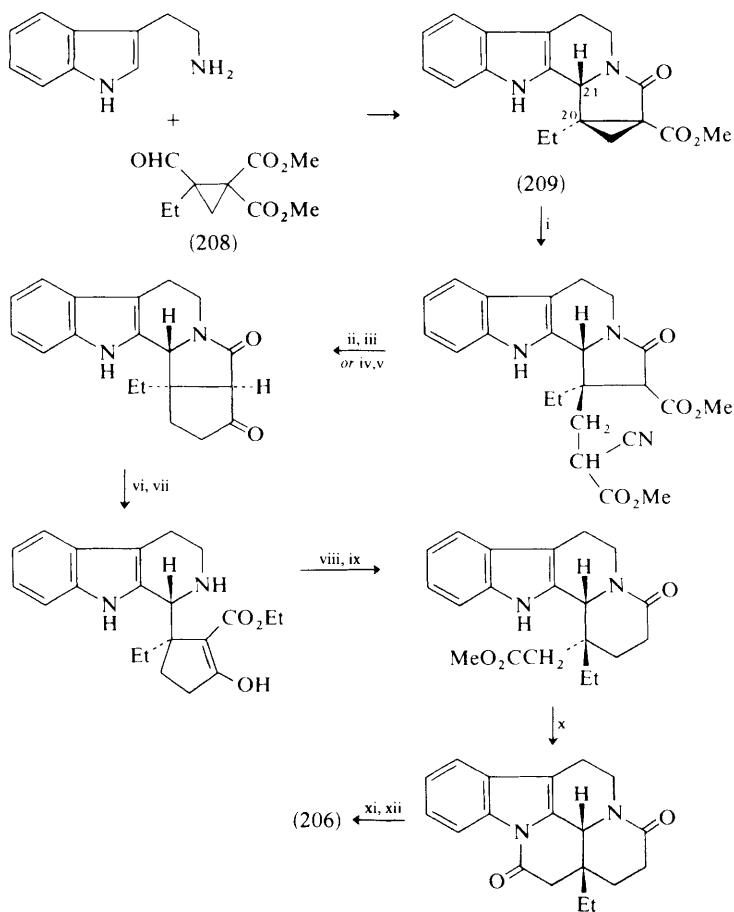
Scheme 32

Winterfeldt's synthesis¹¹¹ follows quite different lines from any previous synthesis, and leads to eburnamonine with a very high degree of stereoselectivity (Scheme 33). The initial stage, which involves the condensation of tryptamine with the cyclopropyl aldehyde-ester (208), gave 85% of pentacyclic lactam ester (209); only 15% of the epimer of (209) was obtained. The correct stereochemical relationship between C-20 and C-21 was thus assured, and this remained undisturbed during the later stages of the synthesis.

An indirect synthesis^{112a} of eburnamonine (vincamone) results from the ring contraction of (–)-homovincamone (210) by Beckmann rearrangement of the derived α -oximino-compound, since (210) has previously been obtained by partial synthesis from (–)-vincadifformine. The initial product of the

¹¹¹ F. Klatter, U. Rosentreter, and E. Winterfeldt, *Angew. Chem.*, 1977, **89**, 916 (*Internat. Edn.*, p. 878).

¹¹² (a) D. Cartier, J. Lévy, and J. Le Men, *Bull. Soc. chim. France*, 1976, 1961; (b) J. Laronze, J. Y. Laronze, J. Lévy, and J. Le Men, *ibid.*, 1977, p. 1195; (c) J. Y. Laronze, J. Laronze, B. Caron, J. Lévy, and J. Le Men, *ibid.*, p. 1207.



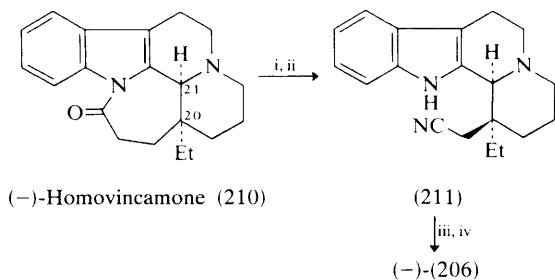
Reagents: *i*, $\text{LiCH}(\text{CN})\text{CO}_2\text{Me}$; *ii*, LiI , DMF; *iii*, KF , AcOH ; *iv*, RO^- ; *v*, H^+ ; *vi*, $\text{Et}_3\text{O}^+ \text{PF}_6^-$; *vii*, hydrolysis; *viii*, MeO^- ; *ix*, re-esterification; *x*, $\text{CF}_3\text{CO}_2\text{H}$; *xi*, $\text{Et}_3\text{O}^+ \text{BF}_4^-$; *xii*, NaBH_4 .

Scheme 33

rearrangement was the nitrile (211) (Scheme 34); in contrast, the C-21 epimer of (210), synthesised together with several other homoeburnane derivatives,^{112b} gives a ureide in the Beckmann rearrangement under somewhat different conditions. The Reims group have also synthesised^{112c} for pharmacological examination a number of E-chanoehomoeburnane derivatives, *i.e.* those lacking ring E.

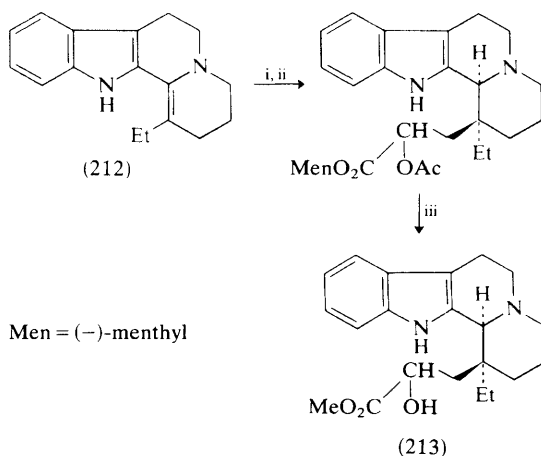
Details of Szántay's synthesis of vincamine have been published.¹¹³ A significant stereoselectivity was introduced into the synthesis by a modification in which the enamine (212) was alkylated by means of the (-)-menthyl ester of α -acetoxyacrylic acid (Scheme 35). Methanolysis of the product gave a methyl

¹¹³ Cs. Szántay, L. Szabó, and G. Kalaus, *Tetrahedron*, 1977, **33**, 1803.



Reagents: i, Nitrosation; ii, POCl_3 ; iii, KOH , MeOH ; iv, HCl .

Scheme 34



Reagents: i, $\text{CH}_2=\text{C}(\text{OAc})\text{CO}_2\text{Men}$; ii, H_2 , Pd/C ; iii, NaOMe .

Scheme 35

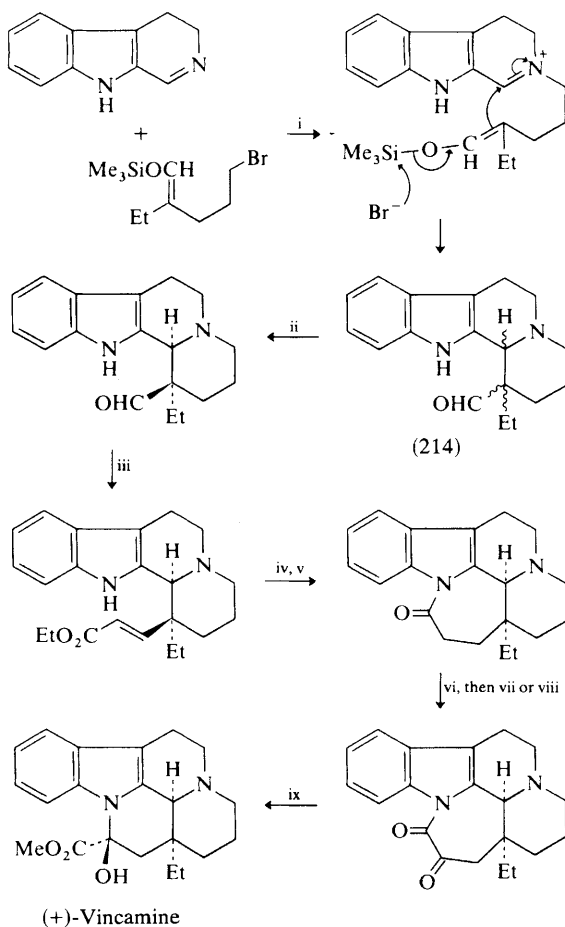
ester (213) with $\sim 40\%$ optical purity; resolution was completed *via* the dibenzoyltartrate salt, and the synthesis finished as before.

Oppolzer's second vincamine synthesis¹¹⁴ proceeds *via* the amino-aldehyde (214) (Scheme 36), the final stage in the preparation of which involved an ingenious new modification of the Mannich reaction; the use of silyl enol ethers as enol equivalents is reported to give much improved yields, and may well be generally applicable. This synthesis is also remarkable in that the *cis*-racemate of (214) could be separated and resolved, and unwanted *cis*-enantiomer and *trans*-epimer could be re-equilibrated with the desired *cis*-enantiomer by reversible Mannich fission on the tosylate of (214). In this way virtually all the amino-aldehyde (214) could be utilised.

Presumably arising out of the last stage in Oppolzer's first vincamine synthesis is a study¹¹⁵ of the addition of alcohols, amines, and thiols to the double bond in

¹¹⁴ W. Oppolzer, H. Hauth, P. Pfäffli, and R. Wenger, *Helv. Chim. Acta*, 1977, **60**, 1801.

¹¹⁵ P. Pfäffli and H. Hauth, *Helv. Chim. Acta*, 1978, **61**, 1682.



Reagents: i, EtNPr_2 , DMF, at 70°C ; ii, (+)-malic acid; iii, $(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}$, NaH, DMF; iv, H_2 , Pd; v, $(\text{Me}_3\text{Si})_2\text{NNA}$; vi, BuONO, $(\text{Me}_3\text{Si})_2\text{NNA}$, PhMe; vii, CH_2O , H_2O , HCl, at $70\text{--}80^\circ\text{C}$; viii, ceric ammonium nitrate, MeOH, at -30°C ; ix, NaOMe, MeOH.

Scheme 36

apovincamine and eburnamenine; the stereochemistry of these reactions was also discussed.

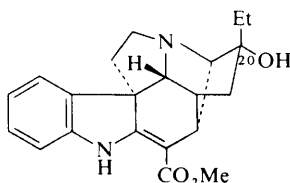
Catharanthine–Ibogamine–Cleavamine Group. The chemistry and pharmacology of alkaloids of *Tabernaemontana iboga* have been reviewed.¹¹⁶ New extractions have resulted in the isolation of coronaridine (previously observed), voacangine, isovoacangine, and ibogamine from the bark of *Ervatamia coronaria*,¹¹⁷ coronaridine and 19-oxocoronaridine from the roots of *Tabernaemontana*

¹¹⁶ J. C. Gagnault and J. Delourme-Houdé, *Fitoterapia*, 1977, **48**, 243.

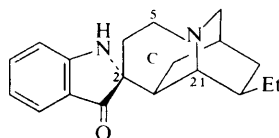
¹¹⁷ C. G. Gonzalez and C. Lorincz, *Rev. Cubana Farm.*, 1976, **10**, 31 (*Chem. Abs.*, 1977, **86**, 185 878).

holstii,^{84a} and ibogamine and isovoacangine from the stem bark of *T. johnstonii*.^{84b} Voacangine, coronaridine, and 19-isoheyanine also occur in the roots of *Hazunta modesta*.⁸⁵ Catharanthine is reported to be produced in the callus tissue culture of *Catharanthus roseus*.^{57b}

The X-ray crystal structure determination¹¹⁸ of pandine (215) defines the configuration of C-20 as *R*, if it is accepted that the absolute configuration at positions 3 and 7 previously proposed is correct.



Pandine (215)



Iboluteine (216)

The ¹³C n.m.r. spectrum of iboluteine (216), coupled with a lanthanide shift study, reveals¹¹⁹ that C-2 has the *R* configuration, and the six-membered ring involved in the spirocyclic linkage adopts a twist boat conformation, owing to the proximity of the carbonyl group to axial hydrogens at positions 5 and 21 in the chair form; these interactions are relieved in the deoxy-dihydro-derivative, in which ring C is a normal chair.

The iboga alkaloids behave differently from the vincadifformine group on photochemical oxidation; iboxyphylline is rapidly oxidised at C-16 to give a hydroxy-indolenine, but only in the presence of oxygen and in the absence of cyanide.¹⁰⁵

Pseudovincadifformine (217), prepared by the known procedure from catharanthine [reduction by NaBH₄ and AcOH, followed by oxidation with Hg(OAc)₂] undergoes the same rearrangement as vincadifformine when oxidised, then treated with triphenylphosphine (Scheme 37).¹²⁰ The products, (20*S*)-pseudovincamine (218) and its 16-epimer, belong to the sub-group C₂ of alkaloids according to an extended biogenetic classification now proposed, a structural group that has so far not been found in Nature.

The chemistry of catharanthine is still being vigorously investigated, in connection with the synthesis of vinblastine and its analogues. Details of some of the earlier work have now become available.¹²¹ New work includes the preparation¹²² of a potentially useful keto-ester (220) from an isoxazolidine derivative (219) obtainable^{22f} from catharanthine. Hydrogenolysis of (219), followed by allylic oxidation and internal Michael addition, affords (220) as a mixture of C-20 epimers (Scheme 38). Other derivatives include¹²³ 15β-hydroxy-15,20-dihydro-

¹¹⁸ A. Ducruix and C. Pascard, *Acta Cryst.*, 1977, **B33**, 1990.

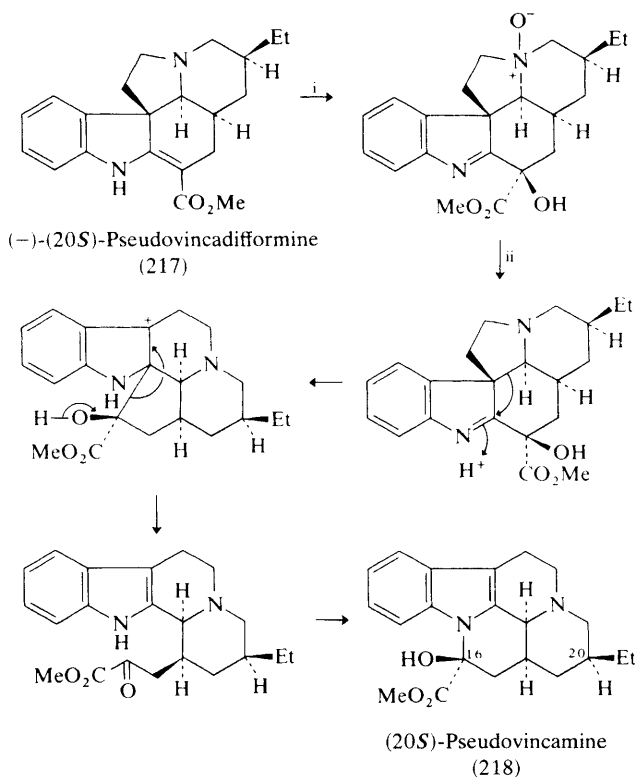
¹¹⁹ E. Wenkert and H. E. Gottlieb, *Heterocycles*, 1977, **7**, 753.

¹²⁰ J. Le Men, C. Caron-Sigaut, G. Hugel, L. Le Men-Olivier, and J. Lévy, *Helv. Chim. Acta*, 1978, **61**, 566.

¹²¹ J. P. Kutney, G. H. Bokelman, M. Ichikawa, E. Jahngen, A. V. Joshua, P. H. Liao, and B. R. Worth, *Canad. J. Chem.*, 1977, **55**, 3227.

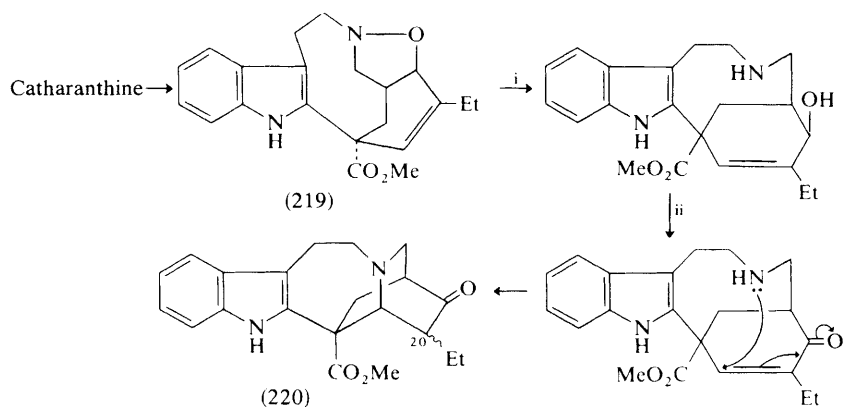
¹²² Y. Langlois, N. Langlois, and P. Potier, *Compt. rend.*, 1977, **284**, C, 809.

¹²³ J. P. Kutney, T. Honda, A. V. Joshua, N. G. Lewis, and B. R. Worth, *Helv. Chim. Acta*, 1978, **61**, 690.



Reagents: i, $\text{O}_2\text{NC}_6\text{H}_4\text{CO}_3\text{H}$; ii, PPh_3 , AcOH , H_2O .

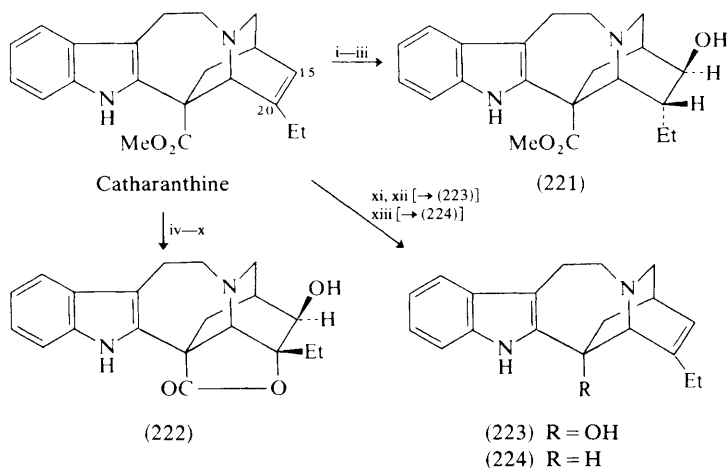
Scheme 37



Reagents: i, Hydrogenolysis; ii, MnO_2 .

Scheme 38

catharanthine (221), the hydroxy-lactone (222), which has the same oxygenation pattern as that proposed^{22*r*} for the dimeric alkaloid vincadioline, and (223), the product of oxidative decarboxylation of catharanthinic acid (Scheme 39). In this



Reagents: i, BH_3 , Me_2S , PhH ; ii, H_2O_2 , NaOH ; iii, THF , NEt_3 , heat; iv, KH , ClCO_2Me ; v, I_2 , base; vi, $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$; vii, KOH ; viii, P_2S_5 ; ix, LiI , py ; x, Raney nickel, EtOH ; xi, 12% NaOH , EtOH ; xii, PhSeCl , CH_2Cl_2 , NEt_3 ; xiii, AcOH , H_2S , dioxan.

Scheme 39

work, and in connection with attempts to prepare 20β -hydroxy-dihydrocatharanthine, which is an obvious precursor for the synthesis of leurosidine, it was observed that displacement of substituents at positions 15 and 20 in the dihydrocatharanthine skeleton is very difficult; α -approach at C-15 appears to be severely hindered, and α -functionalisation at C-20 has only been observed through lactone formation by intramolecular attack by the methoxycarbonyl group. In view of this, the reported formation of 20α -acetoxy-dihydrocatharanthine^{22*h*} by the modified Prévost reaction on catharanthine is surprising; in fact, the Canadian workers have so far been unable to repeat this important preparation.

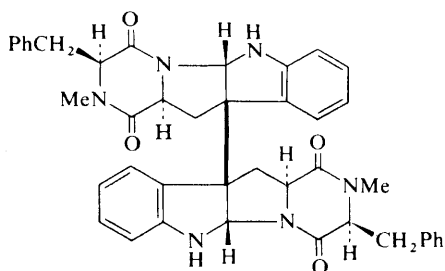
Finally, a smooth (if slow) demethoxycarbonylation of catharanthine [\rightarrow (224)] by means of acetic acid and hydrogen sulphide in dioxan has been reported.¹²⁴

4 Bis-indole Alkaloids

Ditryptophenaline (225) is a dimeric diketopiperazine derivative isolated¹²⁵ from three strains of *Aspergillus flavus*. The structure (relative configuration only) was established by the X-ray method, and is simply derived from two molecules of tryptophan and two of *N*-methylphenylalanine. Ditryptophenaline has no toxic

¹²⁴ Atta-ur-Rahman, S. Firdous, and A. Basha, *Z. Naturforsch.*, 1978, **33b**, 469.

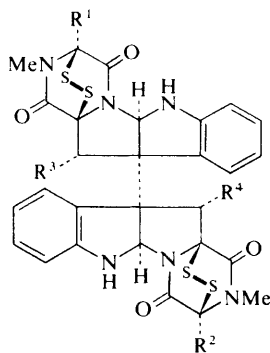
¹²⁵ J. P. Springer, G. Büchi, B. Kobbe, A. L. Demain, and J. Clardy, *Tetrahedron Letters*, 1977, 2403.



Dityryptophenaline (225)

or antibiotic properties, and is obviously not responsible for the toxic effects of *A. flavus*.

Melinacidins II—IV are antibacterial agents, belonging to the epidithia-diketopiperazine group, which are produced by *Acrostalagmus cinnabarinus* var. *melinacidinus*.¹²⁶ Direct comparison established that melinacidin IV is identical with 11 α ,11' α -dihydroxychaetocin (226). The other melinacidins exhibit very similar spectrographic properties, including similar c.d. spectra, and are clearly very closely related, structurally and stereochemically. Melinacidin III (227) is a deoxy-melinacidin IV and melinacidin II a dideoxy-melinacidin IV, of structure (228a) or (228b).



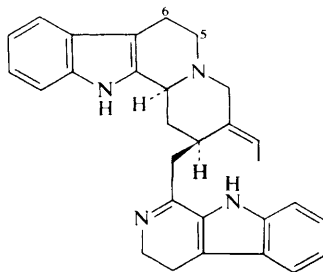
	R ¹	R ²	R ³	R ⁴
Melinacidin IV (226)	CH ₂ OH	CH ₂ OH	OH	OH
Melinacidin III (227)	CH ₂ OH	CH ₂ OH	OH	H
Melinacidin II (228a)	CH ₃	CH ₂ OH	H	OH
or (228b)	CH ₃	CH ₂ OH	OH	H

Analysis of the ¹³C n.m.r. spectrum of geissospermine⁶⁶ reveals that in solution, as in the crystal,^{18c} the molecule adopts a conformation in which the C/D ring junction in the geissoschizine component is *cis*, and C-2 and C-16 are axially disposed to ring D.

Tetrahydropresecamine has been reported to occur in the leaves of *Hunteria elliptica*.⁵⁸ Caracurine V and its mono- and bis-N_b-oxides have been identified

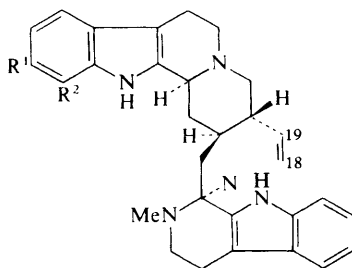
¹²⁶ A. D. Argoudelis and S. A. Mizsak, *J. Antibiotics*, 1977, **30**, 468.

among the other alkaloids of the stem bark of *Strychnos dolichothyrsa*.¹²⁷ Tchibangensine, a new *Strychnos* alkaloid isolated¹²⁸ from the stem and root bark of *S. tchibangensis* Pellegr., has the structure (229), since hydrogenation gives a



Tchibangensine (229)

mixture of ochrolifuanines C and D, and oxidation (CuCl_2) introduces a double bond into the 5,6-position, with formation of usambarensine. Tchibangensine may be identical with an alkaloid isolated earlier from *S. usambarensis*, and identified by synthesis as a 5,6-dihydro-usambarensine.²²ⁱ Further extractions of the leaves of *S. usambarensis*¹²⁹ have resulted in the isolation of fourteen alkaloids. Two non-oxygenated bases are represented by usambarine (known), and a new base, which proves to be 18,19-dihydro-usambarine (230). The remaining bases are phenolic, and include two usambaridine isomers, named usambaridine Br (231) and usambaridine Vi (232), which differ only in the position of the phenolic hydroxy-group. The two dihydro-derivatives of (231) and (232) were also encountered, as was a diphenolic base, strychnobaridine, to which



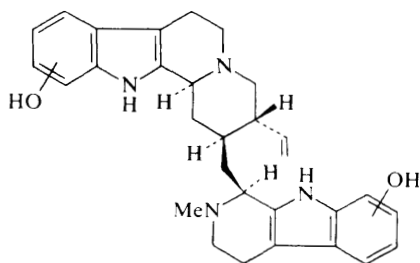
18,19-Dihydro-usambarine (230) $\text{R}^1 = \text{R}^2 = \text{H}$; 18,19-dihydro
 Usambaridine Br (231) $\text{R}^1 = \text{OH}$, $\text{R}^2 = \text{H}$
 Usambaridine Vi (232) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{OH}$

the structure (233; positions of phenolic hydroxy-groups as yet unknown) has been tentatively assigned. Strychnopentamine and its two isomers constitute, at present, a unique group of bases which contain a pyrrolidine ring attached to an usambaridine skeleton. The structure and relative configuration of the crystalline

¹²⁷ R. Verpoorte and A. B. Svendsen, *J. Pharm. Sci.*, 1978, **67**, 171.

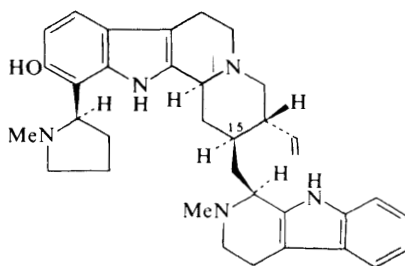
¹²⁸ C. Richard, C. Delaude, L. Le Men-Olivier, and J. Le Men, *Phytochemistry*, 1978, **17**, 539.

¹²⁹ L. Angenot, C. Coune, and M. Tits, *J. Pharm. Belg.*, 1978, **33**, 11.



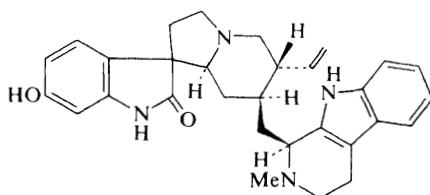
Strychnobaridine (233)

strychnopentamine (234) were deduced^{130a} by the *X*-ray method; the absolute configuration depicted is assumed. Isostrychnopentamines A and B are probably



Strychnopentamine (234)

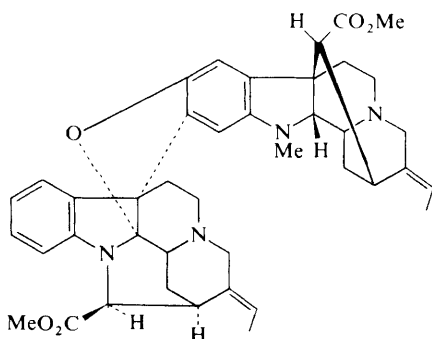
stereoisomers, but no further work has yet been reported. The remaining four alkaloids, strychnofoline, isostrychnofoline, strychnophylline, and isostrychnophylline, are oxindole derivatives, and appear to be the first representatives of this group to be isolated from *Strychnos* species.¹²⁹ Strychnofoline, whose structure was deduced by *X*-ray crystal structure analysis of its ethanol solvate,^{130b} is simply the oxindole analogue (235) of usambaridine Br; again the absolute configuration depicted is based on the usual biogenetic arguments. The structures of the other three oxindole alkaloids have not been discussed.



Strychnofoline (235)

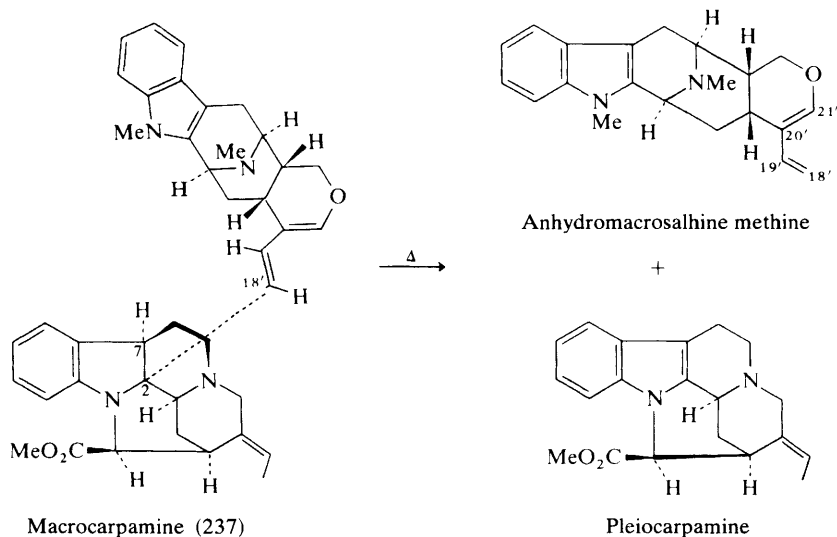
¹³⁰ (a) L. Dupont, J. Lamotte-Brasseur, O. Dideberg, H. Campsteyn, M. Vermeire, and L. Angenot, *Acta Cryst.*, 1977, **B33**, 1801; (b) O. Dideberg, J. Lamotte-Brasseur, L. Dupont, H. Campsteyn, M. Vermeire, and L. Angenot, *ibid.*, p. 1796.

Pleiocraline (236) occurs with pleiocorine in *Alstonia deplanchei*,¹³¹ and shares many of the latter's structural features. Thus, the ¹³C n.m.r. spectrum reveals that pleiocraline also contains a 2,7-dihydropleiocarpamine unit, but, in place of the vincorine unit present in pleiocorine, pleiocraline contains a component closely related to *N*_a-methyl-deacetyldeformo-1,2β*H*-dihydroakuammiline. The ¹³C n.m.r. data also indicate that the nature and positions of attachments of the two monomeric components are the same in pleiocorine and pleiocraline.



Pleiocraline (236)

A 2,7-dihydropleiocarpamine unit is also present in the alkaloid macrocarpamine (237), an amorphous base recently isolated¹³² from the bark of *Alstonia macrophylla* Wall. The second component is anhydromacrosalrhine methine, which is attached to pleiocarpamine by a single bond between C-2 of the latter



Macrocarpamine (237)

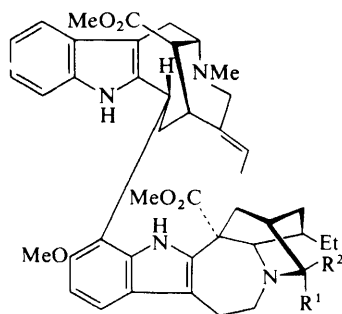
Pleiocarpamine

¹³¹ B. C. Das, J. P. Cosson, and G. Lukacs, *J. Org. Chem.*, 1977, **42**, 2785.

¹³² F. Mayerl and M. Hesse, *Helv. Chim. Acta*, 1978, **61**, 337.

and C-18' of the methine; indeed, pyrolysis of the alkaloid gives a small yield of (\pm)-pleiocarpamine and (-)-anhydromacrosalpine methine. The position of coupling was deduced from the mass, ^{13}C n.m.r., and ^1H n.m.r. spectra. Pertinent data include: in the ^{13}C n.m.r. spectrum, a *singlet* owing to a heterosubstituted sp^3 -hybridised carbon atom, which must be C-2 of the pleiocarpamine unit, further substituted by the methine component; C-7 gives rise to a doublet, and therefore carries a hydrogen atom. The proton n.m.r. spectrum contains signals owing to a *trans*-disubstituted double bond (C-18' and C-19'); one proton is missing from C-18' of the anhydromacrosalpine methine unit, and this must therefore be the other point of attachment of the two units.

Tabernaegantine A has been shown to occur in the roots of *Hazunta modesta*.⁸⁵ A number of dimeric alkaloids have also been isolated from two *Tabernaemontana* species. The roots of *T. holstii* contain^{84a} conoduramine, conodurine, gabunine, and two new alkaloids, 19-oxoconodurine (238) and 19-(2-oxopropyl)-conodurine (239); however, these last two alkaloids may be artefacts, generated either by oxidation of conodurine [\rightarrow (238)] or by oxidation to the carbinolamine stage, followed by condensation with acetone [\rightarrow (239)]. It is of interest that gabunine and (239) showed significant inhibitory activity against



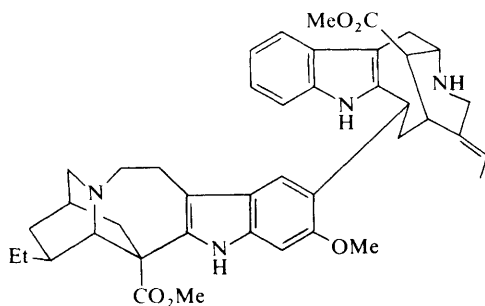
19-Oxoconodurine (238) $\text{R}^1\text{R}^2 = \text{O}$

19-(2-Oxopropyl)-conodurine (239) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_2\text{COMe}$

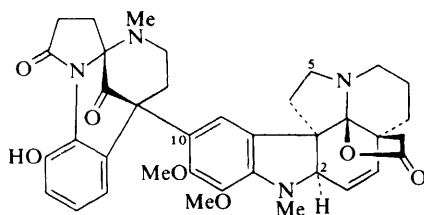
P-399 lymphocytic leukaemia in the mouse, and appear to be responsible, at least in part, for the antileukaemic and cytotoxic activity of extracts of the roots of *T. holstii*.¹³³ A similar activity was observed in extracts of the stem bark of *T. johnstonii*, which yielded^{84b} conodurine, conoduramine, and gabunine, together with three new alkaloids, gabunamine (240), tabernamine, and (tentatively) 19,20-epoxyconoduramine, of which the first two also showed significant cytotoxicity. Evidence relating to the structure of tabernamine has been reported previously in brief,²²ⁱ and some additional evidence is now provided. As would be predicted from its structure, gabunamine (240) gives conoduramine on N_b -methylation, isovoacangine on acid cleavage, and can be synthesised from acid-catalysed condensation of isovoacangine and perivinol.

The oxidation of haplophytine (241) by alkaline hydrogen peroxide simply introduces a carbonyl group at C-5 of the aspidospermine ring system; in contrast,

¹³³ D. G. I. Kingston, *J. Pharm. Sci.*, 1978, **67**, 272.

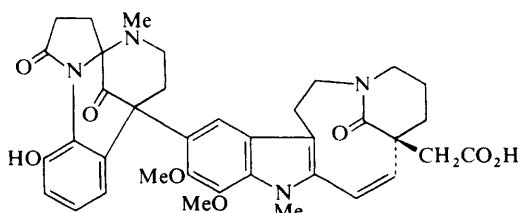


Gabunamine (240)



Haplophytine (241)

alkaline potassium permanganate appears to attack position 2, with formation of a carbinolamine. Hydrolysis of the lactone function, followed by a reverse Mannich cleavage, then leads to a seco-derivative, formulated as (242). The oxidation of the monomeric base aspidophytine (241; but having a hydrogen atom at position 10 instead of the canthiphytine unit) under the same conditions, is exactly analogous.¹³⁴



(242)

The revised structure proposed^{18d} for amataine (243) has been confirmed,¹³⁵ and the evidence obtained in support of it by the French/Swiss group has been thoroughly discussed. Reduction of amataine with sodium borohydride gives a stereoisomer (244) of vobtusine, whereas acid-catalysed hydration of amataine gives hydratoamataine (hydroxyvobtusine) (245), which can be reduced to

¹³⁴ P. Yates, F. N. MacLachlan, and I. D. Rae, *Canad. J. Chem.*, 1978, **56**, 1052.

¹³⁵ V. C. Agwada, J. Naranjo, M. Hesse, H. Schmid, Y. Rolland, N. Kunesch, J. Poisson, and A. Chatterjee, *Helv. Chim. Acta*, 1977, **60**, 2830.

vobtusine (246) by sodium borohydride. The difference between dihydroama-taine (isovobtusine) and vobtusine must reside in the configuration of the spirocyclic centre, in which case the interconversions can be explained as depicted in Scheme 40.

The same group has also provided confirmatory evidence for the structures^{18d} of folicangine and subsessiline lactone,¹³⁶ by correlation of the former with isovoafolidine and of the latter with isovobtusine lactone.

Considerable attention continues to be focussed on the vinblastine group of alkaloids, both in connection with the synthesis of the alkaloids themselves and structural variants that might prove to have useful pharmacological properties. Vinblastine itself is one of the alkaloids produced in the callus tissue culture of *Catharanthus roseus*.^{57b} H.p.l.c. is recommended for the separation of mixtures of *Catharanthus* alkaloids; retention times of the alkaloids differ markedly, and result in good separations of both monomeric and dimeric alkaloids.¹³⁷

The structure proposed earlier for catharinine (vinamidine)^{22k} has now been shown¹³⁸ to be incorrect; catharinine is, in fact, a product of the fission of ring D in leurosine or vinblastine, but in a different sense from that postulated earlier. The structure of catharinine (247) was established by the X-ray crystal structure analysis of the non-vindoline component (248), obtained by the reductive cleavage of catharinine in acid solution. A plausible biogenetic derivation of catharinine from leurosine (249) is illustrated in Scheme 41.

The synthesis of catharine (250),^{139a} to which catharinine was initially believed to be closely related, has in fact been achieved by a process which involves the fission of ring D of the velbanamine component of leurosine (249). This conversion was first reported^{139b} as a result of the accidental over-oxidation that occurred in the preparation of leurosine from anhydrovinblastine by means of *t*-butyl hydroperoxide in the presence of trifluoroacetic acid. The by-product in this reaction was initially regarded as the 21-lactam related to leurosine, but it has now been recognised^{139a} as catharine, and can be prepared equally well by oxidation in the absence of acid (Scheme 41); a radical mechanism appears to be involved. In view of this facile conversion under oxidising conditions, the status of catharine as a *bona fide* natural product is open to question. Indeed, the status of leurosine itself as an alkaloid has been questioned,¹⁴⁰ in view of the ease with which anhydrovinblastine is oxidised to leurosine, even in the absence of specific oxidising agents. For example, anhydrovinblastine is oxidised to leurosine if not stored in an inert atmosphere, and the conversion is even more rapid in solution, particularly in the presence of adsorbents such as silica or alumina. A conversion of 40% has been observed after only 72 hours at room temperature. In view of these results it is perhaps not surprising that anhydrovinblastine has not been isolated from any *Catharanthus* species examined to date.

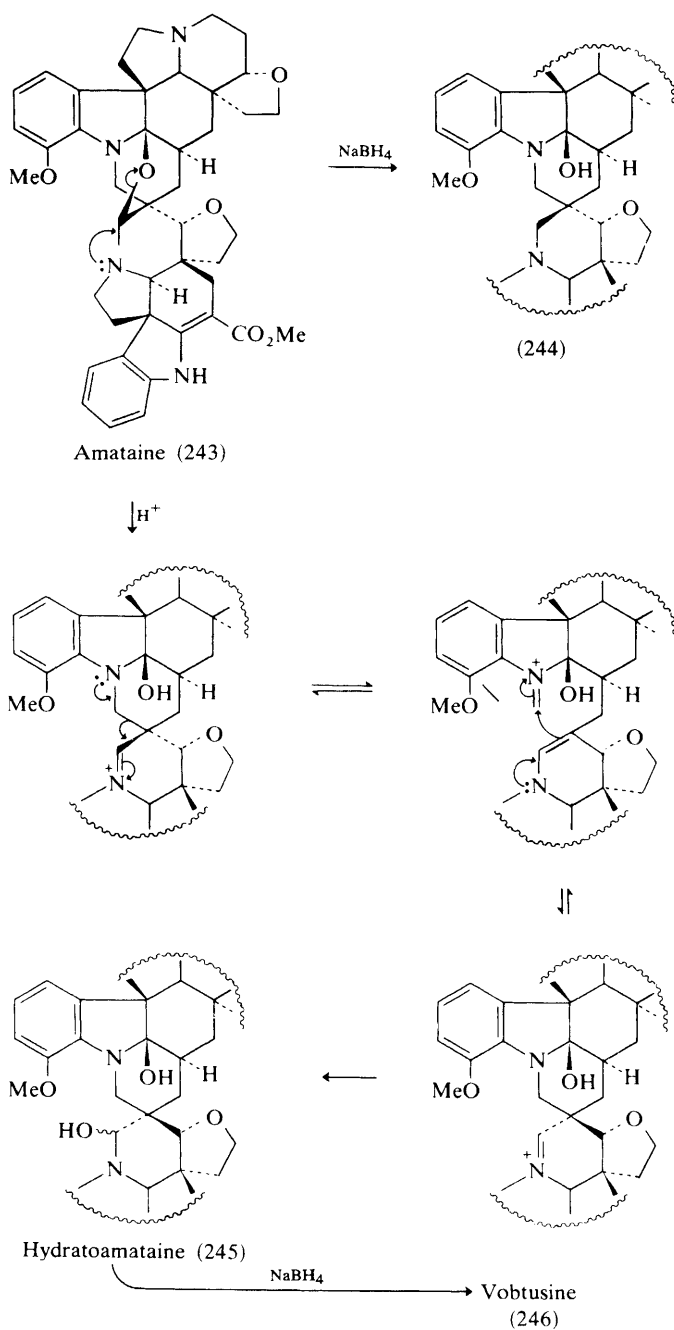
¹³⁶ N. Kunesch, Y. Rolland, J. Poisson, P. L. Majumder, R. Majumder, A. Chatterjee, V. C. Agwada, J. Naranjo, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1977, **60**, 2854.

¹³⁷ S. Görög, B. Herényi, and K. Jovánovics, *J. Chromatog.*, 1977, **139**, 203.

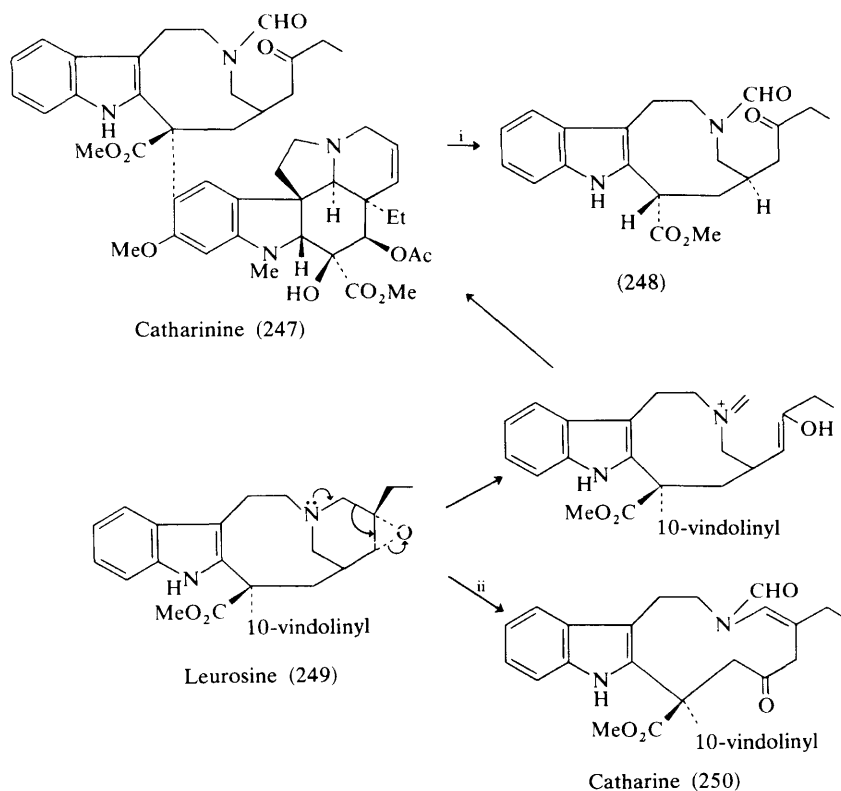
¹³⁸ (a) R. Z. Andriamialisoa, N. Langlois, P. Potier, A. Chiaroni, and C. Riche, *Tetrahedron*, 1978, **34**, 677; (b) S. Tafur, personal communication to authors of ref. 138a.

¹³⁹ (a) J. P. Kutney, J. Balsevich, and B. R. Worth, *Heterocycles*, 1978, **9**, 493; (b) J. P. Kutney, J. Balsevich, and G. H. Bokelman, *ibid.*, 1976, **4**, 1377.

¹⁴⁰ N. Langlois and P. Potier, *J.C.S. Chem. Comm.*, 1978, 102.



Scheme 40



Reagents: i, Sn, SnCl₂, HCl, MeOH; ii, Bu^tOOH, CH₂Cl₂.

Scheme 41

Kutney has reviewed¹⁴¹ the synthetic work in the vinblastine–leurosine series contributed by his own research group up to mid-1976, and the synthesis of leurosine by the same group has been published in detail.¹⁴²

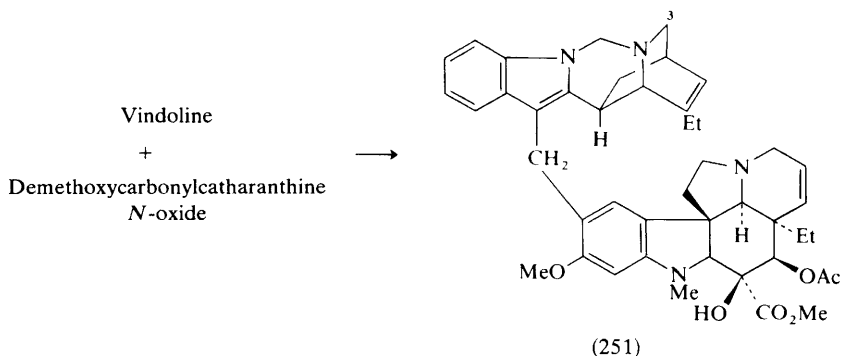
The Polonovski reaction of demethoxycarbonylcatharanthine *N*₆-oxide with trifluoroacetic anhydride in the presence of vindoline leads to a coupling reaction in which 16'-demethoxycarbonylanhydrovinblastine and its C-16' epimer are produced;¹⁴³ a third product was formulated as demethoxycarbonyl-catharanthine with a 10-vindolinyl unit attached to position 3. A re-examination¹⁴⁴ of this last product has shown that it is entirely analogous to that produced in the similar coupling of catharanthine *N*-oxide with vindoline, and has the structure (251).

¹⁴¹ J. P. Kutney, *Lloydia*, 1977, **40**, 107.

¹⁴² J. P. Kutney, A. V. Joshua, P. H. Liao, and B. R. Worth, *Canad. J. Chem.*, 1977, **55**, 3235; J. P. Kutney, J. Balsevich, G. H. Bokelman, T. Hibino, T. Honda, I. Itoh, A. H. Ratcliffe, and B. R. Worth, *ibid.*, 1978, **56**, 62.

¹⁴³ J. P. Kutney, T. Hibino, E. Jahngen, T. Okutani, A. H. Ratcliffe, A. M. Treasurywala, and S. Wunderly, *Helv. Chim. Acta*, 1976, **59**, 2858.

¹⁴⁴ R. Z. Andriamialisoa, Y. Langlois, N. Langlois, and P. Potier, *Compt. rend.*, 1977, **284**, C, 751.

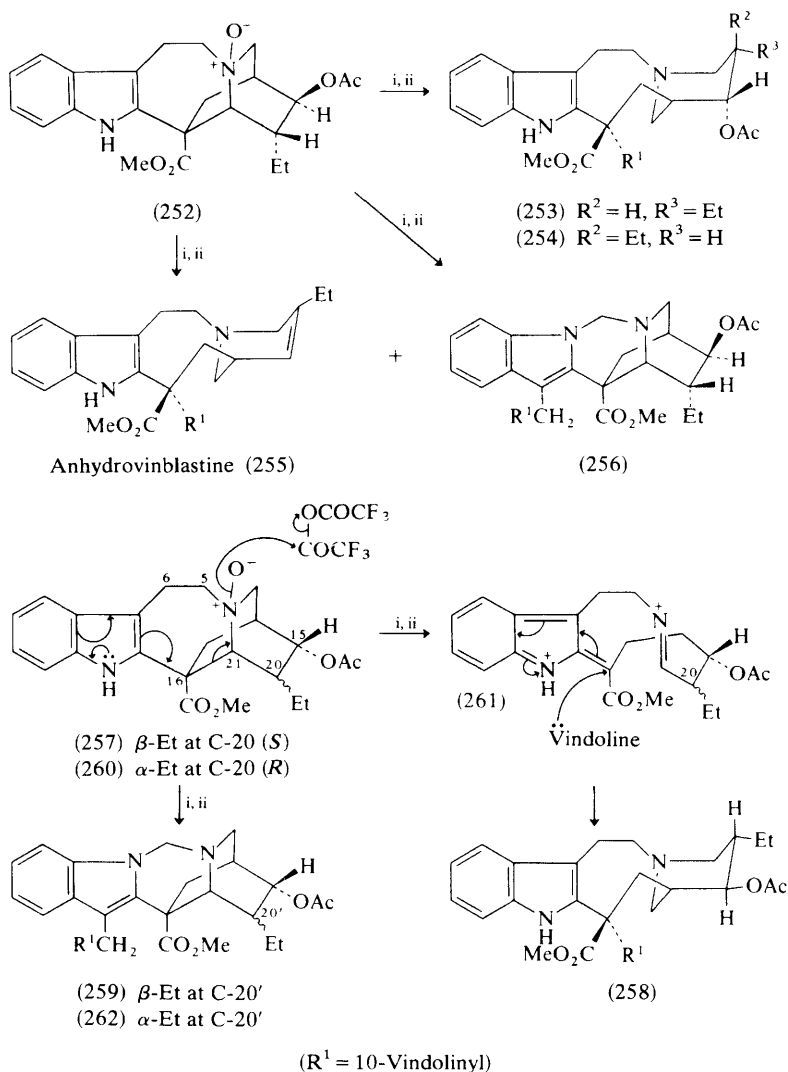


New Polonovski-type coupling reactions reported include that between 15β -acetoxydihydrocatharanthine N_b -oxide (252) [prepared from the β -alcohol described above¹²³] and vindoline, which gave a mixture of $15'\alpha$ -acetoxy- $20'$ -deoxyvinblastine (253) and $15'\alpha$ -acetoxy- $20'$ -deoxyeuroidine (254) (Scheme 42); no product of type (251), resulting from fission of the 5,6-bond in the catharanthine component, was apparently obtained.¹⁴⁵ This result stands in sharp contrast to those obtained by Honma and Ban, who have contributed an independent study¹⁴⁶ of the regiochemical course of the Polonovski coupling reaction between vindoline and appropriate catharanthine derivatives. In their hands the coupling reaction between 15β -acetoxydihydrocatharanthine N_b -oxide (252) and vindoline gave anhydrovinblastine (255) (22%) and the base (256) (32%), obtained by fission of the 5,6-bond of (252); neither (253) nor (254) appears to have been isolated. The isomeric N -oxide (257), in the same coupling reaction, gave an isovinblastine *O*-acetate (258) as a result of fission of the 16,21-bond, followed by nucleophilic attack by vindoline at C-16. A second product, the result of fission of the 5,6-bond, was the base (259). A third isomeric N -oxide (260) gave the same dimeric base (258) as did (257), presumably as a result of epimerization at C-20 in the intermediate immonium ion (261) by appropriate proton exchanges. The second product in this reaction was the base (262), an epimer of (259); the stereoisomerism of the starting materials was preserved in these two products since C-20 was not involved in their formation. In neither of these reactions was anhydrovinblastine formed.¹⁴⁶

It would thus appear that the presence of an α -acetoxy-group at C-15 severely inhibits the fission of the 16,21-bond in the coupling reaction, since the isovinblastine *O*-acetate (258) was obtained in yields of only 6 and 4%, respectively, from (257) and (260). The effect of a β -acetoxy-group is less well defined; Honma and Ban¹⁴⁶ report the formation of anhydrovinblastine (255), but only as the minor product of the reaction, whereas Kutney and Worth¹⁴⁵ report the formation of (253) and (254), but in unspecified yield. For the synthesis of vinblastine derivatives the absence of a C-15 substituent, as in catharanthine and dihydrocatharanthine, seems preferable; for example, catharanthine *N*-oxide was

¹⁴⁵ J. P. Kutney and B. R. Worth, *Heterocycles*, 1977, **6**, 905.

¹⁴⁶ Y. Honma and Y. Ban, *Tetrahedron Letters*, 1978, 155.



Reagents: i, Vindoline, $(CF_3CO)_2O$, at $-50^\circ C$; ii, $NaBH_4$, EtOH.

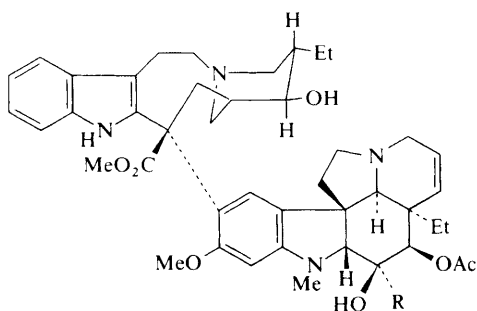
Scheme 42

reported by Potier *et al.*¹⁴⁷ to give a combined yield of 62% of anhydrovinblastine (255) and its C-16' epimer.

The accessibility of anhydrovinblastine (255) affords an independent route to vinblastine derivatives, *via* functionalisation of the 15',20' double-bond. Hydroboration-oxidation of (255), for example, gives¹⁴⁵ a mixture of 15' β -hydroxy-

¹⁴⁷ N. Langlois, F. Guéritte, Y. Langlois, and P. Potier, *J. Amer. Chem. Soc.*, 1976, **98**, 7017.

20'-deoxyvinblastine (263) and the related primary alcohol (264); the former of these products is the alcohol related to Ban's isovinblastine *O*-acetate (258).

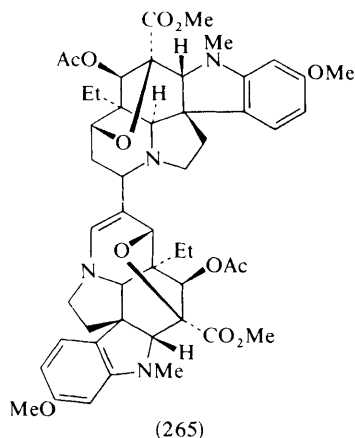


(263) R = CO₂Me

(264) R = CH₂OH

The use of *N*_a-formyl compounds such as vincristine in cancer therapy has stimulated numerous attempts during the past few years to prepare other *N*_a-formyl compounds by oxidation of natural or synthetic relatives of vinblastine, usually by means of chromic acid. The use of a large excess of Jones' reagent at -78 °C is reported to give particularly satisfactory results. Thus, anhydrovinblastine (255) gives an 80% yield of the related *N*_a-formyl derivative; other examples of the use of this oxidant are also cited.¹⁴⁸

The microbial transformation of vindoline by means of *Streptomyces griseus* gives dihydrovindoline ether (previously obtained) and a novel vindoline dimer (265).¹⁴⁹



(265)

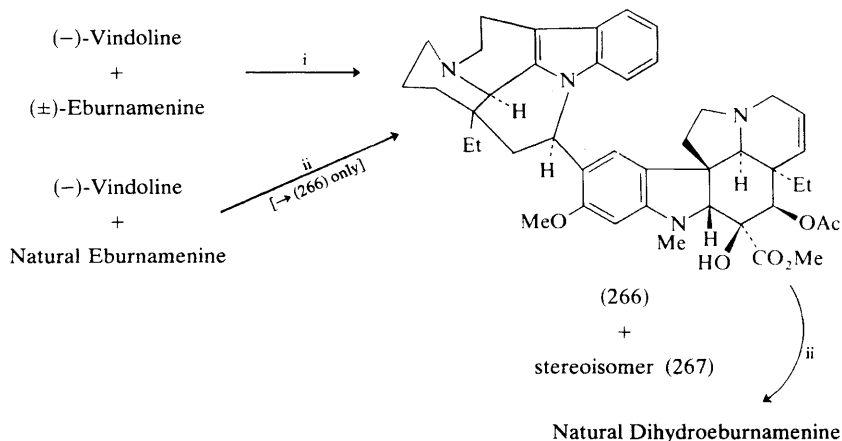
As a variant on the numerous coupling reactions on vindoline that have recently been studied, Takano *et al.*¹⁵⁰ have examined the stereochemical course

¹⁴⁸ J. P. Kutney, J. Balsevich, T. Honda, P. H. Liao, H. P. M. Thiellier, and B. R. Worth, *Heterocycles*, 1978, 9, 201.

¹⁴⁹ T. Nabih, L. Youel, and J. P. Rosazza, *J.C.S. Perkin I*, 1978, 757.

¹⁵⁰ S. Takano, S. Hatakeyama, and K. Ogasawara, *Heterocycles*, 1977, 6, 1311.

of the coupling of (–)-vindoline with synthetic (±)-eburnamenine. The product proved to be a 3 : 4 mixture of (266) and its stereoisomer (267) from the antipodal eburnamenine component (Scheme 43). The stereochemistry of (266) becomes



Reagents: i, 1.5% MeOH, HCl, under N₂, reflux for 3 h; ii, Sn, 4M-HCl.

Scheme 43

clear from its reductive fission to (–)-vindoline and the dihydro-derivative of the naturally occurring enantiomer of eburnamenine, and from its synthesis from vindoline and eburnamenine prepared from natural (–)-eburnamine. Oddly enough, a small yield of (267) was also obtained in this reaction; this may indicate the presence in the natural (–)-eburnamine of a small amount of the (+)-enantiomer.

Finally, details of the synthesis of trichotomine have been published.¹⁵¹

5 Biogenetically Related Quinoline Alkaloids

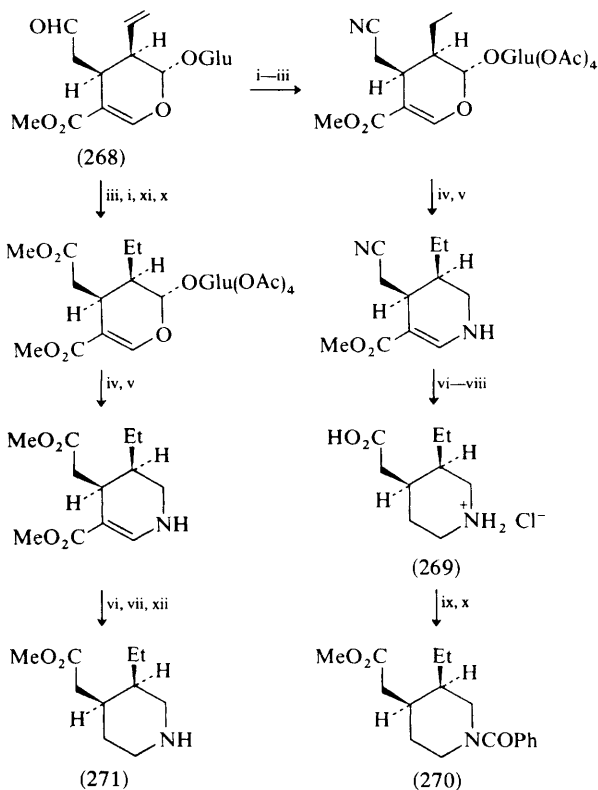
The synthesis¹⁵² of dihydromeroquinene derivatives from secologanin (268) affords a new and convenient stereoconservative synthesis of the *Cinchona* alkaloids. Two routes were developed (Scheme 44); both resulted in the conservation of the easily epimerised centre at C-2 in the secologanin derivatives. The first route resulted in the formation of dihydromeroquinene (cincholoipon) hydrochloride (269), which was identified by conversion into methyl *N*-benzoyldihydromeroquinenate (270); the other afforded methyl dihydromeroquinenate (271), which has previously been converted into quinine.

Details of the extensive contributions of Uskoković and his collaborators on the total synthesis of the *Cinchona* alkaloids have now been given in a series of four comprehensive papers.¹⁵³

¹⁵¹ S. Iwadare, Y. Shizuri, K. Yamada, and Y. Hirata, *Tetrahedron*, 1978, **34**, 1457.

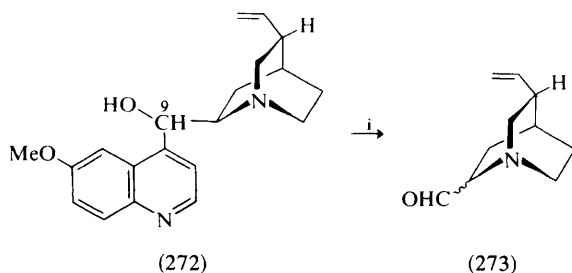
¹⁵² R. T. Brown and J. Leonard, *Tetrahedron Letters*, 1978, 1605.

¹⁵³ M. R. Uskoković, T. Henderson, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Amer. Chem. Soc.*, 1978, **100**, 571; J. Gutzwiller and M. R. Uskoković, *ibid.*, p. 576; G. Grethe, H. L. Lee, T. Mitt, and M. R. Uskoković, *ibid.*, p. 581; G. Grethe, H. L. Lee, T. Mitt, and M. R. Uskoković, *ibid.*, p. 589.



Reagents: i, H_2 , Pd/C; ii, NH_2OH ; iii, Ac_2O , py; iv, NaOMe; v, β -glucosidase, NH_3 , $NaBH_3CN$, pH 6; vi, 2% HCl, heat; vii, $NaBH_4$; viii, 6M-HCl, heat; ix, $PhCOCl$, py; x, CH_2N_2 ; xi, Jones' reagent; xii, esterification.

Scheme 44



Reagents: i, MeOH, N_2 , $h\nu$.

Scheme 45

The photolysis of the *Cinchona* alkaloids in neutral solution results¹⁵⁴ in cleavage of the bond between the aromatic ring and the carbon atom (C-9) carrying the secondary hydroxy-group; quinidine (272), for example, gives 6-methoxyquinoline and the quinuclidine aldehyde (273) in moderately good yield (50—60%) (Scheme 45). This contrasts with photolysis in acid solution, which is reported¹⁵⁵ to result simply in the formation of 9-deoxy-derivatives.

A total synthesis of 10-hydroxy- and 10-methoxy-camptothecins has been described,¹⁵⁶ but adequate details of the work are difficult to obtain; the overall route used appears to be similar to that adopted by the same group in an earlier synthesis of camptothecin.

¹⁵⁴ G. A. Epling and U. C. Yoon, *Tetrahedron Letters*, 1977, 2471.

¹⁵⁵ V. I. Stenberg and E. F. Travecedo, *J. Org. Chem.*, 1970, **35**, 4131.

¹⁵⁶ Shanghai Fifth Pharmaceutical Plant, *K'o Hsueh T'ung Pao*, 1977, **22**, 269 (*Chem. Abs.*, 1977, **87**, 184 742).

13

Diterpenoid Alkaloids

BY S. William PELLETIER & Samuel W. PAGE

1 Introduction

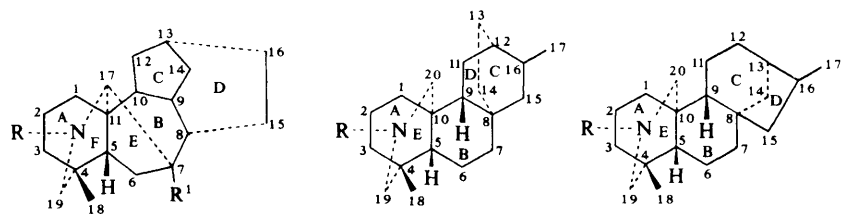
Studies on the diterpenoid alkaloids published during the past twelve months have provided much new structural and synthetic information on these complex plant bases. Twenty diterpenoid bases that are new or previously undetected in plant material have been reported from *Aconitum* and *Delphinium* species, and from *Consolida ambigua* and *Garrya ovata*. An extensive review of diterpenoid alkaloid chemistry has been published.¹

The question of the equilibration of atisine epimers has been further investigated and has created some controversy.

The Wiesner group at the University of New Brunswick has continued to improve their synthetic route for the diterpenoid alkaloids.² This monumental achievement represents a record for stereo- and regio-specific construction – thirteen chiral centres were involved.

There were no new reports on the chemistry of the *Daphniphyllum* alkaloids.

As in the previous Reports, the numbering systems for the aconitine, lycocotinine, atisine, and veatchine skeletons are indicated in structures A, B, C, and D, respectively.



(A) Aconitine skeleton, $R^1 = H$ (C) Atisine skeleton (D) Veatchine skeleton
(B) Lycocotinine skeleton, $R^1 = OR^2$

2 C₁₉ Diterpenoid Alkaloids

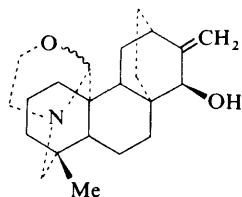
Alkaloids from *Aconitum gigas* Lev. et Van.: Gigactonine and Atisine.—Sakai, Shinma, and Okamoto³ have isolated a new diterpenoid alkaloid, gigactonine,

¹ A. R. Pinder, in 'Rodd's Chemistry of Carbon Compounds', ed. S. Coffey, 2nd edn., Vol. IV, Part G, New York, Elsevier Scientific Publishing Co., 1978, Chapter 34, pp. 323–379.

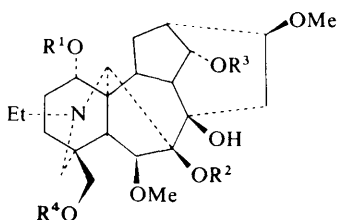
² K. Wiesner, *Chem. Rev.*, 1977, 6, 413.

³ S. Sakai, N. Shinma, and T. Okamoto, *Heterocycles*, 1977, 8, 207.

$C_{24}H_{39}NO_7$, m.pt. 168—169 °C, as a minor constituent of the roots of this plant. Atisine (1) was also isolated as its ternary immonium chloride. From the spectral data (1H and ^{13}C n.m.r., i.r., and mass) and from chemical transformations, structure (2) was assigned to gigactonine. Methylation of (2) gave a mixture of (3), (4), and (5). The monomethyl derivative (3) was identical with the alkaloid delsoleine.



Atisine (1)



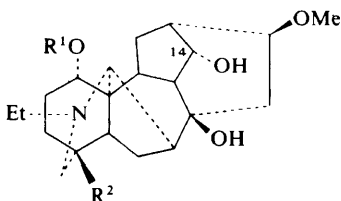
- Gigactonine (2) $R^1 = R^2 = R^4 = H, R^3 = Me$
 Delsoline (3) $R^1 = R^2 = H, R^3 = R^4 = Me$
 (4) $R^1 = H, R^2 = R^3 = R^4 = Me$
 (5) $R^1 = R^2 = R^3 = R^4 = Me$

Alkaloids from *Aconitum miyabei* Nakai: Sachaconitine and Isodelphinine.—

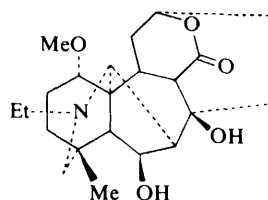
The structure elucidation of these alkaloids, primarily using n.m.r. spectral techniques, has been reported.⁴ These bases had been isolated earlier and partially characterized.⁵

The i.r. and 1H n.m.r. spectra of sachaconitine, $C_{23}H_{37}NO_4$, m.pt. 129—130 °C, indicated the presence of two hydroxy-groups (one α at C-14), a tertiary methyl, an *N*-ethyl, and two methoxy-groups. Comparison of the ^{13}C n.m.r. spectra of sachaconitine with those of isotalatizidine (6), heteratisine (7), and chasmanine (8) established the structure as in (9).

Isodelphinine, $C_{33}H_{45}NO_9$, m.pt. 167—168 °C, had been postulated⁶ to be the C-14 epimer of delphinine (10). The i.r. and 1H n.m.r. data account for one hydroxy-, an *N*-methyl, a benzoyl (at C-14), an acetoxy- (at C-8), and four methoxy-groups. In the 1H n.m.r. spectrum of delphinine (10), the C-14-proton signal is a doublet, while in isodelphinine it is a doublet of doublets. Comparison of the ^{13}C n.m.r. spectra of isodelphinine with those of delphinine (10), deoxy-



Isotalatizidine (6) $R^1 = H, R^2 = CH_2OMe$
 Sachaconitine (9) $R^1 = Me, R^2 = Me$

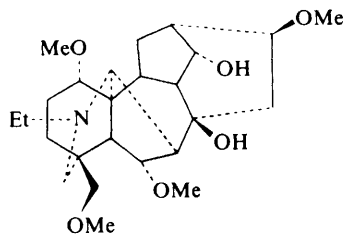


Heteratisine (7)

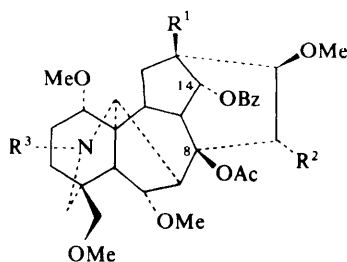
⁴ S. W. Pelletier, N. V. Mody, and N. Katsui, *Tetrahedron Letters*, 1977, 4027.

⁵ N. Katsui and G. Hasegawa, *Bull. Chem. Soc. Japan*, 1960, 33, 1037.

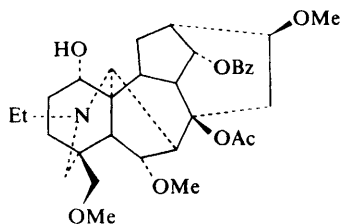
⁶ K. Katsui, *Bull. Chem. Soc. Japan*, 1959, 32, 774.



Chasmanine (8)



Delphinine (10) $R^1 = \text{OH}, R^2 = \text{H}, R^3 = \text{Me}$
 Deoxyaconitine (11) $R^1 = R^2 = \text{OH}, R^3 = \text{Et}$
 Isodelphinine (13) $R^1 = \text{H}, R^2 = \text{OH}, R^3 = \text{Me}$



(12)

aconitine (11), and 8-acetyl-14-benzoxylneoline (12) led to assignment of the hydroxy-group to C-15 and of structure (13) for isodelphinine. This is the first reported example of a C_{19} diterpenoid alkaloid containing a hydroxy-group at C-15 without an additional hydroxy-group at C-13.

Alkaloids of *Consolida ambigua*: Ajacusine, Ajadine, and Ambiguine.—These bases were isolated, along with the C_{20} diterpenoid alkaloid dihydroajaconine, from seeds of the common garden larkspur (*Consolida ambigua*).^{7,8} This plant was earlier identified as *Delphinium ajacis*.⁷ Plants grown from these seeds have been identified as *Consolida ambigua* (L.) P. W. Ball and Heywood by Dr. Carl S. Keener of Pennsylvania State University.⁸

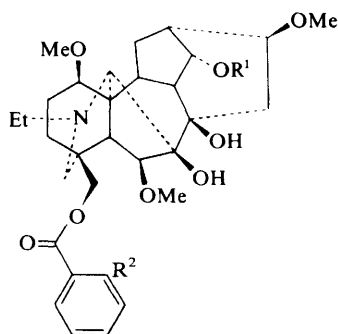
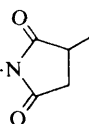
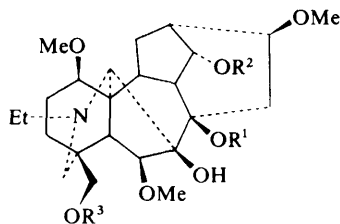
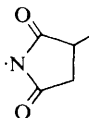
Ajacusine, $C_{43}H_{52}N_2O_{11}$, m.pt. 158—161 °C, gave the known amino-alcohol delectinine (14) on alkaline hydrolysis. From this and spectral data (most importantly, ^{13}C n.m.r. spectral comparisons), structure (15) was assigned to ajacusine.⁷

Ajadine, $C_{35}H_{48}N_2O_{10}$, m.pt. 134—136 °C, was also found to be an ester of (14). From spectral data, it was determined to be the C-14 acetyl-compound (16).⁷

Ambiguine, $C_{28}H_{45}NO_8$, m.pt. 106—108 °C, gave the amino-alcohol (17) on saponification. When acetylated with acetic anhydride in pyridine, compound (17) regenerated ambiguine. From extensive ^{13}C n.m.r. spectral comparisons, structure (18) was assigned to ambiguine.⁸ This is the first known lycotonine-type alkaloid bearing a methoxy-group at C-8.

⁷ S. W. Pelletier and R. S. Sawhney, *Heterocycles*, 1978, **9**, 463.

⁸ S. W. Pelletier, R. S. Sawhney, and N. V. Mody, *Heterocycles*, 1978, **9**, 1241.

Ajacusine (15) $R^1 = \text{Bz}$, $R^2 =$ Ajadine (16) $R^1 = \text{Ac}$, $R^2 = \text{NHCOMe}$ Anthranoyl-lycoctonine (22) $R^1 = \text{Me}$, $R^2 = \text{NH}_2$ Methyl-lycaconitine (41) $R^1 = \text{Me}$, $R^2 =$ Delectinine (14) $R^1 = R^2 = R^3 = \text{H}$ (17) $R^1 = R^3 = \text{Me}$, $R^2 = \text{H}$ Ambiguine (18) $R^1 = R^3 = \text{Me}$, $R^2 = \text{Ac}$

Alkaloids of *Delphinium biternatum* Huth.: 14-Benzoylbrowniine, 14-Benzoyliensiine, 14-Dehydroiliensiine, and Delbiterine.—A comprehensive study of the alkaloids of *D. biternatum* Huth. has been published.⁹ From the aerial parts of the plant, iliensiine (19), acomonine (20), delphatine (21), anthranoyl-lycoctonine (22), browniine (23), dehydrobrowniine (24), and three new alkaloids were isolated. One of these, $\text{C}_{24}\text{H}_{37}\text{NO}_7$, m.pt. 208—210 °C, was identified as 14-dehydroiliensiine (25) on the basis of spectral data and its conversion into iliensiine (19) on reduction with borohydride.

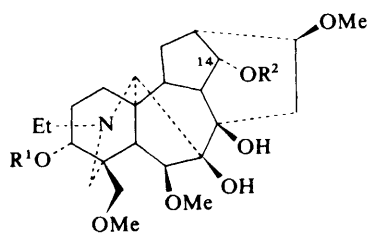
The new alkaloid, $\text{C}_{32}\text{H}_{45}\text{NO}_8$, m.pt. 114—116 °C, gave benzoic acid and browniine (23) on alkaline hydrolysis. The ^1H n.m.r. spectrum contained a

⁹ B. T. Salimov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1978, 106.

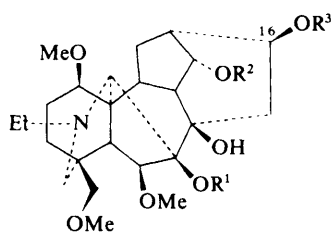
one-proton triplet at 5.00 p.p.m. ($J \approx 5$ Hz), which disappeared after hydrolysis to browniine. Since browniine has only one secondary hydroxy-group, this signal was assigned to the β -proton at C-14. This new base is therefore 14-benzoylbrowniine (26).

On alkaline hydrolysis, the previously unreported ester $C_{31}H_{43}NO_8$, m.pt. 147—149 °C, gave benzoic acid and iliensine (19). The presence of a one-proton triplet at 5.01 p.p.m. ($J \approx 5$ Hz) located the benzoyl group at C-14. Thus, this alkaloid is 14-benzoyl iliensine (27).

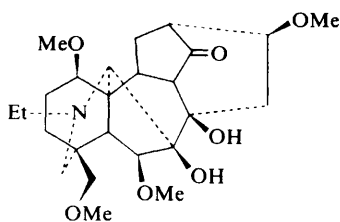
Extraction of the roots of *D. biternatum* with chloroform gave an alkaloid fraction containing browniine (23), delphatine (21), and a new alkaloid named delbiterine (28), $C_{25}H_{41}NO_7$, m.pt. 137—138 °C. Spectral data (i.r., 1H n.m.r., and mass) indicated the presence of an *N*-ethyl, four methoxy- (one at C-1), and three hydroxy-groups on a lycocotinine skeleton. Methylation of (28) with methyl iodide and sodium hydride gave a compound identical with 7,18-di-*O*-methyllycocotinine (29). Acetylation of delbiterine with acetic anhydride in pyridine gave a monoacetate (30). From the 1H n.m.r. spectrum of this monoacetate (30), the location of the secondary hydroxy-group in delbiterine was assigned to C-16.



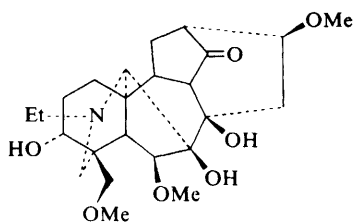
Iliensine (19) $R^1 = H, R^2 = H$
 Acomonine (20) $R^1 = H, R^2 = Me$
 (27) $R^1 = H, R^2 = Bz$



Delphatine (21) $R^1 = H, R^2 = R^3 = Me$
 Browniine (23) $R^1 = R^2 = H, R^3 = Me$
 (26) $R^1 = H, R^2 = Bz, R^3 = Me$
 Delbiterine (28) $R^1 = R^3 = H, R^2 = Me$
 (29) $R^1 = R^2 = R^3 = Me$
 (30) $R^1 = H, R^2 = Me, R^3 = Ac$
 (42) $R^1 = H, R^2 = Ac, R^3 = Me$



14-Dehydrobrowniine (24)



14-Dehydroiliensine (25)

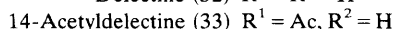
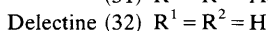
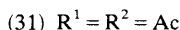
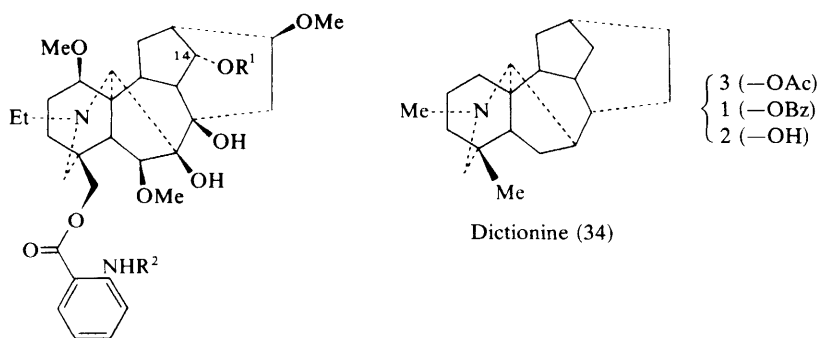
Alkaloids of *Delphinium dictyocarpum*: 14-Acetyldelectine, Delectinine, and Dictionine.—Three new diterpenoid alkaloids have been isolated from plants of

D. dictyocarpum D.C.^{10,11} Four aporphine alkaloids were also isolated from this species.

From the aerial parts of the plants, two new bases, 14-acetyldelectine, $C_{33}H_{46}N_2O_9$, m.pt. 118—120 °C, and dictionine,¹¹ $C_{33}H_{37}NO_{10}$, m.pt. 246—248 °C, were obtained. From the i.r., ¹H n.m.r., and mass spectral data, the first alkaloid was determined to be a lycoctonine-type alkaloid acetylated with anthranilic and acetic acids and having an α -acetoxy-group at C-14 and a β -methoxy-group at C-1. Acetylation of this base with acetic anhydride in pyridine gave a compound identical with the *NO*-diacetate (31) of delectine (32). This established the structure of this new alkaloid as 14-acetyldelectine (33).

The partial structure (34) was assigned for dictionine from the spectral data.

Delectinine, $C_{24}H_{39}NO_7$, m.pt. 167—169 °C, was obtained from the roots of *D. dictyocarpum*.¹¹ The i.r., ¹H n.m.r., and mass spectral data were identical with those for the amino-alcohol hydrolysis product (14) from delectine (32). Direct comparison confirmed this identity, establishing the structure of delectinine as (14).



Alkaloids of *Delphinium iliense*: Dehydrodelcorine and Ilidine.—From a chloroform extract of the above-ground parts of *D. iliense* Huth., Yunusov and co-workers¹² have isolated delcorine (35), lycoctonine (36), deltaline (eldeline) (37), and two additional bases.

One of these unidentified bases, $C_{27}H_{39}NO_7$, occurred in a small amount. From the spectral data, it contained cyclopentanone, *N*-ethyl, four methoxy-, and methylenedioxy-functionalities. Comparison of this alkaloid with dehydrodelcorine (38),¹³ m.pt. 133—134 °C, established their identity.

The other new alkaloid, $C_{25}H_{37}NO_7$, m.pt. 141—143 °C, was named ilidine (39). From the spectral data, it was shown to differ from dehydrodelcorine (38) by

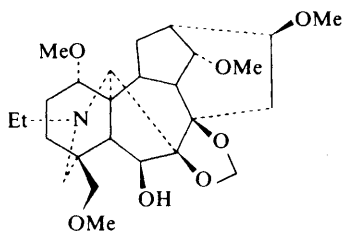
¹⁰ B. T. Salimov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 716.

¹¹ B. T. Salimov, N. D. Abdullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1978, 235.

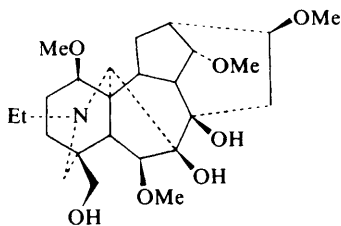
¹² M. G. Zhamierashvili, V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 836.

¹³ A. S. Narzullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 497.

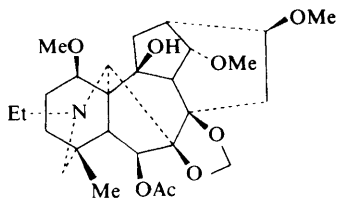
lack of an *O*-methyl group. Methylation of ilidine with methyl iodide and sodium hydride gave *O*-methylilidine, which was identical with dehydrodelcorine (38). The position of the hydroxy-group at C-14 in ilidine was established by comparison of the ^1H n.m.r. spectral data of ilidine and those of the monoacetyl derivative (40).



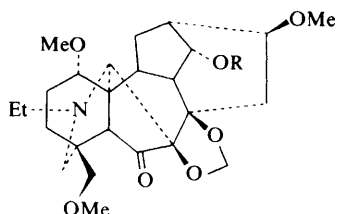
Delcorine (35)



Lycopotonine (36)



Deltaline (Eldeline) (37)



Dehydrodelcorine (38) R = Me
 Ilidine (39) R = H
 (40) R = Ac

Alkaloids of *Delphinium oreophilum*: 14-Acetylbrowniine.—From the aerial parts of this species, total alkaloids were obtained in a yield of 0.8%.¹⁴ Two bases were isolated from this material. One was identified as methyl-lycaconitine (41) by comparison of its perchlorate salt with an authentic sample (see diagram on p. 224).

The second alkaloid, $\text{C}_{27}\text{H}_{43}\text{NO}_8$, m.pt. 129—130°C, was shown from the spectral data to contain two hydroxy-, an *N*-ethyl, an acetoxy- (at C-14), and four methoxy-groups. The spectral and physicochemical data were consistent with the structure of 14-acetylbrowniine (42). The structure of this alkaloid is shown on p. 225.

This base was simultaneously reported as occurring in the seeds of *Delphinium ajacis*¹⁵ (cf. 'Applications of ^{13}C N.M.R. Spectrometry to the C_{19} Diterpenoid Alkaloids'). These are the first reports of this compound being isolated from plant materials.

¹⁴ V. G. Kazlikhin, V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 869.

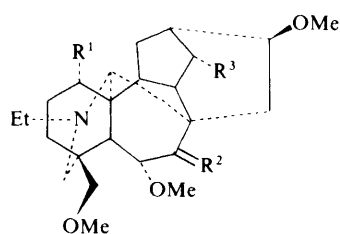
¹⁵ S. W. Pelletier, N. V. Mody, R. S. Sawhney, and J. Bhattacharyya, *Heterocycles*, 1977, 7, 327.

Reactions of Delcosine.—Japanese workers¹⁶ have reported additional chemical studies of anhydrodiacetyl delcosine (43), the product of the treatment of delcosine (44) with acetyl chloride. On hydrogenation, (43) was converted into (45). Delcosine has been isolated from several *Aconitum* and *Delphinium* species.

Reduction of (43) with lithium aluminium hydride gave anhydrodelcosinol (46). Alkaline hydrolysis of (45) gave (47). Hydride reduction of (47), followed by acetylation, yielded (48).

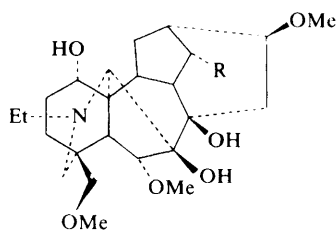
In a reaction sequence analogous to (44) → (43) → (45), deoxy-14-dehydrodelcosine (49) was treated with acetyl chloride, and subsequently hydrogenated to yield (50).

Oxidation of (45) with chromium trioxide in pyridine and subsequent hydrolysis gave (51), while similar oxidation of (47) yielded a mixture of (52) and (53).



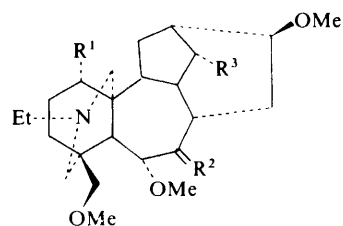
(43) $R^1 = R^3 = \text{OAc}; R^2 = \text{O}$

(46) $R^1 = R^3 = \text{OH}; R^2 = \text{OH}, \text{H}$



Delcosine (44) $R = \text{OH}$

(49) $R = \text{H}$

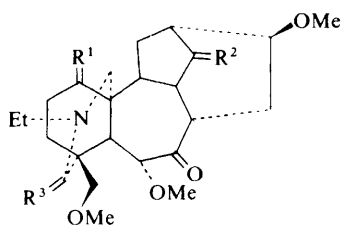


(45) $R^1 = R^3 = \text{OAc}; R^2 = \text{O}$

(47) $R^1 = R^3 = \text{OH}; R^2 = \text{O}$

(48) $R^1 = R^3 = \text{OAc}; R^2 = \text{OAc}, \text{H}$

(50) $R^1 = \text{OAc}; R^2 = \text{O}; R^3 = \text{H}$



(51) $R^1 = R^2 = \alpha\text{-OH}, \text{H}; R^3 = \text{O}$

(52) $R^1 = R^2 = R^3 = \text{O}$

(53) $R^1 = \alpha\text{-OH}, \text{H}; R^2 = \text{O}; R^3 = \text{H}_2$

Applications of ¹³C N.M.R. Spectrometry to the C₁₉ Diterpenoid Alkaloids:

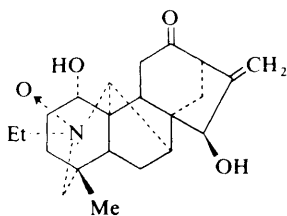
14-Acetylbrowniine.—A review of recent applications of carbon-13 n.m.r. spectrometry to the solution of some of the complex problems of C₁₉ diterpenoid alkaloid chemistry has appeared.¹⁵ Using proton-decoupling techniques and additivity relationships, the carbon-13 chemical shifts for eighteen aconitine and lycoctonine-type alkaloids were assigned. Applications of these methods for the identification and structure elucidation of several new diterpenoid alkaloids were discussed. The new data presented in this work included the identification of

¹⁶ T. Amiya, Y. Kanaiwa, N. Nakano, and T. Shima, *Bull. Chem. Soc. Japan*, 1978, **51**, 248.

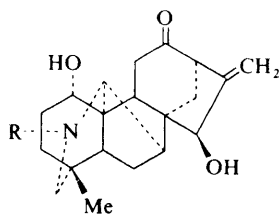
browniine (23), delphatine (21), and 14-acetylbrowniine (42) from the seeds of *Delphinium ajacis* (syn. *Consolida ambigua*).

3 C₂₀ Diterpenoid Alkaloids

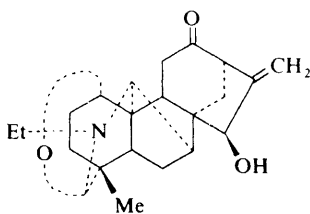
Alkaloids from *Aconitum monticola*: Songorine N-Oxide.—In further studies¹⁷ of the alkaloid fraction from plants of *Aconitum monticola*, songorine N-oxide (54), C₂₂H₃₁NO₄, m.pt. 253—255 °C, has been isolated. Songorine (55), songoramine (56), norsongorine (57), and acomonine (20) were previously reported from this species (cf. this Report, Vol. 7, Chapter 13, p. 250). The structure for songorine N-oxide was assigned from the spectral data and on the basis of reduction of the compound to songorine (55) by zinc and 10% hydrochloric acid.



Songorine N-oxide (54)



Songorine (55) R = Et
Norsongorine (57) R = H



Songoramine (56)

Alkaloids from *Consolida ambigua*: Dihydroajaconine.—With the C₁₉ diterpenoid alkaloids discussed in Section 2, dihydroajaconine, C₂₂H₃₅NO₃, m.pt. 99—100 °C, was isolated from *C. ambigua* (garden larkspur).⁷ It was obtained from the mother liquors of the ajaconine isolation. Structure (58) for dihydroajaconine was proposed on the basis of the spectral data and confirmed by reduction of ajaconine (59) to (58) by borohydride.

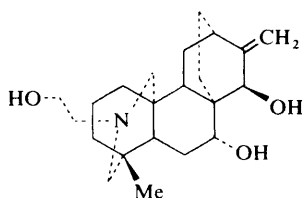
Alkaloids of *Garrya ovata*: Ovatine and Lindheimerine.—From extracts of the leaves and bark of *Garrya ovata* var. *lindheimeri* Torr. (which have shown anti-tumour activity), garryfoline (60) and two new C₂₀ diterpenoid alkaloids have been isolated.¹⁸ The major alkaloid was ovatine, C₂₄H₃₅NO₃, m.pt. 113—

¹⁷ E. F. Ametova, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 867.

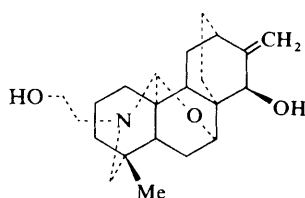
¹⁸ S. W. Pelletier, N. V. Mody, and D. S. Seigler, *Heterocycles*, 1978, 9, 1409.

114 °C. Mild hydrolysis of this base afforded garryfoline (60). From this result and comparisons of the spectral data, ovatine was assigned structure (61), existing as a mixture of C-20 epimers.

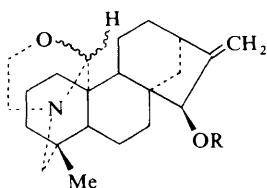
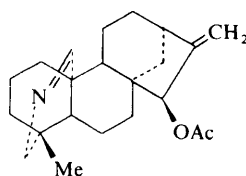
The structure of lindheimerine, $C_{22}H_{31}NO_2$, amorphous, was determined to be (62) from spectral data. Treatment of (60) or (61) with acetic anhydride in pyridine gave (63). On refluxing (63) in chloroform, lindheimerine (62) was obtained in 90% yield from either (60) or (61). Lindheimerine was converted into ovatine (61) in a yield of 98% by treatment with ethylene oxide in acetic acid.



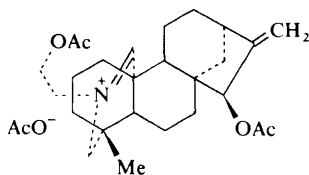
Dihydroajaconine (58)



Ajaconine (59)

Garryfoline (60) R = H
Ovatine (61) R = Ac

Lindheimerine (62)



(63)

Epimerization and Isomerization of the Oxazolidine Ring System in the C_{20} Diterpenoid Alkaloids: X-Ray and ^{13}C N.M.R. Studies.—The nature of the oxazolidine ring system in the atisine- and veatchine-type alkaloids has received considerable attention during the past year.^{19–22} (*cf.* this Report, 1978, Vol. 8, p. 238).

X-Ray crystallographic studies on atisium chloride (64),²² dihydroatisine (65),²² isoatisine (66),²² and veatchine [(67a) and (67b)]^{19,22} established the

¹⁹ W. H. DeCamp and S. W. Pelletier, *Science*, 1977, **198**, 726.

²⁰ S. K. Pradhan, *Tetrahedron Letters*, 1978, **3**, 263.

²¹ N. V. Mody and S. W. Pelletier, *Tetrahedron*, 1978, **34**, 2421.

²² S. W. Pelletier, W. H. DeCamp, and N. V. Mody, *J. Amer. Chem. Soc.*, 1978, **100**, 7976.

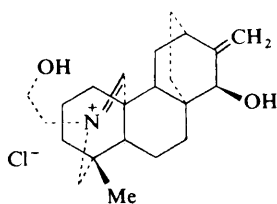
crystal structures of these compounds and resolved some of the disagreements in the interpretation of the observed n.m.r. spectral data.²¹ The structure of atisinium chloride was shown to be as in (64), with the absolute configuration of 4*S*, 5*S*, 8*R*, 10*R*, 12*R*, and 15*S* by the *R*-ratio test.

In the crystalline state, veatchine was shown to exhibit epimeric disorder, existing as a 60:40 mixture of the epimers (67a) and (67b), respectively. By analogy from the determination for atisinium chloride, the absolute configuration for veatchine must be 4*S*, 5*S*, 8*R*, 10*R*, 13*R*, 15*R*, and 20*SR*.

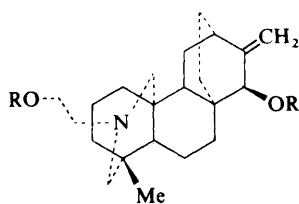
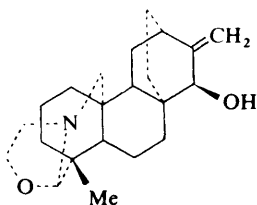
The crystal structure of dihydroatisine was shown to be (65), with ring E having a chair conformation. Its absolute configuration was assigned as 4*S*, 5*S*, 8*R*, 10*R*, 12*R*, and 15*S*.

From the crystal structure, isoatisine was shown *not* to exist as a pair of C-19 epimers, the closure of the oxazolidine ring F having occurred exclusively *endo*. By analogy, the absolute configuration designation for isoatisine must be 4*S*, 5*S*, 8*R*, 10*R*, 12*R*, 15*S*, and 19*S*.

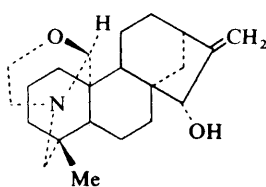
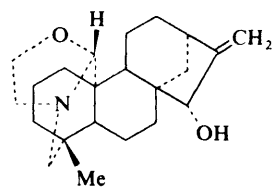
A full report on the ¹³C n.m.r. studies of these and related compounds²¹ and a rebuttal²⁰ of some of the previously published n.m.r. spectral interpretations (*cf.* this Report, 1978, Vol. 8, p. 238) have appeared. The rebuttal was submitted prior to the publication of the *X*-ray crystallographic studies. ¹³C n.m.r. spectral data were reported for atisine (1), atisinone (68), isoatisine (66), isoatisinone (69), dihydroatisine (65), dihydroatisine diacetate (70), atidine (71), atidine diacetate (72), atisine azomethine (73), atisine azomethine acetate (74), atisine dihydro-azomethine (75), atisine *N*-methyl dihydro-azomethine (76), veatchine [(67a) and (67b)], garryine (77), dihydroveatchine (78), dihydroveatchine diacetate (79), veatchine azomethine (80), veatchine azomethine acetate (81), veatchine dihydro-azomethine (82), and veatchine *N*-methyl dihydro-azomethine (83).

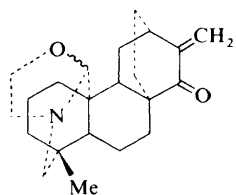


Atisinium chloride (64)

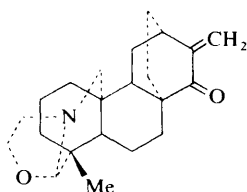
Dihydroatisine (65) R = H
(70) R = Ac

Isoatisine (66)

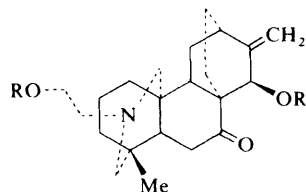
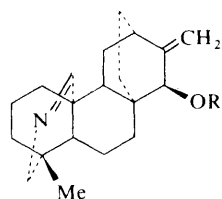
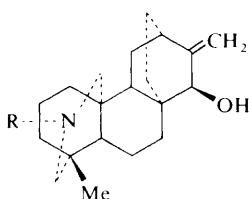
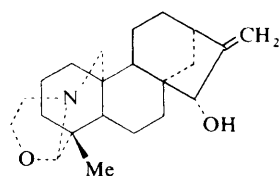
Veatchine (67a) (20*S*)Veatchine (67b) (20*R*)



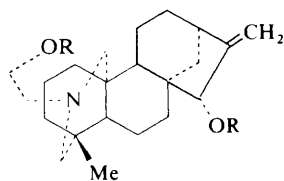
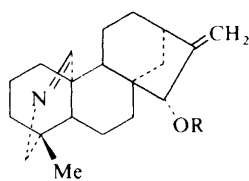
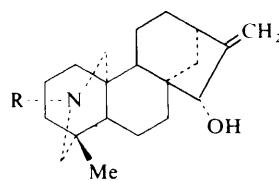
Atisinone (68)



Isoatisinone (69)

Atidine (71) R = H
(72) R = Ac(73) R = H
(74) R = Ac(75) R = H
(76) R = Me

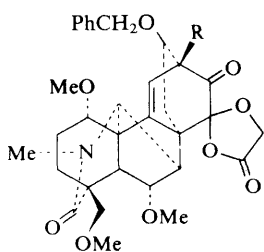
Garryine (77)

(78) R = H
(79) R = Ac(80) R = H
(81) R = Ac(82) R = H
(83) R = Me

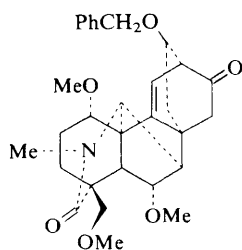
Self-consistent assignments were made for nearly all of the resonances of these compounds. The resonances of the methyl group attached to C-4 in the ¹H n.m.r. spectra of atisine, veatchine, and isoatisine appear as unequal doublets. In the ¹³C n.m.r. spectra this doubling occurs only for veatchine and atisine. Since the oxazolidinone rings of atisine and veatchine are regenerated from the corresponding ternary iminium chloride during isolation, epimers result from the closure of this ring from either side of the trigonal C-20 carbon atom. The existence of C-20 epimers is clearly supported by the n.m.r. and X-ray crystallographic data. The closure of the oxazolidinone ring to C-20 in an *exo*-configuration is evidently slightly favoured. In aprotic solvents, these epimers do not appear to be in equilibrium. However, there remains some uncertainty about deuterium exchange at C-19 and C-20 in the atisine/isoatisine system.^{21,22}

As mentioned previously, in isoatisine (66), closure to C-19 in an *endo*-configuration is clearly favoured. From the X-ray crystallographic structure determination and the ¹³C n.m.r. data, it has been deduced that isoatisine does *not* exist as a mixture of C-19 epimers. The doubling of the 4-methyl singlet in the ¹H n.m.r. spectrum was therefore attributed to the conformational mobility of the oxazolidinone ring. This was supported by the fact that the ¹H n.m.r. spectrum of

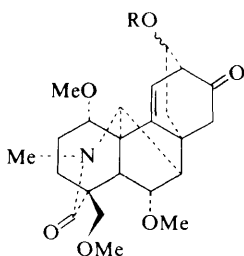
followed by oxidation with chromium trioxide and pyridine proceeded stereospecifically to the saturated keto-acetate (94). This compound was converted into the keto-acetal (95) by treatment with ethylene glycol and toluene-*p*-sulphonic acid, hydrolysis with methanolic sodium hydroxide, and subsequent oxidation with chromium trioxide and pyridine. Reduction of (95) by borohydride followed by methylation gave (96). On heating in 80% acetic acid, (96) was converted into the ketone (97). Bromination of (97) gave (98). This bromo-ketone was refluxed with ethylene glycol and toluene-*p*-sulphonic acid to form the dioxolan (99). On heating with 1,5-diazabicyclo[4.3.0]non-5-ene in a mixture of DMSO and *o*-xylene, (99) rearranged to (100), which was isolated in a yield of 89%. Oxymercuration followed by reduction with borohydride gave (101). On heating (101) in 88% acetic acid, the keto-lactone (102) was obtained. Reduction of (102) with lithium aluminium hydride gave racemic 13-deoxydelphonine (86).



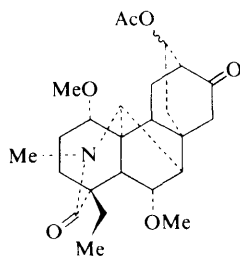
(90a) R = H
(90b) R = Br



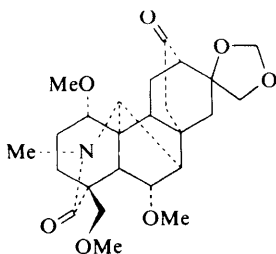
(91)



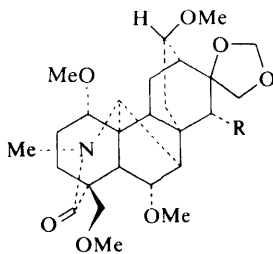
(92) R = H
(93) R = Ac



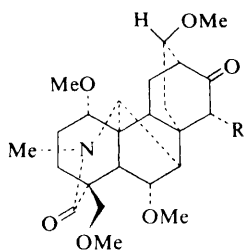
(94)



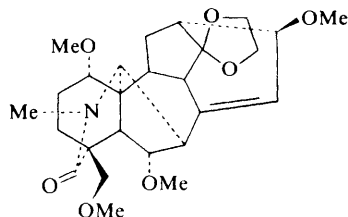
(95)



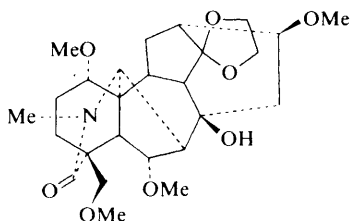
(96) R = H
(99) R = Br



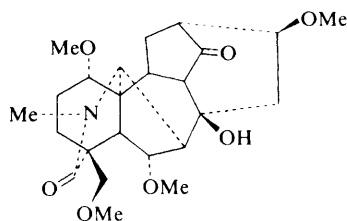
(97) R = H
(98) R = Br



(100)

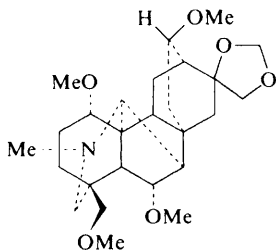


(101)

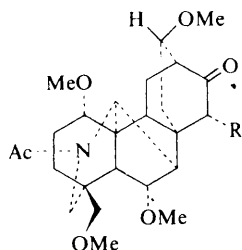


(102)

For a formal synthesis of chasmanine (8), compound (96) was reduced with lithium aluminium hydride to yield (103). Oxidation of (103) with potassium permanganate followed by hydrolysis with 6N hydrochloric acid and acetylation with acetic anhydride in pyridine gave (104). Bromination of (104) gave the bromo-derivative (105). (104) and (105) were identical with the corresponding intermediates of the photochemical synthesis.²



(103)

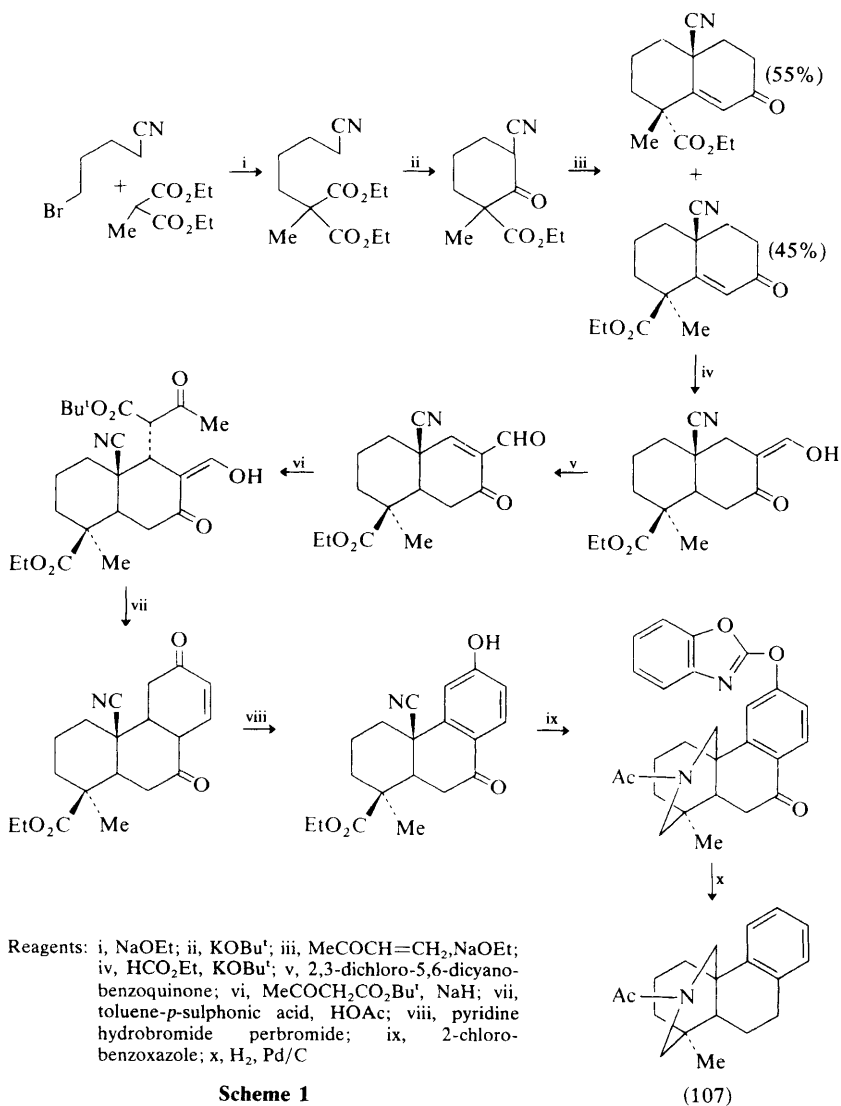
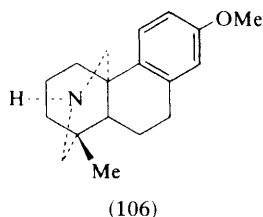


(104) R = H
(105) R = Br

Syntheses Directed toward C₂₀ Diterpenoid Systems.—Sato *et al.*²⁵ have published further details of their synthesis of the tetracyclic intermediate (106). The previous reports of this work have been reviewed. (*cf.* this Report, 1978, Vol. 8, p. 242).

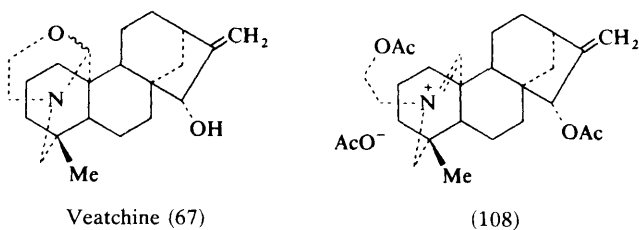
A new synthesis of the tetracyclic diterpenoid alkaloid intermediate (107), using an A → B → C approach, has been reported.^{26,27} Meyer and co-workers, in

²⁷ W. L. Meyer, T. E. Goodwin, R. J. Hoff, and C. W. Sigel, *J. Org. Chem.*, 1977, **42**, 2767.



work directed toward the development of a general diterpenoid synthetic route, included methods for the elaboration of the diterpenoid alkaloids as well as podocarpic acid models. The sequence for the synthesis of amide (107) is outlined in Scheme 1. This amide had previously been formally converted into racemic atisine, veatchine, and garryine.

Degradation of the Oxazolidine Ring of C₂₀ Diterpenoid Alkaloids.—A simple and efficient method for the degradation of the oxazolidine ring system has been developed.²⁸ Treatment of veatchine (67) with acetic anhydride in pyridine, followed by complete removal of the excess pyridine and acetic anhydride, gave the diacetate (108). Without purification, this compound was refluxed in chloro-



form to give (81) in 89% yield. In similar fashion, atisine (1), garryfoline (60), and ovatine (61) were degraded to the corresponding imines in yields of 90%. The analogous imines from the iso-oxazolidines, *i.e.* isoatisine (66) and garryine (77), were formed in yields of about 50%.

Acknowledgment: The authors wish to express appreciation to Dr. Naresh V. Mody for reviewing the manuscript and making several helpful suggestions.

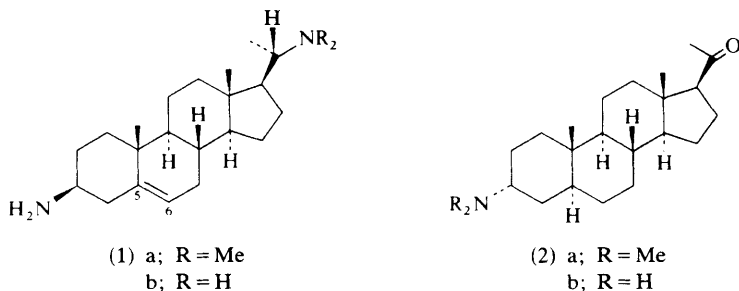
²⁸ N. V. Mody and S. W. Pelletier, *Tetrahedron Letters*, 1978, 3313.

The chemistry of the steroidal alkaloids has been reviewed.¹

1 Alkaloids of the Apocynaceae

The alkaloids konkurchine, conessine, conessidine, holarrhine, and kurchine have been isolated from *Wrightia tomentosa*.² Irehdiamine F (1a) has been isolated from roots of *Vahadenia laurentii* in the first investigation of this species; the crystal and molecular structures of the hydrochloride of this base were investigated by single-crystal X-ray diffraction methods.³ A study has been reported on the nature of the binding of irehdiamine A (1b), and of the 5,6-dihydro-derivative of the latter base, to double-helical DNA.⁴

Primary amines may be converted into their *NN*-dimethyl derivatives by reaction with formaldehyde in the presence of sodium cyanoborohydride. *NN*-Dimethylfuntumine (2a) was prepared from funtumine (2b) in excellent yield by



this procedure.⁵ The epimeric 20-amino-pregnane derivatives (3a) and (3b) have been prepared and caused to react with nitrous acid. In each case the major product was the diol [(3c) and (3d) respectively] in which the configuration at C-20 was retained.⁶ Transformations relevant to the chemistry of the conanine

¹ A. R. Pinder, in 'Rodd's Chemistry of the Carbon Compounds', ed. S. Coffey and M. F. Ansell, Elsevier, Amsterdam, 1978, Volume 4G, p. 381.

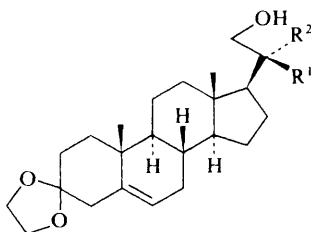
² S. B. Jayaswal, *Indian J. Pharm.*, 1977, **39**, 37 (*Chem. Abs.*, 1977, **87**, 35 872).

³ J. Lamotte, L. Dupont, O. Dideberg, H. Campsteyn, M. Vermeire, C. Delande, and R. Huls, *Acta Cryst.*, 1977, **B33**, 2392.

⁴ J. M. Saucier, *Biochemistry*, 1977, **16**, 5879.

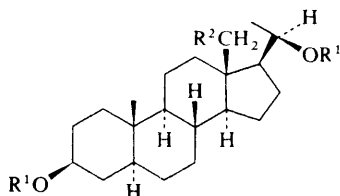
⁵ H. Kapnang, G. Charles, B. L. Sondengam, and J. H. Hemo, *Tetrahedron Letters*, 1977, 3469.

⁶ F. Lobé-Tobo and F. Khuong-Huu, *Bull. Soc. chim. France*, 1976, 1835.

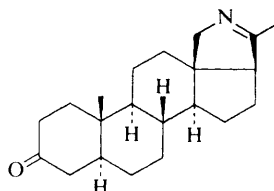


- (3) a; $R^1 = NH_2, R^2 = H$
 b; $R^1 = H, R^2 = NH_2$
 c; $R^1 = OH, R^2 = H$
 d; $R^1 = H, R^2 = OH$

system have been reported.⁷ In particular, the reaction of the iodo-pregnane derivative (4a) with sodium azide, followed by treatment of the product with lithium aluminium hydride, gave the amino-dihydroxy-compound (4b); oxidation of the latter with chromic oxide gave the nor-conanine derivative (5).⁷

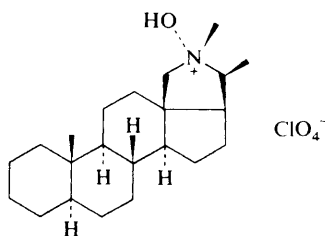


- (4) a; $R^1 = Ac, R^2 = I$
 b; $R^1 = H, R^2 = NH_2$



(5)

An X-ray diffraction study on the hydro-perchlorate salt (6) of conanine N-oxide has been reported.⁸



(6)

2 *Buxus* Alkaloids

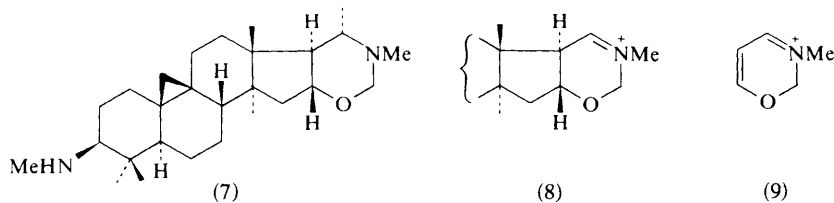
A new alkaloid, buxozine C, $C_{27}H_{46}N_2O$, has been isolated from *Buxus sempervirens*.⁹ The novel structure (7) was assigned to buxozine C on the basis of the

⁷ P. Choay, C. Monneret, and Q. Khuong-Huu, *Tetrahedron*, 1978, **34**, 1529.

⁸ M. Cesario and J. Guilhem, *Crystal Struct. Commun.*, 1977, **6**, 247.

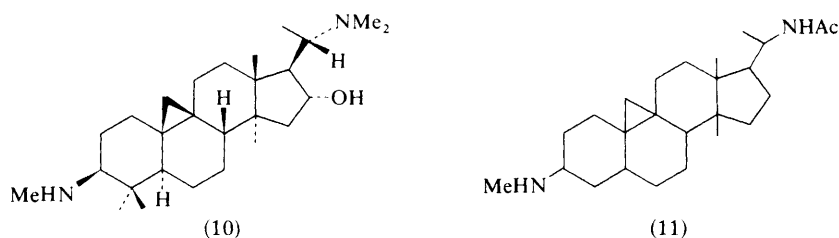
⁹ Z. Votický, L. Dolejš, O. Bauerová, and V. Paulík, *Coll. Czech. Chem. Comm.*, 1977, **42**, 2549; *Phytochemistry*, 1977, **16**, 1860.

following observations: (a) n.m.r. spectroscopy revealed the presence of four tertiary methyl groups, one secondary methyl, two *N*-methyl groups, a cyclopropyl methylene, and a methylene group bound to two heteroatoms; (b) the i.r. spectrum confirmed the presence of a cyclopropyl methylene group and suggested *inter alia* the presence of a secondary amine function; (c) the mass spectrum of buxozine C displayed a molecular ion (m/e 414) and fragment ions at m/e 399 (base peak) [assigned to the ion (8)], m/e 98 [due to ion (9)], and m/e 70, 57, and 44, characteristic of a 3-methylamino-steroid; the m.s. of [N - 2 H]buxozine C was in complete accord with these interpretations. Confirmation of the structure (7)



assigned to buxozine C was gained by hydrogenolysis, which yielded cyclovirobuxine C (10).⁹

The following alkaloids have been isolated from *B. sempervirens* var. *angustifolia*: buxamine E, buxaminol E, buxenine G, buxpiine K, buxtauine M, cyclobullatine A, cyclobuxamine H, cyclobuxine D, cycloprotobuxine C, and cyclovirobuxine D.¹⁰ By comparison, *B. sempervirens* var. *argentea* yielded buxtauine M, cyclobuxamine H, cyclobuxine D, cyclobuxophyllinine M, cyclobuxoviridine L, cycloprotobuxines C and D, cyclovirobuxine D, and irehine, together with two unidentified bases of molecular weights 398 and 426, and a new base named cyclobuxargentine G; the latter alkaloid was tentatively assigned the structure shown (11) on the basis of its i.r. and mass spectra.¹¹ Buxpiine, and an unidentified alkaloid, have been isolated from leaves of flowering *B. hircana*.¹²



3 Alkaloids of the Asclepiadaceae

Two new *N*-methylantraniloyl esters, stephanthranilines C¹³ and A,¹⁴ have been isolated from *Stephanotis japonica*. The mass spectrum of stephanthraniline C, C₂₉H₄₁NO₈, displayed the molecular ion at m/e 531, while the u.v. spectrum

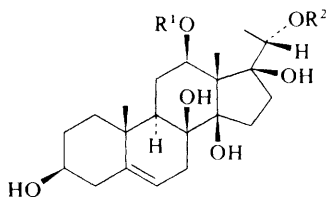
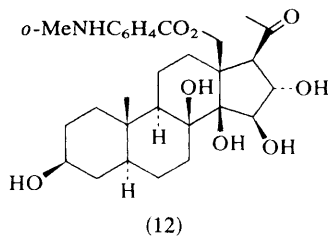
¹⁰ Z. Votický, O. Bauerová, and V. Paulík, *Chem. Zvesti*, 1976, **30**, 351 (*Chem. Abs.*, 1977, **87**, 2424).

¹¹ K. I. Kuchkova, Z. Votický, and V. Paulík, *Chem. Zvesti*, 1976, **30**, 174 (*Chem. Abs.*, 1977, **87**, 2362).

¹² G. M. Orazmuradov and A. M. Aliev, *Khim. prirod. Soedinenii*, 1977, 582 (*Chem. Abs.*, 1977, **87**, 180 702).

provided evidence for an *N*-methylantraniloyl moiety (λ_{\max} 222 and 253 nm). Stephanthraniline C was assigned the structure and stereochemistry indicated in (12) mainly by comparison of its ^1H and ^{13}C n.m.r. spectra with those of model steroid esters.¹³

Stephanthraniline A, $\text{C}_{31}\text{H}_{43}\text{NO}_8$, contained both an *N*-methylantraniloyl ester moiety and an acetoxy-group (8.08 τ). Base-catalysed hydrolysis of the ester gave the known pregnane derivative sarcostin (13a). The n.m.r. spectrum of stephanthraniline A showed, *inter alia*, a one-proton double doublet ($J = 6$ and 11 Hz) at 5.56 τ and a one-proton quartet ($J = 6$ Hz) at 5.21 τ which were assigned to the 12 α - and 20-protons respectively; from these data it may be deduced that C-12 and C-20 of the alkaloid bear acyloxy substituents and hence that the structure of stephanthraniline A must be represented by (13b) or (13c). A decision was made in favour of the former structure (13b) by comparison of the ^{13}C n.m.r. spectrum of 3-*O*-acetylstephanthraniline A with those of model esters derived from sarcostin.¹⁴ Treatment of stephanthraniline A with mild base gave the *N*-methylantraniloyl ester (13d) by hydrolysis of the acetyl ester followed by a well-precedented base-catalysed migration of the remaining ester moiety.¹⁴

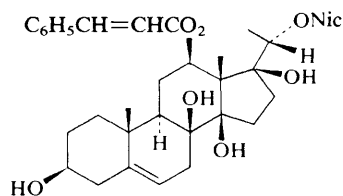


Gagaminin (14) and a new alkaloid tomentomin, $\text{C}_{36}\text{H}_{45}\text{O}_7\text{N}$, have been isolated from leaves of *Marsdenia tomentosa* after acid-catalysed hydrolysis of the crude glycoside extract. Neither alkaloid could be detected in the stem of the plant.¹⁵ The structure (15a) of tomentomin was deduced from the following evidence. Base-catalysed hydrolysis of tomentomin gave the aglycon tomentogenin (15b). The n.m.r. spectrum of tomentomin showed, *inter alia*, a double doublet ($J = 6$ and 11 Hz) at 5.24 τ and a quartet ($J = 6$ Hz) at 5.18 τ , assigned to the 12 α - and 20-protons respectively of a 12 β ,20-diester of tomentogenin. The presence of nicotinoyl and cinnamoyl ester moieties was deduced from the n.m.r., u.v., and i.r. spectra. The mass spectrum of tomentogenin showed no molecular ion but the fragmentation pattern yielded useful structural information. In particular, the existence of a significant fragment ion with m/e 453 ($M - \text{CH}_3\text{CHO}_2\text{CC}_5\text{H}_4\text{N}$) demonstrated that the alkaloid was a 20-*O*-nicotinoyl ester; hence tomentomin (15a) was assigned the structure indicated.¹⁵

¹³ S. Terada, K. Hayashi, and H. Mitsuhashi, *Tetrahedron Letters*, 1978, 1995.

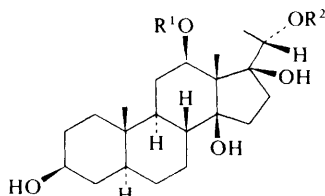
¹⁴ S. Terada, K. Hayashi, and H. Mitsuhashi, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 2802 (*Chem. Abs.*, 1978, **88**, 89 923).

¹⁵ H. Seto, K. Hayashi, and H. Mitsuhashi, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 876 (*Chem. Abs.*, 1977, **87**, 65 331).



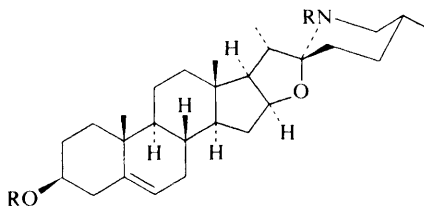
(14)

Nic = Nicotinoyl

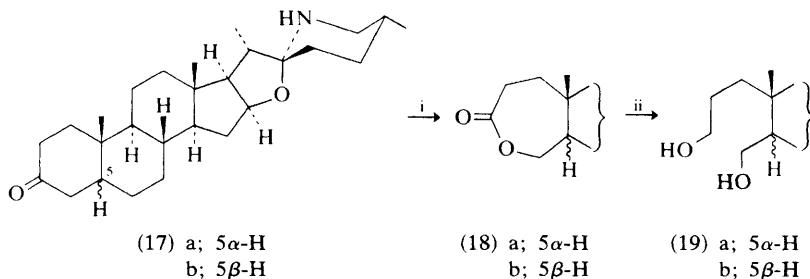
(15) a; $R^1 = C_6H_5CH=CHCO$, $R^2 = Nic$
b; $R^1 = R^2 = H$

4 Solanum Alkaloids

A number of transformations of derivatives of solasodine (16a) have been described.^{16,17} Baeyer–Villiger oxidation of the 5 α - and 5 β -ketones (17a) and

(16) a; $R = H$
b; $R = Ac$

(17b) gave ϵ -lactones (18a) and (18b) respectively; subsequent reduction of these lactones with lithium aluminium hydride gave the diols (19a) and (19b) (Scheme 1).¹⁶ The 16-methyl-pseudosolasodine derivative (20) has been prepared by the

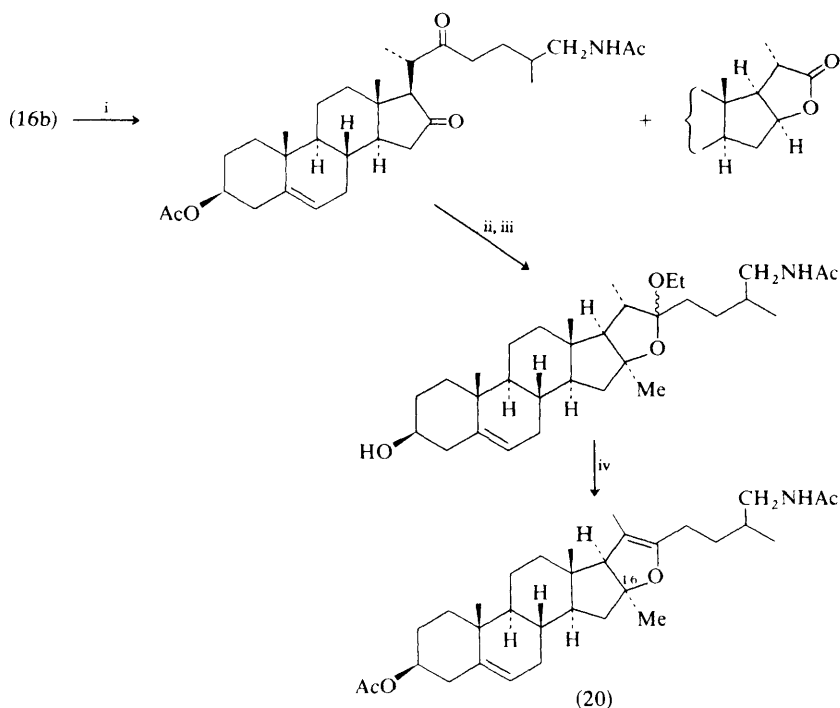
Reagents: i, $PhCO_3H$; ii, $LiAlH_4$.

Scheme 1

route summarised in Scheme 2. 16-Ethyl and 16-phenyl derivatives of pseudo-solasodine were similarly prepared.¹⁷

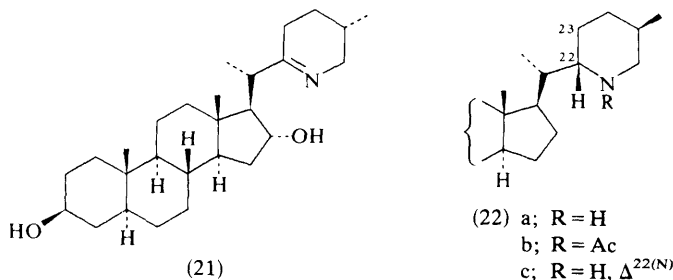
¹⁶ V. V. Kurilskaya, M. P. Irismetov, M. I. Goryaev, V. S. Bazalitskaya, and L. G. Mikhaleva, *Izvest. Akad. Nauk Kazakh. S.S.R., Ser. khim.*, 1977, **27**, No. 3, p. 46 (*Chem. Abs.*, 1978, **88**, 51 090).

¹⁷ L. M. Morozovskaya, E. S. Belenkaya, L. I. Klimova, and G. S. Grinenko, *Khim. Farm. Zhur.*, 1976, **10**, 64 (*Chem. Abs.*, 1977, **87**, 53 483).



Scheme 2

The structure and stereochemistry of 25-isolafloridine (21) were deduced partly from spectroscopic evidence and partly from the results of an *X*-ray crystallographic study on the derived hydrochloride salt.¹⁸ Details of the latter work have now appeared.¹⁹ The piperidine derivative (22a) was formed in 41% yield on treatment of its *N*-acetyl derivative (22b) with di-isobutylaluminium

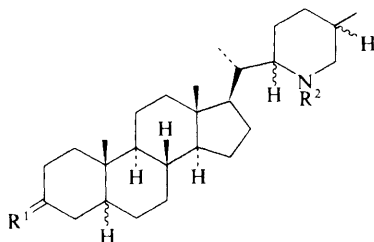


¹⁸ (a) G. J. Bird, D. J. Collins, F. W. Eastwood, B. M. K. C. Gatehouse, A. J. Jozsa, and J. M. Swan, *Tetrahedron Letters*, 1976, 3653; (b) D. M. Harrison, in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London, 1978, Vol. 8, p. 255.

¹⁹ B. M. Gatehouse and A. J. Jozsa, *Acta Cryst.*, 1977, **33B**, 3782.

hydride;²⁰ this conversion represents a considerable improvement over the formation of (22a) by the base-catalysed hydrolysis of (22b), which was utilised earlier as one step in the synthesis of solacongostidine (22c) from solasodine.²¹ The mass spectra of some *Solanum* alkaloids and their derivatives have been discussed.²²

Three new alkaloids, solaquidine,²³ solasodenone,²⁴ and soladunalinidine,²⁵ have been isolated from *Solanum* species. Solaquidine, $C_{29}H_{51}NO_2$, was isolated in 0.0007% yield from green berries of *S. pseudoquina*. The mass spectrum of solaquidine showed a fragment ion with m/e 444 ($M - 1$) but displayed no parent ion. Prominent fragment ions were observed with m/e 98 (base peak), attributable to a methylpiperidine side-chain, and m/e 101 and 127, indicative of a 3,3-dimethoxy-steroid; the latter conclusion was supported by the n.m.r. spectrum, which displayed two three-proton singlets at 6.85 and 6.90 τ (OMe groups). Acetylation of solaquidine followed by chromatography on alumina gave a keto-amide which was assigned structure (23a) on the basis of its spectroscopic properties. Hence solaquidine was assigned the ketal structure (23b).²³ Solaqui-



(23) a; $R^1 = O$, $R^2 = Ac$
 b; $R^1 = (OMe)_2$, $R^2 = H$

dine is unusual in possessing the 3,3-dimethoxy moiety; since methanol was used during the isolation of the base, it is possible that solaquidine is actually an artefact. The isolation and structure determination of four other 22,26-epimino-cholestane derivatives is discussed in Section 5 of this review.

Solasodenone, $C_{27}H_{41}NO_2$, was isolated from roots or leaves of *S. hainanense*. Structure (24a) was assigned to solasodenone on the basis of the following observations: (a) the mass spectrum of the alkaloid showed the molecular ion at m/e 411, and prominent fragment ions with m/e 138 (base peak), 125, and 114, attributable to a spiro-amino-ketal, the presence of which was confirmed by the i.r. spectrum; (b) the i.r. and u.v. spectra demonstrated the presence of an $\alpha\beta$ -unsaturated ketone moiety; (c) the o.r.d. curve and the chemical shifts of the C-18 and C-19 protons in the n.m.r. spectrum were consistent with a 3-oxo- Δ^4 -cholestene skeleton; (d) the n.m.r. spectrum also showed a singlet at 4.26 τ and a

²⁰ R. Tschesche and M. Spindler, *Chem. Ber.*, 1978, **111**, 801.

²¹ G. Adam, D. Voigt, and K. Schreiber, *J. prakt. Chem.*, 1971, **313**, 45.

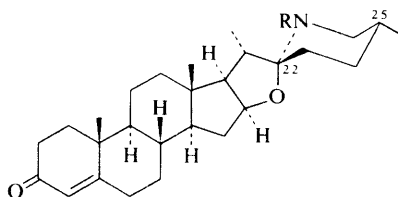
²² J. Tamas and M. Mak, *Kem. Kozl.*, 1976, **46**, 509 (*Chem. Abs.*, 1977, **87**, 102 514).

²³ A. Usubillaga, G. De Castellano, J. Hidalgo, C. Guevara, P. Martinod, and A. Paredes, *Phytochemistry*, 1977, **16**, 1861.

²⁴ G. Adam, H. T. Houng, M. Lischewski, and N. H. Khoi, *Phytochemistry*, 1978, **17**, 1070.

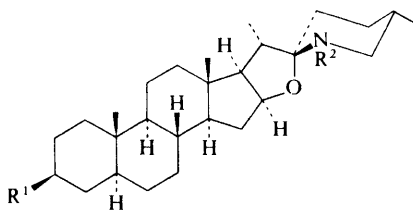
²⁵ G. J. Bird, D. J. Collins, F. W. Eastwood, and J. M. Swan, *Tetrahedron Letters*, 1978, 159.


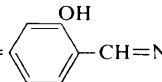
double doublet at 5.70τ ($J = 7$ and 14 Hz), assigned to the C-4 and C-16 protons respectively in (24a); (e) the differences in molecular rotation between solasodenone and its *N*-acetyl- (24b), *N*-chloro- (24c), and *N*-nitroso-derivatives (24d) were consistent with the $22R,25R$ stereochemistry depicted. The structure proposal was confirmed by the preparation of solasodenone (24a) by Oppenauer oxidation of solasodine (16a).²⁴



- (24) a; R = H
 b; R = Ac
 c; R = Cl
 d; R = NO

Soladunalinidine, $C_{27}H_{46}N_2O$, was isolated from the crude aglycon mixture extracted from *S. dunalianum*. The mass spectrum of soladunalinidine (25a) displayed the molecular ion at m/e 414 and showed prominent fragment ions with m/e 138 and 114, characteristic of a spirosoleane system. The n.m.r. spectrum of the base was most revealing, and displayed a close resemblance to that of tomatidine (25b). A six-proton singlet at 9.18τ was assigned to the C-18 and C-19 protons; three-proton doublets at 9.15 and 9.04τ were assigned to the C-27 and C-21 protons respectively, while one-proton multiplets at 6.99 and 5.86τ were attributed to the 3α - and 16α -protons of a 3β -amino-spirosolane skeleton. The ^{13}C n.m.r. spectrum of the new base was also in good agreement with its



- (25) a; $R^1 = NH_2$, $R^2 = H$
 b; $R^1 = OH$, $R^2 = H$
 c; $R^1 = HO$  $CH=N$, $R^2 = H$
 d; $R^1 =$  $CH=N$, $R^2 = H$
 e; $R^1 = NHAc$, $R^2 = Ac$
 f; $R^1 = OAc$, $R^2 = Ac$

formulation as 3β -amino-3-deoxytomatidine (25a). Soladunalinidine formed a *p*-hydroxybenzylidene derivative (25c) and a salicylidene derivative (25d). The c.d. curve of the latter derivative was in agreement with the 3β -configuration proposed for the amino-group of soladunalinidine. Diacetylsoladunalinidine (25e) gave *ON*-diacetyltomatidine (25f) among other products when treated with sodium nitrite in acetic acid, in confirmation of the structure (25a) proposed for soladunalinidine.²⁵ A number of other dibasic *Solanum* alkaloids have been isolated in recent years;²⁶ soladunalinidine is the first 3-amino *Solanum* alkaloid with a spirosoleane skeleton.

The solasodine glyco-alkaloids solasonine and solamargine have been isolated from aerial parts of *S. jasminoides*,²⁷ a new source of these glyco-alkaloids. The same glyco-alkaloids were isolated from immature fruits of *S. oleraceum*²⁸ and from leaves of *S. laciniatum*.²⁹ Solasodine (16a) has been isolated in high yield from mutants of *S. viarum*,³⁰ from a tetraploid variety of *S. khasianum*,³¹ and from diploid, tetraploid, and hexaploid varieties of *S. nigrum*.³² Solasodine has also been isolated from mature fruits of *S. acculeatissimum*,³³ and from *S. mammosum*,³⁴ in 2.8% and 1% yields respectively, and in 0.5% yield from leaves of *S. jasminoides*.³⁵

The tomatidenol glyco-alkaloids soladulcamarine, and α -, β -, and γ -solamarines have been isolated from leaves of *S. dasyphyllum*.³⁶ Tomatidenol (34) and etioline (31d) have been isolated from *S. haranense*.³⁷

Changes in the tomatine content of various parts of the tomato plant have been followed during growth.³⁸ The tomatine content of lateral shoots of the tomato plant varies from 2.3 to 7%.³⁹ The total glyco-alkaloid content of six *Lycopersicon* species has been studied; the highest yield of glyco-alkaloids was obtained from immature fruits of *L. chmielewskii*.⁴⁰

5(6)-Dehydrocommersonine was isolated from root tissue of *S. chacoense*. Tuber tissues of this species were devoid of glyco-alkaloids, while callus of two varieties of *S. tuberosum* yielded typical potato glyco-alkaloids.⁴¹ The occurrence and toxicity of potato glyco-alkaloids have been reviewed.⁴² Studies continue on

²⁶ D. M. Harrison, in ref. 18b, p. 253.

²⁷ S. C. Jain and G. L. Sharma, *Planta Med.*, 1977, **31**, 212.

²⁸ P. Bite and M. Shabana, *Egypt. J. Pharm. Sci.*, 1975, **16**, 85 (*Chem. Abs.*, 1977, **87**, 35 893).

²⁹ J. E. Lancaster, J. D. Mann, and K. E. Blyth, *New Zealand J. Agric. Res.*, 1977, **20**, 395 (*Chem. Abs.*, 1978, **88**, 19 101).

³⁰ V. R. Dnyansagar and A. R. Pingle, *Planta Med.*, 1977, **31**, 21.

³¹ B. Bhatt, *Environ. Exp. Bot.*, 1977, **17**, 121 (*Chem. Abs.*, 1978, **88**, 86 186).

³² P. Khanna and A. K. Rathore, *Indian J. Exp. Biol.*, 1977, **15**, 808 (*Chem. Abs.*, 1977, **87**, 197 345).

³³ P. G. Kadkade and C. Rolz, *Lloydia*, 1977, **40**, 217.

³⁴ L. Telek, H. Delpin, and E. Cabanillas, *Econ. Bot.*, 1977, **31**, 120 (*Chem. Abs.*, 1977, **87**, 58 444).

³⁵ S. C. Jain and G. L. Sharma, *Planta Med.*, 1977, **32**, 233.

³⁶ C. Coune, *Planta Med.*, 1977, **31**, 259.

³⁷ H. Ripperger, *Pharmazie*, 1977, **32**, 537 (*Chem. Abs.*, 1978, **88**, 19 011).

³⁸ A. Ali and E. Schloesser, *Angew. Bot.*, 1977, **51**, 143 (*Chem. Abs.*, 1978, **88**, 71 597); J. Ostrzycka and J. Borkowski, *Herba Pol.*, 1977, **23**, 135 (*Chem. Abs.*, 1978, **88**, 186 182).

³⁹ J. Ostrzycka and J. Czapski, *Herba Pol.*, 1977, **23**, 41 (*Chem. Abs.*, 1978, **88**, 71 498).

⁴⁰ W. H. Courtney and V. N. Lambeth, *Hort. Science*, 1977, **12**, 550 (*Chem. Abs.*, 1978, **88**, 86 090).

⁴¹ R. M. Zacharius and S. F. Osman, *Plant Sci. Lett.*, 1977, **10**, 283 (*Chem. Abs.*, 1978, **88**, 60 085).

⁴² L. Sujkowski and L. Skrzeczowski, *Zesz. Probl. Postepow Nauk Roln.*, 1977, **191**, 151 (*Chem. Abs.*, 1978, **88**, 47 428).

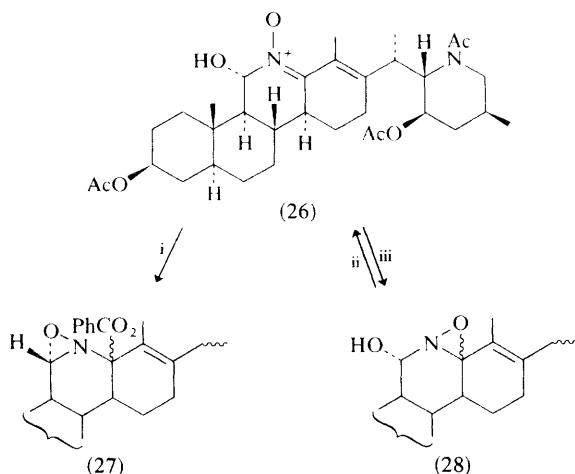
the enzymatic hydrolysis of potato glyco-alkaloids⁴³ and on the variation in the glyco-alkaloid content of potato slices during ageing.⁴⁴

The variation of the glyco-alkaloid content of *S. dulcamara* during growth of the plant has been studied.⁴⁵

5 *Veratrum* and *Fritillaria* Alkaloids

Kutney has reviewed the research of his group on the total synthesis of *Veratrum* and *Fritillaria* alkaloids.⁴⁶

The hydroxy-nitron (26), the preparation of which from jervine was described earlier,⁴⁷ was converted into the oxaziridine (27) on treatment with benzoic anhydride in pyridine.⁴⁸ The alternative oxaziridine (28) was the sole product on irradiation of the nitron at 285 nm. The oxaziridine (28) was reconverted into nitron (26) in quantitative yield on standing at room temperature in the dark (Scheme 3).⁴⁸ Studies continue on the chemistry of C-nor-D-homo-steroids derived by degradation of jervine.⁴⁹



Reagents: i, $(\text{PhCO})_2\text{O}$, pyridine; ii, Δ ; iii, $h\nu$.

Scheme 3

⁴³ A. P. Swain, T. J. Fitzpatrick, E. A. Talley, S. F. Herb, and S. F. Osman, *Phytochemistry*, 1978, **17**, 800.

⁴⁴ T. J. Fitzpatrick, S. F. Herb, S. F. Osman, and J. A. McDermott, *Amer. Potato J.*, 1977, **54**, 539 (*Chem. Abs.*, 1978, **88**, 49 202).

⁴⁵ V. H. Nga, J. Bernath, P. Tetenyi, and I. Zambo, *Herba Hung.*, 1977, **16**, 55 (*Chem. Abs.*, 1977, **87**, 2366).

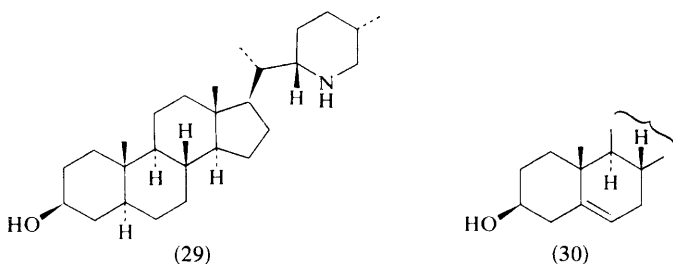
⁴⁶ J. P. Kutney, *Bioorg. Chem.*, 1977, **6**, 371.

⁴⁷ H. Sugimoto, T. Mizuguchi, and T. Masamune, *J.C.S. Perkin I*, 1976, 2365; H. Sugimoto, T. Mizuguchi, S. Honda, and T. Masamune, *ibid.*, 1977, p. 927; cf. D. M. Harrison in ref. 18b, p. 258.

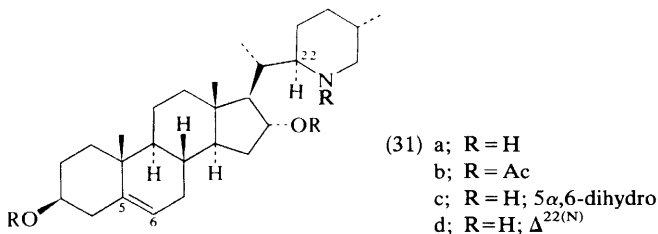
⁴⁸ H. Sugimoto, T. Mizuguchi, and T. Masamune, *Bull. Chem. Soc. Japan*, 1977, **50**, 987.

⁴⁹ A. Murai, N. Iwasa, and T. Masamune, *Chem. Letters*, 1977, 235 (*Chem. Abs.*, 1977, **87**, 39 722); A. Murai, H. Sasamori, and T. Masamune, *ibid.*, p. 669 (*Chem. Abs.*, 1977, **87**, 152 461); H. Sugimoto, S. Sugiyama, N. Yonekura, T. Masamune, and E. Osawa, *J.C.S. Perkin I*, 1978, 612; A. Murai, H. Sasamori, and T. Masamune, *Bull. Chem. Soc. Japan*, 1978, **51**, 234, 243.

Three new 22,26-epiminocholestane derivatives, *i.e.* veramiline,⁵⁰ teinemine,⁵¹ and isoteinemine,⁵¹ have been isolated from *Veratrum* species. Veramiline, $C_{27}H_{45}NO$, from *V. album* subspecies *lobelianum*, formed a digitonide and hence contained a 3β -hydroxy substituent. The base peak in the mass spectrum of veramiline had m/e 98, attributable to a methylpiperidine side-chain. Catalytic hydrogenation of the new base gave a dihydro-derivative⁵⁰ which was shown to be identical to tetrahydroverazine A⁵² (29). The position of the double bond in veramiline was argued on the following basis: (a) the difference in molecular rotation between veramiline and dihydroveramiline was consistent with the conversion of a Δ^5 -steroid into its $5\alpha,6$ -dihydro-derivative; (b) the n.m.r. spectrum of veramiline, especially the chemical-shift values of the C-18 and C-19 protons, was consistent with the presence of a Δ^5 double bond. Hence veramiline was assigned the structure and stereochemistry indicated in (30).⁵⁰



The isomeric alkaloids teinemine, $C_{27}H_{45}NO_2$, and isoteinemine were extracted from aerial parts of budding *V. grandiflorum*, the latter base in only trace amounts.⁵¹ Teinemine (31a) formed an *OON*-triacyl derivative (31b). The mass spectrum of teinemine displayed its base peak at m/e 98, in accord with the postulate that there is a methylpiperidine side-chain. The n.m.r. spectrum of the base showed *inter alia* three-proton singlets at 9.28 and 9.00 τ , assigned to the C-18 and C-19 protons of a 3β -hydroxy- Δ^5 -steroid, a vinyl doublet at 5.31 τ , and one-proton multiplets at 6.48 and 5.92 τ for the 3α - and 16β -protons in (31a). Catalytic hydrogenation of teinemine gave a dihydro-derivative⁵¹ which was identical to the known compound (22*R*)-tetrahydroetioline (31c). Additional evidence for the structure of teinemine was gained by oxidation of dihydro-teinemine (31c) to the 3,16-dione followed by catalytic reduction of the latter to

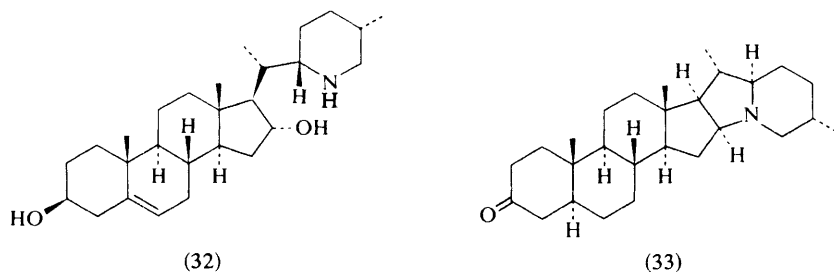


⁵⁰ A. Vassová, Z. Votický, and J. Tomko, *Coll. Czech. Chem. Comm.*, 1977, **42**, 3643.

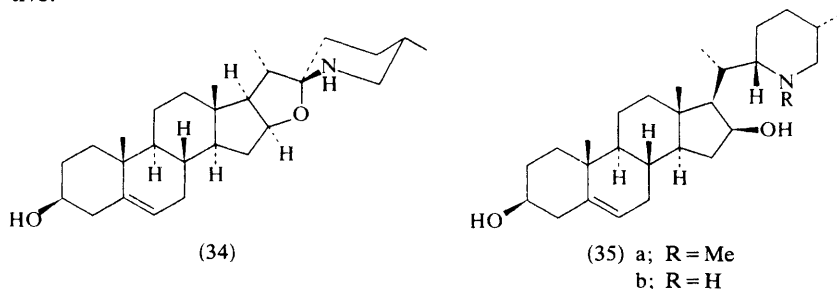
⁵¹ K. Kaneko, M. W. Tanaka, E. Takahashi, and H. Mitsuhashi, *Phytochemistry*, 1977, **16**, 1620.

⁵² G. Adam, K. Schreiber, J. Tomko, and A. Vassová, *Tetrahedron*, 1967, **23**, 167.

yield solanidan-3-one (33). Final proof of the structure of teinimine (31a) was furnished by its partial synthesis by selective hydrogenation of etioline (31d). The minor alkaloid isoteinimine (32) was also formed in low yield in the latter reaction.⁵¹



Extraction of *Fritillaria camtschaticensis*, a known source of solanidine, has yielded tomatidenol (34), solasodine (16a), and a new alkaloid hapepunine, $C_{28}H_{47}NO_2$.⁵³ Hapepunine was assigned the *N*-methyl 22,26-epiminocholestane structure (35a) on the basis of spectroscopic studies similar to those described above for teinimine. This structure proposal was proved by the partial synthesis of hapepunine from tomatidenol (34) *via* the desmethyl derivative (35b). Hapepunine (35a) is the first natural 16 β -hydroxy-22,26-epiminocholestane derivative.⁵³



The circular dichroism spectra of veralosidine, veralosine, veralosinine, and veralosidinine have been interpreted to mean that each of these compounds possesses the (25*S*)-configuration.⁵⁴ This suggestion is at variance with the currently accepted structures for veralosidine (36) and veralosine.⁵⁵

Two new alkaloids with a (25*R*)-cevanine skeleton have been isolated from aerial parts of *Korolkowia sewerzowii*.^{56,57} Ceverine, $C_{29}H_{47}NO_4$, was assigned

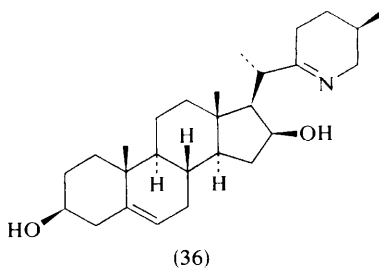
⁵³ K. Kaneko, U. Nakaoka, M. W. Tanaka, N. Yoshida, and H. Mitsuhashi, *Tetrahedron Letters*, 1978, 2099.

⁵⁴ G. P. Moiseeva, R. Shakirov, M. R. Yagudaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 623 (*Chem. Abs.*, 1977, **87**, 136 144).

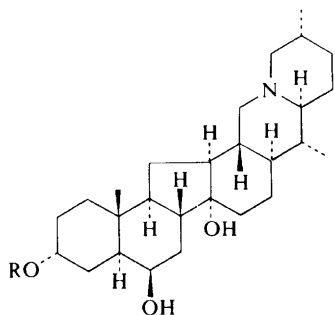
⁵⁵ J. Tomko and Z. Votický, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1973, Vol. 14, p. 21.

⁵⁶ D. U. Abdullaeva, K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 671 (*Chem. Abs.*, 1978, **88**, 170 356).

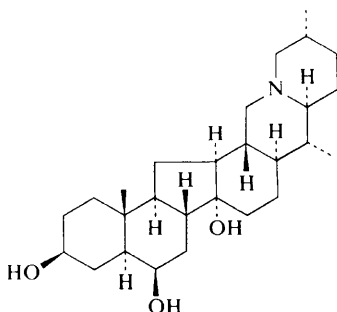
⁵⁷ K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 673 (*Chem. Abs.*, 1978, **88**, 191 175).



structure (37a) on the basis of spectroscopic studies and the formation of korseveriline (37b) on saponification.⁵⁶ The other new base cevedine, $C_{27}H_{45}NO_3$, was assigned the trihydroxy (25*R*)-cevanine structure (38) from the results of spectroscopic studies and its conversion into korseverilinedione on oxidation.⁵⁷



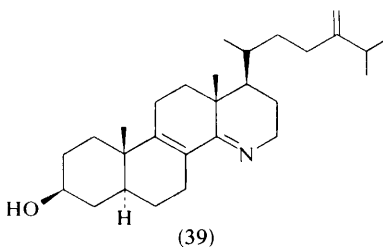
(37) a; R = Ac
b; R = H



(38)

6 Miscellaneous

Several related 24-methylene-15-aza-D-homocholestane derivatives were recently isolated from the fungus *Geotrichum flavo-brunneum*.⁵⁸ Some recent patents describe simple transformations of one such metabolite (39).⁵⁹

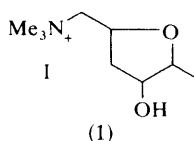


⁵⁸ F. Khuong-Huu and R. Goutarel, in 'The Alkaloids', ed. M. F. Grondon, (Specialist Periodical Reports), The Chemical Society, London, 1977, Vol. 7, p. 283.

⁵⁹ C. D. Jones, U.S. P. 3 972 884 (*Chem. Abs.*, 1977, **86**, 16 845); U.S. P. 4 008 238 (*Chem. Abs.*, 1977, **86**, 171 737); U.S. P. 4 001 246 (*Chem. Abs.*, 1977, **87**, 53 493); J. W. Chamberlin, U.S. P. 4 039 547 (*Chem. Abs.*, 1978, **88**, 38 080).

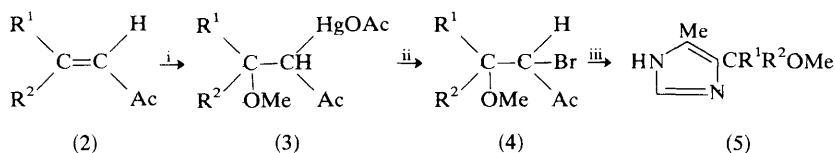
1 Muscarine Alkaloids

The full details of a convenient synthesis of muscarine-type compounds (see Vol. 5, p. 265) have now appeared;¹ the use of a transition-metal carbonyl to aid the cyclocondensation of $\alpha\alpha$ -dibromo-ketones with *NN*-dimethyl-carboxamides gives good yields of 3(2*H*)-furanones, which can be converted into the appropriate muscarine. In this way 4-methylmuscarine iodide (1), as a mixture of its two stereoisomers, was synthesised in 17% overall yield.



2 Imidazole Alkaloids

A synthesis of imidazoles can be achieved by methoxymercuration of an alkene (2), which upon bromination followed by addition of formamidine gives the imidazole (5; $R^1 = H$, $R^2 = H, Me, Et, Pr, \text{etc.}$; or $R^1 = R^2 = Me$)² (Scheme 1). The *N*-alkylation of imidazoles (and pyridazoles) through the use of phase-transfer catalysts has been reported.³



Reagents: i, $Hg(OAc)_2$; ii, Br_2 ; iii, liq. NH_3 , formamidine

Scheme 1

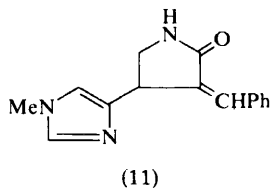
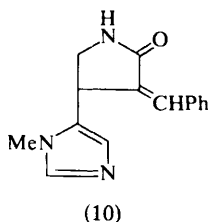
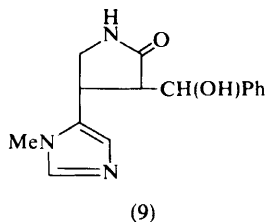
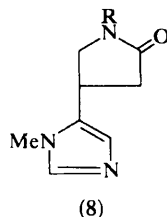
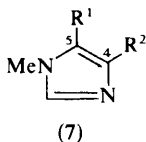
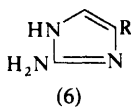
¹ Y. Hayakawa, H. Takaya, S. Makino, N. Hayakawa, and R. Noyori, *Bull. Chem. Soc. Japan*, 1977, **50**, 1990.

² K. Wegner and S. Schunack, *Arch. Pharm.*, 1977, **310**, 380 (*Chem. Abs.*, 1977, **87**, 152 070).

³ H. J. M. Dou and J. Metzger, *Bull. Soc. Chim. France*, 1976, 1861.

2-Aminoimidazole (6; R = H) has been isolated from the leguminous shrub *Mundulea sericea*⁴ while its alanyl derivative enduracididine [6; R = CH₂CH(NH₂)CO₂H] has been obtained from *Lonchocarpus sericeus*.⁵

dl-Isoanantine (10) and *dl*-anantine (11), alkaloids produced by *Cynometra ananta* and *C. lujae* respectively, have been synthesised.⁶ 1-Methyl-5-formylimidazole (7; R¹ = CHO, R² = H) was condensed with carboethoxydiethyl methyl phosphonate under Wittig–Horner conditions to give the $\alpha\beta$ -unsaturated ester (7; R² = CH=CHCO₂Et, R² = H); addition of nitromethane in the presence of tetramethylguanidine gave the nitro-ester [7; R¹ = CH(CH₂NO₂)CH₂CO₂Et, R² = H], which upon reduction gave the lactam (8; R = H). Acetylation of (8; R = Ac) followed by condensation with benzaldehyde in the presence of NaH gave two alcohols (9), which upon dehydration with POCl₃ gave *dl*-isoanantine (10). Starting with the isomeric aldehyde (7; R¹ = H, R² = CHO), *dl*-anantine (11) was synthesised using the same reaction sequence.



3 Peptide Alkaloids

The cyclic dipeptide cyclophenin (12) has been neatly synthesised by condensation of a modified anthranilic acid moiety with phenylpyruvic acid. The reaction strategy (Scheme 2) was patterned on biogenetic considerations.⁷ 2-Nitrobenzamide (13) condensed with phenylpyruvic acid to give the hippuric acid (14); the ester (15), upon *N*-methylation, reduction, and cyclisation, gave the 3,10-dehydro-derivative (18), which had been converted previously into cyclophenin.

Much of the new work on the larger ring peptide alkaloids continues to emanate from Tschesche and his collaborators. From the Rhamnaceae family, the bark of *Scutia buxifolia* has been found to contain scutianines A, B, C, D, and F (19)⁸ as

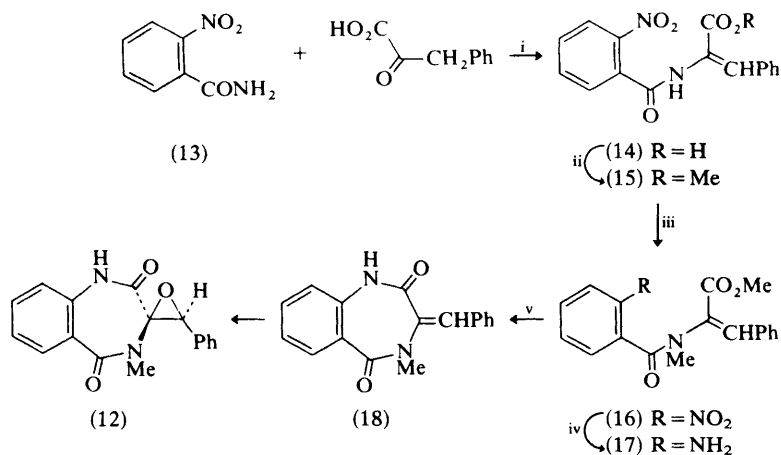
⁴ L. E. Fellows, E. A. Bell, and G. S. King, *Phytochemistry*, 1977, **16**, 1399.

⁵ L. E. Fellows, R. C. Hider, and E. A. Bell, *Phytochemistry*, 1977, **16**, 1957.

⁶ L. Tchissambou, M. Bénèche, and F. Khuong-Huu, *Tetrahedron Letters*, 1978, 1801.

⁷ R. P. Rhee and J. D. White, *J. Org. Chem.*, 1977, **42**, 3650.

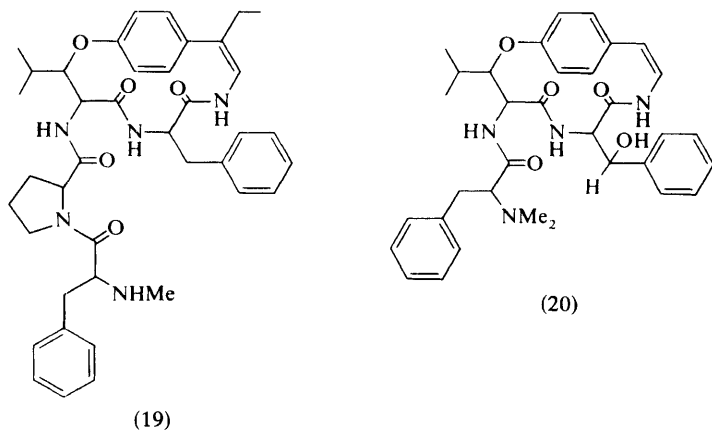
⁸ R. Tschesche, D. Hillebrand, W. Wilhelm, E. Ammermann, and G. Eckhardt, *Phytochemistry*, 1977, **16**, 1025.



Reagents: i, TsOH, PhH; ii, CH₂N₂; iii, NaH, MeI; iv, H₂, Pd, AcOEt; v, piperidine, MeOH

Scheme 2

well as the new, related frangulanine-type alkaloid scutianine G (20).⁹ It is a diastereoisomer of scutianines D and E. In the roots of *Melochia tomentosa*¹⁰ are



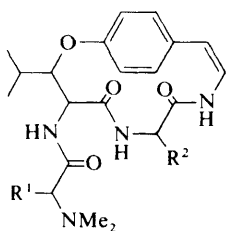
scutianine B (21; R¹ = R² = CH₂Ph) and melonovines A (21; R¹ = CHMe₂, R² = CH₂CHMe₂) and B (21; R¹ = CHMe₂, R² = CH₂C₆H₄OH).

Ziziphus nummularia also produces fourteen-membered-ring cyclopeptides; nummularines G and K, obtained from its bark, have been assigned structures (22) and (23) respectively,¹¹ and they are accompanied by the thirteen-membered-ring compound nummularine H (24), *i.e.* *N*-desmethyljubanine A.¹¹

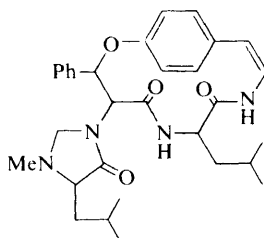
⁹ R. Tschesche and D. Hillebrand, *Phytochemistry*, 1977, **16**, 1817.

¹⁰ G. J. Kapadia, Y. N. Shukla, J. F. Morton, and H. A. Lloyd, *Phytochemistry*, 1977, **16**, 1431.

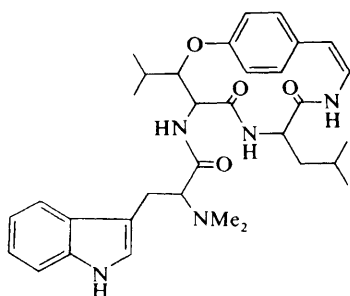
¹¹ R. Tschesche, M. Elgamal, and G. Eckhardt, *Chem. Ber.*, 1977, **110**, 2649.



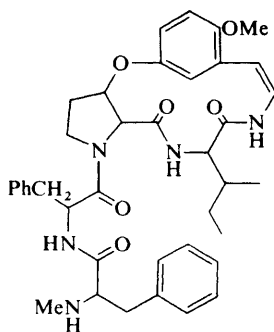
(21)



(22)

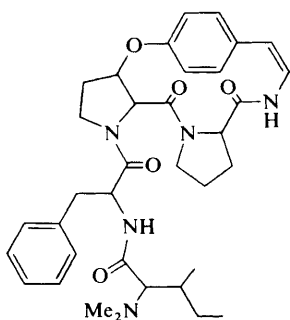


(23)

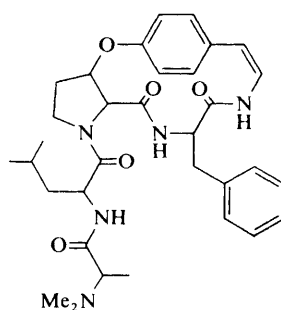


(24)

Of the seven alkaloids isolated from *Ziziphus hysodrica*, only one is new, namely hysodricanine A (25).⁸ In the same publication, an investigation into the bark of *Ziziphus mauritiana* has included the isolation of the known alkaloids mauritines A—F and G together with the new alkaloid mauritine H (26). *Araliorhamnus vaginata* was shown to contain a new aralionin-type alkaloid C (27) as well as the previously reported A, B, and desbenzyl-aralionin A compounds.⁸



(25)

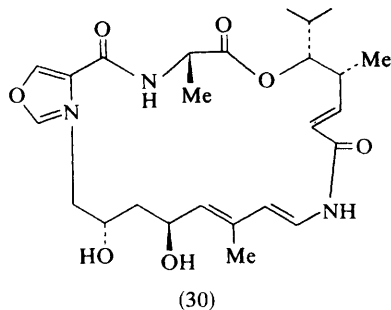
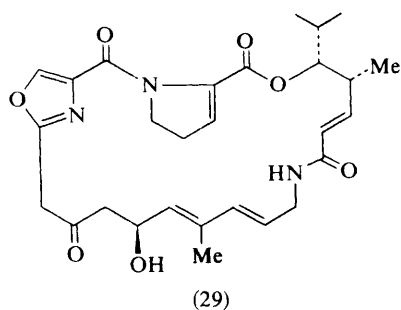
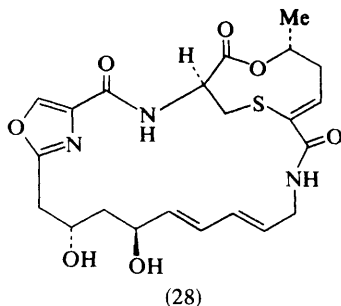
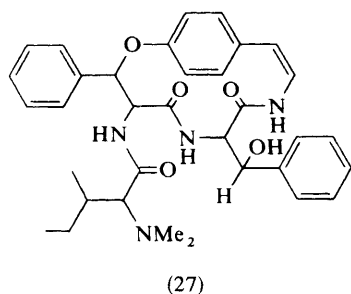


(26)

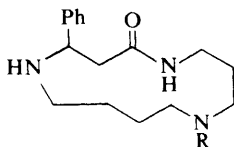
A comparative study of the crystal conformations of griseoviridin (28) and ostreogrycin A (29) with the conformation that these cyclopeptides adopt in solution has been made.¹² The ¹³C and ¹H n.m.r. and the i.r. data showed that for

¹² B. W. Bycroft, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2464.

(28) and (29) one predominant conformation existed which was essentially the same as that adopted in the crystalline state. In the same publication, an analysis of the spectral data of madumycin confirmed its structure as (30).



The structures of two novel spermidine alkaloids celacinnine and celalocinine, obtained from the twigs of *Maytenus serrata*,¹³ have been shown to be (31) and (32) respectively. Celacinnine (31) has also been isolated from the roots of *Tripterygium wilfordii*, and is accompanied by celafurine (33) and celabenzine (34). Only in the fruit of *Maytenus serrata* was the highly active tumour-inhibitory



(31) R = (*E*)-PhCH=CHCO

(32) R = (*Z*)-PhCH=CHCO

(33) R = 3-furoyl

(34) R = COPh

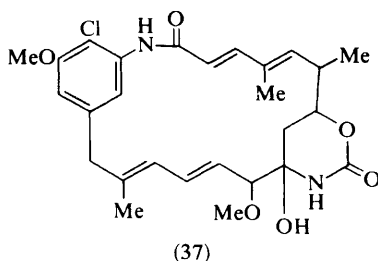
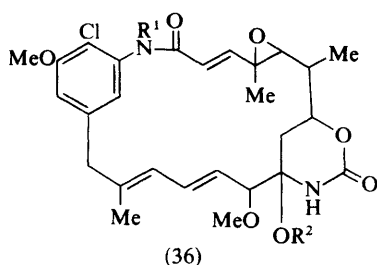
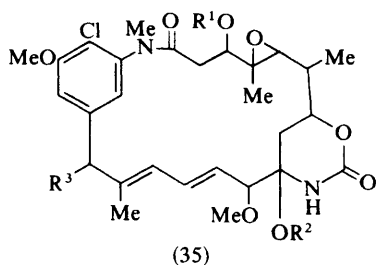
ansa macrolide maytansine found. The stem bark of *Maytenus heterophylla* and leaves of *Pleurostyliia africana* also contain celacinnine.¹⁴ The close relationship

¹³ S. M. Kupchan, H. P. J. Hintz, R. M. Smith, A. Karim, M. W. Cass, W. R. Court, and M. Yatagai, *J. Org. Chem.*, 1977, **42**, 3660.

¹⁴ H. Wagner and J. Burghart, *Planta Medica*, 1977, **32A**, 9.

between the structures of the spermidine alkaloids known to date suggests that they emanate from dicinnamic acid amides (involving tri- or tetra-amines), sometimes with incorporation of other acyl groups. The suggestion has been made that these compounds, unlike many other alkaloids, do not seem to be associated with a particular plant family.¹³

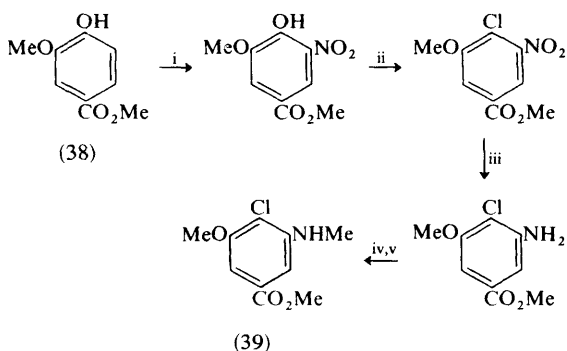
The full account of the work by the late S. M. Kupchan and his collaborators on the maytansinoids includes details of the isolation, structural elucidation, and chemical inter-relationships of those novel ansa macrolides.¹⁵ Of the ten macrolides isolated from *Maytenus serrata*, only maytansine [35; $R^1 = \text{COCH}(\text{Me})\text{N}(\text{Me})\text{COMe}$, $R^2 = R^3 = \text{H}$], maytanprine [35; $R^1 = \text{COCH}(\text{Me})\text{N}(\text{Me})\text{COEt}$, $R^2 = R^3 = \text{H}$], maytanbutine [35; $R^1 = \text{COCH}(\text{Me})\text{N}(\text{Me})\text{COPr}^i$, $R^2 = R^3 = \text{H}$], maytanvaline [35; $R^1 = \text{COCH}(\text{Me})\text{N}(\text{Me})\text{COBu}^t$, $R^2 = R^3 = \text{H}$], and maytanbutacine (35; $R^1 = \text{COPr}^i$, $R^2 = \text{H}$, $R^3 = \text{OAc}$) showed anti-tumour activity. Accompanying these active esters were the maytansides maysine (36; $R^1 = \text{Me}$; $R^2 = \text{H}$), normaysine (36; $R^1 = R^2 = \text{H}$), and maysenine (37).



Progress towards the synthesis of maytansinoids has been made by three independent groups. Meyers' group¹⁶ have described in previous publications approaches towards the synthesis of the 'northern', 'southern', and 'eastern' regions of the macrolide system (Vol. 7, p. 311); now they have described the synthesis of the 'western' zone by a facile conversion of methyl vanillate (38) into the chloro-aniline (39) (Scheme 3). Another route has been described culminating in a synthesis of the *N*-methyl-acetanilide (41) by six steps starting from

¹⁵ S. M. Kupchan, Y. Komoda, A. R. Braufman, A. T. Sneden, W. A. Court, G. J. Thomas, H. P. J. Hintz, R. M. Smith, A. Karim, G. A. Howie, A. K. Verma, Y. Nagao, R. G. Dailey, Jr., V. A. Zimmerly, and W. C. Sumner, Jr., *J. Org. Chem.*, 1977, **42**, 2349.

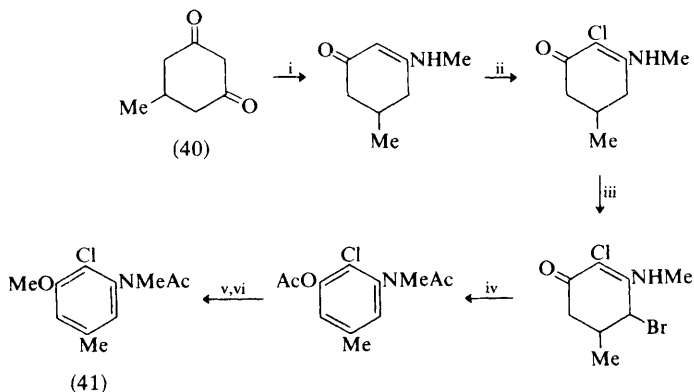
¹⁶ J. M. Kane and A. I. Meyers, *Tetrahedron Letters*, 1977, 771.



Reagents: i, HNO_3 , HOAc , 0°C ; ii, SOCl_2 , DMF ; iii, SnCl_2 , HOAc ; iv, $(\text{CF}_3\text{CO})_2\text{O}$; v, NaH , MeI

Scheme 3

5-methylcyclohexane-1,3-dione (40)¹⁷ (Scheme 4). The Corey group,¹⁸ using the enone ester (42) made by Birch reduction of gallic acid, has converted this (see Scheme 5) into the ester (43), which has in turn been converted into the dial (44).



Reagents: i, MeNH_2 ; ii, NCIS ; iii, Br_2 , CCl_4 ; iv, Ac_2O , TsOH ; v, K_2CO_3 , MeOH ; vi, MeI , K_2CO_3 , MeOH

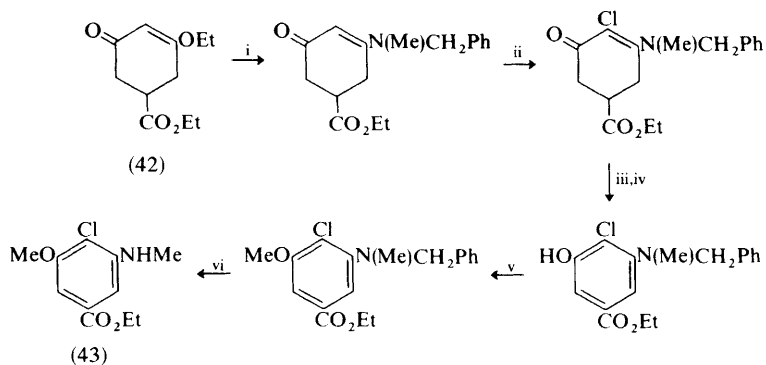
Scheme 4

The willardiine peptides isolated from *Fagus sylvatica*, namely (45; X = Glu or Glu-Phe), have been synthesised by condensing the amine (46) with $\text{PhCH}_2\text{O}_2\text{C-Glu-OMe}$ through the mixed anhydride method, deblocking resulting in the isolation of the alkaloid. Using $\text{PhCH}_2\text{O}_2\text{C-Glu-Phe-OMe}$, the other alkaloid was obtained.¹⁹

¹⁷ J. E. Foy and B. Ganem, *Tetrahedron Letters*, 1977, 775.

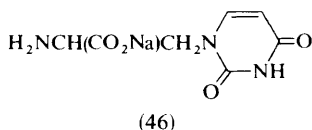
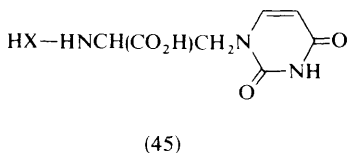
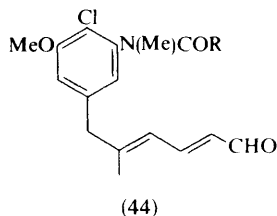
¹⁸ E. J. Corey, H. F. Wetter, A. P. Kozikowski, and A. V. R. Rao, *Tetrahedron Letters*, 1977, 777.

¹⁹ Yu. P. Shvachkin, N. A. Voskova, and G. A. Korshunova, *Zh. Obshch. Khim.*, 1977, 47, 2631 (*Chem. Abs.*, 1978, 88, 136 953).

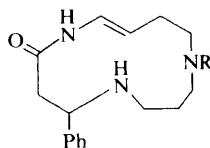


Reagents: i, NMeCH₂Ph; ii, Bu^tOCl, CHCl₃, at -50 °C; iii, LiNEt₂, THF, at -78 °C; iv, PhSeBr; v, MeI, K₂CO₃, acetone; vi, H₂, Pd/C

Scheme 5



A review of the Celastraceae alkaloids has appeared²⁰ and a new structure (47) has been proposed for periphylline,²¹ the alkaloid produced by *Pepiptygia marginata*. This new assignment also modifies the structures for isoperiphylline, dihydroperiphylline (*i.e.* 2,3-dihydro-), and neoperiphylline (*i.e.* 4,5-dehydro-). The synthesis of an eight- and a thirteen-membered-ring compound isomeric with (47) assisted in its structural elucidation.²²



²⁰ R. M. Smith, *Alkaloids* (N.Y.) 1977, **16**, 215.

²¹ R. Hocquemiller, A. Cavé, and H. P. Husson, *Tetrahedron*, 1977, **33**, 645.

²² R. Hocquemiller, A. Cavé, and H. P. Husson, *Tetrahedron*, 1977, **33**, 653.

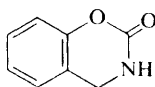
4 Alkaloid-containing Plants and Unclassified Alkaloids

A review of unclassified alkaloids and alkaloidal substances with unknown structures has appeared,²³ while Farnsworth and his collaborators have continued to publish the results of their extensive screening studies on plants.²⁴ A review of plant drugs and their preparation has been published, the data assembled including details of the plant part involved and whether the drug is used as a crude extract or in its pure form. The survey covers the Pharmacopoeias of the member countries of the E.E.C.²⁵ An attempt has been made to correlate alkaloids and plants whereby the characteristics of certain types of compound are linked with various botanical entities.²⁶

Natural sources in which alkaloids have been detected but not characterised include *Anabasis al-ravii*, found in Iraq, from which six alkaloids were isolated.²⁷ A methanol extract of the roots of *Symphoricarpos albus* contained four basic aromatic compounds which are thought to be alkaloids.²⁸

Centaurea saloniitana

From the tar residue obtained from a hot-water extract of the over-ground parts of this plant, *N*-phenyl- β -naphthylamine was isolated.²⁹ This amine was also found in *Reseda lutea*, accompanied by the 1,3-benzoxazine luteanine (48).³⁰



(48)

Haplophyllum latifolium

Haplamidine (49) has been found in the aerial parts of this plant.³¹



(49)

Leonurus artemisia

The Chinese drug I-mu Ts'ao has long been used to treat obstetrical and gynaecological disorders, and recently the alkaloid leonurine has been isolated

²³ R. H. F. Manske, *Alkaloids* (N. Y.), 1977, **16**, 511.

²⁴ G. A. Cordell and N. R. Farnsworth, *Lloydia*, 1977, **40**, 1.

²⁵ R. C. Lomagno and P. Lomagno, *Boll. Soc. Ital. Farm. Osp.*, 1976, **22**, 473 (*Chem. Abs.*, 1977, **87**, 58 436).

²⁶ D. S. Seigler, *Alkaloids* (N. Y.), 1977, **16**, 1.

²⁷ L. M. El-Hakeem and E. Weinert, *Wiss. Z. Martin-Luther-Univ. Halle-Wittenberg, Math.-Naturwiss. Reihe*, 1976, **25**, 65 (*Chem. Abs.*, 1977, **87**, 19 038).

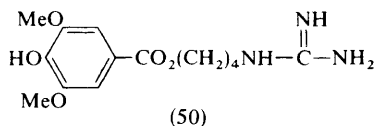
²⁸ M. Szauffer and Z. Kowalewski, *Herba Pol.*, 1976, **22**, 205 (*Chem. Abs.*, 1977, **87**, 98 877).

²⁹ R. I. Evstratova and G. G. Zapesochaya, *Khim. Prir. Soedin.*, 1977, 582 (*Chem. Abs.*, 1977, **87**, 164 248).

³⁰ I. K. Nakhatov, M. M. Tadzhibaev, V. M. Malikov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1977, 424 (*Chem. Abs.*, 1977, **87**, 130 467).

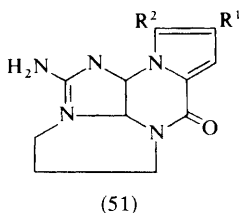
³¹ E. F. Nesmelova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1977, 427 (*Chem. Abs.*, 1977, **87**, 130 469).

from the plant source of this drug;³² it has the interesting amidine structure (50), and the alkaloid possesses uterotonic activity.



Phakellia flabellata

Two weakly basic guanidine compounds have been isolated, monobromophakellin (51; $R^1 = \text{Br}$, $R^2 = \text{H}$) and dibromophakellin (51; $R^1 = R^2 = \text{Br}$); both were found to be present in the sponge as their hydrochlorides.³³



Piper officinarum

The fruit of this plant contains the isobutyl amide of eicosa-2,4,8-trienoic acid.³⁴

Saxidomus giganteus, *Mytilus californianus*, *Gonyaulax catenella*

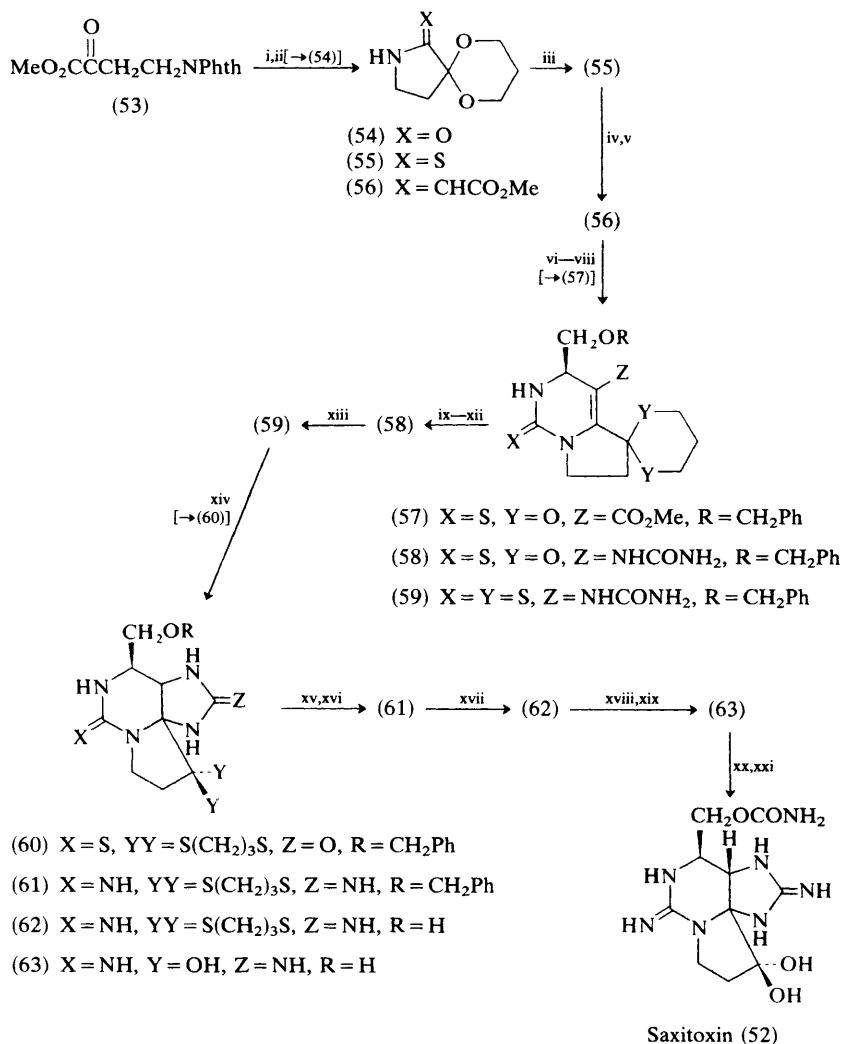
The neurotoxin isolated from these sources is one of the most toxic non-protein substances known; a stereospecific synthesis of *dl*-saxitoxin (52) has now been reported and is shown in Scheme 6.³⁵ The phthalimidobutyrate (53) was converted into the lactam (54) and thence into the thio-lactam (55). Condensation with bromoacetoacetate followed by hydrolysis gave the vinylogous carbamate (56). Addition of benzyloxyacetaldehyde and silicon tetraisothiocyanate gave the thiourea ester (57), whose transformation into the thiourea urea (58) was effected in four steps. Conversion into the more acid-stable thioketal was found to be necessary prior to cyclisation to the tricyclic thicurea (60), which in turn was converted into the diguanidine (61) by steps xv and xvi of Scheme 6. Debenzylation of (61) followed by dethioketalisation gave (63) as its dihydrochloride (steps xviii and xix). Finally, treatment with chlorosulphonyl isocyanate and work-up by hot water produced saxitoxin sulphate, from which (52) was isolated by ion-exchange chromatography.

³² H. W. Yeung, Y. C. Kong, W. P. Lay, and K. F. Cheng, *Plania Medica*, 1977, **31**, 51.

³³ G. Sharma and B. Magdoff-Fairchild, *J. Org. Chem.*, 1977, **42**, 4118.

³⁴ O. P. Gupta, S. C. Gupta, K. L. Dhar, and C. K. Atal, *Phytochemistry*, 1977, **16**, 1436.

³⁵ H. Tanino, T. Nakata, T. Kaneko, and Y. Kishi, *J. Amer. Chem. Soc.*, 1977, **99**, 2818.



Reagents: i, ethylene glycol, TsOH, toluene, reflux; ii, H₂NNH₂ · H₂O, MeOH, reflux; iii, PS₅, PhH; iv, MeCOCHBrCO₂Me, NaHCO₃, CH₂Cl₂, reflux; v, KOH, MeOH, at 50 °C; vi, PhCHOCH₂CHO; vii, Si(NCS)₄; viii, 110 °C, in toluene; ix, H₂NNH₂ · H₂O, MeOH, at r.t.; x, NOCl, CH₂Cl₂, at -50 °C; xi, 90 °C, in benzene; xii, NH₃, PhH, at r.t.; xiii, HS(CH₂)₃SH, MeCN, BF₃ etherate, at r.t.; xiv, CF₃CO₂H, CH₃CO₂H; xv, Et₃O⁺ BF₄⁻, NaHCO₃, CH₂Cl₂, at r.t.; xvi, EtCO₂NH₄, at 135 °C; xvii, BCl₃, CH₂Cl₂, at 0 °C; xviii, NBS, MeCN, H₂O; xix, MeOH, at 100 °C; xx, ClSO₂NCO, HCO₂H, 5 °C; xxi, Sephadex LH-20

Scheme 6

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