THE ALKALOIDS

Edited by
ARNOLD BROSSI

VOLUME 27

THE ALKALOIDS

Chemistry and Pharmacology

Volume 27

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Chemistry and Pharmacology

Edited by
Arnold Brossi
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CONTENTS

Chapter 4. Metabolic Transformations of Alkaloids

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PREFACE

Plants of the genus *Tabernaemontana* produce a great variety of indole alkaloids, as discussed sporadically in earlier volumes under the appropriate classes of indole alkaloids. The chapter "Alkaloids from *Tabernaemontana*" presented here is the first comprehensive review of the chemistry and pharmacology of the indole alkaloids produced by these plants. Indole alkaloids discussed in the chapter "Corynantheine, Yohimbine, and Related Alkaloids" were already reviewed in Volumes 8 and 11. In this updated chapter, besides structure elucidation, spectral properties, and pharmacological properties, great emphasis is given to synthesis of such alkaloids, a discipline much advanced by the Hungarian authors themselves. "Pyrrolidine Alkaloids," discussed in Volumes 1 and 6 more than 20 years ago, are updated, and the chapter now includes discussion of biosynthesis and pharmacology. Properties of alkaloids from black pepper species, important as spices and flavoring agents, are discussed in an addendum. The chapter "Metabolic Transformations of Alkaloids" discusses enzymes involved in alkaloid transformations, and several examples of such reactions in several classes of alkaloids are presented. This topic was discussed in Volume 18 but is now updated and expanded.

Arnold Brossi

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— CHAPTER 1 —

ALKALOIDS FROM *TABERNAEMONTANA**

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I. Introduction

Plants of the genus *Tabernaemontana* L. have been the object of considerable interest in recent years owing to their broad use in traditional medicine and to their controversial botanical classification. This stimulated extensive phytochemical investigations culminating in the isolation of a great number and large variety of constituents, these being almost totally indole alkaloids belonging to different structural classes.

* We dedicate this review to the memory of the late Professor L. Canonica, to whom we owe our interest in the chemistry of natural compounds, in appreciation of his guidance and encouragement over many years.

THE ALKALOIDS, VOL. 27

The chemistry of some of these alkaloids has been diffusely but sporadically covered in previous volumes of this series in relationship to a discussion of constituents of certain species or of some structural classes. However, there is no review collecting comprehensively the chemical aspects and pharmacological characteristics of the isolated alkaloids and highlighting the more recent findings in this field.

This contribution is an attempt to close this gap and therefore the organization of the chapter will be as follows. After a short outline of problems related to the nomenclature and delimitation of genera within the tribe Tabernaemontaneae, a summary of chemically investigated *Tabernaemontana* plants will be presented. Subsequently, the structure elucidation and chemistry of the most relevant alkaloids will be discussed. Finally, some noteworthy pharmacological activities will be outlined.

Other reviews related to this contribution should also be mentioned, in addition to the chapters of this series, which we shall recall later. Some of these deal in general with the problem of classification of indole alkaloids and with chemotaxonomic investigation (*1–5*). The chemistry of indole alkaloids is included in the Royal Society of Chemistry's *Specialist Periodical Reports* and has been extensively reviewed in a one-volume survey edited by J. E. Saxton (*6*), presenting a reasonably complete, although not exhaustive, picture of the state of the art. Other books on indole alkaloid chemistry treating this area cursorily should also be mentioned (*7, 8*). Recently, the genus *Tabernaemontana* was excellently reviewed, particularly with respect to taxonomy, phytochemistry, ethnobotany, and pharmacology (*9*).

II. Taxonomy

Most botanists divide the plant family Apocynaceae into three subfamilies: Plumerioideae, Cerberoideae, and Echitoideae. Alkaloids have been isolated from species belonging to all of these subfamilies; however, indole alkaloids have been found only in the Plumerioideae. This subfamily is further divided into seven tribes, and indole alkaloids are present only in four of these, namely, Carisseae, Tabernaemontaneae, Alstonieae (Plumerieae), and Rauwolfieae.

The four tribes are sufficiently differentiated (*10*); however, the generic limits and nomenclature in the tribe Tabernaemontaneae have had a confusing and exceedingly complex history (*11*), having been the subject of discussion for more than a century. The number of genera recognized within the tribe has varied

considerably, and botanists have considered other genera as sections within the single genus *Tabernaemontana* or split these genera from it. Thus, for example, the name *Tabernaemontana* has been restricted to species found in the Antilles, Central America, and parts of northwestern South America, while species found in Brazil have been assigned to the genus *Peschiera* A. DC. The species from South Asia and Australasia have been grouped under the name of *Ervatamia.*

The problem of classification is related to the occurrence of a large number of species wide spread throughout the world, mainly in the tropics, and to the difficulty of obtaining a quantity of plant parts of adequate quality sufficient for complete botanical investigation. In addition, some species exhibit local variation in some characters (leaf, inflorescence, flower), whereas others (fruit) remain constant. This led in the past and recent years to improper classification or to different and controversial classifications of the same plant.

To have a more complete picture of the tribe Tabernaemontaneae and a more defined taxonomy of the genus *Tabernaemontana,* a world monograph based on examination of living and herbarium specimens and direct comparison has been undertaken by Professor Antony J. M. Leeuwenberg at the University of Wageningen, Holland. The completion of this study will take several years, and only preliminary results have been published (*5,9,12*). From these studies it emerges that many genera are more closely related to the genus *Tabernaemontana* than previously thought. Thus the name *Tabernaemontana* should be used *sensu lato.*

The genera reduced to synonyms of *Tabernaemontana* are the common *Anartia, Bonafusia, Capuronetta, Conopharyngia, Ervatamia, Gabunia, Hazunta, Pagiantha, Pandaca, Peschiera, Rejoua, Sarcopharyngia, Stenosolen,* and the less common *Anacampta, Camerunia, Cadonemma, Leptopharyngia, Merizadenia, Muntafara, Ochronerium, Oistanthera, Pandacastrum, Phrissocarpus, Protogabunia, Taberna,* and *Testupides.*

Plants of the genera *Daturicarpa, Domkeocarpa, Pterotaberna, Tabernanthe* are under study in order to define their position with respect to *Tabernaemontana* (*12*). The genera *Calocrater, Crioceras, Stemmadenia, Voacanga* (= *Orchipeda*), and *Woytkowskia* are to be maintained as distinct from *Tabernaemontana* (*12*).

In this chapter we shall follow Leeuwenberg's classification, and the complete botanical name will be reported only for recognized *Tabernaemontana* species. Supplementing and supporting Leeuwenberg's investigation, the group of Verpoorte at Leiden is presently examining different parts of many species of *Tabernaemontana* from a phytochemical point of view. This work, together with the previous ones, in particular those of French groups in Gif-sur-Yvette and Reims, has led to the examination of about 60 species (out of more than 100 known) and to the isolation of nearly 250 alkaloids, most of them belonging to new structural classes.

III. Indole Alkaloids from Chemically Investigated *Tabernaemontana* Species

A. Classification of Indole Alkaloids of *Tabernaemontana* Species

Indole alkaloids from *Tabernaemontana* plants are all biogenetically derived from tryptophan (tryptamine) and secologanine, which constitute the indole and terpenic portions, respectively, and can be classified into nine main types depending on the structural characteristics of their skeleton (Fig. 1).

According to Kisakürek and Hesse (*4*), eight of these types are named: vincosan, vallesiachotaman, corynanthean, strychnan aspidospermatan (all these

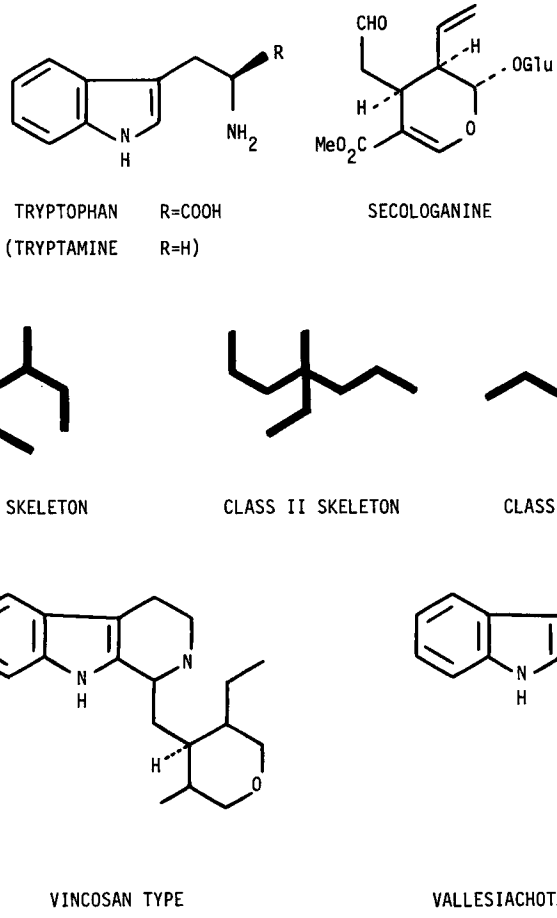
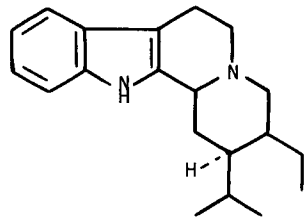
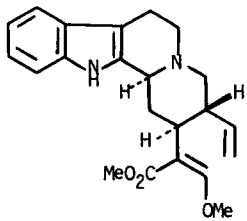


FIG. 1. Classification of indole alkaloids isolated from *Tabernaemontana* plants.

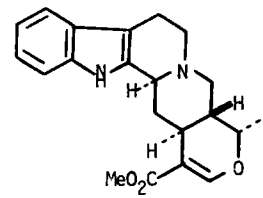


CORYNANTHEAN TYPE

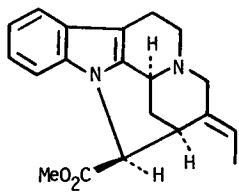
Corynantheine subtype



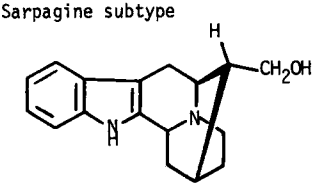
Ajmalicine subtype



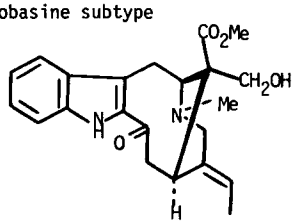
Pleiocarpamine subtype



Sarpagine subtype



Vobasine subtype



Ajmaline subtype

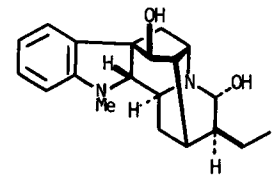
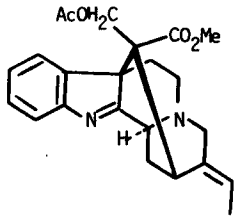
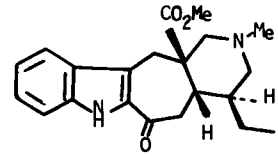


FIG. 1. (*Continued*)

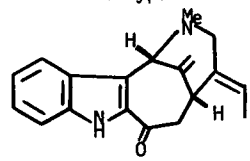
Akuammiline subtype



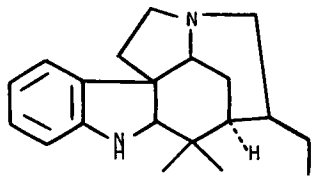
Ervatamine subtype



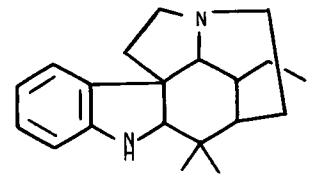
Ervitsine subtype



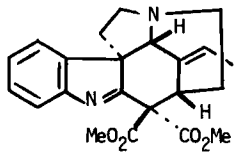
STRYCHNAN TYPE



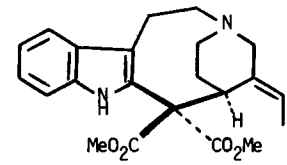
ASPIDOSPERMATAN TYPE



Precondylocarpine subtype



Stemmadenine subtype



Vallesamine subtype

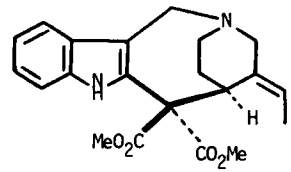
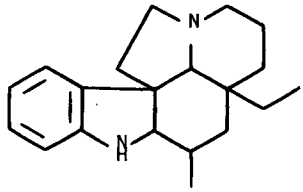
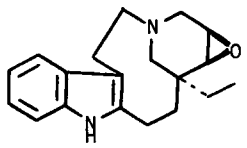


FIG. 1. (*Continued*)

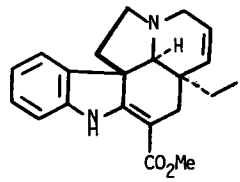
PLUMERAN TYPE



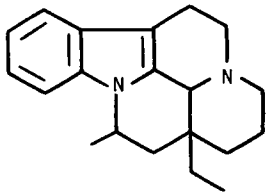
Voaphylline subtype



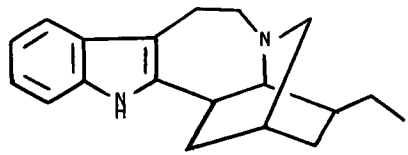
Tabersonine subtype



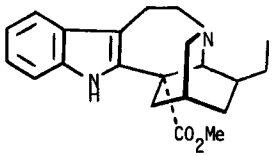
EBURNAN TYPE



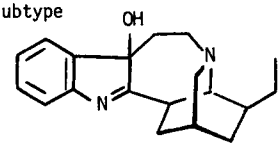
IBOGAN TYPE



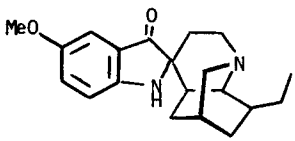
Coronaridine subtype



Coronaridine hydroxyindolenine subtype



Iboluteine subtype



Tabernoxidine subtype

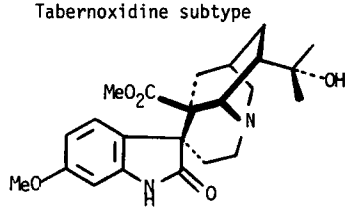


FIG. 1. (*Continued*)

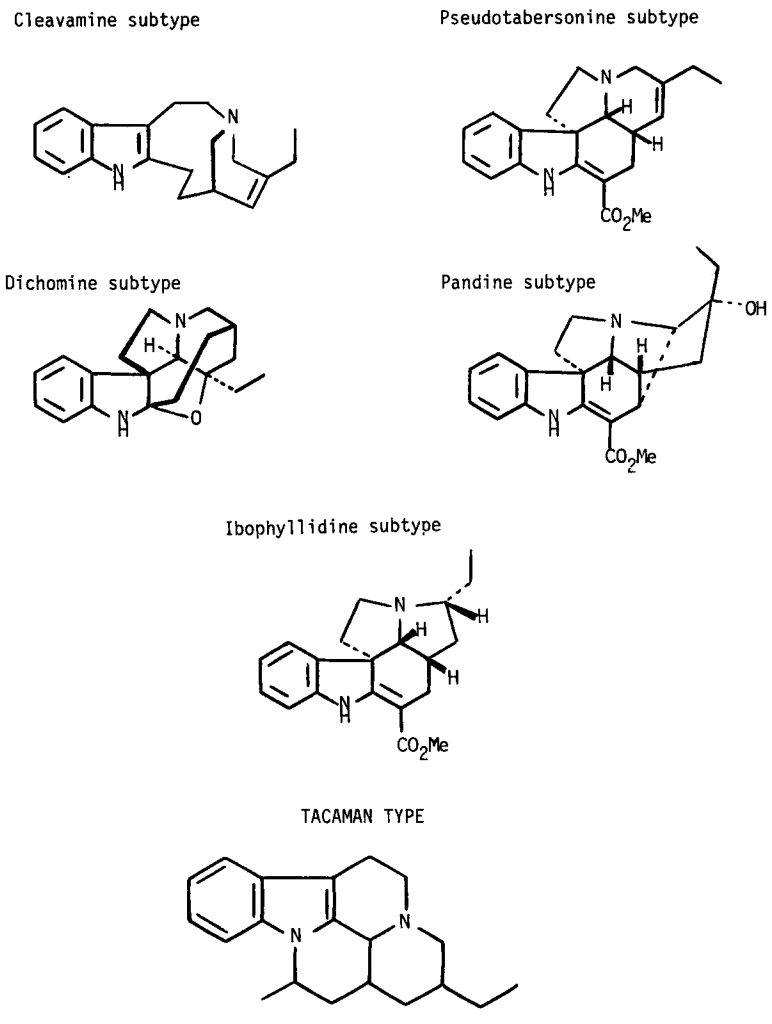


FIG. 1. (*Continued*)

(Text continued from p. 4)

types contain an intact secologanine, class I skeleton), plumeran, eburnan (corresponding to rearranged secologanine, class II skeleton), and ibogan (corresponding to a further rearranged monoterpene, class III skeleton).

The ninth type, tacaman (class III skeleton) has been added by Verpoorte and van Beek in order to account for the isolation of a few tacamines (see below), new indole alkaloids which until now were found only in *Tabernaemontana eglandulosa*.

The nine skeletal types mentioned above are biosynthetically related, or conceivable proposals for their formation *in vivo* are accepted. A discussion on biogenetic relationships among indole alkaloids is outside the scope of this review and summaries on this subject can be consulted (*7, 8, 13*).

No vincosan alkaloids were found in *Tabernaemontana* species, and only a few examples of vallesiachotaman, strychnan, aspidospermatan eburnan, and tacaman alkaloids have been detected.

A greater number of compounds has been found among plumeran, corynanthean and ibogan alkaloids. The last type seems to be characteristic of all *Tabernaemontana* plants, being contained in almost all species.

Alkaloids of plumeran, aspidospermatan, corynanthean, and ibogan types are conveniently subdivided into subtypes depending on further variations of the terpenic portion or, in very few cases, of the indole portion of the fundamental skeleton. The subtypes are named according to the most representative member, even if this is not found in *Tabernaemontana*.

A few alkaloids, clearly originating from tryptophan and secologanine, cannot be accomodated in the previous types. They form the group of miscellaneous monomeric alkaloids.

In addition to monomeric compounds, *Tabernaemontana* plants contain many bisindole alkaloids that are classified on the basis of constituent monomeric units, as in the extensive review by Cordell and Saxton in Volume XX of this series (*14*). This classification is more rational and comprehensive than others (*1, 13, 15*) and will be used as a guide for the representation of structural formulas and for the discussion of the chemistry of single alkaloids.

B. Indole Alkaloids Isolated from *Tabernaemontana* Species

The *Tabernaemontana* plants that have been investigated chemically are listed in Table I, together with the alkaloids found therein, in alphabetical order. For some species, botanical synonyms are listed also.

In Table II the alkaloids are arranged in order of increasing molecular complexity, together with some physical data and occurrence. The structural formulas of the alkaloids are arranged according to the division into types and subtypes outlined above, and are presented in Fig. 2. Within each subtype, compounds are listed in homogeneous groups with increasing molecular weight. Formulas are represented with a defined absolute stereochemistry, which, however, has been determined only for a few compounds, either through chemical correlation or on the basis of chiroptical characteristics. Formulas represent presumed stereochemistry also in those compounds for which there is no clear evidence.

(Text continues on p. 25)

TABLE I

CHEMICALLY INVESTIGATED *TABERNAEMONTANA* PLANTS AND THEIR ALKALOID CONTENT

Plants	Alkaloids	References
T. accedens Müll. Arg. (*Peschiera accedens*)	Accedine (**23**)	*17,20*
	Accedinine (**199**)	*19*
	Accedinisine (**198**)	*19,20*
	N^1-Demethyl-16-epiaccedine (**24**)	*18*
	$N^{4'}$-Demethylvoacamine (**210**)	*19*
	N^1-Methyl-16-epiaffinine (**29**)	*17*
	Voacamidine (**205**)	*19*
	Voacamine (**203**)	*19*
	Voacamine $N^{4'}$-oxide (**204**)	*19*
T. affinis Müll. Arg. (*Peschiera affinis*)	Affinine (**27**)	*21,22*
	Affinisine (**16**)	*21,22,24*
	Coronaridine (**97**)	*24*
	Coronaridine pseudoindoxyl (**148**)	*24*
	19-Epiheyneanine (**123**)	*24*
	Olivacine (**195**)	*23,24*
	Vobasine (**32**)	*21*
T. alba Mill.	Coronaridine (**97**)	*25*
	Tabersonine (**67**)	*25*
T. albiflora (Miq.) Pulle	Coronaridine (**97**)	*26*
	Desethylibophyllidine (**185**)	*26*
	(20*R*)-18,19-Dihydroxypseudovincadifformine (**166**)	*29*
	18-Hydroxycoronaridine (**128**)	*28*
	18-Hydroxy-20-epiibophyllidine (**182**)	*27*
	19-Hydroxyibophyllidine (**180**)	*27*
	(19*R*)-19-Hydroxy-20-epiibophyllidine (**183**)	*27*
	(19*S*)-19-Hydroxy-20-epiibophyllidine (**184**)	*27*
	19-Hydroxy-20-epipandoline (**167**)	*29*
	Ibophyllidine (**178**)	*26*
	20-Epiibophyllidine (**181**)	*26*
T. amblyocarpa Urb.	Akuammidine (**17**)	*30*
	Coronaridine (**97**)	*30,31*
	Heyneanine (**122**)	*31*
	Ibogamine (**134**)	*30,31*
	Isovoacangine (**101**)	*30*
	Isovoacristine (**120**)	*30*
	19-Oxovoacangine (**117**)	*31*
	Tubotaiwine (**61**)	*30*
	Vallesamine (**64**)	*30*
	Voacangine (**100**)	*30,31*
	Voacristine (**118**)	*30*
T. amygdalifolia Jacq.	Cylindrocarpidine (**79**)	*34*
	12-Demethoxycylindrocarpidine (**80**)	*33*
	O-Demethylpalosine (**83**)	*32*

TABLE I (*Continued*)

Plants	Alkaloids	References
	Homocylindrocarpidine (**81**)	*33*
	5-Oxocylindrocarpidine (**82**)	*34*
T. apoda Wr. ex Sauv. (*T. armeniaca, Peschiera apoda*)	Apodine (**84**)	*36*
	Apodinine (**86**)	*43*
	Coronaridine (**97**)	*37,39,40*
	Desoxoapodine (**85**)	*35*
	Heyneanine (**122**)	*42*
	Ibogaine hydroxyindolenine (**146**)	*38*
	Ibogaine pseudoindoxyl (**154**)	*38*
	Ibogamine (**134**)	*37,40,44*
	Isovoacangine (**101**)	*37,44*
	Voacangine (**100**)	*37,38,40,44*
	Voacangine hydroxyindolenine (**143**)	*41,43*
	Voacangine pseudoindoxyl (**149**)	*38,42*
	Voacristine (**118**)	*39,41*
	Voacristine hydroxyindolenine (**144**)	*39,41*
	Voacristine pseudoindoxyl (**150**)	*41*
T. arborea Rose	Isovoacangine (**101**)	*46*
	Tabersonine (**67**)	*46*
	Voacamine (**203**)	*45*
	Voacangine (**100**)	*45,46*
	19-Epivoacorine (**212**)	*45*
T. attenuata (Miers) Urb. (*Anartia meyeri*)	Angustine (**5**)	*47*
	Conopharyngine (**102**)	*47*
	Conopharyngine hydroxyindolenine (**145**)	*47*
	Coronaridine (**97**)	*47*
	Coronaridine hydroxyindolenine (**142**)	*47*
	Heyneanine (**122**)	*47*
	19-Epiheyneanine (**123**)	*47*
	11-Hydroxycoronaridine (**99**)	*47*
	10-Hydroxyheyneanine (**125**)	*47*
	11-Hydroxyheyneanine (**126**)	*47*
	Ibophyllidine (**178**)	*47*
	Isovoacangine (**101**)	*47*
	(6*R*)-3,6-Oxidocoronaridine (**129**)	*47*
	16-Epipleiocarpamine (**15**)	*47*
	Tubotaiwine (**61**)	*47*
	Voacangine (**100**)	*47*
T. aurantiaca Gaud. (*Rejoua aurantiaca*)	Ibogaine pseudoindoxyl (**154**)	*48*
	Voacangine (**100**)	*48*
	Voacangine pseudoindoxyl (**149**)	*48,49*
	Vobtusine (**239**)	*48*
T. australis Müll. Arg. (*Peschiera australis*)	Voacamine (**203**)	*50*
	Voacangine (**100**)	*50*

(*continued*)

TABLE I (*Continued*)

Plants	Alkaloids	References
T. brachyantha Stapf. (*Conopharyngia brachyantha*)	Anhydrovobasindiol (**35**)	*51*
	Normacusine B (**18**)	*51*
	Voacorine (**211**)	*51*
	Isomer of voacorine	*51*
T. bufalina Lour. (*Ervatamia hainanensis*)	Coronaridine (**97**)	*53*
	Coronaridine hydroxyindolenine (**142**)	*53*
	Ervahanine A (**202**)	*52*
	Ervahanine B (**223**)	*52*
	Ervahanine C (**228**)	*52*
	Geissoschizol (**7**)	*53*
	Heyneanine (**122**)	*53*
	(3*S*)-3-(β-Hydroxyethyl)coronaridine (**111**)	*53*
	10-Hydroxyheyneanine (**125**)	*53*
	10-Hydroxygeissoschizol (**8**)	*53*
	Ibogamine (**134**)	*53*
	3-Oxocoronaridine (**105**)	*53*
	Perivine (**25**)	*53*
	Vobasine (**32**)	*53*
T. calcarea Pichon (*Pandaca calcarea, P. caducifolia*)	Apparicine (**66**)	*54*
	Dregamine (**30**)	*54,55*
	Pandine (**176**)	*54,55*
	Pandoline (**164**)	*54,55*
	20-Epipandoline (**165**)	*55*
	Pseudotabersonine (**161**)	*55*
	(20*R*)-Pseudovincadifformine (**162**)	*55*
	Silicine (**46**)	*55*
T. capuronii Leeuwenberg (*Capuronetta elegans*)	14,15-Anhydrocapuronidine (**172**)[a]	*57*
	14,15-Anhydro-1,2-dihydrocapuronidine (**173**)[a]	*57*
	Capuronidine (**170**)	*56*
	Capuronine (**159**)	*56*
	(20*R*)-Capuvosidine (**236**)	*57,58*
	Capuvosine (**235**)	*56,58*
	(20*R*)-Dehydroxycapuvosine (**233**)	*57,58*
	$N^{4'}$-Demethylcapuvosine (**234**)	*57*
	(20*R*)-1,2-Dihydrocapuvosidine (**237**)	*58*
T. cerifera Panch. et Seb. (*Pagiantha cerifera*)	Apparicine (**66**)	*60*
	Ibogaine (**135**)	*59*
	Olivacine (**195**)	*60*
	Voacangine (**100**)	*59*
	Voacangine hydroxyindolenine (**143**)	*59*
	Vobasine (**32**)	*60*
T. chippii Pichon	Voaphylline (**87**)	*61*
	Vobparicine (**200**)	*62*

TABLE I (*Continued*)

Plants	Alkaloids	References
T. citrifolia L. (*T. oppositifolia*)	Akuammidine (**17**)	*64*
	Apparicine (**66**)	*63,64*
	Coronaridine (**97**)	*25,50,63,64*
	Ibogamine (**134**)	*50,64*
	Iboxygaine (**139**)	*64*
	Lochnericine (**74**)	*64*
	3-Oxovoacangine (**108**)	*64*
	3-Oxovoacristine (**127**)	*64*
	Tabersonine (**67**)	*25,64*
	Vallesamine (**64**)	*64*
	Voacamine (**203**)	*50*
	Voacangine (**100**)	*50,63,64*
	Voacangine hydroxyindolenine (**143**)	*64*
	Voacristine (**118**)	*64*
T. coffeoides Boj. (*T. modesta, T. membranacea, Hazunta angustifolia, H. coffeoides, H. membranacea, H. modesta, H. modesta methuenii, H. silicola, H. velutina*)	Akuammidine (**17**)	*69*
	Apparicine (**16**)	*69,70*
	Coronaridine (**97**)	*68*
	Desoxoapodine (**85**)	*70*
	3,14-Dihydroellipticine (**196**)	*67,69,70*
	(20′*S*)-19′,20′-Dihydrotabernamine (**206**)	*71*
	14,15-Dihydroxyvincadifformine (**76**)	*70*
	Dregamine (**30**)	*65–67,69,70*
	Hazuntine (**72**)	*65*
	Hazuntinine (**73**)	*65*
	Heyneanine (**122**)	*69*
	19-Epiheyneanine (**123**)	*68,69*
	10-Hydroxy-11-methoxytabersonine (**69**)	*69*
	(19*R*)-19-Hydroxytabernaelegantine A (**216**)	*67,71*
	Ibogamine (**134**)	*66,67,69,70*
	Isomethuenine (**52**)	*67,69*
	Isoreserpiline (**13**)	*67*
	Isovoacangine (**101**)	*67*
	Lochnericine (**74**)	*70*
	Methuenine (**51**)	*67,69,70*
	Normacusine B (**18**)	*67*
	6-Oxomethuenine (**53**)	*67*
	6-Oxosilicine (**48**)	*67–70*
	6-Oxo-16-episilicine (**49**)	*70*
	3-Oxotabersonine (**68**)	*70*
	Pericyclivine (**19**)	*70*
	Polyneuridine (**20**)	*69*
	Reserpiline (**12**)	*67*
	Silicine (**46**)	*67–70*
	20-Episilicine (**47**)	*67*
	Stemmadenine (**63**)	*67*

(*continued*)

TABLE I (*Continued*)

Plants	Alkaloids	References
	Tabernaelegantine A (**214**)	*67,68,71*
	Tabernaemontanine (**31**)	*65–67,69,70*
	Tabersonine (**67**)	*70*
	Tetraphyllicine (**37**)	*67*
	Tetraphyllicine monomethoxybenzoate (**38**)	*67*
	Tetraphyllicine dimethoxybenzoate (**39**)	*67*
	Tetraphyllicine trimethoxybenzoate (**40**)	*67*
	Vallesamine (**64**)	*70*
	Vincanidine (**56**)	*67*
	Voacangine (**100**)	*68*
	Voacarpine (**26**)	*65,69*
	Voaphylline (**87**)	*69*
	Vobasine (**32**)	*65,67,69,70*
T. contorta Stapf.	Conopharyngine (**102**)	*72*
	Coronaridine (**97**)	*72*
	Ibogaine (**135**)	*72*
	Voacangine (**100**)	*72*
	Voacristine (**118**)	*72*
T. crassa Benth. (*T. durissima, Conopharyngia crassa, C. durissima, C. jollyana, Gabunia odoratissima*)	*O*-Acetylpolyneuridine (**21**)	*77*
	Akuammiline (**41**)	*81*
	Anhydrovobasindiol (**35**)	*81*
	Conoduramine (**226**)	*73,75*
	Conodurine (**230**)	*73,75*
	Conopharyngine (**102**)	*73,79*
	Conopharyngine hydroxyindolenine (**145**)	*77*
	Coronaridine (**97**)	*74–76*
	Coronaridine hydroxyindolenine (**142**)	*76*
	Crassanine (**156**)	*79*
	Gabunine (**229**)	*75*
	Heyneanine (**122**)	*77*
	19-Hydroxyconopharyngine (**121**)	*77–79*
	Ibogamine (**134**)	*75*
	Isovoacangine (**101**)	*73,75*
	3-Oxoconopharyngine (**109**)	*80*
	3-Oxocoronaridine (**105**)	*80*
	5-Oxocoronaridine (**112**)	*74*
	3-Oxoheyneanine (**124**)	*80*
	Perycyclivine (**19**)	*75*
	Perivine (**25**)	*77*
	Tabersonine (**67**)	*76*
	Voacristine (**118**)	*77*
	Vobasine (**32**)	*75*
T. crassifolia Pichon	Ibogamine (**134**)	*82*
	Tabernantine (**136**)	*82*

TABLE I (*Continued*)

Plants	Alkaloids	References
T. debrayi (Mgf.) Leeuwenberg (*Pandaca debrayi*)	Dregamine (**30**)	*54*
	Pandine (**176**)	*54*
	Pandoline (**164**)	*54*
T. dichotoma Roxb. ex Wall (*Ervatamia dichotoma, Pagiantha dichotoma, Rejuoa dichotoma*)	*O*-Acetylvallesamine (**65**)	*89*
	Apparicine (**66**)	*87,89*
	Coronaridine (**97**)	*83,84,86,88,89*
	Dichomine (**177**)	*89,90*
	Heyneanine (**122**)	*84,85*
	19-Epiheyneanine (**123**)	*89*
	Ibogamine (**134**)	*88*
	19-Epiiboxygaine (**140**)	*87*
	Isomethuenine (**52**)	*87,89*
	12-Methoxyvoaphylline (**89**)	*87,89*
	3-(2′-Oxopropyl)coronaridine (**106**)	*89*
	Perivine (**25**)	*87*
	Stemmadenine (**63**)	*88*
	Tabersonine (**67**)	*88*
	Vallesamine (**64**)	*89*
	Voacangine (**100**)	*86,88*
	19-Epivoacristine (**119**)	*87*
	Voacristine hydroxyindolenine (**144**)	*85*
	Voaphylline (**87**)	*88,89*
	Voaphylline hydroxyindolenine (**90**)	*86,88*
	Vobasine (**32**)	*86,87,89*
T. divaricata (L.) R.Br. (*T. coronaria, Ervatamia coronaria, E. divaricata*)	Apparicine (**66**)	*100*
	Coronaridine (**97**)	*50,91,93–95,99*
	Coronaridine hydroxyindolenine (**142**)	*99*
	Dregamine (**30**)	*50,86,94*
	rac-Heyneanine (*rac*-**122**)[b]	*99*
	5-Hydroxy-6-oxocoronaridine (**114**)	*99*
	Ibogamine (**134**)	*95,99*
	Isovoacangine (**101**)	*95*
	Isovoacristine (**120**)	*98*
	Lochnericine (**74**)	*94*
	N^1-Methylvoaphylline (**88**)	*96,97,100*
	3-Oxocoronaridine (**105**)	*93,99*
	5-Oxocoronaridine (**112**)	*99*
	6-Oxocoronaridine (**113**)	*99*
	3-(2′-Oxopropyl)coronaridine (**106**)	*93*
	Tabernaemontanine (**31**)	*50,86,91,92,94*
	Tabersonine (**67**)	*100*
	3,14;4,19-Tetrahydroolivacine (**197**)	*97*
	Voacamine (**203**)	*86,99*
	Voacangine (**100**)	*86,94,95*

(*continued*)

TABLE I (*Continued*)

Plants	Alkaloids	References
	Voacristine (**118**)	*94*
	Voaphylline (**87**)	*94,96,100*
	Vobasine (**32**)	*86*
T. echinata Vell. (*Peschiera echinata*)	Angustine (**5**)	*101*
	Coronaridine (**97**)	*101*
	Decarbometoxyvoacamine (**209**)	*101*
	$N^{4'}$-Demethylvoacamine (**210**)	*101*
	10-Hydroxycoronaridine (**98**)	*101*
	10-Hydroxyheyneanine (**125**)	*101*
	Ibogaine (**135**)	*101*
	Ibogaine hydroxyindolenine (**146**)	*101*
	16-Epiisositsirikine (**10**)	*101*
	Olivacine (**195**)	*101*
	(6*R*)-3,6-Oxidovoacangine (**131**)	*101*
	3-Oxovoacangine (**108**)	*101*
	Pleiocarpamine (**14**)	*101*
	Tubotaiwine (**61**)	*101*
	Voacamidine (**205**)	*101*
	Voacamine (**203**)	*101*
	Voacangine (**100**)	*101*
	Voacangine hydroxyindolenine (**143**)	*101*
	Voacangine pseudoindoxyl (**149**)	*101*
	Voacristine (**118**)	*101*
	19-Epivoacristine (**119**)	*101*
	Vobasine (**32**)	*101*
T. eglandulosa Stapf (*T. chartacea, Gabunia eglandulosa, G. longifera*)	16,17-Anhydrotacamine (**191**)	*105*
	Conopharyngine (**102**)	*72*
	Coronaridine (**97**)	*72,102,103,105*
	16*R*-Decarbomethoxytacamine (**189**)	*105*
	16*S*-Decarbomethoxytacamine (**190**)	*105*
	(20*R*)-1,2-Dehydropseudoaspidospermidine (**168**)	*105*
	Dichomine (**177**)	*105*
	(20*R*)-15,20-Dihydrocleavamine (**157**)	*105*
	(20*S*)-15,20-Dihydrocleavamine (**158**)	*105*
	3-Hydroxycoronaridine (**103**)	*103*
	11-Hydroxycoronaridine (**99**)	*105*
	(20*S*)-Hydroxy-1,2-dehydropseudoaspidospermidine (**171**)	*105*
	3-Hydroxyisovoacangine (**107**)	*103*
	6-Hydroxy-3-oxocoronaridine (**115**)	*102*
	(19*S*)-Hydroxytacamine (**188**)	*105*
	17-Hydroxytacamonine (**193**)	*105*
	Ibogamine (**134**)	*105*
	Isovoacangine (**101**)	*103*
	Norfluorocurarine (**57**)	*105*
	(6*R*)-3,6-Oxidocoronaridine (**129**)	*102*

TABLE I (*Continued*)

Plants	Alkaloids	References
	Perivine (**25**)	*103*
	20*R*-Pseudovincadifformine (**162**)[c]	*105*
	20*S*-Pseudovincadifformine (**163**)[c]	*105*
	Tacamine (**186**)	*104,105*
	16-Epitacamine (**187**)	*105*
	Tacamonine (**192**)	*105*
	Tubotaiwine (**61**)	*105*
	(14*S*,20*R*)-Velbanamine (**160**)[d]	*105*
	Voacamine (**203**)	*103*
	Voacangine (**100**)	*72*
	Voaphylline (**87**)	*105*
	Vobasine (**32**)	*103*
T. elegans Stapf (*Conopharyngia elegans*)	Conoduramine (**226**)	*106*
	Dregamine (**30**)	*106*
	Tabernaelegantine A (**214**)	*106,107*
	Tabernaelegantine B (**219**)	*106,107*
	Tabernaelegantine C (**215**)	*106,107*
	Tabernaelegantine D (**220**)	*106,107*
	Tabernaelegantinine A (**218**)	*107*
	Tabernaelegantinine B (**222**)	*107*
	Tabernaelegantinine C (**217**)	*108*
	Tabernaelegantinine D (**221**)	*108*
	Tabernaemontanine (**31**)	*106*
T. eusepala Aug. DC. (*Pandaca eusepala*)	Apparicine (**66**)	*109*
	(20*S*)-1,2-Dehydropseudoaspidospermidine (**169**)	*109*
	(20*R*)-15,20-Dihydrocleavamine (**157**)	*109*
	(20*S*)-15,20-Dihydrocleavamine (**158**)	*109*
	Ibogaine (**135**)	*109*
	Ibogaine hydroxyindolenenine (**146**)	*109*
	Tubotaiwine (**61**)	*109*
	19-Epivoacristine (**119**)	*109*
	Vobasine (**32**)	*109*
T. flavicans Willd (*Anartia flavicans*)	Ibophyllidine (**178**)	*20,110*
	Ibophyllidine N^4-oxide (**179**)	*20,110*
T. fuchsiaeifolia A. DC. (*Peschiera fuchsiaeifolia*)	Affinisine (**16**)	*111*
	16-Decarbomethoxyvoacamine (**209**)	*113*
	$N^{4'}$-Demethylvoacamine (**210**)	*113*
	Perivine (**25**)	*113*
	Voacamidine (**205**)	*113*
	Voacamine (**203**)	*112*
	Voacangine (**100**)	*112*
	Voachalotine (**22**)	*111,112*
T. glandulosa (Stapf) Pichon	12-Demethoxytabernulosine (**43**)	*20,116*
	3-Ethoxycoronaridine (**104**)	*20,114*

(*continued*)

TABLE I (*Continued*)

Plants	Alkaloids	References
	3-Hydroxycoronaridine (**103**)	*20,115*
	Tabernulosine (**42**)	*20,114,116*
	Vincadiffine (**34**)	*116*
T. heterophylla Vahl	Affinisine (**16**)	*121*
(*T. tenuiflora, Peschiera*	Apparicine (**66**)	*121*
heterophylla, P. diversifolia,	Coronaridine (**97**)	*121*
P. tenuifolia, Stenosolen	16-Decarbomethoxyvoacamine (**209**)	*121*
heterophyllus)	Ervafolene (**248**)	*119,120*
	Ervafolidine (**242**)	*120*
	3-Epiervafolidine (**243**)	*120*
	Ervafoline (**246**)	*118–120*
	19′-Hydroxyervafolene (**249**)	*119,120*
	(19′*R*)-19′-Hydroxyervafolidine (**244**)	*120*
	(19′*S*)-19′-Hydroxy-3-epiervafolidine (**245**)	*120*
	19′-Hydroxyervafoline (**247**)	*119,120*
	Ibogaine (**135**)	*121*
	Ibogamine (**134**)	*121*
	Olivacine (**195**)	*121*
	Pandine (**176**)	*119,121*
	Pandoline (**164**)	*119,121*
	Tabernamine (**201**)	*121*
	3,14;4,19-Tetrahydroolivacine (**197**)	*121*
	Vallesamine (**64**)	*121*
	Voacamine (**203**)	*121*
	Voacangine (**100**)	*119*
	Voacangine hydroxyindolenine (**143**)	*119*
	Voaphylline (**87**)	*119,121*
	Vobasine (**32**)	*121*
T. heyneana Wall.	*O*-Acetylvallesamine (**65**)	*128*
(*Ervatamia heyneana,*	Apparicine (**66**)	*128*
Pagiantha heyneana)	Camptothecine (**3**)	*127*
	Coronaridine (**97**)	*123–126,128*
	Heyneanine (**122**)	*122,125,128*
	10-Hydroxycoronaridine (**98**)	*128*
	Ibogamine (**134**)	*126*
	Isovoacristine (**120**)	*98*
	9-Methoxycamptothecine (**4**)	*127*
	(19*S*)-3,19-Oxidovoacangine (**133**)	*128*
	(6*R*)-3,6-Oxidovoacangine N^4-oxide (**132**)	*128*
	3-Oxocoronaridine (**105**)	*126*
	19-Oxovoacangine (**117**)	*128*
	Tabernoxidine (**155**)	*129*
	Tubotaiwine (**61**)	*128*
	Voacangine (**100**)	*126,128*
	Voacangine hydroxyindolenine (**143**)	*128*

TABLE I (*Continued*)

Plants	Alkaloids	References
	Voacangine pseudoindoxyl (**149**)	*126*
	Voacristine (**118**)	*128*
T. humblotii (Baill.) Pichon (*T. ochrascens, Pandaca ochrascens, P. speciosa*)	Akuammicine (**55**)	*130*
	Akuammidine (**17**)	*130*
	Apparicine (**66**)	*130*
	16-Decarbomethoxyvoacamine (**209**)	*131*
	14,15-Dehydro-16-epivincamine (**94**)	*130*
	Ibogaine (**135**)	*130,131*
	Ibogaine pseudoindoxyl (**154**)	*130,131*
	Ibogaline (**130**)	*130*
	Iboxygaine (**139**)	*131*
	19-Epiiboxygaine (**140**)	*130*
	19-Epiiboxygaline (**141**)	*130*
	Tubotaiwine (**61**)	*130*
	Voacangine (**100**)	*131*
	Voacristine (**118**)	*131*
T. johnstonii (Stapf) Pichon (*Conapharyngia johnstonii*)	Conoduramine (**226**)	*134*
	Conodurine (**230**)	*134*
	19′-20′-Epoxyconoduramine (**227**)	*134*
	Gabunamine (**224**)	*134*
	Gabunine (**229**)	*134*
	Ibogamine (**134**)	*133*
	Isovoacangine (**101**)	*134*
	Pericyclivine (**19**)	*134*
	Perivine (**25**)	*134*
	Tabernamine (**201**)	*133*
	Tubotaiwine (**61**)	*132*
	Tubotaiwine N^4-oxide (**62**)	*132*
T. laeta Mart. (*Peschiera laeta*)	Affinine (**27**)	*136*
	Akuammidine (**17**)	*136*
	Conodurine (**230**)	*136*
	Geissoschizol (**7**)	*135*
	Normacusine B (**11**)	*136*
	Voacamine (**203**)	*136*
	Vobasine (**32**)	*136*
T. longiflora Benth. (*Conopharyngia longiflora*)	Conopharyngine (**102**)	*137*
	Voacangine (**100**)	*137*
	Voaphylline (**87**)	*137*
T. longipes Donn. Sm.	Coronaridine (**97**)	*138,139*
	Tabersonine (**67**)	*138*
	Voacangine (**100**)	*138*
T. lundii A. DC. (*Peschiera lundii*)	Coronaridine (**97**)	*140*
	Ibogaine (**135**)	*140*

(*continued*)

TABLE I (*Continued*)

Plants	Alkaloids	References
	Iboxygaine (**139**)	*140*
	Iboxygaine hydroxyindolenine (**147**)	*140*
	Olivacine (**195**)	*140*
	Voacangine (**100**)	*140*
	Voacristine (**118**)	*140*
	19-Epivoacristine (**119**)	*140*
	Voacristine pseudoindoxyl (**150**)	*140*
	Vobasine (**32**)	*140*
T. macrocalix Müll. Arg. (*Anacampta macrocalix*)	Coronaridine (**97**)	*141*
	Tabersonine (**67**)	*141*
T. macrocarpa Jack (*Ervatamia macrocarpa, Pagiantha macrocarpa*)	Coronaridine (**97**)	*142*
	Voacangine (**100**)	*142*
	Voacangine hydroxyindolenine (**143**)	*142*
	Voaphylline (**87**)	*142*
T. mauritiana Poir. (*Pandaca mauritiana*)	Dregamine (**30**)	*142*
	Tubotaiwine (**61**)	*142*
	Vobasine (**32**)	*143*
T. minutiflora Pichon (*Pandaca minutiflora*)	Condylocarpine (**59**)	*144*
	Coronaridine (**97**)	*144*
	Stemmadenine (**63**)	*144*
	Stereoisomer of 15,20;15′,20′-Tetrahydropresecamine (**253**)	*144*
	Tubotaiwine (**61**)	*144*
	(+)-Vincadifformine (**70**)	*144*
	Vobasine (**32**)	*144*
T. mocquerysii Aug. DC. (*T. boiteaui, Pandaca boiteaui, P. callosa, P. mocquerysii*)	(20*R*)-Capuvosidine (**236**)	*58,147*
	Coronaridine (**97**)	*145*
	16-Decarbomethoxyvoacamine (**209**)	*147*
	19,20-Dehydroervatamine (**50**)	*147*
	(20*S*)-1,2-Dehydropseudoaspidospermidine (**169**)	*147*
	(20*R*)-Dehydroxycapuvosine (**233**)	*58,147*
	(20*R*)-Dehydroxyisocapuvosine (**213**)	*147*
	(20*R*)-1,2-Dihydrocapuvosidine (**237**)	*58*
	(20*S*)-1,2-Dihydrocapuvosidine (**238**)	*147*
	(20*R*)-15,20-Dihydrocleavamine (**157**)	*147*
	(20*S*)-15,20-Dihydrocleavamine (**158**)	*147*
	Ervitsine (**54**)	*146,147*
	Heyneanine (**122**)	*145*
	19-Epiheyneanine (**123**)	*145*
	Methuenine (**51**)	*67,147*
	(20*R*)-Pseudoaspidospermidine (**174**)	*147*
	(20*S*)-Pseudoaspidospermidine (**175**)	*147*
	Tubotaiwine (**61**)	*147*
	Voacamine (**203**)	*147*

TABLE I (*Continued*)

Plants	Alkaloids	References
	Voacangine (**100**)	*145*
	Voacristine (**118**)	*145*
	19-Epivoacristine (**119**)	*145*
T. mucronata Merr. (*Ervatamia mucronata*)	Coronaridine (**97**)	*148*
	Tabernamontanine (**31**)	*148*
T. olivacea Müll. Arg.	Akuammidine (**17**)	*149*
	Condylocarpine N^4-oxide (**60**)	*20,149*
	Coronaridine (**97**)	*149*
	Coronaridine hydroxyindolenine (**142**)	*149*
	Coronaridine pseudoindoxyl (**148**)	*149*
	Heyneanine (**122**)	*149*
	Ibogaine (**135**)	*149*
	Ibogamine (**134**)	*149*
	Voacangine (**100**)	*149*
	Voacangine hydroxyindolenine (**143**)	*149*
	Voacangine pseudoindoxyl (**149**)	*149*
	Voacristine (**118**)	*149*
T. orientalis R.Br. (*Ervatamia lifuana, E. daemeliana*)	Akuammidine (**17**)	*152*
	Apparicine (**66**)	*150*
	Conopharyngine (**102**)	*152,153*
	Coronaridine (**97**)	*152,153*
	16-Decarbomethoxy-19′,20′-dihydrovoacamine (**207**)	*150*
	16-Decarbomethoxy-19′,20′-dihydro-20′-epivoacamine (**208**)	*150*
	16-Decarbomethoxyvoacamine (**209**)	*150*
	19,20-Dehydroervatamine (**50**)	*150*
	Dregamine (**30**)	*150,152,153*
	Ervatamine (**44**)	*150–153*
	20-Epiervatamine (**45**)	*150–153*
	Ibogaine (**135**)	*150*
	Iboxygaine (**139**)	*150,152*
	Isovoacangine (**101**)	*152*
	Pandine (**176**)	*152,153*
	Pandoline (**164**)	*152,153*
	20-Epipandoline (**165**)	*152,153*
	Tabernaemontanine (**31**)	*150,152,153*
	Voacamine (**203**)	*150*
	Voacangine (**100**)	*152,153*
	Voacristine (**118**)	*150*
	Vobasine (**32**)	*150,152,153*
T. pachysiphon Stapf. (*T. cumminsii, T. holstii*)	Affinine (**27**)	*154,160*
	16-Epiaffinine (**28**)	*160*
	Anhydrovobasindiol (**35**)	*160*
	Apparicine (**66**)	*156,160*

(*continued*)

TABLE I (*Continued*)

Plants	Alkaloids	References
	Conoduramine (**226**)	*159,160*
	Conodurine (**230**)	*159,160*
	Conopharyngine (**102**)	*72,154,157,160*
	Conopharyngine hydroxyindolenine (**145**)	*155,160*
	Conopharyngine pseudoindoxyl (**151**)	*157*
	Coronaridine (**97**)	*72,159*
	Decarbomethoxy-15,20;16,17-tetrahydrosecodine (**194**)	*157*
	11-Demethylconoduramine (**225**)	*160*
	Gabunine (**229**)	*159*
	3-Hydroxyconopharyngine (**110**)	*160*
	19-Hydroxyconopharyngine (**121**)	*157,160*
	Ibogaline (**137**)	*160*
	Isositsirikine (**9**)	*160*
	16-Epiisositsirikine (**10**)	*160*
	Isovoacangine (**101**)	*160*
	Lochnericine (**74**)	*160*
	Normacusine B (**18**)	*160*
	3-Oxoconodurine (**231**)	*159*
	3-Oxocoronaridine (**105**)	*159*
	3-(2′-Oxopropyl)conodurine (**232**)	*159*
	Pachysiphine (**75**)	*154*
	Pericyclivine (**19**)	*159,160*
	Perivine (**25**)	*159*
	Tubotaiwine (**61**)	*160*
	Tubotaiwine N^4-oxide (**62**)	*158,160*
	Voacamine (**203**)	*160*
	Voacangine (**100**)	*72,154*
	Vobasine (**32**)	*159,160*
T. pandacaqui Poir. (*T. laurifolia, Ervatamia pandacaqui*)	Coronaridine (**97**)	*161,162*
	Ervafoline (**246**)	*117*
	Ervafolidine (**242**)	*117*
	3-Epiervafolidine (**243**)	*117*
	Ibogamine (**134**)	*162*
	Iboxygaine (**139**)	*162*
	Isovoacangine (**101**)	*162*
	Isovoacristine (**120**)	*162*
	20-Epilochneridine (**58**)	*163*
	Tabernaemontanine (**31**)	*117*
	Tabernanthine (**136**)	*162*
T. penduliflora K. Schum. (*Conopharyngia penduliflora*)	Conopharyngine (**102**)	*72*
	Coronaridine (**97**)	*72*
	Voacangine (**100**)	*72*
T. psorocarpa (Pierre ex Stapf) Pichon	Coronaridine (**97**)	*165*
	14,15-Dehydro-12-methoxyvincamine (**95**)	*164,165*

TABLE I (*Continued*)

Plants	Alkaloids	References
	16-Epiisositsirikine (**10**)	*164,165*
	Isovallesiachotamine (**2**)	*165*
	Tetrahydroalstonine (**11**)	*165*
	Vallesiachotamine (**1**)	*165*
	Voacangine (**100**)	*165*
T. psychotriifolia H.B.K.	Affinine (**27**)	*167*
	Anhydrovobasindiol (**35**)	*166,167*
	Coronaridine (**97**)	*50*
	Olivacine (**195**)	*50*
	Voacamine (**203**)	*50*
	Voacangine (**100**)	*50*
	16-Epivobasinic acid (**33**)	*167*
T. quadrangularis	Coronaridine (**97**)	*168*
	Coronaridine hydroxyindolenine (**142**)	*168*
	Coronaridine pseudoindoxyl (**148**)	*168*
	Heyneanine (**122**)	*168*
	19-Epiheyneanine (**123**)	*168*
	(19*R*)-19-Hydroxyibogamine (**131**)	*168*
	(19*R*)-19-Hydroxyibogamine pseudoindoxyl (**153**)	*168*
	Ibogaine (**135**)	*168*
	Ibogamine (**134**)	*168*
	Ibogamine pseudoindoxyl (**152**)	*168*
	3-Oxocoronaridine (**105**)	*168*
	3-Oxovoacangine (**108**)	*168*
	Voacangine (**100**)	*168*
	Voacangine hydroxyindolenine (**143**)	*168*
T. retusa (Lam.) Pichon (*T. noronhiana, Conapharyngia retusa, Pandaca retusa, Plumeria retusa*)	Coronaridine (**97**)	*82,169,170*
	Coronaridine hydroxyindolenine (**142**)	*82*
	Heyneanine (**122**)	*82,169*
	Ibogamine (**134**)	*82*
	rac-Ibogamine (*rac*-**134**)[b]	*82*
	3-Oxovoacangine (**108**)	*169*
	Pachysiphine (**75**)	*170*
	Tabersonine (**67**)	*170*
	Voacangine (**100**)	*169,170*
	Voacristine (**118**)	*169*
	Voaphylline (**87**)	*170*
T. riedelii Müll. Arg.	Minovincine (**77**)	*171*
	3-Oxominovincine (**78**)	*171*
	(+)-Vincadifformine (**70**)	*171*
	rac-Vincadifformine (*rac*-**70**)[b]	*171*
T. rigida (Miers) Leeuwenberg (*T. macrophylla, Anacampta*	(+)-Apovincamine (**96**)	*171*
	(+)-Vincamine (**91**)	*171*

(*continued*)

TABLE I (*Continued*)

Plants	Alkaloids	References
rigida, Phrissocarpus rigidus)	*rac*-Vincamine (*rac*-**91**)[b]	*171*
	(−)-16-Epivincamine (**92**)	*171*
	rac-16-Epivincamine (*rac*-**92**)[b]	*171*
	Base TR 2 (21-epivincamine) (**93**)[e]	*171*
T. rupicola Benth. (*Anacampta rupicola*)	Voacangine pseudoindoxyl (**149**)	*172*
	Voacristine pseudoindoxyl (**150**)	*172*
T. sananho Ruiz et Pav.	Coronaridine (**97**)	*173*
	Heyneanine (**122**)	*173*
	3-Hydroxycoronaridine (**103**)	*173*
	Ibogamine (**134**)	*173*
	Voacangine (**100**)	*173*
T. sessilifolia Bak. (*Muntafara sessilifolia*)	Apparicine (**66**)	*174*
	Coronaridine (**97**)	*174*
	Dregamine (**30**)	*174*
	6-Hydroxy-3-oxocoronaridine (**115**)	*174*
	6-Hydroxy-3-oxoisovoacangine (**116**)	*174*
	Isovoacangine (**101**)	*174*
	(6*R*)-3,6-Oxidocoronaridine (**129**)	*174*
	(6*R*)-3,6-Oxidoisovoacangine (**130**)	*174*
	Tabernaemontanine (**31**)	*174*
T. siphilitica Leeuwenberg (*T. tetrastachia, Bonafousia tetrastachia, Echites siphilitica*)	Apparicine (**66**)	*179*
	12,12′-Bis-(11-hydroxycoronaridinyl) (**250**)	*177*
	Bonafousine (**251**)	*175,178*
	Coronaridine (**97**)	*177,179*
	Geissoschizine (**6**)	*176*
	12-Hydroxyvincadifformine (**71**)	*179*
	Isobonafousine (**252**)	*178*
	Isovoacangine (**101**)	*177,179*
	Pleiocarpamine (**14**)	*179*
	Tetrahydroalstonine (**11**)	*179*
	Tetrastachyne (**240**)	*179*
	Tetrastachynine (**241**)	*179*
	Tubotaiwine (**61**)	*179*
	Vincadifformine (**70**)[f]	*179*
	Voacangine (**100**)	*177,179*
T. sphaerocarpa Bl. (*Pagiantha sphaerocarpa*)	Dregamine (**30**)	*180*
	Tabernaemontanine (**31**)	*180*
T. stellata Pichon (*Pandaca stellata*)	Coronaridine (**97**)	*82*
T. undulata Vahl (*Bonafusia undulata*)	Coronaridine (**97**)	*136,181*
	19-Epiheyneanine (**123**)	*136*
	Quebrachidine (**36**)	*136*

TABLE I (*Continued*)

Plants	Alkaloids	References
	Voacangine (**100**)	*136*
	Voaphylline (**87**)	*136,181*
T. wallichiana Steud.	Coronaridine (**97**)	*182*
	Isovoacangine (**101**)	*182*
	Voacangine (**100**)	*182*
	Voacristine (**118**)	*182*
Pandacastrum saccharatum[g]	Pandicine (**254**)	*183*

[a] Stereochemistry unknown.
[b] *rac* = racemic.
[c] Isolated as a mixture.
[d] Proposed identification.
[e] Structure not certain.
[f] Stereochemistry not reported.
[g] *Tabernaemontana* nomenclature is not yet available.

(Text continued from p. 9)

Alkaloids of the plumeran type are interesting because compounds with opposite stereochemistry were isolated from different plants. In some cases, a racemic form was also found besides the optically active one. The racemic forms are indicated by the prefix *rac* before the name and relative number. The generally accepted biogenetic numbering system proposed by Le Men and Taylor (*16*) is used through this article. This chapter refers to literature through June 1984.

IV. Structure Elucidation and Chemistry

The great number of different alkaloids found in *Tabernaemontana* precludes a discussion of the structure elucidation and chemistry of all of them. To keep the treatment concise, a major compromise was necessary. The alkaloids that have been reported in previous volumes of this treatise (as indicated in Table I) and their trivial modification will not be mentioned here. This compromise eliminates from the discussion well-established and long-known alkaloids that were isolated not only from *Tabernaemontana* but also from other genera. Moreover, the plumeran alkaloids isolated up to 1976 and eburnan-type and bisindole alkaloids isolated up to 1979 are covered in Volumes XVII and XX. The main efforts of this chapter will be focused on more recently isolated compounds, some of which are structurally and biogenetically relevant and have been found only in plants of the genus *Tabernaemontana*.

(Text continues on p. 64)

TABLE II

INDOLE ALKALOIDS ISOLATED FROM *TABERNAEMONTANA* SPECIES

Alkaloid	MP (°C)	$[\alpha]_D$ (deg)	Volume number[a]	*Tabernaemontana* species
$C_{17}H_{14}N_2$ (MW 246)				
Olivacine (**195**)	318–326	—	XI, XVII	*affinis, cerifera, echinata, heterophylla, lundii, psychotrifolia*
$C_{17}H_{16}N_2$ (MW 248)				
3,14-Dihydroellipticine (**196**)	312	—	VIII	*coffeoides*
$C_{17}H_{18}N_2$ (MW 250)				
3,14;4,19-Tetrahydroolivacine (**197**) (Janetine)	—	—	—	*divaricata, heterophylla*
$C_{18}H_{20}N_2$ (MW 264)				
Apparicine (**66**) (Pericalline)	188–190	−176.5	XI, XVI	*calcarea, cerifera, citrifolia, coffeoides, dichotoma, divaricata, eusepala, heterophylla, heyneana, humblotii, orientalis, pachysiphon, sessilifolia, siphilitica*
$C_{19}H_{22}N_2$ (MW 278)				
14,15-Anhydrocapuronidine (**172**)[b]	—	−54	—	*capuronii*
$C_{19}H_{24}N_2$ (MW 280)				
Ibogamine (**134**)	162–169	−54.7	VII, VIII, XI, XX	*amblyocarpa, apoda, bufalina, citrifolia, coffeoides, crassa, crassifolia, dichotoma, divaricata, eglandulosa, heterophylla, heyneana,*

				olivacea, pandacaqui, quadrangularis, retusa, sananho, johnstonii
(20*R*)-1,2-Dehydropseudoaspidospermidine (**168**)	—	+209	—	*eglandulosa*
(20*S*)-1,2-Dehydropseudoaspidospermidine (**169**)	—	+153	—	*eusepala, mocquerysii*
14,15-Anhydro-1,2-dihydrocapuronine (**173**)[b]	—	+40	—	*capuronii*
$C_{19}H_{26}N_2$ (MW 282)				
(20*R*)-15,20-Dihydrocleavamine (**157**)	135	+68	XVII	*eusepala, eglandulosa, mocquerysii*
(20*S*)-15,20-Dihydrocleavamine (**158**)	—	−87	XVII	*eusepala, eglandulosa, mocquerysii*
(20*R*)-Pseudoaspidospermidine (**174**)	—	—	—	*mocquerysii*
(20*S*)-Pseudoaspidospermidine (**175**)	89	+60	—	*mocquerysii*
$C_{19}H_{28}N_2$ (MW 284)				
Decarbomethoxy-15,20;16,17-tetrahydrosecodine (**194**)	—	—	XVII	*pachysiphon*
$C_{19}H_{20}N_2O$ (MW 292)				
Ervitsine (**54**)	176–177	−160	—	*mocquerysii*
Norfluorocurarine (**57**) (vincanine)	186	−1230	—	*eglandulosa*
$C_{19}H_{22}N_2O$ (MW 294)				
Normacusine B (**18**)	255	+16	VIII	*brachyantha, coffeoides, laeta, pachysiphon*
Methuenine (**51**)	205	+21	—	*coffeoides, mocquerysii*
Isomethuenine (**52**)	—	−178	—	*coffeoides, dichotoma*
Tacamonine (**192**)	—	—	—	*eglandulosa*
$C_{18}H_{20}N_2O_2$ (MW 296)				
Desethylibophyllidine (**185**)	—	+444	—	*albiflora*
$C_{19}H_{24}N_2O$ (MW 296)				
Geissoschizol (**7**)	224–226	−70	—	*bufalina, laeta*
Silicine (**46**)	112	−18	—	*calcarea, coffeoides*
20-Episilicine (**47**)	190	—	—	*coffeoides*

(*continued*)

TABLE II (*Continued*)

Alkaloid	MP (°C)	$[\alpha]_D$ (deg)	Volume number[a]	*Tabernaemontana* species
Voaphylline (**87**) (Conoflorine)	166–168	+24.4	XI, XVII, XX	*chippii, coffeoides, dichotoma, divaricata, eglandulosa, heterophylla, longiflora, macrocarpa, retusa, undulata*
(19*R*)-19-Hydroxyibogamine (**138**)	172–174	−28	—	*quadrangularis*
Ibogamine pseudoindoxyl (**152**)	137–138	−62	—	*quadrangularis*
Capuronidine (**170**)	—	+220	XVII	*capuronii*
(20*S*)-20-Hydroxy-1,2-dehydropseudoaspidospermidine (**171**)	—	—	—	*eglandulosa*
Dichomine (**177**)	—	—	—	*dichotoma, eglandulosa*
(16*R*)-Decarbomethoxytacamine (**189**)	—	—	—	*eglandulosa*
(16*S*)-Decarbomethoxytacamine (**190**)	—	—	—	*eglandulosa*
$C_{19}H_{26}N_2O$ (MW 298)				
Capuronine (**159**)	75	+70	XVII, XX	*capuronii*
(14*S*,20*R*)-Velbanamine (**160**)[c]	—	—	—	*eglandulosa*
$C_{19}H_{20}N_2O_2$ (MW 308)				
6-Oxomethuenine (**53**)	>260	−15	—	*coffeoides*
Vincanidine (**56**)	280	—	VIII, XI	*coffeoides*
$C_{20}H_{24}N_2O$ (MW 308)				
Affinisine (**16**)	194–196	+19	XI, XX	*affinis, fuchsiaeifolia, heterophylla*
Anhydrovobasindiol (**35**) (Taberpsychine)	208	−284	—	*brachyantha, crassa, psychotrifolia*
Tetraphyllicine (**37**)	320–322	+21	VII, VIII, IX	*coffeoides*
$C_{19}H_{22}N_2O_2$ (MW 310)				
N^1-Demethyl-16-epiaccedine (**24**)	170–172	+50	—	*accedens*

6-Oxosilicine (**48**)	>260	−40	—	*coffeoides*
6-Oxo-16-episilicine (**49**)	—	—	—	*coffeoides*
17-Hydroxytacamonine (**193**)	—	—	—	*eglandulosa*
$C_{20}H_{26}N_2O$ (MW 310)				
N^1-Methylvoaphylline (**88**)	—	—	—	*divaricata*
Ibogaine (**135**)	152–153	−53	II, V, VII, VIII, XI, XX	*cerifera, contorta, echinata, eusepala, heterophylla, humblotii, lundii, olivacea, orientalis, quadrangularis*
Tabernanthine (**136**)	215	−35	VII, IX	*crassifolia, pandacaqui*
$C_{19}H_{24}N_2O_2$ (MW 312)				
10-Hydroxygeissoschizol (**8**)	264	—	—	*bufalina*
Voaphylline hydroxyindolenine (**90**)	—	—	—	*dichotoma*
(19*R*)-19-Hydroxyibogamine pseudoindoxyl (**153**)	—	−16	—	*quadrangularis*
$C_{20}H_{15}N_3O$ (MW 313)				
Angustine (**5**)	283–284	—	XXII	*attenuata, echinata*
$C_{20}H_{22}N_2O_2$ (MW 322)				
Pleiocarpamine (**14**)	159	+136	VIII, XI, XII, XIV, XVII, XX	*echinata, siphilitica*
16-Epipleiocarpamine (**15**)	—	—	XI, XVII, XX	*attenuata*
Pericyclivine (**19**)	228	+5	XI, XX	*coffeoides, crassa, pachysiphon, johnstonii*
Akuammicine (**55**)	177.5	−738	V, VI, VII, VIII, XI, XIV, XVII	*humblotii*
Condylocarpine (**59**)	167–168	+876	VII, XVII	*minutiflora*
$C_{20}H_{24}N_2O_2$ (MW 324)				
Accedine (**23**)	148–149	+72	XX	*accedens*

(*continued*)

TABLE II (*Continued*)

Alkaloid	MP (°C)	$[\alpha]_D$ (deg)	Volume number[a]	*Tabernaemontana* species
Affinine (**27**)	264–265	−108	XI	*affinis, laeta, pachysiphon, psychotrifolia*
16-Epiaffinine (**28**)	154	−190	—	*pachysiphon*
Tubotaiwine (**61**)	—	+584	VII, XVII	*amblyocarpa, attenuata, echinata, eglandulosa, eusepala, heyneana, humblotii, mocquerysii, mauritiana, minutiflora, siphilitica, johnstonii*
Ibophyllidine (**178**)	—	+259	XVII	*albiflora, attenuata, flavicans*
20-Epiibophyllidine (**181**)	—	+518	—	*albiflora*
$C_{20}H_{26}N_2O_2$ (MW 326)				
12-Methoxyvoaphylline (**89**)	151–152	—	XVII	*dichotoma*
Iboxygaine (**139**)	235–236	−10	VIII, XI	*citrifolia, humblotii, lundii, orientalis, pandacaqui*
19-Epiiboxygaine (**140**)	163–165	−27	—	*dichotoma, humblotii*
Ibogaine hydroxyindolenine (**146**)	149	+74	—	*apoda, eusepala, echinata*
Ibogaine pseudoindoxyl (**154**) (Iboluteine)	142	−114	—	*apoda, aurantica, humblotii*
$C_{21}H_{24}N_2O_2$ (MW 336)				
Tabersonine (**67**)	193–197 (hydrochloride)	−310	VIII, IX, XVI, XVII, XX	*alba, arborea, citrifolia, coffeoides, crassa, dichotoma, divaricata, longipes, macrocalyx, retusa*
(+)-Apovincamine (**96**)	159–161	+121	XI, XVII, XX	*rigida*
Pseudotabersonine (**161**)	—	+320	XVII	*calcarea*
16,17-Anhydrotacamine (**191**)	—	—	—	*eglandulosa*

$C_{20}H_{22}N_2O_3$ (MW 338)				
Perivine (**25**)	180–181	−121	XIII, XI	*bufalina, crassa, dichotoma, eglandulosa, fuchsiaefolia, pachysiphon, johnstonii*
16-Epivoabasinic acid (**33**)	295	—	—	*psychotriifolia*
Condylocarpine N^4-oxide (**60**)	203–204	+694	—	*olivacea*
$C_{21}H_{26}N_2O_2$ (MW 338)				
N^1-Methyl-16-epiaffinine (**29**)	208–210	−243	—	*accedens*
(+)-Vincadifformine (**70**)	96	+600 ± 5	XI	*minutiflora, riedelii, siphilitica*
Coronaridine (**97**)	230 (hydrochloride)	−9 (hydrochloride)	—	*affinis, alba, albiflora, amblyocarpa, apoda, attenuata, bufalina, citrifolia, coffeoides, contorta, crassa, dichotoma, divaricata, echinata, eglandulosa, heterophylla, heyneana, longipes, lundii, macrocalyx, macrocarpa, minutiflora, mocquerysii, mucronata, olivacea, orientalis, pachysiphon, pandacaqui, penduliflora, psorocarpa, quadrangularis, retusa, sananho, sessilifolia, siphilitica, stellata, undulata, wallichiana*

(*continued*)

TABLE II (*Continued*)

Alkaloid	MP (°C)	$[\alpha]_D$ (deg)	Volume number[a]	*Tabernaemontana* species
(20*R*)-Pseudovincadifformine (**162**)	—	+430	—	*calcarea, eglandulosa*[d]
(20*S*)-Pseudovincadifformine (**163**)	—	—	—	*eglandulosa*[d]
$C_{20}H_{24}N_2O_3$ (MW 340)				
20-Epilochneridine (**58**)	225	+650	—	*pandacaqui*
Tubotaiwine N^4-oxide (**62**)	224	+558	XVII	*pachysiphon, johnstonii*
Vallesamine (**64**)	165	+165	XI	*amblyocarpa, citrifolia, dichotoma, coffeoides, heterophylla*
Ibophyllidine N^4-oxide (**179**)	—	+187	—	*flavicans*
19-Hydroxyibophyllidine (**180**)	—	+91	—	*albiflora*
18-Hydroxy-20-epiibophyllidine (**182**)	—	+368	—	*albiflora*
(19*R*)-19-Hydroxy-20-epiibophyllidine (**183**)	136–138	+431	—	*albiflora*
(19*S*)-19-Hydroxy-20-epiibophyllidine (**184**)	—	+277	—	*albiflora*
$C_{21}H_{28}N_2O_2$ (MW 340)				
Ibogaline (**137**)	143	−43	XI	*humblotii*
$C_{20}H_{26}N_2O_3$ (MW 342)				
Iboxygaine hydroxyindolenine (**147**)	223	+111	—	*lundii*
$C_{20}H_{16}N_2O_4$ (MW 348)				
Camptothecine (**3**)	264–267	+31.3	XIV, XV, XVI, XVII, XXI	*heyneana*
$C_{21}H_{22}N_2O_3$ (MW 350)				
Vallesiachotamine (**1**)	253–255 (acetate)	+160 (acetate)	XI, XIV, XVII	*psorocarpa*
Isovallesiachotamine (**2**)	—	—	—	*psorocarpa*
3-Oxotabersonine (**68**)	151.5–153	−77.4	—	*coffeoides*

$C_{21}H_{24}N_2O_3$ (MW 352)				
Geissoschizine (**6**)	194–196	+115	VIII, XVII	*siphilitica*
Tetrahydroalstonine (**11**)	231	−107	II, VII, VIII, XI, XII, XIV	*psorocarpa, siphilitica*
Akuammidine (**17**)	248.5	+21	V, VII, VIII, XI, XIV	*amblyocarpa, citrifolia, coffeoides, humblotii, laeta, olivacea, orientalis*
Polyneuridine (Normacusine A) (**20**)	243–246	−73	VIII, XI	*coffeoides*
Vobasine (**32**)	111–113	−159	VIII, XI	*affinis, bufalina, cerifera, coffeoides, dichotoma, divaricata, echinata, eglandulosa, eusepala, heterophylla, laeta, lundii, mauritiana, minutiflora, orientalis, pachysiphon*
Quebrachidine (**36**)	276–278	+54	VIII, XI, XIV, XX	*undulata*
19,20-Dehydroervatamine (**50**)	200	+53	—	*mocquerysii, orientalis*
Lochnericine (**74**)	188–191	+473	VIII, XI, XVII	*citrifolia, coffeoides, divaricata*
Pachysiphine (**75**)	163 (hydrochloride)	−455 (hydrochloride)	XVII, XX	*pachysiphon, retusa*
Minovincine (**77**)	—	+340	XVII	*riedelii*
Desoxoapodine (**85**) (Modestanine)	—	−432	XVII	*apoda*
14,15-Dehydro-16-epivincamine (**94**)	—	+40	XX	*humblotii*
3-Oxocoronaridine (**105**)	140	−27	—	*bufalina, crassa, divaricata, heyneana, pachysiphon, quadrangularis*
5-Oxocoronaridine (**112**)	272–275	−10.7	—	*crassa, divaricata*
6-Oxocoronaridine (**113**)	262–267	−33.8	—	*divaricata*

(*continued*)

TABLE II (*Continued*)

Alkaloid	MP (°C)	$[\alpha]_D$ (deg)	Volume number[a]	*Tabernaemontana* species
(6*R*)-3,6-Oxidocoronaridine (**129**) (Eglandine)	—	−57	—	*attenuata, eglandulosa, sessilifolia*
Pandine (**176**)	108–113	+273	XVII	*calcarea, debrayi, heterophylla, orientalis*
$C_{21}H_{26}N_2O_3$ (MW 354)				
Isositsirikine (**9**)	—	−20	XI	*pachysiphon*
16-Epiisositsirikine (**10**)	186–187	−205	—	*echinata, psorocarpa*
Dregamine (**30**)	106–108	−93	VIII, XI	*calcarea, coffeoides, debrayi, divaricata, elegans, mauritiana, orientalis, sessilifolia, sphaerocarpa*
Tabernaemontanine (**31**)	206–208	−52	VIII, XI, XX	*coffeoides, divaricata, elegans, mucronata, orientalis, pandacaqui, sessilifolia, sphaerocarpa*
Ervatamine (**44**)	98	−4	—	*orientalis*
20-Epiervatamine (**45**)	187	−22	—	*orientalis*
Stemmadenine (**63**)	199–200	+324	VIII, XI, XVI, XVII	*coffeoides, dichotoma, minutiflora*
12-Hydroxyvincadifformine (**71**)	—	−427	—	*siphilitica*
(+)-Vincamine (**91**)	232–233	+40 (pyridine)	V, VII, VIII, XI, XVII, XX	*rigida*
(−)-16-Epivincamine (**92**)	186–187	−5	XI, XVII, XX	*rigida*
Base TR_2 (**93**) (probably 21-epivincamine)	209–211	+1.8	XX	*rigida*
10-Hydroxycoronaridine (**98**)	—	—	—	*heyneana, echinata*
11-Hydroxycoronaridine (**99**)	—	−34	—	*attenuata, eglandulosa*
3-Hydroxycoronaridine (**103**)	—	−68	—	*eglandulosa, glandulosa, sananho*

Heyneanine (**122**)	162	−19	XI	*amblyocarpa, apoda, attenuata, bufalina, coffeoides, crassa, dichotoma, divaricata, heyneana, mocquerysii, olivacea, quadrangularis, retusa, sananho*
19-Epiheyneanine (**123**)	170–172	−46	—	*affinis, attenuata, coffeoides, dichotoma, mocquerysii, quadrangularis, undulata*
18-Hydroxycoronaridine (**128**) (Albifloranine)	192–194	−210	—	*albiflora*
Coronaridine hydroxyindolenine (**142**)	113–117	−8	—	*attenuata, bufalina, crassa, divaricata, olivacea, quadrangularis, retusa*
Coronaridine pseudoindoxyl (**148**)	278–279 (hydrochloride)	—	—	*affinis, olivacea, quadrangularis*
Pandoline (**164**)	—	+417	XVII	*calcarea, debrayi, heterophylla, orientalis*
20-Epipandoline (**165**)	—	+462	XVII	*calcarea, orientalis*
Tacamine (**186**)	—	—	—	*eglandulosa*
16-Epitacamine (**187**)	—	—	—	*eglandulosa*
$C_{22}H_{30}N_2O_2$ (MW 354)				
O-Demethylpalosine (**83**)	169	+118	XI	*amygdalifolia*
$C_{21}H_{28}N_2O_3$ (MW 356)				
19-Epiiboxygaline (**141**)	212–215	−48	—	*humblotii*
$C_{21}H_{22}N_2O_4$ (MW 366)				
3-Oxominovincine (**78**)	260	+268	XVII	*riedelii*
Apodine (**84**)	176 (hydrochloride)	−520 (hydrochloride)	XVII	*apoda*

(*continued*)

TABLE II (*Continued*)

Alkaloid	MP (°C)	$[\alpha]_D$ (deg)	Volume number[a]	*Tabernaemontana* species
$C_{22}H_{26}N_2O_3$ (MW 366)				
Voachalotine (**22**)	224	−3	VIII, XI	*fuchsiaefolia*
$C_{21}H_{24}N_2O_4$ (MW 368)				
Voacarpine (**26**)	227–228	+43.5	XI	*coffeoides*
12-Demethoxytabernulosine (**43**)	—	−21	—	*glandulosa*
5-Hydroxy-6-oxocoronaridine (**114**)	285–288	+43.8	—	*divaricata*
6-Hydroxy-3-oxocoronaridine (Eglandulosine) (**115**)	—	−71	—	*eglandulosa, sessilifolia*
3-Oxoheyneanine (**124**)	—	—	—	*crassa*
$C_{22}H_{28}N_2O_3$ (MW 368)				
12-Demethoxycylindrocarpidine (**80**)	—	−49	—	*amygdalifolia*
Voacangine (**100**)	137–138	−42	VII, VIII, XI, XX	*amblyocarpa, apoda, arborea, attenuata, aurantiaca, australis, cerifera, citrifolia, coffeoides, contorta, dichotoma, divaricata, echinata, eglandulosa, fuchsiaefolia, heterophylla, heyneana, humblotii, longiflora, longipes, lundii, macrocarpa, mocquerysii, olivacea, orientalis, pachysiphon, penduliflora, psorocarpa, psychotriifolia, quadrangularis, retusa, sananho, siphilitica, undulata, wallichiana*

Isovoacangine (**101**)	157	−52	XI, XXII	*amblyocarpa, apoda, arborea, attenuata, coffeoides, crassa, divaricata, eglandulosa, johnstonii, orientalis, pandacaqui, sessilifolia, siphilitica, wallichiana*
$C_{21}H_{26}N_2O_4$ (MW 370)				
14,15-Dihydroxyvincadifformine (**76**)	—	—	—	*coffeoides*
10-Hydroxyheyneanine (**125**)	—	−16.6	—	*attenuata, bufalina, echinata*
11-Hydroxyheyneanine (**126**)	—	−22	—	*attenuata*
(20*R*)-18,19-Dihydroxypseudovincadifformine (**166**)	190	+264	—	*albiflora*
19-Hydroxy-20-epipandoline (**167**)	204	+511	—	*albiflora*
(19*S*)-Hydroxytacamine (**188**)	—	—	—	*eglandulosa*
$C_{21}H_{18}N_2O_5$ (MW 378)				
9-Methoxycamptothecine (**4**)	258–260	−76.1	XXI	*heyneana*
$C_{21}H_{22}N_2O_5$ (MW 382)				
Apodinine (**86**)	—	—	—	*apoda*
$C_{22}H_{26}N_2O_4$ (MW 382)				
Vincadiffine (**34**)	230	−121	XI	*glandulosa*
O-Acetylvallesamine (**65**)	171	+151	XI	*dichotoma, heyneana*
10-Hydroxy-11-methoxytabersonine (**69**)	—	—	—	*coffeoides*
Hazuntine (**72**)	152	−450	XVII	*coffeoides*
14,15-Dehydro-12-methoxyvincamine (**95**)	212	+110	—	*psorocarpa*
3-Oxovoacangine (**108**)	252–253.5	—	—	*citrifolia, echinata, quadrangularis, retusa*
19-Oxovoacangine (Voacryptine) (**117**)	175–176	—	XI	*amblyocarpa, heyneana*
(6*R*)-3,6-Oxidoisovoacangine (**130**)	162	−57	—	*sessilifolia*
(6*R*)-3,6-Oxidovoacangine (**131**)	—	—	—	*echinata*
(19*S*)-3,19-Oxidovoacangine (Heyneantine) (**133**)	—	−6	—	*heyneana*

(*continued*)

TABLE II (*Continued*)

Alkaloid	MP (°C)	$[\alpha]_D$ (deg)	Volume number[a]	*Tabernaemontana* species
$C_{23}H_{30}N_2O_3$ (MW 382)				
3-Ethoxycoronaridine (**104**)	—	−59	—	*glandulosa*
(3*S*)-3(β-Hydroxyethyl)coronaridine (**111**)	—	−25.4	—	*bufalina*
$C_{22}H_{28}N_2O_4$ (MW 384)				
3-Hydroxyisovoacangine (**107**)	159–160	−80 ± 24	—	*eglandulosa*
Voacristine (Voacangarine) (**118**)	165	−29	VIII	*amblyocarpa, apoda, citrifolia, contorta, crassa, divaricata, echinata, heyneana, humblotii, lundii, mocquerysii, olivacea, orientalis, retusa, wallichiana*
19-Epivoacristine (**119**)	115	−44.5	XI	*dichotoma, echinata, eusepala, lundii, mocquerysii*
Isovoacristine (**120**)	107	−20	XI	*amblyocarpa, divaricata, heyneana, pandacaqui*
Voacangine hydroxyindolenine (**143**)	134–135	+133.2	—	*apoda, cerifera, citrifolia, echinata, heterophylla, heyneana, macrocarpa, olivacea, quadrangularis*
Voacangine pseudoindoxyl (**149**) (Voaluteine)	208	−115	—	*apoda, aurantiaca, echinata, heyneana, olivacea, rupicola*
$C_{23}H_{26}N_2O_4$ (MW 394)				
O-Acetylpolyneuridine (**21**)	—	—	—	*crassa*
Akuammiline (**41**)	160	+83	V, VII, VIII, X, XIV	*crassa*

$C_{24}H_{30}N_2O_3$ (MW 394)				
3-(2′-Oxopropyl)coronaridine (**106**)	—	−22	—	*divaricata, dichotoma*
$C_{22}H_{26}N_2O_5$ (MW 398)				
Tabernulosine (**42**)	190–191	−27	—	*glandulosa*
6-Hydroxy-3-oxoisovoacangine (**116**)	—	−55	—	*sessilifolia*
3-Oxovoacristine (**127**)	251–252	−35.5	—	*citrifolia*
(6*R*)-3,6-Oxidovoacangine N^4-oxide (**132**)	—	+86.6	—	*heyneana*
$C_{23}H_{30}N_2O_4$ (MW 398)				
Cylindrocarpidine (**79**)	120–121.5	−122	VIII, XI, XVII	*amygdalifolia*
Conopharyngine (**102**)	143	−41	IX, XI	*attenuata, contorta, crassa, eglandulosa, longiflora, orientalis, pachysiphon, penduliflora*
$C_{22}H_{28}N_2O_5$ (MW 400)				
Voacristine hydroxyindolenine (**144**)	179	−22	—	*apoda, dichotoma*
Voacristine pseudoindoxyl (**150**) (Montanine)	274 (hydro-bromide)	−206 (hydro-bromide)	—	*apoda, lundii, rupicola*
Tabernoxidine (**155**)	291–292	—	—	*heyneana*
$C_{23}H_{28}N_2O_5$ (MW 412)				
Reserpiline (**12**)	—	−12	VII, VIII, XI, XIV	*coffeoides*
Isoreserpiline (**13**)	212	−88	VII, VIII, XI, XIV	*coffeoides*
Hazuntinine (**73**)	132	−482	XV, XVII	*coffeoides*
5-Oxocylindrocarpidine (**82**)	213	−39	XI	*amygdalifolia*
3-Oxoconopharyngine (**109**)	284–286	−48 ± 2	—	*crassa*
$C_{24}H_{32}N_2O_4$ (MW 412)				
Homocylindrocarpidine (**81**)	—	−82	—	*amygdalifolia*
$C_{23}H_{30}N_2O_5$ (MW 414)				
3-Hydroxyconopharyngine (**110**)	—	—	—	*pachysiphon*

(*continued*)

TABLE II (*Continued*)

Alkaloid	MP (°C)	$[\alpha]_D$ (deg)	Volume number[a]	*Tabernaemontana* species
19-Hydroxyconopharyngine (**121**)	—	−36.4	—	*crassa, pachysiphon*
Conopharyngine hydroxyindolenine (**145**) (Jollyanine)	161–163	−56	—	*attenuata, crassa, pachysiphon*
Conopharyngine pseudoindoxyl (**151**)	—	—	—	*pachysiphon*
Crassanine (**156**)	191	+21	—	*crassa*
$C_{28}H_{30}N_2O_3$ (MW 442)				
Tetraphyllicine monomethoxybenzoate (**38**)	—	—	—	*coffeoides*
$C_{29}H_{32}N_2O_4$ (MW 472)				
Tetraphyllicine dimethoxybenzoate (**39**)	—	—	—	*coffeoides*
$C_{30}H_{34}N_2O_5$ (MW 502)				
Tetraphyllicine trimethoxybenzoate (**40**)	—	—	—	*coffeoides*
$C_{35}H_{40}N_4O_3$ (MW 564)				
Bonafousine (**251**)	199–200	−35	XX	*siphilitica*
Isobonafousine (**252**)	—	+19	—	*siphilitica*
$C_{39}H_{44}N_4O_2$ (MW 600)				
Vobparicine (**200**)	—	—	—	*chippii*
$C_{40}H_{48}N_4O_2$ (MW 616)				
Tabernamine (**201**)	—	−51	XX	*heterophylla, johnstonii*
(20*R*)-Capuvosidine (**236**)	—	−7	XX	*capuronii, mocquerysii*
$C_{40}H_{50}N_4O_2$ (MW 618)				
(20′*S*)-19′,20′-Dihydrotabernamine (**206**)	—	—	—	*coffeoides*
(20*R*)-Dehydroxyisocapuvosine (**213**)	—	—	XX	*mocquerysii*
(20*R*)-Dehydroxycapuvosine (**233**)	—	−98	XX	*capuronii, mocquerysii*
(20*R*)-1,2-Dihydrocapuvosidine (**237**)	—	—	XX	*capuronii, mocquerysii*
(20*S*)-1,2-Dihydrocapuvosidine (**238**)	—	—	XX	*mocquerysii*

$C_{39}H_{48}N_4O_3$ (MW 620)					
$N^{4'}$-Demethylcapuvosine (**234**)	—	−85	XX		*capuronii*
$C_{40}H_{44}N_4O_3$ (MW 628)					
Ervafolene (**248**)	—	+236		—	*heterophylla*
$C_{40}H_{50}N_4O_3$ (MW 634)					
Capuvosine (**235**)	236	−53	XX		*capuronii*
$C_{40}H_{44}N_4O_4$ (MW 644)					
Ervafoline (**246**)	258	+279		—	*heterophylla, pandacaqui*
19′-Hydroxyervafolene (**249**)	248	+284		—	*heterophylla*
$C_{41}H_{48}N_4O_3$ (MW 644)					
Accedinisine (**198**)	235	−60	XX		*accedens*
$C_{41}H_{50}N_4O_3$ (MW 646)					
16-Decarbomethoxyvoacamine (**209**)	228	—	XX		*echinata, fuchsiaefolia, heterophylla, humblotii, mocquerysii, orientalis*
$C_{41}H_{52}N_4O_3$ (MW 648)					
16-Decarbomethoxy-19′,20′-dihydrovoacamine (**207**)	215	+22	XX		*orientalis*
16-Decarbomethoxy-19′,20′-dihydro-20′-epivoacamine (**208**)	180	−18	XX		*orientalis*
$C_{40}H_{44}N_4O_5$ (MW 660)					
19′-Hydroxyervafoline (**247**)	258	+247		—	*heterophylla*
$C_{41}H_{48}N_4O_4$ (MW 660)					
Accedinine (**199**)	—	−81	XX		*accedens*
$C_{40}H_{46}N_4O_3$ (MW 662)					
Ervafolidine (**242**)	240	+20		—	*heterophylla, pandacaqui*
3-Epiervafolidine (**243**)	>260	+52		—	*heterophylla, pandacaqui*
$C_{42}H_{50}N_4O_4$ (MW 674)					
Ervahanine (**202**)	—	−97		—	*bufalina*

(*continued*)

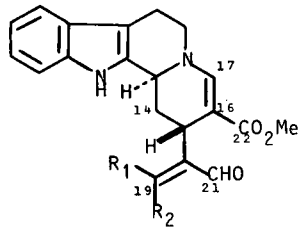
TABLE II (*Continued*)

Alkaloid	MP (°C)	$[\alpha]_D$ (deg)	Volume number[a]	*Tabernaemontana* species
Ervahanine B (**223**)	—	−123	—	*bufalina*
Ervahanine C (**228**)	—	−62	—	*bufalina*
$C_{40}H_{46}N_4O_6$ (MW 678)				
(19′*R*)-19-Hydroxyervafolidine (**244**)	260	+33	—	*heterophylla*
(19′*S*)-19-Hydroxy-3-epiervafolidine (**245**)	260	+74	—	*heterophylla*
$C_{42}H_{56}N_4O_4$ (MW 680)				
15,20;15′,20′-Tetrahydropresecamine (**253**)[b]	—	+57	XX	*minutiflora*
$C_{42}H_{50}N_4O_5$ (MW 690)				
$N^{4'}$-Demethylvoacamine (**210**)	227	−67	XX	*accedens, echinata, fuchsiaefolia*
Gabunamine (**224**)	—	—	XX	*johnstonii*
11-Demethylconoduramine (**225**)	—	—	—	*pachysiphon*
Gabunine (**229**)	244–246	−105	XI	*crassa, pachysiphon, johnstonii*
$C_{43}H_{52}N_4O_5$ (MW 704)				
Voacamine (**203**)	224	−52	VII, XI, XX	*accedens, arborea, australis, citrifolia, divaricata, echinata, eglandulosa, fuchsiaefolia, heterophylla, laeta, mocquerysii, orientalis*
Voacamidine (**205**)	—	−168	VIII, XI, XX	*accedens, echinata, fuchsiaefolia*
Conoduramine (**226**)	218	−77	VIII, XI, XX	*crassa, elegans, pachysiphon, johnstonii*
Conodurine (**230**)	222–225	−101	VIII, XX	*crassa, laeta, pachysiphon, johnstonii*
$C_{42}H_{50}N_4O_6$ (MW 706)				
Tetrastachyne (**240**)	—	−248	—	*siphilitica*

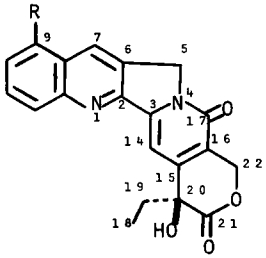
Tetrastachynine (**241**)	—	0	—	*siphilitica*
12,12′-Bis(11-hydroxycoronaridinyl) (**250**)	—	—	XX	*siphilitica*
$C_{43}H_{54}N_4O_5$ (MW 706)				
Tabernaelegantine A (**214**)	231	−31.8	XX	*elegans, coffeoides*
Tabernaelegantine C (**215**)	171	−36.8	XX	*elegans*
Tabernaelegantine B (**219**)	199	+14.4	XX	*elegans*
Tabernaelegantine D (**220**)	206	+11.3	XX	*elegans*
$C_{42}H_{50}N_4O_6$ (MW 718)				
3-Oxoconodurine (**231**)	217–218	—	XX	*pachysiphon*
Vobtusine (**239**)	302	−352	VII, VIII, XI, XX	*aurantiaca*
$C_{43}H_{52}N_4O_6$ (MW 720)				
Voacamine $N^{4'}$-oxide (**204**)	216–219	−55	XX	*accedens*
Voacorine (**211**)	273	−42	VII, VIII, XX	*brachyantha*
19-Epivoacorine (**212**)	265	−44	XX	*arborea*
19′,20′-Epoxyconoduramine (**227**)	—	—	XX	*johnstonii*
$C_{43}H_{54}N_4O_6$ (MW 722)				
(19*R*)-19-Hydroxytabernaelegantine A (**216**)	268	−33	—	*coffeoides*
$C_{44}H_{53}N_5O_5$ (MW 731)				
Tabernaelegantinine C (**217**)	177	—	XX	*elegans*
Tabernaelegantinine D (**221**)	259	—	XX	*elegans*
$C_{44}H_{50}N_4O_7$ (MW 746)				
Pandicine (**254**)	—	—	—	*Pandacastrum saccharatum*
$C_{46}H_{56}N_4O_6$ (MW 760)				
3-(2′-Oxopropyl)conodurine (**232**)	203–204	—	XX	*pachysiphon*
$C_{46}H_{58}N_4O_6$ (MW 762)				
Tabernaelegantinine A (**218**)	160	−53.7	XX	*elegans*
Tabernaelegantinine B (**222**)	215	+39.1	XX	*elegans*

[a] Volume of this treatise in which the alkaloid has been previously discussed.
[b] Stereochemistry unknown.
[c] Tentatively identified.
[d] Isolated as a mixture.

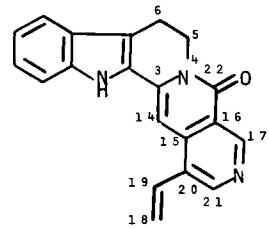
VALLESIACHOTAMAN TYPE



	R_1	R_2
1	Me	H
2	H	Me



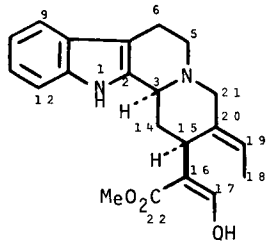
	R
3	H
4	OMe



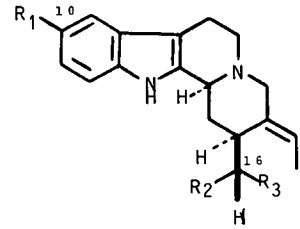
5

CORYNANTHEAN TYPE

Corynantheine subtype



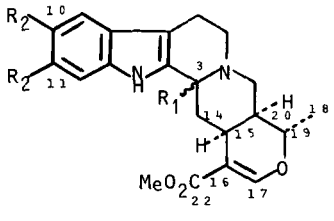
6



	R_1	R_2	R_3
7	H	CH_2OH	H
8	OH	CH_2OH	H
9	H	CO_2Me	CH_2OH
10	H	CH_2OH	CO_2Me

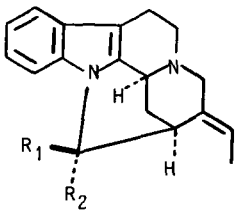
FIG. 2. Structural formulas of indole alkaloids isolated from *Tabernaemontana* plants.

Ajmalicine subtype



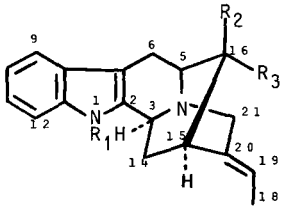
	R_1	R_2
11	α-H	H
12	β-H	OMe
13	α-H	OMe

Pleiocarpamine subtype



	R_1	R_2
14	CO_2Me	H
15	H	CO_2Me

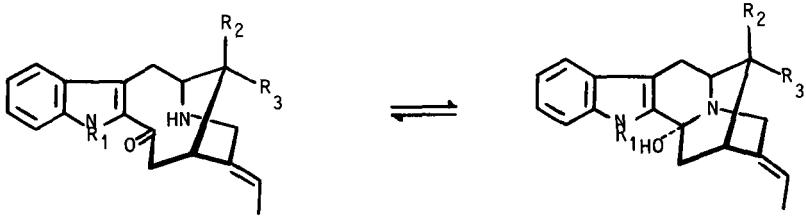
Sarpagine subtype



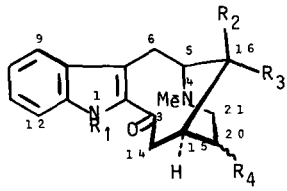
	R_1	R_2	R_3
16	Me	H	CH_2OH
17	H	CO_2Me	CH_2OH
18	H	H	CH_2OH
19	H	H	CO_2Me
20	H	CH_2OH	CO_2Me
21	H	CH_2OAc	CO_2Me
22	Me	CH_2OH	CO_2Me

FIG. 2 (*Continued*)

Vobasine subtype

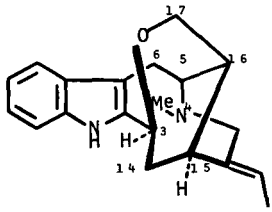


	R_1	R_2	R_3
23	Me	H	CH_2OH
24	H	CH_2OH	H
25	H	CO_2Me	H
26	H	CO_2Me	CH_2OH



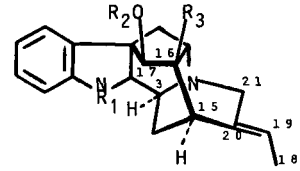
	R_1	R_2	R_3	R_4
27	H	CH_2OH	H	=CH-Me
28	H	H	CH_2OH	=CH-Me
29	Me	H	CH_2OH	=CH-Me
30	H	CO_2Me	H	α-Et
31	H	CO_2Me	H	β-Et
32	H	CO_2Me	H	=CH-Me
33	H	H	CO_2H	=CH-Me
34	H	CO_2Me	CH_2OH	=CH-Me

FIG. 2 (*Continued*)



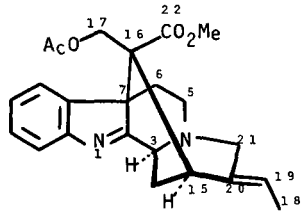
35

Ajmaline subtype



	R_1	R_2	R_3
36	H	H	CO_2Me
37	Me	H	H
38	Me	$COC_6H_4(OMe)$	H
39	Me	$COC_6H_3(OMe)_2$	H
40	Me	$COC_6H_2(OMe)_3$	H

Akuammiline subtype



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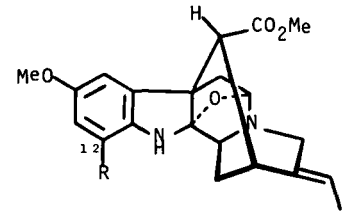
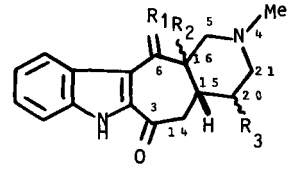


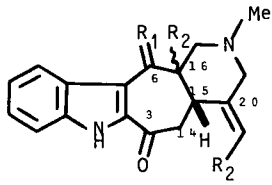
	R
42	OMe
43	H

Ervatamine subtype



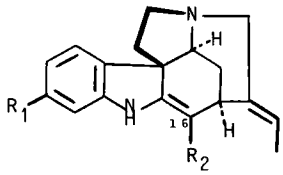
	R_1	R_2	R_3
44	H_2	β-CO_2Me	β-Et
45	H_2	β-CO_2Me	α-Et
46	H_2	β-H	α-Et
47	H_2	β-H	β-Et
48	O	β-H	α-Et
49	O	α-H	α-Et

FIG. 2 (*Continued*)



	R_1	R_2
50	H_2	β-CO_2Me
51	H_2	β-H
52	H_2	α-H
53	O	β-H

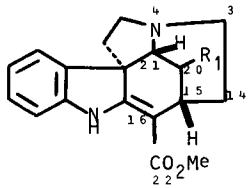
STRYCHNAN TYPE



	R_1	R_2
55	H	CO_2Me
56	OH	CHO
57	H	CHO

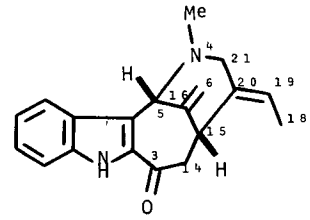
ASPIDOSPERMATAN TYPE

Precondylocarpine subtype

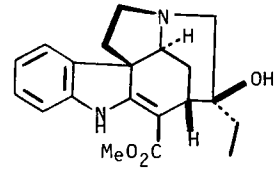


	R_1	
59	=CH-Me	-
60	=CH-Me	$N_4 \rightarrow O$
61	α-Et	-
62	α-Et	$N_4 \rightarrow O$

Ervitsine subtype

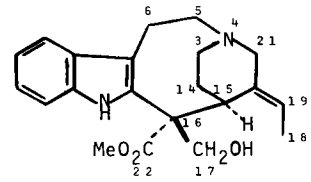


54



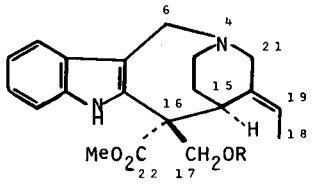
58

Stemmadenine subtype



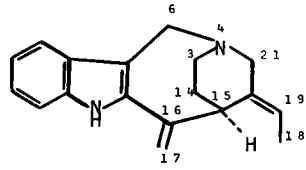
63

FIG. 2 (*Continued*)



	R
64	H
65	Ac

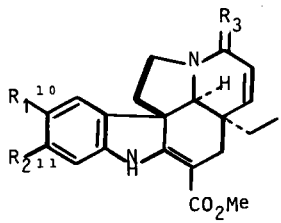
Vallesamine subtype



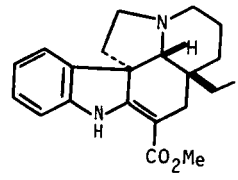
66

PLUMERAN TYPE

Tabersonine subtype



	R_1	R_2	R_3
67	H	H	H
68	H	H	O
69	OH	OMe	H



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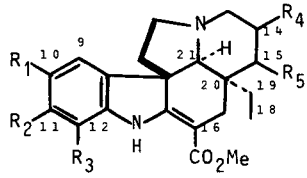
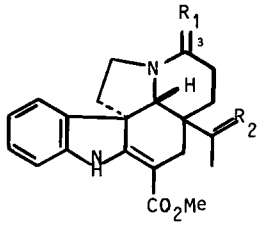
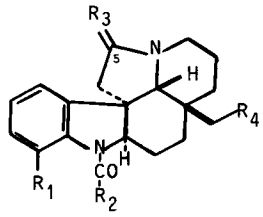


	R_1	R_2	R_3	R_4	R_5
71	H	H	OH	H	H
72	H	OMe	H	~O~	
73	OMe	OMe	H	—O—	
74	H	H	H	---O---	
75	H	H	H	—O—	
76	H	H	H	ξ-OH	ξ-OH

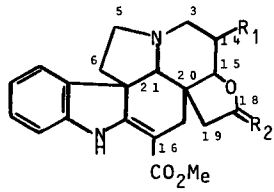
FIG. 2 (*Continued*)



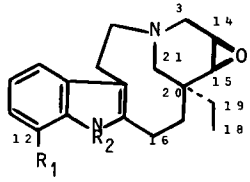
	R_1	R_2
77	H_2	O
78	O	O



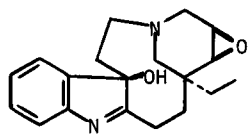
	R_1	R_2	R_3	R_4
79	OMe	Me	H_2	CO_2Me
80	H	Me	H_2	CO_2Me
81	OMe	Et	H_2	CO_2Me
82	OMe	Me	O	CO_2Me
83	OH	Et	H_2	Me



	R_1	R_2
84	H	O
85	H	H_2
86	OH	O



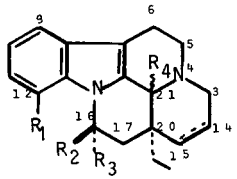
	R_1	R_2
87	H	H
88	H	Me
89	OMe	H

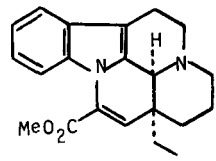


90

FIG. 2 (*Continued*)

EBURNAN TYPE



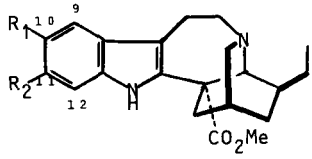


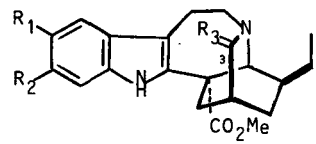
96

	R_1	R_2	R_3	R_4
91	H	OH	CO_2Me	α-H
92	H	CO_2Me	OH	α-H
93	H	OH	CO_2Me	β-H
94	H	CO_2Me	OH	α-H Δ^{14}
95	OMe	OH	CO_2Me	α-H Δ^{14}

IBOGAN TYPE

Coronaridine subtype

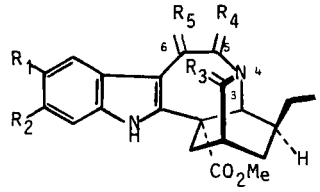




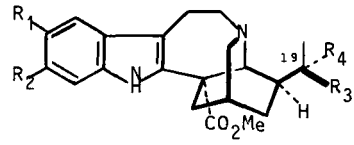
	R_1	R_2
97	H	H
98	OH	H
99	H	OH
100	OMe	H
101	H	OMe
102	OMe	OMe

	R_1	R_2	R_3
103	H	H	OH,H
104	H	H	OEt,H
105	H	H	O
106	H	H	H,CH_2Ac
107	H	OMe	OH,H
108	OMe	H	O
109	OMe	OMe	O
110	OMe	OMe	OH,H
111	H	H	H,CH(OH)Me

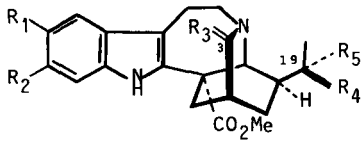
FIG. 2 (*Continued*)



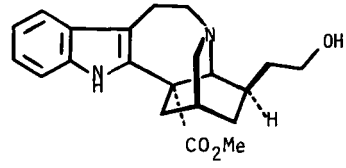
	R_1	R_2	R_3	R_4	R_5
112	H	H	H_2	O	H_2
113	H	H	H_2	H_2	O
114	H	H	H_2	H,OH	O
115	H	H	O	H_2	H,OH
116	H	OMe	O	H_2	H,OH



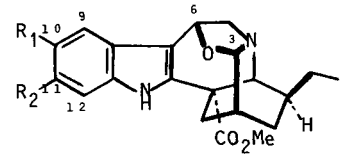
	R_1	R_2	R_3	R_4
117	OMe	H	O	
118	OMe	H	H	OH
119	OMe	H	OH	H
120	H	OMe	H	OH
121	OMe	OMe	OH	H



	R_1	R_2	R_3	R_4	R_5
122	H	H	H_2	H	OH
123	H	H	H_2	OH	H
124	H	H	O	H	OH
125	OH	H	H_2	H	OH
126	H	OH	H_2	H	OH
127	OMe	H	O	H	OH

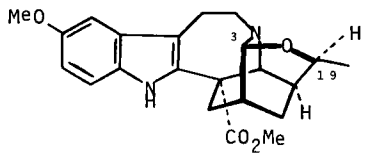


128

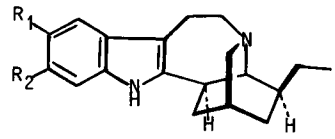


	R_1	R_2	
129	H	H	-
130	H	OMe	-
131	OMe	H	-
132	OMe	H	$N_4 \rightarrow O$

FIG. 2 (*Continued*)

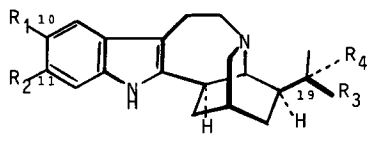


133

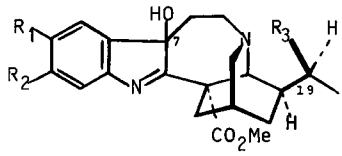


	R_1	R_2
134	H	H
135	OMe	H
136	H	OMe
137	OMe	OMe

Coronaridine hydroxyindolenine subtype

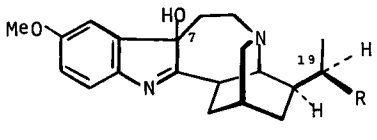


	R_1	R_2	R_3	R_4
138	H	H	OH	H
139	OMe	H	H	OH
140	OMe	H	OH	H
141	OMe	OMe	OH	H

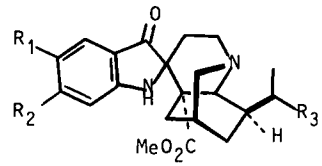


	R_1	R_2	R_3
142	H	H	H
143	OMe	H	H
144	OMe	H	OH
145	OMe	OMe	H

Iboluteine subtype

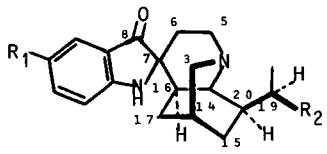


	R
146	H
147	OH



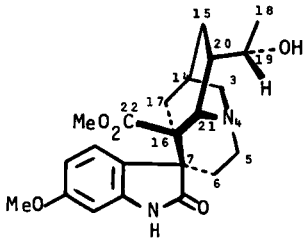
	R_1	R_2	R_3
148	H	H	H
149	OMe	H	H
150	OMe	H	OH
151	OMe	OMe	H

FIG. 2 (*Continued*)

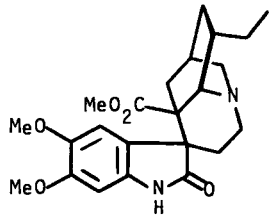


	R_1	R_2
152	H	H
153	H	OH
154	OMe	H

Tabernoxidine subtype

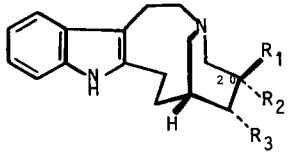


155



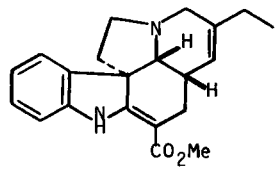
156

Cleavamine subtype



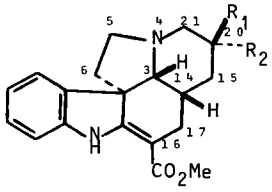
	R_1	R_2	R_3
157	H	Et	H
158	Et	H	H
159	H	Et	OH
160	Et	OH	H

Pseudotabersonine subtype

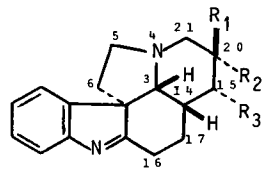


161

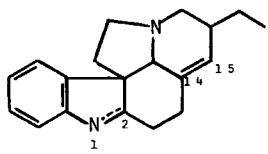
FIG. 2 (*Continued*)



	R_1	R_2
162	H	Et
163	Et	H
164	Et	OH
165	OH	Et
166	H	$CH(OH)CH_2OH$
167	OH	CH(OH)Me

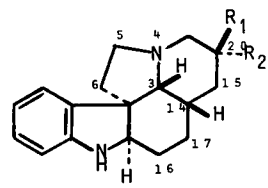


	R_1	R_2	R_3
168	H	Et	H
169	Et	H	H
170	H	Et	OH
171	OH	Et	H



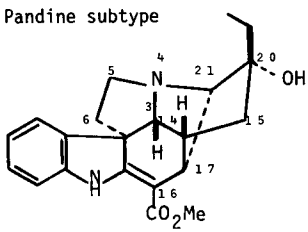
172 Δ^1

173 -



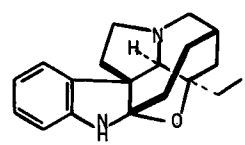
	R_1	R_2
174	H	Et
175	Et	H

Pandine subtype



176

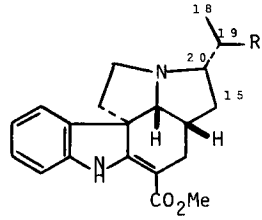
Dichomine subtype



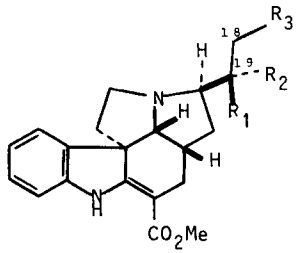
177

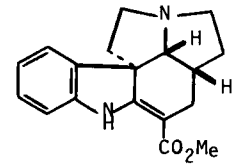
FIG. 2 (*Continued*)

Ibophyllidine subtype



	R	
178	H	-
179	H	$N_4 \rightarrow O$
180	OH	-

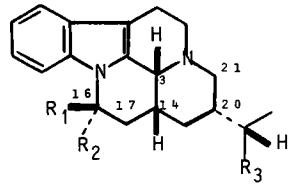


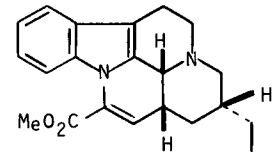


185

	R_1	R_2	R_3
181	H	H	H
182	H	H	OH
183	OH	H	H
184	H	OH	H

TACAMAN TYPE

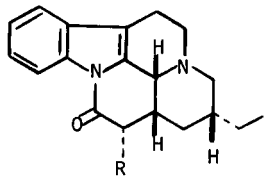




191

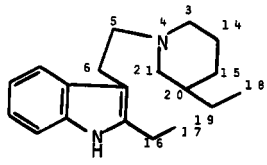
	R_1	R_2	R_3
186	CO_2Me	OH	H
187	OH	CO_2Me	H
188	CO_2Me	OH	OH
189	OH	H	H
190	H	OH	H

FIG. 2 (*Continued*)

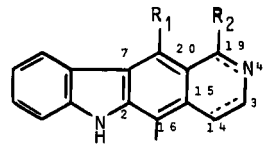


	R
192	H
193	OH

MISCELLANEOUS TYPE

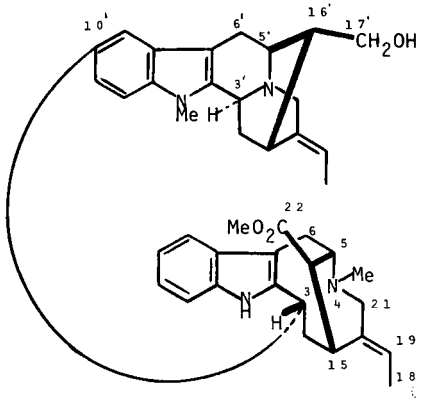


194

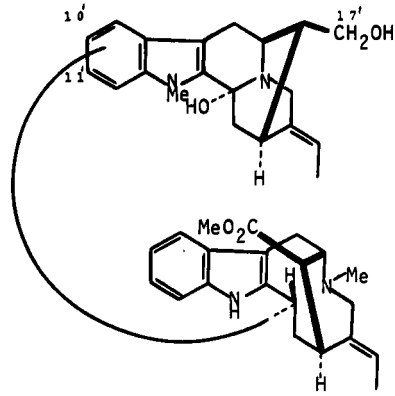


	R_1	R_2	
195	H	Me	$\Delta^{3,14;4,19}$
196	Me	H	$\Delta^{4,19}$
197	H	Me	-

CORYNANTHEAN CORYNANTHEAN TYPE



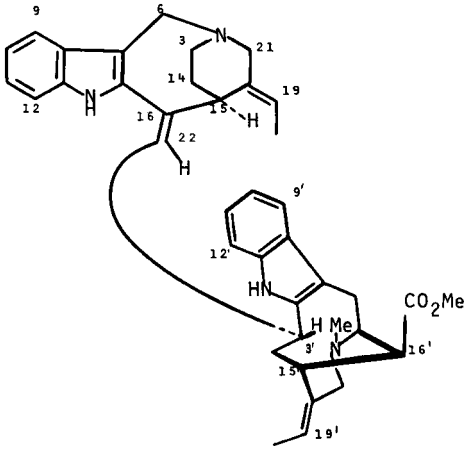
198



199

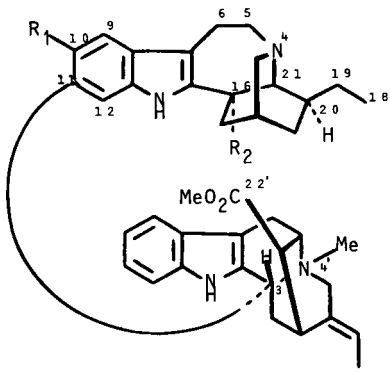
FIG. 2 (*Continued*)

ASPIDOSPERMATAN-CORYNANTHEAN TYPE

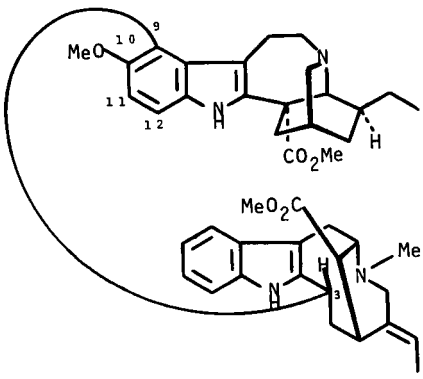


200

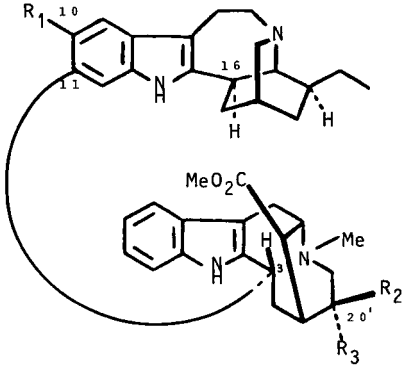
IBOGAN CORYNANTHEAN TYPE



	R_1	R_2	
201	H	H	
202	H	CO_2Me	
203	OMe	CO_2Me	
204	OMe	CO_2Me	$N_{4'} \rightarrow O$

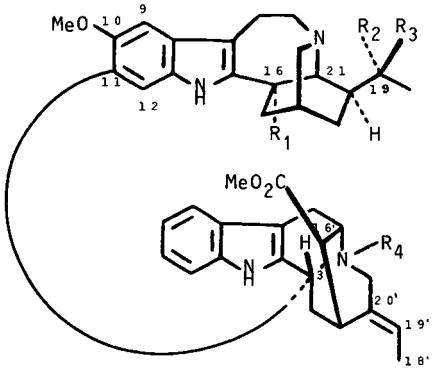


205

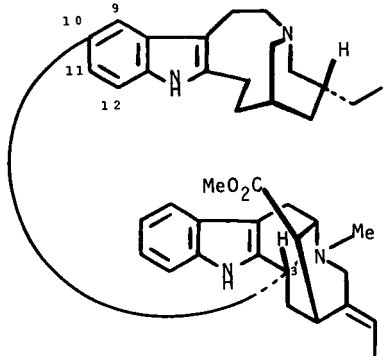


	R_1	R_2	R_3
206	H	Et	H
207	OMe	H	Et
208	OMe	Et	H

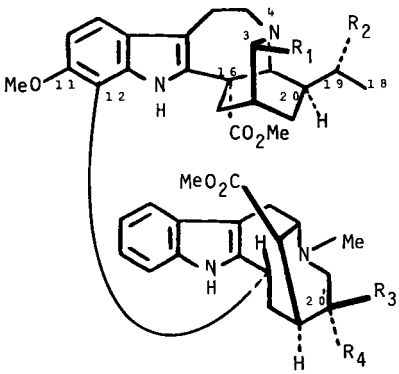
FIG. 2 (*Continued*)



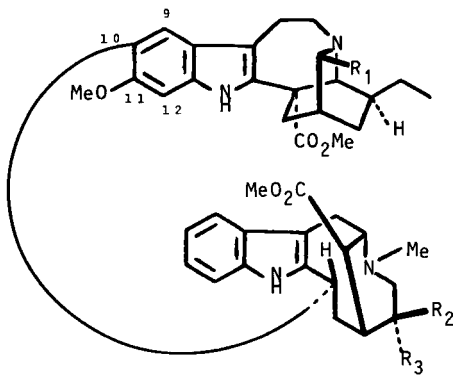
	R_1	R_2	R_3	R_4
209	H	H	H	Me
210	CO_2Me	H	H	H
211	CO_2Me	H	OH	Me
212	CO_2Me	OH	H	Me



213

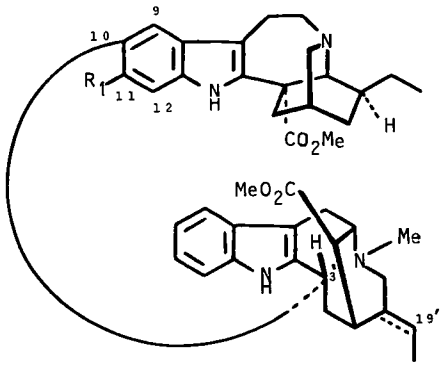


	R_1	R_2	R_3	R_4
214	H	H	Et	H
215	H	H	H	Et
216	H	OH	Et	H
217	CN	H	H	Et
218	CH_2Ac	H	Et	H

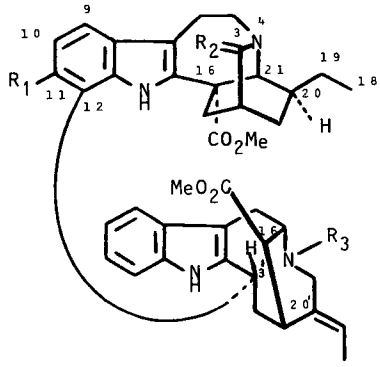


	R_1	R_2	R_3
219	H	Et	H
220	H	H	Et
221	CN	H	Et
222	CH_2Ac	Et	H

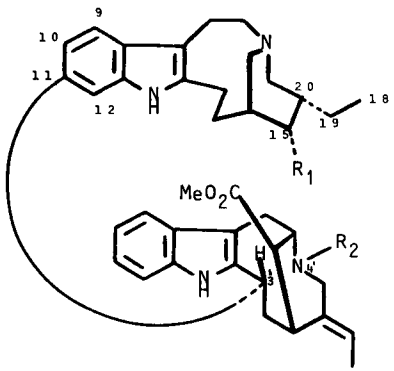
FIG. 2 (*Continued*)



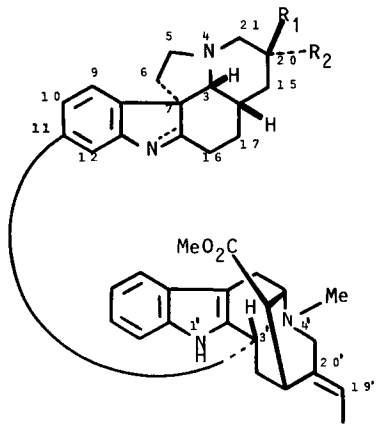
	R_1	R_2	
223	H	Me	$\Delta^{19'}$
224	OMe	H	$\Delta^{19'}$
225	OH	Me	$\Delta^{19'}$
226	OMe	Me	$\Delta^{19'}$
227	OMe	Me	19',20'-epoxy



	R_1	R_2	R_3
228	H	H_2	Me
229	OMe	H_2	H
230	OMe	H_2	Me
231	OMe	O	Me
232	OMe	H,CH_2Ac	Me



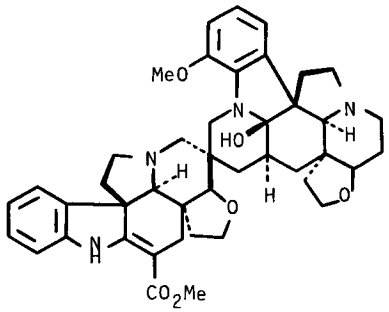
	R_1	R_2
233	H	Me
234	OH	H
235	OH	Me



	R_1	R_2	
236	H	Et	Δ^{1}
237	H	Et	(NH,2αH)
238	Et	H	(NH,2αH)

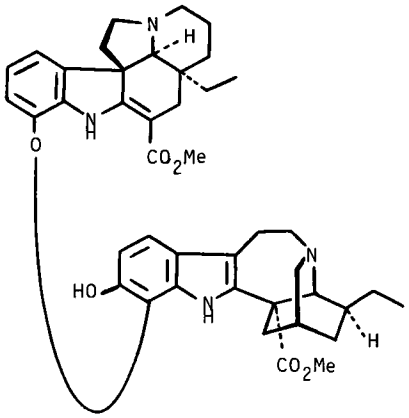
FIG. 2 (*Continued*)

PLUMERAN-PLUMERAN TYPE



239

PLUMERAN-IBOGAN TYPE



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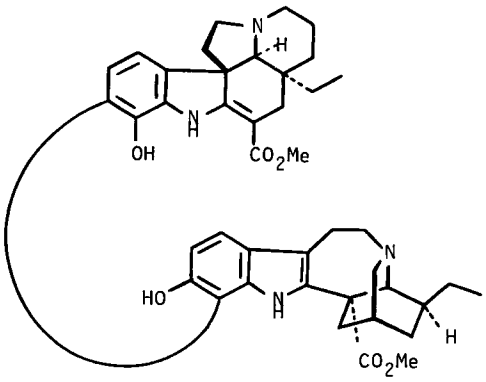

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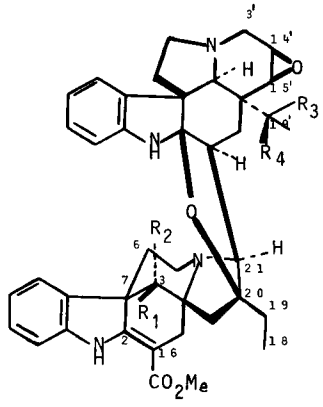
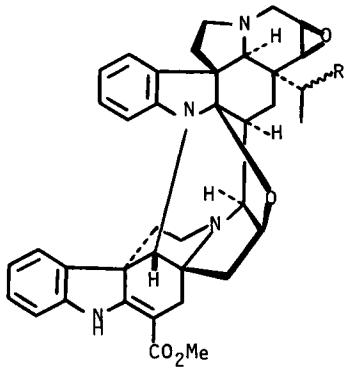
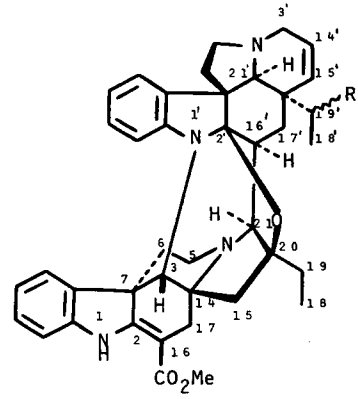


	R_1	R_2	R_3	R_4
242	H	OH	H	H
243	OH	H	H	H
244	H	OH	OH	H
245	OH	H	H	OH

FIG. 2 (*Continued*)

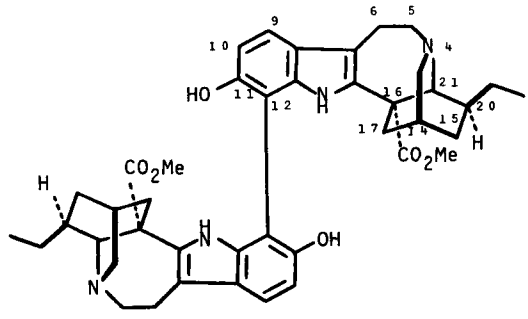


	R
246	H
247	OH



	R
248	H
249	OH

IBOGAN–IBOGAN TYPE

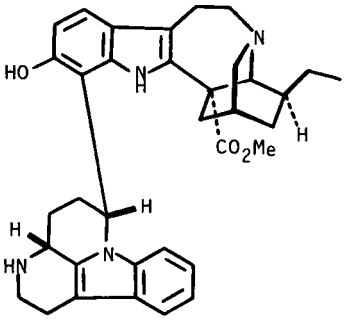


250

FIG. 2 (*Continued*)

IBOGAN-MISCELLANEOUS TYPE

(IBOGAN-CANTHINONE TYPE)



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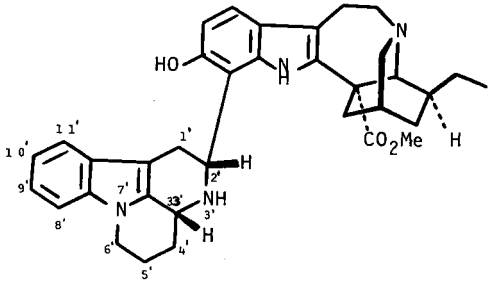
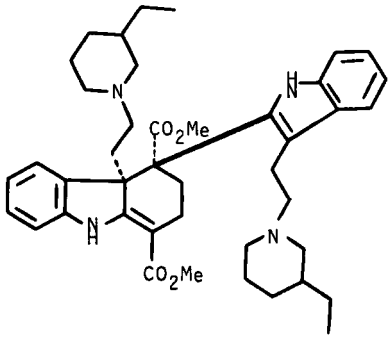


252

MISCELLANEOUS MISCELLANEOUS TYPE

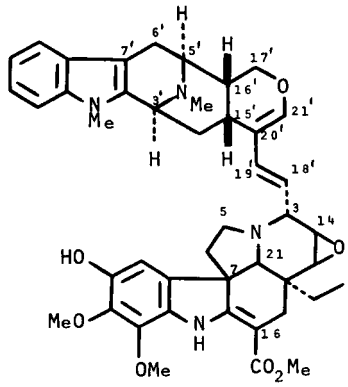
(SECODINE-SECODINE TYPE)



253

PLUMERAN MISCELLANEOUS TYPE

(PLUMERAN-MACROLINE TYPE)



254

FIG. 2 (*Continued*)

(Text continued from p. 25)

A. Corynanthean-Type Alkaloids

1. Corynantheine-Subtype Alkaloids

The already known geissoschizol (**7**, $C_{19}H_{24}N_2O$, MP 224–226°C, $[\alpha]_D$ −70°) (*184*) and its 10-hydroxy derivative (**8**, $C_{19}H_{24}N_2O_2$, MP 264°C) (*184*), were isolated from the roots of *T. bufalina (Ervatamia hainanensis)* (*53*). The detailed analysis of the ^{1}H-NMR spectra of **7** and **8** diacetate were reported (Table III) and the assignment of all of the protons was made by application of consecutive double-resonance experiments.

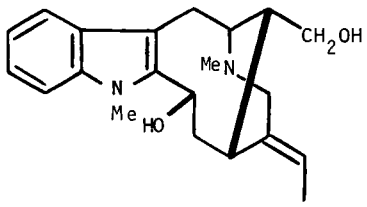
The ^{1}H-NMR data of isositsirikine (**9**, $C_{21}H_{26}N_2O_3$, $[\alpha]_D$ −20°), isolated from the stem bark of *T. psorocarpa* (*65*) were in agreement with those previously reported by Kan *et al.* (*185*) from 16-epiisositsirikine (**10**). The structure was confirmed through direct comparison with an authentic sample obtained by $NaBH_4$ reduction of geissoschizine (**6**). The stereochemistry at C-16 of isomeric isositsirikines has been revised by Scott (*186*), and structure **10** represents the correct C-16 configuration for 16-epiisositsirikine. The proton resonances of **10** are reported in Table III in comparison with the data of isositsirikine. The CMR data of **10** are also available.

2. Sarpagine-Subtype Alkaloids

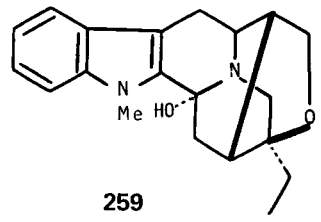
Tabernaemontana psychotrifolia from Venezuela, in addition to yielding the known affinine (**27**, $C_{20}H_{24}N_2O_2$,) has also afforded 16-epivobasinic acid (**33**) and anhydrovobasindiol (taberpsychine) (**35**) (*167*).

16-epivobasinic acid (**33**, $C_{20}H_{22}N_2O_3$, MP 295°C), was previously prepared by Renner *et al.* (*187*) but never before reported as a natural product. Prolonged treatment of **33** with diazomethane yielded 16-epivobasine in which the C-16 configuration was established by a CO_2Me chemical shift at 3.53 ppm versus 2.63 ppm in vobasine (**32**).

The structure of anhydrovobasindiol (**35**, $C_{20}H_{24}N_2O$, MP 208°C, $[\alpha]_D$ −243°) was based almost entirely on chemical evidence. Hydrogenation of **35** gave a dihydro derivative ($C_{20}H_{26}N_2O$, MP 191–193°C), which formed a methiodide on reaction with MeI. Hofmann elimination with *tert*-BuOK in *tert*-BuOH



258



259

TABLE III

^{1}H-NMR DATA FOR GEISSOSCHIZOL (**7**), 10-HYDROXYGEISSOSCHIZOL (**8**) (DIACETATE) (*53*), ISOSITSIRIKINE (**9**), AND 16-EPIISOSITSIRIKINE (**10**) (*185*)

Proton	Chemical shifts (ppm)			
	7	**8** (diacetate)[a]	**9**	**10**
H-3	4.24 br s	4.22 br s	4.31 br s	3.9 br s
H-5α[b]	3.08 ddd	3.06 ddd	3.15 ddd	2.84 ddd
H-5β[b]	3.27 m	3.23 m	3.27 dd	3.17 dd
H-6α	2.68 br d	2.56 br d	2.65 br d	2.68 br d
H-6β	3.05 m	3.05 m	3.0 m	3.0 m
H-9	7.52	7.16	7.48	7.48
H-10	7.14	—	7.10	7.09
H-11	7.18	6.86	7.17	7.14
H-12	7.38	7.28	7.38	7.31
H-14α[c]	2.33 m	2.27 m	2.26 m	2.27 m
H-14β[c]	2.21 m	2.04 m	2.22 m	2.25 m
H-15	3.0 m	2.85 m	3.10 m	3.38 m
H-16,H-16′	1.55 m	1.56 m	2.52 m	2.66 m
H-17	3.60 br dd	3.97 br dd	3.55 br dd	3.92 br dd
H-17′	3.56 br dd	3.93 br dd	3.50 br dd	3.87 br dd
H-18	1.67 d	1.63 d	1.67 d	1.63 d
H-19	5.56 br q	5.54 br q	5.64 br q	5.52 br q
H-21	3.68 br d	3.57 br d	3.54 br d	3.08 br d
H-21	3.01 br d	2.95 br d	2.93 br d	3.80 br d
CO_2Me	—	—	3.82 s	3.57 s
NH	8.20 br s	8.07 br s	8.67 br s	8.23 br s

Coupling constants (Hz)

7: $J_{5\alpha,5\beta} = 12$, $J_{5\alpha,6\alpha} = 4$, $J_{5\alpha,6\beta} = 12$, $J_{5\beta,6\alpha} = 1$, $J_{5\beta,6\beta} = 5$, $J_{6\alpha,6\beta} = 15$, $J_{16,17} = 7$, $J_{16,17'} = 5$, $J_{18,19} = 6.5$, $J_{19,21\alpha} < 0.5$, $J_{19,21\beta} < 0.5$, $J_{21\alpha,21\beta} = 12$

8: $J_{5\alpha,5\beta} = 12$, $J_{5\alpha,6\alpha} = 4$, $J_{5\alpha,6\beta} = 12$, $J_{5\beta,6\alpha} = 1$, $J_{5\beta,6\beta} = 5$, $J_{6\alpha,6\beta} = 15$, $J_{16,17} = 7$, $J_{16,17'} = 5$, $J_{18,19} = 6.5$, $J_{19,21\alpha} < 0.5$, $J_{19,21\beta} < 0.5$, $J_{21\alpha,21\beta} = 12$

9: $J_{5\alpha,5\beta} = 12$, $J_{5\alpha,6\alpha} = 4$, $J_{5\alpha,6\beta} = 12$, $J_{5\beta,6\alpha} = 1$, $J_{5\beta,6\beta} = 5.5$, $J_{6\alpha,6\beta} = 15$, $J_{16,17} = 7$, $J_{16,17'} = 5$, $J_{17,17'} = 12$, $J_{18,19} = 6.5$, $J_{19,21\alpha} < 0.5$, $J_{19,21\beta} < 0.5$, $J_{21\alpha,21\beta} = 12$

10: $J_{5\alpha,5\beta} = 12$, $J_{5\alpha,6\alpha} = 4$, $J_{5\alpha,6\beta} = 12$, $J_{5\beta,6\alpha} = 1$, $J_{5\beta,6\beta} = 5.5$, $J_{6\alpha,6\beta} = 15$, $J_{16,17} = 5$, $J_{16,17'} = 5$, $J_{17,17'} = 12$, $J_{18,19} = 6.5$, $J_{19,21\alpha} < 0.5$, $J_{19,21\beta} < 0.5$, $J_{21\alpha,21\beta} = 12$

[a] Acetate signals at 2.03 and 2.33 ppm.

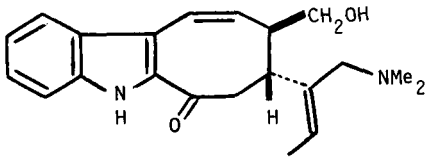
[b,c] Assignments may be reversed.

gave dihydrotaberpsychinemethine (**255,** MP 153–155°C), showing in its ^{1}H-NMR spectrum an ABMNX system for the H—C=C(H)—CH—CH_2O grouping at 6.69, 5.55, ~2.75, 4.21, and 3.79 ppm, respectively. A minor product was also isolated having structure **256** on the basis of the presence of a pair of doublets (4.98 and 5.63 ppm, J = 1 Hz), typical of a terminal methylene grouping.

Achenbach and Schaller have reported the isolation from the root bark of *T. accedens* of three monomeric alkaloids in addition to several bisindole alkaloids (*17*).

The first component was easily recognized as the N^1-methyl derivative **29** ($C_{21}H_{26}N_2O_2$, MP 208–210°C, $[\alpha]_D$ −243°) of 16-epiaffinine **28.**

The second compound (accedine, $C_{20}H_{24}N_2O_2$, MP 148–149°C, $[\alpha]_D$ +72°) showed no carbonyl absorption in the IR, and ^{1}H-NMR and mass spectra were in full agreement with the almost total existence of ring-closed carbinolamine structure **23.** The configuration at C-16 was determined by correlation with **32.** Reductive methylation (CH_2O–H_2/Pd) of **23** afforded **29,** which on $LiAlH_4$ reduction gave the diol **257** identical in all respects to the product obtained from



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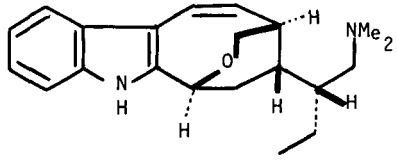
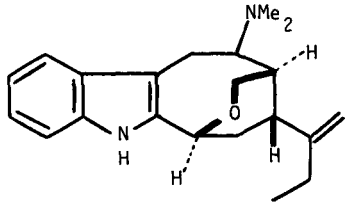


256

vobasine (**32**) by N^1-methylation, C-16 epimerization, followed by $LiAlH_4$ reduction. Additional proof of the configuration at C-16 resulted from the formation of cycloaccedine (**258,** MP 204–205°C, $[\alpha]_D$ +62°) on treatment with concentrated HCl (70°C, 24 hr).

The last monomeric alkaloid, N^1-demethyl-16-epiaccedine (**24,** $C_{19}H_{24}N_2O_2$, MP 170–172°C, $[\alpha]_D$ +50°), existed as an equilibrium mixture of carbinolamine and open-chain carbonyl forms in which the latter are present in amounts of ~10% in MeOH and 25% in chloroform. Hofmann degradation of **24** methiodide



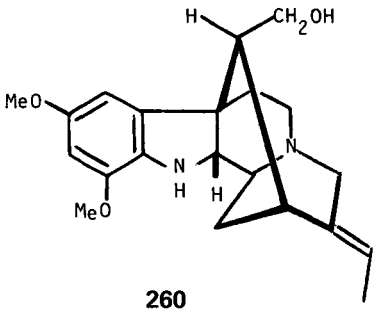
257

gave **259,** identical to the product obtained from affinine methiodide, thus establishing the stereochemistry at the double bond and the absolute configuration.

3. Akuammiline-Subtype Alkaloids

In the course of chemical investigation on *Tabernaemontana,* Achenbach *et al.* (*116*) isolated from *T. glandulosa,* from Sierra Leone and Nigeria, two new alkaloids, tabernulosine (**42**) and 12-demethoxytabernulosine (**43**).

Tabernulosine (**42,** $C_{22}H_{26}N_2O_5$, MP 190–191°C, $[\alpha]_D$ −27°) showed in the ^{1}H-NMR spectrum (180 MHz) signals for a CO_2Me, two meta-related methoxy groups, and an ethylidene system Me—CH=C . Another important feature was the presence of a downfield doublet (J = 2.5 Hz) at 4.78 ppm. Further detailed analysis of the ^{1}H-NMR spectrum by means of extensive decoupling experiments, led to evidence in the tabernulosine structure of the presence of a six-membered heteroring analogous to that in alkaloids from Picralima and Vinca plants. Structure **42** is in agreement with the CMR spectrum and, in particular, C-2 and C-5 resonate downfield (102.0 and 87.5 ppm, respectively), indicating the presence of an oxygen bridge. The position of the two methoxyls was established through comparison of aromatic carbon shifts with those of the model compounds, 4,6-dimethoxy- and 5,7-dimethoxy-2,3-dihydroindoles. The behavior of **42** toward reducing agents is noteworthy. Treatment with excess $LiAlH_4$ led to reductive elimination of the ether bridge, giving indoline **260,** while reduction with $NaBH_3CN$ afforded only **261.** Interestingly, $NaBH_4$ gave mainly



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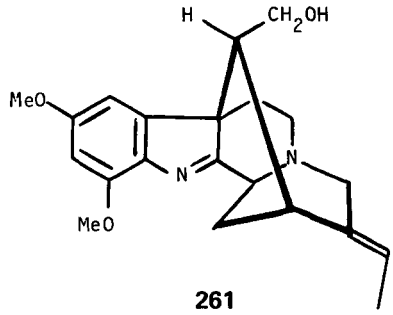

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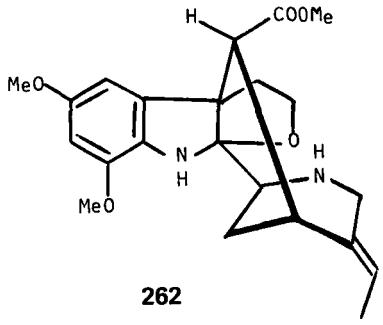
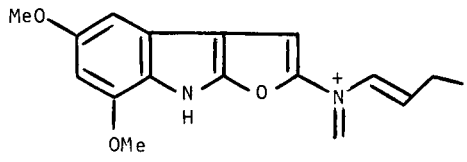


262

262, which contains an aspydodasycarpin ring system, as indicated by ^{1}H-NMR and mass spectroscopy.

On the basis of Klyne's rule (*188*) for the determination of the absolute configuration of aspidospermidine alkaloids, the positive Cotton effects [λ_{max} 252 ($\Delta\epsilon$ +0.66), 263 (+0.41), and 268 nm (+0.49)] suggested an absolute configuration at C-7 as shown in **42.** The mass spectrum of **42** exhibited a peculiar fragmentation pattern. In particular, the base peak at *m/z* 299 is formed via two different processes, leading to the formation of ions **263** and **264** in a 7:3 ratio.



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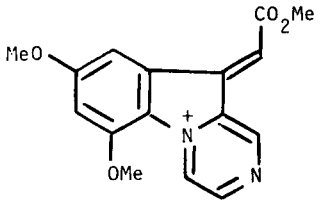


264

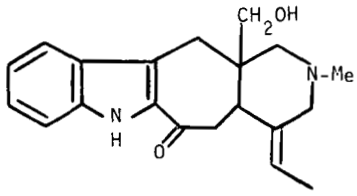
The minor component from *T. glandulosa* was shown to be 12-demethoxytabernulosine (**43**) on the basis of UV and ^{1}H-NMR spectra, which showed an aromatic pattern compatible with the presence of protons in the 1, 2, and 4 positions.

4. Ervatamine-Subtype Alkaloids

In 1971, Knox and Stobbe isolated, from *T. orientalis (Ervatamia orientalis),* ervatamine (**44,** $C_{21}H_{26}N_2O_3$, MP 98°C), 20-epi-ervatamine (**45,** $C_{21}H_{26}N_2O_3$, MP 187°C, $[\alpha]_D$ −22°), and 19,20-dehydroervatamine (**50,** $C_{21}H_{24}N_2O_3$, MP 200°C, $[\alpha]_D$ +53°C), which were the first examples of a novel class of 2-acylindole alkaloids, lacking the most common indolylethylamine moiety (*151*).

The structural relationship among the above alkaloids was indicated by catalytic hydrogenation of **50,** followed by mild CrO_3–pyridine oxidation. This led to a mixture containing **44** as the major product and **45.** The main work on structure elucidation was performed on **50,** and this involved an interesting combination of chemical degradation and spectroscopy.

The UV spectrum of **50** [λ_{max} 242 (log ϵ 4.11) and 315 nm (4.28)] and its IR spectrum (1650 cm^{-1}) were typical for that of an acylindole chromophore. In the ^{1}H-NMR spectrum, signals for the CO_2Me and NMe groups at 3.56 and 2.27 ppm, respectively, and an ethylidene grouping quartet at 5.44 ppm and a doublet at 1.58 ppm (J = 6.5 Hz) were observed. $LiAlH_4$ reduction of **50** gave a mixure of diols, which was converted to a single ketol (**265,** $C_{20}H_{24}N_2O_2$, $[\alpha]_D$ +67°)



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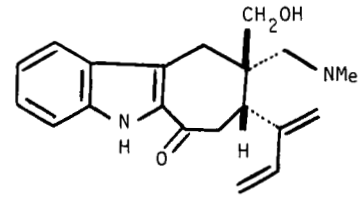

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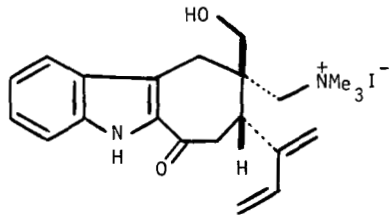

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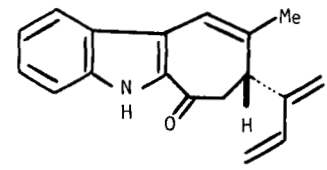

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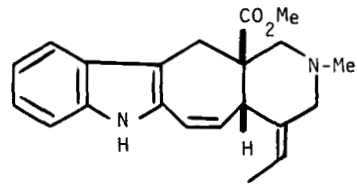


269

by a carefully controlled CrO_3–pyridine oxidation. The ^{1}H-NMR spectrum of the O-acetate of **265** indicated a clean AB system for the C-22 methylene, demonstrating that the CO_2Me group in **50** is on a quaternary carbon. In order to gain information about the skeleton, a Hofmann degradation sequence was envisaged. Reaction of **265** methiodide with *tert*-BuOK in *tert*-BuOH gave **266** ($C_{21}H_{26}N_2O_2$, MP 138°C, $[\alpha]_D$ +4°) via a vinylogous Hofmann elimination. This product had a new chromophore, which showed a broadened short wavelength UV absorption (230–240 nm) attributable to a diene chromophore. In the

^{1}H-NMR spectrum of **266,** the five vinylic protons gave rise to a dd at 6.30 ppm (J = 17.5 and 10.5 Hz), two doublets at 5.33 ppm (J = 10.5 Hz) and 5.10 ppm (J= 17.5 Hz), and two broadened singlets at 5.15 and 4.95 ppm.

Quaternization of **266** with MeI to give **267** proceeded slowly because of strong hydrogen bonding between the OH group and the N^4 atom. Hofmann elimation of **267** led to the neutral product **268** ($C_{18}H_{17}NO$, MP 141–144°C, $[\alpha]_D$ +255°), which is considered to arise from the loss of formaldehyde and Me_3N in a Grob fragmentation, followed by double bond isomerization [vinylic H-6 at 6.88 ppm and Me-5 at 2.06 ppm ($J \approx 1$ Hz)].

The conclusive information about the ring system in **50** was derived from $NaBH_4$ reduction, and subsequent smooth dehydration (glacial AcOH) to the α-vinylindole **269,** recognized by UV maxima (237 and 321 nm) and by the presence of two additional vinyl protons as separated dd at 6.44 ppm (J = 11.0 and 2.5 Hz) and at 5.52 ppm (J = 11.0 and 3.5 Hz).

The configurations of the stereo centers for ervatamine alkaloids were established by chemical correlations (*189, 190*) with the vobasine series and supported further by an X-ray diffraction study of **44** (*191*).

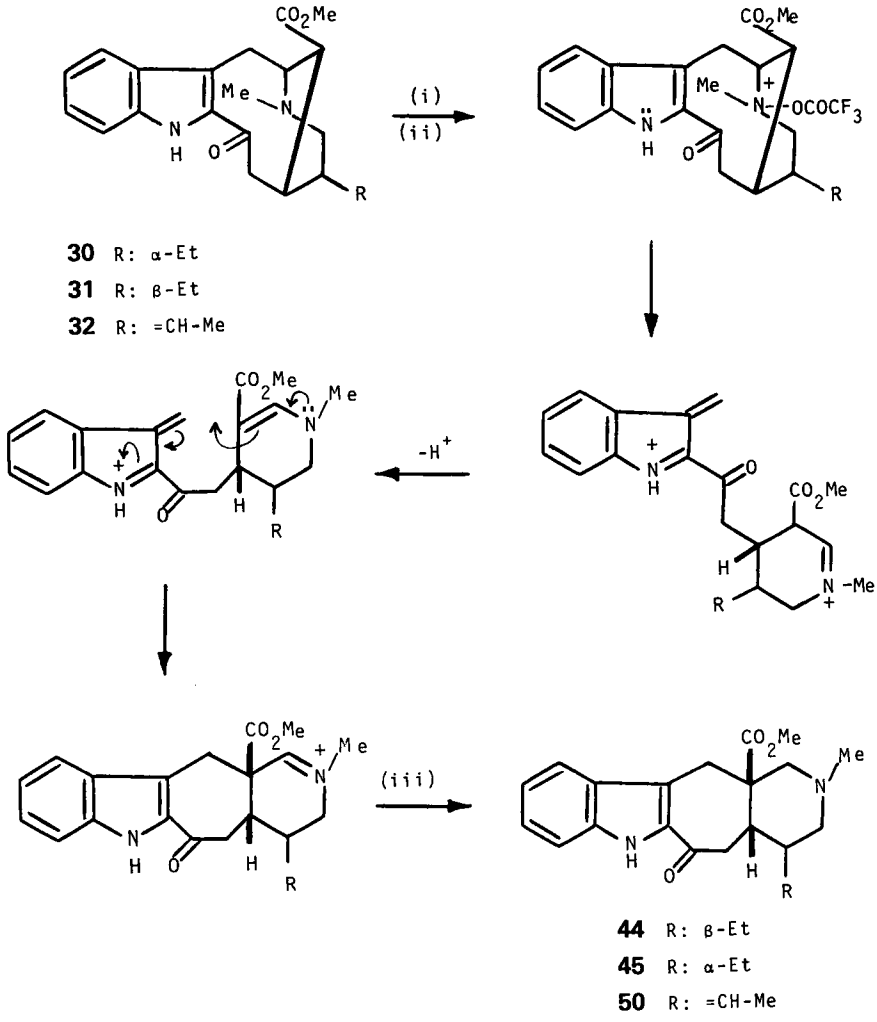
Laboratory transformations took advantage of fragmentation of dregamine (**30**), tabernaemontanine (**31**), and vobasine (**32**) as N^4 oxide induced by treatment with trifluoroacetic anhydride (Polonovski–Potier reaction) (*192*) and reductive capture of the intermediate iminium ion (Scheme 1).

The above sequence mimics the proposed biosynthesis of *Ervatamia* alkaloids and in this context Thal and Mansuy (*190*) set out to determine whether an enzyme preparation would be able to promote the same transformation. By incubation of dregamine hydrochloride with a suspension of liver microsomes from a rat pretreated with phenobarbital (as a good inducer of *P*-450 cytochromes) in the presence of NADPH and O_2, 20-epiervatamine (**45**) was formed together with the major metabolite N^1-demethyldregamine. It is well known that microsomal reaction on tertiary amines results in *N*-oxide formation or N-dealkylation. Thus it is likely that **45** was derived either from a rearrangement of dregamine N^4-oxide, catalyzed by the iron cytochrome *P*-450 or from one-electron oxidation of **30.**

Ervatamine (**44**) had a different conformation in solution with respect to **45** and **50.** This was deduced from the different rate of N-methylation and from a careful inspection of ^{1}H-NMR spectra. These studies led to proposed conformation **270** for **44** and conformations **271a,b** for **45** and **50,** respectively.

Some alkaloids of the ervatamine group lacking the ester group were isolated from various *Tabernaemontana (Hazunta)* species (Table I), but particularly from *T. coffeoides* (*67*). The structure of silicine (**46,** $C_{19}H_{24}N_2O$, MP 112°C, $[\alpha]_D$ −18°) rested on the identity with decarbomethoxy-20-epiervatamine, and the absolute configuration was established by X-ray crystallography (*193*).

Jones oxidation coverted **46** in good yield to 6-oxosilicine (**48,** $C_{19}H_{22}N_2O_2$,

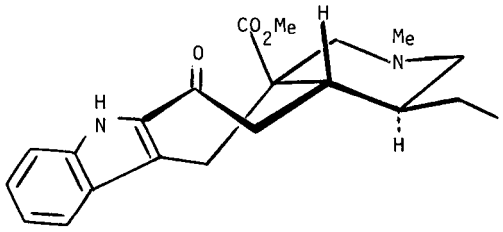


30 R: α-Et
31 R: β-Et
32 R: =CH-Me

44 R: β-Et
45 R: α-Et
50 R: =CH-Me

SCHEME 1. Reagents: (i) H_2O_2, $CHCl_3$, EtOH; (ii) TFAA, O°C; (iii) $NaBH_4$.

MP >260°C, $[\alpha]_D$ −40°), which is also a natural product from *T. coffeoides* (*67*). Its UV spectrum [λ_{max} 227(19200), 260(17700), and 335(13200) in acid solution] indicated a 2-acylindole chromophore perturbed by the presence of a carbonyl group in position 6. Its IR spectrum exhibited two carbonyl absorptions at 1670 and 1615 cm^{-1} for the carbonyl functions located at positions 3 and 6, respectively, while in the ^{1}H-NMR spectrum (pyridine-d_5) the aromatic proton H-9 was shifted downfield by the neighboring C-6 carbonyl.



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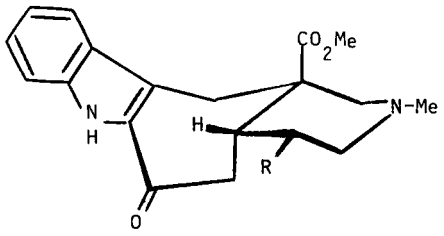


271a R: α-Et,β-H

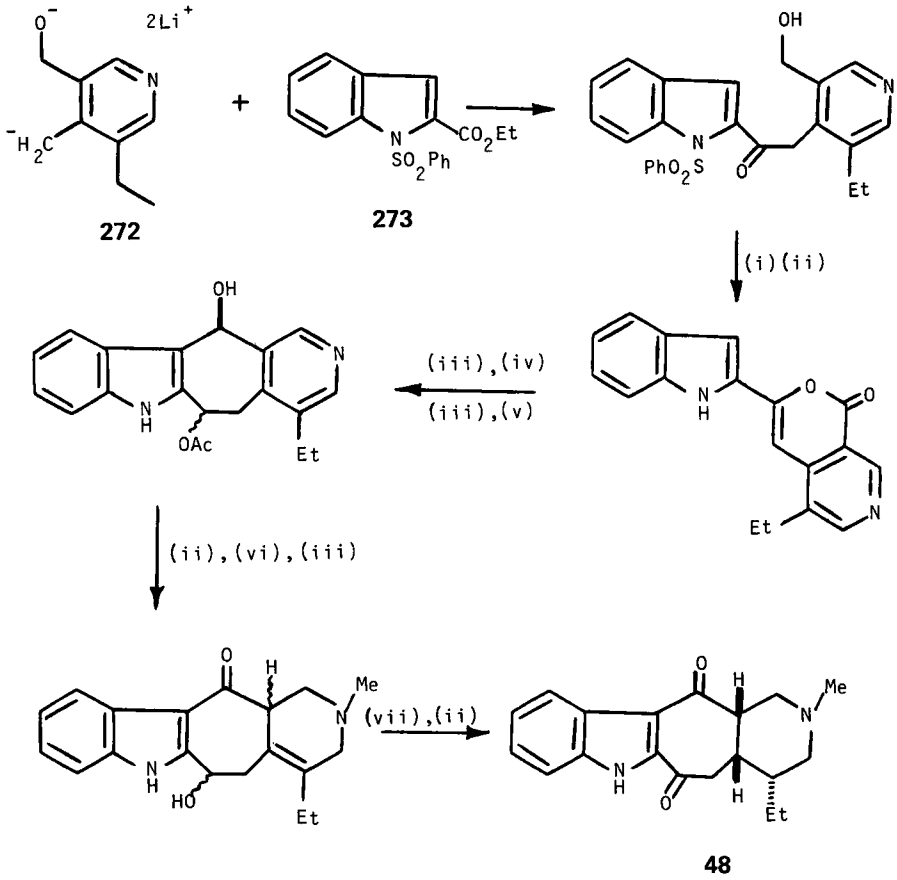
271b R: =CH-Me

Methuenine (**51,** $C_{19}H_{22}N_2O$, MP 205°C, $[\alpha]_D$ +21°) represented the 19,20-dehydro derivative of silicine, and its hydrogenation over the PtO_2 Adams catalyst, followed by CrO_3-pyridine oxidation gave, in fact, a mixture of silicine **46** and the natural 20-episilicine (**47,** $C_{19}H_{24}N_2O$, MP 190°C). The last compound gave the same mass spectrum as **46** but differed in the chemical shift of 18-methyl at 0.87 ppm versus 0.95 ppm in **46.**

Another natural compound, 6-oxomethuenine (**53,** $C_{19}H_{20}N_2O_2$, MP >260°C, $[\alpha]_D$ −15°), was obtained by Jones oxidation of **51** and gave the same UV spectrum as **48** in either acid or alkaline medium.

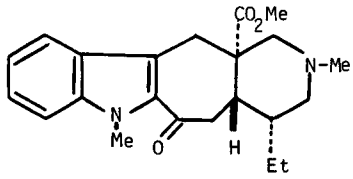
Isomethuenine (**52,** $C_{19}H_{22}N_2O$, $[\alpha]_D$ −178°) probably indicated as "Alkaloid M" by Potier *et al.* during the chemical investigation of several *Tabernaemontanae* (*67*), was recently isolated by Verpoorte *et al.* from *T. dichotoma* (*87*) and spectroscopically characterized.

The French group at Gif-sur-Yvette has paid great attention to the synthesis of ervataminelike alkaloids. The structure assigned to 6-oxosilicine has also been confirmed by Husson *et al.* (*194*) through total synthesis of the racemic compound. The first key step of this approach is the formation of the C-3—C-14 bond by acylation of the N,O-dilithiated species **272** with the N-protected carbomethoxyindole **273.** The second key step is the construction of ring C by alumina-induced intramolecular oxyalkylation of the indole β position by the



SCHEME 2. Reagents: (i) HO^-; (ii) MnO_2; (iii) $NaBH_4$; (iv) Ac_2O–pyridine; (v) alumina; (vi) MeI; (vii) PtO_2–H_2.

aldehyde function (Scheme 2). Interestingly, the overall stereochemistry is governed by cis reduction of a pyridinium intermediate. N^1-Methyl-16,20-epiervatamine (**274**) and 15,20-dehydroervatamine (**275**) has also been obtained through rather similar approaches (*194, 195*).



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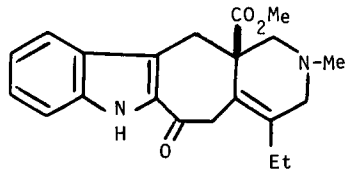

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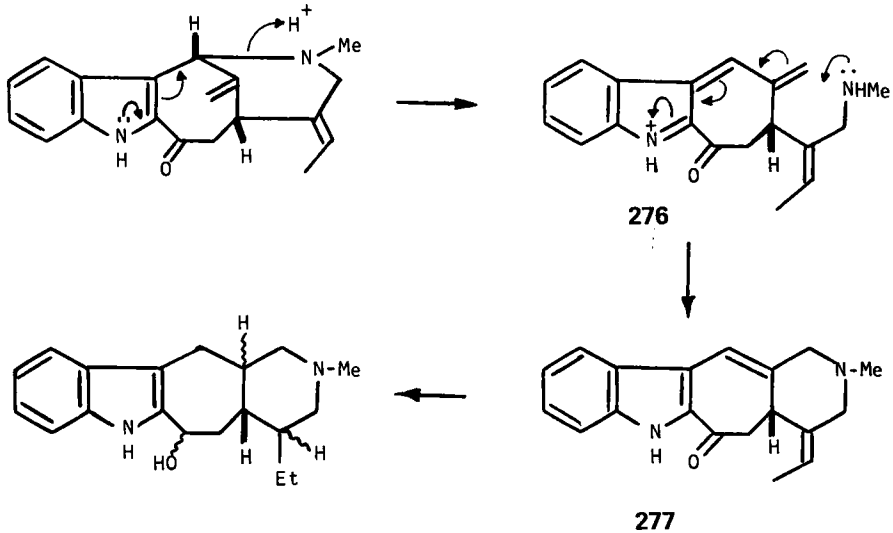
5. Ervitsine-Subtype Alkaloids

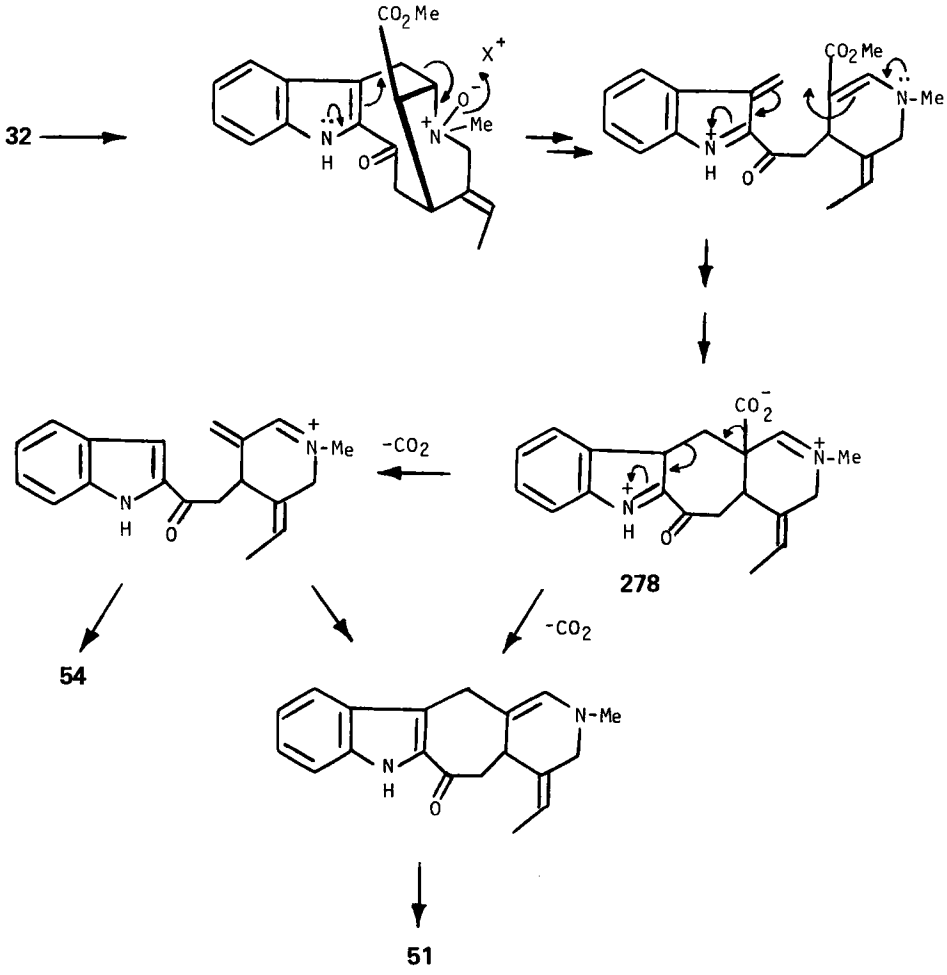
The root bark of *T. mocquerysii (Pandaca boiteaui)* was chemically investigated by Husson *et al.* (*146*) and was shown to contain, in addition to methuenine (**51**), a new acylindole alkaloid belonging to a novel structural class. It was named ervitsine (**54,** $C_{19}H_{20}N_2O$, MP 176–177°C, $[\alpha]_D$ −160°C) and gave a UV spectrum (λ_{max} 236 and 318 nm) analogous to that of a 2-acylindole. Its ^{1}H-NMR spectrum indicated the presence of an ethylidene grouping with signals at 1.63 (3H) and 5.30 ppm (1H) coupled with J = 7Hz, a single NMe group at 2.30 ppm, an isolated proton at 5.16 ppm, and an unusual exocyclic methylene group displaying singlets at 5.03 and 5.17 ppm. The structure of **54** was determined by X-ray analysis and corroborated by an interesting chemical correlation with methuenine (**51**). In fact, by acid treatment (50% AcOH, 24 hr at reflux) **54** undergoes a retro-Mannich fragmentation to form the intermediate **276,** which can recyclize to give 5,16-dehydromethuenine (**277**). Hydrogenation of the latter gave a mixture of three epimers, one of which was identical with that obtained by similar hydrogenation of **51** (Scheme 3).

Although there is no *in vivo* correlation, the cooccurrence of **51** and **54** in *T. mocquerysii* suggests **278** as a reasonable common intermediate formed by vobasine (**32**) (Scheme 4) through its N^4-oxide or other biological equivalent(s).

So far, only the ring system of ervitsine has been synthesized. Exploiting the regiospecific alkylation of a 2-cyano-3-piperideine derivative **279,** Husson *et al.* (*196*) obtained **280,** whose stereochemistry was determined by X-ray analysis (Scheme 5).



SCHEME 3

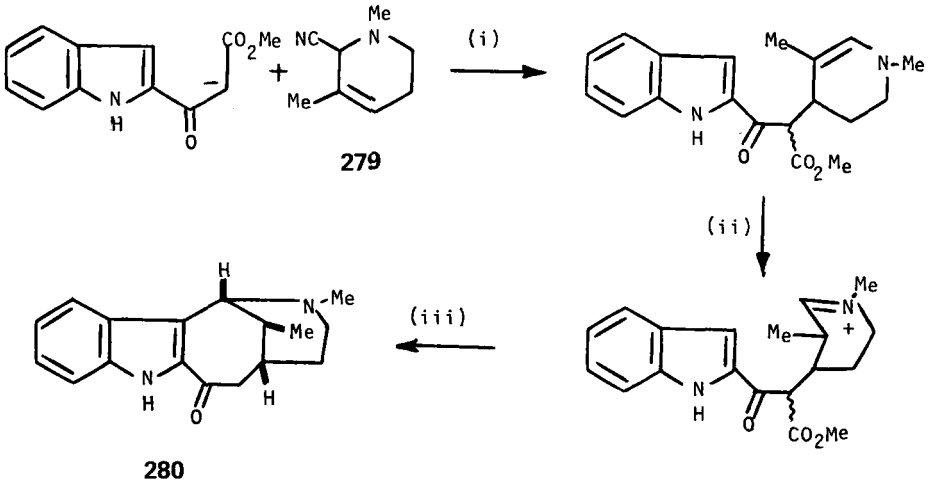


SCHEME 4

B. PLUMERAN-TYPE ALKALOIDS

1. Voaphylline-Subtype Alkaloids

From the seeds of *T. dichotoma,* Verpoorte *et al.* (*88*) isolated voaphylline hydroxyindolenine (**90,** $C_{19}H_{24}N_2O_2$) by preparative TLC. Because the solution of voaphylline (**87**) in chloroform always shows the presence of an extra spot in the TLC of the 7-hydroxyindolenine derivative, **90** is probably an artifact of the isolation procedure. Furthermore, the fully assigned 300-MHz ^{1}H-NMR spectrum of **90,** compared with that of voaphylline (**87**) is reported. The relative



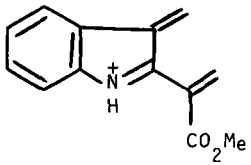
SCHEME 5. Reagents: (i) $AgBF_4$, THF; (ii) pTSA, PhMe; (iii) AcOH–H_2O–H_2SO_4.

stereochemistry in **90**, deduced by X-ray diffraction study (*197*), represents the absolute stereochemistry since $NaBH_4$ reduction of **90** led to **87**.

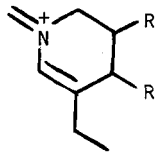
2. Tabersonine-Subtype Alkaloids

Among plumeran alkaloids isolated from the leaves of *T. coffeoides (Hazunta modesta)*, two minor compounds were not previously discussed (*70*). One was recognized as 3-oxotabersonine (**68**, $C_{21}H_{22}N_2O_3$, MP 151.5–153°C, $[\alpha]_D$ −77.4°) identical to the product isolated by Sakai from the seeds of *Amsonia elliptica* (*198*). Compound **68** was also obtained in 32% yield by $KMnO_4$ oxidation of tabersonine (**67**).

The second alkaloid ($C_{21}H_{26}N_2O_4$) was recovered in very small amount and shown to belong to the tabersonine subtype from the UV absorptions (β-anilinoacrylic chromophore) and from the peaks at *m/z* 156 (**281**) and 214 (**282**) in its MS. On acetylation, a diacetate (M^+ · 454) was formed and the peak at *m/z* 156 was shifted 84 amu to *m/z* 240 (**283**). These data are compatible with a 14,15-dihydroxyvincadifformine structure (**76**) for this compound; however,



m/z 214 (**282**)



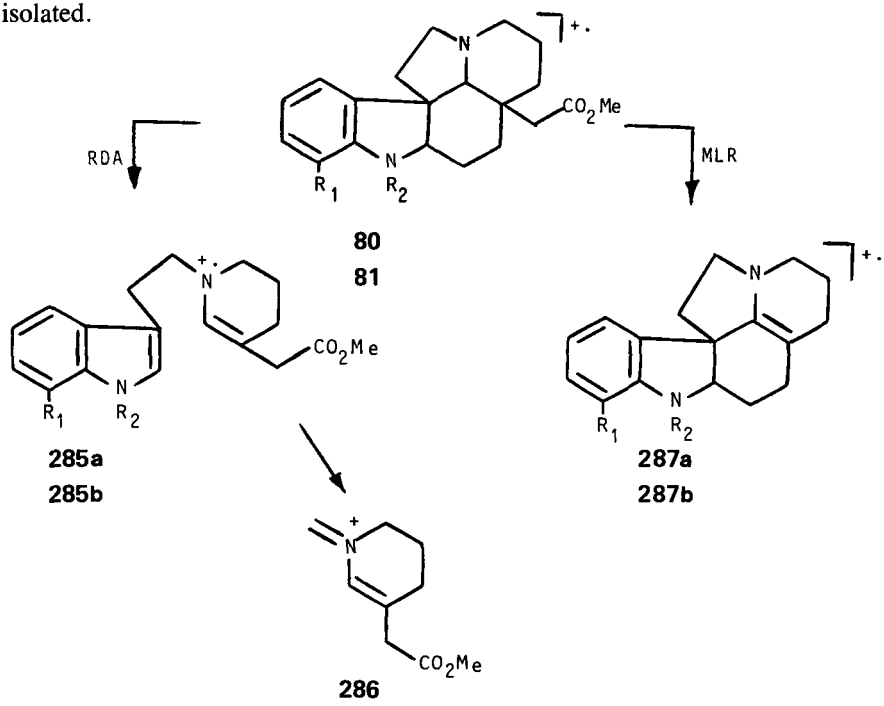
m/z 156 (**281**) R:OH
m/z 240 (**283**) R:OAc
m/z 124 (**284**) R:H

paucity of material prevented the determination of stereochemistry at C-14 and C-15.

12-Hydroxyvincadifformine (**71**, $C_{21}H_{26}N_2O_3$, $[\alpha]_D$ −427°) was isolated from *T. siphilitica (Bonafousia tetrastachya)* and characterized by the presence of a base peak at *m/z* 124 (**284**) in the mass spectrum and by comparison of the CMR spectrum with that of vincadifformine (**70**) (*179*).

In addition to the previously discussed cylindrocarpidine (**79**, $C_{23}H_{30}N_2O_4$, MP 120–121.5°C, $[\alpha]_D$ −122°), the root bark of *T. amygdalifolia* has also afforded two novel *N*-acylindolines: 12-demethoxycylindrocarpidine (**80**, $C_{22}H_{28}N_2O_3$, $[\alpha]_D$ −49°) and homocylindrocarpidine (**81**, $C_{24}H_{32}N_2O_4$, $[\alpha]_D$ −82° (*33*). Their structures were based mainly on high-resolution mass spectra. Besides fragments **285a,b** (retro Diels-Alder fragmentation, RDA) and **286**, typical for plumeran alkaloids, the two compounds gave ions **287a,b** by loss of $H_2C{=}C(OH)OMe$ (McLafferty rearrangement, MLR) (Scheme 6). Compound **81** was obtained by propionylation of N^1-deacetylcylindrocarpidine, thus establishing the position of the methoxy group and the absolute configuration.

Plumeran alkaloids containing a lactone ring are present only in *T. apoda* from Cuba (*43*). In addition to apodine (**24**), a novel alkaloid of structure **86** ($C_{21}H_{22}N_2O_5$) assigned on the basis of mass spectroscopic studies, has been isolated.



SCHEME 6. a: R_1 = H; R_2 = COMe. b: R_1 = H; R_2 = COEt.

C. Ibogan-Type Alkaloids

1. Coronaridine-Subtype Alkaloids

Coronaridine subtype alkaloids are widely spread in *Tabernaemontana*. The iboga skeleton is particularly susceptible to oxidation at aminomethylenes C-3 and C-5 and at benzylic C-6. Very often, the fundamental compounds are accompanied by the oxidation products at these positions.

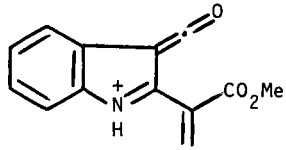
a. Coronaridine Derivatives. 3-Hydroxycoronaridine (**103,** $C_{21}H_{26}N_2O_3$, oil, $[\alpha]_D$ −68°) has been isolated from many *Tabernaemontanae* (Table I), and its structure was deduced from its mass spectrum and confirmed by $NaBH_4$ reduction to **97.** On the analogy with other 3-hydroxy iboganes (see below), **103** is a mixture of epimers and can be obtained by iodine-mediated oxidation of coronaridine (**97**).

Achenbach and Raffelsberger (*114*) isolated from *T. glandulosa* an amorphous alkaloid ($C_{23}H_{30}N_2O_3$, $[\alpha]_D$ −59°), which was identified as 3-ethoxycoronaridine (**104**) on the basis of its hydrolysis to **103.** This compound was considered to be a true natural compound and not an artifact. From its ^{1}H-NMR spectrum, **104** was shown to be a 17:3 mixture of C-3 epimers.

3-Oxocoronaridine (**105,** $C_{21}H_{24}N_2O_3$, MP 140° $[\alpha]_D$ −27°) is relatively widespread in *Tabernaemontanae* (Table I) and it was obtained by mild oxidation (Corey reagent) to **103.** The fully assigned ^{1}H-NMR spectrum of **105** has also been reported (Table IV).

A new amorphous alkaloid has been recently isolated from the Chinese plant *T. bufalina (Ervatamia hainanensis)* collected on Hainan Island (*53*). Its mass spectrum showed a molecular ion at *m/z* 382, corresponding to $C_{23}H_{30}N_2O_3$. From the fragmentation pattern, this compound would appear to be a coronaridine derivative in which a C_2H_5O unit is attached to the aliphatic moiety of the molecule. The structure **111** with (*S*) configuration at C-3 was determined by a detailed analysis of its ^{1}H-NMR spectrum (Table IV) in comparison with the data of other ibogan alkaloids.

Two other closely related alkaloids from the root bark of *T. divaricata* were studied by Rastogi *et al.* and shown to be isomeric with 3-oxocoronaridine (*99*). The first compound (MP 272–275°C, $[\alpha]_D$ −10.7°) displayed in its ^{1}H-NMR spectrum an AB system centered at 3.91 ppm (J = 15 Hz). This was indicative of



m/z 228 **(288)**

TABLE IV

^{1}H-NMR DATA FOR ALIPHATIC PROTONS OF CORONARIDINE (**97**) (*28*), 3-OXOCORONARIDINE (**105**) (*53*), (3*S*)-3(β-HYDROXYETHYL)CORONARIDINE (**111**) (*53*), 18-HYDROXYCORONARIDINE (**128**) (*28*), AND HEYNEANINE (**122**) (*28*)

	Chemical shifts (ppm)				
Proton	**97**	**105**	**111**[e]	**128**	**122**
H_R-3[a]	2.90 br d	—	—	2.94 br d	2.98 br d
H_S-3[a]	2.80 br d	—	2.75 br d	2.78 br d	2.81 br d
H_R-5[b]	3.4 m	4.5 m	3.45 m	3.4 m	3.45 m
H_S-5[b]	3.2 m	3.3 m	3.35 m	3.2 m	3.15 m
H_R-6[c]	3.15 m	3.2 m	3.2 m	3.15 m	3.1 m
H_S-6[c]	3.0 m	3.1 m	3.0 m	3.05 m	3.05 m
H-14	1.89 m	2.01 m	1.73 m	1.95 m	2.03 m
H_R-15	1.73 br dd	1.63 m	1.58 m	1.68 m	1.56 br dd
H_S-15	1.14 br dd	1.77 m	1.32 m	1.82 m	1.92 br dd
H_R-17[d]	1.91 br d	2.32 br d	1.92 br d	1.97 br d	1.98 br d
H_S-17[d]	2.58 br d	2.64 br d	2.67 br d	2.60 br d	2.60 br d
H-18	0.89 t	0.98 t	0.91 t	3.68 m	1.10 d
H-18′	—	—	—	3.80 m	—
H-19	1.45 dq	1.44 dq	1.48 dq	1.83 m	4.17 br q
H-19′	1.55 dq	1.54 dq	1.60 dq	1.83 m	—
H-20	1.33 br dt	1.42 m	1.36 br dd	1.47 br dd	1.47 br dd
H-21	3.54 d	4.51 d	3.70 d	3.62 d	3.86 d
CO_2Me	3.70 s	3.73 s	3.75 s	3.73 s	3.73 s
NH	7.75 br s	7.96 br s	7.75 br s	7.86 br s	7.83 br s

Coupling constants (Hz)

97: $J_{3R,3S} = 9$, $J_{3R,14} = 3$, $J_{3S,14} = 3$, $J_{14,17R} = 3$, $J_{14,17S} = 3$, $J_{15R,15S} = 12.5$, $J_{15R,20} = 10$, $J_{15S,20} = 5$, $J_{17R,17S} = 12$, $J_{18,19} = 7$, $J_{18,19'} = 7$, $J_{19,20} = 7$, $J_{19',20} = 7$, $J_{20,21} < 0.2$

105: $J_{14,17R} = 3$, $J_{14,17S} = 3$, $J_{15R,15S} = 12$, $J_{17R,17S} = 12$, $J_{18,19} = 7$, $J_{19,20} = 7$, $J_{19',20} = 7$, $J_{20,21} < 0.2$

111: $J_{3S,14} = 3$, $J_{14,17R} = 3$, $J_{14,17S} = 3$, $J_{15R,15S} = 12$, $J_{15R,20} = 10$, $J_{15S,20} = 5$, $J_{17R,17S} = 12$, $J_{18,19} = 7$, $J_{19,20} = 7$, $J_{19',20} = 7$, $J_{20,21} < 0.2$

128: $J_{3R,3S} = 9$, $J_{3R,14} = 3$, $J_{3S,14} = 3$, $J_{14,17R} = 3$, $J_{14,17S} = 3$, $J_{15R,15S} = 12.5$, $J_{15R,20} = 10$, $J_{15S,20} = 5$, $J_{17R,17S} = 12$. $J_{18,18'} = 12$, $J_{20,21} < 0.2$

122: $J_{3R,3S} = 9$, $J_{3R,14} = 3$, $J_{3S,14} = 3$, $J_{14,17R} = 3$, $J_{14,17S} = 3$, $J_{15R,15S} = 12.5$, $J_{15R,20} = 10$, $J_{15S,20} = 5$, $J_{17R,17S} = 12$, $J_{18,19} = 7$, $J_{19,20} = 7$, $J_{20,21} < 0.2$

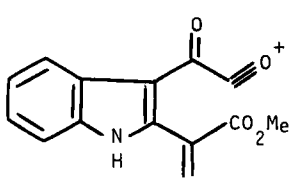
[a,b,c,d] Assignments may be reversed.

[e] CH(OH)-Me, 3.57 m; CH(OH)Me 1.17 d.

a 5-oxocoronaridine structure (**112**), and, in fact, it could be isolated in 5% yield by $KMnO_4$ oxidation of **97.** The second alkaloid (MP 262–267°C, $[\alpha]_D$ −33.8°) had a structurally diagnostic peak in its mass spectrum at *m/z* 228, attributable to ion **288.** The structure of 6-oxocoronaridine as **113** was further supported by the finding, in addition to the signals at 3.88 and 3.09 ppm (J = 12 Hz) for diastereotopic C-3H_2, of an AB system at 3.33 and 1.80 ppm. These signals are due to C-5H_2 protons and the high-field occurrence of one of these is determined by the shielding effect of C-6 carbonyl.

Further oxidation products of **97** are 3,6-oxidocoronaridine (eglandine) (**129,** $C_{21}H_{24}N_2O_3$, $[\alpha]_D$ −57°) and 6-hydroxy-3-oxocoronaridine (eglandulosine) (**115,** $C_{21}H_{24}N_2O_4$, $[\alpha]_D$ −71°) isolated from *T. eglandulosa* (*102*) and *T. sessilifolia (Muntafara sessilifolia)* (*174*).

Another variant in the oxidation pattern of coronaridine is furnished by 5-hydroxy-6-oxocoronaridine (**114,** $C_{21}H_{24}N_2O_4$, MP 285–288°, $[\alpha]_D$ +43.8°). The UV spectrum (λ_{max} 218, 248, and 310 nm) exhibited the characteristic bathochromic shift of a 3-acylindole on addition of alkali. Diagnostically important fragment ions occurred at *m/z* 256($C_{14}H_{10}NO_4$), 230 ($C_{13}H_{12}NO_3$), and 202 ($C_{12}H_{12}NO_2$) corresponding to structures **289, 290,** and **291,** respectively. The



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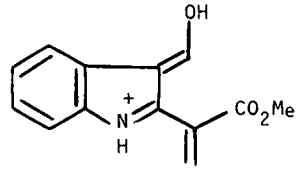

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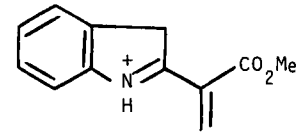

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^{1}H-NMR spectrum of **114** is characterized by the presence of a singlet at 5.26 ppm (H-5) and an "AB quartet" centered at 3.32 ppm (J = 12 Hz) for C-3H_2. Furthermore, H-9 appeared to be shifted at 8.77 ppm because of the neighboring carbonyl group (*99*).

A rare and biogenetically interesting example of the ethyl chain functionalization of the iboga skeleton is represented by 18-hydroxycoronaridine (albifloranine) (**128,** $C_{21}H_{26}N_2O_3$, MP 192–194°C, $[\alpha]_D$ −210°) isolated from *T. albiflora* (*28*). The base peak in its mass spectrum appeared at *m/z* 323 (M^+ · −31), and this suggested that a hydroxy group was present at C-18. A detailed ^{1}H-NMR study of **128** in comparison with **97** and heyneanine (**122**) was reported and shown in Table IV.

Finally, two phenolic derivatives of coronaridine were isolated: 10-hydroxycoronaridine (**98,** $C_{21}H_{26}N_2O_3$) from the wood and stem bark of *T. heyneana (Ervatamia heyneana)* (*128*) and 11-hydroxycoronaridine (**99,** amorphous, $[\alpha]_D$ −34°) from *T. attenuata* (*47*). Both gave characteristic UV spectra with bathochromic shifts on addition of alkali, in agreement with the proposed

TABLE V

^{13}C-NMR CHEMICAL SHIFTS OF CORONARIDINE (**97**) (*47*, *199*), 11-HYDROXYCORONARIDINE (**99**) (*47*), HEYNEANINE (**122**) (*199*), 19-EPIHEYNEANINE (**123**) (*199*), AND TABERNOXIDINE (**155**) (*129*)

	97	**99**	**122**	**123**	**155**
C-2	136.5[a]	136.4	136.5[a]	135.9[a]	180.2
C-3	53.1	51.5	52.1[b]	52.0[b]	47.0
C-5	51.5	53.1	51.1[b]	50.9[b]	52.5
C-6	22.2	22.0	21.3	21.6	29.9
C-7	110.3	110.0	110.7	109.6	50.3
C-8	128.8	123.1	129.5	128.4	123.4
C-9	118.3	119.1	119.3	118.3	124.9
C-10	119.0	109.2	119.3	120.3	105.6
C-11	121.8	152.2	123.2	122.1	159.4
C-12	110.3	96.5	111.4	110.4	95.7
C-13	135.6[a]	135.0	136.3[a]	135.6[a]	142.9
C-14	27.2	27.3	26.7	26.0	25.8
C-15	32.0	31.9	22.9	28.6	25.1
C-16	55.1	54.9	56.8	54.1	49.9
C-17	36.3	36.2	36.8	36.5	25.3
C-18	11.6	11.6	20.2	22.1	21.3
C-19	26.6	26.6	72.3	70.7	70.1
C-20	38.9	39.1	39.5	40.2	40.3
C-21	57.2	57.6	59.7	54.7	50.3
CO_2Me	175.9, 52.4	—, 52.6	175.7, 52.8	174.8, 52.6	174.0, 51.5, 55.0 (OMe)

[a,b] In any vertical column, signals with the same superscript may be reversed.

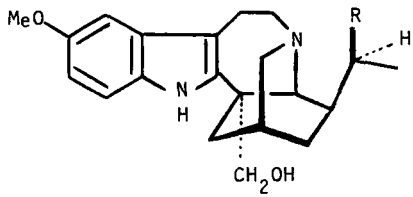
structures. The aromatic proton pattern was, for **98**, H-9 at 6.87 ppm, H-11 at 6.68 ppm, H-12 at 7.20 ppm, and for **99**, H-9 at 7.23 ppm, H-10 at 6.60 ppm, and H-12 at 6.75 ppm. In the case of **99**, the structure was corroborated by comparison of CMR data with those of coronaridine (**97**) (Table V) (*199*).

b. Voacangine Derivatives. Among derivatives of voacangine (**100**), isolated from *Tabernaemontana* species, 3,6-oxidovoacangine (10-methoxyeglandine) (**131**), its N^4-oxide (**132**), and 3,19-oxidovoacangine (heyneatine) (**133**) are to be mentioned.

3,6-Oxidovoacangine ($C_{22}H_{26}N_2O_4$, amorphous) gave a mass spectrum quite similar to that of voacangine (**100**), with the diagnostic presence of the peak at *m/z* 368 [$M^{+\cdot} - 14$], reminiscent of the behavior of other 3,6-oxidoiboga alkaloids such as eglandine (**129**). The methoxy group was located at C-10 from ^{1}H-NMR data (*101*).

The corresponding N^4-oxide (**132**, $C_{22}H_{26}N_2O_5$, $[\alpha]_D$ +86.6°) isolated from *T. heyneana (Ervatamia heyneana)* shows loss of 16 amu from $M^{+\cdot}$ and subsequent fragmentation similar to that of other 3,6-oxidovoacangines (*128*). Skeletal

assignment was substantiated by the observation of a dd at 4.11 ppm (J = 8.8 and 7.2 Hz) for H-6 and by $LiAlH_4$ reduction to afford **292.**



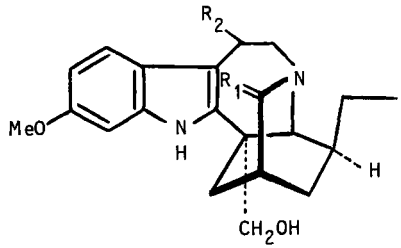
292 R:H

293 R: OH

A unique member of the 3,19-oxide derivative group within iboga alkaloids is represented by heyneatine (**133,** $C_{22}H_{26}N_2O_4$, $[\alpha]_D$ −6°), isolated from *T. heyneana* (*128*). The similarity of its UV spectrum and aromatic portion with that of **100** indicated a 10-methoxyindole chromophore. A doublet (3H) at 1.12 ppm and a singlet (1H) at 4.0 ppm suggested that an ether bridge connects C-19 and C-3. $LiAlH_4$ reduction of **133** afforded **293,** whereas $NaBH_4$ treatment yielded voacristine [(19*S*)-voacangarine] (**118**), confirming the carbinolamine–ether substitution at C-3 and C-19. Heyneatine is thus (19*S*)-3,19-oxidovoacangine.

c. Isovoacangine Derivatives. 3-Hydroxyisovoacangine (**107,** $C_{22}H_{28}N_2O_4$, M.P. 159–160°C, $[\alpha]_D$ −80±24°) was isolated by Hesse *et al.* from *T. eglandulosa* as a 12:1 mixture of the two 3-epimers (*103*). It was deeply investigated from a spectroscopic and chemical point of view. Reaction with acetone formed 3-(2′-oxopropyl)isovoacangine, while $NaBH_4$ reduction gave **101,** which could in turn be oxidized to **107** by I_2 in benzene.

Two new 3,6-difunctionalized isovoacangines were found in *T. sessilifolia* (*174*). The major compound (**116,** $C_{22}H_{26}N_2O_5$, amorphous, $[\alpha]_D$ −55°) had in its mass spectrum fragments from the aliphatic portion similar to those of **115,** whereas fragments from the indole moiety were shifted 30 amu. $LiAlH_4$ reduction



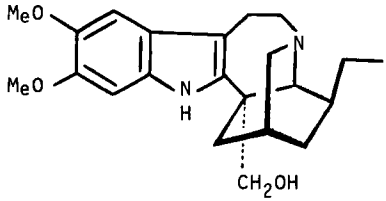
294 R_1: H_2; R_2: H

295 R_1: O; R_2: H

296 R_1: O; R_2: OH

gave isovoacanginol (**294**) besides the corresponding 3-oxo derivative (**295**) and 3-oxo-6-hydroxyisovoacanginol (**296**), thus confirming the location of a methoxy group at C-11. The structure of (6*R*)-3,6-oxidoisovoacangine (**130,** MP 162°C, $[\alpha]_D$ −57°) was assigned to the minor component of *T. sessilifolia* on the anology with spectroscopic data of **101** and on formation of **294** by $LiAlH_4$ reduction.

d. Conopharyngine Derivatives. Two derivatives of conopharyngine oxygenated at C-3 have been reported. 3-Oxoconopharyngine (**109,** $C_{23}H_{28}N_2O_5$, MP 284–286°C, $[\alpha]_D$ −48 ± 2°), was known since 1968 and isolated from *T. crassa (Conopharyngia jollyana)* in 0.01% yield (*80*). $LiAlH_4$ reduction furnished conopharyngol (**297**), identical to the product obtained from **102.** Decarbomethoxylation of **109** gave the corresponding 3-oxoibogaline derivative **298** (MP 253–254°C), which was subsequently reduced with $LiAlD_4$ to give ibogaline-3-d_2. The location of the deuterium label was established by comparison of the mass spectrum of this compound with that of ibogaine-3-d_2 of known structure.



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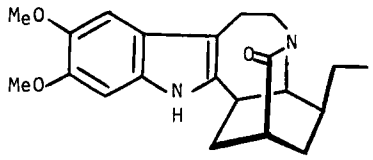

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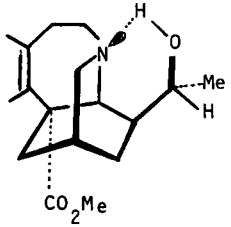
An accurate chemical investigation of the root and stem bark of *T. pachysiphon* from Nigeria gave an amorphous alkaloid, ($C_{23}H_{30}N_2O_5$, $M^{+\cdot}$ 414), showing a single spot on TLC in all of the solvents used (*160*). Its UV spectrum [λ_{max} 223, 273 (sh), 285 (sh), 302, 306, and 311 nm (sh)] is fairly characteristic for a 10,11-dimethoxyindole. Mass spectral behavior with the concomitant presence of $M^{+\cdot}$, $[M-2]^{+\cdot}$, $[M-16]^{+\cdot}$, and $[M-18]^{+\cdot}$ suggested that this compound might be 3-hydroxyconopharyngine (**110**). In its ^{1}H-NMR spectrum, the most characteristic signals were a broad singlet ($W_{\frac{1}{2}}$ 6 Hz) integrating for 0.4H at 4.43 ppm and a doublet (J = 1.6 Hz) for 0.6H (H-3). These data suggested that **110** was actually a mixture of (3*R*) and (3*S*) isomers in a 3:2 ratio. As final proof of the correctness of this assignment, **110** afforded **102** as the sole product upon $NaBH_4$ reduction.

e. 19-Hydroxy Derivatives of Iboga Alkaloids. 19-Hydroxycoronaridine (**122,** $C_{21}H_{26}N_2O_3$, MP 162°C, $[\alpha]_D$ −19°), known as heyneanine, is a widespread alkaloid in *Tabernaemontana* (Table I). Its 19-epimer (**123,** MP 170–172°C, $[\alpha]_D$ −46°) was also isolated from many *Tabernaemontanae* (Table I). The only appreciable difference in the spectroscopic features was the resonance

of 18-Me at 1.28 ppm and H-19 at 3.88 ppm versus 1.11 and 4.13 ppm in **122.** Chemical correlation established the identity of the carbon skeleton. In fact, reduction of the O-tosyl derivative of **123** with $LiAlH_4$ gave the corresponding alcohol, coronaridinol, as the major product. The difference in the above chemical shift originates from the locking of the side chain in a fixed conformation by the intramolecular hydrogen bond whose existence was ascertained through the invariance of the IR band at 3470 cm^{-1} on dilution in chloroform. Thus, depending on the C-19 configuration, the substituents (H, Me) and C-19 are exposed to two possible environments, **299** and **300** for **123** and **122,** respectively. In the (19*R*) series, C-18H_3 undergoes a deshielding effect of the N^4-lone pair, while in the (19*S*) series, H-19 experiences this effect. An additional support to this assignment comes from the analysis of the CMR spectrum of **123** and **122** in comparison with that of **97** (Table V). The most characteristic feature of these spectra was the downfield shift of C-15 and the upfield shift of C-21 in 19-epiheyneanine (**123**) versus heyneanine (**122**). This is cleanly explained by the shielding effect of the differently oriented Me groups in the fixed conformation.

Potier *et al.* isolated two phenolic derivatives of heyneanine from *T. attenuata*



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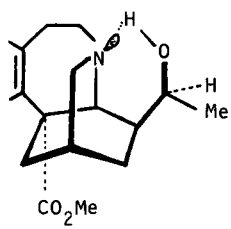

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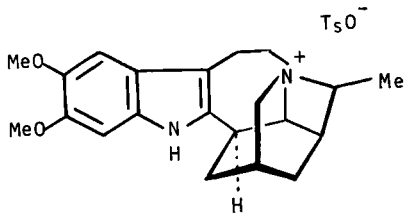


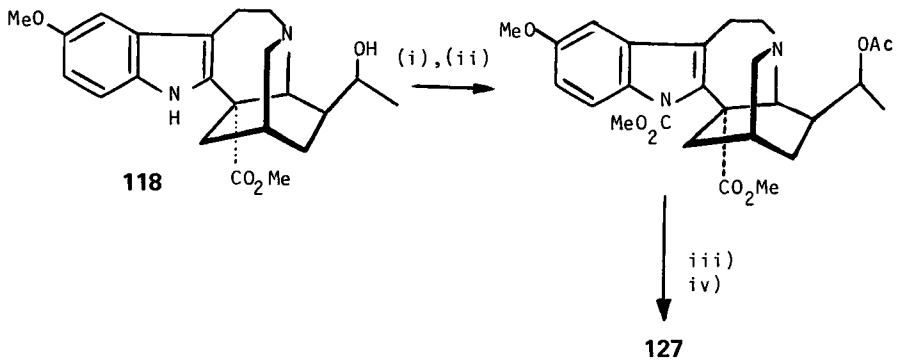
301

(Anartia meyeri) from French Guiana. 10-Hydroxyheyneanine (**125,** $C_{21}H_{26}N_2O_4$, $[\alpha]_D$ −16.6°) and 11-hydroxyheyneanine (**126,** $[\alpha]_D$ −22°) were characterized from their ^{1}H-NMR spectra and CMR data (*47*). Compound **125** was also isolated from *T. bufalina* (*53*).

In addition to other conopharyngine derivatives, *T. crassa* contained 19-hydroxyconopharyngine (**121,** $[\alpha]_D$ −36.4°) (*77, 79*). Decarbomethoxylation of **121,** induced by hydrazine hydrate, followed by treatment with tosyl chloride in pyridine, gave the aziridinium salt **301,** MP 217–220°C. Finally, $LiAlH_4$ reduction of **301** gave ibogaline (**137**), whereas $LiAlD_4$ treatment afforded ibogaline-*19-*d_2. Mass spectral data showed that the deuterium label was located on C-19, thus the OH group in **121** is linked to C-19.

3-Oxovoacristine (**127,** MP 251–252°C, $[\alpha]_D$ −35.5°) was recently isolated by Kutney *et al.* from *T. citrifolia* from Cuba (*64*). The structure was based on the usual spectroscopic properties (^{1}H-NMR and MS) and unambiguously proved by its synthesis from voacristine (**118**) as shown in Scheme 7.

Other examples of 19-hydroxy alkaloids are (19*R*)-19-hydroxyibogamine



SCHEME 7. Reagents and conditions: (i) Ac_2O, pyridine, room temp; (ii) KH, THF, O°C, $ClCO_2Me$; (iii) I_2, $NaHCO_3$, H_2O–C_6H_6; (iv) 1% KOH MeOH, room temp.

(**138,** $C_{19}H_{24}N_2O$, MP 172–174°C, $[\alpha]_D$ −28°) from *T. quadrangularis* (*168*), while from *T. humblotii (Pandaca ochracens)* besides ibogaine **135** and ibogaline **137,** the respective (19*R*)-hydroxy derivatives, 19-epiiboxygaine (**140**) and 19-epiiboxygaline (**141**) have been isolated (*130*). Compound **138** was known before its isolation as a degradation product of 19-epiheyneanine (**123**). The position of the hydroxy group and the configuration at C-19 in **140** were determined by ^1H NMR and chemical correlation to ibogaine (**135**) and ibogaline (**137**), respectively.

2. Coronaridine Hydroxyindolenine- and Iboluteine-Subtype Alkaloids

Another position of facile oxidation of the iboga skeleton is C-7, and very often these alkaloids are accompanied by the corresponding 7-hydroxyindolenines and by the products of further rearrangement to 3-oxoindoles (pseudoindoxyls). Both compounds are fairly well characterized by typical UV absorptions. 7-Hydroxyindolenines are formed by aeration of a chloroform solution of the alkaloids and by action of other mild oxidizing agents. This led to the common opinion that they are artifacts formed by the autoxidation of chloroform solutions during the isolation procedures. However, some 7-hydroxyindolenines were obtained in the absence of chlorinated solvents, and this makes the distinction very subtle between natural and isolated artifactual alkaloids.

Up to now, six 7-hydroxyindolenines were isolated from *Tabernaemontana* species (Table I): coronaridine hydroxyindolenine (**142,** $C_{21}H_{26}N_2O_3$, MP 113–117°C, $[\alpha]_D$ −8°), voacangine hydroxyindolenine (**143,** $C_{22}H_{28}N_2O_4$, MP 134–135°C, $[\alpha]_D$ +133.2°), voacristine hydroxyindolenine (**144,** $C_{22}H_{28}N_2O_5$, MP 179°C, $[\alpha]_D$ −22°), conopharyngine hydroxyindolenine (jollyanine) (**145,** $C_{23}H_{30}N_2O_3$, MP 161–163°C, $[\alpha]_D$ −56°), ibogaine hydroxyindolenine (**146,**

$C_{20}H_{26}N_2O_2$, MP 149°C, $[\alpha]_D$ +74°), and iboxygaine hydroxyindolenine (**147**, $C_{20}H_{26}N_2O_3$, MP 223°C, $[\alpha]_D$ +111°.

Iboga alkaloids devoid of the 19-hydroxy group are significantly more stable toward oxidation than are the corresponding hydroxy bases. Abstraction of the hydroxy proton of 7-hydroxyindolenines by bases leads to concomitant carbon migration and formation of pseudoindoxyls. In some cases the rearrangement is better accomplished by warm HCl. The interrelationship among indoles, 7-hydroxyindolenines, and pseudoindoxyls has been exhaustively treated by Cordell (see Ref. *6*).

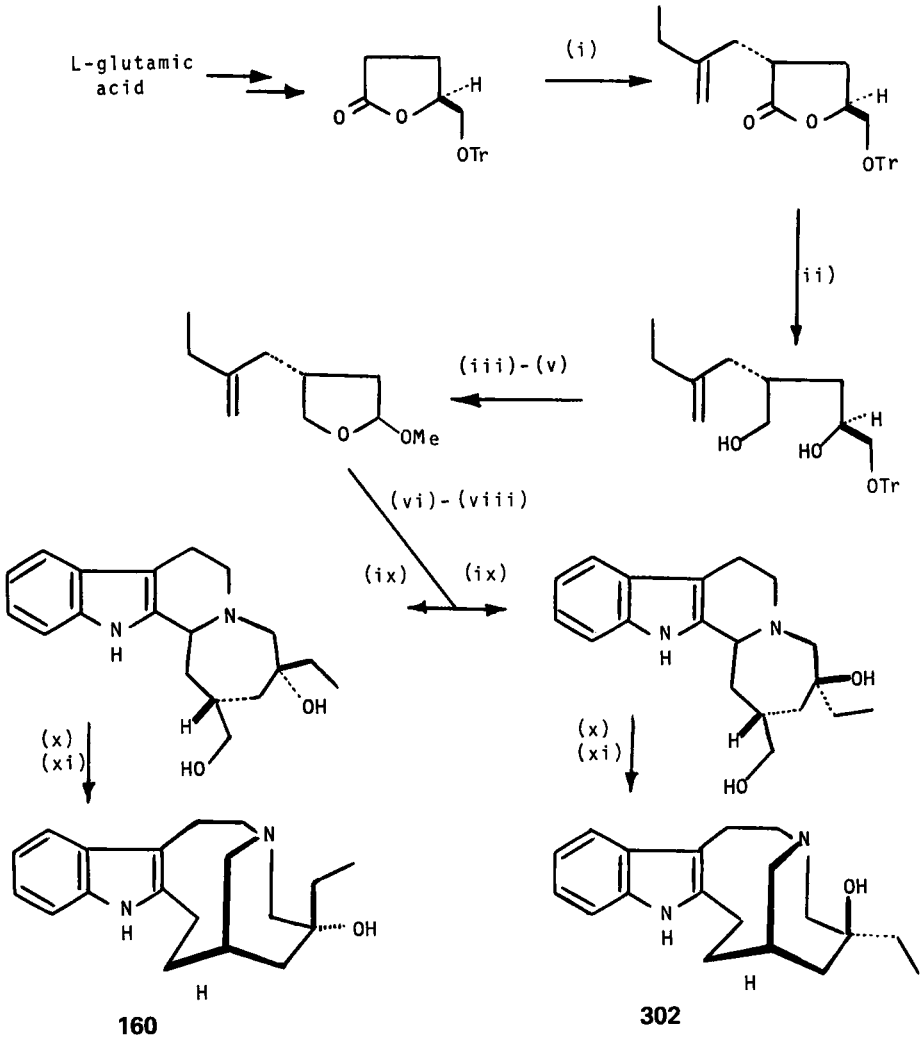
3. Tabernoxidine (**155**)

Only three examples of ibogan-type oxindole alkaloids are known, and two of them, crassanine (**156**) and tabernoxidine (**155**), were found in *Tabernaemontana*. Crassanine ($C_{23}H_{30}N_2O_5$, MP 191°C, $[\alpha]_D$ +21°) was isolated in minute amounts by Cava *et al.* from *T. crassa* (*79*). Its IR spectrum indicated the presence of two carbonyl groupings (1739 and 1709 cm^{-1}), while its UV spectrum was almost superimposable on that of known 10,11-dimethoxyoxindoles such as kisantine (*200*). In addition to the carbomethoxy methyl at 3.47 ppm and two aromatic methoxyls at 3.83 ppm (6H), the ^{1}H-NMR spectrum of **156** exhibited two singlets (1H) at 6.50 and 7.01 ppm and the low-field oxindole NH at 9.30 ppm. The latter values are similar to those recorded for kisantine, and on this basis Cava *et al.* proposed the structure **102** for crassanine. To date, no evidence is available on the configuration at the C-7 spiro center.

Recently, tabernoxidine (**155**, $C_{21}H_{28}N_2O_5$, MP 291–292°C) was isolated from *T. heyneana* (*129*). Its UV spectrum displayed maxima at 220, 258, 286, and 293 nm, indicating an oxindole chromophore. Its ^{1}H-NMR spectrum suggested a 1,2,4-trisubstituted benzene ring and contained two methoxy signals at 3.78 and 3.43 ppm, a doublet (J = 6.5 Hz) at 1.06 ppm, and a methine proton at 4.10 ppm assigned to a CHCH(OH)Me grouping. The latter values are those expected for a (19*S*) configuration [cf. heyneanine (**122**)]. The CMR spectrum of **155** is reported in Table V. The structure with relative stereochemistry (shown in formula **155**) was established by a single-crystal X-ray analysis, and for the first time the configuration at the spiro center of an ibogan oxindole was determined. Crystallographic data confirmed both the intramolecular bond (2.71 Å) between C-19-OH and the bridgehead N^4 and the previously portrayed spatial distribution of groups for **122.**

4. Cleavamine-Subtype Alkaloids

(14*S*, 20*R*)-Velbanamine (**160**, $C_{19}H_{26}N_2O$, (M^+ · 298), λ_{max} 287 nm) was isolated from leaves and twigs of *T. eglandulosa* (*105*). The minute amounts of material precluded spectroscopic examination. The structure and stereochemistry



SCHEME 8. Reagents and conditions: (i) 2-ethylallyl bromide, LDA; (ii) $LiAlH_4$, THF; (iii) MeOH–HCl; (iv) $NaIO_4$, MeOH; (v) $HC(OMe)_3$, pTSA, MeOH; (vi) mCPBA, CH_2Cl_2; (vii) tryptamine, 160°C, MeOH, sealed tube; (viii) aq. AcOH; (ix) silica gel chromatography; (x) MsCl, pyridine, O°C; (xi) Na, liq. NH_3.

of **160** were ascertained only by direct comparison with an authentic sample of (−)-velbanamine, enantioselectively synthesized by Takano and Ogasawara (*201*), starting from L-glutamic acid and thus having a (14*S*, 20*R*) configuration. This elegant approach is outlined in Scheme 8 and was also suitable for the synthesis of (+)-isovelbanamine (**302**).

Racemic 15,20-dihydrocleavamines (**157** and **158**) were obtained by the same

authors through an adaptation of their earlier approach to quebrachamine (*202*). The CMR spectra of **157, 158,** and **160** have been discussed in comparison to those of other cleavamines and dihydrocleavamines bearing a carbomethoxy substituent at C-16 (*203*). This study allowed the determination of the preferred conformation of the monocyclic azocyclononane and the piperidine ring.

5. Pseudotabersonine-Subtype Alkaloids

Two new pseudotabersonine-related alkaloids were isolated by Husson *et al.* from the stem bark of *T. albiflora* from French Guiana (*29*) and characterized as (20*R*)-18,19-dihydroxypseudovincadifformine (**166,** $C_{21}H_{26}N_2O_4$, MP 190°C, $[\alpha]_D$ +264°) and 19-hydroxy-20-epipandoline (**167,** $C_{21}H_{26}N_2O_4$, MP 204°C, $[\alpha]_D$ +511°. Both compounds exhibited similar UV maxima attributed to a β-anilinoacrylic chromophore, and their mass spectra showed, in addition to a molecular ion at *m/z* 370, a base peak at *m/z* 156 formed by retro-Diels–Alder fragmentation in ring C, followed by C-6—C-5 bond cleavage.

Structures **166** and **167** were deduced from a detailed analysis of 400-MHz ^{1}H-NMR spectra in comparison with that of the known pandoline **164** and 20-epi-pandoline **165** (Table VI). The assigned chemical shifts and coupling constants for all protons were in agreement with the relative stereochemistry represented in **166** and **167,** only the configuration at C-19 being undetermined. The orientation of the two-carbon chain at C-20 in **166** was deduced from the coupling constant values of H-20, while the same chemical environment at C-20 in **167** and **165** was suggested by the similar shift of surrounding H-21, H-15, and H-3. Compounds **166** and **167** exhibited a strong positive optical rotation and therefore they belonged to the same steric series as pandoline and 20-epipandoline.

Tabernaemontana eglandulosa is a small liane distributed in the forests of central Africa. The root bark yielded many coronaridine-subtype alkaloids, whereas the leaves afforded the already discussed (14*S*, 20*R*)-velbanamine (**160**), some new pseudotabersoninelike alkaloids, and many other structurally new compounds discussed later.

One of the main alkaloids was (20*R*)-1,2-dehydropseudoaspidopermidine (**168**) (*105*), having an indolenine UV chromophore (λ_{max} 221, 265, and 330 nm) and a mass spectrum with a base peak at *m/z* 137, analogous to that of (20*S*)-1,2-dehydropseudoaspidospermidine (**169**), previously isolated from *T. eusepala* (*109*) and *T. mocquersii* (*147*). The ^{1}H-NMR spectrum at 300 MHz of **168** was compared with that of the closely related (20*S*)-hydroxy-1,2-dehydro-pseudoaspidospermidine (**171**) from the same plant (see below). An accurate analysis allowed the determination of the chemical shifts and coupling constants of most of the protons, except H-14, H-15, H-19, and H-20, and indicated that the conformation of all of the rings was the same as in **171.** In order to determine the C-20 configuration, it was necessary to measure the coupling constants of

TABLE VI

^{1}H-NMR DATA FOR ALIPHATIC PROTONS OF PANDOLINE (**164**) (*29*), 20-EPIPANDOLINE (**165**) (*29*), (20*R*)-18,19-DIHYDROXYPSEUDOVINCADIFFORMINE (**166**) (*29*), 19-HYDROXY-20-EPIPANDOLINE (**167**) (*29*), AND (20*S*)-HYDROXY-1,2-DEHYDROPSEUDOASPIDOSPERMIDINE (**171**) (*105*)

	Chemical shifts (ppm)				
Proton	**164**	**165**	**167**	**166**	**171**
H-3	2.89 d	3.05 d	3.02 d	2.94 d	2.82 dd
H-5α	2.95 ddd	2.90 ddd	2.90 ddd	2.98 ddd	3.18 ddd
H-5β	2.79 ddd	2.77 ddd	2.77 ddd	2.67 ddd	2.88 ddd
H-6α	2.06 ddd	2.00 ddd	1.98 ddd	1.98 ddd	2.31 ddd
H-6β	1.81 ddd	1.78 ddd	1.77 ddd	1.79 ddd	1.82 ddd
H-14	1.52 m	1.52 m	1.53 m	1.56 m	1.53 ddddd
H-15α	1.87 br d	1.92 br d	1.87 br d	1.68 br d	1.83 ddd
H-15β	1.58 dd	1.67 dd	1.72 dd	1.88 ddd	1.41 ddd
H-16	—	—	—	—	2.97 ddd
H-16′	—	—	—	—	2.78 ddd
H-17α	2.59[a] m	2.41 dd	2.25 dd	2.47 dd	2.52 dddd
H-17β	2.61[a] m	2.48 dd	2.47 dd	2.53 dd	1.75 ddddd
H-18	0.96 t	0.98 t	1.27 d	3.58 dd	0.97 t
H-18′	—	—	—	3.73 dd	—
H-19	1.47 br q	1.75 br q	4.17 br q	3.87 m	1.77 dq
H-19′	1.54 br q	1.85 br q	—	—	1.96 dq
H-20	—	—	—	1.80 m	—
H-21α	2.98 d	3.12 d	3.48 d	3.36 dd	3.12 dd
H-21β	2.57 d	2.57 d	2.44 d	2.73 dd	2.36 d
CO_2Me	3.77 s	3.76 s	3.75 s	3.77 s	—
NH	8.94 br s	8.90 br s	8.88 br s	8.91 br s	—

Coupling constants (Hz)

164: $J_{3,14} = 4$, $J_{5\alpha,5\beta} = 10$, $J_{5\alpha,6\alpha} = 6$, $J_{5\alpha,6\beta} = 0.5$, $J_{5\beta,6\alpha} = 12.5$, $J_{5\beta,6\beta} = 5$, $J_{6\alpha,6\beta} = 12.5$, $J_{14,15\alpha} = 2.5$, $J_{14,15\beta} = 6$, $J_{14,17\alpha} = 12$, $J_{14,17\beta} = 5$, $J_{15\alpha,15\beta} = 15$, $J_{17\alpha,17\beta} = 14$, $J_{18,19} = 7$, $J_{18,19'} = 7$, $J_{19,19'} = 14$, $J_{21\alpha,21\beta} = 12$

165: $J_{3,14} = 4$, $J_{5\alpha,5\beta} = 10$, $J_{5\alpha,6\alpha} = 6$, $J_{5\alpha,6\beta} = 0.5$, $J_{5\beta,6\alpha} = 12.5$, $J_{5\beta,6\beta} = 5$, $J_{6\alpha,6\beta} = 12.5$, $J_{14,15\alpha} = 2.5$, $J_{14,15\beta} = 6$, $J_{14,17\alpha} = 12$, $J_{14,17\beta} = 5$, $J_{15\alpha,15\beta} = 15$, $J_{17\alpha,17\beta} = 14$, $J_{18,19} = 7$, $J_{18,19'} = 7$, $J_{19,19'} = 14$, $J_{21\alpha,21\beta} = 12$

167: $J_{3,14} = 4$, $J_{5\alpha,5\beta} = 10$, $J_{5\alpha,6\alpha} = 6$, $J_{5\alpha,6\beta} = 0.5$, $J_{5\beta,6\alpha} = 12.5$, $J_{5\beta,6\beta} = 5$, $J_{6\alpha,6\beta} = 12.5$, $J_{14,15\alpha} = 2.5$, $J_{14,15\beta} = 6$, $J_{14,17\alpha} = 12$, $J_{14,17\beta} = 5$, $J_{15\alpha,15\beta} = 15$, $J_{17\alpha,17\beta} = 14$, $J_{18,19} = 7$, $J_{21\alpha,21\beta} = 12$

166: $J_{3,14} = 4$, $J_{5\alpha,5\beta} = 10$, $J_{5\alpha,6\alpha} = 6$, $J_{5\alpha,6\beta} = 0.5$, $J_{5\beta,6\alpha} = 12.5$, $J_{5\beta,6\beta} = 5$, $J_{6\alpha,6\beta} = 12.5$, $J_{14,15\alpha} = 2.5$, $J_{14,15\beta} = 6$, $J_{14,17\alpha} = 12$, $J_{14,17\beta} = 5$, $J_{15\alpha,15\beta} = 15$, $J_{15\alpha,20} = 2.5$, $J_{15\beta,20} = 6$, $J_{17\alpha,17\beta} = 14$, $J_{18,18'} = 11$, $J_{18,19} = 7$, $J_{18',19} = 4$, $J_{19,20} = 7$, $J_{20,21\alpha} = 3$, $J_{20,21\beta} = 5$, $J_{21\alpha,21\beta} = 12$

171: $J_{3,14} = 2.9$, $J_{3,17\beta} < 1$, $J_{5\alpha,5\beta} = 8.4$, $J_{5\alpha,6\alpha} = 6.7$, $J_{5\alpha,6\beta} = 2$, $J_{5\beta,6\alpha} = 11.4$, $J_{5\beta,6\beta} = 4.8$, $J_{6\alpha,6\beta} = 12.1$, $J_{14,15\alpha} = 1.9$, $J_{14,15\beta} = 5.6$, $J_{14,17\alpha} = 12.9$, $J_{14,17\beta} = 5.6$, $J_{15\alpha,15\beta} = 13.6$, $J_{15\alpha,21\alpha} = 1.8$, $J_{15\beta,19} = 0.5$, $J_{16\alpha,16\beta} = 15.4$, $J_{16\alpha,17\alpha} = 11.0$, $J_{16\alpha,17\beta} = 3.7$, $J_{16\beta,17\alpha} = 6.5$, $J_{16\beta,17\beta} = 9.9$, $J_{17\alpha,17\beta} = 12.2$, $J_{18,19} = 7.5$, $J_{18,19'} = 7.5$, $J_{19,19'} = 14.8$, $J_{21\alpha,21\beta} = 10.5$

[a] Assignment may be reversed.

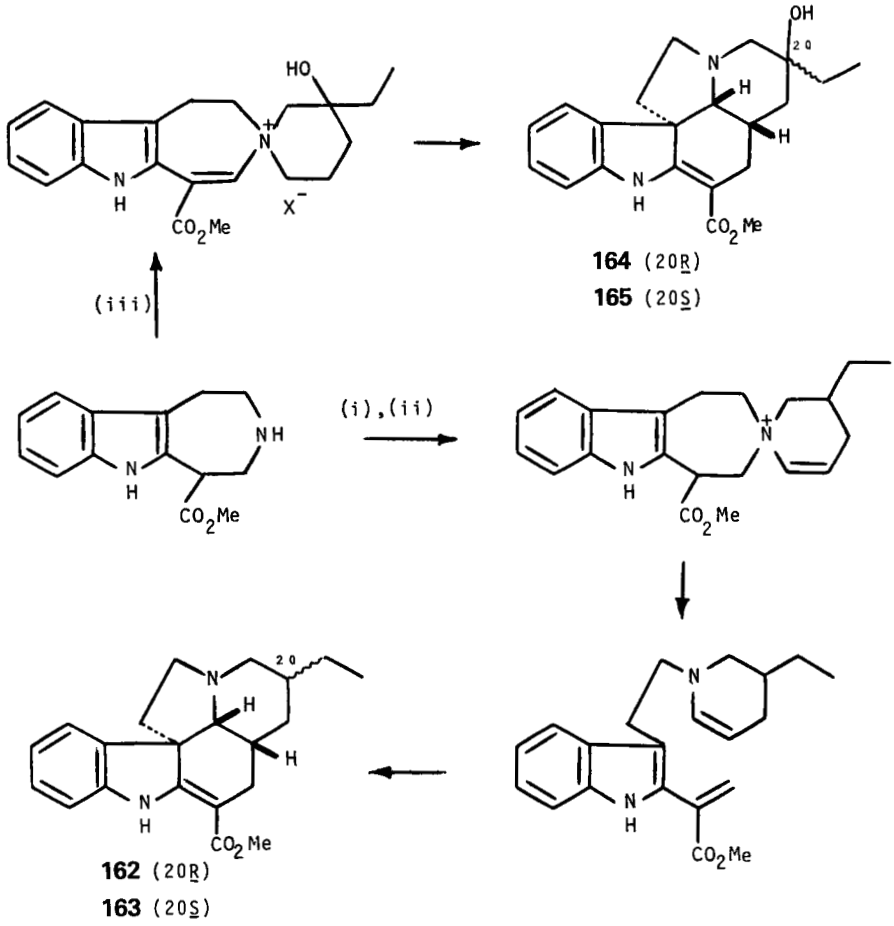
H-21α and H-21β with H-20. However, these signals were obscured by H-16α and H-17α, respectively. On the assumption that H-16α and H-17α have the same shift, shape, and spectral width in **168** and **171,** the signals of the latter were subtracted by means of a computer from the mixed signals of H-16α and H-21α, and H-17α and H-21α in the spectrum of **168.** The resulting pattern indicated that H-21α is a broad doublet (J_{gem} = 11 Hz, $W_{1/2}$ 4.5 Hz) and that H-21β is a dd (J = 11 Hz, $W_{1/2}$ 3.9Hz). From these values it could be deduced that H-20 is β-equatorially oriented. In the opposite α-axial orientation, H-21α would have appeared as a ddd with J ~11, 3.5, and 1.6 Hz and H-21β as a dd (J = 11 Hz). The absolute configuration of (20*R*)-1,2-dehydropseudoaspidospermidine depicted in **168** is based on the positive optical rotation as in the previously isolated (20*S*) epimer **169**.

The minor alkaloid (20*S*)-hydroxy-1,2-dehydropseudoaspidospermidine (**171,** $C_{19}H_{24}N_2O$), with similar UV spectrum as **168,** had almost all of the mass peaks shifted 16 amu, suggesting the presence of an additional oxygen atom in the molecule (*105*). The lack of signal below 3.2 ppm ruled out the presence of an oxymethine proton and suggested that OH is on a quaternary carbon, most likely C-20 as in several indole alkaloids of this group (e.g., pandolines, velbanamines). The ^{1}H-NMR resonances at 300 MHz were assigned by means of homonuclear decoupling experiments (Table VI). From the coupling constants, particularly those between H-3 and H-14 (J = 2.9 Hz) and between H-15α and H-21α (J = 1.8 Hz, "W" path), the authors deduced that **171** had a ring C and D conformation identical to that of pandoline **164** and 20-epipandoline (**165**). As a consequence, the configuration at C-20 could be determined by the shift of diastereotopic C-19H_2, taking advantage of the large difference between H-19 and H-19′ resonances in **164** and **165.** These protons were found in **171** at 1.77 and 1.96 ppm, indicating the same (20*S*) configuration as in **165.** From the similarity of CD spectra, **171** was shown to have the same absolute configuration as that of **168** and of other pseudoaspidosperidines from *Tabernaemontana* species.

Tabernaemontana eglandulosa gave also a very small amount of a mixture of the known (20*R*)-pseudovincadifformine (**162**) and its new (20*S*) epimer **163.** The amount isolated was too small for a separation of the epimers, and they were recognized by comparison of the spectral data (^{1}H NMR) with those of a racemic mixture of **162** and **163,** synthesized by Kuehne (Scheme 9). (*204*).

Treatment of an indoloazepine ester with 4-(bromomethyl)hexanal, followed by addition of triethylamine at 40°C, afforded a mixture of *rac*-**162** and *rac*-**163** in the same ratio as the natural mixture, indicating a possible common intermediate. The same reaction scheme with 4-ethyl-4,5-epoxypentanal gave a 1:1 mixture of *rac*-**164** and *rac*-**165.**

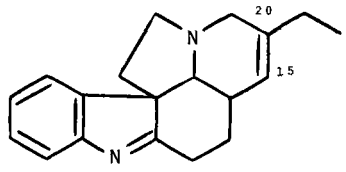
In addition to monomeric capuronine (**159**), capuronidine (**170**), and other dimeric alkaloids, Husson *et al.* isolated from *T. capuronii (Capuronetta ele-*



SCHEME 9. Reagents and conditions: (i) $BrCH_2CH(Et)CH_2CHO$, MeOH; (ii) NEt_3, 40°C; (iii) CH_2—C(Et)CH_2CHO (O), N_2, MeOH, reflux.

gans) two minor amorphous pseudoaspidospermidine alkaloids, namely, 14,15-anhydrocapuronidine (**172,** $C_{19}H_{22}N_2$, $[\alpha]_D$ −54°) and its 1,2-dihydro derivative (**173,** $C_{19}H_{24}N_2$) (*57*).

Compound **172** exhibited typical indolenine UV absorptions and mass spectral fragmentation very similar to those of 15,20-anhydrocapuronidine (**303**), obtained by concentrated H_2SO_4 dehydration of **170.** Upon reduction with $NaBH_4$, the indolenine **172** was converted to its 1,2-dihydro derivative, identical to the natural product **173.** Catalytic hydrogenation gave a tetrahydro derivative, characterized by a peak at *m/z* 190 in the mass spectrum, typical of pseudoaspidospermatane alkaloids.

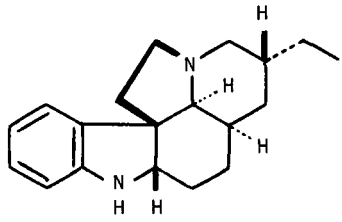


303

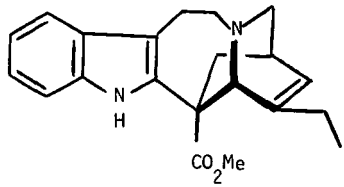
The ^{1}H-NMR spectrum showed a multiplet a 5.77 ppm for the olefinic proton, a singlet at 3.62 ppm for the aminomethine C-3, a triplet at 0.95 ppm for the methyl, and an octet at 1.29 ppm for the methylene of the ethyl chain. Irradiation of the latter signal was crucial for the structure delucidation because it allowed the detection of a quintet for H-20 at 3.50 ppm. As a consequence, the double bond could not be located between C-15 and C-20, and, moreover, the chemical shift of C-19H_2 was too far upfield compared with the same signal in pseudotabersonine (**161**). Irradiation of H-20 resulted only in the simplification of the C-19H_2 signal to a quartet and in a slight modification of the multiplet at 3.23 ppm (C-21H_2). No modification of the H-15 signal was observed, suggesting a quasi-orthogonal relationship between the two protons.

A chemical correlation with other known alkaloids was impossible; however, the cooccurrence with **159** and **170** gave the presumption of the same absolute stereochemistry for **172** and **173.**

Finally, the last new alkaloid belonging to this subtype was found in *T. mocquerysii,* besides (20*S*)-1,2-dehydropseudoaspidospermidine **169,** already discussed in Volume 17 of this series and (20*R*)-pseudoaspidospermidine **174** (*147*). The new compound, (20*S*)-pseudoaspidospermidine (**175,** $C_{19}H_{26}N_2$, MP 89°C, $[\alpha]_D$ +60°), was identical in all respects, except optical rotation, with the pseudoaspidospermidine (**304,** $[\alpha]_D$−60°), obtained by chemical elaboration of (+)-catharanthine (**305**) (*109*).



304 ≡ ent-**175**



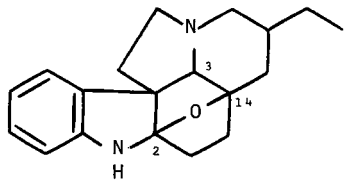
305

6. Dichomine-Subtype Alkaloids

A unique alkaloid possessing a novel type of ibogan skeleton was isolated from the leaves of *T. dichotama* (*90*) and *T. eglandulosa* (*105*). The new com-

pound, named dichomine (**177**, $C_{19}H_{24}N_2O$, M^+ at 296), displayed an unusual UV spectrum with maxima at 206, 228, and 288 nm and major fragments in the mass spectrum at *m/z* 267 and 124. The most characteristic signals the in ^{1}H-NMR spectrum were a somewhat broad singlet at 4.59 ppm (1H), a sharp singlet at 3.81 ppm (1H), and a triplet (3H) at 0.63 ppm. The signal at 4.59 ppm was shown to have no coupling constant with any other proton and could be assigned to an OH or an NH. However, it was too sharp to be an OH and it was thought to be an NH, with an unusual upfield position attributable to a neighboring oxygen atom. The singlet at 103.6 ppm in the CMR spectrum was in agreement with an indoline C-2 with oxygen and carbon substituents. In addition to the six aromatic carbons, the CMR spectrum contained signals at 80.1 ppm (s), 77.7 ppm (d), 67.6 ppm (s), 59.8 ppm (t), and 49.3 ppm (t). Another six signals (t) were found in the zone between 36 and 27 ppm and one for a methyl group at 8.1 ppm.

These data, together with the molecular formula, indicated that the oxygen must be present as an ether bridge. If the doublet at 77.7 ppm is due to an aminomethine, the second carbon of the ether bridge should give rise to the singlet at 80.1 ppm. The only biosynthetically reasonable structures that could explain this spectral behavior are 2,14-oxidopseudoaspidospermidine (**306**) (without stereochemistry) or the new structure **173.** Structure **306** was easily



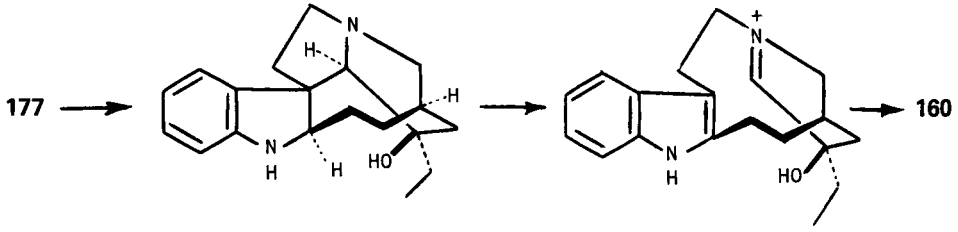
306

ruled out because irradiation of Me-18 at 0.63 ppm reduced the signals of diastereotopic C-19H_2 to two doublets at 1.33 and 1.42 ppm (J = 13.7 Hz) without additional coupling.

Examination of Dreiding models showed that **177** is a highly strained and rigid molecule and that only the relative arrangement of groups as in structure **177** or its enantiomer is possible.

This structure received support from the determination of coupling constants of all signals in the ^{1}H-NMR spectrum. In particular, the predicted small angle between H-14 and both H-3β and H-17β, and the nearly orthogonal disposition of H-14 with respect to H-3α and H-17α are confirmed by the large and small values of respective coupling constants. H-14 bisects the C-15H_2 angle, and, in fact, the two coupling constants are almost identical.

The absolute configuration of dichomine was determined by chemical correlation. Reduction with $LiAlH_4$ in THF gave a product identical to (14*S*, 20*R*)-velbanamine (**160**) through sequential carbinolamine C—O reductive cleavage

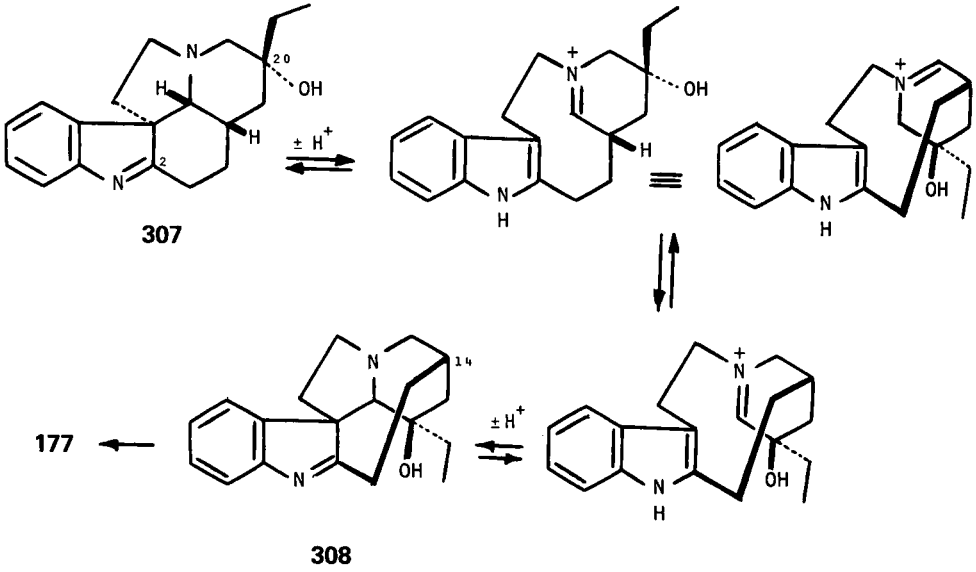


SCHEME 10

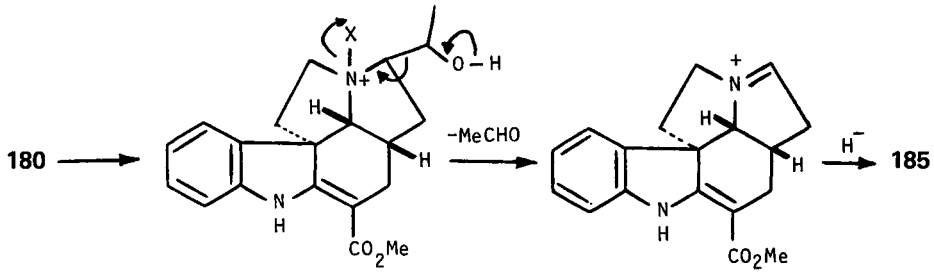
and iminium intermediate reduction (Scheme 10). The absolute configuration at C-14 is thus identical to that of all other iboga-type alkaloids isolated from *T. dichotoma* and *T. eglandulosa* and from all other *Tabernaemontana* species. A reasonable biogenetic scheme to **177** starts from 1,2-dehydro-(20*R*)-hydroxy-pseudoaspidospermidine (**307**), which is isomerized through the intervention of iminium ions to the indolenine **308** (Scheme 11). The basic carbon skeleton of **308** is strongly strained and therefore not stable. It can be trapped into a stable form only if a hydroxy group is present at C-20 with the proper (*R*) configuration to form an ether linkage to C-2.

7. Ibophyllidine-Subtype Alkaloids

Continuing with the chemical investigation of stem bark of *T. albiflora (Tabernaemontana albiflora)*, Husson *et al.* (*26, 27*) isolated six new alkaloids possessing the 21-



SCHEME 11



SCHEME 12

norpandolane skeleton and closely related to the known ibophyllidine **178** (*205*): 19-hydroxyibophyllidine **180,** $C_{20}H_{24}N_2O_3$, $[\alpha]_D$ +91°), 20-epiibophyllidine (**181,** $C_{20}H_{24}N_2O_2$, $[\alpha]_D$ +518°), 18-hydroxy-20-epiibophyllidine (**182,** $C_{20}H_{24}N_2O_3$, $[\alpha]_D$ +368°), (19*R*)-19-hydroxy-20-epiibophyllidine (**183,** $C_{20}H_{24}N_2O_3$, MP 136–138°C, $[\alpha]_D$ +431°), (19*S*)-19-hydroxy-20-epiibophyllidine (**184,** $C_{20}H_{24}N_2O_3$, $[\alpha]_D$ +277°), and desethylibophyllidine (**185,** $C_{18}H_{20}N_2O_2$, $[\alpha]_D$ +444°).

The structures of all of these compound are based on a detailed examination of their 400-MHz ^{1}H-NMR spectra and on comparison with **178** (Table VII). The chemical shifts of H-3 and H-20, which resonated at 3.51 and 3.18 ppm in **178** and at 3.89 and 2.78 ppm in **181,** supplied the key to establish the C-20 configuration in these compounds.

For the first time, an alkaloid of this type was isolated that lacked the ethyl chain. Compound **185** might biogentically arise from 19-hydroxyibophyllidine (**180**) through a Polonovski fragmentation process (Scheme 12). The strong positive optical rotation of all of these ibophyllidine-related alkaloids suggests that they belong to the same steric series as ibophyllidine (**178**).

Taking advantage of the reaction scheme previously depicted for the isomeric pseudovincadifformines (**162** and **163**), Kuehne and Bohnert realized the stereospecific synthesis of *rac*-**178** (*206*), *rac*-**181** (*206*), and *rac*-**185** (*207*).

Ibophyllidine N^4-oxide (**179,** $C_{20}H_{24}N_2O_3$, oil, $[\alpha]_D$ +187°) was isolated from *T. flavicans* too, besides ibophyllidine (**178**). It was recognized from the downfield shift of H-3 at 5.68 ppm and found identical to the product of N-oxidation (30% H_2O_2–EtOH) of **178** (*110*).

D. TACAMAN-TYPE ALKALOIDS

Of the 27 alkaloids isolated from *T. eglandulosa,* eight were found to belong to a new structural type, never found before in nature, the tacaman type (*105*).

Tacamine (**186,** $C_{21}H_{26}N_2O_3$), the first isolated and most representative al-

TABLE VII

^{1}H-NMR DATA FOR ALIPHATIC PROTONS OF IBOPHYLLIDINE (**178**) (*26*), 19-HYDROXYIBOPHYLLIDINE (**180**) (*27*), 20-EPIIBOPHYLLIDINE (**181**) (*26*), 18-HYDROXY-20-EPIIBOPHYLLIDINE (**182**) (*27*), (19*R*)-19-HYDROXY-20-EPIIBOPHYLLIDINE (**183**) (*27*), (19*S*)-19-HYDROXY-20-EPIIBOPHYLLIDINE (**184**) (*27*), AND DEETHYLIBOPHYLLIDINE (**185**) (*26*)

	Chemical shifts (ppm)						
Proton	**178**	**180**	**181**	**182**	**183**	**184**	**185**
H-3	3.51 d	3.61 d	3.89 d	3.86 d	3.84 d	3.92 d	3.75 d
H-5α	2.77 d	2.87 ddd	2.97 ddd	3.03 br dd	2.94 br dd	3.12 m	2.89 ddd
H-5β	3.15 m	3.31 m	3.36 td	3.38 td	3.30 td	3.53 td	3.36 td
H-6α	2.27 td	2.35 m	2.04 m	2.1 m	2.05 m	2.12 td	2.03 td
H-6β	2.2 m	2.3 m	1.64 ddd	1.70 dd	1.64 dd	1.76 dd	1.64 ddd
H-14	2.03 m	2.08 m	2.04 m	2.04 m	2.04 m	2.05 m	2.02 m
H-15α	1.29 dt	1.40 dt	1.76 br dd	1.76 br dd	1.60 br dd	1.84 br dd	1.74 ddt
H-15β	2.18 m	2.18 m	1.95 br dd	2.16 m	2.1 m	1.98 ddd	2.12 m
H-17α	1.81 dd	1.85 dd	1.93 dd	1.90 dd	1.8 dd	1.93 dd	1.84 dd
H-17β	3.12 dd	3.18 dd	2.76 dd	2.83 dd	2.76 dd	2.82 dd	2.78 dd
H-18	1.03 t	1.26 d	0.96 t	4.03 m	1.10 d	1.23 d	—
H-18′	—	—	—	3.76 m	—	—	—
H-19	1.57 ddq	3.96 m	1.47 ddq	1.62 br dd	3.85 m	3.63 m	—
H-19′	1.92 ddq	—	1.75 ddq	2.1 m	—	—	—
H-20	—	—	2.78 m	3.30 m	2.90 m	2.98 m	2.73 td
H-20	3.18 m	3.34 m	—	—	—	—	3.28 ddd
CO_2Me	3.75 s	3.78 s	3.75 s	3.74 s	3.75 s	3.76 s	3.74 s
NH	9.12 br s	9.13 br s	9.05 br s	9.05 br s	9.03 br s	9.02 br s	9.03 br s

Coupling constants (Hz)

178: $J_{3,14} = 7.5$, $J_{5\alpha,5\beta} = 10$, $J_{5\alpha,6\alpha} = 7$, $J_{5\alpha,6\beta} = 7$, $J_{14,15\alpha} = 6$, $J_{14,17\alpha} = 11$, $J_{14,17\beta} = 6.5$, $J_{15\alpha,15\beta} = 12.5$, $J_{15\alpha,20\beta} = 12.5$, $J_{17\alpha,17\beta} = 15$, $J_{18,19} = 7$, $J_{18,19'} = 7$, $J_{19,19'} = 14$, $J_{19,20\beta} = 7$, $J_{19',20\beta}\beta = 7$

180: $J_{3,14} = 7.5$, $J_{5\alpha,5\beta} = 10$, $J_{5\alpha,6\alpha} = 7$, $J_{5\alpha,6\beta} = 7$, $J_{14,15\alpha} = 6$, $J_{14,17\alpha} = 11$, $J_{14,17\beta} = 6.5$, $J_{15\alpha,15\beta} = 12.5$, $J_{15\alpha,20\beta} = 12.5$, $J_{17\alpha,17\beta} = 15$, $J_{18,19} = 7$, $J_{19,20\beta} = 9$

181: $J_{3,14} = 6.5$, $J_{5\alpha,5\beta} = 12.5$, $J_{5\alpha,6\alpha} = 6$, $J_{5\alpha,6\beta} = 0.5$, $J_{5\beta,6\alpha} = 12.5$, $J_{5\beta,6\beta} = 5.5$, $J_{6\alpha,6\beta} = 12.5$, $J_{14,15\alpha} = 0.5$, $J_{14,17\alpha} = 11.5$, $J_{14,17\beta} = 6$, $J_{15\alpha,15\beta} = 12.5$, $J_{15\alpha,20\alpha} = 6$, $J_{15\beta,20\alpha} = 9$, $J_{17\alpha,17\beta} = 14.5$, $J_{18,19} = 7$, $J_{18,19'} = 7$, $J_{19,19'} = 14$, $J_{19,20\alpha} = 7$, $J_{19',20\alpha} = 7$

182: $J_{3,14} = 6.5$, $J_{5\alpha,5\beta} = 12.5$, $J_{5\alpha,6\alpha} = 6.5$, $J_{5\alpha,6\beta} = 0.5$, $J_{5\beta,6\alpha} = 12.5$, $J_{5\beta,6\beta} = 5.5$, $J_{6\alpha,6\beta} = 12.5$, $J_{14,15\alpha} = 0.5$, $J_{14,17\alpha} = 11.5$, $J_{14,17\beta} = 6$, $J_{15\alpha,15\beta} = 12.5$, $J_{15\alpha,20\alpha} = 6$, $J_{17\alpha,17\beta} = 15$, $J_{18,18'} = 12$, $J_{18,19} = 3$, $J_{18,19'} = 12$

183: $J_{3,14} = 6.5$, $J_{5\alpha,5\beta} = 12.5$, $J_{5\alpha,6\alpha} = 6$, $J_{5\alpha,6\beta} = 0.5$, $J_{5\beta,6\alpha} = 12.5$, $J_{5\beta,6\beta} = 5.5$, $J_{6\alpha,6\beta} = 12.5$, $J_{14,15\alpha} = 0.5$, $J_{14,17\alpha} = 11.5$, $J_{14,17\beta} = 5.5$, $J_{15\alpha,15\beta} = 12.5$, $J_{15\alpha,20\alpha} = 6$, $J_{17\alpha,17\beta} = 14.5$, $J_{18,19} = 7$, $J_{19,20\alpha} = 8$

184: $J_{3,14} = 6.5$, $J_{5\alpha,5\beta} = 12.5$, $J_{5\alpha,6\alpha} = 7$, $J_{5\alpha,6\beta} = 0.5$, $J_{5\beta,6\alpha} = 12.5$, $J_{5\beta,6\beta} = 5.5$, $J_{6\alpha,6\beta} = 12.5$, $J_{14,15\alpha} = 0.5$, $J_{14,17\alpha} = 11.5$, $J_{14,17\beta} = 6$, $J_{15\alpha,15\beta} = 12.5$, $J_{15\alpha,20\alpha} = 6$, $J_{15\beta,20\alpha} = 8$, $J_{17\alpha,17\beta} = 15$, $J_{18,19} = 7$, $J_{19,20\alpha} = 6.5$

185: $J_{3,14} = 6.5$, $J_{5\alpha,5\beta} = 12.5$, $J_{5\alpha,6\beta} = 6$, $J_{5\alpha,6\beta} = 0.5$, $J_{5\beta,6\alpha} = 12.5$, $J_{5\beta,6\beta} = 5.5$, $J_{6\alpha,6\beta} = 12.5$, $J_{14,15\alpha} = 0.5$, $J_{14,15\beta} = 9$, $J_{14,17\alpha} = 11.5$, $J_{14,17\beta} = 6$, $J_{15\alpha,15\beta} = 12.5$, $J_{15\alpha,20\alpha} = 5.5$, $J_{15\alpha,20\beta} = 0.5$, $J_{15\beta,20\alpha} = 9$, $J_{15\beta,20\beta} = 7$, $J_{17\alpha,17\beta} = 14.5$, $J_{20\alpha,20\beta} = 11.5$

TABLE VIII
^{13}C-NMR CHEMICAL SHIFTS OF TACAMINE (**186**) AND 16-EPITACAMINE (**187**) (*104, 105*)

	186	**187**
C-2	130.9	130.9
C-3	54.2	54.0
C-5	50.7	50.4
C-6	17.0	16.7
C-7	106.1	106.2
C-8	128.8	128.1
C-9	118.4	118.0
C-10	121.6	121.4
C-11	120.2	120.0
C-12	110.4	112.4
C-13	134.4	135.9
C-14	32.1	33.2
C-15	31.1	29.6
C-16	81.8	82.6
C-17	40.2	42.6
C-18	11.5	11.2
C-19	26.9	26.8
C-20	38.3	37.3
C-21	50.5	50.2
CO_2Me	174.3, 54.2	172.3, 53.0

kaloid of this type gave a yellow color with ceric sulfate, which slowly changed to orange. The UV maxima at 227, 279, and 282 nm with a shoulder at 290 nm was characteristic of an indole chromophore. The mass spectrum gave a molecular peak at *m/z* 354 with major fragments at 339, 295, 293, 292, 252, and 223. Such a fragmentation is typical for alkaloids of the Eburnea type, and the similarity was confirmed by the CMR spectrum (Table VIII), which showed shifts for aromatic carbons almost identical to those of vincamine (**91**). The shifts of aliphatic carbons were quite different, suggesting a change in this part of the molecule. The ^{1}H-NMR spectrum at 300 MHz was extensively examined by means of homonuclear decoupling experiments (Table IX). The most characteristic signals were that for a methoxy group at 3.83 ppm, a multiplet for four aromatic protons between 7.10 and 7.50 ppm, and a triplet for an Me—CH_2 group at 0.86 ppm. In addition, all chemical shifts and coupling constants for aliphatic protons were assigned, and, in particular, it was noted that the two protons at C-19 are coupled not only with Me-18 but also with another vicinal proton, thus indicating the presence of a CH_3CH_2CH grouping.

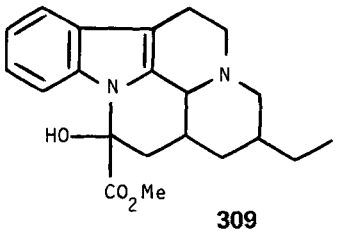
The only reasonable explanation for these data is represented by gross structure **309.** This could be derived from a pseudotabersonine-subtype precursor by a sequence of electrophilic hydroxylation at C-16, followed by acid-catalyzed

TABLE IX

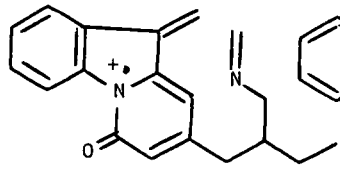
^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) of the Aliphatic Protons of Tacaman-Type Alkaloids (*105*)

	Tacamine (**186**)		16-Epitacamine (**187**)		19*S*-Hydroxytacamine (**188**)		16,17-Anhydrotacamine (**191**)	
Proton	δ	*J*	δ	*J*	δ	*J*	δ	*J*
H-3	4.35 dddd	5.8, 2.3, 1.9, <0.5	4.11 m	—	4.40 m	—	4.49 m	—
H-5α	3.34 ddd	14.0, 6.5, 0.6	3.02 m	—	3.37 m	—	3.35 m	—
H-5β	3.43 ddd	14.0, 11.2, 5.5	3.07 m	—	3.46 m	—	3.35 m	—
H-6α	3.00 dddd	16.3, 11.2, 6.5, 2.3	2.90 m	—	3.02 m	—	3.01 dddd	16.3, 8.8, 8.5, 2.8
H-6β	2.59 dddd	16.3, 5.5, 1.9, 0.6	2.48 m	—	2.63 m	—	2.81 m	—
H-14	2.40 ddddd	12.7, 5.8, 4.2, 4.0, 3.1	2.08 m	—	2.46 m	—	2.58 dddd	12.6, 7.2, 3.0, 2.0
H-15α	1.14 ddd	13.2, 12.7, 12.6	0.69 ddd	12.7, 12.7, 12.7	1.29 ddd	13.0, 13.0, 13.0	0.52 ddd	13.0, 12.6, 12.6
H-15β	1.67 ddddd	13.2, 4.0, 3.0, 1.6, <0.5	1.31 m	—	1.62 br d	13.0	1.73 br d	13.0
H-16	—	—	—	—	—	—	—	—
H-17α	2.62 dd	14.3, 4.2	2.67 dd	14.9, 2.9	2.65 dd	14.3, 4.0	6.39 d	7.2
H-17β	2.19 dd	14.3, 3.1	2.22 dd	14.9, 4.2	2.21 dd	14.3, 3.1	—	—
H-18	0.86 t	7.3	0.77 t	7.3	1.16 d	6.3	0.85 t	7.4
H-19	1.20 ddq	14, 7.3, 6.5	0.98 m	—	3.44 dd	6.6, 6.3	1.10 m	—
H-19′	1.20 ddq	14, 7.3, 6.5	0.98 m	—	—	—	1.10 m	—
H-20	1.48 dddddd	12.6, 10.7, 6.5, 6.5, 3.5, 3.0	1.30 m	—	1.7 m	—	1.54 m	—
H-21α	2.15 dd	10.9, 10.7	2.06 dd	10.9, 10.9	2.31 dd	11.0, 11.0	2.23 dd	11.1, 11.1
H-21β	2.66 ddd	10.9, 3.5, 1.6	2.43 br d	10.9	2.99 br d	11.0	2.71 ddd	11.1, 3.5, 1.9
CO_2Me	3.83 s	—	3.67 s	—	3.84 s	—	3.94 s	—

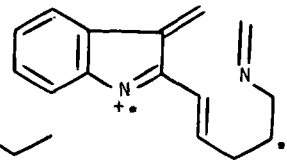
Proton	16*R*-Decarbomethoxytacamine (**189**)		16*S*-Decarbomethoxytacamine (**190**)		Tacamonine (**192**)		17-Hydroxytacamonine (**193**)	
	δ	*J*	δ	*J*	δ	*J*	δ	*J*
H-3	4.20 m	—	4.35 m	—	4.33 m	—	4.65 m	—
H-5α	3.14 m	—	3.38 m	—	3.30 m	—	3.37 m	—
H-5β	3.20 m	—	3.40 m	—	3.38 m	—	3.37 m	—
H-6α	2.91 m	—	3.02 dddd	15.9, 11.0, 6.7, 2.4	2.89 m	—	2.93 m	—
H-6β	2.50 m	—	2.65 br d	15.9	2.48 br ddd	17.0, 7.1, 3.1	2.52 br d	16
H-14	2.24 m	—	2.39 m	—	2.45 m	—	2.62 m	—
H-15α	0.37 ddd	12.7, 12.7, 12.7	1.13 ddd	12.8, 12.5, 12.5	0.56 ddd	12.6, 12.6, 12.6	0.40 ddd	12.4, 12.4, 12.4
H-15β	1.53 br d	—	1.77 br d	12.8	1.66 br d	12.6	1.66 m	—
H-16	5.58 dd	9.5, 5.4	6.06 dd	4.0, 1.2	—	—	—	—
H-17α	2.45 ddd	13.9, 5.4, 3.2	2.26 ddd	15.5, 3.5, 1.2	2.99 dd	17.0, 4.9	—	—
H-17β	1.89 ddd	13.9, 9.5, 3.6	2.40 ddd	15.5, 4.0, 4.0	2.66 dd	17.0, 2.3	4.36	2.6
H-18	0.81 t	7.2	0.88 t	7.3	0.85 t	7.4	0.85 t	7.3
H-19	1.02 m	—	1.13 m	—	1.10 m	—	1.12 m	—
H-19′	1.02 m	—	1.13 m	—	1.10 m	—	1.12 m	—
H-20	1.40 m	—	1.58 m	—	1.52 m	—	—	—
H-21α	1.92 dd	11.0, 11.0	2.26 dd	10.9, 10.9	2.03 dd	11.0, 10.9	2.06 dd	10.9, 10.9
H-21β	2.50 m	—	2.77 br d	10.8	2.64 ddd	10.9, 3.7, 1.7	2.62 br d	10.9



309



m/z 292 (310)

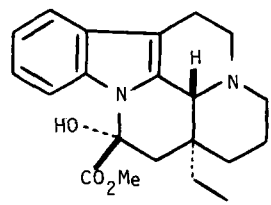


m/z 223 (311)

skeletal rearrangement, analogous to that proposed by Wenkert for the formation of vincamine from vincadifformine (*208*).

The CMR data are in agreement with the proposed skeleton, and ions at *m/z* 292 and 223, characteristic of tacamine, can be represented by structures **310** and **311**, respectively. The cis C/D and D/E ring junctions were suggested by the similarity of the shifts of C-6 and C-21 to those of C-6 and C-3 in vincamine and by the relative small coupling between H-3 and H-14. The shift values of C-18 and C-19 suggested an equatorial orientation of the ethyl chain at C-20, and this was supported by the analysis of the splitting pattern of H-20. In agreement with an axial β orientation, H-20 had a large coupling constant with H-21α (J = 10.7 Hz) and H-21β (J = 5 Hz) and with H-15α (J = 12.6 Hz) and H-15β (J = 3 Hz).

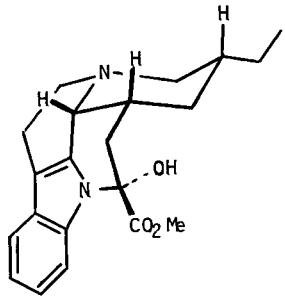
The absolute configuration of the molecule, including that at C-16, was determined by analysis of the CD spectrum in comparison with the data of alkaloids of the vincamine class. It has been suggested that unequivocal assignment of configuration at C-21 and C-16 of vincamine alkaloids could be made by observation of Cotton effects between 250 and 300 nm and below 250 nm in the ORD and CD spectra, respectively. The influence of the center at C-20 is of minor importance because of its relatively long distance from the indole chromophore. The CD spectrum of tacamine [**186** $\lambda_{max}(\Delta\epsilon)$ 272(−5.0), 250(−3.9), 238(−6.3), 234(0), 227(+14.8), 212 nm (0)], (*209*) is the same in character as that of 16-epi-21-epivincamine (**312**) and roughly the mirror image of the spectrum of (+)-



312

vincamine. Therefore, tacamine must possess the conformation and the same configuration at C-3 and C-16 as those of the enantiomer of (+)-vincamine, namely, a 3β-H orientation and a 16β-CO_2Me (equatorial) and a 16α-OH (axial) orientation.

Formula **313** represents the conformation and absolute configuration of tac-



313

amine. The enantiomer of **186** was synthesized by Le Men and associates, starting from (+)-catharanthine (*210*). However, a positive correlation with tacamine was impossible owing to the lack of ^{13}C-NMR and CD data and low resolution of the ^{1}H-NMR spectrum.

The second most abundant alkaloid in *T. eglandulosa* decomposed readily and quantitatively to tacamine in solution or on a TLC plate. The UV and mass spectra were similar to those of tacamine, indicating a very close but less stable structure. The mass spectrum was characterized by a base peak owing to the easy loss of a CO_2Me fragment, and this fact together with the slow epimerization suggested that the molecule might be 16-epitacamine in which the bulky CO_2Me group occupied the less favorable axial orientation. This hypothesis was confirmed by ^{1}H-NMR and CMR data. The chemical shift of most protons changed with respect to tacamine; however, the coupling constants of the aliphatic protons remained unaffected and therefore the relative stereochemistry of the molecule should be the same. The CMR data fitted with those predicted on the basis of extrapolation of the difference between vincamine and 16-epivincamine.

Finally, the CD spectrum showed negative Cotton effects at 272 and 283 nm and a positive Cotton effect at 240 nm, indicating the same configuration at C-3 as in tacamine but opposite configuration at C-16. In fact, the spectrum was similar to that of 21-epivincamine and the mirror image of 16-epivincamine. The absolute configuration of 16-epitacamine is therefore represented by structure **187.**

The UV maxima of 16,17-anhydrotacamine (**191**), λ_{max} 228, 273, and 312 nm) were similar to those of 16,17-anhydrovincamine (apovincamine) (**96**), and the analogy was confirmed by mass spectroscopy, with the molecular ion at *m/z* 336, 18 amu less than tacamine, and by ^{1}H NMR (Table IX). The signals for H-17α and H-17β of the latter were missing and, instead, one olefinic proton (d, J = 7.2 Hz) appeared at 6.39 ppm. In addition, H-14 changed from a ddddd to a dddd, and H-15 resonated upfield at 0.52 ppm because of its position under the shielding influence of the indole ring. Compound **191** was prepared from tacamine **186** by dehydration in refluxing MeOH/HCl, and, because the latter

survived isolation conditions, the possibility that **191** is an artifact is greatly reduced.

The most characteristic feature of (19*S*)-hydroxytacamine (**188**), which possesses a tacamine-like UV absorption and has an additional oxygen atom, was the change of the methyl signal splitting pattern from a triplet at 0.86 ppm to a doublet at 1.16 ppm, indicating the presence of a hydroxy group at C-19. H-19 could not be observed in the ^{1}H-NMR spectrum because it was obscured by the H-5α and H-5β signals. However, the (*S*) configuration at C-19 was based on the fact that H-15α, H-21α, and H-21β are deshielded with respect to tacamine by 0.15, 0.16, and 0.33 ppm, respectively, while H-15β is not affected at all. The OH group is thus nearest to H-21β. This automatically means that the configuration is (*S*) because the relatively large Me group is the least sterically hindered when it is as far as possible from H-15α, H-15β, H-21α, and H-21β. From the CD spectrum, (19*S*)-hydroxytacamine has the same absolute configuration at C-3 and C-16 as in tacamine.

(16*R*)- and (16*S*)-Decarbomethoxytacamines (**189** and **190**) are minor alkaloids and their UV spectra were those of an unchanged indole chromophore as for tacamine. The absence of the CO_2Me group was indicated by MS ($M^{+\cdot}$ 296) and, particularly, by the lack of a typical signal in the ^{1}H-NMR spectrum (Table IX).

The detailed analysis of the other signals of the ^{1}H-NMR spectrum led readily to the recognition of H-3, H-5α, H-6β, H-6α, H-5β, H-14, H-15α, H-15β, H-20, H-21α, and H-21β, indicating that the ring junction and the orientation of the ethyl chain at C-20 were the same as in tacamine. The most characteristic and diagnostic difference was the appearance of a dd at 5.58 ppm (J = 9.5 and 5.4 Hz) in the spectrum of **189** and at 6.06 ppm (J = 4.0 and 1.2 Hz) in the spectrum of **190.** Because these coupling constants were also found in the signals of H-17α and H-17β, it was deduced that the two alkaloids were the isomeric 16-decarbomethoxytacamines.

The coupling constants values of H-16 allowed the determination of the configuration at C-16. In **189,** H-16 must be axially oriented, antiperiplanar with axial H-17, because one of the coupling constants is 9.5 Hz. On the other hand, H-16 in **190** must be equatorially oriented. The different configuration at C-16 deeply influences the chemical shift of H-15α, which is strongly shielded in **189** with respect to **190** (0.37 ppm versus 1.13 ppm).

Molecular models show that in both compounds H-15α must experience a diamagnetic ring current because it is situated under the pyrrole ring. However, in **190** the diamagnetic effet is contrasted by a van der Waals deshielding effect between electronegative 16α-OH and H-15α, and, as a consequence, this last proton occupies an expected position.

The absolute configuration at C-3 was derived from the CD spectrum, which also substantiated the difference at C-16 of the isomers. If the ethyl chain is not taken into account, the 16-decarbomethoxytacamines can be considered the mir-

ror images of 16-decarbomethoxyvincamines (vincanols), and the CD spectra must also be their mirror images. Both CD spectra showed a negative Cotton effect near 270–280 nm and an opposite Cotton effect at a shorter wavelength (<250 nm). Considering the data of vincaminols (*211*), it can be concluded that both isomers possess a 3β-H configuration and that in **189** the 16-OH is equatorial (H-16 axial) and in **190** the C-160H is axial (H-16 equatorial).

The third major component of *T. eglandulosa* was named tacamonine and was shown immediately to possess structure **192** on the basis of the modified UV spectrum with maxima at 242, 265, 294, and 303 nm, reminiscent of those of eburnamonines. The molecular peak in the mass spectrum was at *m/z* 292, and signals for CO_2Me and H-16 were absent in the proton spectrum. In addition, the close proximity of the new carbonyl group shifted H-9 (0.9 ppm) and H-17α and H-17β (0.4 ppm) downfield with respect to tacamine. By contrast with other tacamines, the CD spectrum of **192** was qualitatively and quantitatively different from that of eburnamonine. The authors explained this on the basis of the relatively larger influence of the asymmetric C-20 in eburnamonine compared to C-14 in tacamonine, because C-16 is no longer a stereo center. From the negative Cotton effect and on biogenetic reasoning, it is concluded that tacamonine has the same 3β-H as other tacamines. *ent*-Tacamonine (pseudovincamone) was synthesized by Lévy *et al.* before its isolation from natural sources (*212*).

17-Hydroxytacamonine (**193**) was a trace component of the tacamine mixture, and it has a UV spectrum similar to that of tacamonine. The presence of an additional oxygen was inferred by the mass spectrum, showing a $M^{+\cdot}$ at 316 and by the ^{1}H-NMR spectrum, which resembled that of tacamonine except that no protons at C-17 could be observed at the usual position, but, instead, a doublet at 4.36 ppm (J = 2.6 Hz) had appeared. These observations could be accounted for by the presence of an OH at C-17 with an equatorial orientation because of the small coupling constant between H-17 and H-14 and the preferred orientation of the bulky group.

The presence of an extra stereo center at C-17 perturbs the *N*-acylindole chromophore in an unpredictable way, creating differences in the 240–300-nm zone of the CD spectrum and preventing the application of the analogy principle for determining absolute configuration. On biogenetic grounds it is assumed that structure **193** represents the absolute configuration of 17-hydroxytacamonine.

E. Bisindole Alkaloids

1. Corynanthean–Aspidospermatan-Type Alkaloids

From 250 g of root bark of *T. chippii*, a small tree growing in the high forest or bush and occurring in the Ivory Coast and Ghana, nearly 4 mg of the new bisindole alkaloid vobparicine (**200**, $C_{39}H_{43}N_4O_2$) were isolated (*62*). The dimeric nature of this compound suggested by the molecular formula was con-

firmed by its ^{1}H-NMR spectrum, which showed the presence of two NH and eight aromatic protons. The singlets at 2.47 and 2.61 ppm, the quartet at 5.41 ppm, and the doublet at 1.67 (J = 6.8 Hz) were reminiscent of the signals for CO_2Me, NMe, and C=CHMe groupings of vobasine (**32**); while the AB system at 4.49 and 4.39 ppm (J = 17.5 Hz), the quartet at 5.39 ppm, and the doublet at 1.68 ppm (J = 6.8 Hz) corresponded to the aminomethylene C-6H_2 and C=CHMe of apparicine (**66**).

The presence of vobasinol-like and apparicine-like monomeric units was further substantiated by UV, mass, and CMR spectra. The UV spectrum [λ_{max} 222, 290 (sh), 296 (sh), and 304 nm] was the summation of UV spectra of **32** and **66.** The high-resolution mass spectrum showed, in addition to the molecular ion at 600.3464, characteristic fragments at m/z 337, 336, 227, 194, 182, 180, and 122 for the vobasine portion and at m/z 263, 249, 233, 220, 208, 167, and 107 for the apparicine portion.

Almost all of the signals in the CMR spectrum could be superimposed on those of vobasinol (**314**) and apparicine (**66**). Diagnostically useful differences were found in the shift of C-3 of **314** and in the shift and multiplicity of C-22 of apparicine (downfield doublet, 112.2→123.0 ppm).

All of these data suggested that the point of attachment of the two units involves the nonaromatic carbons C-3′ of vobasinol and C-22 of **66.** In fact, H-22 appears at 5.96 ppm as a doublet (J = 10.1 Hz) coupled with H-3′ at 4.53 ppm.

The differentiation between two possible Z and E configurations at the double bond was based on a careful inspection of Dreiding models and some nuclear Overhauser effect (NOE) measurements. The rather large coupling value between H-22 and H-3′ suggested either a small (0–30°) or large angle (150–180°) between these two protons. The small angle conformation in both Z and E isomers resulted in severe steric compression, eliminating this possibility. In the large angle conformation, the Z isomer showed H-22 and H-3′ somewhat proximate to H-1′ and H-1, respectively, while the E-isomer indicated interaction between H-3′, H-14, and H-15. Irradiation of H-3′ gave a small NOE for the high field NH and no NOE for H-14 and H-15. All of these data fit with structure **200** for vobparicine.

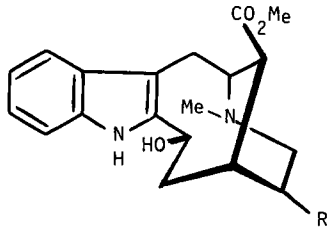
Predictably, vobparicine originates from attack of the strongly nucleophilic C-22 of **66** on C-3 of **314.** In fact, when a mixture of vobasinol and excess apparicine was refluxed for 2 hr in 1.5% methanolic HCl under nitrogen, vobparicine was formed, identical in all respects with the natural product. Vobparicine was considered to be a genuine alkaloid because the conditions for its synthesis were not achieved during isolation procedure.

2. Ibogan–Corynanthean-Type Alkaloids

a. Ervahanine A (202), Ervahanine B (223), and Ervahanine C (228). *Ervatamia hainanensis* (*T. bufalina* according to Leeuwenberg's classi-

fication) is a small shrub distributed in the southern part of China over forest regions of 100–500-m elevation, and locally named *Hainan gou ya hua* and *Du gen mu*. The roots collected in the Hainan Island yielded, in addition to corynanthean- and ibogan-type monomers, three isomeric bisindole alkaloids named ervahanines A (**202**), B (**223**), and C (**228**) (*52*). The mass spectra of these compounds were identical and showed fragments at *m/z* 194, 182, 180, 136, and 122, characteristic of a voacamine-type structure. The ^{1}H-NMR spectra exhibited typical signals of a vobasine-like moiety (CO_2Me and ethylidene chain) and a coronaridine-like unit (CO_2Me and ethyl chain). Thus ervatamines belong to the restricted series of voacamine congeners in which the iboga portion is devoid of aromatic methoxy substituent(s).

Along these indications, **202** was obtained by condensation of vobasinol (**314**)



314 R: =CH-Me

315 R: β-Et; α-H

and coronaridine (**97**) under Büchi's conditions (*213*) for the synthesis of voacamine (**203**), together with minor amounts of ervahanine B (**223**). The third isomer was not formed under these conditions. The position of attachment of the vobasine unit to the aromatic ring of coronaridine was based on the inspection of ^{1}H-NMR spectra in comparison with authentic 10- and 11-substituted indoles as tabernamine (**201**) and capuvosine (**235**). It is interesting to note that H-9 was the

TABLE X
^{1}H-NMR DATA FOR ERVAHANINE A (**202**), ERVAHANINE B (**223**), AND ERVAHANINE C (**228**)

	Chemical shifts (ppm) (*52*)		
Proton	**202**	**223**	**228**
H-3	4.63 dd	4.62 dd	4.82 dd
H-5	4.03 dd	4.02 dd	4.13 br dd
H^R-6	3.24 dd	3.24 dd	3.1 dd
H^S-6	3.48 dd	3.50 dd	3.48 dd
H-9	7.57 dd	7.58 br dd	7.66 d
H-10,11,12	7.1 m	7.1 m	7.1 m
H^R-14	2.68 br d	2.71 br d	2.76 br d

(*continued*)

TABLE X (*Continued*)

Proton	Chemical shifts (ppm) (*52*)		
	202	**223**	**228**
H^S-14	1.96 ddd	1.92 ddd	1.98 ddd
H-15	3.77 m	3.74 m	3.84 m
H-16	2.73 dd	2.72 dd	2.80 m
H-18	1.63 d	1.63 d	1.66 d
H-19	5.30 br q	5.30 br q	5.34 br q
H^R-21	3.73 br d	3.73 br d	3.82 br d
H^S-21	2.90 d	2.88 d	2.95 d
N-Me	2.57 s	2.58 s	2.67 s
CO_2Me	2.45 s	2.45 s	2.52 s
NH	7.48 s	7.49 s	7.60 s
H^R-3′[a]	2.88 br d	2.88 br d	2.88 br d
H^S-3′[a]	2.75 br d	2.78 br d	2.30 br d
H^R-5′[b]	3.35 m	3.33 m	3.32 m
H^S-5′[b]	3.15 m	3.15 m	3.12 m
H^R-6′[c]	3.10 m	3.09 m	3.06 m
H^S-6′[c]	2.98 m	2.95 m	2.98 m
H-9′	7.39 d	7.31 d	7.34 m
H-10′	6.98 dd	—	7.0 m
H-11′	—	6.98 dd	7.1 m
H-12′	7.00 s	7.16 d	—
H-14′	1.83 m	1.84 m	1.80 m
H^R-15′	1.68 br dd	1.70 br dd	1.72 m
H^S-15′	1.12 m	1.12 m	1.06 m
H^R-17′[d]	1.81 br d	1.83 br d	1.80 m
H^S-17′[d]	2.51 br d	2.53 br d	2.54 br d
H-18′	0.88 t	0.88 t	0.87 t
H^R-19′	1.42 dq	1.42 dq	1.40 dq
H^S-19′	1.54 dq	1.54 dq	1.52 dq
H-20′	1.30 m	1.29 m	1.22 m
H-21′	3.50 s (d)	3.48 s (d)	3.45 s (d)
CO_2Me	3.66 s	3.64 s	3.76 s
NH	7.72 s	7.77 s	8.02 br s

Coupling constants (Hz)

202: $J_{3,14R} = 12$, $J_{3,14S} \sim 3$, $J_{5,6R} = 10$, $J_{5,6S} = 5$, $J_{5,16} \sim 2$, $J_{6R,6S} = 14$, $J_{9,10} \sim 8$, $J_{14R,14S} = 14$, $J_{14R,15} = 12$, $J_{14S,15} \sim 3$, $J_{15,16} \sim 2$, $J_{18,19} = 7$, $J_{19,21R} \sim 1$, $J_{19,21S} < 0.2$, $J_{21R,21S} = 12$, $J_{3'R,3'S} = 9$, $J_{3'R,14'} \sim 3$, $J_{3'S,14'} \sim 3$, $J_{9',10'} = 8$, $J_{10',12'} = 2$, $J_{14',17'R} \sim 3$, $J_{14',17'S} \sim 3$, $J_{15'R,15'S} = 12.5$, $J_{15'R,20'} \sim 10$, $J_{15'S,20'} \sim 5$, $J_{17'S,17'R} = 12$, $J_{18',19'R} = 7$, $J_{18',19'S} = 7$, $J_{19'R,20'} \sim 7$, $J_{19'S,20'} \sim 7$, $J_{20',21'} < 0.2$

223: $J_{3,14R} = 12$, $J_{3,14S} \sim 3$, $J_{5,6R} = 10$, $J_{5,6S} = 5$, $J_{5,16} \sim 2$, $J_{6R,6S} = 14$, $J_{9,10} \sim 8$, $J_{14R,14S} = 14$, $J_{14R,15} = 12$, $J_{14S,15} \sim 3$, $J_{15,16} \sim 2$, $J_{18,19} = 7$, $J_{19,21R} \sim 1$, $J_{19,21S} < 0.2$, $J_{21R,21S} = 12$, $J_{3'R,3'S} = 9$, $J_{3'R,14'} \sim 3$, $J_{3'S,14'} \sim 3$, $J_{9',11'} = 2$, $J_{11',12'} = 8$, $J_{14',17'R} \sim 3$, $J_{14',17'S} \sim 3$, $J_{15'R,15'S} = 12.5$, $J_{15'R,20'} \sim 10$, $J_{15'S,20'} \sim 5$, $J_{17'R,17'S} = 12$, $J_{18',19'R} = 7$, $J_{18',19'S} = 7$, $J_{19'R,20'} \sim 7$, $J_{19'S,20'} \sim 7$, $J_{20',21'} < 0.2$

228: $J_{3,14R} = 12$, $J_{3,14S} \sim 3$, $J_{5,6R} \sim 10$, $J_{5,6S} = 5$, $J_{6R,6S} = 14$, $J_{9,10} = 8$, $J_{14R,14S} = 14$, $J_{14R,15} = 12$, $J_{14S,15} \sim 3$, $J_{18,19} = 7$, $J_{19,21R} \sim 1$, $J_{19,21S} < 0.2$, $J_{21R,21S} = 12$, $J_{3'R,3'S} \sim 9$, $J_{9',10'} = 8$, $J_{14',17'R} = 3$, $J_{14',17'S} \sim 3$, $J_{15'R,15'S} = 12$, $J_{17'R,17'S} = 12$, $J_{18',19'R} = 7$, $J_{18',19'S} = 7$, $J_{19'R,20'} \sim 7$, $J_{19'S,20'} \sim 7$, $J_{20',21'} < 0.2$

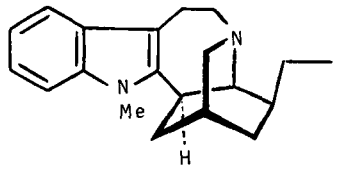
[a,b,c,d] Assignments may be reversed.

more deshielded proton, followed by H-12 and then by H-10 and/or H-11, which possess similar shifts. To make a full assignment of proton signals of **202, 223,** and **228,** comparison was made with the spectra of **32** and **97,** and results are shown in Table X.

b. 19-Hydroxytabernaelegantine A (216) and 19′,20′-Dihydrotabernamine (206). *T. coffeoides (Hazunta modesta)* from Madagascar has yielded a large number of monomeric indole alkaloids of different structural types and also three bisindole alkaloids. One of these was the previously discussed tabernaelegantine A (**214**) first isolated from *T. elegans* (*106, 107*). The second was the closely related (19*R*)-19-hydroxytabernaelegantine A (**216,** $C_{43}H_{54}N_4O_6$, MP 268°C, $[\alpha]_D$ −33°), and the third was identified as (20*S*)-19′,20′-dihydrotabernamine (**206,** $C_{40}H_{50}N_4O_2$) (*71*).

Both compounds displayed a typically indolic UV spectrum and a mass spectral fragmentation pattern for bisindole alkaloids of the dihydrovobasine–iboga type. The molecular ion at *m/z* 722 for **216,** 16 amu higher than tabernaelegantine A, indicated the presence of an additional oxygen somewhere in the molecule. Analysis of the spectrum showed the peaks for the dihydrovobasine portion as usual values, but peaks from the alicyclic part of the iboga portion were 2 amu less than in tabernaelegantine A. These facts, together with the presence of an [M − 18] peak at *m/z* 704 and of a doublet for Me-18 at 1.18 ppm (J = 6Hz), suggested that the additional oxygen was a hydroxy function (ν_{max} 3450 cm^{-1}) at C-19 in the iboga portion. The CMR spectrum confirmed this hypothesis and established (i) the (*R*) configuration at C-19 from the shift of C-15 and C-21 as for heyneanine (**122**) (ii) the β orientation of the ethyl chain at C-20′ [(*S*) configuration] from the shift of C-14′ and C-16′, identical to those of tabernaemontanine (**31**), and (iii) the point of attachment between C-3′ of the dihydrovobasine portion and C-12 of the 19-hydroxyisovoacanginyl portion as in tabernaelegantine A (**214**).

The mass spectral behavior of **206** (M^+· 618) and the ^{1}H-NMR spectrum indicated the absence of CO_2Me and OMe groups and suggested that **206** had a tabernaelegantine-like structure in which the iboga portion is ibogamine itself. In fact, **206** was obtained by condensation of tabernaemontaninol (**315**) and ibogamine under Büchi's conditions. In order to define the point of linkage of C-3′ to the aromatic portion, an ingenious although indirect method was used. Selective methylation of N^1 in **206** led to a complex mixture. N^1-methyl-(20′*S*)-19′,20′-dihydrotabernamine ($C_{41}H_{52}N_4O_2$, MP 270°C, $[\alpha]_D$ −68°) was obtained by replacing N^1-methylibogamine (**316**) in the above condensation. Seven aromatic protons were present among which an ABX system for 1,2,4-related protons was observed at 7.38 (d, J = 8 Hz), 6.94 (dd, J = 8 and 2 Hz), and 7.01 ppm (broad d, J = 2 Hz). Irradiation of N^1-Me of the ibogamine half resulted in a 9% increase in the area of the signal at 7.01 ppm, which is then attributed to H-12. As a consequence, the natural compound possesses structure **206.**



316

c. 11-Demethylconoduramine 255. 11-Demethylconoduramine (**225**, $C_{42}H_{50}N_4O_5$) was obtained by Verpoorte *et al.* from the root bark and stem bark of *T. pachysiphon* together with other known alkaloids related to conoduramine (**226**) and conodurine (**230**) (*160*). The UV spectrum of **225** showed a mainly indolic structure with maxima at 224, 286, and 294 nm and a shoulder at 303 nm, shifted to 323 nm on addition of base. In the mass spectrum, a molecular ion was observed at *m/z* 690, 14 amu less than conoduramine. Fragments at *m/z* 194, 182, 180, and 122 and at 208, 148, 136, and 122 (belonging to the vobasine half and the iboga half, respectively) suggested that no changes had taken place in the aliphatic part of both halves. Therefore, the loss of mass must have occurred in the aromatic iboga portion. The ^{1}H-NMR spectrum was almost superimposable on that of **226** except for the lack of the 11-methoxy group at 3.97 ppm. Thus the structure **225** was proposed for this alkaloid; however, any chemical correlation with conoduramine failed. Prolonged treatment with CH_2N_2, even in the presence of BF_3, left starting material unaffected, probably because of steric hindrance by the vobasine half.

3. Plumeran–Ibogan-Type Alkaloids

a. Tetrastachyne (240) and Tetrastachynine (241). From the leaves of *T. siphilitica (Bonafousia tetrastachya)* from French Guiana, Ahond *et al.* isolated three new alkaloids in addition to the known 12,12′-bis(11-hydroxycoronaridinyl) (**250**) and bonafousine **251.** The new alkaloids were tetrastachyne (**240**, $C_{42}H_{50}N_4O_6$, $[\alpha]_D$ −248°) and tetrastachynine (**241**, $C_{42}H_{50}N_4O_6$, $[\alpha]_D$ 0°) belonging to the rare plumeran–ibogan type and an isomer of bonafousine (see below) (*179*). Both alkaloids afforded a molecular ion at *m/z* 704 accompanied by a variable proportion of an intermolecular transmethylation ion at *m/z* 720, similar to that observed for other dimers (voacamines, tabernaelegantines). Significant fragment ions were observed at *m/z* 136 and 125 and at 124, characteristic of iboga and *Aspidosperma* moieties, respectively. In the UV spectrum, an almost typical hydroxyindole chromophore was observed for both compounds, which exhibited the characteristic bathochromic shift on addition of alkali. Their IR spectra were also quite similar and indicated the presence of NH, OH, saturated, and unsaturated ester functions.

Methylation of **240** with diazomethane yielded a monomethyl ether whose UV

spectrum remained unchanged on addition of alkali, suggesting that one oxygen is engaged in an ether linkage. On the other hand, a dimethyl ether was obtained by methylation of **241,** and its mass spectrum contained a remarkable peak at *m/z* 367 [$M^{+\cdot} - 367$], which indicated that the two monomeric units contained the same number of oxygen atoms (CO_2Me + phenolic OH).

The only recognizable signals in the ^{1}H-NMR spectrum of methoxytetrastachyne were two triplets attributable to two ethyl chains at 0.65 and 0.86 ppm, two CO_2Me groups at 3.57 and 3.72 ppm, an aromatic methoxyl at 3.69 ppm, and AB system of ortho-coupled aromatic protons at 6.89 and 7.29 ppm (J = 8.5 Hz), and a three-spin system for contiguous protons at 6.41 (dd, J = 8.5, 1.5 Hz), 6.70 (dd, J = 8.5, 8 Hz), and 6.97 ppm (dd, J = 8, 1.5 Hz).

The key to establishing the structure of these alkaloids was supplied by analysis of the CMR spectra. In the region below 75 ppm, all saturated carbons appeared at virtually the same chemical shift in both compounds and comparison with the data of **250** and 12-hydroxyvincadifformine (**71**), also found in the leaves of *T. siphilitica,* indicated that the bisindole alkaloids contained unsubstituted aliphatic moieties of the above compounds. Examination of the sp^2-carbon zone of **240** revealed, in addition to C-2 and C-16, the presence of six carbons, three of which (C-8, C-9, and C-10) had the same chemical shift as in 12-hydroxyvincadifformine. C-11, C-12, and C-13 showed small but diagnostic shifts attributable to the etherification of 12-OH. The other signals were in agreement with those of an 11-hydroxycoronaridine substituted at C-12 by an oxygen. Six aromatic carbons of **241** corresponded to those of **250,** indicating a C—C bond linkage between the two halves. The others carbons were those expected for an 11-substituted 12-hydroxyvincadifformine. The alkaloids were thus assigned isomeric structures **240** and **241,** presumably derived by attack of a phenoxy radical of 12-hydroxyvincadifformine to 11-hydroxycoronaridine.

b. Ervafoline and Ervafolidine Alkaloids. Examination of the leaves of *T. heterophylla (Stenosolen heterophyllus),* a shrub native to French Guiana, led to the further isolation of several monomeric and bisindole alkaloids (*120*). Among the latter, ervafoline (**246**), 19′-hydroxyervafoline (**247**), ervafolene (**248**), 19′-hydroxyervafolene (**249**), ervafolidine (**242**), 3-epiervafolidine (**243**), (19′*R*)-19′-hydroxyervafolidine (**244**), and (19′*S*)-19′-hydroxy-3-epiervafolidine (**245**) represent the first members of a new group of bisindole alkaloids, formed by plumeran-type and modified ibogan-type units. In addition, **246–249** are unique among dimeric alkaloids because three bonds link the two halves of the molecule. Ervafoline (**246**), ervafolidine (**242**), and 3-epiervafolidine (isoervafolidine) (**243**) were also previously isolated from *Ervatamia pandacaqui* (*117*).

Ervafoline Series. Ervafoline (**246,** $C_{40}H_{44}N_4O_4$ (high resolution mass spectrometry), MP 285°C, $[\alpha]_D$ +279°) showed UV maxima at 252, 306, and 326 nm owing to the presence of β-anilinoacrylic and dihydroindole chromphores. In the

^{1}H-NMR spectrum ($CDCl_3$ containing a small amount of TFA) only one indolic NH at 9.20 ppm and two three-proton triplets at 0.97 and 1.06 ppm were observed, attributable to the presence of two ethyl chains. The CMR spectrum revealed the presence of a quaternary N—C—O as a singlet at 103.4 ppm and an oxirane ring with doublets at 51.7 and 57.0 ppm, similar to the signals of C-14 and C-15 of hazuntinine (**73**) or pachysiphine (**75**).

Ervafoline did not fragment under the acidic conditons used for the cleavage of other bisindole alkaloids. The complete structure and relative stereochemistry of ervafoline, as shown in formula **246,** were determined by a single-crystal X-ray study.

With the structure determined, a detailed analysis of the 400-MHz ^{1}H-NMR spectrum was performed in comparison with other ervafolines (Table XI) (*214*). Characteristic were the singlet at 3.86 ppm for H-3 and the multiplet at 5.64 ppm for aromatic H-12′. The unusual shift of the latter proton is due to the anisotropic effect of the neighboring aromatic ring in the lower part (part B) of the dimer.

19′-Hydroxyervafoline (**247,** $C_{40}H_{44}N_4O_5$, MP 258°C, $[\alpha]_D$ +247°) was found to have the same UV absorptions as **246** and a molecular ion at *m/z* 660, 16 amu higher than **246,** indicating the presence of an additional oxygen. Analysis of the mass spectrum showed highly diagnostic peaks at *m/z* 214 and 154, ascribed to ions **282** and **317,** respectively. Another fragment was observed at *m/z* 333, shifted 1 amu higher on deuteration. The structure of this ion was not given; however, it was also present in the mass spectrum of **246** and considered a characteristic feature of ervafoline alkaloids, derived from part B. The presence of fragments at *m/z* 154 and 333 indicated that the additional oxygen, unlike the case of ervafoline, was embodied in the upper part (part A) of the dimer.

Acetylation of **247** furnished a monoacetate (M^+ · 702) whose ^{1}H-NMR spectrum demonstrated the presence of a hydroxy group at C-19 (quintet at 5.07 ppm and doublet at 1.38 ppm for H-19 and Me-18, respectively). Exhaustive double-

TABLE XI

^{1}H-NMR DATA FOR ALIPHATIC PROTONS OF ERVAFOLINE (**246**) (*214*), 19′-HYDROXYERVAFOLINE (**247**), ERVAFOLENE (**248**), AND 19′-HYDROXYERVAFOLENE (**249**) (*119*)

	Chemical shifts (ppm)			
Proton	**246**	**247**	**248**	**249**
H-3	3.86 s	3.84 s	3.90 s	3.87 s
H^R-5	2.8[a] m	2.83 br dd	2.9[a] m	2.8[a] m
H^S-5	3.5[a] m	3.4 m	3.5[a] m	3.4[a] m
H^R-6	1.8 m	1.8 m	1.8 m	1.8 m
H^S-6	1.68 ddd	1.74 br dd	1.7 m	1.8 m
H^R-15	2.11 d	2.10 d	2.15 d	2.12 d

TABLE XI (*Continued*)

Proton	Chemical shifts (ppm)			
	246	**247**	**248**	**249**
H^S-15	2.00 d	2.00 d	2.01 d	2.00 d
H^R-17	2.94 d	2.94 d	2.95 d	2.94 d
H^S-17	2.49 d	2.49 d	2.50 d	2.49 d
H-18	0.96 t	0.96 t	0.96 t	0.96 t
H^R-19	1.78[b] br q	1.8 br q	1.8 br q	1.76 br q
H^S-19	1.80[b] br q	1.8 br q	1.8 br q	1.76 br q
H-21	3.54 d	3.54 d	3.50 d	3.49 d
CO_2Me	3.75 s	3.76 s	3.78 s	3.75 s
NH	9.20 s	9.18 br s	9.24 br s	9.22 s
H^R-3′	3.10 br d	3.15 br d	3.18 br d	3.15 br d
H^S-3′	3.47 dd	3.46 dd	3.38 dd	3.38 dd
H^R-5′	3.10[c] m	3.0[a] m	3.0[b] m	3.0[b] m
H^S-5′	3.15[c] m	3.1[a] m	3.1[b] m	3.1[b] m
H^R-6′	2.15 br dd	2.17 br dd	2.34 br dd	2.35 br dd
H^S-6′	1.24 br dd	1.24 br dd	1.2 m	1.15 br dd
H-14′	3.25 br dd	3.25 br dd	5.92 ddd	6.02 ddd
H-15′	3.03 d	3.03 d	5.75 br d	5.66 br d
H-16′	3.10 br d	3.28 br dd	3.12 br d	3.58 br dd
H^R-17′	1.92 dd	1.82 dd	—[e]	1.82 dd
H^S-17′	1.35 dd	1.90 dd	—[e]	1.52 dd
H^R-18′	0.97 t	1.38 d	0.90 t	1.23 d
H^R-19′	1.51[d] dq	3.9 br q	1.5[c] m	3.9 br q
H^S-19′	1.63[d] dq	—	1.6[c] m	—
NH	2.58 s	2.58 s	2.75 s	2.95 s

Coupling constants (Hz)

246: $J_{5R,6S} \sim 1$, $J_{5S,6S} = 6.5$, $J_{6R,6S} = 13.5$, $J_{15R,15S} = 12$, $J_{17R,17S} = 17.5$, $J_{18,19R} = 7.5$, $J_{18,19S} = 7.5$, $J_{21,16'} = 0.3$, $J_{3'R,3'S} = 14$, $J_{3'R,14'} < 0.3$, $J_{3'S,14'} = 1.5$, $J_{5'R,6'R} = 12$, $J_{5'R,6'S} \sim 0.5$, $J_{5'S,6'R} = 6$, $J_{5'S,6'S} = 6$, $J_{6'R,6'S} = 15$, $J_{14',15'} = 4.5$, $J_{16',17'R} = 2.5$, $J_{16',17'S} = 12$, $J_{17'R,17'S} = 13$, $J_{18',19'R} = 7$, $J_{18',19'S} = 7$, $J_{19'R,19'S} = 14$

247: $J_{15R,15S} = 12$, $J_{17R,17S} = 17$, $J_{18,19R} = 7.5$, $J_{18,19S} = 7.5$, $J_{21,16'} < 0.3$, $J_{3'R,3'S} = 14$, $J_{3'R,14'} < 0.3$, $J_{3'S,14'} = 1.5$, $J_{5'R,6'R} = 12$, $J_{5'R,6'S} \sim 0.5$, $J_{5'S,6'R} = 6$, $J_{5'S,6'S} = 6$, $J_{6'R,6'S} = 15$, $J_{14',15'} = 4.5$, $J_{16',17'R} \sim 2.5$, $J_{16',17'S} = 12$, $J_{17'R,17'S} = 13$, $J_{18',19'} = 7$

248: $J_{15R,15S} = 12$, $J_{17R,17S} = 17.5$, $J_{18,19R} = 7.5$, $J_{18,19S} = 7.5$, $J_{21,16'} < 0.3$, $J_{3'R,3'S} = 14$, $J_{3'R,14'} < 0.5$, $J_{3'S,14'} = = 5$, $J_{3'R,15'R} < 0.5$, $J_{3'S,15'} < 0.3$, $J_{5'R,6'R} = 12$, $J_{5'R,6'S} \sim 0.5$, $J_{6'R,6'S} = 15$, $J_{14',15'} = 9.5$, $J_{16',17'S} = 12$, $J_{18',19'R} = 7$, $J_{18',19'S} = 7$

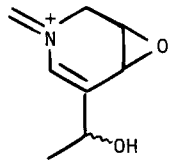
249: $J_{15R,15S} = 12$, $J_{17R,17S} = 17$, $J_{18,19R} = 7.5$, $J_{18,19S} = 7.5$, $J_{21,16'} < 0.3$, $J_{3'R,3'S} = 14$, $J_{3'R,14'} < 0.5$, $J_{3'S,14'} = 5$, $J_{3'R,15'} < 0.5$, $J_{3'S,15'} < 0.3$, $J_{5'R,6'R} = 12$, $J_{5'R,6'S} \sim 0.5$, $J_{5'S,6'R} = 6$, $J_{5'S,6'S} = 6$, $J_{6'R,6'S} = 15$, $J_{14',15'} = 9.5$, $J_{16',17'R} \sim 2.5$, $J_{16',17'S} = 12$, $J_{17'R,17'S} = 13$, $J_{18',19'} = 7$

[a,b,c,d] Assignments may be reversed.

[e] Obscured by impurities.

resonance experiments and comparison with **246** allowed the assignment of all the protons of 19′-hydroxyervafoline (**247**) (Table XI).

Ervafoline (**248,** $C_{40}H_{44}N_4O_3$, $[\alpha]_D$ +236°), isolated as an amorphous compound, had the same UV spectrum as that of **246** and **247.** The IR spectrum revealed the presence of a carbonyl group (1690 cm^{-1}) and a double bond (1620 cm^{-1}). In addition to the molecular ion at *m/z* 628, structurally useful fragments were observed at *m/z* 414 [$M^{+\cdot}$ − 214], 333 (see above), 214, and 122. From the simultaneous presence of peaks at *m/z* 333 and 122 (**318**), it would appear



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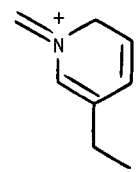


318

that ervafolene is a derivative of ervafoline where the 14′, 15′-epoxy group is replaced by a carbon–carbon double bond. This is confirmed by the finding in the ^{1}H-NMR spectrum at 400-MHz (Table XI) of a ddd at 5.92 ppm ($J_{14',15'}$ = 9.5 Hz, $J_{3'S,14'}$ = 5 Hz, $J_{3'R,14'}$ <0.5 Hz) for H-14′ and a broadened d at 5.75 ppm for H-15′ and by the disappearance of the two signals at 3.25 and 3.03 ppm for H-14′ and H-15′, respectively, in ervafoline (**246**).

The ^{1}H-NMR spectrum of 19′-hydroxyervafolene (**249,** $C_{40}H_{44}N_4O_4$, MP 248°C, $[\alpha]_D$ +284°) indicated clearly that it possessed the same double bond as in **248,** while the doublet at 1.23 ppm (J = 7 Hz) attributable to Me-18 was reminiscent of the secondary OH at C-19′, as in **247.** Catalytic hydrogenation afforded a dihydro derivative ($M^{+\cdot}$ 646) and acetylation gave a monoacetate ($M^{+\cdot}$ 686), furnishing chemical evidence of the presence of both the double bond and the hydroxy group. Structure **249** was further supported by complete analysis of the proton spectrum.

Ervafolidine Series. Ervafolidine (**242,** $C_{40}H_{46}N_4O_5$, MP 240°C, $[\alpha]_D$ +20°) showed λ_{max} 234(sh), 248, 306, and 324 nm, typical of the β-anilinoacrylic and dihydroindole chromophores. The IR spectrum substantiated the presence of a C=CCO_2Me grouping (1685 and 1610 cm^{-1}). Compound **242** was therefore closely related to **246,** containing one additional oxygen atom and two hydrogens, suggesting the hydrolytic cleavage of one ring or bond. The mass spectrum showed peaks at *m/z* 108 and 138, typical of an epoxy-substituted piperidine nucleus as found in part A of ervavoline, while the absence of peaks at m/z 333 suggested a change in part B.

Examination of the ^{1}H-NMR spectrum in comparison with that of **246** indicated the presence of two ethyl chains (Me—CH_2 signals at 0.82 and 1.08 ppm with J = 7 Hz) and also confirmed the presence of an epoxy ring (H-15′ at 2.92

ppm as a doublet, $J = 4.5$ Hz, coupled with a broadened dd at 3.26 ppm ascribed to H-14′).

On acetylation, a monoacetate (M^+ · 704) was formed in which a 1H singlet appeared at 5.20 ppm (versus 3.87 ppm in **242**), suggesting the presence of a secondary hydroxyl surrounded by two nonprotonated carbons. This feature, coupled with biogenetic reasoning (see below) led to structure **242** for ervafolidine, and it was further supported by comparison of the 400-MHz ^{1}H-NMR spectrum with that of 3-epiervafolidine (**243**) (see below) whose structure was based on X-ray analysis.

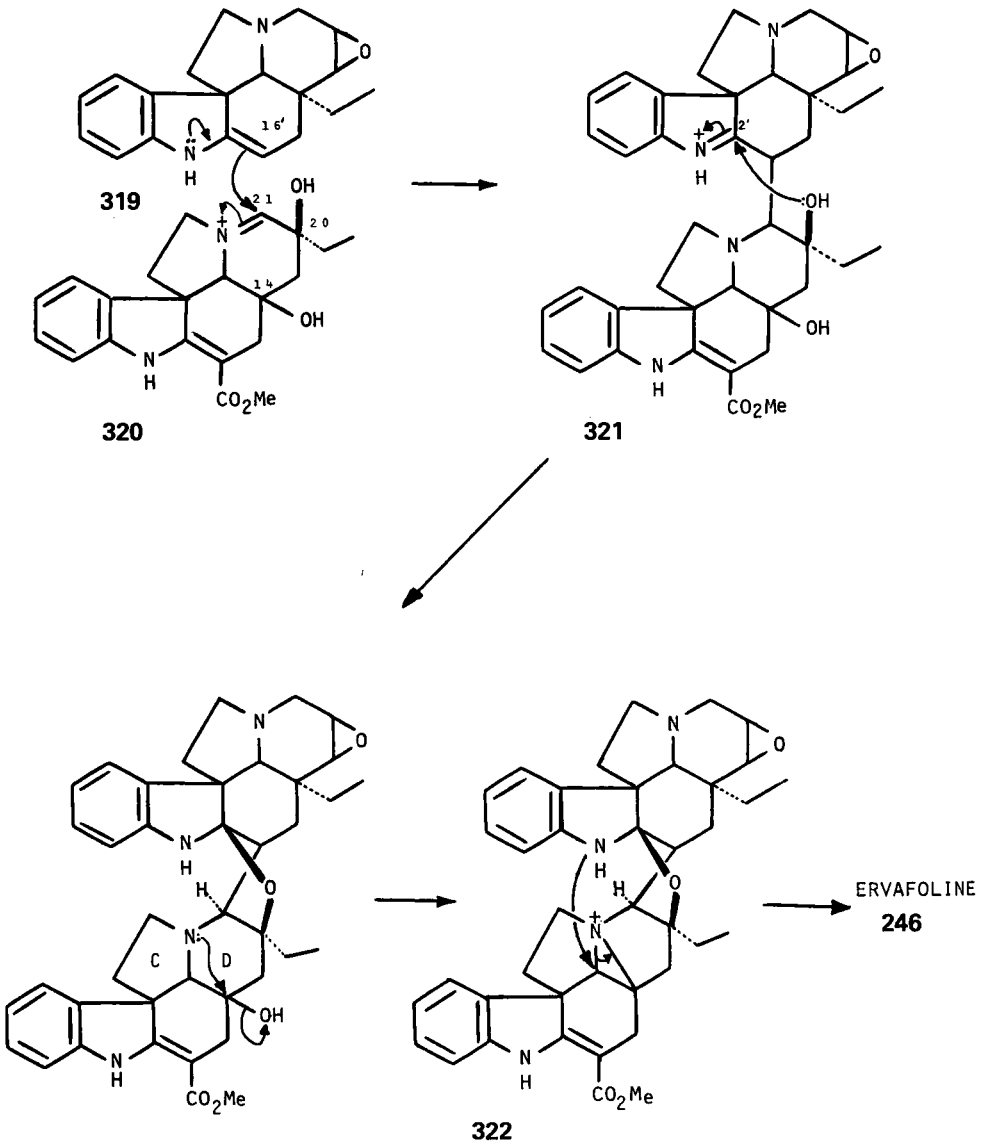
3-Epiervafolidine ($C_{40}H_{46}N_4O_5$) was a crystalline compound (MP >256°C, $[\alpha]_D$ +52°) and could be analyzed by X-ray crystallography, resulting in formula **243.** The only significant difference between it and ervafolidine was the downfield shift of H-3 in the ^{1}H-NMR spectrum at 4.14 ppm as a doublet (J = 5Hz) attributable to the coupling with the hydroxy proton. This is a characteristic feature of alkaloids of this series with a (3*S*) configuration.

(19′*R*)-19′-Hydroxyervafolidine (**244,** $C_{40}H_{46}N_4O_6$, MP 260°C, $[\alpha]_D$ +33°) gave a UV spectrum identical to that of **242** and **243.** The additional oxygen was placed on an ethyl chain as seen in the ^{1}H NMR spectrum, which contained a doublet (J = 7 Hz) at 1.19 ppm coupled with a quartet at 3.74 ppm, suggesting the group MeCHOH. On acetylation, **244** furnished a diacetate (M^+ · 762) whose ^{1}H-NMR spectrum showed two singlets for $MeCO_2$, at 1.74 and 1.88 ppm, while H-19′ and H-3 resonated at 4.83 and 5.51 ppm, respectively. The close analogy between spectroscopic characteristics of **244** and **242** suggested a strict relationship between the two molecules. Formula **244** with a (19′*R*) configuration was corroborated by X-ray analysis.

(19′*S*)-19′-Hydroxy-3-epiervafolidine (**245,** $C_{40}H_{46}N_4O_6$, MP 260°C $[\alpha]_D$ +74°) was easily recognized to be epimeric at C-3 with respect to **244** from the great similarity of the spectra and from the diagnostic difference in the H-3 shift (4.16 ppm, d). Other differences were found in the chemical shifts of H-16′ and H-17′, and these were also interpreted as originating from an epimeric configuration at C-19′.

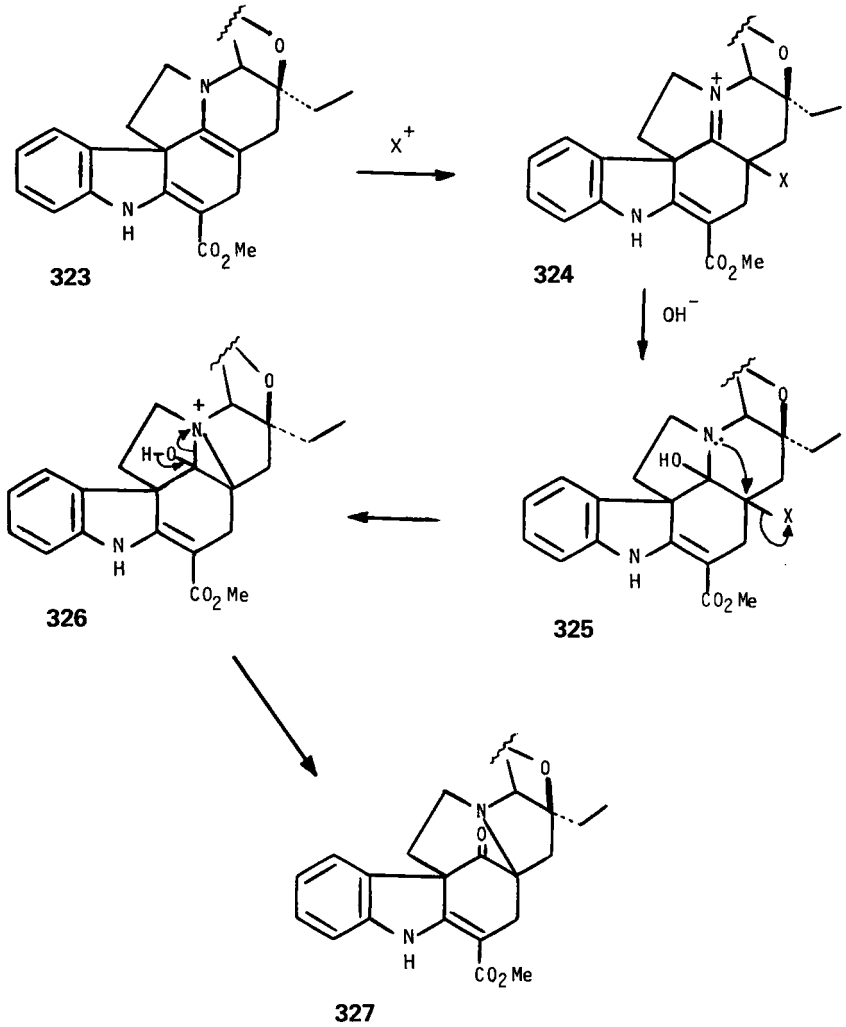
A difference in conformation of molecules in the ervafolene and ervafolidine series emerged from X-ray analysis. In ervafolene (**246**), where C-3 is linked to $N^{1'}$, a cis relationship between N^4 lone pair and the bond between C-14 and C-17 was observed. Also the lone pair of $N^{4'}$ was cis to the ethyl chain at C-20′. In 3-epiervafolidine and (19′*R*)-19′-hydroxyervafolidine, the molecule adopted an identical conformation with the lone pair of N^4 and $N^{4'}$, trans with respect to the C-14—C-17 bond and the ethyl chain, respectively. The absolute configurations depicted in formulas **242–249** were deduced from relative configurations and based on the assumption that the ibogan half of the molecule was derived from 20-epipandoline (**165**) whose absolute configuration is known.

Biogenetic Considerations. The structural novelty of ervafoline–ervafolidine



SCHEME 13

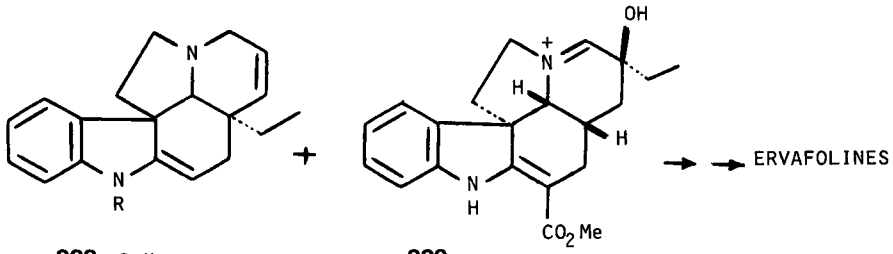
alkaloids raised some interesting biogenetic problems. According to the structure, ervafoline could reasonably be derived from a nucleophilic attack of the epoxyenamine **319** on the iminium salt of a properly modified 20-epipandoline **320** with the formation of a C—C bond between positions 16′ and 21. The intermediate indoleninium ion **321** could be intramolecularly captured by the



SCHEME 14

tertiary β-oriented C-20-OH of the 20-epipandoline unit. Finally, the contraction of ring D and enlargement of ring C could be envisaged as having been derived from an N^4-assisted internal displacement of C-14-OH to form an aziridinium ion (**322**), which could undergo nucleophilic opening by attack of the $N^{1'}$ of the upper half (Scheme 13).

Alternatively, the ring C/D enlargement–contraction to form the spiroindolenine moiety could take place via an electrophilic attack on bisindolenamine **323** to afford the iminium ion **324** or its equivalent carbinolamine **325.** Ring closure to hydroxyaziridinium ion **326,** followed by C—C fragmentation could



328 R=H
335 R=Me

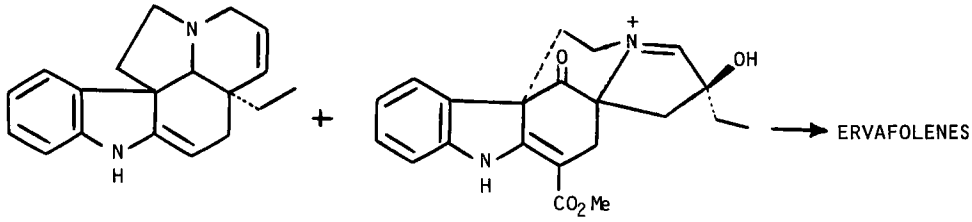
329

SCHEME 15

lead to the spiroketone **327.** This compound could be the key intermediate for the production of either ervafoline alkaloids (intramolecular reductive amination of C-3 carbonyl by $N^{1'}$) or ervafolidine alkaloids (nonstereodiscerning reduction of the C-3 carbonyl) (Scheme 14).

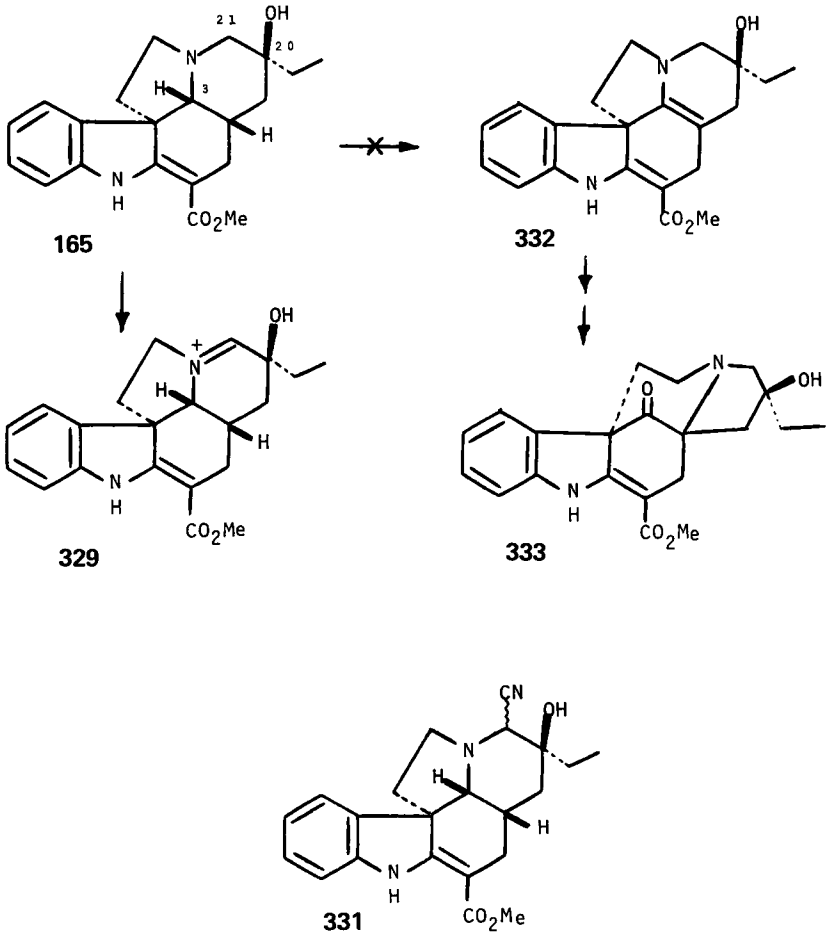
Synthetic Approach. The above biogenetic proposals have inspired two interesting strategies for the synthesis of ervavoline–ervafolene ring systems. In the first approach (Scheme 15), the enamine **328,** derived from decarbomethoxylation of tabersonine, should react with the iminium salt **329** (see below), derived from 20-epipandoline **165,** followed by ring contraction. The second convergent approach (Scheme 16) would involve an initial contraction of ring D of 20-epipandoline, followed by oxidation to the iminium ion **330** (see below) and condensation with the imine **328.** It is worth mentioning that monomeric alkaloids having the skeleton of **330** are unknown, and this could suggest that the ring contraction–enlargement process takes place after the dimerization step.

The formation of iminium ions of 20-epipandoline occurred only under Polonovski–Potier conditions. Thus on treatment of the *N*-oxide of **165** with trifluoroacetic anhydride followed by an aqueous solution of KCN, the iminium ion **329** was obtained, readily isolated as the corresponding α-amino nitrile **331** (Scheme 17). The reaction was completely regioselective and no traces of the enamine **332** could be obtained. This made the synthesis of spiroketone **333**



328 **330**

SCHEME 16

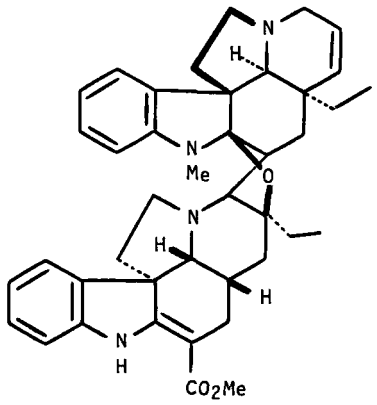


SCHEME 17

impossible, and as a consequence the second route was abandoned. The synthesis along the lines of the first approach met only partial success and could lead no further than the model compound **334.**

Coupling of the more activated enamine **335,** obtained in two steps from tabersonine, with 21-cyano-20-epipandoline (**331**) in the presence of $AgBF_4$ in THF solution gave the dimer **334** in 20% yield. Its structure was based on spectral data, particularly CMR. Diagnostic were the chemical shifts for C-2′ at 104.1 ppm (versus 103.4 ppm in ervafoline) and the upfield shift of C-6′ at 35.3 ppm (ascribed to the γ effect).

The stereochemical outcome at C-2′, C-16′, and C-21′ was the same as in the natural products. It is dictated by the stereochemistry of C-20 in 20-epipan-



334

doline, and it is the result of the most favored course in the condensation of the two reacting species. Although till now the desired rearrangement could not be achieved, this strategy allowed preparation of a derivative whose natural occurrence cannot be a priori ruled out.

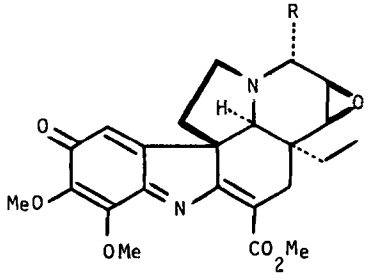
4. Ibogan–Canthione-Type Alkaloids

Isobonafousine (**252,** $C_{36}H_{42}N_4O_3$, $[\alpha]_D$ +19°), from the leaves of *T. siphilitica (Bonafousia tetrastachya)*, is the second bisindole alkaloid containing an ibogan unit and a hexahydrocanthinone unit. The UV spectrum and mass spectral fragmentations were identical to those of bonafousine (**251**). In particular, the mass spectrum showed peaks at *m/z* 211, 184, 170, and 169 attributable to the canthinone half and peaks at *m/z* 136, 135, 122, and 121 attributable to the aliphatic part of the coronaridine unit. A transmethylation ion was also observed as in **251** and other dimers. The ^{1}H-NMR spectrum indicated a CO_2Me grouping (2.91 ppm versus 3.24 ppm in **251**), strongly shielded by the indole moiety of the canthinone unit. The CMR spectrum showed the invariant presence of all carbons of 12-substituted 11-hydroxycoronaridine, whereas the carbons of canthinone had the same multiplicity but slightly different shifts. In fact, the C-1 triplet near 21 ppm was missing, and, instead, another methylene appeared at 29.4 or 29.7 ppm in the vicinity of C-5′. This suggested that 11-hydroxycoronaridine was linked to C-2′ and occupied an equatorial orientation because C-3′a at 50.1 ppm was not affected. The CD curves of **252** and **251** were identical, and thus the absolute stereochemistry of isobonafousine is that represented in formula **252.**

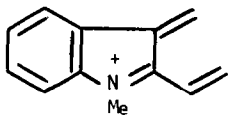
5. Plumeran–Macroline-Type Alkaloids

From the leaves of *Pandacastrum saccharatum,* a species of the Apocynaceae now classified under *Tabernaemontana,* Das *et al.* isolated a novel bisindole

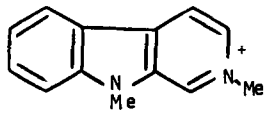
alkaloid, pandicine (**254**, $C_{44}H_{50}N_4O_7$), as an amorphous, air-sensitive compound possessing a hitherto unknown highly oxygenated tabersonine skeleton linked at its C-3 position to the C-18 position of a modified macroline moiety (*183*). Pandicine showed UV maxima at 231, 234, 250(sh), 297, 307, and 342 nm. On acid treatment, the maxima were observed at 228, 265, 297, 304, and 342 nm, while in alkaline medium there was a bathochromic shift to the visible. Compound **253** was easily oxidized to the iminoquinone **336** [λ_{max} 233, 260,



336 R: as in **254**



337



338

288(sh) and 396 nm; H-9 at 5.63 ppm versus 6.34 ppm in **253**], which was responsible for the brown color of pandicine and precluded the determination of optical rotation. Its mass spectrum displayed peaks at *m/z* 170 and 197 attributable to ions 337 and 338, respectively, characteristic of a macroline skeleton (*215*). Complementary peaks at *m/z* 290 and 456 [$M^{+\cdot} - 290$] might be attributed to retro-Diels–Alder opening of ring C in a plumeran skeleton, followed by cleavage of the C-5—C-6 bond.

The structure elucidation of pandicine is based almost completely on CMR analysis. Comparison with the spectrum of criophylline (*216*) revealed the presence of all of the aliphatic carbons of the 3-substituted 14β,15β-epoxytabersonine half. Only C-3 has a different shift owing to the change of the substituent at this center. The assignment of the aromatic carbon signals of the substituted tabersonine was based on chemical shift additivity rules and oxidation to iminoquinone **336.** The two aromatic methoxyls resonated at unusual downfield positions, 60.5 and 61.0 ppm, and these values were consistent with an ortho arrangement that forces the sterically crowded OMe out of the plane of the aromatic ring. The carbons belonging to the macroline portion of **254** showed a

resemblance with those of villalstonine (*217*) except for C-18′, C-19′, C-20′, and C-21′, reflecting a structural modification in this region of the molecule.

The C-18′, C-19′, and C-21′ protons showed signals at 5.05 ppm (dd, J = 16, 8 Hz), 5.85 ppm (d, J = 16 Hz), and 6.41 (s), compatible with an exocyclic trans-substituted C-18′/C-19′ double bond conjugated with a dihydropyran system. Irradiation of H-18′ provided the key to the linkage between the macroline and substituted tabersonine moieties. In fact, the H-3 signal at 3.95 ppm (J = 8, 1 Hz) was simplified to a doublet (J = 1 Hz) coupled in turn to the AB system of H-14 and H-15 at 3.15 ppm (J = 3, 1 Hz) and 3.07 ppm (J = 3 Hz), respectively). These results led to formula **254** for pandicine. Although there is no proof for the relative stereochemistry of the two units, the one depicted in formula **254** is based on the configuration of the naturally occurring monomers of macroline and 10,11-dimethoxy-14β,15β-epoxytabersonine (hazuntinine).

V. Pharmacology

Tabernaemontana plants are mentioned in ethnobotanical literature for their broad use in traditional medicine or for nonmedicinal purposes, mainly as sources of wood, rubber, arrow poison, birdlime, and others (*9*). Ethnopharmacological data are available for about 70 species, some of them not yet chemically investigated.

The most common medicinal use of many different species from all tropical regions is based on their antimicrobial action against infections or wounds, inflamation of nails, eyes, and throat, and against syphilis and Hansen's disease. Antiparasitic activity against dysentery, diarrhea, and intestinal worms, as well as activity for the treatment of skin ulcers and abscesses has also been reported. Some species are used as analgesics against headache, toothache, and pains in general. Other species showed purgative and febrifuge activity as well as central nervous system (CNS) action, mainly tonic and stimulant activity. These activities are most probably due to the presence of alkaloids, which are the main secondary metabolites in the plants. Although much attention has been paid to isolation and structure elucidation of alkaloids, relatively little pharmacological research has been carried out on either crude extracts or isolated alkaloids (*9*).

The extracts of *T. affinis, T. arborea, T. divaricata, T. heyneana,* and *T. pandacaqui* showed some degree of antitumor activity, whereas the extracts of *T. malaccensis, T. dichotoma,* and *T. crassa* exhibited hypotensive effects (*9*). Recently a systematic antimicrobial, antiamoebic, and antiviral screening of 19 different *Tabernaemontana* species has been carried out with positive results (*218*).

Pharmacological activity has been studied for about 40 *T.* alkaloids. Some of these have been studied during a plant antitumor screening program carried out under the auspices of the National Cancer Institute of the U.S. National Institute

of Health, and it was found that some alkaloids exhibited antimicrobic, cytostatic, and antiviral activities. The results of pharmacological screening are not of special interest except for camptothecine (**3**), its 9-methoxy analog (**4**), and vincamine (**91**), each of which has been studied in several clinical trails. It is noteworthy that these alkaloids are not characteristic of this species, being found in larger quantities in other plants.

A. Cytotoxicity

Cytotoxicity has been evaluated against the cell culture KB of the human carcinoma of the nasopharynx and lymphocyte carcinoma of the mouse P388. Alkaloids tested are reported in Table XII. These data indicate that dimeric

TABLE XII
CYTOTOXICITY OF *TABERNAEMONTANA* ALKALOIDS AS THE ED_{50} (μg/ml)

Alkaloid	*P*-388 cells	KB cells	References
Apparicine (**66**) (NSC 85631)	3.8	—	*128*
Camptothecine (**3**) (NSC 94600)	0.053	0.17	*127,128*
9-Methoxycamptothecine (**4**) (NSC 176323)	0.0036	—	*127,128*
Conoduramine (**266**)	20	19	*134,219*
Conodurine (**230**)	26	31	*134,219*
3-(2′-Oxopropyl)conodurine (**232**)	2.4	—	*159*
Coronaridine (**97**) (NSC 127490)	0.43	—	*128*
10-Hydroxycoronaridine (**98**)	25	—	*128*
Gabunamine (**244**)	1.3	5.8	*134,200*
Gabunine (**229**)	3.2	—	*134,159,200*
Heyneanine (**122**) (NSC 306218)	7.4	—	*127*
Ibogamine (**134**)	—	>100	*200*
Lochnericine (**74**)	—	1.1	*220*
Olivacine (**195**)	—	0.4	*221*
Perivine (**25**)	20	70	*134,219*
Tabernamine (**201**)	2.1	—	*134,219*
Tubotaiwine (**61**)	23.0	—	*158*
Tubotaiwine *N*-oxide (**62**)	1.8	—	*158*
O-Acetylvallesamine (**65**)	26	—	*128*
Vallesiachotamine (**1**)	1.1	3.56	*222*
Voacamidine (**205**)	14	—	*219*
Voacamine (**203**)	2.6	—	*219*
$N^{4'}$-Demethylvoacamine (**210**)	0.3	0.95	*219*
Voacangine (**100**)	6.8	5100	*219*
Voacangine hydroxyindolenine (**143**)	26	—	*128*
(6*R*)-3,6-Oxidovoacangine *N*-oxide (**132**)	3.2	—	*128*
(19*S*)-3,19-Oxidovoacangine (**133**)	16	—	*128*
19-Oxovoacangine (**117**)	27.0	—	*128*
Isovoacangine (**101**)	18	—	*134,219*
19-Epivoacorine (**212**)	1.7	—	*134,219*
Voacristine (**118**)	50	—	*128*
Vobasine (**32**)	—	100	*219*

compounds are much more active than the monomers from which they are derived and that $N^{4'}$-demethylation produces a marked increase of cytotoxicity. In fact, one of the most active compounds seems to be $N^{4'}$-demethylvoacamine (**210**). However, its activity is far from being comparable with that of camptothecine (**3**) and its 9-methoxy analog (**4**), originally isolated from the trunk of the Chinese tree *Camptotheca acuminata*. Camptothecine inhibits the growth of a wide range of experimental tumors (Walker 256 carcinosarcoma, L5178Y lymphoma, plasma cell tumor YPC-1, L1210 mouse leukemia, and others). The results of preliminary *in vivo* and *in vitro* experiments were very promising and prompted clinical trials; however, severe side effects, nausea, vomiting, diarrhea, hemorrhagic cystitis, and low incidence of positive response limited clinical application. Camptothecine is used in the People's Republic of China in the treatment of papillary cancer of the bladder and psoriasis. For a general survey of pharmacological activities of camptothecine and analogs, see Ref. *223*.

Olivacine (**195**) is also active against L1210 leukemia at 10 mg/kg.

B. Antimicrobial, Antiprotozoal, and Antiviral Activity

Conoduramine (**266**), conodurine (**230**), and voacamine (**203**), from *T. pachysiphon* have been found to be strongly active against Gram-positive *Bacillus subtillis* and *Streptococcus aureus* at a minium inhibitory concentration value of 4–20 μg/mL and 20–50 μg/mL, respectively. A moderate action was shown against Gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* (*160*). According to Achenbach *et al.* (*115*), 3-hydroxycoronaridine (**103**) exhibits strong antibiotic activity and the recently isolated dimeric vobparicine (**200**) shows strong activity against Gram-positive bacteria (*62*). Other *T.* alkaloids, such as affinisine (**16**), apparicine (**66**), ibogamine (**134**), iboxygaine (**139**), isovocangine (**101**), and tabernanthine (**136**), show antimicrobial activity, however, at too high a concentration to be of practical use (*224*). Olivacine (**195**) is the only alkaloid that has been found to inhibit the growth of the protozoa *Crithidia fasciculata* and *Trypanosoma cruzi* in culture (*225*). Lochnericine (**74**) and perivine (**25**) were shown to be inactive *in vitro* against Vaccinia VI and Polio III viruses. Apparicine (pericalline) (**66**) represents the most active indole alkaloid that was tested against Polio III virus, but it was inactive against Vaccinia VI (*226*).

C. Miscellaneous Pharmacological Activity

Affinine (**27**) shows a little CNS depression and no analgesic, antipyretic, antiedema and diuretic activity (*21*). Affinisine (**16**) is a CNS depressant at 50 mg/kg po in the mouse and possesses a moderate analgesic activity and no

diuretic activity (*21*). Apparicine (**66**), isolated also from *Catharanthus* and *Aspidosperma* species, shows a pronounced analeptic property (*227*). Coronaridine (**97**), also present in *Catharanthus ovalis* and *C. roseus*, was widely investigated for pharmacological activity; however, it has shown poor properties. As with the closely related catharanthine, it shows pronounced diuretic action, some analgesic effect, and CNS activity (*227*). Interestingly, it was found partially to prevent pregnancy in adult female rats, owing to some estrogenic activity (*126*). Dregamine (**30**) shows a little pharmacological activity as a local anesthetic, convulsant, and respiratory stimulant (*228*). Ervatamine (**44**), as the hydrochloride, affects membrane potential in frog nerve fibers by selectively blocking Na^+ channels and competes with benzocaine for the receptors for local anesthetics (*229*).

Ibogaine (**135**), also isolated from *Tabernanthe iboga* and other plants, has remarkable CNS stimulating properties and hallucinogenic activities. This explains the use of *T. iboga* by African hunters to help them stay motionless for long periods without loss of concentration. The closely related ibogaline (**137**) shows strong CNS stimulating properties, whereas the other analogs, ibogamine (**134**), iboxygaine (**139**), tabernanthine (**136**), voacangine (**100**), isovoacangine (**101**), voacristine (**118**), and conopharyngine (**102**), show a more or less pronounced CNS activity. All of these alkaloids cause bradycardia and blood pressure lowering (*228*).

Perivine **25** exhibits an enhanced local anesthetic activity with respect to cocaine in the rabbit-cornea test (*230*). Tabersonine (**67**) shows 25% of the hypotensive activity of reserpine on cats, (±)-vincadifformine shows 50% activity, whereas (−)-vincadifformine (*ent*-70) is inactive (*231*).

(+)-Vincamine (**91**) is the major alkaloid of *V. minor*, a plant used against headache and vertigo. It exerts a sedative CNS action and produces a fall in blood pressure. The principal activity is a moderate cerebral vasodilation. Clinical studies have demonstrated that i.v. administration of **91** to humans reduces the arterial blood pressure and increases cerebral blood flow and oxygen consumption. The improved cerebral hemodynamic conditions significantly and positively affect the state of patients with advanced arteriosclerosis with beneficial effects on memory, concentration, and behavior. It has thereafter been introduced under several trade names as a pharmaceutical in many European countries (*232*). Vobasine (**32**) has been widely studied; it exhibits a weak CNS depressive, analgesic, and antipyretic action (*21*).

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— CHAPTER 2 —

CORYNANTHEINE, YOHIMBINE, AND RELATED ALKALOIDS

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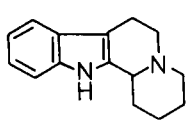
I. Introduction

During the past two decades a great number of papers have been published on the isolation, structure elucidation, synthesis and transformation, biogenesis, chemotaxonomy, and pharmacology of indole alkaloids. In this chapter we summarize the new results that appeared from 1968 to mid 1984 for the corynantheine–yohimbine group of monoterpene indole alkaloids with greater emphasis on their chemistry, excluding the related oxindoles and heteroyohimbines.

THE ALKALOIDS, VOL. 27

In 1965 and 1968, information regarding alkaloids of this type was reviewed in *The Alkaloids* (*1–4*). The approach in summarizing the previous results in four different chapters of this series is based on the chemotaxonomy of alkaloids in question. Now we wish to follow the new editorial policy of *The Alkaloids,* so the organization of this chapter is based on the system of chemical structure. First, we sum up the literature of simple alkaloids having the indolo[2,3-*a*]quinolizine ring system (**1**), then the mono- as well as the disubstituted indolo[2,3-*a*]quinolizine alkaloids, and finally to give a summary of the development of our knowledge about the yohimbine- and reserpine-type alkaloids, both having the dodecahydroindolo[2,3-*a*]benzo[*g*]quinolizine skeleton (**2**).



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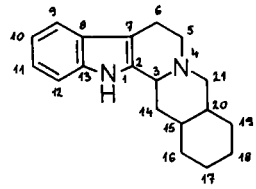

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Two important books on the biogenesis of indole alkaloids have been published (*5, 6*), therefore we do not intend to cover the literature of the biogenesis of corynantheine- and yohimbine-type alkaloids. Our chapter begins with the structure elucidation of the alkaloids isolated during the past two decades and proceeds with the synthesis, transformation, as well as spectroscopy of the alkaloids in question.

It should be mentioned that during the last 13 years the Royal Chemical Society published 13 volumes of *Special Periodical Reports on Alkaloids* (*7*), which in very brief form reconsidered the publications on alkaloid chemistry and biochemistry that appeared in the preceding years. Recently, this reviewing has been continued in *Natural Product Reports.*

The structures, primary sources, and literature of indole- as well as other type alkaloids are given in *Encyclopedia of the Alkaloids* (*8*). Two chapters on both corynantheine and yohimbine alkaloids have appeared in a volume of *Indoles* (*9*). The numbering system as well as the assignment of the relative configurations of stereo centers of alkaloids reported throughout this chapter follow the generally accepted biogenetic numbering system (*10*)*.

Botanical sources are listed as cited in the original references.

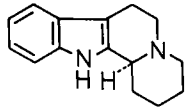
* Instead of "chirality center" we use the more recently introduced "stereo center" terminology (*10a*). According to the IUPAC 1957 Rules we should have depicted our compounds "upside down," but for the convenience of the reader we adhered to the traditional formulas.

II. Structural Elucidations

A. Simple Indoloquinolizine Alkaloids

1. Octahydroindoloquinolizine

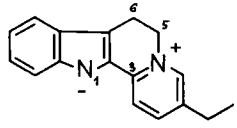
The simplest member of the indolo[2,3-*a*]quinolizine alkaloid group has been found in *Dracontomelum magniferum* B1. (*11*); it possesses structure (−)-**1**. No name has as yet been given for this levorotatory alkaloid.



(−)-**1**

2. 5,6-Dihydroflavopereirine

5,6-Dihydroflavopereirine (**3**) has been isolated from *Strychnos usambarenis* Gilg (*12*). The zwitterionic structure of the alkaloid has been proved by spectroscopic investigation and by direct comparison of the alkaloid with a synthetic 5,6-dihydroflavopereirine (**3**) sample.



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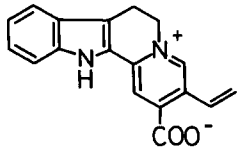
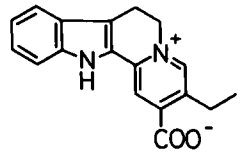
3. Vincarpine and Dihydrovincarpine

Two new zwitterionic alkaloids with a 5,6-dihydroindolo[2,3-*a*]quinolizine ring system have been isolated from *Vinca major* L. var. *elegantissima* Hort (*13*). The structures of vincarpine (**4**) and dihydrovincarpine (**5**) have been determined on the basis of their spectral data and via some derivatives obtained by either catalytic or hydride reduction. Interestingly, the ^{1}H-NMR spectrum of vincarpine in TFA solution corresponds to structure **6** derived by lactonization of **4** in the presence of acid.



4 Vincarpine



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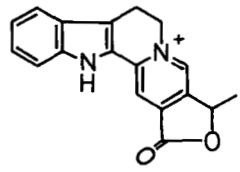

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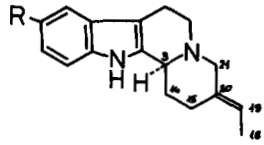
4. Deplancheine and 10-Methoxydeplancheine

(+)-Deplancheine (**7**) was isolated first from the stem and bark of *Alstonia deplanchei* van Heurck and Muell. Arg. by Husson *et al.* (*14*). The structure of this novel type of alkaloid has been established from spectral evidence; the trans annellation of rings C and D is supported by the presence of characteristic Bohlmann bands in the IR spectrum and also by the chemical shift of the C-3 proton below 3.7 ppm. The ethylidene side chain was also indicated by the ^{1}H-NMR spectrum [δ 1.52 (3H, d, J =6 Hz), 5.30 (1H, q, J = 6 Hz)] and its *E* configuration was confirmed by regio- and stereospecific total synthesis (*14*). 10-Methoxydeplancheine (**8**) has been found in the leaves of *Alstonia lanceolifera* S. Moore (*15*).

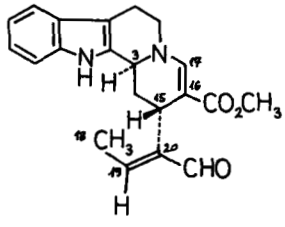


7 R=H Deplancheine

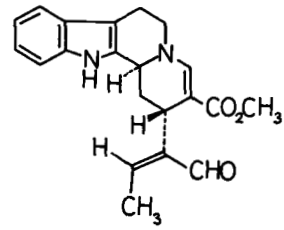
8 R=OCH_3

5. Vallesiachotamine and Isovallesiachotamine

Vallesiachotamine (**9**) (*4*), isolated first from *Vallesia dichotoma* Ruiz and Pav., and characterized as a mixture of formyl rotamers (*16*), proved to be really a mixture of two geometrically isomeric alkaloids: vallesiachotamine (**9**) and isovallesiachotamine (**10**) (*16a*). Recently **9** and **10** were isolated from *Strychnos*



9 Vallesiachotamine



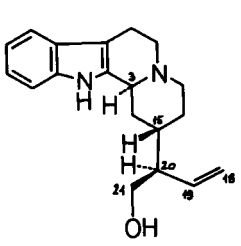
10 Isovallesiachotamine

tricalysiodes Hutch. and M. B. Moss (*17*) separated, and characterized in full spectroscopic detail. Isovallesiachotamine (**10**) has been found alone in *Rhazya stricta* Decaisne (*18*).

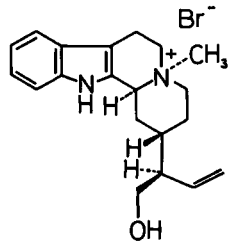
B. Corynanthe Alkaloids

1. Antirhine and Antirhine N_b-Metho Salts

Antirhine (**11**) was isolated first from *Antirhea putaminosa* (F. Muell.) Bail. in 1967 (*19*). Final determination of the stereostructure of antirhine, including conformational analysis, has been reported by Bisset and Phillipson (*20*). They established that the thermodynamically more stable conformer possesses a *cis*-quinolizidine ring junction as shown in formula **11′**; however, some of the conformer with a trans junction (**11″**) is also present.



11 Antirhine



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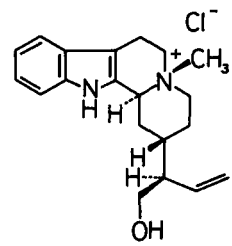

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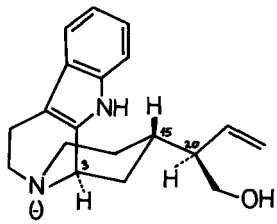
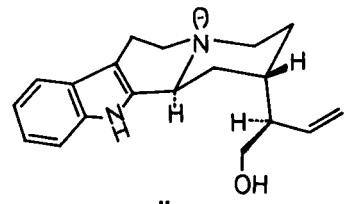


11′



11″

Antirhine methobromide (**12**) has been isolated from *Strychnos camptoneura* Gilg and Busse (*20*); however, it is not certain that this is the naturally occurring form of the alkaloid. In view of ^{1}H-NMR evidence, α orientation was suggested for the N_b-methyl group of **12.**

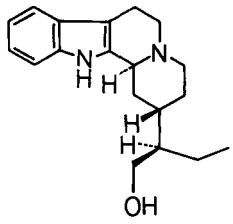
The other antirhine N_b-metho salt, namely, antirhine N_b-β-methochloride (**13**) has been isolated from *Amsonia elliptica* Roem. and Schult. (*21*). Demethylation

of this new quaternary alkaloid, isolated also from *Hunteria eburnea* Pichon (*22*), with sodium thiophenoxide afforded a tertiary base identical with antirhine. Restoring the quaternary nitrogen by methylation of **11** resulted in antirhine N_b-α-methochloride (*22*).

The isolation of isoantirhine, having a side chain containing an ethylidene group, and methoxyantirhine, having a methoxy substituent on ring A, has also been reported (*23, 24*); however, no physical or spectroscopic data are available.

2. 18,19-Dihydroantirhine and Its N_b-Metho Salt

An investigation of *Aspidosperma marcgravianum* (*23*) led to the isolation of 18,19-dihydroantirhine (**14**). The quaternary N_b-β-methochloride derivative of **14** (compound **15**) was previously found in *Hunteria eburnea* Pichon (*22*).



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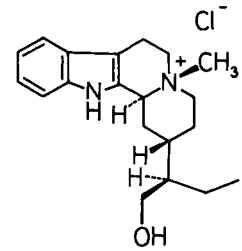
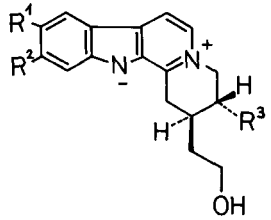


15

3. 3,4,5,6-Tetradehydro Derivatives of Corynantheol

3,4,5,6-Tetradehydro-18,19-dihydrocorynantheol (**16**) has been isolated from *Aspidosperma marcgravianum* (*23*). The structure of **16** has been determined on the basis of spectral data and by comparing the alkaloid with a semisynthetic



16 $R^1=R^2=H$; $R^3=-CH_2CH_3$

17 $R^1=OCH_3$; $R^2=H$; $R^3=-CH_2CH_3$

18 $R^1=R^2=OCH_3$; $R^3=-CH_2CH_3$

19 $R^1=OCH_3$; $R^2=H$; $R^3=-CH=CH_2$

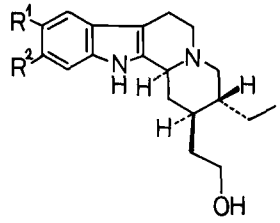
20 $R^1=R^2=OCH_3$; $R^3=-CH=CH_2$

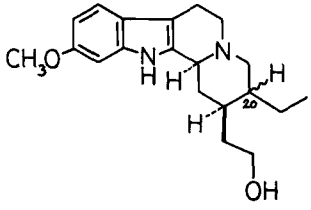
sample obtained from 18,19-dihydrocorynantheol (**21**) via lead tetraacetate oxidation.

A complex mixture of 10-methoxy-3,4,5,6-tetradehydro-18,19-dihydrocorynantheol (**17**), 3,4,5,6-tetradehydroochropposinine (**18**), 10-methoxy-3,4,5,6-tetradehydrocorynantheol (**19**), and 3,4,5,6,18,19-hexadehydroochropposinine (**20**) has been isolated from the root bark of *Neisosperma glomerata* (Blume) Fosberg and Sachet (*25*). The approximative structure elucidation of alkaloids **17–20** was performed by ^{1}H-NMR and mass spectral analysis of the unseparated mixture.

4. 10-Hydroxydihydrocorynantheol, Ochropposinine, and Ochromianine

Recently three new derivatives of 18,19-dihydrocorynantheol (**21**) have been isolated from natural sources. 10-Hydroxydihydrocorynantheol (**22**) has been found in *Ochrosia moorei* F. Muell. (*26*), and its structure has been determined by chemical analysis and by IR, ^{1}H-NMR, and mass spectra. Ochropposinine (**23**) was isolated first in 1972 from *Ochrosia oppositifolia* K. Schum. (*27, 28*) and recently from *Ochrosia moorei* (*26*) by Potier's group. The relative configuration of C-20 as well as the absolute configuration of **23** have been elucidated. Ochromianine (**24**) isolated from *Ochrosia miana* H.Bn. ex Guill. (*29*) could be described very probably as 11-methoxycorynan-17-ol. The relative configuration of C-20 has not as yet been determined exactly.





21 $R^1=R^2=H$

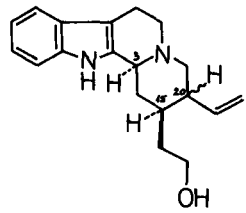
22 $R^1=OH$; $R^2=H$

23 $R^1=R^2=OCH_3$ Ochropposinine

24 Ochromianine

5. Normelionine-B

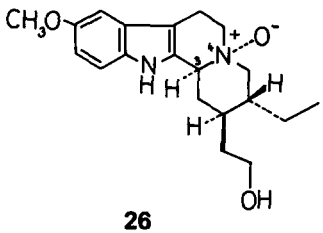
The alkaloid normelionine-B (**25**) has been isolated from the root bark of *Strychnos nux-vomica* L. (*30*); however, its structure has not been established completely. The relative steric positions of hydrogens attached to the C-3, C-15, and C-20 stereo centers are assumed to be α,α,β or α,α,α, respectively.



25 Normelionine-B

6. *N*-Oxides of 10-Methoxydihydrocorynantheol

Ahond *et al.* recently reported the isolation of two epimeric *N*-oxides of 10-methoxydihydrocorynantheol from the trunk bark of *Ochrosia moorei* (*26*). The absolute configuration of the stereo centers at the annellation of rings C and D are 3*S*,4*R* in **26** and 3*S*,4*S* in **27.**



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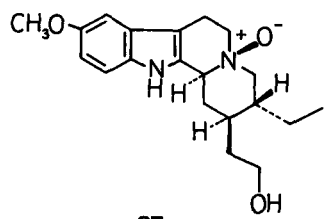
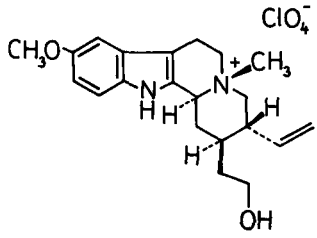


27

The *N*-oxide of the alkaloid dihydrocorynantheol (**21**) has also been mentioned as a natural product from the leaves of *Mitragyna parvifolia* (Roxb.) Korth.; however, it was detected only by mass spectroscopy and no further evidence for the structure has been given (*31*).

7. 10-Methoxycorynantheol α- and β-Metho Salts

Sakai *et al.* reported the isolation of 10-methoxycorynantheol β-metho-perchlorate (**28**) from *Ochrosia nakaiana* Koidz. and determined its structure by means of spectroscopic investigation (*32*). 10-Methoxycorynantheol α-meth-



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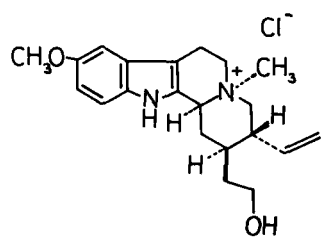
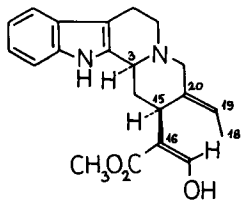


29

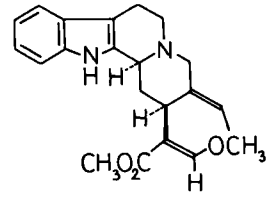
ochloride (**29**) has been found in the bark of *Neisosperma glomerata* (Blume) Fosberg and Sachet (*25*). The relative steric position of the *N*-methyl group has been proved by comparative ^{1}H-NMR studies.

8. Geissoschizine and Geissoschizine Methyl Ether

Geissoschizine (**30**) (*1*) is one of the most widely investigated monoterpene indole alkaloids. Since the first structure elucidation, carried out by Rapoport



30 Geissoschizine

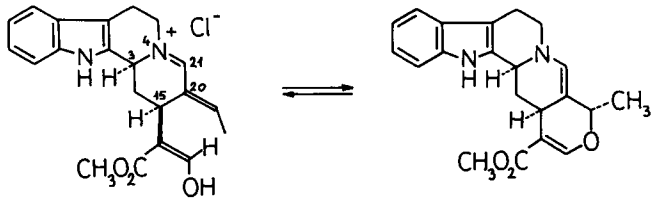


31

and co-workers (*33*) as well as by Janot (*34*), a great number of publications have appeared on the total synthesis (see Section III) and conformational analysis of this alkaloid. Independently, two research groups have concurred (*35, 36*) in that the preferred conformation of geissoschizine in solution possesses a cis C/D ring junction and that ring D is boat shaped. ^{1}H-NMR (*309*) and ^{13}C-NMR data (*37*) support this suggestion. In contrast, geissoschizine has a trans C/D quinolizidine conformation in crystalline form (*37*). Geissoschizine methyl ether (**31**) has been isolated from *Uncaria rhynchophylla* Miq. as a new alkaloid (*38*). The configurations of the Δ^{16} and Δ^{19} double bonds are assumed to be *E* in the molecule (*38*).

9. 4,21-Dehydrogeissoschizine

Kan-Fan and Husson reported the isolation and structure elucidation of 4,21-dehydrogeissoschizine chloride (**32**) from the leaves of *Guettarda eximia* (*39*). It has been suggested that this alkaloid is a biosynthetic intermediate of several

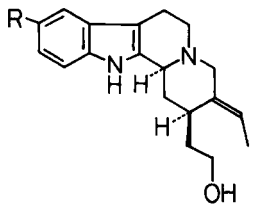


32 **33**

heteroyohimbine alkaloids as well as other geissoschizine-type alkaloids (*39, 40*). Proof of structure **32** is based on spectral data and chemical transformations; sodium borohydride reduction of **32** leads to a mixture of geissoschizine, isositsirikine (**46**), and 16-epiisositsirikine (**47**). 4,21-Dehydrogeissoschizine (**32**) has also been converted to cathenamine (**33**) (*39, 40*).

10. 10-Hydroxygeissoschizol, Isogeissoschizol, 10-Methoxyisogeissoschizol, and Acetylgeissoschizol

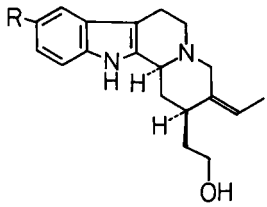
The previously known geissoschizol (**34**) and 10-methoxygeissoschizol (**35**) as well as 10-hydroxygeissoschizol (**36**) have been recently isolated from *Amsonia elliptica* Roem. and Schult. (*21, 41*) and from the stem bark of *Rauwolfia vomitoria* Afz. (*42*). Isogeissoschizol (**37**) and 10-methoxyisogeissoschizol (**38**) have been isolated from the leaves of *Aspidosperma marcgravianum* (*23*), both with a *Z* ethylidene substituent at position C-20. Acetylgeissoschizol (**39**) has been detected in the stem bark of *Rauwolfia vomitoria* (*43*) together with **30, 34, 35,** and **36.**



34 R=H Geissoschizol

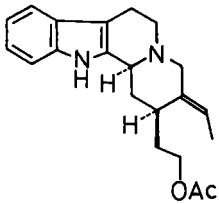
35 R=OCH_3

36 R=OH



37 R=H

38 R=OCH_3

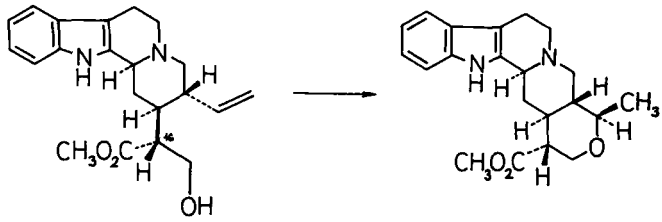


39

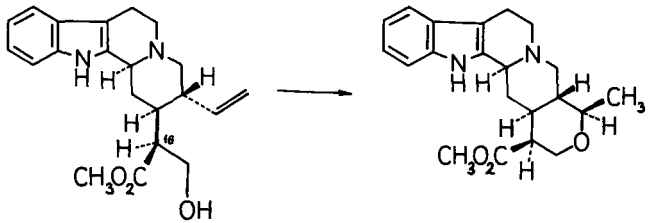
11. Sitsirikine and 16-Episitsirikine

The structure of (−)-sitsirikine (**40**), isolated from *Vinca rosea* (syn. *Catharanthus roseus*) (L.) G. Don by Kutney and Brown (*44*), was assigned from chemical and spectral data and verified by a correlation with corynantheine via the corresponding 18,19-dihydro derivatives. This transformation determined the configuration at the stereo centers connected with the ring system; however, it did not establish the configuration at C-16 in the side chain. Later Brown and Leonard established the C-16 configuration of (−)-sitsirikine as *R* by cyclizing it to (16*R*)-cyclositsirikine (**41**). (−)-16-Episitsirikine (**42**) has correspondingly been transformed to the epimeric (16*S*)-cyclositsirikine (**43**) (*45*) (see also Section V). The specific rotation ($[\alpha]_D$) of (−)-sitsirikine was found to be −58° and that of (−)-16-episitsirikine is −22° in methanolic solution.

In 1978, a French group reported the isolation of (+)-sitsirikine and (+)-16-



40 Sitsirikine **41**

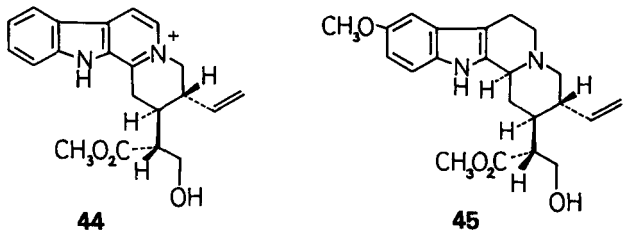


42 16-Episitsirikine **43**

episitsirikine from the seeds of *Aspidosperma album* (Vahl) R. Bent. showing $[\alpha]_D$ +23° (MeOH) and +218° (MeOH), respectively (*46*). According to the specific rotations and because of insufficient spectral data reported for these alkaloids, it may be suggested by us that the compound with $[\alpha]_D$ +23° would rather correspond to (+)-16-episitsirikine than to (+)-sitsirikine. The alkaloid with specific rotation +218°, however, needs more investigation for completing its structure elucidation.

12. 3,4,5,6-Tetradehydrositsirikine and 10-Methoxysitsirikine

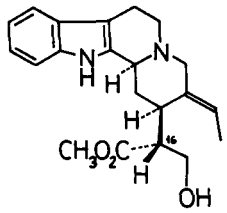
Alkaloids 3,4,5,6-tetradehydrositsirikine (**44**) and 10-methoxysitsirikine (**45**) have recently been isolated from *Aspidosperma oblongum* by Robert *et al.* (*24*) and characterized in full spectral detail.



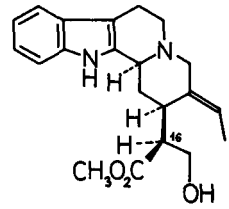
44 **45**

13. (*E*)-Isositsirikine, 16-Epi-(*E*)-isositsirikine, and 16-Epi-(*Z*)-isositsirikine

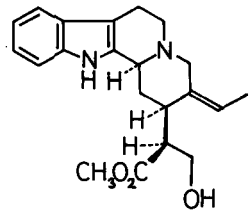
The isolation of (−)-(*E*)-isositsirikine (**46**), containing ethylidene side chain at C-20 with an *E* configuration, from *Catharanthus roseus* (L.) G.Don has been mentioned first by Kutney and Brown (*44*); however, no definite stereo arrangement was suggested for stereo center C-16. Later Kutney and co-workers (*47*) isolated (−)-16-epi-(*E*)-isositsirikine (**47**) from *Aspidosperma cuspa*. At that time, both new alkaloids (**46** and **47**) were characterized in full detail, suggesting that the absolute configuration of C-16 in (−)-(*E*)-isositsirikine (**46**) is (*R*), and consequently it is (*S*) in (−)-16-epi-(*E*)-isositsirikine (**47**). This structure elucidation was supported by Scott and co-workers (*48*), converting geissoschizine (**30**) enzymatically to the levorotatory (−)-(16*R*)-(*E*)-isositsirikine (**46**).



46 Isositsirikine



47 16-Epi-(E)-isositsirikine



48

16-Epi-(Z)-isositsirikine

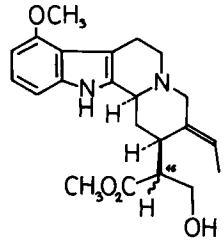
(−)-16-Epiisositsirikine (**47**) has also been isolated from *Tabernaemontana pachysiphon* Stapf (*49*), *T. psychotrifolia* (*49a*), and from *T. psorocarpa* (*49b, 50*) and characterized in full detail (*49b*).

Recently, Cordell and collaborators (*51*) reported the discovery of (−)-16-epi-(*Z*)-isositsirikine (**48**) from the leaves of *Catharanthus roseus* (L.) G.Don and *Rhazya stricta* Decaisne, the first isositsirikine-type alkaloid with *Z* geometry in the C-20 ethylidene side chain. Moreover, they gave reliable structure assignments for (−)-(*E*)-isositsirikine (**46**) and (−)-16-epi-(*E*)-isositsirkine (**47**).

Though the isolation of isositsirikine and 16-epiisositsirikine from *Aspidosperma oblongum* (*24*) and also their *N*-oxide derivatives from *A. marcgravianum* (*23*) has been reported, the stereochemical assignment of C-16 was, however, uncertain.

14. Strychnorubigine and 10-Methoxyisositsirikine

The methoxy-substituted, isositsirikine-type alkaloid strychnorubigine (**49**) has been isolated from the root bark of *Strychnos rubiginosa* DC. (*52*). With the exception of the configuration at C-16, the structure of **49** has been established from chemical analysis and by IR, MS, as well as NMR spectra.



49

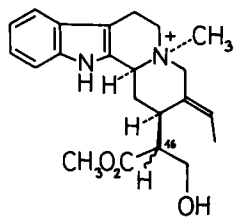
Strychnorubigine

The structural formula of aspexcine, isolated first from *Aspidosperma excelsum* Benth. and identified as a 10-methoxyisositsirikine (*4*), had to be corrected. Recently, Verpoorte *et al.* (*53*) established that, instead of a corynane skeleton, aspexcine has a 10-methoxy, normal yohimbane structure.

At the same time, "10-methoxyisositsirikine" has been isolated from *Aspidosperma oblungum* by Robert *et al.* and proved to be different from aspexcine in reported spectral data (*24*). The isositsirikine structure was verified by ^{1}H-NMR and MS spectra. However, on the basis of the assigned 16*S* configuration, it should be correctly named as 10-methoxy-16-epiisositsirikine.

15. Diploceline and 16-Epidiploceline

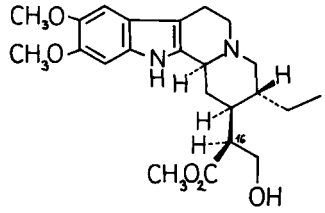
Since the configuration at C-16 is undetermined, both quaternary alkaloids diploceline and 16-epidiploceline, isolated from the root bark of *Strychnos gossweileri* Exell (*54*), could be represented by formula **50.** The absolute configurations of the C-3 and C-15 have been determined by CD measurements, and the cis junction of C/D rings is supported by ^{1}H-NMR data [δ 4.58 (C3—H), δ 3.58 (N—CH_3) for diploceline].



50

16. 10,11-Dimethoxy-19,20-dihydro-16-episitsirikine

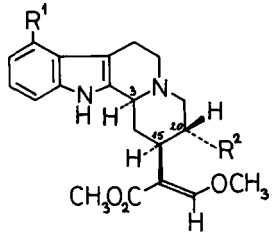
10,11-Dimethoxy-19,20-dihydro-16-episitsirikine (**51**), with 16*S* absolute configuration, has been found in *Ochrosia moorei* F. Muell. and characterized in full detail by Ahond *et al.* (*26*).



51

17. Corynantheine-Type Alkaloids

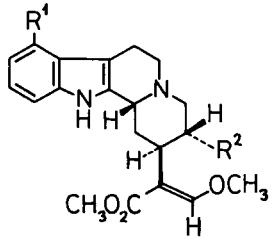
The corynantheine-type alkaloids can be subdivided into four groups, depending on the relative configurations of stereo centers attached to ring D, i.e., normal (hydrogens at positions 3, 15, and 20 are α, α, and β, respectively); pseudo (β, α, β); allo (α, α, α), and epiallo (β, α, α). It is a common structural feature of the corynantheinie-type alkaloids that a β-methoxyacrylic group is connected to C-15, in which the geometry of the enol–ether double bond has always been found to be *E*.



52	R^1=H; R^2=-CH=CH_2	Corynantheine
53	R^1=OCH_3; R^2=-CH=CH_2	Paynantheine
54	R^1=H; R^2=-CH_2CH_3	Dihydrocorynantheine
55	R^1=OCH_3; R^2=-CH_2CH_3	Speciogynine
56	R^1=OH; R^2=-CH_2CH_3	Gambirine

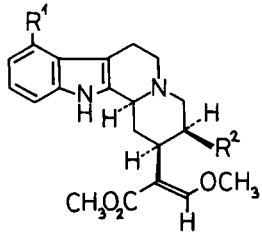
Normal Series. After 1967, only one new alkaloid was isolated in the normal series: the *N*-oxide of dihydrocorynantheine (**54**) (*55*).

Pseudo Series. Hirsuteine (**57**) has been detected first in *Mitragyna parvifolia* Korth. (*56*), and later it has been isolated and characterized in full detail from



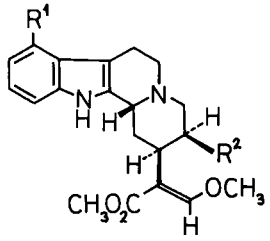
57 R^1=H; R^2=-CH=CH_2 Hirsuteine
58 R^1=H; R^2=-CH_2CH_3 Hirsutine
59 R^1=OCH_3; R^2=-CH=CH_2 Isopaynantheine
60 R^1=OCH_3; R^2=-CH_2CH_3 Mitraciliatine

Uncaria rhynchophylla Miq. (*57*). The *N*-oxide of hirsutine (**58**) has been found in *Uncaria tomentosa* DC. (*55*), and 3-isopaynanthiene (**59**) has been isolated from *Mitragyna speciosa* Korth. (*58*).



61 R^1=H; R^2=-CH_2CH_3 Corynantheidine
62 R^1=OCH_3; R^2=-CH_2CH_3 Mitragynine

Allo Series. Only two members of allo series of alkaloids are known: corynantheidine (**61**) and mitragynine (**62**). No new alkaloid has been isolated since 1967.

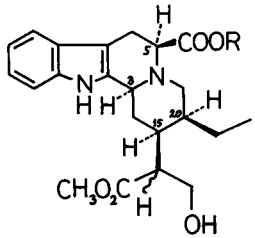


63 R^1=OCH_3; R^2=-CH_2CH_3 Speciociliatine
64 R^1=H; R^2=-CH=CH_2 Epiallocorynantheine
65 R^1=H; R^2=-CH_2CH_3 3-Isocorynantheidine

Epiallo Series. Previously, only speciociliatine (**63**) was known as a corynantheine-type alkaloid having an epiallo skeleton. Two new alkaloids in this series were isolated during the last decade, i.e., epiallocorynantheine (**64**) from *Uncaria attenuata* (*59*) and 3-isocorynantheidine (**65**) from *Mitragyna speciosa* Korth. (*58*).

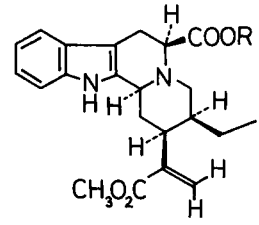
18. Adirubine and Anhydroadirubine

Adirubine (**66**), the first member of a new series of 5β-carboxy alkaloids having a corynane skeleton, has been isolated from *Adina rubescens* by Brown *et al.* (*60*). The first structure elucidation of adirubine, based on spectral data only, was incomplete (*60*). Final determination of the steric arrangement around ring D was performed by correlation with 5β-methoxycarbonyldihydromancunine, and it proved to be allo (3α, 15α, 20α) (*61*).



66 R=H Adirubine

67 R=CH_3



68 R=H

69 R=CH_3

In 1975, Brown and Charalambides (*62*) reported the isolation of anhydroadirubine (**68**), also from *Adina rubescens,* as a methyl ester derivative (**69**).

The isolation of a trace alkaloid of *Rauwolfia oreogiton* Mgf. has been reported (*63*) and provisionally identified as 19,20-dehydroadirubine acetate. However, the structure determination needs more confirmation.

C. Yohimbane Alkaloids

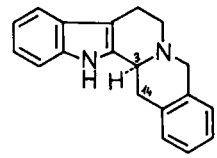
1. Anhydroalstonatine

The quaternary alkaloid anhydroalstonatine (**70**), which has a completely aromatic yohimbane ring system, has been isolated from *Alstonia venenata* R.Br. (*64*).

2. Demethoxycarbonyl-3,14-dihydrogambirtannine

The simple hexadehydroyohimbane alkaloid demethoxycarbonyl-3,14-dihydrogambirtannine (**71**) has been isolated from *Ochrosia lifuana* Guill. and

70 Anhydroalstonatine



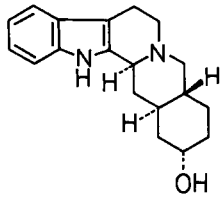
71

from *Ochrosia miana* H.Bn. ex Guill. (*65*). The same alkaloid has also been isolated from the fruits of *Strychnos usambarensis* Gilg (*66*).

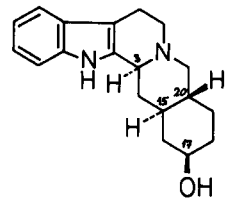
3. Yohimbine-Type Alkaloids

Similarly to the corynantheine-type alkaloids, yohimbines could also be divided into four groups according to the relative configurations of the stereo centers C-3, C-15, and C-20.

Normal Series. Among yohimbines with a normal skeleton, there are three alkaloids in which the methoxycarbonyl substituent at C-16 is lacking, namely, yohimbol (**72**), its N_b-methochloride, and the recently discovered 17-epiyohimbol (**73**) isolated from *Hunteria zeylanica* (*67*).



72 Yohimbol



73 17-Epiyohimbol

The following yohimbine alkaloids, containing a methoxycarbonyl substituent at C-16 and a hydroxy group at C-17, were known when the previous review on that topic appeared in *The Alkaloids* (*4*): yohimbine (**74**), β-yohimbine (**75**), corynanthine (**76**) (known also as rauhimbine), 11-methoxy-β-yohimbine (**77**), and 19,20-dehydroyohimbine (**78**).

New normal yohimbine-type alkaloids, isolated or characterized, together with their primary sources, are listed in Table I. Note that aspexcine, isolated from *Aspidosperma excelsum* Benth., has earlier been characterized as a 10-methoxyisositsirikine. This alkaloid, however, proved to be identical with excelsinine (**81**) (*53*) (see Section II.B. 14.).

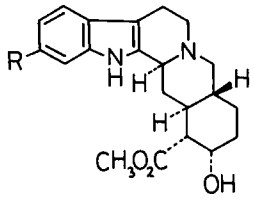
Pseudo Series. Besides the previously known pseudoyohimbine (**88**), there is only one additional alkaloid found in *Rauwolfia capuroni* Mgf. (*68*) that belongs to the pseudo series, namely, 11-methoxypseudoyohimbine (**89**).

Allo Series. Only three alkaloids belonging to the allo-type yohimbines, that

TABLE I

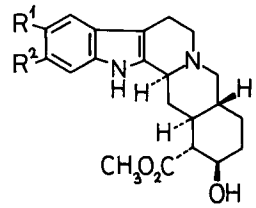
RECENTLY ISOLATED YOHIMBINE ALKALOIDS WITH NORMAL OR PSEUDO SKELETONS AND THEIR PRIMARY SOURCES

Alkaloid	Source (Ref.)	mp (°C)	$[\alpha]_D$	Spectral data (Ref.)	Molecular formula
Normal series					
11-Methoxyyohimbine (**79**)	*Rauwolfia capuroni* Mgf. (*68*)	200–202	+90°	(*68*)	$C_{22}H_{28}N_2O_4$
10-Methoxy-β-yohimbine (**80**)	*Aspidosperma oblongum* (*24*)	—	+29°	(*24*)	$C_{22}H_{28}N_2O_4$
Excelsinine (aspexcine) (**81**)	*Aspidosperma excelsum* Benth. (*53,69*)	199–201	−63.4°	(*53,69*)	$C_{22}H_{28}N_2O_4$
19,20-Dehydro-β-yohimbine (**82**)	*Aspidosperma oblongum* (*24*)	—	−45°	(*24*)	$C_{21}H_{24}N_2O_3$
3,4-Dehydro-β-yohimbine (**83**)	*Aspidosperma oblongum* (*24*)	—	+114°	(*24*)	$C_{21}H_{24}N_2O_3$
3,4,5,6-Tetradehydro-β-yohimbine (**84**)	*Amsonia elliptica* Roem. and Schult. (HCl salt) (*21,41*)	273–275	+127.2°	(*21*)	$C_{21}H_{23}N_2O_3Cl$
O-Acetylyohimbine (**85**)	*Aspidosperma excelsum* Benth. (*69*)	274–275 (HCl salt)	—	(*53,69,70*)	$C_{23}H_{28}N_2O_4$
Poweridine (**86**)	*Ochrosia poweri* Bail. (*70a*)	226	−4.9°	(*70,70a*)	$C_{24}H_{30}N_2O_5$
5β-Carboxycorynanthine (**87**)	*Adina rubescens* (*71*), methyl ester	235	−29°	(*71*)	$C_{23}H_{28}N_2O_5$
β-Yohimbine *N*-oxide	*Aspidosperma oblongum* (*24*)	230	—	(*24*)	$C_{21}H_{26}N_2O_4$
Pseudo series					
11-Methoxy-φ-yohimbine (**89**)	*Rauwolfia capuroni* Mgf. (*68*)	267–268	+30°	(*68*)	$C_{22}H_{28}N_2O_4$



74 R=H Yohimbine

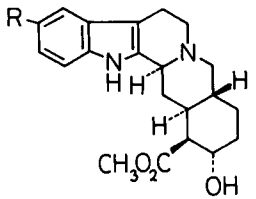
79 R=OCH_3



75 R^1=R^2=H β-Yohimbine

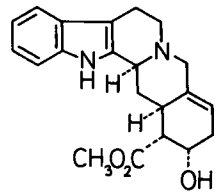
77 R^1=H; R^2=OCH_3

80 R^1=OCH_3; R^2=H



76 R=H Corynanthine

81 R=OCH_3



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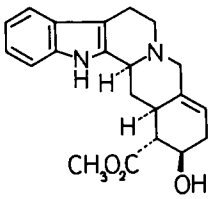

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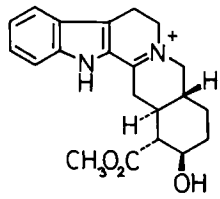

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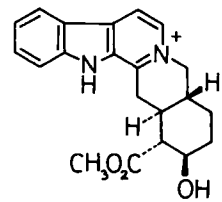

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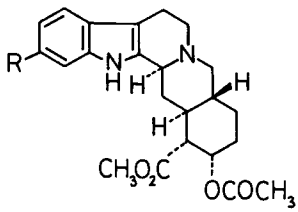
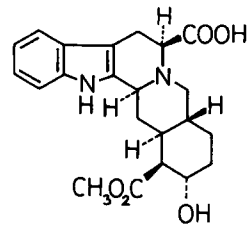


85 R=H

86 R=OCH_3



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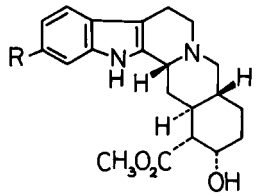
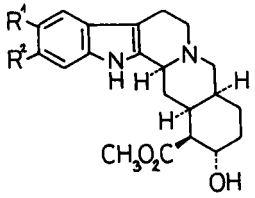


88 R=H Pseudoyohimbine

89 R=OCH_3

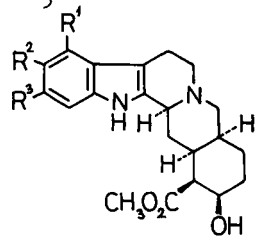


90 $R^1=R^2$ α-Yohimbine

91 $R^1=R^2=OCH_3$ Seredine

94 $R^1=OCH_3$; $R^2=H$

95 $R^1=H$; $R^2=OCH_3$



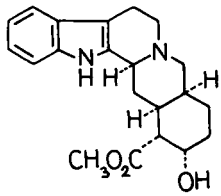
92 $R^1=R^2=R^3=H$

96 $R^1=OCH_3$; $R^2=R^3=H$ Alstovenine

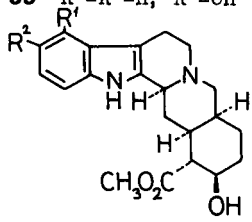
97 $R^1=R^2=H$; $R^3=OCH_3$

98 $R^1=H$; $R^2=R^3=OCH_3$

99 $R^1=R^3=H$; $R^2=OH$ Powerine



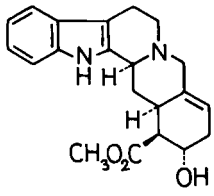
93 Alloyohimbine



100 $R^1=R^2=H$

101 $R^1=H$; $R^2=OCH_3$

102 $R^1=OCH_3$; $R^2=H$



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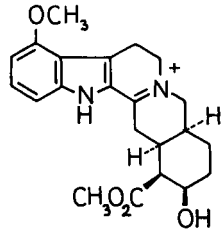

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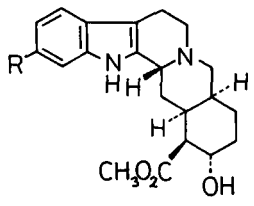
TABLE II

RECENTLY ISOLATED YOHIMBINE ALKALOIDS WITH ALLO OR EPIALLO SKELETONS AND THEIR PRIMARY SOURCES

Alkaloid	Source (Ref.)	mp (°C)	$[\alpha]_D$	Spectral data (Ref.)	Molecular formula
Allo series					
10-Methoxy-α-yohimbine (**94**)	*Aspidosperma oblongum* (*24*)	—	−13°	(*24*)	$C_{22}H_{28}N_2O_4$
11-Methoxy-α-yohimbine (**95**)	*Neissosperma glomerata* (*78*)	218	−46°	(*78*)	$C_{22}H_{28}N_2O_4$
Alstovenine (**96**)	*Alstonia venenata* R.Br. (*79,80*)	172 (*79*), 169–171 (*80*)	+10.2° (*79*); +9.4° (*80*)	(*79–81*)	$C_{22}H_{28}N_2O_4$
11-Methoxy-17-epi-α-yohimbine (**97**)	*Neissosperma glomerata* (*78*)	223	−68°	(*78*)	$C_{22}H_{28}N_2O_4$
10,11-Dimethoxy-17-epi-α-yohimbine (**98**)	*Neissosperma glomerata* (*78*)	259	−50°	(*78*)	$C_{23}H_{30}N_2O_5$
Powerine (**99**)	*Ochrosia poweri* Bail. (*70a*)	188–189	−216°	(*70a,81a*)	$C_{21}H_{26}N_2O_3$
17-Epialloyohimbine (**100**)	*Aspidosperma oblongum* (*24*)	—	−8°	(*24,73,81b*)	$C_{21}H_{26}N_2O_3$
10-Methoxy-17-epi-alloyohimbine (**101**)	*Aspidosperma oblongum* (*24*)	—	+4°	(*24*)	$C_{22}H_{28}N_2O_4$
16-Epialstovenine (**102**)	*Alstonia venenata* (*81*)	227–230	+72°	(*81*)	$C_{22}H_{28}N_2O_4$
19,20-Dehydro-α-yohimbine (**103**)	*Aspidosperma oblongum* (*24*)	—	+90°	(*24*)	$C_{21}H_{24}N_2O_3$
3,4-Dehydroalstovenine (**104**)	*Alstonia venenata* R.Br. (*82*)	HCl salt: 216	+38.5° (H_2O)	(*82,82a*)	$C_{22}H_{27}N_2O_4Cl$
O-Acetylalloyohimbine (**93**-OAc)	*Rauwolfia nitida* (*83*)	—	−89°	(*83*)	$C_{23}H_{28}N_2O_4$
Epiallo series					
Quaternatine (**106**)	*Alstonia quaternata* (*84*)	168	−105°	(*84*)	$C_{22}H_{28}N_2O_4$
Venenatine (**107**)	*Alstonia venenata* R.Br. (*79,80*)	130 (*79*), 123–126 (*80*)	−82° (*79*); −76° (*80*)	(*79–81*)	$C_{22}H_{28}N_2O_4$
Venoxidine (Venenatine *N*-oxide)	*Alstonia venenata* R.Br. (*85*)	218–219	−82.4°	(*82a*)	$C_{22}H_{28}N_2O_5$
16-Epivenenatine (**108**)	*Alstonia venenata* R.Br. (*81*)	188–190	−52.7°	(*81*)	$C_{22}H_{28}N_2O_4$

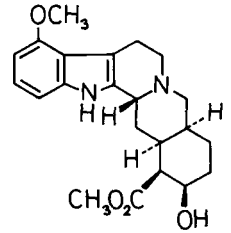
is, α-yohimbine (**90**), seredine (**91**), and alloyohimbine, have previously been known. After the first total synthesis of the four possible allo stereoisomer yohimbines reported by Szántay and coworkers (*72–75*), the formula for the stereostructure of alloyohimbine, given in the original literature (*76, 77*) as **92,** had to be corrected. Chemical evidence as well as direct comparison of alloyohimbine with synthetic samples containing the C-16 and C-17 substituents either in the β,β (compound **92**) or α,α positions (compound **93**) unambigously pointed out that the correct stereostructure of alloyohimbine should be represented by formula **93.** Yohimbine alkaloids, containing the alloyohimbane skeleton, isolated and characterized since the last review on this topic, together with their primary sources, are listed in Table II.

Epiallo Series. Among alkaloids containing the epiallo yohimbane skeleton, only 3-epi-α-yohimbine (**105**) was formerly known. In the past decade, four additional members of this alkaloid subgroup have been isolated, namely, quaternatine (**106**) from *Alstonia quaternata* (*84*), venenatine (**107**) and its *N*-oxide (venoxidine) from *Alstonia venenata* R.Br. (*79, 80, 82a, 85*) and 16-epivenenatine (**108**) also from *Alstonia venenata* R.Br. (*81*).

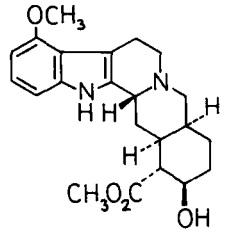


105 R=H 3-Epi-α-yohimbine

106 R=OCH_3 Quaternatine



107 Venenatine



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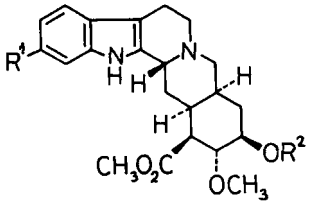
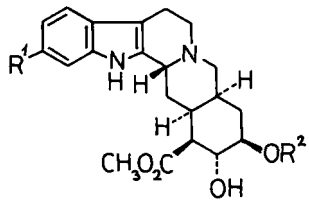
16-Epivenenatine

4. Reserpine-Type Alkaloids

The previously known reserpine-type alkaloids (*3*) are shown below. They are: reserpine (**109**), deserpidine (**110**), rescinnamine (**111**), veneserpine (**112**), pseudoreserpine (**113**), raunescine (**114**), rescidine (**115**), raugustine (**116**), and isoraunescine (**117**). It should be mentioned that all reserpine-type alkaloids are trisubstituted at ring E and that the substituents at C-16, C-17, and C-18 are all in equatorial positions on the epiallo yohimbane ring system existing predominantly





109 R^1=OCH_3; R^2=TMB Reserpine

110 R^1=H; R^2=TMB Deserpidine

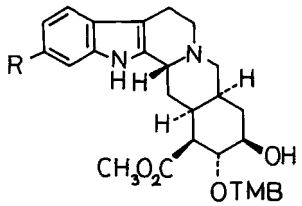
111 R^1=OCH_3; R^2=TMC Rescinnamine

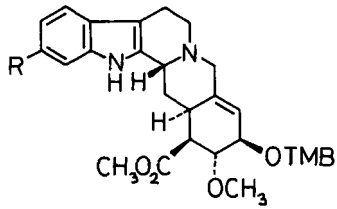
112 R^1=OCH_3; R^2=MYR Veneserpine

113 R^1=OCH_3; R^2=TMB ψ-Reserpine

114 R^1=H; R^2=TMB Raunescine

115 R^1=OCH_3; R^2=TMC Rescidine



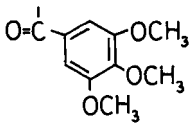


116 R=OCH_3 Raugustine

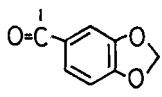
117 R=H Isoraunescine

118 R=OCH_3 Raujemidine

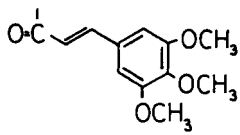
119 R=H Deserpideine



TMB



MYR

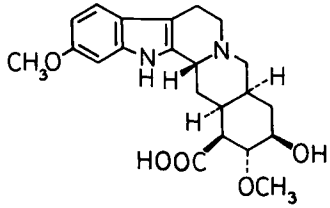


TMC

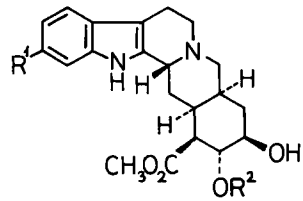
in the E_{c2} conformation. Additionally, there are two alkaloids known, in which a $\Delta^{19,20}$ double bond is present, namely, raujemidine (**118**) and deserpideine (**119**). The *N*-oxide of reserpine (renoxide) is also a known alkaloid.

The isolation of a new reserpine-type alkaloid from *Rauwolfia vomitoria* Afz. named neonorreserpine has recently been reported; however, the stereochemistry of its substituents attached to ring E has not yet been established (*86*).

Reserpic acid (**120**) has been isolated from *Rauwolfia vomitoria* Afz. (*87*). The authors stated that the compound was not a secondary product of the isolation, however, the question is still open.



120



121 R^1=OCH_3; R^2=CH_3

122 R^1=H; R^2=CH_3

123 R^1=R^2=H

The isolation of methyl reserpate (**121**) from *Rauwolfia vomitoria* Afz. (*42*) and *R. obscura* K. Schum. (*88*) and of methyl deserpidate (**122**) from *Rauwolfia obscura* K.Schum. (*89*) has been reported by Court and coworkers. It should be mentioned that these compounds may not be primary products but only artifacts formed by hydrolysis of reserpine (**109**) and deserpidine (**110**), respectively.

The same research group several times reported the isolation of "18-hydroxyyohimbine" (*83, 90–93*) and "18-hydroxy-α-yohimbine" (*90*) from different *Rauwolfia* species. In this series of communications the stereochemical structure of "18-hydroxyyohimbine" has been represented (*83, 92*) by formula **123,** which could be considered as methyl raunescidate that might have been formed by simple hydrolysis of raunescine (**114**). The chemical structure of "18-hydroxy-α-yohimbine" has, unfortunately, not been given by the authors in their publiction (*90*). Since yohimbine (**74**) and α-yohimbine (**90**) have normal and alloyohimbine skeletons, respectively, the name "18-hydroxyyohimbine" for a compound that belongs to the epiallo series (**123**) is misleading. Therefore, it would be desirable not to use the "18-hydroxyyohimbine alkaloids" terminology for reserpine-type alkaloids but to name them as the methyl esters of the corresponding trisubstituted reserpic acid derivatives.

The application of chromatographic techniques to isolation, purification, structure elucidation, and identification procedures has created new possibilities and resulted in considerable progress in the important field of alkaloid research.

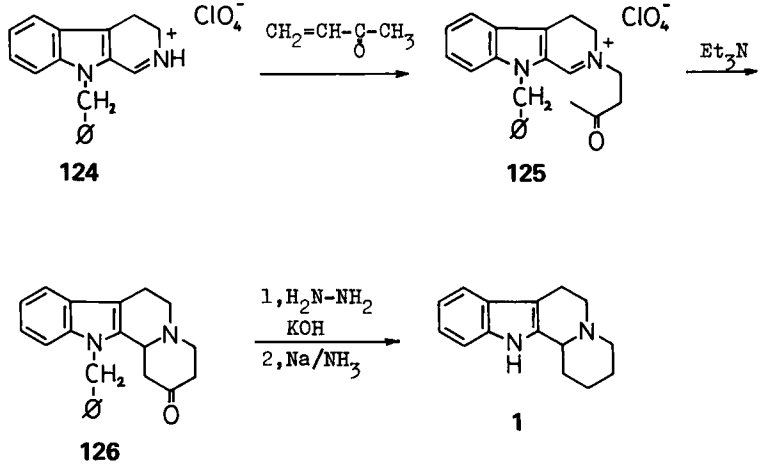
Publications and reviews on thin-layer chromatography of alkaloids have been summarized by Svendsen and Verpoorte (*93a*).

III. Synthesis

A. Synthesis of Simple Indoloquinolizine Alkaloids

1. Octahydroindoloquinolizine

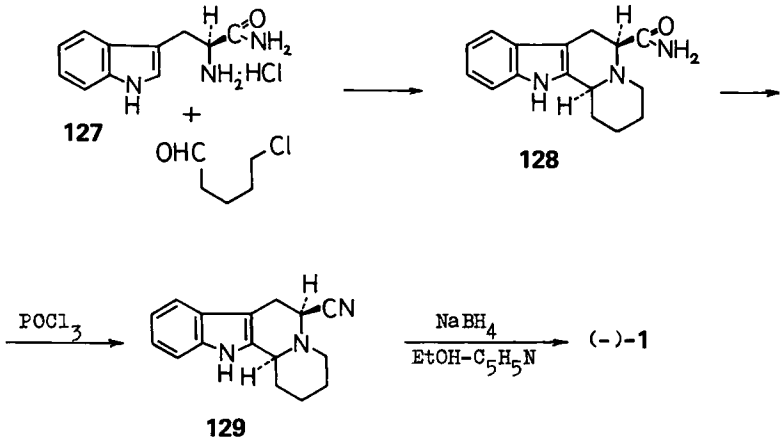
1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (**1**) had been synthesized several times (*94–96*) before its levorotatory antipode was found as a naturally occurring compound in *Dracontomelum magniferum* B1. (*11*). The first preparation of (−)-**1**, still unnamed, has been reported by Novák and Szántay (*97*). 9-Benzyl-3,4-dihydro-β-carboline perchlorate (**124**) was treated with methyl vinyl ketone to supply **125**, which was cyclized by base treatment to tetracyclic derivative **126**. Wolff–Kishner reduction of **126**, followed by debenzylation, resulted in racemic octahydroindoloquinolizine (**1**). Enantiomers of (±)-**1** were separated by resolution with D-camphorsulphonic acid (*97*).



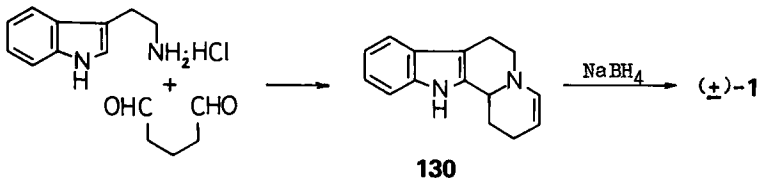
124 **125** **126** **1**

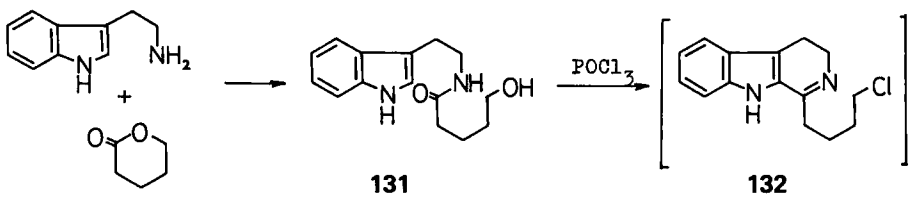
An interesting example of asymmetric induction has been used for the synthesis of (−)-**1** from L-tryptophan. Pictet–Spengler cyclization of the corresponding amide (**127**) with 5-chloropentanal afforded (−)-**128** as the sole product. Removal of the unwanted carboxamide function was achieved in good yield by sodium borohydride reduction of the corresponding α-amino nitrile (−)-**129**, resulting in (−)-**1** (*98*).

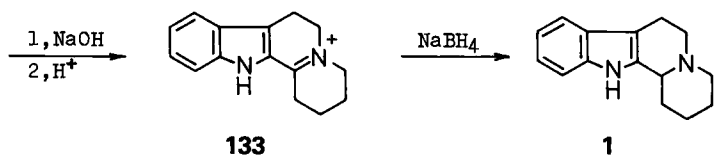
A one-pot synthesis of racemic octahydroindoloquinolizine (**1**) was reported



by Gribble (*99*). An aqueous solution of tryptamine hydrochloride and glutaraldehyde was allowed to stand at room temperature for 7–10 days, and then treated with sodium borohydride. Workup provided (±)-**1** in 55% yield. Similarly (±)-**1** has been synthesized from tryptamine and δ-valerolactone by simple reaction steps, as outlined below (*100*).

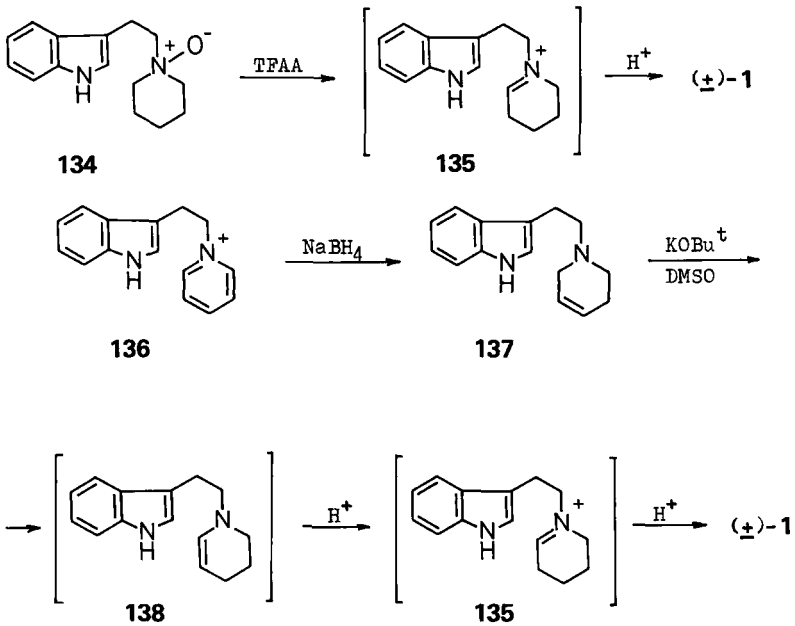






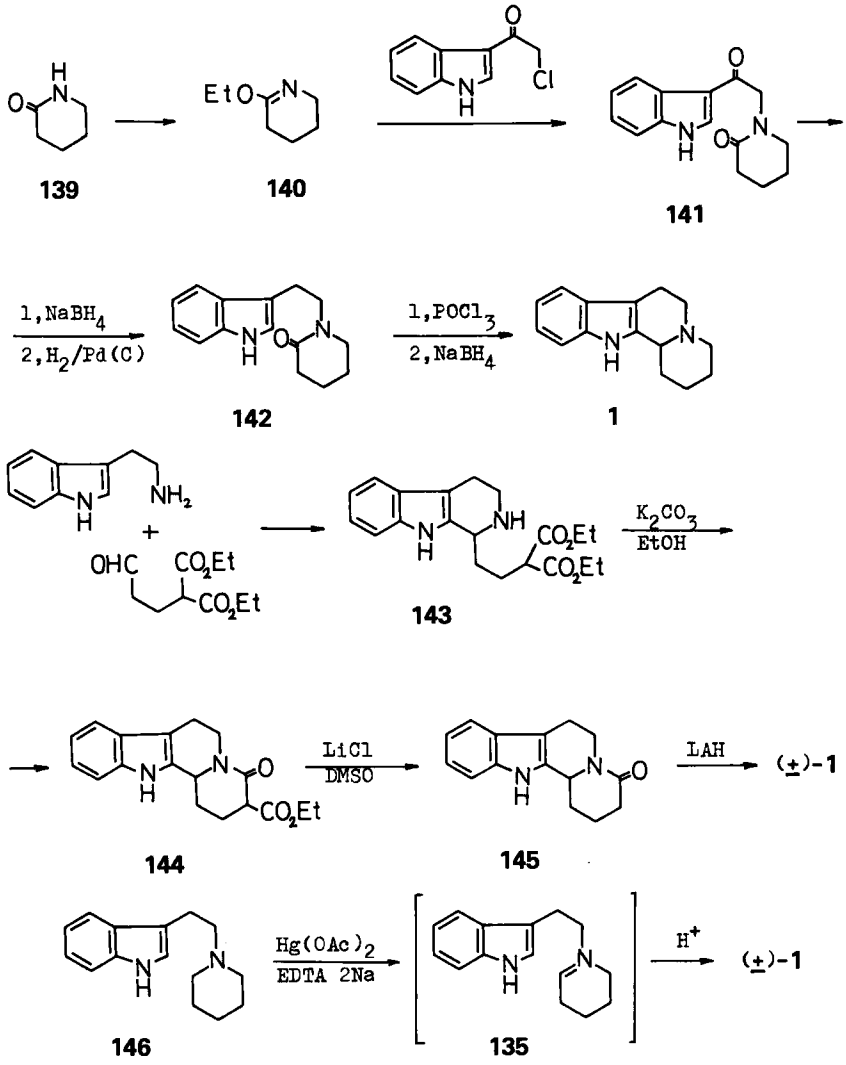
Utilizing Wenkert's cyclization process, a number of new approaches have been elaborated for the synthesis of simple indolo[2,3-*a*]quinolizine derivatives. For example, treatment of *N*-[2-(indol-3-yl)ethyl]piperidine *N*-oxide (**134**) with trifluoroacetic anhydride gave piperideinium intermediate **135** in a Polonovski-type reaction, which could be cyclized in acidic medium to (±)-**1** (*101*).

According to another approach, treatment of *N*-[2-(indol-3-yl)ethyl]-1,2,5,6-tetrahydropyridine (**137**), obtained from the corresponding pyridinium salt **136** by borohydride reduction, first with potassium *tert*-butoxide, and then with acetic acid, led to (±)-**1** via key intermediate **135** in 78% yield (*102*).



A new route has been developed for the efficient formation of the variably substituted indolo[2,3-*a*]quinolizine ring system, starting from a properly substituted 2-piperidone (*103, 104*). For the preparation of octahydroindoloquinolizine (**1**), the unsubstituted 2-piperidone **139** was treated with triethoxonium tetrafluoroborate. Then the corresponding lactim ether **140** was alkylated with 3-chloroacetylindole followed by a subsequent two-step reduction process and Bischler–Napieralski ring closure. Finally, reduction of the C=N bond afforded (±)-**1** (*104*).

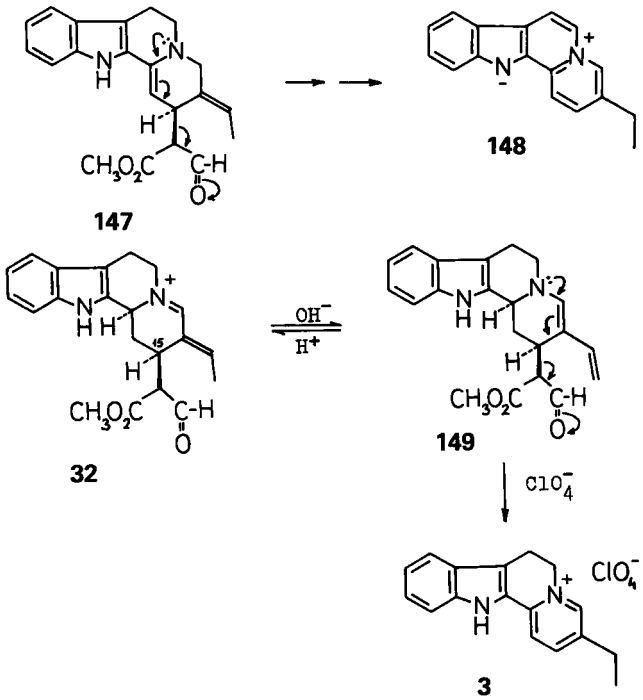
A convenient synthesis of (±)-**1** has been reported by Sakai *et al.* (*105*). The condensation of tryptamine with diethyl (2-formylethyl)malonate led to lactam ester **144.** Deethoxycarbonylation of **144,** followed by lithium aluminum hydride reduction, gave racemic octahydroindoloquinolizine (**1**).



Oxidative cyclization of *N*-[2-indol-3-yl)ethyl]piperidine (**146**) with 3 molar equivalents of mercuric acetate and EDTA disodium resulted in (±)-**1** in 85% yield (*106*).

2. Flavopereirine and 5,6-Dihydroflavopereirine

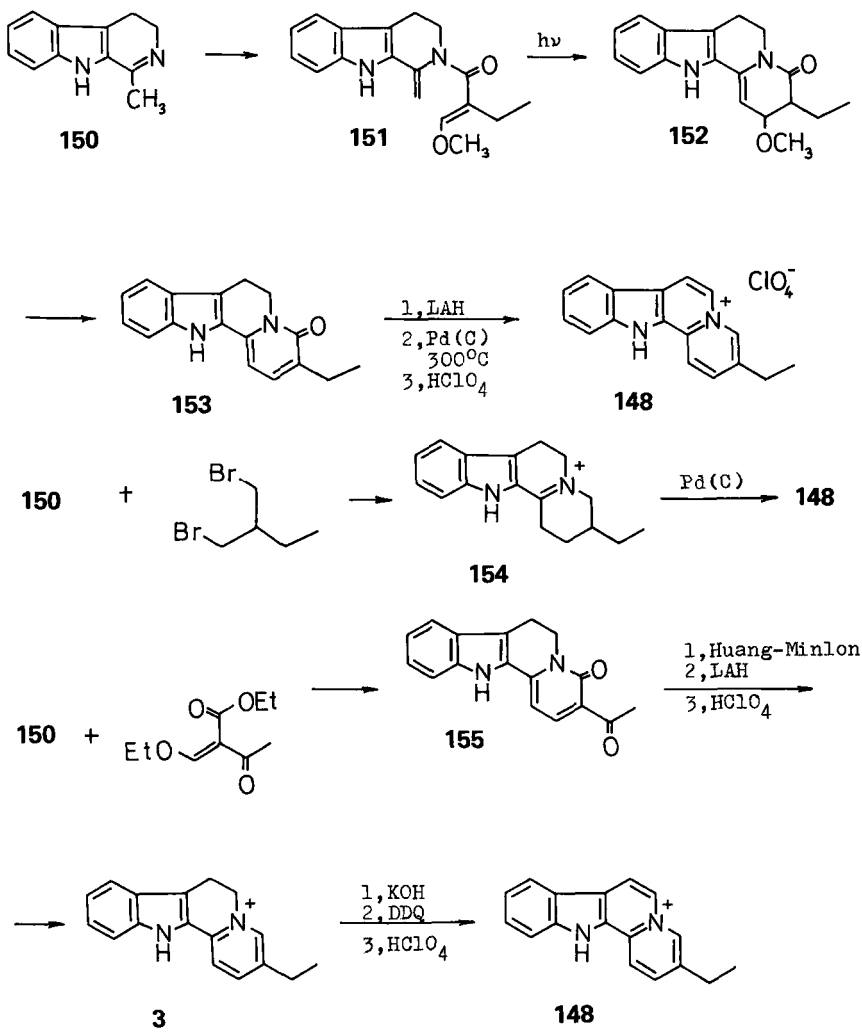
3,14-Didehydrogeissoschizine (**147**) has been proposed to be the biogenetic precursor of simple indolo[2,3-*a*]quinolizine alkaloids such as flavopereirine (**148**)



(*107*). The above assumption has been supported by *in vitro* transformation of 4,21-didehydrogeissoschizine (**32**) to 5,6-dihydroflavopereirine (**3**) (*108*). Treatment of **32** with base supplied dienamine **149,** which loses the β-aldehydo ester unit attached to C-15 in a retro-Mannich reaction. Finally, two subsequent [1,5]-sigmatropic hydrogen migrations led to 5,6-dihydroflavopereirine (**3**), isolated as the perchlorate salt.

A new total synthesis of flavopereirine perchlorate (**148**) has been reported by Ninomiya *et al.* (*109*) via enamide photocyclization. Harmalane (**150**) was acylated with 3-methoxyethacryloyl chloride to enamide **151** which was irradiated in benzene solution without purification to yield the unstable lactam **152.** The latter was treated with hydrochloric acid, resulting in dehydrolactam **153** in a yield of 35% from harmalane (**150**). Lithium aluminum hydride reduction of **153,** followed by dehydrogenation, afforded flavopereirine (**148**), isolated as its perchlorate (*109*).

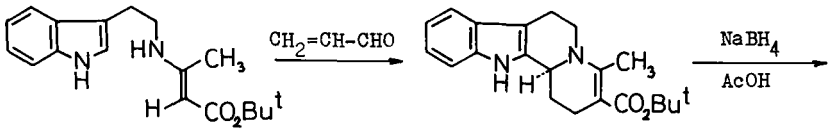
A straightforward synthesis of flavopereirine (**148**) was published by Danieli *et al.* (*110*). Reflux of harmalane (**150**) with 1-bromo-2-(bromomethyl)butane led to the corresponding 3-ethylhexahydroindolo[2,3-*a*]quinolizinium salt **154,** which, after dehydrogenation and treatment with perchloric acid, supplied flavopereirine perchlorate (**148**) in 57% overall yield. In a similar approach, flavopereirine (**148**) and 5,6-dihydroflavopereirine (**3**) perchlorates have been syn-



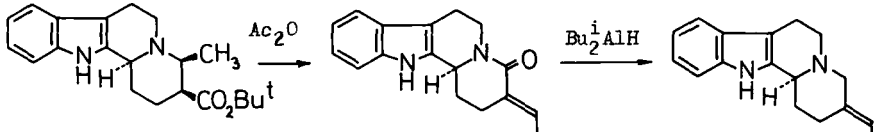
thesized from 3-acetyl-4-oxo-6,7-dihydro-12*H*-indolo[2,3-a]quinolizine (**155**) obtained in one step by the reaction of harmalane (**150**) and ethyl ethoxymethyleneacetoacetate (*111*).

3. Deplancheine

Interestingly enough, racemic deplancheine (**7**) had been synthesized 6 years before the isolation of the alkaloid from the stem bark of *Alstonia deplanchei* van Heurck and Müll. Arg. (*14*). Winterfeldt and co-workers (*112*) treated enamine



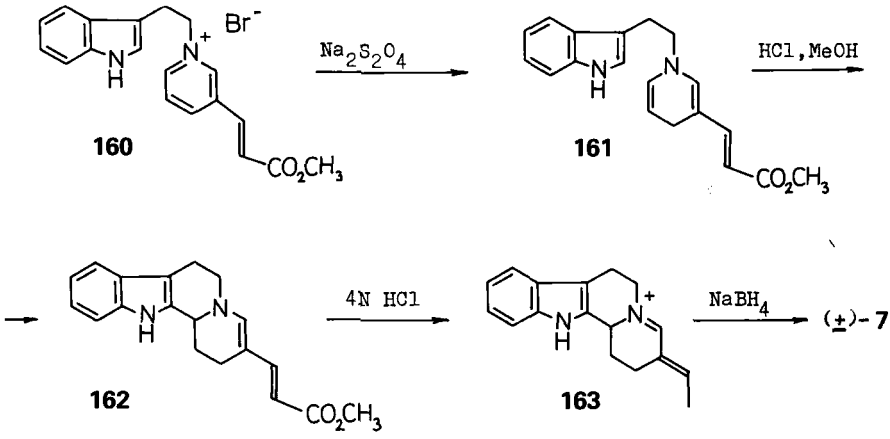
156 157



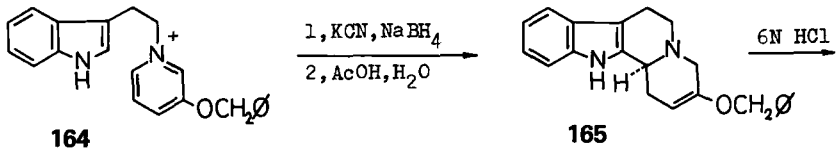
(±)-158 (±)-159 (±)-7

156, obtained from tryptamine and *tert*-butyl acetoacetate, with acrolein to yield the cyclic vinylogous urethane **157.** Reduction of **157** with sodium borohydride in glacial acetic acid afforded **158** stereoselectively. Treatment of **158** with acetic anhydride led to the unsaturated lactam **159,** utilizing the cyclic β-amino acid rearrangement to an α-methylenelactam observed first by Rapoport *et al.* (*113, 114*). To complete the synthesis, **159** was reduced by diisobutylaluminum hydride, supplying deplancheine in racemic form (*112*).

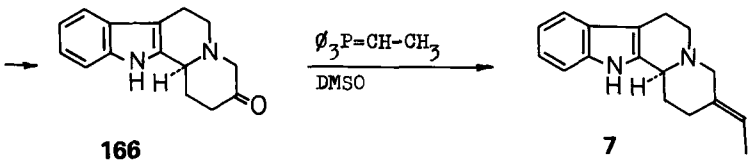
After its isolation, the structure of alkaloid deplancheine (**7**) was unambiguously proved by several total syntheses. In one of the first approaches (*14*), 1,4-dihydropyridine derivative **161,** obtained by sodium dithionite reduction of *N*-[2-(indol-3-yl)ethyl]pyridinium salt **160,** was cyclized in acidic medium to yield quinolizidine derivative **162.** Upon refluxing **162** with hydrochloric acid, hydrolysis and decarboxylation took place. In the final step of the synthesis, the conjugated iminium salt **163** was selectively reduced to racemic deplancheine.



160 161 162 163



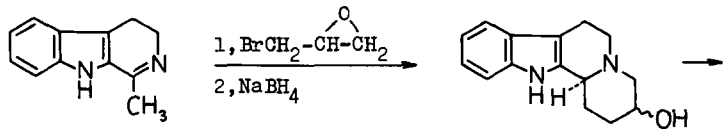
164 **165**



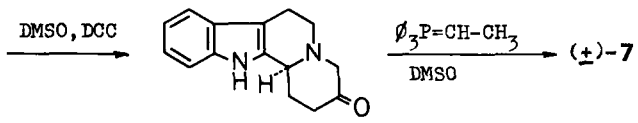
166 **7**

(±)-Deplancheine has also been achieved (*115*) from the easily available pyridinium salt **164,** utilizing a Wittig reaction to establish the desired ethylidene side chain at C-20.

(±)-Ketone **166,** the key intermediate of deplancheine was obtained in 63% overall yield by the reaction of harmalane (**150**) with 1-bromo-2,3-epoxypropane, followed by sodium borohydride reduction and Moffat oxidation (*116*). Methods for the elaboration of the exocyclic, *E*-configurated double bond are reviewed (*117*).



150 **167**

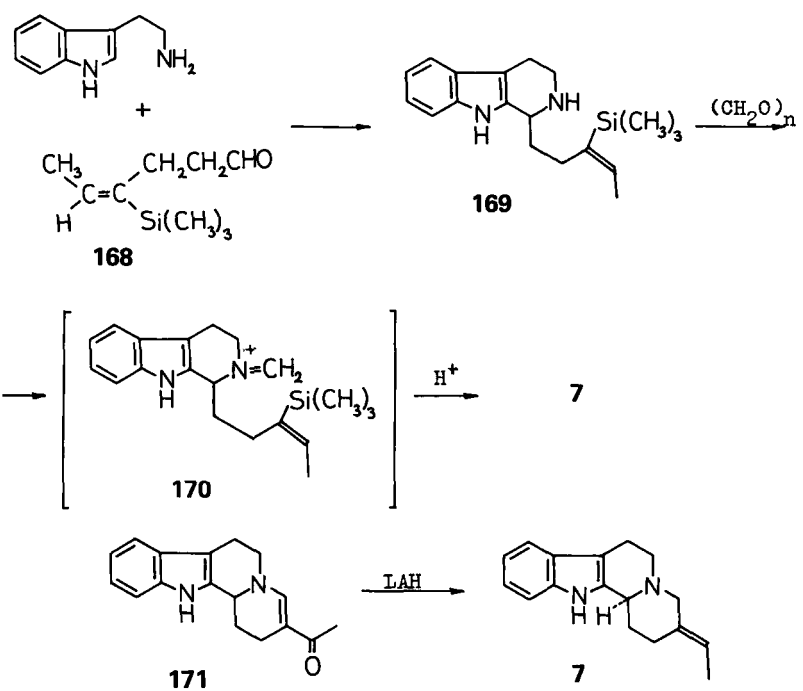


166

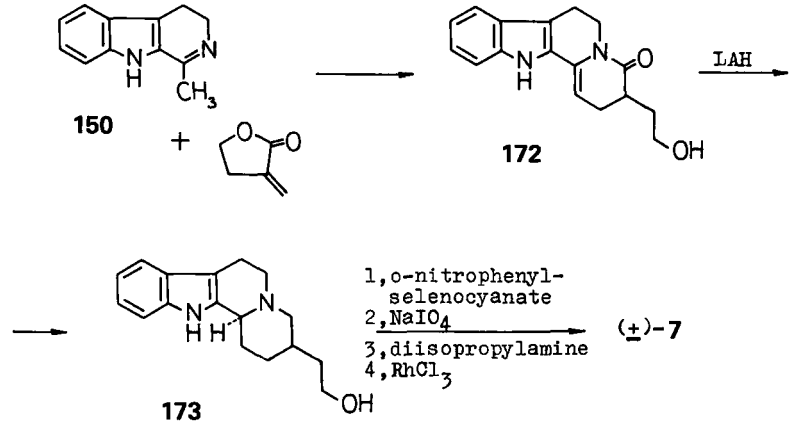
An alternative total synthesis of (±)-deplancheine, applying stereocontrolled formation of the exocyclic double bond, has also been reported (*118*). The final ring closure was reached in this case by an acid-catalyzed iminium ion–vinylsilane cyclization (**170→7**).

A short synthesis of (±)-deplancheine has been reported by Hämeilä and Lounasmaa (*119*) by lithium aluminum hydride reduction of 3-acetylindolo[2,3-*a*]quinolizine derivative **171.**

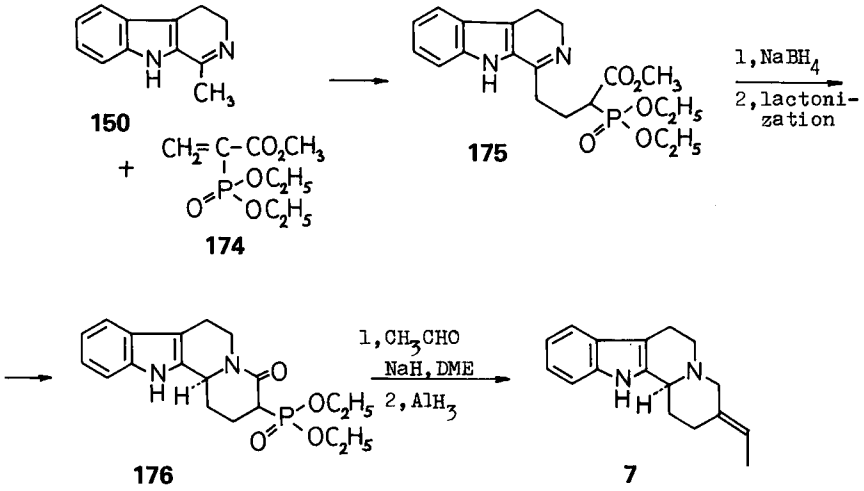
Two new approaches to achieve (±)-deplancheine have been developed by



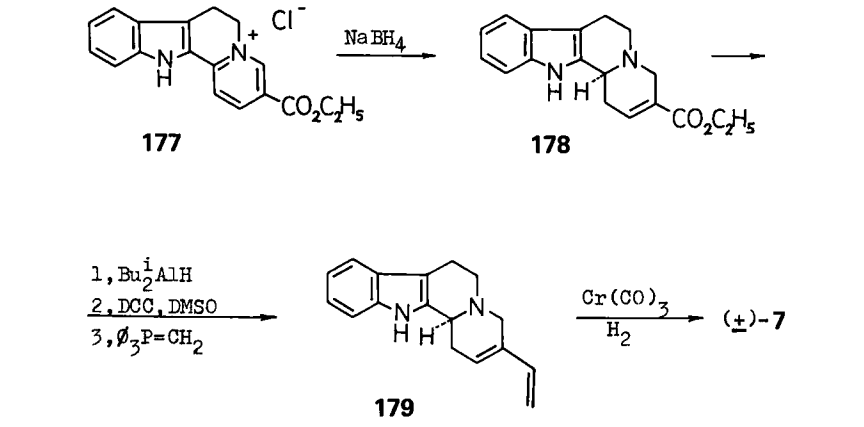
Danieli *et al.* (*116*), both of which utilize an alkylation process of 1-methyl-3,4-dihydro-β-carboline (**150**) in the key ring-forming step. In the first one, treatment of **150** with α-methylene-γ-butyrolactone gave enamide **172,** which, when reduced with lithium aluminum hydride, afforded indolo[2,3-*a*]quinolizine derivative **173.** The desired ethylidene substituent at C-20 has been developed from the hydroxyethyl side chain in a four-step sequence as shown below.



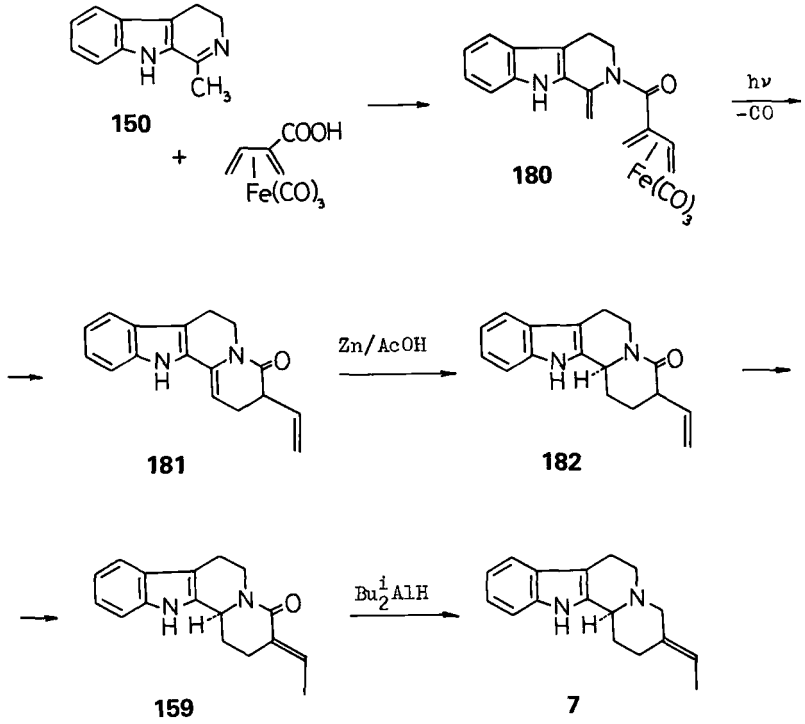
In the other approach, again harmalane (**150**) was treated with methyl 2-(diethylphosphono)acrylate (**174**), resulting in iminophosphonate **175.** By its sodium borohydride reduction and subsequent lactonization, the amidophosphonate **176** has been obtained, Wittig–Horner reaction of **176** with acetaldehyde followed by selective reduction of the carbonyl group of the enamide function supplied (±)-deplancheine in good yield (*116*).



Recently, a multistep synthesis of (±)-deplancheine was developed by Rosenmund and Casutt (*120*), starting from tryptamine and coumalic ester. In the key step of this approach, 1,4-addition of hydrogen to diene **179** was achieved with full stereoselectivity by means of hydrogen in the presence of toluenetricarbonylchromium catalyst.

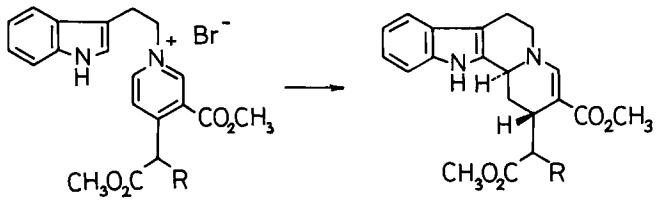


A highly stereoselective synthesis of (±)-deplancheine has been developed (*121*), utilizing a photocyclization process for the preparation of enelactam **181,** which was reduced by zinc in acetic acid to lactam **182.** In the latter, the double bond was shifted to the 19,20 position stereoselectively with an *E* geometry by the use of nonacarbonyldiiron catalyst to supply **159,** previously synthesized and transformed to (±)-**7** by Winterfeldt *et al.* (*112*).



4. Synthesis of Vallesiachotamine Models

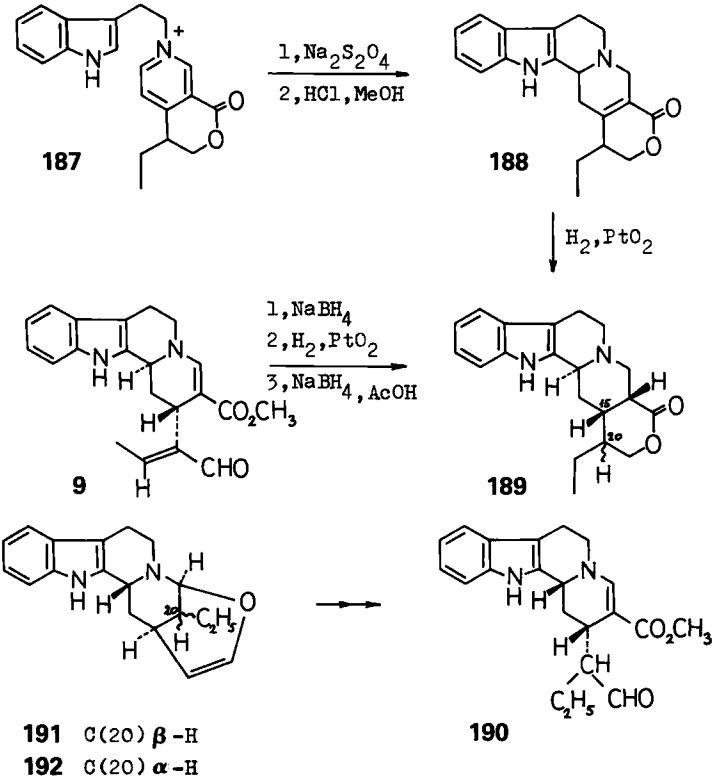
A series of papers have been published by Lounasmaa *et al.* (*122–128*) on the synthesis of different alkaloid-like indolo[2,3-*a*]quinolizidine derivatives by means of reduction and subsequent cyclization of *N*-[2-(indol-3-yl)ethyl]piridinium salts, developed as a general method for indole alkaloid synthesis by Wenkert and co-workers (*129, 130*). Aimed at the total synthesis of vallesiachotamine (**9**), valuable model studies were reported (*131–133*). Reduction of pyridinium salts **183** and **184** with sodium dithionite and subsequent acid-induced cyclization represents a convenient method for preparing vallesiachotamine-type derivatives **185** and **186,** respectively.



183 R=H **185** R=H

184 R=CH_2CH_3 **186** R=CH_2CH_3

When pyridinium salt **187** was transformed to an indolo[2,3-*a*]quinolizidine compound in a similar way and the unsaturated lactone **188** was hydrogenated over platina catalyst, a mixture of vallesiachotamine-type compounds (**189** diastereomers) epimeric at C-20 was formed (*134*). These compounds have also been prepared in optically active form from vallesiachotamine (**9**), thus producing the first chemical correlation between synthetic and natural vallesiachotamine derivatives (*134*).



191 C(20) β-H

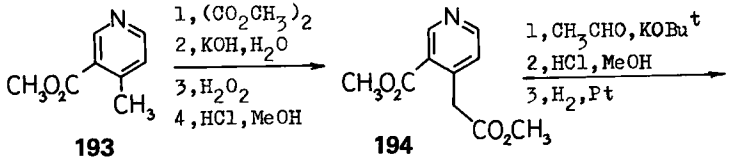
192 C(20) α-H

Dihydro-3-epivallesiachotamine (**190**) has been prepared from 20-epidihydromancunine (**191**), obtained as a side product during the transformation of demethylhirsutine to dihydromancunine (**192**) (*135*).

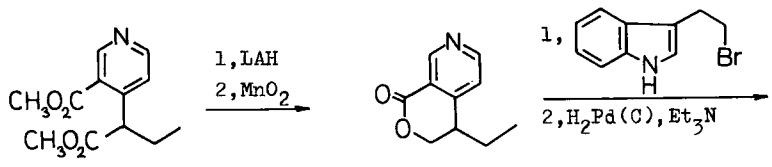
B. Synthesis of Corynanthe Alkaloids

1. Antirhine and 18,19-Dihydroantirhine

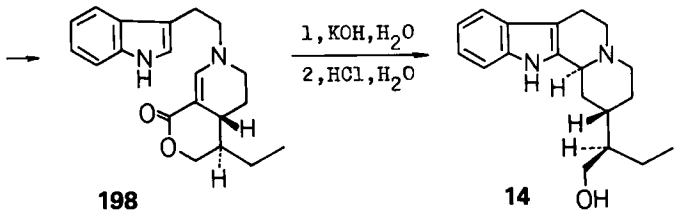
Several total syntheses of antirhine (**11**) and 18,19-dihydroantirhine (**14**) have been developed during the last decade. Wenkert *et al.* (*136*) employed a facile route to (±)-18,19-dihydroantirhine, using lactone **196** as a key building block. Base-catalyzed condensation of methyl 4-methylnicotinate (**193**) with methyl oxalate, followed by hydrolysis, oxidative decarboxylation with alkaline hydrogen peroxide, and final esterification, resulted in methyl 4-(methoxycarbonylmethyl)nicotinate (**194**). Condensation of **194** with acetaldehyde and subsequent reduction afforded nicotinic ester derivative **195**, which was reduced with lithium aluminum hydride, and the diol product obtained was oxidized with manganese dioxide to yield the desired lactone **196**. Alkylation of **196** with tryptophyl bromide (**197**) resulted in a pyridinium salt whose catalytic reduction



193 **194**



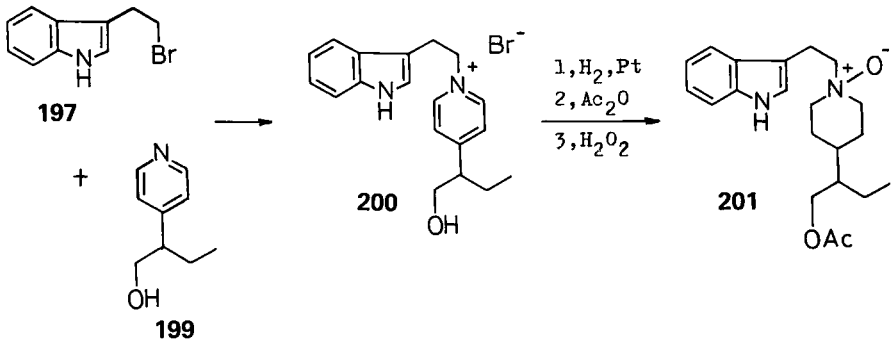
195 **196**



198 **14**

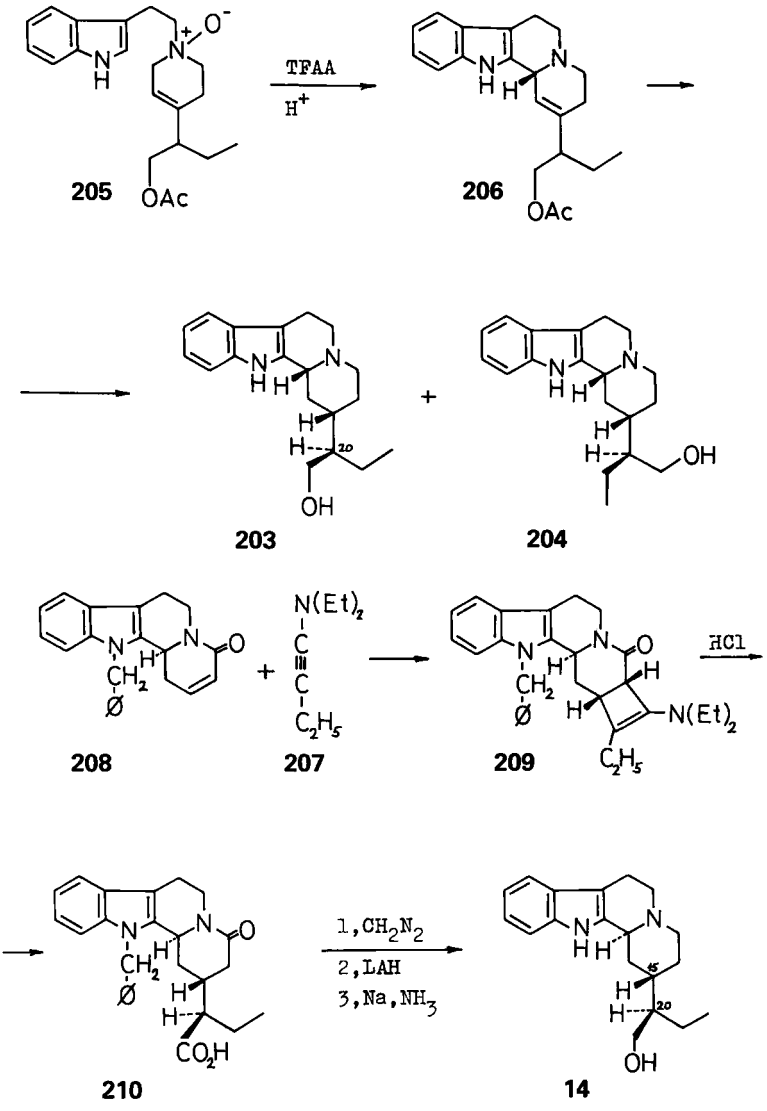
led to the thermodynamically favored C-15, C-20-*trans*-tetrahydropyridine **198** selectively. Finally, alkaline hydrolysis, followed by decarboxylation and acid-catalyzed cyclization, afforded (±)-18,19-dihydroantirhine (*136*).

Another route to (±)-18,19-dihydroantirhine makes use of the modified Polonovski reaction for the final cyclization step, resulting in the C-3, C-15-*trans*-indoloquinolizine selectively. The product obtained via this sequence, however, proved to be an inseparable mixture of (±)-18,19-dihydroantirhine and its C-20 epimer (**202**) (*137*).



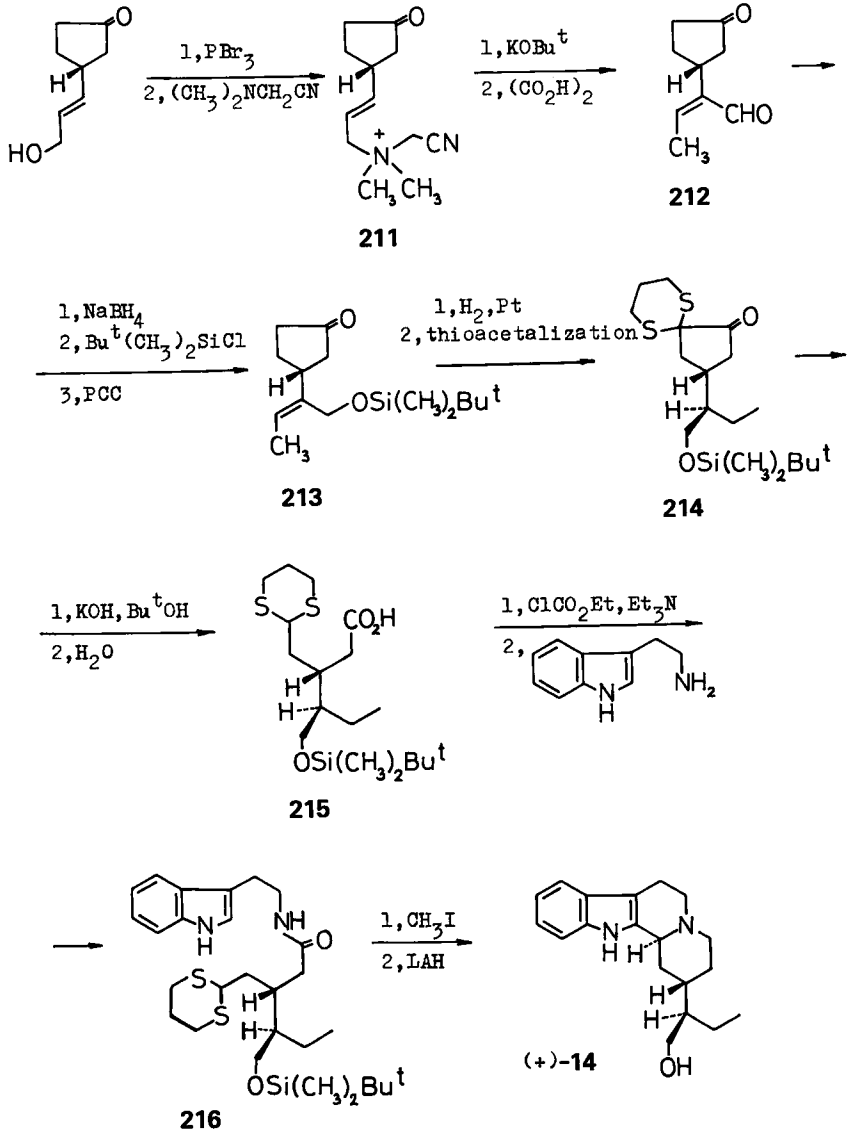
Also, a mixture of (±)-3-epi-18,19-dihydroantirhine (**203**) and its C-20 epimer (**204**) has been obtained (*138*) by hydrogenation and subsequent deacetylation of **206,** prepared earlier via a modified Polonovski reaction (*101*).

A highly stereoselective synthesis of (±)-18,19-dihydroantirhine has been developed by Ficini and co-workers (*139*). The control in the formation of all three stereo centers and the efficiency of the particular reaction steps leads to a remarkable overall yield of 40% starting from lactam **208.** In the key step of the synthesis, ynamine **207** attacks the unsaturated lactam **208** at C-15 in a perpendicular direction, involving a transition state in which ring D of **208** exists in a flattened half-chair conformation, leading to **209** with established relative configurations at C-3, C-15, and C-16. The relative configuration of the would-be C-20 stereo center could be controlled during the hydrolysis of the cylobutane–enamine system of **209,** when the proton addition in the introductory step occurs at C-20 on the more accessible exo face of the molecule. Finally, esterification



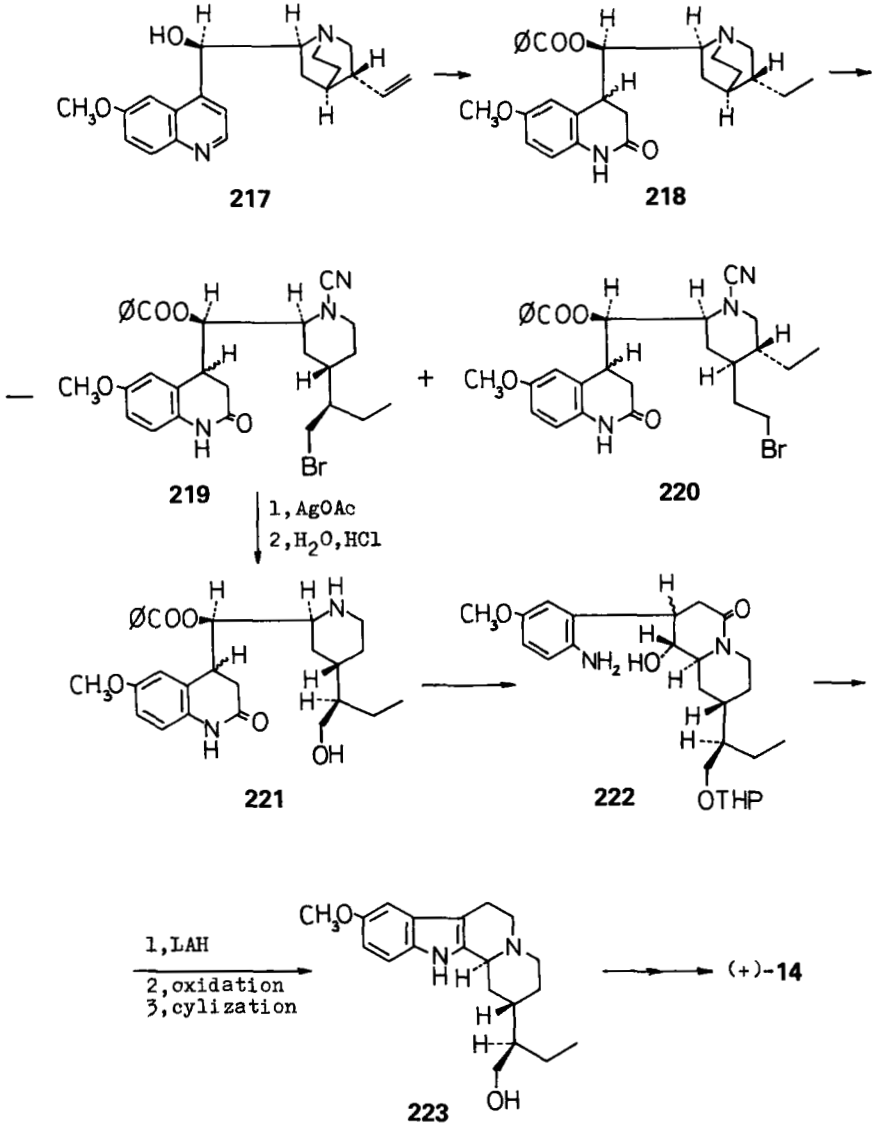
with diazomethane, reduction with lithium aluminum hydride, and debenzylation of the indole nitrogen yielded (±)-18,19-dihydroantirhine (*139*).

Recently, an enantioselective total synthesis of (±)-18,19-dihydroantirhine has been reported by Kametani's group (*140*). They started from the chiral cyclopentanone derivative **211,** obtained from the previously prepared (*R*)-1,2-isopropylideneglyceraldehyde (*141*). Utilizing a number of reaction steps, **211** was transformed to **215** with the desired stereochemistry at the future C-15 and



C-20 positions. The final cyclization gave the C-3, C-15-trans arrangement of the hydrogen atoms attached to those centers, furnishing the dextrorotatory antipode of 18,19-dihydroantirhine (*140*).

The transformation of quinine (**217**) to (±)-18,19-dihydrohunterburnine (**223**) as well as (±)-18,19-dihydroantirhine was reported by Sawa and Matsumura (*142*). Normal and allo *N*-cyanobromides **219** (C-4—Hβ and C-4—Hα, respec-

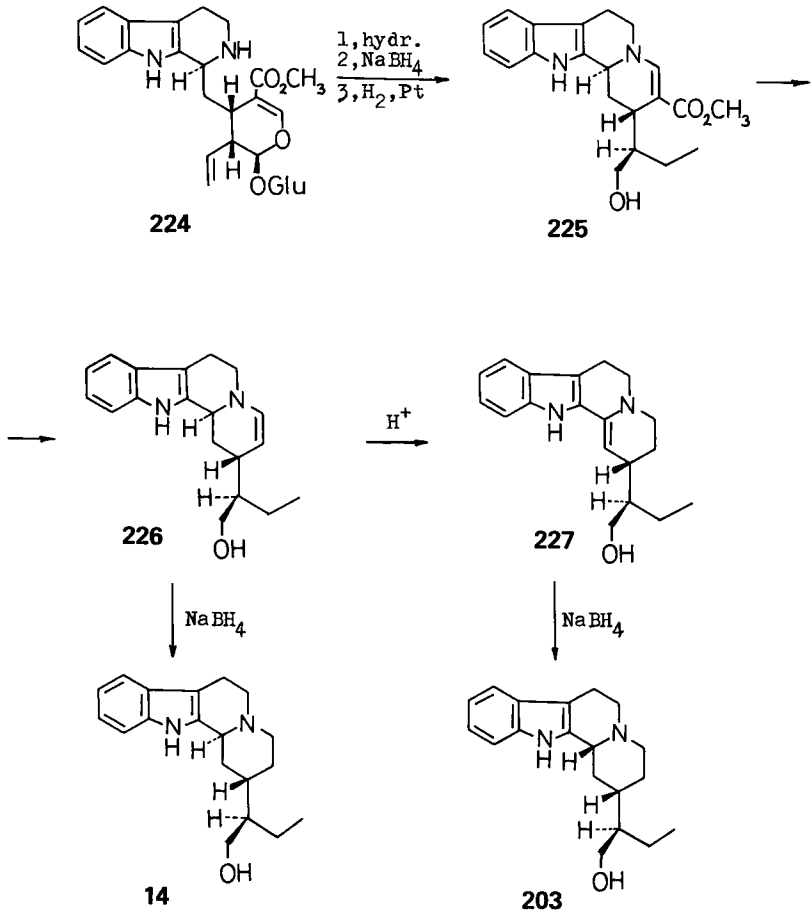


tively) were prepared by the von Braun reaction of the corresponding 9-benzoyl-2′-oxohexahydroquinines (**218**), obtained from natural quinine (**217**). Simple substitution, hydrolysis, and protecting-group introduction reactions, followed by the lactam ring conversion, yielded two diastereomeric quinolizidones (**222**), which were reduced with lithium aluminum hydride and oxidized by a modified Oppenauer method. The final cyclization was carried out in acidic

media to yield (±)-18,19-dihydrohunterburnine (**223**) (*142*). Demethylation of **223** and hydrogenolysis of the corresponding tetrazolyl ether gave (+)-18,19-dihydroantirhine, the absolute configuration of which was established by Johns (*19, 143*).

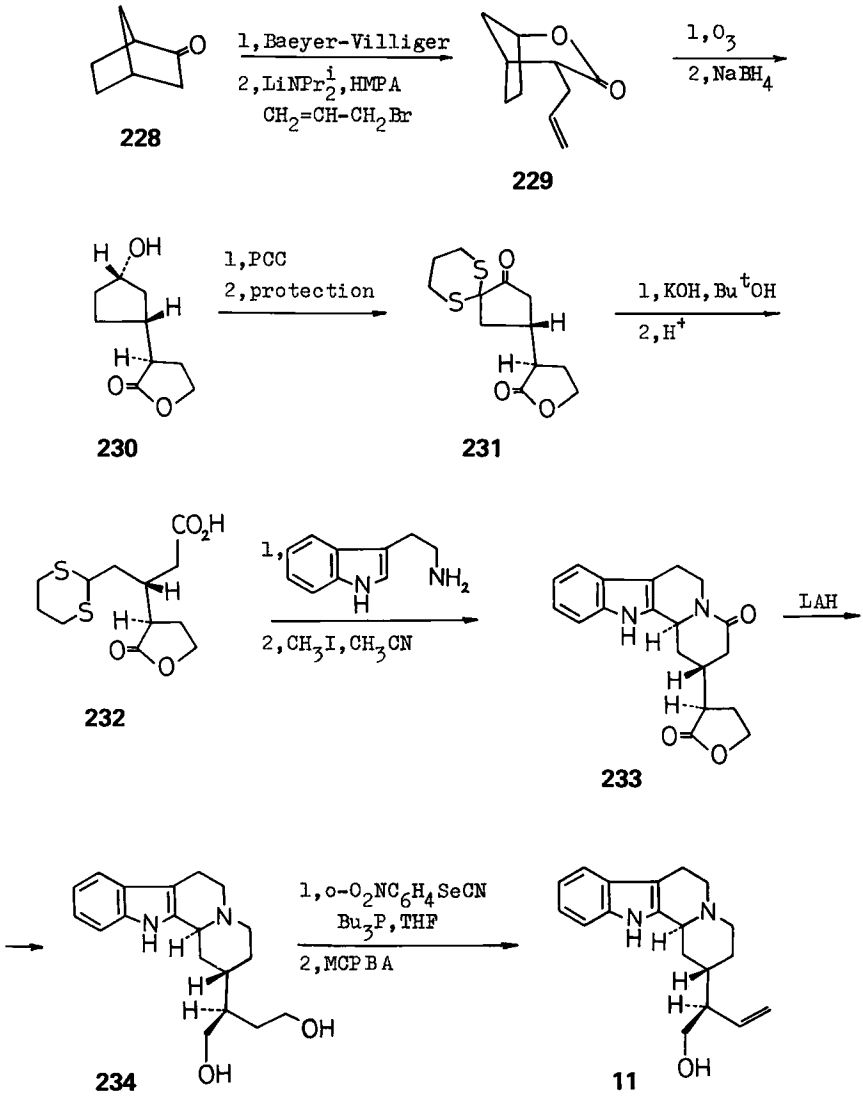
18,19-Dihydroantirhine has also been reached from indole alkaloid strictosidine (**224**). Mild hydrolysis of **224,** followed by subsequent sodium borohydride and catalytic reduction, supplied vallesiachotamine derivative **225.** Hydrolysis and decarboxylation of **225** gave enamine **226,** which could be izomerized to **227** by the use of acid. Sodium borohydride reduction of the thermodynamically less stable enamine **226** afforded (+)-18,19-dihydroantirhine selectively, while **227** yielded uniformly 3-epi-18,19-dihydroantirhine (**203**) (*144*).

The first synthesis of (±)-antirhine (**11**) has been published by Takano and co-



224 **225** **226** **227** **14** **203**

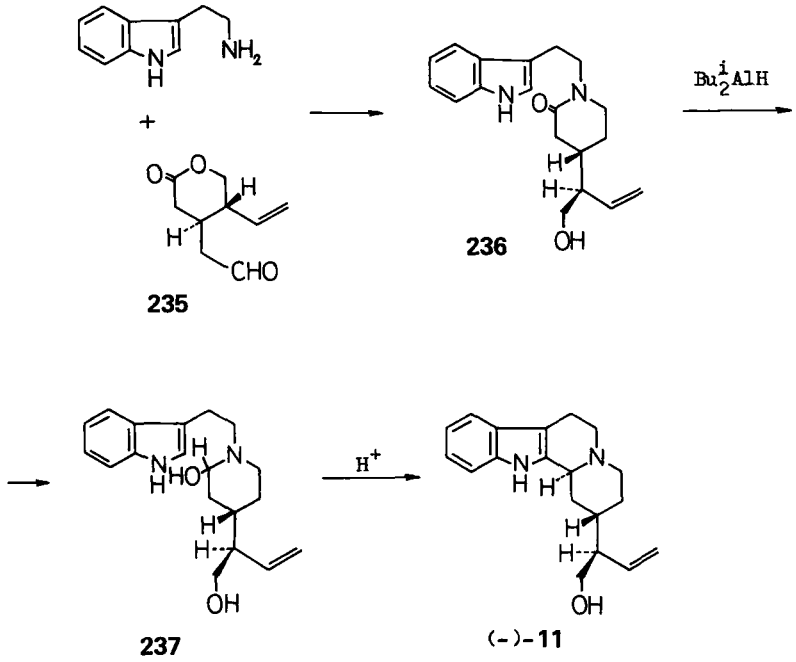
workers (*145*). The key building block (**232**) of the synthesis, prepared from (±)-norcamphor (**228**) as shown below, proved to be suitable for assuring all of the relative configurations at C-3, C-15 and C-20. Moreover, the proper substitution at C-20 could also be reached. Condensation of **232** with tryptamine, followed by cyclization, resulted in lactam **233**, which was reduced with lithium aluminum hydride to indolo[2,3-*a*]quinolizine derivative **234** with cis C/D ring annellation. Finally, the less-hindered hydroxy group was eliminated by the use



228 **229** **230** **231** **232** **233** **234** **11**

of *o*-nitrophenyl selenocyanate and *m*-chloroperbenzoic acid, affording (±)-antirhine (*145*).

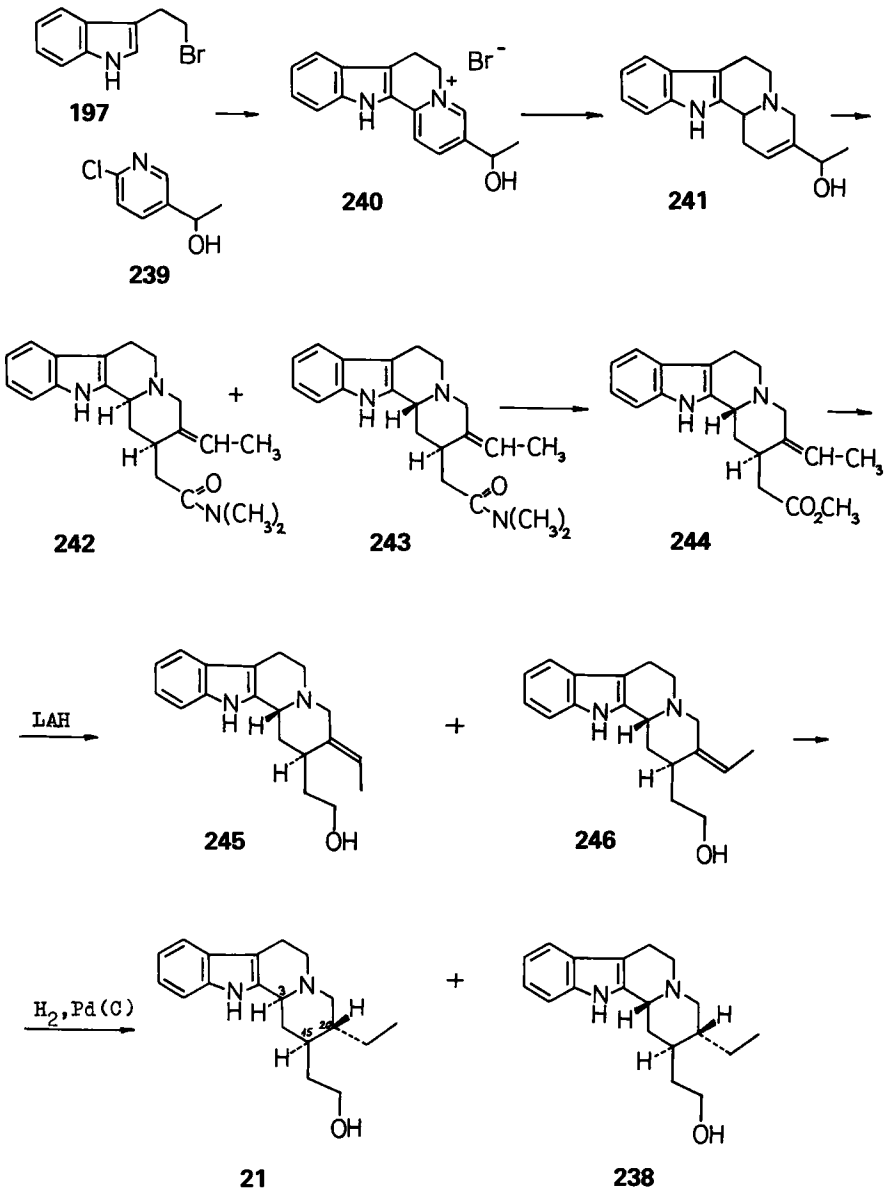
Takano's group reported the first enantioselective total synthesis of (−)-antirhine as well (*146*). Chiral product **235** was prepared via a number of stereoselective reactions. Reductive condensation of **235** with tryptamine, using sodium cyanoborohydride at pH 6, supplied lactam **236,** which was reduced by diisobutylalminum hydride to hemiacetal **237.** The latter could be cyclized to (−)-antirhine by simple acid treatment (*146*).



2. Dihydrocorynantheol and Its Stereosiomers

Dihydrocorynantheol (**21**), first isolated from *Aspidosperma marcgravianum* (*147*), is the simplest corynanthe alkaloid. The members of this type of alkaloid have three stereo centers in the D ring of the indolo[2,3-*a*]quinolizine skeleton. This substitution pattern allows four possible relative arrangements for the C-3, C-15, and C-20 stereo centers, the names of which are normal, pseudo, allo, and epiallo, respectively.

Dihydrocorynantheol, which belongs to the normal series and its C-3 epimer **238** with pseudo relative configuration have been synthesized by Ziegler and Sweeny (*148*). Alkylation of 2-chloro-5-(α-hydroxyethyl)pyridine (**239**) with



tryptophyl bromide (**197**), followed by sodium borohydride reduction, resulted in a diastereomeric mixture of allylic alcohols **241.** Heating the alcohols **241** with dimethylacetamide dimethyl acetal gave a separable mixture of amides **242** and **243.** The latter (**243**), after hydrolysis and esterification, furnished **244,** which

could be reduced by lithium aluminum hydride to a mixture of 3-epigeissoschizol (**245**) and 3-epiisogeissoschizol (**246**). Prolonged hydrogenation over palladium–charcoal resulted in the saturation of the carbon–carbon double bond and a partial epimerization at C-3, supplying (±)-dihydrocorynantheol and (±)-hirsutinol (**238**) in good yield (*148*).

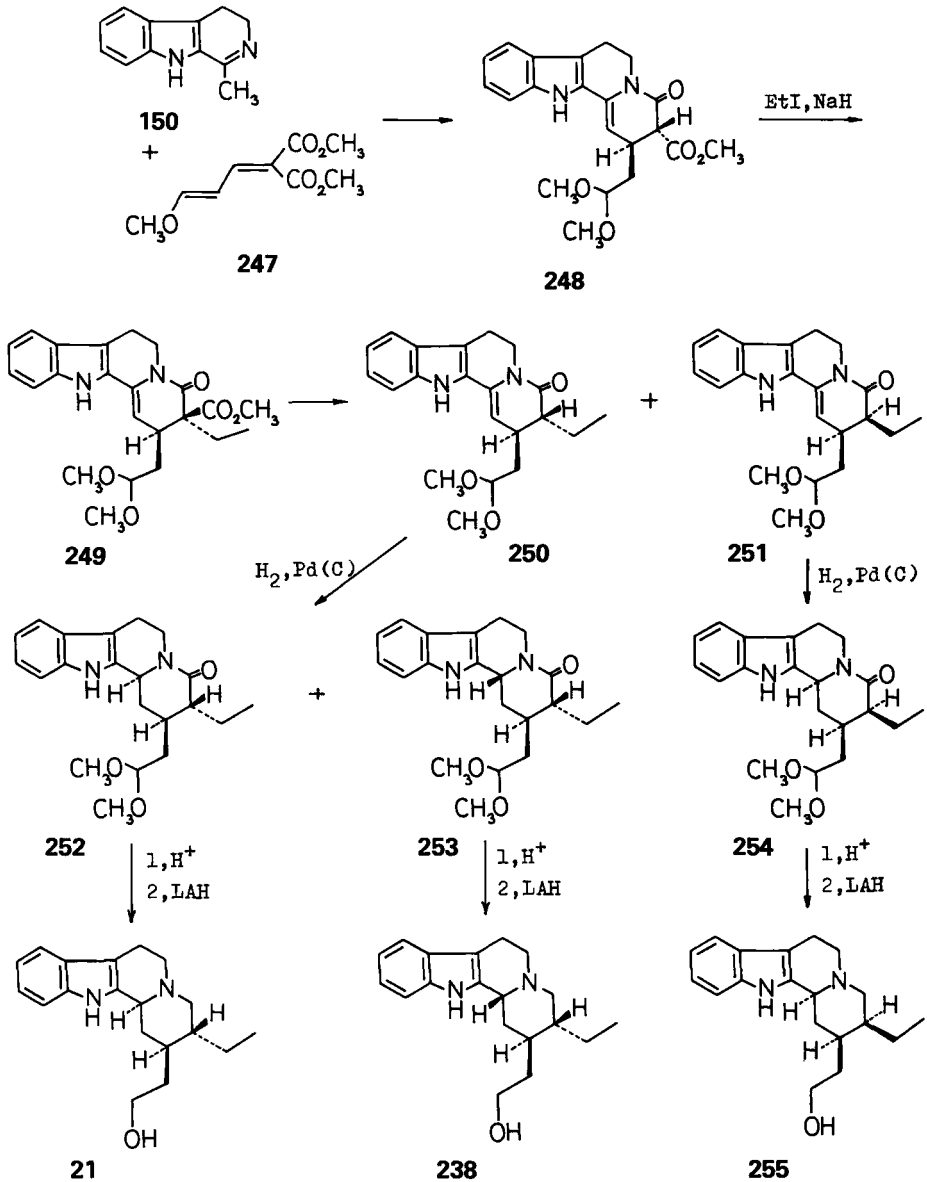
The utilization of the Robinson annellation method for the synthesis of corynanthe-type alkaloids has been thoroughly investigated by Kametani and coworkers (*149–152*). The tetracyclic ring system was efficiently formed via the Michael addition of dimethyl 3-methoxyallylidenemalonate (**247**) to the enamine derived from 3,4-dihydro-1-methyl-β-carboline (**150**). Alkylation of **248,** followed by hydrolysis and decarboxylation, resulted in a mixture of stereosiomeric enamides **250** and **251.** Hydrogenation of **250** afforded two lactams in a ratio of 2:1 in favor of the pseudo stereoisomer **253** over the normal isomer **252.** On the other hand, catalytic reduction of **251** gave **254** as the sole product in nearly quantitative yield. Deprotection of **254,** followed by lithium aluminum hydride reduction, yielded (±)-corynantheidol (**255**) with allo relative configuration of stereo centers at C-3, C-15 and C-20. Similar transformations of **252** and **253** lead to (±)-dihydrocorynantheol and (±)-hirsutinol (**238**), respectively, from which the latter is identical with (±)-3-epidihydrocorynantheol (*149–151.*).

Direct hydrogenation of key intermediate **248** over the Adams catalyst and subsequent lithium aluminum hydride reduction yielded the two stereoisomeric alcohols **256** and **257,** which were separately transformed to (±)-corynantheal (**258**) and (±)-3-epicorynantheal (**259**), respectively, by Moffatt oxidation, followed by Wittig reaction with methyltriphenylphosphonium bromide and, finally, by demasking the aldehyde function (*151, 152*).

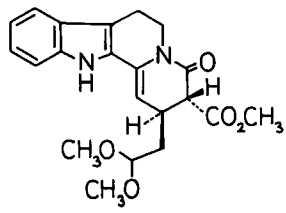
Experience gathered during the synthesis of (±)-antirhine (**11**) (*145*) provided Takano's group with a useful method for the synthesis of corynantheidol-type alkaloids. By the use of a number of stereoselective transformations, δ-lactone **260** was prepared from (±)-norcamphor (**228**). Reduction of **260** to the corresponding lactol followed by reductive alkylation with tryptamine supplied **261,** which, after hydrolysis of the dithian protecting group, was cyclized by the Pictet–Spengler reaction to yield (±)-3-epicorynantheidol **262** and (±)-corynantheidol (**255**) in 63 and 8% yields, respectively (*153*).

The transformation of the major product **262** to (±)-corynantheidol has also been realized via complete C-3 epimerization performed by mercuric acetate oxidation and subsequent sodium borohydride reduction (*153*).

Similarly to δ-lactone **260,** γ-lactone **263,** prepared also from (±)-norcamphor (**228**), proved to be another useful intermediate for the synthesis of all four corynantheidol stereoisomers as well as of the corresponding 18,19-didehydro derivatives. Cleavage of the α-diketone monothioketal moiety in **263** and the formation of amide **265** by its reaction with tryptamine, followed by Bischler–Napieralski cyclization and sodium borohydride reduction, resulted in a mixture



of epimeric lactams **266** and **267.** Transformation of **266** to (±)-corynantheidol (allo) and (±)-3-epicorynantheidol (epiallo) was carried out by the use of simple reaction steps elaborated previously, including C-3 epimerization. On the other hand, from **267,** (±)-hirsutinol (**238** pseudo) and (±)-dihydrocorynantheol (**21** normal) could be prepared (*154*).



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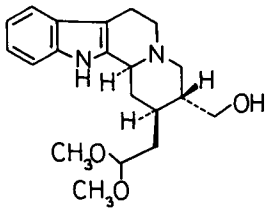

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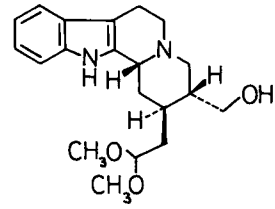

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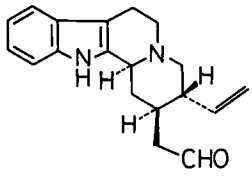

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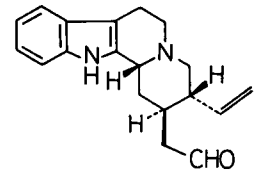

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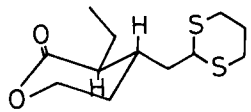

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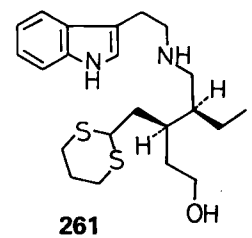

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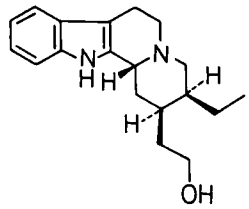

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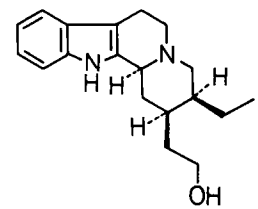

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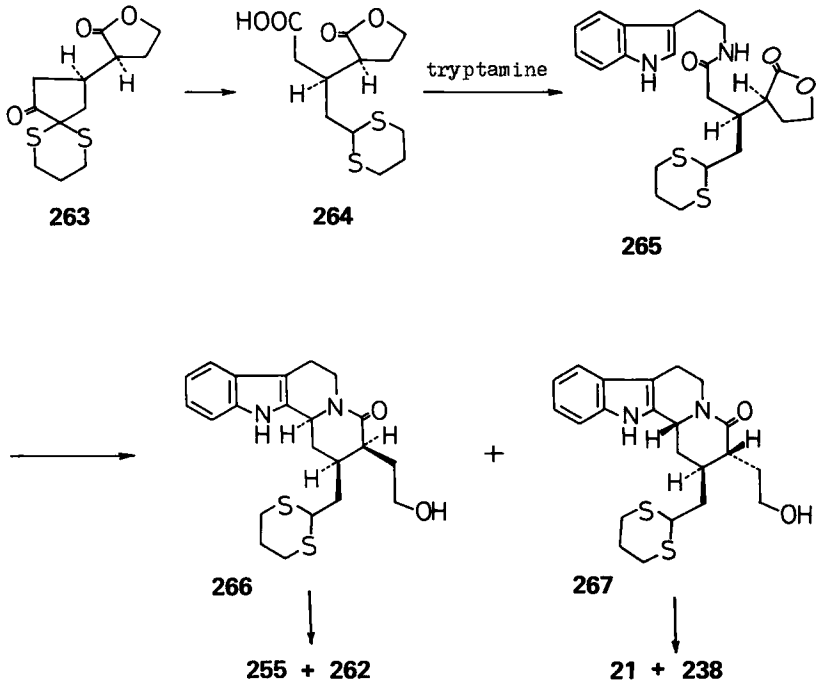


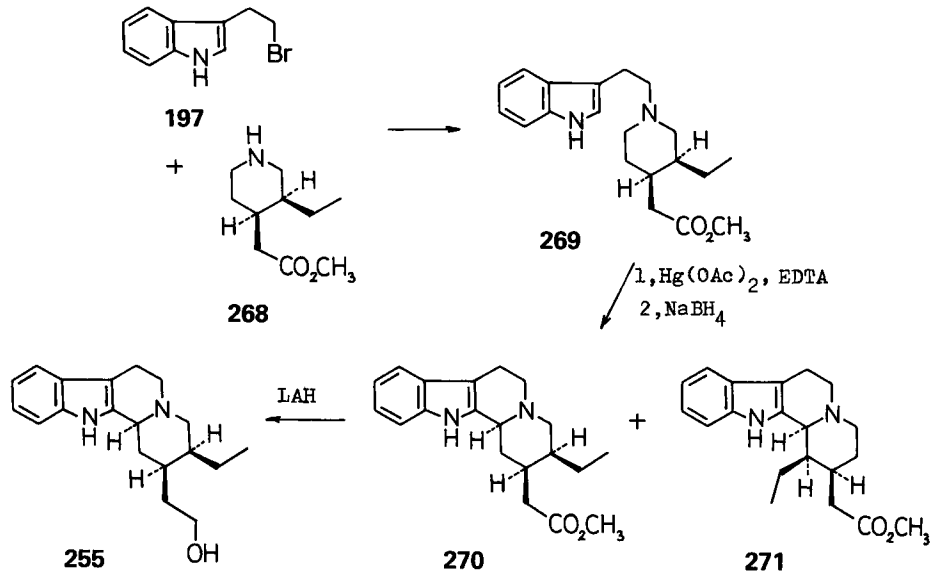
From lactams **266** and **267** the 18,19-didehydro alkaloid corynantheal (**258**) and its stereosiomers with pseudo and epiallo configurations have also been prepared in racemic form (*154*).

(±)-Corynantheidol (**255**) has been prepared by Hanaoka *et al.* (*155*), who started from piperideine derivative **268** and tryptophyl bromide (**197**). The key cyclization step, resulting in indolo[2,3-*a*]quinolizine **270** as the major product besides **271**, was carried out by mercuric acetate oxidation in the presence of the disodium salt of ethylenediaminetetraacetic acid (EDTA), followed by sodium borohydride reduction. Finally, lithium aluminum hydride reduction of **270** provided (±)-corynantheidol in good yield (*155*).

3. Geissoschizine and Related Alkaloids

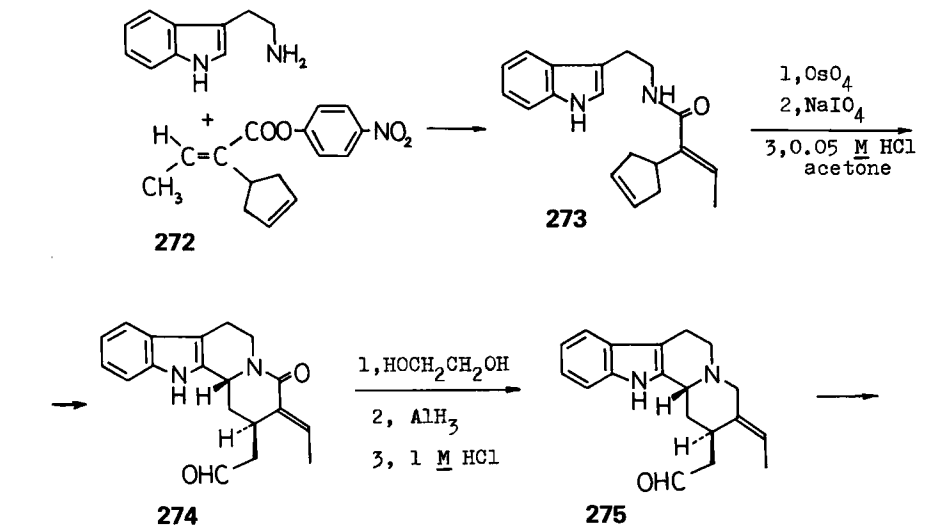
The total synthesis of (±)-geissoschizine (**30**) was reported by Yamada *et al.* (*156*) in 1974. The geometrically pure *p*-nitrophenyl ester **272** was condensed with tryptamine, and then the resulting amide **273** was transformed to lactam aldehyde **274** by hydroxylation with osmium tetroxide, metaperiodate oxidation, and Pictet–Spengler cyclization.

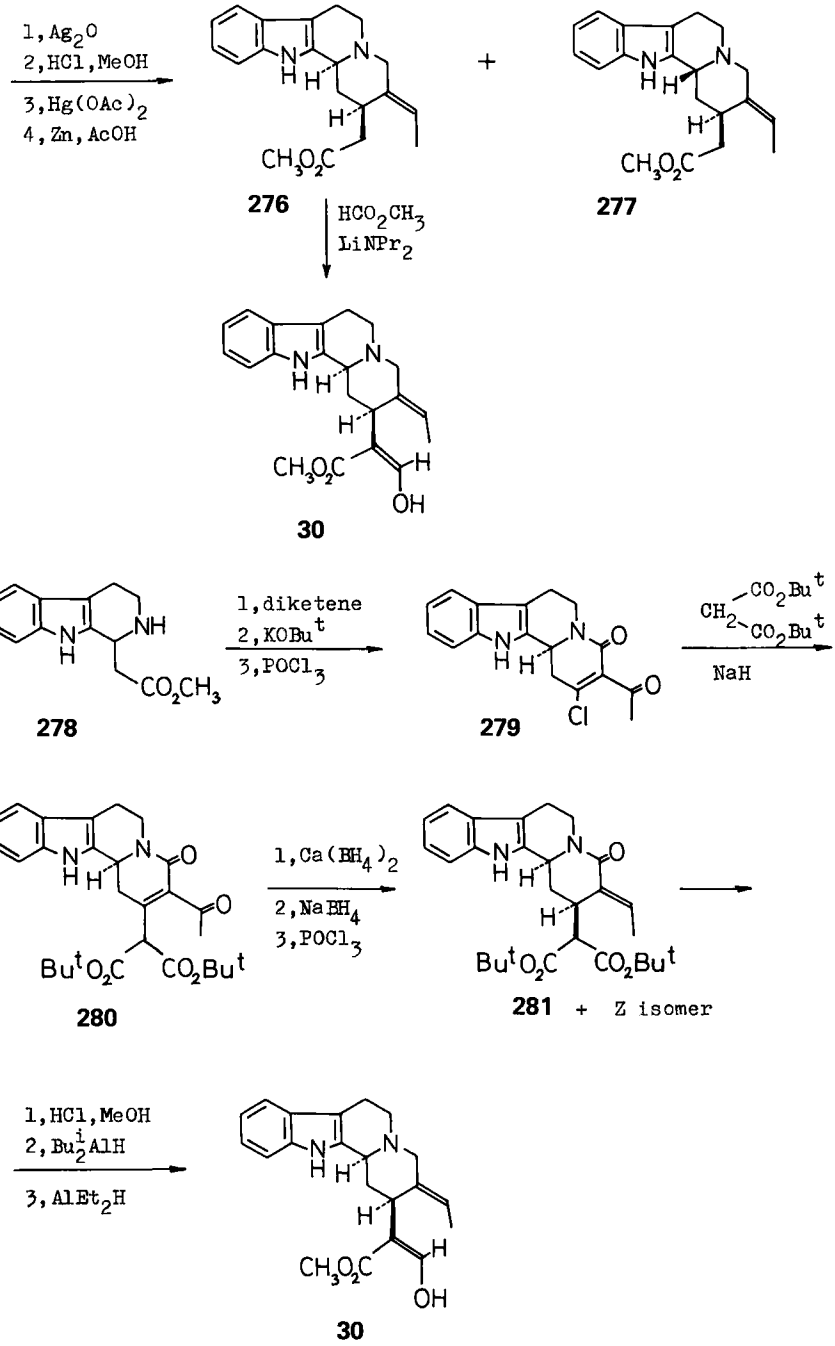
Temporary protection of the aldehyde function and reduction with aluminum hydride gave (±)-3-epigeissoschizal (**275**), from which silver oxide oxidation, followed by esterification, resulted in methyl (±)-epigeissoschizoate (**277**).

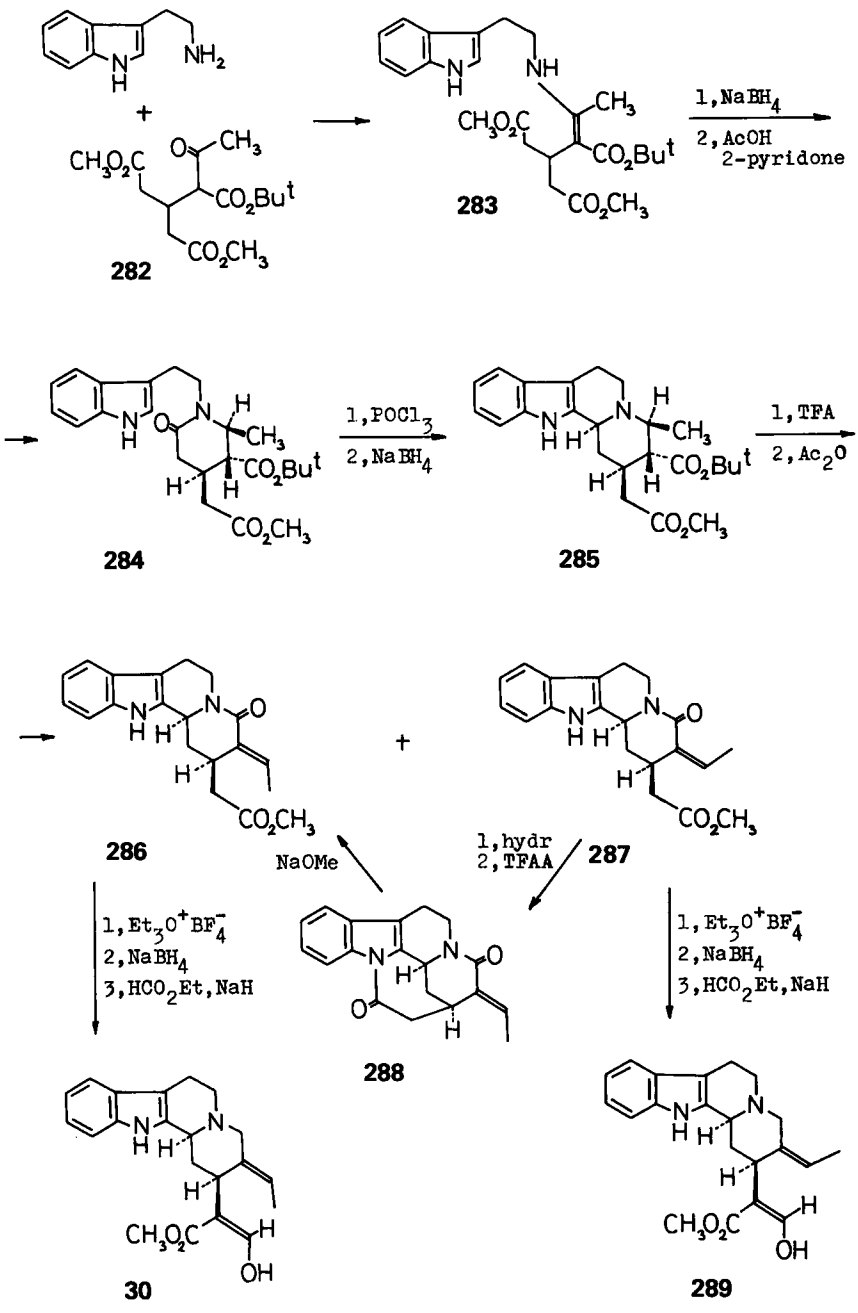


Using the mercuric acetate oxidation–zinc powder reduction method, **277** and methyl (±)-geissoschizoate (**276**) were obtained in about a 3:1 ratio. Formylation of **276** with methyl formate in the presence of lithium diisopropylamide yielded (±)-geissoschizine as the sole product (*156*).

Two total syntheses of (±)-geissoschizine have been reported by Winterfeldt and co-workers (*157–160*). The first one takes advantage of the greater stability of the double bond of the *E* isomer in the side chain of lactam **281**, obtained from




1, Ag_2O
2, HCl, MeOH
3, $Hg(OAc)_2$
4, Zn, AcOH
276
277
HCO_2CH_3
$LiNPr_2$
30
1, diketene
2, $KOBu^t$
3, $POCl_3$
278
279
$CH_2(CO_2Bu^t)_2$
NaH
1, $Ca(BH_4)_2$
2, $NaBH_4$
3, $POCl_3$
280
281 + Z isomer
1, HCl, MeOH
2, Bu^i_2AlH
3, $AlEt_2H$
30

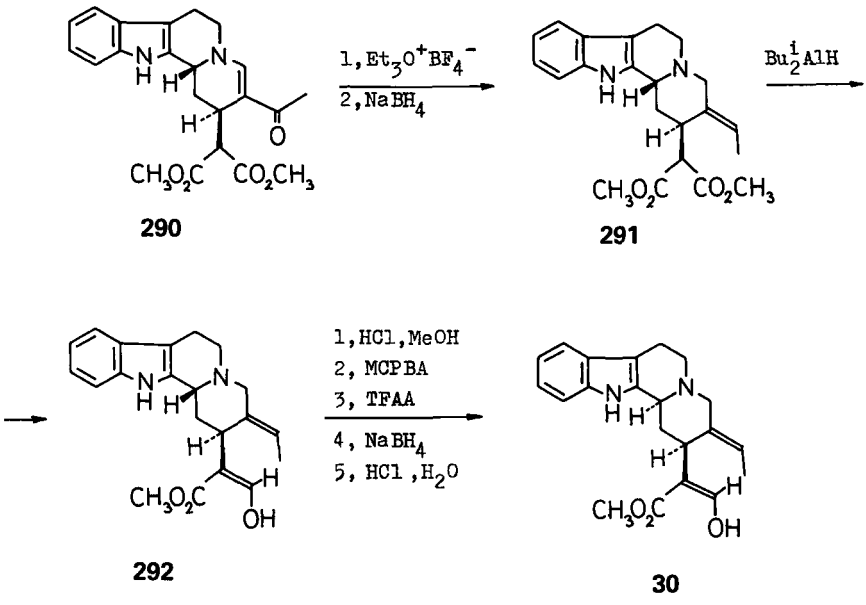

1, NaBH4
2, AcOH
2-pyridone
1, POCl3
2, NaBH4
1, TFA
2, Ac2O
NaOMe
1, hydr
2, TFAA
1, Et3O+BF4−
2, NaBH4
3, HCO2Et, NaH
282
283
284
285
286
287
288
289
30

tetrahydro-β-carboline derivative **278** by the use of simple reaction steps. Selective two-stage reduction of the dimethyl ester corresponding to **281** resulted in (±)-geissoschizine (*157*).

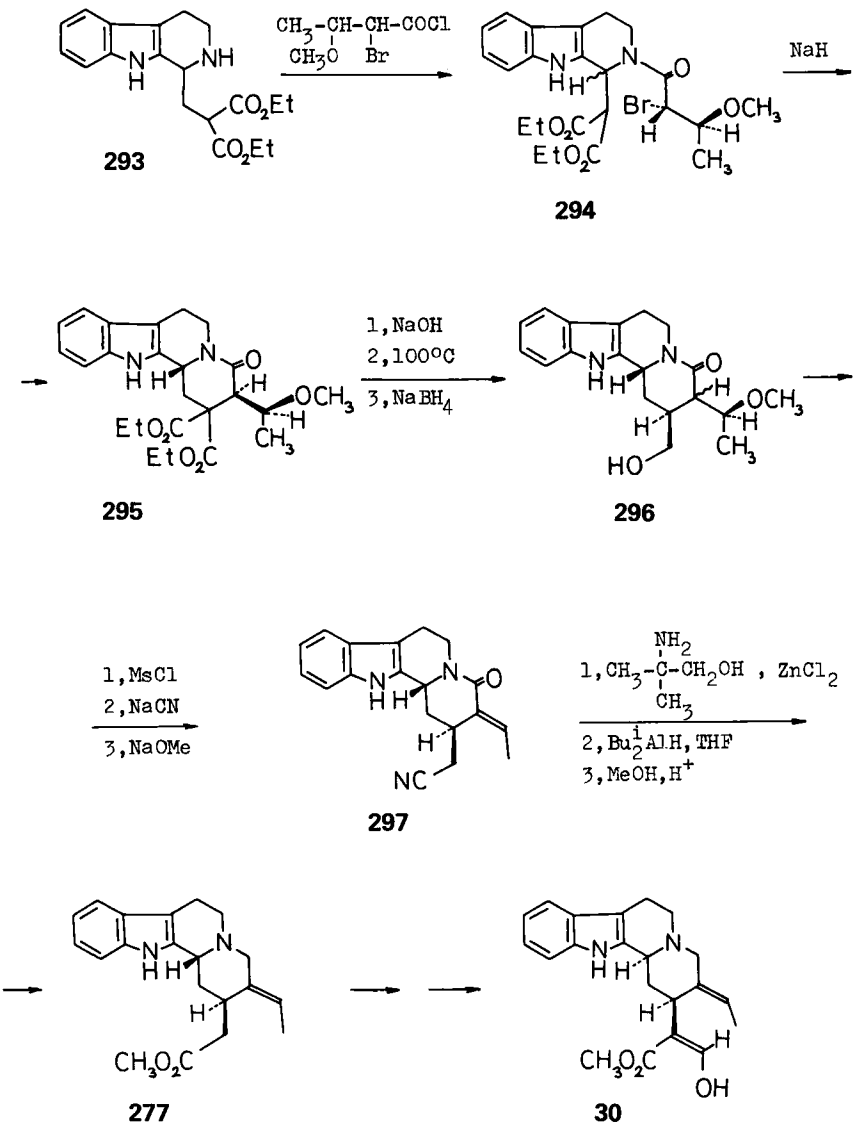
During the second synthesis, lactam **284,** obtained from building block **282** and tryptamine, was cyclized and reduced to indolo[2,3-*a*]quinolizine derivative **285.** Rearrangement of **285** gave a mixture of geometrically isomeric ethylidene lactams **286** and **287.** The synthesis proved to be stereoconvergent through intermediate **288,** inasmuch as the ring closure of **287** to dilactam **288** is accompanied by a spontaneous isomerization of the double bond in question. Removal of the lactam carbonyl group of **286,** followed by formylation, yielded (±)-geissoschizine (*158*). In addition, the Borch reduction and formylation of **287** could supply the *Z*-configured (+)-isogeissoschizine (**289**) (*159*).

(±)-Geissoschizine has also been synthesized by Wenkert and co-workers (*161*). The previously prepared intermediate keto ester **290** (*130*) was converted by Borch reduction to **291** in moderate yield. Further selective reduction of **291** resulted in (±)-3-epigeissoschizine (**292**), which was finally epimerized to (±)-geissoschizine (*161*).

Harley-Mason *et al.* (*162*) have reported a linear synthesis of (±)-geissoschizine. Acylation of **293** with *erythro*-2-bromo-3-methoxybutyroyl chloride gave a diastereomeric mixture of C-3-epimer amides **294,** only one of which could be cyclized to tetracyclic ester **295.** Hydrolysis and decarboxylation, fol-



290 **291** **292** **30**

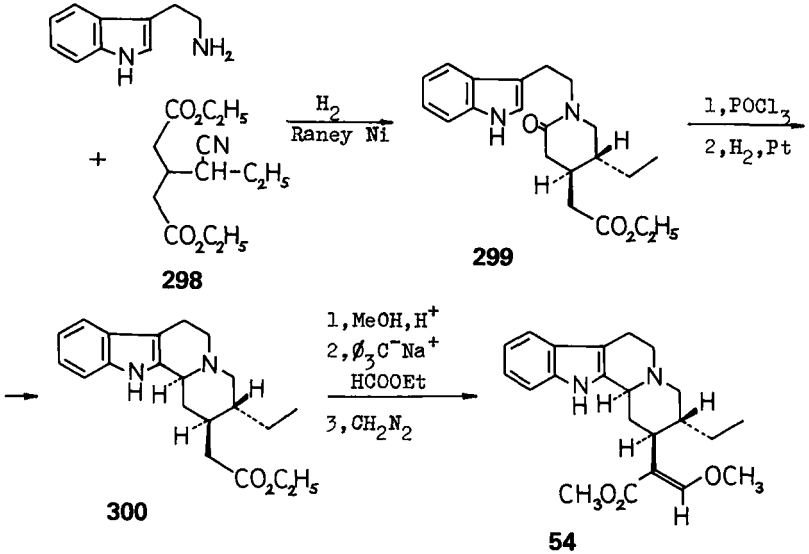


lowed by reduction, yielded two C-20-epimer alcohols (**296** diastereomers), which were transformed to a uniform product (**297**) with the desired *E* configuration of the exocyclic double bond. Removal of the lactam carbonyl, followed by methanolysis of the masked nitrile group, resulted in methyl (±)-3-isogeissoschizoate (**277**), which has already been converted to (±)-geissoschizine by Yamada and co-workers (*156*).

4. Corynantheine, Dihydrocorynantheine, Corynantheidine, and Hirsutine

The first total synthesis of (±)-dihydrocorynantheine (**54**) (*163*) and (±)-corynantheine (**52**) (*164*) with normal stereo arrangement of the C-3, C-15, and C-20 hydrogens (α, β, α, respectively) was published in full detail by van Tamelen and co-workers in 1969. [In preliminary form it has been published earlier (*165, 166*).]

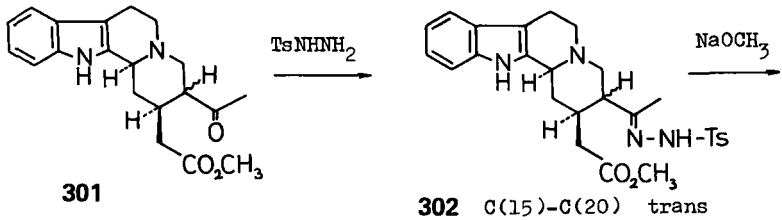
Lactam **299** was prepared from tryptamine and cyano diester **298** by reductive alkylation in about 12% yield. Phosphorus oxychloride cyclization of **299,** followed by catalytic reduction, resulted in the corresponding trans disubstituted indolo[2,3-*a*]quinolizine **300.** After transesterification, formylation and methylation were carried out in two subsequent steps with ethyl formate in the presence of triphenylmethylsodium and with an excess of diazomethane to supply (±)-dihydrocorynantheine (*163*).



298 **299** **300** **54**

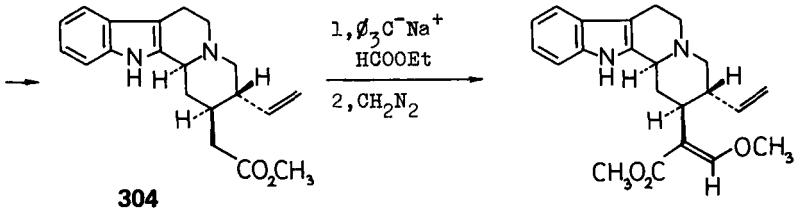
On the other hand, (±)-corynantheine was achieved from key intermediate **301,** used previously in the synthesis of ajmaline (*167*). The *trans*-tosylhydrazone derivative **302** afforded the desired vinyl-substituted indolo[2,3-*a*]quinolizine **304** in moderate yield along with the corresponding ethylidene-substituted isomer. Formylation and methylation of **304** afforded finally (±)-corynantheine (*164*).

Lactam **299** has later been synthesized by another route from ethyl *trans*-5-ethyl-2-oxo-4-piperidineacetate and 3-chloroacetylindole, which represents a new formal total synthesis of (±)-dihydrocorynantheine and related alkaloids (*104*).



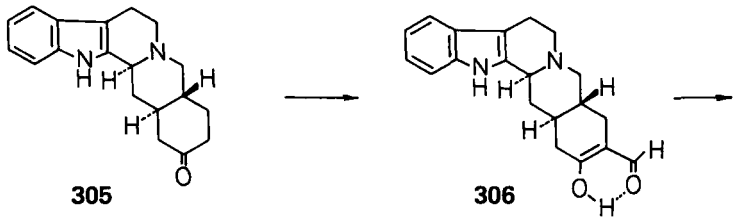
301

302 C(15)-C(20) trans
303 C(15)-C(20) cis

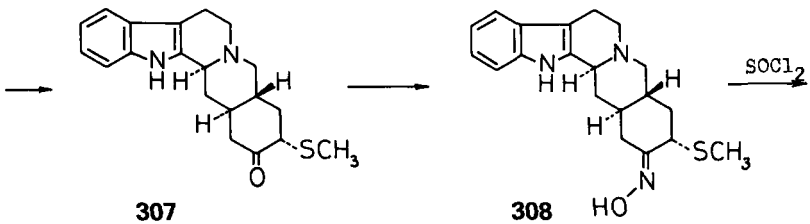


304 **52**

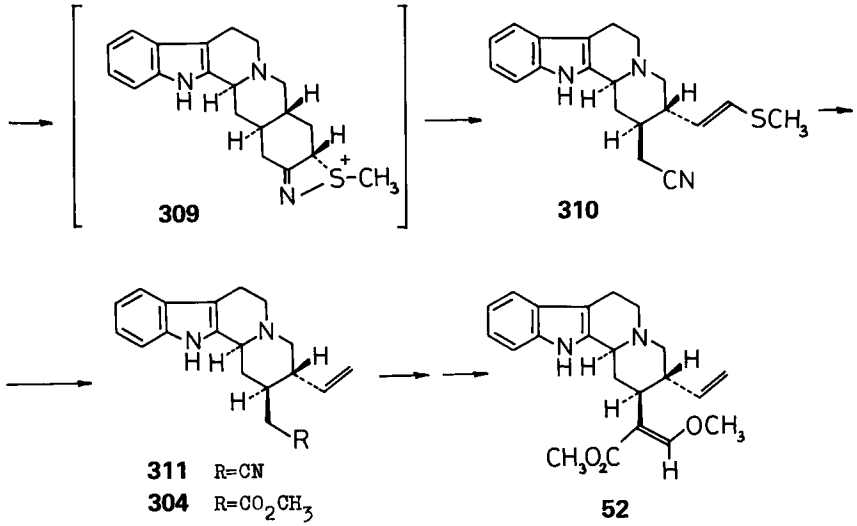
The natural antipode of corynantheine (3*S*, 15*S*, 20*R*) has elegantly been prepared by Autrey and Scullard (*168*), starting from yohimbone (**305**), synthesized and resolved previously by Swan (*169*). Yohimbone (**305**) was converted to 18-formylyohimbone (**306**) and then through **307** to oxime **308.** On reaction with thionyl chloride, **308** underwent a Beckmann fragmentation to the trans-substituted indolo[2,3-*a*]quinolizine **310,** which after desulfurization and esterification resulted in the levorotatory methyl corynantheate (**304**). This product



305 **306**



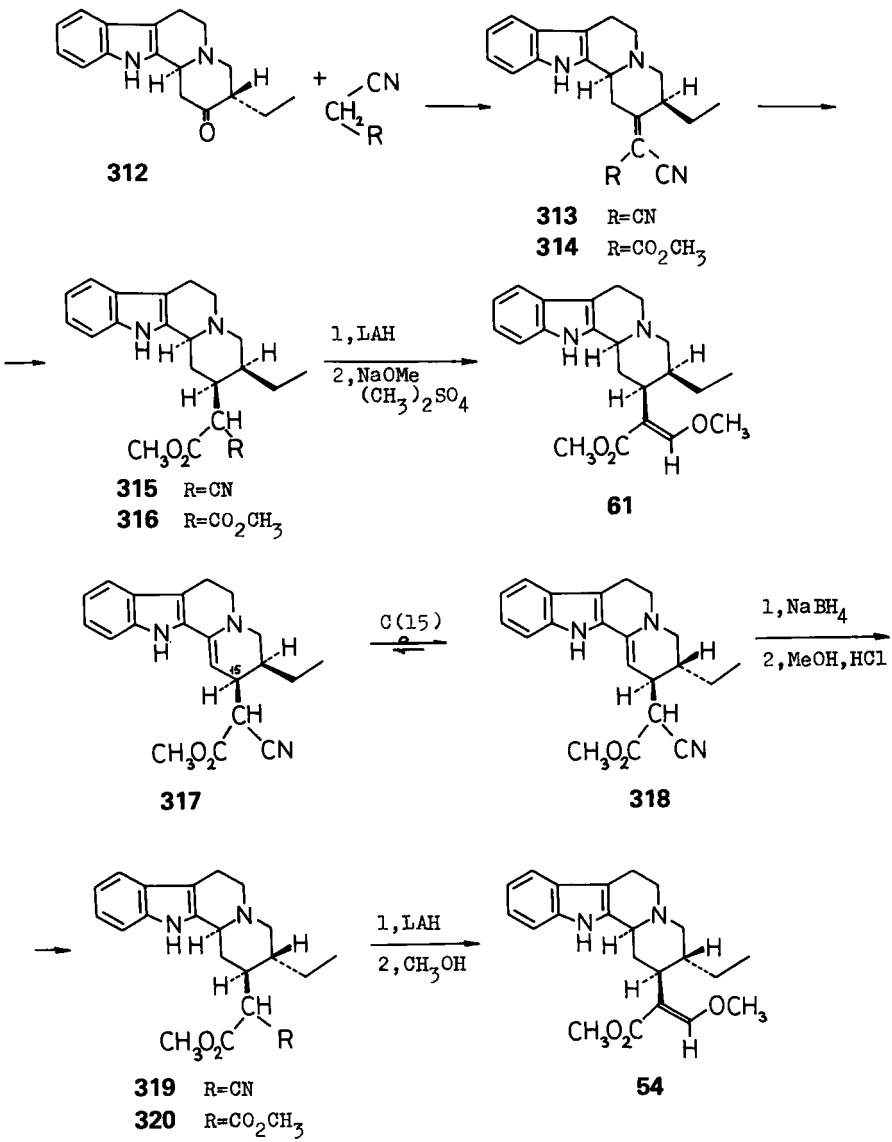
307 **308**



was transformed to natural (+)-corynantheine by formylation and methylation in rather poor yield (*168*).

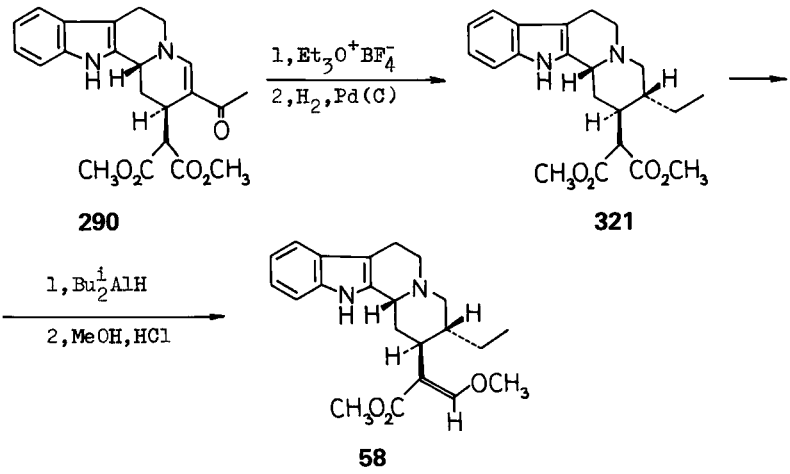
The stereoselective total synthesis of both (±)-corynantheidine (**61**) (*170, 171*) (allo stereoisomer) and (±)-dihydrocorynantheine (*172*) (normal stereoisomer) has been elaborated by Szántay and co-workers. The key intermediate leading to both alkaloids was the allo cyanoacetic ester derivative **315,** which was obtained from the previously prepared ketone **312** (*173*) by the Knoevenagel condensation accompanied by complete epimerization at C-20 and by subsequent stereoselective sodium borohydride reduction. (±)-Corynantheidine was prepared by modification of the cyanoacetate side chain; esterification furnished diester **316,** which underwent selective lithium aluminum hydride reduction. The resulting sodium enolate of the α-formyl ester was finally methylated to racemic corynantheidine (*171*).

(±)-Dihydrocorynantheine was obtained via similar steps from normal cyanoacetic ester **319** (*172*). Stereoselective transformation of the allo cyanoacetic ester **315** to the normal stereoisomer **319** was achieved by utilizing a unique epimerization reaction of the corresponding quinolizidine–enamine system (*174*). Oxidation of allo cyanoacetic ester **315** with lead tetraacetate in acetic acid medium, followed by treatment with base, yielded the cis-disubstituted enamine **317,** which slowly isomerized to the trans isomer **318.** It has been proved that this reversible eipmerization process occurs at C-15. The ratio of trans/cis enamines (**318/317**) is about 9:1. The sodium borohydride reduction of **318** furnished the desired cyanoacetic ester derivative **319** with normal stereo arrangement. The details of the C-15 epimerization mechanism are discussed by Bárczai-Beke *et al.* (*174*).



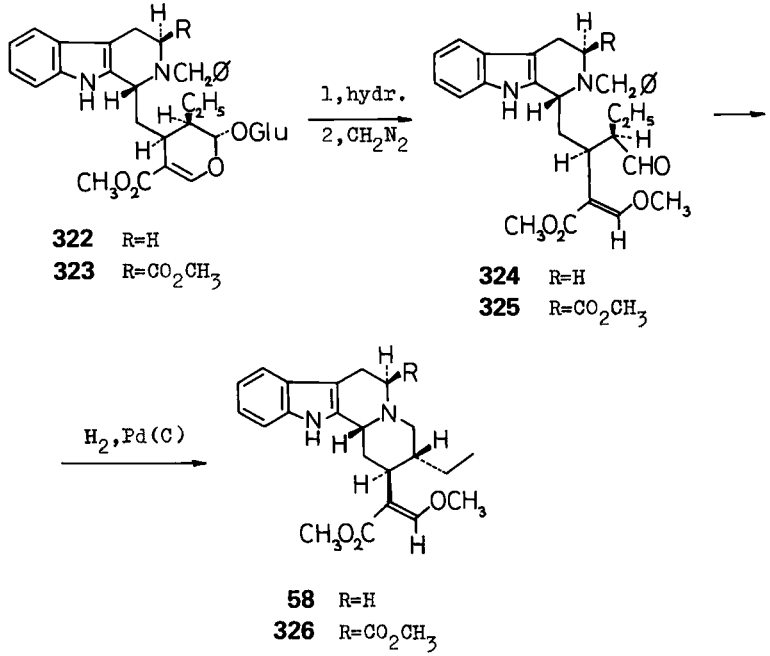
Hirsutine (**58**), the pseudo isomer of corynantheidine and dihydrocorynantheine, has been elegantly synthesized by Wenkert and his collaborators (*161*). The reaction of keto diester **290** with Meerwein's reagent, followed by hydrogenation, resulted in pseudo-type diester **321,** which on reduction and methylation gave (±)-hirsutine (*161*).

The synthesis of corynantheine-type alkaloids along a biogenetic route has been widely investigated by Brown *et al.* (*175, 176*).



290 321 58

Condensation of N_b-benzyltryptamine or N_b-benzyl-L-tryptophan with dihydrosecologanin gave N_b-benzyl-18,19-dihydrovincoside (**322**) or its 5β-meth-

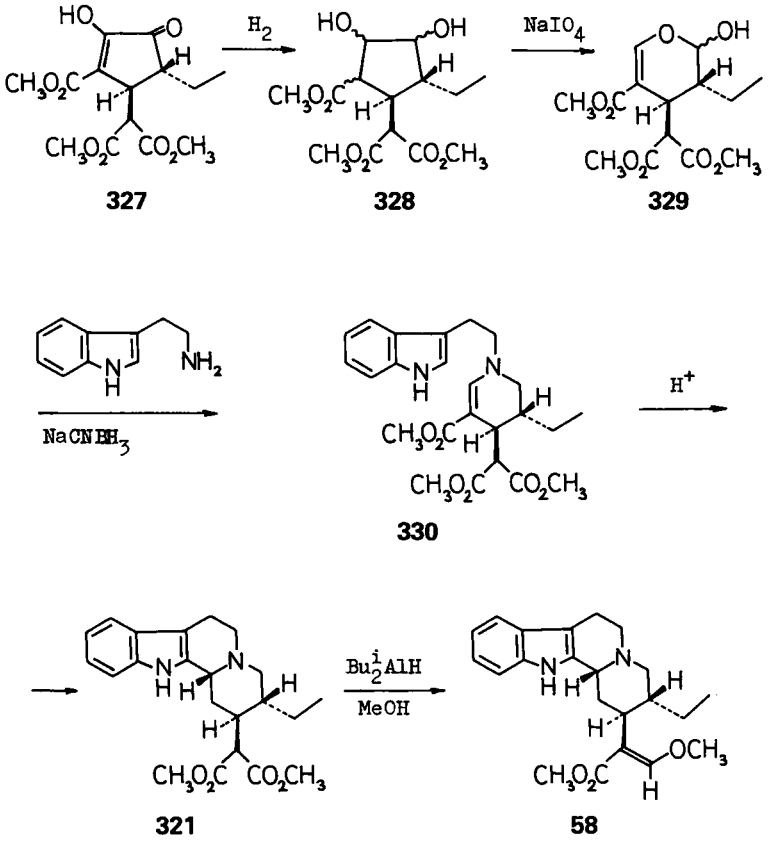


322 R=H
323 R=CO_2CH_3

324 R=H
325 R=CO_2CH_3

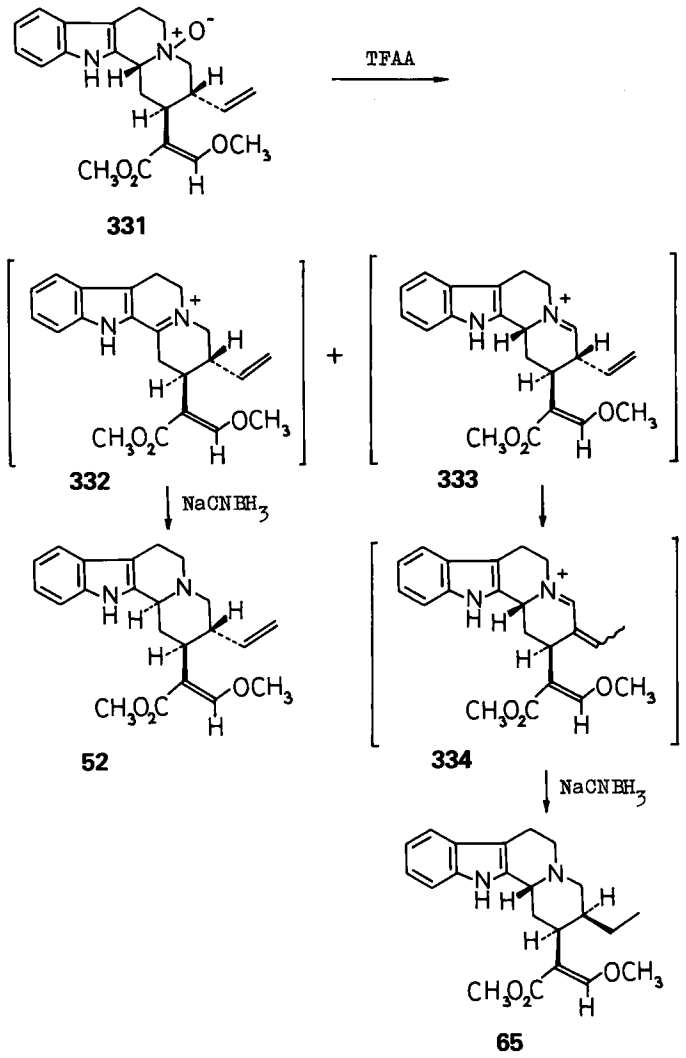
58 R=H
326 R=CO_2CH_3

oxycarbonyl derivative (**323**). Removal of the sugar unit and subsequent opening of ring E by formation of an enol ether resulted in **324** or **325**, respectively, which compounds upon hydrogenation in acidic medium could be cyclized to hirsutine (*177*) or 5β-methoxycarbonylhirsutine (**326**) (*178*).



A stereoselective total synthesis of (±)-hirsutine has been developed by Brown *et al.* (*179*). Catalytic hydrogenation of hydroxycyclopentenone **327,** prepared previously (*180*), afforded a mixture of isomeric diols **328,** which were quantitatively cleaved by sodium periodate to supply **329.** Reductive amination of **329** with tryptamine resulted in tetrahydropyridine **330,** which upon treatment with aqueous methanol in the presence of hydrochloric acid gave indolo-[2,3-*a*]quinolizine **321** with pseudo-stereochemistry. Conversion of **321** to (±)-hirsutine was accomplished in a similar manner by Wenkert *et al.* (*161*) via selective reduction with diisobutylaluminum hydride and methylation with methanol (*179*).

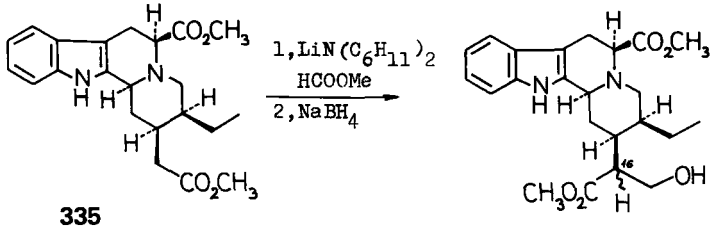
An interesting transformation was discovered by Sakai and Shinma (*181*) during the chemical investigation of corynanthe alkaloid *N*-oxides. Polonovski reaction and sodium cyanoborohydride reduction of hirsuteine *N*-oxide (**331**) gave corynantheine (**52**) and 3-isocorynantheidine (**65**), the latter likely formed by reduction of the conjugated iminium intermediate **334.**



5. Adirubine

Adirubine (**66**), the first member of a new series of C-5-carboxy alkaloids with a corynane skeleton, has been isolated from *Adina rubescens* by Brown and coworkers (*60*). The allo stereostructure of the alkaloid has been determined by the same authors (*61*). The configuration of C-16, however, has not as yet been elucidated.

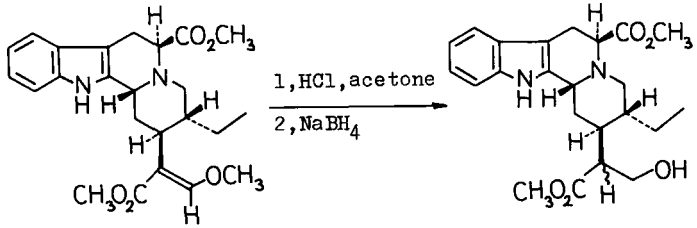
Until now, only one nonstereospecific total synthesis of methyl adirubine (**67**) has been published by van Tamelen and Dorschel (*182*). Tetracyclic diester



335 **67** + C(16) epimer

(±)-**335** with proper stereochemistry was obtained after separation of a complex mixture of at least six stereosiomers prepared by a process that consists of a number of reaction steps lacking high stereoselectivity. Diester **335** was finally transformed to a mixture of racemic methyl adirubine and its C-16 epimer by formylation and subsequent reduction (*182*).

The synthesis of the optically active C-3 epimer of methyl adirubine has been accomplished by Brown and Chapple (*178*) from 5β-methoxycarbonylhirsutine (**326**), prepared from N_b-benzyl-L-tryptophan and dihydrosecologanin via cleav-



326 **336**

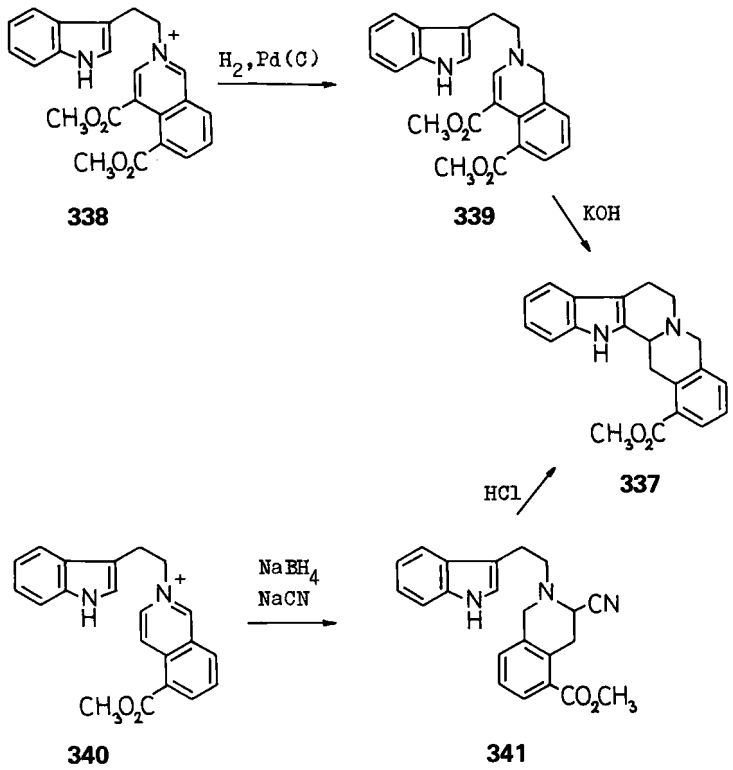
age of the enol ether function with acid and reduction with sodium borohydride, affording **336** (*178*).

C. Synthesis of Yohimbane Alkaloids

1. Dihydrogambirtannine, Oxogambirtannine, and Demethoxycarbonyldihydrogambirtannine

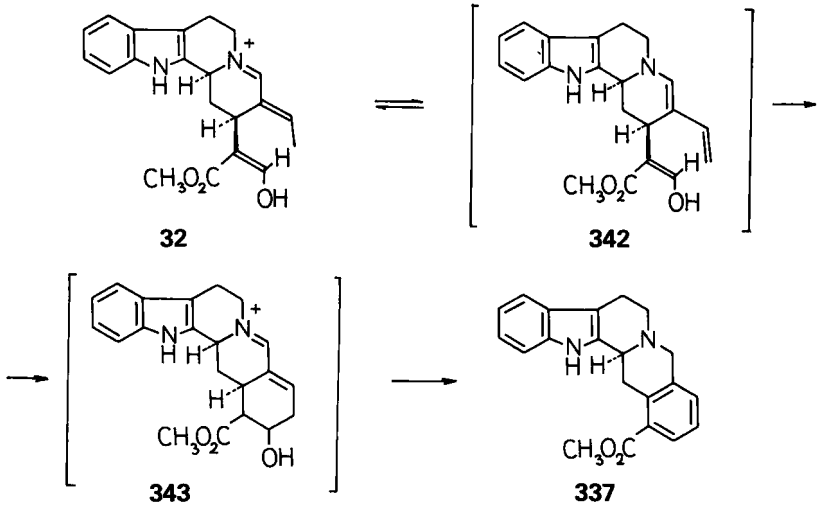
(±)-Dihydrogambirtannine (**337**) has been achieved via two routes from *N*-[2-(indol-3-yl)ethyl]isoquinolinium salts. Wenkert and co-workers (*183*) first synthesized the stable intermediate **339**, which could be hydrolyzed, decarboxylated, and cyclized in one step by the use of aqueous alkali to (±)-**337**. In a very similar approach, Beisler (*184*) caused the isoquinolinium salt **340** to react with sodium borohydride and sodium cyanide, and the resulting intermediate **341** was immediately treated with strong acid. This one-pot reaction gave (±)-dihydrogambirtannine in an overall yield of 83%.

By investigating the biogenetic connection between the yohimbane and cory-



338 339 337 340 341

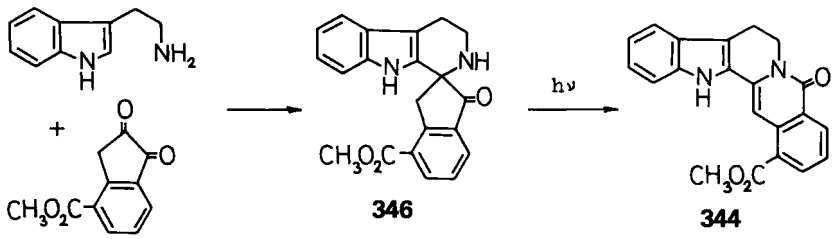
nanthe skeletons, the formation of dihydrogambirtannine has been observed from 4,21-dehydrogeissoschizine (**32**) under very mild conditions (*185*). Dihydrogambirtannine (**337**) was also formed as a side product during the synthesis of



32 342 343 337

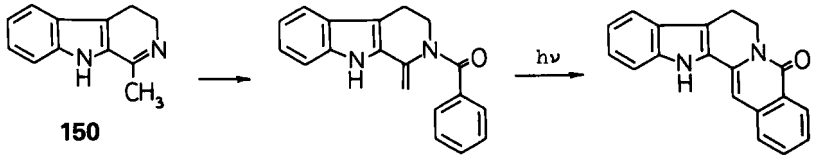
yohimbine (**74**) and β-yohimbine (**75**), starting from tryptamine and secoxyloganin (*186*).

Oxogambirtannine (**344**) has been synthesized by Irie *et al.* (*187*) via photoinduced rearrangement of spirotetrahydro-β-carboline **346,** obtained by Pictet–Spengler condensation of tryptamine and indandione (**345**).



345 **346** **344**

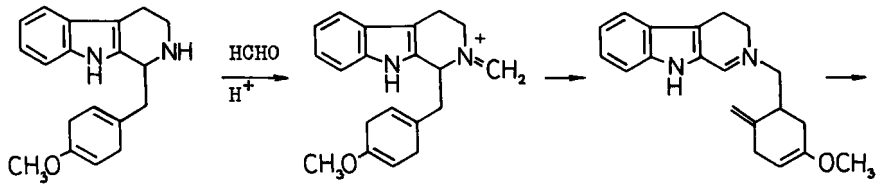
Simple synthesis of demethoxycarbonyloxogambirtannine (**347**) was reported by Ninomiya and co-workers (*188*) via enamide photocyclization. N-Benzoylation of harmalane (**150**) afforded enamide **348,** which could be photocyclized to **347** in 37% yield.



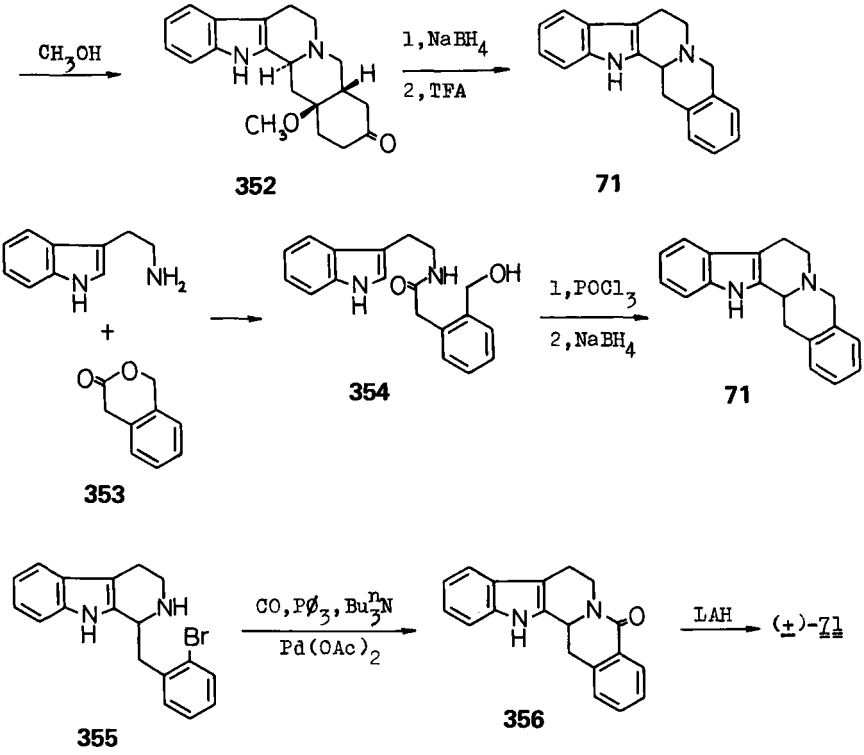
150 **348** **347**

(±)-Demethoxycarbonyldihydrogambirtannine (**71**) was synthesized several times (*189–191*) before its isolation as a natural product from *Ochrosia lifuana* Guill. as well as *Ochrosia miana* H.Bn. ex Guill. (*65*). In the last decade, (±)-**71** was elegantly synthesized by Wilcock and Winterfeldt (*192*) from an appropriately substituted cyclohexadienyltetrahydronorharmane derivative **349** via the Cope rearrangement, cyclization, reduction, and acid-treatment sequence.

A simple synthesis of (±)-**71** was carried out from tryptamine and isochroman-3-one **353** through the formation of amide **354,** followed by Bischler–Napieralski ring closure and reduction, in an overall yield of 45% (*193*).



349 **350** **351**



Palladium-catalyzed amidation was also used for the synthesis of (±)-demethoxycarbonyldihydrogambirtannine as shown above (*194*).

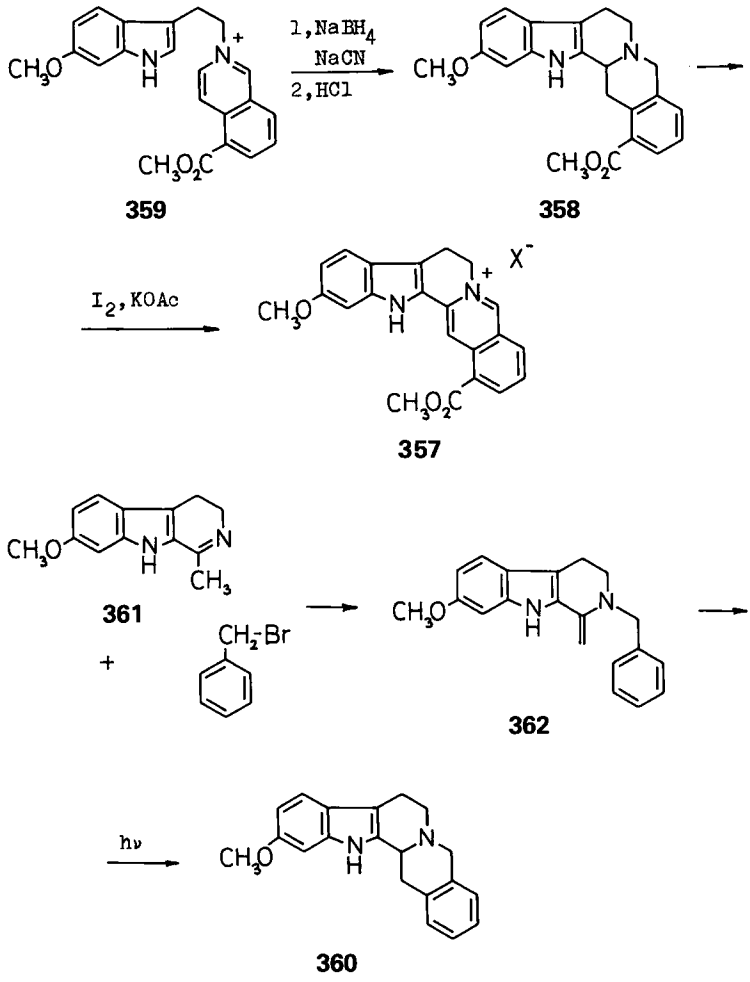
2. Alstoniline and Tetrahydroalstoniline

Beisler's method for the synthesis of (±)-dihydrogambirtannine (**337**) (*184*) has been extended for the preparation of alstoniline hydrochloride (**357**) as well as (±)-tetrahydroalstoniline (**358**) (*195*).

Demethoxycarbonyldihydroalstoniline (**360**) was synthesized by photocyclization of enamine **362,** prepared from harmaline (**361**) and benzyl bromide (*196*).

3. Synthesis of Yohimbine-Type Alkaloids

Preliminary synthetic studies resulted in a number of different approaches for the preparation of the four basic stereoisomeric yohimbane skeletons. They are as follows: (±)-yohimbane (**363**) (*109, 197–206*), (±)-pseudoyohimbane (**364**) (*201*), (±)-alloyohimbane (**365**) (*109, 202–204, 207*), (±)-3-epialloyohimbane (**366**), (*109, 205, 207, 208*).

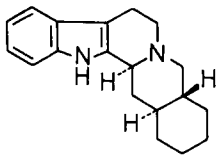


359 **358** **357** **361** **362** **360**

4. Yohimbol and 17-Epiyohimbol

Yohimbol (**72**) and 17-epiyohimbol (**73**) could be prepared from yohimbone (**305**) either with sodium borohydride or by the Meerwein–Ponndorf reduction. On prolonged reduction of yohimbone (**305**) under Meerwein–Ponndorf conditions, an equilibrium is established between yohimbol (**72**) and 17-epiyohimbol (**73**) in favor of the latter (*209*).

The first total synthesis of (±)-yohimbone (**305**) has been reported by Swan (*169*). Birch reduction of key intermediate 17-methoxyhexadehydroyohimbane (**368**), obtained from phenylhydrazine and **367**, led to tetradehydroyohimbane derivative **369**, which upon acid treatment gave yohimbenone (**370**). When **370**



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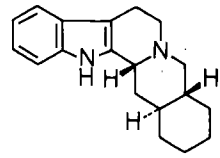

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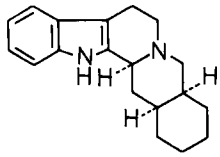

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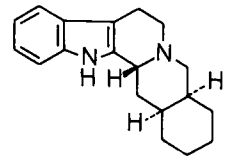

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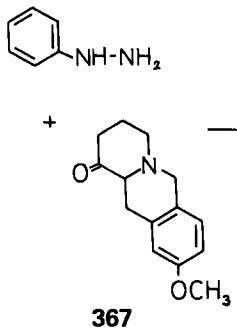

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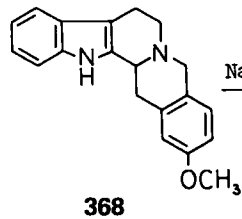

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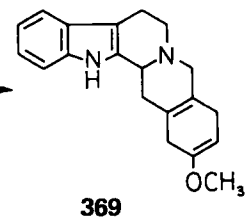

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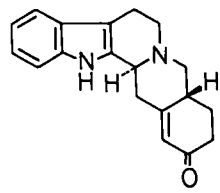

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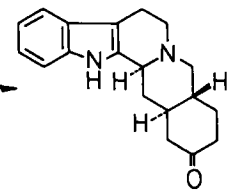

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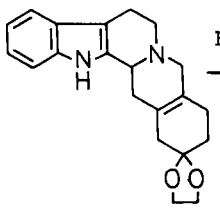

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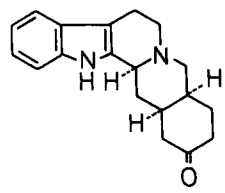

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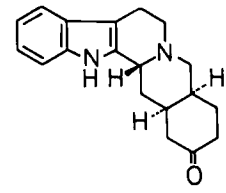

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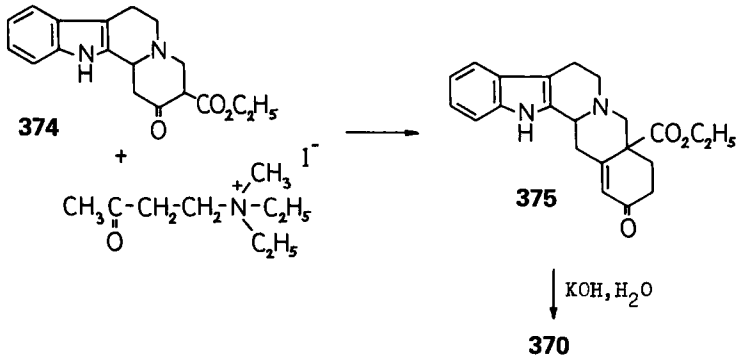
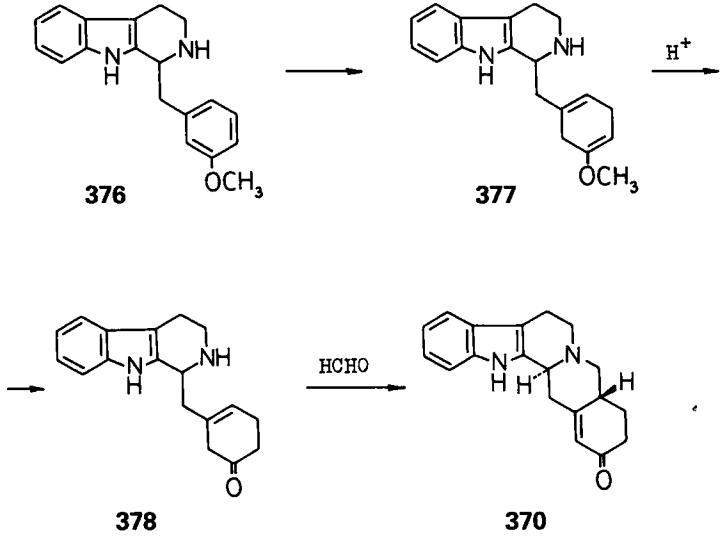
was hydrogenated over the Adams catalyst in acid solution, (±)-yohimbone (**305**) could be prepared (*169*). On the other hand, high-pressure hydrogenation of ethylene ketal **371,** obtained from yohimbenone (**370**), followed by hydrolysis, resulted in (±)-alloyohimbone (**372**) as well as (±)-epialloyohimbone (**373**) (*210, 211*).

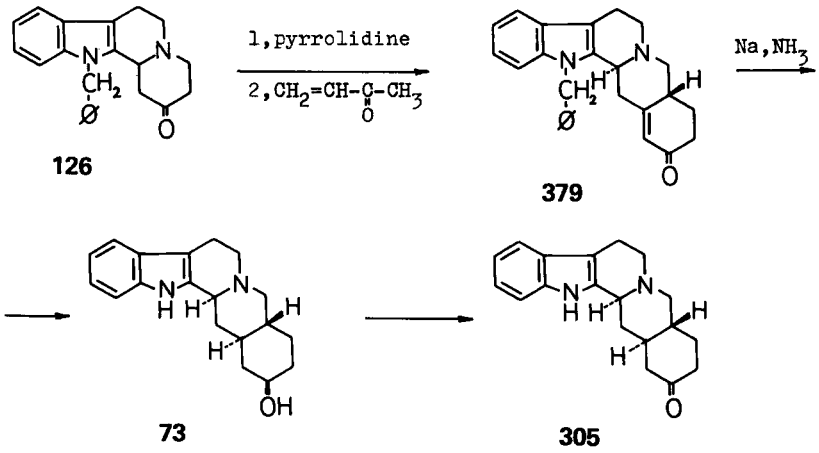
(±)-Yohimbenone (**370**) has been synthesized by Kline (*212*) via the Robinson reaction of the **374** tetracyclic compound with 4-diethylaminobutan-2-one methiodide, followed by hydrolysis and decarboxylation of intermediate **375.**



(±)-Yohimbenone has also been prepared by Benson and Winterfeldt (*213*) from enol ether **377,** obtained by Birch reduction of **376,** via subsequent acid hydrolysis to **378** and formaldehyde cyclization to **370.**

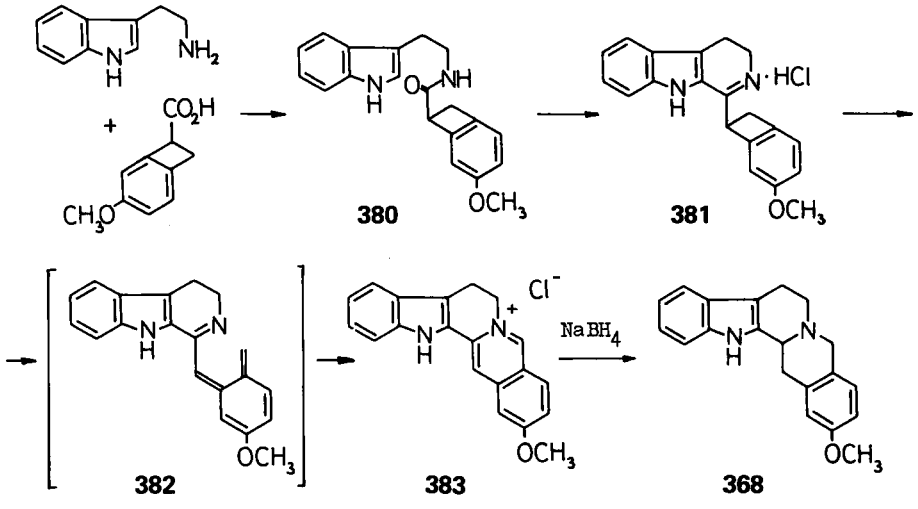


Simple synthesis of (±)-17-epiyohimbol (**73**) has been reported by Mori *et al.* (*214*). *N*-Benzyloctahydroindolo[2,3-*a*]quinolizinone (**126**), prepared according to the procedure of Novák and Szántay (*97*) was coverted to the corresponding pyrrolidine enamine, which was treated with methyl vinyl ketone to give *N*-benzylyohimbenone (**379**). Reduction of **379** with sodium in liquid ammonia



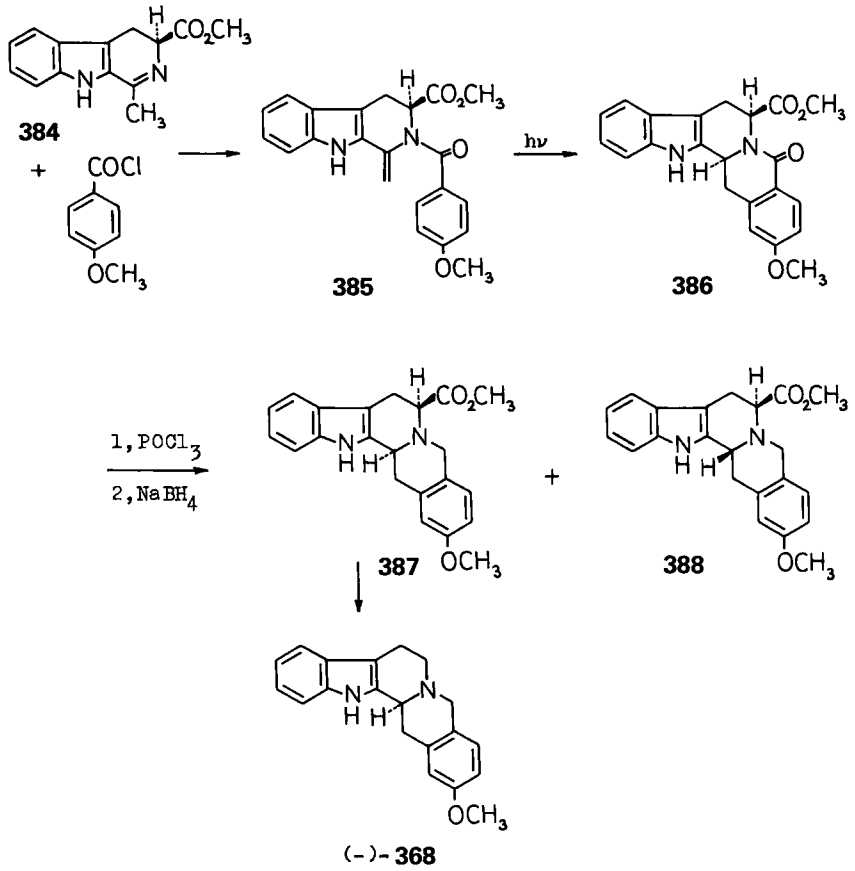
gave stereoselectively (±)-17-epiyohimbol. Oppenauer oxidation of **73** was also carried out, resulting in (±)-yohimbone (**305**) (*214*).

Key intermediate **368** of Swan's (±)-yohimbone (**305**) synthesis (*169*) has also been achieved by Kametani *et al.* (*215*). Thermolysis of 3,4-dihydro-1-(5-methoxybenzocyclobutanyl)-β-carboline hydrochloride (**381**) afforded deca-

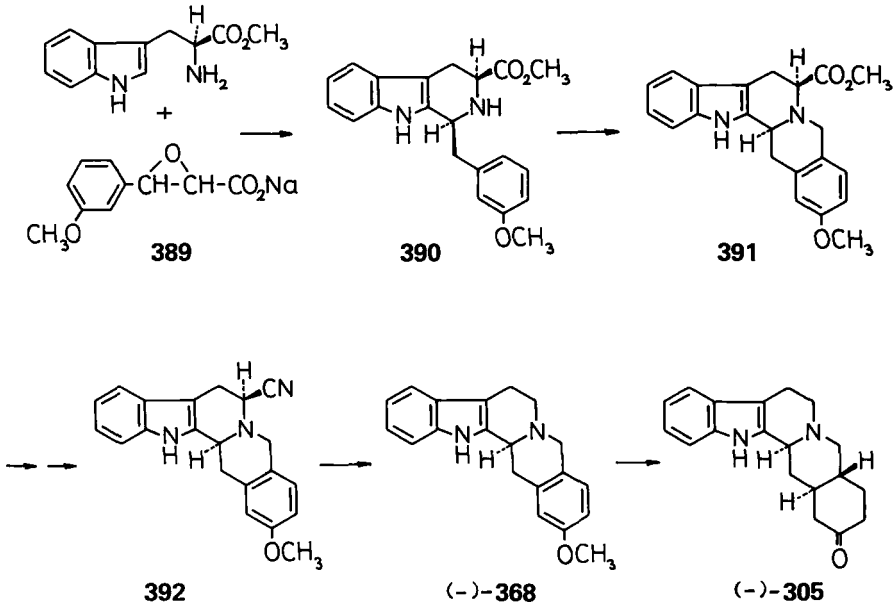


dehydroyohimbane **383** in 70% yield, which on reduction with sodium borohydride supplied 17-methoxyhexadehydroyohimbane (**368**) (*215*).

Attempts have been made for the enantioselective synthesis of (−)-yohimbane. Kametani *et al.* (*216*) reported the total synthesis of key intermediate (−)-**368** starting from L-tryptophan, using enamide photocyclization. However, the optical purity of (−)-17-methoxyhexadehydroyohimbane obtained was only 17% owing to the partical racemization of intermediates throughout the reaction sequence.



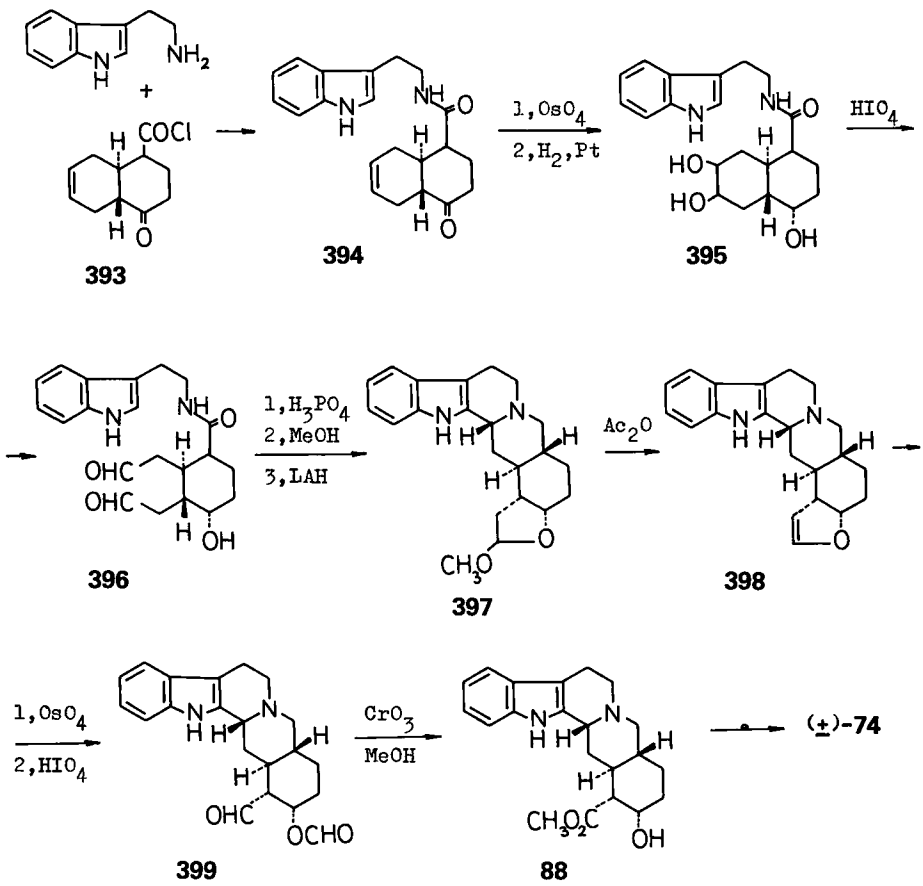
Okamura and Yamada (*217*) were more successful when they performed the 1,3-transfer of chirality in a Pictet–Spengler reaction of methyl L-tryptophan and sodium 3-(3-methoxyphenyl)glycidate (**389**). Thus (3*S*, 15*S*, 20*R*)-(−)-yohimbone (**305**) has been prepared in optically pure form.



5. Yohimbine, β-Yohimbine, and Pseudoyohimbine

The first total synthesis of D/E-trans annellated yohimbines, e.g., (±)-yohimbine (**74**) and (±)-pseudoyohimbine (**88**), was published in preliminary form by van Tamelen and co-workers (*218*) in 1958, while full details (*219*) appeared only in 1969. Key building block **393,** prepared from butadiene and *p*-quinone, was condensed with tryptamine, yielding unsaturated amide **394,** which was subsequently transformed to dialdehyde derivative **396.** Cyclization of the latter resulted in pseudoyohimbane **397.** Final substitution of ring E was achieved via pyrolysis, oxidation, and esterification steps. As a result of the reaction sequence, (±)-pseudoyohimbine was obtained, from which (±)-yohimbine could be prepared via C-3 epimerization.

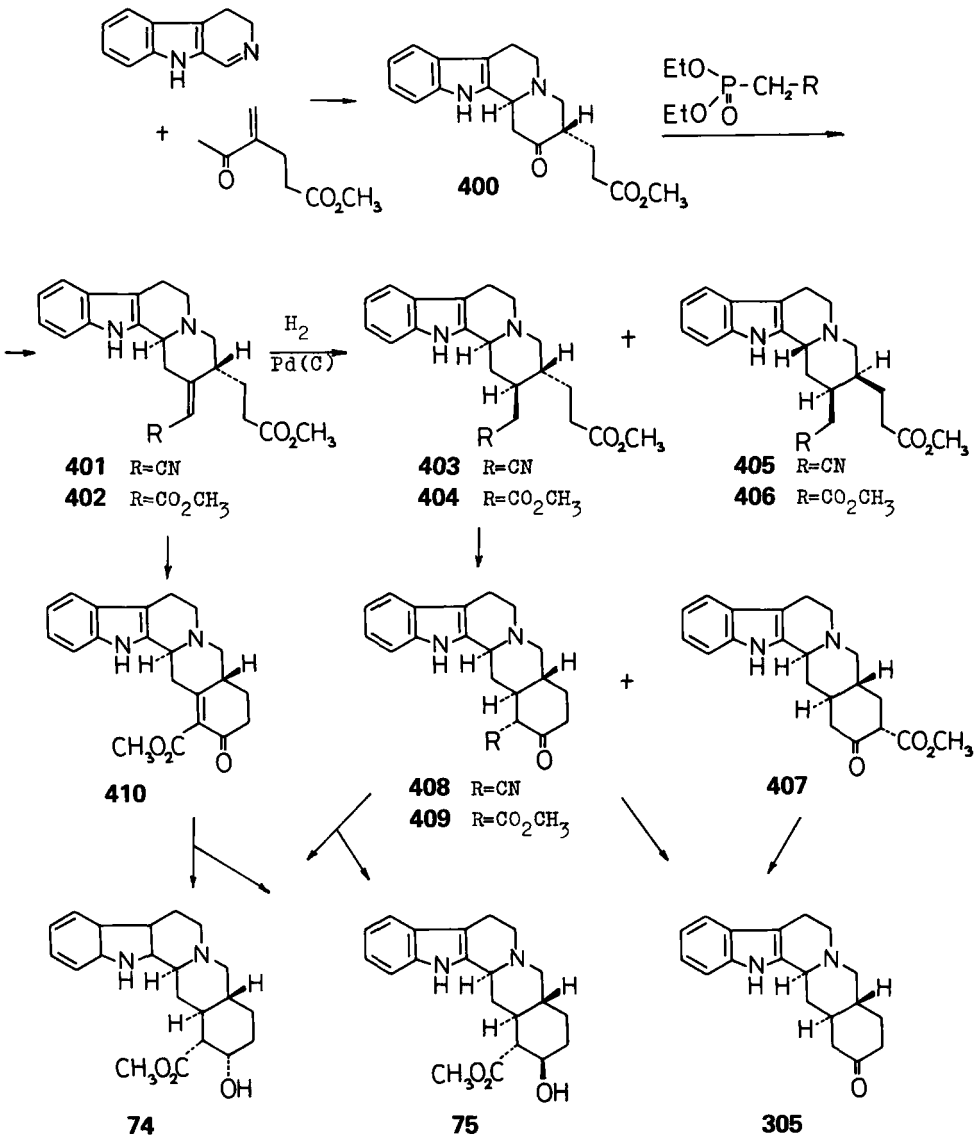
In 1969, Szántay and co-workers published a linear synthesis of (+)-yohimbine and (−)-β-yohimbine (**75**) in full detail (*220*). Tetracyclic key intermediate **400,** obtained from 3,4-dihydro-β-carboline and a properly substituted α,β-unsaturated ketone (*173*), was treated with a proper phosphonoacetic acid derivative to give unsaturated nitrile **401** or unsaturated ester **402.** Catalytic reduction of the latter resulted almost exclusively in **404** with normal stereo arrangement, while reduction of **401** supplied a mixture of normal and epialloindolo[2,3-*a*] quinolizines **403** and **405,** respectively. Dieckmann ring closure of diester **404** gave 18α-methoxycarbonylyohimbone (**407**) as the thermodynamically favored



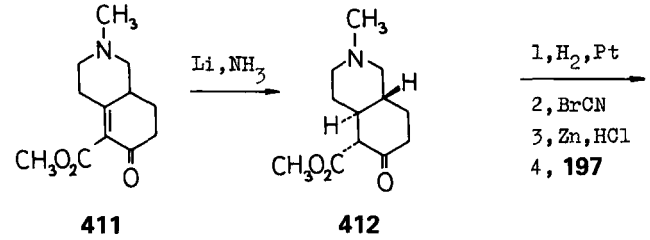
393 **394** **395** **396** **397** **398** **399** **88**

main product. The target (±)-yohimbinone (**409**) could be isolated from the reaction mixture only as a minor product. Sodium borohydride reduction of **409** completed the total synthesis, resulting in (±)-yohimbine and (±)-β-yohimbine. Hydrolysis and decarboxylation of both **407** and **409** gave (±)-yohimbone (**305**). Regioselective Dieckman ring closure could be achieved from nitrile ester **403,** supplying 16α-cyanoyohimbone (**408**), which has also been transformed to (±)-yohimbine and (±)-β-yohimbine. Resolution of the racemic alkaloids obtained (**74** and **75**) has been performed by the use of *N*-acetyl-L-leucine and L-camphor-sulphonic acid, respectively (*75, 220*).

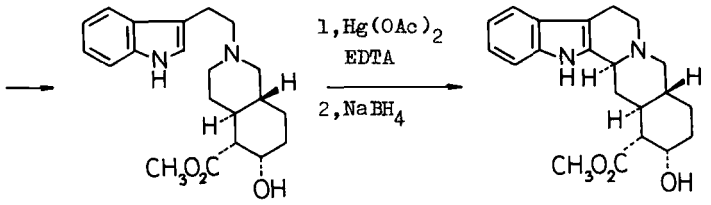
The reaction sequence was later modified (*74, 221*) by carrying out the Dieckmann ring closure on unsaturated ester **402.** The process took place with total regioselectivity, thus resulting in 15,16-didehydroyohimbinone (**410**) as the sole product. Finally, catalytic reduction of **410** yielded (±)-yohimbine and (±)-β-yohimbine in a single step (*74*).



An efficient synthesis of (±)-yohimbine has been published by Stork and Guthikonda (*222*). Reaction of the pyrrolidine enamine of *N*-methylpiperidone with methyl 3-oxo-4-pentenoate gave **411** in good yield. Reduction of **411** with lithium in liquid ammonia furnished *trans-N*-methyldecahydroisoquinolone **412.** This building block was transformed in simple reaction steps to secoyohimbane **413** from which (±)-yohimbine could be obtained by oxidative cyclization with



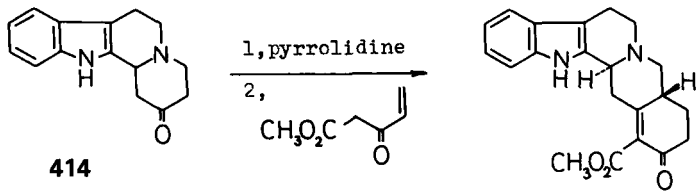
411 **412**



413 **74**

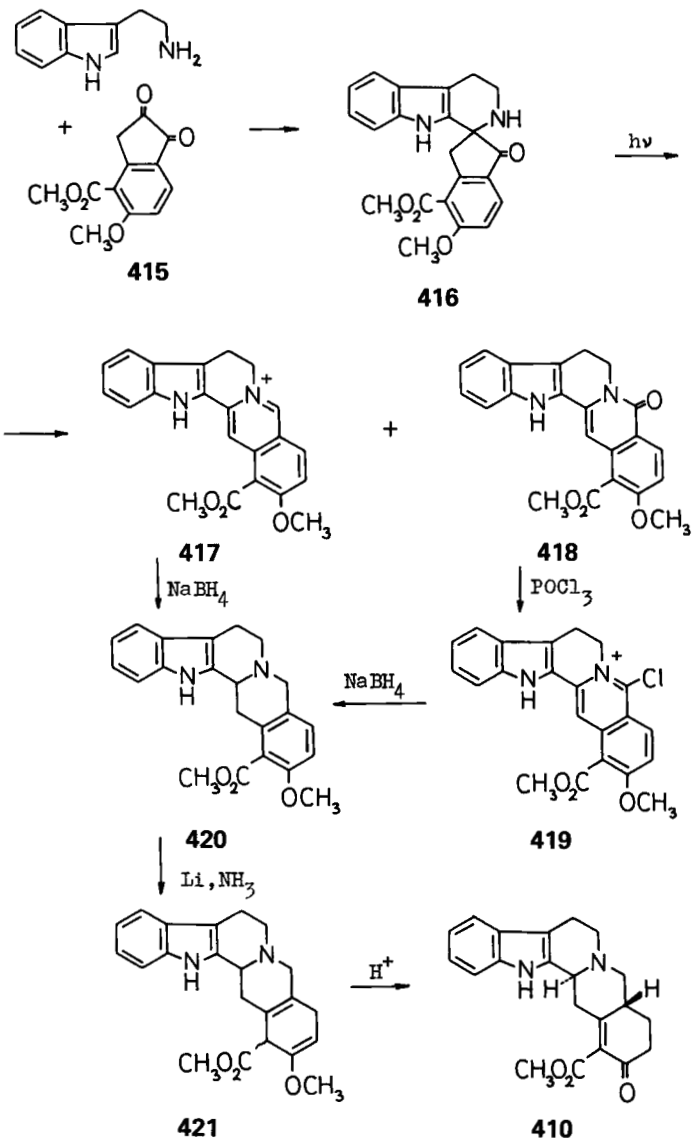
2 equiv of mercuric acetate in the presence of ethylenediaminetetraacetate (EDTA) disodium salt, followed by sodium borohydride reduction. (±)-β-Yohimbine as well as (±)-pseudoyohimbine (**88**) have also been synthesized by the same route (*222*).

Kametani and his collaborators presented two different approaches for the synthesis of (±)-yohimbine and (±)-β-yohimbine (*223–226*). The first one (*223, 224*) utilizes Stork's method for the Robinson reaction of the enamine derived from octahydroindolo[2,3-*a*]quinolizin-2-one (**414**) to produce 15,16-didehydroyohimbinone (**410**), prepared first by Szántay *et al.* (*74, 221*).



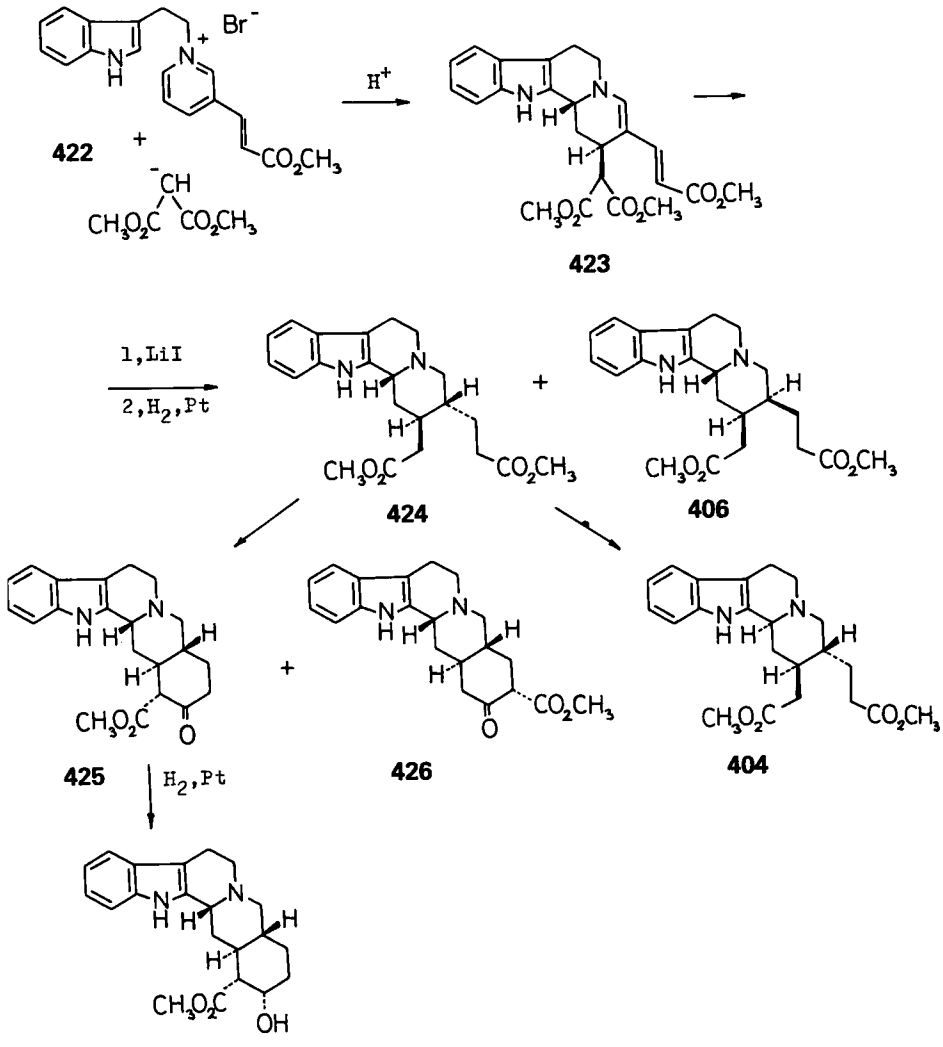
414 **410**

The second approach (*224–226*) employs *O*-methylhexadehydroyohimbine (**420**), prepared from spiroindeno-2-(1′-tetrahydro-β-carboline)-1-one derivative **416** by photolysis and subsequent reduction, as the key intermediate. The side product (**418**) of the photolysis was also utilized for the preparation of **420** via subsequent phosphoryl chloride treatment and sodium borohydride reduction. Birch reduction of **420** resulted in enol ether **421**, which could be transformed to 15,16-didehydroyohimbinone (**410**), prepared previously by Szántay *et al.* (*74, 221*) as a universal precursor of the synthesis of yohimbine-type alkaloids.



The general method for the synthesis of different indoloquinolizine alkaloids via *N*-tryptophyl 3-substituted pyridinium salts, developed by Wenkert and his collaborators, has been extended for the synthesis of yohimbine alkaloids (*227–229*).

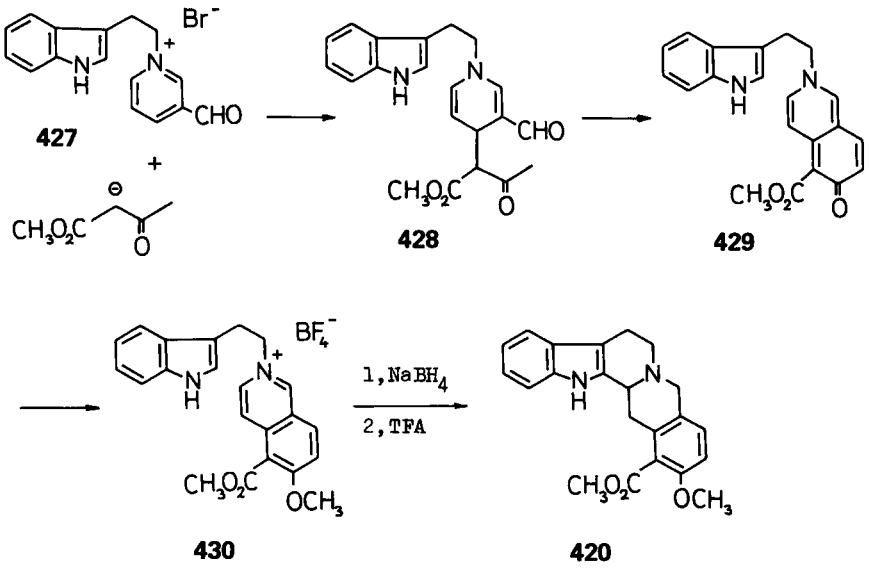
Pyridinium salt **422,** prepared from nicotinaldehyde, was alkylated with dimethyl sodiomalonate and subsequently cyclized with hydrogen bromide to triester **423.** Lithium iodide-induced demethylation, followed by decarboxylation



and hydrogenation over a platinum catalyst, produced diesters **424** and **406** in a ratio of 12:1. The major product (**424**) proved to be the pseudo isomer and the minor component (**406**) had epiallo stereo arrangement. Dieckmann condensation of **424** led to (±)-pseudoyohimbinone (**425**) and its isomer (±)-**426.** Catalytic hydrogenation of keto ester **425** gave (±)-pseudoyohimbine (**88**) as the sole product (*227, 228*). The acid-catalyzed C-3 epimerization of pseudo diester **424** resulted in an equilibrium of the normal and pseudo diesters **404** and **424,** respectively, in a ratio about 2:1. Since **404** has been converted to (±)-yohim-

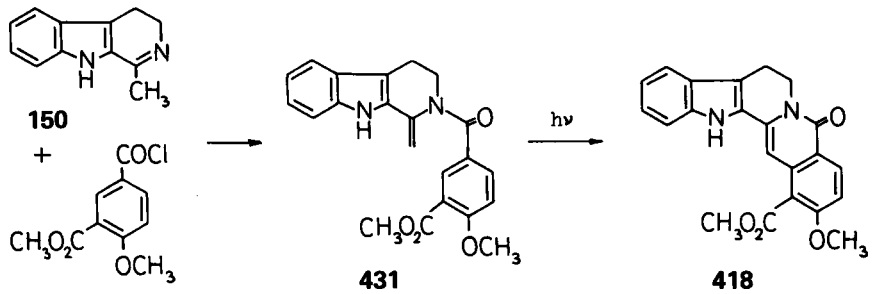
bine and (±)-β-yohimbine by Szántay *et al.* (*75, 220*), the present synthesis of **404** represents a new formal total synthesis of yohimbine alkaloids **74** and **75.**

Another formal total synthesis of (±)-yohimbine has been worked out by Wenkert *et al.* (*229*) by preparing *O*-methylhexadehydroyohimbine (**420**), which was first prepared by Kametani and co-workers (*224–226*) as a key intermediate toward (±)-yohimbine. In Wenkert's approach, pyridinium salt **427** was γ-alkylated with acetoacetic ester anion. The product **428** then underwent intramolecular condensation, affording tetracyclic quinone **429.** Methylation of **429**



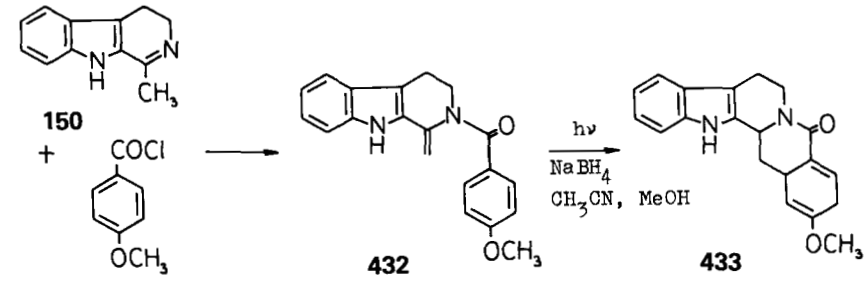
with trimethyloxonium tetrafluoroborate was followed by selective sodium borohydride reduction to the corresponding dihydro intermediate whose treatment with trifluoroacetic acid completed the synthesis of (±)-*O*-methylhexadehydroyohimbine (*229*).

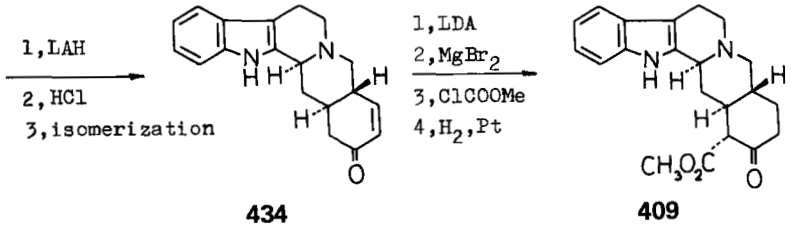
Ninomiya and co-workers have also published a formal total synthesis of (±)-yohimbine (*230*). Photocyclization of unstable enamide **431,** obtained from har-



malane (**150**), afforded pentacyclic amide **418,** synthesized earlier by Kametani *et al.* (*224*).

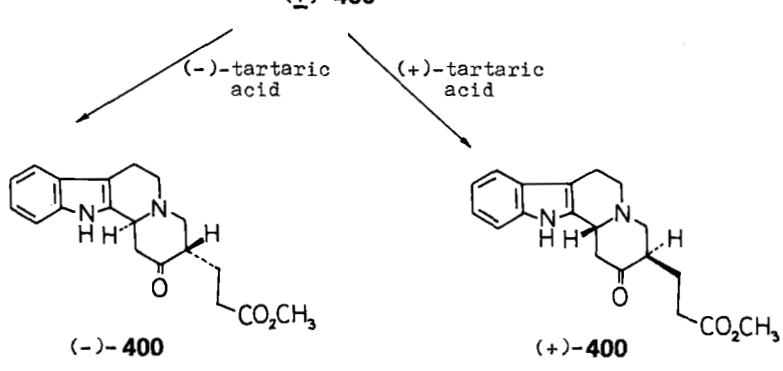
The total synthesis of (±)-yohimbine via regioselective functionalization of 18,19-dehydroyohimbinone (**434**) has been reported by Ninomiya *et al.* (*231*). Key intermediate **434** was prepared by enamide photocyclization of **432,** fol-





434 **409**

lowed by lithium aluminum hydride reduction, cleavage of the enol ether function with acid treatment, and isomerization of the carbon–carbon double bond, resulting in conjugated enone **434** (*205*). Acylation of the corresponding magnesium enolate, prepared *in situ* from the lithium enolate of **434,** followed by catalytic reduction, supplied exclusively (±)-yohimbinone (**409**) (*231*).



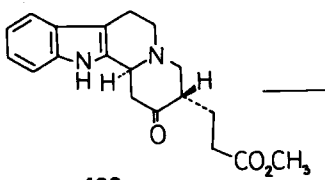
More recently, Szántay and co-workers (*232*) succeeded in performing the enantioselective total synthesis of both natural and "unnatural" antipodes of yohimbine and β-yohimbine. Utilizing second-order asymmetric induction, either the levorotatory or dextrorotatory antipode of key tetracyclic intermediate **400** could be obtained by the use of (−)- or (+)-tartaric acid, respectively.

Natural (+)-yohimbine and (−)-β-yohimbine have been obtained via the route described for racemic compounds [(−)-**400** → (+)-**402** → (−)-**410** → (+)-**74** + (−)-**75**], and similarly the corresponding unnatural antipodes (−)-**74** and (+)-**75** have been obtained from tetracyclic keto ester (+)-**400** (*232*).

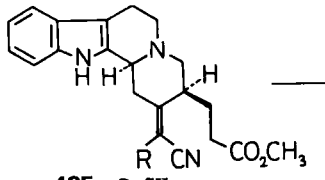
6. Alloyohimbine, α-Yohimbine, 17-Epialloyohimbine, and 3-Epi-α-yohimbine

The first total synthesis of (±)-alloyohimbine (**93**) and (±)-α-yohimbine (**90**), as well as two further stereoisomers still having the alloyohimbane skeleton, was accomplished by Szántay *et al.* (*72, 73*) in 1973. To assure the allo stereoarrangement of the yohimbane skeleton, the previously prepared tetracyclic keto ester **400** (*173*) was condensed with methyl cyanoacetate or malononitrile. Inasmuch as the reaction is accompanied by entire epimerization at C-20, the sodium borohydride reduction of products **435** or **436** supplies uniformly the cis-substituted indolo[2,3-*a*]quinolizine derivatives **437** and **438,** respectively. Hydrolysis, decarboxylation, and esterification gave nitrile ester **439** and diester **440.** Dieckmann condensation of **439** afforded 16-cyanoalloyohimbone (**441**), while the same reaction involving **440** yielded a mixture of isomers **442** and **443.** Hydrolysis and decarboxylation of both products (**442** and **443**) furnished (±)-alloyohimbone (**372**). By simple borohydride reduction of the keto–enol tautomeric mixture of (±)-alloyohimbinone (**442**) or via reduction of 16-cyanoalloyohimbone (**441**), followed by hydrolysis and esterification of the C-16 nitrile group to an ester function, all four stereoisomers of yohimbine with alloyohimbane skeleton (**90, 92, 93,** and **100**) could be prepared in racemic form. Of these four stereoisomers one proved to be identical with (±)-alloyohimbine (**93**) and another with (±)-α-yohimbine (**90**). It is worth mentioning that 10 years after its total synthesis 17-epialloyohimbine (**100**) was found as an alkaloid of *Aspidosperma oblongum* (*24*); however, the stereoisomer represented by formula **92** has not yet been found in nature. Spectroscopic and chemical investigation of natural alloyohimbine as well as its four stereoisomers (**90, 92, 93,** and **100**), prepared by Szántay *et al.* (*72, 73*), led to the recognition that the formula for the structure of alloyohimbine should be revised from the formerly suggested **92** to **93** (*72, 73, 75*).

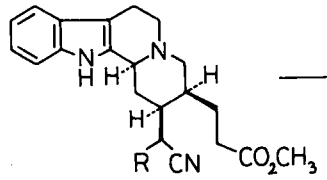
Two yohimbine stereoisomers [(±)-**445** and (±)-**446**] having epialloyohimbane skeletons have been synthesized from the previously prepared (*220*) epiallo nitrile ester **405,** using the following reaction sequence: Dieckmann condensa-



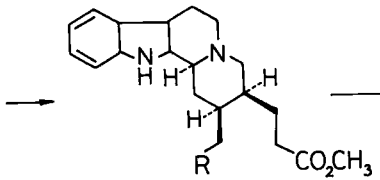
400



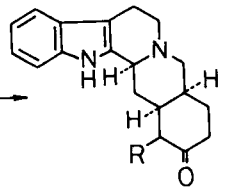
435 R=CN
436 R=CO_2CH_3



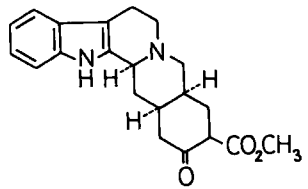
437 R=CN
438 R=CO_2CH_3



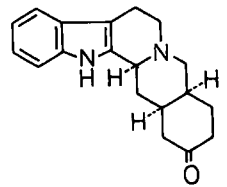
439 R=CN
440 R=CO_2CH_3



441 R=CN
442 R=CO_2CH_3



443



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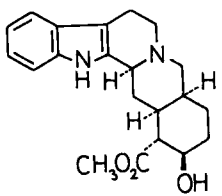
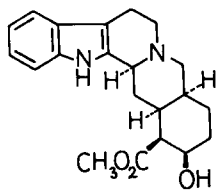
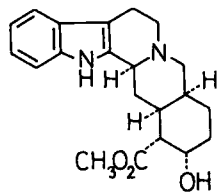


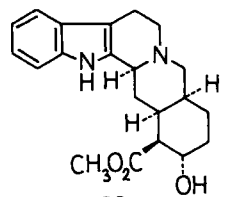
100



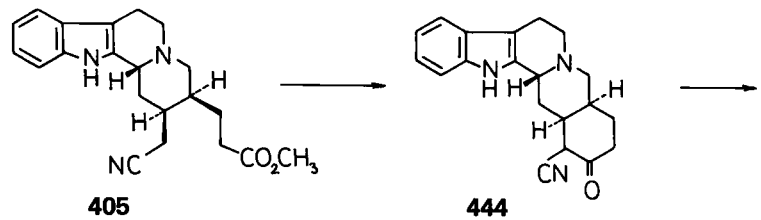
92



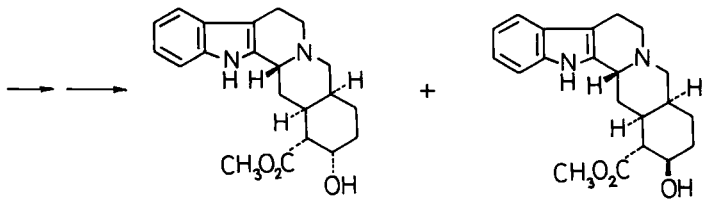
93



90



405 444



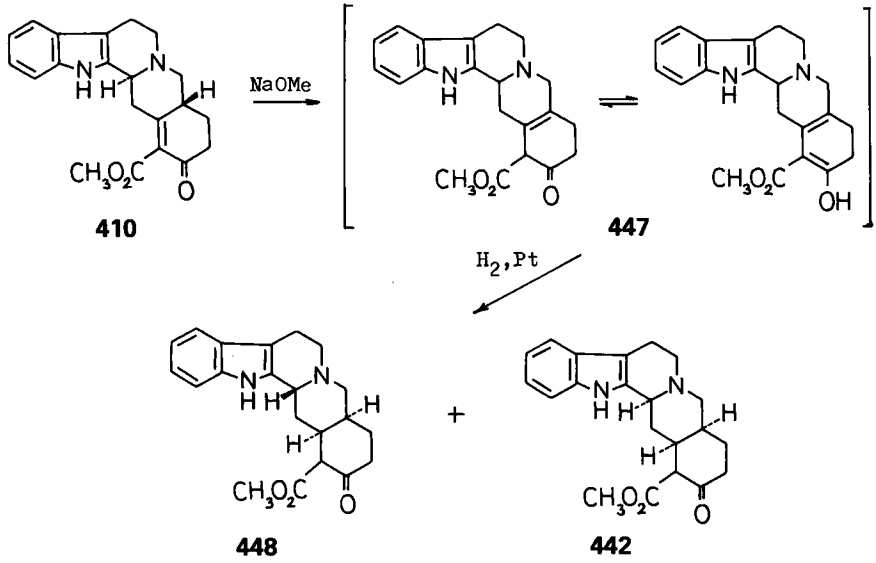
445 446

tion to **444**, sodium borohydride reduction, separation of the stereoisomers, followed by transformation of the C-16 nitrile group to an ester (*72*). Epimerization of **445** at C-3 furnished (±)-alloyohimbine (**93**) (*72*).

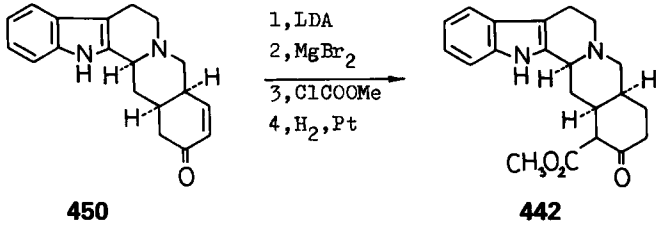
Szántay and co-workers (*74*) extended the utilization of 15,16-didehydroyohimbinone (**410**), obtained by regioselective Dieckman condensation of **402,** for the preparation of yohimbine stereoisomers with D/E-cis ring junction. Having been treated with base, this key intermediate (**410**) rearranges to 15,20-didehydro derivative **447,** which could be converted by a two-step reduction through intermediates (±)-alloyohimbinone (**442**) and (±)- epialloyohimbinone (**448**) to D/E-cis annellated alkaloids (±)-alloyohimbine (**93**), (±)-α-yohimbine (**90**), and (±)-3-epi-α-yohimbine (**105**), (±)-17-epialloyohimbine (**100**), as well as the not naturally occurring stereoisomers (±)-17-epi-α-yohimbine (**92**), (±)-3-epialloyohimbine (**445**), and (±)-3,17-epialloyohimbine (**446**).

The transformations of D/E-cis annellated yohimbines, utilizing C-3 and C-16 epimerizations have also been studied by the Hungarian group, and, as a result, (±)-3,17-epi-α-yohimbine (**449**), not directly available from **448** by reduction, has been synthesized (*81b*) (see p. 213).

Wenkert and his collaborators (*228*) have also synthesized (±)-alloyohimbine (**93**) and (±)-α-yohimbine (**90**) by the use of *N*-tryptophylpyridinium salt **422** as starting material. Minor isomer diester **406,** having epiallo relative stereo arrangement, was oxidized with mercuric acetate in the presence of EDTA, and the resulting imminium salt was immediately reduced with sodium borohydride, yielding allo diester **440,** previously synthesized by Szántay *et al.* (*73*). Since cyclization and reduction have transformed this compound to (±)-alloyohimbine (**93**) and (±)-α-yohimbine (**90**), this approach constitutes a formal total synthesis



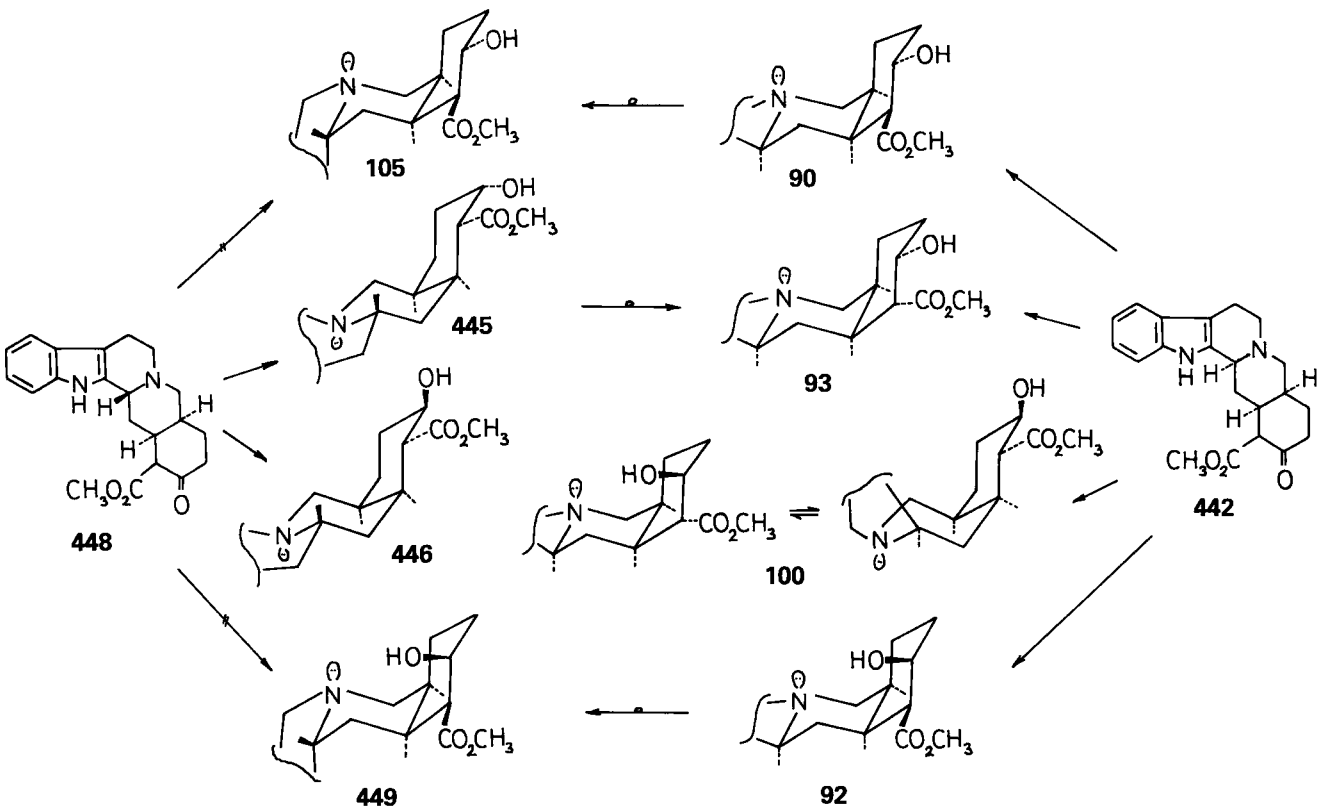
of these alkaloids. Another formal total synthesis of these D/E-cis annellated yohimbine alkaloids (**93, 90**) has been reported by Ninomiya and co-workers (*231*). Acylation of 18,19-didehydroalloyohimbone (**450**) at C-16 and subsequent reduction yielded (±)-alloyohimbinone (**442**), prepared first by Szántay's group (*73*).

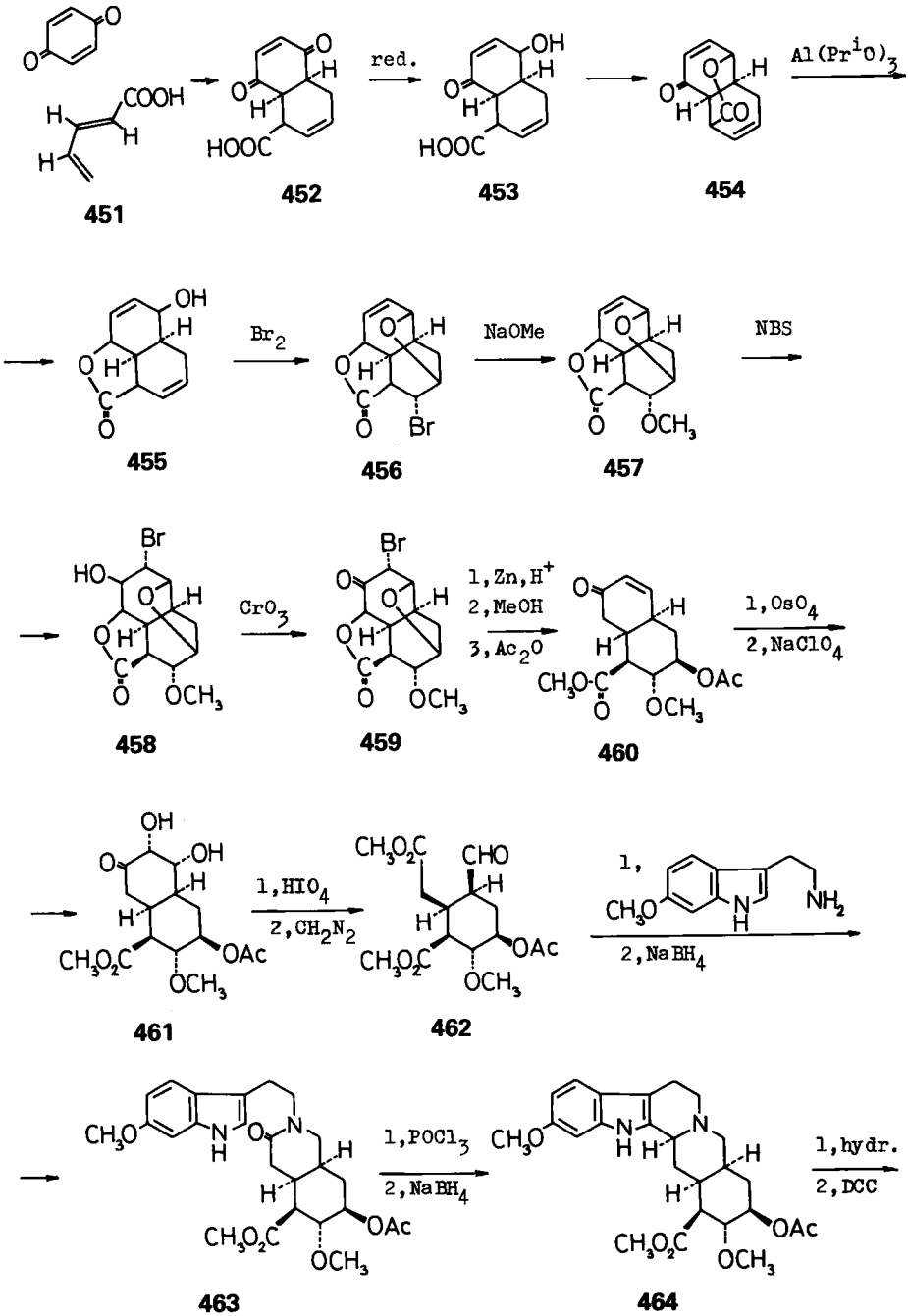


7. Reserpine, Deserpidine, and Related Alkaloids

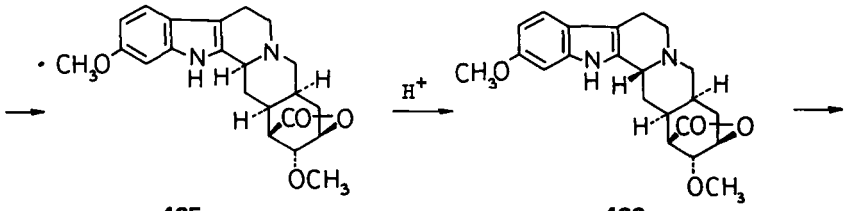
The first total synthesis of (−)-reserpine (**109**) was published in 1956 and 1958 by Woodward and co-workers (*233, 234*). Although this ingenious work has already been reviewed in *The Alkaloids* (*3*), it is worthwhile to present the reaction sequence to recapitulate this convergent approach.

The stereospecific preparation of aldehyde ester **462,** already comprising five of the six stereo centers of the molecule and, furthermore, the stereoselective construction of the epialloyohimbane skeleton with E_{c2} conformation are regarded the remarkable features of Woodward's approach.

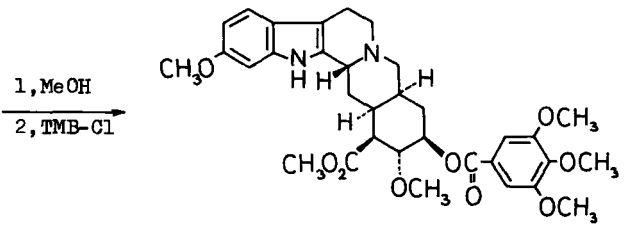

105
90
445
93
448
446
442
100
449
92



451 **452** **453** **454** **455** **456** **457** **458** **459** **460** **461** **462** **463** **464**



465 466



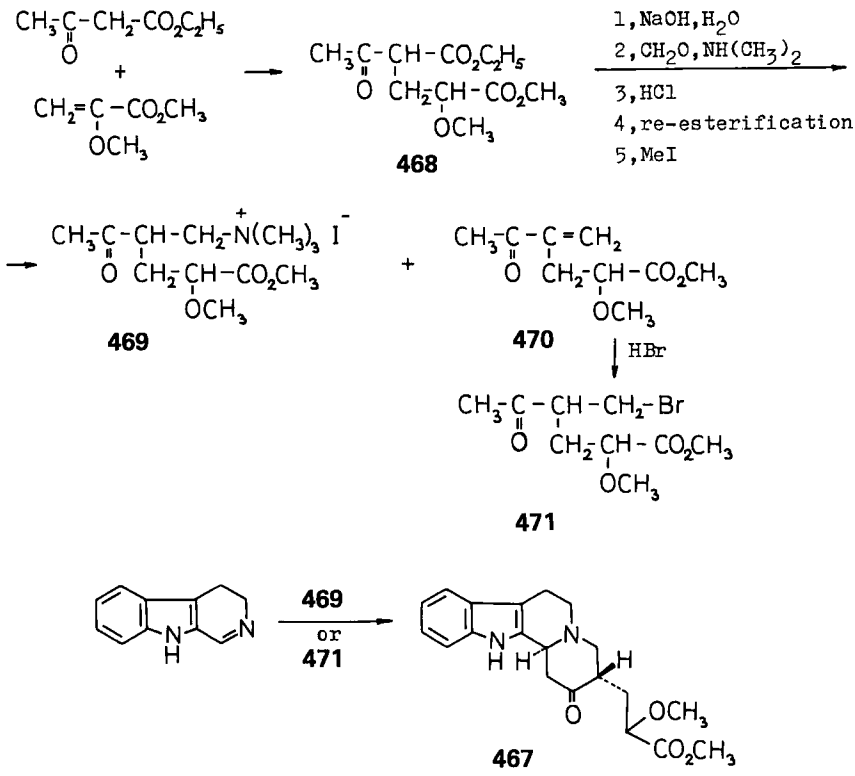
109

Certain steps of Woodward's synthesis of reserpine have been modified by French (*235, 236*) and Czech (*237–243*) research groups. Deserpidine (**110**) has also been synthesized by the use of key building block **462** (*240–242*). Some approaches aiming toward the preparation of similar ring-E products have appeared (*244–249*); however, no alkaloid total synthesis was reported during the two decades following Woodward's work.

After an interval of more than 20 years, a second synthesis of (±)-deserpidine and the achievement of some stereoisomers of (±)-raunescine (**114**) have been reported by Szántay and co-workers (*250, 255*). The basic idea of this linear total synthesis was similar to that utilized by them for the synthesis of yohimbine alkaloids. First, tetracyclic key intermediate **467** was prepared (*253*), in which the methoxy substituent of the side chain, on the one hand, represents the future C-18—O bond of the end product and will, on the other hand, control the regioselectivity of the Dieckmann ring closure.

The addition product of ethyl acetoacetate and methyl α-methoxyacrylate was hydrolyzed, and the resulting dicarboxylic acid was treated with dimethylamine hydrochloride and aqueous formaldehyde. The product of the Mannich reaction was decarboxylated, reesterifed, and finally treated with methyl iodide to supply quaternary salt **469** as the main product. During the above one-pot process, elimination also took place, yielding unsaturated ketone **470,** which was later utilized as its hydrogen bromide adduct **471.** Reaction of 3,4-dihydro-β-carboline either with **469** or **471** furnished the desired indolo[2,3-*a*]quinolizine derivative **467** as a mixture of two diastereomeric racemates.

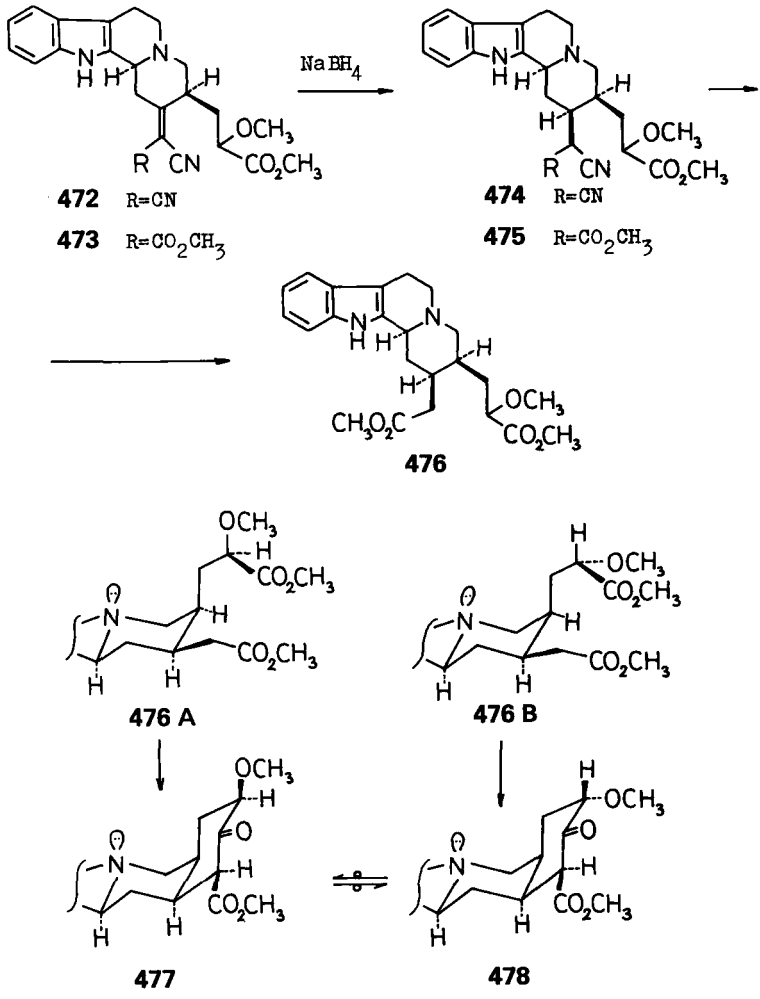
Performing a Knoevenagel condensation of intermediate **467** with methyl



cyanoacetate or malononitrile, followed by sodium borohydride reduction, as well as hydrolysis, decarboxylation, and esterification resulted in allo diester **476,** which could be separated into its diastereomeric components (**476A** and **476B** racemates). Dieckmann ring closure of **476A** gave allo pentacycle **477,** while the same reaction of **476B** yielded a mixture. In addition to the expected product **478,** the C-18 epimeric compound **477** also has been formed as a result of subsequent epimerization.

Reduction of the enolizable keto ester **477** supplied two alcohols, **479** and **480,** from both of which the same unsaturated ester **481** could be obtained by easy water elimination. Accordingly, the reduction of **478** yielded alcohols **482, 483,** and **484** in addition to **479** and **480** derivable from **477,** formed by previous C-18 epimerization of **478.** Water elimination of **482** gave 18α-methoxyapoalloyohimbine (**485**). By demethylating the three major products **479, 480,** and **482,** the corresponding C-18-hydroxy derivatives **486, 487,** and **488** could be prepared.

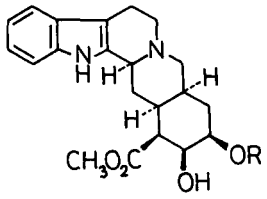
Water elimination from both **486** and **487** stereoisomers resulted in 18β-hydroxyapoalloyohimbine (**489**). By this step, stereo centers at C-16 and C-17



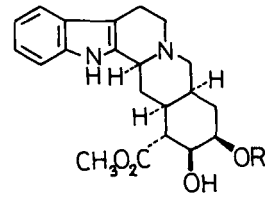
were destroyed, and the product **489** was proved suitable to supply the proper substitution pattern of ring E by stereoselective methanol addition. Since esterification of the hydroxyl group of **490** with trimethoxybenzoyl chloride and the transformation of the alloyohimbine skeleton to epiallo by C-3 epimerization have already been performed, preparation of **490** represents a new total synthesis of (±)-deserpidine (**110**) (*255*).

When **486** was treated with trimethoxybenzoyl chloride, (±)-3-epi-17-epiraunescine (**491**) was formed as the sole product in rather good yield (*255*).

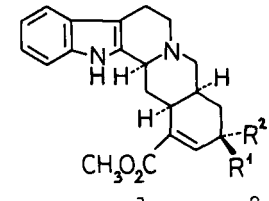
It should be noted that dialcohols **486, 487,** and **488,** obtained during the synthesis are stereoisomers of "18-hydroxy-α-yohimbine," which has an al-



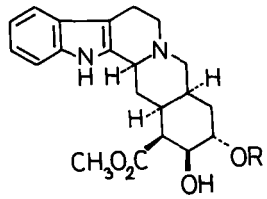
479 R=CH_3
486 R=H



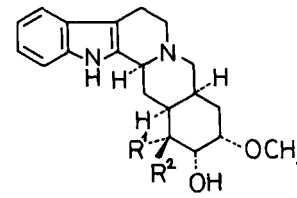
480 R=CH_3
487 R=H



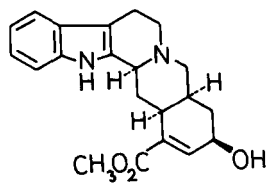
481 R^1=OCH_3; R^2=H
485 R^1=H; R^2=OCH_3



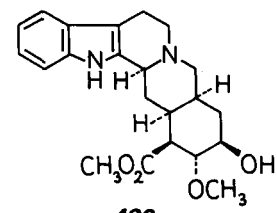
482 R=CH_3
488 R=H



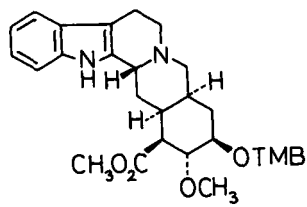
483 R^1=CO_2CH_3; R^2=H
484 R^1=H; R^2=CO_2CH_3



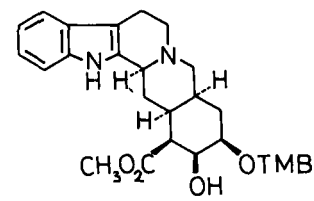
489



490



110

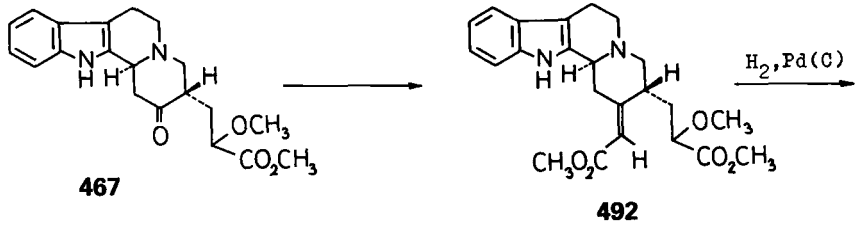


491

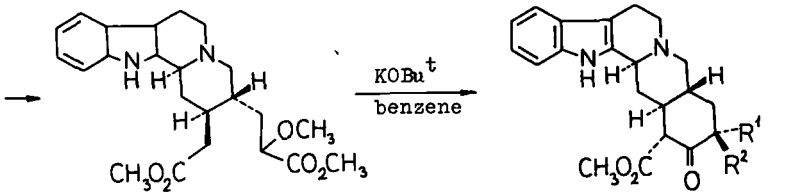
loyohimbane skeleton and has been reported by Iwu and Court (*90*) as a natural substance. Unfortunately the exact steric structure of "18-hydroxy-α-yohimbine" has not been given in the reference cited.

Szántay and co-workers (*254*) have synthesized all four possible stereoisomers of 18-hydroxyyohimbine and a number of stereoisomeric raunescine analogs having normal yohimbine skeletons.

Tetracyclic keto ester **467,** prepared earlier (*253*), was treated with the anion of diethyl methoxycarbonylmethylphosphonate in dimethylformamide. The reaction supplied the unsaturated ester **492,** which was catalytically hydrogenated to diester **493.** Dieckmann condensation of **493** yielded two nonenolizable keto esters (**494** and **495**), which could be separated by fractional crystallization. Sodium borohydride reduction of 18α-methoxyyohimbinone (**494**) gave two alcohols (**496** and **497**) in a ratio of about 10:1; at the same time, reduction of 18β-methoxyyohimbinone (**495**) furnished another two stereoisomeric alcohols (**498** and **499**) in approximately equal amounts. Demethylation of the four stereoisomers (**496–499**) resulted in the corresponding 18-hydroxyyohimbines (**500–503**)

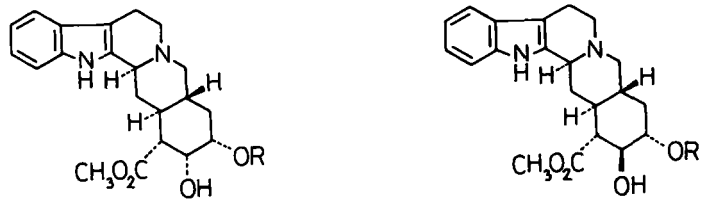


467 **492**



493 **494** R^1=OCH_3; R^2=H

495 R^1=H; R^2= OCH_3



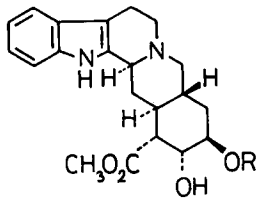
496 R=CH_3

500 R=H

504 R=THB

497 R=CH_3

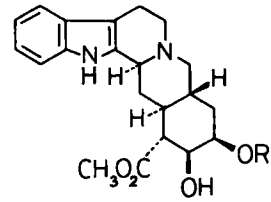
501 R=H



498 R=CH_3

502 R=H

505 R=TMB



499 R=CH_3

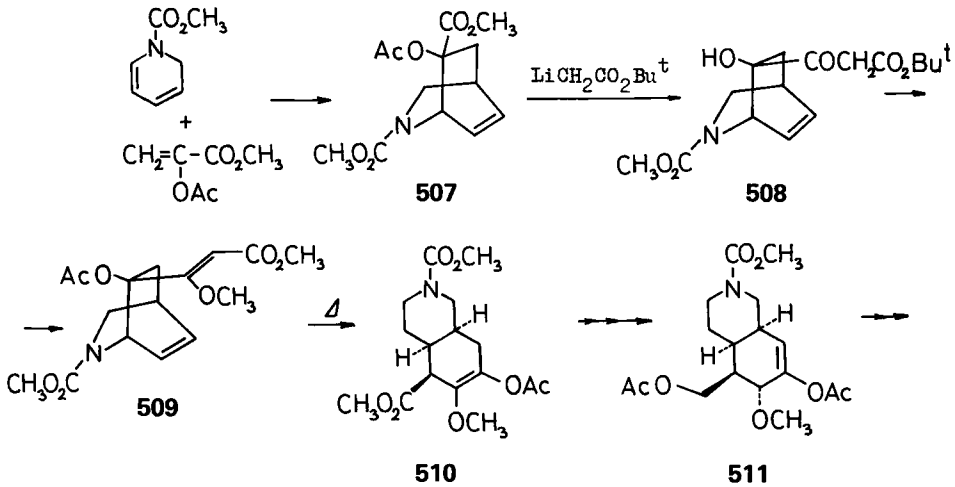
503 R=H

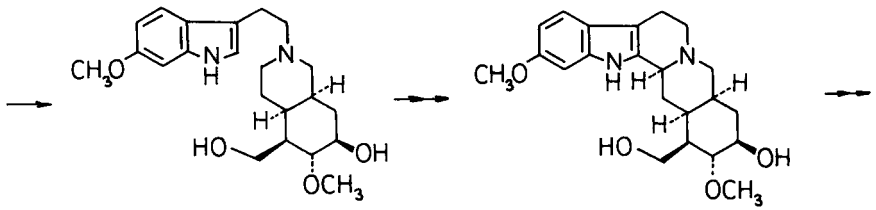
506 R=TMB

with retention of the relative steric positions of substituents on ring E. Stereoisomers, with normal yohimbane skeletons, of alkaloid raunescine (**114**) have also been prepared via acylation of dialcohols **500, 502,** and **503** with trimethoxybenzoyl chloride in pyridine, resulting in compounds **504, 505,** and **506,** respectively, in racemic form (*254*).

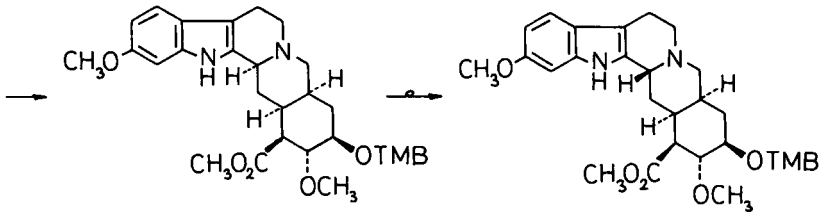
An approach in constructing the basic reserpine skeleton via the amino Claisen rearrangement of zwitterionic vinylisoquinuclidenes has been investigated (*256, 257*).

A new multistep synthesis of (±)-reserpine (**109**) has been published by Wender *et al.* (*258*). The key building block of the synthesis is *cis*-hexahydroisoquinoline derivative **510,** prepared by the extension of the previously elaborated (*259*) Diels–Alder addition–Cope rearrangement sequence. Further manipulation of **510** gave 2,3-secoreserpinediol derivative **512,** which already possesses the required stereochemistry in ring E. Oxidative cyclization of **512** yielded 3-isoreserpinediol (**513**), which was transformed by the use of simple reaction





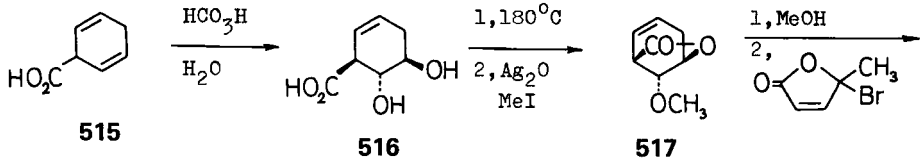
512 513



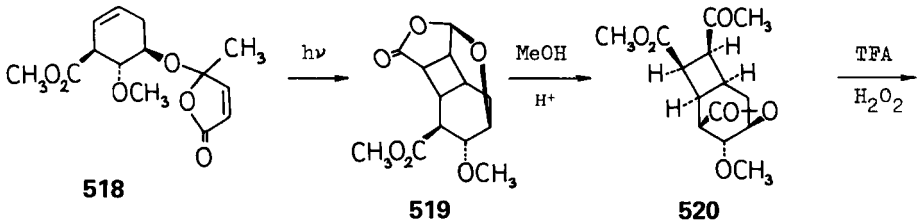
514 109

steps to (±)-3-isoreserpine (**514**) (*258, 259*). Since natural 3-isoreserpine has already been converted to (−)-reserpine (*260, 261*), the synthesis of racemic 3-isoreserpine represents a new total synthesis of (±)-reserpine.

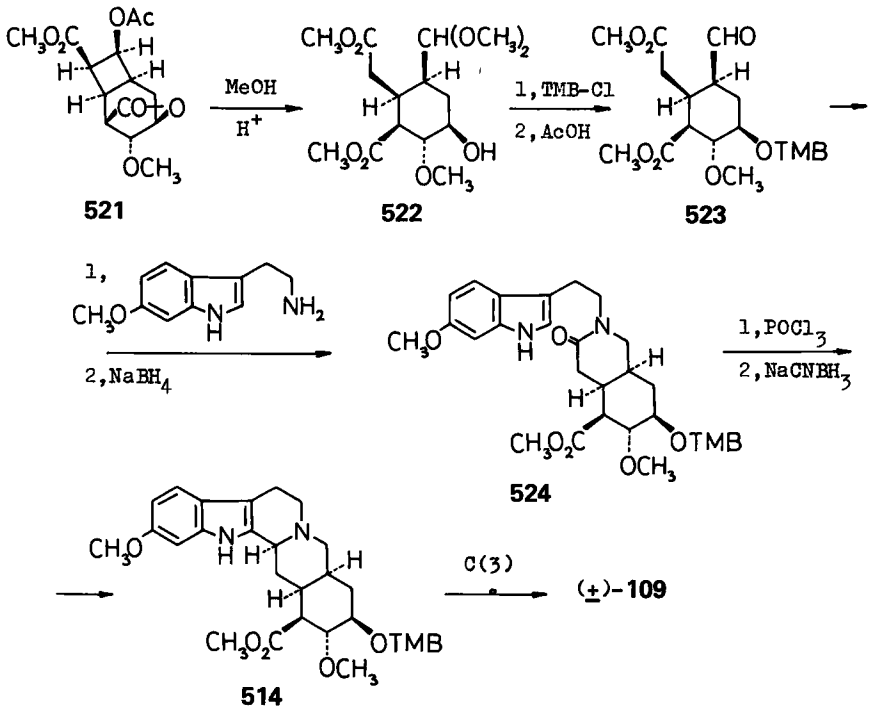
A new method, reported by Pearlman (*262*), for the preparation of Woodward's key building block also constitutes a new synthesis of reserpine as well as deserpidine. In the key step of the synthesis an internal [2π + 2π] photocyclization of dienone **518** gave cyclobutane derivative **519** with the established stereochemistry. Methanolysis and subsequent peracid treatment of **520** yielded lactone ester **521**. Repeated methanolysis and retroaldol fission of the cyclobutane



515 516 517



518 519 520

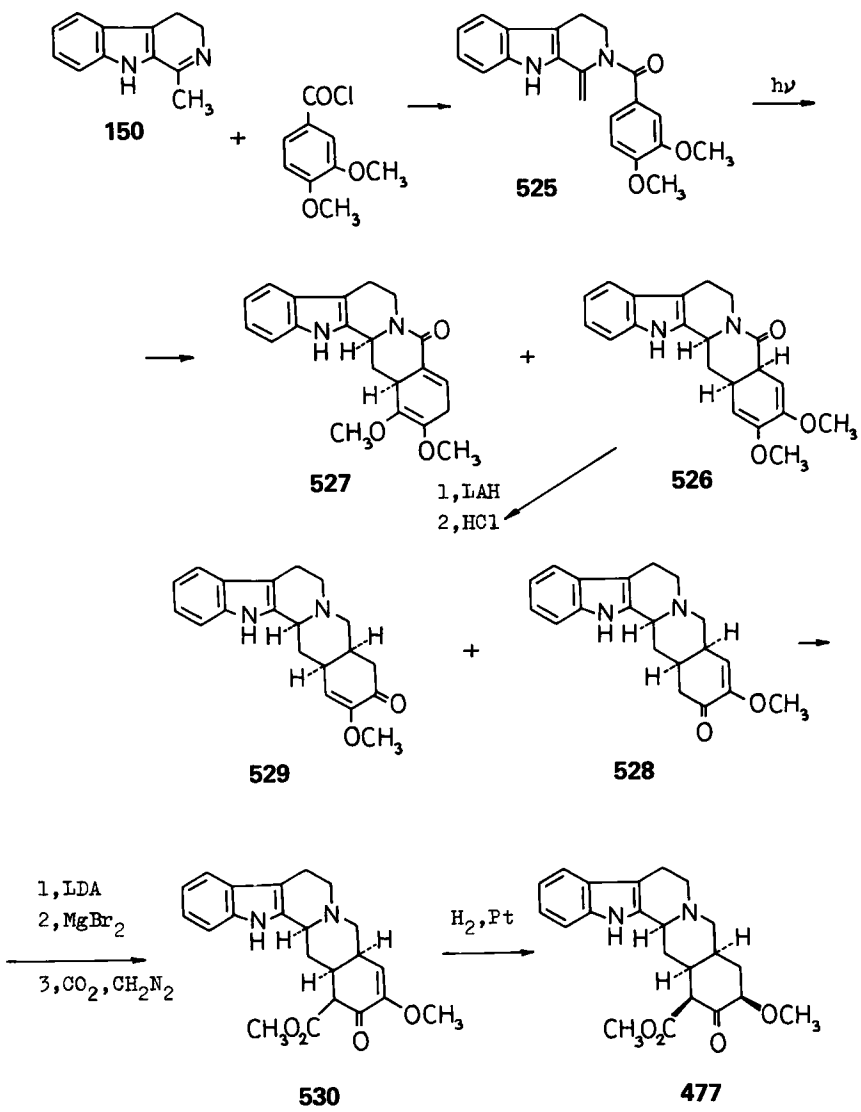


521 **522** **523** **524** **514**

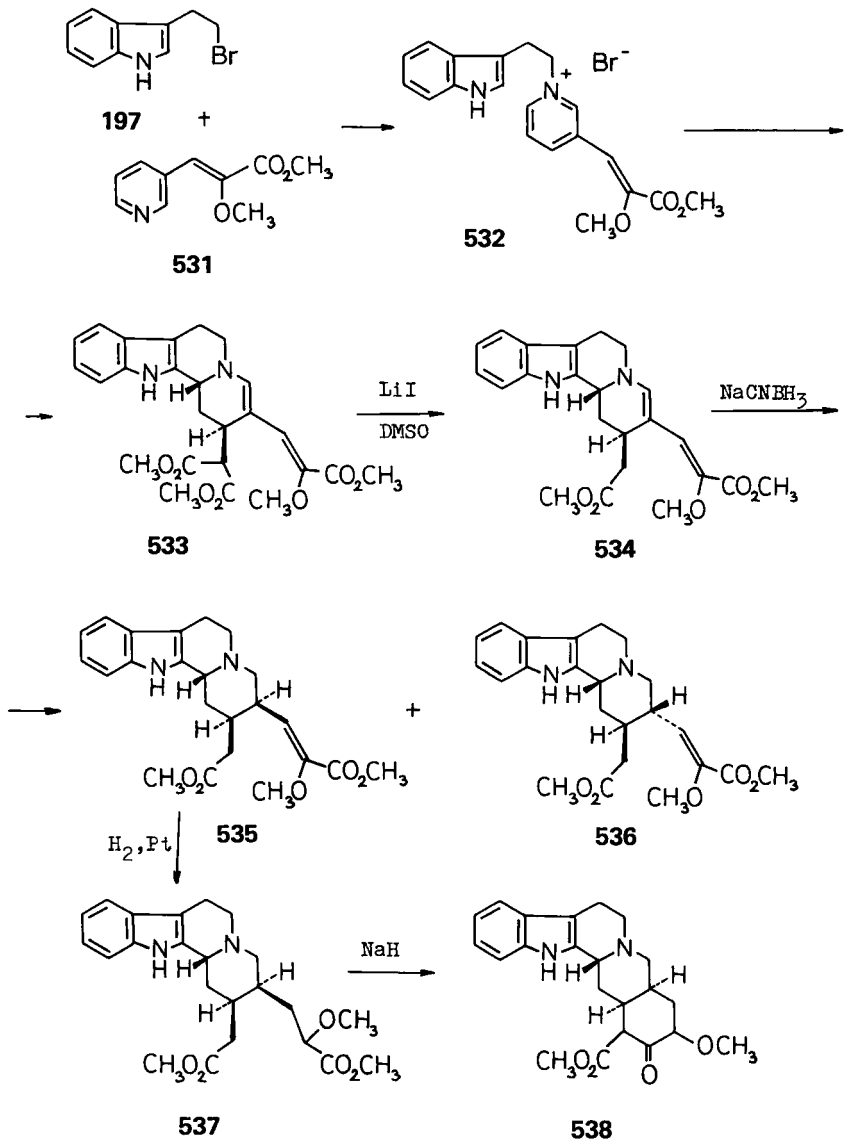
ring resulted in acetal **522,** which was transformed to key building block **523.** Repeating the original Woodward's procedure, (±)-3-epireserpine (**514**) has finally been prepared (*262*).

A formal total synthesis of (±)-deserpidine was completed by Ninomiya *et al.* (*263*) via reductive photocyclization of enamide **525,** prepared from harmalane (**150**) and veratroyl chloride. The photocyclization led to a mixture of two isomeric lactams (**526** and **527**). Treatment of dienol ether **526** with lithium aluminum hydride and then with hydrochloric acid resulted in partial hydrolysis of one of the two enol ether groups, yielding a mixture of ketones **528** and **529.** C-Acylation of **528** via lithium enolate with carbon dioxide, followed by esterification, gave unsaturated keto ester **530.** Catalytic hydrogenation of **530** afforded (±)-18β-methoxyalloyohimbinone (**477**), previously prepared by Szántay *et al.* (*255*) during the synthesis of (±)-deserpidine.

A new approach to (±)-deserpidine has been published by Wenkert (*264*) in preliminary form. The characteristic feature of the synthesis is the addition of a nucleophile to a pyridinium salt, followed by acid-induced ring closure. For the preparation of the desired pyridinium salt **532,** nicotinaldehyde was condensed with methyl methoxyacetate, and the methyl acrylate derivative **531** was alky-



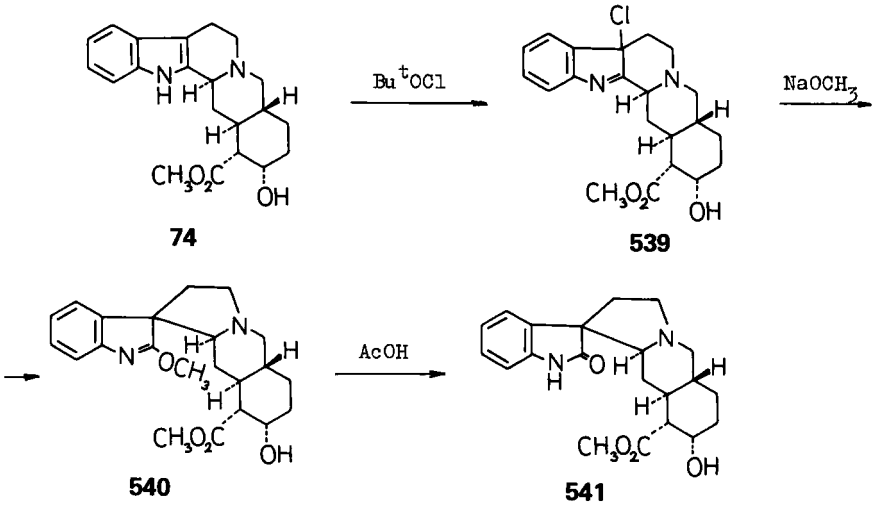
lated with tryptophyl bromide. As nucleophile, dimethyl sodiomalonate was treated with **532.** The resulting triester **533** was then demethoxycarbonylated to unsaturated diester **534,** the sodium cyanoborohydride reduction of which furnished epiallo as well as pseudo diesters **535** and **536,** respectively. Hydrogenation of **535,** followed by condensation, supplied 18-methoxyepialloyohimbinone (**538**) from which (±)-deserpidine can be reached (*264*).



IV. Transformations, Reactions

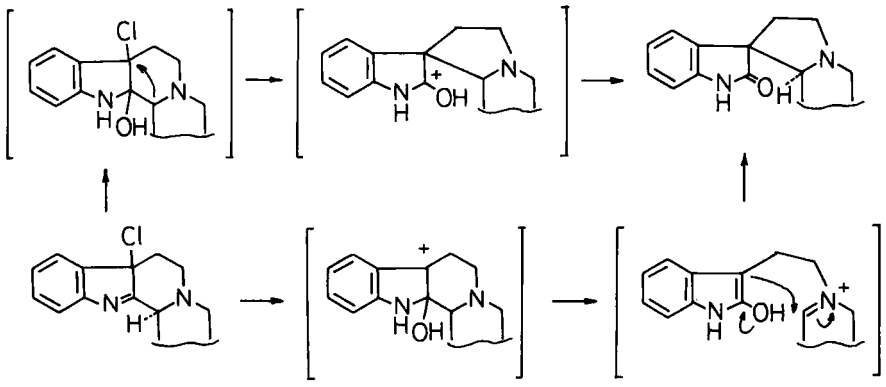
The conversion of indole alkaloids to oxindole derivatives has been studied extensively. Since this review does not deal with the literature of oxindole alkaloids, only the most important transformations of the alkaloids having indoloquinolizine as well as yohimbane skeletons are to be mentioned.

Chlorination of yohimbine (**74**) at the β position of the indole moiety with *tert*-butyl hypochlorite and treatment of the resulting chloride (**539**) with base in



methanol gave imino ether **540**, which could be hydrolyzed in refluxing aqueous acetic acid to spirooxindole **541** (*265*). Interestingly enough, the base-catalyzed rearrangement could be performed only with D/E trans yohimbine alkaloids; it failed, however, with D/E-cis yohimbines. The latter alkaloids could be transformed to the corresponding D/E-cis yohimbinoid oxindoles by the use of lead tetraacetate oxidation, followed by acetic acid treatment in methanol (*266*).

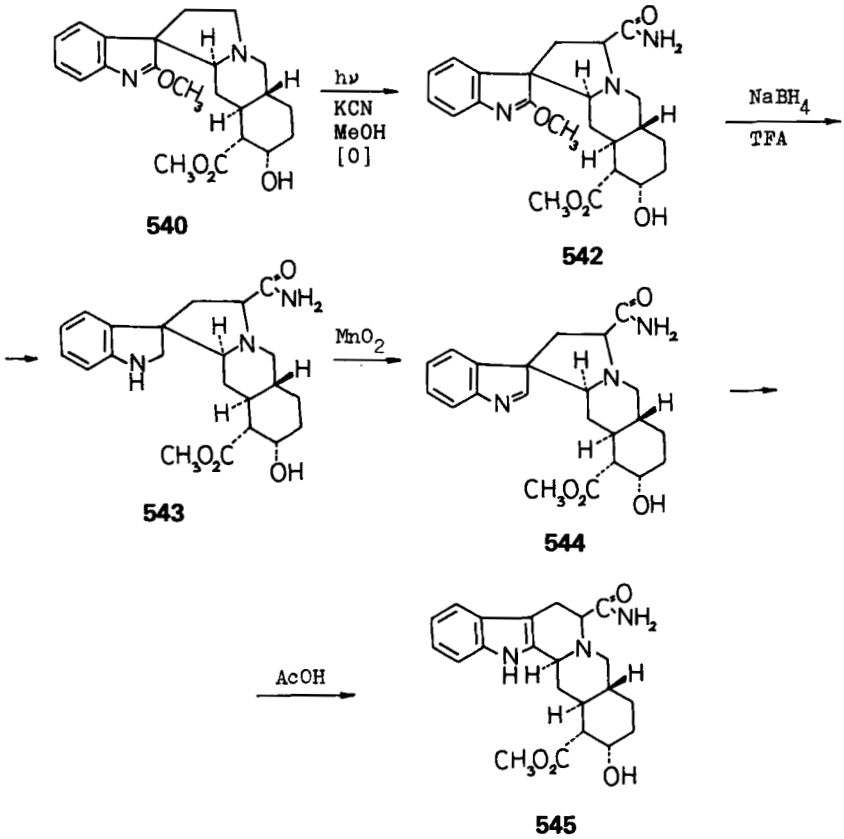
Zinnes and Shavel found that chloroindolenines, derived from various yohimbine alkaloids, gave directly the corresponding oxindoles by being refluxed in aqueous methanol at pH 6 (*267, 268*). This procedure can be applied for both D/E-cis and D/E-trans yohimbine alkaloids (*267–269*).



Two possible mechanisms for the formation of the oxindoles from 3-chloroindolenines have been proposed (*267, 268*) as shown on p. 225.

In 1980 a review appeared concerning the preparation and synthetic use of 3-haloindolenines (*270*).

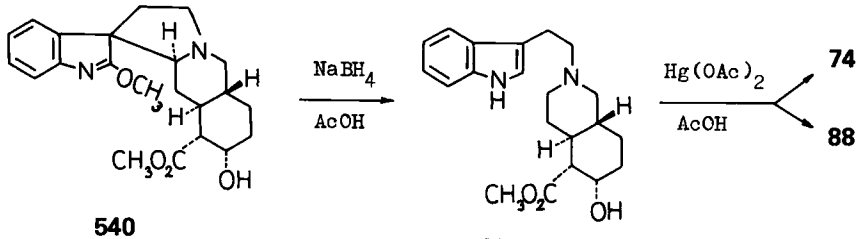
Photooxidation of imino ether **540** in the presence of potassium cyanide led to the α-amino carboxamide **542,** which could be transformed by simple reaction steps to 5-carboxamidoyohimbine (**545**) (*271*).



540 **542** **543** **544** **545**

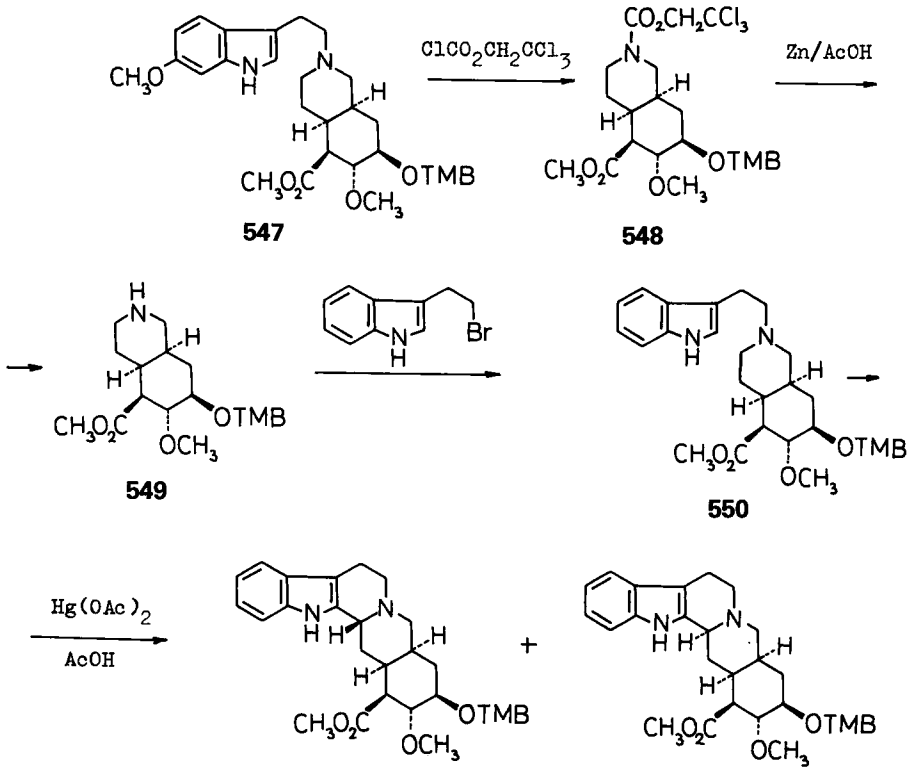
Reduction of imino ether **540** with sodium borohydride led to 2,3-seco-2,3-dihydroyohimbine (**413**), which could be recyclized by mercuric acetate oxidation, followed by acid treatment, yielding yohimbine (**74**) and pseudoyohimbine (**88**) (*271–272*).

A simple method was developed for the cleavage of the C-2—C-3 bond of indole alkaloids by the use of formic acid–formamide as reagent. Thus 2,3-seco derivatives of yohimbine (**74**), hirsutine (**58**), and reserpine (**109**) were prepared



540 **413**

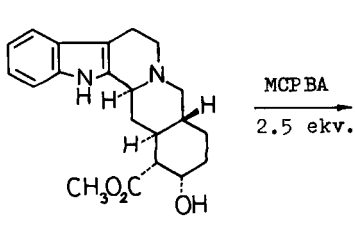
(*273*). The transformation of reserpine to deserpidine (**110**) via 2,3-seco-2,3-dihydroreserpine (**547**) has been accomplished (*274*). 2,3-Seco-2,3-dihydroreserpine (**547**) was treated with trichloroethyl chloroformate, resulting in



547 **548** **549** **550** **110** **551**

urethane **548** in 63% yield, which could be cleaved to piperidine derivative **549**, using zinc and acetic acid. The resulting **549** was then alkylated by tryptophylbromide (**197**), and 2,3-seco-2,3-dihydrodeserpidine (**550**) was obtained. Mercuric acetate oxidation, followed by acid treatment, gave deserpidine and 3-isodeserpidine (**551**) (*274*).

Treatment of chloroindolenine N_b-oxide (**552**), derived from yohimbine (**74**), with ethanolic potassium hydroxide gave 3-hydroxyyohimbine N_b-oxide (**553**). The same type of reaction occured, when **552** was treated either with methanolic sodium methoxide or with methanolic potassium cyanide, the products being 3-methoxyyohimbine N_b-oxide (**554**) and 3-cyanoyohimbine N_b-oxide (**555**), respectively (*275*).



74 **552**

553 R=OH

554 R=OCH_3

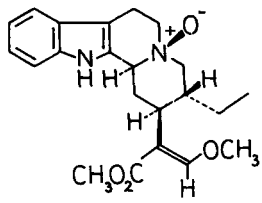
555 R=CN

556 **557**

558

The preparation and stereochemistry of some indole alkaloid *N*-oxides was studied by Sakai and co-workers (*276*). The N-oxidation of yohimbine (**74**) with *m*-chloroperbenzoic acid under mild reaction conditions led to two isomeric *N*-oxides (**556** and **557**) in a ratio of 10:1. MCPBA oxidation of pseudoyohimbine (**88**) afforded a single product (**558**).

Similarly to the above results, from dihydrocorynantheine (**54**) also two isomeric *N*-oxides (**559** and **560**) could be prepared; at the same time, from hirsutine (**58**) only one (**561**) could be obtained. On the basis of spectral evidence, the authors concluded that the major *N*-oxide derived from yohimbine and dihydrocorynantheine maintained the original stereo arrangement and they have the C/D-trans ring junction (*276*).



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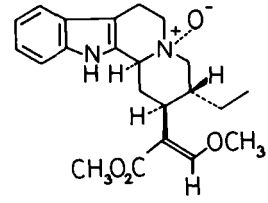

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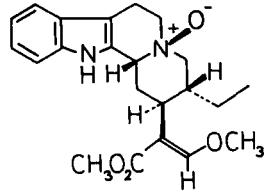
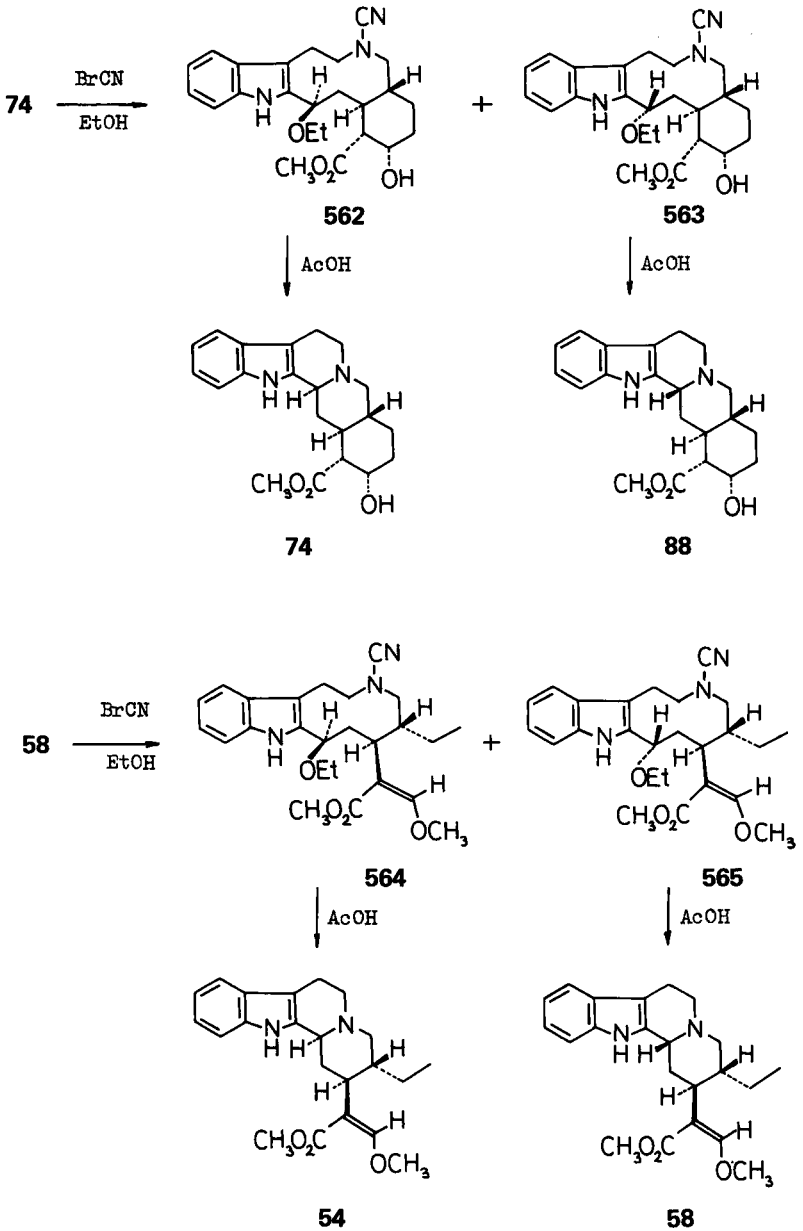


561

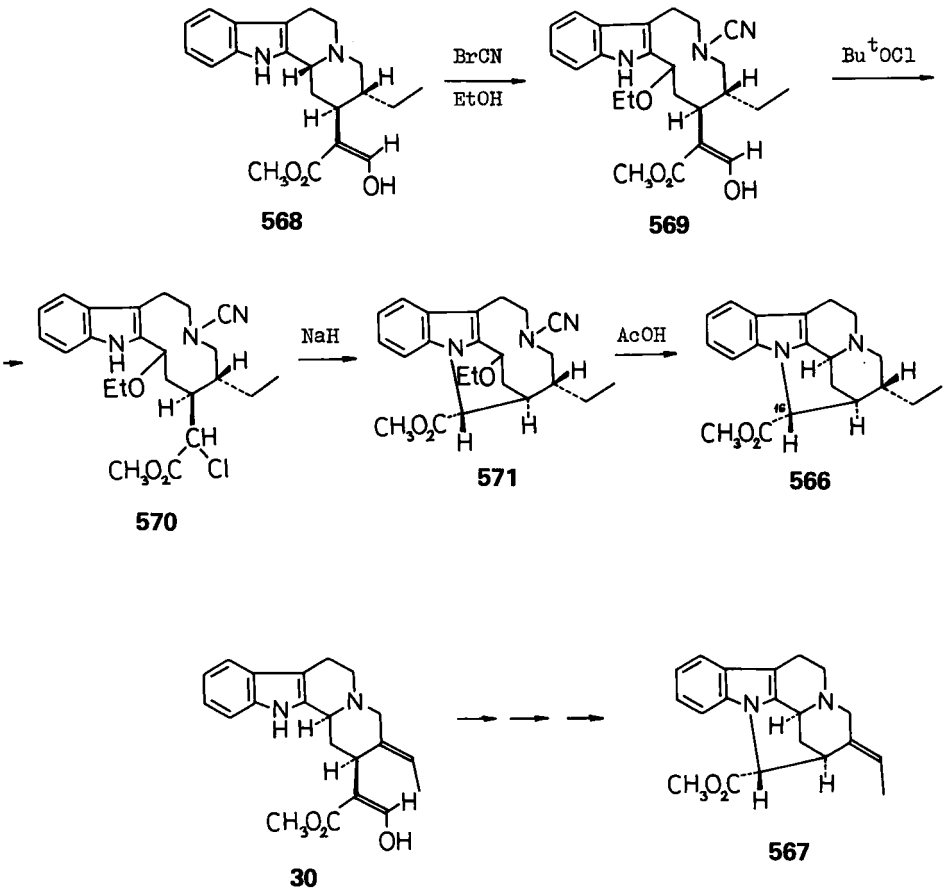
Reaction of yohimbine (**74**) with cyanogen bromide in ethanol–chloroform afforded an isomeric mixture of (3*R*)- and (3*S*)-ethoxy-3,4-secocyanamide derivative (**562** and **563**, respectively) (*277, 278*). It was found that the relative amounts of **562** and **563** depend on the molar ratio of ethanol to the substrate applied during the reaction. Stereospecific ring closures of **562** and **563** with hot acetic acid yielded yohimbine and pseudoyohimbine (**88**), respectively.

A similar result was obtained for hirsutine (**58**), which gave the corresponding (3*R*)- and (3*S*)-ethoxy-3,4-secocyanamide (**564** and **565**) upon treatment with cyanogen bromide. Both products could be cyclized; **564** gave dihydrocorynantheine (**54**), while **565** afforded hirsutine (**58**) stereospecifically (*278*).

During the synthesis of C-mavacurine-type alkaloids, Sakai and Shinma,reported the transformation of hirsutine to 19,20β-dihydro-16-epipleiocarpamine



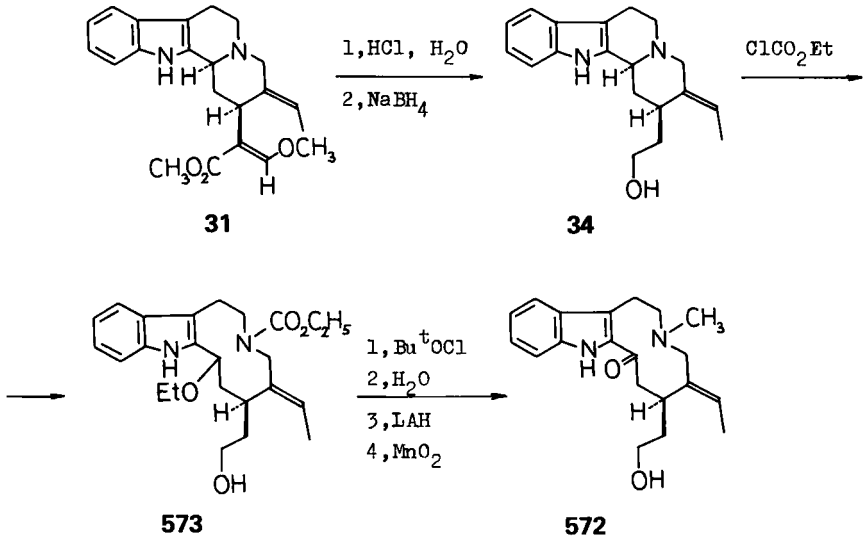
(**566**) (*279*) as well as the preparation of 16-epipleiocarpamine (**567**) starting from geissoschizine (**30**) (*280*). First, demethylhirsutine (**568**) was subjected to a C/D-ring-cleavage reaction, using cyanogen bromide. The resulting 3,4-seco compound **569** was then oxidized with *tert*-butyl hypochlorite in about 90% yield



to **570,** which was cyclized to **571** by treatment with sodium hydride in dimethyl sulfoxide. During these chemical transformations intermediates **569, 570,** and **571** occurred as a mixture of diastereomers. The final ring closure of **571** was performed in aqueous acetic acid to give 19,20β-dihydro-16-epipleiocarpamine (**566**). However, the desired pleiocarpamine derivative with a β-methoxycarbonyl function at C-16 could not be achieved (*279*). A similar reaction sequence starting from geissoschizine (**30**) led to 16-epipleiocarpamine (**567**) (*280*).

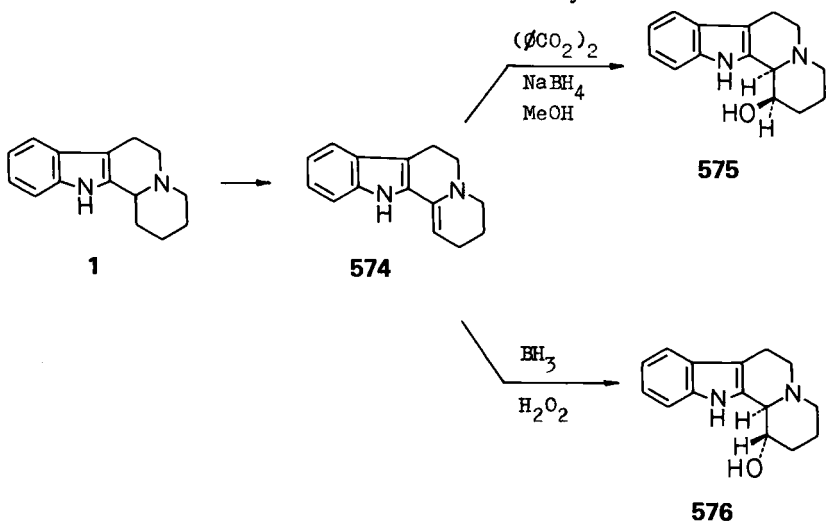
Cryptopine-type indole alkaloid burnamicine (**572**) has been synthesized from geissoschizine methyl ether (**31**) (*281*). In the first step, geissoschizol (**34**) was prepared, and then cleavage of the C/D ring fusion was carried out by means of ethyl chloroformate. Finally, C-3 carbonyl and *N*-methyl groups were developed by simple oxidation, reduction, and repeated oxidation steps.

The oxidation of hexahydroindolo[2,3-*a*]quinolizin (**574**) with benzoyl peroxide, followed by reduction and removal of the benzoyl group, gave the cis alcohol (**575**), while hydroboration–oxidation of the same enamine (**574**) yielded



31 **34** **573** **572**

the trans alcohol (**576**) (*282*). Accordingly, benzoyl peroxide oxidation of 3,14-didehydroyohimbine (**577**), followed by reduction and methanolysis, afforded 14β-hydroxyyohimbine (**578**) and 14α-hydroxypseudoyohimbine (**579**) in both cases with a formal trans water addition. Considerably different results were

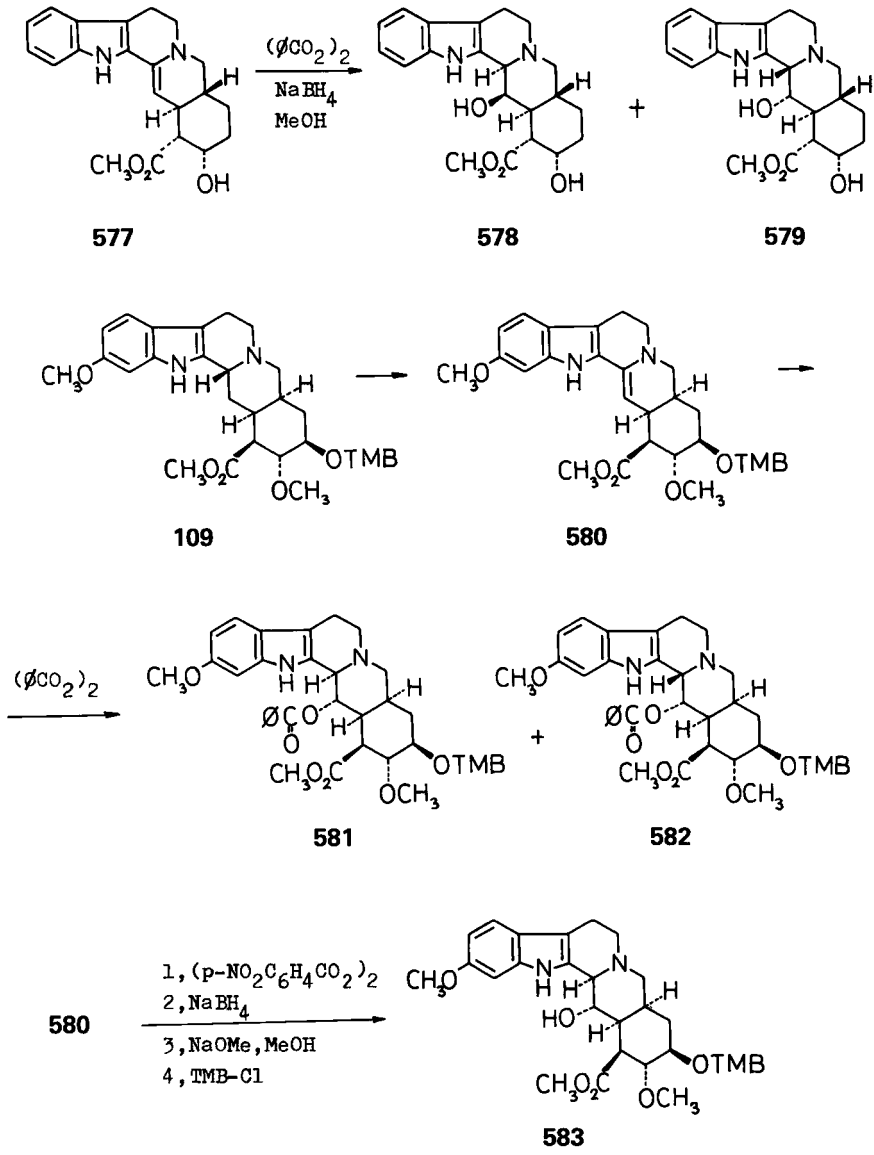


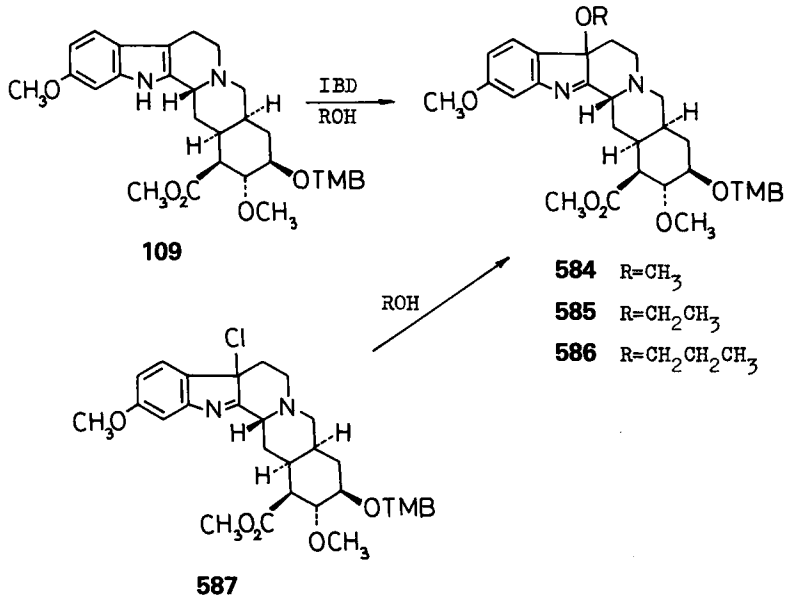
1 **574** **575** **576**

experienced in the hydroxylation reaction of 3,14-didehydroreserpine (**580**). Treatment of enamine **580** with benzoyl peroxide, followed by sodium borohydride reduction, resulted in 14α-benzoyloxyisoreserpine (**581**) and 14α-benzoyloxyreserpine (**582**); however, an attempt to remove the O-benzoyl group was

unsuccessful. 14α-Hydroxyisoreserpine (**583**) could be prepared from **580** via *p*-nitrobenzoyl peroxide oxidation, followed by reduction, methanolysis, and acylation with 3,4,5-trimethoxybenzoyl chloride (*283*).

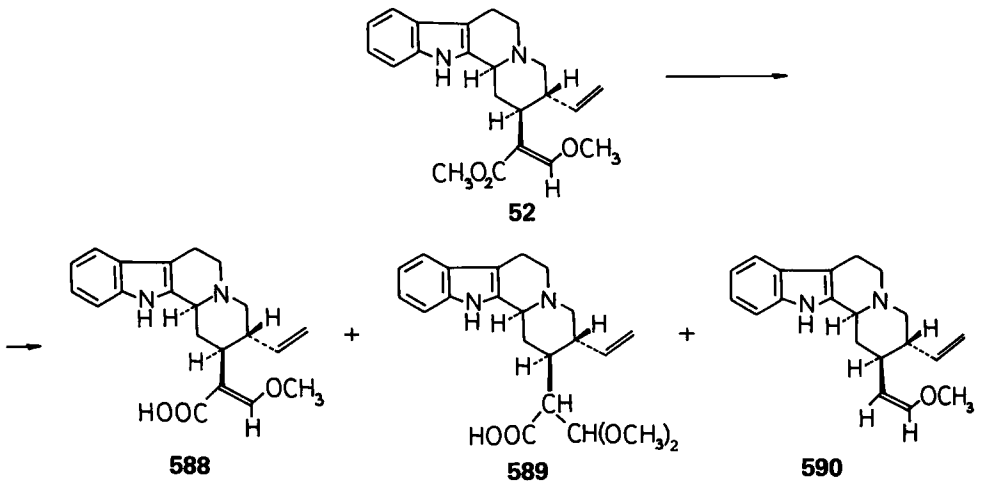
Oxidation of reserpine (**109**) with iodosobenzene diacetate in alcoholic medium (*284*) afforded in a single step the corresponding 7-alkoxyindolenine derivatives

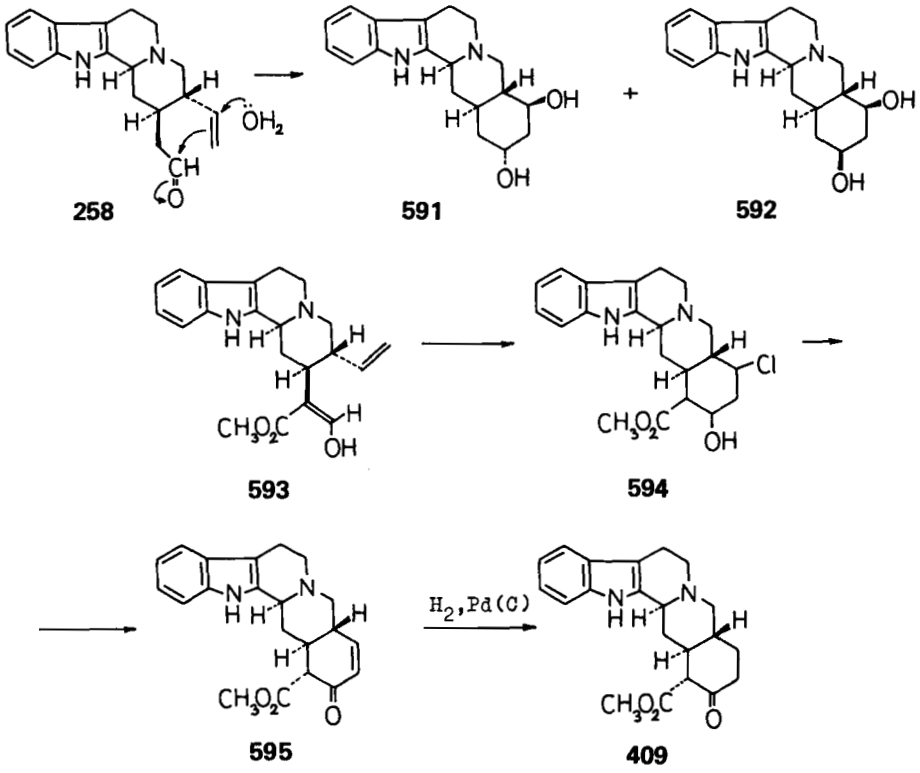




584–586, which could previously be obtained by solvolysis of 7-chloro-7*H*-reserpine (**587**).

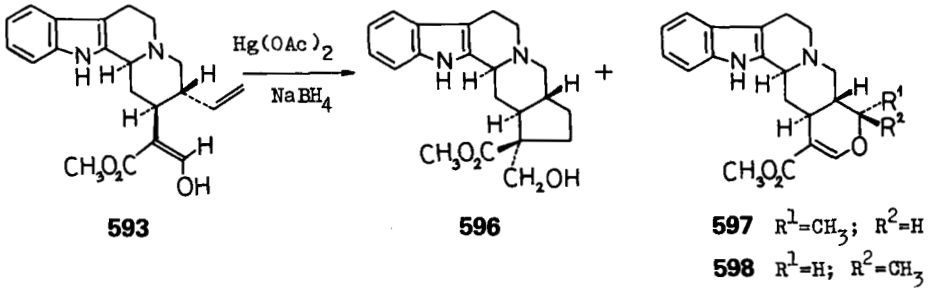
A series of publications appeared regarding the transformation of corynanthe-type alkaloids to yohimbane derivatives (*285–287*). The saponification of corynantheine (**52**) in methanol yielded a complex mixture of corynantheic acid (**588**), two C-16-epimer acetal acids (**589**), and demethoxycarbonylcorynantheine (**590**). All four compounds upon hydrolysis in acid resulted in cory-

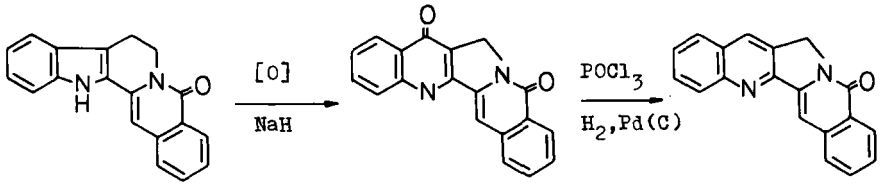




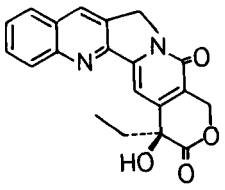
nantheal (**258**). Acid-catalyzed ring closure of **258** gave two isomers of 17,19-dihydroxyyohimbane (**591** and **592**) (*285*). Utilizing this formation of ring E, which might have great importance in biosynthetic implications, yohimbinone (**409**) has been prepared from demethylcorynantheine (**593**) (*286*).

On the other hand, oxymercuration of demethylcorynantheine (**593**), followed by sodium borohydride reduction, gave 18-*abeo*-(17→16)-yohimbane derivative **596** as the major product besides small quantities of ajmalicine (**597**) and 19-epiajmalicine (**598**) (*287*).





347 **599** **600**



601

Witkop and Goodwyn reported (*288*) that ozonolysis of yohimbine (**74**) and its derivatives led to the corresponding quinolone derivatives. This reaction has been thoroughly investigated by Winterfeldt (*289*). For example, autooxidation of lactam **347** resulted in quinolone **599,** which upon treatment with phosphoryl chloride, followed by catalytic reduction, gave pyrrolo[3,4-*b*]quioline derivative **600** (*290*). This transformation was also used as a key step in the biomimetic synthesis of camptothecin (**601**), performed by Winterfeldt *et al.* (*291, 292*).

A series of publications by Albright *et al.* report the investigation of methods for the oxidation of hydroxy groups in yohimbine-type alkaloids and the functionalization of yohimbone (**305**) at the C-18 position (*293–297*).

The microbiological transformation of several yohimbines and derivatives resulted almost exclusively in aromatic-ring hydroxylated compounds (*298, 299*).

V. Spectroscopy

A. Circular Dichroism and Optical Rotatory Dispersion Spectra

It has been shown that CD measurement is a proper tool to determine the absolute configuration of the C-3 stereo center in corynantheine and yohimbine alkaloids (*300*). The chiroptical properties of stereoisomeric yohimbanes and 17-ketoyohimbanes also have been studied. Cotton effects due to aromatic and ketone absorptions have been considered in terms of the appropriate sector and

octant rules, respectively (*301*). The configuration of N-4 in quarternary metho salts of yohimbine (**74**) and β-yohimbine (**75**) has also been determined by CD measurement (*302*).

B. Infrared Spectroscopy

A review has appeared regarding the infrared and nuclear magnetic resonance spectroscopic investigations of quinolizidine alkaloids (*303*). The connection between the C/D ring junction and the existence of Bohlmann bands in the IR spectra of indolo[2,3-*a*]quinolizidines has been reinvestigated and interpreted (*304*).

C. Nuclear Magnetic Resonance Spectroscopy

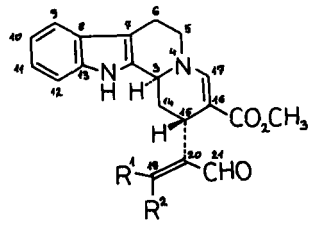
In addition to the *Annual Reports on NMR Spectroscopy* monograph reviewing ^{1}H-NMR and ^{13}C-NMR spectroscopy of alkaloids in three volumes (*305*), several books and reviews appeared concerning the ^{13}C-NMR spectroscopy of naturally occurring substances (*306–308*). Therefore we would like to present only a limited number of examples of the exceptional applicability of these physical methods for structure elucidation and conformational analysis of complex molecules.

The configuration at C-16 of sitsirikine (**40**) and 16-episitsirikine (**42**) could not be established directly on the basis of their ^{1}H-NMR spectra, since the

TABLE III

^{1}H-NMR (90 MHz) Data for Vallesiachotamine (**9**) and Isovallesiachotamine (**10**) (*17*)

Proton	Chemical shift (δ) and coupling constant (Hz)	
	Vallesiachotamine (**9**)	Isovallesiachotamine (**10**)
1-H	7.95 brs	8.25 brs
3-H	4.49 dd, $J_1 = 12$, $J_2 = 4$	4.28 dd, $J_1 = 12$, $J_2 = 2$
5-H	2.88 m	2.85 m
6-H	3.72 m	3.65 m
9–11-H	7.10–7.40 m	7.10–7.40 m
12-H	7.50 dd, $J_1 = 8$, $J_2 = 2$	7.48 dd, $J_1 = 8$, $J_2 = 2$
14-H	2.10 m	1.86 m (2.10)
15-H	4.00 dd, $J_1 = 5$, $J_2 = 1$	4.04 dd, $J_1 = 5$, $J_2 = 1$
17-H	7.68 s	7.78 s
18-H	2.08 d, $J = 7$	2.18 d, $J = 7$
19-H	6.68 q, $J = 7$	6.56 q, $J = 7$
21-H	9.38 s	10.30 s
16-CO_2CH_3	3.64 s	3.66 s



9 $R^1=CH_3$; $R^2=H$

10 $R^1=H$; $R^2=CH_3$

chemical shifts and coupling constants of C-17 methylene protons do not show significant difference. This problem, however, could be solved easily by ^{1}H-NMR (300 MHz) analysis of cyclositsirikine (**41**) and 16-epicyclositsirikine

TABLE IV

^{1}H-NMR DATA FOR GEISSOSCHIZINE (**30**) (270 Hz) (*309*) AND GEISSOSCHIZOL (**34**) (400 Hz) (*310*)

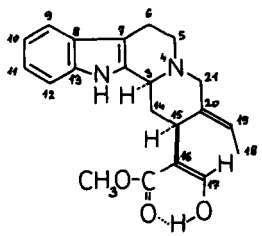
	Geissoschizine (**30**)		Geissoschizol (**34**)	
Proton	Chemical shift (δ)	Coupling constant (Hz)	Chemical shift (δ)	Coupling constant (Hz)
1-H	7.80 sbr	$J_{3\alpha,14\beta}$ = 11.5	8.21 sbr	$J_{5\alpha,5\beta}$ = 12
3α-H	4.51 dd		4.24 br	
5α-H	—	$J_{3\alpha,14\alpha}$ = 2	3.08[a] ddd	$J_{5\alpha,6\alpha}$ = 4
5β-H	2.70–3.33		3.27[a] m	
6α-H	—	$J_{14\alpha,14\beta}$ = 13	2.68 dbr	$J_{5\alpha,6\beta}$ = 12
6β-H	—		3.05 m	
9-H	7.50	$J_{14\beta,15\alpha}$ = 6.5	7.52	$J_{5\beta,6\alpha}$ = 1
10-H	7.13		7.14	
11-H	7.18	$J_{14\alpha,15\alpha}$ = 11.5	7.18	$J_{5\beta,6\beta}$ = 5
12-H	7.33		7.38	
14α-H	2.12 ddd	$J_{18,19}$ = 7	2.33[b] m	$J_{6\alpha,6\beta}$ = 15
14β-H	2.64 ddd		2.21[b] m	
15α-H	3.85 ddbr	$J_{15\alpha,21\alpha}$ = 1	3.00 m	$J_{16,17}$ = 7
16-H	—		1.55 m	
		$J_{18,21\beta}$ = 2	1.55 m	$J_{16,17'}$ = 5
17-H	7.85 s		3.60 ddbr	
		$J_{19,21\beta}$ = 2	3.56 ddbr	$J_{18,19\alpha}$ = 6.5
18-H	1.83 dd		1.63 d(d)	
19-H	5.42 qbr	$J_{21\alpha,21\beta}$ = 12.5	5.56 qbr	$J_{19,21\beta}$ < 0.5
21α-H	3.20 dbr		3.68 dbr	
21β-H	3.97 dt		3.01 dbr	$J_{21\alpha,21\beta}$ = 12
OCH_3	3.70 s		—	

[a,b] Values with identical superscripts are interchangeable.

TABLE V

^{1}H-NMR (300 MHz) SPECTRA OF CYCLOSITSIRIKINE (**41**) AND 16-EPICYCLOSITSIRIKINE (**43**) (*45*)

	Cyclositsirikine (**41**)		16-Epicyclositsirikine (**43**)	
Proton	Chemical shift (δ)	Coupling constant (Hz)	Chemical shift (δ)	Coupling constant (Hz)
3α-H	3.33 dd	$J_{3\alpha,14\beta}$ = 10	3.39 dd	$J_{3\alpha,14\beta}$ = 10
5α-H	2.62 td	$J_{3\alpha,14\alpha}$ = 3	2.69 td	$J_{3\alpha,14\alpha}$ = 3
5β-H	3.05 m	$J_{5\alpha,6\beta}$ = 12	3.16 m	$J_{5\alpha,6\beta}$ = 11
6α-H	2.70 m	$J_{5\alpha,5\beta}$ = 12	2.77 m	$J_{5\alpha,5\beta}$ = 12
6β-H	3.00 m	$J_{5\alpha,6\alpha}$ = 3.5	3.00 m	$J_{5\alpha,6\alpha}$ = 4.5
9–12-H	7.0–7.5	$J_{5\beta,5\alpha}$ = 12	7.0–7.5	$J_{5\beta,5\alpha}$ = 12
14α-H	2.1 m	$J_{5\beta,6\beta}$ = 5	2.1 m	$J_{5\beta,6\beta}$ = 5
14β-H	1.34 q	$J_{5\beta,6\alpha}$ = ~2	1.38 q	$J_{5\beta,6\alpha}$ = ~2
15α-H	1.82 qd	$J_{6\alpha,6\beta}$ = 14	1.78 m	$J_{6\alpha,6\beta}$ = 15
16-H	2.53 td	$J_{14\alpha,14\beta}$ = 14	2.59 m	$J_{14\alpha,14\beta}$ = 14
17α-H	3.54 t	$J_{14\alpha,15\alpha}$ = 3	3.77 dd	$J_{14\alpha,15\alpha}$ = 3
17β-H	4.12 dd	$J_{14\beta,15\alpha}$ = 11	4.36 dd	$J_{14\beta,15\alpha}$ = 11
18-Me	1.20 d	$J_{15\alpha,20\beta}$ = 11	1.30 d	$J_{15\alpha,20\beta}$ = 11
19α-H	3.25 m	$J_{15\alpha,16\beta}$ = 11	3.22 m	$J_{15\alpha,16\alpha}$ = 4.5
20β-H	1.5 m	$J_{16\beta,17\alpha}$ = 11	1.63 m	$J_{16\alpha,17\alpha}$ = 3
21α-H	2.1 t	$J_{16\beta,17\beta}$ = 4.5	2.1 t	$J_{16\alpha,17\beta}$ = ~1
21β-H	3.0 dd	$J_{17\alpha,17\beta}$ = 11	3.1 dd	$J_{17\alpha,17\beta}$ = 12
CO_2CO_3	3.72 s	$J_{18,19\alpha}$ = 7	3.71 s	$J_{18,19\alpha}$ = 7
		$J_{19\alpha,20\beta}$ = 10		$J_{19\alpha,20\beta}$ = 10
		$J_{20\beta,21\alpha}$ = 11		$J_{20\beta,21\alpha}$ = 11
		$J_{20\beta,21\beta}$ = 3.5		$J_{20\beta,21\beta}$ = 4.5
		$J_{21\alpha,21\beta}$ = 11		$J_{21\alpha,21\beta}$ = 11



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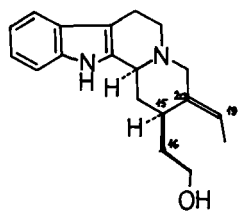
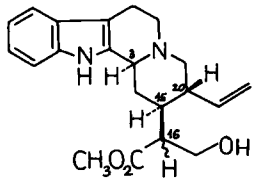


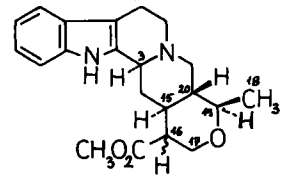
34

(**43**), obtained via oxymercuration and subsequent sodium borohydride reduction of **40** and **42**, on the basis of the characteristic coupling constants (*45*). (See Table V).

The sodium borohydride reduction of the preequilibrated mixture obtained from 4,21-dehydrogeissoschizine chloride (**32**) resulted in four isositsirikine isomers (**46, 47, 48, 602**) besides tetrahydroalstonine and 19-epiajmalicine. A

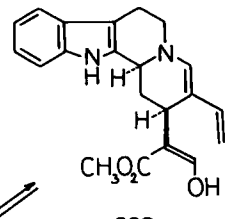


1, $Hg(OAc)_2$
2, $NaBH_4$



40 16β-H (R)
42 16α-H (S)

41 16β-H (R)
43 16α-H (S)



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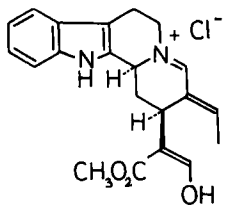

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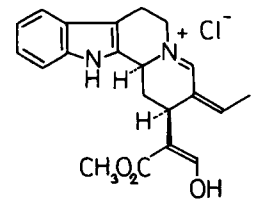
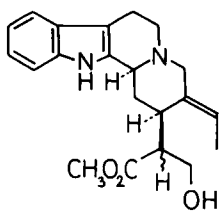


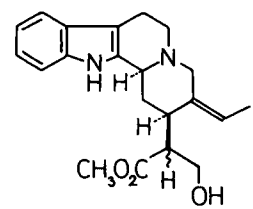
604

$NaBH_4$

$NaBH_4$



46 16R
47 16S



602 16R
48 16S

thorough ^{1}H-NMR spectroscopic investigation of (*E*)-isositsirikine (**46**), 16-epi-(*E*)-isositsirikine (**47**), (*Z*)-isositsirikine (**602**), and 16-epi-(*Z*)-isositsirikine (**48**) was carried out by Kan *et al.* (*311*). (See Table VI).

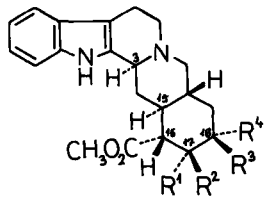
The ^{1}H-NMR spectra of yohimbines have been investigated in a series of

TABLE VI

^{1}H-NMR (400 MHz) DATA OF ISOSITSIRIKINES (**311**)

Proton	(*E*)-Isositsirikine (**46**)		16-Epi-(*E*)-isositsirikine (**47**)	
	Chemical shift (δ)	Coupling constant (Hz)	Chemical shift (δ)	Coupling constant (Hz)
3α-H	4.31 br s	$J_{5\alpha,5\beta}$ = 12	3.90 br s	$J_{5\alpha,5\beta}$ = 12
5α-H	3.15 ddd	$J_{5\alpha,6\alpha}$ = 4	2.84 ddd	$J_{5\alpha,6\alpha}$ = 4
5β-H	3.27 dd	$J_{5\alpha,6\beta}$ = 12	3.17 dd	$J_{5\alpha,6\beta}$ = 12
6α-H	2.65 br d	$J_{5\beta,6\alpha}$ = 1	2.68 br d	$J_{5\beta,6\alpha}$ = 1
6β-H	3.0 m	$J_{5\beta,6\beta}$ = 5.5	3.0 m	$J_{5\beta,6\beta}$ = 5.5
9–12-H	7.1–7.48	$J_{6\alpha,6\beta}$ = 15	7.09–7.48	$J_{6\alpha,6\beta}$ = 15
14α-H	2.26[a] m	$J_{16,17}$ = 7	2.27[b] m	$J_{16,17}$ = 5
14β-H	2.22[a]	$J_{16,17'}$ = 5	2.25[b] m	$J_{16,17'}$ = 5
15α-H	3.10 m	$J_{17,17'}$ = 12	3.38 m	$J_{17,17'}$ = 12
16-H	2.52 m	$J_{18,19}$ = 6.5	2.66 m	$J_{18,19}$ = 6.5
17-H	3.55 br dd	$J_{19,21\alpha}$ < 0.5	3.92 br dd	$J_{19,21\alpha}$ < 0.5
17′-H	3.50 br dd	$J_{19,21\beta}$ < 0.5	3.87 br dd	$J_{19,21\beta}$ < 0.5
18-H	1.67 d	$J_{21\alpha21\beta}$ = 12	1.63 d	$J_{21\alpha,21\beta}$ = 12
19-H	5.64 br q		5.52 br q	
21α-H	3.54 br d		3.08 br d	
21β-H	2.93 br d		3.80 br d	
CO_2CH_3	3.67 s		3.57 s	
NH	8.67 br s		8.23 br s	
	(*Z*)-Isositsirikine (**602**)		16-Epi-(*Z*)-isositsirikine (**48**)	
	Chemical shift (δ)	Coupling constant (Hz)	Chemical shift (δ)	Coupling constant (Hz)
3α-H	3.64 br d	$J_{3\alpha,14\alpha}$ = 4	3.44 br d	$J_{3\alpha,14\alpha}$ = 4
5α-H	2.74 m	$J_{3\alpha,14\beta}$ = 12	2.63 ddd	$J_{3\alpha,14\beta}$ = 12
5β-H	3.19 dd	$J_{5\alpha,5\beta}$ = 12	3.11 dd	$J_{5\alpha,5\beta}$ = 12
6α-H	2.76 br d	$J_{5\alpha,6\beta}$ = 12	2.73 br d	$J_{5\alpha,6\beta}$ = 12
6β-H	3.0 m	$J_{5\beta,6\alpha}$ = 1	3.0 m	$J_{5\beta,6\alpha}$ = 1
9–12-H	7.1–7.48	$J_{5\beta,6\beta}$ = 5.5	7.06–7.45	$J_{5\beta,6\beta}$ = 5.5
14α-H	2.17 ddd	$J_{6\alpha,6\beta}$ = 15	2.26 ddd	$J_{6\alpha,6\beta}$ = 15
14β-H	1.72 ddd	$J_{14\alpha,14\beta}$ = 12	1.42 ddd	$J_{14\alpha,14\beta}$ = 12
15α-H	2.66 m	$J_{14\alpha,15\alpha}$ = 4	2.82 m	$J_{14\alpha,15\alpha}$ = 4
16-H	3.01 m	$J_{14\beta,15\alpha}$ = 12	2.94 m	$J_{14\beta,15\alpha}$ = 12
17-H	3.94 br dd	$J_{16,17}$ = 7	3.95 br dd	$J_{16,17}$ = 7
17′-H	3.85 br dd	$J_{16,17'}$ = 5	3.88 br dd	$J_{16,17'}$ = 5
18-H	1.74 d	$J_{17,17'}$ = 12	1.67 d	$J_{17,17'}$ = 12
19-H	5.48 br q	$J_{18,19}$ = 6.5	5.36 br q	$J_{18,19}$ = 6.5
21α-H	2.91 br d	$J_{19,21\alpha}$ < 0.5	2.76 br d	$J_{19,21\alpha}$ < 0.5
21β-H	3.82 br d	$J_{19,21\beta}$ < 0.5	3.85 br d	$J_{19,21\beta}$ < 0.5
CO_2CH_3	3.76 s	$J_{21\alpha,21\beta}$ = 12	3.72 s	$J_{21\alpha,21\beta}$ = 12
NH	7.91 br s		8.21 br s	

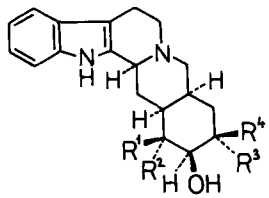
[a,b] Data with identical superscripts are interchangeable.



500 $R^1=R^4=OH$; $R^2=R^3=H$

502 $R^1=R^3=OH$; $R^2=R^4=H$

503 $R^2=R^3=OH$; $R^1=R^4=H$



486 $R^1=CO_2CH_3$; $R^4=OH$; $R^2=R^3=H$

487 $R^2=CO_2CH_3$; $R^4=OH$; $R^1=R^3=H$

488 $R^1=CO_2CH_3$; $R^3=OH$; $R^2=R^4=H$

publications (*72–75, 81b, 293, 301*). Recently, the ^{1}H-NMR data of normal and allo 18-hydroxyyohimbine stereoisomers (**500, 502, 503** and **486, 487, 488,** respectively) were reported (*254, 255*). (See Table VII).

Invention of Fourier transform instruments and consequent development of ^{13}C-NMR techniques have supplied the chemist with excellent tools in characterizing complex molecules and making fine stereochemical distinctions. During the last two decades following the fundamental work of Wenkert (*130, 228, 308*), substantial amounts of ^{13}C-NMR data of corynantheine and yohimbine alkaloids have been published. Some numerical values of interest are cited in Tables VIII, IX, X, and XI.

In comparison with other spectroscopic methods, ^{13}C-NMR spectroscopy affords the most valuable information for the stereochemical and conformational analysis of quinolizidine compounds. On the basis of the results, summarized in a review by Tourwé and van Binst (*313*) as well as in a series of publications (*314–318*), the steric structure elucidation of indolo[2,3-*a*]quinolizidine alkaloids has been facilitated.

TABLE VII

CHARACTERISTIC ^{1}H–NMR (100 MHz) DATA OF NORMAL AND ALLO 18–HYDROXYYOHIMBINES (*254,255*)

Compound	Chemical shift (δ), coupling constant (Hz), and relative steric position	
	17-H	18-H
500	4.18 t (eq) $J_{16\beta,17\beta} = J_{17\beta,18\beta} = 2$	3.65 m (ax) $J_{17\beta,18\beta} + J_{18\beta,19\alpha} + J_{18\beta,19\beta} = 16$
502	4.02 t (eq) $J_{16\beta,17\beta} = J_{17\beta,18\alpha} = 3$	3.98 q (eq) $J_{17\beta,18\alpha} = J_{18\alpha,19\alpha} = J_{18\alpha,19\beta} = 3$
503	3.76 dd (ax) $J_{16\beta,17\alpha} = 10.5$, $J_{17\alpha,18\alpha} = 2.5$	4.04 q (eq) $J_{17\alpha,18\alpha} = J_{18\alpha,19\alpha} = J_{18\alpha,19\beta} = 3$
486	4.30 t (eq) $J_{16\alpha,17\alpha} = J_{17\alpha,18\alpha} = 3$	3.56 m (ax) $J_{17\alpha,18\alpha} + J_{18\alpha,19\alpha} = 3+4$, $J_{18\alpha,19\beta} = 13$
487	4.32 t (eq) $J_{16\beta,17\alpha} = J_{17\alpha,18\alpha} = 3$	3.70 m (ax) $J_{17\alpha,18\alpha} + J_{18\alpha,19\alpha} = 3+4$, $J_{18\alpha,19\beta} = 11$
488	4.10 t (eq) $J_{16\alpha,17\alpha} = J_{17\alpha,18\beta} = 3$	3.90 q (eq) $J_{17\alpha,18\beta} = J_{18\beta,19\alpha} = J_{18\beta,19\beta} = 3$

TABLE VIII

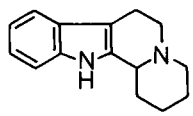
^{13}C-NMR Data for Octahydroindoloquinolizine (**1**) (*130,312*) and Deplancheine (**7**) (*14*)

Carbon	Octahydroindoloquinolizine (**1**)	Deplancheine (**7**)
2	135.2	134.0*
3	60.3	60.2
5	55.8	52.9
6	21.6	21.6
7	108.1	108.3
8	127.6	127.4
9	118.1	118.2
10	119.3	119.3
11	121.2	121.3
12	110.8	110.7
13	136.1	136.1
14	30.0	30.2
15	24.3	25.9
18	—	12.7
19	—	119.3
20	25.7	134.7*
21	53.5	63.5

TABLE IX

^{13}C-NMR Data for Geissoschizine (**30**) (*36*)

Carbon	Geissoschizine (**30**)
2	132.8
3	53.6
5	50.5
6	20.4
7	108.1
8	126.4
9	118.2
10	119.6
11	121.9
12	110.9
13	136.5
14	33.8
15	27.7
16	107.5
17	161.5
18	13.1
19	121.9
20	133.1
21	59.1
C=O	170.5
OCH_3	51.2



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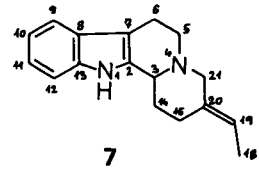

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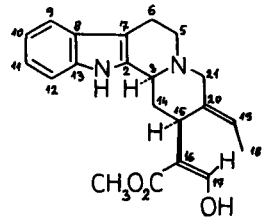

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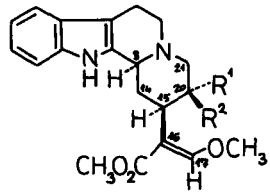
TABLE X
^{13}C-NMR SPECTRA OF CORYNANTHEINE (**52**) DIHYDROCORYNANTHEINE (**54**), AND CORYNANTHEIDINE (**61**) (*308*)

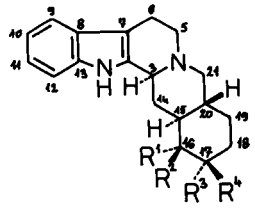
Carbon	**52**	**54**	**61**
2	135.2	135.2	136.0
3	59.9	60.2	61.2
5	52.6	53.1	53.4
6	21.8	21.9	21.9
7	107.5	107.5	107.9
8	127.4	127.4	127.7
9	117.9	117.9	117.9
10	120.9	120.9	121.0
11	119.0	119.0	119.2
12	110.8	110.8	110.9
13	136.2	136.2	136.2
14	33.1	33.8	29.8
15	38.8	38.7	40.8
16	111.7	111.7	111.8
17	159.8	159.8	160.7
18	115.4	11.3	12.8
19	139.2	24.4	19.1
20	42.4	39.3	40.0
21	61.3	61.3	57.9
C=O	168.9	168.9	169.5
OCH_3	51.1	51.1	51.2
$=CH-O\underline{C}H_3$	61.3	61.3	61.2



52 R^1=-CH=CH_2; R^2=H

54 R^1=-CH_2CH_3; R^2=H

61 R^1=H; R^2=-CH_2CH_3

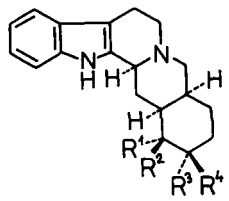


74 R^1=CO_2CH_3; R^3=OH; R^2=R^4=H

75 R^1=CO_2CH_3; R^4=OH; R^2=R^3=H

76 R^2=CO_2CH_3; R^3=OH; R^1=R^4=H

605 R^2=CO_2CH_3; R^4=OH; R^1=R^3=H

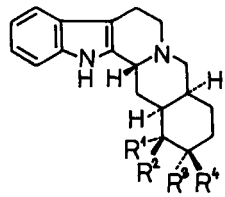


90 R^2=CO_2CH_3; R^3=OH; R^1=R^4=H

92 R^2=CO_2CH_3; R^4=OH; R^1=R^3=H

93 R^1=CO_2CH_3; R^3=OH; R^2=R^4=H

100 R^1=CO_2CH_3; R^4=OH; R^2=R^3=H



105 R^2=CO_2CH_3; R^3=OH; R^1=R^4=H

449 R^2=CO_2CH_3; R^4=OH; R^1=R^3=H

446 R^1=CO_2CH_3; R^4=OH; R^2=R^3=H

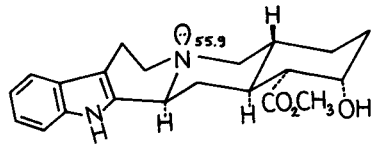
445 R^1=CO_2CH_3; R^3=OH; R^2=R^4=H

Finally, it is worth mentioning that ^{15}N-NMR spectra of yohimbine (**74**), reserpine (**109**), and isoreserpine (**514**) also have been investigated (*319*). The ^{15}N chemical-shift differences between C/D-cis- and trans-fused compounds could be explained by a hyperconjugative interaction between the antiperiplanar C—H bonds and the nitrogen lone pair characteristic for trans-fused compounds only.

TABLE XI

^{13}C-NMR DATA FOR YOHIMBINE STEREOISOMERS (*81b,130*)

Carbon	74	75	76	605	90	92	93	100	105	449	446	445
2	134.3	134.0	135.8	134.7	134.3	135.2	134.4	134.4	131.7	133.4	135.1	134.5
3	59.8	59.0	60.5	59.9	60.1	61.6	60.1	56.9	53.7	54.4	54.4	54.3
5	52.1	52.3	52.6	52.8	53.2	53.5	52.8	52.7	50.8	51.4	53.3	53.3
6	21.5	21.3	21.6	21.7	21.7	21.9	21.3	19.6	16.5	17.0	21.7	21.6
7	107.5	107.4	106.3	107.8	108.1	108.3	107.1	107.9	107.3	107.2	107.1	108.6
8	127.0	126.9	127.0	127.3	127.1	127.6	126.8	127.8	127.2	127.7	127.1	127.6
9	117.7	117.7	117.5	118.2	117.9	118.1	117.5	118.0	117.6	117.7	117.6	118.1
10	118.8	118.8	118.4	119.3	119.1	119.3	118.6	119.5	118.9	118.8	118.6	119.5
11	120.8	120.9	120.4	121.3	121.1	121.2	120.5	121.4	121.0	120.8	120.6	121.4
12	110.6	110.7	111.1	111.0	110.6	110.8	110.6	111.2	110.8	111.1	111.0	110.8
13	135.8	135.8	136.1	136.2	135.7	136.1	135.8	136.3	135.6	135.9	136.3	136.1
14	33.8	33.8	33.6	33.9	27.6	29.4	31.0	30.2	23.6	25.9	32.5	32.7
15	36.4	41.6	34.7	41.6	37.9	37.6	37.4	35.3	32.5	31.4	36.2	30.0
16	52.6	57.1	51.1	51.7	54.6	49.8	50.6	51.8	54.1	49.4	50.6	45.2
17	66.9	71.6	65.9	71.0	66.0	65.8	66.7	69.4	65.7	65.9	72.1	67.1
18	31.4	33.5	28.2	29.5	33.2	31.9	30.2	31.1	33.5	31.9	30.3	27.3
19	23.1	27.5	23.5	28.3	24.5	20.6	24.8	23.7	23.9	20.1	27.2	22.5
20	40.2	39.1	36.5	33.9	36.4	36.9	32.0	33.5	35.6	36.7	33.6	33.9
21	61.0	60.5	62.0	61.8	60.4	60.8	59.6	54.1	49.4	50.9	55.0	54.7
OMe	51.7	51.6	51.1	51.4	51.8	51.9	51.5	52.0	51.7	51.8	51.6	52.0
C=O	175.1	175.0	172.7	173.0	174.4	175.6	174.0	174.8	174.7	175.2	175.2	176.0



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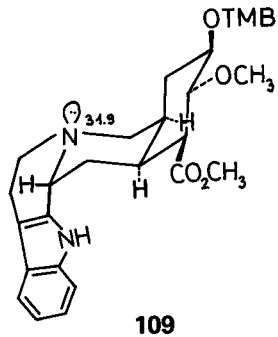

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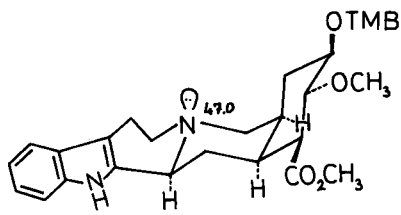
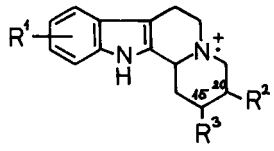


514

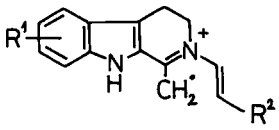
D. Mass Spectroscopy

Results and data gathered on mass spectroscopy of various indole alkaloids have been summarized by Hesse (*320*). The derivation of the characteristic fragments of indolo[2,3-*a*]quinolizidines has been interpreted by Gribble and Nelson (*321*), who investigated C-3, C-5, C-6, C-20, and C-21 deuterated derivatives of octahydroindolo[2,3-*a*]quinolizine (**1**). Kametani *et al.* have observed and proved, with labeled compounds, a methyl transfer from the ester function of reserpine derivatives to the basic nitrogen atom during mass-spectroscopic measurement (*322*).

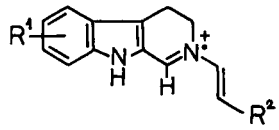
Correlation between stereo arrangement and mass fragmentation of corynantheidine alkaloids has been observed by Beckett and co-workers (*323*). Their findings, interconnecting the relative abundances of X and Y type fragments with the stereochemistry of corynantheidine and 9-methoxycoryantheidine stereoisomers, proved relevant only for compounds containing an α,β carbon–carbon double bond in the side chain attached to C-15. Szántay and collaborators extended this observation (*324, 325*), having found another characteristic fragment (Z) to compare with X, which arises in the mass spectrum of every 15,20-disubstituted indolo[2,3-*a*]quinolizidine derivative. Thus the correlation that the I_X/I_Z ratio is always about twice as high in the case of normal and pseudo stereoisomers as that in allo and epiallo compounds can be applied for all 15,20-disubstituted indoloquinolizines investigated.



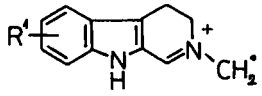
M



Y



X



Z

After further systematic investigation, the correlation has been modified again by comparing the abundances of Z and M fragments as a function of the stereoarrangement of the isomers. In this comparison, however, 15,20-cis-disubstituted allo and epiallo stereoisomers supply higher I_Z/I_M ratios than do the corresponding trans compounds (normal, pseudo). By this modification, the correlation can be applied not only to corynantheines but to yohimbines as well (*326*). (See Tables XII and XIII).

TABLE XII

I_X/I_Y, I_X/I_Z, AND I_Z/I_M FRAGMENT RATIOS OF CORYNANTHEIDINE ALKALOIDS (*325,326*)

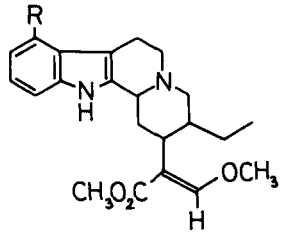
Compound	Stereo arrangement	R	I_X/I_Y[a]	I_X/I_Z	I_Z/I_M
Dihydrocorynantheine (**54**)	Normal	H	2.3	0.37	1.1
Hirsutine (**58**)	Pseudo	H	2.8	0.37	1.2
Corynantheidine (**61**)	Allo	H	0.62	0.13	2.2
3-Isocorynantheidine (**65**)	Epiallo	H	0.26	0.11	1.8
Speciogynine (**55**)	Normal	OCH_3	2.0	0.30	0.73
Mitraciliatine (**60**)	Pseudo	OCH_3	3.0	0.29	0.84
Mitragynine (**62**)	Allo	OCH_3	0.45	0.10	1.20
Speciociliatine (**63**)	Epiallo	OCH_3	0.25	0.09	2.00
Dihydrocorynantheol (**21**)	Normal	H	—	2.22	0.11
Hirsutinol (**238**)	Pseudo	H	—	2.10	0.12
Corynantheidol (**255**)	Allo	H	—	1.12	0.20
3-Isocorynantheidol (**262**)	Epiallo	H	—	1.13	0.18
10-OCH_3-Dihydrocorynantheol (**606**)	Normal	OCH_3	—	2.34	0.05
10-OCH_3-Hirsutinol (**607**)	Pseudo	OCH_3	—	2.25	0.04
10-OCH_3-Corynantheidol (**608**)	Allo	OCH_3	—	0.85	0.12
10-OCH_3-3-Isocorynantheidol (**609**)	Epiallo	OCH_3	—	1.12	0.09

[a] Y fragment could not be found in mass spectra of corynantheidols.

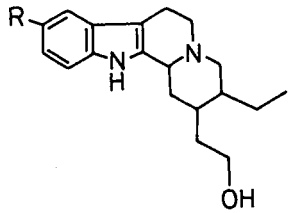
TABLE XIII

I_X/I_Z AS WELL AS I_Z/I_M FRAGMENTS;
RATIOS OF 15,20-DISUBSTITUTED SYNTHETIC INTERMEDIATES (*326*)

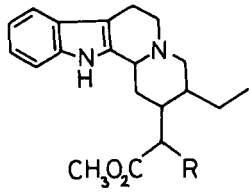
Compound	Stereo arrangement	R	I_X/I_Z	I_Z/I_M
Nitrile ester **319**	Normal	CN	1.70	0.09
Nitrile ester **610**	Pseudo	CN	1.80	0.09
Nitrile ester **315**	Allo	CN	0.78	0.15
Ester **300**	Normal	H	2.50	0.10
Ester **270**	Allo	H	0.70	0.21
Ester **611**	Epiallo	H	0.60	0.29
Diester **404**	Normal	H	2.50	0.11
Diester **440**	Allo	H	1.00	0.25
Diester **406**	Epiallo	H	0.93	0.28
Diester **493**	Normal	OCH_3	1.25	0.15
Diester **476**	Allo	OCH_3	0.62	0.53



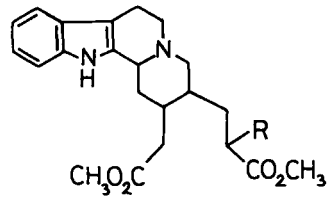
R=H **54, 58, 61, 65**
R=OCH_3 **55, 60, 62, 63**



R=H **21, 238, 255, 262**
R=OCH_3 **606-609**



R=CN **319, 610, 315**
R=H **300, 270, 611**



R=H **404, 440, 406**
R=OCH_3 **493, 476**

VI. Pharmacology

Among naturally occurring compounds the indole alkaloids play important roles as biologically active substances. There are two interesting groups of monoterpene indole alkaloids, namely, the yohimbines and reserpines, which already have found medicinal application in human therapy. Consequently, comprehensive screening and thorough investigation of them has been published during the past two decades. The great number of articles points far beyond our main objective of informing alkaloid chemists of the biological activities of corynantheidines and yohimbines. We therefore restricted ourselves to a short account of the more significant pharmacological effects of the title alkaloids themselves and to those of some important derivatives of the yohimbine and reserpine groups only. The discussion of this section follows the order of the earlier parts dealing with structure elucidation and synthesis of the alkaloids in question.

Octahydroindoloquinolizidine. Racemic octahydroindoloquinolizidine (**1**) improves muscle-tone-caused hypothermia and inhibits spontaneous motor activity (*327*). It has been shown that **1** and its 11-methoxy derivative are useful as antiphlogistics (*328*).

Flavopereirine. Flavopereirine (**3**) shows selective inhibition activity in the *in vitro* synthesis of cancer DNA (*329*).

Dihydrocorynantheol. Dihydrocorynantheol (**21**) exhibits antimicrobal activity against gram-positive bacteria (*330*).

16-Epi-(Z)-isositsirikine. 16-Epi-(*Z*)-isositsirikine (**48**) displays *in vivo* antineoplastic activity in the KP as well as P 388 test systems (*51*).

Hirsutine. Hirsutine (**58**) shows ganglion-blocking activity in cat superior cervical ganglion preparation (*331*), and it has a long-lasting depressive effect (*332*). Hirsutine also inhibits the ganglionic transmission of the dog urinary bladder (*333, 334*).

Mitragynine. Mitragynine (**62**) ethanedisulfonate exhibits analgesic and antitussive properties in animals (*335*). It has only weak respiratory depressant activity.

Yohimbine Stereoisomers and Derivatives. Yohimbine (**74**) has been proved to be a sympathicolytic agent, which was formerly used as an aphrodisiac with questionable results. It was Starke who discovered yohimbine as the first example of a preferentially presynaptic α-adrenolytic agent (*336, 337*). Later it was demonstrated thoroughly that yohimbine and especially α-yohimbine (**90**) are highly selective antagonists of the α_2-adrenoceptor, while corynanthine (**76**) displays the highest selectivity for the α_1-adrenoceptor (*338, 339*). Therefore, yohimbine and its naturally occurring diastereomers could be used as valuable tools for the subclassification of α-adrenoceptors, including the differentiation between the high and low affinity sites (*340, 341*). Because of their blockade on the inhibitory presynaptic α_2-adrenoceptors at sympathetic nerve endings, yohimbine and α-yohimbine have antidepressant activities utilized in different psychopharmacological drug compositions (*342*).

The anticonvulsant effect, as well as the hypertensive activity of yohimbine have also been studied (*343, 344*). It has been shown that yohimbine produces significant increases in subjective anxiety, autonomic symptoms, and blood pressure (*345*).

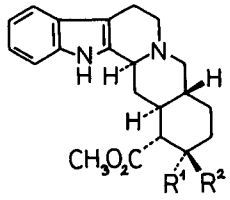
The pharmacological and biochemical properties of yohimbine stereoisomers have been reviewed (*338, 346*).

Among methoxy-substituted yohimbine alkaloids, only 11-methoxy-α-yohimbine (**95**) and 11-methoxy-3-epi-α-yohimbine (**106**) were tested for α-adrenergic activity, and they showed only weak α_2-adrenoceptor blocking effect (*347*). On the other hand, venenatine (**107**) has reserpinelike activity and shows synergism with reserpine (**109**). Furthermore, alstovenine (**96**) displays monoamine oxidase inhibitor activity (*348*).

Several semisynthetic derivatives of yohimbine alkaloids show interesting pharmacological activity. For example, 17-methylthiomethoxyyohimbane stereoisomers (**612** and **613**) are valuable central nervous system depressants (*349*) and several hydrazides of yohimbinecarboxylic acid (**614** and **615**-type compounds) are useful cardiac stimulants, respiratory analeptics, and antihypertensives (*350–353*).

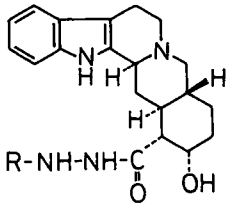
Different N_a-substituted normal as well as pseudo yohimbane derivatives have antiflammatory and analgesic activity (*354, 355*).

Compounds containing condensed yohimbane and pyrazole/or pyrimidine ring systems (**616, 617**) are potent central nervous system depressants (*294, 297*).

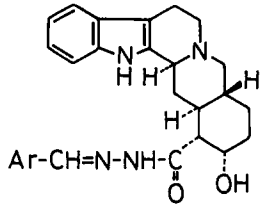


612 R^1=OCH_2SCH_3; R^2=H

613 R^1=H; R^2=OCH_2SCH_3



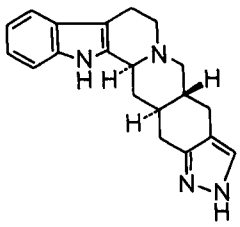
614



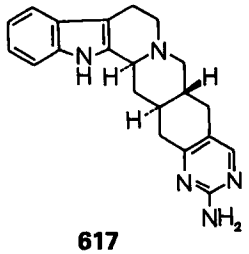
615

17-Alkoxyhexadehydroyohimbanes (**618**) and 17-alkoxydecadehydroyohimbanes (**619**) have analgesic and hypotensive activities (*356, 357*). On the other hand, 16,17,18-trialkoxyhexadehydroyohimbanes (**620**) are useful as hypotensive and vasodilating agents (*358*).

Reserpine and Related Alkaloids. *Rauwolfia* alkaloid reserpine (**109**) and a few semisynthetic derivatives or analogs are widely used drugs for treatment of high blood pressure or psychiatric disorders (*359, 360*). It was Bein (*361*) who first demonstrated the hypotensive action of the crude reserpine. The world-wide



616



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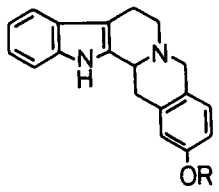

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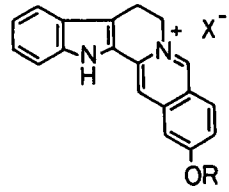

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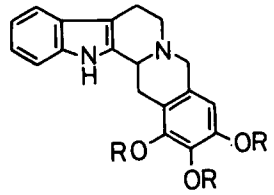

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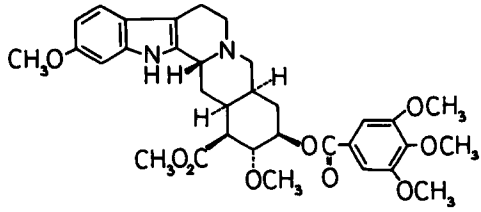


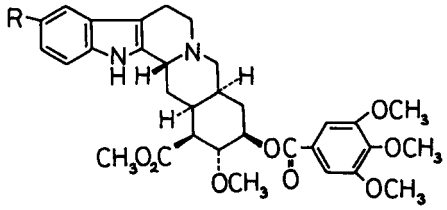
109 Reserpine

intensive investigation of the pharmacology of reserpine have been reviewed several times (*362–366*).

It is generally agreed that the hypotensive activity of reserpine is attributed to the diminution in sympathetic arteriolar vasoconstrictor tone. Reserpine has been proved to inhibit the vasoconstrictor amines selectively, and therefore even its single dose results in a slowly developing fall in arterial pressure accompanied by bradycardia. Some brain functions are inhibitied by reserpine as well, the respiratory center is, however, stimulated. The sedative or tranquilizing activity of reserpine is in connection with the depletion of serotonin in the stores of brain tissues. The mechanism of action acceptedly involves at least two factors: (1) a short central stimulation by liberation of serotonine and noradrenaline and (2) a long-lasting central depressing effect, which is mainly due to a reserpine-inhibited catecholamine uptake (*363, 365*). Reserpine also inhibits, in some cases, the experimentally induced thrombus formation.

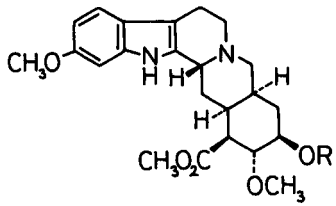
Because of the side effects (psychic depression, gastrointestinal disorders) of reserpine, extended research work has been carried out to find a proper analog or

derivative possessing more specific antihypertensive action. The chemical modification of reserpine, encompassing exchange of ester groups at C-16 and C-18, substitution of the indole nitrogen, substitution of aromatic ring A or hetero ring C, functionalization of the tertiary nitrogen atom, and other subtle—mainly stereochemical—manipulations, facilitated studying the structure–activity relationship. A great number of these alterations and results have been reviewed earlier (*363*, *364*). Despite the efforts made, besides the two natural analogs deserpidine (**110**) and rescinnamine (**111**), only a few semisynthetic derivatives proved to be successful by that time to be developed as medicines. Examples are syrosingopine (**621**) and 10-methoxydeserpidine (Methoserpidine) (**622**), whose chemical and pharmacological investigation has been continued up to now (*367–370*).

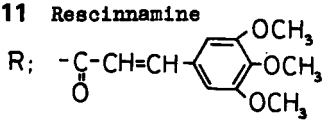


110 Deserpidine R=H

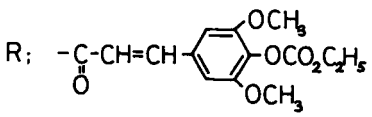
622 Methoserpidine R=OCH_3



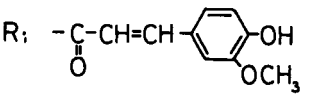
111 Rescinnamine



621 Syrosingopine



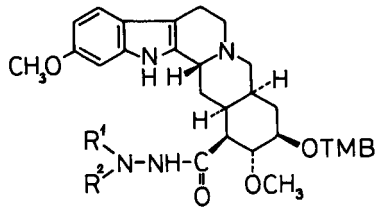
623 Rescimetol



Rescinnamine-type derivatives containing differently substituted cinnamoyloxy functions at C-18 have been investigated extensively by Japanese researchers (*371–376*). Rescimetol (**623**), an effective antihypertensive agent

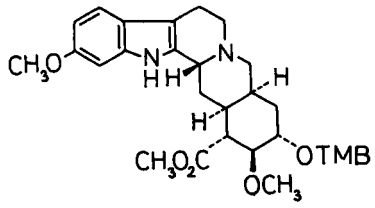
with fewer central and gastric side effects than those of reserpine, is the most promising member of this series.

Pharmacological investigation of a great number of C-18-acyloxy analogs of reserpine showed that alteration at this site of the molecule exerts smaller or greater modification of the original activity, and sometimes lower toxicity is observed (*377–379*). Even methyl reserpate (**121**), having a free secondary OH group at C-18, showed the characteristic hypotensive and sedative effect (*380*). By transforming the C-16 ester function of reserpine to a hydrazide or substituted hydrazides, a series of new compounds (**624**) with basically unchanged biological properties have been synthesized (*381*).



624

No significant loss of activity has been experienced when the relative configurations of all three substituents of ring E have been altered (**625**) simultaneously (*382*). It is well known, however, that the C-3 epimer (**514**) of reserpine is practically inactive (*363*).



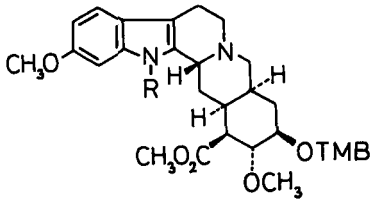
625

16,17,18-Epireserpine

Alkylation with nitrogen-containing groups at the indole nitrogen did not influence the hypotensive effect of reserpine (*383*). Moreover, one member of this series, N_a-diethylaminoethylreserpine (Bietaserpine) (**626**), has found practical utilization as an antihypertensive agent in human therapy (*384–386*).

Quaternarization of the tertiary N_b atom with fluorine-containing alkyl groups furnished a series of quaternary salts. However, none of them was reported to be more active than the parent alkaloid (*387*).

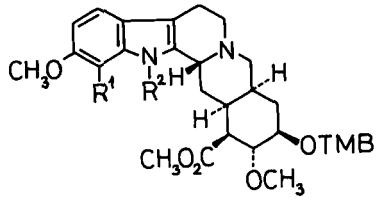
Electrophilic substitution on ring A of both reserpine and deserpidine was one of the earliest reactions to be investigated on this field. Beside halogenation



626 R=$CH_2CH_2N(C_2H_5)_2$

Bietaserpine

(*363*), nitration of reserpine has been reported (*388*). The process affords a mixture of three mononitro derivatives of which 12-nitroreserpine (**627**) is reported to have longer-lasting hypotensive effect than has reserpine, though higher doses are required. Pharmacological tests of 1-nitroreserpine* (**628**) have shown the same order of hypotensive activity as that of reserpine, giving only mild sedation without the undesired side effects.



627 $R^1=NO_2$; $R^2=H$

628 $R^1=H$; $R^2=NO_2$

The worldwide scientific interest and the great number of articles in this field are well correlated with statistical data, pointing out that among drugs from higher plants reserpine and its analogs have stood high on the list during the past two decades (*389*). Though the efforts to synthesize new derivatives have decreased slightly, further chemical, pharmacological, and mainly pharmacodynamical investigations unequivocally indicate continued interest.†

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* The structure of **628,** however, has not been proved unambiguously.

† See also addendum, page 407.

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— CHAPTER 3 —

PYRROLIDINE ALKALOIDS

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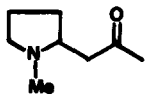
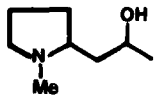
I. Introduction

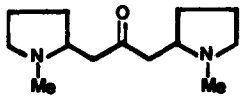
Two reviews on pyrrolidine alkaloids have appeared in volumes I (*1*) and VI (*2*) of this series. At that time, the only alkaloids mentioned were hygrine (**1**), hygroline (**2**), cuscohygrine (**3**), stachydrine (**4**), and betonicine (**5**). Carpaine,



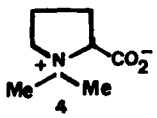
1 HYGRINE



2 HYGROLINE

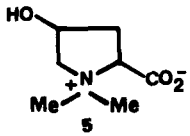


3 CUSCOHYGRINE



4

STACHYDRINE



5

BETONICINE

originally thought to be a pyrrolidine, was later shown to be a piperidine and has migrated into the appropriate section.

After 1960, many new isolations of these bases were reported, much chemistry and biology has been added to the original body, and about 80 new alkaloids from the vegetable and animal kingdoms have joined the list. These are the reasons why it was felt that the time had come to update the preceding reviews.

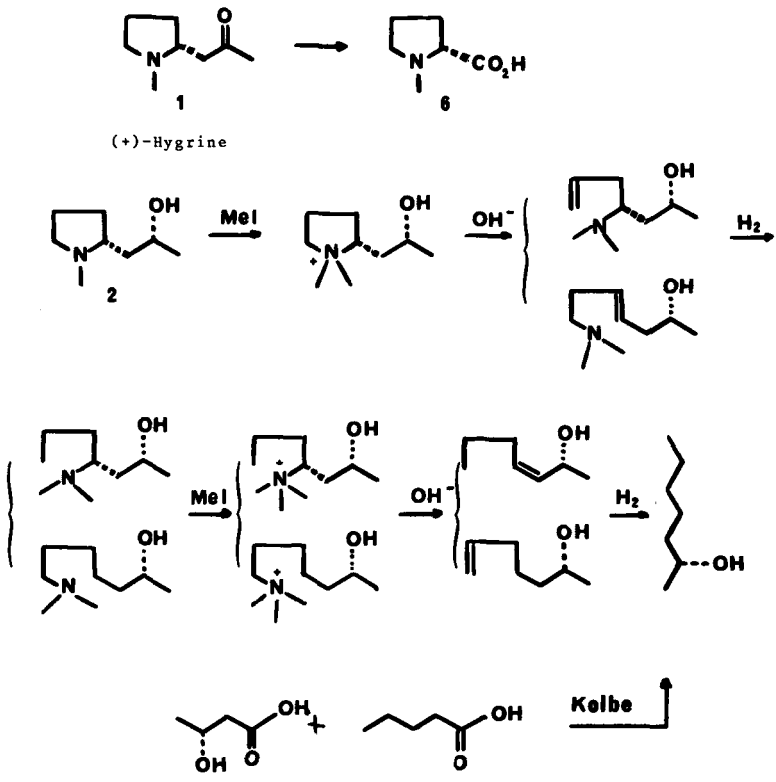
We have chosen to classify the new bases according to their sources and that often has led to homogeneous subsets. To gain concision, we have treated the similar structures of ficine, vochysine, and phyllospadine in the same section even though the Moraceae, Vochysiaceae, and Zosteraceae are unrelated.

The pyrrolidine ring is part of numerous natural products, and we have restricted the field to those alkaloids that contain an isolated pyrrolidine ring. We have thus excluded the so-called *Sceletium* (mesembrine) and *Dendrobium* (dendrobine) alkaloids, which have also been reviewed (*3–5*). The pyrrolidine ring is frequently encountered in proline residues of cyclopeptide alkaloids; these have been reviewed already (*7*) and will not be discussed here.

II. Hygrine and Hygroline

Hygrine (**1**) and hygroline (**2**) were known compounds when the first reviews on pyrrolidine alkaloids in this series were written. Since 1950, the configurations of **1** and **2** have been determined and new sources of the alkaloids have been found.

The establishment of the stereochemistries of **1** and **2** is an outstanding example of what could be done in the field with the weaponry of that time (*8*). Chromic



SCHEME 1. Determination of the absolute configuration of hygroline.

acid oxidation of (+)-hygrine yielded (+)-hygric acid (**6**) whose known absolute configuration settled the case of the only stereo center of **1** (*R* in the sense of Cahn, Ingold, and Prelog). Hygrine and hygroline having been previously correlated, only the configuration of the alcohol-bearing carbon of **2** remained to be determined. Thus a series of Hoffman degradations, followed by catalytic hydrogenations, transformed **2** to (−)-2-heptanol [(+)-2-heptanol was similarly obtained from (+)-pseudohygroline]. The absolute configuration of 2-heptanol, which could be established by analogies with known compounds, was then definitively proved by synthesis from (−)-β-hydroxybutyric acid and valerianic acid under Kolbe conditions. (+)-Hygroline is thus the (*R,R*) compound.

New sources of hygrine are the roots of *Nicandra physaloides* (L.) Gaertn. (Solanaceae) (*9, 10*), *Dendrobium chrysanthum* Wall. (Orchidaceae) (*11*), and *Cochlearia arctica* Slecht (Cruciferae) (*12*). Hygroline was also isolated from this latter source as well as from *Carallia brachiata* (Lour.) Merr. (Rhizophoraceae), a plant from eastern Asia, New Guinea, and Queensland (*13*), and

Gynotroches axillaris Bl. (Rhizophoraceae—Queensland) (*14*). Reference *11* contains the first reported ^1H NMR and mass spectra of hygroline.

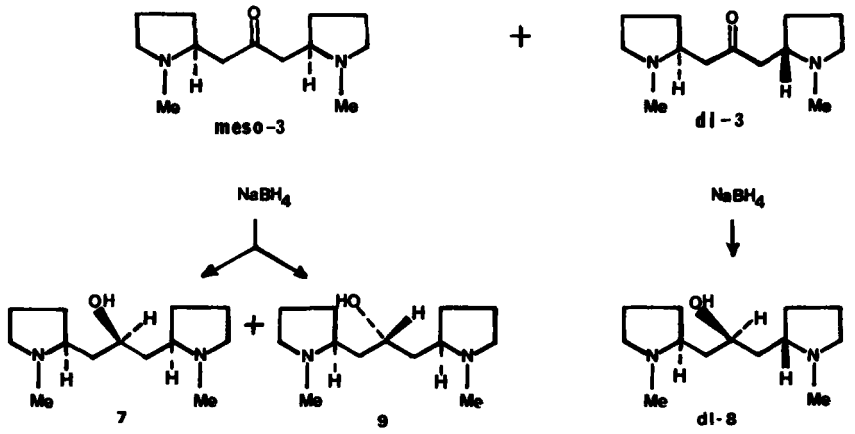
Syntheses of hygrine will be detailed in a separate section but it is worth noting here that the intriguing problem of the Hess synthesis of hygrine has been solved (*15, 16*). Hygrine is no longer synthesized from 2-(β-hydroxypropyl) pyrrolidine, HCl, and CH_2O!

III. Cuscohygrine and Dihydrocuscohygrine

The relationship between cuscohygrine and the tropane alkaloids, their co-occurrence, and their important pharmacological properties justify the numerous citations of cuscohygrine in the literature. The presence of cuscohygrine has been noted in the following families, genera, and species:

Solanaceae
- *Cyphomandra betacea* Sendt. (*17*)
- *Datura bernhardii* Lundström (*18*)
- *Datura candida* (Persoon) Safford (*19*)
- *Datura ceratocaula* Jacq. (*20*)
- *Datura cornigera* Hook. (*19*)
- *Datura ferox* L. (*19*)
- *Datura innoxia* Mill. (*19, 21, 22*)
- *Datura leichhardtii* Muell. ex Benth. (*17, 18*)
- *Datura metel* L. var. *fastuosa* (Bernh.) Danert (*19*)
- *Datura meteloides* Dun. (*19, 21, 22*)
- *Datura sanguinea* R. and P. (*19*)
- *Datura stramonium* L. (*18, 19, 21, 22*)
- *Mandragora officinarum* L. (*23*)
- *Salpichroa origanifolia* (Lam.) Baillon. (*24*)
- *Scopolia carniolica* Jacq. (*25*)
- *Scopolia lurida* (Link and Otto) Dun. (*26, 27*)
- *Scopolia tangutica* Max. (*28, 29*)
- *Solandra grandiflora* Sw. (*30*)
- *Solandra guttata* Don. (*30*)
- *Solandra hartwegii* N.Br. (*30*)
- *Solandra hirsuta* Dun. (*30*)
- *Solandra macrantha* Dun. (*30*)
- *Solanum carolinense* Mill. (*31*)
- *Withania sommifera* Dunal (*32, 33*)

Convolvulaceae
- *Convolvulus erinaceus* C. A. Mey. (*34*)



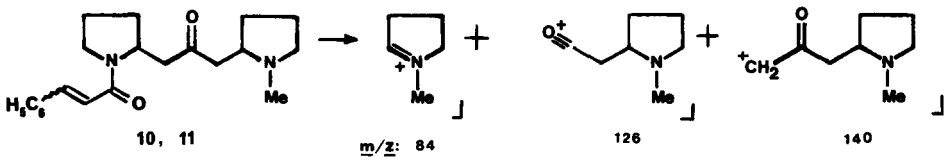
SCHEME 2

The amount of cuscohygrine is the main difference between the two commercial varieties of coca leaves: *Erythroxylum coca* Lam. var. *coca* and var. *spruceanum* (Erythroxylaceae). Coca leaves collected in Bolivia and in Peru have cuscohygrine as the main alkaloid besides cocaine, whereas the opposite situation occurs with material collected in Java (*35*).

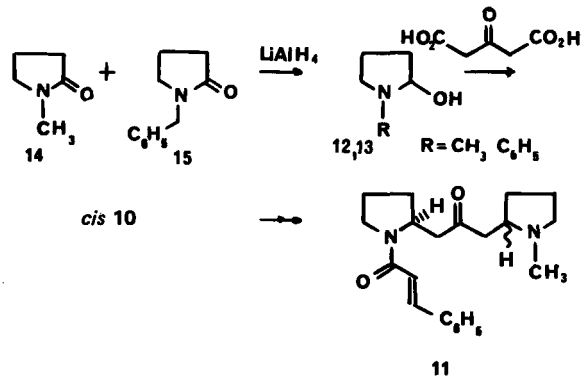
Cuscohygrine (**3**) and (−)-dihydrocuscohygrine (**8**) have been isolated from peruvian coca leaves (*36*); as previously noted, cuscohygrine was optically inactive. The isolation of three isomeric alcohols (**7**, **8**, and **9**) after $NaBH_4$ reduction of **3** indicated that the natural product was a mixture of meso and racemic forms. Natural (−)-dihydrocuscohygrine corresponded to the reduction product of medium polarity; it is the reduction product of the levorotatory form of cuscohygrine. The zero optical rotation of cuscohygrine and its existence as a mixture of diastereoisomers may be related to the easy racemization of the stereo center of N-C(R)H-CH_2CO systems through a retro Michael–Michael equilibrium.

N-cis- and *N-trans*-cinnamoylnorcuscohygrine (**10** and **11**) (*cis-* and *trans*-dendrochrysines) have been found in the orchid *Dendrobium chrysanthum* Wall. (*37*). The structure determination of these products was based on IR, UV, and NMR spectra for the cinnamoyl residue and on mass spectrometry (*N*-methylpyrrolidin-2yl group).

This hypothesis was confirmed by a biomimetic synthesis from a mixture of



SCHEME 3. MS fragmentation of the cinnamoyl cuscohydrines.



SCHEME 4. Total synthesis of the dendrochrysines.

the hemireduction products (**12** and **13**) of *N*-methyl- and *N*-benzylpyrrolidin-2-ones (**14** and **15**) and acetonedicarboxylic acid (see below). The absolute configuration of **10** was determined by comparison of its CD spectrum with those of *N-cis*-cinnamoyl-L-prolinol and of *N-cis*-cinnamoyl-L-2-methylpyrrolidine. The configuration of the relevant carbons were found to be identical; the configuration of the second stereo center remains to be determined.

IV. The Betaines: Stachydrine and Hydroxystachydrines

Stachydrine (**4**) and 3-hydroxystachydrine (**16**) have been isolated from numerous vegetable sources, listed below in alphabetical order of family, genus and species. They are

Capparidaceae

Boscia madagascariensis Moust., leaves (**4** + **16**) (*38*)
Boscia senegalensis Lam., leaves (**4** + **16**) (*38*)
Cadaba farinosa (Forsk.), stem (**4** + **16**) (*38, 39*)
Cadaba fruticosa Druce, leaves (**4**) (*40*)
Cadaba rotundifolia Forsk, leaves (**16**) (*39*)
Capparis assamica Hook., leaves (**4**) (*38*)
Capparis biloba Hutch. and Dalz., leaves (**4** + **16**) (*38*)
Capparis corymbosa Lam., leaves (**4**) (*38*)
Capparis decidua Edgew., root bark (**4**) (*41*)
Capparis erythrocarpa I. Sert., leaves (**4** + **16**) (*38*)
Capparis flavicans Wall., leaves (**4** + **16**) (*38*)
Capparis horrida L., leaves (**4**) (*38*)
Capparis micracantha DC., leaves (**4**) (*38*)
Capparis moonii Wight, fruit (**4**) (*42*)
Capparis spinosa L., leaves and cortex (**4**) (*43*)

Capparis pyrifolia Lam., leaves (**4** + **16**) (*38*)
Capparis tomentosa Lam., fruit (**4**) (*38, 44*)
Capparis zeylanica Lam., leaves (**4** + **16**) (*38*)
Cladostemon paradoxus Br. and Watke, leaves (**4**) (*38*)
Courbonia glauca, rhizome (**4**) (*45*)
Cratevea erythrocarpa Gagnep (**4**) (*38*)
Cratevea adansonii DC. (**4**) (*38*)
Cratevea graveana Baill. (**4**) (*38*)
Cratevea nurvala Buch. Ham. (**4**) (*38*)
Maerua angolensis DC. (**4** + **16**) (*38*)
Ritcheia capparoides Britten (**4**) (*38*)
Ritcheia reflexa Gilg. and Benedict (**4**) (*38*)
Steriphoma paradoxum Endl. (**4** + **16**) (*38*)
Stixis obtusifolia Baill. (**4**) (*38*)
Stixis scandens Lour. (**4**) (*38*)
Stixis suavolens Roxb. (**4**) (*38*)
Thylachium africanum Lour. (**4** + **16**) (*38*)
Tirana purpurea Pierre (**4** +**16**) (*38*)

Compositae
Achillea millifolium L. (**4**) (*46*)
Onopordon acanthium L. (**4**) (*47*)

Labiatae
Eremostachys speciosa Rupr. (**4**) (*48*)
Lagochilus hirtus Fish. and Mey. (**4**) (*49*)
Lagochilus inebrians Bunge (**4**) (*48*)
Lagochilus platycalyx Fisch and Mey. (**4**) (*48*)
Lagochilus pubescens Vved. (**4**) (*48*)
Lagochilus setulosus Vved. (**4**) (*48*)
Lamium album L. (**4**) (*48*)
Leonorus cardiaca L. (**4** + **14**) (*50*)
Leonorus quinquelobus Gilib. (**4** + **15**) (*51*)
Leonorus sibiricus L. (**4** + **16**) (*52*)
Leonorus turkestanicus Knorr. (**4** + **12**) (*48*)
Marrubium alternidens K. H. Rechinger (**4**) (*48*)
Marrubium vulgare L. (**4**) (*53*)
Sideritis montana L. (**4**) (*48*)
Stachys balansae Boiss. (**4**) (*54*)
Stachys betoniciflora Rupr. (**4**) (*55*)
Stachys hissarica Regel (**4**) (*48*)
Scutellaria immaculata Nevski ex Juzepczuk (**4** + **2**) (*48*)

Leguminosae
Desmodium triflorum DC., root (**4**) (*56*)

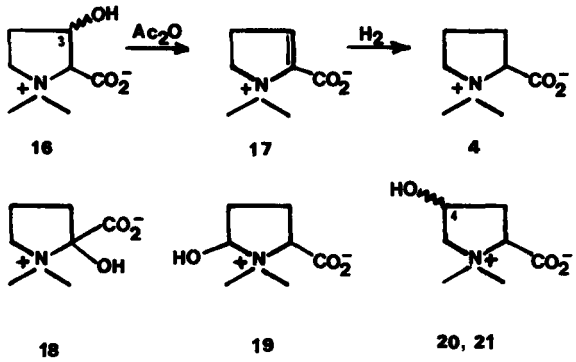
Liliaceae

Asphodelus microcarpus Viviani (**4**) (*57*)

The occurrence of stachydrine and of 3-hydroxystachydrine in the Capparidaceae has been proposed as a criterion for chemotaxonomic classification of this family (*38*). As shown in the above list, it is not a sufficient clue to define the family *sensu stricto* but it allows a distinction, among the family, of genera with or without betaines.

The many isolations of stachydrine have not generated much novel chemistry about this alkaloid. One can mention, however, ^{1}H-NMR and ^{13}C-NMR data on stachydrine by Atta-ur-Rahman (*40*). From the pharmacological standpoint, stachydrine has been found to reduce the systolic rate in frogs (*58*).

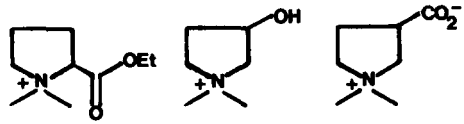
Assignment of configuration of 3-hydroxystachydrine (**16**) is often not discussed. In their isolation of **16** in the fruit of *Courbonia virgata,* A. Brogn., Cornforth, and Henry have shown it to be a mixture of the cis and trans com-



pounds (*59*). This determination was based on a dehydration reaction (Ac_2O), which gave the same Δ-2 pyrrolinium salt (**17**). The fact that one of the betaines could be isomer **18, 19, 20,** or **21** was refuted on the basis that **18** and **19** would be unstable and **20** or **21** would be identical with betonicine or turicine.

The ethyl ester of (−)-stachydrine (**22**) has been isolated from the root of *Courbonia virgata* (*60*); it is not considered to be an extraction artifact from stachydrine. (−)-3-Hydroxy-1,1-dimethylpyrrolidinium (**23**) is not a betaine even though it may exist in a neutral form; it has been isolated for the first time from a natural source, *Courbonia glauca,* in 1973 (*45*).

The methanolic extract of the red alga *Griffithsia flosculosa* Batt. (Ceramiaceae) contains a betaine whose mass spectrum is similar to that of stachydrine (*61*). The substances were not identical by TLC, and it was considered that



22 23 24

the novel compound could be β-stachydrine (**24**); this was proved by a synthesis from β-proline according to Witkop's method (*62*).

The 4-Hydroxystachydrines: Betonicine and Turicine. Betonicine (**20**) and turicine (**21**) are the betaines corresponding to the cis and trans isomers of 4-hydroxyproline. Betonicine has been isolated from *Achillea millefolium* L. (Compositae) (*63*) and probably from *A. atrata* L. (Compositae) (*46*); it is also the major alkaloid of *Marrubium vulgare* (Labiateae) (*64*). In a study of *Combretum micranthum* G.Don (Combretaceae), three alkaloids, combretines A, B, and C, were isolated (*65*). Combretine A (MP 253–257°C (dec), $[\alpha]_D$ +37°) is thought to be the enantiomer of betonicine (MP 254–256°C, $[\alpha]_D$ −36,6°); combretine B (MP 248–249°C, $[\alpha]_D$ 0°) is probably the racemic form of betonicine. Although the plant is frequently used in folk medicine (kinkeliba), none of the bases from *C. micranthum* shows appreciable physiological activity. Two groups of authors, at least, (*62, 64*) seem to consider that turicine is an extraction artifact of betonicine.

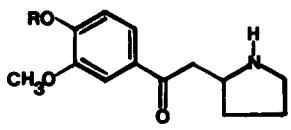
V. Occurrence of Pyrrolidine Alkaloids

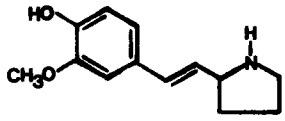
A. Acanthaceae

Hesse and coworkers have isolated four new pyrrolidine bases from the roots of *Ruspolia hypercrateriformis* M.R., a plant from tropical Africa belonging to the family Acanthaceae (*66, 67*). There are three monomers: ruspolinone (**25,** $C_{14}H_{19}NO_3$), norruspolinone (**26,** $C_{13}H_{17}NO_3$), and norruspoline (**27** $C_{13}H_{17}NO_2$), and there is one dimer, hypercratine (**28,** $C_{25}H_{30}N_2O_5$).

Structures of alkaloids **25, 26,** and **27** were established by spectroscopic means (UV, IR, NMR, and mass) and by chemical correlations. All three compounds had a zero optical rotation, which might be attributed to an easy racemization of their unique stereo centers; this was also observed for hygrine.

The structure of hypercratine was deduced from spectroscopic data, including 200 MHz ^1H NMR and ^{13}C NMR. The mass spectrum of the acylated derivative of **28** was dominated by fragments at *m/z* 70 and 112, explained by an α cleavage of the pyrrolidine ring. The complexity of the NMR spectra and the distance between the C-2 and C-2′ stereo centers have not permitted establishing the configuration of these centers. The nature of the substituents on atoms C-6′ or C-7′ remains yet to be settled [alternative structures **28** and **28′**].

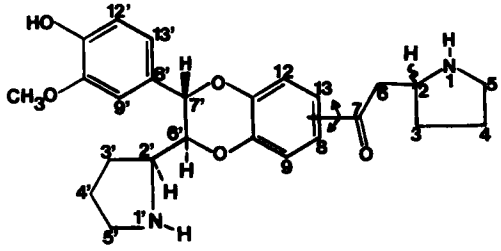




27 NORRUSPOLINE

25 R = CH_3 RUSPOLINONE

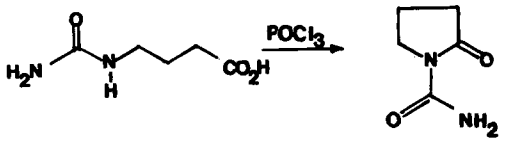
26 R = H NORRUSPOLINONE



28 HYPERCRATINE (7-8 OR 7-13 BOND)

B. Annonaceae

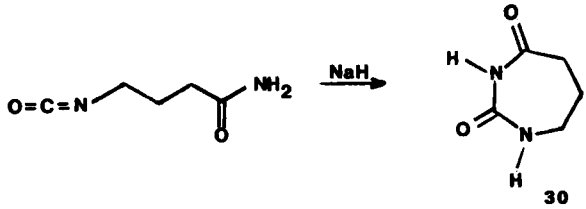
Whereas the Annonaceae are characterized primarily by benzylisoquinoline alkaloids, two pyrrolidine alkaloids have recently been found in species belonging to this family. Squamolone (**29**) was isolated from *Annona squamosa* L. by Chinese workers in 1962 (*68*). Despite careful spectroscopic investigation and a total synthesis (Eq. 1), squamolone was assigned the incorrect diazepine formula **30.** The correct structural formula (**29**) was later established by an unambiguous synthesis of **30** (Eq. 2). Compounds **29** and **30** proved to have very similar spectroscopic properties, which could justify the early confusion (*69*).



(1)

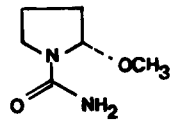
29

SQUAMOLONE



30 (2)

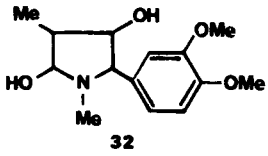
Later, squamolone was isolated from *Hexalobus crispiflorus* A.Rich. along with aporphine alkaloids, and the methoxyurea **31** (*70*) *H. crispiflorus* was collected in Nigeria. The genus *Hexalobus* consists of five species growing in southern and tropical Africa and Madagascar. The possibility of **31** being an extraction artifact of an unknown precursor has been considered.



31

C. CAMPANULACEAE

Approximately 30 species belong to the genus *Codonopsis;* they grow in eastern and central Asia, in the Himalayas and in Malaysia. The two alkaloids codonopsine and codonopsinine have been isolated from *C. clematidea* C. B. Clarke by Yunusov *et al.* Carbinolamine structural formula **32** was first proposed for codonopsine (*71*), but it was corrected to **33** to explain chemical degradation experiments (*72*). Codonopsinine was isolated soon afterward and given formula **34** (*73*), later corrected to **35** (one carbon methoxy shift) following chemical evidence (*74*). In 1972, a definitive ^{1}H-NMR study of these alkaloids was published by the same group of authors; this has allowed precise determination of



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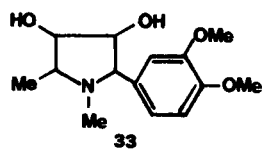

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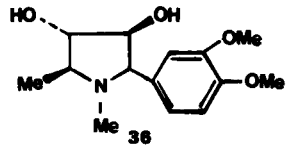
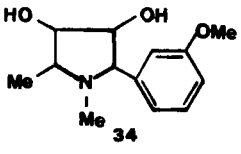


36

CODONOPSINE



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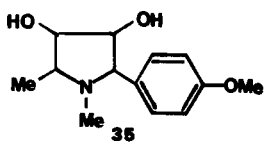

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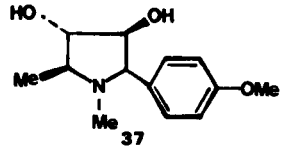


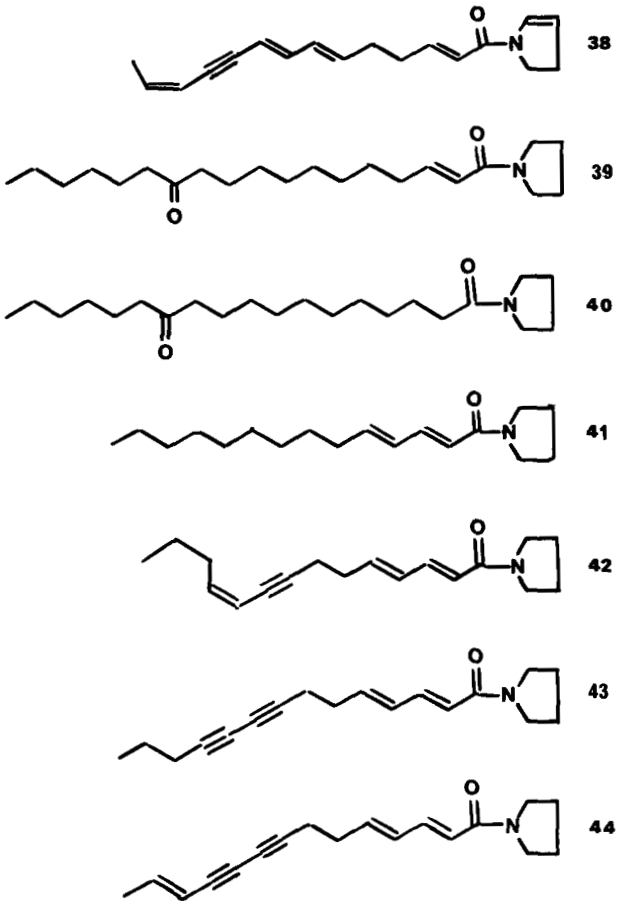
37

CODONOPSININE

the relative stereochemistry of the pyrrolidine ring substituents (actual formulas **36** and **37**) (*75*). Khanov *et al.* have demonstrated that codonopsine decreases blood pressure in cats in doses >20 mg/kg (*76*).

D. Compositae

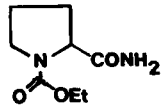
The genus *Achillea* (Compositae) has provided a large variety of amides derived from long-chain unsaturated acids. Investigations by Bohlmann and coworkers led to the isolation of the following bases: tetradeca-(2*E*,6*E*,8*E*,12*Z*)-tetraen-10-ynoic acid 2′,3′-dehydropyrrolideide (**38**) from *A. tomentosa* L. (*77*),



ACHILLEA PYRROLIDINE ALKALOIDS

2,3-dehydrolycaonic acid pyrrolidide (**39**), lycaonic acid pyrrolidide (**40**) from *A. lycaonica* Boiss. and Heldr. (*78*) tetradeca-(2*E*,4*E*)-dienoic acid pyrrolidide (**41**), tetradeca-(2*E*,4*E*,10*Z*)-trien-8-ynoic acid pyrrolidide (**42**), tetradeca-(2*E*,4*E*)-dien-8,10-diynoic acid pyrrolidide (**43**), and tetradeca-(2*E*,4*E*,12*E*)-trien-8,10-diynoic acid pyrrolidide (**44**) from *A. nana* L. (*79*).

Besides sesquiterpene lactones, an alkaloid analyzed as $C_8H_{14}N_2O_3$ (**45**), was isolated from the leaves of *Arnica montana* L. (*80*). Distinction between the two possible structures **45** (amide–urethane) and **46** (ester + urea) was accomplished by a selective synthesis from prolinamide.



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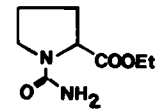
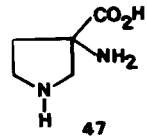


46

E. Cucurbitaceae

Cucurbitine (**47**) is the active principle from the seeds of *Cucurbita moschata* Duch., which are used in Chinese folk medicine. The structure of this unique α-amino acid was established through a combination of chemical and spectroscopic techniques (*81*, *82*). A single-crystal X-ray analysis of the perchlorate of cucurbitine has confirmed the original hypothesis and has established the absolute configuration of **47** (*83*).



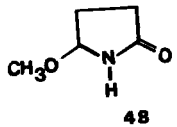
47

CUCURBITINE

Cucurbitine was later found in several species of *Cucurbita*, including the seeds of the common pumpkin (*84*, *85*). It inhibited the growth of immature *Schistosoma japonica in vitro* and appeared to be promising in the treatment of bilharziasis.

F. Dennstaedtiaceae

Pterolactam (**48**) was isolated from bracken (*Pteridium aquilinum* Kuhn), a fern belonging to a monotypic genus (*86*). Its IR spectrum strongly resembles the IR spectrum of 2-pyrrolidone; the structure of **48** was established by ^{1}H-NMR spectroscopy. It is interesting to note that **48** possesses a weak but definitive optical rotation ($[\alpha]_D$ −2.0°).



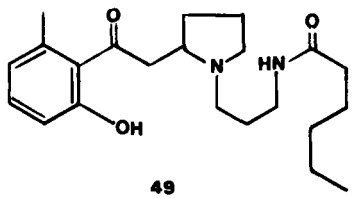
48

PTEROLACTAM

G. Elaeocarpaceae

Peripentadenia is a monotypic genus of the family Elaeocarpaceae represented by *Peripentadenia mearsii* (C. T. White) L. S. Smith, a tree growing in rain forests of northern Queensland. Besides unidentified minor alkaloids, the species yields one major alkaloid, peripentadenine (**49**) (*87*). Its molecular formula, $C_{22}H_{34}N_2O_3$, was established by high-resolution mass spectroscopy; the presence of phenol, ketone, secondary amide, and tertiary amine functionalities was deduced from examination of spectroscopic data.

Chemical degradations have allowed the identification of both extremities of peripentadenine, hexanoic acid (present as an amide) and 2-hydroxy-6-methylacetophenone. ^{13}C NMR showed that the rest of the molecule included two nitrogen atoms, six methylenes, and one methine arranged in a (3-propylamino)-1-pyrrolidine unit substituted at C-2. This formula was definitively proved by chemical degradations as well as by two total syntheses. As noted before in the cases of hygrine and of the ruspolinone alkaloids, peripentadenine is optically inactive.

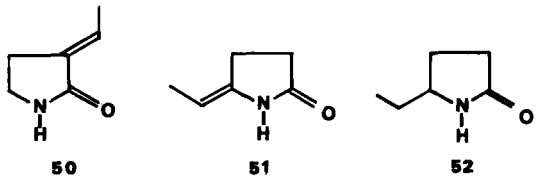


49

PERIPENTADENINE

H. Fumariaceae

Corydalis is a genus of the family Fumariaceae that is represented by some 320 species growing in the temperate climates of the northern hemisphere. *Corydalis pallida* Pers. var. *tenuis* from Japan was simultaneously examined for alkaloids by two groups of investigators (*88, 89*). Besides benzylisoquinoline-type alkaloids, *trans*-3-ethylidene-2-pyrrolidone (**50**) (alkaloid P) was present. The alternative formula **51** was ruled out by the nonidentity of the hydrogenation product of **50** with an authentic sample of 5-ethyl-2-pyrrolidone (**52**). Alkaloid



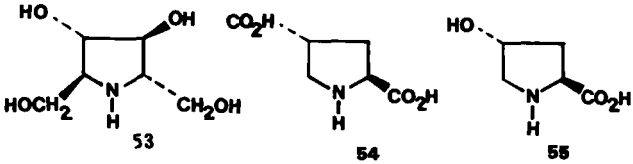
50 51 52

CORYDALACTAM

50, for which the name corydalactam is proposed, was known before as a synthetic material (*90*); two more syntheses of it were later performed by Kametani and Ihara (*91, 92*).

I. Leguminosae

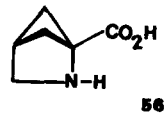
A systematic investigation of the free amino acids of the Leguminosae led to the isolation of a novel ninhydrin-positive compound from the leaves of *Derris elliptica* Benth. (Papilionidae) (*93*). This substance was analyzed as $C_6H_{13}NO_4$ (microanalysis and high resolution mass spectrometry) and was shown to be an amino alcohol. The absence of a carbonyl in the IR, the loss of 31 mass units in the mass spectrum, and a positive periodate cleavage reaction were best embodied into a dihydroxydihydroxymethylpyrrolidine structure. The relative simplicity of the NMR spectra (three peaks in the ^{13}C spectrum; four spin-system in the ^1H spectrum) pointed out a symmetrical structure. Inasmuch as the material was optically active ($[\alpha]_D$ 56.4, $c = 7$, H_2O), meso structures were ruled out, and the 2*R*, 3*R*, 4*R*, 5*R* relative configuration was retained (*93*). This structure (**53**) was further confirmed by an X-ray determination (*94*).



53 54 55

In another legume, *Afzelia bella* Harms (Caesalpinoidene), the same authors have isolated the new *trans*-4-carboxy-L-proline (**54**) along with *trans*-4-hydroxy-L-proline (**55**) as free amino acids. The structure of the diacid **54** is based on mass, ^1H, and ^{13}C-NMR spectroscopy (*95*); the proposed absolute configuration of **54** was also demonstrated by X-ray diffraction (*96*). Compound **54** is probably identical with the diacid independently isolated from the red alga *Chondria coerulescens* (Crouan) Falk. (Rhodomelaceae) (*97*).

From the seeds of the legume *Atelia herbert smithii* Pittier (Papilionidae), which seems to repel insect predators, Bell *et al.* have isolated the new amino acid 2,4-methanoproline (**56**) (*98*). This structure has been established by spectroscopic means and confirmed by X-ray diffraction.

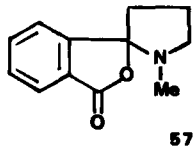


56

2,4 - METHANOPROLINE

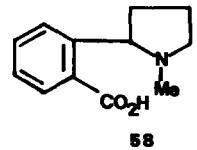
J. Malpighiaceae

Shihunine (**57**), previously isolated from *Dendrobium lohohense* Tang and Wang (*99, 100*) and *D. pierardii* Roxb. (Orchidaceae) (*101*), has been found as a racemate in *Banisteriopsis caapi* Morton (*102*). This plant species also contained the optically active dihydroshihunine **58**, a compound only known before as a racemic synthetic material. Both **57** and **58** were identified by direct comparison with authentic samples. The absolute configuration of (+)-(**58**) was determined as 2*S* by comparison of the CD spectra of **58** and of the α-phenylethylamines (*102*).



57

SHIHUNINE

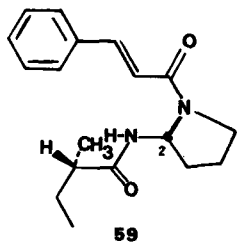


58

DIHYDROSHIHUNINE

K. Meliaceae

The pyrrolidine bases **59** and **60** were independently determined in two species of *Aglaia*. They were named odorine (**59**) and odorinol (**60**), after *Aglaia odorata* Lour. (*103, 104*), and roxburghilin (**59**) and hydroxyroxburghilin (**60**), after *Aglaia roxburghiana* Miq. (*105*); the compounds were demonstrated to be identical (*104*).



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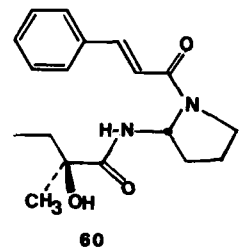


60

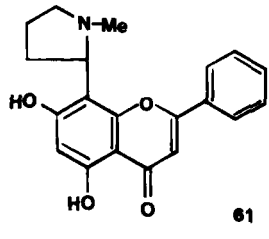
ODORINE - ROXBURGHILIN ODORINOL-HYDROXYROXBURGHILIN

Structures of these unusual aminal bisamides were determined by spectroscopic evidence and chemical degradations. The study of the constituent of *A.*

odorata was justified by its use as a medicinal plant (treatment of human cough, inflammation and traumatic injury) (*106*). The discovery that odorinol possessed significant *in vivo* activity against P-388 lymphocytic leukemia growth prompted its synthesis from L-proline (*104*) and a structural determination by X-ray methods (*106*). Although odorine C-2′ underwent partial racemization on standing in chloroform solutions, odorine is not a mixture of diastereoisomers; the configurational stability of this carbon atom is attributed to its bisamide nature.

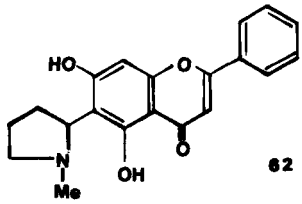
L. Moraceae, Vochysiaceae, and Zosteraceae

Although unrelated, these three families are the source of unique alkaloids that share common features. They are ficine (**61**) and isoficine (**62**) from *Ficus pantoniana* King (Moraceae) (*107*), vochysine (**63**) from the fruit of *Vochysia guianensis* (Aubl.) Poir. (Vochysiaceae) (*108*), and phyllospadine (**64**) from the seaweed *Phyllospadix iwatensis* Makino (Zosteraceae) (*109*).



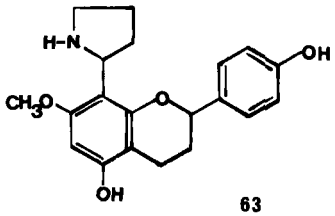
61

FICINE



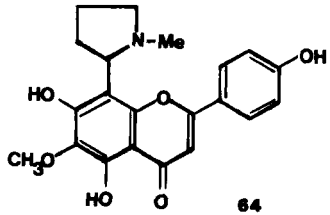
62

ISOFICINE



63

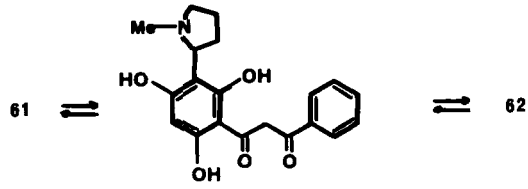
VOCHYSINE



64

PHYLLOSPADINE

All four bases consist of two units: a pyrrolidine and a flavonoid (or flavan), and their spectra present characteristics of both parts. Thus the UV and IR spectra resemble the spectra of the parent flavonoid (chrysine for **61** and **62**, hispidulin for **64**, and 4′,5-dihydroxy-7-methoxyflavan for **63**). The mass spectra of **61**, **62**, and **63** do not easily give a molecular ion but rather show fragments pertaining to the flavonoid and to the pyrrolidine parts [*m/e* 84 and 83 (**61** and



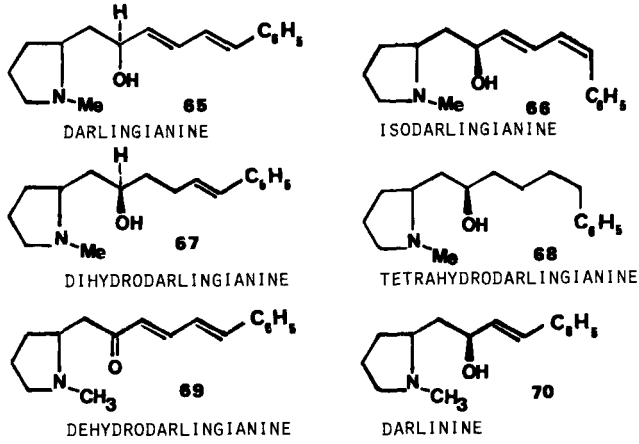
SCHEME 5. The ficine–isoficine interconversion.

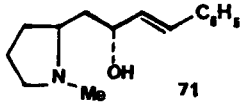
62) and 69 (**63**)]. The mass spectrum of phyllospadine triacetate displays a molecular ion, which has been analyzed (509.1695, $C_{27}H_{27}NO_9$); its intensity is unspecified.

The ^{1}H-NMR spectra of **61–64** as well as the ^{13}C-NMR spectra of **63** also show a superimposition of the signals corresponding to the two moieties of the molecules. Examination of the signals of the aromatic protons, and chemical correlations (degradation or synthesis) led to the proposed structures **61–64.** The interconversion ficine–isoficine, an acid-catalyzed process, is probably related to the Wessely–Moser rearrangement; it indeed involves opening of the B ring and not a pyrrolidine migration (Scheme 5). Of these compounds, **63** is an optically inactive material, and the optical rotations of **61, 62,** and **64** were not reported after their isolation; it now appears that natural ficine is levogyre ($[\alpha]_D$ −60°) (*109a*).

M. PROTEACEAE

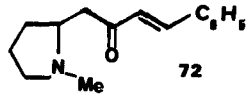
Darlingia darlingiana (F. Muell.) L.A.S. Johnson, is a tall tree from the rain forests of northern Queensland. Besides a tropene and two pyranotropanes, Bick *et al.* have reported the isolation and structure elucidation of eight pyrrolidine





71

EPIDARLININE



72

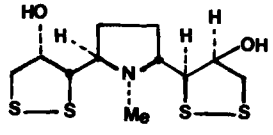
DEHYDRODARLININE

alkaloids (*110*). Five of them are diversely hygrogenated C_{17} alkaloids (C_8 hygrine unit + C_9 cinnamaldehyde unit): darlingianine (**65**, $C_{17}H_{23}NO$), isodarlingianine (**66**, $C_{17}H_{23}NO$), dihydrodarlingianine (**67**, $C_{17}H_{25}NO$), tetrahydrodarlingianine (**68**, $C_{17}H_{27}NO$), and dehydrodarlingianine (**69**, $C_{17}H_{21}NO$). The three other bases are C_{15} alkaloids: darlinine (**70**), epidarlinine (**71**, $C_{15}H_{21}NO$), and dehydrodarlinine (**72**).

Dehydrodarlingianine (**69**) and dehydrodarlinine (**72**) were synthetized by base-catalyzed reaction of hygrine with cinnamaldehyde and benzaldehyde, respectively. The relative stereochemistry of darlingianine (**65**) was established by X-ray diffraction (*111*). The structure of the other bases was established by chemical correlations as well as by spectroscopic methods. The absolute configurations of these bases remain to be determined.

N. Rhizophoraceae

The genus *Cassipourea* is the largest in the family Rhizophoraceae and is present in tropical areas in America, Africa, India, Madagascar, and Sri Lanka. Along with pyrrolizidine alkaloids, Warren and Wright have isolated a new base (**73**) from *C. gerrardii* Alston called gerrardine ($C_{11}H_{19}NO_2S_4$, MP 180°C). An unusual feature of the structure of **73** is the presence of two 1,2-dithiolan rings.



73

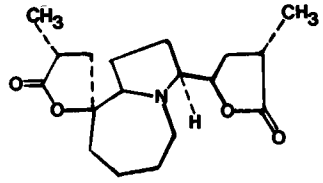
GERRARDINE

The gross structure of **73** was determined by a combination of spectroscopic and chemical means (*112*); stereochemistry was proved by single-crystal X-ray diffraction (*113*). Much later, **73** was also found in *C. guianensis* from Brazil (*114*). It was characterized by PMR and CMR data as well as by X-ray analysis. Gerrardine showed activity against *Salmonella* spp. (*115*), *Candida albicans* T.A., *Escherichia coli,* and *Klebsiella pneumoniae* D.T. (*114*).

O. Stemonaceae

Croomia is one of the two genera of the family Stemonaceae; it is represented by three species growing in Japan and the United States. The main alkaloid

isolated from the roots and rhizomes of *Croomia heterosepala* Okuyama is croomine (**74**, $C_{18}H_{27}NO_4$, $[\alpha]_D$ +9.8°) (*116*). The presence of a pyrrolidine unit



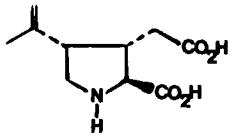
74

CROOMINE

in **74** was inferred from a dehydrogenation experiment (Ag_2O) yielding a tetradehydrocroomine derivative with a positive Ehrlich's pyrrole test. Although a correct total planar formula for **74** was deduced from conventional spectroscopic techniques, an X-ray structure determination was performed on the methiodide derived from **74.** The structure was solved by the heavy-atom method until an *R* value of 0.08; correction for anomalous iodine dispersion allowed the determination of the absolute configuration as depicted in the figure.

P. Algae

The known anthelmintic properties of the seaweed *Digenea simplex* Agardh were traced back to α-kainic acid (**75**) after several decades of intense work by Japanese workers (*117, 118*). A structure was rapidly proposed for this relatively small molecule ($C_{10}H_{15}NO_4$) on the basis of chemical (*119*) and X-ray evidence (*120*). α-Allokainic acid was isolated soon after from the same source, and its structure was established as **76** (*121, 122*).



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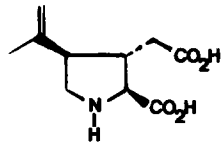
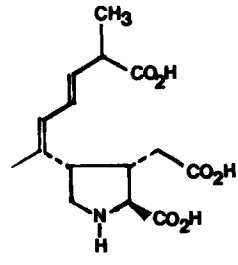
α—KAINIC ACID



76

ALLOKAINIC ACID



77

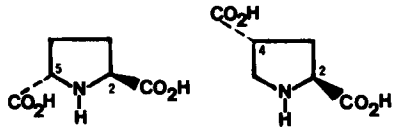
DOMOIC ACID

α-Kainic acid was later found to be present in the red alga from Sicily, *Centroceras clavulatum* Mont. C. Ag. (*123*), and in the Corsican alga *Alsidium helminthochorton* (Latour) Kützing (Rhodomelaceae) (*124*).

Although isolated in 1959 (*125*) from the now rare red alga *Chondria armata* Okamura (Rhodomelaceae), domoic acid (**77**) was given a tentative structure

only in 1966 (*126*). The last uncertainties were removed in 1982 by a total synthesis of (−)-domoic acid and by an X-ray crystallographic study (*127*).

A systematic investigation of amino acids present in algae was undertaken by Italian workers mainly for chemotaxonomic reasons. Besides known compounds, two simple new amino acids were isolated: pyrrolidine-2,5-dicarboxylic acid (**78**) from *Schizymenia dubyi* (Chauv.) J. Ag. (Nemastomaceae) and pyr-



78 **79**

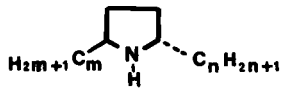
rolidine-2,4-dicarboxylic (**79**) from *Chondria coerulescens* Falk. from *C. dasiphylla* (Wood) Falk (Rhodomelaceae) and *Ceramium rubrum* (Ceramiaceae) (*123*). Both compounds were identified by spectroscopic means and also by chemical correlation by dehydrogenation (Se) to the corresponding pyrroledicarboxylic acids. Absolute configurations of **78** and **79** rest on molecular rotation rules. It is worth noting that **79** was simultaneously isolated from a vascular plant, *Afzelia bella* (Caesalpinoideae) (*95*).

Q. Ants

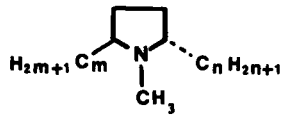
A large number of chemicals, which are used for communication, attack or defense, are secreted by ants. In general, these substances are small molecules, and their availability in minute amounts (50 μg per ant) does not allow the use of the traditional isolation and characterization procedures. Thus all of the structural work on ant substances rests on gas chromatography (GC), mass spectroscopy, and chemical synthesis. Two review articles have been published on the chemicals from the glands of ants (*128, 128a*) and we shall mention here only the work relevant to the pyrrolidine field.

Besides piperidine alkaloids, a total of 19 pyrrolidines have been found in the secretions of thief ants and fire ants of the genera *Solenopsis* and *Monomorium*. Among these, compounds **80–84** are simple pyrrolidines with two saturated linear all-carbon side chains; only in *Solenopsis latinode* is there a secondary amine (**82**) and its methylated analog (**85**). One or two terminal unsaturations are present in compounds **86–91**, which all possess a (hex-1-en)-6-yl chain and a 5-, 7-, or 9-carbon saturated chain. Compounds **93, 94, 96, 97,** and **98** are the Δ-1-pyrrolines corresponding to pyrrolidines **80, 82, 90** (**93** and **96** corresponding to **80, 94** to **82,** and **97** and **98** to **90**).

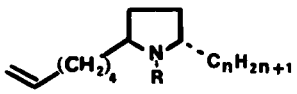
The mass spectra of **80–91** show weak odd molecular ions and strong fragments owing to α cleavage of the side chains (*129*). The secondary nature of the nitrogen atom is proved by acetylation, which gives less polar materials 42 amu



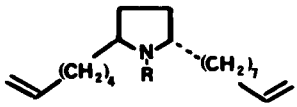
80 $m = 2$	$n = 7$	*Solenopsis punctaticeps*	(*129*)
81 $m = 4$	$n = 5$	*Solenopsis punctaticeps*	(*129*)
		Monomorium sp.	(*128*)
82 $m = 4$	$n = 7$	*Solenopsis fugax*	(*130*)
		Solenopsis punctaticeps	(*129*)
		Monomorium latinode	(*131*)
83 $m = 5$	$n = 6$	*Solenopsis molesta*	(*132*)
		Solenopsis texanas	(*132*)
84 $m = 6$	$n = 9$	*Monomorium* sp.	(*133*)



85 $m = 4$	$n = 7$	*Monomorium latinode*	(*131*)



86 $n = 5$	R = H	*Monomorium pharaonis*	(*134*)
87 $n = 7$	R = H	*Monomorium* sp.	(*131*)
88 $n = 9$	R = H	*Monomorium* sp.	(*133*)
89 $n = 9$	R = Me	*Monomorium* sp.	(*131*)

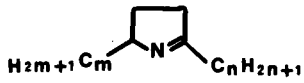


90 R = H	*Monomorium* sp.	(*133*)
91 R = Me	*Monomorium* sp.	(*131*)

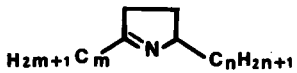
heavier. The linearity of the side chain is demonstrated by catalytic hydrogenolysis (1% Pd, 320°C) of a mixture of **80–82, 92, 93,** and **95** to the linear C_{11}–C_{15} hydrocarbons, identified by their GC retention times and mass spectra (*129*). These reactions also produce pyrroles, which give in their mass spectra intense molecular ions accompanied by ions corresponding to benzylic cleavage (Scheme 6).

The presence of an imine function in **92–98** is proved by reduction ($NaBH_4$ or $NaBD_4$) to pairs of compounds showing typical mass spectral behavior for 2,5-disubstituted pyrrolidines. The location of their imine double bond is based on a detailed study of the mass spectrum fragmentation. While the natural occurrence of imines **92–98** is not to be questioned, it is worth noting that in the introduction system of many GC-coupled mass spectrometers, dehydrogenation of secondary amines may take place; suggestions are given to circumvent these problems (*135*).

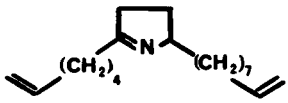
A remarkable feature of the structural work on the derivatives with unsaturated side chains is the method by which the double bonds were located. Thus a micromethod has been devised, based on the Markovnikov selectivity of olefin



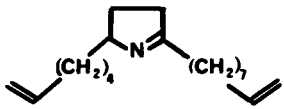
92 $m = 2$ $n = 5$ *Solenopsis punctaticeps* (*129*)
93 $m = 2$ $n = 7$ *Solenopsis punctaticeps* (*129*)
94 $m = 4$ $n = 7$ *Monomorium latinode* (*131*)



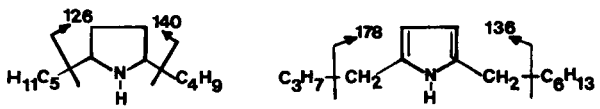
95 $m = 2$ $n = 5$ *Solenopsis punctaticeps* (*129*)
96 $m = 2$ $n = 7$ *Solenopsis punctaticeps* (*129*)



97 *Monomorium* sp. (*133*)



98 *Monomorium* sp. (*133*)



81

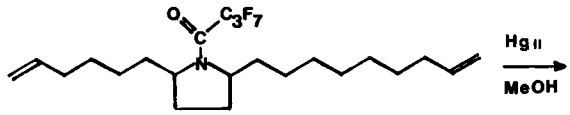
SCHEME 6. MS behavior of pyrrolidines and pyrroles.

oxymercuration. For example, treatment of butyramide (**99**) with mercury salts in methanol gives the methyl ether **100**, whose mass spectrum is dominated by fragments at m/z 59, corresponding to $CH_3—CH—^{+}OCH_3$ units. This unambiguously places the double bonds in terminal positions (*133*).

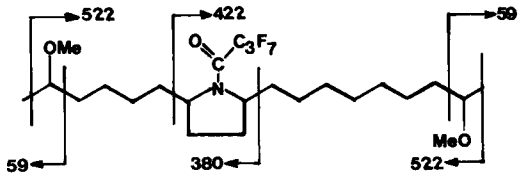
All of this structural work is backed up by total synthesis, which will be developed later. These syntheses often produce mixtures of cis–trans isomers. The natural products have a trans configuration and have the longest GC retention times. This attribution is based on an analogy with the hydrogenation of 2,5-dimethylpyrrole.

R. MISCELLANEOUS ORIGIN

Some alkaloids do not fall into the simple classification that we have used, nor do they fall into the categories that we have decided to exclude. In this chapter,



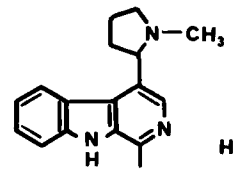
99



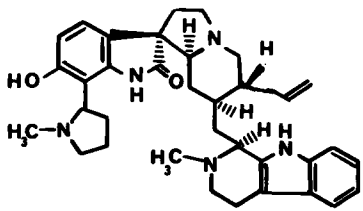
100

SCHEME 7. Location of unsaturations in ant pyrrolidine alkaloids.

we wish to sample some alkaloids that deserve mention with regard to the field. Among indole alkaloids, several compounds have been found that possess an extra pyrrolidine ring and often an odd number of nitrogen atoms. Their origin is at the crosspoint of the biosynthetic tryptophan and ornithine pathways. Examples of these bases are brevicolline (**101**) from *Carex brevicollis* DC. (Cyperaceae) (*136*), strychnophylline (**102**) (*137*), isostrychnophylline (**103**) (*137*), and strychnopentamine (**104**) (*138, 139*), all from *Strychnos usambarensis* Gilg (Loganiaceae).

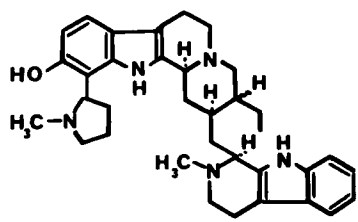


101 BREVICOLLINE



102 STRYCHNOPHYLLINE

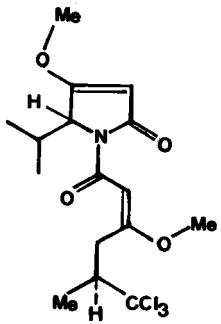
103 ISOSTRYCHNOPHYLLINE



104 STRYCHNOPENTAMINE

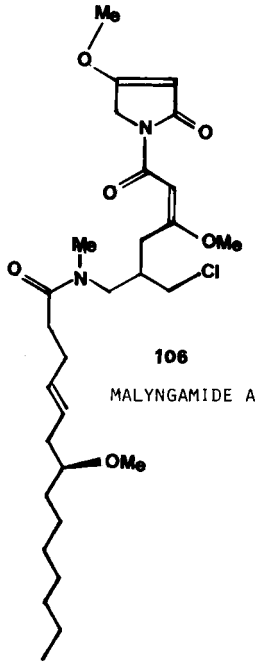
Marine organisms have provided very complex molecules possessing a pyrrolidinone ring as part of a urea function: dysidin (**105**) (*140*), malyngamide A (**106**) (*141*) and pukeleimides A, B, C, D, E, F, and G (**107–113**) (*142, 143*).

The culture broths of several microorganisms have yielded a series of unique



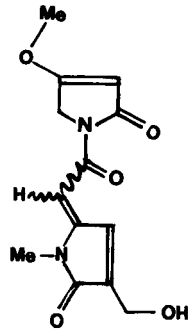
105

DYSIDIN



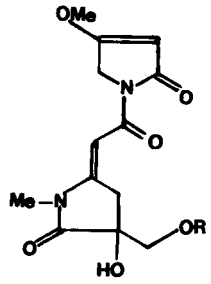
106

MALYNGAMIDE A



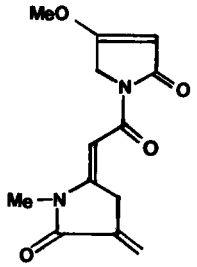
107 (E) A
108 (Z) B

PUKELEIMIDES

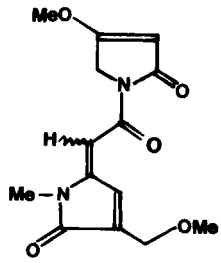


109 R = CH_3 C
110 R = H D

PUKELEIMIDES



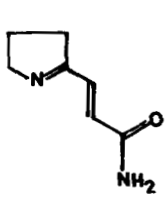
111 PUKELEIMIDE E



112 (Z) PUKELEIMIDE F
113 (E) PUKELEIMIDE G

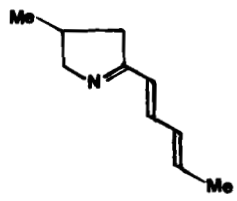
antibiotics containing pyrrolidine rings: desdanine (**114**) from *Streptomyces caelestis* (*144*), alkaloid A (**115**) from *Streptomyces* sp. NA-337 (*145*), ikarugamycin (**116**) from *S. phaeochromogenes* var. *ikaruganensis* (*146*), and mycosporine Z (**117**) from the fungus *Botrytis cinerea* (*147*).

Last but not least, a very intriguing terpenoid pyrrolidine alkaloid, polyzonimine was "milked" from the millipede *Polyzonium rosalbum* (*148*). The structural formula of polyzonimine (**118**) is based on an X-ray crystallographic analysis of its perchlorate and by a total synthesis.



114

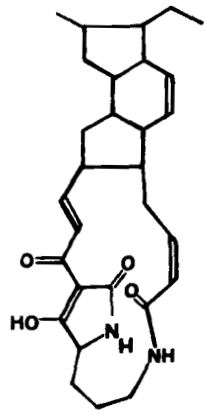
DESDANINE



115

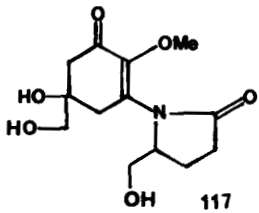
ALKALOID A

FROM S. SP. NA 337



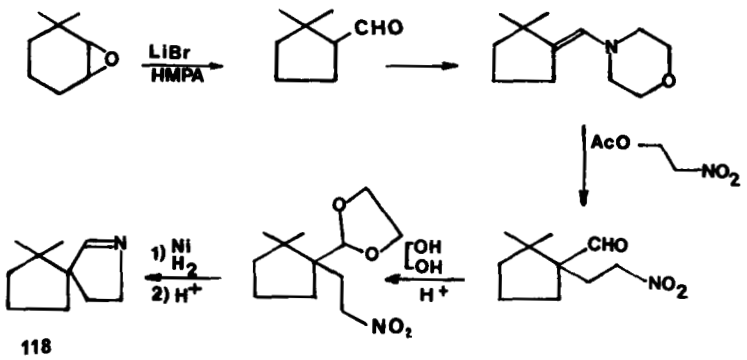
116

IKARUGAMYCIN



117

MYCOSPORINE Z



118

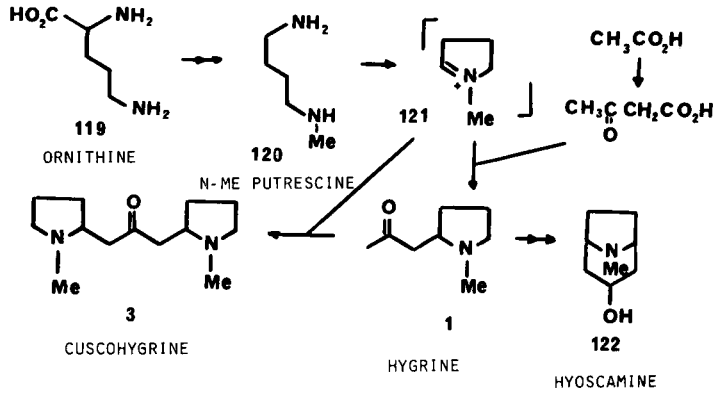
SYNTHESIS OF POLYZONIMINE

VI. Biosynthesis of Pyrrolidine Alkaloids

A. Biosynthesis of Hygrine and Cuscohygrine

The pivotal role of hygrine in the biosynthesis of cuscohygrine and of the tropane alkaloids has justified numerous investigations. The following scheme represents the now generally admitted pattern of formation of these bases.

Ornithine (**119**) is first converted to putrescine or *N*-methylputrescine (**120**)

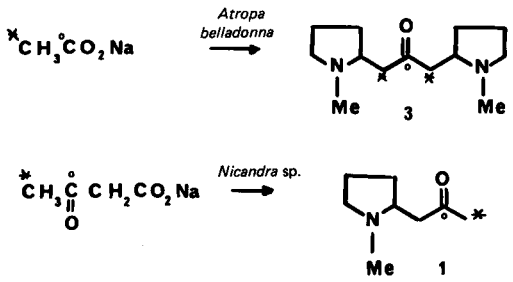


SCHEME 8. Biosynthesis of hydgrine and cuscohygrine.

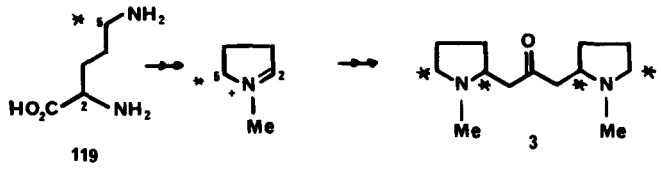
(via *N*δ-methylornithine) and then oxidized to a Δ-1-pyrrolinium salt (**121**), which condenses with an acetoacetate unit to give, after decarboxylation, hygrine (**1**). A second Mannich reaction transforms hygrine to cuscohygrine (**3**) (bimolecular process) or to tropanes such as hyoscamine (**122**) (intramolecular reaction).

The broad lines of the scheme were proved in the late 1960s by the incorporation of ornithine-2-^{14}C-δ-^{15}N, putrescine-1,4-$^{14}C_2$, *N*-methylputrescine-*4-t*, sodium acetoacetate-*3*-^{14}C, sodium acetate-*1*-^{14}C, and sodium acetate-*t* into cuscohygrine in *Scopolia lurida* (*149*). At the same, ornithine-2-^{14}C and acetate-*1*-^{14}C were fed into hygrine in *Nicandra physaloides* (*150*). The *in vivo* transformation of labeled hygrines to cuscohygrine was demonstrated in *Datura stramonium* (*150*). The mechanisms of incorporation of acetate and of acetoacetate into hygrine and cuscohygrine have been clarified as depicted in Scheme 9 (*151–153*).

More recently, E. Leete has demonstrated that in the incorporation of ornithine-*5*-^{14}C into cuscohygrine (*154*), scrambling of the label occurs unexpect-



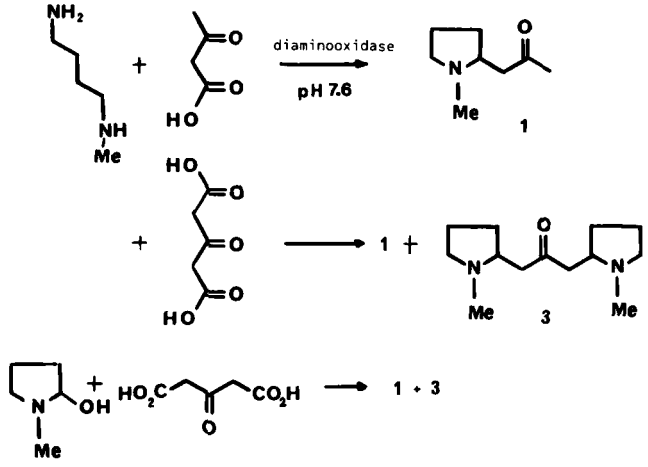
SCHEME 9. Incorporation of acetate and acetoacetate in hygrine and cusecohygrine.



SCHEME 10

edly. This fact can be traced back to a symmetrical intermediate along the biosynthetic pathway (Scheme 10).

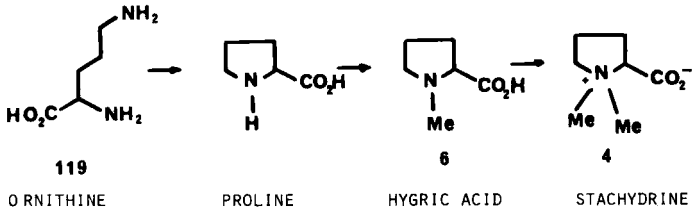
The viability of these biosynthetic schemes were supported by several enzymatic (*155*, *156*) or chemical (*157*) biomimetic syntheses of cuscohygrine and of hygrine (Scheme 11).



SCHEME 11. Biomimetic syntheses of hygrine and cuscohygrine.

B. BIOSYNTHESIS OF STACHYDRINE

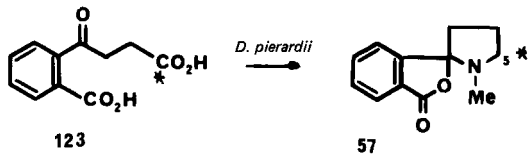
The biosynthesis of stachydrine in alfalfa *Medicago sativa* L. (Papilionoideae) has been investigated by Marion *et al.* who found evidence for the following sequence: ornithine → proline → hygric acid → stachydrine (Scheme 12) (*158*, *159*). The timing of each event has been discussed with regard to the age of the plant. Even though the young plant can synthesize stachydrine from hygric acid, it does not have the coenzymes for the transformation of ornithine to hygric acid. At the time of flowering, however, all of the necessary coenzymes are present to synthesize stachydrine from ornithine. This now explains the difficulties encountered in the early feeding experiments.



SCHEME 12. Biosynthesis of stachydrine (*153*, *159*).

C. BIOSYNTHESIS OF SHIHUNINE

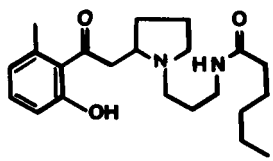
Unlike the preceding compounds, shihunine does not arise from ornithine. In feeding the orchid *Dendrobium pierardii* with acetate-*1*-^{14}C, radioactive shihunine was obtained; since the label was mainly located at C-5, a polyketide pathway was excluded. Orthosuccinylbenzoic acid (**123**), itself of the shikimic-α-ketoglutaric acid offspring, was found to be a direct precursor of shihunine (14.4% incorporation) by feeding experiments with ^{14}C- and ^{13}C-labeled material (*160*). It is worth noting that the experiment with ^{13}C is one of the rare incorporations traced by ^{13}C in nonmicrobial organisms.



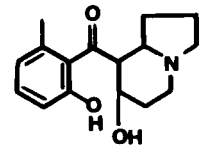
SCHEME 13. Biosynthesis of shihunine (*160*).

D. BIOSYNTHETIC HYPOTHESIS FOR THE OTHER ALKALOIDS

Although no experiment has yet been reported to support the idea, it seems clear that a majority of the pyrrolidine alkaloids arise from the ornithine, putrescine, and proline pool. This could be the case for ficine (**61**) and isoficine (**62**), vochysine (**63**), and phyllospadine (**64**) but also of the *Darlingia* alkaloids, which share common features with hygrine; this assertion probably also holds for the ruspolinone (**25**) and odorine–roxburghlin (**59**) families. Peripentadenine, isolated from a plant of the family Elaeocarpaceae, bears resemblance to other alkaloids of the elaeocarpus type such as isoelaeocarpicine (**124**) (*161*). It cannot be excluded, however, that spermidine may be a biosynthetic intermediate instead of putrescine. The question of the origin of ant alkaloid substances remains so far without an obvious answer.



49 PERIPENTADENINE



124 ISOELAEOCARPICINE

VII. Synthesis of Pyrrolidine Alkaloids

Many of the aforementioned alkaloids have been the goal of total synthesis. In some cases, syntheses were demanded to settle structure problems, in other cases to provide material for biological evaluation or, finally, to illustrate new chemical methodologies. Some examples of the first category of syntheses have been given in the preceding chapter (squamolone, polyzonimine) and others can be found in the rich chemistry of ant pyrrolidine alkaloids. The second class of syntheses may be exemplified by biologically active materials such as shihunine, a constituent of the Chinese drug *Tsung Huan-tsao,* domoic acid, or cucurbitine. General approaches to polysubstituted pyrrolidines have provided access to kainic acid (ene reaction, [2 + 3] cycloadditions) or to ant chemicals (alkylation of nitroamines or of urethanes). We have arbitrarily decided to classify these syntheses into two sets: those that functionalize a pyrrolidine ring and those in which this ring is synthesized.

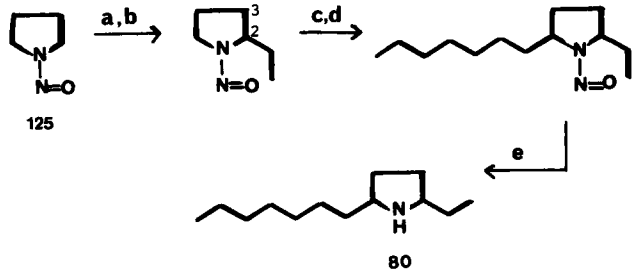
A. Syntheses Starting with a Pyrrolidine Ring

Pyrrolidine itself is not sufficiently activated to allow direct C—C bond formation at positions 2 or 3. However, under certain conditions the nitrogen atom may stabilize a reactive carbanion or carbocation (iminium ion). Both approaches have been fruitful.

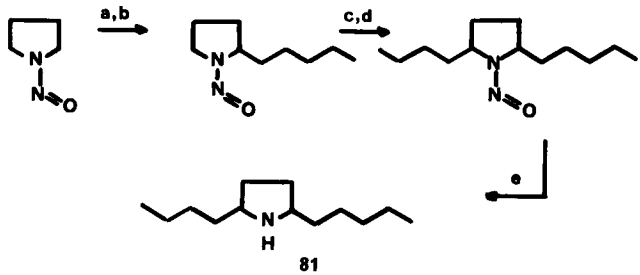
1. Syntheses via Carbanions α to Nitrogen

Two examples of synthesis of ant venom alkaloids via the Seebach (*162*) *N*-nitroso methodology have been published (*163, 164*). They start with *N*-nitrosopyrrolidine (**125**), which is sequentially alkylated at positions 2 and 5 (Schemes 14 and 15).

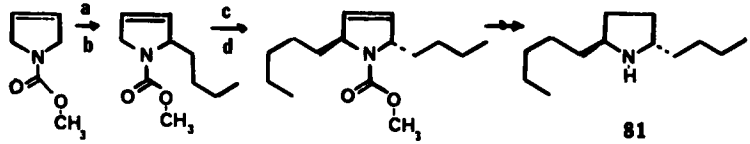
It is possible to deprotonate allylurethanes and to alkylate these anions regiospecifically α to nitrogen. An application of this sequence has led to a novel synthesis of 2-butyl-4-pentylpyrrolidine (*165*). A salient feature of this approach is its stereoselectivity (> 95% trans), much better than the one obtained with the *N*-nitroso method (1:1 mixtures) (Scheme 16).



SCHEME 14. (a) LDA, THF, HMPA; (b) EtI, 64%; (c) LDA, THF, HMPA; (d) n-$C_7H_{15}I$, 75%; (e) HCl, C_6H_6, 80%.



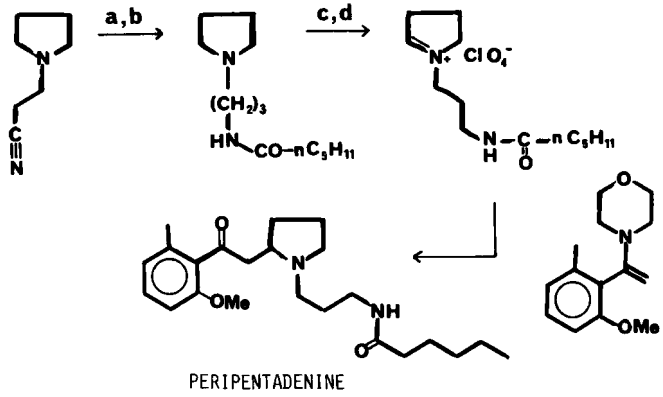
SCHEME 15. (a) LDA, THF, HMPA; (b) n-C_5H_{11}, 70%; (c) LDA, THF, HMPA; (d) n-C_4H_9I, 75%; (e) HCl, toluene, 90%.



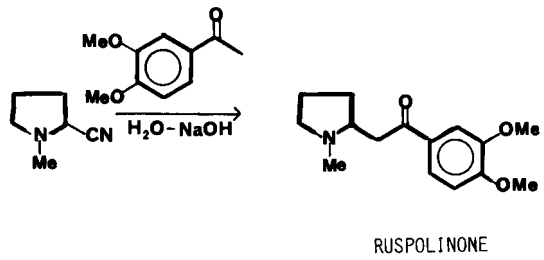
SCHEME 16. (a) LDA; (b) n-C_4H_9Br; (c) LDA; (d) n-$C_5H_{11}Br$; 38% overall.

2. Syntheses via Δ-1-Pyrrolidinium Ions or Equivalents

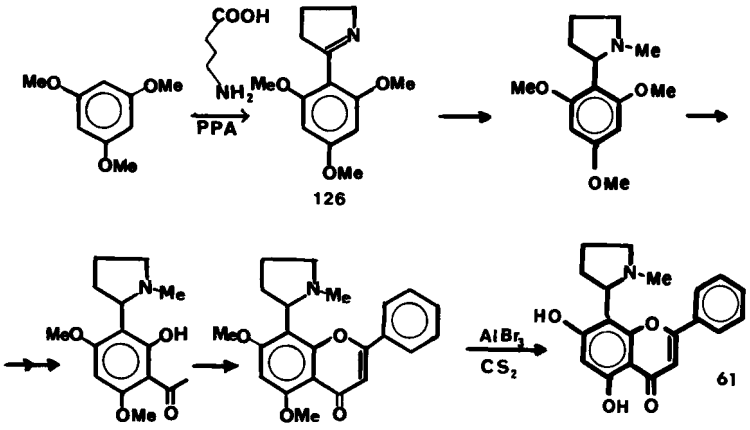
The alkylation α to nitrogen via iminium ions is a well known process related among others to the Mannich reaction. Many variations of this reaction have been described, depending on the way in which the cation is generated. In the synthesis of peripentadenine (Scheme 17), the iminium ion is formed by a mercury(II) oxidation of the corresponding pyrrolidine (*87*), while in the ruspolinone synthesis use is made of an amino nitrile as a masked iminium ion (Scheme 18) (*166*). Sequences of this type are also the basis of the now classic syntheses of hygrine, cuscohygrine, and related compounds.



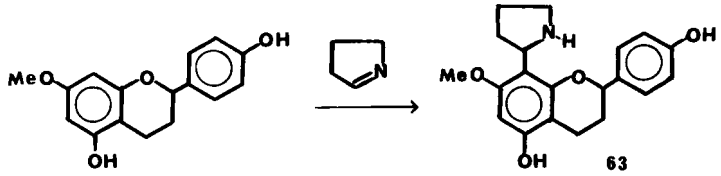
SCHEME 17. (a) $LiAlH_4$; (b) n-$C_5H_{11}COCl$; (c) $Hg(OAc)_2$; (d) $HClO_4$.



SCHEME 18

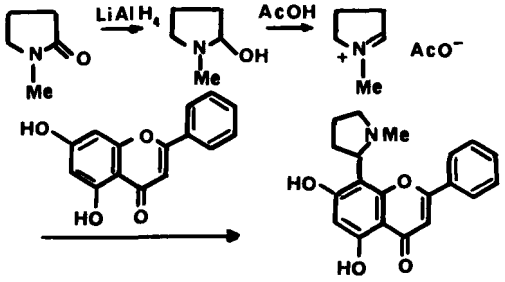


SCHEME 19. Synthesis of ficine (*167*).



VOCHYSINE

SCHEME 20



FICINE

SCHEME 21

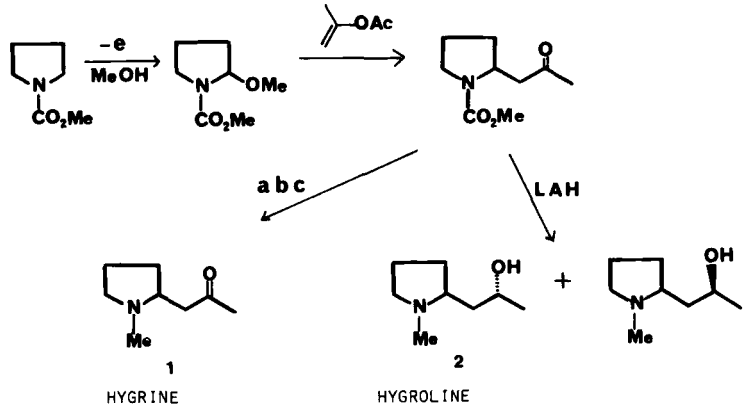
The syntheses of flavanoid alkaloids also rest on Δ-1-pyrroline chemistry and on Friedel–Crafts-type reactions. In Govindachari's pioneering synthesis of ficine (*167*), pyrrolidine **126** is formed by condensation of trimethoxybenzene and γ-aminobutyric acid in the presence of PPA (Scheme 19). Although the mechanism of this reaction has not been precisely determined, it may involve a Δ-1-pyrrolinium cation. These conditions were later used by Koch *et al.* in their synthesis of vochysine (Scheme 20) (*108*).

This kind of approach was later much improved by Leete through the use of the hemireduction product of *N*-methylpyrrolidone (Scheme 21) (*109a*).

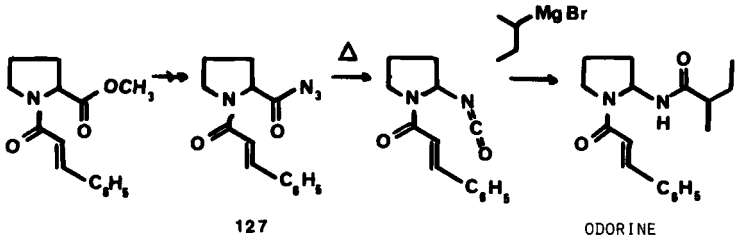
Electrochemistry offers a new and promising alternative for the generation of masked iminium ions. This approach is illustrated by the elegant syntheses of hygrine and hygroline (Scheme 22) (*168*).

3. Syntheses from Proline Derivatives

The bisamide odorine–roxburghilin and its dihydro derivative have been synthesized twice via Curtius rearrangement of a proline azide (**127**). The two syntheses followed similar lines and differed only in the preparation of the azide and in the solvent for rearrangement (*104, 105*). The stereospecificity of the Curtius rearrangement was an important argument for the determination of the absolute configuration of odorine (Scheme 23).



SCHEME 22. Electrochemical syntheses of hygrine and hygroline. (a) $HOCH_2CH_2OH$, H; (b) $LiAlH_4$; (c) H; 96% overall.

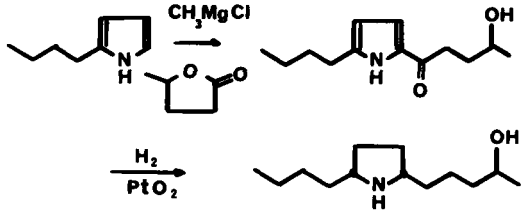


SCHEME 23

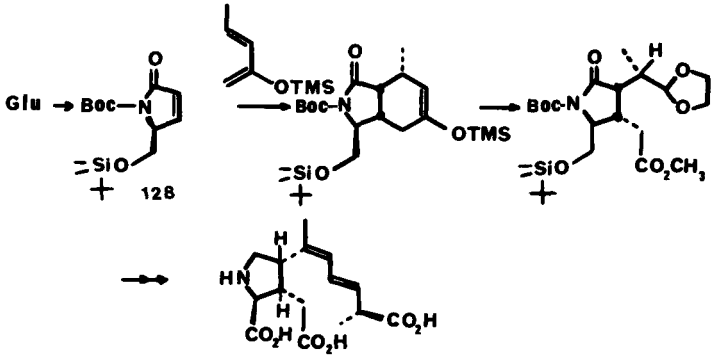
4. Miscellaneous Syntheses Starting from a Five-Membered Nitrogen-Containing Ring

Pyrrole itself is an obvious precursor of pyrrolidine by catalytic hydrogenation. One example of construction of an ant pyrrolidine analog from a pyrrole has been published (Scheme 24) (*169*).

The synthesis of domoic acid (**77**) by Ohfune is an illustration of the use of a



SCHEME 24



77

DOMOIC ACID

SCHEME 25. Synthesis of domoic acid.

pyroglutamic acid derivative (**128**) as a precursor of a proline nucleus. The control of the stereochemistry of the three stereo centers of the five-membered ring of domoic acid was realized by a Diels–Alder reaction, followed by cleavage of the remaining double bond (Scheme 25) (*127*).

B. Syntheses in Which the Pyrrolidine Ring is Constructed

1. The Hofmann–Loeffler Reaction

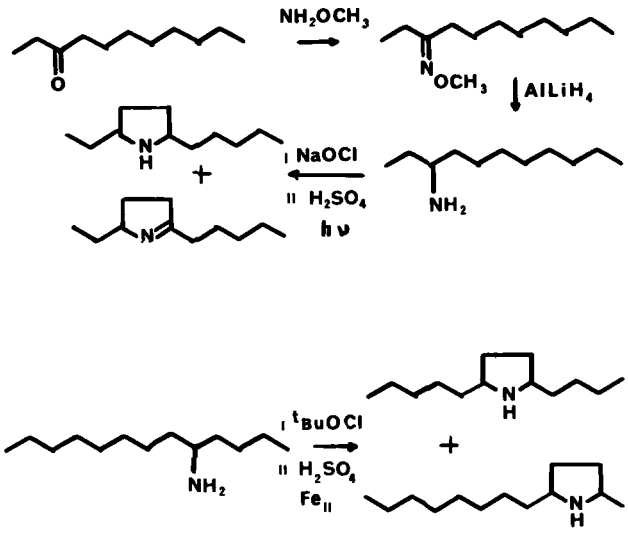
The Hofmann–Loeffler photolytic rearrangement of chloroamines has been used in early syntheses of ant pyrrolidines (Scheme 26) (*129, 164*). This reaction, however, suffers from lack of stereo- and regioselectivity.

2. By Reductive Amination of 1,4-Diketones

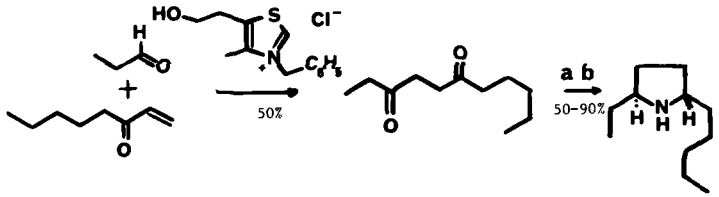
The reductive amination of 1,4-diketones in the presence of an equivalent of ammonia opens an avenue to 2,4-disubstituted pyrrolidines. Since Stetter's thiazolium salt chemistry allows the preparation of 1,4-diketones from α,β unsaturated enones and aldehydes, a large variety of pyrrolidines may be prepared. Two examples of such syntheses have recently been published by the T. H. Jones group (Scheme 27) (*132, 170*).

3. By Dieckmann Reactions

The early syntheses of allokainic acid had as a key step a ring closure of a diester derived from glycine. The presence of the masked isopropenyl chain



SCHEME 26



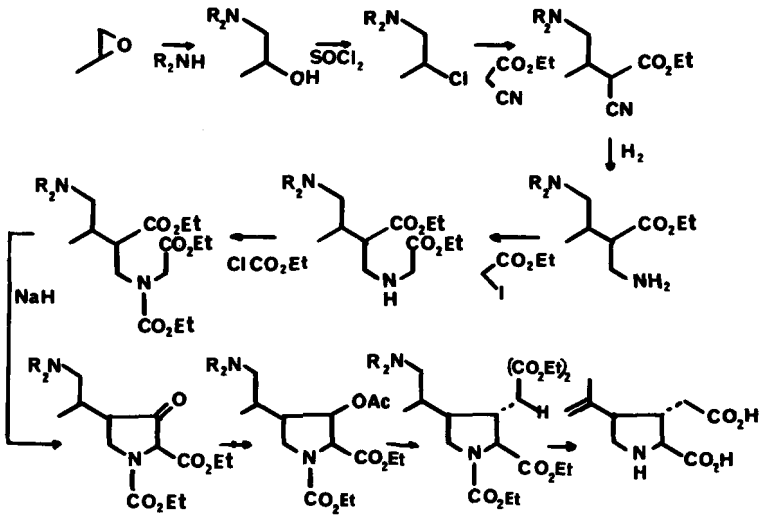
SCHEME 27. (a) $NaBH_3CN$, NH_4OAc, KOH, MeOH; (b) $NaBH_4$.

allowed distinction between the two ester α positions and thus orientated the cyclization. It is worth noting that protection of the nitrogen atom as a urethane is important to avoid retro-Michael reactions (Scheme 28) (*171*, *172*).

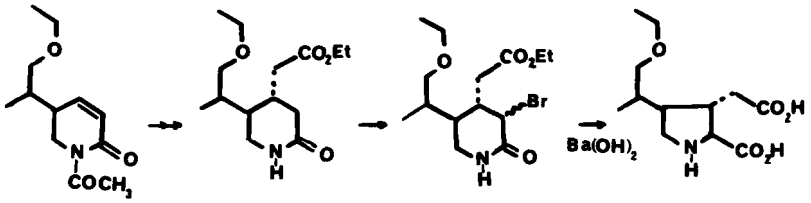
4. By Ring Contraction of a Piperidone Derivative

Two types of ring contractions have been used in the synthesis of pyrrolidines. The older one, an analogous Favorskii process, is the key step of Honjo's α-allokainic acid synthesis. The general lines of this approach are given in Scheme 29 (*173*).

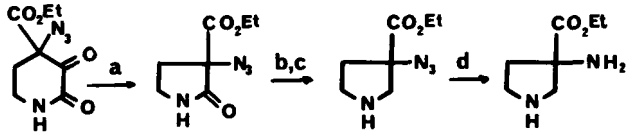
A different reaction involving the decarbonylation of an α-keto amide (**129**) is the basic idea of Monteiro's synthesis of cucurbitine (Scheme 30) (*174*).



SCHEME 28



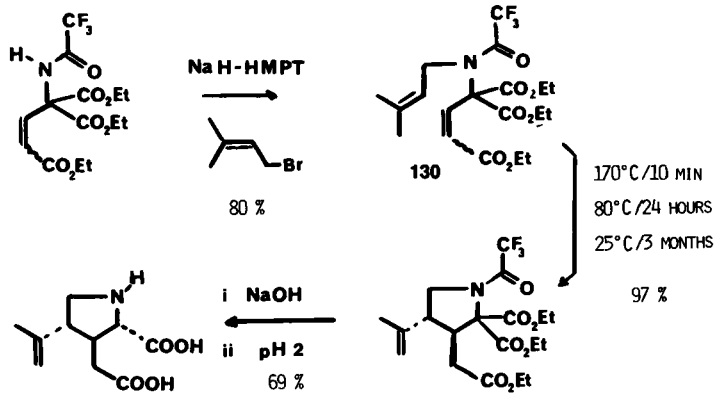
SCHEME 29



SCHEME 30. (a) CH_3CO_3H; (b) $Et_3O^+BF_4^-$; (c) B_2H_6; (d) PtO_2.

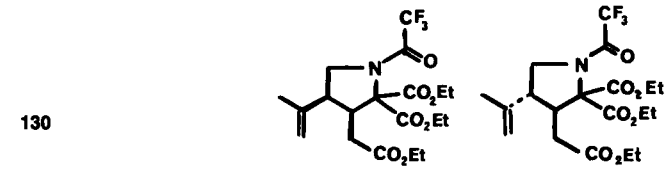
5. Via an Ene Reaction

The ene reaction offers great possibilities in the synthesis of 3,4 disubstituted pyrrolidines or piperidines (*175*). An illustration of this reaction is a short and selective synthesis of allokainic acid by Oppolzer and Andres (*176*) (Scheme 31). In subsequent work, the influence of the double-bond geometry in the



SCHEME 31. (*176*).

starting material (**130**) and of the reaction parameters was studied to select the best substrate and conditions (Scheme 32) (*177*).

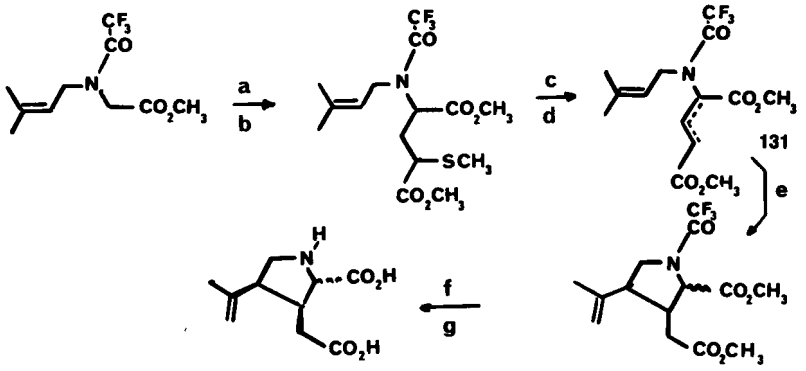


(Z) - ENOPHILE	THERMAL	25%	75%
	Et_2AlCl (-78°C)	0%	100%
(E) - ENOPHILE	THERMAL	50%	50%
	Et_2AlCl (-78°C)	11%	89%

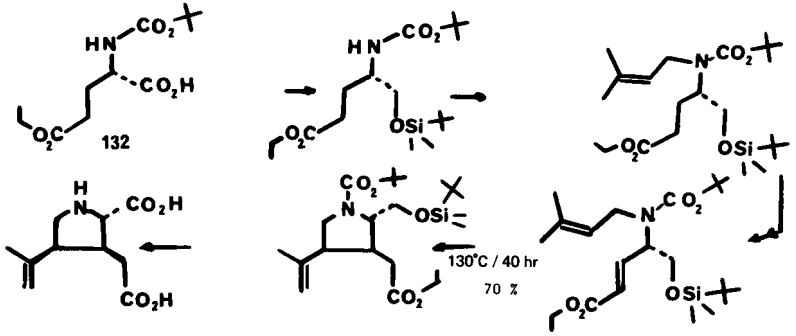
SCHEME 32. (*177*).

The low percentage of obtaining products belonging to the α-kainic acid series (at best 50%) was attributed to unfavorable transition states with repulsion between one of the aminomalonate ester groups and the isoprenyl chain. These difficulties were circumvented by using a simple α-amino ester (**131**) in lieu of the aminomalonate group; this has led to a simple synthesis of α-kainic acid (Scheme 33) (*178*).

The main lines of this approach were later embodied in an enantioselective synthesis of (−)-α-allokainic acid (Scheme 34) (*179*). The sole stereo center of the ene reaction starting material was derived from a glutamic acid derivative (**132**); to avoid loss of optical activity via double bond migration (see Scheme 33), the α acid function of kainic acid had to be reduced before the pyrolysis step



SCHEME 33. (a) LICA; (b) $CH_2C(SMe)CO_2Me$; (c) MCPBA; (d) 130°C, 36 hr; (f) OH^-; (g) H^+, 60%.



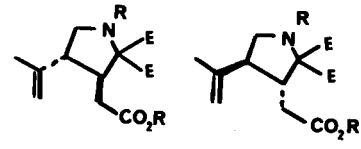
SCHEME 34

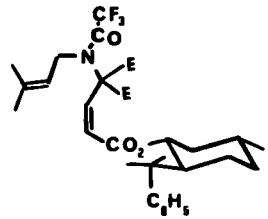
and then reoxidized at the end of the sequence (*179*). The completion of this total synthesis of (−)-α-kainic acid provided the first unambiguous determination of the absolute configuration of the natural product.

This sequence was obviously not amenable to a synthesis of optically active α-allokainic acid given the fact that an aminomalonate group was necessary. After unfruitful assays with menthyl esters, the Swiss group was rewarded by the discovery that the phenylmenthyl group (*180*) brings sufficient asymmetry to the reaction intermediate to afford products with a high percentage of favorable diastereoisomer (Scheme 35) (*181*).

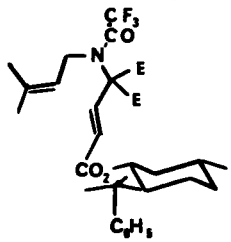
6. Via [3 + 2] Dipolar Additions

Pyrrolidines are attainable by [3 + 2] cycloaddition of azomethine ylides and olefins; one such reaction is exemplified by a total synthesis of α-allokainic acid (Scheme 36) (*182*).



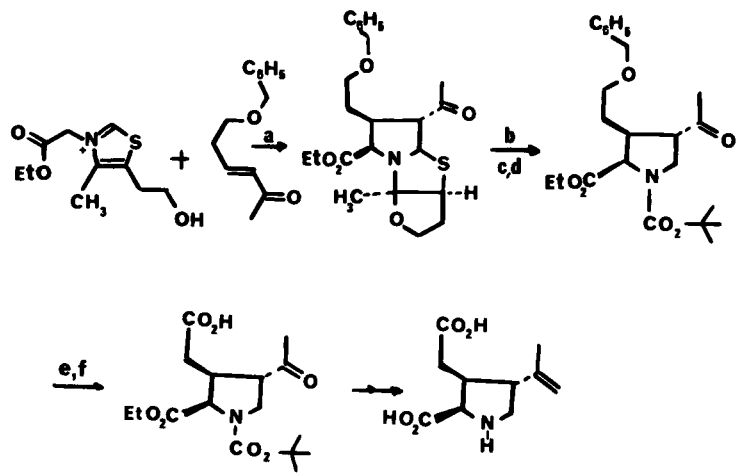


THERMAL	50%	50%
Et_2AlCl	95%	5%

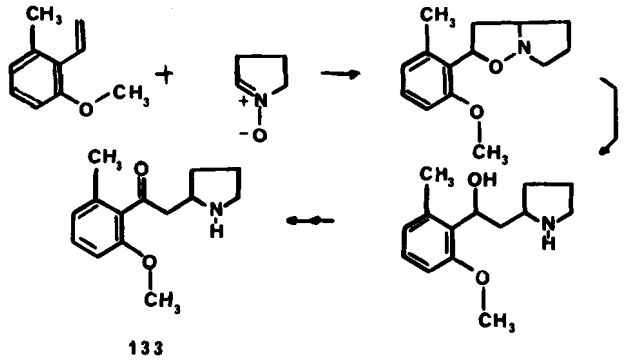


Et_2AlCl	15%	85%

SCHEME 35. Asymmetric synthesis of α-allokainic acid (*182*).



SCHEME 36. (a) Et_3N; (b) Bu_3SnH; (c) HCl, EtOH; (d) *t*-BuOCOCOO-*t*-Bu; (e) H_2, Pt/C; (f) Jones.



133

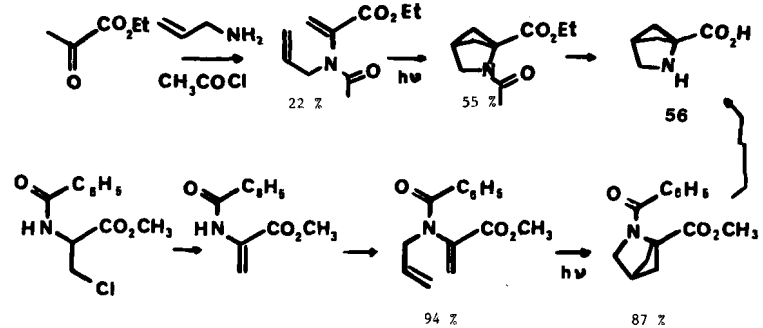
SCHEME 37

Nitrone cycloadditions may also lead to pyrrolidine according to another type of cycloaddition. The power of the method is illustrated by the synthesis of the peripentadenine intermediate **133** en route to *Elaeocarpus* alkaloids (Scheme 37) (*185*).

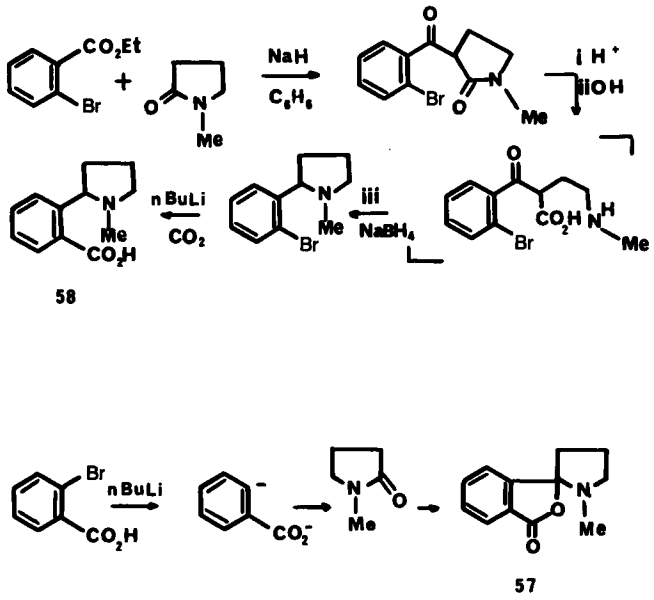
7. Miscellaneous

The presence of a pyrrolidine unit in complex systems such as the azabicyclo[2.1.1]hexane unit of 2,4-methanoproline (**56**) lends itself to synthesis pertaining to the 1,3-disubstituted cyclobutane part of the molecule. Thus two syntheses of **56** have been published, relying on the [2 + 2] photochemical synthesis of cyclobutanes. A nontrivial problem of the synthesis of these compounds is liberation of the target molecule from its protective groups (Scheme 38).

Several syntheses of shihunine (**57**) and of dihydroshihunine (**58**) have now been published and they all illustrate general synthetic methodology toward



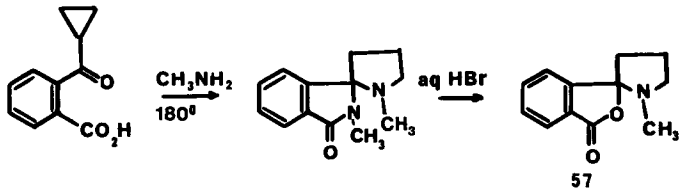
SCHEME 38. Synthesis of 2,4-methanoproline.



SCHEME 39. Dihydroshihunine and shihunine syntheses.

pyrrolidines. The first two routes, by Leete, showed different ways of incorporating a pyrrolidone into a complex system (Scheme 39) (*186*).

Curiously, the synthesis of shihunine via a phenylcyclopropylimine (*187*) is the sole example of a "simple" pyrrolidine alkaloid obtained according to this general pyrroline synthesis (*188*) (Scheme 40).



SCHEME 40. The cyclopropylimine approach to shihunine.

VIII. Biological Activities of Pyrrolidine Alkaloids

The chemical diversity of pyrrolidine alkaloids indicates a broad spectrum of biological activities, which, however, does not allow, at the present time, structure–activity relationship studies. The available data are inhomogeneous, ranging from investigations of pure compounds to reports of use in folk medecine.

A review article has been published on the biological activities of the alkaloids of *Erythroxylum* sp. (*189*). Whereas hygrine **1** has no anesthetic action, cuscohygrine (**3**) was found to inhibit the delayed-type hypersensitivity response to 2,4-dinitrofluorobenzene in mice. Several plant species containing cuscohygrine are widely used in the preparation of drugs, but the presence of very active alkaloids, such as cocaine and scopolamine along with **3**, does not allow the definition of the role of **3** in the alkaloid mixture. Such is the case, for example, of the *Erythroxylum* species used in the preparation of narcotics (*190*). Other cuscohygrine-containing plants used in folk medicine are *Datura inoxia* (*190*), *Whitana somnifera* (*33*), the latter a sedative drug in India, and *Datura stramonium*, used in Mexico as a narcotic in the treatment of asthma and of earache in children (*191*).

Soviet workers have studied the activity of stachydrine (**4**) and found it to slow down by 20% the systolic rate of frogs (at doses 0.02–2.5 mg per frog). It produces a positive effect on the central nervous system of the frog under conditions of hypoxia (*58*). Stachydrine is present in *Desmodium triflorum* whose total alkaloid mixture produces such significant actions as antispasmodic, sympathomimetic, CNS stimulant, and curarimimetic (*56*). These actions are consistent with the reported uses of the plant by natives of the Himalayas. *Capparris* species, which contain stachydrine, are used worldwide. *Capparis spinosa* is used in Israel (*192*) in the treatment of rheumatism, external pains, male and female sterility, and cough and lung complaints; it is used in India in cases of jaundice and asthma (*193*). *Capparis decidua* is used in some parts of India (*41, 194*) against rheumatism, gout, cough, asthma, and ulcers; it is also diaphoretic, alexeteric, and anthelmintic. *Capparis tomentosa* is toxic to camels (*44*) but is used in Rwanda as a diuretic and abortefact (*195*). *Capparis mooni* extracts have been marketed as antitubercular agents in India (*42*) but their activity has not been definitively established in subsequent studies performed in the USSR. *Capparis erythrocarpa* has found use in Tanzania against children's convulsive fever (*196*). The leaves of *Capparis zeylanica* are supposed to have a counter-irritant action (*197*). *Courbonia glauca* is reported as a fish poison in Rhodesia (*45*). The role of stachydrine in these activities, if any, is difficult to determine precisely, and these ethnopharmacological studies must be used as bases for further biological and chemical investigations.

This approach has been chosen to investigate the active principles of kinkeliba, a decoction of the leaves of *Combretum micranthum*, used against tropical fevers, bilious alimentary disorders, colic, and vomiting. No appreciable activity could be demonstrated for the isolated alkaloids (hydroxystachydrines) (*65*).

The reported use in the Middle East of the seeds of *Cucurbita* species as tenifuge (*198*) was traced back to the imino acid cucurbitine (**47** (*81*).

Besides these relations of biological activities, based on traditional plant use, there are reports of investigations of the following pure compounds: codonopsine

(**36**), which decreases blood pressure in cats (*76*); odorinol (**60**), an inhibitor of the growth of P-388 lymphocytic leukemia in mice (*106*); gerrardine (**73**), an antifungal (MIC ~ 50 μg/ml against *Candida albicans*) (*144*); α-kainic acid (**75**) is responsible for the anthelmintic properties of the seaweed *Digenea* simplex (*117, 118*).

Finally, the report by Angenot *et al.* of an exceptional increase of antimitotic activity in strychnopentamine (**104**) caused by the presence of a supplementary pyrrolidine ring, is worth noting (*199*). Chemists might use this fact as an reason to promote interesting new syntheses of pyrrolidine alkaloids or creation of unnatural molecules containing pyrrolidine.

IX. Addendum: Pyrrolidine Alkaloids from Black Pepper

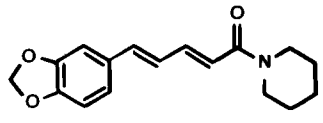
The preparation of a special chapter in this series on the constituents of pepper (*6*) led us to ignore pepper alkaloids. After publication of the chapter, we discovered that it dealt with the alkaloids of red pepper species (*Capsicum,* Solanaceae), which are not pyrrolidines, and the purpose of this addendum is to provide a survey of the pyrrolidine alkaloids contained in black pepper species *Piper,* Piperaceae.

The Piperaceae are represented by four genera and approximately 2000 species (*200*) growing in intertropical areas; among these, *Piper* is one of the largest genera known in the vegetable kingdom. Several species of *Piper* have an economic importance: *Piper nigrum* L. (black pepper) is a well-known condiment, called black gold in the middle ages. It is cultivated in the India–Malaysia area along with *Piper betle* L., the leaves of which are used with the nuts of *Areca catechu* L. in the preparation of a chewing condiment appreciated in the Orient.

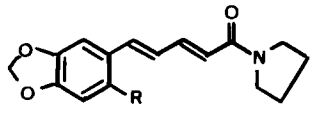
The chemistry of pepper has long been studied and the pungent principle of black pepper—a piperidine alkaloid, piperine **134**—was isolated as early as 1877 (*201*). Its synthesis from the acid and piperidine was accomplished in 1882. (*202*). The corresponding pyrrolidine alkaloid trichostachyne (**135**) was isolated some 100 years later from several *Piper* species (see below). The cooccurence of piperidine and pyrrolidine alkaloids is a common feature of the chemistry of pepper. In many cases, the crude alkaloid extract is first cleaved with acids or bases and then each alkaloid is reconstituted by selective amidation. For the sake of unity, this chapter will be limited to comments on pyrrolidines, even in cases where they are minor alkaloids.

Piper guineense Schum. and Thonn is a creeper found in humid and shady forests from Guinea to Uganda and Angola; it is known as the source of the "Ashanti pepper." Its fruit and roots contain the above-mentioned piperine **134** and trichostachyne (**135**) (*203, 204*). In the root was also found wisanidine (**136**) named after the Nigerian vernacular name of the species, *wisa osoro* (*205*). The

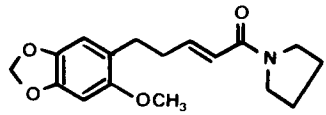
structure of this compound ($C_{17}H_{19}O_4N$, MP 171–173°C) was established as 6-methoxytrichostachyne after spectroscopic studies. It was synthesized from pyrrolidine and wisanic acid chloride. An alkaloid with the same structure was independently isolated from the seeds of *Piper guineense* and named okolasine (after the place of collection, Okola, Cameroon) (*206*). Physical and spectroscopic data seem to indicate that the two bases are but one compound. Wisanidine is accompanied in the seeds by its dihydro derivative **137** (*201*). Compounds **136** and **137** were also chemically correlated (DDQ dehydrogenation).



134 PIPERINE



135 R = H TRICHOSTACHINE
136 R = O CH$_3$ WISANIDINE = OKOLASINE

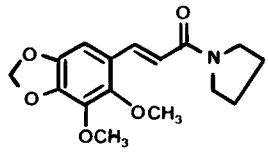


137
DIHYDROWISANIDINE

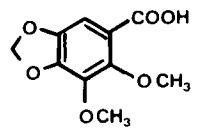
Piper methysticum Forst is a bush tree from Polynesia, known under the local name of *kawa-kawa;* its roots are used in the preparation of an inebriating social beverage called *kava,* the active principles of which are not alkaloids. Two alkaloids were isolated from the root: 1-cinnamoylpyrrolidine (**138**) and 1-(*m*-methoxycinnamoyl)pyrrolidine (**139**) (*208*). Their structures were determined by spectroscopic means as well as by total synthesis.

R = H **138**
R = O CH$_3$ **139**

These alkaloids bear close resemblance to peepuloidine (**140**), the main alkaloid of *Piper peepuloides* Roxb., a medicinal plant from India. The main structural problem with **140** was the location of the five benzenic substituents,



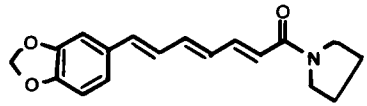
140
PEEPULOIDINE



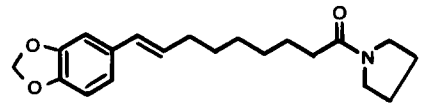
DILL-APIOLIC ACID

which could not be determined by ^{1}H-NMR spectroscopy. The problem was finally solved by oxidative degradation ($KMnO_4$) to a known compound, dillapiolic acid (*209*).

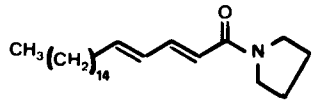
Piper trichostachyon C.DC. from India contains a variety of pyrrolidine alkaloids in its stem and leaves. Among these one finds trichostachyne (**135**) (*210*), its C_2 homolog 1-piperettylpyrrolidine (**141**) (*211*), tricholein (**142**) (*212*), and a long-chain dienamide: trichonine or 1-pyrrolidinyl-(*E,E*)-eicosa-2,4-dienamide (**143**) (*213*).



141 1 - PIPERETTYL PYRROLIDINE



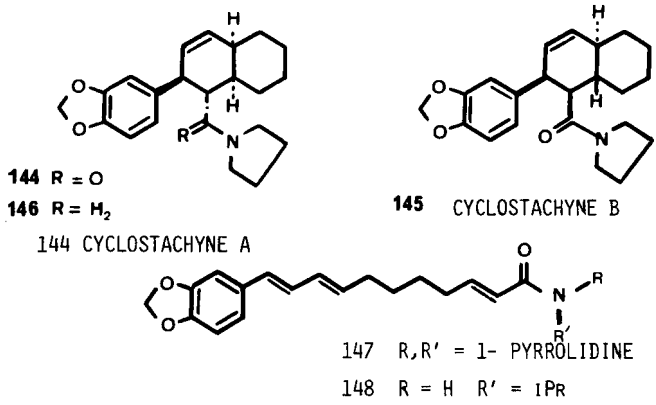
142 TRICHOLEINE



143

TRICHONINE

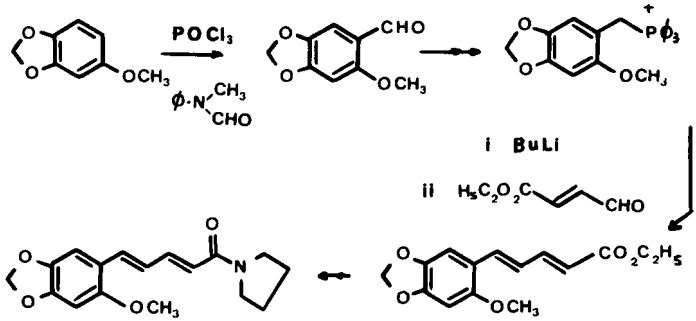
The stems of *P. trichostachyon* have yielded long-chain unsaturated amides and two fascinating pyrrolidine alkaloids containing cis- and trans-fused decalin systems: cyclostachin A (**144**) and B (**145**). These structures were proposed on the basis of spectroscopic studies (^{1}H NMR) and on an X-ray crystal analysis of derivative **146** (*214*). This unambiguously demonstrated the relative configurations of the four stereo centers of **144** and also the fact that it was a racemate, an idea already supported by ORD and CD data. Cyclostachin B differed from **144** by the simultaneous inversion of two contiguous stereo centers (*215*). Although apparently unimportant, these structural features are of particular significance with regard to the biosynthesis of **144** and **145.** The location of the decalin double bond, the existence of **144** and **145** as racemates, and the configurations of the four stereo tertiary centers plead for a Diels–Alder origin for these compounds. Their possible precursor in that case would be the (*E,E,E*)-triene **147** and the two alternative approaches of the dienophile toward the diene would lead to isomers **144** and **145.** Despite the fact that **147** was not isolated from the plant, the idea was supported by the isolation of the related triene piperstachine **148** and by the successful *in vitro* preparation of **144** and **145.** The fact that these cycload-



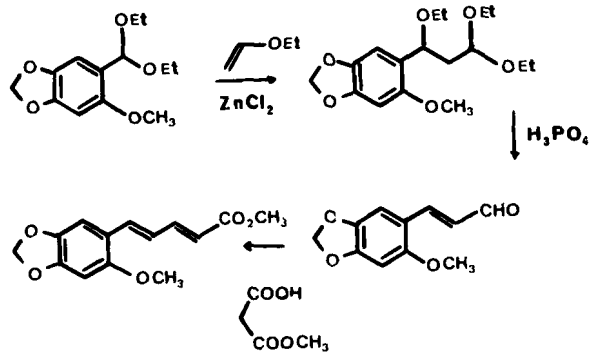
ditions could only be performed in boiling xylene was used by the authors as an evidence of the natural origin of the cyclostachines. Doubt can be raised on this assumption following the recent discoveries of low-temperature Diels–Alder reactions performed in water (*216*).

The total syntheses of these pepper alkaloids are not those of pyrrolidines but rather syntheses of their acid parts. Thus dihydrowisanidine (**137**) has been prepared by a series of reactions, the key step of which is the formation of the carbon–carbon double bond by a Wittig–Horner reaction (*217, 218*). Schemes 41 and 42 summarize two syntheses of okolasine from sesamolmethyl ether (*219*); of course, routes to okolasine also yield the corresponding piperidine alkaloid wisanine. Molybdenum-catalyzed elimination of allylic acetate (**149**) yielded (*E,E*)-diene ester **150** en route to trichonine (*220*); worthy of note is the use of an aluminum amide in the preparation of amide **143** from ester **150** (Scheme 43).

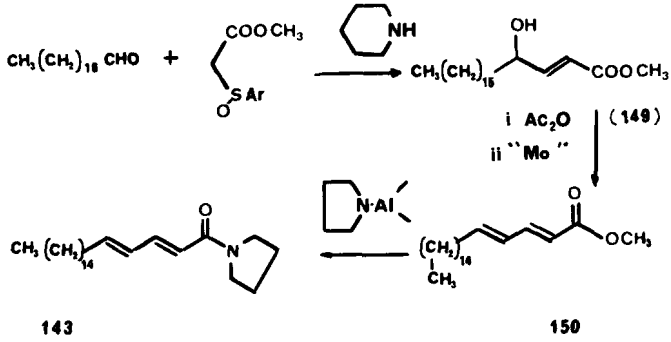
The Indian *Piper* species have been the subject of a review article describing their chemistry and biological activities (*221*).



SCHEME 41



SCHEME 42



SCHEME 43

Acknowledgment

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Note Added in Proof

The results announced in Ref. *150* have been reexamined and criticized by E. Leete, *Phytochemistry* **24,** 953 (1985).

— CHAPTER 4 —

METABOLIC TRANSFORMATIONS OF ALKALOIDS

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I. Introduction

The alkaloids are an enormously complex grouping of nitrogen-containing organic compounds that have long fascinated chemists, biochemists, pharmacognosists, pharmacologists, plant physiologists, and others interested in their myriad of interesting physical, chemical, and biological properties. They are widespread in their natural occurrence, being found in plants, mammals, arthropods, marine species, club mosses, fungi, and bacteria (*1*). Alkaloids continue to be of great interest as drugs themselves, or as the prototype compounds from which many drugs are derived. Their broad occurrences in nature, their structural and biosynthetic diversities, and widely differing types of biological activities have rendered the alkaloids extremely difficult to categorize and define. Pelletier discards the classical restrictive definition of an alkaloid in favor of a much simpler description as follows (*1*): "An alkaloid is a cyclic organic compound

THE ALKALOIDS, VOL. 27

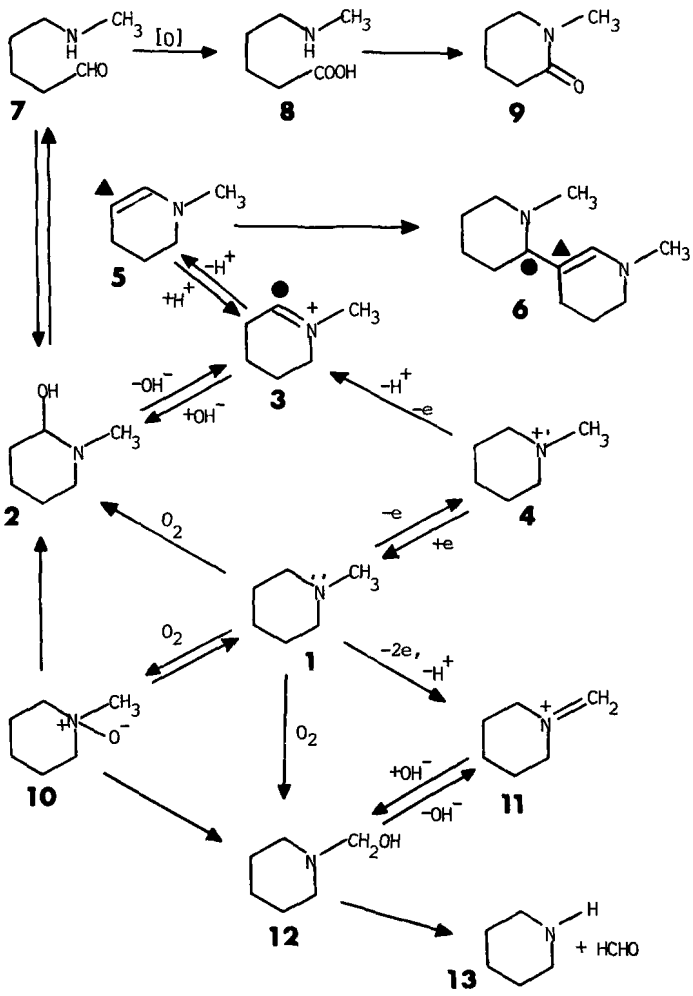
containing nitrogen in a negative oxidation state which is of limited distribution among living organisms." This simple definition accommodates all of the compounds traditionally considered among the alkaloids, and it extends the group to include amides, amine oxides, quaternary ammonium salts, and others not previously included.

This review is concerned with the metabolism of alkaloids by microbial, mammalian, and plant metabolic systems. This topic was last covered in *The Alkaloids* in 1981 in an excellent and detailed review by Holland (*2*). Microbial transformations of the alkaloids have also been described by others (*3–7*). Most of these reviews provide descriptions of the results obtained when alkaloid substrates undergo biotransformation reactions in a microbial or enzymatic system. We present an updated survey of biotransformations among the various classes of alkaloids and have attempted to focus attention on both the fascinating chemical and biochemical mechanisms of alkaloid biotransformation reactions—and on the metabolic systems that catalyze them. In this regard, the properties of many of the enzyme systems known to catalyze chemical transformations of alkaloids are described in a separate section of the chapter. The last section is devoted to a survey of biotransformations obtained with specific groups of alkaloids. This section is purposely organized according to structural types of alkaloids such as the isoquinolines, quinolines, indoles, and others. This organization is used because it fits a historical pattern for the consideration of such compounds and because it offers a convenient and logical means of describing the useful chemistry obtained with organic nitrogen compounds.

Chemistry and Biochemistry of Alkaloid Bioconversions

Nature seems to be an inexhaustible source of new alkaloid structures, which may serve as exciting new prototypic compounds for the development of useful pharmacologic agents. The alkaloids provide new targets for modern spectral analyses, and they challenge organic chemists to develop innovative synthetic methodology. In the same way, the alkaloids provide stimulating challenges to biochemists interested in biochemical mechanisms involved in their formation and biotransformation in living systems. While the structural complexities of many alkaloids render routine chemical and biochemical studies difficult, this feature often offers unique opportunities for the observation and discovery of new chemical and biochemical mechanisms. These opportunities serve as the basis for most contemporary applications of biocatalysis in natural products chemistry (*8*).

Microorganisms, plants, and mammalian systems all contain enzymes capable of catalyzing chemical transformations with alkaloid substrates. Interesting and useful enzyme reactions that may occur with alkaloids include oxidations, reduc-



SCHEME 1. Possible pathways of biotransformation of the nitrogen heterocycle *N*-methylpiperidine (**1**).

tions, hydrolyses, and conjugation reactions. The myriad of reactions possible with alkaloids can perhaps best be appreciated by considering the several predictable ways in which a very simple nitrogen heterocycle such as *N*-methylpiperidine (**1**), might be transformed by enzymes. These are summarized in Scheme 1.

All of the transformations illustrated in Scheme 1 are oxidative in nature and are typical of reactions catalyzed by well-known enzyme systems found in microorganisms, plants, and mammals. Monooxygenase activation and introduction of molecular oxygen may result in the formation of carbinolamine **2**, which

serves as a branch point in the generation of products. The carbinolamine may open to form the equivalent amino aldehyde **7**, which can be further oxidized to **8** and condensed to form the lactam **9**, or it may lose OH to form a reactive iminium species such as **3**. An alternative pathway to the formation of **3** would involve the initial one-election oxidation of **1** to form the radical cation **4**, which, upon loss of a proton and a second electron, forms the iminium derivative. Isomerization of the iminium **3** to the enamine **5** provides two intermediates that undergo enamine dimerization to form **6**. The carbons involved in the carbon–carbon bond forming reaction are indicated by the darkened symbols. An alternate path by which *N*-methylpiperidine may be oxidized is also illustrated in Scheme 1. The central intermediate is the carbinolamine **12**, which would form by direct introduction of molecular oxygen into the methyl group, by initial one-electron oxidation followed by loss of a second electron and a proton to form iminium **11**, or by initial N-oxidation to **10** and subsequent rearrangement to **12**. Carbinolamines such as **12** are chemically unstable, and they eliminate formaldehyde to yield the N-demethylated analog **13**. Thus with a very simple substrate such as *N*-methylpiperidine, one could expect to form a few stable metabolic products (i.e., **9, 6, 10,** and/or **13**) by any of several possible combinations of enzymatic and nonenzymatic pathways. In many cases, the only way of distinguishing among the range of mechanistic possibilities illustrated here would be to isolate the enzyme(s) responsible. This is due to the fact that many of the intermediates postulated in Scheme 1 (i.e., **2, 3, 5, 11,** and **12**) are intrinsically unstable and subject to rapid decomposition and low steady-state concentrations in reaction media.

1. Enzymes as Reagents in Alkaloid Chemistry

Much activity is evident in the application of enzymes in synthetic and natural products chemistry (*9–26*). Surprisingly, this is not a new field of endeavor, but rather one that was extensively developed for application in solving synthetic chemical problems in the steroid field. The earliest work in this field took place during the early twentieth century, and serious industrial application of biocatalysis began in the late 1940s (*8*). The successes obtained in steroid chemistry clearly underlined the potential for biocatalysis to contribute in other areas of natural products chemistry including that with the alkaloids.

In essence, an enzyme-catalyzed equivalent exists for almost every type of chemically catalyzed reaction, and thousands of these have been documented in comprehensive monographs and reviews (*9–26*). Many reactions have been observed in relatively specialized areas, particularly with groups of organic compounds such as the steroids, other terpenoids, antibiotics, aromatics, and alkaloids. Specific chemical reactions have been accomplished with intact and growing microbial cells, with plant and mammalian tissue preparations, and with

cell-free enzyme preparations of varying degrees of purity. With isolated enzyme systems, reactions are usually one-step in nature, whereas with whole-cell or tissue preparations it is possible to obtain multistep conversions.

It is useful to compare the catalytic properties of enzymes and traditional chemical reagents used in synthetic or natural products chemistry. Most enzyme reactions are achieved under very mild reaction conditions such as pH 7.0 at room temperature. They require no strong acids, bases, or exogenous heavy metals of possible environmental concern. Unwanted side reactions are minimized in sensitive molecules owing to mild reaction conditions, and it is unnecessary to employ troublesome blocking groups commonly used in organic synthesis. A major difference between traditional catalysts and enzymes is found in the highly specific ways in which enzymes interact with substrate molecules. Because enzymes are chiral catalysts with rigid substrate binding properties, they often effect reactions of high stereo- or enantiospecificity. They may discriminate between racemic molecules and achieve other chemical transformations of value in asymmetric synthesis. A major aim among many recent studies in biocatalysis has been to identify enzyme systems or whole microbial cells that catalyze biotransformation reactions with predictable stereochemical outcomes. Noteworthy limitations of biocatalysis include the instability of some enzyme systems when removed from their cellular environments, the expense of cofactors required in some types of biotransformation reactions, and the low solubilities of some organic substrates in aqueous media. Some of these drawbacks may be overcome by the use of whole cells that generate cofactors *in situ*, by preparing immobilized biocatalysts, or by using enzymes in nonaqueous solvents (*8, 16, 17, 24*).

Many possibilities exist for the exploitation of biocatalysis in alkaloid chemistry (*8*). Biocatalysts may achieve highly selective transformations of prototype compounds leading to products that are rare or only available in very low yield by conventional chemical approaches. Interesting new analogs may be prepared without having to resort to new and lengthy total synthetic chemical methods. In addition, biocatalysis can be readily adapted as mimics of plant, microbial, and mammalian metabolic systems by affording metabolites of alkaloids similar to those formed in biosynthetic processes. Indeed, biocatalysis with alkaloids affords rich opportunities for displaying novel biochemical reactions or unusual rearrangements that contribute to our understanding of biosynthetic or biodegradative pathways.

2. Microbial Models of Mammalian Metabolism

Alkaloids are of high pharmacologic, toxicologic, and environmental importance. Metabolic disposition studies are indispensable when attempting to under-

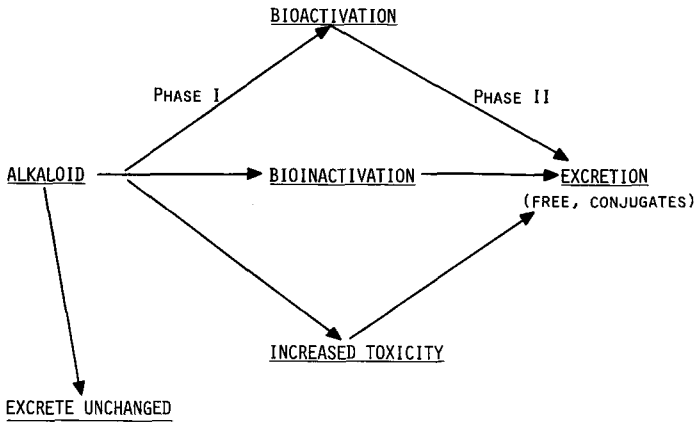


FIG. 1. Some of the possible effects of enzyme transformations on the activities of alkaloids in mammalian systems.

stand how compounds such as the alkaloids elicit biological effects in mammals. When alkaloids are ingested or administered to animals (including man), they seldom escape from undergoing enzymatic transformation by many of the enzyme systems traditionally associated with the field of drug metabolism. Metabolic changes in the structures of alkaloids and other xenobiotics may result in one or more of the following phenomena: conversion from inactive to active forms (bioactivation), conversion from active to inactive forms (bioinactivation), conversion to a toxic and less useful form, conversion to a metabolite with different biological activity. These possibilities are illustrated in Fig. 1. Common mammalian Phase I and Phase II biotransformation reactions have been summarized (*27*) and they include: for Phase I, oxidations, reductions, and hydrolyses; and for Phase II, conjugation reactions such as glucuronidation, sulfate conjugation, glycine conjugation, acetylation, and O-methylation.

Most mammalian metabolism studies are performed in test animals such as rats, mice, and guinea pigs prior to generating similar information in humans. One problem facing investigators is that different species may metabolize a given alkaloid substrate in more than one way. Metabolic disposition studies may also be rendered analytically difficult because of the small amounts of alkaloid metabolites obtained (tens of micrograms) and the need for complete ^{13}C and ^{1}H NMR and other spectral analyses in the elucidation of metabolite structures. This problem has been complicated with compounds such as the Catharanthus alkaloids, for example, because the parent alkaloids are difficult to prepare synthetically, and presumed metabolites are unknown. Microbial transformation systems offer attractive adjuncts to methods used in usual drug metabolism studies through their ready abilities to produce quantities of metabolites identical to those formed by mammals.

The concept of microbial models of mammalian metabolism was elaborated by Smith and Rosazza for just such a purpose (*27–32*). In principle, this concept recognizes the fact that microorganisms catalyze the same types of metabolic reactions as do mammals (*32*), and they accomplish these by using essentially the same type of enzymes (*29*). Useful biotransformation reactions common to microbial and mammalian systems include all of the known Phase I and Phase II metabolic reactions implied, including aromatic hydroxylation (accompanied by the NIH shift), N- and O-dealkylations, and glucuronide and sulfate conjugations of phenol to name but a few (*27–34*). All of these reactions have value in studies with the alkaloids.

Strategy in Using Microbial Models of Mammalian Metabolism. In using the microbial models concept, it is possible to employ microoorganisms as mimics of mammalian metabolic systems by conducting parallel metabolic experiments, either by using mammalian and microbial systems at the same time, or by using microorganisms prospectively to predict the types of metabolites that might be formed by mammals. In either case, one would hope to obtain essentially the same range of metabolites with both types of metabolic system. The value of parallel experiments was extensively underlined by Smith and Rosazza in several reviews (*27–32*). The predictive value of microbial metabolic systems has been emphasized many times. Clark *et al.* (*35*) present a recent example of this in their studies on the metabolism of the antimalarial compound Primaquine. In microbial transformation experiments, a carboxylic acid metabolite was the major compound produced by the fungus *Aspergillus flavus*. In subsequent experiments, the carboxylic acid metabolite was also identified as the major metabolite of primaquine in the plasma in rats and rhesus monkeys largely because analytical standards of the microbially produced carboxylic acid allowed these investigators to search specifically for the previously unidentified compound. It is only fair to mention that while the end products of metabolism of microorganisms and mammals may be the same for a given compound, the pathways to metabolite formation and patterns of metabolites formed might also be significantly different. Cerniglia *et al.* have investigated this possibility extensively in studies on the mechanism of aromatic hydroxylation of polycyclic aromatic hydrocarbons (*36–38*). The stereochemistries of dihydrodiol intermediates formed with naphthlene, anthracene, and phenanthrene are different in the fungus *Cunninghamella elegans* and rat liver, and the positions of oxidation about the aromatic ring differ as well.

Smith and Rosazza have suggested that microbial transformation experiments could best be carried out by using a series of perhaps 10 metabolitically prodigious microorganisms as microbial models. Microorganisms for such work may be selected on the basis of considerable literature precedence for their abilities to catalyze the desired biotransformation reaction (i.e., O-dealkylation, N-dealkylation, aromatic hydroxylation, and reductions). The alkaloid substrate

is incubated with each microorganism, using methods previously described (*31*), and metabolites are detected through simple screening experiments coupled with suitable chromatographic analysis. When parallel metabolic experiments are performed, metabolites common to both mammals and microorganisms may be prepared by simple fermentation scaleup techniques, thus obviating the need for time-consuming total or partial synthetic organic chemical approaches. By using large-scale fermentation vessels, it is possible to prepare sufficient quantities of metabolites for complete chemical and spectral identification as well as for biological evaluation. We initially felt that it might be unlikely for a single microorganism to catalyze all of the Phase I and Phase II biotransformations commonly observed in a mammalian liver. However, some microorganisms have demonstrated an uncanny ability to mimic mammalian metabolic systems. For example, *Cunninghamella echinulata* (NRRL 3655) accomplishes allylic hydroxylation, carbon–carbon bond fission via epoxide intermediates, and ester and glucoside conjugation, all with a single substrate (*39*). This same microorganism also achieves aromatic hydroxylation and O- and N-demethylation with other compounds. In similar fashion, *Streptomyces griseus* (UI-1158) accomplishes aromatic hydroxylation, O- and N-demethylation, O-methylation, carbon–carbon bond fission, and N-oxidation reactions with substrates ranging from alkaloids to coumarins (*8*). Convenient source listings of useful microorganisms may be gleaned by an examination of our literature citations on microbial models of mammalian metabolism and by examination of other primary and secondary sources that address and organize the literature of microbial transformation according to specific reactions.

3. Microbial Models of Plant Metabolism

All of the principles and ideas covered in the previous section may be translated directly to the use of microorganisms as tools in the production of compounds of plant biosynthetic or biodegradative importance. Just as one finds microbial systems to be of value in preparing metabolites in mammalian systems, it may be possible to use microbial transformations to prepare derivatives of alkaloids that might be found rarely or only in very small quantities in plants. In this way, abundant prototype alkaloids may be used as microbial transformation substrates to provide a range of metabolites. As in the mammalian case, metabolism studies using plant tissues, tissue cultures, or cell-free extracts may be conducted in parallel with microbial metabolic systems. Metabolites common to both would be prepared in quantity by relatively simple fermentation scale-up methods.

4. Alkaloids in Mammalian Systems

It seems reasonable to include a mention of the topic of alkaloids in mammalian systems, since these compounds apparently form in mammals by reac-

tions typical to those commonly found in plants and probably microorganisms. The topic of mammalian alkaloids was reviewed by Collins in *The Alkaloids* in 1983, where aspects of the formation, detection, metabolism, and effects of tetrahydroisoquinoline and tetrahydro- or aromatic carbolines were considered (*40*).

II. Enzymes That Catalyze Alkaloid Transformations

A. General Considerations

The biotransformation reactions of alkaloids that we shall consider are catalyzed by enzymes, either in purified form or as constituents of intact organisms. Although alkaloids are structurally defined as cyclic organic compounds containing nitrogen in a negative oxidation state (*1*), biotransformation reactions need not be limited only to these structural features. Indeed, most alkaloids have many different functional groups that are susceptible to enzyme-catalyzed reactions. Accordingly, we shall consider enzymes capable of catalyzing biotransformation of the many organic functional groups commony found in the structures of alkaloids.

Enzymatic transformation of alkaloids in mammals is usually considered to be part of a detoxication process in which an alkaloid is converted to a more polar chemical derivative, which is more readily excreted and less toxic. Although this is generally true, several recent reviews (*41–45*) indicate that xenobiotics may also be metabolized to form toxic products. Thus knowledge of the structural changes brought about by such biotransformations is increasingly important in guiding the design of drugs, antimicrobial agents, and agricultural chemicals. It also contributes much to a basic understanding of the molecular events in chemical cytotoxicity.

While the enzymes involved in detoxication processes are nonspecific in the classical sense of intermediary metabolism, they often have distinct specificities both for organic functional groups and for the electronic, steric, and stereochemical environments where these functional groups are located. Enzyme specificity based on organic functional groups and their environments leads to a wide diversity in the alkaloid substrates possible and therefore the products obtained from biotransformation. This section of the chapter will concentrate principally on the enzymes themselves, including general concepts of substrate specificity and mechanism.

B. Groups of Enzymes

Enzymes involved in alkaloid transformations have been arbitrarily divided into two major classes or types of biotransformations. The classification used here is that which has evolved from early descriptions of mammalian detoxica-

TABLE I
SUMMARY OF ENZYMES AND REACTIONS IN PHASE I METABOLISM

Enzymes	Reactions
Oxidoreductases	
Cytochromes *P*-450	Aryl and alkyl hydroxylations, epoxide formation, oxidative dealkylation of heteroatoms, reduction, dehalogenation, desulfuration, deamination, aryl N-oxygenation, oxidation of sulfur
FAD-containing monoxygenase	Oxidation of nucleophilic nitrogen and sulfur, oxidative desulfurization
Peroxidases	Oxidation of aromatic hydrocarbons, phenols, amines, and sulfides; oxidative dealkylation, reduction of *N*-oxides
Alcohol dehydrogenase	Alcohol oxidation; reduction of ketones
Monoamine oxidase	Oxidative deamination
Xanthine oxidase and aldehyde oxidase	Oxidation of heterocyclic aromatic amines, *N*-oxide reduction
Aldehyde dehydrogenase	Aldehyde oxidation
Aldehyde reductase	Aldehyde reduction
Ketone reductases	Ketone reduction
NADPH-cytochrome *P*-450 reductase	Reduction of quinones, quinonimines, nitroaromatics, azoaromatics, and oxidized aromatic heterocycles
Copper oxidases (ceruloplasmin, laccase)	Oxidation of phenols and amines
Hydrolases	
Epoxide hydrolase	Hydrolysis of epoxides and arene oxides
Amidases and esterases	Hydrolysis of amides and esters
Glycosidases	Hydrolysis of glycosides

TABLE II
SUMMARY OF ENZYMES AND REACTIONS IN PHASE II METABOLISM

Enzymes	Reactions
Acetyltransferases	Acetylation of amines and arylhydroxamic acids
Glucuronyltransferases	Glucuronidation of alcohols, phenols, hydroxylamines, thiols, amines, ureides, thioureides, and carboxy groups
Glutathione transferases	Glutathione conjugation of aryl and alkyl halides, β-unsaturated ketones, epoxides, benzylsulfates, organic nitrate esters, organic thiocyanates, and reduction of organic peroxides
Methyltransferases	Methylation of amines, thiols, and phenols
Sulfotransferases	Sulfation of alcohols, phenols, amines, and hydroxamic acids
Amino acid acylases	Peptide bond formation between glycine or glutamine and carboxylic acids
Glucosylases	Glucoside formation from alcohols, phenols, and carboxylic acids

tion reactions (*46*). Phase I reactions include oxidation, reduction, and hydrolysis, while Phase II reactions are those primarily involving conjugation of the alkaloid or its phase II metabolite. A listing of the enzymes important in bioconversions of alkaloids is presented in Table I (Phase I) and Table II (Phase II).

C. Oxidoreductases

1. Cytochromes *P*-450

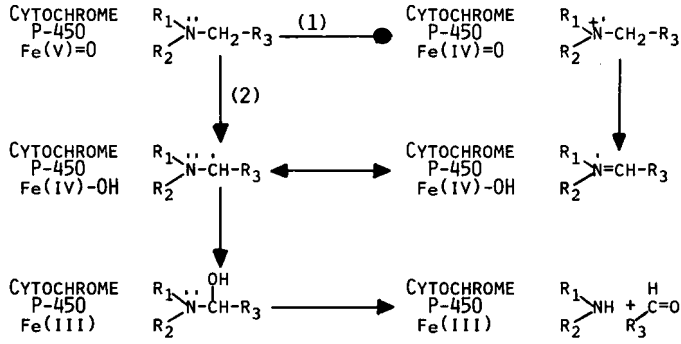
The cytochromes *P*-450 are a group of heme-containing proteins that form carbon monoxide complexes that exhibit maximum absorption of visible light at ~450 nm. These proteins are present in many animals, plants, and microorganisms, with the most extensively studied enzymes being those from mammalian liver and the bacterium *Pseudomonas putida*. Synthesis of different isoenzyme forms of cytochrome *P*-450 may be selectively induced by pretreatment of animals or microorganisms with various chemicals such as phenobarbital, 3-methylcholanthrene, β-naphthoflavone, and pregnenolone-16-carbonitrile. Such isoenzymes have distinct but overlapping specificity for substrates. The specificity (*47–51*), distribution (*47, 50, 51*) genetics (*52–55*), and mechanism (*48–50, 52*) of the cytochromes *P*-450 have been reviewed. These enzymes are classified as monooxygenases because they catalyze the general reaction in Eq. (1) where one atom of molecular oxygen is inserted into the organic chemical substrate (RH), and the other is reduced to form water. In addition

$$O_2 + NAD(P)H + RH + H^+ \rightarrow ROH + NAD(P)^+ + H_2O \quad (1)$$

to a cytochrome *P*-450, this reaction also requires additional proteins that function in the transfer of electrons from reduced pyridine nucleotides to the cytochrome *P*-450. The NADPH-cytochrome *P*-450 reductase is required in hepatic microsomes, while both an iron–sulfur protein and an FAD-containing reductase are required with *P*-450 systems in adrenal mitochondria and in bacteria such as *Pseudomonas putida* (*53*).

While the cytochrome *P*-450 monooxygenase reaction described in Eq. (1) often involves hydroxylation of carbon, many other reactions are catalyzed by these enzyme systems. These reactions include oxidation of nitrogen and sulfur, epoxidation, dehalogenation, oxidative deamination and desulfuration, oxidative N-, O-, and S-dealkylation, and peroxidative reactions (*56*). Under anaerobic conditions, the enzyme system will also catalyze reduction of azo, nitro, *N*-oxide, and epoxide functional groups, and these reductive reactions have been recently reviewed (*56, 57*). Furthermore, the NADPH-cytochrome *P*-450 reductase is capable of catalyzing reduction of quinones, quinonimines, nitroaromatics, azoaromatics, bipyridyliums, and tetrazoliums (*58*).

Early steps involved in the mechanism of cytochrome *P*-450 oxidations have



SCHEME 2. Simplified scheme for oxidative N-dealkylation incorporating a cytochrome *P*-450 perferryl oxygen intermediate and substrate radicals.

been described (*49, 59*). These include the binding of substrate to the *P*-450 enzyme and the transfer of electrons to the hemoprotein. Mechanistic events in the later stages of the catalytic cycle have been of more recent concern (*49, 50, 60*). These include oxygen activation by the formation of a reduced oxygenated heme intermediate and subsequent transfer of oxygen to the substrate. Current evidence points to a stepwise oxidative mechanism including homolytic cleavage of molecular oxygen and formation of discrete radical and/or cationic substrate intermediates (*49, 50, 60*). An example demonstrating one way in which alkaloid substrates may undergo oxidation via cytochrome *P*-450 enzymes involves the formation of radical cation intermediates such as those shown schematically in Scheme 2.

Although pathway 2 in the oxidation process (Scheme 2) may be considered analogous to mechanisms proposed for carbon hydroxylations catalyzed by cytochrome *P*-450, abstraction of an electron from the lone pair on nitrogen (pathway 1) would be a more likely first step in these types of reactions. It is reasonable to assume that the nature of substituents R_1, R_2, and R_3 would greatly influence the rate and path of reaction. The mechanistic possibilities in Scheme 2 are undoubtedly simplistic in their representation of the active oxygen species of cytochrome *P*-450 and are by no means comprehensive. However, these pathways do serve to illustrate.the role of radical substrate intermediates in cytochrome *P*-450-catalyzed reactions. More detailed analyses of mechanistic studies on these and other cytochrome *P*-450-mediated reactions can be found in recent reviews on the subject (*49, 50, 60*).

2. Microsomal FAD-Containing Monooxygenase

The FAD-containing monooxygenase catalyzes oxidation of nucleophilic nitrogen and sulfur atoms in a diverse array of organic compounds. The enzyme

has been purified to homogeneity from hog (*61 62*), rat (*63*), rabbit (*64*), and mouse (*65*) liver microsomes, and from rabbit lung microsomes (*64*). The substrate specificity (*66*) and kinetic mechanism (*67*) of the enzyme isolated from hog liver microsomes have been extensively studied. While the liver microsomal enzymes from various species are fairly similar in physical and catalytic properties (*61–65*), there are catalytic and antigenic differences between the liver and lung enzymes in the rabbit (*64*).

Nucleophilic nitrogen and sulfur atoms of alkaloids and other organic compounds are often oxygenated in reactions catalyzed by the hepatic microsomal FAD-containing monooxygenase. Tertiary amines are converted to amine oxides, and lipophilic amines are generally better substrates for the enzyme (*66*). Secondary amines follow similar substrate requirements. However, the products are hydroxylamines, which may be further oxidized to nitrones in a reaction catalyzed by the same FAD-containing monooxygenase. Nitrones usually undergo nonenzymatic hydrolysis to form aldehydes and primary hydroxylamines (*68*). 1,1-Disubstituted hydrazines and N-substituted aziridines are also substrates for the enzyme (*69*). Nucleophilic sulfur compounds are among the best substrates known for the monooxygenase. These include thiocarbamates, thioamides, thiols, sulfides, and disulfides. In general, nitrogen- and sulfur-containing compounds that are capable of delocalization of the heteroatom electrons in an aromatic ring (e.g., pyridine, thiophene) are not substrates for oxidation catalyzed by the FAD-containing monooxygenase (*66*). The relative substrate specificities of the FAD-containing monooxygenase and the cytochromes *P*-450 have been recently reviewed (*70*).

3. Peroxidases

The peroxidases are a group of hemoproteins that catalyze oxidation of organic chemical substrates by hydroperoxides. Peroxidases are found in a variety of plant, microbial, and mammalian tissues. In addition to the plant peroxidases, the large group of peroxidases capable of catalyzing alkaloid oxidations includes chloroperoxidase, catalase, myeloperoxidase, lactoperoxidase, thyroid peroxidase, intestinal peroxidase, and prostaglandin endoperoxide synthetase. The most extensively studied enzyme in this class is horseradish peroxidase (HRP). HRP reacts with hydrogen peroxide, organic hydroperoxides, or peracids to form distinct intermediates labeled as compounds I and II. These intermediates are described in the accepted catalytic sequence for HRP as shown below where the oxidation state of heme iron is in parentheses.

$$\text{HRP}(\text{Fe}^{3+}) + \text{H}_2\text{O}_2 \rightarrow \text{HRP-I}(\text{Fe}^{4+})^{+\cdot} + \text{H}_2\text{O} \quad (2)$$

$$\text{HRP-I}(\text{Fe}^{4+})^{+\cdot} + \text{AH}_2 \rightarrow \text{HRP-II}(\text{Fe}^{4+}) + \text{AH}\cdot \quad (3)$$

$$\text{HRP-II}(\text{Fe}^{4+}) + \text{AH}_2 \rightarrow \text{HRP}(\text{Fe}^{3+}) + \text{AH}\cdot \quad (4)$$

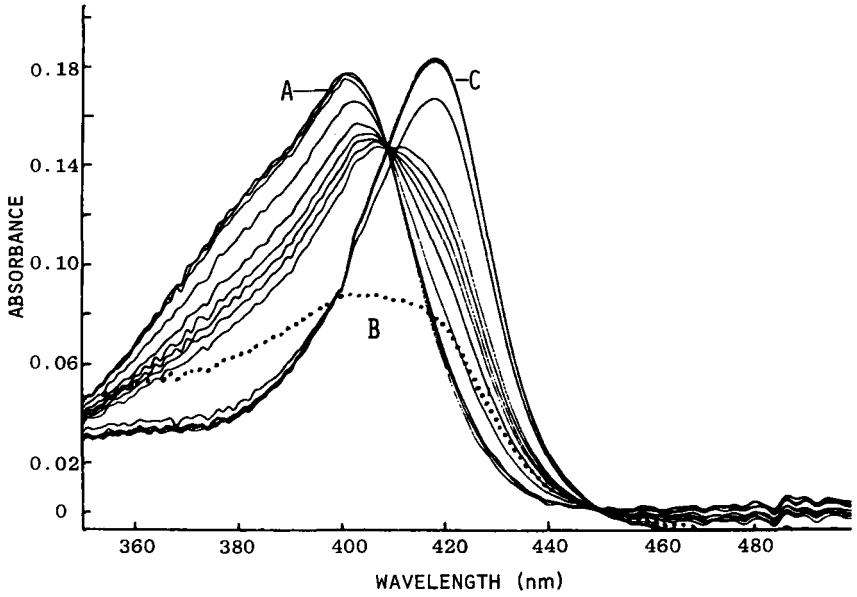
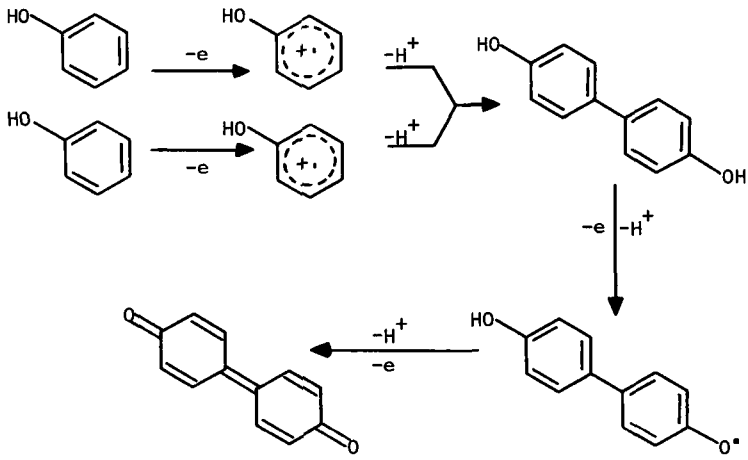


FIG. 2. Titration of 4.7 μ*M* horseradish peroxidase (Curve A) with equimolar hydrogen peroxide to form HRP-compound I (Curve B), followed by addition of 7.0 μ*M* vindoline (Curve C). Spectra were recorded every 15 sec.

The structure of HRP-I has been identified as an Fe(IV) porphyrin π-cation radical by a variety of spectroscopic methods (*71–74*). The oxidized forms of HRP present differences in their visible absorption spectra (*75–77*). These distinct spectral characteristics of HRP have made this a very useful redox protein for studying one-electron transfers in alkaloid reactions. An example is illustrated in Fig. 2 where the one-electron oxidation of vindoline is followed by observing the oxidation of native HRP (curve A) with equimolar H_2O_2 to HRP-compound I (curve B). Addition of vindoline to the reaction mixture yields the absorption spectrum of HRP-compound II (curve C) (*78*). This methodology can yield useful information on the stoichiometry and kinetics of electron transfer from an alkaloid substrate to HRP. Several excellent reviews on the properties, mechanism, and oxidation states of peroxidases have been published (*79–81*).

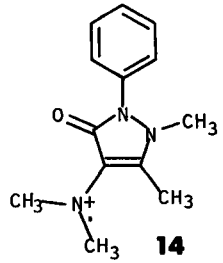
Enzymatic transformations of alkaloids by peroxidases most probably occur by single-step oxidations catalyzed by the HRP-I and HRP-II forms of the enzyme. The catalysis of one-electron oxidations of compounds containing aromatic hydrocarbon, hydrazine, phenol, hydroxamic acid, and amine functional groups has been recently reviewed (*45, 58, 82*). A brief summary of those HRP reactions that involve functional groups most commonly occurring in alkaloids is presented below.



SCHEME 3. Phenolic coupling reactions caused by one-electron oxidations.

a. Phenol Oxidation. The reactions illustrated in Scheme 3 are representative of a variety of oxidative couling reactions that can also occur with more complex phenols.

b. Oxidation of Amines. Peroxidases catalyze one-electron oxidation of arylamines and aliphatic amines and oxidative dealkylation of tertiary amines. Indirect evidence with stopped-flow spectrophotometry led Chance (*83*) to propose a free radical intermediate in the oxidation of *p*-aminobenzoic acid. Later ESR experiments by Yamazaki and Piette directly confirmed amino cation radicals as intermediates in the HRP-catalyzed oxidation of *p*-phenylenediamine (*84*). An example of an amino cation free radical (**14**) formed in amine oxidation



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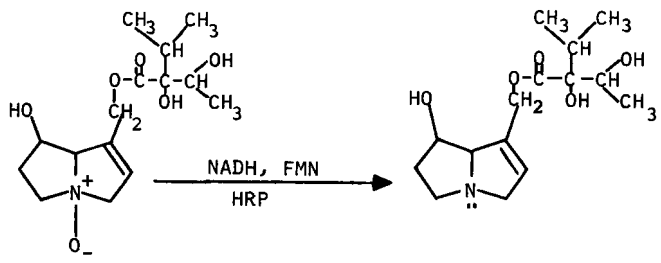
is seen in the HRP/H_2O_2 oxidation of aminopyrine (*85*). In those cases, as in aminopyrine where the tertiary amine has a small alkyl group (methyl), further one-electron oxidation leads to an intermediate, which is hydrolyzed to yield formaldehyde and the secondary amine. The kinetics and stoichiometry of N-demethylation by peroxidases has been recently studied for both horseradish

peroxidases (*86*) and chloroperoxidase from *Caldariomyces fumago* (*87*). When the nitrogen is constrained in a heterocyclic ring system, reactions other than N-dealkylation predominate. An excellent example of this type of reaction involving a heterocyclic amine is the oxidation of vindoline catalyzed by HRP (*78*). This reaction sequence is outlined in Section III,A,3. Similar radical reactions catalyzed by peroxidases may occur with many other alkaloids.

c. Oxidation of Aromatic Hydrocarbons. The major peroxidase of interest in the oxidation of aromatic hydrocarbons is prostaglandin endoperoxide synthetase (PES). PES is distinct from other peroxidases in that the same protein first catalyzes oxidation of arachidonic acid to a hydroperoxide and later reduction of the hydroperoxide with concomitant oxidation of another chemical substrate. The hydroperoxidase site of PES catalyzes the oxidation (referred to as cooxidation) of a variety of chemicals containing amine, phenol, and aromatic hydrocarbon functional groups. Polycyclic hydrocarbons such as benzo[*a*]pyrene, 7,12-dimethylbenzanthracene, oxophenylbutazone, and phenylbutazone are hydroxylated in PES-catalyzed reactions (*88*). While the substrate specificity and mechanism for cooxidation of aromatic hydrocarbons by PES have not been fully elucidated, this enzyme might prove to be important in the mammalian metabolism of alkaloids, especially in those tissues that contain little or no cytochrome *P*-450.

Peroxidases have also been utilized for preparative-scale oxidations of aromatic hydrocarbons. Procedures have been optimized for hydroxylation of L-tyrosine, D-(−)-*p*-hydroxyphenylglycine, and L-phenylalanine by oxygen, dihydroxyfumaric acid, and horseradish peroxidase (*89*). Lactoperoxidase from bovine milk and yeast cytochrome *c* peroxidase will also catalyze such hydroxylation reactions (*89*).

d. N-Oxide Reduction. In addition to the oxidative reactions catalyzed by peroxidases, we have observed that peroxidase catalyzes reduction of an alkaloid *N*-oxide. As seen in Scheme 4, horseradish peroxidase catalyzes the anaerobic reduction of indicine *N*-oxide in a reaction requiring a reduced pyridine nucleotide (NADH or NADPH) and a flavin coenzyme (FAD, FMN, or riboflavin).

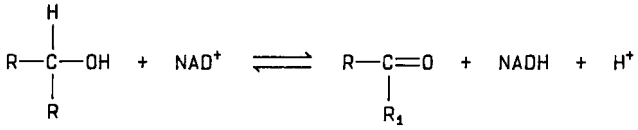


SCHEME 4. Reduction of indicine *N*-oxide catalyzed by horseradish peroxidase.

Rat liver microsomes and cytosol also catalyze this reaction with the same cofactor requirements (*90*).

4. Alcohol Dehydrogenases

Alcohol dehydrogenases catalyze oxidation of alcohols in a reaction dependent on the pyridine nucleotide NAD^+ [Eq. (5)]. Since the reaction is reversible, alcohol dehydrogenases also catalyze the reduction of aldehydes by



R = alkyl or aryl
R^1 = alkyl, aryl, or H (5)

NADH. The enzymes are widely distributed in nature, being found in microorganisms, plants, and animals. Catalytic mechanism, specificity, and physical properties of the alcohol dehydrogenases have been reviewed in detail (*91–93*).

In general, primary and seconday aliphatic and aromatic alcohols are good substrates for alcohol dehydrogenases, while tertiary alcohols and sterically hindered secondary alcohols are poor substrates. Although α,β-unsaturated alcohols are better substrates than the corresponding saturated alcohols in the oxidation reaction, saturated aldehydes are better substrates for the reductive reaction (*92*). Polyalcohols such as glycerol, ethylene glycol, and long chain diols are also substrates for alcohol dehydrogenase. Alcohol dehydrogenase catalyzes reduction of aromatic ketones, but does not catalyze reduction of long-chain aliphatic ketones (*92*).

Alcohol dehydrogenase purified from horse liver contains two atoms of zinc per subunit of molecular weight 40,000. The catalytically active enzyme is a dimer of two identical subunits. One atom of zinc is essential to the catalytic mechanism of the enzyme, while the role of the second zinc atom is less certain (*93*). Owing partly to its availability and partly to its catalytic versatility, horse-liver alcohol dehydrogenase (HLADH) has been used as a catalyst for a variety of enantioselective reactions with organic chemicals. Jones and coworkers have been instrumental in describing the utility of HLADH in organic synthesis, and have proposed a model for predicting the specificity of the enzyme for new organic molecules (*94*). These principles might prove useful in predicting new HLADH-catalyzed transformations of alkaloids.

5. Monoamine Oxidase

Monoamine oxidase (MAO) is a mammalian flavin-containing enzyme that catalyzes oxidation of primary amines. While the neurotransmitter amines are

most often considered the substrates for MAO, other primary amines can also be oxidized in MAO-catalyzed reactions. The general reaction is as follows:

$$RCH_2NH_2 + O_2 + H_2O \rightleftarrows RCHO + NH_3 + H_2O_2 \quad (6)$$

The enzyme is present in neural cells, platelets and such organs as heart, liver, and intestine. Details on the specificity, catalytic mechanism, and properties of MAO have been reviewed (*95*).

6. Xanthine Oxidase and Aldehyde Oxidase

Xanthine oxidase and aldehyde oxidase are metalloflavoproteins that catalyze hydroxylation of a wide variety of heterocyclic compounds in addition to aliphatic and aromatic aldehydes. Both proteins contain molybdenum, FAD, and iron as prosthetic groups and have molecular weights of approximately 300,000. Although aldehyde oxidase was originally named for its ability to catalyze oxidation of aldehydes, the best substrates for the enzyme are nitrogen-containing heterocycles. Xanthine oxidase and aldehyde oxidase have complementary specificities for heterocycles, with the overall reaction involving hydroxylation of carbon according to the following general mechanism [Eqs. (7) and (8)], where

$$RH + H_2O \rightarrow ROH + 2e^- + 2\,H^+ \quad (7)$$

$$A + 2\,e^- + 2\,H^+ \rightarrow AH_2 \quad (8)$$

R is an electron-donor substrate such as purine or xanthine and A is an electron acceptor such as O_2 or NAD^+. It is thought that the *in vivo* mammalian form of xanthine oxidase uses NAD^+ as acceptor and is therefore more appropriately named xanthine dehydrogenase. No evidence exists for a dehydrogenase form of aldehyde oxidase. The specificities of xanthine oxidase and aldehyde oxidase have been extensively catalogued (*96*), and the mechanism and properties of these enzymes have been reviewed (*97, 98*).

7. Aldehyde Dehydrogenase

While most alkaloids do not contain aldehydes when they enter mammalian, microbial, or plant tissues, this functional group may become important when formed as a metabolite of alcohols (via alcohol dehydrogenase) or amines (via oxidative dealkylation and oxidative deamination). Aldehyde dehydrogenases catalyze oxidation of aldehydes to the corresponding carboxylic acids. The physical properties, catalytic mechanism, and specificity of this group of enzymes has been reviewed (*99*). The general reaction catalyzed by aldehyde dehydrogenase is seen in Eq. (9).

$$RCHO + NAD^+ + H_2O \rightarrow RCOOH + NADH + H^+ \quad (9)$$

The mechanism proposed for the aldehyde dehydrogenases includes an enzyme-bound hemiacetal intermediate, possibly via a thioester bond with a cysteine (*100*). The specificity of the enzyme for aldehydes is quite broad. Apparent K_m values for many aliphatic and aromatic aldehydes are in the micromolar range, with the highest reaction velocities observed for aldehydes with electron-withdrawing substituents on the α carbon for aliphatic aldehydes and in the para position for aromatics (*99*).

8. Carbonyl Reductases

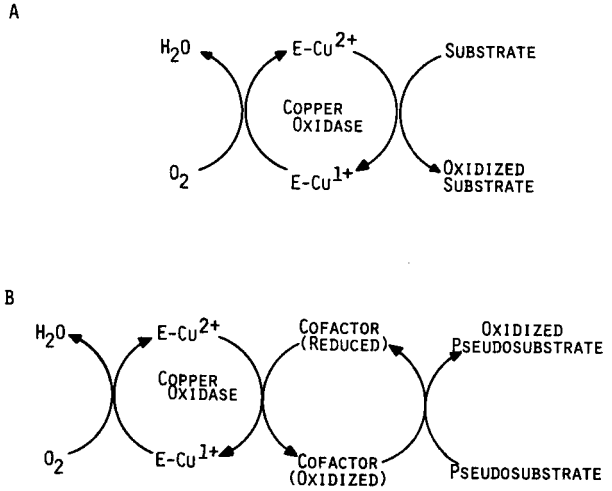
The carbonyl reductases catalyze reduction of aldehydes and ketones by reduced pyridine nucleotides (NADH and/or NADPH). As mentioned earlier, alcohol dehydrogenase can perform this function in the presence of a high ratio of NADH to NAD^+. Other enzymes capable of carbonyl reduction include the aldehyde and ketone reductases. The aldehyde and ketone reductases have a ubiquitous species distribution, with the enzymes present in organisms ranging from bacteria to vertebrates. The mammalian carbonyl reductases have been extensively reviewed (*101*).

Aldehyde reductases are a group of isoenzymes that catalyze the NADPH-specific reduction of aldehydes. Ketones do not serve as substrates for these enzymes. The best substrates for aldehyde reductase are aromatic aldehydes and those aldehydes obtained through metabolism of biogenic amines. The species distribution, specificity, and inhibition of aldehyde reductases have been reviewed (*102*).

As with the aldehyde reductases, ketone reductases are specific for NADPH as reductant. Also, some isoenzymes of ketone reductase have not been purified to homogeneity and therefore not fully characterized. It is clear, however, that the ketone reductases catalyze reduction of aromatic, aliphatic, cyclic, and unsaturated ketones to the corresponding alcohols. The ketone reductases also catalyze reduction of aromatic and aliphatic aldehydes to primary alcohols. The distribution and specificity of ketone reductases has been reviewed (*103*).

9. Copper Oxidases

Copper oxidases are widely distributed in nature, and enzymes from plants, microbes, and mammals have been characterized (*104, 105*). The "blue" copper oxidases, which include laccases, ascorbate oxidases, and ceruloplasmin, are of particular interest in alkaloid transformations. The principle differences in specificity of these copper oxidases are due to the protein structures as well as to the distribution and environment of copper(II) ions within the enzymes (*106*). While an *in vivo* role in metabolism of alkaloids has not been established for these enzymes, copper oxidases have been used *in vitro* for various alkaloid transformations.



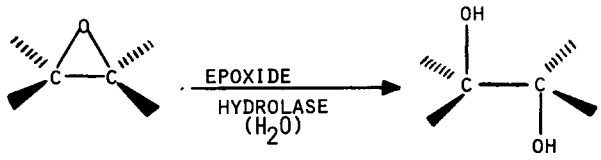
SCHEME 5. Oxidation of substrates and pseudosubstrates catalyzed by copper oxidases.

Laccases from plant and fungal sources and mammalian ceruloplasmin catalyze the oxidation of alkaloid substrates by molecular oxygen. True substrates interact directly with the active sites of copper oxidases (as in reaction sequence A, Scheme 5). Pseudosubstrates (as in sequence B, Scheme 5) require substances that are loosely defined as cofactors to interface with the enzyme. These cofactors are substrates for the enzyme, which can then be reduced by any of the much larger class of pseudosubstrates. Substrates for the laccases and ceruloplasmin include iron(II) and a large group of bifunctional aromatic amines and phenols such as hydroquinones, aminophenols, epinephrine, and 5-hydroxyindole and their derivatives, and various phenothiazines (*105*, *106*). The range of pseudosubstrates for these enzymes is much broader, since the only requirement is the ability of the substance to reduce the oxidized cofactor. Since the pseudosubstrate does not have to bind to the active site of a copper oxidase, the number of alkaloids that could serve as reductants is potentially very large.

D. HYDROLASES

1. Epoxide Hydrolase

As with several other functional groups considered earlier, epoxides are most commonly found in alkaloid metabolites rather than the original compound. These epoxides may arise via oxidation of alkenes or aromatic hydrocarbons. Epoxide hydrolase catalyzes hydrolysis of epoxides to the more hydrophilic diol. As seen in Scheme 6, this is usually a stereospecific reaction that always yields a



SCHEME 6. Stereochemical features of the epoxide hydrolase reaction.

trans diol. The enzyme is widely distributed among vertebrates and invertebrates, and is found in the microsomes, nuclei, and cytosol of many tissues. However, most work on substrate specificity and mechanism has been accomplished with liver microsomal epoxide hydrolase. The catalytic and physical properties of this enzyme have been reviewed elsewhere (*107, 108*). Bacterial and fungal epoxide hydrolases have also been reviewed (*109*).

2. Amidases and Esterases

Carboxylesterases and amidases catalyze hydrolysis of carboxy esters and carboxy amides to the corresponding carboxylic acids and alcohols or amines. In general those enzymes capable of catalyzing hydrolysis of carboxy esters are also amidases, and vice versa (*110*). The role of these enzymes in metabolsim of drugs and insecticides has been reviewed (*111, 112*). In addition to the interest in mammalian metabolism of drugs and environmental chemicals, microbial esterases have been used for enantioselective hydrolyses (*113, 114*).

Mammalian esterases have been classified into three groups according to specificity for substates and inhibitors (*110*). In terms of overall hydrolytic activity in mammals, the most important class of esterases is that of the B-esterases, which are principally active with aliphatic esters and amides. A-Esterases are important for aromatic esters and organophosphorus esters, and C-esterases are active with acetyl esters. In general, the specificity of mammalian esterases is determined by the nature of substituent groups (acetyl, alkyl, or aryl) rather than the heteroatom (O, N, or S) that is adjacent to the carboxy group. That is, the same esterase would likely catalyze hydrolysis of an ester, amide, or thioester as long as the substituents were identical except for the heteroatom (*110*).

3. Glycosidases

Glycosidases catalyze the hydrolysis of the glycoside linkage in glucosides, glucuronides, or other carbohydrate conjugates of alkaloids. The role of intestinal microorganisms in hydrolysis of glycosides to release pharmacologically or toxicologically active substances has been reviwed (*115*). The utility of other microbial glycosidases, as well as plant glycosidases, in organic synthesis has also been reviewed (*113*).

E. Phase II Enzymes

1. Acetyltransferases

Acetyltransferases catalyze the acetylation of amino, hydroxyl, and thiol functional groups. Acetylation of hydroxy and thiol groups is comparatively rare and of much less importance in alkaloid metabolism than reactions with amino functional groups. The types of amines that are acetylated include arylamines (the major route of metabolism in many species), aliphatic amines, hydrazines, sulfonamides, and the α-amino group of cysteine conjugates. The purification, physical properties, and specificity of the *N*-acetyltransfereases have been reviewed (*116–118*).

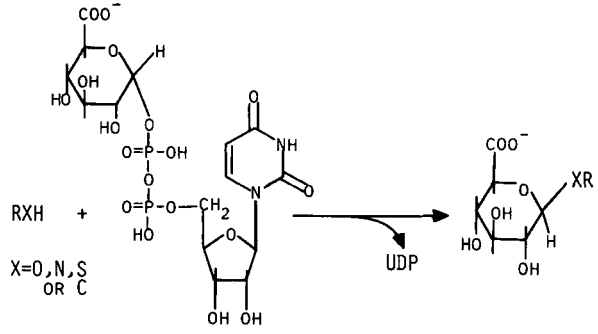
N-Acetyltransferases catalyze the transfer of an acetyl moiety from coenzyme A (CoASAc) to an acceptor amine as seen in Eq. (10). The nature of the

$$RNH_2 + CoASAc \rightarrow RNHCOCH_3 + CoASH \qquad (10)$$

substituent R varies from NH in hydrazines and SO in sulfonamides to aryl groups and short aliphatic groups connected to an aromatic ring. Furthermore, the same *N*-acetyltransferases that catalyze acetylation of arylamines also catalyze the O-acetylation of arylhydroxamic acids (*119*). While the exact number of *N*-acetyltransferases active with arylamines and arylhydroxamic acids is not yet known, it is clear that there are multiple forms of the enzyme and that their levels are under genetic control (*116*).

2. UDP-Glucuronyltransferases

Formation of glucuronide conjugates is a major metabolic conversion for many lipid-soluble compounds. The product glucuronides are more water soluble and usually more readily excreted. The glucuronic acid donor in this reaction is



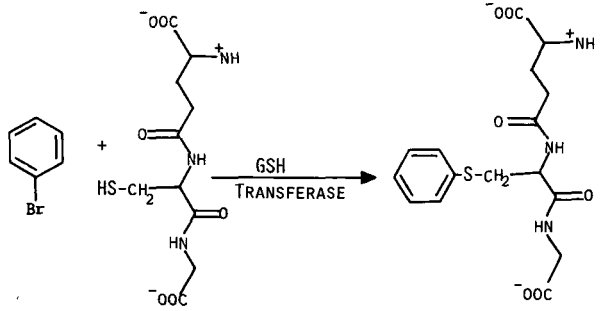
SCHEME 7. General glucuronidation reaction catalyzed by UDP-glucuronyl transferases.

uridinediphosphoglucuronic acid (UDP-glucuronic acid), and the reaction is catalyzed by UDP-glucuronyltransferase. The general reaction is shown in Scheme 7.

UDP-glucuronyltransferase catalyzes an S_N2 nucleophilic displacement of the UDP moiety, with a broad specificity for the nucleophilic atom and a preference for lipophilic R groups. While the specificity for nucleophilic nitrogen, oxygen, and sulfur is quite broad, the only known instances of C-glucuronide formation are in metabolism of phenylbutazone and sulfinpyrazone. The broad range of nitrogen- oxygen- and sulfur-containing substates for glucuronidation is in part due to the presence of multiple forms of UDP-glucuronyltransferase with distinct but overlapping specificities. Uniform terminology and assay conditions for these enzymes have been agreed to by several laboratories working with UDP-glucuronyltransferases (*120*). Substrate specificity, multiplicity, and other properties of UDP-glucuronyltransferases have been reviewed (*121–123*).

3. Glutathione Transferases

These enzymes catalyze the reaction of electrophiles with glutathione (GSH) to form a glutathione conjugate. Bromobenzene is used in Scheme 8 as an example to illustrate the reaction. This reaction yields a polar GSH-conjugate, which can either be excreted as such or carried further through the mercapturic acid pathway before excretion. The mercapturate pathway involves hydrolysis of the peptide between the γ-glutamyl and cysteine amino acids, followed by hydrolysis of the cysteinylglycine peptide bond, leaving a cysteine conjugate that is acetylated in a reaction catalyzed by a specific *N*-acetyltransferase. The role of this pathway in detoxication has been reviewed (*124, 125*). Reviews on the mechanism, physical properties, and specificity of the glutathione transferases are also available (*126, 127*). In general, glutathione transferases catalyze reaction of glutathione with electrophilic carbon, nitrogen, oxygen, and sulfur in an otherwise diverse array of organic molecules. As with the glucuronyl trans-



SCHEME 8. Conjugation of bromobenzene with glutathione.

ferases, there has been an attempt to standardize the nomenclature of the many glutathione transferase isoenzymes isolated from various species, tissues, and cell fractions (*128*).

4. Methyltransferases

The methyltransferases catalyze transfer of a methyl group from *S*-adenosylmethionine to the nitrogen, oxygen, or sulfur atoms of appropriate acceptor molecules. Methyltransferases are widely distributed in nature, and their properties and varying degrees of specificity for acceptor molecules have been reviewed elsewhere (*129–132*). Catechol O-methyltransferase is very specific for catechols, and especially active with biogenic amines having catechol functionalities (*129–130*). Histamine *N*-methyltransferase is specific for histamine and as such is of lesser interest in alkaloid metabolism (*130*). The indolethylamine *N*-methyltransferases are relatively nonspecific for methyl acceptors and many physiologic and nonphysiologic amines serve as substrates (*130, 132*). Likewise, thiol *S*-methyltransferase is relatively nonspecific, with a variety of sulfides and thiophenols acting as methyl acceptors (*130, 131*). Although acceptors for these various transferases vary more or less, depending on the enzyme, all are extremely specific for *S*-adenosylmethionine as methyl donor in the reaction (*129–132*).

5. Sulfotransferases

The sulfotransferases catalyze formation of sulfate esters of compounds having hydroxy or amino groups. The donor in this transfer of a sulfuryl group is 3′-phosphoadenylsulfate, also named previously as 3′-phosphoadenosine-5′-phosphosulfate (PAPS). An example of this reaction is seen in Eq. (11) for phenol as the sulfuryl (SO_3) acceptor, with the products of the reaction being phenyl sulfate and adenosine 3′,5′-bisphosphate (PAP).

$$\text{PAPS} + C_6H_5OH \rightleftarrows C_6H_5OSO_3^- + \text{PAP} \qquad (11)$$

Substrates for the sulfotransferases include such varied compounds as primary and secondary alcohols, hydroxysteroids, phenols, organic hydroxylamines, and amines. As is the case with formation of glutathione and glucuronide conjugates, the formation of a sulfate ester usually renders a substance more polar and more readily excreted. Several reviews on the multiple forms of sulfotransferases and their specificities and properties are available (*133–135*).

6. Amino Acid Acylases

Conjugation with amino acids is a major route of metabolism for carboxylic acids including aromatic, heteroaromatic, arylacetic, cinnamic, and aryloxyacetic acids. Although a wide range of amino acid conjugates has been ob-

served, the major amino acid conjugates involve glycine or glutamine in a peptide (amide) bond to the carboxylic acid. The enzymes involved in the conjugation of carboxylic acids with amino acids are found in the mitochondria of a wide range of species and tissues. The species differences and enzymology of amino acid conjugation reactions have been reviewed (*136, 137*). In general, two types of enzymes are involved in amino acid conjugation, indicative of the fact that two reactions are involved. The first group of enzymes are called ATP-dependent acid:CoA ligases (AMP), or acyl-CoA synthetases, and catalyze formation of a thioester bond between coenzyme A and the carboxylic acid. The second group of enzymes are termed acyl-CoA:amino acid *N*-aryltransferases and catalyze formation of the amino acid conjugate with release of coenzyme A.

7. Glucosylases

Although formation of glucosides of hydroxy and carboxyl groups is relatively rare in mammals, it is a common reaction in insects (*138*), plants (*139*), and microorganisms (*140*). However, mammalian metabolism of heterocyclic nitrogen-containing compounds to *N*-glucosides has been reported (*141, 142*). It is likely that the glucosyl donor in all of these reactions in uridinediphosphoglucose. While these reactions have been described in various species, detailed information on the properties and specificities of the enzymes involved is not yet available.

III. Survey of Alkaloid Transformations

This section of the review will consider various types of biotransformations of alkaloids from both chemical and biochemical perspectives. We have attempted to avoid serious repetition of published work previously covered by Holland (*2*) in this series by presenting material published since 1980 and by inclusion of a few examples that were not mentioned earlier. For convenience, we have organized our review in essentially the same style used by Holland.

A. The Indole Alkaloids

1. Ellipticine and Derivatives

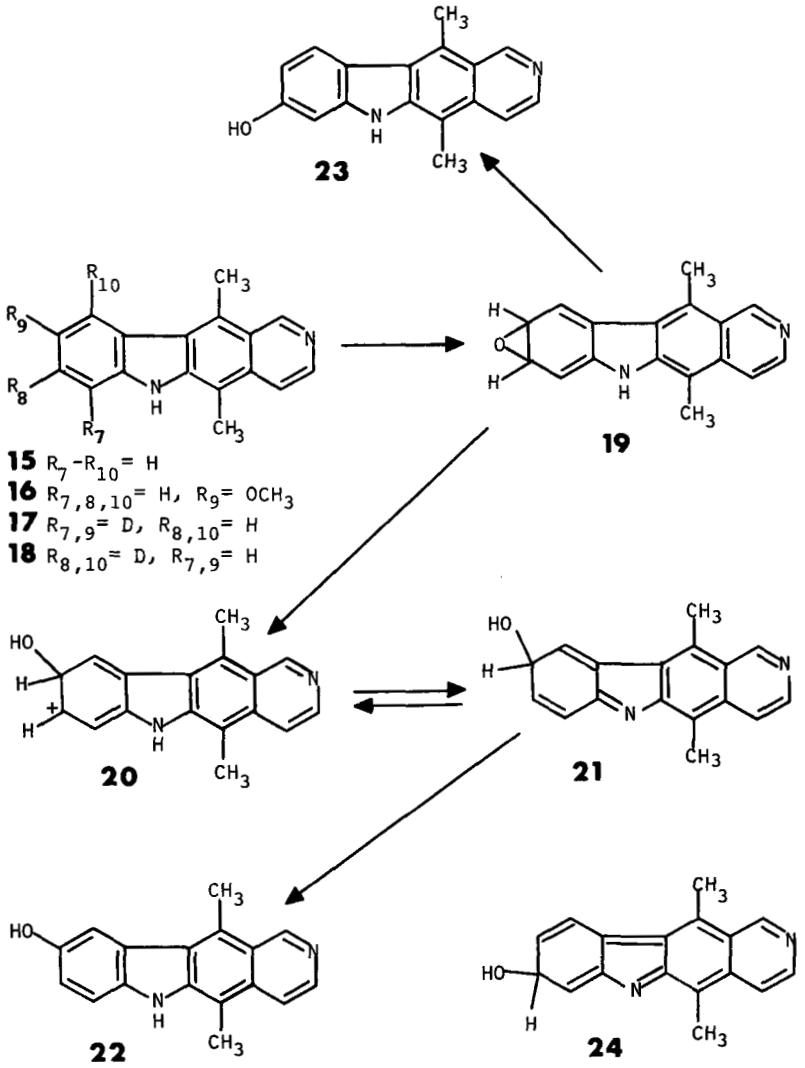
The antitumor alkaloid ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) has been isolated from many species of *Ochrosia* and *Aspidosperma*. Ellipticine and its derivatives are highly active versus several experimental neoplasms, and the compound has been widely subjected to studies devoted to its total synthesis, the preparation of derivatives, and metabolism. Metabolic transformation studies with ellipticines have been conducted, using microorganisms, *in vivo* and *in vitro*

mammalian metabolic systems, and cell-free enzymes including peroxidases from both plants and mammals. The biological properties of ellipticine and related alkaloids is authoritatively discussed by Suffness and Cordell in Volume 25 of this treatise.

Microbial transformations of ellipticine (**15**) and 9-methoxyellipticine (**16**) were reported by Chien and Rosazza (*143, 144*). Of 211 cultures screened for their abilities to transform 9-methoxyellipticine (**16**), several, including *Botrytis alii* (NRRL 2502), *Cunninghamella echinulata* (NRRL 1386), *C. echinulata* (NRRL 3655), and *Penicillium brevi-compactum* (ATCC 10418), achieved O-demethylation of **16** in good yield (Scheme 9). *P. brevi-compactum* was used to prepare 9-hydroxyellipticine (**22**) from the methoxylated precursor, and 150 mg of product was obtained from 400 mg of starting material (37% yield). The structure of the metabolite was confirmed by direct comparison with authentic 9-hydroxyellipticine (*143*). O-Demethylation is a common microbial metabolic transformation with **16** and many other alkaloids (*143*). Meunier *et al.* have also demonstrated that peroxidases catalyze the O-demethylation reaction with 9-methoxyellipticine (*145*).

Screening experiments were conducted with 224 cultures to show that *Aspergillus alliaceus* (NRRL 315), *A. fumigatus* (UI 51), and *Penicillium purpurogenum* (UI 193) consistently formed metabolites of ellipticine in good yield (*144*). An *A. alliaceus* incubation containing 3 g of ellipticine (**15**) afforded 560 mg of 9-hydroxyellipticine (**22**) and 250 mg of 8-hydroxyellipticine (**23**). In ^{1}H-NMR spectra, different ABX splitting patterns for protons 7, 8, and 10 for **22** and 7, 9, and 10 for **23** and the observed spectral differences for 7-hydroxyellipticine reported by others enabled clear-cut structural assignments of these metabolites. Microbial hydroxylation of aromatic substrates usually obeys the rule of electrophilic aromatic substitution. Thus it was not surprising to learn that 9-hydroxylation predominated with ellipticine. Precedence for the hydroxylation of indoles at positions equivalent to 8 and 9 of ellipticine exists in the microbial transformation of yohimbines and acronycine (*144*). Interestingly, the ratio 4:1 of 9-:8-hydroxylation was constant in all experiments (*146*). This suggested the possibility that both metabolites could arise through a common arene oxide intermediate (**19**), which could give either metabolite depending on the manner of epoxide ring opening (*144*).

Reinhold and Bruni studied the metabolism of 7,9-dideuterioellipticine (**17**) in rats and found that deuterium originally at position 9 was completely lost during the mammalian hydroxylation process (*147*). Proton and carbon-13 NMR and mass spectral analyses confirmed the complete elimination of deuterium at position 9, thus ruling out the occurrence of an NIH shift mechanism in the hydroxylation of ellipticine. An oxygen-insertion process was rationalized to account for the mechanism of aromatic hydroxylation in rats since this would not be expected to display the NIH shift but should demonstrate an isotope effect. It was



SCHEME 9. Metabolism of ellipticine by *Aspergillus alliaceus* NRRL 315.

also suggested that if an arene oxide formed, it could be sufficiently unstable to open and isomerize to the phenol with complete loss of deuterium.

The possibility that an NIH shift mechanism could occur with *Aspergillus alliaceus* NRRL 315 during the 8- and 9-hydroxylation of ellipticine was tested by incubating the microorganism with both 7,9-(**17**) and 8,10-(**18**) dideuterioellipticines, isolating 8- and 9-hydroxylated metabolites from both substrates, and

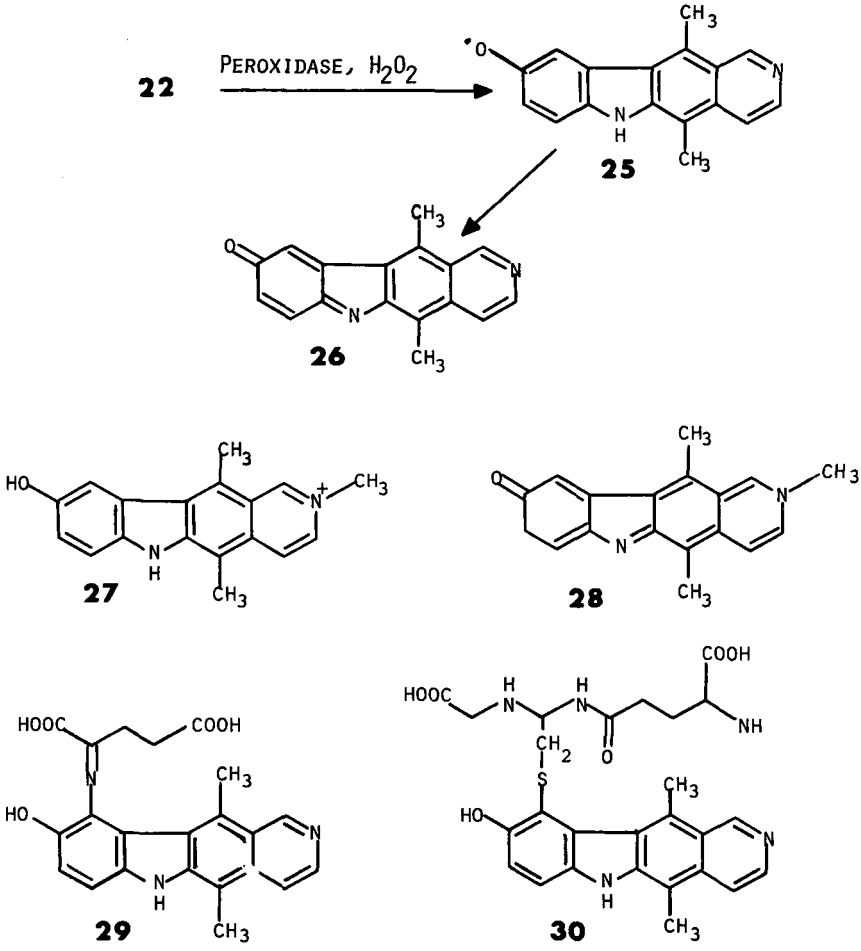
evaluating these for deuterium retention by 360-MHz NMR spectroscopy and mass spectrometry (*148*). Within the limits of detection of these analytical tools, it was impossible to observe evidence for deuterium migration and retention (i.e., the NIH shift) in any of the four isolated metabolites. Several possible explanations of these results can be put forth. Daly *et al.* (*149*) indicated that the presence of an ionizable functional group at a position para to the hydroxylated position can result in the formation of alternate and stabilizing intermediates such as **21** and **24** (Scheme 9). The stabilized intermediates would tautomerize to form hydroxylated products with complete elimination of deuterium at the oxidized position. Such processes are normally pH dependent. The available analytical data cannot rule out other direct hydroxylation mechanisms including addition–rearrangement (*150*) or direct insertion of oxygen into a carbon–hydrogen bond (*151*). While such processes may occur with accompanying large isotope effects, this is not always the case (*152*). Isotope effects may be too small to be of significance in the experiments performed by Reinold and Bruni and by us to be measurable, and competing direct and indirect hydroxylation mechanisms may occur at the same time during the hydroxylation process.

Oxidations of 9-Hydroxyellipticine. 9-Hydroxyellipticine is the major metabolite of ellipticine formed by mammalian cytochrome *P*-450 hydroxylation (*147, 153*). The reaction is a good example of a bioactivation process because 9-hydroxyellipticine is many times more active as an antineoplastic agent than is ellipticine itself (*154*). Auclair, Meunier, Paoletti, and co-workers have extensively studied further oxidations of 9-hydroxyellipticine and its derivatives (*155–158*).

The classic oxidizing systems of human myeloperoxidase and horseradish peroxidase were exploited for their well-known abilities to oxidize phenolic substrates. Under conditions of incubations, the following oxidation pathway was defined (*155*). Peroxidases are first converted to the oxidized

$$\text{peroxidase} + H_2O_2 \rightarrow \text{compound I} + H_2O$$
$$\text{compound I} + \text{9-OH-E} \rightarrow \text{9-OH-E.} + \text{compound II}$$
$$\text{compound II} + \text{9-OH-E} \rightarrow \text{9-OH-E.} + \text{peroxidase}$$
$$\text{9–OH–E.} + \text{9–OH–E.} \rightarrow \text{9–OH–E} + \text{9–oxoellipticine}$$

peroxidase compound I, which is essentially an Fe(IV)-porphyrin π-cation radical form of the enzyme. Compound I removes an electron from 9-hydroxyellipticine (**22**) to form an unstable radical (**25**). The same reaction is catalyzed by peroxidase compound II, an Fe(IV) form of the enzyme also capable of removing an electron from 9-hydroxyellipticine. The last reaction results in the formation of the 9-oxoellipticine derivative **26** as shown in Scheme 10. Evidence for the formation of **26** was furnished by monitoring absorbance at 515 nm for the formation of the quinonimine. Free radical intermediates were detected by EPR, and standard radical preparations were prepared by using elemental iodine in dimethyl sulfoxide containing 9-hydroxyellipticine. The same kinds of reactions



SCHEME 10. Oxidations of 9-hydroxyellipticine by peroxidases.

occur with 9-hydroxy-*N*-methylellipticine (**27**), and delocalization of the positive charge through resonance stabilization can occur through compounds such as **28.** These types of molecular structures are highly reactive and capable of undergoing nucleophilic attack with suitable molecules.

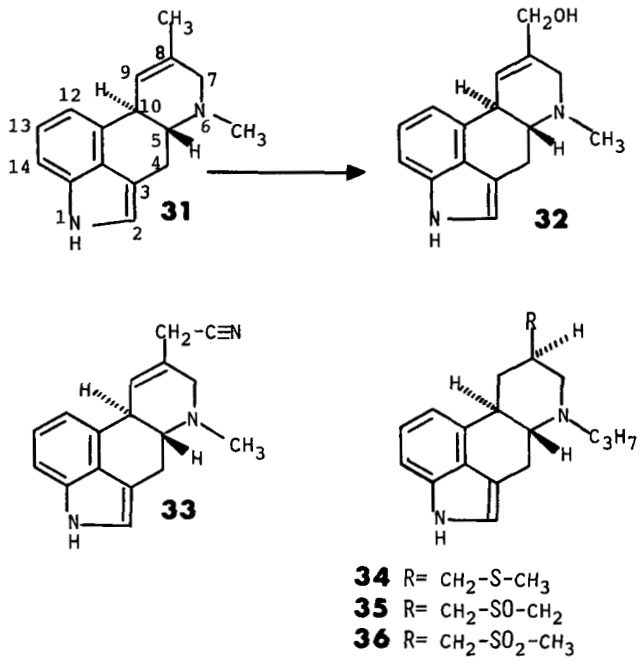
The reactivity of compounds such as **28** was clearly demonstrated by the peroxidase-catalyzed covalent binding of N^2-methyl-9-hydroxyellipticine (**27**) to proteins (*156*). Using horseradish peroxidase and hydrogen peroxide, tritiated-**27** was converted to the 9-oxoellipticine derivative in the presence of bovine serum albumin (BSA) and human antibovine IgG *in vitro*. Covalent binding to these proteins was confirmed by gel electrophoresis, combustion, and liquid scintillation analysis. Dissolution of the BSA-ellipticinium derivative with pronase and

subsequent HPLC resulted in the identification of a major fluorescent and radioactive peak identical to an aspartic acid–*N*-methyl-9-hydroxyellipticinium adduct (**29**). The synthetic adduct was prepared by treating 250-mg quantities of aspartic acid or glycine with 50 mg of **27** in the presence of horseradish peroxidase and hydrogen peroxide. Direct evidence for the occurrence of similar biotransformations *in vivo* came through the identification of a 10-*S*-glutathione conjugate (**30**) with *N*-methyl-9-hydroxyellipticinium acetate. Rats received the drug intravenously, and both the 9-O-glucuronide (major metabolite) and a possible 10-*S*-glutathione conjugate (**30**) (minor metabolite) were isolated from bile (*157*). Similar results were obtained with the methyl isomer olivacine. Auclair and co-workers also demonstrated that 9-hydroxylated ellipticines can undergo autoxidation in alkaline aqueous solution initially to a superoxide anion and the drug free radical. This initial step is followed by dismutation of both superoxide anion and free radicals of the drug to generate hydrogen peroxide and 9-oxoellipticines (*158*). These properties may be important in the well-known cytotoxic activities of these drugs.

2. Clavines, Ergolines, and Lysergic Acid Derivatives

Useful derivatives of ergot alkaloids such as methysergide or bromocriptine are prepared semisynthetically from natural lysergic acids. Sieben *et al.* developed a microbiological synthesis of such compounds beginning with much more stable ergolines as starting materials (*159*). The microorganism *Claviceps fusiformis* strain SD 58 catalyzes allylic hydroxylation of the 17-methyl group of agroclavine (**31**) to form elymoclavine (**32**) (Scheme 11). Numerous agroclavine derivatives and isomers were prepared and evaluated as potential substrates for the agroclavine hydroxylase of the microorganism. Hydroxylation occurred in yields of 35–75% with derivatives such as 1-alkyl, 1-benzyl-, 1-hydroxymethyl-, 2-bromo- or 2-iodo-, 2,3-dihydro-, and 6-ethyl-6-noragroclavine. However, *C. fusiformis* could not hydroxylate compounds lacking either the 8,9 double bond or a tertiary N^6 nitrogen.

The microbial models of mammalian drug metabolism strategy were exploited in studies were semisynthetic, dopaminergic ergot alkaloid derivatives Lergotrile (**33**) and Pergolide (**34**) (Scheme 11). Both of these compounds were developed for their potential application in treating disorders such as Parkinsonism, galactorrhea, and acromegaly. Lergotrile (**33**) is converted to demethyllergotrile in guinea pigs, and the compound is also hydroxylated at position 13 by both guinea pigs and humans. Of 38 microorganisms screened for their abilities to transform **33,** five, including *Cunninghamella echinulata* (UI 3655), *Streptomyces rimosus* (ATCC 23955), *S. platensis* (NRRL 2364), *S. spectabilis* (UI C-632), and *S. flocculus* (ATCC 25453), produced *N*-demethyllergotrile as the major microbial transformation product (*160*). *Streptomyces platensis* was used to produce de-

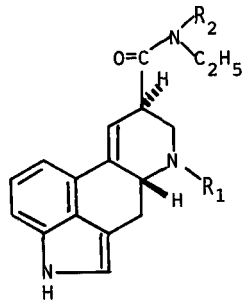


SCHEME 11. Microbial transformations of agroclavine (**31**), lergotrile (**33**), and pergolide (**34**).

methyllergotrile in 50% yield for chromatographic, spectral, and physical identification.

Pergolide (**34**) was metabolized to the equivalent sulfoxide **35** by most of 58 microorganisms examined for their abilities to transform the alkaloid substrate (*161*). Cultures were selected based on their reported abilities to oxidize sulfur or indoles. Several microorganisms including *Aspergillus alliaceus* (UI 315), *A. niger* (ATCC 16888), *Calonectria decora* (ATCC 14767), and all six *Cunninghamella* strains examined formed pergolide sulfone (**36**). *Helminthosporium* species (NRRL 4671) was used for preparative-scale conversion of Pergolide to pergolide sulfoxide (**35**). Pergolide sulfoxide was characterized by triphenylphosphine reduction back to **34,** melting point, and spectral comparison to synthetic **35.** Unlike other reports in the literature, the sulfoxidation by *Helminthosporium* sp. was not stereospecific. Stereoslectivity in sulfoxidation of Pergolide by other microorganisms was not examined.

Ishii and coworkers examined microbial transformations of lysergic acid and related compunds in order to clarify the metabolic pathway of LSD in mammals (*162–164*). *Steptomyces lavendulae* (IFM 1031) accomplished selective N-demethylation at position N^6 of lysergic acid diethylamide (LSD) (**37**) to afford nor-LSD (**38**) (*162*). On the other hand, *S. roseochromogenes* (IFM 1081) ac-

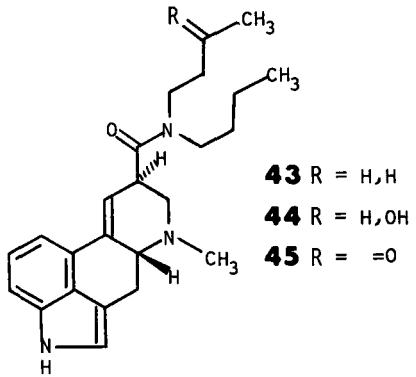


37 R_1=CH_3, R_2= C_2H_5
38 R_1=H, R_2= C_2H_5
39 R_1=CH_3, R_2= $CH{=}CH_2$
40 R_1=CH_3, R_2= $CHOH{-}CH_3$
41 R_1=CH_3, R_2= $CH_2{-}CH_2OH$
42 R_1=CH_3, R_2= H

SCHEME 12. Microbial transformation of lysergic acid derivatives.

complished selective oxidative N-dealkylation at the amide-nitrogen position of **37** to give mixtures of **39, 41,** and **42** as metabolites, with no production of nor-LSD (**38**). Other cultures including *S. massasporeus* (ISP 5035), *S. platensis* (ISP 5041), *S. rimosus* (ISP 5060), *S. fulvissimus* (ISP 5593), and *Cunninghamella echinulata* (IAM 8209) produced all of the metabolites mentioned above from LSD. Lysergic acid ethylamide (**42**) was the most common metabolite formed in microbial transformation experiments. The sequence of metabolic events was tested by incubating compounds **41** and **39** with *S. roseochromogenes*. While the lysergic acid ethyl-2-hydroxyethylamide derivative (**41**) was not metabolically transformed to other metabolites, lysergic acid ethylvinylamide (**39**) gave both **41** and lysergic acid ethylamide (**42**) in 20 and 50% yields, respectively, thus confirming the intermediacy of the vinyl-LSD derivative in the biotransformation sequence (Scheme 12). It is interesting to note that lysergic acid ethylvinylamide (**39**) was identified in a mixture of mammalian metabolites of LSD, using the microbial metabolite as an analytical reference standard, thus confirming the prospective value of the microbial models of mammalian metabolism approach (*163*).

This work was extended to a study of the microbial transformation of amide congeners of lysergic acid by *Streptomyces roseochromogenes* (*164*). In general, it was determined that the length of the alkyl chain on the amide group of lysergic acid amide substrates greatly influenced the mode of biotransformation by the microorganism. Alpha oxidation occurred in cases where N-alkyl chains were short; and omega-1 (ω-1) oxidation occurred when the N-alkyl group was longer. Lysergic acid dimethylamide and lysergic acid diallylamide were oxidized at the carbon position α to the amide nitrogen atom to give the corresponding N-dealkylated products. Compounds such as lysergic acid di-*n*-butylamide (**43**) and lysergic acid di-*n*-propylamide, however, are oxidized to give pairs of ω-1 hydroxylation products as shown in Scheme 13. The microorganism failed to achieve the oxidation of isolysergic acid diethylamide, the C-8 epimer of lysergic acid dimethylamide, and different yields of epimeric hydroxylated metabolites



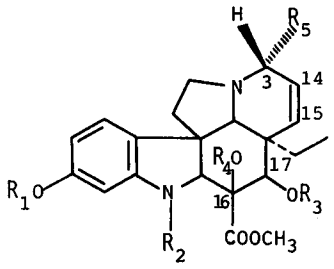
SCHEME 13. Metabolism of lysergic acid amide congeners by *Streptomyces roseochromogenes*.

(such as **44**) were obtained. This suggested that the hydroxylation reaction is stereoselective, and an enzyme model was proposed to explain the observed differences in hydroxylated metabolite yields. It is difficult to assess whether the hydroxylation reaction itself was stereoselective for two reasons: (1) mass balance experiments did not account for 100% of starting materials and products; and (2) the observed differences in amounts of isomeric alcohols **44** could be explained by the presence of oxidoreductases of *S. roseochromogenes*, which either selectively oxidize one alcohol isomer to the corresponding ketone **45** or which selectively reduce ketones back to unequal mixtures of alcohol products.

3. Catharanthus (Vinca) Alkaloids

Extensive biotransformation studies have been conducted with the Aspidosperma alkaloid vindoline, but much less work has been done with monomeric Iboga and dimeric alkaloids from this plant. The long-standing interest in this group of compounds stems from the clinical importance of the dimeric alkaloids vincristine and vinblastine, both of which have been used for more than 2 decades in the treatment of cancer. Few mammalian metabolites of dimeric Catharanthus alkaloids have been characterized. Thus the potential role of alkaloid metabolism in mechanism of action or dose-limiting toxicities remains unknown. The fact that little information existed about the metabolic fate of representative Aspidosperma and Iboga alkaloids and Vinca dimers prompted detailed microbial, mammalian enzymatic, and chemical studies with such compounds as vindoline, cleavamine, catharanthine, and their derivatives. Patterns of metabolism observed with the monomeric alkaloids would be expected to occur with the dimeric compounds.

a. Aspidosperma Alkaloids. Vindoline (**46**) is an abundantly available monomeric Vinca alkaloid. The structure of this alkaloid is found as one-half of



46 $R_1=R_2=CH_3$, $R_3=Ac$, $R_4=R_5=H$

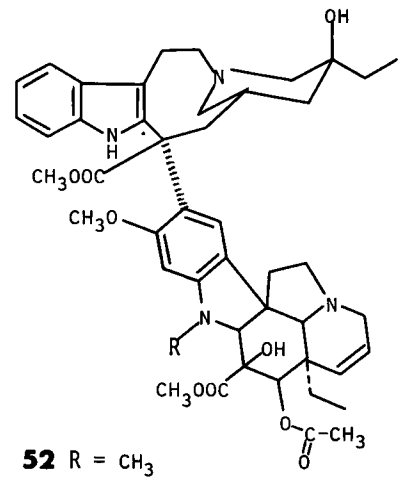
47 $R_2=CH_3$, $R_3=Ac$, $R_1=R_4=R_5=H$

48 $R_1=CH_3$, $R_2=R_4=R_5=H$, $R_3=Ac$

49 $R_1=R_2=CH_3$, $R_3=R_4=R_5=H$

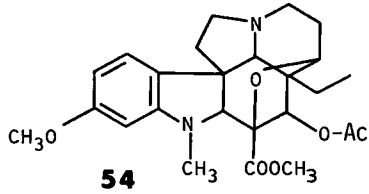
50 $R_1=R_2=CH_3$, $R_3=R_4=Ac$, $R_5=H$

51 $R_1=R_2=CH_3$, $R_3=R_4=Ac$, $R_5={}^2H$



52 R = CH_3

53 R = CHO

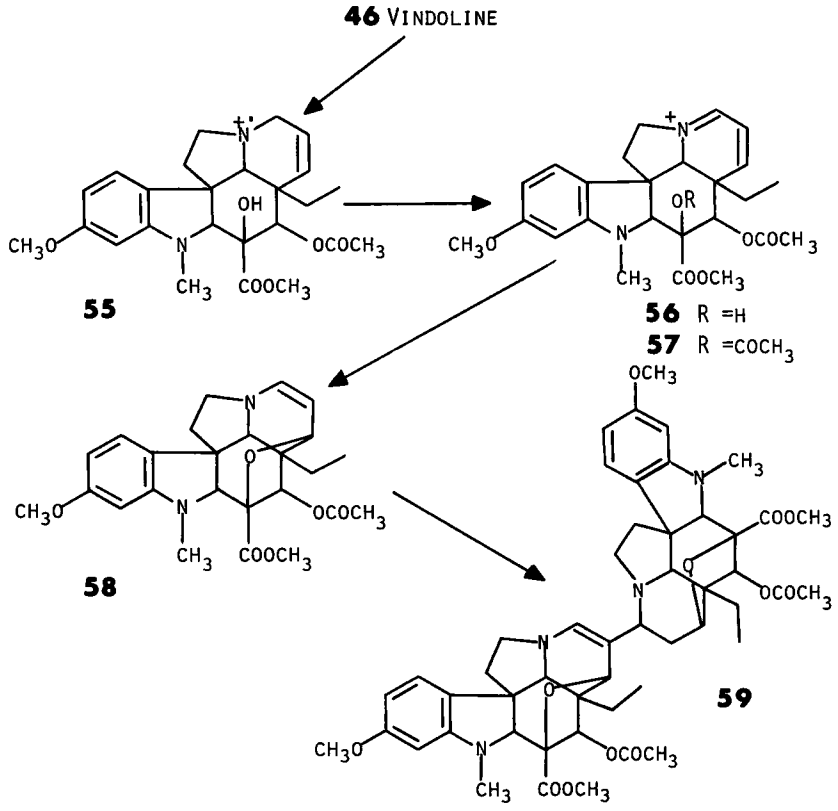


54

SCHEME 14. The structures of vindoline (**46**) and derivatives, vinblastine and vincristine (**52** and **53**), and dihydrovindoline ether (**54**).

the clincally active dimeric compounds vinblastine (**52**) and vincristine (**53**) (Scheme 14). One of the first major metabolites of vindoline observed in our laboratory was the phenolic derivative **47**, produced by O-demethylation of the alkaloid by cultures of the fungus *Sepedonium chrysospermum* (ATCC 13378) (*165*). The O-demethyl derivative was obtained in 650-mg yield from a 2-g incubation of vindoline. Although O-demethylvindoline is not biolgically active, this compound provides a novel new synthetic product for use in the synthetic preparation of new types of Catharanthus alkaloids and for biomimetic type syntheses of dimers.

Earlier biotransformation studies with vindoline were reported from the Eli Lilly Laboratories (*166–168*), and microbial transformation products included *N*-demethylvindoline (**48**), deacetylvindoline (**49**), and a structurally novel com-



SCHEME 15. Pathways of oxidation of vindoline by *Streptomyces griseus*, copper oxidases, and peroxidases.

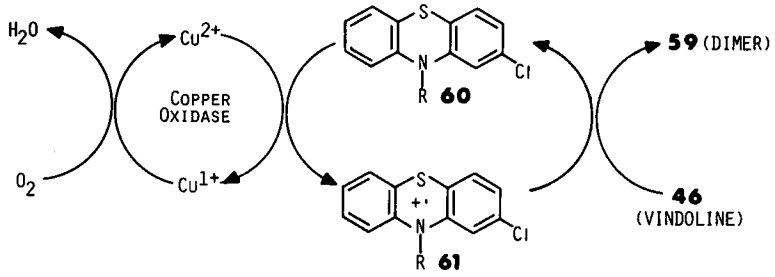
pound known as dihydrovindoline ether (**54**). The metabolic origin of **54** was of considerable mechanistic interest to us since it was possible to postulate several pathways for its formation from vindoline (*169–171*). *Streptomyces griseus* (UI 1158) formed dihydrovindoline ether (**54**), and the major metabolite was identified as the dihydrovindoline ether dimer **59** by ^{13}C- and ^{1}H-NMR and mass spectrometry (*169*) (Scheme 15). The enamine intermediate **58** was postulated as a logical precursor of **59,** and Gustafson isolated this unstable compound for characterization by direct NMR spectral measurement of the olefinic proton signals, and by mass-spectral analysis of the product obtained when **58** was deuterated by sodium borodeuteride (*170*).

The precursor to the enamine **58** was identified as iminium intermediate **56** in studies using *Streptomyces griseus*, copper oxidases (*172, 173*), and peroxidases (*78*). Although it was impossible to isolate the highly unstable iminium derivative itself, the 16-O-acetyl derivative **57** was stable and isolable. Thus when 16-

O-acetylvindoline (**50**) (Scheme 14) was incubated with these metabolic systems, the trapped iminium derivative **57** could not undergo intramolecular cyclization to form **58** and the dimer. The iminium compound was reduced with sodium borodeuteride to give the monodeuterated derivative **51** (Scheme 14) as the sole product (*173*). This compound was identified by mass spectrometry, and by high-field ^1H and ^2H NMR as 3-α-deuterio-16-O-acetylvindoline. Mass-spectral fragmentation patterns provide abundant information about the structures of aspidosperma alkaloids such as 16-O-acetylvindoline. Key fragments in the mass spectrum at *m/e* 136 and 122, which are derived from the piperidine ring of 16-O-acetylvindoline, showed that the deuterium atom was located on the piperidine ring. The logical location for deuterium was at position 3 because monodeuterated acetylvindoline could only be obtained by 1,2-deuteride attack. The ^1H-NMR spectral properties of vindoline at 360 HMz have been reported (*174*). Proton signal multiplicites and coupling constants give a clear picture of the relative positions of each proton attached to carbons 3, 14, and 15 of 16-acetylvindoline, and the monodeuterio-16-O-acetylvindoline derivative. Measured dihedral angles for protons at 3β/14 (44°) and 3α/14 (77°) for the preferred conformer of acetylvindoline are consistent with observed coupling constants of 5.1 and 2.0 Hz, respectively, for these vicinal protons. In the spectrum of **51,** geminal coupling between H-3β and H-3α was absent and the signal for H-3β occurred as a doublet at 3.30 ppm with $J = 5.1$ Hz attributed to coupling only with H-14. The signal for H-3α was absent in the spectrum of **51.** The signal at 5.84 ppm for proton H-14 was a doublet of doublets attributed to coupling only between protons H-3β and H-15. These results clearly fix the position of the deuterium atom at 3α, the expected position if $NaBD_4$ reduction occurred from the least-hindered face of iminium **57.**

Further proof of the identity of the iminium intermediate was obtained by hydrolysis of the 16-O-acetyl functional group to form **56,** which goes on to give the dimer **59** by intramolecular etherification and formation of the enamine. These findings were highly significant in providing the first direct evidence for the existence of iminium intermediates in the metabolism of nitrogen heterocycles such as vindoline. The stability of the iminium derivative enabling its isolation and chromatography and its reactivity with hydride reagents were cited as evidence to suggest that such metabolites could react with other nucleophiles of biological significance. The mechanism by which *Streptomyces griseus* catalyzes the oxidation of vindoline remains unknown because to date it has not been possible to isolate an active cell-free enzyme system from the microorganism capable of accomplishing the biotransformation of vindoline.

Eckenrode *et al.* demonstrated that copper oxidases could oxidize vindoline through the same sequence of intermediates found in the metabolism of the alkaloid by *Streptomyces griseus*. Laccase from *Polyporus anceps*, laccase from the lacquer tree, and the mammalian (human serum) equivalent copper oxidase



SCHEME 16. The flow of electrons during the oxidation of vindoline by copper oxidases.

known as ceruloplasmin all catalyzed the biotransformation reaction (*172*). This finding was important because the mechanism of oxidation of alkaloids by copper oxidases suggests the involvement of radical–cation intermediates in the oxidation pathway as shown in Scheme 16 (*172*). Vindoline is a direct substrate for the copper oxidases, but the reaction rates were greatly enhanced when chlorpromazine (**60**) was used as a "cofactor." The importance of this observation is that the reaction is actually a free-radical oxidation process facilitated by the copper component of the copper oxidases. When chlorpromazine is oxidized to its equivalent radical–cation species (**61**), enzyme incubation mixtures become red with a measured absorption maximum at 529 nm. The observed red color provided indirect evidence for the involvement of a chlorpromazine radical cation and later vindoline radical ions (i.e., **55** in (Scheme 15) during the alkaloid oxidation process. Knowing this, it was possible to mimic the copper-oxidase reaction, using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with 16-O-acetylvindoline as substrate.

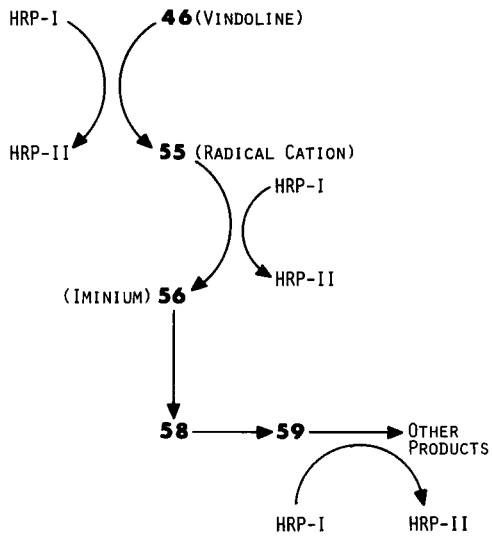
Two additional systems were exploited in order to confirm the involvement of free-radical processes during vindoline oxidations. These were the enzyme peroxidase and photochemistry. Horseradish peroxidase (HRP) oxidized both vindoline and 16-O-acetylvindoline in the presence of hydrogen peroxide. Vindoline was converted to the enamine dimer **59** (*78*). During the reaction, the following sequence of redox reactions occurs:

$$\underset{[Fe(III)]}{\text{HRP (native)}} + H_2O_2 \rightarrow \underset{[Fe(IV)]^{+\cdot}}{\text{HRP-I}} + H_2O$$

$$\underset{[Fe(IV)]^{+\cdot}}{\text{HRP-I}} + \underset{\mathbf{46}}{\text{vindoline}} \rightarrow \underset{[Fe(IV)}{\text{HRP-II}} + \underset{\mathbf{55}}{\text{vindoline}^{+\cdot}}$$

$$\text{HRP-II} + \text{vindoline} \rightarrow \text{HRP (native)} + \text{vindoline}^{+\cdot}$$

The form of the enzyme with the greatest oxidation potential is known as horseradish peroxidase, compound I (HRP-I), which consists of a radical cation stabilized throughout the highly conjugated protoporphyrin IX ring system. In the presence of vindoline, HRP-I is reduced to HRP-II, an Fe(IV) form of the enzyme. The vindoline cation radical **55** thus formed eliminates a second elec-



SCHEME 17. The course of oxidation of vindoline by horseradish peroxidase.

tron and a proton to produce the iminium product **56,** which undergoes intramolecular etherification and dimerization. The transformation of native HRP to HRP-I and the subsequent reduction of HRP-I to HRP-II is easily followed by visible spectroscopy where these three enzyme forms exhibit absorption maxima at 403, 412, and 418 nm, respectively. The availability of this simple spectral tool to measure the different oxidation states of the enzyme enabled a determination of the stoichiometry of the oxidation reaction as 4.77 mol of HRP-I reduced per mol of vindoline oxidized (Scheme 17) (*78*). It is noteworthy that HRP-II could not serve to oxidize vindoline.

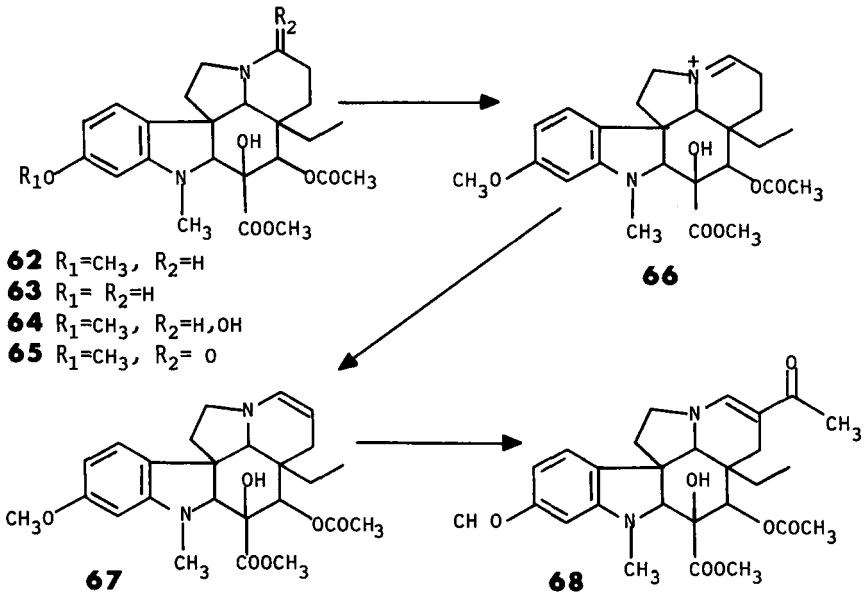
Final confirmation of the free-radical oxidation of vindoline involved the use of photochemistry of vindoline and 16-O-acetylvindoline. Photochemistry presents a pure case for the involvement of radical species in organic reactions. Our work was prompted by a report from Danieli *et al.* (*175*) who examined the dye-sensitized photooxygenation of aspidosperma alkaloids vincadifformine and tabersonine. Solutions of vindoline in methanol (1 mg/ml) held in pyrex containers were exposed to high-energy light from a Hanovia UV lamp. Although vindoline was rapidly consumed in the reaction, no discernible alkaloid products were accumulated. The same results were obtained when vindoline was dissolved in solutions containing photosensitizing agents that are used to catalyze photochemical reactions much as chlorpromazine serves as a "cofactor" with the copper oxidases. Under these conditions, vindoline is completely consumed in the reaction, and no alkaloid products accumulate. When 16-O-acetylvindoline was photolyzed in methanol, a single product was obtained quantitatively. This

compound was isolated and completely characterized as the iminium derivative **57** by ^{1}H NMR and by reduction to a deuterated derivative (*176*). This confirmed the involvement of free-radical processes in vinca alkaloid transformations and may represent a "Photochemical Model of Microbial Models of Mammalian Metabolism."

Recent work in our laboratories has confirmed the existence of a similar pathway in the oxidation of vindoline in mammals (*177*). The availability of compounds such as **59** as analytical standards, along with published mass spectral and NMR spectral properties of this compound, served to facilitate identification of metabolites formed in mammalian liver microsome incubations. Two compounds are produced during incubations with mouse liver microsome preparations: 17-deacetylvindoline, and the dihydrovindoline ether dimer **59.** Both compounds were isolated and completely characterized by spectral comparison to authentic standards. This work emphasizes the prospective value of microbial and enzymatic transformation studies in predicting pathways of metabolism in mammalian systems. This work would also suggest the involvement of cytochrome *P*-450 enzyme system(s) in the oxidation process. Whether the first steps involve direct introduction of molecular oxygen at position 3 of vindoline or an initial abstraction of electrons, as in Scheme 15, remains unknown. The establishment of a metabolic pathway in mammals, identical to those found in Streptomycetes, with copper oxidases and peroxidases again confirms the prospective value of the microbial models of mammalian metabolism concept.

In this regard, studies on the biotransformation of 14,15-dihydrovindoline (**62**) by *Streptomyces griseus* provided results of mechanistic interest when a carbinolamine (**64**) and related compounds were isolated and characterized as major metabolites of the alkaloid (*178*). Gram quantities of dihydrovindoline were incubated with growing cultures and resting cells of the microorganism to provide sufficient quantities of metabolites for complete chemical characterization. One of the first metabolites characterized was the O-demethyldihydrovindoline derivative **63**, the structure of which was determined by mass spectrometry [(M $-$ CH_3) fragment from the molecular ion and from the characteristic indole peak at *m/e* 188] and ^{1}H NMR where the methoxy signal at 3.7 ppm was absent (*179*) (Scheme 18).

Among other metabolites formed in small-scale incubations, it appeared that **64** formed within 24 hr of substrate addition and that the lactam **65** and the vinylogous amide **68** formed later. The structure of the vinylogous amide **68** was based on the high-resolution mass spectrum (*m/e* 456.2265 for $C_{25}H_{32}N_2O_6$). The mass spectrum also indicated that an acetyl functional group had been added to the piperidine ring. The ^{13}C-NMR spectrum displayed a doublet at 146.943 ppm and a singlet at 106.853 ppm, and these were attributed to olefinic signals at positions 3 and 14 was shown. The carbonyl resonance peak for the 17-acetyl grouping of **62** was absent in the metabolite spectrum and was replaced with a



SCHEME 18. Oxidations of 14,15-dihydrovindoline (**62**) *Streptomyces griseus*.

new carbonyl resonance at 191.972. The chemical shift of the carbon atom is characteristic for α,β-unsaturated ketone moieties, and all carbon assignments were in agreement with those previously reported for a mercuric acetate oxidation product of 16-acetyl-14,15-dihydrovindoline. The origin of the acetyl group and the mechanism of its formation by *Streptomyces griseus* is unknown. The acetyl group could be derived either from an intramolecular transfer of the 17-acetyl group of **62** to position 14 or from acetate pools found in *S. griseus*.

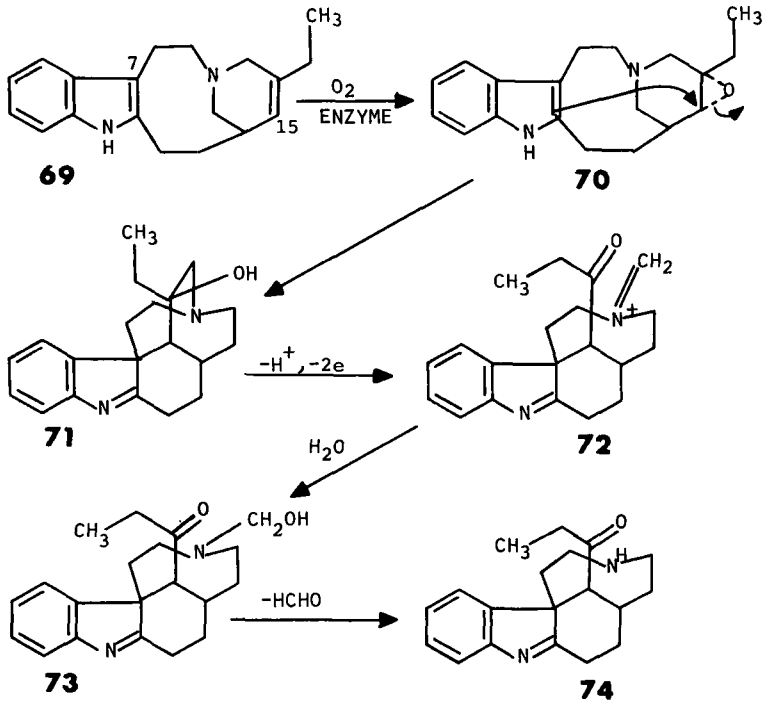
The structure of the 3-oxo derivative **65** was determined by high resolution mass spectrometry, which demonstrated that a single oxygen atom had been incorporated into the alkaloid skeleton. Peaks in the mass spectrum at *m/e* 174 and 188 provided evidence that the additional oxygen atom was not in the dihydroindole portion of the molecule, while a peak at *m/e* 138 supported the presence of an oxygenated piperdine ring. This metabolite was also chemically compared with authentic oxodihydrovindoline derivatives previously prepared and provided for comparison by J. P. Kutney.

The carbinolamine metabolite **64** was unstable in organic solvents and on routine chromatography. It was impossible to obtain molecular ions in the mass spectra by electron impact, chemical ionization, field desorption, or fast-atom bombardment techniques. The apparent molecular ion occurred at *m/e* 456, consistent with a carbinolamine such as **64**, which eliminates water to form an [M − 18] peak. The ^{1}H-NMR spectrum of this metabolite was similar to that of

the starting material, but no olefinic signals were observed in its spectrum. In addition, the chromatographic mobilities of the new metabolite were significantly different from those for vindoline and 14,15-dihydrovindoline. The ^{13}C-NMR spectrum of the metabolite was identical to that for **62** except for one signal. A triplet (methylene) at 52.3 ppm in **62** was replaced by a doublet (methine) at 89.440 ppm in the spectrum of **64.** This was assigned to the carbon atom at position 3 of the metabolite, which is assumed to exist as a carbinolamine. Similar assignments have been made for other alkaloid carbinolamine compounds (*178*). Confirmation of the identity of the metabolite as **64** was obtained by reduction of the compound with $NaBD_4$ in CH_3OD. The reduced metabolite was chromatographically identical to dihydrovindoline, and a single deuterium atom was located (by mass spectrometry) in the piperidine ring.

The results with **62** were interesting for several reasons. This was the first time we observed a carbinolamine directly. The vinylogous acetyl compound **68** also is supportive of an oxidation pathway as shown in Scheme 18. Neither **66** nor **67** was identified in this work, but their requirement as intermediates in the proposed pathway is obvious.

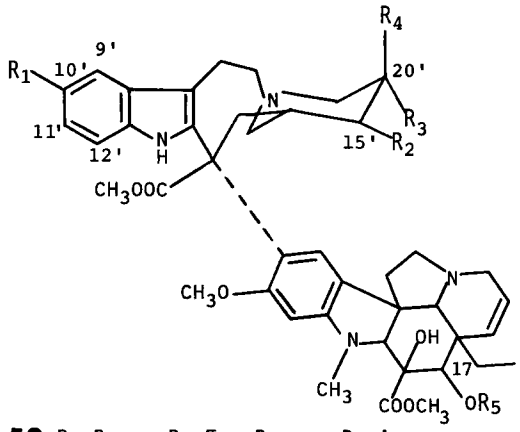
b. Cleavamine and Vinca Dimers. Metabolic transformation studies with Iboga alkaloids are rare. A preliminary report of an unusual biotransformation reaction observed when cleavamine (**69**) is oxidized by *Polyporus anceps* laccase has appeared (*171*). Functionalized cleavamines are found in the structures of dimeric alkaloids, and this Iboga alkaloid derivative was an excellent substrate for copper oxidases (*171*) as evidenced by oxygen-uptake experiments. Iboga alkaloids were oxidized at approximately twice the rate of Aspidosperma derivatives such as vindoline. When cleavamine was incubated with the laccase from *P. anceps* in preparative (1 g) scale, two metabolites were isolated, and the structure of the major one was identified. The high-resolution mass spectrum indicated an empirical formula of $C_{18}H_{22}N_2O$ (*m/e* 282.1725) or a compound containing one fewer carbon atom than cleavamine. Mass-spectral fragment ions indicated the loss of an ethyl group and an ethyl ketone, confirming the presence of a carbonyl functional group observed in the IR spectrum (1705 cm^{-1}). The metabolite identified as **74** also exhibited spectral differences in the UV spectrum where the indole UV absorption band was absent. The ^{1}H-NMR spectrum showed a four-proton multiplet in the aromatic region for the indolinene ring protons and an upfield triplet for the C-18 methyl-group protons. The triplet was indicative of the fact that the ethyl side chain of **69** was intact. The absence of an olefinic signal in the ^{1}H-NMR spectrum strongly suggested that bond formation took place between positions 7 and 15 to generate the requisite indolinene ring. The ^{13}C-NMR spectrum was in complete agreement with all observations for the metabolite structure as **74.** With structural information in hand, it was important to propose a mechanism for the formation of **74** consistent with the changes in cleavamine, including the loss of a carbon atom. The pathway shown in Scheme



SCHEME 19. Oxidation of cleavamine by *Polyporus anceps* laccase.

19 was based in part on a known acid-catalyzed transformation of leurosine to vincathicine. Oxidation of **69** to an epoxide (**70**) may occur with molecular oxygen, with or without enzyme activation, followed by an intramolecular condensation involving indole-ring electrons. The next step involves fission of a carbon–carbon bond to form an iminium intermediate **72,** which upon hydration to the unstable carbinolamine **73** loses formaldehyde to give **74.** Verification of the proposed pathway requires preparation of intermediates for reaction with laccase.

Leurosine (**75**) (Scheme 20) is the most abundant of the dimeric antitumor alkaloids isolated from *Catharanthus roseus* G. Don. Several species of *Streptomyces* produced a common metabolite of the alkaloid, and *S. griseus* (UI 1158) was incubated with 400 mg of leurosine sulfate to obtain 28 mg of pure metabolite (*180*). The metabolite was identified as **76** primarily on the basis of its ^{1}H-NMR spectrum. The mass spectrum indicated that the metabolite contained one oxygen atom more than **75.** The ^{1}H-NMR spectrum contained all of the aromatic proton signals of the vindoline portion of the molecule, and aromatic proton signals for the Iboga portion of the compound occurred as a doublet of doublets



52 R_1=R_2=H, R_3=ET, R_4=OH, R_5=Ac

75 R_1=H, R_2-R_3=O, R_4=ET, R_5=Ac

76 R_1=OH, R_2-R_3=O, R_4=ET, R_5=Ac

77 R_1=R_2=R_5=H, R_3=ET, R_4=OH

78 R_1=H, R_2-R_3=15',20'-OLEFIN, R_4=ET, R_5=Ac

SCHEME 20. Structures of dimeric Catharanthus alkaloids and their microbial or enzymatic transformation products.

at 6.74 ppm (J = 2, 10 Hz, 1H), a doublet at 6.90 ppm (J = 2 Hz, 1H), and a doublet at 6.98 ppm (J = 10 Hz, 1H). These signals are consistent with the presence of an H_a, H_m, H_x system and indicated that the hydroxy group was attached at either position 10′ or 11′ of the indole ring. The assignment at position 10′ is based on the magnitude of the upfield shift of the proton signal at position 9′ from 7.49 ppm in leurosine at 6.90 ppm in the metabolite. A similar shift has been observed in other hydroxylated indole alkaloids (*180*).

Mammalian metabolic transformation studies of dimeric vinca alkaloids have been largely unsuccessful in identifying other than the simplest of structural changes caused by enzymatic systems. The metabolism of vinblastine (**52**) (Scheme 20) was studied in human neoplastic (rhabdomyosarcoma xenograft) and mouse tissues after the alkaloid was injected *in vivo* or examined *in vitro*, using liver microsomal preparations (*181*). An acidified-ethanol extraction procedure coupled with high-performance liquid chromatography, using an octadecyl reversed-phase system, was used to identify deacetylvinblastine (**77**) as the major metabolite. No metabolites were detected in the tumor itself, and none was formed by microsomes prepared from tumor tissue. Mouse liver microsomes were capable of hydrolyzing vinblastine to the deacetylvinblastine derivative. These methods are being used to study vinca alkaloid metabolism in a series of

tumor xenografts. Anhydrovinblastine (**78**) (Scheme 20) is a compound readily prepared by the chemical linking of catharanthine and vindoline. Biotransformation studies with **78** have been conducted, using intact *Catharanthus roseus* cell suspension cultures and crude enzyme preparations from them. When 500 mg of **78** was incubated with 5.5 L of cell line "916" in a Microferm fermentor, it was transformed to the natural bisindole alkaloid leurosine (**75**) (106 mg recovered) and 29.7 mg of another dimeric alkaloid known as catharine. Neither leurosine nor catharine was produced by callus tissues per se. The use of such "biosynthetically advanced" alkaloid precursors together with tissue cultures capable of enzymatically transforming them to useful compounds may represent an attractive approach to the synthesis of other vinca dimers (*182*).

Another cultured cell line of *Catharanthus roseus* (EU4A), which does not produce detectable amounts of vinblastine and other bisindole alkaloids, was also examined for its ability to transform **78** (*183*). Cell-free extracts of the culture line were prepared, and the 35,000 × *g* supernatant solution was used. Incubations with 21′-tritioanhydrovinblastine yielded a mixture from which radioactive vinblastine (**52**) was isolated. The labeled vinblastine was reisolated after unlabeled carrier was added and rigorously purified by successive thin-layer chromatography, reversed-phase HPLC, and crystallization to constant specific activity. Boiled extracts could not produce labeled **52**, thus supporting the involvement of enzymes in the conversion process.

Rusling *et al.* described an interesting voltametric study of vinblastine, catharanthine, and vindoline (*184*). Each of these compounds gave oxidation waves in mixed aqueous/organic media by cyclic, normal-pulse, and differential-pulse voltametry. Although each of these compounds was oxidized by these techniques, no products were isolated and characterized. The results were consistent with the suggestions that alkaloid salts first undergo deprotonation and that electron transfer takes place on the alkaloid base. Interestingly, it was suggested that alkaloid bases are most likely oxidized through cation radicals prior to secondary transformations or other second-order processes. These findings through voltametry support the extensive enzymatic transformation studies with vindoline and suggest that similar enzymatic oxidative pathways will be unrecovered.

4. Miscellaneous Indole Alkaloids

The metabolic fate of 11-bromo-[15-3*H*]vincamine (**79**) (Scheme 21) was studied in rats, dogs, and humans (*185*). Complex mixtures of metabolites were present in rat plasma after animals received oral doses of the alkaloid. However, in dog and human plasma, the major compound was unchanged **79.** The major identified metabolite was 11-bromovincaminic acid (**80**) in human and dog urines.

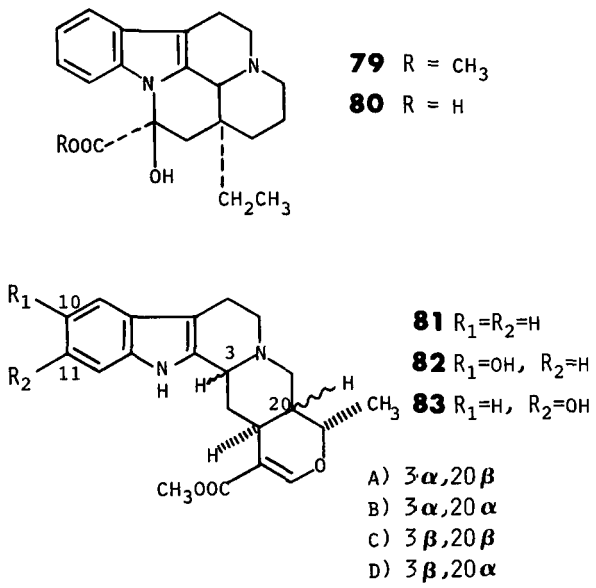
TABLE III
MICROBIAL TRANSFORMATION PRODUCTS OBTAINED FROM SUBSTRATES **81a–81d** BY VARIOUS MICROORGANISMS

Microorganism	Yield (%)						
	82a	**83a**	**82b**	**83b**	**82c**	**82d**	**83d**
Cunninghamella elegans ATCC 9245	92	—	—	—	78	56	—
C. blakesleeana ATCC 8688a	27	18	—	—	65	49	—
Mucor griseo-cyanus	12	21	—	15	—	—	—
MRRS 10-IBI	19	13	23	72	—	—	—
Streptomyces platensis ATCC 13895	—	5	—	—	—	41	32
S. rimosus ATCC 10970	—	5	—	—	—	13	5
S. rimosus IBI-A6	12	5	—	—	—	15	5

Microbial transformations of four heteroyohimbine stereoisomers [ajmalicine (**81a**) tetrahydroalstonine (**81b**), isoajmalicine (**81c**), and akumigine (**81d**)] yielded mixtures of 10- and 11-hydroxylation products (*186*) (Scheme 21). Microorganisms known for their abilities to metabolize indole alkaloids, steroids, and antibiotics were intitially screened, and seven cultures were further used for preparative-scale incubations with alkaloid substrate. The microorganisms used and yields (by HPLC) of metabolites obtained from **81a–81d** are shown in Table III.

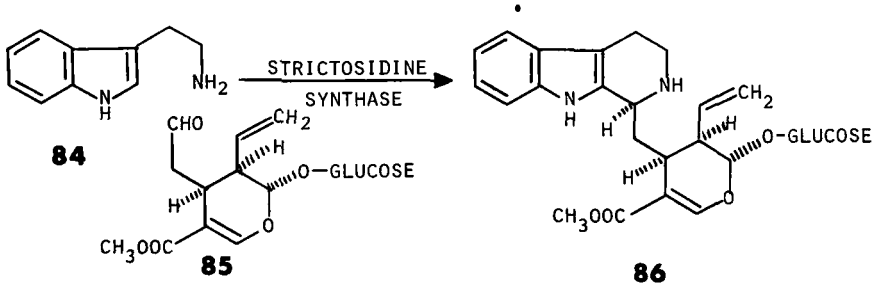
Each of the metabolites isolated from fermentation reaction mixtures gave a molecular ion at *m/e* 368 ($C_{21}H_{24}N_2O_4$) by high resolution mass spectrometry, or 16 mass units higher than the starting material. Other mass spectral fragments were consistent with metabolites hydroxylated on the aromatic ring. Confirmation of this finding was obtained by analysis of AMX spectral patterns for aromatic protons in the 200-MHz ^{1}H-NMR spectrum. The assignment of metabolite structures to either 10- or 11-hydroxy categories was based on the well-known observation that in 11-hydroxy indole derivatives, the two ortho protons (H-10 and H-12) have a larger chemical shift difference than that between protons H-9 and H-11 in 10-hydroxy compounds. The structures of 10-hydroxylated metabolites (**82a–d**) were confirmed by regiospecific Fremy's salt oxidation of dihydroindole substrates, which yield 10-hydroxylated products. A fungus isolated from the roots of *Rauwolfia vomitoria* (MRRS 10-IBI) accomplishes the regiospecific 11-hydroxylation of **81b,** but it would not oxidize the closely related alkaloids **81c** and **81d.** The 11-hydroxylation reaction is difficult to achieve by chemical methods.

Considerable success has been achieved in isolating plant tissue culture enzymes responsible for specific steps in the biosynthesis of a range of indole alkaloids (*187–191*). While the subject of biosynthesis is beyond the scope of this review, the value of such enzymes in catalyzing biotransformation reactions



SCHEME 21. *Structures of vincamine* (**79**) *and heteroyohimbines* (**81a–d**) *and their metabolites.*

in vitro is well illustrated by Pfitzner and Zenk who prepared an immobilized Strictosidine synthase and used it in the gram-scale synthesis of strictosidine (*187*) (Scheme 22). The enzyme was obtained from cell cultures of *Catharanthus roseus,* partially purified from strictosidine glucosidases by a gel-filtration step and immobilized on a cyanogen bromide-activated Sepharose matrix. Properties of the immobilized alkaloid-synthesizing enzyme were determined, and a preparative-scale synthesis of strictosidine (**86**) was achieved by passing 15 m*M* solutions of tryptamine hydrochloride (**84**) and secologanin (**85**) through the column at pH 6.5 and 37°C. A 1 × 6-cm column containing 2 g of the Sepharose-bound enzyme gave a total of 6 g of strictosidine during a 12-day reaction period.



SCHEME 22. The enzymatic synthesis of strictosidine (**86**) by immobilized strictosidine synthase.

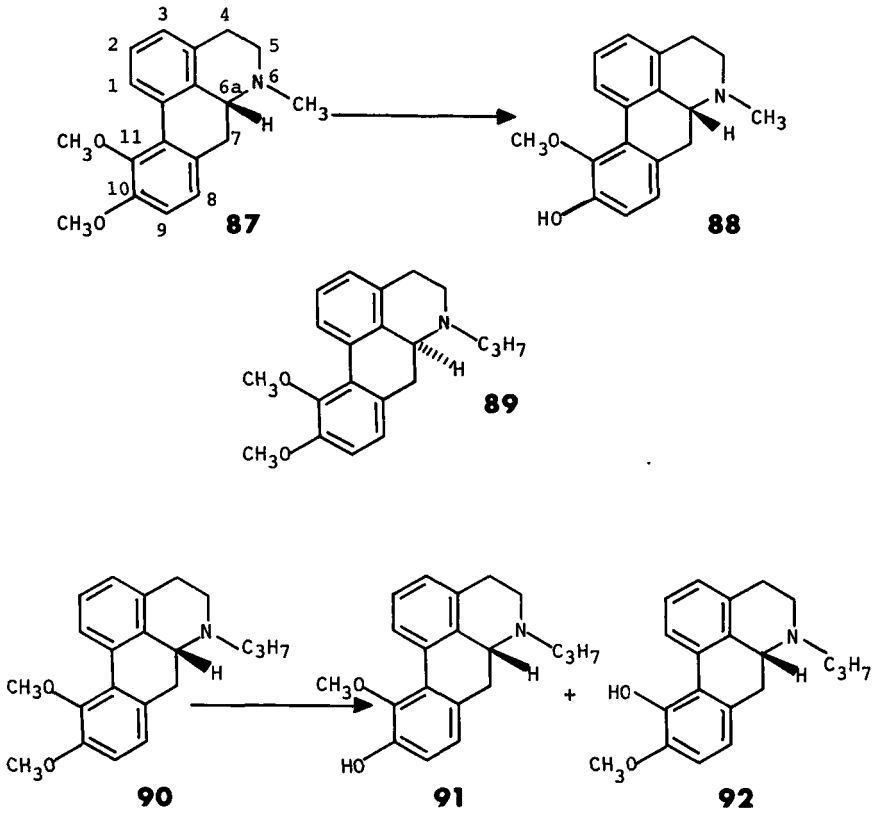
B. Isoquinoline Alkaloids

Isoquinoline alkaloids possess the isoquinoline moiety as a common structural feature, and many of the compounds in this group are pharmacologically active. They include an impressive array of functionalized structures such as the aporphines, simple isoquinolines and tetrahydroisoquinolines, and structurally complex compounds such as the morphinans. Most isoquinolines are highly oxygenated and possess methyl ether, phenolic, *N*-alkyl, and other functional groups that serve as the focus for metabolic attack by enzymes and microorganisms. Common reactions observed with these alkaloids include hydroxylation, O- and N-dealkylation, and phenolic oxidative couplings. Several excellent examples of the use of microorganisms and their enzymes as useful reagents in organic synthesis are found among the isoquinoline alkaloids.

1. The Aporphines

Davis and his group at the University of Texas have established microorganisms as useful tools in the preparation and resolution of a variety of aporphine alkaloid substrates. The fungus *Cunninghamella elegans* ATCC 9245 was exploited for its abilities to accomplish the regiospecific O-demethylation of 10,11-dimethoxyaporphines. Following the analytical demonstration that 10,11-dimethoxyaporphine (**87**) could be selectively and quantitatively O-demethylated at the less sterically hindered 10 position to produce isoapocodeine (**88**) (*192*), Smith and Davis accomplished the reaction in preparative scale to obtain **88** in 59% yield (*193*) (Scheme 23). From 1.4 g of **87,** it was possible to obtain 880 mg of **88** as the hydrochloride salt. The optimum pH for the O-demethylation reaction was between pH 3.0 and 6.0, and ascorbic acid added to the incubation medium prevented unwanted oxidation of the phenolic product. This biotransformation reaction is the only direct route to isoapocodeine, and chemical methods for the preparation of **88** are poor.

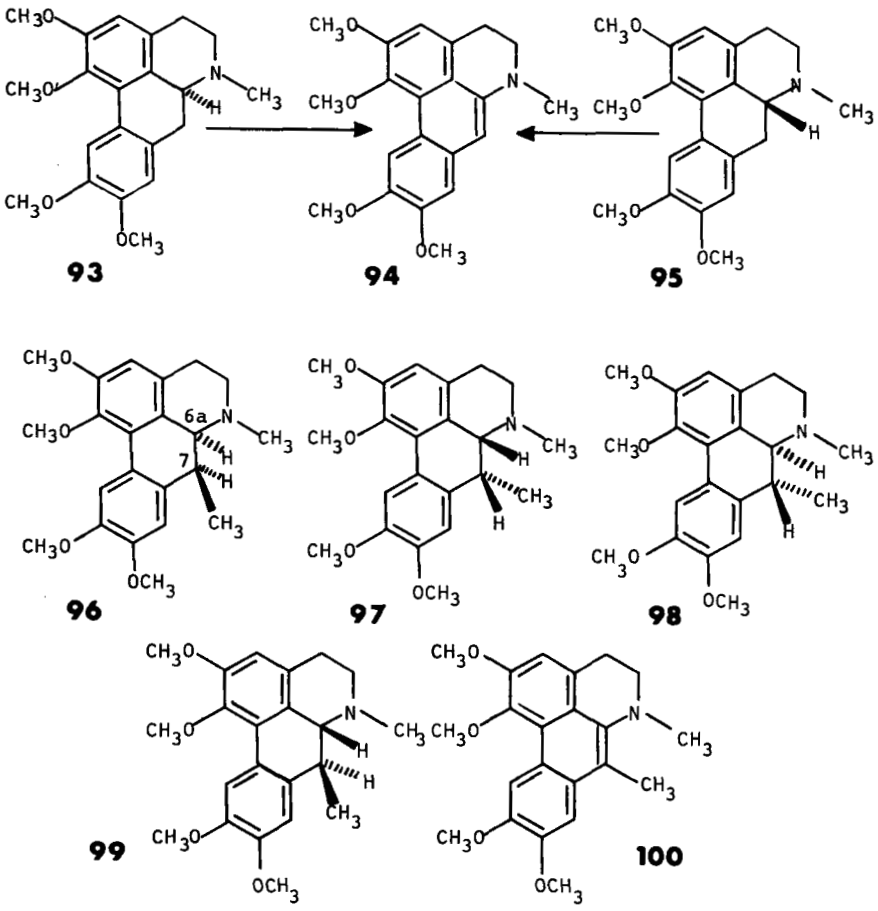
The O-demethylation reaction was further explored, using racemic aporphines such as **87** and the *n*-propyl analog **90** (*194*). Interestingly, *Cunninghamella elegans* displayed both regiospecificity for dealkylation at the 10 position, and high stereoselectivity of (*R*)-(−)-aporphine enantiomers. For example, while the (6a*R*)-(−) isomer **87** is quantitatively converted to isoapocodeine (**88**), the (6a*S*)-(+) isomer **89** gives no products. The same was true with *n*-propyl-10,11-dimethoxyaporphine (**90**) where only the (*R*)-(−) isomers would react. With **90,** however, regiospecificity was apparently compromised when reactions were conducted for longer periods of time. While **91** was the major product obtained during the first 48 hr of incubation, mixtures of **91** and **92** (67:33 by GC) were obtained from longer reaction periods. The O-demethylation reaction affords a nondestructive method for the resolution of racemic aporphines yielding (*S*)-(+)



SCHEME 23. O-Dealkylation reactions of aporphines by *Cunninghamella elegans* ATCC 9245.

compounds unchanged and the (*R*)-(−) isomer as the phenol. Chemical methylation of O-dealkylated products (i.e., **88** and **91**) would produce the other enantiomer in optically pure form.

Davis and Rosazza have also examined the oxidation of aporphines to dehydroaporphines as a means of destructive resolution. *Fusarium solani* ATCC 12823 stereospecifically and quantitatively oxidized (*S*)-(+)-glaucine (**93**) to 6a,7-dehydroglaucine (**94**) (*195*) (Scheme 24), (*R*)-(−)-Glaucine (**95**) was not oxidized by the microorganism, and racemic mixtures of (*RS*)-glaucines were oxidized to the extent of 50%. Unused and recovered glaucine substrate was previously shown (by optical rotation measurements) to be gradually enriched in the unnatural (*R*)-(−)-glaucine enantiomer (*196*). Davis and Talaat used *F. solani* to resolve (6a*RS*)-glaucine preparatively (1.5 g) to obtain 700 mg of 96% ee, (6a*R*)-(−)-glaucine (**95**) (*197*). The (*R*)-(−) isomer **95** was then used as a probe in screening experiments to identify microorganisms capable of stereoselectively



SCHEME 24. Dehydrogenations of glaucine and 7-methylglaucine isomers by *Fusarium solani* ATCC 12823 and *Aspergillus flavipes* ATCC 1030.

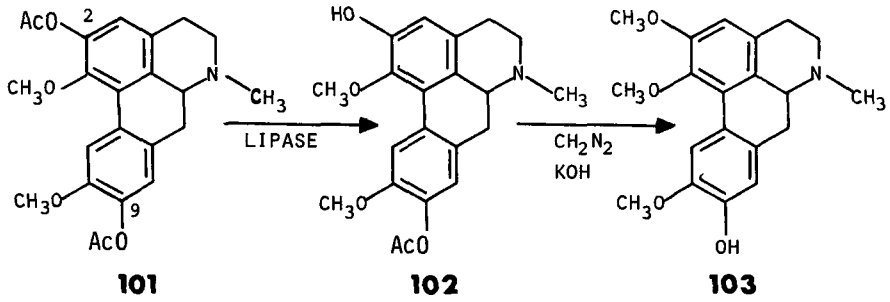
oxidizing this aporphine isomer. *Aspergillus flavipes* ATCC 1030 was able to accomplish the dehydrogenation reaction only with (*R*)-(−)-glaucine. Thus both *R* and *S* organisms are available for the destructive resolution of racemic mixtures of aporphines.

Kerr and Davis used an ingenius chemical probe to shed light on the stereochemical features of the glaucine dehydrogenation reaction (*198*). Racemic *cis*-7-methylglaucines (**96, 97**) and *trans*-7-methylglaucines (**98, 99**) were prepared by condensing glaucine with formaldehyde, followed by reduction (Scheme 24). The two diastereomeric sets of enantiomers were readily separated from one another, and the relative stereochemistries at positions 6a and 7 were

established by ^{1}H- and ^{13}C-NMR as well as by chemical reactivity. When the 7-methyl substrates were incubated with both *Fusarium solani* and *Aspergillus flavipes*, only racemic *cis*-7-methylglaucine (**96, 97**) was oxidized to dehydro-7-methylglaucine (**100**). The corresponding trans compounds were not oxidized. In both cases, the reactions gave **100** in 50% yield. Based on the previously observed stereoselectivities for these microorganisms, dehydrogenation reactions most likely proceed by cis elimination of the (6a*S*,7*S*)-hydrogen atoms of **96** for *F. solani*, and the (6a*R*,7*R*)-hydrogen atoms of **97** for *A. flavipes* (*198*).

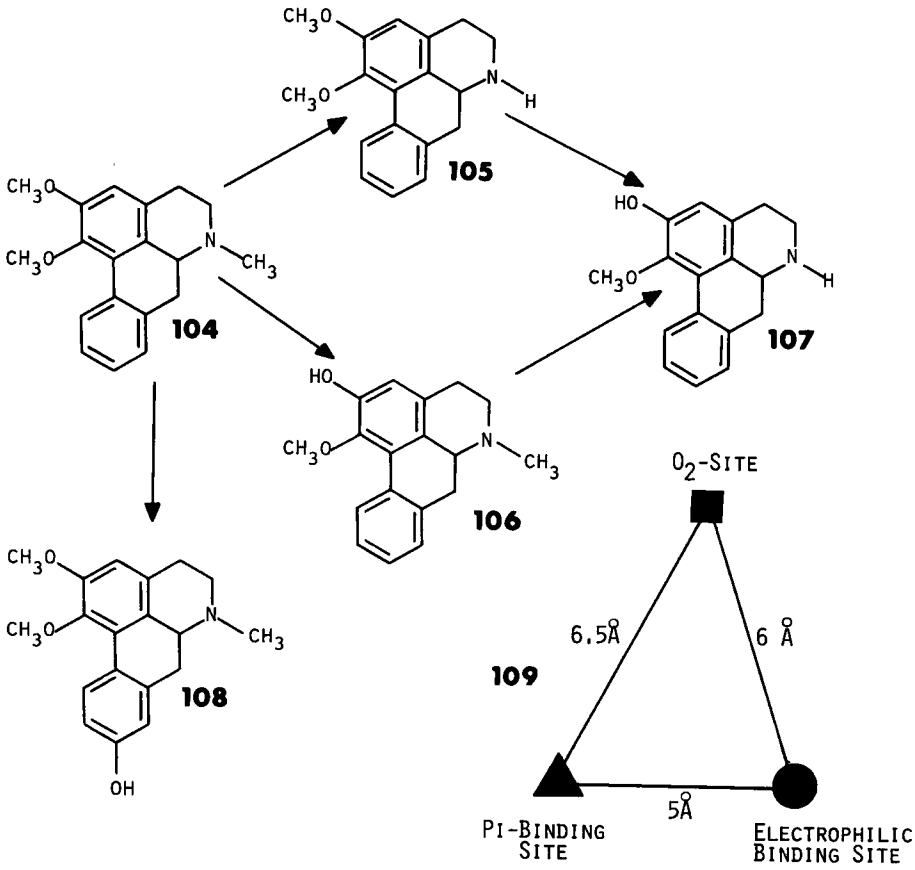
Esterases are highly attractive enzymes for use in synthetic organic chemical manipulations. They are usually stable, may be isolated in crude or partially pure form, and are commercially available and cheap. Such enzymes do not require expensive cofactors, and they may be immobilized for use (*8*). We have used commercially available lipase (i.e., esterase) from *Candida cylindraceae* (Sigma Chemical Company) in the regioselective and quantitative hydrolysis of boldine 2,9-diacetate (**101**) to provide 9-acetylboldine (**102**). Methylation of **102**, followed by base hydrolysis of the 9-acetyl group, afforded *N*-methyllaurotetanine (**103**) in excellent yield (*199*) (Scheme 25). The structure of **102** was confirmed by direct physical and spectral comparison with authentic *N*-methyllaurotetanine. The high regioselectivity displayed by enzymes such as the esterases extend the use of simple blocking groups to widespread application in other combined chemical/biochemical syntheses of alkaloids and other substrates.

Nuciferine (**104**) has proved to be an interesting organic substrate for biotransformation with cultures of *Streptomyces griseus* (M. E. Gustafson and J. P. Rosazza, unpublished results). This microorganism has afforded numerous O- and N-dealkylation products with a variety of aporphine, benzylisoquinoline, benzyltetrahydroisoquinoline, and tetrahydroisoquinoline alkaloid substrates including papaverine, *d*-tetrandrine, 10,11-dimethoxyaporphine, and glaucine (*8*). When incubated with nuciferine (400 mg), *S. griseus* provided *N*-nornuciferine (**105**) in 38% yield, 2-*O*-demethylnuciferine (**106**) (7% yield), and *N*-nor-2-*O*-



101 **102** **103**

SCHEME 25. Use of lipase (esterases) in the combined chemical and biochemical synthesis of *N*-methyllaurotetanine (**103**).



SCHEME 26. Microbial transformation of nuciferine (**104**).

demethylnuciferine (**107**) (5% yield) (Scheme 26). A small quantity of 9-hydroxynuciferine (**108**) was also obtained from the same incubation. Structure proofs of the various compounds were made simple by ^{1}H NMR. Signals for the protons in the two methoxy groups are at 3.85 ppm (C-1 methoxy) and 3.65 ppm (C-2 methoxy), and the *N*-methyl group resonates at 2.65 ppm. Thus simple absence of one of these signals, coupled with high-resolution mass spectrometry, afforded sufficient evidence for the proof of structures **104–107.** Similarly, the aromatic protons of nuciferine are well resolved with H-3 (6.6 ppm) and H-11 (8.3 ppm) isolated from protons 8–10 (multiplet centered at 7.3 ppm). The proton signal at position H-11 served as a clear indicator for the position of hydroxylation in the aromatic ring. Proof of the structure of **108** included a molecular ion 16 mass units in excess of nuciferine itself, the observation of

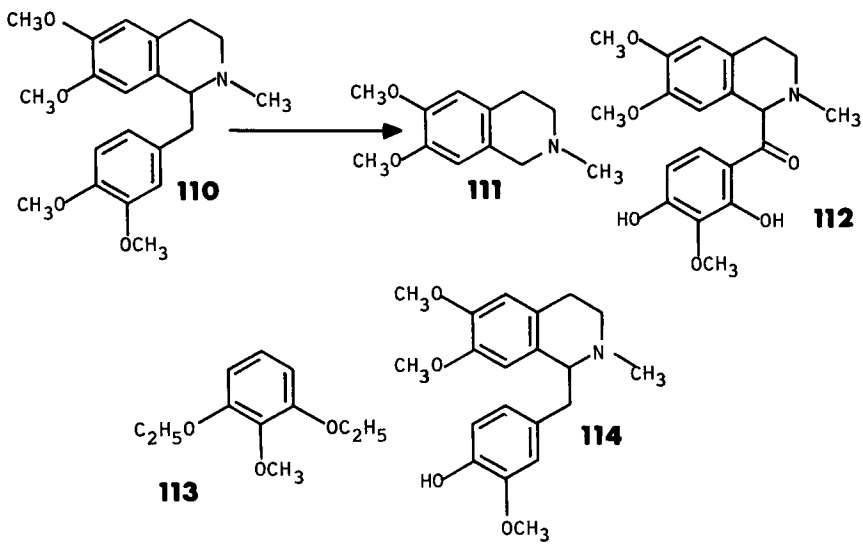
proton signals for one aromatic proton (6.6 ppm, H-3), two methoxy groups and one *N*-methyl group, and the 11-proton as a doublet (8.15 ppm, $J = 9.2$ Hz). In all other nuciferine metabolites and nuciferine itself, the H-11 signal appears as a doublet of doublets at the same chemical shift. The observed coupling constant suggests coupling of the 11-proton with the adjacent 10-proton, but no meta coupling. Together, these results support the identity of the phenolic metabolite as **108.**

Streptomyces griseus catalyzed three of the most useful types of oxidation reactions (i.e., O- and N-dealkylation and aromatic hydroxylation) with nuciferine. Previous work with glaucine indicated that similar oxidative reactions were all catalyzed with the same enzyme of the bacterium. A model of the enzyme system of *S. griseus* (**109**), which accomplished these reactions, was proposed, based on the pattern of metabolites obtained with nuciferine and on previous O- and N-dealkylation results with glaucine and 10,11-dimethoxyaporphine with this microorganism (*8*). The enzyme model incorporates electrophilic and π-binding sites and a separate oxygenation site. Association of either the nitrogen or oxygen atoms of alkaloid substrates with the electrophilic binding site would orient the alkaloid in such a way as to achieve N- or O-dealkylation or aromatic hydroxylation.

2. Benzylisoquinolines

Cannonica and co-workers examined the biotransformation of laudanosine (**110**) by a strain of *Pseudomonas putida* (*200*). The microorganism used in this work was isolated by an enrichment technique from waste-water treatment plants, using a culture medium containing laudanosine as the sole carbon and nitrogen source. When *P. putida* was incubated with 0.5% solutions of **110,** four major metabolites were obtained. The major product (15% yield) was identified as *O*-methylcorypalline (**111**), along with the new compound identified as **112,** and two additional products, which appear to be tautomeric forms of **112,** based on their chemical reactivities (Scheme 27). The structure of metabolite **112** was based on mass spectrometry, which indicated loss of one methoxy group and the addition of two oxygen atoms, all on the benzylic portion of the molecule, and NMR spectroscopy, indicating the presence of four aromatic protons (versus five on the substrate laudanosine). Two aromatic protons gave singlets, while the other two gave doublets, indicating their ortho disposition to one another. Permanganate degradation of the diethyl ether derivative of **112** and presumed tautomers gave **113,** thus confirming the arrangement of atoms on the benzylic aromatic ring.

These transformation reactions are similar in part to those previously observed for laudanosine (*201*) and for the aporphine–benzylisoquinoline alkaloid thalicarpine (*202*). Laudanosine underwent regiospecific O-demethylation at

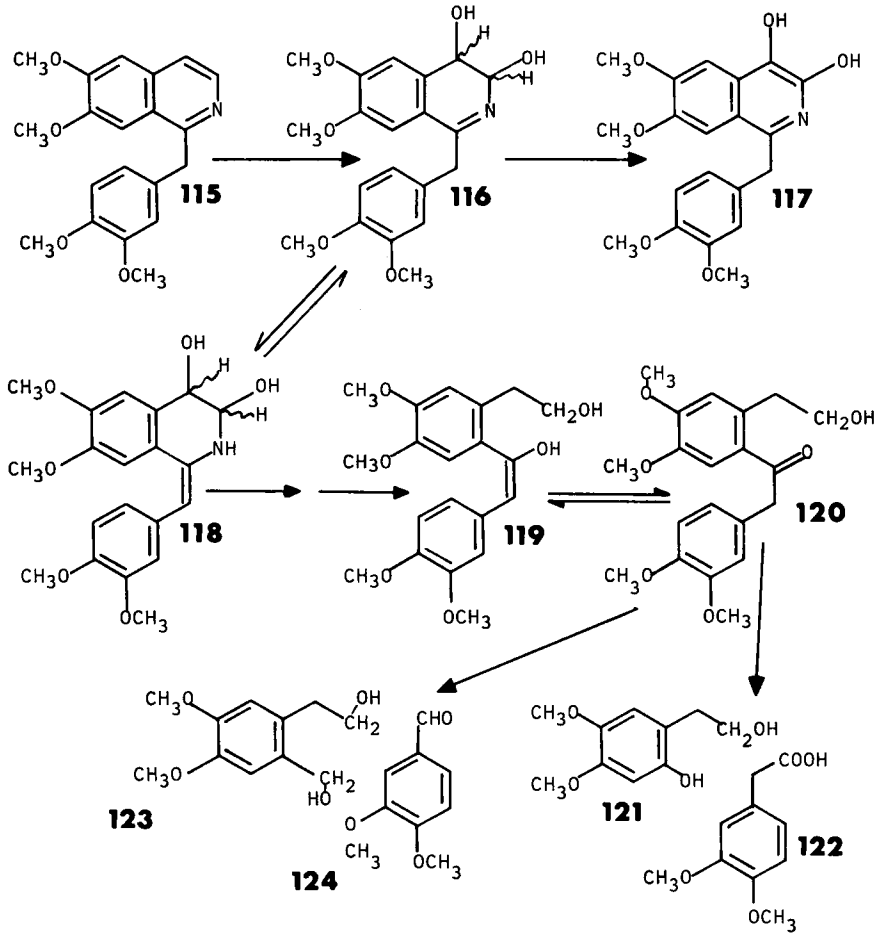


SCHEME 27. Biotransformations of laudanosine (**110**) by *Pseudomonas putida*.

position 4′ by *Cunninghamella blakesleeana* ATCC 8688a to form pseudocodamine (**114**), the structure of which was determined by chemical ethylation and permanganate degradation to 4-ethoxy-3-methoxybenzoic acid (*201*). Carbon–carbon bond fission between positions 1 and 9 of laudanosine represents an interesting reaction previously observed with the benzyltetrahydroisoquinoline portion of the dimeric alkaloid thalicarpine (*202*). The mechanism of such oxidative bond fission reactions is unknown and may be of biosynthetic and toxicologic importance with the benzylisoquinoline alkaloids.

The biodegradation of the benzylisoquinoline alkaloid papaverine (**115**) was studied, using a *Nocardia* species isolated by soil enrichment procedures by Haase-Aschoff and Lingens (*203*). The soil from which the microorganism was isolated was incubated with dilute solutions of papaverine for a year to favor the growth of organisms capable of degrading the alkaloid. When grown in the presence of 0.01–0.1% papaverine hydrochloride, the microorganism secreted numerous metabolites into the culture medium. These were isolated, and most were identified by spectral and physical techniques. The identities of the metabolites were suggestive of the pathway of degradation shown in part in Scheme 28.

The first step involves dioxygenase attack of the isoquinoline ring to give **116** as a branch intermediate. Loss of two protons and electrons from **116** gives the catechol **117** as a minor metabolite. Isomerization of the double bond of **116** to **118,** loss of water, and ammonolysis gives the enol–keto tautomers **119** and **120.** The latter compound serves as a second branch point in the degradation process. Enzymatic Baeyer–Villiger oxidation of **120** gives **121** and **122,** both of which



SCHEME 28. Pathways for the biodegradation of papaverine by *Nocardia* sp.

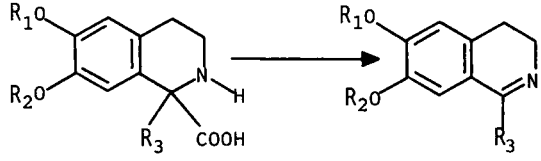
may be further oxidized. Hydroxylation of **120,** followed by retrobenzoin condensation was used to rationalize the formation of metabolites **123** and **124.** In these experiments, the microorganism displays the enzymatic machinery developed during the enrichment culture selection experiment, which permits the organism to use papaverine as the sole source of carbon, nitrogen, and energy.

Peroxidase and laccase enzymes were used to catalyze the decarboxylation of various tetrahydroisoquinoline-1-carboxylic acids to give high yields of the corresponding 3,4-dihydroisoquinolines (*204*). Compounds such as **125** (Scheme 29) are derived from Pictet–Spengler ring closure via α-keto acid and aryl amine condensation and are of biogenetic importance. The possible relevance of iso-

quinolinecarboxylic acids to important biosynthetic pathways had never been established because decarboxylation of such compounds had not been demonstrated under physiological conditions. Feasibility for these experiments was shown by the successful anodic oxidation of isoquinolinecarboxylic acids and by their air oxidation in basic media. In both anodic or air oxidation, free phenolic functional groups were required at positions 6 or 7 for the decarboxylation reaction.

Laccase from *Polyporus versicolor* was used in preliminary experiments because its known mechanism of oxidation involves one- and possibly two-electron oxidation steps but not hydroxylation. Various tetrahydroisoquinoline-1-carboxylic acids including **125, 127, 129, 131,** and **133** (Scheme 29) were uniformly and rapidly converted to their corresponding dihydroisoquinoline derivatives with the copper oxidase. Horseradish peroxidase–hydrogen peroxide also catalyzed the same decarboxylation reaction. The rates of reactions were conveniently followed by measuring the increase in absorbance at 350 nm caused by the formation of dihydroisoquinoline products such as **126.** Although the decarboxylation reactions were obtained with either enzyme system, further oxidations to other products such as aporphines were not observed. As with anodic oxidations, 6- or 7-phenolic substituents were a requisite for the decarboxylation reaction. Dimethoxytetrahydroisoquinolines do not undergo this reaction, thus underlining the free radical nature of the oxidation process.

The subject of metabolism of tetrahydroisoquinolines and related alkaloids in mammalian metabolic systems has recently been reviewed (*205, 206*). The formation of biogenic amine-derived alkaloids in mammals and their transformation by O-methylation reactions have been described.



125 R_1=H, R_2=R_3=CH_3 **126** R_1=H, R_2=R_3=CH_3

127 R_1=R_3=H, R_2=CH_3 **128** R_1=R_3=H, R_2=CH_3

129 R_1=H, R_2=CH_3, R_3=CH_2-C_6H_5 **130** R_1=H, R_2=CH_3, R_3=CH_2-C_6H_5

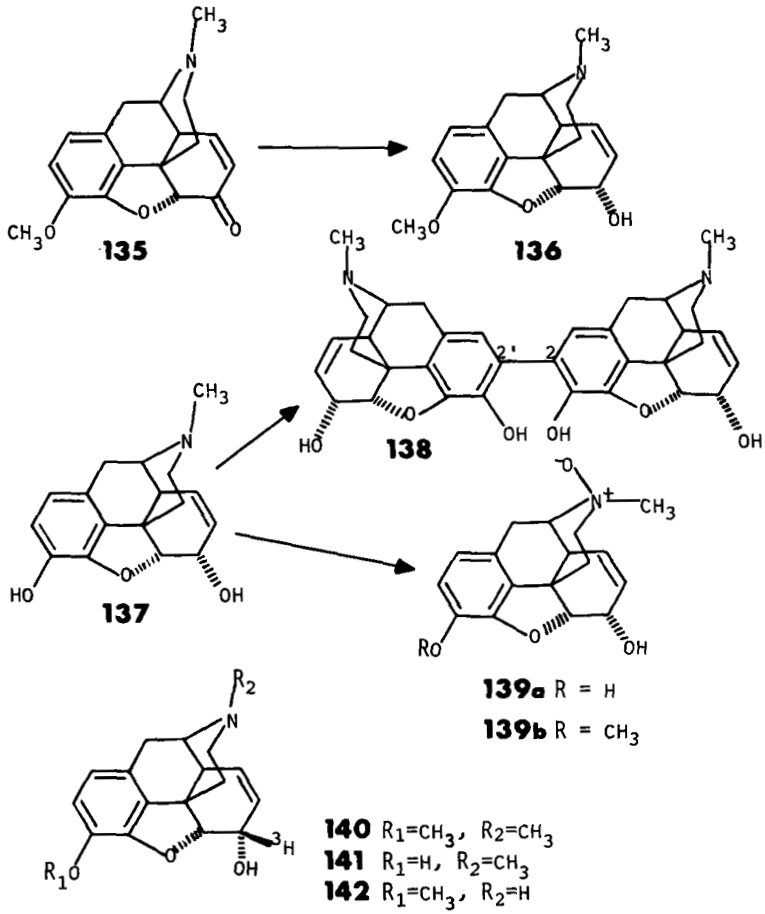
131 R_1=H, R_2=CH_3, R = CH_2 (OMe, OMe, OMe) **132** R_1=H, R_2=CH_3, R = CH_2 (OMe, OMe, OMe)

133 R_1=CH_3, R_2=H, R_3=CH_2-C_6H_5 **134** R_1=CH_3, R_2=H, R_3=CH_2-C_6H_5

SCHEME 29. Oxidative decarboxylation of tetrahydroisoquinoline-1-carboxylic acids by fungal laccase and horseradish peroxidase.

3. Morphinan Alkaloids

Biotransformations of morphinan alkaloids have been reported for plant, fungal, and mammalian enzymatic systems with emphasis on rather specific reactions such as the reduction of ketones, N- and O-demethylation, and peroxidative transformations. Furuya *et al.* used immobilized tissue culture cells of *Papaver somniferum* to accomplish the selective reduction of codeinone (**135**) to codeine (**136**) (*207*) (Scheme 30). Suspension cultures of a well-established cell line of *P. somniferum* were grown for one week as a source of cell mass for immobilization in calcium alginate. The cells continued to live in the alginate matrix for 6 months maintaining their biological activity. The reduction of co-



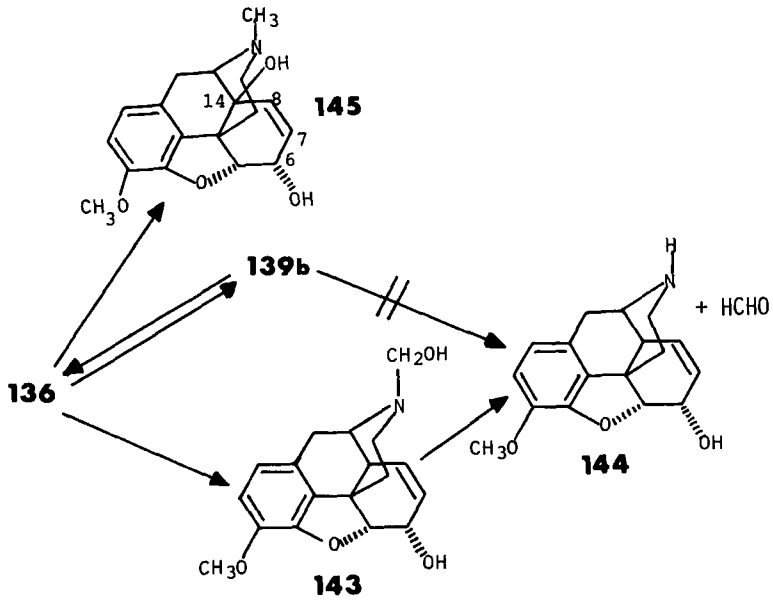
SCHEME 30. Biotransformation of codeinone and morphine by immobilized *P. somniferum* cells and peroxidases.

deinone was more efficient with immobilized cells versus cell cultures. Immobilized cells were active when used either in a shake flask or in a column bioreactor. However, the reduction reaction was less efficient when conducted in columns. This was explained by the reduced aeration obtained in columns versus shaken vessels. Incubation parameters were optimized to give highest yields at 20°C and 3.375 vvm aeration. The successful application of immobilized cell cultures in this reaction is being further explored for possible use in the biotransformation of thebaine to codeine.

Morphine levels decrease in poppy latex, presumably because of the action of plant enzymes such as phenolases, monooxygenases, and peroxidases on the phenolic alkaloid substrate. This may lead to the formation of a variety of previously identified alkaloid derivatives in the plant. Vagujfalvi and Petz-Stifter examined the reaction of morphine (**137**) with horseradish peroxidase and a crude poppy enzyme fraction and were able to identify *N*-oxides and pseudomorphine as major metabolites (*208*) (Scheme 30). Rates of oxidation reactions were influenced by the presence or absence of phenolic compounds and ascorbic acid. With horseradish peroxidase, hydrogen peroxide, and *p*-coumaric acid, pseudomorphine (2,2′-bimorphine) (**138**) was the major product (8–10% yield), while traces of *N*-oxides (**139**) were formed. The *N*-oxides were the major products (in 3–4% yield) when reactions were conducted in the presence of phenolic acids *and* ascorbic acid. The differences in the pathways of oxidation by peroxidases and plant enzymes were explained by proposing the formation of free radicals of the phenolic carboxylic acid, which generate morphine radicals resulting in the dimerization reaction. Ascorbic acid may serve to quench radicals once formed, thus preventing the dimerization process.

The dealkylation of codeine has been studied recently with microsomal enzyme preparations from rat liver and from the fungus *Cunninghamella bainieri*. Using a radiometric thin-layer chromatography assay, Duquette *et al.* incubated 6-(3*H*)-codeine (**140**) with the 165,000 × *g* pellets from Sprague–Dawley rat-liver homogenates to obtain 6-tritiomorphine (**141**), and 6-tritio-*N*-norcodeine (**142**) (Scheme 30) (*209*). The profiles for N-demethylation and O-demethylation showed maxima at pH 8.0 and 7.8, respectively, and kinetic parameters for N-demethylation were markedly higher than those for the O-demethylase. It is suggested that the two dealkylation reactions are catalyzed by different enzyme systems. *N*-Oxides of morphinan substrates previously identified in extracts of guinea pigs incubations were apparently not obtained with the rat-liver enzyme preparations (*210*).

Screening experiments identified *Cunninghamella bainieri* C43 and other microorganisms capable of accomplishing N-dealkylation reactions with a variety of drugs (*211*), and Gibson *et al.* obtained an active cell-free extract from this fungus, which was used to examine the mechanism of microbial N-demethylation of codeine (*212*). Two generally accepted mechanisms for the N-dealkyla-



SCHEME 31. N-Dealkylation of codeine by cell-free extracts of *Cunninghammella bainieri*.

tion of codeine were considered: formation of an unstable carbinolamine (**143**), which loses formaldehyde to produce the *N*-norcodeine product **144**, or formation of an intermediate *N*-oxide **139b** (Scheme 31). The isolated microsomal enzyme was prepared by disruption of cells and surfactant solubilization. The carbon monoxide-reduced UV difference spectrum indicated the presence of a cytochrome *P*-450 enzyme in the microsomal preparation, and the N-demethylation reaction required NADPH, NADH, and iron. Semicarbazide was used to trap formaldehyde formed during the N-demethylation reaction. Both codeine (**136**) and the *N*-oxide (**139b**) were transformed to norcodeine (**144**) by the enzyme mixture. It would appear that codeine *N*-oxide undergoes reduction back to codeine when it is converted to **144**, and that the *N*-oxide derivative does not serve as a direct-line intermediate in the N-demethylation reaction. Heimbrook *et al.* (*213*) have provided recent evidence suggesting that both *N*-oxide and tertiary amine substrates such as **139b** and **136** may undergo direct oxidation by cytochromes *P*-450 in N-demethylation reactions. Both types of substrates may associate with *P*-450 to form essentially the same reactive intermediate: the *N*-oxide with *P*-450–Porphyrin–Fe(III), and the tertiary amine with reduced *P*-450 following one-electron transfer from the reductase. The carbinolamine forms only after a carbon–hydrogen bond breaks to form a free radical intermediate on the *N*-methyl group.

Kunz *et al.* at DuPont examined the oxidation of codeine by cultures of

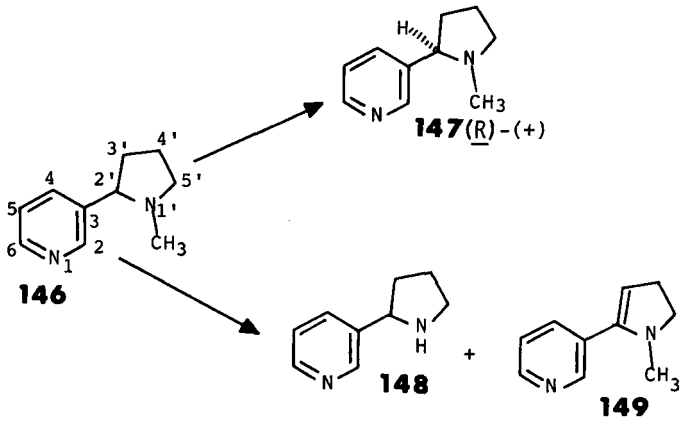
Streptomyces griseus (ATCC 10137) (*214*). Although other workers had reported the conversion of morphine and codeine to 14-hydroxymorphine and 14-hydroxycodeinone by cultures of *Arthrobacter* and *Pseudomonas*, rigorous chemical evidence was not provided for the identification of these products. Incubation of codeine with *S. griseus* resulted in the isolation of two metabolites identified as *N*-norcodeine (**144**) and 14-hydroxycodeine (**145**) (Scheme 31). Their identities were established by chromatography (TLC, GC), gas chromatography/mass spectrometry, and high-field ^{1}H-NMR spectroscopic analyses of the metabolites. The 14-hydroxylation reaction previously observed with thebaine, codeine, and morphine is difficult to achieve chemically with codeine and morphine. The N-demethylation reaction is similar to that reported earlier for fungi and mammalian metabolic systems, whereas the 14-hydroxylation reaction may be unique to bacteria.

C. Pyridine Alkaloids

Nearly all of the microbial and mammalian transformation studies with this group of alkaloids have been focused on nicotine. Microorganisms have been used to resolve racemic nicotine to make available unnatural (*R*)-(+)-nicotine for biological evaluation. Highly significant work has detailed the mechanism of nicotine oxidation in mammals, and has resulted in the identification of reactive intermediates formed as the alkaloid is transformed by hepatic monooxygenases. The chemistry and pharmacology of the pyridine alkaloids is discussed by Strunz and Findlay in Volume 26 of this treatise.

Three groups of investigators used *Pseudomonas* species to resolve racemic nicotine (*215–217*). Traditional chemical methods used for the resolution of nicotine involve formation of *d*-tartaric acid salts and tedious fractional crystallization. DeTraglia and Tometsko recognized that while the oxidative degradation of nicotine by microorganisms was well described in the literature, the stereoselective features of nicotine oxidations had not been explored (*215*). Cells of *Pseudomonas putida* NRRL B-8061 were placed in dialysis sacs, immersed in pH 6.5 phosphate buffer containing 3.1 *mM*(*S*)-(−)-nicotine or racemic nicotine (**146**), and incubated at 30°C. Samples taken at time intervals were subjected to UV and circular dichroism measurements to determine the extent and stereoselectivity of the oxidation reaction. The microorganism selectively oxidized (*S*)-(−)-nicotine, and optically pure (*R*)-(+)-nicotine (**147**), the "unnatural" alkaloid isomer, was obtained qunatitatively when racemic nicotine was used. Similar results were obtained by others, using different *P. putida* strains (*216, 217*) (Scheme 32).

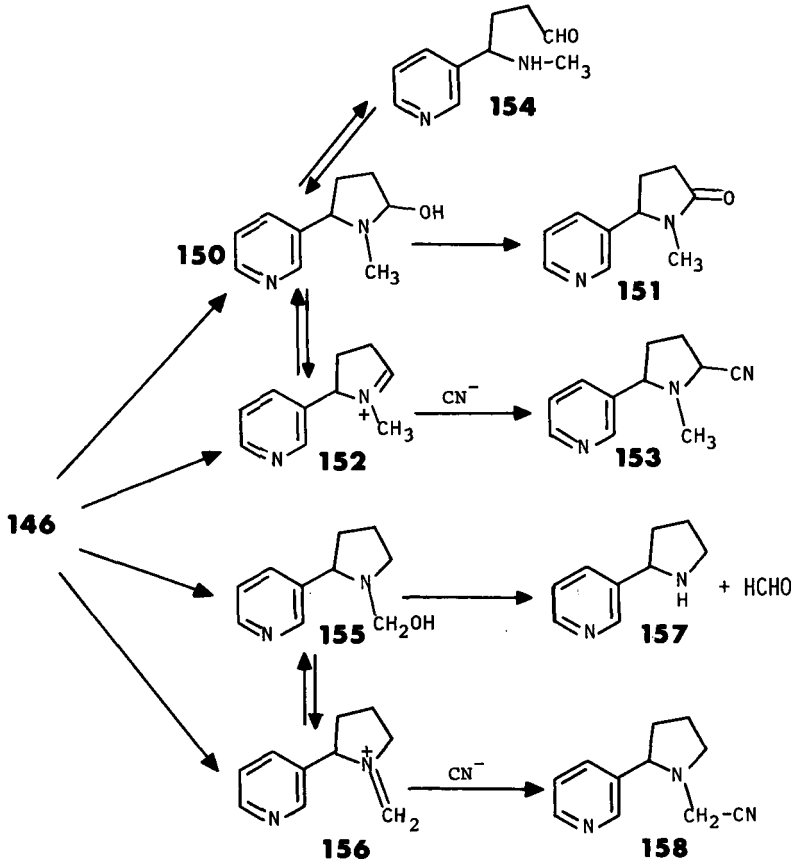
Several species of fungi were examined for their abilities to degrade (*S*)-(−)-nicotine (*218*). *Pellicularia filamentosa* JTS-208 and *Cunninghamella echinulata* IFO-4444 gave low yields of nornicotine (**148**) and *N*-methylmyosine



SCHEME 32. Oxidative transformations of nicotine by microorganisms.

(**149**). After long incubation times, exceeding 2 weeks, *C. echinulata* gave **148** and **149** in 3.47 and 7.95% yields, respectively (by HPLC). Only one of eight cultures pathogenic to tobacco was able to degrade nicotine. The microbial transformation reaction would of be little preparative value, but this work claims to be the first demonstration of pyrrolidine oxidative pathways of nicotine in fungi.

Castagnoli and his group studied the biotransformation of nicotine by rabbit liver microsomal fractions with emphasis on the identification of reactive iminium–carbinolamine intermediates produced as the alkaloid undergoes metabolic oxidation (*219*). Cotinine (**151**) and nornicotine (**157**) are major and minor mammalian metabolites of nicotine, which most probably form through carbinolamine precursors **150** and **155,** respectively (Scheme 33). Liver incubation reactions conducted in the presence of 0.01 *M* sodium cyanide led to the characterization of two isomeric cyanonicotine compounds, the production of which were used to confirm the existence of reactive iminium species during the process of metabolic oxidation of nicotine. Cyano adducts are thought to arise from nucleophilic attack by cyanide ion on iminium intermediates such as **152** and **156.** The structure of one cyano adduct was shown to be *N*-(cyanomethyl)nornicotine (**158**) by synthesis and mass spectrometry. Experiments using nicotine-(*N*-methyl-d_3) and a 10-fold excess of formaldehyde in reaction mixtures indicated that **158** apparently forms without carbon–nitrogen bond cleavage and subsequent reformation of the carbinolamine **155.** The other cyano adduct was shown to be 5′-cyanonicotine (**153**). The location of cyano functional groups was established by the use of several different deuterated nicotine analogs and by mass-spectrometric evaluation of the incubation products. These included nicotine-5′,5′-d_2, nicotine 2′,5′,5′-d_3, and nicotine (*N*-methyl-d_3). The loss or retention of deuterium from



SCHEME 33. Pathways of mammalian hepatic metabolism of nicotine.

cyano adducts produced when the deuterated substrates were incubated with rabbit liver microsomes confirmed the positions of cyano groups in **153** and **158.** Similar experiments with tritium-labeled 1-benzylpyrrolidine led to the NADPH-dependent incorporation of label into macromolecular fractions isolated from hepatic microsomal incubations (*220*). This experiment demonstrated that metabolically generated iminium ions, such as those proposed for nicotine, are capable of alkylating nucleophilic functional groups *in vivo*.

Hibberd and Gorrod incubated nicotine-Δ-1′-(5′)-iminium (**152**) with hepatic homogenates prepared from mouse, rat, hamster, rabbit, guinea pig, and human fetal liver to demonstrate the involvement of such reactive chemical intermediates in the oxidation of nicotine to cotinine (**151**) (*221*). The iminium ion (**152**) was converted to (**151**) more rapidly than nicotine, thus confirming the intermediacy of the ion between nicotine and cotinine. A series of inconclusive

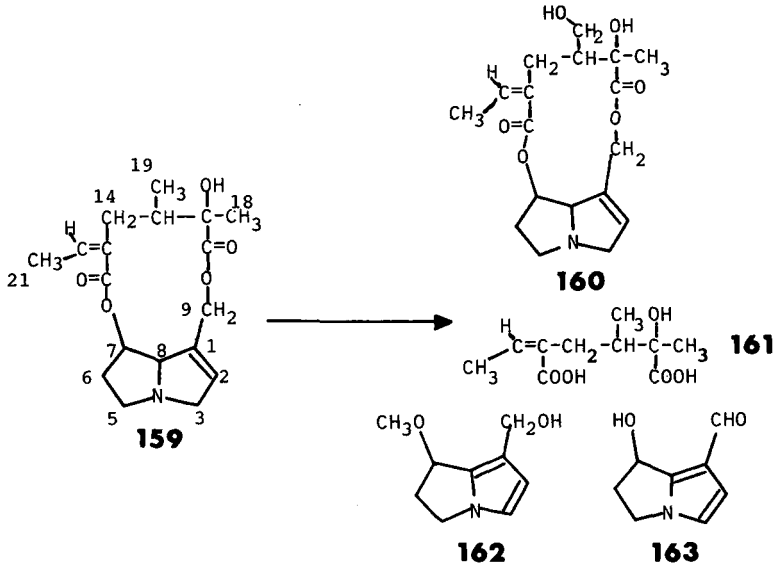
inhibition studies was used to suggest that the carbinolamine intermediate **150** is oxidized to continine by aldehyde oxidase. Aldehyde oxidase was also implicated in this conversion by Castagnoli *et al.* who compared the abilities of 10,000 × *g* supernatant and 100,000 × *g* microsomal fractions to form cotinine (*220*).

D. Pyrrolizidine Alkaloids

Extensive metabolic work continues with the pyrrolizidine alkaloids many of which are known toxic principles of plants responsible for conditions such as irreversible hemorrhagic liver necrosis, megalocytosis, and cancer. Considerable interest remains in the metabolism of pyrrolizidine alkaloids and their *N*-oxides to "metabolic" pyrroles thought to participate in molecular events associated with the above-mentioned toxicities. The chemistry and pharmacological properties of the pyrrolizidine alkaloids is authoritatively discussed by Wrobel in Volume 26 of this treatise.

Segall and coworkers described the *in vitro* mouse hepatic microsomal metabolism of the alkaloid senecionine (**159**) (Scheme 34). Several pyrrolizidine alkaloid metabolites were isolated from mouse liver microsomal incubation mixtures and identified (*222, 223*). Preparative-scale incubations with mouse liver microsomes enabled the isolation of metabolites for mass spectral and ^{1}H-NMR analysis. Senecic acid (**161**) was identified by GC–MS comparison with authentic **161.** A new metabolite, 19-hydroxysenecionine (**160**), gave a molecular ion consistent with the addition of one oxygen atom to the senecionine structure. The position to which the new oxygen atom had been added was made evident by the ^{1}H-NMR spectrum. The three-proton doublet for the methyl group at position 19 of senecionine was absent in the NMR spectrum of the metabolite and was replaced by two signals (one proton each) at 3.99 and 3.61 ppm for a new carbinol methylene functional group. All other ^{1}H-NMR spectral data were consistent for the structure of **160** as the new metabolite (*222*).

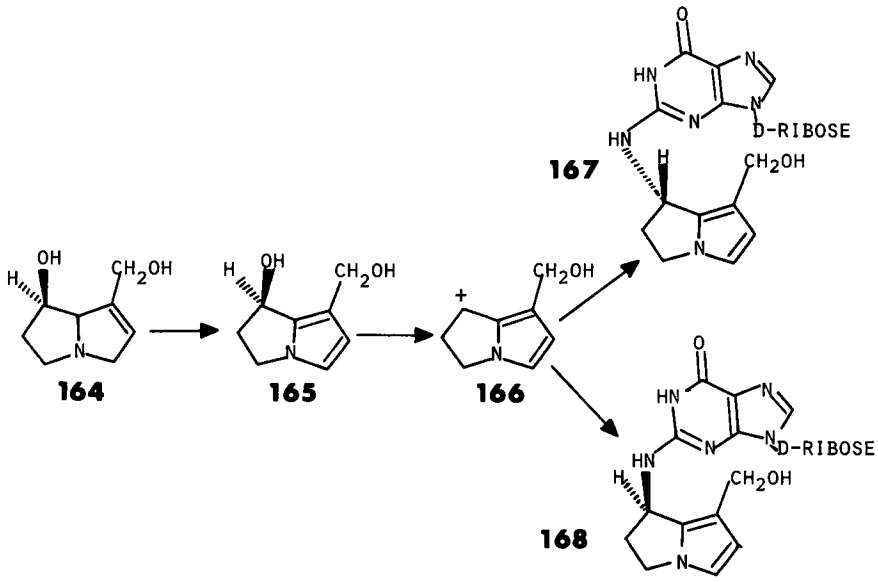
Two metabolites of lower molecular weight were identified as 7-methoxydehydroretronecine (**162**) and 1-formyl-7α-hydroxy-6,7-dihydro-5*H*-pyrrolizine (**163**) (*223*). The molecular ion for **162** at *m/e* 167 indicated an empirical formula of $C_9H_{13}NO_2$, and the presence of OH and CH_3O functional groups was indicated by fragments obtained by losses of water and methanol. The ^{1}H-NMR spectrum was also consistent with the metabolite structure as **162,** a known compound. The metabolite was not an artifact of reaction mixture workup since it was formed whether ethanol or methanol were used in the reaction. The second metabolite (**163**) is also a known compound, the structure of which was confirmed by mass spectrometry (*m/e* 151 and fragments obtained by losses of carbon monoxide, formaldehyde, and water) and ^{1}H-NMR spectrometry, indicating an aldehyde resonance at 9.69 ppm (Scheme 34). The absence of nuclear spin coupling between H-7 and the aldehyde proton proved that the structure was



SCHEME 34. The transformation of senecionine by mouse liver monooxygenase preparations.

163. Incubation mixtures containing calf thymus DNA resulted in senecionine and a related compound being bound to a macromolecular liver fraction (*224*). The binding of the compounds was dependent on the presence of oxygen, the enzyme system, and an NADPH-generating system, thus demonstrating that metabolites such as those formed from senecionine (Scheme 34) may interact with macromolecules to result in alkaloid-associated toxicities.

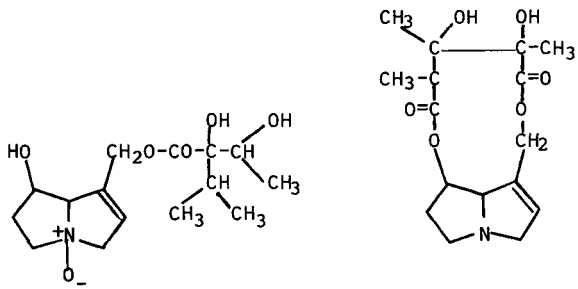
Few attempts have been made to demonstrate that pyrrolizidinepyrroles in fact do react with typical cellular nucleophiles. Pyrroles that are metabolically derived from pyrrolizidine alkaloids are generally considered to be carcinogenic and potentially antimitotic. To examine the ways in which pyrrolizidinepyrroles react with nucleophiles, dehydroretronecine (**165**), the pyrrole structure expected from retronecine (**164**) was treated *in vitro* with deoxyguanosine under physiological conditions (i.e., 25 *mM* phosphate buffer, pH 7.4, and 37°C) for 12 hr (*225*). Two reaction products were obtained in nearly equal proportions (Scheme 35). The two adducts of **165** were isolated and characterized as 7α- and 7β-(deoxyguanosine-*N*-2-yl)dehydrosupinidines (**167**) and (**168**), respectively. The compounds were subjected to physical (pK_a determination), chemical (reaction with mild alkali and with 4-[*p*-nitrobenzyl]pyridine) and spectral (MS and 270-MHz ^{1}H-NMR) analyses. The ^{1}H-NMR spectra of the adducts were similar, and the N-1 proton signal was not observed in the spectrum of either isomer, a common observance with nucleosides. The C-8 proton signal occurred as a sharp



SCHEME 35. The *in vitro* chemical reaction of dehydroretronicine (**165**) with deoxyguanosine.

singlet at 7.95 ppm for one isomer and at 7.89 ppm for the other, thus indicating that C-8 and N-7 positions were not involved in covalent bond formation. Pyrrole proton signals were also evident in the spectra of both isomers. The proton signal for position 7 was coupled to an exchangeable proton and was shifted downfield by 0.4 ppm, thus confirming the position of bond formation as isomeric at position 7 (*225*). The facile reaction of metabolic pyrroles such as **165** with biologically significant nucleophiles supports the putative involvement of these compounds in pyrrolizidine alkaloid toxicity.

Indicine *N*-oxide (**169**) (Scheme 36) is a clinically important pyrrolizidine alkaloid being used in the treatment of neoplasms. The compound is an attractive drug candidate because it does not have the acute toxicity observed in other pyrrolizidine alkaloids. Indicine *N*-oxide apparently demonstrates increased biological activity and toxicity after reduction to the tertiary amine. Duffel and Gillespie (*90*) demonstrated that horseradish peroxidase catalyzes the reduction of indicine *N*-oxide to indicine in an anaerobic reaction requiring a reduced pyridine nucleotide (either NADH or NADPH) and a flavin coenzyme (FMN or FAD). Rat liver microsomes and the 100,000 × *g* supernatant fraction also catalyze the reduction of the *N*-oxide, and cofactor requirements and inhibition characteristics with these enzyme systems are similar to those exhibited by horseradish peroxidase. Sodium azide inhibited the *N*-oxide reduction reaction, while aminotriazole did not. With rat liver microsomes, *N*-octylamine decreased



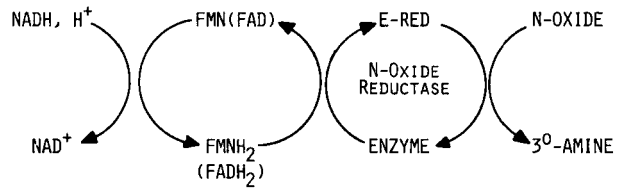
169 **170**

SCHEME 36. Structure of indicine *N*-oxide (**169**) and monocrotaline (**170**).

the rate of *N*-oxide reduction to 60% of controls. *n*-Octylamine is a well-known inhibitor of cytochrome *P*-450, thus implicating this well-known enzyme in the microsomal reduction reaction. *N*-Oxide reductase activity was retained when horseradish peroxidase, hepatic supernatant, and microsomal preparations were used with an ultrafiltration membrane (mol wt 10,000 cutoff). Coenzyme requirement studies and the sensitivity of the supernatant enzyme to inhibitors suggested that the enzymatic reaction requires a reduced flavin, which in turn reduces peroxidase, which then reduces indicine *N*-oxide (*90*).

Monocrotaline (**170**) has been the subject of extensive metabolic study with mammalian and microbiological systems. Pyrrolizidine alkaloids such as monocrotaline require metabolic activation to the corresponding pyrrole derivatives or dehydro alkaloids before they are capable of forming covalent bonds with critical macromolecules within the cell. The X-ray structure of dehydromonocrotaline has recently been determined (*226*), and the ability of dihydroretronicine derived from monocrotaline to react with deoxyguanosine has been demonstrated *in vitro* (*225*).

Microbial transformation experiments were conducted with monocrotaline and monocrotaline *N*-oxide as substrates (*227*). Numerous microbial genera were screened for their abilities to transform these compounds, but few new metabolites of these compounds were detected in fermentation extracts. Several *Streptomyces* species consumed the alkaloid substrates to form "metabolic pyrroles" as shown by spectrophotometric and chromatographic measurements of the pyrrolizidinepyrroles following sonication of cells, extraction, and reaction of extracts with *p*-dimethylaminobenzaldehyde reagent. Many microorganisms achieved the facile reduction of monocrotaline *N*-oxide to monocroaline. These included 15 *Streptomyces*, two *Aspergillus*, one *Penicillium*, two *Mucor*, and two *Candida* strains. *Streptomyces lincolnensis* ATCC 25466 achieved *N*-oxide reduction in the most efficient manner, and this organism was selected for further study. A preparative-scale incubation provided sufficient monocrotaline from

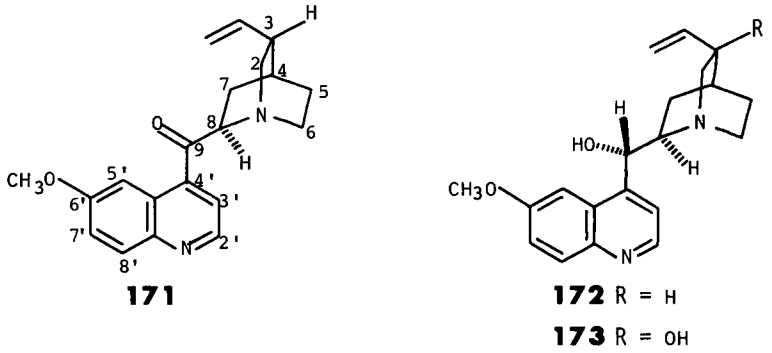


SCHEME 37. The flow of electrons in the *N*-oxide reductase system of *Streptomyces lincolnensis*.

monocrotaline *N*-oxide for complete chemical and spectral characterization. Attempts to purify the *N*-oxide reductase enzyme system from *S. lincolnensis* have been made. After passage of the *S. lincolnensis* cells through a French Press, the reductase activity resided in the 100,000 × *g* (1.5 hr) supernatant fraction. Addition of FMN to the supernatant enhanced the *N*-oxide reduction reaction. The catalytic activity was nondialyzable, heat labile, and eluted in the void volume of Sephadex G-25, and the enzyme was purified 30-fold by ion-exchange chromatography. The *S. lincolnensis* enzyme system accomplished the reduction under oxygen and nitrogen, and it is selective for aliphatic *N*-oxide substrates. The results of inhibition studies, chelated iron, catalase, and superoxide dismutase experiments suggested the involvement of a metal atom, possibly iron, in the *N*-oxide reductase. A scheme for the reduction of *N*-oxides by the enzyme system of *S. lincolnensis* has been proposed (Scheme 37). The stereoselective features of microbiol *N*-oxide reductases with rigid nitrogen heterocyclic *N*-oxide isomers, such as those observed with morphinan alkaloids, have not yet been explored.

E. QUINOLINE ALKALOIDS

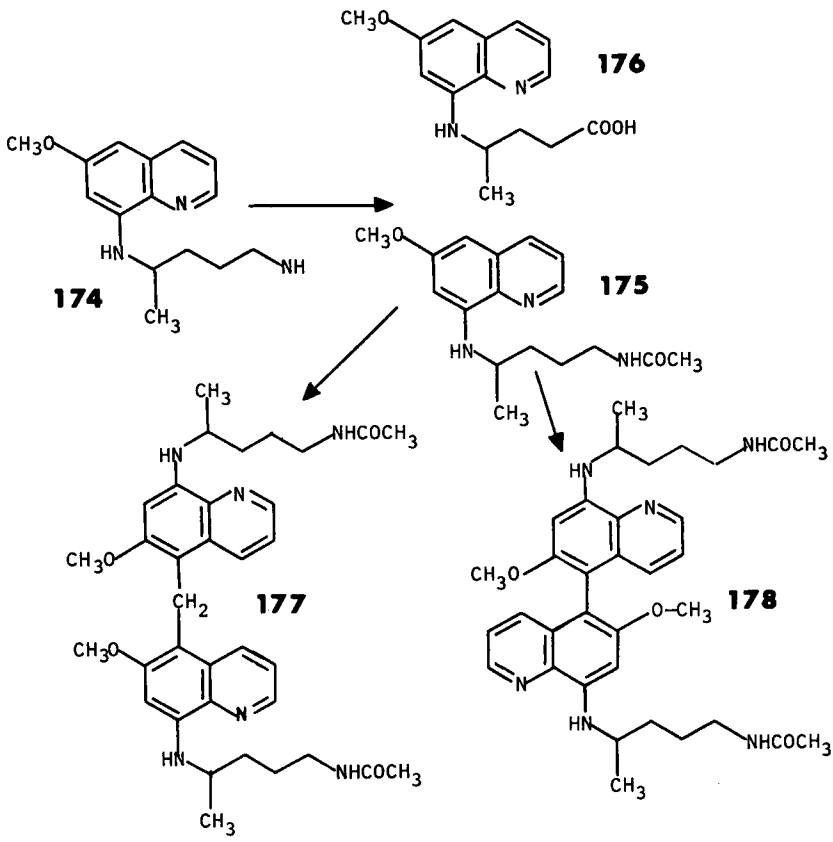
Biotransformations of quinidine, quininone, and of the synthetic quinoline antimalarial primaquine have been reported. Quinidine sulfate is a minor Cinchona alkaloid of value in cardiovascular medicine. Microbial transformations were explored as a possible means of preparing the alkaloid, using semisynthetically prepared quininone (**171**) (Scheme 38) as starting material. Ray *et al.* (*228*) screened 450 microorganisms to find two that were able to accomplish the reduction reaction. One of these was a strain of *Hansenula anomala,* which was used to catalyze the stereospecific reduction of **171** to quinidine (**172**) in 50% yields. Although the alkaloid was isolated and crystalized, no physical or spectral data supporting its identity were provided. Eckenrode examined microbial transformations as a means of obtaining mammalian metabolites of quinidine (*229*). Several microorganisms accumulated a common, polar metabolite of the alkaloid and these included: *Aspergillus fumigatus* (MR 51), *Cunninghamella elegans* (NRRL 1393), *C. blakesleeana* (NRRL 1369), *C. bainieri* (NRRL 3065), *C. echinulata* (NRRL 3655), *Stemphylium consortiale* (UI 4136), and



SCHEME 38. Biotransformations of quininone (**171**) and quinidine (**172**).

two *Streptomyces griseus* strains designated ATCC 10137 and 13273. *Streptomyces griseus* (ATCC 13273) was used to prepare the metabolite that was isolated and identified as the 3-hydroxylated derivative **173** (Scheme 38). Mass spectrometry indicated a molecular ion 16 mass units higher than that of quinidine and provided a quinuclidine fragment at *m/e* 152 for the metabolite versus *m/e* 136 for quinidine, indicating that the oxygen atom was introduced into this portion of the metabolite structure. ^{1}H-NMR comparisons of the metabolite and quinidine indicated differences in the vinyl proton signals. The ^{13}-NMR spectrum contained a new singlet at 70.7409 ppm for a carbinol carbon, and the resonance for C-3 at 39.89 ppm in quinidine was absent in the spectrum. The orientation of the hydroxy group as syn to C-5 as shown in **173** was confirmed by ^{13}C NMR. As in most enzymatic hydroxylation reactions, the oxidation of quinidine by *S. griseus* proceeded with retention of configuration at the hydroxylated carbon atom. The microbial metabolite was identical to one of the primary mammalian metabolites of quinidine.

Clark and co-workers at the University of Mississippi School of Pharmacy investigated microbial and mammalian transformations of the synthetic quinoline compound primaquine. Primaquine (**174**) (Scheme 39) is a 6-methoxy-8-aminoquinoline derivative used in the treatment of vivax malaria in combination with other antimalarial drugs (*230*). Its toxicity, thought due in part to metabolism, limits its use. Two major metabolites of primaquine were first identified by microbial transformation experiments. *N*-Acetylprimaquine (**175**) was produced by *Streptomyces griseus* ATCC 10137, *S. griseus* ATCC 23337, and by *S. roseochromogenes* (ATCC 13400) in yields of 57, 34, and 57%, respectively. The identity of this microbial metabolite was established spectrally and by synthesis of the compound, using primaquine and acetic anhydride/pyridine. The second major metabolite (88% yield) was produced by *Aspergillus flavus* (ATCC 9170) and identified as a carboxylic acid derivative (**176**). This metabolite is most likely formed as a product of oxidative deamination (*230*). Yields of **176**



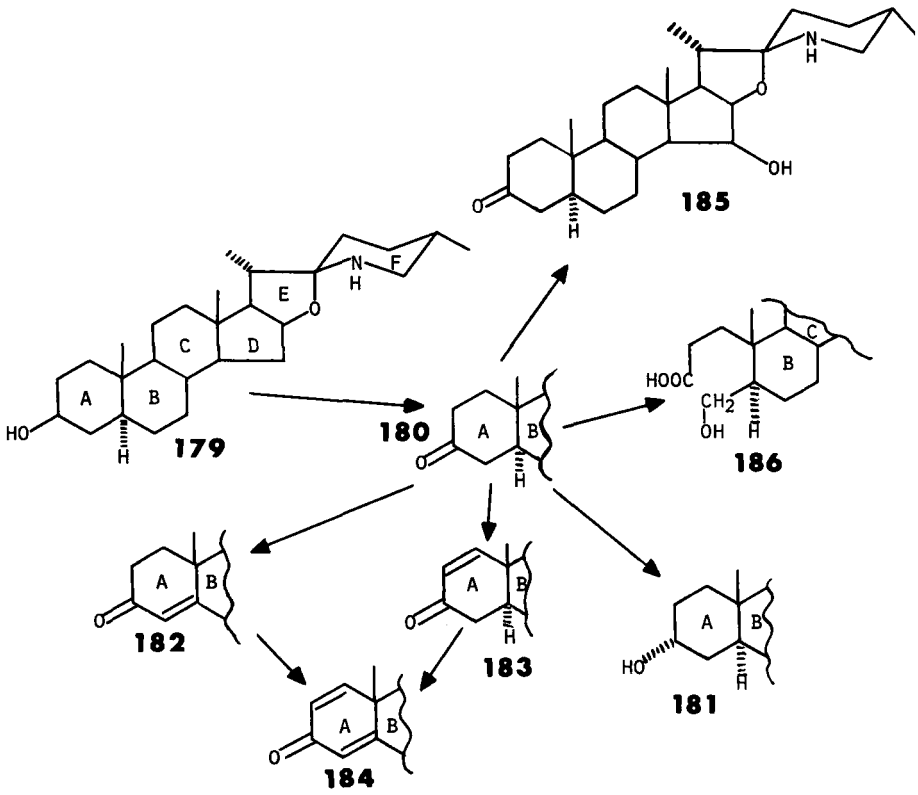
SCHEME 39. Biotransformations of the quinoline antimalarial primaquine (**174**).

were eight times higher when resting microbial cells of the *Aspergillus* were used in the biotransformation reaction. The structure of **176** was confirmed by total synthesis and by spectral analysis. Clark and coworkers later studied the metabolism of primaquine in rats (*231*). Interestingly, the major mammalian metabolite formed following intravenous, intraperitoneal, or oral administration of primaquine to animals was the carboxylic acid derivative **176.** This result underlines the value of prospective microbial transformation experiments in predicting the outcome of mammalian metabolism work.

When *N*-acetylprimaquine (**175**) was incubated for prolonged periods of time with *Candida tropicalis* (ATCC 20021) (*232*) and *Streptomyces rimosus* (ATCC 23955) (*233*), two unusual minor dimeric metabolites were obtained. These were identified as the methylene-linked compound **177** formed by *C. tropicalis* and the biaryl-linked compound **178** formed by *S. rimosus*. Both dimeric metabolites were prepared synthetically to confirm their identities.

F. Steroidal Alkaloids

Belic *et al.* examined microbial transformations of the steroidal alkaloid tomatidine (**179**) as a continuation of earlier investigations on microbes capable of transforming steroidal sapogenins to 16-keto compounds (*234*). Tomatidine (720 mg) was incubated with resting cells of the fungus *Gymnoascus reesii* CBS 39264 suspended in 0.4% NaCl at pH 4.7 for varying periods of time both with and without inhibitors such as dipyridyl. The organisms completely degraded tomatidine within 120 hr but accumulated a number of metabolites on shorter (24–48 hr) incubation times. These were isolated and identified in most cases by direct chemical, spectral, and physical comparisons with authentic samples. The major metabolite (42% yield) was identified as tomatidone (**180**) along with minor products tomatanin-3α-ol (**181**) and 4-tomatiden-3-one (**182**) identified as its *N*-acetyl derivative. Although **181** was shown as arising directly from tomatidine, a more likely explanation for its formation is through stereospecific reduction of tomatidone (**180**). Three other metabolites were less rigorously characterized as 1-tomatiden-3-one (**183**), 1,4-tomatidien-3-one (**184**) and 15β-



Scheme 40. Transformations of the steroidal alkaloid tomatidine by *Gymnoascus reesii*.

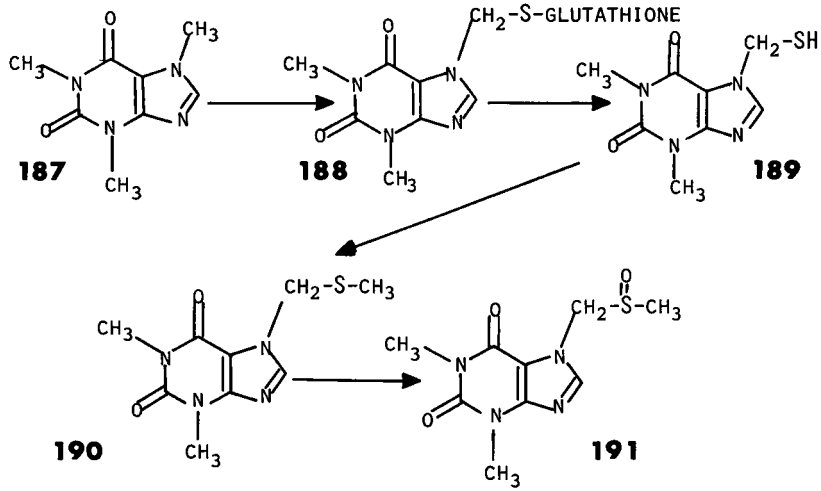
hydroxytomatidone (**185**). The metabolites identified in this work are similar to those formed earlier by *Nocardia* species. However, *Nocardia* accumulates 1,4-tomatadien-3-one even during prolonged incubations. Based on the identification of various tomatidine metabolites, a scheme for the biotransformation of this alkaloid was proposed (Scheme 40).

In an extension of the previous work, Gaberc-Porekar *et al.* identified an unusual metabolite of tomatidine by the same microorganism (*235*). This compound was characterized as 4-hydroxy-3,4-secotomatidin-3-oic acid (**186**) identified as *N*-acetyl-3,4-tomatidinecarbolactone, which was produced during the N-acetylation process. The seco metabolite contained one additional oxygen atom (by mass spectrometry) and ^{1}H-NMR spectroscopy indicated that the E and F rings of tomatidine and the metabolite were identical. Major changes in the NMR spectrum included the upfield shifting of the 19-methyl group signal and the presence of a propionyl moiety. The metabolite structure implies the involvement of a Baeyer–Villiger oxidation of the ketone of tomatidone to form the seco product. This represents a new microbial degradation pathway of steroidal alkaloids.

G. Miscellaneous Alkaloids

1. Caffeine

Rafter and Nilsson described the conversion of caffeine (**187**) to sulfur-containing metabolites by the action of the intestinal microflora of rats (*236*). Pre-

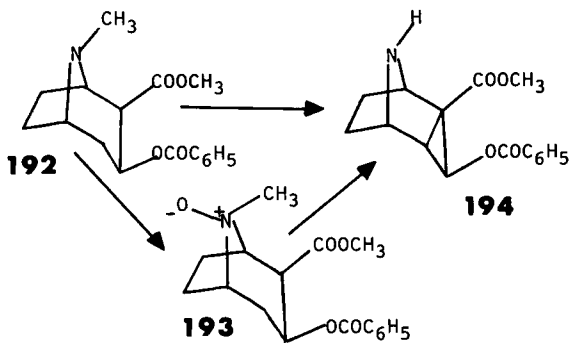


Scheme 41. A proposed pathway for the conversion of caffeine (**187**) to caffeine methyl sulfoxide (**191**) by gut microflora.

vious work demonstrated the existence of sulfur-containing metabolites including sulfides, sulfoxides, and sulfones of caffeine in extracts of urines from several types of animals. The mechanisms involved in the formation of such compounds are unclear, and it was suggested that the origin of the sulfur atom in xenobiotic metabolites could be through cysteine, methionine, or glutathione. Radioactive caffeine was administered to conventional (ordinary) and germ-free rats, and the major metabolite obtained from urine extracts was caffeine methyl sulfoxide (**191**). The nature of the metabolite was established by HPLC and mass spectrometry. Significant quantitative differences were observed in the amounts of **189** formed by conventional versus germ-free animals (a ratio of 42/1). This finding confirmed the involvement of rat intestinal microflora in the conversion reaction. Based on previous work with other xenobiotics, a scheme for the biotransformation of caffeine by gut-microflora mammalian enzymes was proposed as shown in Scheme 41. This work underlines the potential of the gut microflora to be engaged in complex biotransformations of xenobiotics.

2. Cocaine

Cocaine-mediated hepatotoxicity has been associated with the conversion of cocaine to norcocaine and further oxidation products. The enzymes involved in *in vitro* hepatic oxidative N-demethylation of cocaine (**192**) were investigated (*237*), and two different enzymatic pathways appear to be important in the formation of the hepatotoxic metabolite. Cytochrome *P*-450 monooxygenases accomplish the direct N-demethylation of cocaine to norcocaine (**194**) as confirmed by induction and inhibition studies (Scheme 42). The second pathway for cocaine N-demethylation involves formation of cocaine *N*-oxide (**193**) as an intermediate and two enzymes. A flavin-containing monooxygenase is first thought to convert cocaine to cocaine *N*-oxide, followed by cytochrome *P*-450-



SCHEME 42. Two pathways for the N-demethylation of cocaine by mammalian liver microsomal enzyme preparations.

TABLE IV

A SUMMARY OF ALKALOID TRANSFORMATIONS CATALYZED BY MICROBIAL, MAMMALIAN, AND PLANT ENZYME SYSTEMS

Alkaloid	Enzymatic reaction	Biocatalyst	Reference
Agroclavine	Allylic hydroxylation	*Claviceps*	*159*
Isoajmalicine	Aromatic hydroxylation	*Cunninghamella* (2), *Mucor*, MRRS, *Streptomyces* (3)	*186*
Akumagine	Aromatic hydroxylation	*Streptomyces*	*186*
Alstonine, tetrahydro-	Aromatic hydroxylation	*Streptomyces*	*186*
Aporphine, 10,11-dimethoxy-	O-Demethylation	*Cunninghamella*	*192*
Aporphine, *n*-propyl-10,11-dimethoxy-	O-Demethylation	*Cunninghamella*	*194*
Boldine, 2,9-diacetyl-	Ester hydrolysis	*Candida* lipase	*199*
Caffeine	Sulfur conjugation	Rat intestinal microflora	*236*
Cleavamine	Intramolecular cyclization	*Polyporus anceps* laccase	*171*
Cocaine	N-Demethylation	Liver *P*-450 and FAD monooxygenases	*237*
Codeine	O-Demethylation and N-demethylation	*Cunninghamella*, rat–liver microsomes	*209*
	14-Hydroxylation	*Streptomyces*	*214*
Codeine *N*-oxide	N-Demethylation	*Cunninghamella P*-450 enzyme	*212*
Codeinone	Reduction	*Papaver somniferum*	*207*
Ellipticine	Aromatic hydroxylation	*Aspergillus* (2), *Penicillium*, liver microsomes	*144* *147*
Ellipticine, 9-hydroxy-	Phenol oxidation	Peroxidase	*155*
Ellipticine, 9-methoxy-	O-Demethylation	*Cunninghamella* (2), *Penicillium*, *Botrytis*. peroxidase	*143* *145*
(−)-Glaucine	Dehydrogenation	*Fusarium*	*195,196*
(+)-Glaucine	Dehydrogenation	*Aspergillus*	*197*
Glaucine, 7-methyl-*cis* and *trans*-	Dehydrogenation	*Fusarium*, *Aspergillus*	*198*
Indicine *N*-oxide	*N*-Oxide reduction	Peroxidase, rat liver microsomes	*90*
Isoquinoline-1-carboxylic acid, tetrahydro-	Decarboxylation	Laccase, peroxidase	*204*
Laudanosine	O-Demethylation C—C bond fission	*Pseudomonas*	*200*

Lergotrile	N-Demethylation	*Cunninghamella, Streptomyces* (5)	*160*
Leurosine	Aromatic hydroxylation	*Streptomyces*	*180*
Lysergic acid derivatives	N-Demethylation	*Streptomyces* (4), *Cunninghamella,* rat liver *P*-450	*162,164*
Monocrotaline *N*-oxide	*N*-Oxide reduction	*Streptomyces*	*227*
Morphine	N-Oxidation, dimerization	Peroxidase	*208*
Nicotine	Resolution of racemates	*Pseudomonas*	*215–217*
	N-Demethylation, pyrrole oxidation	*Pellicularia, Cunninghamella*	*218*
	N-Dealkylation, pyrrole oxidation, iminium formation	Liver microsomes	*220*
Norpseudoephedrine	Ketonization (hydroxylation at a carbinol carbon)	Dopamine-β-hydroxylase	*238*
Nuciferine	N-Demethylation, O-demethylation, aromatic hydroxylation	*Streptomyces*	*8*
Papaverine	Diooxygenase ring fission	*Nocardia*	*203*
Pergolide	Sulfur oxidation	*Aspergillus* (2), *Calonectria, Cunninghamella* (6), *Helminthosporum*	*161*
Primaquine	N-Acetylation, oxidative deamination	*Streptomyces* (2), *Aspergillus*	*230*
Primaquine, *N*-acetyl-	Dimerization	*Candida*	*232*
		Streptomyces	*233*
Quinidine	Allylic hydroxylation	*Aspergillus, Cunninghamella* (4), *Stemphylium, Streptomyces*	*229*
Quininone	Reduction	*Hansenula*	*228*
Senecionine	Ester hydrolysis, oxidation, methylation	Mouse liver microsomes	*222,223*
Tomatidine	A-Ring oxidation and fission	*Gymnoascus*	*234*
Tryptamine	Condensation with secologanin	Strictosidine synthase	*187*
Vinblastine	Ester hydrolysis	Human neoplastic tissue, liver microsomes	*181*
Vinblastine, anhydro–	Epoxidation	*Catharanthus roseus*	*182*
	Hydration		*183*
Vincamine, 11-bromo-	Ester hydrolysis	Dogs, rats, humans	*185*

(*continued*)

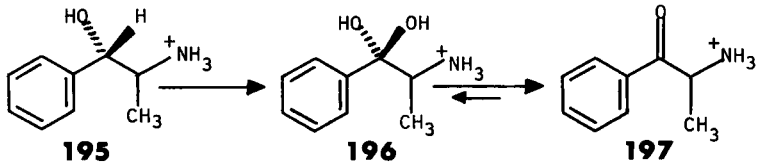
TABLE IV (*Continued*)

Alkaloid	Enzymatic reaction	Biocatalyst	Reference
Vindoline	Iminium formation	*Streptomyces*, laccases	*169*
	Intramolecular etherification and dimerization	Ceruloplasmin, peroxidase	*172,173,174*
		Mouse liver	*177*
Vindoline, 16–O–acetyl–	Iminium formation	Copper oxidases	*173,174*
		Streptomyces, peroxidases, photochemistry	*176*
Vindoline, 14,15-dihydro-	Imine formation, carbinolamine, O-demethylation	*Streptomyces*	*178*

catalyzed N-demethylation to form **194.** A model reaction in which **193** was N-demethylated by the action of ferrous sulfate was also presented. This reaction, similar to those proposed in the N-demethylation of a wide range of alkaloid substrates involves the formation of reactive iminium intermediates.

3. Norpseudoephedrine

The leaves of *Catha edulis* (Khat) have long been chewed as a central nervous system stimulant. Cathine, also known as (+)-norpseudoephedrine (**195**) and the related ketone compound cathinone (**197**) are active principles of the plant, and recent evidence suggests that cathinone is the more potent stimulant compound. The configuration of the hydroxy group at the β position is *S*, opposite to the *R* configuration found in most functional neurotransmitters such as norepinephrine. May *et al.* suggested that the enzyme dopamine-β-hydroxylase, which is responsible for the stereospecific *R* hydroxylation at the β carbon of phenethylamines could possibly hydroxylate (*S*)-β-phenethanolamines. The resulting *gem*-diol **196** would exist in equilibrium in aqueous solution predominently as the ketone (*238*) (Scheme 43). In principle, the available C—H bond of compounds such as **195** would be stereotopically equivalent to the pro-*R* hydrogen atom of dopamine. Incubation of (*S*)-(+)-norpseudoephedrine (**195**) with highly purified adrenal dopamine β-hydroxylase in mixtures containing ascorbic acid or ferrocyanide as reductants resulted in the accumulation of cathinone (**197**) as indicated by HPLC. The reaction consumed oxygen, and the stoichiometry of the reaction indicated the involvement of a monooxygenase. This reaction represents a novel oxidative method for the formation of a ketone from an alcohol functional group.



195 **196** **197**

SCHEME 43. The conversion of (*S*)-(+)-norpseudoephedrine (**195**) to cathinone (**197**) by dopamine-β-hydroxylase.

H. SUMMARY AND CONCLUSIONS

Table IV summarizes most of the information considered in this review of alkaloid transformations and considers the alkaloids studied, the reactions observed and described, and the biocatalysts that accomplish biotransformation reaction. Only the generic names of microorganisms involved in alkaloid transformations have been given in this table, and the parentheses () contain the

numbers of species found to accomplish a specific biotransformation reaction. The table presents an impressive listing of alkaloids studied during the five-year period covered in this review. Nevertheless, many classes of alkaloids are conspicuously absent from this listing, including simple piperidine, quinolizidines, Ipecac, diketopiperazines, Iboga alkaloids, other bisindole alkaloids, terpene-derived alkaloids, and others. A rich array of oxidation, reduction, conjugation, and complex rearrangement reactions have been documented, catalyzed by known (i.e., copper oxidase, peroxidases, flavins, cytochrome *P*-450) and unknown enzyme systems of many microorganisms, plants, and mammals. Future developments and directions in the field of alkaloid biotransformations will draw upon deeper insights into the unknown enzymes catalyzing reactions and the further unraveling of bioorganic mechanisms by which complex nitrogen heterocycles undergo structural changes.

Acknowledgments

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Addendum to Chapter 2

Structural Elucidations

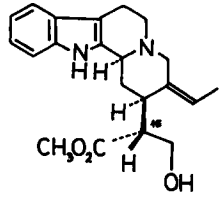
(*Z*)-Isositsirikine (**602**), with (*R*) absolute configuration at stereo center C-16, has been isolated from the leaves, fruit, and stem bark of *Alstonia sphaerocapitata* Boit (*390*).

Three new alkaloids have been isolated from *Nauclea officinalis* Pierre ex Pitard: naucleficine (**630**), nauclefoline (**631**), and nauclefidine (**632**) (*391*).

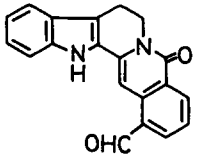
Syntheses

An improved procedure for the synthesis of octahydroindoloquinolizine (**1**) from 3-(2-piperidino-ethyl)indole by oxidative cyclization process has been reported (*392*).

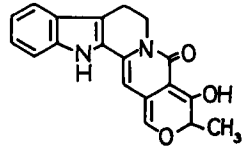
The total synthesis of vallesiachotamine (**9**) and isovallesiachotamine (**10**) has been completed elegantly by Wenkert and Spitzner (*393*) by utilizing the addition of a silicon-stabilized anion to pyridinium salt **633** to achieve the properly substituted indoloquinolizidine **634** by cyclization, from which **9** and **10** could be prepared in racemic form by simple reaction steps.



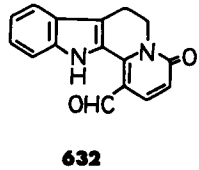
602 Z-Isositsirikine



630



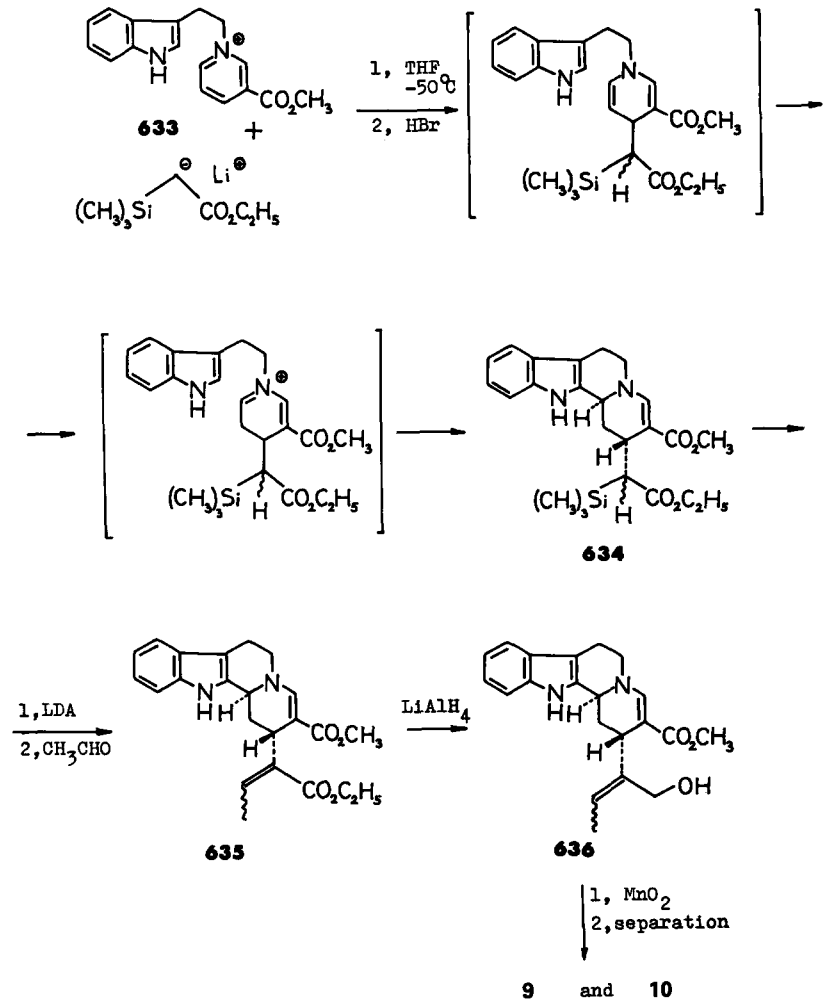
631



632

Scheme A

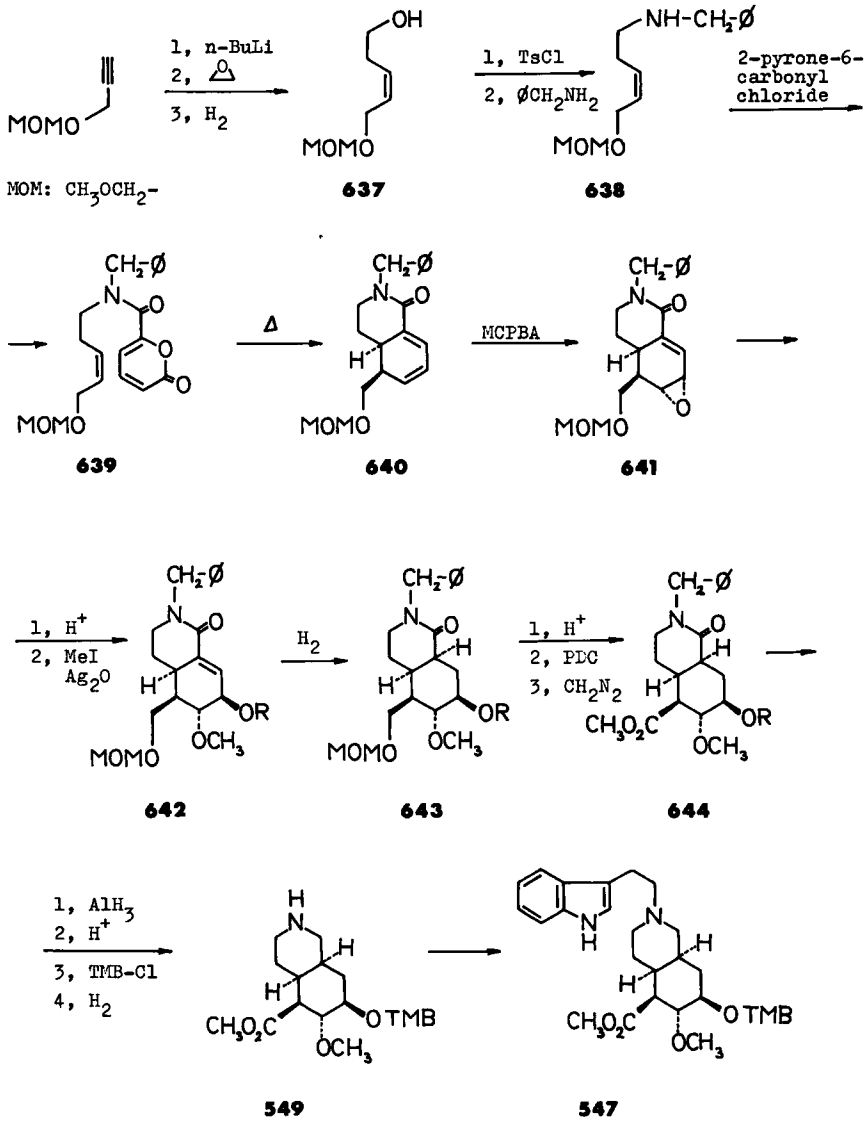
THE ALKALOIDS, VOL. 27



SCHEME B

After completing the enantioselective total synthesis of (+)-18,19-dihydroantirhine [(+)-**14**](*140*), Kametani *et al.* reported (*394*) the synthesis of (−)-antirhine [(−)-**11**] by using (3*S*)-[3-hydroxy-(*E*)-prop-1-enyl]cyclopentanone as a chiral synthon.

Racemic dihydrocorynantheol (**21**) has been prepared by Danieli *et al.* (*395*). The levorotatory antipode of dihydrocorynantheol [(−)-**21**] at the same time has been synthesized by Kametani *et al.* (*396*) via the chiral synthon **215** utilized previously (*140*) for the synthesis of (+)-18,19-dihydroantirhine.



SCHEME C

A new strategy has been developed for the construction of pentacyclic skeletons of alkaloids such as (−)-alloyohimbane [(−)-**365**] starting from optically active carbohydrate levoglucosenone (*397*).

Ninomiya *et al.* (*398*) reported the total synthesis of 19,20-dehydroyohimbine (**78**), 19,20-dehydro-β-yohimbine (**82**), as well as 19,20-dehydro-α-yohimbine

(**103**), starting from the previously prepared 18,19-dehydro-alloyohimbone (**450**)(*231*) via regioselective acylation at C-16 and subsequent migration of the double bond from the conjugated position to the 19,20-unconjugated position, followed by sodium borohydride reduction.

A new convergent total synthesis of reserpine (**109**) has been developed by Martin and co-workers (*399*). In the first phase of the synthesis they constructed the trisubstituted *cis*-decahydroisoquinoline **549** as the key intermediate by utilizing a number of stereoselective reaction steps as shown in Scheme C. N-Alkylation with 6-methoxytryptophyl bromide and subsequent oxidative cyclization of **547** resulted in reserpine (**109**) and 3-epireserpine (**514**).

SPECTROSCOPY

The 400-MHz NMR chemical shifts and most of the main coupling constants of reserpine (**109**), deserpidine (**110**), rescinnamine (**111**), and methyl reserpate (**121**) have been reported by Lounasmaa *et al.* (*400*).

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INDEX

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E

F

G

H

I

J

K

L

M

P

U

V

W

X

Y

Z

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