INDOLES

Part Four

The Monoterpenoid Indole Alkaloids

This is the twenty-fifth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors



INDOLES

Part Four

The Monoterpenoid Indole Alkaloids

Edited by

J. Edwin Saxton

Department of Organic Chemistry
The University of Leeds
United Kingdom

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

In the postwar years, and particularly during the 30 years since the isolation of reserpine in 1952, enormous interest has been shown in the monoterpenoid indole alkaloids, an interest which even now shows few signs of abating. The result is that these alkaloids now constitute probably the largest single group in the whole of the alkaloid field, with well over 1000 members, the vast majority of whose structures have been securely established. This impressive array of structures underlines the apparently limitless ingenuity of nature in the construction of alkaloids from two simple precursors, namely, tryptophan (which usually undergoes little structural modification in its incorporation into the final alkaloid) and a monoterpene unit derived in the first place from mevalonic acid, via geraniol. In parallel with this intensive activity in isolation and structure elucidation there has been a predictable surge of interest in the laboratory synthesis of these alkaloids, and in their biosynthesis, the details of which are now reasonably well understood.

The chemistry of these alkaloids has been reviewed comprehensively and periodically in the monographs edited by the late Dr. R. H. F. Manske and annually in the Royal Society of Chemistry's Specialist Periodical Reports. Hence in order to acquire a true perspective of the area the reader is obliged to consult several volumes. In contrast, space limitations do not permit detailed treatment of this vast field in a one-volume survey of alkaloids, and the recent texts that fall into this category, superb as they are, can only provide a cursory treatment of this fascinating area.

This volume therefore constitutes an attempt to provide a one-volume summary of the chemistry, biosynthesis, and pharmacology of the monoterpenoid indole alkaloids which, although not exhaustive, nevertheless gives a reasonably complete picture of the present state of the art, and with copious references to the original literature allows the reader to trace all the recent significant work. Since emphasis has been placed on the publications of the last 30 years the older, classical work on the *Strychnos* and *Cinchona* groups has not been discussed in detail, and attention has naturally been focused on the alkaloids of the corynantheine, heteroyohimbine, yohimbine, aspidospermine, and catharanthine groups, as well as the bisindole alkaloids, which were comparatively little known in 1952 and which have yielded to structural investigation by modern methods in the intervening years.

Many of the monoterpenoid indole alkaloids exhibit a well-defined pharmacological activity, and several of them have found clinical use. Indeed, the possibility of discovering new alkaloids with useful pharmacological activity still provides the stimulus to investigations in this area as much as the intellectual rewards of structure elucidation and synthesis do. In the final chapter of this book the pharmacology and biochemistry of these alkaloids are discussed in some detail.

In general the literature has been surveyed to mid-1981, although a few later references have also been included.

The Editor warmly thanks Mrs. M. Romanowicz for secretarial assistance, and Mr. T. Lanigan for his original suggestion that there was a need for a volume of this kind.

J. EDWIN SAXTON

Leeds, United Kingdom
August 1983

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CHAPTER I

Structural and Biosynthetic Relationships

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I. INTRODUCTION

The individual chapters in this volume attest to the rich variety of structures obtaining within the largest group of alkaloids, those that contain an indole, or related, fragment and a rearranged monoterpene unit,* and that are found most frequently in plants of the Apocynaceae, Loganiaceae, and Rubiaceae families.[2] The purpose of this account is to attempt a correlation of the various types within a framework of structural relationships. Any such classification must depend on a recognition of the biosynthetic pathways thus far delineated, so it is with a consideration of these pathways that we begin.

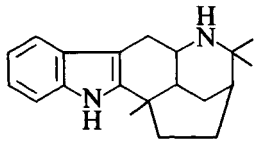
The subject has been reviewed extensively and the reader is referred to some of these reviews for alternative treatment.[3]

* The *Aristotelia* indole alkaloids, for example, **1**, are distinct from those under discussion here. They have a regular monoterpene unit. A possible biosynthetic scheme has been proposed.[1]

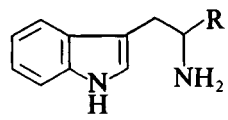
II. BIOSYNTHESIS

A. *Corynanthe-Strychnos, Aspidosperma*, and *Iboga* Alkaloids

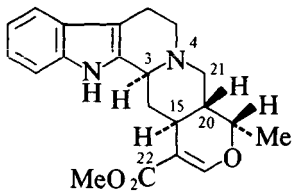
Common to all the terpenoid indole bases is a tryptamine unit (as **2b**, cf. **3–6**), which in a convincing variety of alkaloids has been found to have its genesis in tryptophan (**2a**)[4–7] via tryptamine (**2b**).[7,8] Modifications to the tryptamine fragment are generally slight. Those observed involve oxygenation of the benzene ring, oxindole formation, and rarely, loss of one or both carbon atoms from the tryptamine side chain, as in alkaloids such as apparicine and uleine (Section II. D). The most extensive modification occurs in the quinoline derivatives camptothecin (Section II. F) and the *Cinchona* alkaloids (Section II. E).



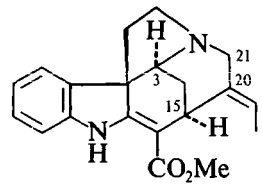
1



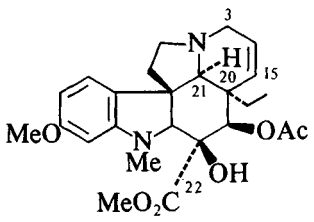
2a: R = CO_2H
2b: R = H



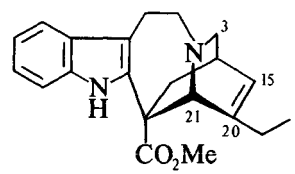
Ajmalicine (3)



Akuammicine (4)



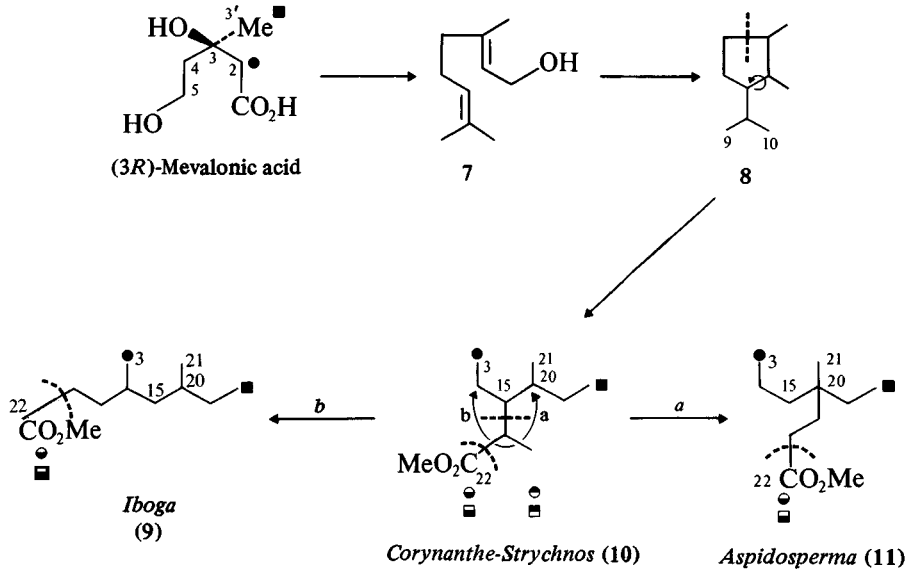
Vindoline (5)



Catharanthine (6)

The enormous variation in terpenoid indole structure is associated therefore not with the tryptamine unit, but with the remaining 9 or 10 carbon atoms. Following the original brilliant concept,[9] it has been shown that these atoms are monoterpenoid in origin. Such an origin is not immediately apparent by inspection because the alkaloidal C_9/C_{10} units are formed from a fragmented cyclic monoterpene. Indeed, other sources for these units were examined and were excluded experimentally.[10]

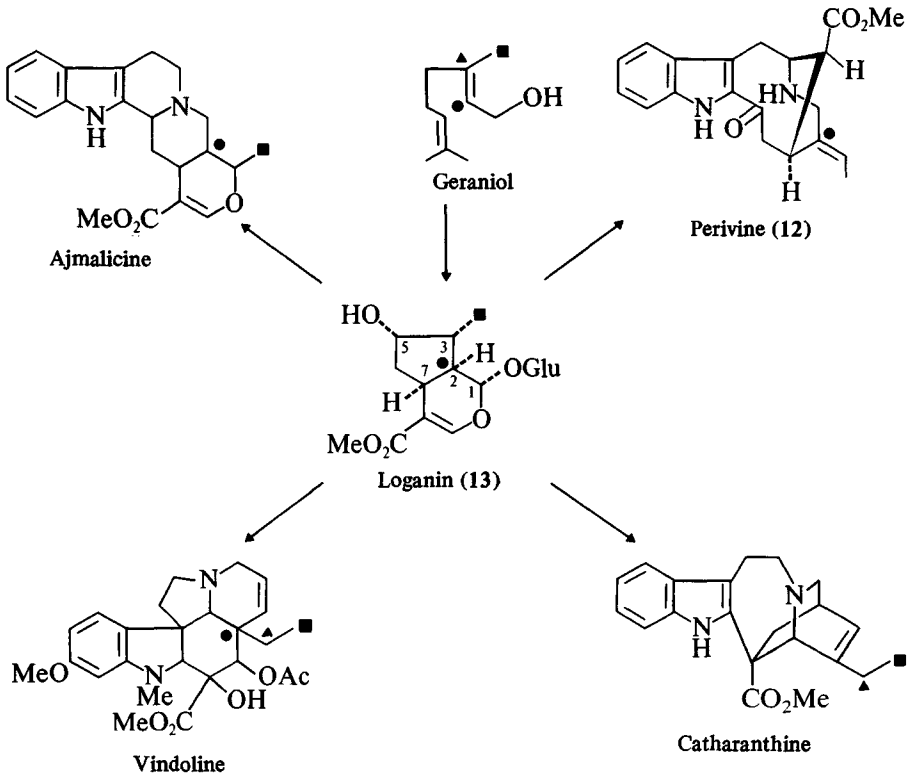
Close examination of the various alkaloidal C_9/C_{10} terpenoid units reveals broadly three major types: first, that of the *Corynanthe-Strychnos* group, for example, ajmalicine (**3**) and akuammicine (**4**) where the unit is simplified as in **10**; second, that of the *Aspidosperma* group, for example, vindoline (**5**) with the C_9/C_{10} unit represented by **11**; and third, that of the *Iboga* group, for example, catharanthine (**6**), which is a third variant (**9**). The relationship of these skeletal types to a common cyclopentane monoterpene skeleton is illustrated in Scheme 1, in which the tenth atom (C-22), which is sometimes missing, is depicted as a carbomethoxy group.



Scheme 1

Essential proof that these C_9/C_{10} units are terpenoid in origin and related in the way shown has come with extensive and rigorous experimentation. It was established that the C_9/C_{10} units of representatives of the three groups of alkaloids are each derived from two molecules of mevalonic acid[5,11–14] linked initially in the normal head-to-tail fashion, elaborated along a pathway which includes geraniol (**7**)/nerol (**14**)[12–15] and the cyclopentane monoterpene, loganin (**13**)[15,16] (cf. Scheme 1). Not only was loganin (**13**), in contrast to three other cyclopentanoid monoterpenes, a specific precursor, but also its biosynthesis from geraniol and its presence in *Catharanthus roseus* G. Don (syn. *Vinca rosea* L.), the plant used for most of the experiments, could be demonstrated (Scheme 2; **12** has, like **3**, the skeleton of type **10**). These results secure loganin as an intermediate in alkaloid biosynthesis; it stands as a key compound along the biosynthetic pathway.

As observed in other systems, the biosynthesis of the alkaloidal monoterpene unit is from (3*R*)-mevalonic acid, not the (3*S*) isomer.[14] The transformation of C-2 or C-3′ of mevalonate through C-9 and C-10 of the intermediate **8** into alkaloids

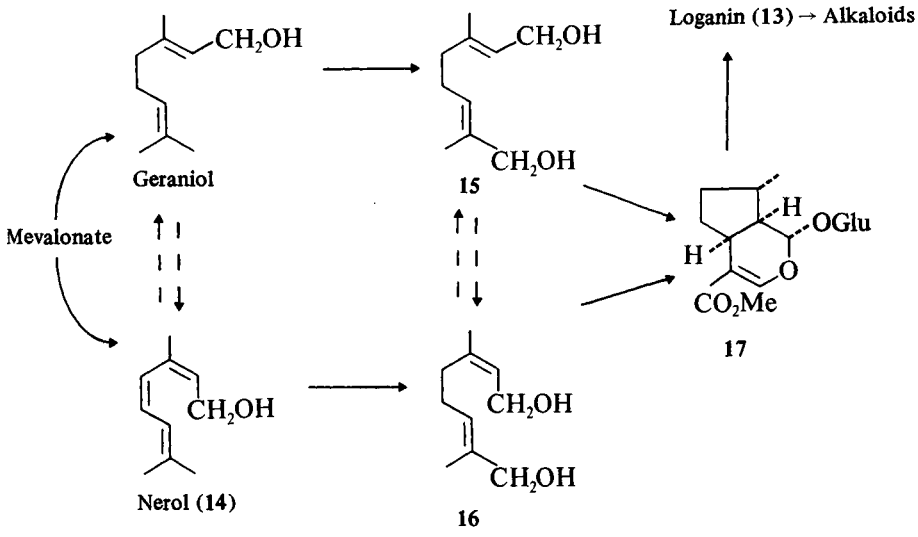


Scheme 2

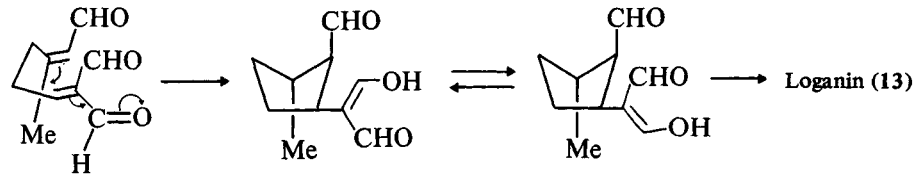
was observed to occur with loss of identity between these termini, as observed in the biosynthesis of cyclopentanoid monoterpenes.[17]

Further experimental results established[18] that deoxyloganin (**17**) is to be sited as an intermediate in biosynthesis before loganin (**13**), and the hydroxy derivatives **15** and **16**, of geraniol (**7**) and nerol (**14**), respectively, must also be included in the pathway[17a,19] (Scheme 3). The failure of various other derivatives of geraniol and nerol to act as precursors[17a,19] restricts the range of possible intermediates beyond **15** and **16**, and leads to a plausible mechanism for cyclization via a trialdehyde (Scheme 4), which accounts for the observation that label passing from mevalonate through C-9 and C-10 of the acyclic terpenes becomes equally distributed between the corresponding positions in loganin and the alkaloids.[17a,20]

Alkaloid derivation from loganin (**13**) must involve cyclopentane ring cleavage (cf. **8** → **10** in Scheme 1), which may be rationalized in terms of either of the two mechanisms shown in Scheme 5, to give secologanin (**18**). Actual involvement of this fragmented terpene in alkaloid biosynthesis is proved by the observations that it is a natural constituent of *C. roseus*, is derived from loganin (**13**) in this plant, and is a precursor for representative terpenoid indole alkaloids.[21] From secologanin the pathway leads logically to the *Rhazya stricta* Decaisne base, strictosidine (**19**),

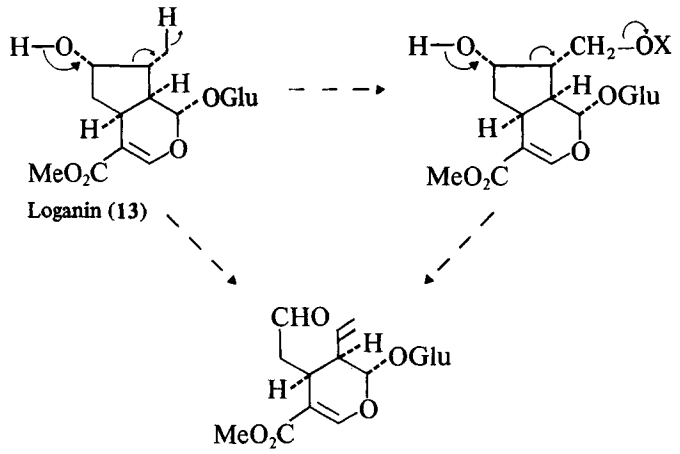


Scheme 3



Scheme 4

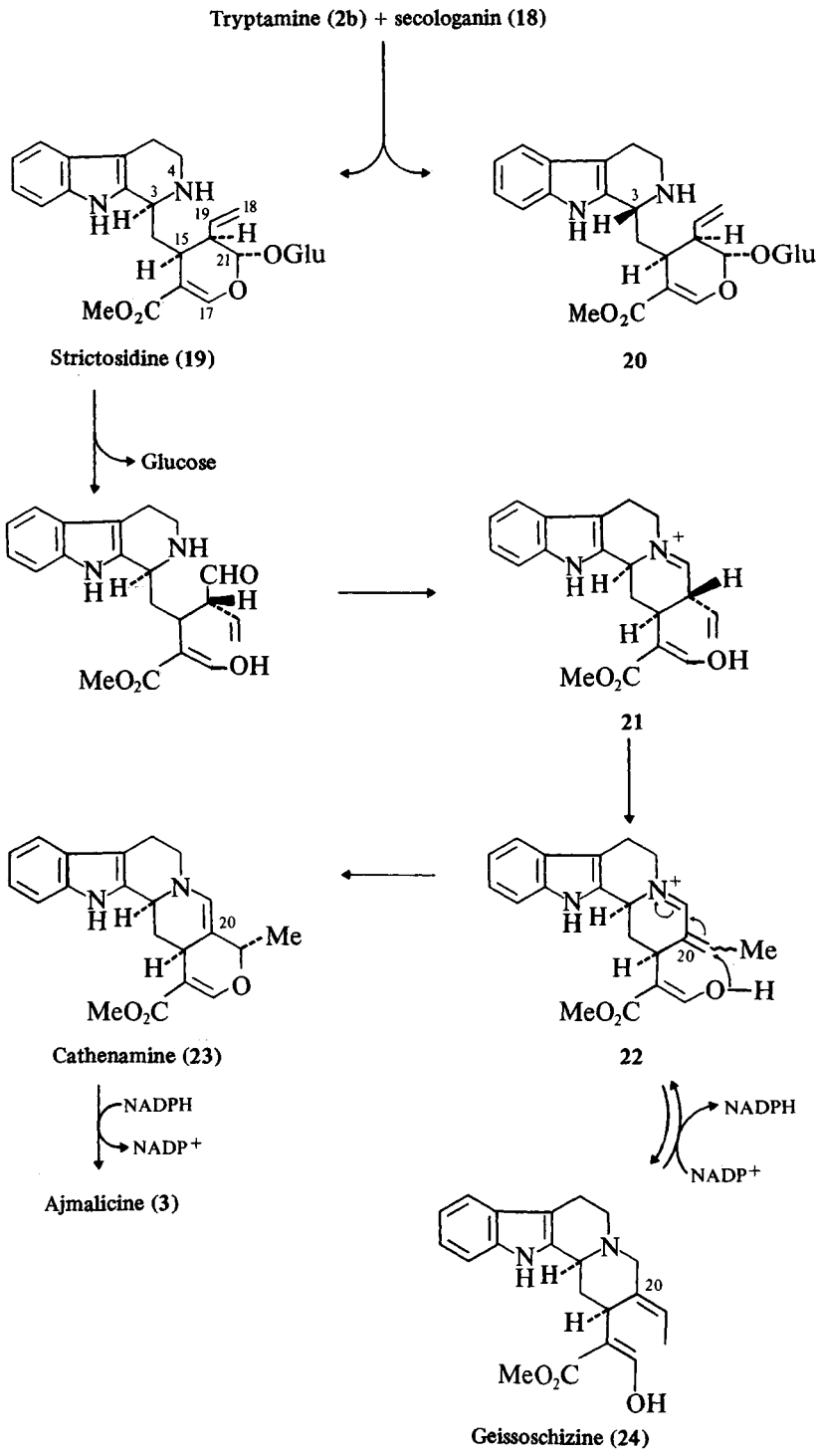
as the first alkaloid; it is one of two epimeric bases obtained by chemically condensing secologanin (**18**) with tryptamine (**2b**) (Scheme 6).[8,22] Both this base and its C-3 epimer, vincoside (**20**), were shown to be natural constituents of *C. roseus* and to be derived from loganin (**13**).[8,23] The earliest results indicated that vincoside (**20**), not strictosidine (**19**), was the terpenoid indole alkaloid precursor,[8] though this involved C-3 epimerization (cf. **3** and **4**). However, recent results obtained with enzyme preparations from plant tissue cultures,[24–30] as well as with whole plants, have shown unambiguously that strictosidine (**19**) is the true intermediate in the formation of the *Corynanthe-Strychnos* type with both the 3α (e.g., **3**, **25**, and **26**) and 3β configuration (e.g., **27** and **28**), as well as vindoline (**5**), catharanthine (**6**), and a variety of other alkaloids.[29–33] In the case of the 3β alkaloids the incorporation of strictosidine occurs, not surprisingly, with loss of the C-3 proton; this proton is retained through the formation of alkaloids with 3α configuration.[31] (The ipecac alkaloids include a C_9/C_{10} terpenoid unit derived along a pathway related to that described above.[33–35] Here the alkaloids, with opposite stereochemistry at positions equivalent to those at C-3 in terpenoid indole alkaloids, are derived by contrast from precursors of the same chirality[33,35].)



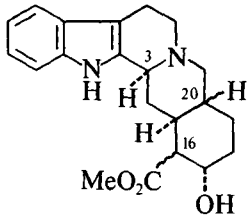
Scheme 5

Recent work with enzyme preparations from plant tissue cultures (notably *C. roseus*) has provided exciting results which precisely define the early steps up to and beyond strictosidine. It has been found that tryptamine (**2b**) and secologanin (**18**) condense together under enzyme catalysis to give strictosidine (**19**) stereospecifically. The enzyme that carries out the condensation has been isolated, purified, and characterized.[36] Subsequent modification of strictosidine (**19**) first requires loss of the glucose moiety; two strictosidine-specific glucosidases have been isolated and characterized.[37] Biosynthesis with the enzyme preparations stops with the formation of strictosidine (**19**) in the presence of a β-glucosidase inhibitor.[29,30] In the absence of inhibitor biosynthesis can proceed normally and the alkaloids ajmalicine (**3**), its C-19 epimer (**29**), and tetrahydroalstonine (**30**) are formed.[25–27] The enzyme preparation requires reduced pyridine nucleotide (NADPH or NADH); in the absence of coenzyme, 20,21-dehydroajmalicine (**23**) (cathenamine) is found to accumulate[26,27] and has been identified as an alkaloid of *Guettarda eximia* plants.[38] Moreover, cathenamine is enzymatically converted into **3**, **29**, and **30** in the presence of NADPH.[26,27] Cathenamine is thus very probably a normal intermediate in alkaloid biosynthesis in intact plants.

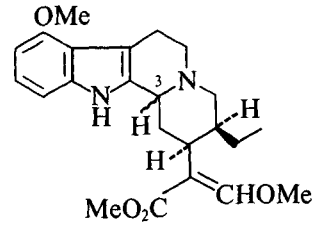
Two further compounds, **21** and **22**, have been identified as biosynthetic intermediates. The latter, 4,21-dehydrogeissoschizine (**22**), has, like cathenamine (**23**), been isolated from *G. eximia* plants.[39] On incubation with an enzyme preparation in the presence of NADPH, **22** was converted into **3**, **29**, and **30**. In the absence of NADPH, cathenamine (**23**) was formed; under NADPH-regenerating conditions, geissoschizine (**24**) was formed. From this evidence and the observation that unlabeled **22** diluted the incorporation of radioactivity from [1-^{14}C]-tryptamine into **3**, **29**, and **30** and that **22** was formed from radioactive tryptamine plus secologanin, it is clear that **22** is a normal biosynthetic intermediate.[40] The evidence implicating **21** as an intermediate is more circumstantial and comes from the


Tryptamine (2b) + secologanin (18)
Strictosidine (19)
20
Glucose
21
Cathenamine (23)
22
NADPH
NADP+
Ajmalicine (3)
NADPH
NADP+
Geissoschizine (24)

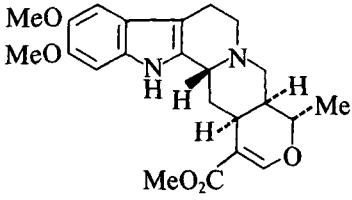
Scheme 6



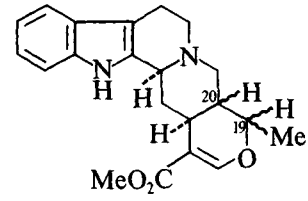
	16H	20H
α-Yohimbine (25)	α	α
Yohimbine (34)	β	β
Corynanthine (35)	α	β



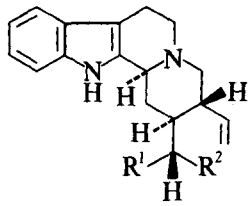
	3H
Mitragynine (26)	α
Speciociliatine (28)	β



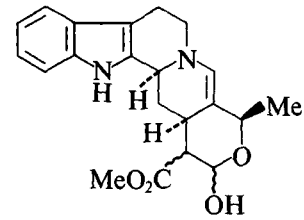
Reserpiline (27)



	19-H	20-H
29	α	β
Tetrahydroalstonine (30)	β	α



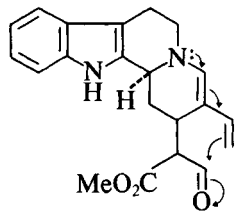
Sitsirikine (31): $R^1 = CO_2Me$, $R^2 = CH_2OH$
Isositsirikine (32): $R^1 = CH_2OH$, $R^2 = CO_2Me$



33

isolation of sitsirikine (**31**) and isositsirikine (**32**) as new and exclusive products from a *C. roseus* enzyme preparation incubated with strictosidine (**19**) and potassium borohydride.[41] Also potentially involved in this area of biosynthesis is **33**, isolated from *G. eximia*, and convertible chemically into cathenamine (**23**).[42] It is a reasonable substrate biochemically for obtaining different stereochemistries at C-19 and C-20. Within the enzyme system ajmalicine (**3**) is not converted into the epimers **29** or **30**, and so the differing stereochemistries at these centers must be irreversibly set up at an earlier stage, that is, possibly through **33**.

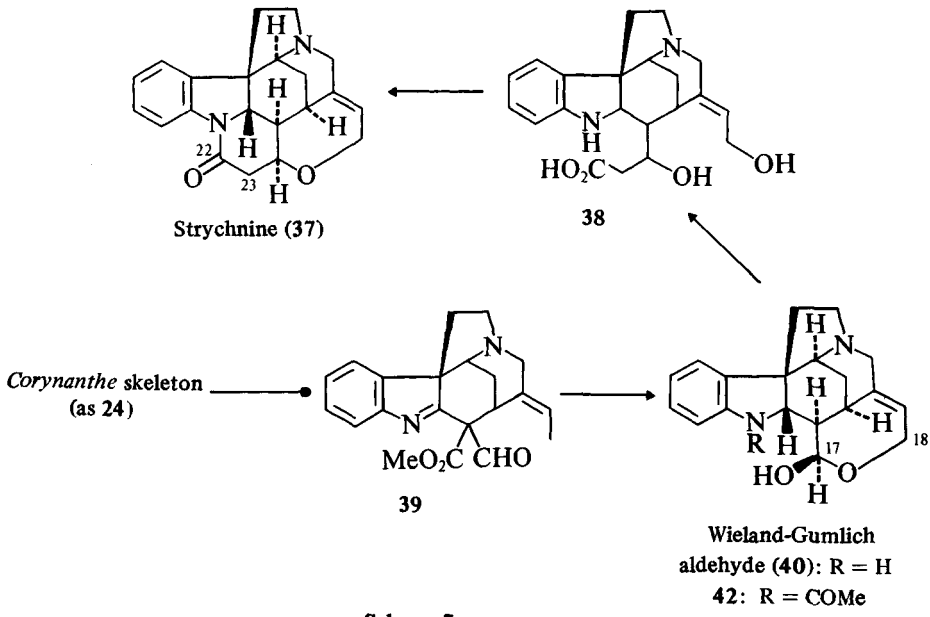
The *Corynanthe*-type alkaloids, represented by ajmalicine (**3**) and mitragynine



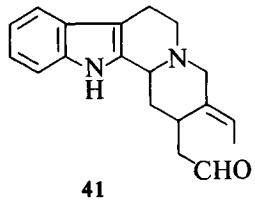
36

(26), are the simplest variation of the strictosidine skeleton. Only slightly more complex are alkaloids of the yohimbine (25, 34) type which have a further carbocyclic ring. α-Yohimbine (25) and its stereoisomers yohimbine (34) and corynanthine (35) have been shown to have a genesis along the strictosidine pathway, as expected.[31,43] Plausibly an intermediate of type 36 is involved.

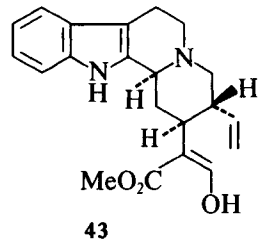
Simple rearrangement of strictosidine (19) affords the *Strychnos* skeleton, exemplified by akuammicine (4), the known biosynthetic steps to which have already been referred to; further results are given below. Strychnine (37) is slightly more complex in that it has an additional C_2 unit (C-22 and C-23). It has, however, the expected origins in tryptophan (2a), and in mevalonate via geraniol (7); the C_2 unit arises from acetate.[44] A search[45] for later intermediates in strychnine biosynthesis has revealed that geissoschizine (24; but see discussion below) and the Wieland-Gumlich aldehyde (40) are precursors, and negative results with geissoschizal (41) and diaboline (42) have suggested, respectively, that 39 (i.e., skeletal rearrangement before loss of C_1 unit) and 38 may be intermediates. The deduced pathway is illustrated in Scheme 7.



Scheme 7



41

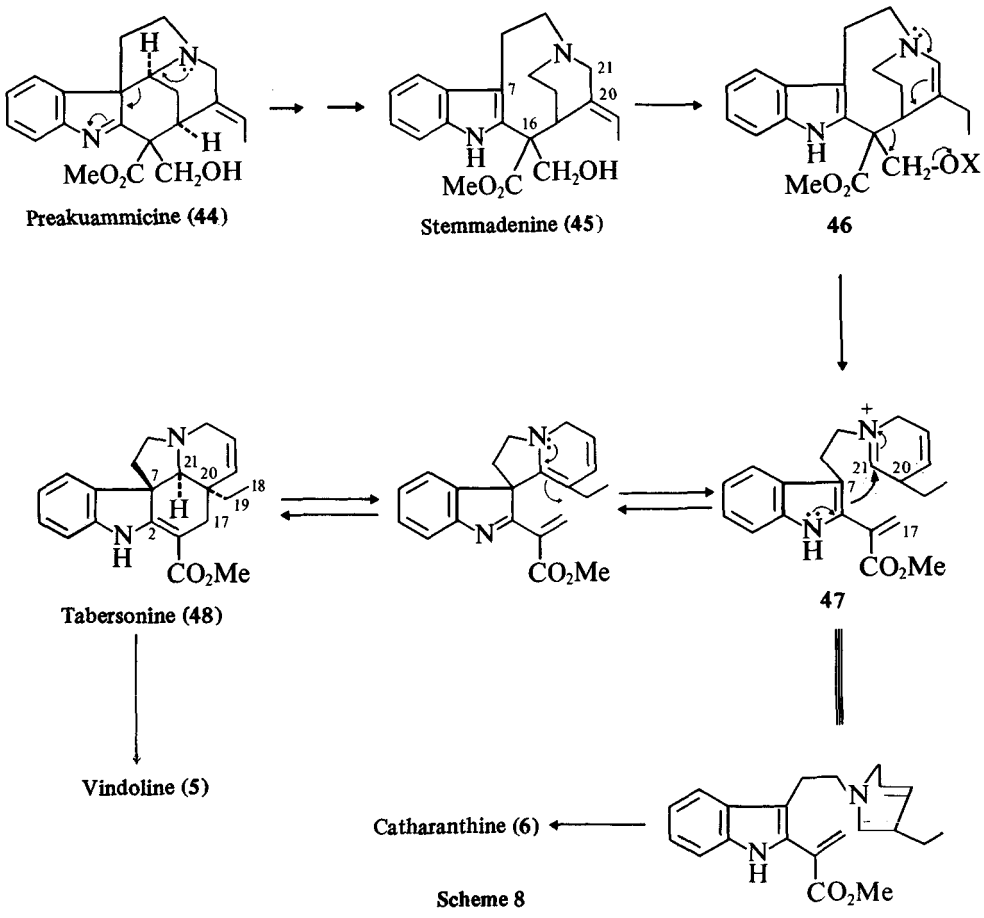


43

All the alkaloids so far mentioned have a biogenesis via strictosidine (**19**). It is implicit in their close structural relationship to **19** and clear from the foregoing experimental results that alkaloids with the *Corynanthe* skeleton are the first to be formed, followed by those of the *Strychnos* type. It is a reasonable hypothesis that the other skeletons are elaborations of the *Corynanthe* skeleton, and this is supported by the results of biosynthetic experiments. First, alkaloids with *Corynanthe*-type structures appear in *C. roseus* seedlings before bases of the *Iboga* and *Aspidosperma* type.[46] Second, it has been found that the *Corynanthe* base, geissoschizine (**24**) (but not its double-bond isomer, **43**),[14] is an intact precursor for representatives of the *Aspidosperma* and *Iboga* groups,[4] and also those with the *Strychnos* skeleton, represented by akuammicine (**4**)[47] and strychnine (**37**).[45]

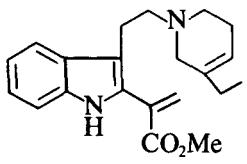
Although the above results with geissoschizine (**24**) in whole plants indicate that it is an intermediate in the elaboration of more complex alkaloids, experiments with a cellfree preparation from a *C. roseus* tissue culture which synthesizes *Corynanthe* bases indicate that here at least **24** is on a shunt from the main pathway, entering this pathway by an $NADP^+$-dependent reaction just prior to cathenamine (**23**)[48] (see Scheme 6). The deduced relationship, however, between the *Corynanthe* skeleton and those of the *Iboga* and *Aspidosperma* alkaloids still stands; one may conclude either that a compound *related* to geissoschizine (**24**) is directly involved or that, for plants producing more complex alkaloids, geissoschizine (**24**) is not at a terminus of biosynthesis but is an intermediate. The observed[14] loss of tritium from C-2 of loganin (**13**) (= C-20 in **24**) in the formation of the three alkaloid groups is accommodated through the intermediacy of **22**, where the equivalent site, C-20, like that of geissoschizine (**24**), is devoid of a hydrogen atom.

The results of orthodox feeding experiments and those in which the sequence of alkaloid formation is obtained by noting the appearance of precursor label in individual alkaloids in relation to time have led to the conclusion[46,49] that preakuammicine (**44**), stemmadenine (**45**), and tabersonine (**48**) are further important intermediates in the biosynthesis of both catharanthine (**6**) (*Iboga* type) and vindoline (**5**) (*Aspidosperma* type). The formation of tabersonine (**48**) may be rationalized in terms of the pathway illustrated in Scheme 8. Central to this hypothetical route is the enamine (**47**) arrived at by fragmentation of stemmadenine (**45**). Although alternative cyclization paths from this enamine could give both the *Iboga* type (as **6**) and the *Aspidosperma* type (as **5**), such a simple idea is argued against by the incorporation of tabersonine (**48**) into catharanthine (**6**),[46] unless the conversion of **47** into **48** is reversible (Scheme 8). The validity of **47** as a biosynthetic intermediate is supported by the isolation of simple derivatives of



Scheme 8

secodine (**49**) from plants and by the specific incorporation of labeled secodine (**49**) into vindoline (**5**); the tritium loss from secodine, labeled in the dihydropyridine ring, on translation into vindoline (**5**), is consistent with involvement of secodine (**49**) via a more highly oxidized intermediate (as **47**).[50] It is to be noted that, since tritium from C-1 of loganin (equivalent to C-21 in **45**) is retained on formation of **5** and **6**, the double shift in the conversion of **45** into **46** leaves that particular proton unaffected.[14] Necessary further clarification of the biosynthesis of *Iboga* and *Aspidosperma* alkaloids probably depends now on work with isolated enzymes leading to the sort of clarity obtaining to date for the



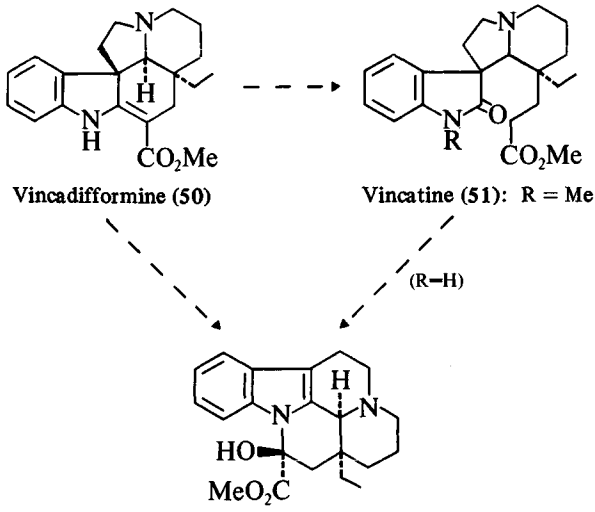
Secodine (49)

biosynthesis of the *Corynanthe* alkaloids. Exciting prospects are thus opened up by the development of strains of *C. roseus* cultures which will indeed synthesize *Strychnos, Iboga*, and *Aspidosperma* alkaloids.[51]

It is a puzzling feature, particularly of the *Aspidosperma* alkaloids,[52] but also of bases of the *Iboga*[53] and vincamine (**52**) series, that both enantiomeric series occur naturally, sometimes in the same plant. The chirality from earlier biosynthetic intermediates is lost on reaching secodine (**49**), which is achiral, but this does not explain the subsequent biological stereospecificity in both stereochemical senses. The natural occurrence of enantiomeric forms of akuammicine (**4**) has been given a chemical rationale.[54]

B. Vincamine

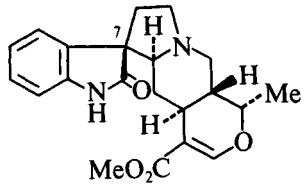
The terpenoid skeleton (**11**) in vincamine (**52**) is the same as in the *Aspidosperma* bases, for example, **5** and **50**, suggesting that vincamine is related biosynthetically to this group of alkaloids [see Scheme 9[55,56]; for the laboratory conversion of vincadifformine (**50**) into vincamine see Chapter VIII]. This has been supported in a provisional way with the reported incorporations of tryptophan, stemmadenine (**45**), and tabersonine (**48**).[57] It is additionally to be noted that both vincatine (**51**)[58] and vincadifformine (**50**)[59] occur with vincamine (**52**) in *Vinca minor* L.



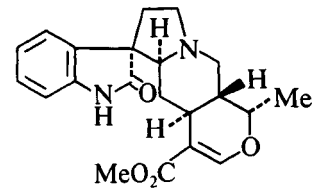
Scheme 9

C. Oxindole Alkaloids

Derivation of the oxindole alkaloids mitraphylline (**53**) and isomitraphylline (**54**) from the corresponding indole derivatives has been indicated by the apparent



Mitraphylline (53)

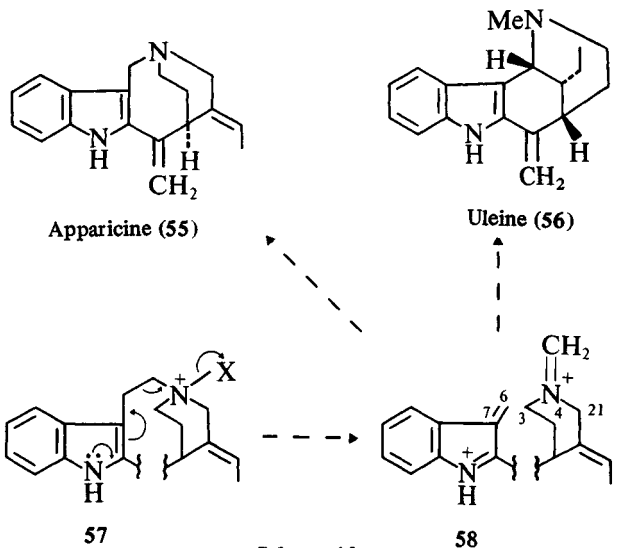


Isomitraphylline (54)

transformation of ajmalicine (3) and 3-isoajmalicine into these alkaloids in *Mitragyna parvifolia* Korth.[60] Some conclusions have also been reached about interrelationships of oxindole alkaloids in *Mitragyna* species.[61]

D. Apparicine and Uleine

Apparicine (55), vallesamine (59), and uleine (56) are exceptional terpenoid indole alkaloids in that their biosynthesis must involve modification to the normal tryptamine side chain with loss of C-1. Definitive evidence on the course of uleine biosynthesis is lacking,[62] but it appears that apparicine (55) does arise from tryptophan (2a) with the expected loss of C-2 (= C-1 in tryptamine).[63] Stemmadenine (45) and secodine (49) are precursors, which means that rearrangement to the apparicine skeleton is a late step in biosynthesis.[64] Secure details on the biosynthesis of these intriguing metabolites must await further work, but a key step probably involves a cleavage of the type shown in Scheme 10,[65,66] with subsequent bonding of C-6 to N-4 (for 55) or C-7 to C-21 (for 56). Such a sequence has been given chemical validity by the laboratory conversion [H_2O_2; $(CF_3CO)_2O$; hydrolysis] of stemmadenine (45) into vallesamine (59).[66] Vallesamine, preliminary



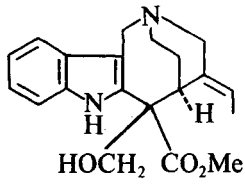
Apparicine (55)

Uleine (56)

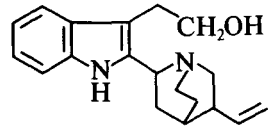
57

58

Scheme 10



Vallesamine (59)



60

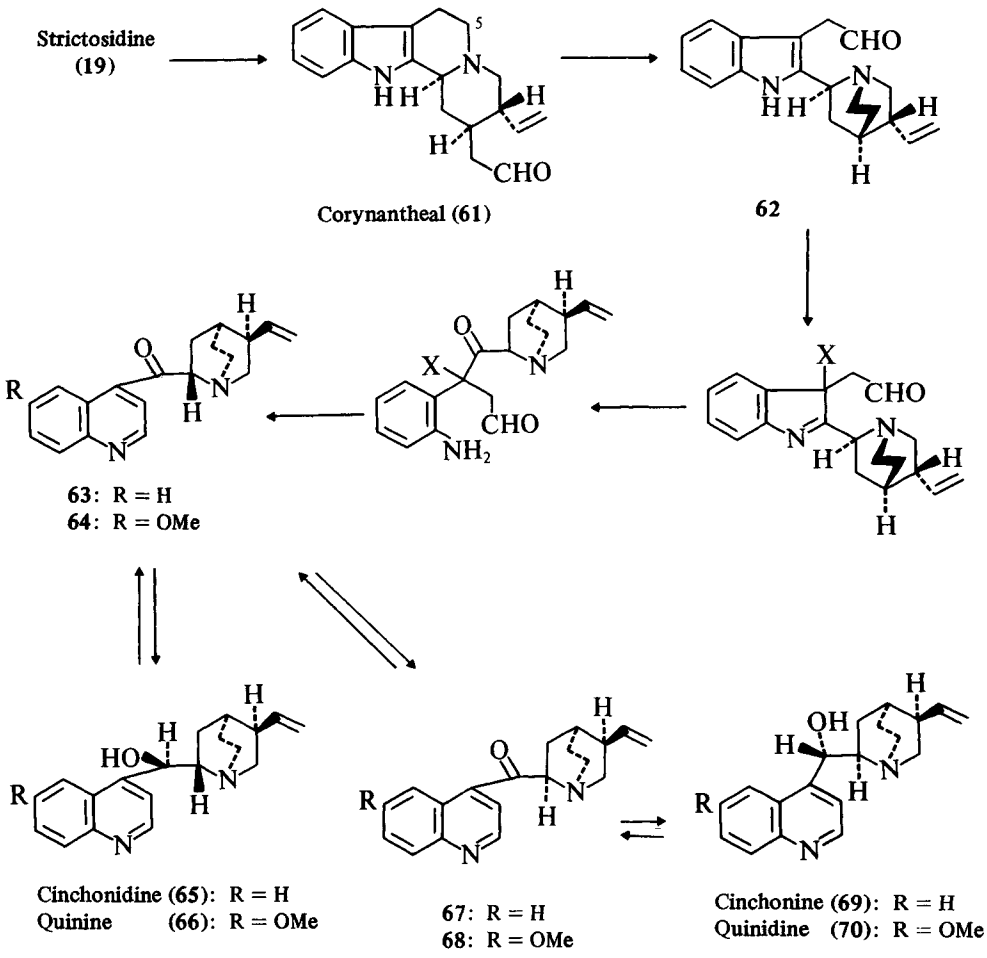
in vivo evidence indicates, is a precursor for apparicine. If the chemical sequence is an accurate reflection of the biosynthesis of **55** and **59**, then the reported[64] incorporation of secodine (**49**) is puzzling.

E. *Cinchona* Alkaloids

The structure **60** for the *Cinchona* alkaloid cinchonamine suggested at an early stage that there was a biogenetic relationship between the terpenoid indole bases and the *Cinchona* alkaloids with a quinoline moiety, for example, quinine (**66**).[67,68] Indeed it was likely that alkaloids of the former type would prove to be precursors for the quinoline bases. These ideas, the results of tracer experiments show, are correct. The incorporation of tryptophan,[69,70] geraniol (**7**),[12,70,71] loganin (**13**),[72] and strictosidine (**19**),[31] establishes an early biosynthetic pathway in common with the *Corynanthe* alkaloids (Section II. A). The labeling was, moreover, in accord with hypothesis (Scheme 11). Corynantheal (**61**), but not **43**, was found to be a precursor, and is likely to be the last of the *Corynanthe*-type intermediates.[73] The next intermediate is probably the aldehyde **62**, since the corresponding alcohol, cinchonamine (**60**), was not incorporated and half the label from [1-$^3H_2$]-tryptamine (labeling site corresponds to C-5 of **61**) was retained. This also excludes the corresponding carboxylic acid as an intermediate. No information is available on the rearrangement steps that follow **62**, but biosynthesis proceeds plausibly along the pathway shown in Scheme 11. The pathway leads to the ketone, cinchonidinone (**63**), the intermediacy of which in biosynthesis is indicated by its natural occurrence in *Cinchona* plants, and its conversion into *Cinchona* alkaloids[74]; **68** is also naturally occurring. It appears that the conversion of **63** into **65** is reversible, that in vivo epimerization occurs via **63** $\rightleftarrows$ **67**, and that **63** is a substrate for aromatic hydroxylation leading to different quinoline alkaloids.

F. Camptothecin

Camptothecin (**72**) represents a course of in vivo modification to the terpenoid indole skeleton leading to a quinoline alkaloid different from that of the *Cinchona* bases (Section II. E). The biosynthetic pathway to camptothecin (**72**) follows the route to *Corynanthe*-type alkaloids with strictosidine (**19**) as the last common intermediate.[75,76] Biosynthesis proceeds then via the lactam **71**, derived from

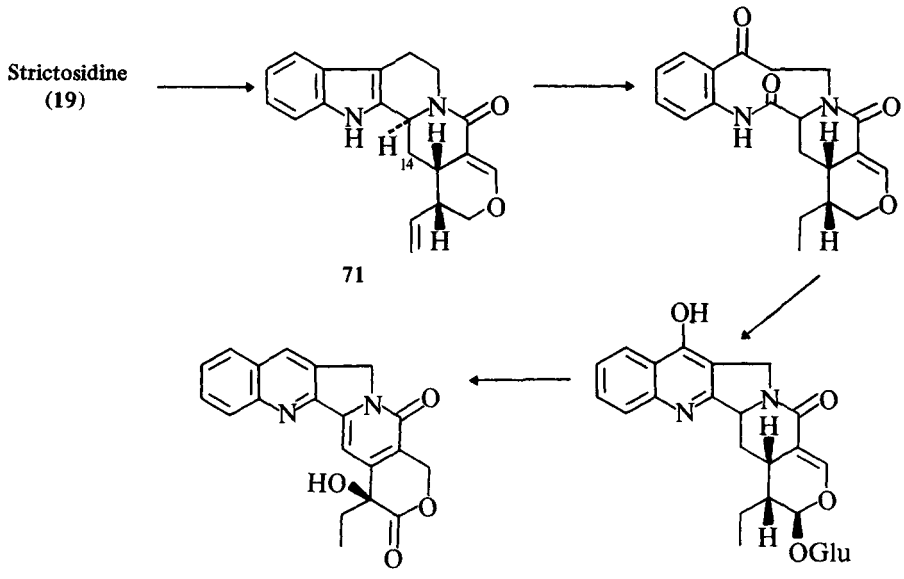


Scheme 11

strictosidine (**19**), with plausible intermediates as shown in Scheme 12, to camptothecin (**72**).[75] Desaturation of ring D is necessarily involved in this sequence and a proton is lost from C-14 (see **71**). The results of further experiments show, not without analogy, that it is lost nonstereospecifically, indicating that removal of this particular proton is probably not enzyme mediated.[77]

G. Bisindole Alkaloids

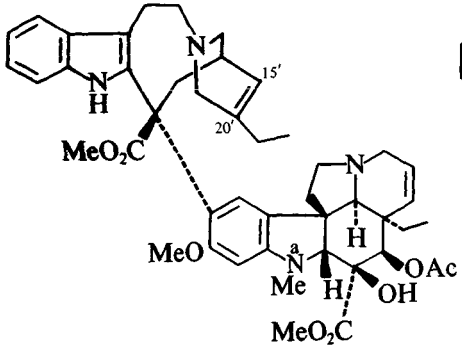
By inspection it seems manifest that bisindole alkaloids, for example, vinblastine (**74**), have a biogenesis from monomeric terpenoid indole alkaloids, such as vindoline (**5**) and catharanthine (**6**). Investigations have been dogged, however, by poor incorporations.[78] Recently more careful work and the use of cellfree preparations have given positive results. Anhydrovinblastine (**73**), which was shown to



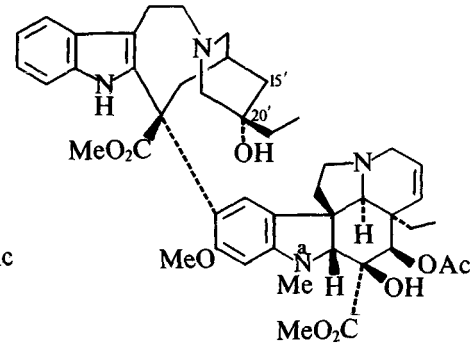
Scheme 12

be a natural product of *Catharanthus roseus*, has been found to be specifically and efficiently labeled by radioactive vindoline (**5**) and catharanthine (**6**) in whole plants[79] and in a cellfree preparation.[80] In cellfree preparations vinblastine (**74**) was formed from **73**[81,82]; 20′-deoxyleurosidine (as **73**, but saturated between C-15′ and C-20′) also acts as a precursor for **74**.[83] Leurosine (**75**) was also generated from **5**, **6**, and **73**, but the ready chemical conversion of **73** into **75**[84] leads to the question whether this is a real biosynthesis. Both anhydrovinblastine (**73**) and leurosine (**75**) were found to be efficient precursors for catharine (**76**).[82]

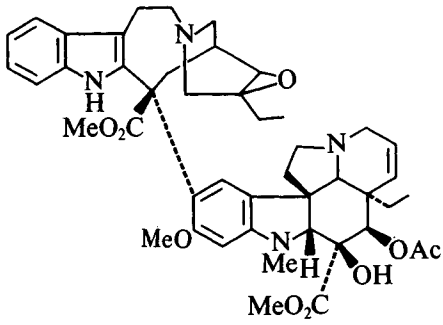
The chemical fusion of vindoline (**5**) and catharanthine (**6**) to give **73** occurs on treating catharanthine N_b-oxide with trifluoroacetic anhydride in the presence of vindoline (**5**), followed by reduction ($NaBH_4$).[85] The probable mechanism for the chemical reaction is shown in Scheme 13, and it is likely that the in vivo coupling resembles this route.



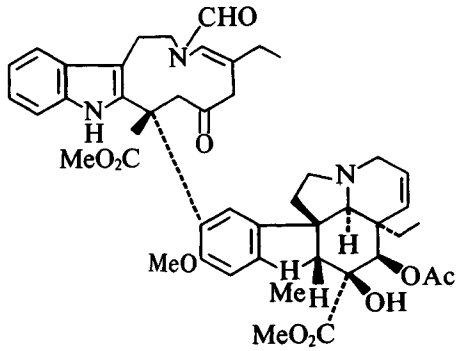
Anhydrovinblastine (73)



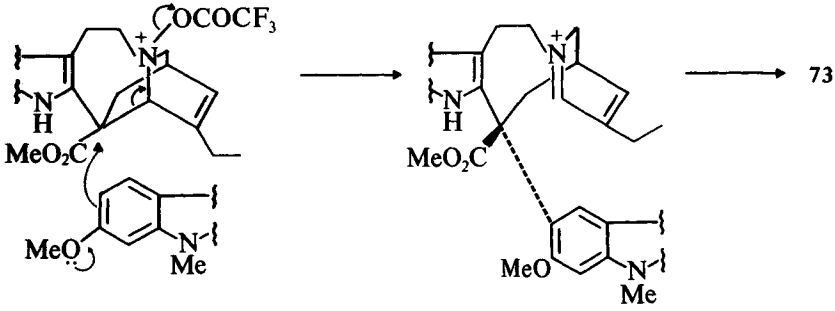
Vinblastine (74)



Leurosine (75)



Catharine (76)

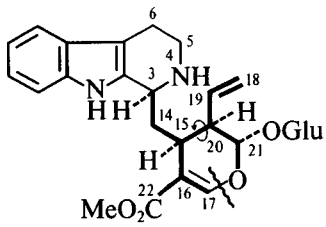


Scheme 13

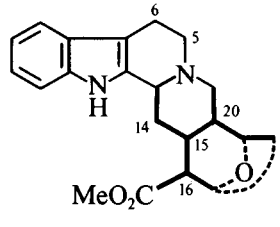
III. STRUCTURAL RELATIONSHIPS

The extensive studies so far conducted have revealed the gross topography of terpenoid indole alkaloid biosynthesis, together with some detail. The framework on which structural relationships (cf. Ref. 56) can be built is clearly defined, and is summarized in Scheme 14 (cf. Schemes 1, 6, and 8); the fragments shown with heavy outline are the basic terpenoid units derived from that in strictosidine (**19**), the first of the alkaloids to be formed in vivo. Almost all other terpenoid indole alkaloids are derived from it. An exception is adirubine (**82**),[86] which should derive from **83**, formed from tryptophan (**2a**) rather than tryptamine (**2b**) (cf. Scheme 6), plus secologanin (**18**). (N.B. **83**, which is naturally occurring,[87] is known[88] not to be a precusor for a variety of alkaloids without a carboxy group at C-5.) The **83** skeleton appears again in the more extensively modified form of adifoline (**84**).[89] It is interesting to note that, so far as is known, biosynthesis via **83** stops at these primitive alkaloids,[86,89,90] and does not yield the more advanced *Aspidosperma* and *Iboga* types.

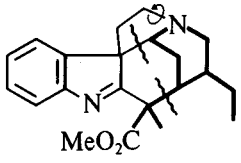
The following discussion centers on the alkaloids represented by **77–81**, with a description of major elaborations of these basic skeletons. Generally, no further



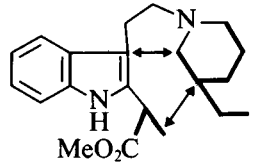
Strictosidine (19)



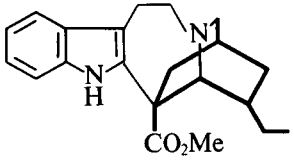
Corynanthe type (77)



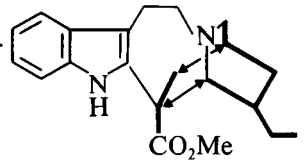
Strychnos type (78)

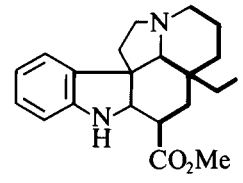


Secodine type (79)



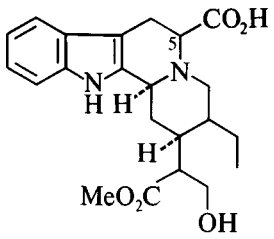
Iboga type (80)



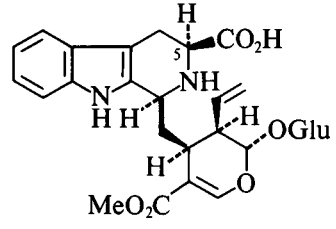


Aspidosperma type (81)

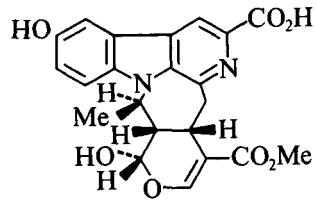
Scheme 14



Adirubine (82)



83



Adifoline (84)

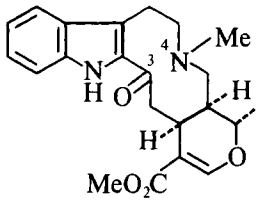
mention is made of those alkaloids for which the discussion in Section II adequately relates them and their close relatives to **19** or **77–81**.

The biochemical reactions that afford the various alkaloids involve, as for secondary metabolites generally, apparently simple reactions, and chiefly those with enamines and carbanions. Reaction naturally centers on N-4 (see **19**, Scheme 14) and adjacent carbon atoms; C-15 and C-16 are also commonly involved. These reactions are generally accessible in the laboratory and can give (as seen above) a guide to the actual biochemical pathways. This guide may or may not, however, turn out to be reliable when in vivo experiments are carried out. The fact that particular alkaloids co-occur in the same plants may indicate a close relationship, but on the other hand, crucial biosynthetic intermediates may not be detected, and abundant alkaloids may be those at the termini of divergent pathways.

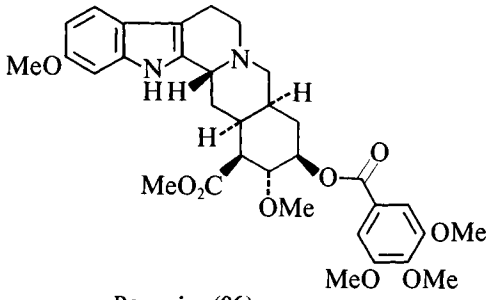
A. Alkaloids with a Nonrearranged Secologanin Skeleton

Alkaloids in this group, for example, **3**, **4**, **26**, and **34**, are those with structures correlating with **77** and **78**. They are widespread and numerous, which is not surprising considering their close biogenetic relationship to strictosidine (**19**). Apart from an unrearranged secologanin (**18**) skeleton, they have in common *S* chirality at C-15 (see **3** and **4**).[56] An examination of the biosynthetic pathway indicates that this is the one center not affected by biochemical reactions.

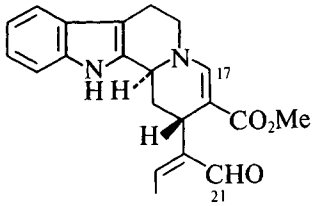
Biogenesis of alkaloids like ajmalicine (**3**) follows simply from strictosidine (**19**) by condensation of C-21 with N-4 (see Section II. A), and picraphylline (**85**) may be derived from a precursor related to **3** by simple oxidative fission of the C-3, N-4 bond. Formation of the carbocyclic ring E in yohimbine (**34**) from the *Corynanthe* skeleton (as **23**) has already been discussed (Section II. A), and alkaloids like reserpine (**86**) surely arise in a similar way. Vallesiachotamine (**87**),[91] on the other hand, must derive, without intervention of *Corynanthe* intermediates, directly from strictosidine (**19**) by condensation of N-4 with the masked aldehyde group at C-17, rather than with the one at C-21. A similar independent derivation from strictosidine (**19**) is to be found in cadambine (**88**),[92] in which the fundamental linkage is between N-4 and C-18 of **19**. Linkage of C-19 to N-4 leads to alkaloids exemplified by cadamine and isocadamine (**89**);[93] in these alkaloids the tetrahydropyran ring of **19** is transformed into a pyridine ring, which occurs also in other alkaloids, for example, naufoline (**90**).[16] Cyclization of N-4 onto C-18 or



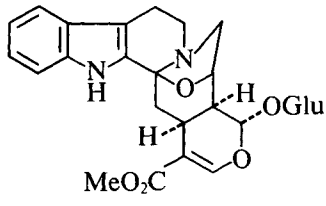
Picraphylline (85)



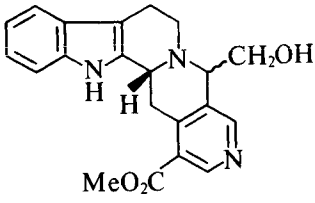
Reserpine (86)



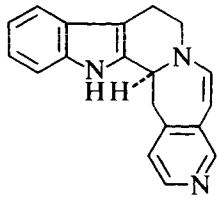
Vallesiachotamine (87)



Cadambine (88)



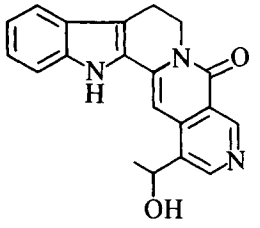
Cadamine and Isocadamine (89)



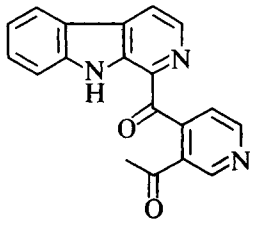
Naufoline (90)

C-19 (in **19**) to give **88–90**, among other products, suggests a biosynthetic intermediate in which the C-18, C-19 double bond in **19** has become an epoxide.

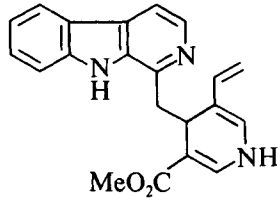
Two further pyridine alkaloids are angustoline (**91**)[95] and pauridianthine (**92**).[96] The former alkaloid corresponds to the vallesiachotamine (**87**) skeleton, and **91** and **92** may represent successive steps of derivation from **87**. A priori, however, it is more likely that **92** and alkaloids like lyaline (**93**)[97] arise more directly from **19**.



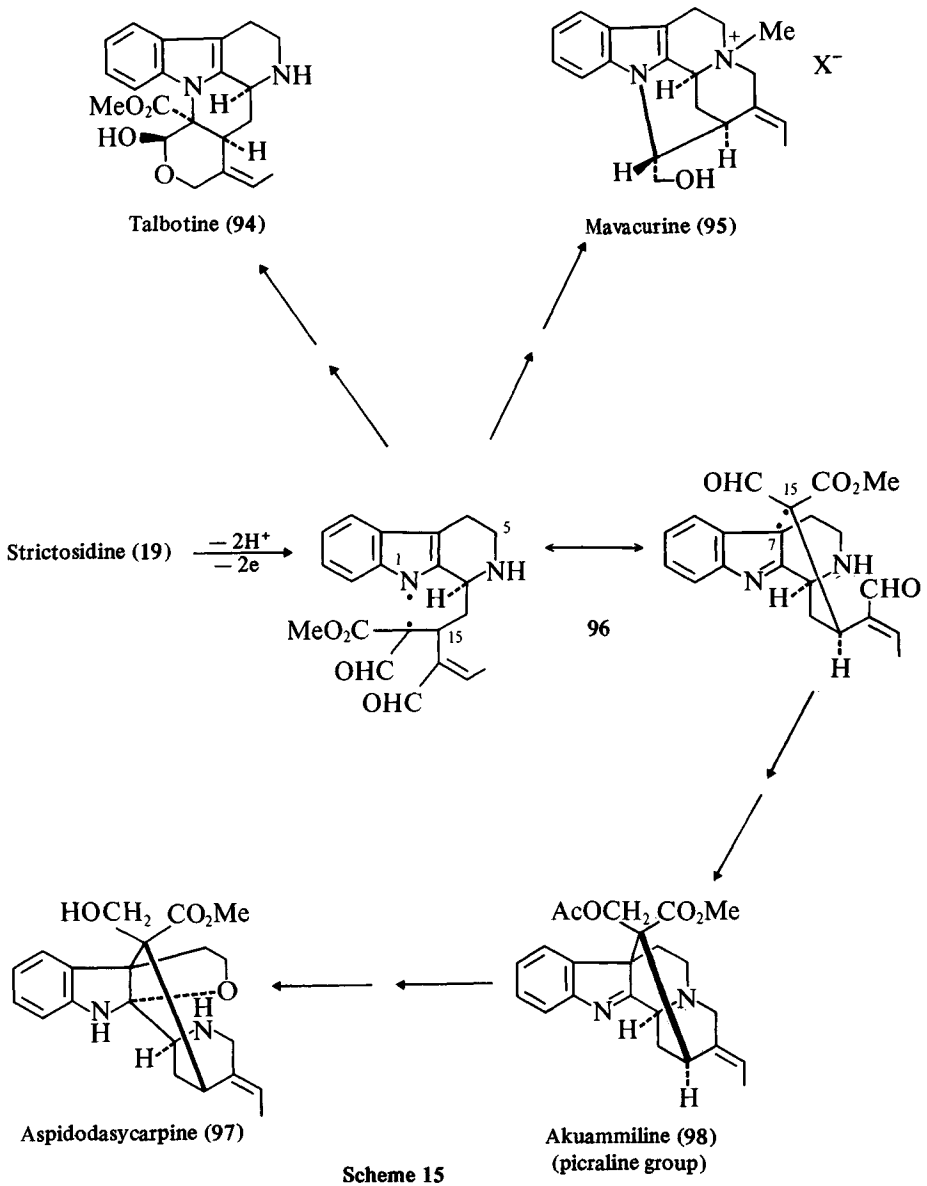
Angustoline (91)



Pauridianthine (92)

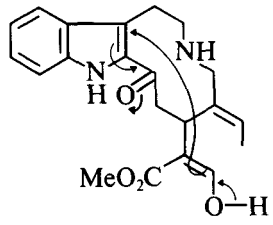


Lyaline (93)



Scheme 15

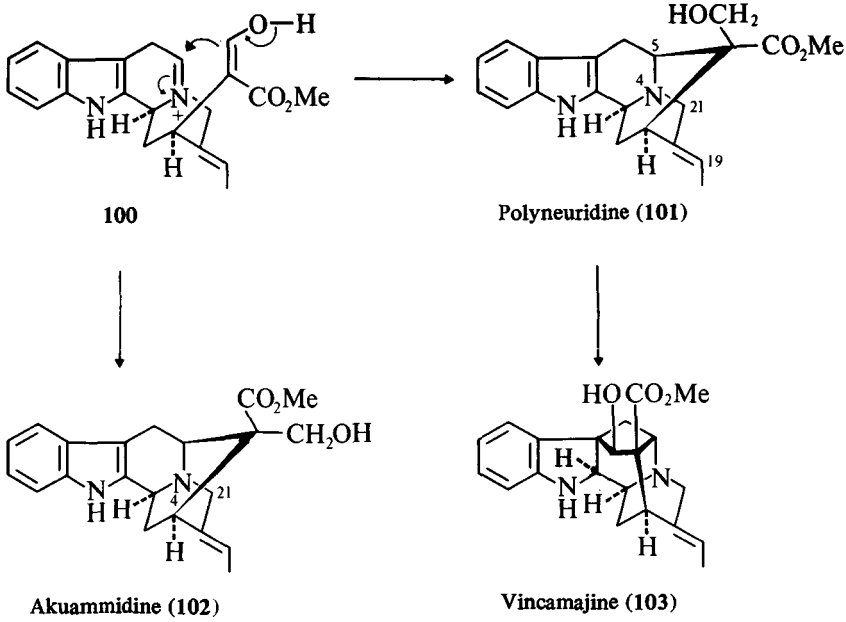
Starting from the ajmalicine (**3**)-geissoschizine (**24**) skeletons, reaction of the pendant group at C-15 (see **96**) with N-1, C-7, or C-5 leads to different alkaloids, represented by **94**, **95**, **98**, **101**, and **103**. Formation of alkaloids represented by talbotine (**94**),[98] mavacurine (**95**),[99] and akuammiline (**98**) (picraline alkaloids)[100] may be rationalized in a unified way[56] (Scheme 15) through a diradical **96**, seen as the key intermediate derived from strictosidine (**19**), which by radical coupling can afford these alkaloid types. Only **94** necessarily derives directly from **19**; the others



99

may form in a similar way from a *Corynanthe* intermediate. An alternative biogenesis for akuammiline (**98**) and related alkaloids involves cyclization of **99**, which is related to picraphylline (**85**) (N.B. **85**, **98**, and their relatives co-occur in *Picralima* species).[100]

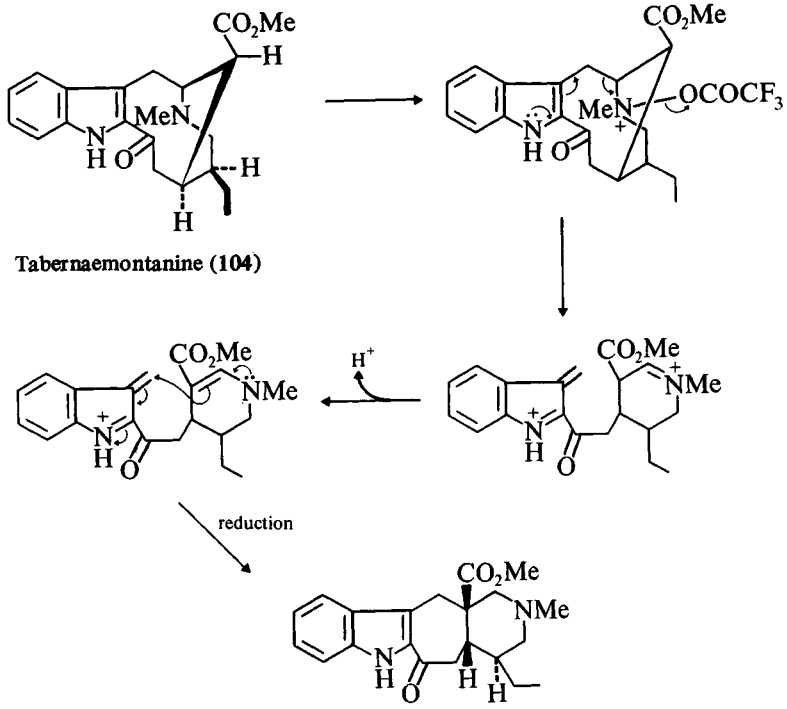
A similar cyclization with the C-17 aldehyde in the *Corynanthe* base **100** may lead to the sarpagine [e.g., polyneuridine (**101**) and akuammidine (**102**)] and ajmaline [e.g., vincamajine (**103**)] groups of alkaloids (Scheme 16). Further transformation of the **100/101** skeleton affords alkaloids like tabernaemontanine (**104**). The chemical conversion[101] of **104** into ervatamine (**105**) (Scheme 17) indicates a possible biogenetic relationship between alkaloids with structures represented by **104** and those represented by **105**. The *Pandaca boiteaui* Mgf. alkaloids, methuenine (**108**) and ervitsine (**107**), could be derived in a similar way (Scheme 18) from **106** (cf. **105** in Scheme 17);[102] **108** may derive directly from **106** without ring opening.



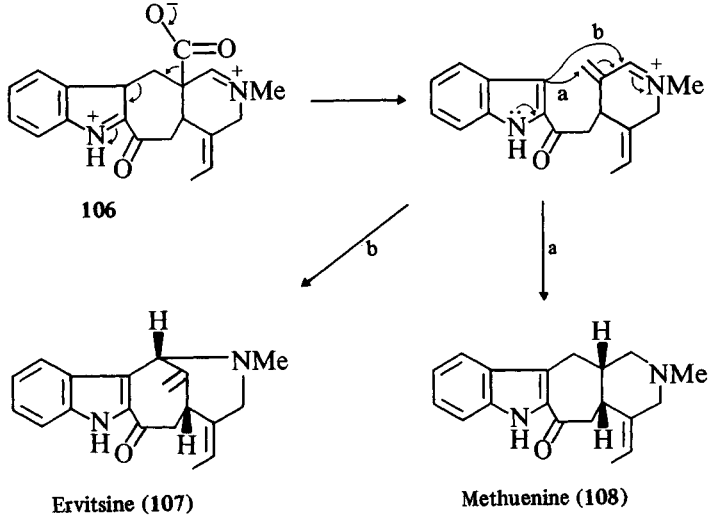
100 **Polyneuridine (101)**

Akuammidine (102) **Vincamajine (103)**

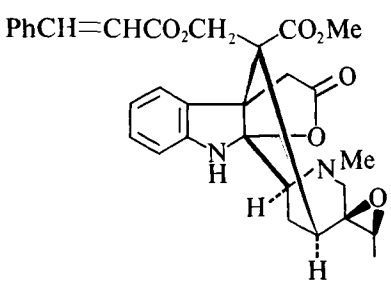
Scheme 16



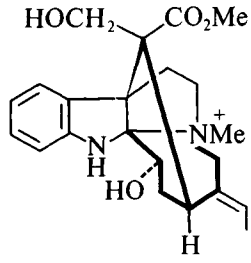
Scheme 17



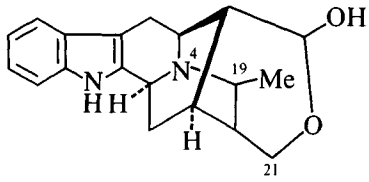
Scheme 18



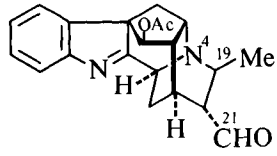
Lanciferine (109)



Echitamine (110)



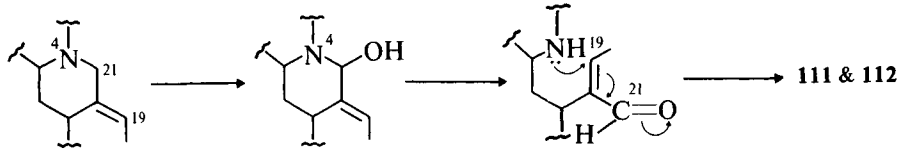
Peraksine (111)



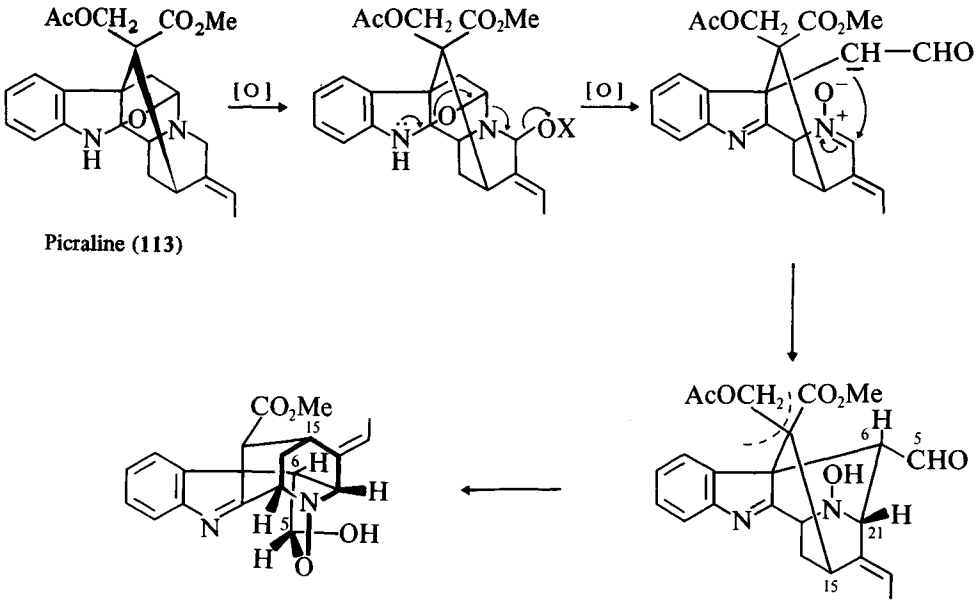
Perakine (112)

Lanciferine (**109**)[103] and echitamine (**110**)[104] represent further elaborations of the skeleton **98**, as do peraksine (**111**) and perakine (**112**)[105,106] of the skeletons **101/103**. For these last two alkaloids C-19 rather than C-21 (cf. **101**) is linked to N-4, and the simplest hypothesis is that rearrangement occurs (Scheme 19)[106,107] at a late stage of biosynthesis. Quite the most extravagant elaboration of the skeletons under discussion is found in nareline (**114**); its possible biogenesis from picraline (**113**) is illustrated in Scheme 20.[108] A simpler transformation of talpinine (**115**) (N-4, C-21 cleavage) affords talcarpine (**116**), a reaction carried out chemically; both alkaloids are found in the same plant (*Pleiocarpa talbotii* Wernham).[109]

An important development occurs with the formation in plants of preakuammicine (**44**) from the *Corynanthe* skeleton. From **44** biosynthesis drives through stemmadenine (**45**) to alkaloids with rearranged secologanin skeletons, for example, **5** and **6** (Section II. A). Conversion of the *Corynanthe* skeleton into those represented by **44** requires a reordering of the bonds to the indole nucleus. It has been suggested[55] that rearrangement could occur via an intermediate of type **98** but, in the light of the biosynthetic evidence so far, this is not so. The evidence, however, is in support of a simple rearrangement or one via an oxindole, for example, **117** (Scheme 21).[110]



Scheme 19



Picraline (113)

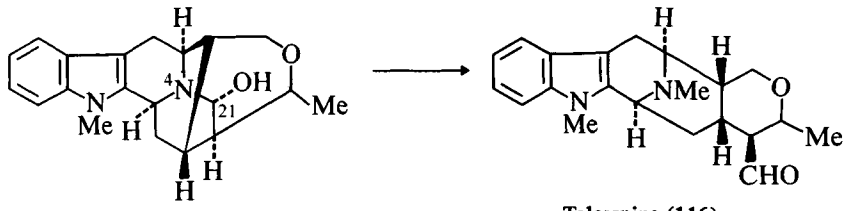
Nareline (114)

Scheme 20

The relationship of alkaloids, represented by akuammicine (**4**) and strychnine (**37**), to preakuammicine (**44**) is manifest (the biosynthesis of these alkaloids is covered in Section II. A). Alkaloids like **118**, strychnofendlerine (**119**),[111] and holstiine (**120**)[112] are oxidation products of the preakuammicine (**44**) skeleton.

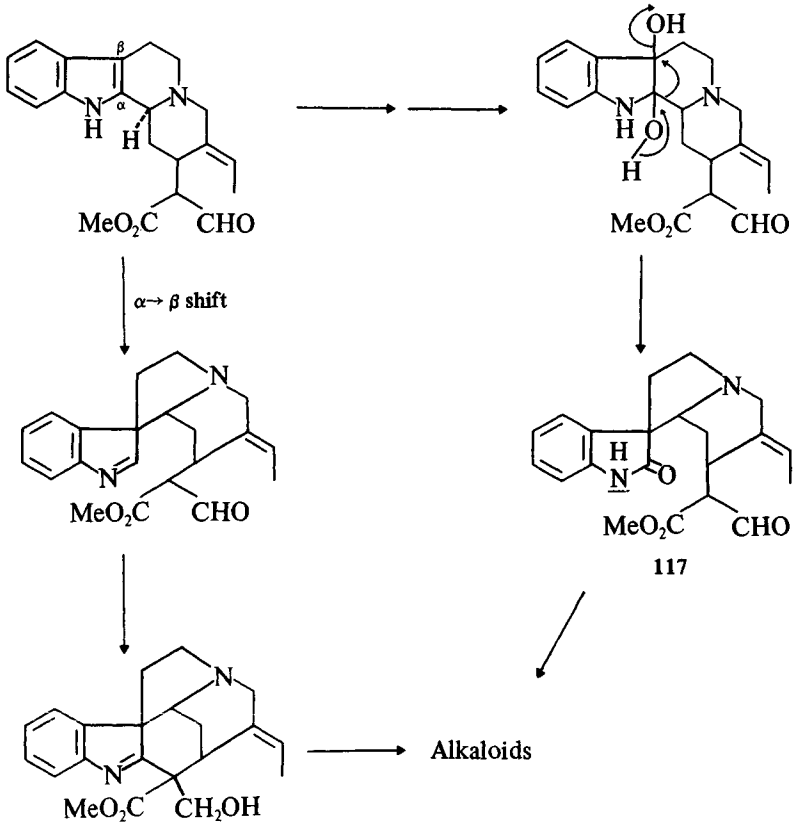
The reordering of the bonding of **44**, found in condylocarpine (**122**) and dichotine (**124**),[113] can be rationalized[114] as occurring from the stemmadenine (**45**) relative **121** (Scheme 22); there is chemical analogy for the sequence to **122**.

Three novel alkaloids, hunteracine (**125**),[115] andranginine (**126**),[116,117] and goniomine (**127**), can also be seen as stemmadenine (**45**) derivatives. The first alkaloid (**125**) can be related to **45** by loss of the C-16 substituents, C-7 hydroxylation, and nucleophilic closure of N-4 onto the indole α position. The transformation[116] of precondylocarpine acetate (from **123**) into andranginine (**126**) (for details see Chapter VII) indicates a possible biogenetic relationship of **126** to alkaloids of type **123**. Goniomine (**127**) can also be derived hypothetically from precondylocarpine (**123**)[118] as shown in Scheme 23.



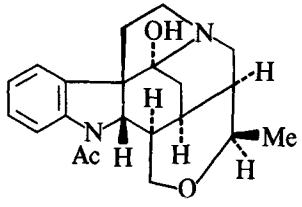
Talpinine (115)

Talcarpine (116)

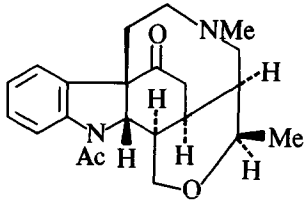


Preakuammicine (44)

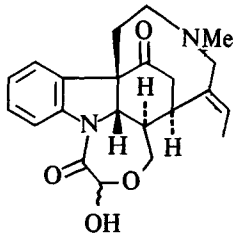
Scheme 21



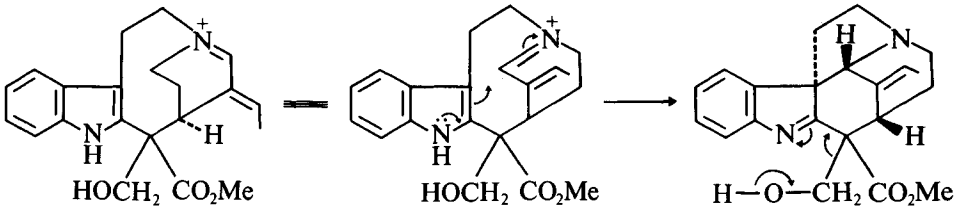
118



Strychnofendlerine (119)

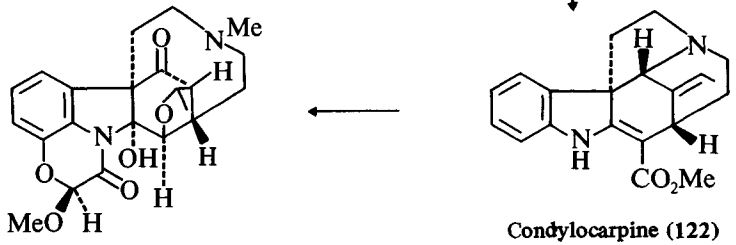


Holstiine (120)



121

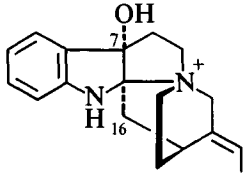
Precondylocarpine (123)



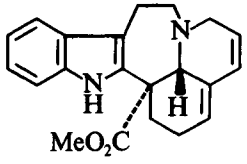
Dichotine (124)

Condylocarpine (122)

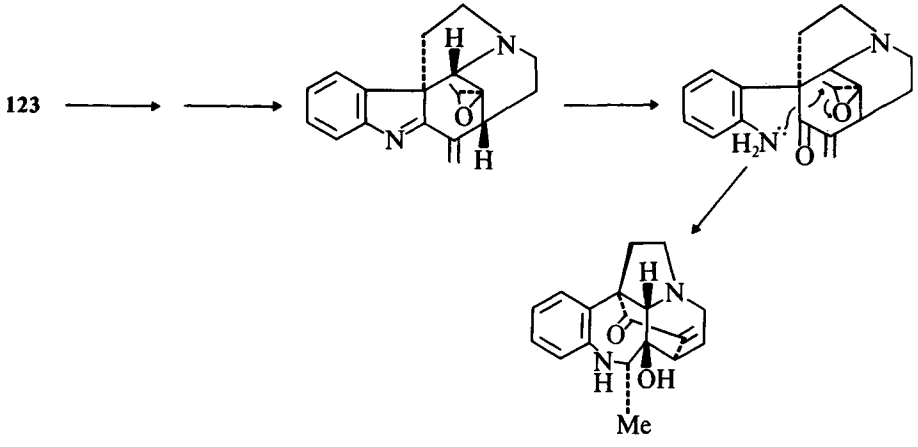
Scheme 22



Hunteracine (125)

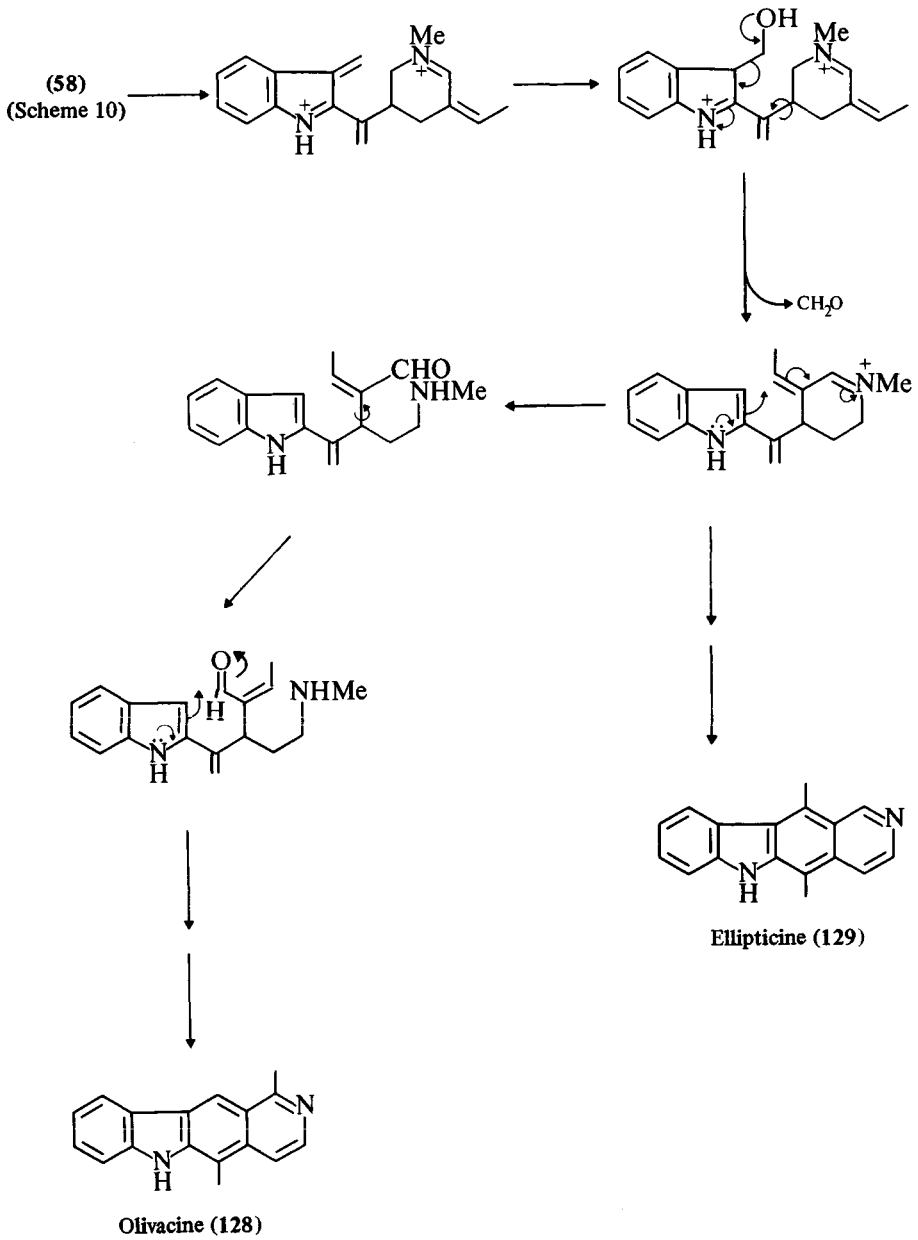


Andranginine (126)



Goniomine (127)

Scheme 23

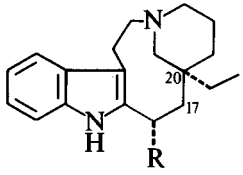


Scheme 24

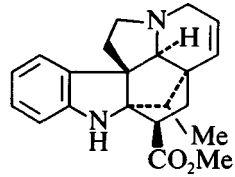
The relationship of apparicine (**55**) and uleine (**56**) to the stemmadenine (**45**) skeleton has already been discussed (Section II. D). Olivacine (**128**) and ellipticine (**129**) are two examples in which the original tryptamine side chain is completely lost. A possible biogenesis is indicated in Scheme 24.[65,119]

B. Alkaloids with a Rearranged Secologanin Skeleton

It will be apparent from the discussion in Section II. A that, for the *Aspidosperma* [e.g., vindoline (**5**)] and *Iboga* [e.g., catharanthine (**6**)] groups of alkaloids, with rearranged secologanin skeletons, biosynthesis funnels through derivatives of secodine (**49**) from stemmadenine (**45**); it is through fragmentation to **47** and recombination that rearrangement occurs (cf. Scheme 8). In the formation of vindoline (**5**) and tabersonine (**48**) from **47** two bonds must be formed (C-7, C-21 and C-17, C-20). Although the natural occurrence of alkaloids such as quebrachamine (**130**) and vincadine (**131**) suggests that the 17,20 bond is the first to be forged, quebrachamine is possibly not an *Aspidosperma* precursor,[7] which indicates that initial bond formation for **48**, for example, is from C-7 to C-21 (Scheme 8). The alkaloids vindolinine (**132**)[120] and pleiocarpine (**134**) can be derived from



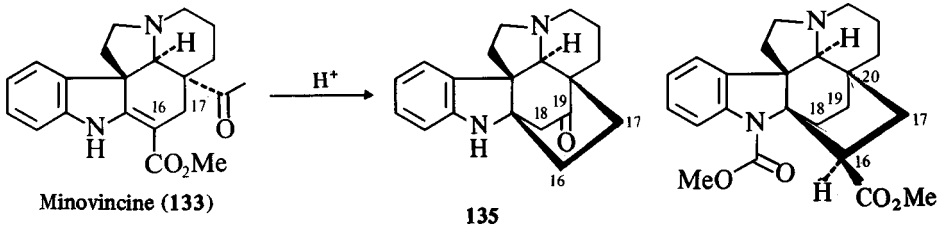
(+)-Quebrachamine (**130**): R = H
(+)-Vincadine (**131**): R = CO_2Me



Vindolinine (**132**)

tabersonine (**48**) by C-2, C-19 and C-2, C-18 bond formation, respectively. Support for the derivation of pleiocarpine (**134**) alkaloids from a tabersonine (**48**) derivative comes from the in vitro conversion of minovincine (**133**) into 19-oxo-aspidofractinine (**135**)[121] (Scheme 25). A further chemical sequence (Scheme 26) relates the pleiocarpine alkaloids to the heptacyclic kopsane alkaloids.[122]

Vincamine (**52**) is one of several alkaloids with the same basic skeleton which is related biosynthetically to the tabersonine skeleton (Section II. B). A slightly

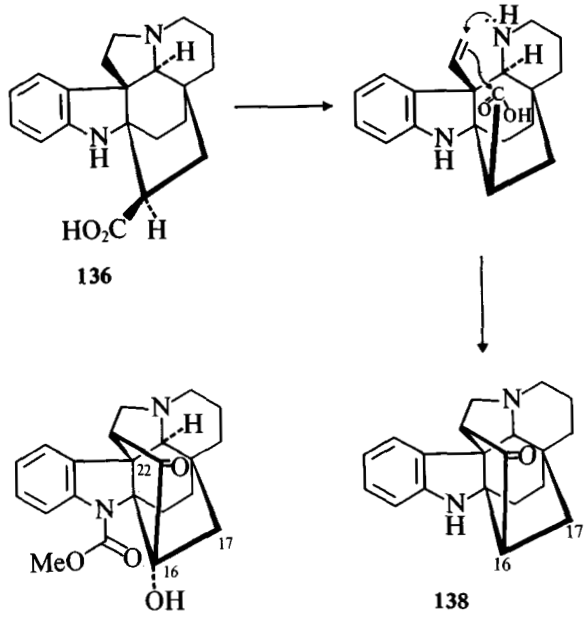


Minovincine (**133**)

135

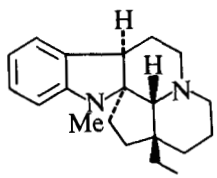
Pleiocarpine (**134**)

Scheme 25

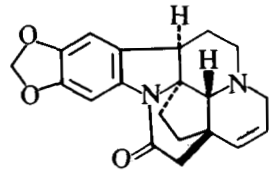


Scheme 26

different arrangement is found in vallesamidine (**139**) and schizozygine* (**140**),[56,123] with the latter representing a later stage of biosynthesis than the former, along a pathway similar to that for vincamine (**52**) (see Scheme 9).



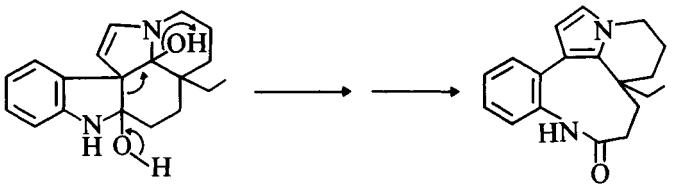
Vallesamidine (139)



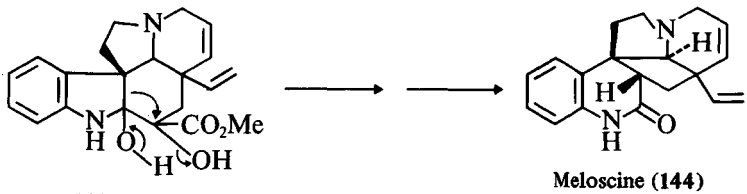
Schizozygine (140)

The most curious *Aspidosperma* variation is rhazinilam (**142**),[124] which may be an artifact derived from **141**. Meloscine (**144**)[125] clearly includes a simple *Aspidosperma* terpenoid skeleton. The unusual dihydroquinolone group could arise via the *Aspidosperma* derivative **143** [cf. the biosynthesis of the quinoline alkaloid, camptothecin (**72**) (Scheme 12)].

* Note that the absolute configuration implied in structure **140** for schizozygine is opposite to that depicted in structure **52**, Chapter IX. There is at present no direct, unequivocal evidence relating to this point; the configuration illustrated here (**140**) is merely given for convenience [cf. (−)-vallesamidine (**139**)], following the authors of Ref. 56.

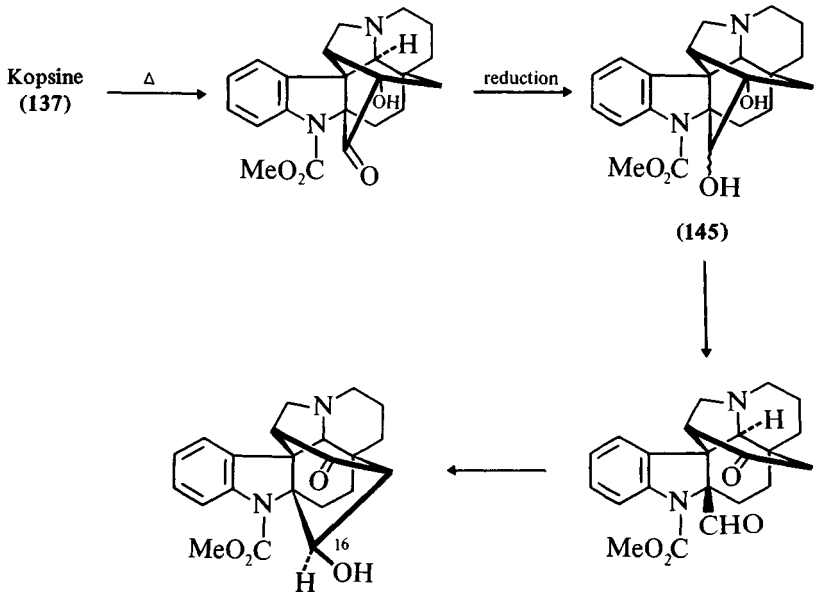


141 Rhazinilam (142)



143 Meloscine (144)

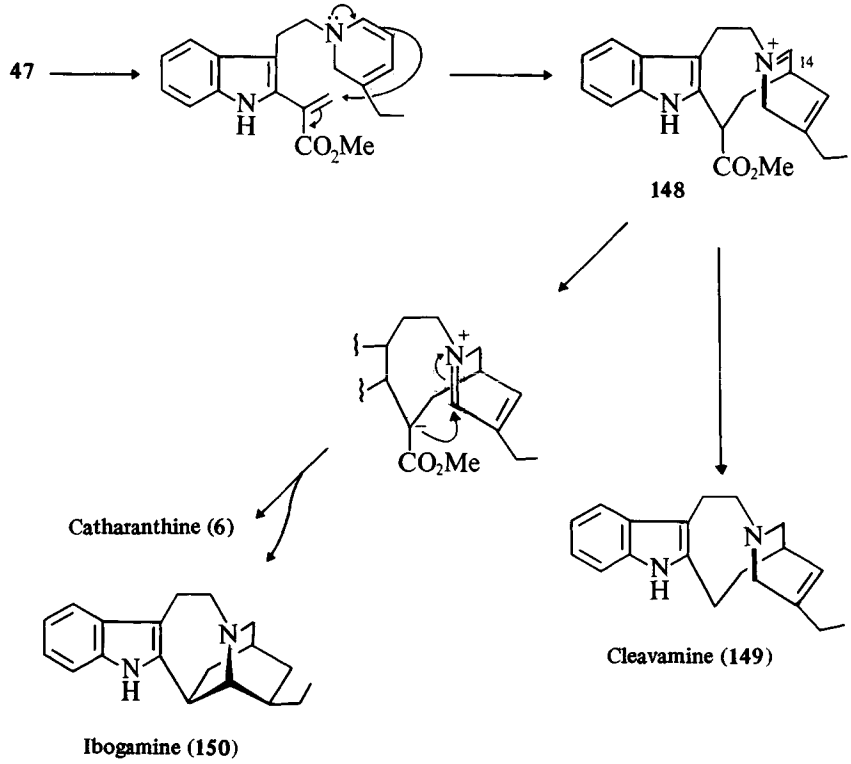
Fruticosine (**146**) and fruticosamine (**147**) have terpenoid skeletons showing further rearrangement. They co-occur naturally with kopsine (**137**),[126,127] which is chemically convertible into **146** and **147** (Scheme 27).[127,128] These facts strongly indicate a biogenetic link between **146/147** and the kopsine (**137**), hence *Aspidosperma*, skeleton. However, dihydroisokopsine (**145**) was found not to be incorporated into **146** or **147**.[56]



Fruticosine (**146**)
Fruticosamine (**147**), C-16 epimer

Scheme 27

The secodine skeleton (**49**) serves as the starting point not only for *Aspidosperma* alkaloids, but also for the *Iboga* alkaloids, e.g., catharanthine (**6**), with slightly different secologanin skeleton (see Scheme 14), the biosynthesis of which has already been discussed (Section II. A). Cleavamine (**149**) and related alkaloids are obviously close relatives of **6**. The natural occurrence of these alkaloids indicates that catharanthine (**6**), ibogamine (**150**), and congeners probably arise from **47** through **148**, which has the cleavamine (**149**) skeleton (Scheme 28). Pandoline (**152**)[129] may also arise through **148** ≡ **151**, with, however, the opposite stereochemistry at C-14. The formation of iboxyphylline (**153**) and ibophyllidine (**154**) from pandoline (**152**) seems probable[130] (Scheme 29).

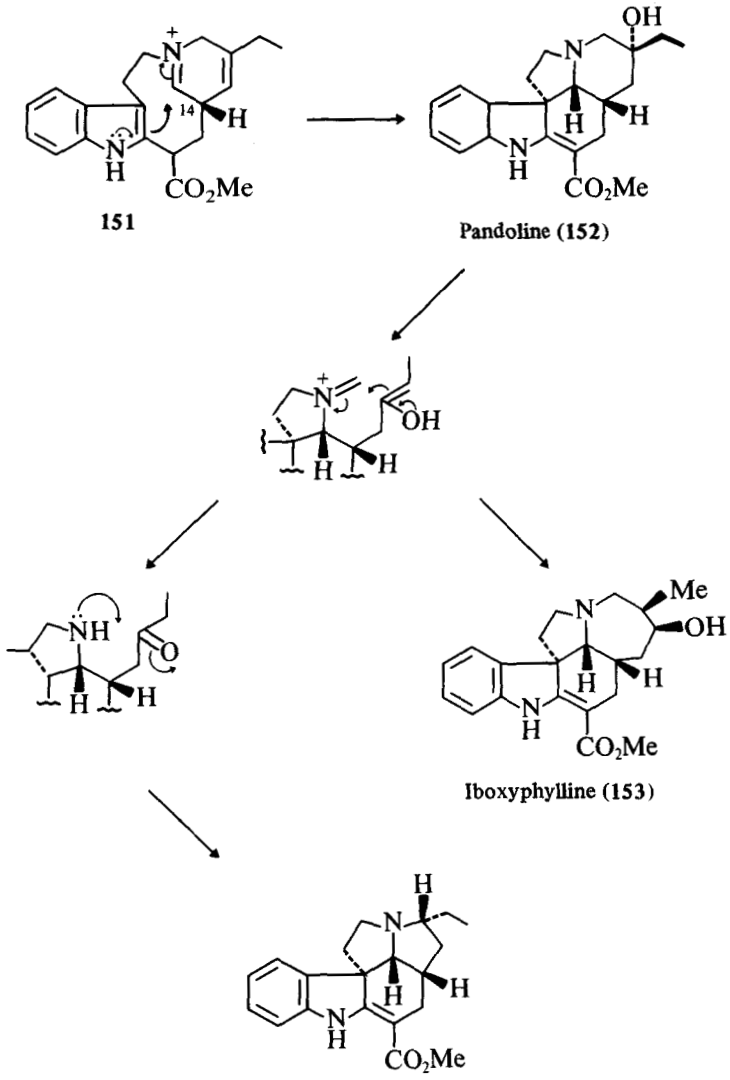


Scheme 28

C. Oxindole Alkaloids

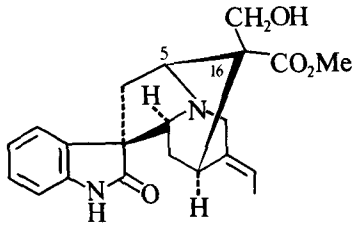
Oxindole alkaloids are found mainly as variants on the *Strychnos* skeleton (**78**), but are to be thought of, in some cases at least, as the products of rearrangement on the *Corynanthe* skeleton (**77**), for example, mitraphylline (**53**) and isomitraphylline (**54**). At the new asymmetric center (C-7), both *R* and *S* configurations are observed.

Rare oxindole variants are found in voachalotine oxindole (**155**)[131] and

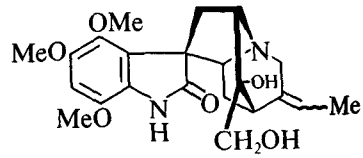


Scheme 29

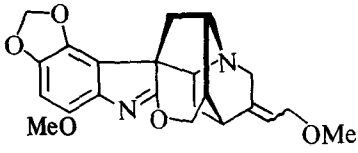
chitosenine (**156**).[132] The latter alkaloid co-occurs with other obviously related alkaloids, for example, gardfloramine (**157**). These alkaloids are related structurally to the sarpagine group (e.g., **101**), in which the *Corynanthe* skeleton (**77**) has been modified by the formation of an additional C-5 to C-16 bond, as well as oxindole formation. Gelsemine (**158**) is one of four similar alkaloids isolated from *Gelsemium sempervirens*.[133] These bases are unique, convoluted oxindoles derived from the *Corynanthe* skeleton with additional bonds at positions 5,16 and (rarely encountered) 6,20.



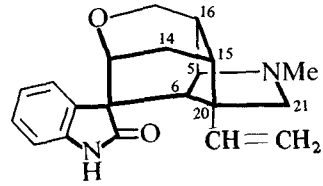
Voachalotine oxindole (155)



Chitosenine (156)



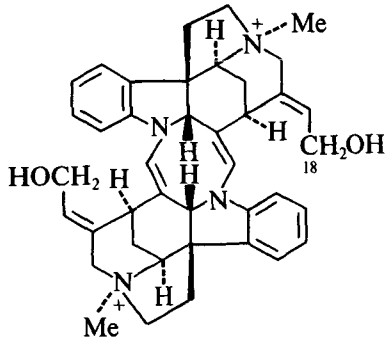
Gardfloramine (157)



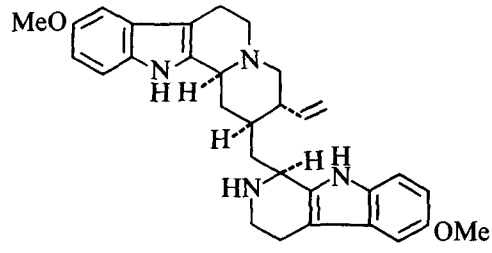
Gelsemine (158)

D. Bisindole Alkaloids

The fusion of two monomeric terpenoid indole fragments yielding bisindole alkaloids may occur with two units of the same base, as in *C*-toxiferine (**159**), two units of a different type, as in vinblastine (**74**), or one terpenoid indole fragment and a quite different unit as, for example, in isocinchophyllamine (**160**). The common monomeric structural types discussed above are represented in the bisindole alkaloids. Linkage between the two units occurs through the available reactive functionality of the terpenoid fragment and may also involve the aromatic residue.

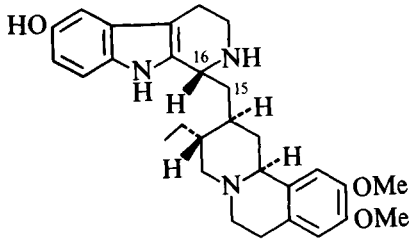


C-Toxiferine (159)

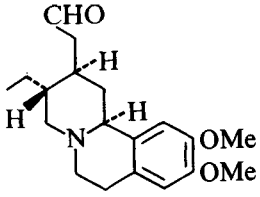


Isocinchophyllamine (160)

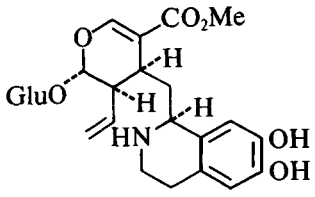
Calabash curare is prepared from the bark of South American *Strychnos* species. Nearly two score bisindole alkaloids have been isolated from the curare and the *Strychnos* species along with a large number of monomeric bases. The structures of the bisindole bases, for example, *C*-toxiferine (**159**), are all related, and in some cases have been chemically related, to the Wieland-Gumlich aldehyde (**40**) or its 18-deoxy derivative and their respective N-4 dimetho salts.[134] Variations on **159** are associated essentially with further bond formation across the central ring and bonding through the C-18 oxygen functions.



Tubulosine (161)



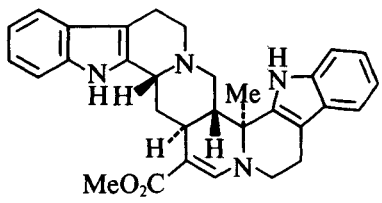
162



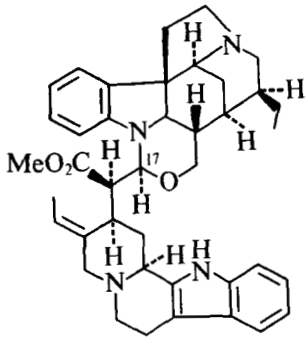
163

Tubulosine (**161**) is representative of a group of bases reminiscent of the ipecac alkaloids, in which **162**, derived from desacetylisoipecoside (**163**) (cf. Refs. 33 and 35), has condensed with tryptamine (**2b**).[135]

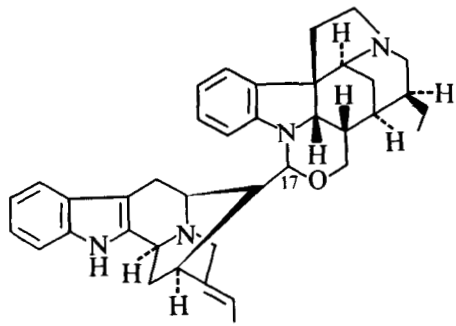
Condensation of tryptamine with a *Corynanthe* derivative leads to isocinchophyllamine (**160**),[136] and in a different way to a group of alkaloids represented by roxburghine D (**164**).[137] The *Corynanthe* fragment is to be found in geissospermine (**165**),[138] as is one of the *Strychnos* type. Both this alkaloid and geissolosimine (**166**), with *Strychnos* and sarpagine units, implicate a C-17 aldehyde function in the bonding of the two components; these alkaloids are found together in *Geissospermum vellosii* Allem.[139]



Roxburghine D. (164)

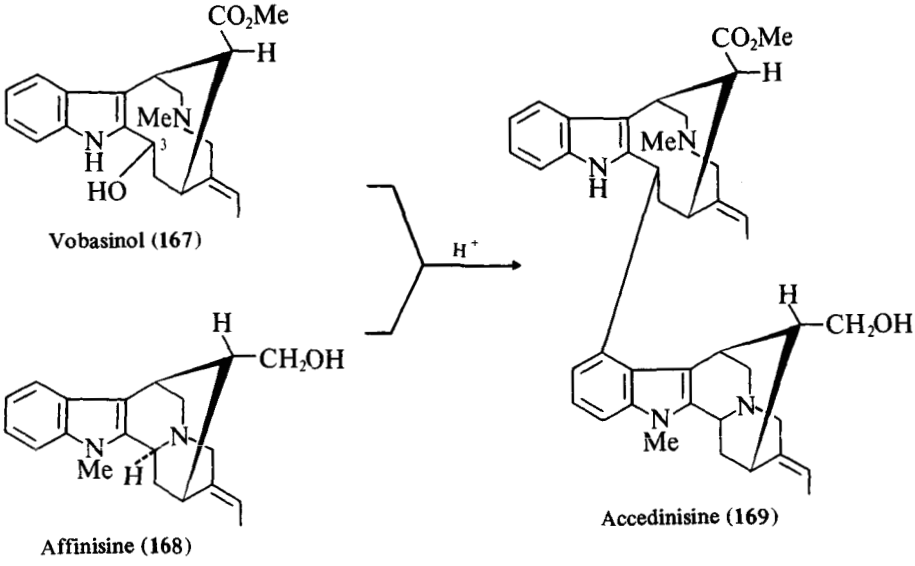


Geissospermine (165)



Geissolosimine (166)

A number of alkaloids, for example, accedinisine (**169**)[140] and voacamine (**171**),[141] are simply formed chemically from monomeric alkaloids, one of which bears a hydroxy group at C-3, the site of linkage (Schemes 30 and 31). This emphasizes a simple biochemical link between monomeric alkaloid and bisindole. No such simple relationship is apparent for haplophytine (**172**).[142] On the other hand, the complex alkaloid, borreverine (**174**), is formed from the simple base, borrerine (**173**), by acid treatment; these alkaloids co-occur in *Borreria verticillata*.[143]



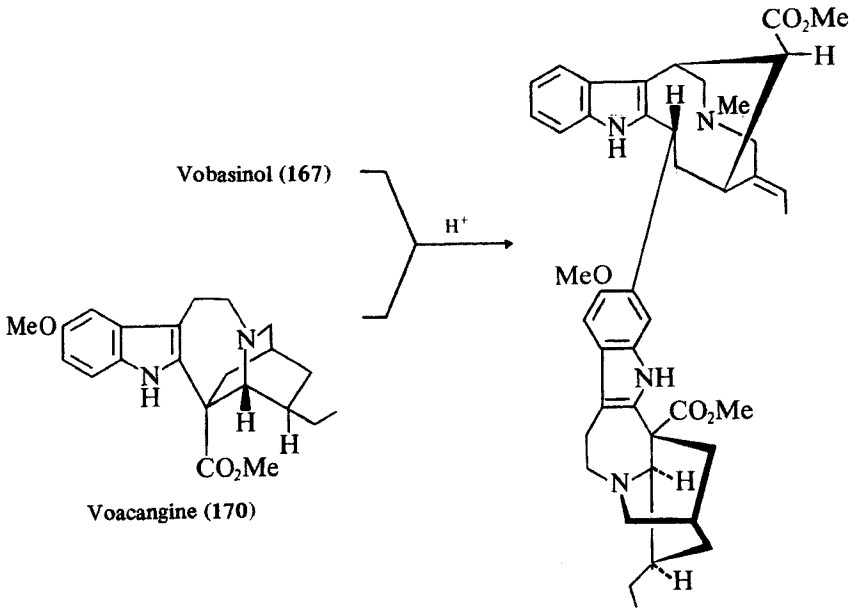
Vobasinol (167)

Affinisine (168)

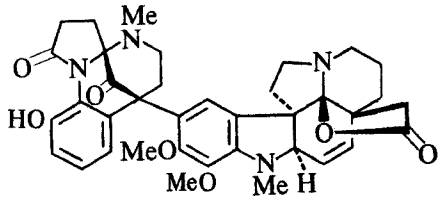
Accedinisine (169)

Scheme 30

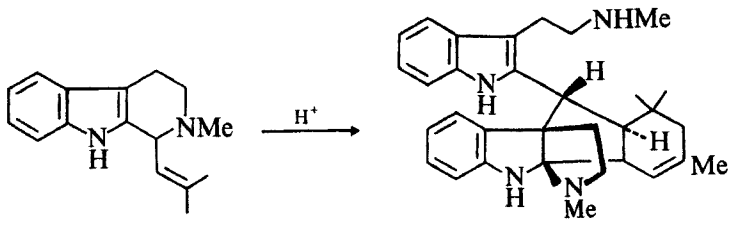
Closely related to secodine (**49**) are the dimeric alkaloids, secamine (**175**) and presecamine (**176**); **49** gives a diastereoisomeric mixture of presecamines (**176**) on standing without solvent, whereas **176** gives **175** rapidly on treatment with acid.[144]



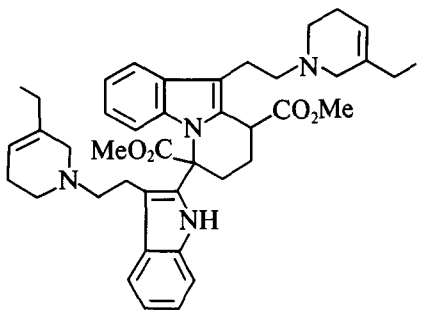
Scheme 31



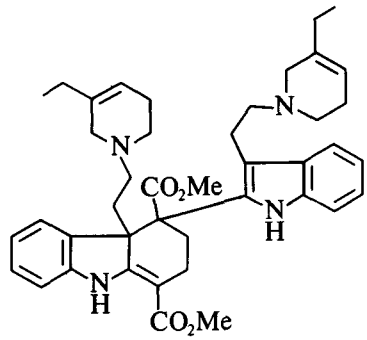
Haplophytine (172)



Borrerine (173) Borreverine (174)

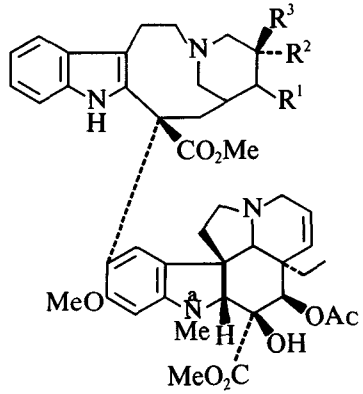


Secamine (175)



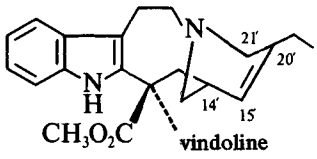
Presecamine (176)

A possible biogenesis of anhydrovinblastine (**73**) and vinblastine (**74**) is suggested by a chemical synthesis discussed above (Section II. G). It has been observed[145] that anhydrovinblastine (**73**), in acetonitrile solution, undergoes a spontaneous sequence of oxidation-reduction reactions leading to antitumor *Catharanthus* alkaloids, leurosine (**75**), catharine (**76**), catharinine (vinamidine, **180**),[146] vinblastine (**74**), leurosidine (**177**), and the deoxy derivatives **178** and **179**. Alkaloid formation is rationalized in Scheme 32. The relative yields of the alkaloids were strikingly similar to their relative abundance in *Catharanthus* species, with the exception of naturally occurring vincristine (**74**, N_a-formyl instead of N_a-methyl group), which was not one of the in vitro products from **73**. These results raise the question as to how much the formation of these alkaloids is enzymatically controlled in vivo.



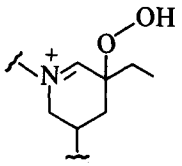
	R^1	R^2	R^3
Leurosidine (177)	H	OH	Et
178	H	Et	H
179	H	H	Et

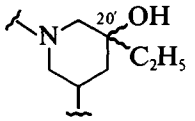
Linkages between monomeric fragments different from those discussed so far are found in alkaloids represented by pycnanthine (**181**),[147] vobtusine (**182**),[148] and villalstonine (**183**).[149] The nature of the monomeric units is clear. For **181** see



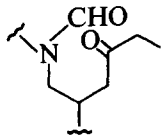
Anhydrovinblastine (73)

[o]

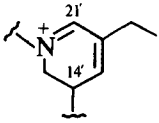


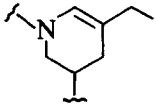


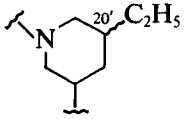
20'*S* Vinblastine (74)
20'*R* Leurosidine (177)



Vinamidine (catharinine) (180)

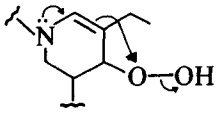


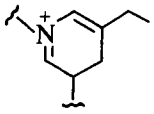


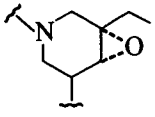


20'*R* Deoxyleurosidine (178)
20'*S* Deoxyvinblastine (179)

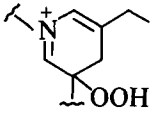
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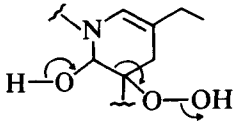


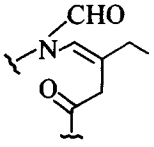




Leurosine (75)



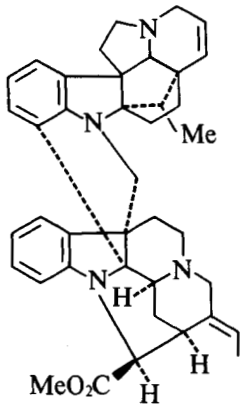




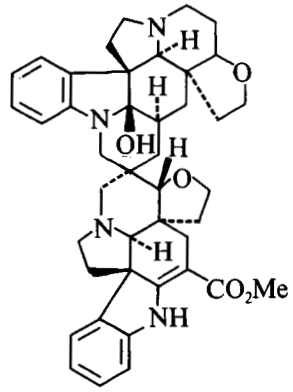
Catharine (76)

Scheme 32

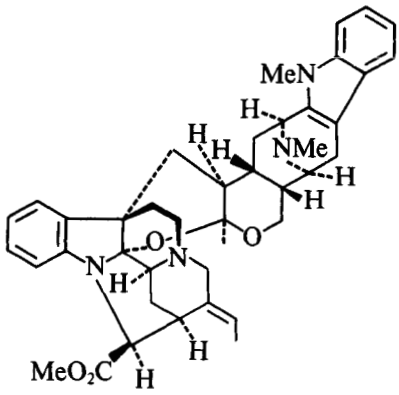
95 and **132**; for **182** see **5**. In the case of **183** one of these units is the unusual base macroline (**184**), which is possibly a fragmented akuammidine (**102**) derivative (C-21, N-4 cleavage).



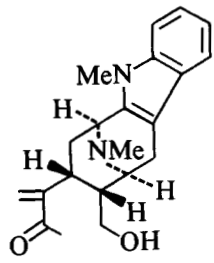
Pycnanthine (181)



Vobtusine (182)



Villalstonine (183)



Macroline (184)

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CHAPTER II

Alkaloids of *Aristotelia* Species

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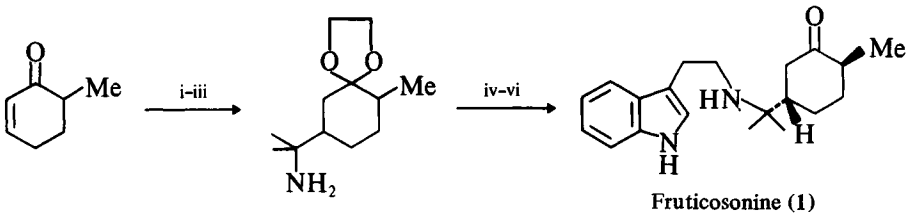
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I. ALKALOIDS DERIVED FROM TRYPTAMINE AND AN UNREARRANGED MONOTERPENE UNIT

In view of the extremely widespread occurrence of tryptamine derivatives and simple, unrearranged monoterpenes in higher plants it is surprising that few alkaloids have been encountered in which these two structural features are combined. Indeed, it was not until 1975 that the structure of the first such alkaloid, aristoteline, was established. Since that time several other alkaloids have been added to the group; all are closely related structurally, and all of them have been isolated from the *Aristotelia* genus, which belongs to the Elaeocarpaceae, a family that has previously yielded a number of alkaloids belonging to the indolizidine group.[1] The *Aristotelia* species investigated to date include *A. serrata* W. R. B. Oliver (the New Zealand wineberry),[2] *A. peduncularis* (Labill.) Hook. f.,[3] which is endemic in Tasmania, *A. fruticosa* Hook. f.,[4] from New Zealand, and the Chilean species, *A. chilensis* (Mol.) Stuntz.[5]

The simplest alkaloid of the group is fruticosonine (**1**), $C_{20}H_{28}N_2O$, mp 120–121° $[\alpha]_D^{20}$ +45.7° ($CHCl_3$), which may well represent an early stage in the biosynthesis of the more complex alkaloids of this group, since in principle it can readily be generated from tryptamine and a monoterpenoid unit, for example, geraniol. Its structure (**1**) was determined by X-ray crystallography, and confirmed by the total synthesis of racemic fruticosonine (Scheme 1);[4] this constitutes the only synthetic work recorded so far in this series.

Aristoteline (**2**), $C_{20}H_{26}N_2$, mp 164°, $[\alpha]_D^{20}$ +16° (MeOH), occurs in the roots of *A. serrata*,[2] together with several other alkaloids, in *A. chilensis*,[5] together with



Fruticosonine (1)

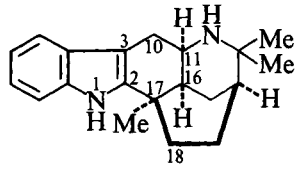
Scheme 1. Reagents: i, Me_2CHNO_2, EtONa; ii, $(CH_2OH)_2$, TsOH; iii, $NaBH_4$, Pd/C, MeOH; iv, indole β-glyoxylyl chloride; v, $LiAlH_4$; vi, $H_3\overset{+}{O}$.

aristotelone, and in *A. peduncularis*.[6a] Its structure and absolute configuration were established[2] by the X-ray crystal structure determination of aristoteline hydrobromide; supporting evidence was also provided by the mass spectral fragmentation.[5] Aristotelone, the minor alkaloid of *A. chilensis*, exhibits a uv spectrum of indoxyl type, and is almost certainly the indoxyl relative (**3**) of aristoteline. Such a structure is consistent with the mass spectral fragmentation (Scheme 2); unfortunately, paucity of material prevents unequivocal proof of structure.

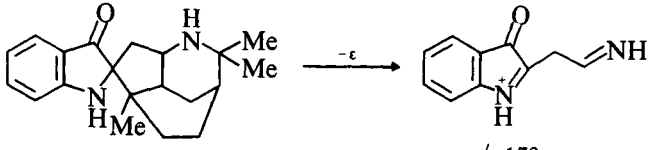
More recent extractions of *A. serrata* have resulted in the isolation of two alkaloids, named makomakine and makonine from the Maori name, *makomako*, for this plant.[6b] Makomakine, mp 99–100°, $[\alpha]_D^{19}$ +131.2° ($CHCl_3$), is isomeric with aristoteline, and proves to be a β-substituted indole derivative containing an additional, secondary nitrogen atom, two quaternary methyl groups, and an exocyclic methylene group. Since reaction with 47% hydrobromic acid converts it into aristoteline (**2**) (Scheme 3), makomakine must have the structure and absolute stereochemistry shown in **4**, and it is presumably a biogenetic precursor of aristoteline.[6b]

The cyclization of makomakine may give aristoteline directly, but it could also be envisaged as proceeding via the spirocyclic indolenine derivative **5**. Such a mechanism is consistent with the behavior of indole derivatives, and with the ultimate formation of aristoteline (**2**), since in the intermediate **5** the fully substituted carbon (C-17) would obviously migrate to position 2 in preference to the primary carbon C-10. Such a structure (**5**) is attributed to aristoserratenine, another minor alkaloid of *A. serrata*;[7] in consonance with this formulation aristoserratenine exhibits an indolenine uv spectrum and has the molecular formula $C_{20}H_{26}N_2$, by high resolution mass spectrometry. Proton and ^{13}C nmr spectra indicate the presence of an indolenine system unsubstituted at C-2, the sequence of protons in the reduced part of the molecule resembles that in aristoteline, and the mass spectra of the two alkaloids are also very similar. Since acid-catalyzed rearrangement of aristoserratenine affords aristoteline (in 47% yield), the structure and stereochemistry of aristoserratenine are as indicated in **5**; only the configuration at the spirocyclic center (C-3) remains to be established.[7]

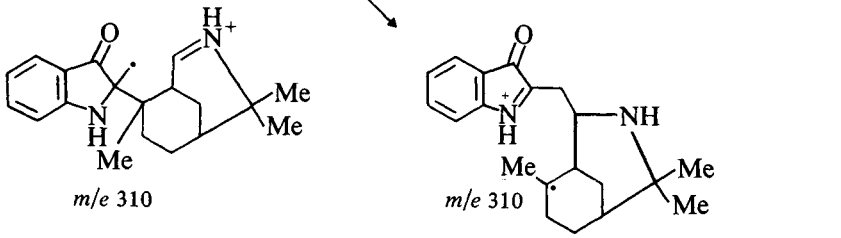
Tasmanine, $C_{20}H_{26}N_2O$, mp 250°, $[\alpha]_D^{20}$ −132° ($CHCl_3$), one of the minor alkaloids of *A. peduncularis*, proves to be the oxindole analogue (**6**) of aristoserratenine.[6a] In addition to the oxindole function the molecule contains three methyl groups attached to fully substituted carbon atoms, four methylene groups,



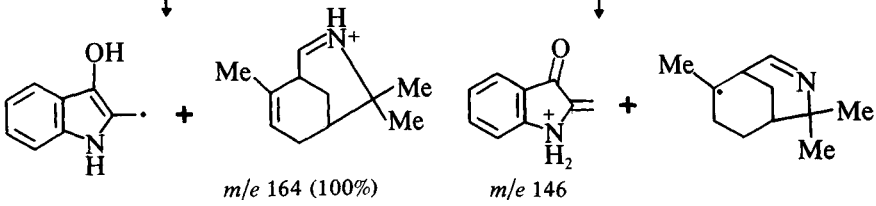
Aristoteline (2)



Aristotelone (3) *m/e* 173

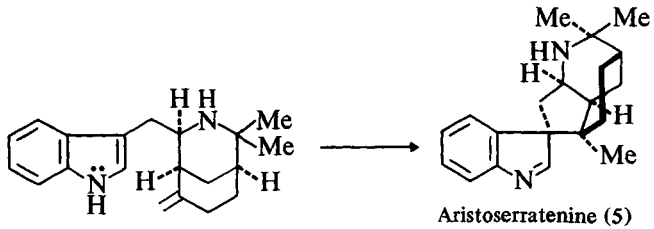


m/e 310 *m/e* 310



m/e 164 (100%) *m/e* 146

Scheme 2



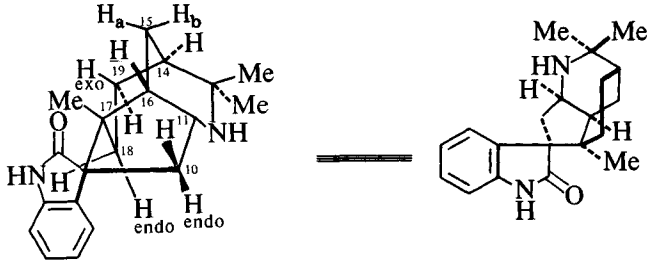
Makomakine (4) Aristoserratenine (5)

HBr H^+

Aristoteline (2)

Scheme 3

and three methine groups, but no unsaturation. The structure (**6**) was deduced from a complete analysis of the ^1H and ^{13}C nmr spectra, together with double resonance experiments. The stereochemistry depicted in **6** follows from inspection of the appropriate chemical shifts (see Table I). For example, the deshielding of the C-16 proton by the oxindole carbonyl group (cf. the chemical shift of the C-14 proton) and the substantial shielding of the C-18 exo proton (cf. the chemical shift of the C-18 endo proton) by the aromatic ring are clearly in favor of the stereochemistry of the spirocyclic center as shown in **6**. A similar set of signals in the nmr spectrum of aristoserratenine (see Table I) presumably indicates the same configuration at C-3 in this alkaloid, as depicted in **5**.*

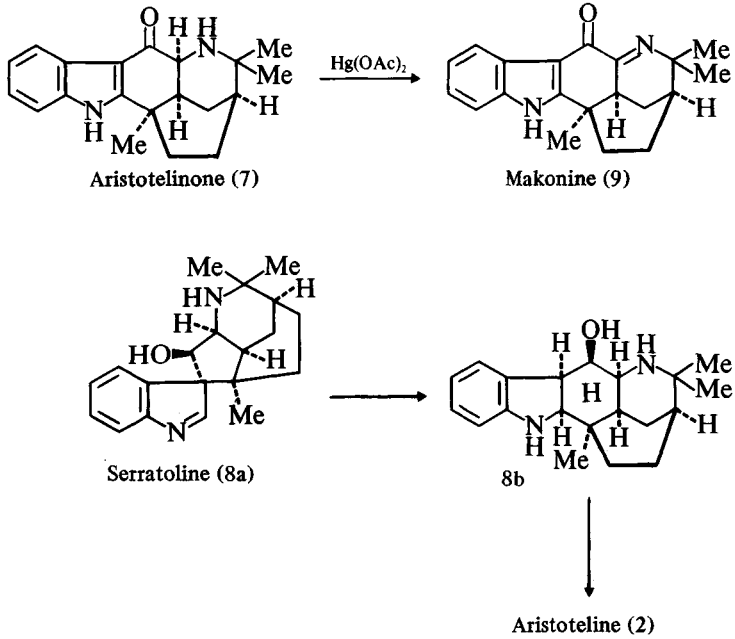


Tasmanine (**6**)

TABLE I. NMR SPECTRA OF ARISTOSERRATENINE (**5**) AND TASMANINE (**6**)

	Chemical shifts (δ values, ppm)	
Proton	Aristoserratenine (**5**)	Tasmanine (**6**)
C-10H (exo)	2.37	2.55
C-10H (endo)	1.87	1.77
C-11H	3.83	3.77
C-16H	2.02	2.56
C-15H_a	2.17	2.11
C-15H_b	1.66	1.56
C-14H	1.39	1.31
C-19H (exo)	1.61	1.53
C-19H (endo)	1.99	1.94
C-18H (exo)	1.00	0.75
C-18H (endo)	3.16	3.00

* The stereochemistry of aristoserratenine must be regarded as still *sub judice*, since further examination reveals that the small differences in the chemical shifts recorded in Table I could be due *either* to a difference in functional group (indolenine vs. oxindole) *or* to a different configuration at the spirocyclic center (C-3). A nuclear Overhauser effect on the C-2H signal following irradiation of the C-18 endo proton appears to favor the opposite configuration for aristoserratenine to that depicted in **5**, and it should also be noted that aristoserratenine is dextrorotatory ($[\alpha]_D^{25}$ + 58°), cf. tasmanine. The definitive solution to this problem must await further evidence, and in particular the chiroptical data for aristoserratenine and tasmanine.[7]



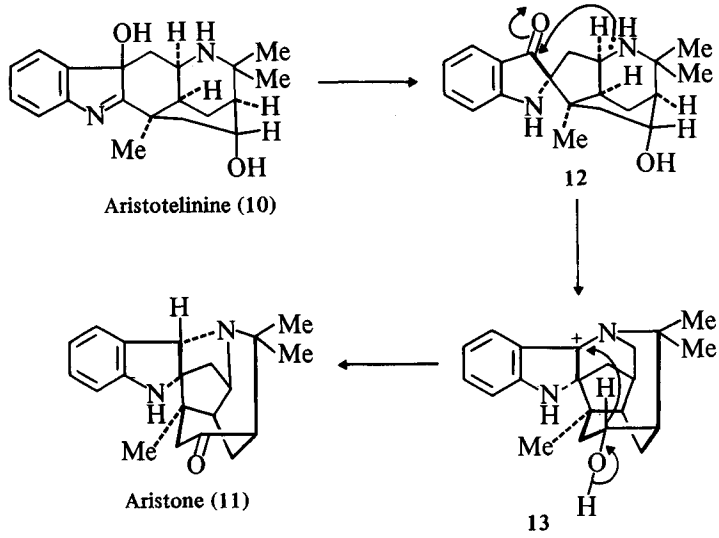
Scheme 4

Aristotelinone (7), $[\alpha]_D^{19}$ + 122.7° (MeOH:$CHCl_3$) (Scheme 4), another minor alkaloid of *A. serrata*,[8] is a 3-acylindole which can be reduced by means of lithium aluminum hydride to aristoteline, and it therefore has the structure and stereochemistry expressed in **7**. The ^1H nmr spectrum of serratoline, mp 157–160°, $[\alpha]_D$ − 68.25° ($CHCl_3$), also from *A. serrata*, shows a particular resemblance to that of one of the two hydroxy compounds obtained as by-products in the reduction of aristotelinone (**7**). However, serratoline exhibits an additional singlet at δ7.30 ppm, the broad NH signal is absent, and its uv spectrum is that of an indolenine. These data suggest that serratoline has the constitution **8a**, a conclusion that is confirmed by reduction (with $NaBH_4$) and concomitant rearrangement to an indoline derivative (**8b**), the acid-catalyzed dehydration of which is accompanied by a proton shift to give aristoteline (**2**).[8]

Makonine, $C_{20}H_{22}N_2O$, mp 310–312°, $[\alpha]_D^{19}$ + 431° (MeOH:$CHCl_3$), shares many of the characteristics of aristotelinone, but has one additional olefinic carbon atom, and the nonindolic nitrogen atom appears to be tertiary. Its structure (**9**) becomes clear from its formation by oxidation of aristotelinone (**7**) with mercuric acetate.[6b]

Two further alkaloids that occur in *A. chilensis* in extremely small amounts are aristotelinine (**10**) and aristone (**11**). The structures of both alkaloids were determined by the X-ray method; aristotelinine has the constitution of the hydroxyindolenine analogue of a hydroxyaristoteline, and in view of the minute amounts of alkaloid isolated it seems possible that it is an artifact, derived from a hydroxyaristoteline as yet undetected in the plant. Aristone (**11**) can be derived from

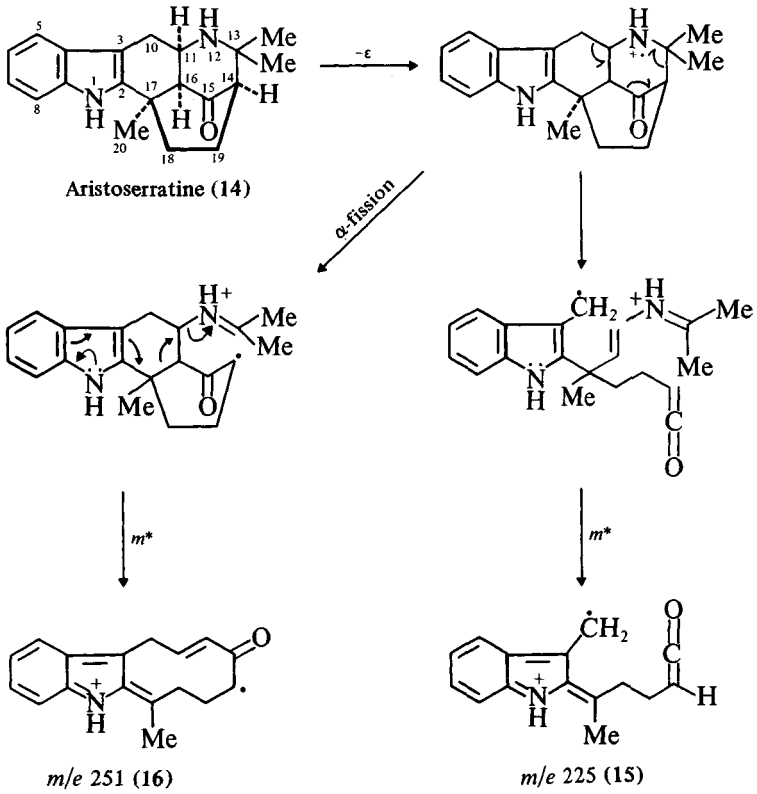
aristotelinine by rearrangement to the related indoxyl derivative (**12**), which is a hydroxyaristotelone, followed by interaction of N_b with the indoxyl carbonyl group and intramolecular hydride transfer in the carbonium ion (**13**) thus generated (Scheme 5).[9,10]



Scheme 5

Aristoserratine (**14**), mp 199°, $[\alpha]_D^{19}$ + 22.5° ($CHCl_3$) (Scheme 6), occurs in small amounts in *A. serrata* and in *A. peduncularis*.[11] Its spectroscopic properties indicate that it is in all probability an oxoaristoteline; since the carbonyl absorption is observed at ν_{max} 1710 cm^{-1} the carbonyl group is not situated at C-10, and the only possible positions (since the molecule contains three methyl groups) are positions 15, 18, and 19. That the carbonyl group is situated at C-15 was deduced by analysis of its ^1H nmr spectrum and confirmed by the ^{13}C nmr spectrum.

In the mass spectrum aristoserratine fragments to give a base peak at *m/e* 225, which appears as a less intense peak at *m/e* 227 in the sodium borohydride reduction product. The corresponding ion in the mass spectrum of aristoteline (**2**) occurs at *m/e* 211. The ready formation of the ion (**15**) at *m/e* 225 is the result of fission of an activated 13,14 bond, and is regarded as confirmation of the presence of the carbonyl group at C-15. Another important ion (**16**) which results from initial fission of the activated 13,14 bond is observed at *m/e* 251. So far it has not proved possible to reduce aristoserratine to aristoteline for final proof of structure and stereochemistry. However, aristoserratine exhibits three Cotton effects, at 302, 278, and 227 nm. Of these, the positive Cotton effect at 302 nm, which corresponds with the $n \rightarrow \pi^*$ transition of the carbonyl group, is consistent with the absolute configuration shown in **14**, according to the octant rule. The two negative Cotton effects at 278 and 227 nm are attributed to the indole chromophore. Aristoteline (**2**) exhibits only one Cotton effect, corresponding to the one at 227 nm, and



Scheme 6

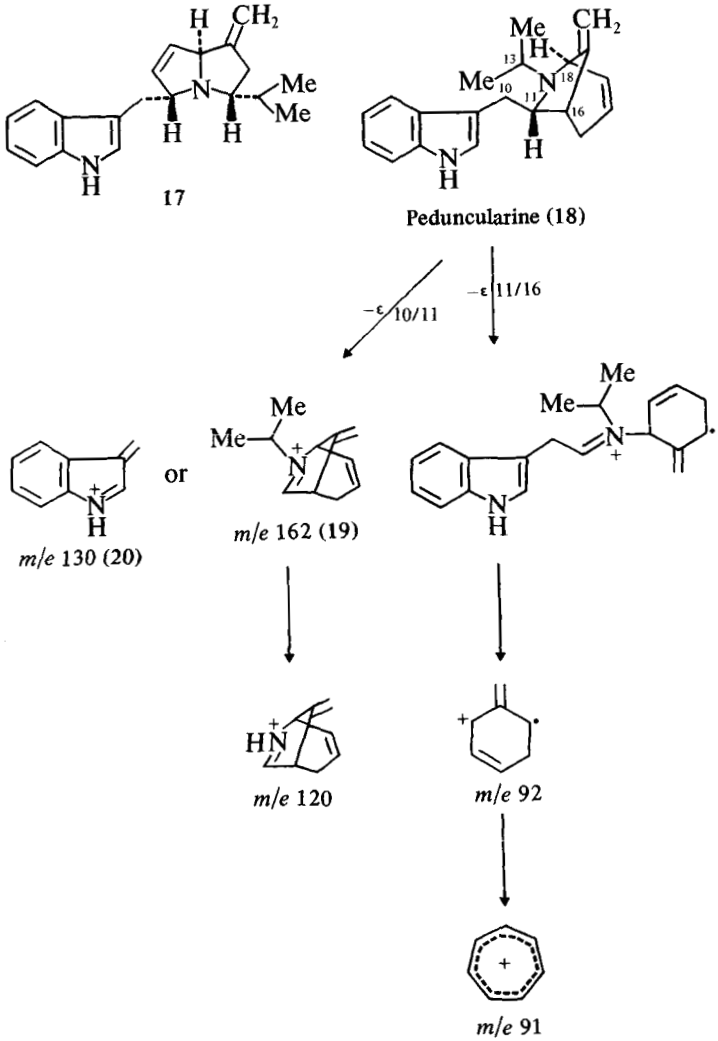
since it is also negative, the absolute configuration expressed in **14** for aristoserratine is confirmed.[11]

The first *Aristotelia* species to be investigated was *A. peduncularis*, which yielded from its roots and lower stems the alkaloid peduncularine, $C_{20}H_{24}N_2$, mp 155–157°, $[\alpha]_D^{19}$ −24° (MeOH), of an apparently new type;[3] subsequently, two further bases, sorelline, $C_{20}H_{24}N_2$, mp 165–168°, $[\alpha]_D^{22}$ +157° ($CHCl_3$), and hobartine, $C_{20}H_{26}N_2$, mp 149–150.5°, $[\alpha]_D^{22}$ −20° ($CHCl_3$), were isolated.[12]

The initial work on peduncularine revealed that it was an indole derivative attached, via a methylene group at the β position, to a $C_{11}H_{16}N$ unit, the latter containing a tertiary nitrogen atom, an isopropyl group, and at least two double bonds, since the nmr spectrum exhibited four olefinic protons which disappeared on hydrogenation. Consequently, the nonindolic fragment contains not more than two rings. Two of the olefinic protons are contained in a methylene group, and the remaining two were deduced to be present as vicinal protons in a five-membered ring. The methine proton of the isopropyl group was observed to resonate at low field, but it was erroneously maintained that peduncularine did not contain an *N*-isopropyl group, partly at least on the evidence that the $M^+ - 15$ peak was much weaker than expected for such a grouping. On this and other evidence the structure

17 was proposed, in which the β-indolylmethyl unit is attached to a pyrrolizidine ring system.[3]

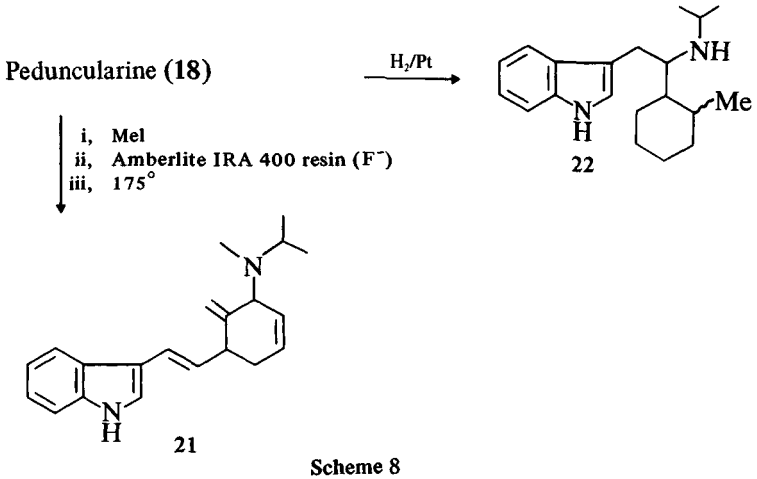
A later reexamination[13] of peduncularine showed, however, that structure **17** is untenable, and that the correct structure is **18** (Scheme 7). In accordance with **18**, the base peak (at *m/e* 162) in the mass spectrum, the only significant fragment peak at low potential, is due to the ion **19**, which arises by fission of the doubly activated 10,11 bond.* At higher potential, the familiar ion at *m/e* 130 (**20**) is also observed, but since it is not accompanied by its homologue, peduncularine does not



Scheme 7

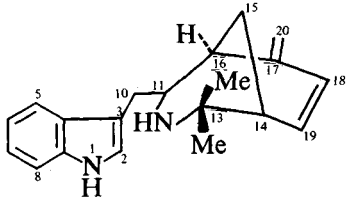
* The numbering system used here for peduncularine, sorrelline, and hobartine is based on the postulated biogenetic relationship between these alkaloids and the major *Aristotelia* alkaloids (Section II).[6a]

contain either an unsubstituted ethanamine chain or a methylene group at the indole α position. In contrast to the earlier conclusion it was now shown that the isopropyl group is attached to N_b, since the methine proton of this isopropyl group resonates at δ 3.02 ppm, consistent with its proximity to nitrogen, and it undergoes a shift in the presence of the europium shift reagent comparable with that observed for the protons at C-11 and C-18, which are similarly placed. The remaining features of the structure were deduced from a more detailed analysis of the ^1H and ^{13}C nmr spectra, and from chemical degradation. This included the Hofmann degradation, which gave the conjugated derivative (**21**) of a 3-vinylindole, and hydrogenation, which gave the base **22** by predictable hydrogenolysis of the doubly activated 12,18 bond, followed by hydrogenation (Scheme 8).[13]

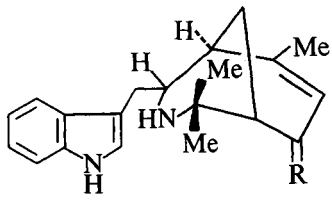


Scheme 8

The structures of sorelline (**23**) and hobartine (**24**) were elucidated following a detailed analysis of their ^1H and ^{13}C nmr spectra, and their mass spectra.[12] Both structures show a very close resemblance to those of the majority of *Aristotelia* alkaloids, and both contain an unrearranged monoterpene unit, hobartine (**24**) simply being the 19,20-dihydro derivative of sorelline (**23**). Hobartine is isomeric with aristoteline (**2**) and makomakine (**4**), and in fact is $\Delta^{17,18}$-2,17-secoaristoteline.



Sorelline (23)

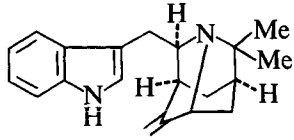


Hobartine (24): R = H_2
Serratenone (25): R = O

Serratenone, $C_{20}H_{24}N_2O$, $[\alpha]_D^{19}$ −45.3° ($CHCl_3$), is a closely related base which occurs to the extent of 0.003% of the dry weight of *A. serrata*.[7] The molecule con-

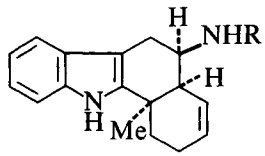
tains an indole nucleus (uv spectrum) containing a free position 2 (nmr spectrum and positive Ehrlich test), and a conjugated ketone system (ν_{max} 1650 cm^{-1}), in which the vinylic α proton is allylically coupled to a methyl group and a further methine proton. This enone system is insulated from the indole nucleus, since the uv spectrum of serratenone is identical with the summation spectrum of tryptamine and mesityl oxide. A detailed examination of the nmr and mass spectra revealed the complete structure of serratenone to be **25**, that is, an allylic oxidation product of hobartine.[7]

Aristofruticosine, $C_{20}H_{24}N_2$, a minor base of *A. fruticosa*, is an isomer of peduncularine, and also contains an indole nucleus with a free 2-position (nmr spectrum and Ehrlich test). Since the nonindole component of the aristofruticosine molecule has only one unit of unsaturation it must be tricyclic, and connected to the indole nucleus via a methylene group at position 3, since the mass spectrum exhibits a strong peak at *m/e* 130 (**20**), accompanied by the complementary ion at *m/e* 162. The sequence of the protons in the nonindole component was established by a series of double resonance experiments and confirmed by the ^{13}C nmr spectrum. The structure (**26**) thus deduced for aristofruticosine resembles that of peduncularine, except that the 13,14 bond has remained intact.[7]



Aristofruticosine (26)

Aristomakinine, $C_{17}H_{20}N_2$, $[\alpha]_D^{19}$ −72° ($CHCl_3$), occurs to the extent of only 0.0004% of the dry weight of *A. serrata*. Its uv spectrum is typically indolic, and since there are no protons at positions 2 or 3 of the indole nucleus (nmr spectrum, negative Ehrlich test), it must be a disubstituted indole. Aristomakinine contains three replaceable hydrogen atoms, accounted for by the indole NH and a primary amino group. Two olefinic protons are present, but in contrast to all the other *Aristotelia* alkaloids there are no signals owing to a geminal dimethyl group; since aristomakinine has three carbon atoms less than the typical *Aristotelia* alkaloids it would appear that carbon atoms 13, 21, and 22 are missing. Hence a possible structure for aristomakinine is **27**; this was proved by condensation with acetone followed by reduction with sodium borohydride, which gave *N*-isopropylaristomakinine, identical with aristomakine, another minor alkaloid of *A. serrata*, for which the structure and stereochemistry (**28**) had been independently deduced.[7]



Aristomakinine (27): R = H
Aristomakine (28): R = $CHMe_2$

II. BIOGENETIC RELATIONSHIPS AMONG THE *ARISTOTELIA* ALKALOIDS

The *Aristotelia* alkaloids form a closely knit group whose biogenesis can be conceived as arising from the condensation of tryptamine with a regular monoterpenoid unit such as geraniol or (better) nerol (**29**), or a close relative.[14] Initial condensation could give rise to an intermediate **30** which could be transformed into fruticosonine (**1**), makomakine (**4**), aristoteline (**2**), aristoserratenine (**5**), tasmanine (**6**), aristotelinone (**7**), makonine (**9**), aristotelone (**3**), and serratoline (**8a**), by obvious oxidation, cyclization, and rearrangement stages (Scheme 9). Fission of the 13,14 bond in aristoteline (**2**) with concomitant introduction of the 14,19 double bond affords aristomakine (**28**), which on dealkylation gives rise to aristomakinine (**27**).

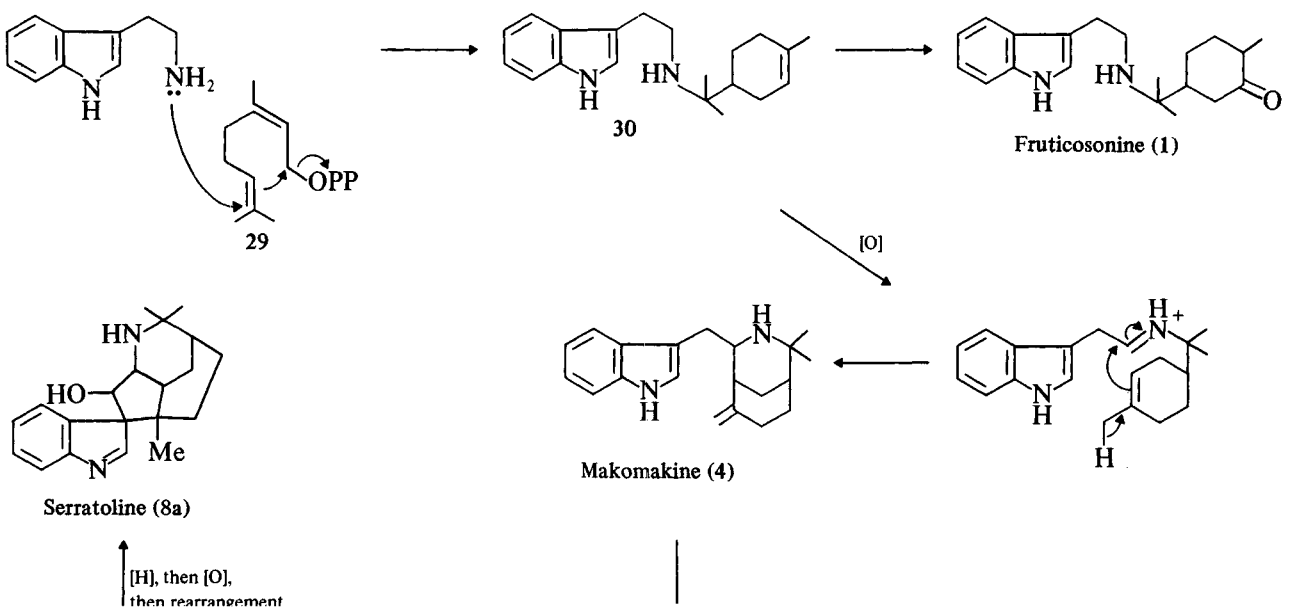
An oxidative rearrangement sequence on a hydroxyaristoteline (OH at C* in **2**), similar to that shown in **2** → **31** → **3**, would give rise to an indoxyl (**12**), via aristotelinine (**10**), from which aristone (**11**) can be generated, as outlined in Scheme 5.

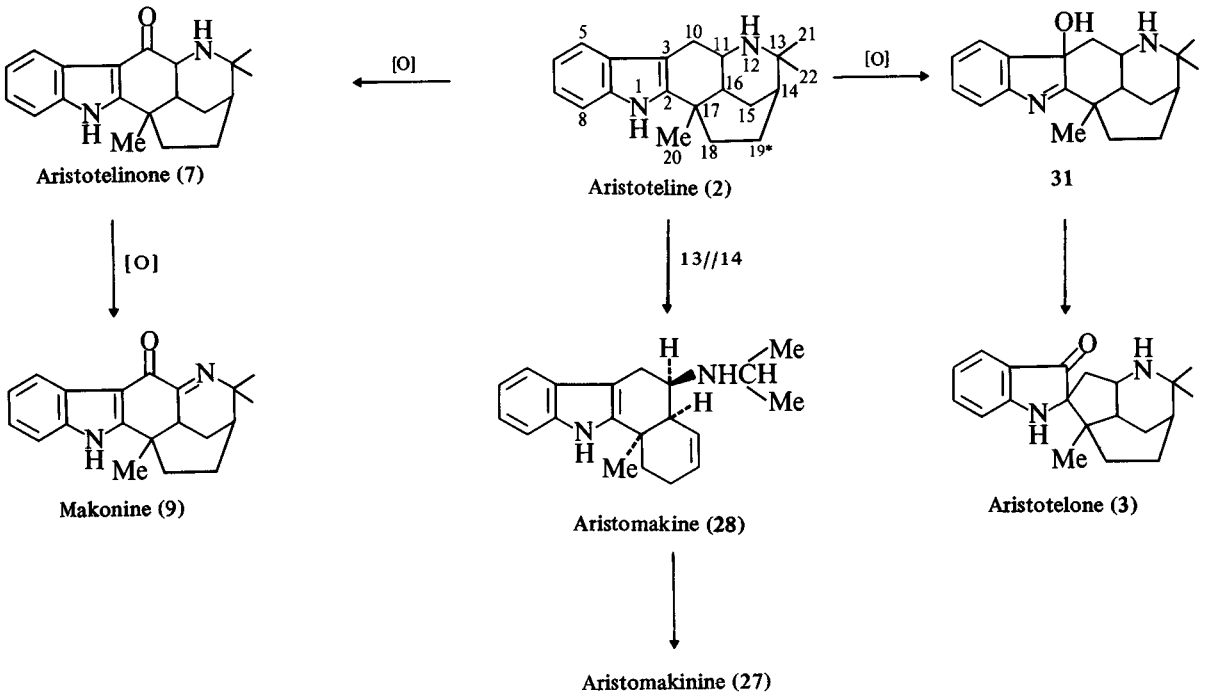
Isomerization of makomakine (**4**) gives hobartine (**24**), whereas oxidation gives sorelline (**23**), and formation of a bond between N_b and C-18 in sorelline can give rise to the skeleton of aristofruticosine (**26**). Oxidation of one of the geminal methyl groups in sorelline affords an intermediate, the fragmentation of which gives the skeleton of peduncularine (**18**).[14] A more acceptable pathway to peduncularine, however, consists in the biosynthesis of **32** from 10-hydroxynerol (**33**), a known precursor[15] of secologanin-derived indole alkaloids in *Catharanthus roseus*, by a route analogous to that postulated for sorelline. The isopropyl group on N_b in peduncularine is thus predicted to arise from the isopropylidene group of geraniol or nerol, via the appropriate 10-hydroxy derivative (Scheme 10).

III. ALKALOIDS OF *BORRERIA* SPECIES*

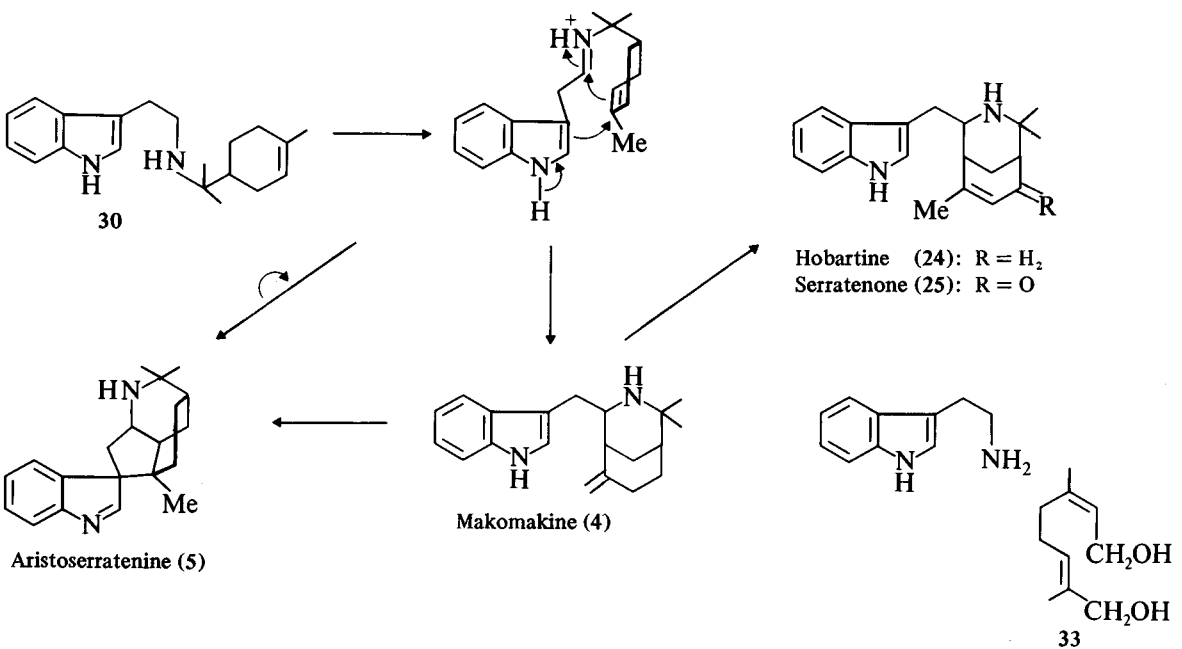
Two further alkaloids may appropriately be mentioned at this point. These are borreline (**34**), $C_{17}H_{18}N_2O$, mp 215–216°, $[\alpha]_D$ −235° (MeOH), isolated from a Guyanese *Borreria* species,[16] later identified as *B. capitata* R. et P.,[17] and borrecapine (**35**), $C_{20}H_{24}N_2O$, mp 203–205°, $[\alpha]_D$ −75° (MeOH).[17] The structure (**34**) of borreline was deduced from its spectroscopic properties and confirmed by X-ray crystal structure analysis.[16] The biogenetic origin of this molecule is not immediately apparent, but it became clear that the nontryptamine component is a degraded monoterpene unit when the structure (**35**) of borrecapine was deduced.[17] Borrecapine is clearly derived from tryptamine and an unrearranged monoterpene unit, combined in a different sense from that observed in the *Aristotelia* alkaloids.

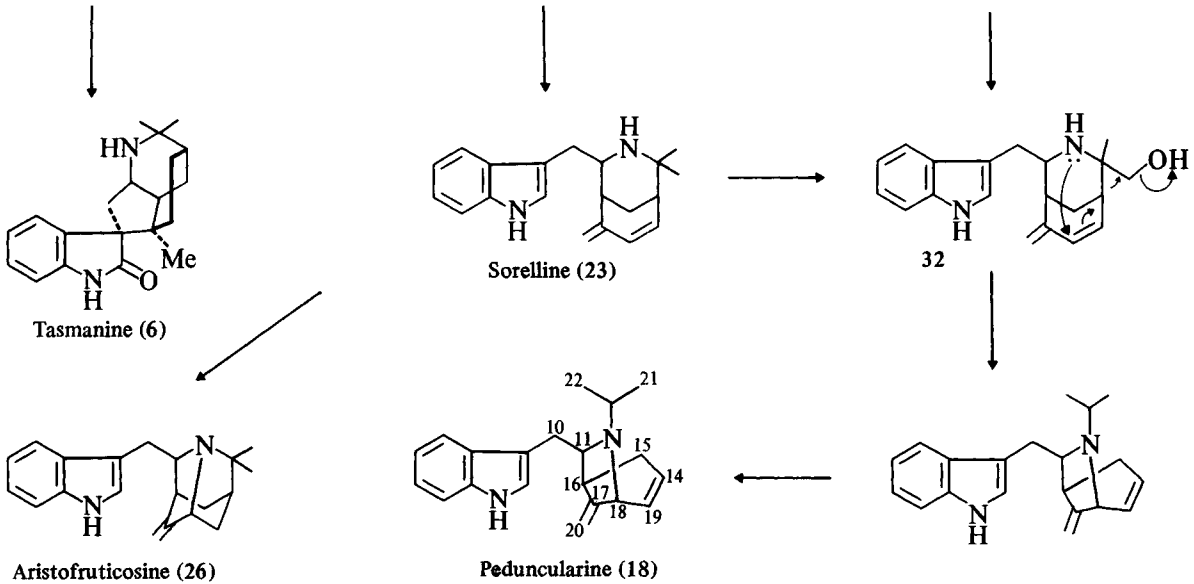
* For bisindole alkaloids of *Borreria* species, see Chapter XI.


NH2
OPP
29
30
HN
Fruticosonine (1)
O
[O]
Makomakine (4)
Serratoline (8a)
HO
Me
[H], then [O],
then rearrangement

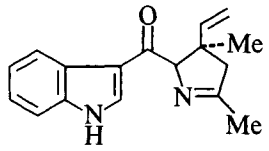

[O]
[O]
[O]
13//14
Aristotelinone (7)
Aristoteline (2)
31
Makonine (9)
Aristomakine (28)
Aristotelone (3)
Aristomakinine (27)

Scheme 9

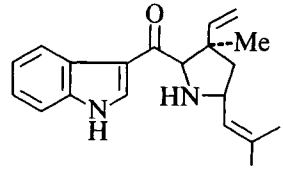

30
Hobartine (24): R = H2
Serratenone (25): R = O
Makomakine (4)
Aristoserratenine (5)
33


HN
Me
N
H
O
Tasmanine (6)
H
N
N
H
Sorelline (23)
H
N
N
H
OH
32
N
N
H
Aristofruticosine (26)
22
21
10
11
N
15
16
17
14
18
19
20
N
H
Peduncularine (18)
N
N
H

Scheme 10



Borreline (34)



Borrecapine (35)

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CHAPTER III

The Corynantheine-Heteroyohimbine Group

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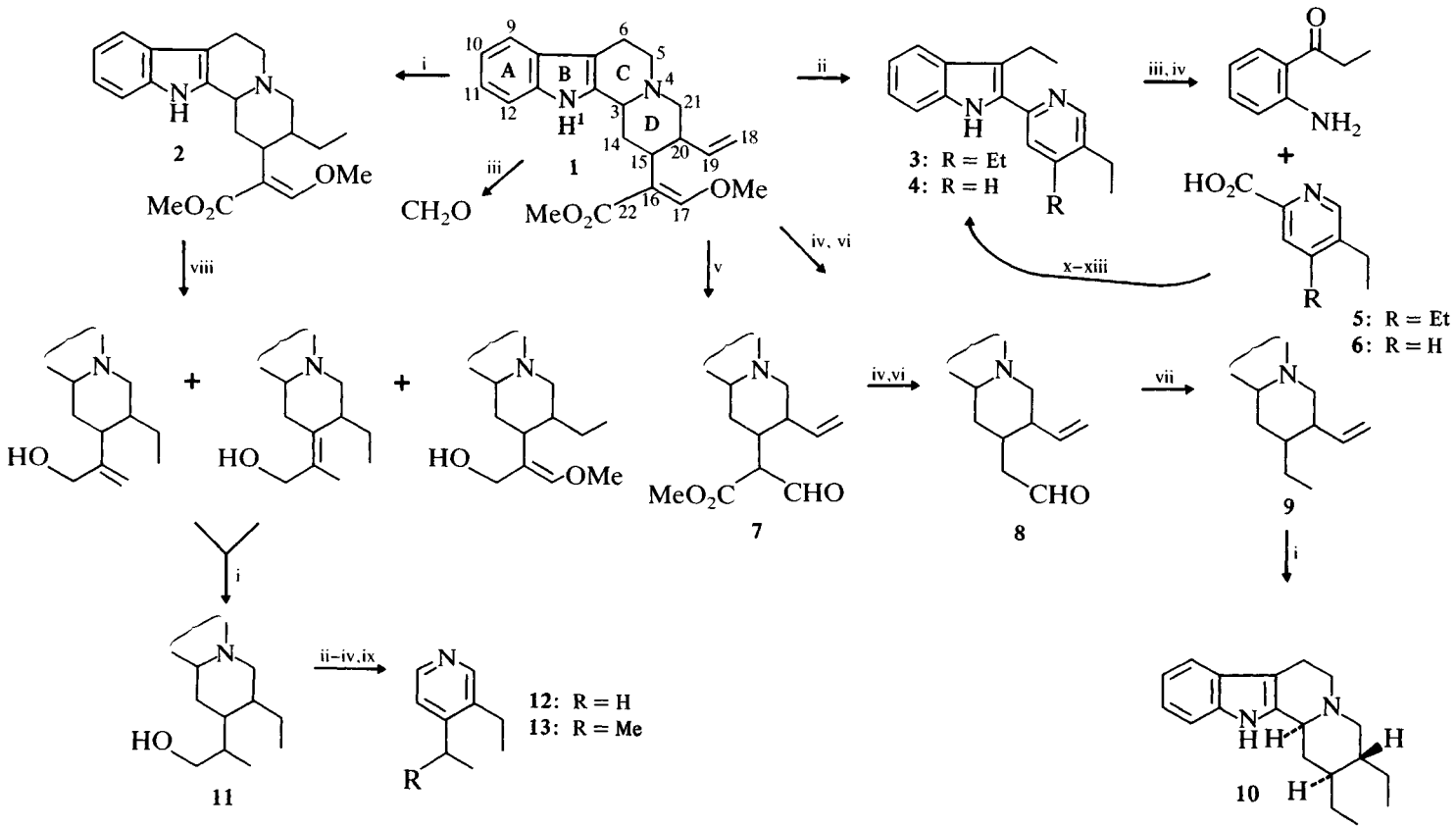
I. INTRODUCTION

As a consequence of biosynthetic studies, the common derivation from secologanin and tryptophan or tryptamine of the several glycosidic indole alkaloids, their aglycones, and related indolopyridines discovered in the past few years is now transparently obvious. Again, the large number of well-known secoyohimbine and heteroyohimbine alkaloids represented by corynantheine (**16**) and ajmalicine (**54**) are among the less convoluted derivatives of secologanin. Inasmuch as they all contain a similar unrearranged secologanin unit, and in many cases have actually been intercorrelated by chemical transformations, it is convenient to discuss these apparently disparate alkaloids together. Their structural elucidations, interconversions, and syntheses constitute a large body of fascinating chemistry of which we can examine only a relatively small proportion in detail. The main criteria for selection have involved the need to demonstrate overall structural relationships between alkaloids, the increasing range of chemical and spectroscopic methods developed over the years for structure elucidation, and the synthetic challenge presented by the structures. In general the discussion of topics follows their historical sequence, but with occasional benefit of hindsight.

II. CORYNANTHEINE AND CONGENERS

A. Corynantheine (16) and Dihydrocorynantheine (17)

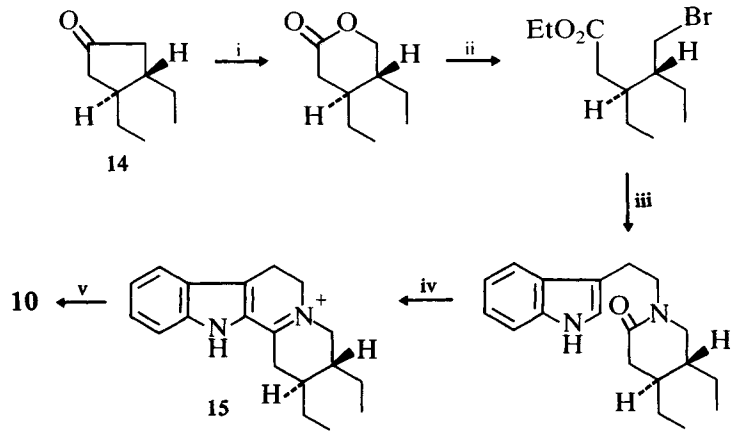
Corynantheine, $C_{22}H_{26}N_2O_3$, was originally isolated from samples of commercial yohimbehe bark, but the first definite plant source identified was *Pseudocinchona africana* A. Chev.[1,2] Discordant results in early work were eventually found to be due to the co-occurrence of varying amounts of the dihydro derivative.[3] The structure was elucidated largely by the degradations and transformations outlined in Scheme 1.[4–7] Corynantheine is a monoacidic base, has a uv spectrum differing somewhat from that of a simple indole, and possesses two methoxyls, one being in a carbomethoxy group. The basic skeleton was revealed by selenium dehydrogenation to alstyrine (corynanthyrine) (**3**), whose structure was established by ozonization and subsequent hydrolysis to *o*-aminoacetophenone and 4,5-diethylpyridine-2-carboxylic acid (**5**), and by synthesis from **5**.[4,5] Some desethylalstyrine (**4**) was also obtained as a by-product. The presence of the β-methoxyacrylate system was established by hydrolysis and decarboxylation to an aldehyde, corynantheal (**8**), and thus accounted for the additional chromophore causing an inflection in the



Scheme 1. Reagents: i, H_2, cat.; ii, Se, Δ; iii, O_3; iv, aq. OH^-; v, HCl, Me_2CO; vi, H_3O^+; vii, N_2H_4, Δ; viii, $LiAlH_4$; ix, Δ; x, conversion into the corresponding nitrile; xi, PrMgBr; xii, $PhNHNH_2$; xiii, H^+, Δ.

indolic uv absorption at about 250 nm.[4,6] Wolff-Kishner reduction of the aldehyde afforded corynantheane (**9**), which now contained a *C*-methyl group (Kuhn-Roth) whereas corynantheal possesses none. Catalytic hydrogenation of corynantheine and its derivatives to dihydro analogues indicated one reducible double bond, which the production of formaldehyde on ozonization showed to be a terminal vinyl group. Accordingly, corynantheine must be tetracyclic rather than pentacyclic like the yohimbines (see Chapter IV), and the gross structure **1** was suggested as being more compatible with production of desethylalstyrine by loss of the ester side chain than the alternative arrangement. Confirmation was obtained by the isolation of a small amount of 3-ethyl-4-isopropylpyridine (**13**) in addition to 3,4-diethylpyridine (**12**) on degradation of dihydrocorynantheine via **11**. Formation of **13** proved conclusively that in corynantheine the vinyl group must be attached to C-20, and the β-methoxyacrylate group – which was the only possible precursor of the isopropyl unit in **13** – must be at C-15.[7]

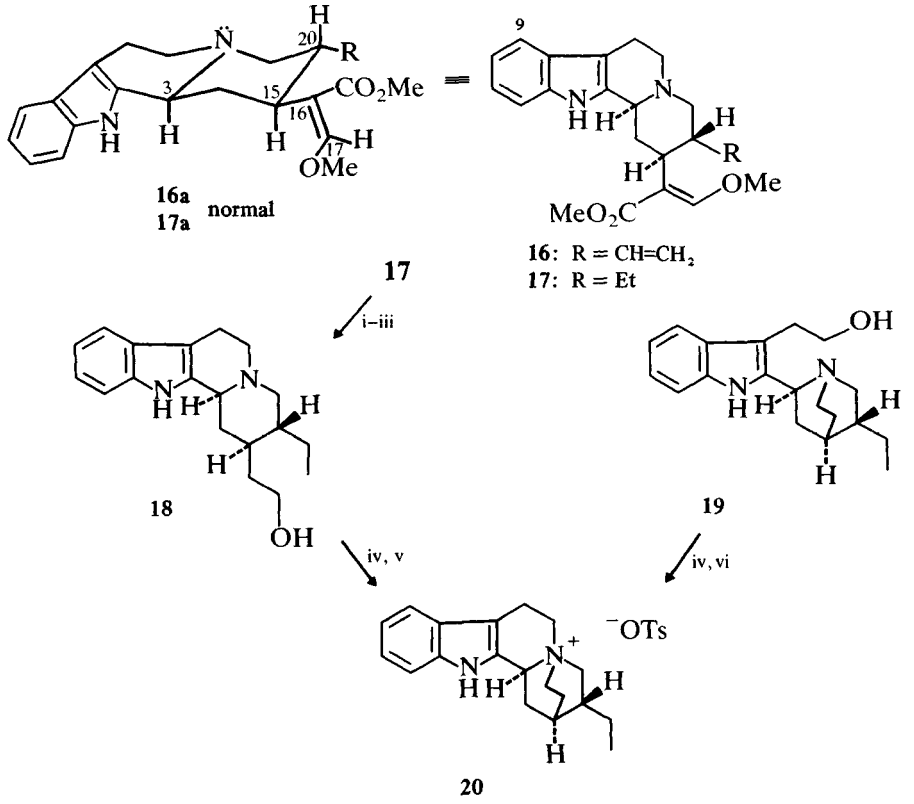
The relative stereochemistry of corynantheine was elucidated by a stereospecific synthesis of (±)-dihydrocorynantheane (**10**) from trans-3,4-diethylcyclopentanone (**14**) outlined in Scheme 2.[8] By analogy with the yohimbane series (see Chapter IV) catalytic reduction of the 3-dehydro intermediate (**15**) should give the more stable product in which H-3 is cis to H-15 and hence trans to H-20. Since no inversion of C-3 was anticipated in the production of dihydrocorynantheane from corynantheine, the latter must have the same stereochemistry. This conclusion was supported by the observation in the ir spectrum of corynantheine of trans-quinolizidine bands in the 2700–2800 cm^{-1} region in accord with a trans C/D ring junction and an axial, α* H-3. The corresponding favored conformation for corynantheine would then be **16a** with ring D in a chair with all substituents equatorial. That **16** also represents the absolute stereochemistry of corynantheine was established by two independent correlations with *Cinchona* alkaloids of known absolute configuration. In the first,



Scheme 2. Reagents: i, $PhCO_3H$; ii, HBr, EtOH; iii, tryptamine; iv, $POCl_3$; v, H_2, Pt.

* The designations α (down) and β (up) have the same meanings as in the steroid convention.

the tosylate of dihydrocorynantheol (**18**), obtained by obvious reactions from dihydrocorynantheine (**17**), was converted to the same quaternary salt **20** as that afforded by tosylation of cinchonamine (**19**) (Scheme 3).[10] In the second, cinchonine was transformed in a multistep sequence into dihydrocorynantheane (**10**).[11]



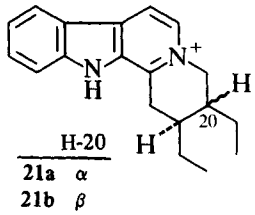
Scheme 3. Reagents: i, OH^-, ii, H_3O^+; iii, $NaBH_4$; iv, TsCl; v, DMF, Δ; vi, AgOTs.

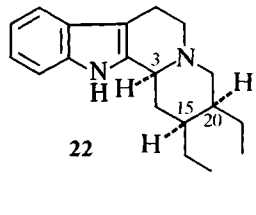
One stereochemical feature remaining to be determined was the geometric arrangement about the 16,17 double bond. Eventually, from a comparison of the chemical shift of H-17 in corynantheine with that in heteroyohimbines, and from an X-ray structure of a related alkaloid, mitragynine (see Section II. C), it was concluded that the ester and methoxyl groups were trans to each other.[12,15] Indeed this *E* configuration appears to be constant in all alkaloids related to corynantheine, since H-17 invariably appears at δ 7.4 ± 0.1.

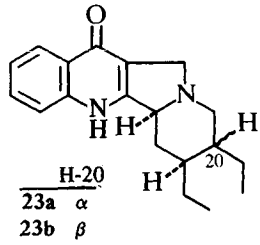
B. Corynantheidine (24)

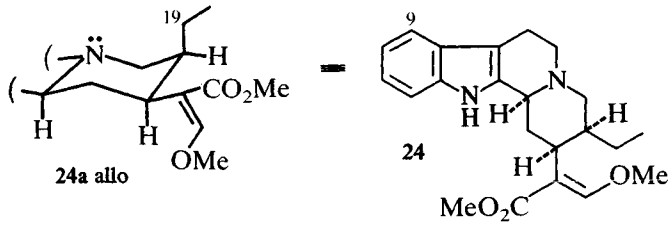
Corynantheidine, $C_{22}H_{28}N_2O_3$, also isolated from *P. africana*, was readily recognized as a stereoisomer of dihydrocorynantheine from the similarity of its uv

and ir spectra and chemical reactions: degradation with selenium to alstyrine, hydrolysis and decarboxylation to an aldehyde, corynantheidal ($C_{19}H_{24}N_2O$), and Wolff-Kishner reduction of the aldehyde to corynantheidane ($C_{19}H_{26}N_2$).[13] Since the ring C dehydrogenation products (**21a, b**) of corynantheidane and dihydrocorynantheane were not identical, they must be epimeric at C-20, given the invariability of the H-15 α configuration for all known indole alkaloids. On the basis of parallel molecular rotation changes of the same sign and order of magnitude on dehydrogenation to **21** or on oxidation to the quinolones **23a, b**, the chirality at C-3 was determined to be the same in both corynantheidane and dihydrocorynantheane. Later, this deduction was confirmed and extended to an absolute 3α(*S*) configuration from the positive Cotton effect in the 270–300 nm region of the ord and cd spectra.[14,15] Hence corynantheidane could be formulated as **22**, and corynantheidine as **24**.





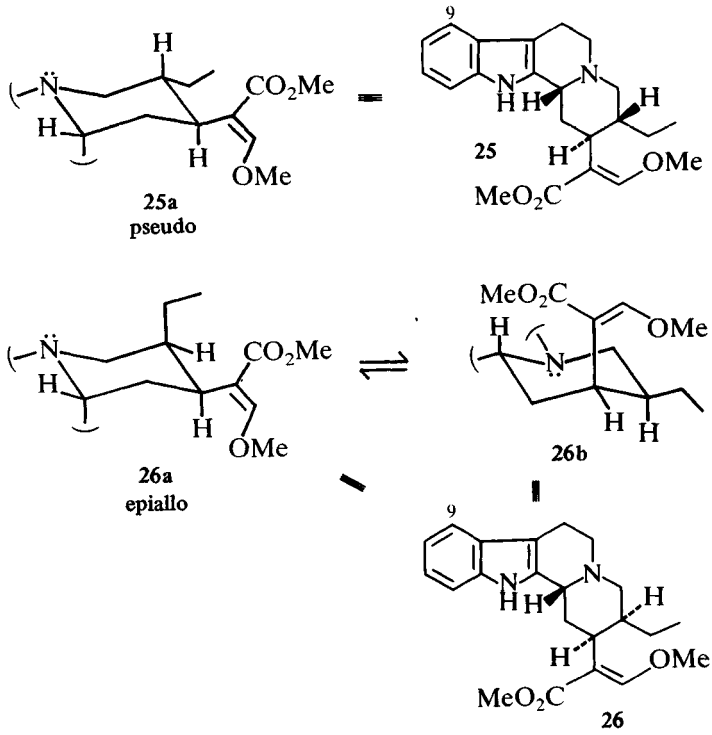




C. Other Corynantheine Analogues

If an identical absolute α(*S*) configuration at C-15 is assumed, there are four stereochemical series for corynantheine-type alkaloids, namely, normal (3α, 20β), pseudo (3β, 20β), allo (3α, 20α), and epiallo (3β, 20α), the preferred conformations being **17a, 25a, 24a**, and **26a/b**, respectively.[16] A 9-methoxycorynantheidine structure had been suggested for mitragynine from *Mitragyna speciosa* Korth on the

basis of chemical degradations and comparisons of ir, nmr, and mass spectra with those of dihydrocorynantheine and corynantheidine.[17] This allocation to the allo series was confirmed by an X-ray structure determination on the hydriodide salt.[12] However, three other stereoisomers of mitragynine were also known – speciogynine, speciociliatine, and mitraciliatine – one of which must belong to each of the three remaining stereochemical series, since all had the same 16,17 *E* configuration.[15] In order to make valid stereochemical assignments for these alkaloids various criteria based on spectral data were utilized. In addition to displaying the well-known trans-quinolizidine (Bohlmann) bands in the 2700–2800 cm^{-1} region,[9] an H-3 which is axial and trans to the lone pair on N-4 occurs below δ 3.8 in the nmr spectrum, whereas an equatorial (to ring D) H-3 in a cis-quinolizidine is observed downfield in the δ 4.1–4.5 region.[18] Furthermore, the summed couplings should result in a much larger bandwidth (~ 14 Hz) for an axial than for an equatorial (~ 8 Hz) H-3.



A further nmr criterion was the symmetry and degree of resolution of the C-18 methyl triplet, which in 100 MHz spectra was noticeably better for corynantheidine compared with dihydrocorynantheine. This phenomenon was attributed to a deshielding of the axial C-19 methylene group by the nitrogen lone pair in the former (**24a**), which did not occur with the equatorial ethyl group in the latter, and thus could be used to differentiate between C-20 conformations and hence configurations.[16]

Finally, the absolute configuration at C-3 in indole alkaloids could be established from the sign of the Cotton effect in the 270–300 nm region of ord and cd spectra.[14,15] The normal and allo series with an $\alpha(S)$ H-3 exhibited a positive Cotton effect, whereas the pseudo and epiallo with β(R) H-3 showed a negative Cotton effect.

Application of these criteria determined the stereochemistry of speciogynine (**17**, 9-OMe), mitraciliatine (**25**, 9-OMe), and speciociliatine (**26**, 9-OMe) as summarized in Table I.[15] These deductions were corroborated by chemical evidence, based on the observation that alkaloids in which the lone pair on the basic nitrogen had a trans-diaxial relationship to H-3 were oxidized to the 3-dehydro derivatives much faster than those with a cis axial-equatorial arrangement.[19a] Again these techniques helped to elucidate the structures of hirsutine (**25**), paynantheine (**16**, 9-OMe), gambirine (**17**, 9-OH), and other related alkaloids,[19] and some were employed in the wider context of *Corynanthe* alkaloids in general. Hirsuteine (the 3β epimer of corynantheine) and 3-isocorynantheidine (**26**) have recently been isolated.[145]

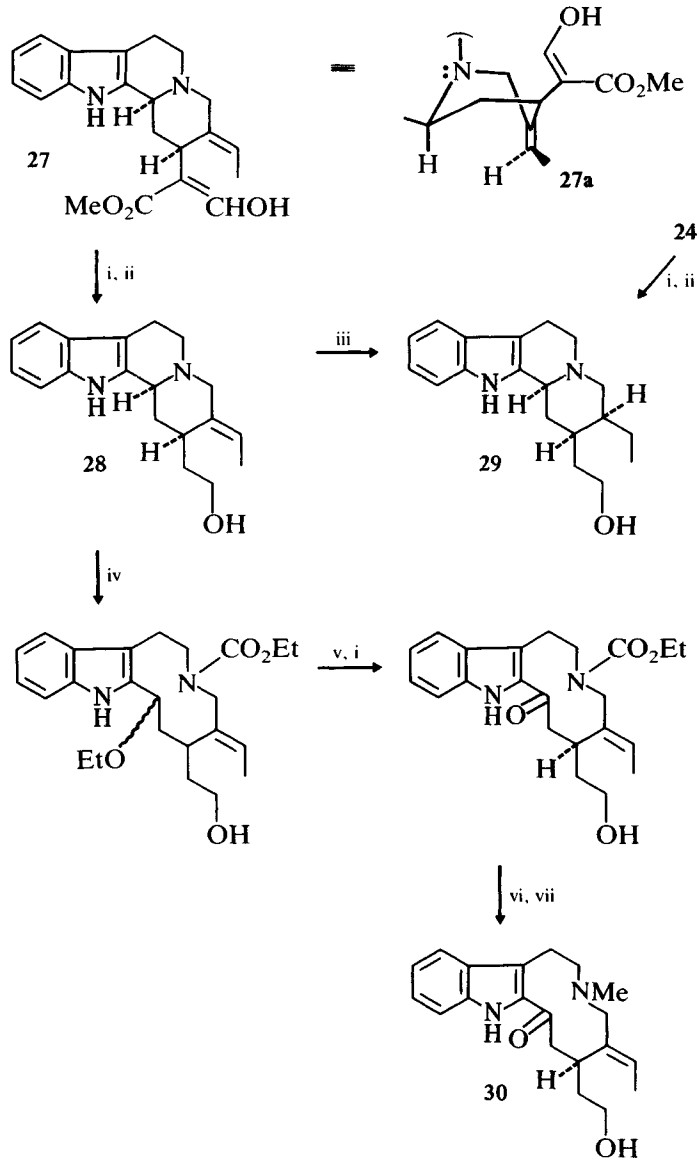
TABLE I. STEREOCHEMICAL ASSIGNMENTS FROM SPECTRAL DATA

Series	Trans-Quinolizidine ir bands	Cotton effect	Chemical shift (δ)		Symmetry of Me-18	Name (Structure)
			H-3	H-17		
Normal	Present	+ ve	3.8	7.40	Unsym.	Dihydrocorynantheine (17)
				7.37		Speciogynine (17, 9-OMe)
Pseudo	Absent	− ve	4.45	7.35	Unsym.	Hirsutine (25)
				7.33		Mitraciliatine (25, 9-OMe)
Allo	Present	+ ve	3.8	7.47	Sym.	Corynantheidine (24)
				7.45		Mitragynine (24, 9-OMe)
Epiallo	Absent	− ve	4.1	7.43	Sym.	Speciociliatine (26, 9-OMe)

D. Geissoschizine (27) and Related Alkaloids

Geissoschizine, $C_{21}H_{24}N_2O_3$, was originally obtained by cleavage of geissospermine (Chapter XI) with hydrochloric acid, but has since been isolated as such and as its *O*-methyl ether from various plants.[20,23b] It was found to contain one *O*-methyl and one *C*-methyl, ozonolysis demonstrating that the latter was in an ethylidene group. The ir spectrum showed the presence of NH, OH, and C=O functions, and the uv absorption was that of an indole together with another (base-sensitive) chromophore. On heating with dilute acid geissoschizine was hydrolyzed and decarboxylated to an aldehyde, which was reduced by sodium borohydride to an alcohol, geissoschizol, $C_{19}H_{24}N_2O$. This sequence suggested a β-aldehydo methyl ester which, as its β-hydroxyacrylate tautomer, would also account for the additional uv chromophore. Catalytic hydrogenation of geissoschizol (**28**) afforded the known corynantheidol (**29**) obtained from corynantheidine, and thus established the

structure and stereochemistry **27** for geissoschizine, apart from the geometry about the double bond (Scheme 4).[21] The ethylidene group was eventually found to have the *E* configuration common to virtually all alkaloids of this type, the resulting non-bonded interactions between the C-15 and C-20 substituents forcing geissoschizine to adopt a flexible ring D boat conformation (**27a**) with a cis C/D ring junction.[22] Interestingly, a trans C/D conformation is preferred in the crystalline state.



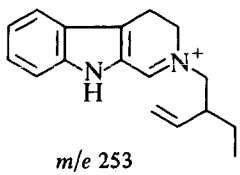
Scheme 4. Reagents: i, H_3O^+; ii, $NaBH_4$; iii, H_2, cat.; iv, $ClCO_2Et$, EtOH, Na_2CO_3; v, Bu^tOCl; vi, $LiAlH_4$; vii, MnO_2.

Sakai and co-workers[23a,b] have converted geissoschizol (**28**) via a novel C-3, N-4 cleavage reaction with ethyl chloroformate into the related 2-acylindole alkaloid burnamicine (**30**) from *Hunteria eburnea* Pichon, and hence confirmed its structure[23c] (Scheme 4).

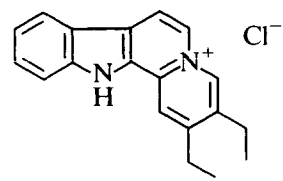
E. Sitsirikine (33), Dihydrositsirikine (34), and Isositsirikine (36)

Sitsirikine and its dihydro derivative were isolated from *Vinca rosea* L. (*Catharanthus roseus* G. Don) as a mixture separable only with difficulty, although catalytic hydrogenation readily afforded pure dihydrositsirikine, $C_{21}H_{28}N_2O_3$,[24a] which was also found in *Pausinystalia yohimbe* Pierre.[24b] Its uv spectrum was indolic and the ir spectrum showed bands for C=O, NH, and OH groups. The base was shown to contain an ethyl group by production of propionic acid in a modified Kuhn-Roth oxidation, and one methoxyl group by the Zeisel method. In addition to confirming the presence of these groups, the nmr spectrum of dihydrositsirikine displayed a two-proton multiplet at δ 3.9, which shifted to δ 4.4 in the monoacetate derivative, thus indicating a primary alcohol. The likely presence of a methyl ester was confirmed by reduction with lithium aluminum hydride to a diol, $C_{20}H_{28}N_2O_2$, in which the two primary hydroxyls were shown to have a 1,3 relationship by condensation with acetone to give an acetonide derivative. Consequently, dihydrositsirikine must contain a β-hydroxy ester unit.

In an early application of mass spectrometry to structure determination, the fragmentation pattern of dihydrositsirikine revealed the essential framework of the molecule by comparison with that of the known yohimbine alkaloids (see Chapter IV). A molecular ion at *m/e* 356 confirmed the formula, and ions characteristic of a tetrahydro-β-carboline were apparent at *m/e* 355 (M-1), 184, 170, 169, and 156. However, a striking difference from yohimbine was in the occurrence of a strong peak at *m/e* 253 (M-103) attributable to ion **31** formed by ready loss of the β-hydroxyester group. Confirmation of the tetracyclic skeleton and the location of substituent groups was obtained by dehydrogenation with palladium and DDQ to flavocoryline hydrochloride (**32**). On the basis of the above evidence, the gross



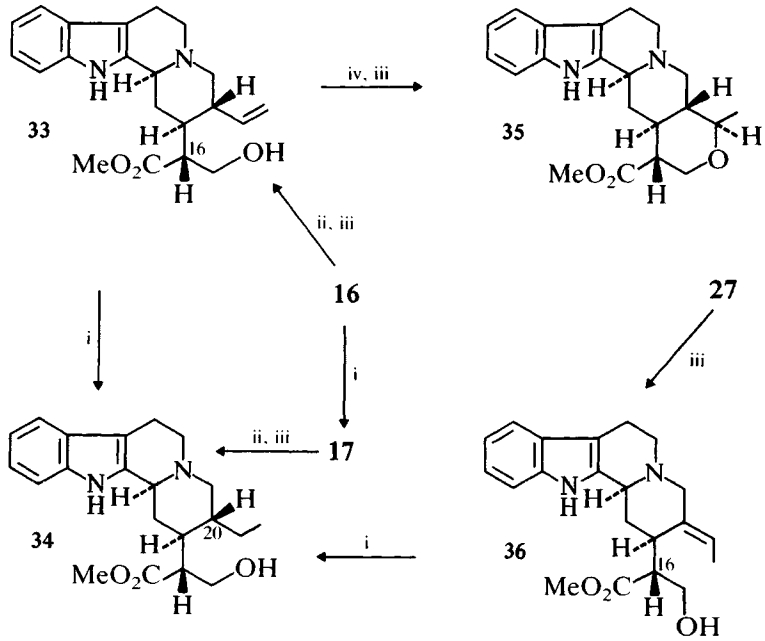
m/e 253
31



32

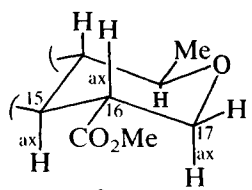
structure **34** was considered likely for dihydrositsirikine, and, furthermore, the presence of trans-quinolizidine bands in the ir spectrum indicated that H-3 had an α configuration. Final confirmation of the structure and the stereochemistry, except for the C-16 chirality, was provided by a correlation with dihydrocorynantheine (**17**) (Scheme 5). Acid-catalyzed cleavage of the enol ether in **17**

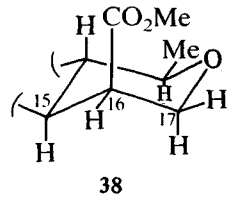
afforded a β-aldehydo ester which on reduction with sodium borohydride gave dihydrositsirikine (**34**) as the major product.



Scheme 5. Reagents: i, H_2, cat.; ii, HCl, Me_2CO; iii, $NaBH_4$; iv, $Hg(OAc)_2$.

Sitsirikine could then be formulated as **33** (except for C-16 chirality), a structure which accounted for its molecular ion at *m/e* 354, the presence of three vinyl protons in its nmr spectrum, and the production of formaldehyde on ozonolysis. In a later study, Brown and Leonard established the configuration at C-16 by converting sitsirikine to the cyclic ether **35** to prevent rotation about the 15,16 bond.[25a] At 300 MHz H-16 could then be observed to have trans-trans triaxial couplings to H-15 and H-17 axial as in **37**, in accord with an *R* configuration. As a check that no epimerization had occurred, the 16 epimer of the ether was also prepared from corynantheine via 16-episitsirikine (**33**, 16*S*) and shown by nmr data and base-catalysed epimerization to have the stereochemistry indicated in **38**. Hence the complete structure of sitsirikine must be **33**, and dihydrositsirikine is **34**.



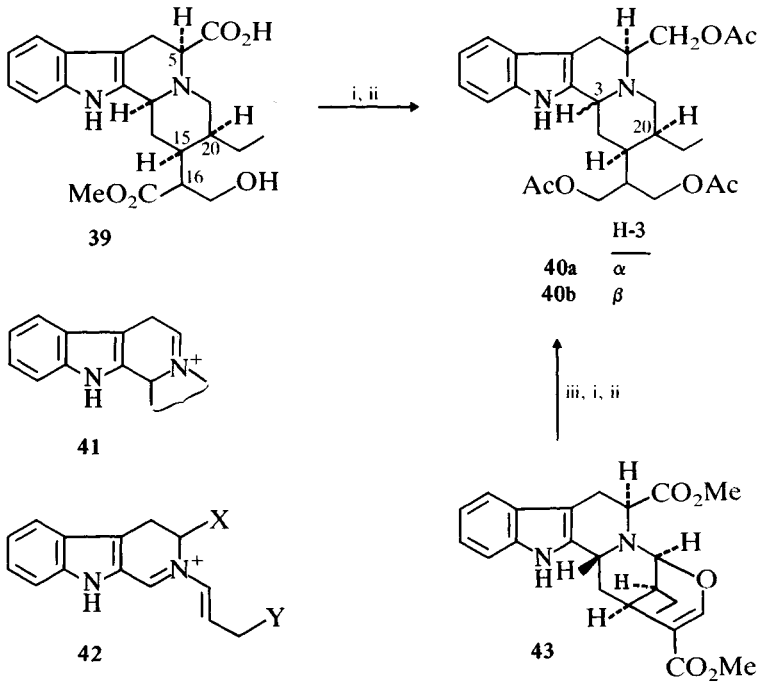


Isositsirikine was also isolated from *V. rosea* and shown to have structure **36**, in a very similar fashion by a parallel series of transformations, and by uv, ir, nmr, and mass spectral data.[24a] One distinctive feature was the ethylidene group detectable from nmr signals at δ 5.47 (1H, quartet, $J = 7$ Hz) and δ 1.4 (3H, doublet, $J = 7$ Hz). The essential features of the structure and the *E* configuration about the 19,20 double bond were confirmed by reduction of geissoschizine to isositsirikine (**36**) and its 16 epimer, the C-16 chirality being determined by hydrogenation to **34**.[25] 16-Epi-isositsirikine has been isolated from *Aspidosperma cuspa* Blake.[25b]

F. Adirubine (39)

The first *Corynanthe* type alkaloid retaining the carboxyl group of tryptophan to be discovered was adirubine, $C_{22}H_{28}N_2O_5$, found in the bark of *Adina rubescens* Hemsl.[26a] The presence of a carboxyl group was established by formation of a methyl ester, a primary hydroxyl group by acetylation and deacetylation, and a methyl ester by reduction to a triol, $C_{21}H_{30}N_2O_3$. These features were substantiated by appropriate spectral data, and in addition the nmr spectrum showed a three-proton triplet at δ 0.83 for an ethyl group. The basic tetracyclic structure and the location of substituents were deduced from the mass spectral fragmentation patterns of adirubine and its derivatives, which had many similarities to those of the corresponding dihydrositsirikine derivatives, particularly in the loss of the C-15 substituent. However, a striking difference was the very facile loss of the carboxyl and derived groups, from which an attachment at C-5 was inferred since cleavage would then generate a favorable immonium ion (**41**) (Scheme 6). This supposition was confirmed by the identical mass spectral behavior of model compounds. Again, the ethyl group was located at C-20 from the observation that a fragment **42** was common to a range of derivatives of adirubine and dihydrositsirikine. On the basis of this and other supporting evidence adirubine was formulated as the gross structure **39** (without stereochemistry).

The absolute stereochemistry at C-3 was readily established as α(*S*) from a positive Cotton effect in the cd spectrum of methyl adirubine acetate, and H-15 was consequently also α since it exhibited trans-quinolizidine ir bands at 2760 and 2735 cm^{-1}, and the nmr signal for H-3 was below δ 3.8 (cf. Section II. C); H-5 was shown to retain the configuration of L(*S*)-tryptophan since it was not epimerized by prolonged treatment of methyl adirubine with sodium methoxide.[26b] Evidence for the C-20 configuration was provided by the epimerization of adirubine triol triacetate in refluxing acetic acid largely to the 3β isomer, as shown by the change in sign of the cd Cotton effect. Such behavior was in accord with established allo-epiallo rather than normal-pseudo relationships,[27] and consequently with structures **40a** and **40b**. Confirmation of the basic structure and 20α stereochemistry was afforded by the preparation of **40b** from 5-carbomethoxydihydromancunine (**43**), a compound of known stereochemistry synthesized from methyl L-tryptophanate and dihydrosecologanin.[28a] A second corroboration was by the total synthesis of methyl adirubine, during which the nmr method of Trager et al.[16] for C-20 configurational assignments was used (cf. Section II. C).[28b]

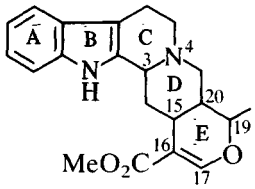


Scheme 6. Reagents: i, $LiAlH_4$; ii, Ac_2O, py; iii, $NaBH_4$.

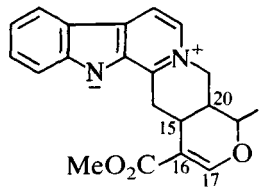
III. AJMALICINE AND RELATED HETEROYOHIMBINES

A. Ajmalicine (54) and Tetrahydroalstonine (55)

Ajmalicine was first found in *Rauwolfia serpentina* (L.) Benth. ex Kurz but was subsequently isolated from yohimbehe bark and a large number of apocynaceous plants under a variety of names (δ-yohimbine, raubasine, tetrahydroserpentine, Alkaloid F, vincaine, vinceine).[29] At first it was thought to be an isomer of yohimbine, but eventually the formula $C_{21}H_{24}N_2O_3$ was established. It contained one *C*-methyl (Kuhn-Roth) and one *O*-methyl (Zeisel), which was present in a methyl ester since hydrolysis gave an acid, $C_{20}H_{22}N_2O_3$. The uv spectrum was very similar to that of corynantheine with absorption in the 250 nm region superimposed on the indole curve, and this additional chromophore was likewise attributed to a methyl β-alkoxyacrylate system, which was confirmed by ir bands at 1695 and 1630 cm^{-1}. Again like corynantheine, ajmalicine yielded alstyrine on heating with selenium but, since it contained no reducible double bond, was formulated as the gross pentacyclic structure **44**.[30] Furthermore, serpentine, a yellow anhydronium base also isolated[29a] from *R. serpentina*, must correspond to **45** since its tetrahydro derivative was identical with ajmalicine.[31]

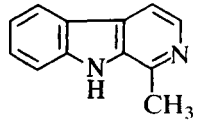


44

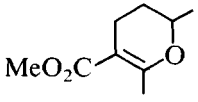


45

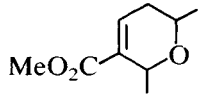
Tetrahydroalstonine, $C_{21}H_{24}N_2O_3$, was originally known as the hydrogenation product of the strong base alstonine, $C_{21}H_{20}N_2O_3$, a major constituent of dita bark (*Alstonia constricta* F. Muell.) but was later found to occur naturally in *Alstonia* and other apocynaceous species.[32] Both alstonine and tetrahydroalstonine contain a *C*-methyl group and a methyl ester. The uv spectrum of alstonine, and its degradation to alstyrine (**3**) with selenium, and to harman (**46**) on fusion with potassium hydroxide, suggested the part structure of rings A–D in **44** with substituents at C-15 and C-20. On the other hand, the uv spectrum of tetrahydroalstonine was that of an indole plus an additional chromophore in the 250 nm region which was removed on reduction with lithium aluminum hydride to tetrahydroalstonol, $C_{20}H_{24}N_2O_2$, or with sodium and butanol to hexahydroalstonol, $C_{20}H_{26}N_2O_2$. Since the ester carbonyl band in the ir spectrum of tetrahydroalstonine is low (about 1700 cm^{-1}) it is conjugated with the double bond revealed by the reduction reactions. Initially, a structure with the double bond between C-15 and C-16 was proposed, but summation uv spectra of 2,3-dimethylindole with the pyrans **47** and **48** showed that only the former fitted the spectrum of tetrahydroalstonine. Hence the gross structure (**44**) of tetrahydroalstonine is the same as ajmalicine, and alstonine is likewise a stereoisomer of serpentine (**45**).[33]



46

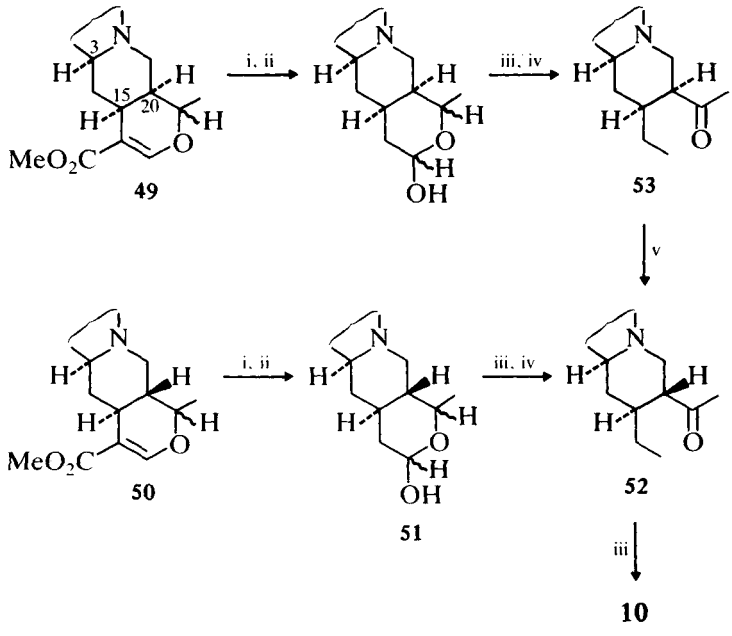


47



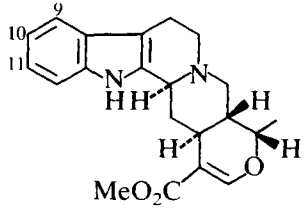
48

Because ajmalicine and tetrahydroalstonine were produced by catalytic or sodium borohydride reduction of their tetradehydro derivatives, in all probability H-3 and H-15 were cis in both. Again, H-3 was axial since ajmalicine could be oxidized with mercuric acetate to a 3-dehydro compound, which was reduced as above to ajmalicine or by zinc and acetic acid to 3-isoajmalicine.[9a] Accordingly in their ir spectra ajmalicine and tetrahydroalstonine exhibited trans-quinolizidine bands in the 2800 cm^{-1} region whereas their corresponding C-3 epimers, 3-isoajmalicine and akuammigine, did not.[9] Consequently, the former pair must belong to the normal or allo series and the latter to the pseudo or epiallo series

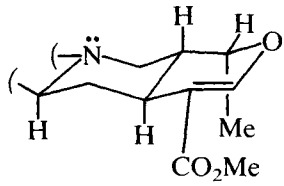


Scheme 7. i, KOH, EtOH; ii, HCl; iii, N_2H_4, NaOH, Δ; iv, $Al(OPr^i)_3$, Me_2CO; v, NaOMe.

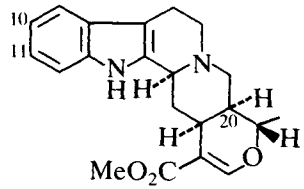
(cf. Section II. C). After an erroneous assignment based on comparative rates of dehydrogenation, eventually ajmalicine was proved to have a D/E trans (**50**) and tetrahydroalstonine a D/E cis ring junction (**49**) by conversion into dihydrocorynantheane (**10**) as shown in Scheme 7.[34] Hydrolysis and decarboxylation of ajmalicine to **51**, Wolff-Kishner reduction, and Oppenauer oxidation afforded dihydrocorynantheone (**52**), subsequently reduced to **10**, a compound of established normal stereochemistry. In a similar sequence tetrahydroalstonine yielded the 15,20 cis base corynantheidone (**53**), which was converted to the more stable trans isomer **52** only on treatment with sodium methoxide. Furthermore, since dihydrocorynantheane had been correlated with cinchonamine (Section II. A) these results also established the absolute stereochemistry of both heteroyohimbines. The only unknown stereochemical feature was the configuration at C-19 in each alkaloid, which was obtained from nmr data. In the case of tetrahydroalstonine, H-19 displayed a large (9 Hz) coupling with H-20 compatible only with a trans diaxial relationship as in **55a**, whereas with ajmalicine a much smaller axial-equatorial coupling (2.5 Hz) was evident, corresponding to **54a**.[35] Corroborative evidence was afforded by comparison of rates of methiodide formation: ajmalicine, in which N-4 is readily accessible, reacted much more rapidly than tetrahydroalstonine (**55a**) in which the axial C-19 hinders approach to N-4.[35] The absolute stereochemistry at C-19 in ajmalicine was also determined by application of Hudson's rule after conversion of ring E to a γ-lactone.[36] Hence ajmalicine is fully represented by the normal structure and stereochemistry **54** and tetrahydroalstonine is its allo 20 epimer **55**.



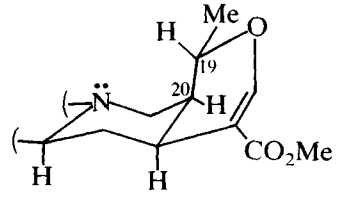
54 normal



54a



55 allo



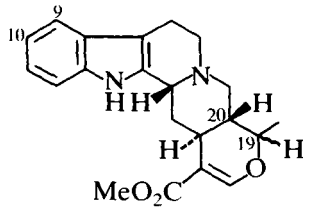
55a

B. Other Stereoisomers of Ajmalicine

All eight possible stereoisomers of ajmalicine are now known as natural products, their structures and stereochemistry having been elucidated by combinations of chemical and spectroscopic methods. The structures of 3-isoajmalicine (**57**) and akuammigine (**59**), isolated from *Picralima* species, followed from correlations with **54** and **55** by inversion of C-3.[34] One interesting feature of akuammigine is that both cis- and trans-quinolizidine conformers **59a** and **59b** are comparable in energy since both exist in solution, as shown by ^{13}C nmr spectra.[37,38] Again, in the ^{1}H nmr spectrum the coupling between H-19 and H-20 is a weighted average between trans diaxial and diequatorial forms at room temperature, the H-19 signals for the separate **a** ($J = 7$ Hz) and **b** ($J \approx 1$ Hz) conformers being observed on cooling to $-45°C$.[39]

Mayumbine from *Corynanthe (Pseudocinchona) mayumbensis* (R. Good) N. Halle was long thought to have the epiallo structure **58**, but has recently been shown to be 19-epiajmalicine (**60**).[38] A key piece of nmr information was the trans diaxial coupling between H-19 and H-20 evident in conformation **60a**. This base was previously known only as a racemate from total synthesis[42] or in optically active form by partial synthesis from desmethylcorynantheine (**62**) (Scheme 8)[40,41] or *N*-4-benzylvincoside (Section VIII. B).[40] The same was true of 3-iso-19-epiajmalicine (**54**) until it was recently isolated from *Uncaria attenuata* ssp. *bulusanensis* and correlated with the synthetic product.[43]

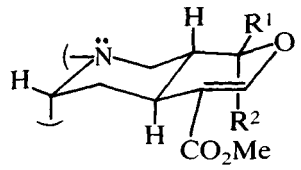
A new alkaloid with the actual structure **58** – 3-isorauniticine – was also isolated from *C. mayumbensis*, the cis relationship of H-19 and H-20 being indicated by a small 1 Hz coupling.[38] The ^{13}C nmr spectrum of 3-isorauniticine was very close to that of one conformer of its 19-epimer akuammigine (particularly C-3, 5, and 6), a trans-quinolizidine system (**58b**) being substantiated by Bohlmann ir bands and



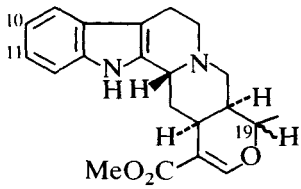
H-19	
56	α
57	β

pseudo

=



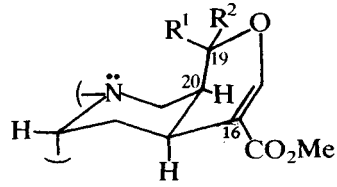
	R¹	R²
56a	Me	H
57a	H	Me



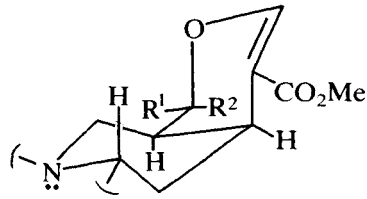
H-19	
58	α
59	β

epiallo

=

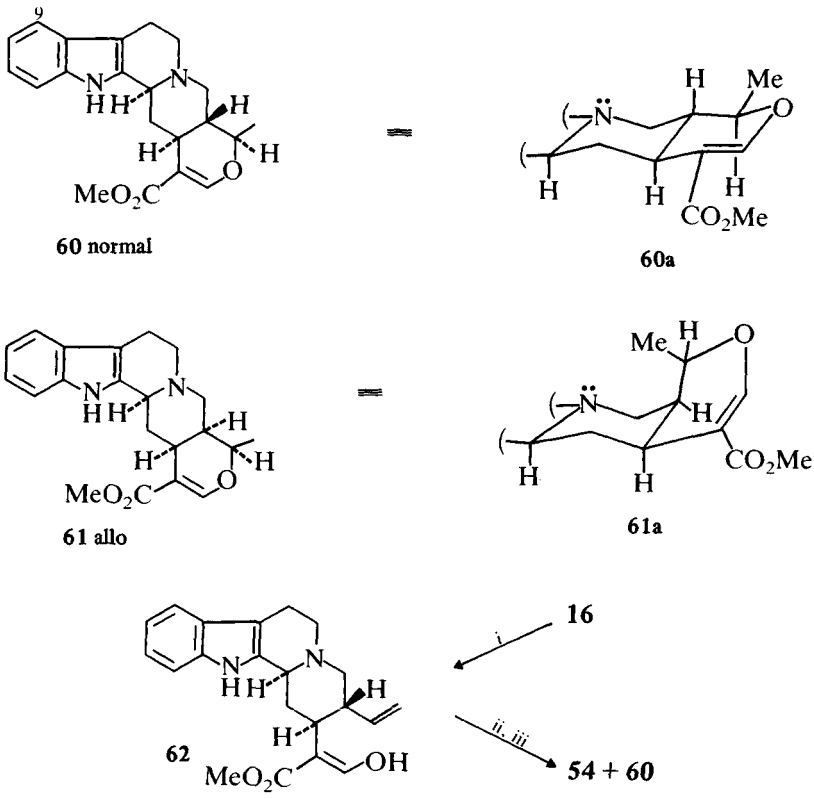


	R¹	R²
58a	Me	H
59a	H	Me



	R¹	R²
58b	Me	H
59b	H	Me

the position of H-3 below δ 3.8 in the nmr spectrum. Presumably the alternative epiallo conformation (**58a**) is not favored for 3-isorauniticine because of non-bonded interactions with the methyl group (R^1 = Me) on C-19 which do not occur in the case of akuammigine (**59a**, R^1 = H). Confirmation of structure **58** was obtained by oxidation with mercuric acetate and reduction of the 3-dehydro salt with zinc and acid to give rauniticine (**61**). This alkaloid had previously been isolated from *Rauwolfia nitida* Jacq., and assigned the stereochemistry **61a** from spectral data and from chemical evidence which included a relatively slow rate of N-4 methylation (like tetrahydroalstonine) and irreversible C-3 epimerization on heating with acid.[44]



Scheme 8. Reagents: i, HCl, Me_2CO; ii, $Hg(OAc)_2$; iii, $NaBH_4$.

C. *ar*-Methoxyheteroyohimbines

Several simple derivatives of the heteroyohimbines are known with aromatic methoxy groups at positions 9, 10, and/or 11: tetraphylline (**54**, 11-OMe),[45b,c,e] cabucine (**54**, 10-OMe),[45g] raumitorine (**56**, 10-OMe),[35,45a,c] rauvanine (**56**, 10,11-$(OMe)_2$),[45d] mitrajavine (**57**, 9-OMe),[45f] raufloricine (**57**, 10-OMe),[45h] aricine (**55**, 10-OMe),[35,45c,e] reserpinine (**55**, 11-OMe),[35,45a,c] isoreserpiline (**55**, 10,11-$(OMe)_2$),[35,45c,e] raunitidine (**61**, 11-OMe),[35,44] isoreserpinine (**59**, 11-OMe),[35,45c] and reserpiline (**59**, 10,11-$(OMe)_2$).[35,45c] The structures were largely determined as above by degradation to methoxyalstyrines, and by application of similar spectroscopic and chemical criteria to determine stereochemistry.

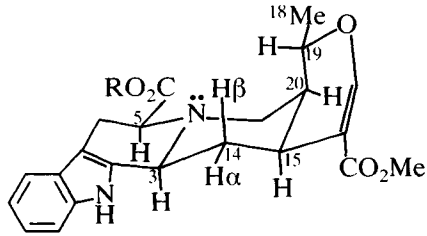
In the more recent studies mass spectra have been useful particularly because constant increments of 30 m.u. for each methoxyl group occur in characteristic ions[46] (cf. yohimbines, Chapter IV). For example, the basic structure of 10,11-dimethoxyajmalicine from *Cabucula striolata* M. Pichon was evident from mass spectral peaks at *m/e* 412 (M^+), 244, 230, 229, and 216.[45h] The substitution pattern in the indole ring was established with only two para aromatic protons appearing as

singlets in the 60 MHz nmr spectrum, which also showed appropriate signals for H-17 (δ 7.52), CO_2Me (δ 3.70), two aromatic methoxyls (δ 3.84, 3.88), H-19 (δ 4.38, $J = 3$, 7 Hz), and the 18-methyl (δ 1.16, $J = 7$ Hz). Twin ir bands at 1690 and 1618 cm^{-1} were attributed to the β-alkoxyacrylate ester.

From the observation of Bohlmann bands in the ir spectrum and the lack of an H-3 signal downfield from δ 3.8, the stereochemistry at C-3 and C-15 was assumed to be cis and α.[9,18] A D/E junction was deduced from the occurrence of the 18-methyl nmr doublet in the same position as typical trans D/E heteroyohimbine alkaloids (δ 1.2) rather than those with a cis D/E junction (δ 1.4),[35b] and the small cis a-e coupling of H-19 and H-20 completed the parallel with ajmalicine and led to structure **54** (10,11-$(OMe)_2$).

D. 5α*H*-Carboxytetrahydroalstonine (63)

A more unusual structure in that it was derived from tryptophan rather than tryptamine was 5α*H*-carboxytetrahydroalstonine (**63**) from *A. rubescens*, the first carboxyheteroyohimbine to be discovered.[47] A small quantity (~ 10 mg) was isolated as the methyl ester for which a formula $C_{23}H_{26}N_2O_5$ was established by mass measurement, and the presence of indole, methyl β-alkoxyacrylate, and saturated methyl ester functions was shown by uv, ir, and nmr data. As with adirubine (Section II. F) characteristic mass spectral fragments at *m/e* 351 (M-CO_2Me), 349, 182, 169, 168, and 156 were immediately indicative of a tetrahydro-β-carboline substituted at C-5 by a carbomethoxy group. A three-proton doublet ($J = 6.5$ Hz) at δ 1.40 and a multiplet ($J = 10$, 6.5 Hz) at δ 4.46 in the nmr spectrum were readily attributed to the 18-methyl and H-19 in a heteroyohimbine alkaloid. Detailed examination of the 220 MHz nmr spectrum together with decoupling experiments enabled most of the protons to be assigned to the gross structure **64**.



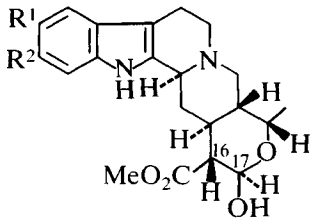
	R
63	H
64	Me

From the cd spectrum the absolute configuration of H-3 was α(*S*); and, in addition to trans-quinolizidine ir bands, its cis relation to H-15 could be deduced conclusively from the nmr spectrum: H-3 appeared at δ 3.8 with a trans diaxial coupling (10 Hz) to H-14β which in turn had a similar coupling with H-15 at δ 2.8. Furthermore, the couplings of other protons including H-20 to H-15 appeared to

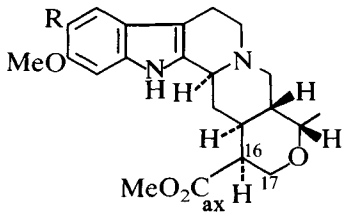
be small (< 3 Hz), and an allo stereochemistry seemed likely, but alternative conclusive proof of the configuration at C-20 and at C-19 was obtained in the following manner. From their large coupling it was evident that H-19 and H-20 were trans and diaxial: a choice between the two alternatives was made by reference to the empirical observation that the chemical shift of H-19 in all 19α, 20β-heteroyohimbine alkaloids and related synthetic derivatives invariably lies between δ 3.5 and 3.8, whereas in the 19β,20α series it occurs in the range δ 4.2–4.5, as in the present case. Finally, H-5 in the methyl ester must have the axial α configuration since it was not epimerized by sodium methoxide, and therefore the parent alkaloid was 5α*H*-carboxytetrahydroalstonine (**63**).

E. Other Heteroyohimbine Derivatives

Accompanying the corresponding heteroyohimbines in *C. striolata* were bases in which water had been added to the β-alkoxyacrylate system: ajmalicinine (**65**), cabucinine (**66**), and 10,11-dimethoxyajmalicinine (**67**), dehydration with *p*-tosyl chloride in pyridine yielding the parent alkaloids.[45g,h] The relative stereochemistry at the two additional chiral centers was revealed by a trans diaxial coupling (8.5 Hz) between H-16 and H-17 in the nmr spectrum of the *O*-acetates. The *Rauwolfia* alkaloid tetraphyllinine is another water adduct of ajmalicine and hence a stereoisomer of (**65**).[48]



	R^1	R^2
65	H	H
66	OMe	H
67	OMe	OMe



	R
68	H
69	OMe

A (so far) unique pair of 16,17-dihydroheteroyohimbines are herbaceine (**69**) and herbaine (**68**) from *Vinca herbacea* Waldst. et Kit.[49] The uv spectrum of herbaceine, $C_{23}H_{30}N_2O_5$, showed only a 5,6-dimethoxyindole chromophore and a saturated carbonyl ir band at 1715 cm^{-1} was proved to be a methyl ester by hydrolysis to an acid ($C_{22}H_{28}N_2O_5$) and lithium aluminum hydride reduction to an alcohol ($C_{22}H_{30}N_2O_4$). Methylation of the acid gave epiherbaceine rather than herbaceine, an isomerization better achieved by refluxing the latter with sodium methoxide in methanol. The mass spectrum showed strong peaks at *m/e* 414 (M^+) 413, 244, 230, and 229, characteristic of a tetrahydro-β-carboline moiety with two aromatic methoxyls. Since herbaceine gave no evidence for a hydroxylic proton, the remaining oxygen atom was probably ethereal, in accord with a 16,17-

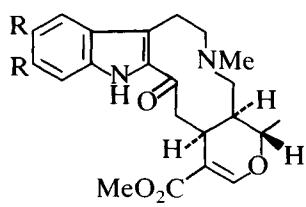
dihydroheteroyohimbine structure. Final evidence was afforded by the nmr spectrum, which in addition to signals confirming the methoxyl and *C*-methyl protons displayed a two-proton multiplet at δ 3.97 attributed to the C-17 methylene group. The normal stereochemistry at positions 3, 15, and 20 was proposed on the basis of Bohlmann ir bands and the rate of reaction with methyl iodide which was somewhat closer to those of yohimbine/corynanthine than α-yohimbine/alloyohimbine. Again, the chemical shift of the 18-methyl group and the 19,20 coupling were identical with those of ajmalicine, and since the base-catalyzed epimerization of herbaceine implied an axial β-carbomethoxy group at C-16, its structure could be formulated as **69**. It would seem likely that herbaine (**68**) has a similar structure.[49b] The most direct way of confirming these structures would obviously be by selective reduction of the 16,17 double bond in the corresponding heteroyohimbines. Previously, this process was not feasible because of the resistance of the conjugated β-alkoxyacrylate system, but has recently been achieved by the use of a nickel(III) chloride/sodium borohydride combination to furnish analogues of **68/69** from ajmalicine, tetrahydroalstonine, and reserpiline.[50a]

Recently a novel 14β-hydroxy derivative of 3-isorauniticine (**58**), presumably formed by oxidation/reduction of the corresponding 3,14 enamine, has been isolated.[50b,c]

F. Picraphylline (70)

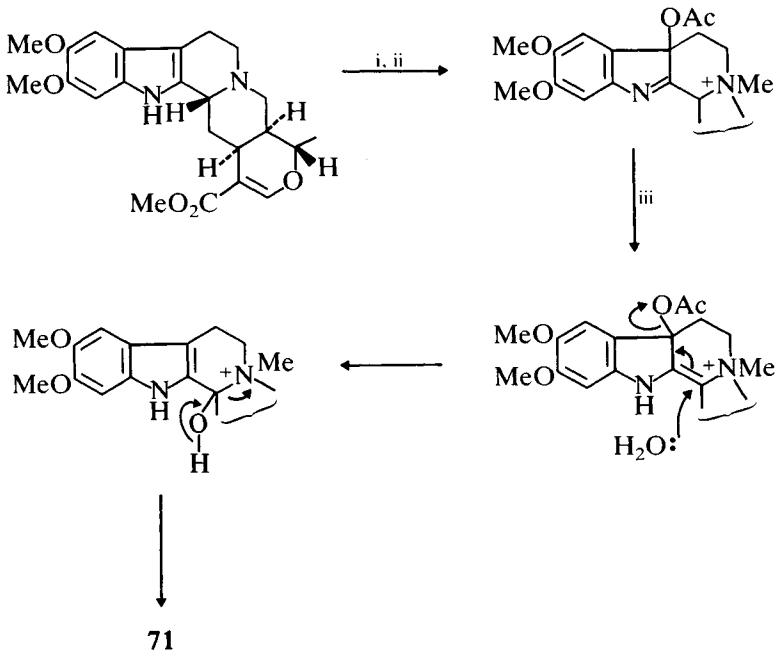
The uvspectrum of picraphylline (**70**), $C_{22}H_{26}N_2O_4$, a base from *Picralima nitida* Th. and H. Durand, is that of a 2-acylindole (λ_{max} 313, 238 nm) plus an additional chromophore.[51a] Reduction of the 2-acyl group with potassium borohydride gave an epimeric mixture of alcohols, $C_{22}H_{28}N_2O_4$, whose uv absorption suggested that the latter chromophore was a β-alkoxyacrylate system, a deduction substantiated by ir bands at 1695 and 1630 cm^{-1}. The nmr spectrum of picraphylline revealed similarities to ring E of a heteroyohimbine with signals for methoxyl (δ 3.72), H-17 (δ 7.55), and a C-18 methyl doublet (δ 1.30) but, additionally, had an *N*-methyl peak at δ 2.0. Comparison of the mass spectrum with those of burnamicine (**30**) and heteroyohimbine alkaloids led to the suggestion of structure **70**, which was confirmed when pyrolysis of the hydrochlorides of the epimeric alcohols yielded tetrahydroalstonine (**55**).

The constitution of the 10,11-dimethoxy derivative (**71**) of picraphylline, isolated from *Ochrosia balansae*, was established in an analogous manner by con-



	R
70	H
71	OMe

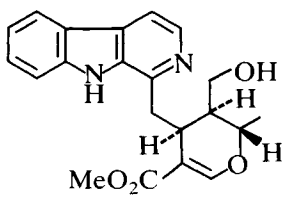
version to reserpiline.[51b] Furthermore, although it was not possible to carry out the reverse sequence from reserpiline, 10,11-dimethoxypicraphylline was prepared in low yield from isoreserpiline (Scheme 9).



Scheme 9. Reagents: i, $Pb(OAc)_4$; ii, MeI; iii, aq. AcOH, NaOAc.

G. Alstonidine (72)

By the usual chemical methods, alstonidine (**72**), $C_{22}H_{24}N_2O_4$ (from *Alstonia constricta* F. Muell), was shown to contain *C*-methyl, *N*-methyl, hydroxyl, and methyl ester groups. From the uv spectrum it was evidently a β-carboline derivative, and the ir spectrum indicated a β-alkoxyacrylate function. Definitive formulation of a cleaved heteroyohimbine skeleton **72** was only possible after a detailed examination of the nmr spectra of alstonidine and its *O*-acetate.[51] In particular, with the aid of decoupling experiments,[52] all the complex couplings to H-20 in alstonidine



72

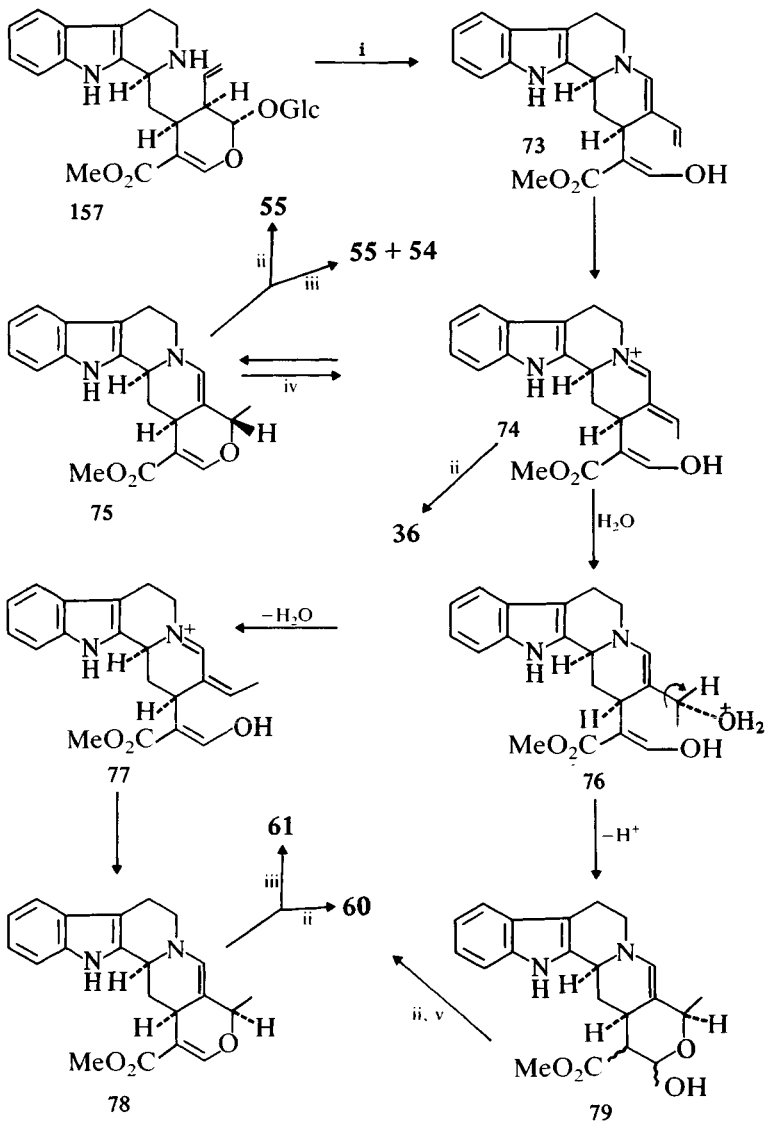
O-acetate could be analyzed to reveal the stereochemical relationship to alstonine with a trans diaxial coupling of 10 Hz to H-19; a value of 4.2 Hz for the H-15 coupling, consistent only with a cis geometry, was obtained by matching the observed spectrum with theoretical spectra computed from different $J_{15,20}$ values.

H. Cathenamine (75) and 19-Epicathenamine (78)

Recently, the labile 20,21-dehydro precursor for heteroyohimbine alkaloids, cathenamine (**75**), has been isolated from *Guettarda eximia* (Rubiaceae) and from the incubation of tryptamine and secologanin with a cell free extract of *Catharanthus roseus*.[53] Its structure was evident from mass and nmr spectra and its reduction by sodium borohydride to tetrahydroalstonine (**55**). In vitro glucolysis of strictosidine (**157**) in pH 6.5 buffer also afforded cathenamine together with its previously unknown 19 epimer (**78**), the necessary precursor for the 19α*H*-heteroyohimbines (Scheme 10).[54] Accordingly, reduction of **78** produced 19-epiajmalicine (**60**) and rauniticine (**61**). An interesting feature of this reaction sequence is the exclusive initial formation of the 19β*H* epimer cathenamine, which was attributed by Brown to a kinetic preference in protonation of **73** to give the *E*-ethylidene intermediate **74** which can undergo cyclization only from the upper (β) face.[55] In this respect it is relevant that on treatment of **75** with acid, **74** can be isolated, its ethylidene stereochemistry being established by reduction to isositsirikine (**36**).[56a] Again, 19-epicathenamine was shown to be formed from cathenamine on standing, but no deuterium from D_2O and no ^{18}O from $^{18}OH_2$ was incorporated during the epimerization.[54,55] It was therefore deduced that the *Z*-ethylidene (**77**) required by steric constraints for formation of **79** was produced by rapid reversible addition of water to the *E*-alkene (**74**). These results also excluded the intermediacy of water adducts such as **79** which have been found in *G. eximia*[56b] and were also formed in the in vitro reactions.

IV. OXINDOLE ALKALOIDS

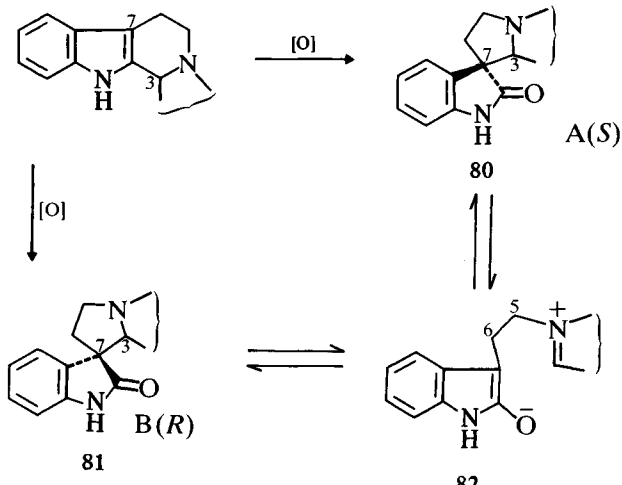
In a large number of plants, particularly from *Mitragyna* and related genera, oxidation of the indole system in secoyohimbines and heteroyohimbines occurs to give analogous oxindole alkaloids, and indeed the same can be achieved in the laboratory (Scheme 11). In this process another chiral center is created at C-7 and two stereoisomeric series arise – the A isomers with C-7 in the *S* configuration (**80**) and the B isomers with C-7 in the *R* configuration (**81**). In general, the A and B isomers can be interconverted via the ring-opened form **82** by heating in acetic acid or pyridine, but an additional complication is that C-3 may also be isomerized at the same time. In order to distinguish between configurations at the spiro center (and at C-3) various experimental criteria have been evolved including pK_a, equilibration in acidic and basic media, nmr chemical shifts, and cd spectra. Perhaps the last is the most generally applicable, a negative Cotton effect in the 290 nm region denoting an A(*S*) configuration and a positive effect a B(*R*) configuration.[57]



Scheme 10. Reagents: i, β-glucosidase, pH 6; ii, $NaBH_4$; iii, $NaCNBH_3$, pH 6; iv, H^+; v, CF_3CO_2H or p-$MeC_6H_4SO_3H$.

Particularly useful in view of the ease of inversion of C-3 is the finding that its chirality can also be established from the sign of the cd curve at about 260 nm, a positive effect denoting an α(*S*) and a negative a β(R) configuration.

The facility with which the C-3,C-7 bond opens also affects the mass spectra of oxindole alkaloids, in which the only major diagnostic fragments are those produced by simultaneous or subsequent cleavage of the 5,6 bond in **82**.[69]



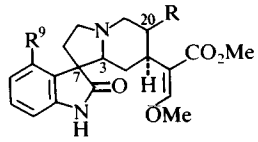
Scheme 11

A. Tetracyclic Oxindole Alkaloids

The secoyohimbine oxindole alkaloids related to dihydrocorynantheine can likewise be classified as normal, pseudo, allo, and epiallo, on the basis of their configurations at C-3 and C-20 relative to C-15, as in Table II. Examination of the likely conformers for the normal series shows no serious nonbonded interactions for either **83** or **84**, but by contrast, in the pseudo series, major destabilizing interactions are evident in both possible conformers **86a** and **86b** of the A isomer and likewise **87a** and **87b** of the B isomer. Consequently, since in any equilibration the C-7,C-3 bond is broken, only the normal isomers are obtained, and indeed no pseudo oxindole alkaloid has yet been isolated from natural sources. Again, in the preferred conformers **85a** and **85b** of the allo series, there are only small interactions with the axial ethyl group, but considerably larger destabilizations in the epiallo series with the axial oxindole moiety in **88a/89a** or β-alkoxyacrylate group in **88b/89b**. Hence although the difference in energy is less marked than in the normal/pseudo case, equilibration would result in a predominance of allo over epiallo configurations, a situation which is again reflected in vivo.

Rhynchophylline, $C_{22}H_{28}N_2O_4$, and its stereoisomer isorhynchophylline, were originally isolated from *Ourouparia rhynchophylla* Matsumura (*Uncaria rhynchophylla* Miq) and subsequently from several *Mitragyna* species. Their relationship was apparent from interconversion on heating in acidic or basic solution. Oxindole and β-alkoxyacrylate chromophores were identified from uv and ir spectra, and these and other features were established by a series of chemical analyses and transformations similar to those used on corynantheine (Scheme 12).[58] Rhynchophylline was converted into rhynchophyllal (**90**) and rhynchophyllane (**91**): palladium-charcoal dehydrogenation of the latter gave 3,4-diethylpyridine, whereas the former gave 3-ethyloxindole and 3-ethyl-4-methylpyridine, thus proving

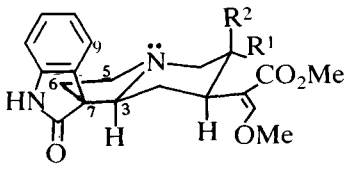
TABLE II. TETRACYCLIC OXINDOLE ALKALOIDS



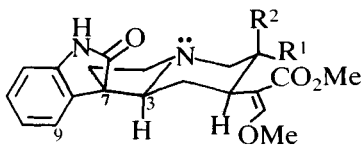
Series	C-7	R^9	R	Name	Ref.
Normal	A(*S*)	H	Et	Isorhynchophylline	57d
(H-3α, H-20β)	B(*R*)	H	Et	Rhynchophylline	57d
	A	H	$CH{=}CH_2$	Corynoxeine	64
	A	OH	Et	Rotundifoline	57d, 61a
	B	OH	Et	Isorotundifoline	57d, 61a
	A	OH	$CH{=}CH_2$	Rotundifoleine	61b
	B	OH	$CH{=}CH_2$	Isorotundifoleine	61b
	A	OMe	Et	Rhynchociline	57d, 61a
	B	OMe	Et	Ciliaphylline	57d, 61a
	A	OMe	$CH{=}CH_2$	Isospecionoxine	61a
	B	OMe	$CH{=}CH_2$	Specionoxine	61a
Allo	A	H	Et	Corynoxine	57b, d, 63
(H-3α, H-20α)	B	H	Et	Corynoxine B	57d, 63
	A	OH	Et	Mitrafoline	61b
	B	OH	Et	Isomitrafoline	61b
	B	OMe	Et	Mitragynine oxindole B	57d
Epiallo	A	OH	Et	Isospeciofoline	61b
(H-3β, H-20α)	B	OH	Et	Speciofoline	61b

the orientation of the C-15 and C-20 substituents. The point of attachment of the oxindole in ring D was shown to be either C-3 or C-21 by oxidation of isorhynchophyllane (**91**) (obtained by a similar route from isorhynchophylline) to a dilactam (**92**), whose ir spectrum displayed a δ-lactam carbonyl absorption at 1625 cm^{-1} in addition to an oxindole band at 1715 cm^{-1}. Eventual proof of the constitution **91** for rhynchophyllane, which also established the relative stereochemistry at C-15 and C-20, was afforded by synthesis of (±)-N_a-methylrhynchophyllane (**93**) from the aldehyde **94**, prepared from *threo*-3,4-diethyl-5-hydroxyvalerolactone.[59] Finally, the relationship with dihydrocorynantheine was confirmed by its conversion into rhynchophylline via the chloroindolenine **95** and imido ether **96** (Scheme 13).[60]

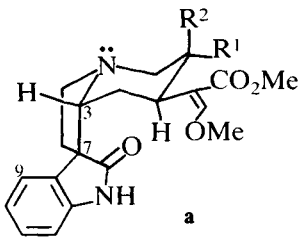
Assignment of the C-7 and C-3 stereochemistry indicated for rhynchophylline in **83** and isorhynchophylline in **84** was based upon their relative pK_a values and equilibration studies. When heated in acetic acid, rhynchophylline predominates because its conjugate acid is stabilized by hydrogen bonding between the protonated nitrogen and the oxindole carbonyl as in **97**, an explanation which also accords with its being a stronger base (pK_a 6.32) than isorhynchophylline (pK_a 5.20). In pyridine the reverse is found, since now rhynchophylline is destabilized by repulsion between the lone pair of electrons and the carbonyl group. The signs of Cotton



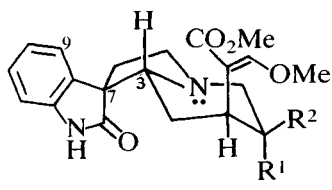
	R^1	R^2
83 normal A(*S*)	Et	H
85a allo A	H	Et



	R^1	R^2
84 normal B(*R*)	Et	H
85b allo B	H	Et

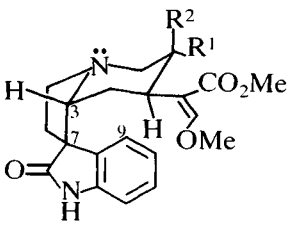


a

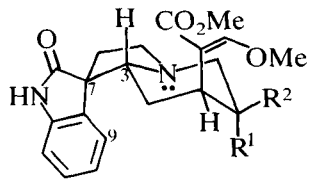


b

	R^1	R^2
86 pseudo A	Et	H
88 epiallo A	H	Et



a

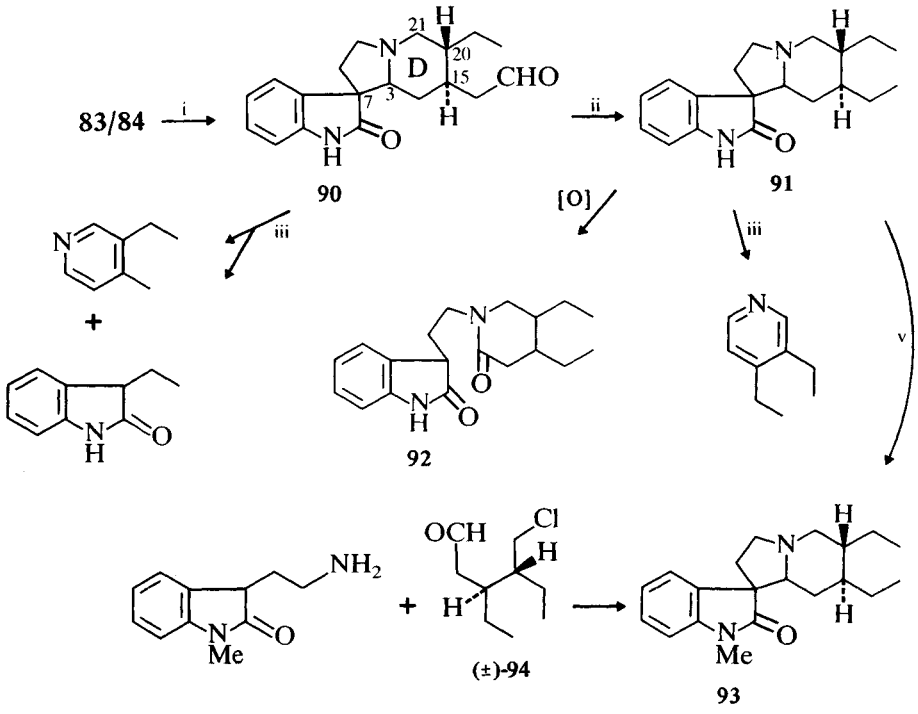


b

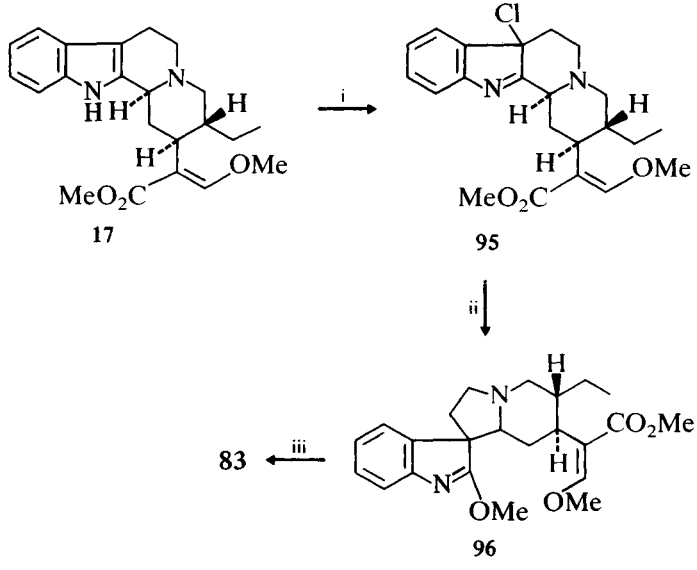
	R^1	R^2
87 pseudo B	Et	H
89 epiallo B	H	Et

effects in cd spectra lead to the same conclusions. Yet another criterion is the chemical shift of H-9 which occurs at δ 7.20 in rhynchophylline and at δ 7.40 in isorhynchophylline, the deshielding in the latter case being attributable to the close proximity of the aromatic proton to the lone pair of electrons on N_b in the A isomer.[57c] Finally, there are constant differences of about 2 ppm in ^{13}C chemical shifts for C-3 and C-9 between A and B stereoisomers which can act as indicators for the C-7 configuration.[37]

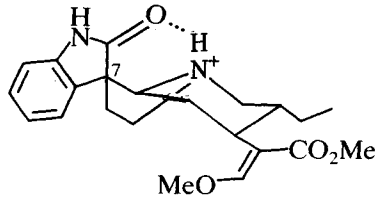
Corynoxine, an alkaloid from *Pseudocinchona africana*, was formulated as an isomer of rhynchophylline on the basis of chemical degradations and spectral data.[57b] When heated in acetic acid it was largely converted into another isomer, corynoxine B, whereas in pyridine the equilibrium favored corynoxine, but in neither case was any rhynchophylline produced, ruling out a pseudo configuration. Hence corynoxine must belong to the allo or epiallo series, a deduction supported by the symmetry of the 18-methyl triplet in its nmr spectrum (cf. Section II. C)



Scheme 12. Reagents, H_3O^+; ii, N_2H_4, NaOH, Δ; iii, Pd-C, Δ; iv, $Hg(OAc)_2$; v, MeI, NaOMe.



Scheme 13. Reagents: i, Bu^tOCl; ii, MeOH; iii, aq. AcOH, Δ.



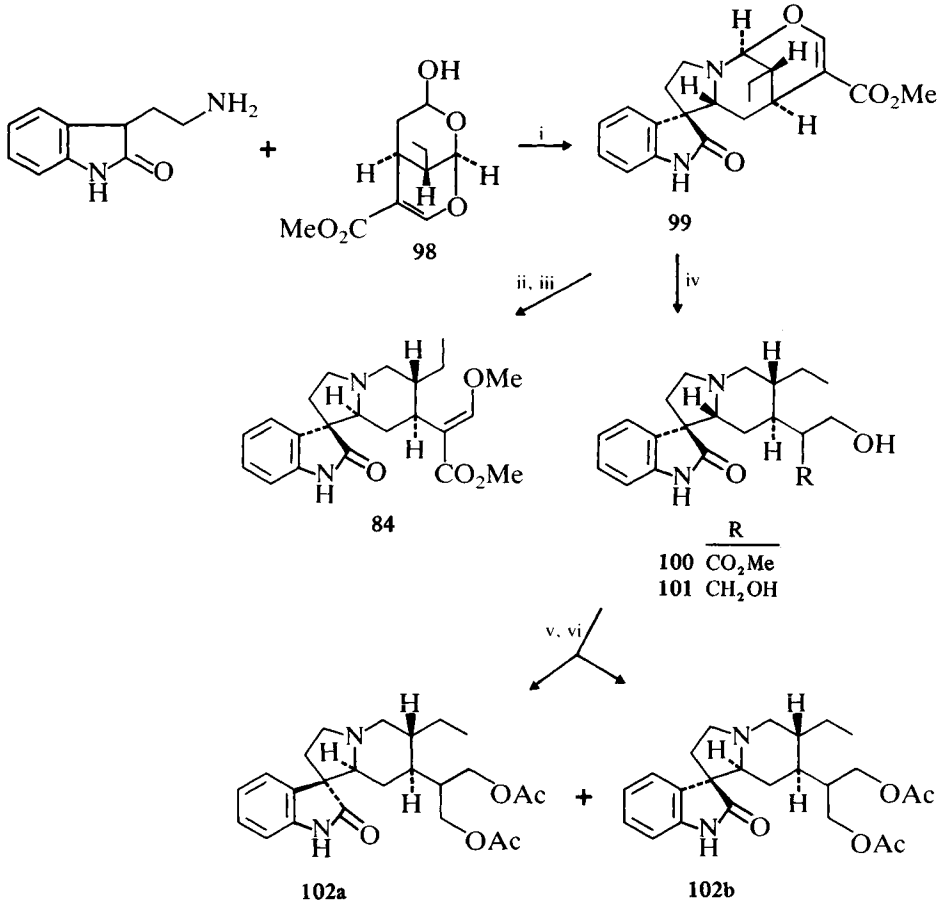
97

in accord with an axial ethyl group, and confirmed by a partial synthesis from corynantheidine.[61] Stereochemistry at C-7 and C-3 in corynoxine was assigned from the signs of the Cotton effects in the cd spectrum, and from the deshielding of H-9 relative to corynoxine B, as described above. Thus corynoxine had the allo A structure **85a** and its C-7 epimer was the allo B, **85b**.[57b,d,61]

Rhynchociline and ciliaphylline were *ar*-methoxy derivatives of rhynchophylline isolated from *Mitragyna ciliata* Aubrev. et Pellgr. and shown to be an A/B pair by interconversion. In the nmr spectra of the two bases there were three adjacent aromatic protons, one of which was moved downfield by more than 1 ppm in the spectrum of *N*-acetylciliaphylline and hence must be attached to C-12. Consequently the methoxy group must be at C-9. Since equilibration produced no further isomers and the 18-methyl triplet in the nmr spectra was unsymmetrical, the alkaloids belong to the normal series and are 9-methoxyrhynchophyllines. Unfortunately, the usual criteria for assigning C-7 stereochemistry were not valid, but a distinction was possible from the difference in chemical shift of the aromatic methyl signal on changing from deuterochloroform to acetic acid. A protonated N-4 would be expected to have a greater deshielding effect on the methoxyl group of the A isomer (0.2 ppm) than the B isomer (0.08 ppm) because it is closer in the former case. On this basis rhynchociline had the A configuration (**83**, 9-OMe) and ciliaphylline the B configuration (**84**, 9-OMe).[57d] An analogous pair of 9-hydroxy bases, rotundifoline and isorotundifoline, were assigned to the normal series from the usual equilibration and nmr criteria. Although isorotundifoline behaves as a typical phenol, rotundifoline is virtually nonphenolic in character, a difference attributed to the presence in the latter of a strong intramolecular hydrogen between N-4 and the 9-hydroxyl group. Consequently, rotundifoline must belong to the A series and is formulated as **83** (9-OH) and its 7-epimer is **84** (9-OH).[57d]

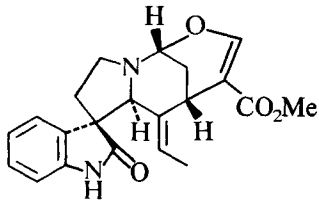
Only the allo oxindoles are known in the parent and 9-methoxy[57d] series but all four 9-hydroxy derivatives of **89**, **88**, **85a**, and **85b** have been isolated from *Mitragyna speciosa* and identified from chemical and spectral data: speciofoline (epiallo B), isospeciofoline (epiallo A), mitrafoline (allo A) and isomitrafoline (allo B), respectively.[61b] Again, two isomers predominated during the interconversion of the four in acidic or basic media, were essentially nonphenolic, and could be formulated as 9-hydroxy derivatives of **85a** and **89b** in which hydrogen bonding to N-4 could occur.

Because of the nonbonded interaction in the pseudo series it had been axiomatic that oxindole alkaloids related to **86/87** would be too unstable to exist. Indeed,



Scheme 14. Reagents: i, Et_3N, EtOH; ii, H_2, Pd-C; iii, CH_2N_2; iv, $NaBH_4$; v, Ac_2O, py; vi, AcOH, Δ.

none has been isolated from natural sources and, moreover, oxidation of pseudo indole alkaloids invariably gave only normal oxindole products. However, oxindole bases **99**, **100**, and **101** of pseudo B configuration have been prepared from 2-oxytryptamine and dihydrosecologanin aglucone (**98**) as shown in Scheme 14, their structures being established from cd and nmr spectra and by correlation with dihydrositsirikine derivatives **102a, b** of known stereochemistry.[65a] Incidentally, secologanin aglucone, on the other hand, yielded the very different and novel structure condoxine (**103**).[146] As anticipated, these 3β bases were readily converted to 3α normal structures on warming in acetic acid solution. Since catalytic hydrogenation of 2-oxodihydromancunine (**99**) afforded isorhynchophylline (**84**) in good yield, this route represented a short and efficient partial synthesis of both the rhynchophylline isomers.[65b] Another possible pseudo base has been reported as a transient intermediate during the isomerization of isorotundifoline.[61b]

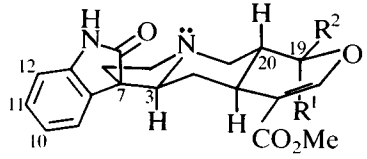


103

B. Pentacyclic Oxindole Alkaloids

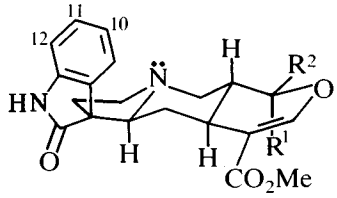
Since the oxindole alkaloids derived from the heteroyohimbines have four variable chiral centers at C-3, C-7, C-19, and C-20, a total of 16 diastereoisomers is theoretically possible. The twelve normal (**104–107**), allo (**108–111**), and epiallo (**112–115**) structures are all known, and together with various *ar*-methoxy derivatives are listed in Table III. In general, their structural and stereochemical features have been elucidated from chemical and spectroscopic data[57,61,62a,b] in a manner rather similar to the tetracyclic oxindole alkaloids or the corresponding indolic heteroyohimbines as appropriate, and in many cases direct correlations with the latter have been made (as in Scheme 15 below). However, even more than with the tetracyclic oxindoles, the pseudo series is again strongly disfavored by severe steric interactions found in **116**, the only conformation possible because of the fifth ring.

Among the first structures to be determined were mitraphylline (**105**) and isomitraphylline (**104**), largely by classical methods. Thus, for example, drastic degradation with zinc dust gave a key 3-spirocyclopropanooxindole **117** and 3,4-diethylpyridine; hydrolysis, decarboxylation, and Wolff-Kishner reduction gave mitraphyllane (**118**) in analogous fashion to heteroyohimbine alkaloids and, eventually, the gross structure **119** was proposed for both alkaloids.[66] Comparison of nmr spectra suggested that the stereochemistry at C-15, 19, and 20 was the same as in ajmalicine (**54**), a deduction which was confirmed by a conclusive partial synthesis of **104** and **105** from this alkaloid via hydrolysis of its 7-chloroindolenine derivative.[60] Since a pseudo configuration could be excluded on steric grounds, H-3 was α in both isomers. Finally, mitraphylline was formulated as the normal B isomer (**105**) since it was a strong base (cf. **97**) than isomitraphylline which, consequently, was the A isomer (**104**). The other normal pair were formosanine (**107**) and isoformosanine (**106**) which, after an initial erroneous assignment, were shown to have a trans diaxial relationship between H-19 and H-20 from a 9 Hz coupling in their nmr spectra. Since the cd curves were virtually superimposable on those of the mitraphyllines, formosanine and its 7-epimer were formulated as oxindole derivatives of the then unknown 19-epiajmalicine, structures which were confirmed by preparation from synthetic material according to the general procedure for heteroyohimbines (**120**) given in Scheme 15.[57b,62b,67] Again the stronger base, formosanine, was allocated the B configuration, an assignment corroborated by a positive cd band at 290 nm compared with a negative band for isoformosanine.



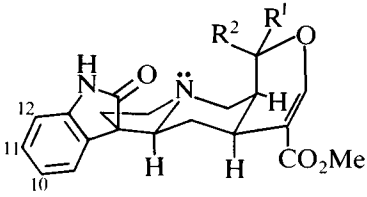
normal B

	R¹	R²
105	Me	H
107	H	Me



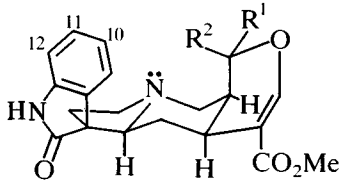
normal A

	R¹	R²
104	Me	H
106	H	Me



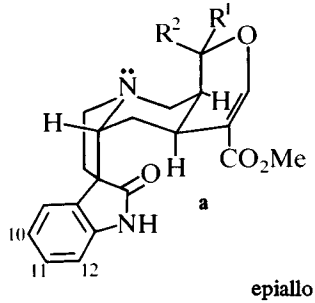
allo B

	R¹	R²
109	Me	H
111	H	Me

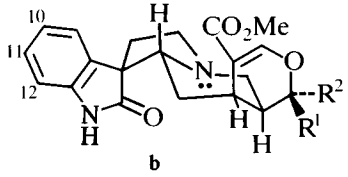


allo A

	R¹	R²
108	Me	H
110	H	Me



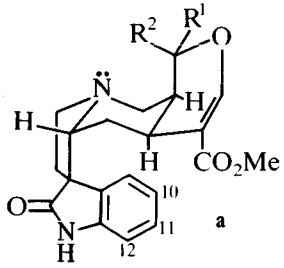
a



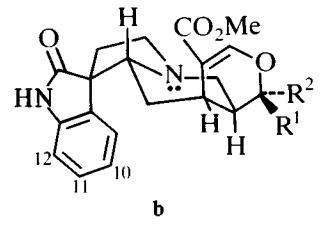
b

epiallo A

	R¹	R²
112	Me	H
114	H	Me



a

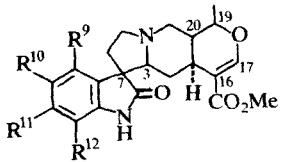


b

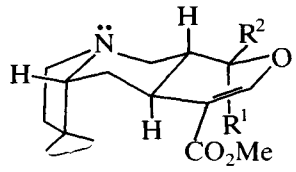
epiallo B

	R¹	R²
113	Me	H
115	H	Me

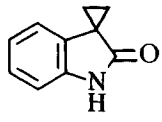
TABLE III. PENTACYCLIC OXINDOLE ALKALOIDS



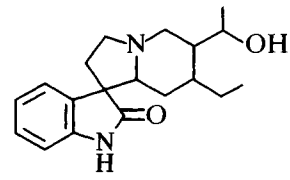
Series	C-7	H-19	R^9	R^{10}	R^{11}	R^{12}	Name	Ref.
Normal	A(*S*)	α	H	H	H	H	Isoformosanine (uncarine A)	62a, b
(H-3α, H-20β)	B(*R*)	α	H	H	H	H	Formosanine (uncarine B)	62a, b
	A	α	H	OMe	OMe	H	Rauvanine oxindole A	57c
	B	α	H	OMe	OMe	H	Rauvanine oxindole B	57c
	A	β	H	H	H	H	Isomitraphylline	62a, b
	B	β	H	H	H	H	Mitraphylline	62a, b
	A	β	H	OMe	OMe	H	Herbaline (16αH,17-dihydro)	62d
	A	β	OMe	H	H	H	Javaphylline	62h
	B	β	OMe	H	H	H	Isojavaphylline	62h
Allo	A	α	H	H	H	H	Rauniticine-allo-oxindole A	57c, 62a
(H-3α, H-20α)	B	α	H	H	H	H	Rauniticine-allo-oxindole B	57c, 62a
	A	β	H	H	H	H	Isopteropodine (uncarine E)	62a, b, c
	B	β	H	H	H	H	Pteropodine (uncarine C)	62a, b, c
	A	β	H	OMe	OMe	H	Isocarapanaubine	57a, c
	B	β	H	OMe	OMe	H	Carapanaubine	57c, 62a
	A	β	H	H	OMe	OMe	Isomajdine (elegantine)	62e, f, g
	B	β	H	H	OMe	OMe	Majdine	62e, f, g
Epiallo	A	α	H	H	H	H	Rauniticine-epiallo-oxindole A	57c, 62a
(H-3β, H-20α)	B	α	H	H	H	H	Raunicitine-epiallo-oxindole B	57c, 62a
	A	β	H	H	H	H	Speciophylline (uncarine D)	62b
	B	β	H	H	H	H	Uncarine F	62b
	A	β	H	OMe	OMe	H	Rauvoxinine	57c, 62a
	B	β	H	OMe	OMe	H	Rauvoxine	57c, 62a
	A	β	H	H	OMe	OMe	Isoelegantissine (majdine 4)	62f, g
	B	β	H	H	OMe	OMe	Elegantissine (majdine 3)	62f, g



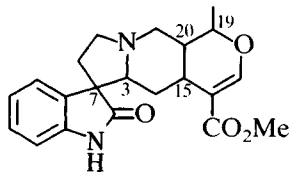
116 pseudo



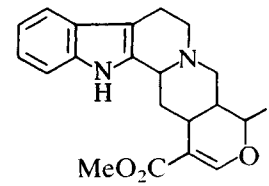
117



118



119



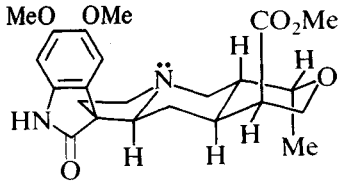
120

Scheme 15. Reagents: i, Bu^tOCl; ii, H^+, aq. MeOH.

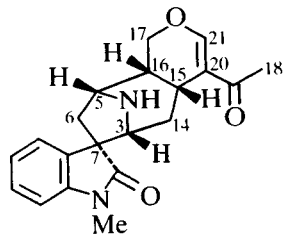
The four naturally occurring allo-epiallo isomers pteropodine (uncarine C) (**109**), isopteropodine (uncarine E) (**108**), speciophylline (uncarine D) (**112**), and uncarine F (**113**) were all interconvertible and could be synthesized from tetrahydroalstonine (**55**).[62b] A diequatorial coupling for H-19 and H-20 of 1.5 Hz for speciofoline and uncarine F was compatible only with the epiallo conformations **112b/113b** rather than **112a/113a**, whereas the pteropodine isomers had couplings of 11 Hz in accordance with allo conformations. Another four interconvertible oxindoles were obtained by oxidation of rauniticine (**61**) and assigned C-7 and C-3 configurations as above. However, in this case these were two major and two minor isomers, the former being designated as the epiallo bases **114b/115b** and the latter as the allo structures **110/111**, which an axial 19-methyl group renders less stable. Accordingly in the nmr spectra the methyl group in the allo pair is deshielded and occurs at markedly lower field than in the epiallo pair owing to its proximity to the N-4 lone pair.[57c,62a]

Various *ar*-methoxy derivatives of these representative alkaloids that have been isolated and whose structures have been established by analogous equilibration and spectroscopic methods are given in Table III. A so far unique oxindole alkaloid is the 16,17-dihydro derivative herbaline (**121**) from *Vinca herbacea*.[62d] Assignment of configuration at the additional chiral center at C-16 was possible from its epimerization on treatment with base to an isomer with the more stable equatorial orien-

tation of the carbomethoxy group. Other structural and stereochemical features were inferred from nmr data but could not be confirmed by synthesis from an appropriate heteroyohimbine since the ring E double bond could not be hydrogenated selectively. However, such a correlation should now be feasible since a suitable reduction method has recently been (cf. Section III.E) devised.[50a] Another unique oxindole alkaloid is alstonisine (Alkaloid C) from *Alstonia muelleriana* Domin. for which the highly modified structure **122** has been established by the X-ray method.[68] Various *N*-4-oxide derivatives of oxindole alkaloids have also been isolated and characterized.[70]



121



122

V. ALKALOID GLYCOSIDES AND RELATED COMPOUNDS

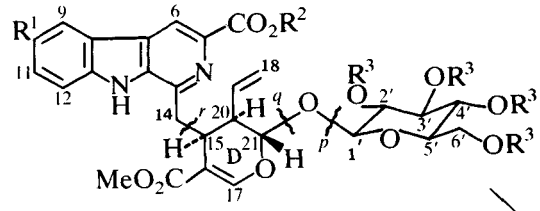
In vivo condensation of secologanin with tryptamine and tryptophan derivatives yields not only the biological precursors for the variegated skeleta of 1300 or so monoterpenoid indole alkaloids but also a related group of alkaloid glycosides and aglucones formed by less drastic modifications. To date, the only major sources have been a relatively few plants of the Rubiaceae: *Adina cordifolia* (Roxb.) Hook. f. ex Brandis, *A. rubescens* Hemsl., *Anthocephalus cadamba* Miq., *Nauclea latifolia* Sm., *N. diderichii* Merrill, *Pauridiantha lyalli* (Baker) Bremek, *Palicourea alpina* (Sw) DC, and in the Apocynaceae, *Rhazya stricta* Dcne, *R. orientalis*, A.DC., *Catharanthus roseus* G. Don (*Vinca rosea L.*), and *Vinca major L.* However, the number of sources is rapidly increasing with the wider use of isolation techniques appropriate for these polar, water-soluble compounds.

A. Tryptophan Derivatives

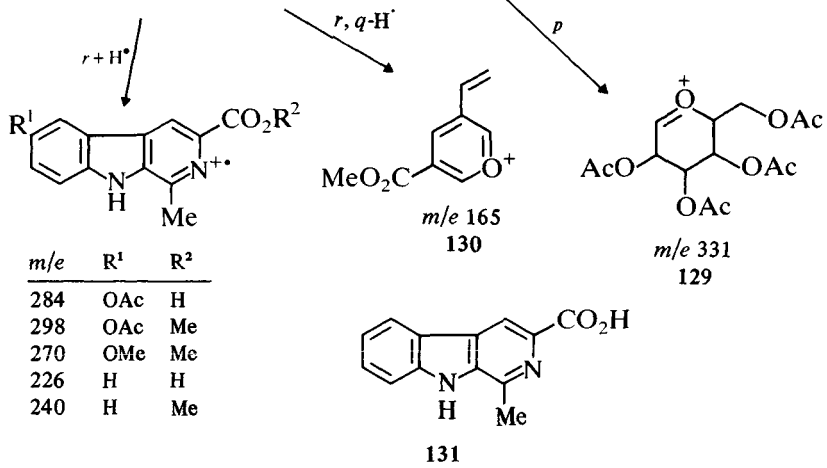
1. *Cordifoline (123) and Related Alkaloids*

The first indole alkaloid containing the secologanin moiety to be isolated was cordifoline, obtained as its pentaacetate ($C_{38}H_{40}N_2O_{17}$) after acetylation of an extract of the heartwood of *A. cordifolia*.[71a] It was shown to contain carboxyl, phenolic, and olefinic groups by conversion to methylcordifoline pentaacetate, dimethylcordifoline tetraacetate, and methyldihydrocordifoline pentaacetate.

Remaining features of the molecule were elucidated largely by spectroscopic methods. In particular the mass spectra of cordifoline derivatives (**124–126**) were very informative in the early stages of the structural investigation, the major fragments being rationalized in terms of only three cleavages, *p*, *q*, and *r*, in Scheme 16.



	R¹	R²	R³
123	OH	H	H
124	OAc	H	Ac
125	OAc	Me	Ac
126	OMe	Me	Ac
127	H	H	H
128	H	Me	Ac



m/e	R¹	R²
284	OAc	H
298	OAc	Me
270	OMe	Me
226	H	H
240	H	Me

m/e 165
130

m/e 331
129

131

Scheme 16.

A strong peak at *m/e* 331 ($C_{14}H_{19}O_9$) common to all these compounds was attributed to an oxonium ion (**129**), which was the parent of related ions at *m/e* 271, 169, 127, and 109 formed by loss of acetic acid and ketene; complementary ions were found at M-331 and M-347 corresponding to cleavages *p* and *q* of a hexoside. From nmr spectra it was evident that the sugar was an aldohexose, and furthermore the protons 1′–4′ had only trans diaxial couplings corresponding to glucose. Subsequent cleavage of the free glycoside with β-D-glucosidase confirmed its identity.

The substituted carboline partial structure was represented by a major ion at *m/e* 284 ($C_{15}H_{14}N_2O_4$) for cordifoline pentaacetate, together with lesser fragments at *m/e* 240 and 198 formed by loss of carbon dioxide and ketene; corresponding ions at *m/e* 298 and 270 were given by the other derivatives. Further information about this system was afforded by the nmr spectrum which showed phenolic acetate, indolic NH, and four aromatic protons attributable to H-6, H-9, and H-12 and either H-10 or H-11. Comparison of the uv spectrum [λ_{max} 239, 271, 305, 338 nm] and its characteristic bathochromic shift in acid solution with that of harman-3-carboxylic acid (**131**) revealed a marked correspondence, which was

enhanced by a summation spectrum of **131** with loganin, a compound with a β-alkoxyacrylate chromophore. Since the acetoxy substituent would have little effect upon the uv absorption, a basic β-carboline structure was thus present; subsequently the phenolic group was located at C-10 by reference to adifoline[71b] (see Section V. A. 3).

The remainder of the molecule was represented by a mass spectral ion at *m/e* 165, ($C_9H_9O_3$) corresponding to the pyrylium ion **130**, which shifted to *m/e* 167 after hydrogenation. A vinyl group was indicated by three olefinic protons in the nmr spectra, which were replaced by an ethyl group in the dihydro derivative. The presence of the system $MeO_2C-\underset{|}{C}=CH-O-\underset{|}{C}-$ suggested by the uv absorption was confirmed by twin ir bands at 1680 and 1635 cm^{-1} and nmr signals at δ 7.49 (H-17) and 5.85 (OMe).

Most importantly, the hydrogen atoms around ring D were located in the nmr spectrum of cordifoline pentaacetate and their assignments confirmed by decoupling (see Table IV). One key feature was the small allylic interaction between H-17 and H-15 which fixed their relative positions within ring E to ring D. Furthermore, H-20 had a cis axial-equatorial coupling (3.5 Hz) with H-15, and a trans diaxial coupling (5 Hz) with H-21, which thus indicated their relative stereochemistry. Consequently,

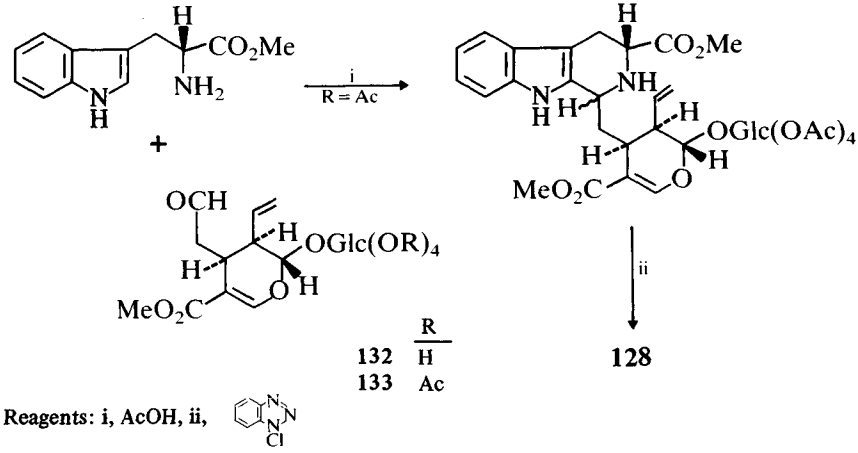
TABLE IV. ^1H CHEMICAL SHIFTS FOR CORDIFOLINE PENTAACETATE IN $CDCl_3$ AT 300 MHz

H	δ	Multiplicity[a]	*J* (Hz) (coupled proton)
6	8.83	s	–
9	7.92	d	2 (11)
11	7.39	dd	9 (12), 2 (9)
12	7.71	d	9 (11)
14a	3.85 [b]4.05	br. d	13 (14b), ~ 1 (15)
14b	3.18	dd	13 (14a), 11 (15)
15	3.30	m	11 (14b), 3.5 (20), ~ 1 (14a), ~ 1 (17)
17	7.55	d	~ 1 (15)
18a, b	5.20	m	17, 10 (19)
19	5.77	dt	17 (18a), 10 (18b), 10 (20)
20	2.62	m	10 (19), 5 (21), 3.5 (15)
21	5.41	d	5 (20)
22-CO_2Me	3.90	s	–
10-OAc	2.40	s	–
1′	4.90 [b]5.20	d	8 (2′)
2′	4.88 [b]5.35	dd	10 (3′) 8 (2′)
3′	5.22 [b]5.64	t	10 (4′), 10 (2′)
4′	5.06	t	10 (5′), 10 (3′)
5′	3.85 [b]3.88	dt	10 (4′), 3 (6′a, b)
6′a, b	4.24	d	3 (5′)
Ac	2.09	s	–
Ac	2.02	s	–
Ac × 2	1.98	s	–

[a] s = singlet, d = doublet, t = triplet, m = multiplet, br. = broadened.
[b] On addition of 20% v/v C_6D_6.

the pentaacetate could be formulated as **124**, and because cordifoline also gave a pentapropionate, it must correspond to **123**.

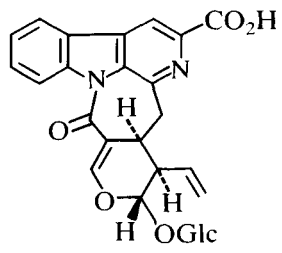
In later studies, deoxycordifoline (**127**) has been isolated from *A. cordifolia* and *A. rubescens*, the features of its structure being determined in an analogous manner to cordifoline.[73] Eventually, the proposed structure was confirmed by the partial synthesis of the methyl tetraacetate **128** from methyl D-tryptophanate and secologanin tetraacetate (**133**) outlined in Scheme 17.[72] Since the cd spectra of **128** and **124** were virtually identical, this sequence also established the absolute configuration of cordifoline as shown in **123**.



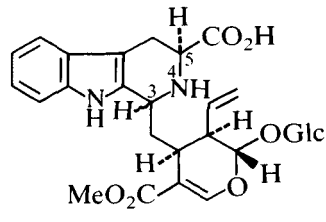
Scheme 17.

Another glycoalkaloid isolated as a tetraacetate ($C_{35}H_{34}N_2O_{14}$) from *A. rubescens* had a uv spectrum [λ_{max} 245, 287, 306, 326, and 337 nm] that did not correspond to any known system, but on treatment with alkali afforded a chromophore similar to that of **131**.[74] Subsequent treatment of its methyl ester with sodium methoxide followed by reacetylation yielded **128**. Given that no indolic NH was apparent in ir or nmr spectra, the only feasible structure compatible with the mass spectral fragmentation was that of deoxycordifoline *N*-1-lactam (**134**), which was substantiated by synthesis of 2-carbomethoxy-4,5-dihydrocanthin-6-one as a model uv chromophore.

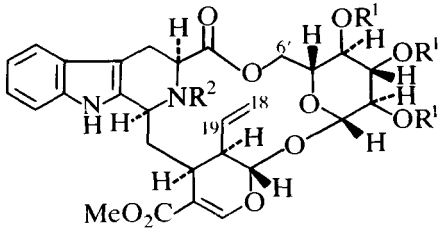
Obviously, the biological precursors of deoxycordifoline would be one or both of the corresponding tetrahydro derivatives **135/136** formed by condensation between L-tryptophan and secologanin (**132**). Although the 3β epimer (**136**) has not been found in nature, the 3α alkaloid (**135**) and both the easily derived 3α and 3β lactams (**137/138**) have been isolated from *R. orientalis* and *A. rubescens*. Partial syntheses from **132** established their structures apart from the configurations at C-3, which were readily assigned from cd spectra, the 3α lactam (**137**) displaying a diagnostic positive Cotton effect at about 270 nm and the 3β lactam a negative effect.[75] Furthermore, analogous cd behavior was exhibited by the noncyclized N-4 acetamides of **135** and **136**.



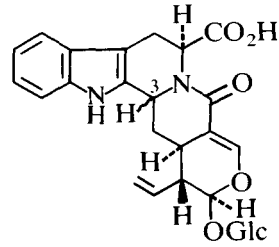
134



	H-3
135	α
136	β



	R^1	R^2	
139	H	H	
140	Ac	Ac	18,19-dihydro
141	H	Ac	18,19-dihydro



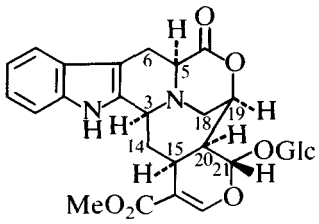
	H-3
137	α
138	β

A rather more unusual natural derivative of 3α,5α*H*-tetrahydrodeoxycordifoline was the macrocyclic lactone macrolidine (**139**), whose relationship was evident from spectral data and cleavage of the lactone ring with sodium methoxide to the methyl ester of **135**.[76] That the primary hydroxyl at C-6′ in the sugar was involved in the lactone ring was deduced from the observation that on Zemplen deacetylation of **140** to **141** the chemical shift of the two 6′ protons at about δ 4.0 and 4.6 remained essentially constant, whereas the secondary protons at C-2′, 3′, and 4′ moved from δ 4.9–5.3 to δ 3.4–3.8.

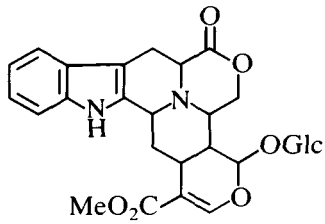
2. *Rubenine* (*142*)

Yet another glycosidic alkaloid isolated in small amounts from the heartwood of *A. rubescens* was rubenine (**142**), $C_{28}H_{32}N_2O_{11}$.[77] It afforded a tetraacetate whose spectral data demonstrated the presence of indole, methyl β-alkoxyacrylate, and hexoside functions. A series of ions in the mass spectrum at *m/e* 183, 182, 169, and 168, rather than the more usual 184, 183, 170, and 169 for a tetrahydro-β-carboline, indicated a substituent α to N-4. Ready losses of CO and CO_2 from the molecular ion suggested a lactone, and, accordingly, cleavage with sodium methoxide followed by reacetylation gave a methyl ester pentaacetate. Hydrolysis of rubenine with β-glucosidase furnished glucose and an aglucone, which had an ir band at

1740 cm^{-1} indicative of a δ-lactone. Furthermore, the newly liberated hydroxyl had to be linked to the β-alkoxyacrylate via a hemiacetal (**143**), because addition of alkali now had a marked effect on the uv absorption in the 275 nm region attributable to ionization of a β-hydroxyacrylate chromophore, that is, **143** → **144** → **145** in Scheme 18. As anticipated, reduction of the aglucone with sodium borohydride yielded a diol (**146**).

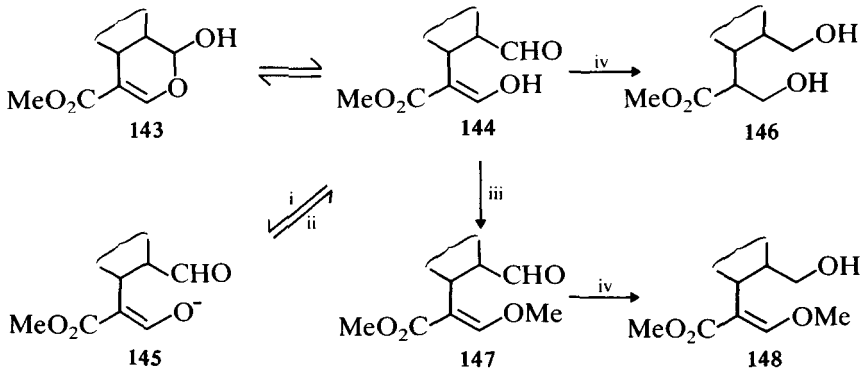


142



149

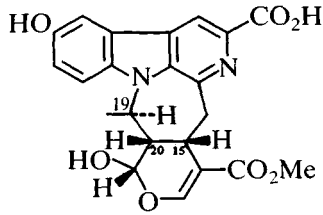
Two plausible gross structures **142** and **149** could be advanced for rubenine at this stage, the latter eventually being excluded when nmr analysis revealed that the δ-lactone was derived from a secondary rather than a primary alcohol. With the aid of spin decoupling, assignments could be made for virtually all the protons and their relative stereochemistry. Thus the couplings to H-20 (δ 2.2) were a trans a-a with H-21 (δ 5.35), cis a-e with H-15 (δ 3.20), and cis a-e with H-19 (δ 5.15), which was further strongly coupled with Hβ-18 (δ 3.75) but only weakly with Hα-18 (δ 3.60); Hβ-14 (δ 1.80) had large trans a-a interactions with both H-3 (δ 4.33) and H-15, with which Hα-14 was only weakly coupled; H-5 (δ 4.15) had a substantial coupling with Hα-6 (δ 3.15) and a small one with Hβ-6 (δ 3.50). These data were compatible only with structure **142** for rubenine, which the cd spectrum confirmed as also representing the absolute configuration. The novel N-4, C-18 bond in a seven-membered ring is presumably formed in vivo from nucleophilic attack of N-4 on an 18,19-epoxy derivative of **135**.[77]



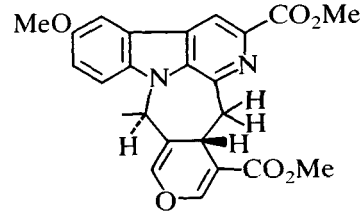
Scheme 18. *i*, OH^-; *ii*, H^+; *iii*, CH_2N_2; *iv*, $NaBH_4$.

3. *Adifoline (150) and Deoxyadifoline (152)*

The aglycone part structure **143** of the yellow alkaloid adifoline (**150**), $C_{22}H_{20}N_2O_7$, from *A. cordifolia*, were evident from a series of chemical reactions (Scheme 18) and accompanying spectral data.[71b] The uv, nmr, and mass spectra of adifoline and its derivatives revealed a phenolic carboxy-β-carboline unit identical with that of cordifoline (Section V. A. 1); reduction with lithium aluminum hydride changed the uv spectrum to one similar to that of 7-methoxyharman, thus locating the phenolic group at C-10. On standing in trifluoroacetic acid, adifoline was dehydrated to anhydroadifoline, which with diazomethane gave a dimethyl derivative assigned structure **151** from spectral data. Adifoline was consequently formulated as **150**, the stereochemical details being determined from an nmr analysis.

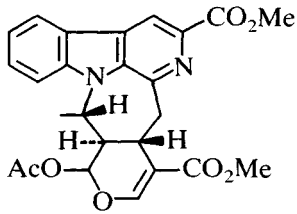


150

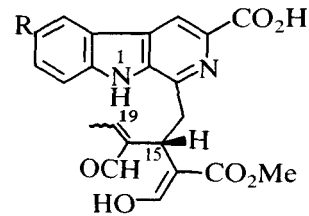


151

Merlini and Nasini subsequently isolated a deoxy analogue of adifoline as the methyl ester acetate derivative for which they deduced structure **152**.[73a] It is apparent that the two alkaloids differ in stereochemistry at C-19 and C-20, $J_{15,20}$ in the deoxy compound being 9.0 Hz (trans a-a) compound with 6.0 Hz (cis a-e) in the case of adifoline. However, the occurrence of two diastereomeric series is not surprising, since the seven-membered ring is presumably formed by a non-selective Michael addition of N-1 to C-19 in a rearranged aglucone (**153**) of cordifoline or deoxycordifoline.[74]



152



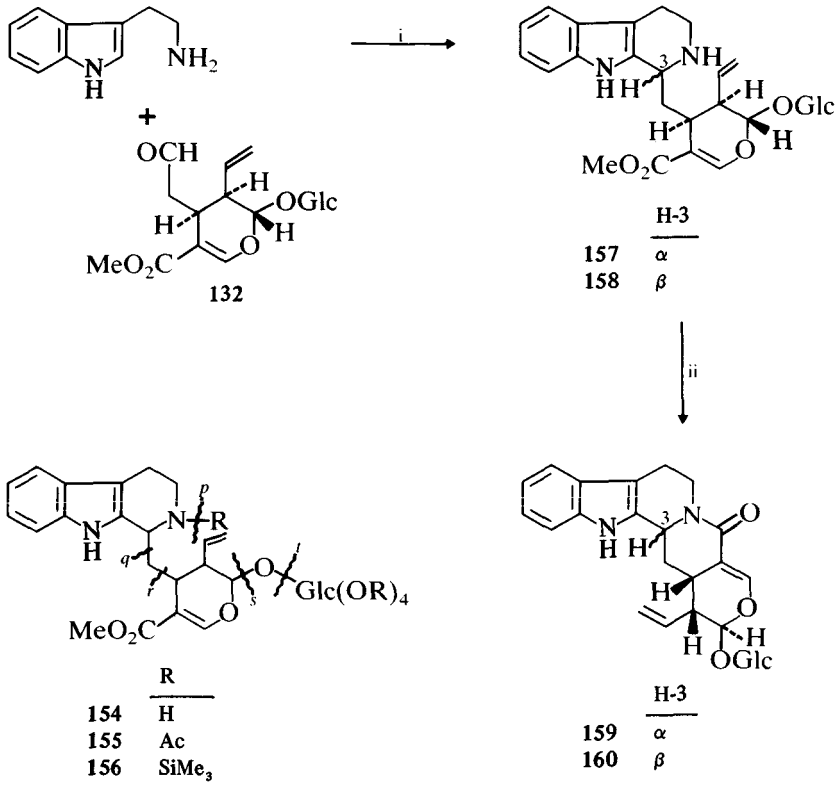
153 R = H or OH

B. Tryptamine Derivatives

1. *Strictosidine (157), Vincoside (158), and Related Alkaloids*

During an investigation on the constituents of *R. stricta*, an alkaloid glycoside was isolated, strictosidine, for which the gross structure **154** (Scheme 19) was

deduced largely by analogy with cordifoline[78] (Section V. A. 1). Functional groups in the base and derived pentaacetate (**155**) were detected from the uv, ir, and nmr and mass spectra. In particular, strong peaks in the mass spectra of **155** and **156** were attributable to cleavages *p* and *q*; other major ions due to cleavage *r*, *s*, and *t* revealed a similar fragmentation to corresponding cordifoline derivatives in accord with a common secoiridoid moiety (cf. Scheme 16).



Scheme 19. Reagents: i, pH 3.5; ii, Na_2CO_3.

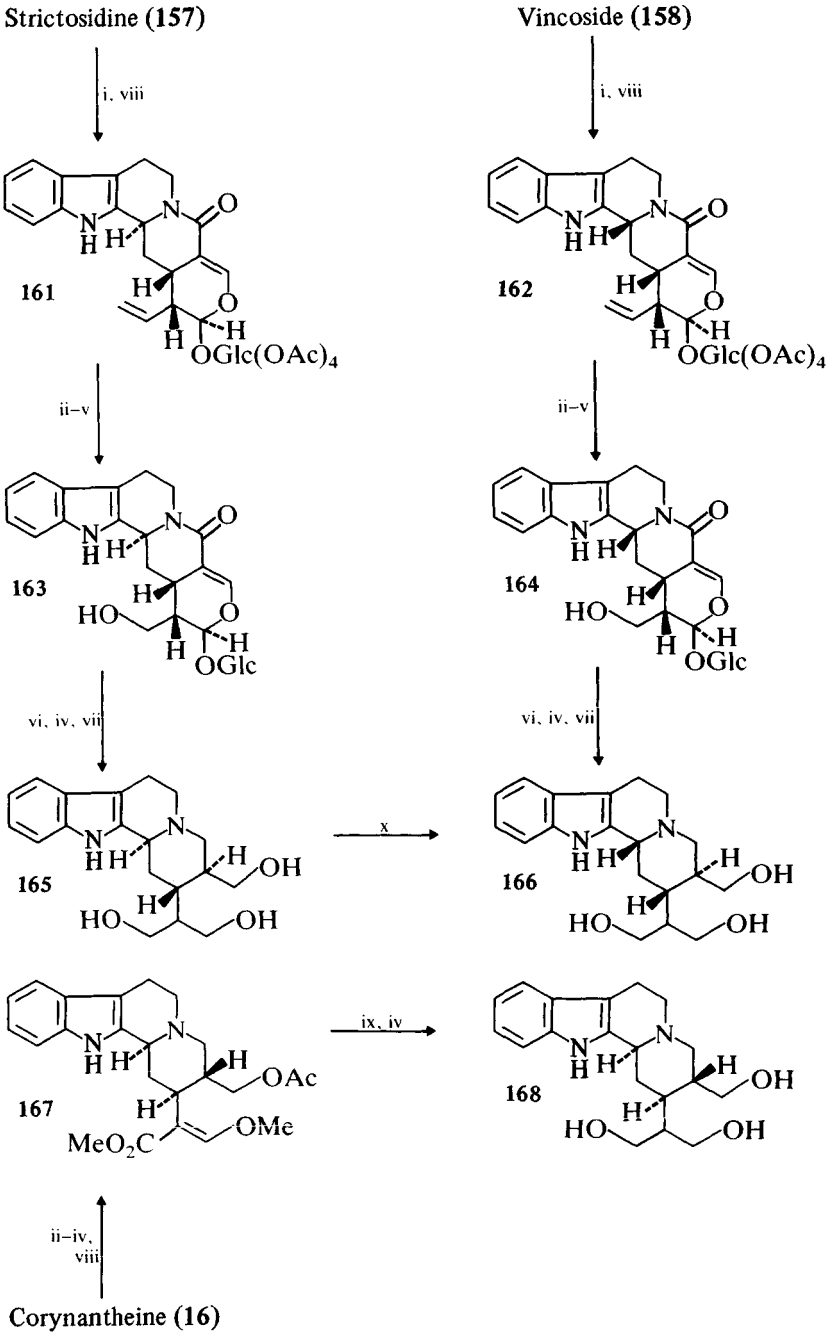
In contemporary work, secologanin (**132**) had been obtained, its structure and stereochemistry being established by correlation with ipecoside.[79] Condensation with tryptamine afforded two C-3 isomers (**157/158**), one corresponding to strictosidine (isovincoside), the other being its C-3 epimer, vincoside. Although the latter could be isolated as a hydrochloride salt, it was unstable as the base, in marked contrast to its epimer: aqueous sodium carbonate at room temperature very rapidly converted vincoside into its lactam (**159** or **160**), whereas in order to obtain strictosidine lactam (**159** or **160**) it was necessary to heat for a considerable time. Both lactams have since been isolated from natural sources, vincoside lactam from *A. rubescens*[80] and strictosidine lactam (strictosamide) from *R. stricta*[81] and *N. latifolia*.[82]

Hence the only remaining unknown feature in these alkaloids was the configuration at C-3. After an early erroneous assignment, the matter was clarified independently by three groups which established strictosidine as the 3α(*S*) isomer (**157**) and vincoside as the 3β(*R*) isomer (**158**). In one investigation, chemical and chiroptical correlations were made between vincoside, strictosidine, and corynantheine (**16**), an alkaloid of rigorously established absolute configuration (Section II. A) as outlined in Scheme 20.[80] The key observation was that vincoside must have 3β(*R*) stereochemistry since it was converted to a triol (**166**), which was found to be the enantiomer of a triol (**168**) obtained from corynantheine of 3α(*S*) stereochemistry; independent evidence for the C-3 configuration was the strong negative Cotton effect in the ord curve of **166** in accord with a 3β chirality, mirrored by a positive effect for **168**. Strictosidine taken through the identical reaction sequence produced an isomeric triol **165** with 3α stereochemistry as shown by ord; subsequent acid-catalyzed epimerization of H-3 in the usual manner then afforded **166**. A second approach was to correlate strictosidine with dihydroantirhine (**170**) of known stereochemistry via dihydrovallesiachotamine (**169**) (Scheme 21), exploiting a prior observation that vallesiachotamine was readily formed from strictosidine.[81,83] Particular care was needed to check that no inversion of C-3 had occurred and a second more complex correlation with the lactam was also made. Finally, parallel molecular rotation differences showed that C-3 in vincoside had the same *R* chirality as the corresponding center in ipecoside, whose absolute stereochemistry had been determined by X-ray crystallography.[84]

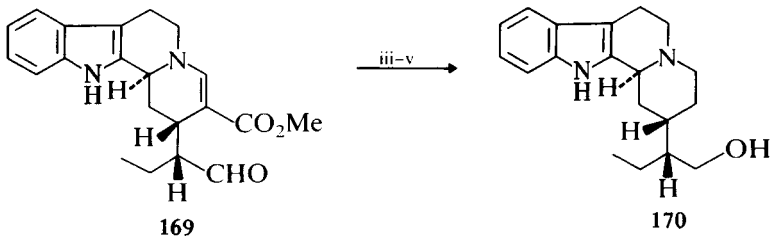
Removal of the sugar from strictosidine under weakly acidic condition afforded the known alkaloid vallesiachotamine (**171**), and, likewise by spontaneous rearrangement of the aglucone, vincoside gave the 3β epimer (**172**).[78,85,86] In this process two geometrical isomers of the ethylidene group are generated and hence vallesiachotamine is actually a mixture, thus explaining the anomalous nmr behavior reported in the original isolation. On the other hand, with methanolic hydrochloric acid, strictosidine is converted into a novel N-1 cyclized base, nacycline (**173**).[86]

2. *Rubescine (174) and 10-β-D-Glucosyloxyvincoside lactam (175)*

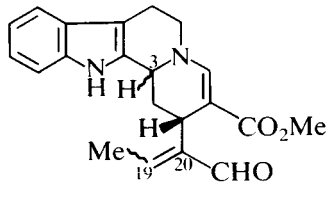
A neutral glycoalkaloid found in *A. rubescens* was rubescine (**174**). The relationship to vincoside lactam was immediately apparent when it was methanolyzed to **160** and methyl caffeate. The position of substitution of the caffeate ester on the sugar was located by 220 MHz nmr analysis of the tetrahydro derivative where only H-3′ was found in a low field position attributable to acylation.[87a] Another neutral alkaloid, isolated as the octaacetate, was found to be a bishexoside from its mass spectrum where two successive losses of 330 m.u. from its molecular ion at *m/e* 1012 were apparent. Eventually the structure of 10-glucosyloxyvincoside lactam (**175**) was proposed on the basis of uv, ir, nmr, and mass spectral data and confirmed by partial synthesis of the aglucone from 5-hydroxytryptamine (serotonin) and secologanin.[87b]



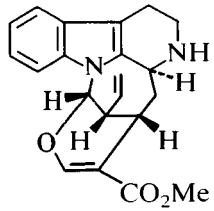
Scheme 20. Reagents: i, Na_2CO_3; ii, OsO_4; iii, $NaIO_4$; iv, $NaBH_4$; v, NaOMe; vi, β-glucosidase; vii, $LiAlH_4$; viii, Ac_2O, py; ix, HCl, Me_2CO; x, AcOH, Δ.



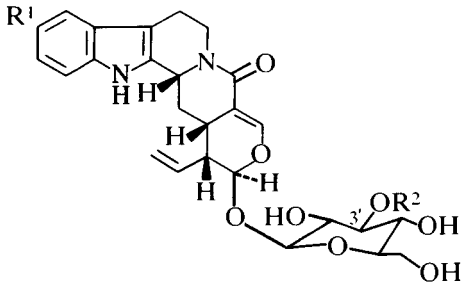
Scheme 21. Reagents: i, H_2, cat.; ii, hydrolysis; iii, OH^-; iv, H^+; v, $NaBH_4$.

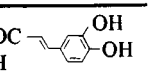


	H-3
171	α
172	β



173

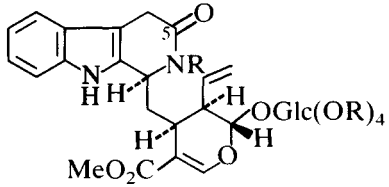


	R^1	R^2
174	H	
175	β-D-Glc	H

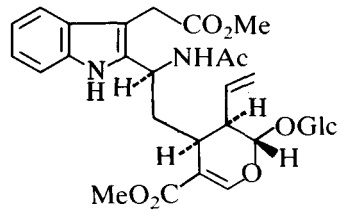
3. *5-Oxostrictosidine (176), Lyaloside (179), Pauridianthoside (180), and Palinine (181)*

The structure **(176)** of the 5-oxo derivative of strictosidine from *A. rubescens* was deduced from uv, ir, nmr, cd, and mass spectral data and its chemical

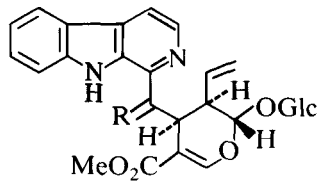
reactions.[88] One particularly informative transformation was cleavage in the imide derivative (**177**) with sodium methoxide to give **178**, which provided an essential clue to the nature of ring C.



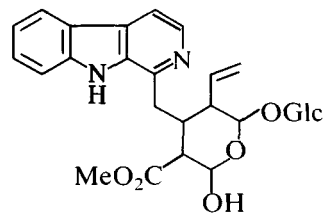
	R
176	H
177	Ac



178



	R
179	H_2
180	O

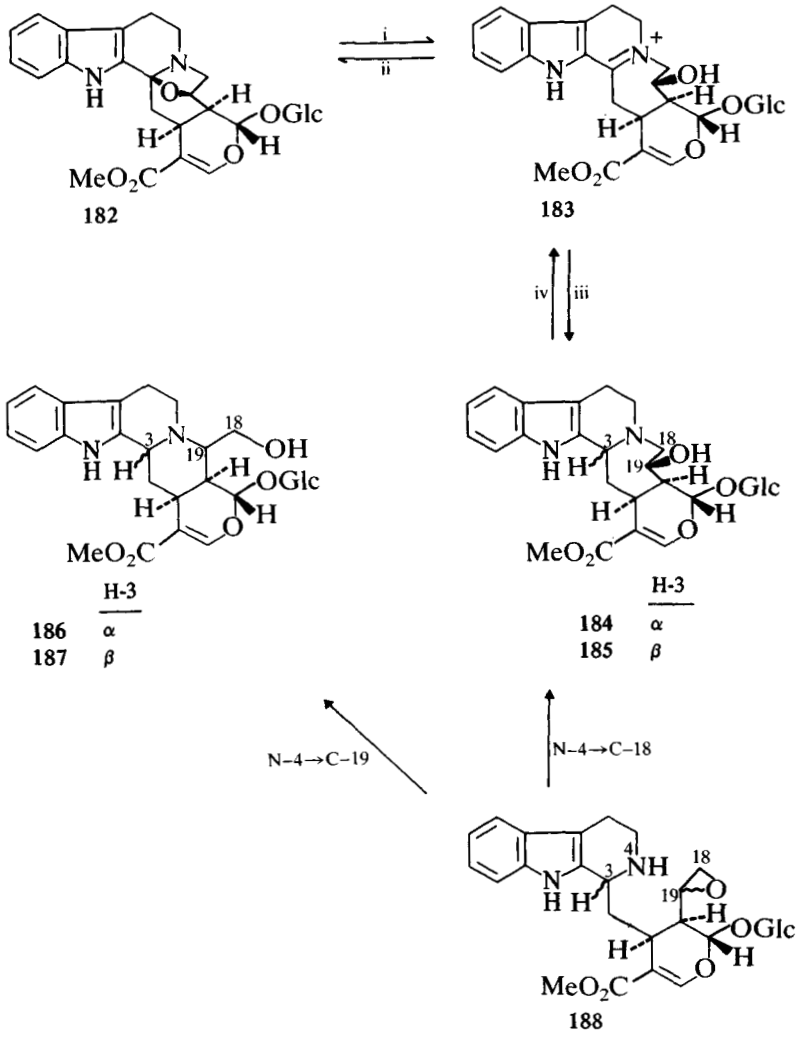


181

An alternative mode of oxidation of ring C was represented by the β-carboline bases lyaloside (**179**) and pauridianthoside (**180**) from *Pauridiantha lyalli*.[89] The authors proposed configurations for these alkaloids at C-20 and C-21 which differed from those of secologanin derivatives on the basis of $J_{15,20}$ and $J_{20,21}$ couplings of 3.5 and 5.0 Hz, respectively, but in fact these values are virtually identical with those of cordifoline, for example (Section V. A. 1). Hence these alkaloids should be formulated as the strictosidine derivatives **179** and **180**. The β-carboline alkaloid palinine from *Palicourea alpina* is presumably a water adduct (**181**) of lyaloside.[90]

4. *Cadambine (182), 3α- (184) and 3β-Dihydrocadambine (185), 3α- (186) and 3β-Isodihydrocadambine (187)*

Extracts of the wood and leaves of *Anthocephalus cadamba* have yielded five related indole glucosides: cadambine (**182**), its 3-epimeric dihydro derivatives (**184**) and (**185**), and two epimeric isodihydrocadambines (**186**) and (**187**);[91] **184** has also been isolated from *N. diderichii*.[92] A striking feature of the uv spectrum of cadambine was the reversible change from an indole to a 3,4-dihydro-β-carbolinium chromophore (**183**) on addition of acid (Scheme 22). The relationship between three of the alkaloids became apparent when reduction of cadambine gave 3α- and 3β-dihydrocadambine, whereas mild oxidation of the 3α-dihydro derivative regenerated cadambine.[91] Further chemical reactions with supporting spectral data



Scheme 22. Reagents: i, H^+; ii, OH^-; iii, $NaBH_4$; iv, $Hg(OAc)_2$.

and, in particular, a complete nmr analysis of virtually all the protons led to the formulation of structure **182** for cadambine. Cd data confirmed that **182** was the absolute configuration, and also distinguished the 3α- and 3β-dihydrocadambines.

Structural assignments for the epimeric pair of isodihydrocadambines (**186**) and (**187**) likewise depended largely on the full range of spectroscopic methods.[91b,c] One distinguishing characteristic in the mass spectra of various derivatives was the invariable presence of a major ion attributable to cleavage of the 18,19 bond, a process facilitated by the lone pair on N-4.

All four dihydro isomers have novel N-4,C-18 or N-4,C-19 bonds and can be visualized as arising from alternative modes of attack by N-4 on 18,19-epoxides

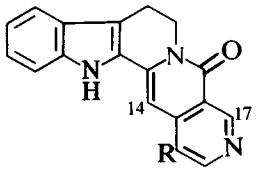
(**188**) of strictosidine and vincoside. It is evident that an *R*-epoxide would be the correct precursor for the dihydrocadambines but since the configuration at C-19 is as yet unknown for **186/187** a similar prediction cannot be made for the isodihydrocadambines. Again, since strictosidine is apparently the universal source of all indole alkaloids, the 3β derivatives may actually be formed via dehydro intermediates such as **183**.

VI. INDOLOPYRIDINE ALKALOIDS

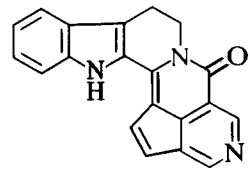
During the past 10 years there has appeared an increasing number of alkaloids composed of tryptamine and substituted pyridine moieties, the latter being derived from a secologanin aglucone unit by insertion of nitrogen (Table V, structures **189–208**). In some cases the full C_{10} unit is present; in others it has been modified by removal of the ester, vinyl, or other groups. It is significant that most of the indolopyridines occur together with structurally related glycoalkaloids whose aglycones constitute obvious precursors for the pyridine units by condensation with ammonia, either endogenous or used in extraction procedures. Subsequent modification can then be rationalized in simple combinations of oxidation, addition of water, β-dicarbonyl or retro-aldol cleavages, etc., all of which can occur spontaneously, and hence in many cases the alkaloids are artifacts. In this context it is noteworthy that 18,19-dihydroangustine (**190**) has been prepared from the aglucone

TABLE V. INDOLOPYRIDINE AND RELATED ALKALOIDS

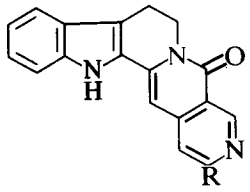
Name	Structure	Ref.	Original source
Angustine	**189**	93a, b, d	*Strychnos angustiflora*
Angustoline	**191**	93a, b	*S. angustiflora*
Angustidine	**195**	93a	*S. angustiflora*
Nauclefine (parvine)	**194**	93b	*Nauclea latifolia*
Naucletine	**192**	93b	*N. latifolia*
Naulafine	**193**	93c	*N. latifolia*
Lyaline	**196**	94a	*Pauridiantha lyalli*
Lyadine	**197**	94a	*P. lyalli*
Lyalidine	**198**	94b	*P. lyalli*
Hydroxylyalidine	**199**	94b	*P. lyalli*
Pauridianthinol	**200a**	94a	*P. lyalli*
Pauridianthine	**200b**	94a, d	*callicarpoides*
Pauridianthinine	**201**	94d	*callicarpoides*
Cadamine	**203a**	95a	*Anthocephalus cadamba*
Isocadamine	**203b**	95a	*A. cadamba*
Nauclechine	**204**	94c	*N. latifolia*
Decarbomethoxynauclechine	**205**	94c	*N. latifolia*
Naufoline	**206**	94c	*N. latifolia*
Naucleonidine	**207**	95b	*N. diderichii*
Naucleonine	**208**	95b	*N. diderichii*
Mostueine	**202a**	96b	*Mostuea brunonis*
Decussine	**202b**	96c, d	*S. decussata*



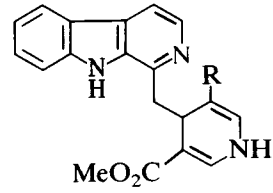
	R
189	$CH{=}CH_2$
190	Et
191	CH(OH)Me
192	COMe



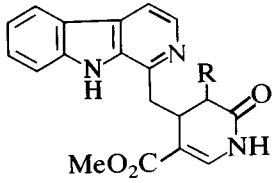
193



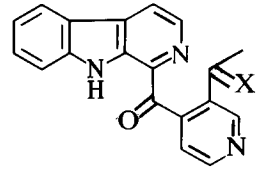
	R
194	H
195	Me



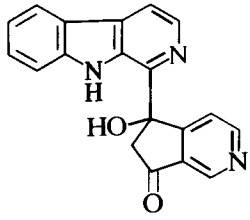
	R
196	$CH{=}CH_2$
197	CH(OH)Me



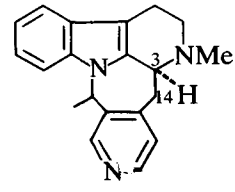
	R
198	CHMe
199	CH(OH)Me



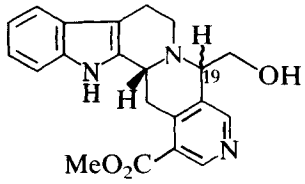
	X
200a	H, OH
200b	O



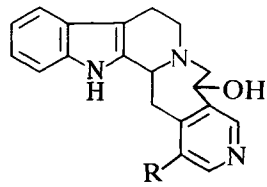
201



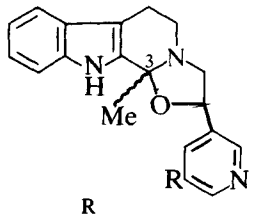
202a
202b: 3,14 dihydro



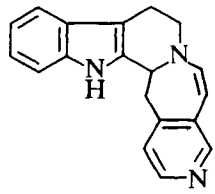
	H-19
203a	α
203b	β



	R
204	CO_2Me
205	H

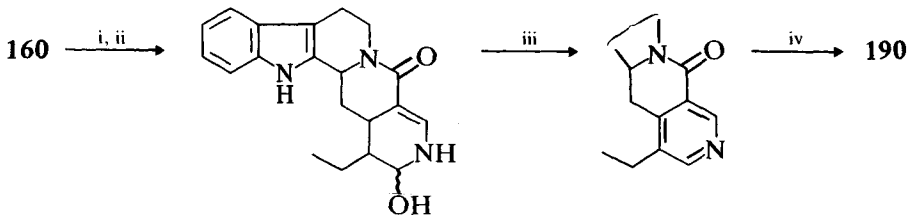


	R
207	CO_2Me
208	H



206

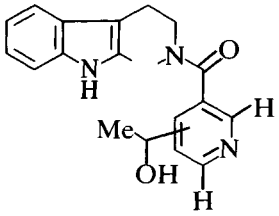
of dihydrovincoside lactam by treatment with ammonia and subsequent oxidation (Scheme 23).[96a]



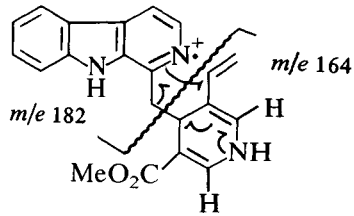
Scheme 23. Reagents: i, β-glucosidase; ii, NH_3; iii, S, xylene, Δ; iv, CF_3CO_2H, O_2.

Structure determination for these alkaloids has usually been readily accomplished with the aid of modern spectroscopic techniques, particularly nmr and mass spectra. Thus, for example, with the highly unsaturated skeleton of angustoline the high resolution nmr spectrum revealed in addition to the protons of the tryptamine unit and the methylcarbinol group, two pyridine α protons, one of which was ortho to a carbonyl group, and one unsaturated proton. These data were in accord with part structure **209**, which could be extended to the complete structure **191** from the observation of a long range W-coupling between the last two protons above, attributed to H-17 and H-14, respectively.[93a] Again, with lyaline (**196**) and its congeners, nmr evidence for the 1,4-dihydropyridine moiety was obtained when on addition of D_2O the coupling of the α protons with NH was removed.[94a] In this case the mass

spectral fragmentation was also extremely informative, cleavage of the 14,15 bond in the molecular ion (**210**) occurring very readily as indicated to give important peaks at *m/e* 182, corresponding to harman, and at *m/e* 164, corresponding to the pyridine residue.

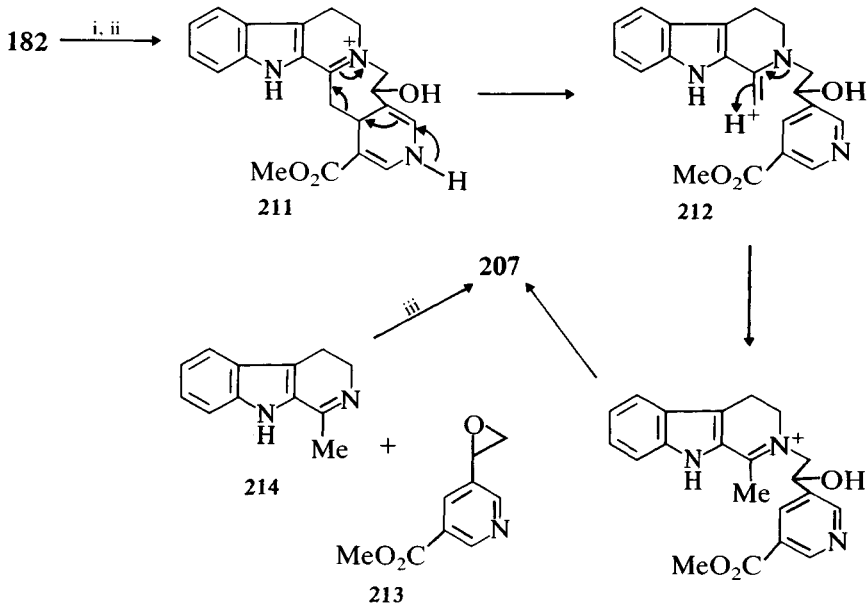


209



210

One of the most interesting compounds is naucleonidine, inasmuch as its origin from a parent glycoalkaloid is not immediately apparent. Its structure was formulated as **207** on the basis of spectral data and, in particular, uv behavior analogous to cadambine, and confirmed by synthesis from the dihydro-β-carboline **214** and epoxypyridine **213**.[95b] Doubling of some nmr signals was eventually attributed to the presence of diastereoisomers formed by reversible opening of the ether ring. The most likely precursor would seem to be cadambine (**182**) as outlined in Scheme 24: reaction of ammonia with the aglucone would lead to a dihydropyridine (**211**), which could then aromatize by cleavage of the 14,15 bond, giving **212**; subsequent protonation and cyclization of the alcohol would generate **207**.



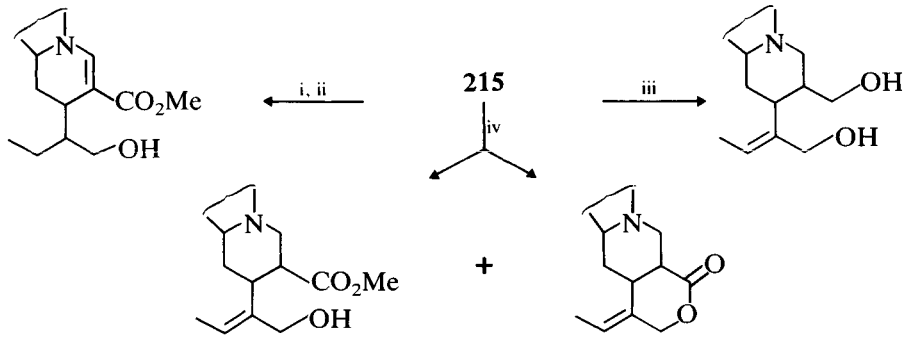
Scheme 24. Reagents: i, hydrolysis; ii, NH_3; iii, $CHCl_3$, N_2, heat 72 hours.

VII. MODIFIED CORYNANTHE ALKALOIDS

A. Natural Bases

Alkaloids in which the basic *Corynanthe* skeleton has been extensively rearranged are properly the subject of other chapters, but it is appropriate to discuss a few of the simpler modifications here. Thus vallesiachotamine, mentioned above as a glycolysis product of strictosidine, was originally isolated from *Vallesia dichotoma* Ruis et Pav.[85]

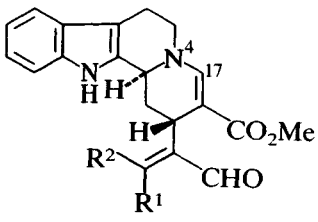
Its uv spectrum was a composite of an indole and another chromophore eventually shown to be a β-aminoacrylate, and the ir and nmr spectra revealed the presence of aldehyde, methyl ester, and ethylidene groups. Although the mass spectral fragmentation of vallesiachotamine itself was not immediately informative, those of various reduction products summarized in Scheme 25 had the peaks at *m/e* 184, 170, 168, and 156 characteristic of a tetrahydro-β-carboline moiety. Furthermore the implications of these chemical transformations and associated spectral data,



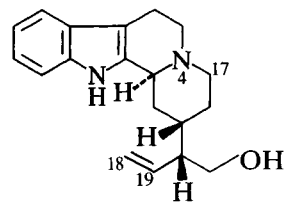
Scheme 25. Reagents: i, $NaBH_4$; ii, H_2, cat.; iii, $LiAlH_4$; iv, $NaBH_4$, AcOH.

together with biogenetic speculation, led to the formulation of vallesiachotamine as **215** (without stereochemistry) containing a novel N-4,C-17 bond. Support for this assignment was obtained from nmr spectra with the aid of decoupling to establish the sequence N–CH–CH_2–CH–C=C–; it was later substantiated by the production of vallesiachotamine from strictosidine which was also established the configurations at C-3 and C-15. An initially puzzling feature of the nmr spectrum was the doubling of some signals, but this was subsequently realized as attributable to the presence of both *E* and *Z* geometrical isomers **215a** and **215b**: the former was identified from the chemical shift of its aldehydic proton at δ 10.2, the signal appearing at δ 9.3 for the latter.[97] In all likelihood vallesiachotamine is formed by spontaneous rearrangement of strictosidine aglucone as in vitro (Scheme 26).

An identical N-4,C-17 bond is found in antirhine (**216**), an alkaloid from *Antirhea putaminosa* (F. v. Muell) Bail, which is presumably derived as in Scheme 26.[98a,b] Its constitution was deduced from uv, ir, nmr, and mass spectral data, and

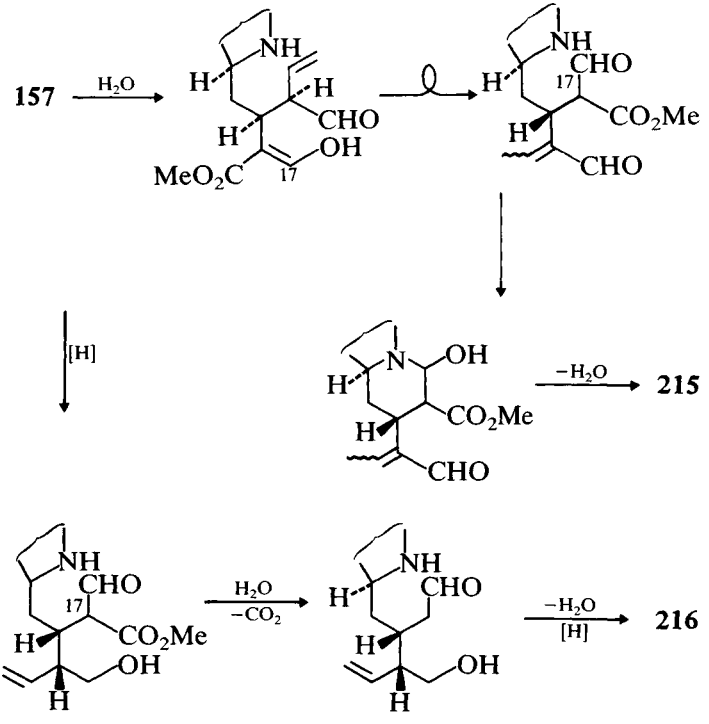


	R^1	R^2
215a	H	Me
215b	Me	H

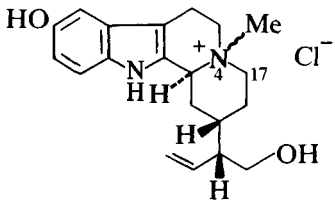


216

confirmation of both structure and absolute stereochemistry was achieved when tosylation of 18,19-dihydroantirhine (**170**) afforded the known quaternary salt **20** (cf. Scheme 3). As mentioned above, 19,20-dihydrovallesiachotamine (**169**) was later converted into **170** (Scheme 21), thus correlating both vallesiachotamine and strictosidine. Another analogous pair of alkaloids are the hunterburnine α- and β-methochlorides (**217**) whose structures were determined by the X-ray method;[99a–d] their absolute configurations were eventually obtained by synthesis from quinine.[99e]

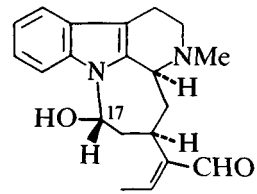


Scheme 26.

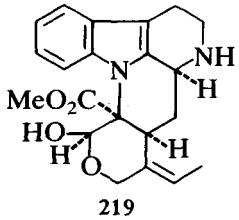


NMe

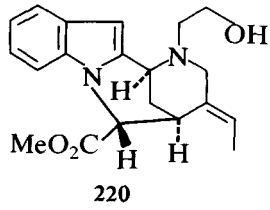
217a α
217b β



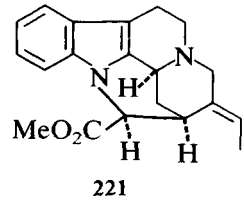
218



219

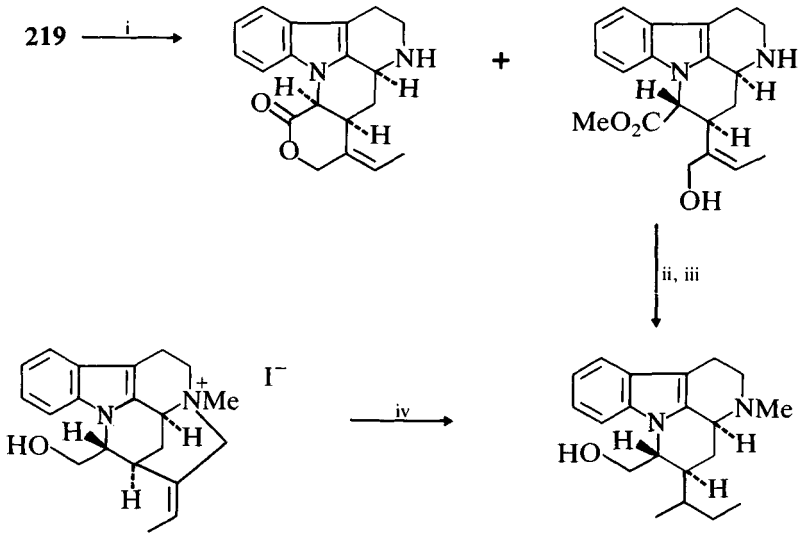


220



221

Elucidation of the structure of akagerine (**218**), a *Strychnos* alkaloid, was also achieved by X-ray diffraction.[100] Again, it can readily be derived from strictosidine except that in this case cyclization of the C-17 aldehyde occurs to N-1 since N-4 is blocked by methylation. An alternative bonding by N-1 is via oxidative coupling to C-16 as in talbotine (**219**)[101] and vinoxine (**220**),[102] two recently discovered variants on the theme of the *Pleiocarpa* alkaloids exemplified by pleiocarpamine

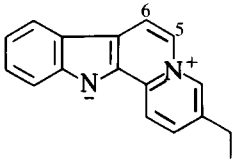


222

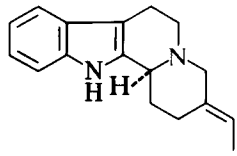
Scheme 27. Reagents: i, NaOMe; ii, H_2, Pd–C, CH_2O; iii, $LiAlH_4$; iv, Emde reduction.

(**221**).[103] The constitution of talbotine was elucidated by a correlation with ϵ_1-mavacurine, the Emde reduction product of the known alkaloid mavacurine (**222**) (Scheme 27). Its absolute stereochemistry was established by applying Horeau's method to the *O*-methyl ether, since the usual procedure of comparing molecular rotation differences on acetylation proved erroneous.[101]

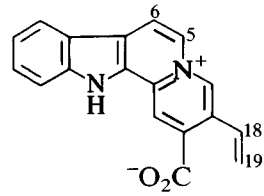
Even more drastic skeletal modification is the loss of the C_3 substituent group from C-15 in flavopereirine (melinonine-G) (**223**), a simple yellow quaternary base from *Geissospermum laeve* (Vellozo) Baillon, and its 5,6-dihydro derivative **224** from *S. usambarensis*.[104] A similar alkaloid is deplancheine (**225**), which had actually been synthesized before its recent discovery in *Alstonia deplanchii* van Heurck et Mueller Arg.[105,141] Instead of being lost as a unit, the three carbons (C-16, 17, and 22) may be removed consecutively, giving rise to the zwitterionic alkaloids vincarpine (**227**),[106] dihydrovincarpine (**228**),[106] and flavocarpine (**226**),[107] where C-16 is retained.



223
224: 5,6-dihydro

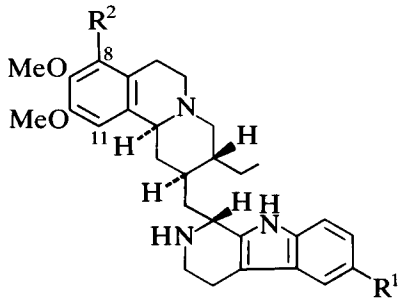


225



226
227: 5,6-dihydro
228: 5,6,18,19-tetrahydro

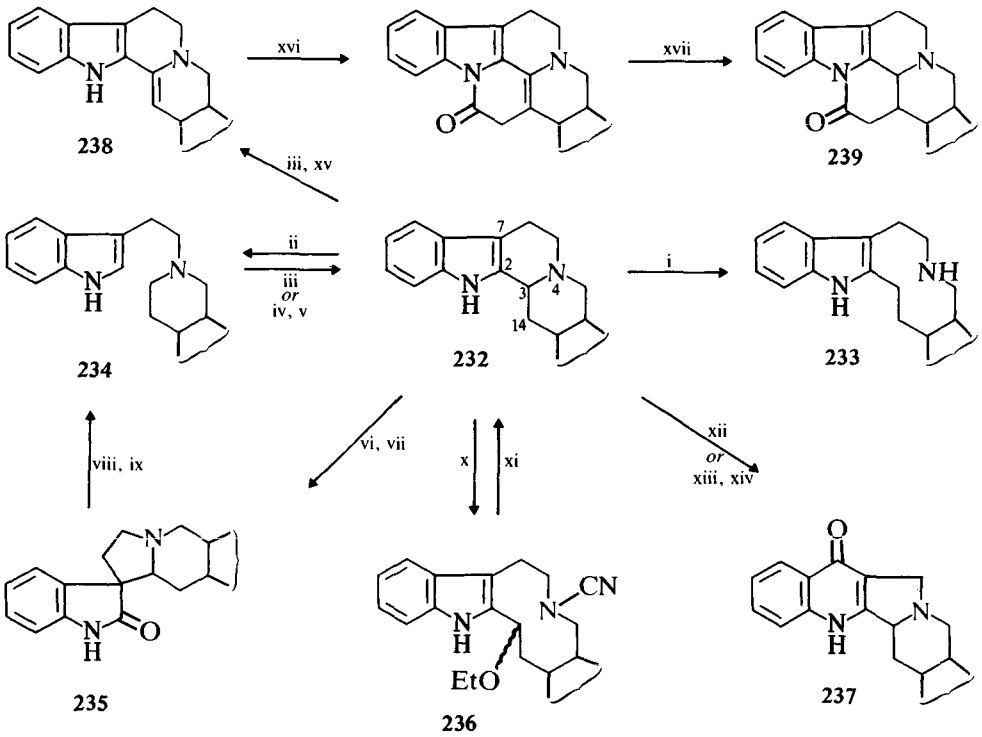
Strictly speaking, the indole alkaloids of *Alangium lamarckii* Thw. – tubulosine (**229**), deoxytubulosine (**230**), and alangimarckine (**231**) – are more closely related to the isoquinoline alkaloid emetine than *Corynanthe* alkaloids, in that the tryptamine unit is condensed with the equivalent of C-17 rather than C-3, and indeed the structures were largely elucidated by comparison with emetine.[108] The location of the phenolic group in alangimarckine at C-8 rather than C-11 as previously supposed was eventually established by synthesis.[108d]



	R^1	R^2
229	OH	H
230	H	H
231	H	OH

B. Transformation Products

In the continuous search for compounds of therapeutic value several chemical reactions of indoles have been applied to the β-carboline moiety (**232**) of *Corynanthe* alkaloids generally in addition to the yohimbine type (see Chapter IV). Some of the transformations have been mentioned above at various stages, and others are outlined in Scheme 28. Thus with metal and acid,[109] reductive cleavage of the 3,4 bond to give **233** occurs, whereas formic acid yields the 2,3-seco products **234**,[110] – the latter can be recyclized by various oxidative methods, including the Polonovski reaction.[111] Under some oxidation conditions an alternative N-4,C-21 immonium is produced from **234**, resulting in the unnatural "inside" isomers.[110c] The conversion of indole into oxindole alkaloids (see Section IV) is well established, and now the reverse process from **235** is feasible via reduction of the imino ether obtained with Meerwein's reagent to **234**.[112] A very useful cleavage of the 3,4 bond in **232** can be achieved with cyanogen bromide (or ethyl chloroformate), the product **236** subsequently being used to synthesize various alkaloids, for example, burnamicine (**30**) from geissoschizol as described in Scheme 4, and derivatives of



Scheme 28. Reagents: i, Zn, AcOH; ii, HCO_2H, DMF, Δ; iii, $Hg(OAc)_2$; iv, H_2O_2; v, $(CF_3CO)_2O$; vi, $Pb(OAc)_4$ or Bu^tOCl; vii, H_3O^+, MeOH; viii, $Et_3O^+ BF_4^-$; ix, $NaBH_4$, AcOH; x, CNBr, EtOH, K_2CO_3; xi, AcOH, Δ; xii, $KOBu^t$, DMSO, O_2; xiii, $NaIO_4$; xiv, Et_3N; xv, OH^-; xvi, $ClCH_2CO_2Me$, Δ; xvii, $NaBH_3CN$, AcOH.

pleiocarpamine (**221**) from hirsutine, dihydrocorynantheine, and geissoschizine.[113] The indole 2,7 bond has also been cleaved by oxidation with oxygen in presence of a strong base[114] or with sodium periodate,[115] the intermediate ketolactam cyclizing to a quinolone (**237**) spontaneously in the former case, or on treatment with triethylamine in the latter. Conversion of a heteroyohimbine into an eburnamonine analogue (**239**) was achieved via the 3,14-enamine **238** produced by mercuric acetate oxidation.[116]

VIII. SYNTHESES

The variety of structures offered by the *Corynanthe* alkaloids, ranging from the simple achiral skeleton of flavopereirine to compounds with several different functionalities and stereochemical features such as geissoschizine or formosanine, has obviously presented a continuing challenge to practitioners of organic synthesis at all levels. A large number of syntheses have been achieved and are listed in Table VI, but we can discuss only a few in detail.

A. Total Syntheses

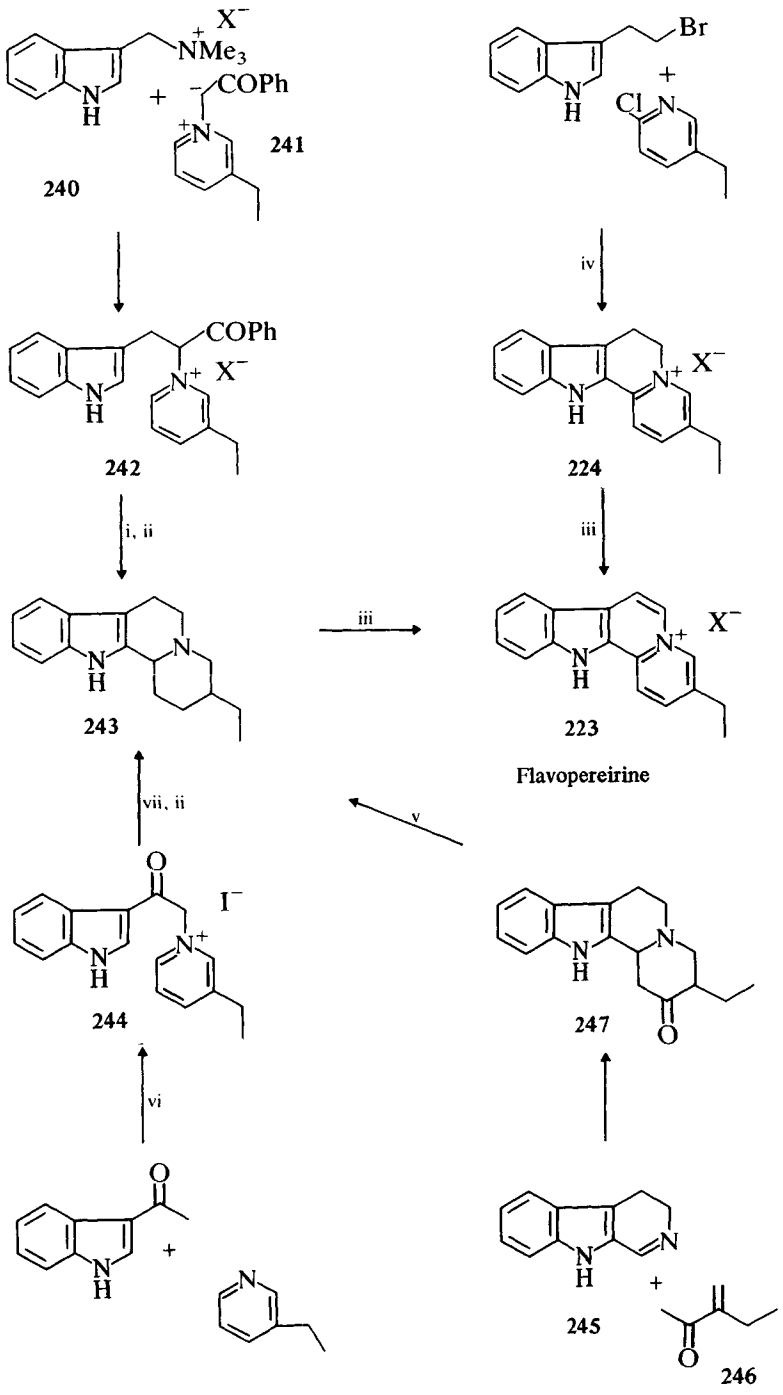
In view of their lack of chirality, it is perhaps hardly surprising that the simple indolo[2,3a]quinolizines have attracted much attention, flavopereirine itself having been synthesized several times[139] by various routes, some of which are outlined in Scheme 29. One common approach is via pyridinium salts which are cyclized to the indole to produce ring C in various ways. Thus **242** was obtained by reaction of a pyridinium ylide **241** with a quaternary salt of gramine (**240**), and afforded **243** on catalytic hydrogenation after alkaline cleavage of the phenacyl group.[139c] The requisite bond formation presumably occurred by nucleophilic attack of the indole on an intermediate dihydro- or tetrahydropyridine, as in **248** → **249**. A similar approach[139i] was by reduction of the quaternary iodide **244**, obtained by coupling of 3-acetylindole and 3-ethylpyridine with iodine. In both cases dehydrogenation of **243**, for example, by consecutive treatment with mercuric acetate and palladium-charcoal, yielded flavopereirine (**223**). An even simpler cyclization method used a 2-chloropyridine and tryptophyl bromide to form 5,6-dihydroflavopereirine (**224**) directly.[139e] An alternative route[139j] is based on the Wolff-Kishner reduction to **243** of the ketone **247**, conveniently produced by addition of dihydro-β-carboline (**245**) to an α,β-unsaturated ketone (**246**), a procedure due to Openshaw and Whittaker.[120b] The ready availability of this tetracyclic ketone (**247**) with two chiral centers was exploited in syntheses of more complex alkaloids described below.

Before its isolation deplancheine (**225**) had actually been prepared by Winterfeldt[141] as a model compound for his synthetic approach to geissoschizine (see below). Two recent syntheses[105a,b] were from pyridinium salts **250** and **251** via dihydropyridine intermediates, the latter route having the interesting feature of apparently generating stereoselectively an *E* configuration in the ethylidene group (Scheme 30). Presumably the dienamine produced on hydrolysis and

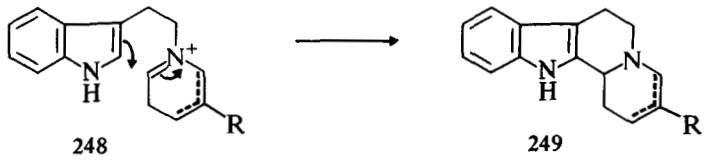
TABLE VI. SYNTHESES OF SOME CORYNANTHE ALKALOIDS AND RELATED SYSTEMS

Alkaloid	Ref.
Flavoperereirine (223)	139
Dihydroflavopereirine (224)	139
Flavocarpine (226)	140
Deplancheine (225)	105, 141
Angustidine (194)	134a, b, 135
Naucletine (192)	134a
Angustoline (191)	134a, c
Nauclefine (parvine) (193)	136, 137, 138b
Angustine (189)	137, 138a
Dihydroangustine (190)	135
Naucleonine (208)	95b, c
Naucleonidine (207)	95b, c
Akagerine (218)	100c
Antirhine (216)	98c
Dihydroantirhine (170)	142
Mavacurine (222)	125
Dihydrocorynantheane (10)	8
Dihydrocorynantheol (18)	121
Corynantheidol (29)	119
Dihydrocorynantheine (17)	22d, 117, 118, 120, 122, 123, 144
Corynantheidine (24)	120, 122a, 144
Hirsutine (25)	123, 124d, 144
3-Isocorynantheidine (26)	123, 144
Corynantheine (16)	118
Geissoschizine (27)	118, 124
Sitsirikine (33)	25a
Adirubine (39)	28b
Ajmalicine (54)	42b, 55, 126, 128, 129
Tetrahydroalstonine (55)	42, 55, 127–131
Akuammigine (59)	42, 55, 127, 128, 131
19-Epiajmalicine (60)	40, 42a, b, 54, 127–129
3-Iso-19-epiajmalicine (56)	40, 42a, 127
Rauniticine (61)	54
Cathenamine (75)	54
19-Epicathenamine (78)	54
N-Methylrhynchophyllane (93)	59
Rhynchophyllol (90)	64
Rhynchophyllines (83/84)	65, 132
Mitraphyllines (104/105)	133
Formosanines (106/107)	40, 42a, 127, 133
Condoxine (103)	146

decarboxylation of **252** is protonated while in the preferred transoid conformation to give a conjugated immonium system (**253**) with an *E* orientation of the alkene (cf. **73** → **74** in Scheme 10 and Refs. 54, 55); an additional factor may be a destabilizing "peri" interaction between H-21 and the methyl group in the alternative *Z* geometrical isomer.

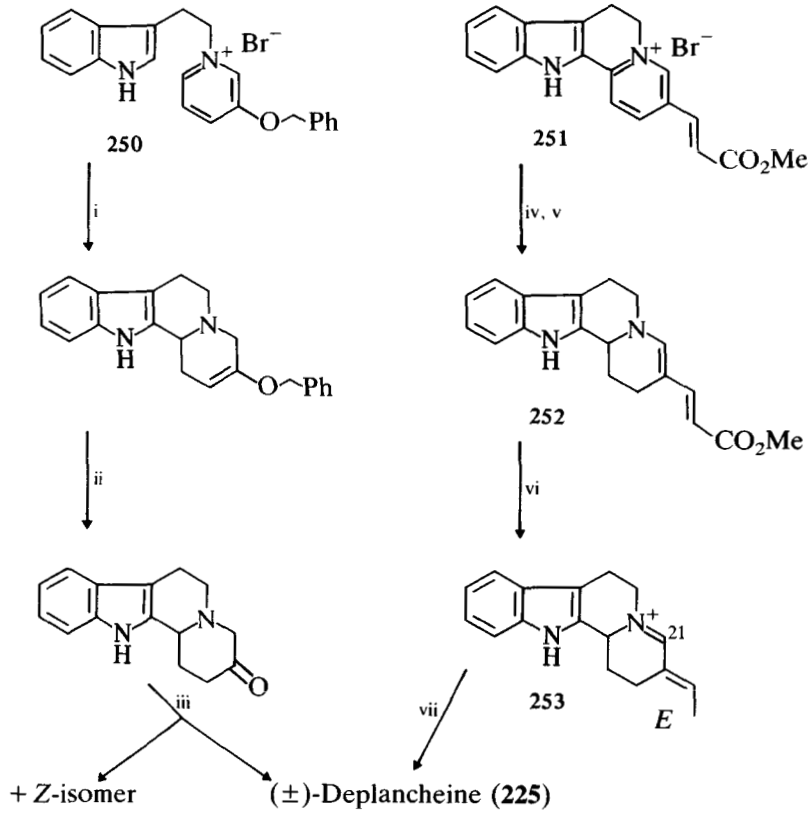


Scheme 29. Reagents: i, OH^-, EtOH; ii, H_2, cat.; iii, dehydrogenation; iv, Δ; v, N_2H_4, OH^-, Δ; vi, I_2; vii, $LiAlH_4$, THF.

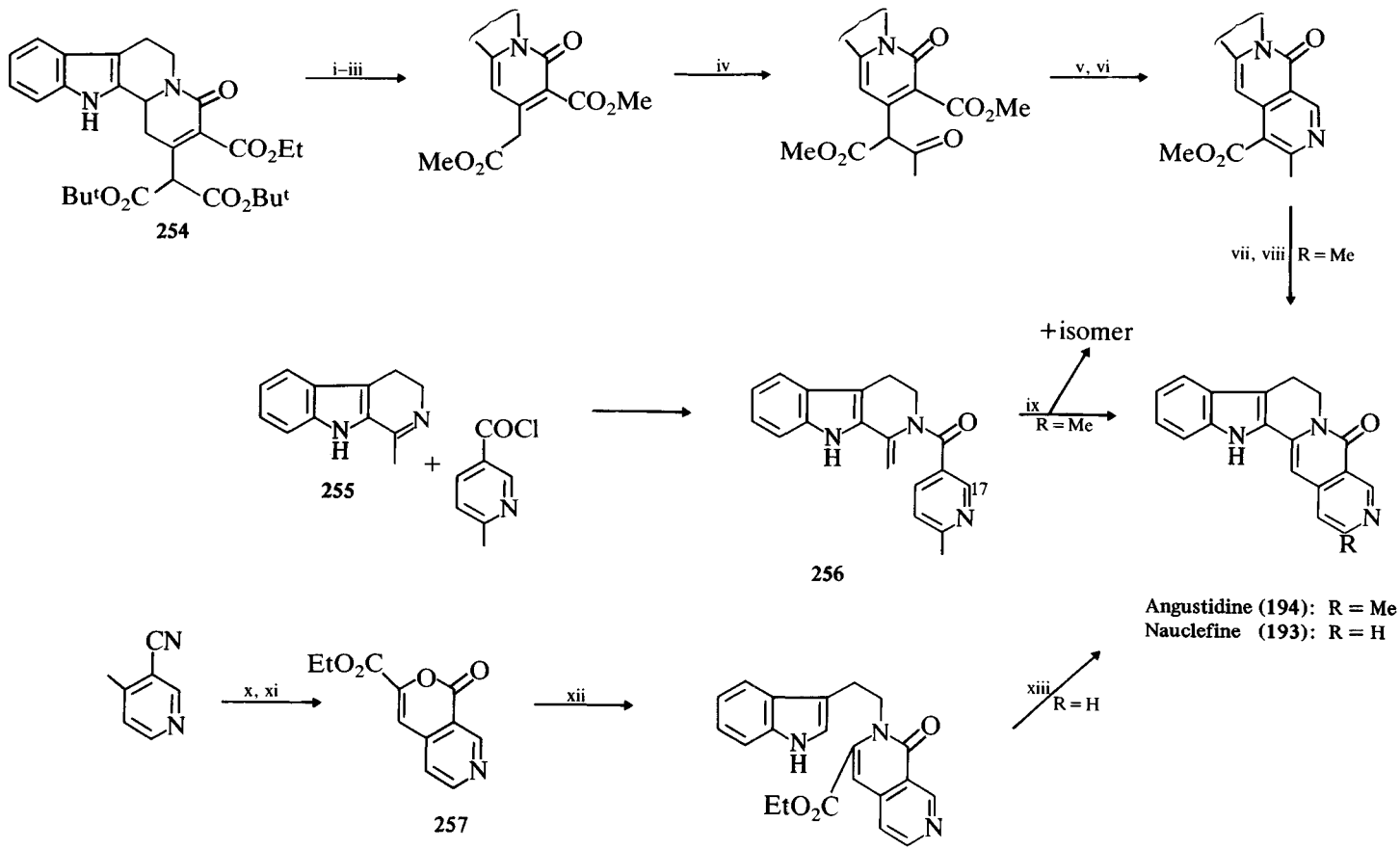


248 249

Several general routes to indolopyridine alkaloids have been devised (Schemes 23 and 31). As in the biogenetically patterned preparation of dihydroangustidine (**190**) from the aglucone of dihydrovincoside lactam mentioned above (Scheme 23),[96] Winterfeldt's synthesis of angustidine (**194**) from the lactam **254** also inserted ammonia into a β-dicarbonyl compound to create the pyridine ring (Scheme 31).[135] An alternative synthetic route to indolopyridine alkaloids starting from a pyridine was based on Wenkert's dihydrogentianine synthesis[119] (cf. Scheme 33), the key intermediate **257** being prepared in an entirely analogous manner from 4-methylnicotinonitrile.[137] After condensation of **257** with tryptamine, ring C was closed with concomitant loss of the carboethoxy group by heating in acid. How-



Scheme 30. Reagents: i, $LiAlH_4$, THF; ii, HCl; iii, $Ph_3P{=}CHMe$; iv, $Na_2S_2O_4$; v, HCl, MeOH; vi, aq. HCl, Δ; vii, $NaBH_4$.

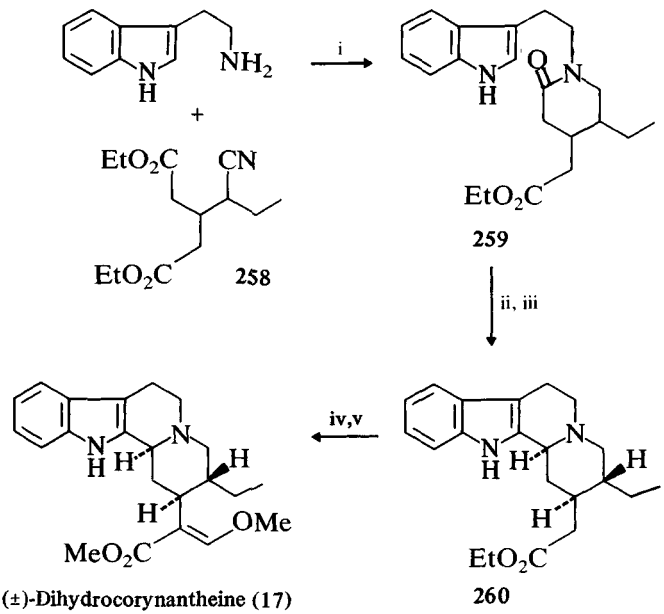


Scheme 31. Reagents: i, $SOCl_2$; ii, CF_3CO_2H; iii, H^+, MeOH; iv, NaH, Ac_2O; v, Bu^i_2AlH; vi, NH_3; vii, OH^-; viii, quinoline, Δ; ix, *hν*; x, $CH_2(CO_2Et)_2$, $KOBu^t$; xi, H_3O^+; xii, tryptamine; xiii, HCl, AcOH, Δ.

ever, the shortest and most direct route is that of Ninomiya et al., who exploited their enamide photocyclization in a neat synthesis of angustidine (**194**) and its congeners.[134] Irradiation of **256**, readily prepared from the dihydro-β-carboline **255** and 6-methylnicotinoyl chloride, gave **194** in 20% yield together with an isomer produced by the alternative cyclization to C-17. Subsequently it was found that formation of the unwanted isomer could be suppressed by quaternizing the pyridine nitrogen with a benzyl group.[136b]

Since these molecules were either achiral or had only one chiral center, the question of stereochemistry did not arise, except for the geometrical isomerism of deplancheine. However, the majority of *Corynanthe* alkaloids possessed three or more chiral centers and hence their syntheses involved major problems in stereoselectivity in the production of diastereoisomers as well as regioselectivity. These difficulties are evident in the first total synthesis of one of these alkaloids – dihydrocorynantheine (**17**) by van Tamelen et al. in 1957[117a,b] (Scheme 32). Reductive amination of the nitrile ester **258** with tryptamine yielded **259**, together with an isomeric lactam, which had to be separated. Bischler-Napieralski cyclization of the former, followed by catalytic hydrogenation, gave the tetracyclic base **260**, which was transformed by Claisen formylation with methyl formate and subsequent methylation into racemic dihydrocorynantheine. Obtainment of **17** thus largely depended on its being one of the more stable normal diastereomeric series.

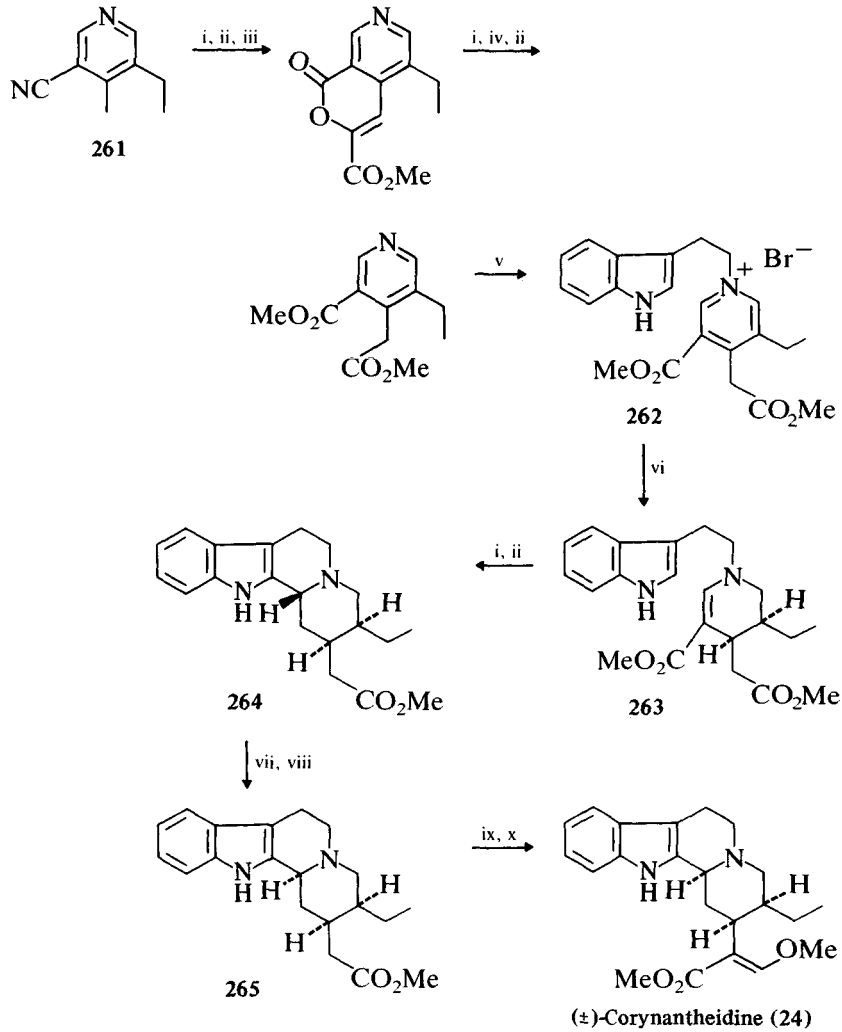
The allo epimer of dihydrocorynantheine, corynantheidine (**24**), was obtained by Wenkert and co-workers in a typical application of his elegant general approach using substituted pyridinium salts as synthetic intermediates (Scheme 33).[119a,120d]



(±)-Dihydrocorynantheine (17)

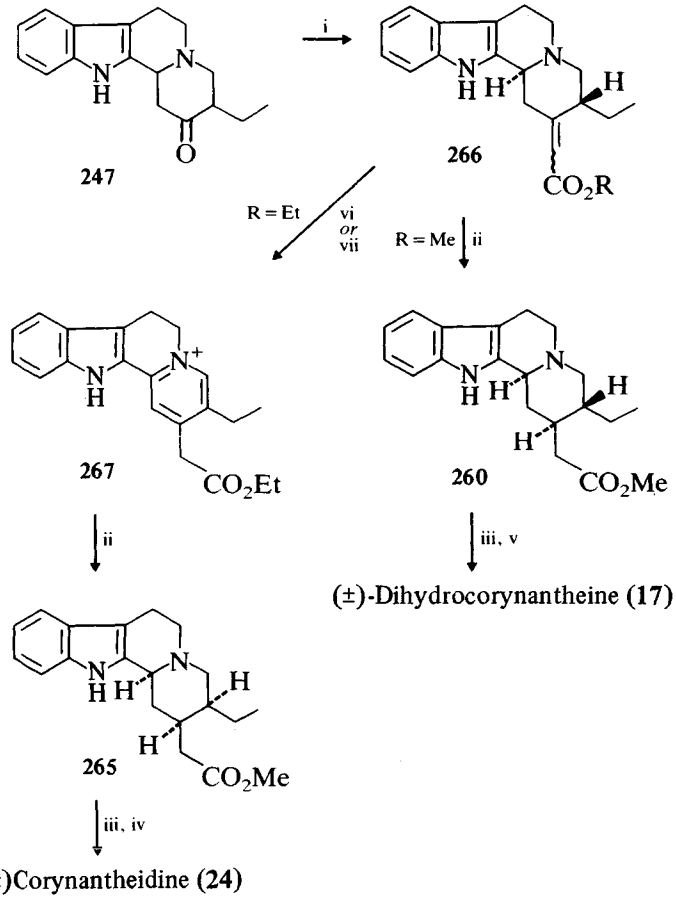
Scheme 32. Reagents: i, H_2, Raney Ni; ii, $POCl_3$; iii, H_2, Pt; iv, $NaCPh_3$, HCO_2Me; v, methylation.

Thus the pyridinium bromide **262**, prepared from 5-ethyl-4-methylnicotinonitrile (**261**), was reduced to the tetrahydropyridine **263** by controlled catalytic hydrogenation, which it was anticipated would also give predominantly cis 15,20 stereochemistry. On subsequent hydrolysis and decarboxylation of the β-aminoacrylate ester, an immonium species was produced which promptly cyclized onto the indole to afford a tetracyclic base isolated as **264** after remethylation. This process yielded the wrong stereochemistry at C-3 and hence it was inverted by a dehydrogenation/reduction sequence to give the allo base **265**, which was then converted into corynantheidine.



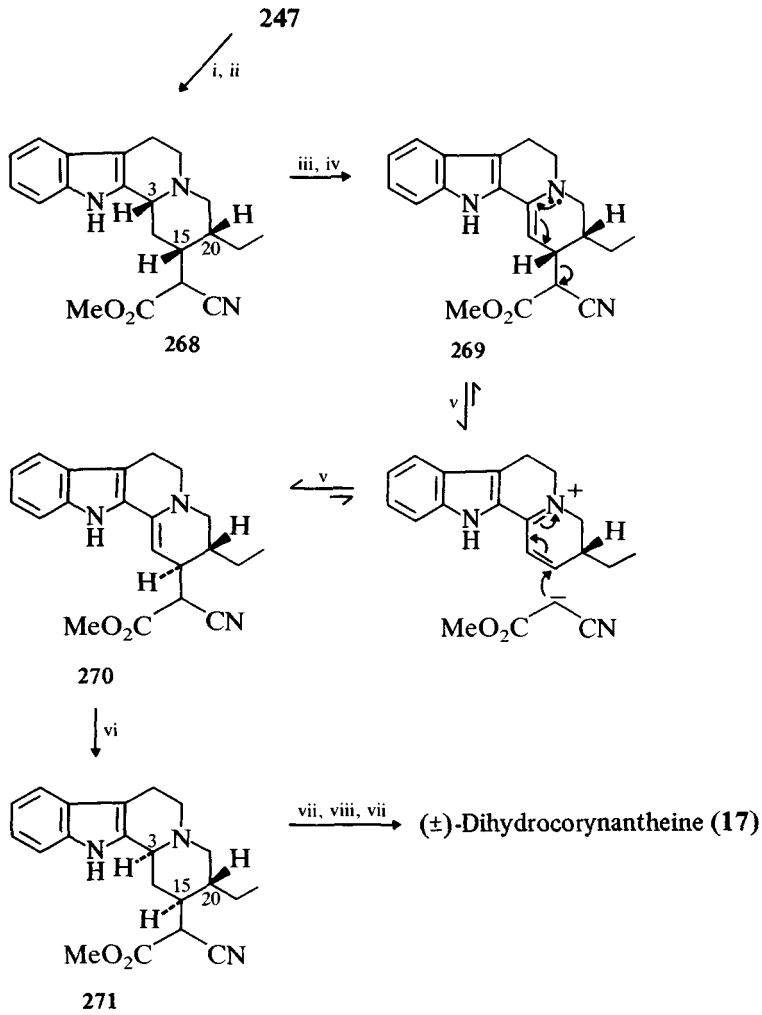
Scheme 33. Reagents: i, aq. KOH; ii, MeOH, HCl; iii, $(CO_2Me)_2$, $KOBu^t$; iv, H_2O_2; v, tryptophyl bromide, Et_2O; vi, H_2, Pd-C, MeOH, Et_3N; vii, Pd, maleic acid; viii, $NaBH_4$; ix, $HC(OEt)_3$, NaH; x, CH_2N_2.

Both dihydrocorynantheine and corynantheidine were synthesized by Weisbach and co-workers[120a] from the readily available tetracyclic ketone **247** mentioned above, as indicated in Scheme 34. Condensation of **247** with a trialkylphosphonate gave an unsaturated ester **266** which was hydrogenated from the less hindered α face to give **260**, convertible as before to (±)-dihydrocorynantheine. Attempts to epimerize C-3 or C-20 in **266** directly were of no avail, and hence it was dehydrogenated to the achiral quaternary salt **267**, which was reduced to the all-cis corynantheidine precursor **265** by catalytic hydrogenation.



Scheme 34. Reagents: i, $(RO)_2PO^-CHCO_2R$; ii, H_2, Pd-C; iii, HCO_2Me, $NaCPh_3$; iv, CH_2N_2; v, MeOH, HCl; vi, $Hg(OAc)_2$; vii, EtO^-, then I_2, NaOAc.

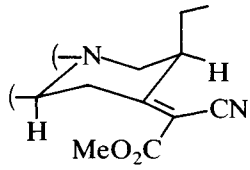
The same ketone **247** was also used by Szántay and co-workers to prepare **268**, a common intermediate in his synthetic route to this pair of alkaloids (Scheme 35).[122a] One intriguing difference, however, was that condensation with cyanoacetic ester rather than the phosphonate resulted in opposite configurations at C-20, presumably because the larger C-15 substituent interacts unfavorably with an



Scheme 35. Reagents: i, $NCCH_2CO_2Me$, NaH; ii, $NaBH_4$; iii, $Pb(OAc)_4$; iv, aq. NH_3; v, CH_2Cl_2, Ar; vi, $NaBH_4$, AcOH; vii, MeOH, HCl; viii, $LiAlH_4$, $-70°$.

equatorial ethyl group, which thus prefers an axial orientation as in **272**; as before, subsequent reduction with borohydride then occurs from the less-hindered face cis to H-3. An interesting feature is the exploitation of an unusual epimerization of the 3,14-dehydro intermediate **269** to **270**, via the indicated (slow) elimination and addition of the cyanoacetic ester unit. The net result after reduction of **270** was inversion of both C-3 and C-15 in **268** to give a base (**271**) with normal stereochemistry. Conversion of **271** into a diester and controlled reduction afforded the corresponding aldehydo ester, subsequent methylation giving (±)-dihydrocorynantheine. In rather similar fashion **268** was converted into (±)-corynantheidine.

Introduction of a vinyl rather than an ethyl group at C-20 was eventually achieved

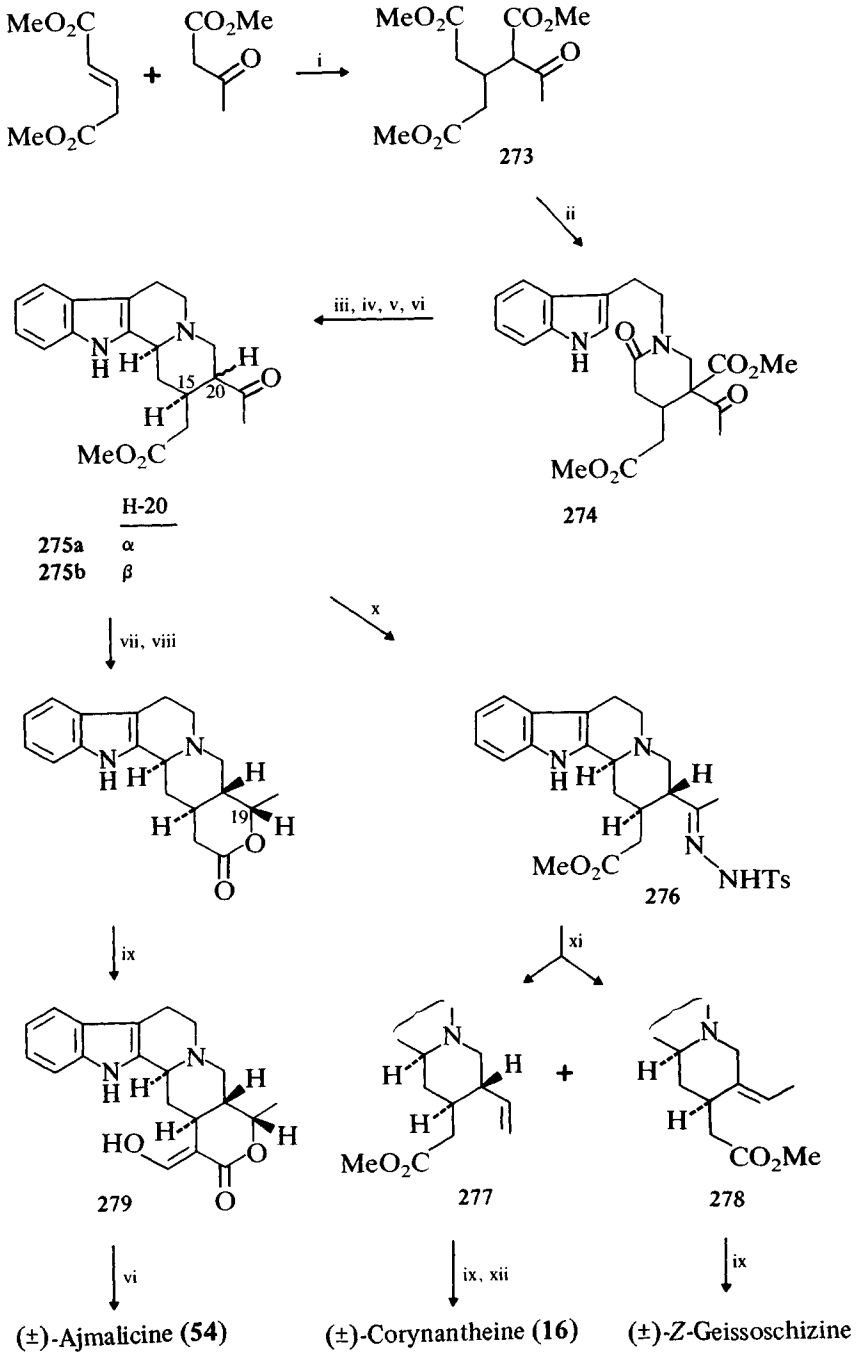


272 (racemate)

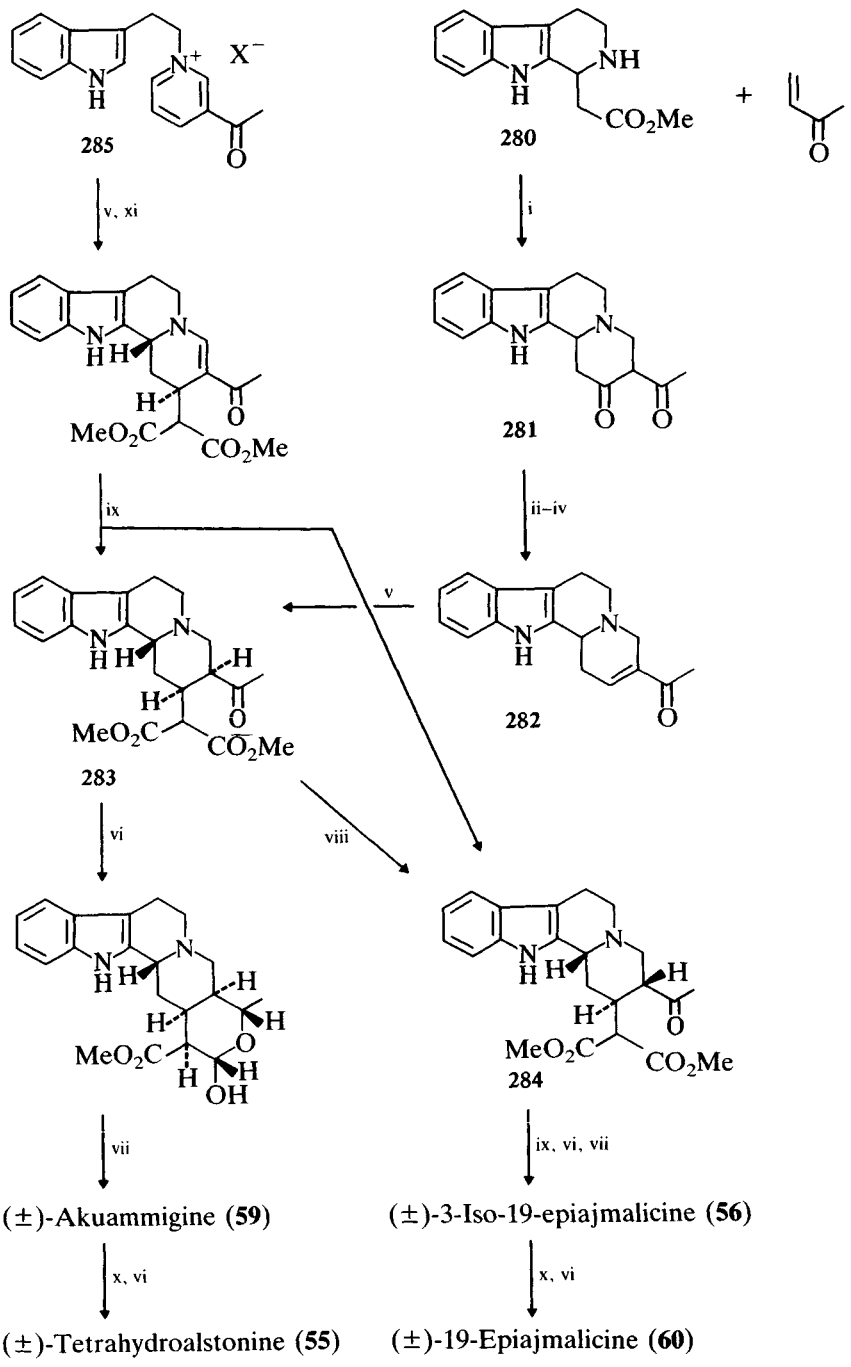
by van Tamelen and co-workers in a variant of his dihydrocorynantheine synthesis (Scheme 36).[118] The keto ester **273**, obtained from dimethyl glutaconate and methyl acetoacetate, was condensed with tryptamine and formaldehyde to give the key intermediate **274**. In a series of standard reactions **274** was converted into a mixture of 15,20 trans and cis tetracyclic isomers (**275**) in a ratio of about 3:2, the major product **275b** being identified by conversion into a known derivative of dihydrocorynantheine. After separation by chromatography, the tosylhydrazone of the trans keto ester was decomposed with alkali to a mixture of vinyl (**277**) and 19,20-ethylidene (**278**) isomers, the former being converted into (±)-corynantheine (**16**) by formylation and subsequent methylation. Similar treatment of the latter afforded a product which was isomeric but not identical with geissoschizine (**27**). It was formulated as the *Z* isomer and provided the first intimation that natural geissoschizine possessed an *E* configuration of the 19,20 double bond. Furthermore, an alternative sequence of reactions from the keto ester **275b** effected the first total synthesis of a heteroyohimbine alkaloid, ajmalicine (**54**).[126] Reduction of the ketone to an alcohol with sodium borohydride, lactone formation, and formylation afforded the hydroxymethylene derivative **279** which rearranged to (±)-ajmalicine on acid-catalyzed methanolysis of the lactone.

An elegant series of syntheses of ajmalicine and some of its stereoisomers have been performed by Winterfeldt and co-workers from a key α,β-unsaturated ketone (**282**) obtained from the amino ester **280** and MVK, via the β-diketone **281** (Scheme 37).[42a,127] The product (**283**) of kinetically controlled addition of malonate to **282** was used to obtain the alkaloids with a D/E cis ring junction such as akuammigine (**57**), whereas the thermodynamically preferred adduct (**284**) led to the D/E *trans* series exemplified by 3-iso-19-epiajmalicine (**56**). Application of the usual procedures for C-3 inversion then yielded the 3α-epimers, and oxidation of **56** gave the oxindole alkaloids (±)-formosanine (**107**) and isoformosanine (**106**). Both **283** and **284** have also been obtained by Wenkert from the pyridinium salt **285** in a shorter but less stereoselective route.[128]

In their approaches to the *Cinchona* alkaloids (see Chapter XII) Uskoković and co-workers[42b] devised a synthesis from 3-ethyl-4-methylpyridine of a meroquinene (cis-3-vinyl-4-piperidineacetic acid) derivative (**287**), in which the ethyl group of **286** was functionalized by the Hoffmann-Loeffler-Freytag reaction. This product has now been utilized in synthesis of (±)-akuammigine and tetrahydroalstonine via the 2,3-seco compound **289** as outlined in Scheme 38, a notable feature being that only one stereoisomer is produced on cyclization of **288** to **289**.[42b] A parallel series of reactions on the trans isomer of **286** has also been carried out but in this case

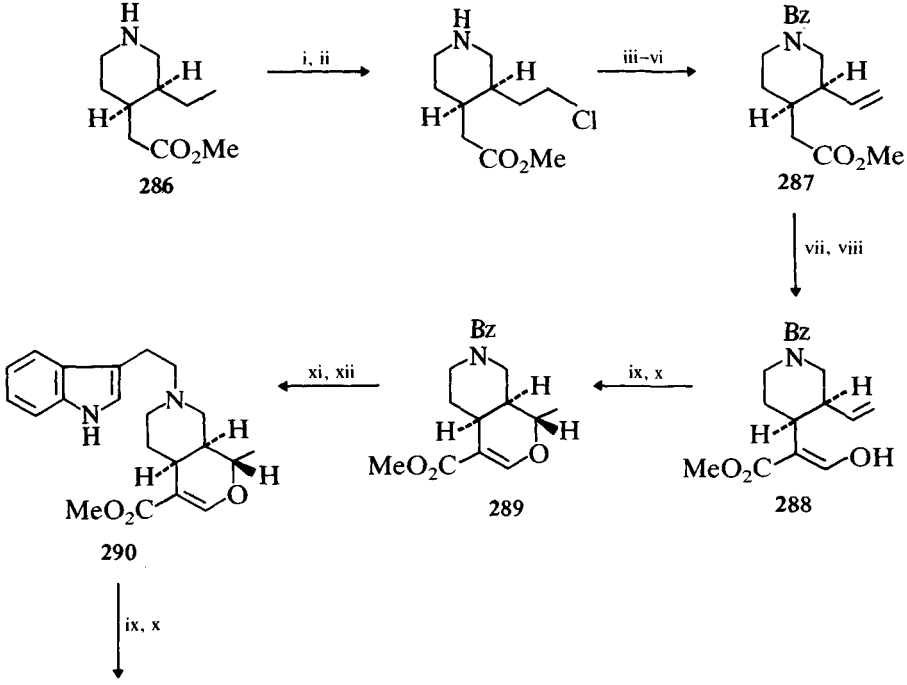


Scheme 36. Reagents: i, base, ii, tryptamine, CH_2O, Bu^tOH; iii, $POCl_3$; iv, H_2, Pd-C; v, H_3O^+; vi, MeOH, H^+; vii, $NaBH_4$; viii, DCC; ix, HCO_2Me, $NaCPh_3$; x, H_2NNHTs; xi, NaOMe; xii, CH_2N_2.



Scheme 37. Reagents: i, $KOBu^t$; ii, $POCl_3$, DMF; iii, $LiAl(OBu^t)_3H$; iv, H_3O^+; v, $CH_2(CO_2Me)_2$, NaOMe; vi, $NaBH_4$; vii, PPA; viii, NaOMe; ix, H_2, cat.; x, $Pb(OAc)_4$; xi, HCl, PhH.

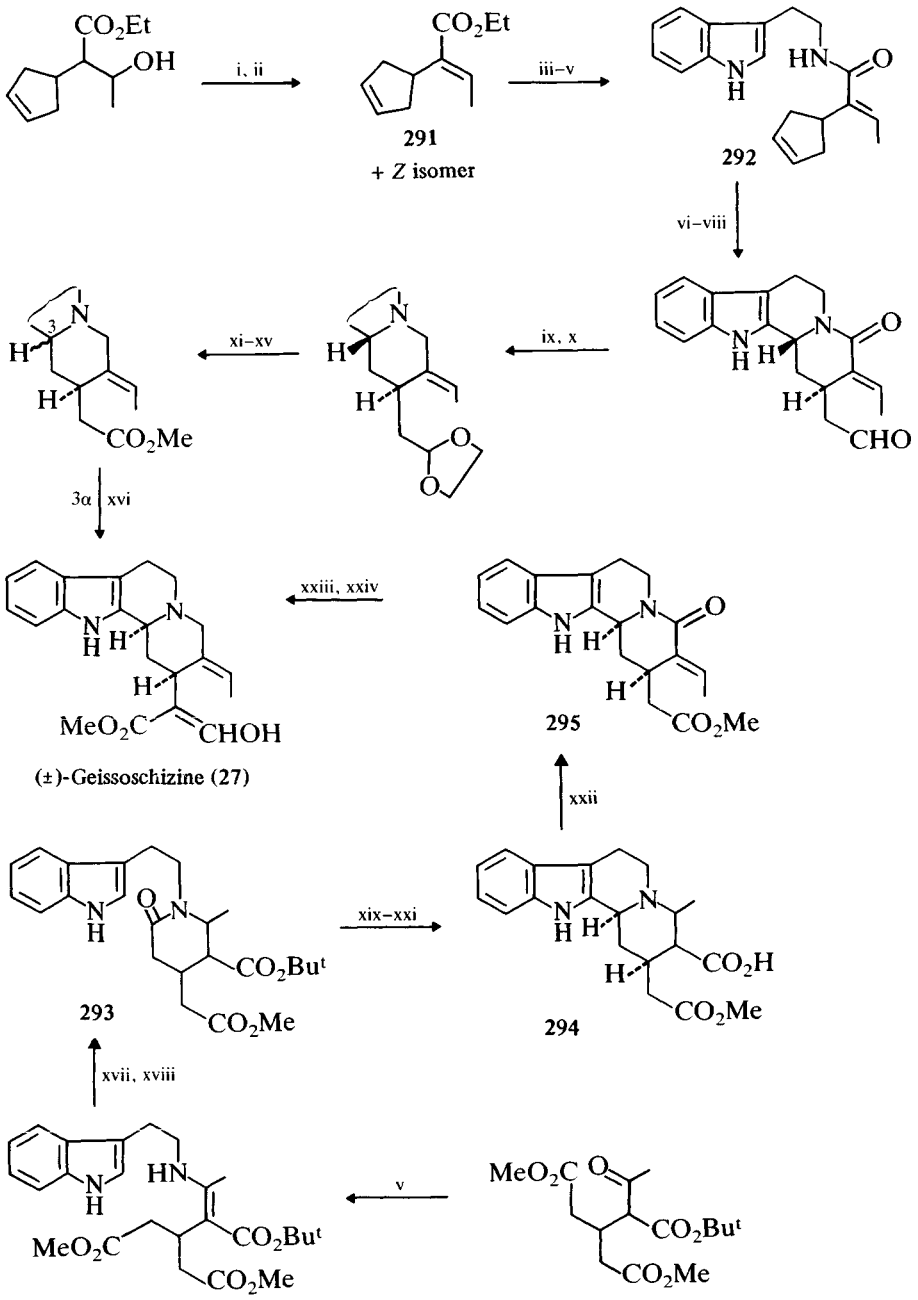
less stereoselectivity was found in the closure of the heterocyclic ring and both ajmalicine and 19-epiajmalicine were produced.



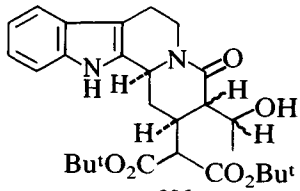
(±)-Akuammigine (**59**) + (±)-Tetrahydroalstonine (**55**)

Scheme 38. Reagents: i, NCS; ii, CF_3CO_2H, *hν*; iii, BzCl; iv, KOH, MeOH; v, $KOBu^t$, DMSO; vi, CH_2N_2; vii, $(Me_2N)_2CHOBu^t$; viii, H^+; ix, $Hg(OAc)_2$; x, $NaBH_4$; xi, hydrolysis; xii, tryptophyl bromide, K_2CO_3.

Although the original study by van Tamelen and his co-workers had afforded only the unnatural *Z* isomer of geissoschizine, in later work they circumvented the geometric problem by separating out the pure *E* isomer (**291**) of an early intermediate in another synthetic route (Scheme 39).[124a] Since this was successful, it established the geometry of the double bond in geissoschizine. A distinctive feature of the synthesis was the use of a cyclopentene as a masked dialdehyde in **292**, a neat device which van Tamelen had previously used in making rhynchophyllol.[64] Other total syntheses of (±)-geissoschizine have been reported,[124] one of which, by Winterfeldt and co-workers, is outlined in Scheme 39. The critical stage was the rearrangement of the acid **294** to the lactam **295** in acetic anhydride by elimination and recyclization. Initially this sequence was carried out on stereochemically homogeneous material but later it was found that a mixture of stereoisomers was equally effective in giving the *E* isomer **295** as the major product. The greater stability of the *E* relative to the *Z* configuration was also exploited in the second synthesis at a stage involving dehydration of the β-hydroxylactam **296**.

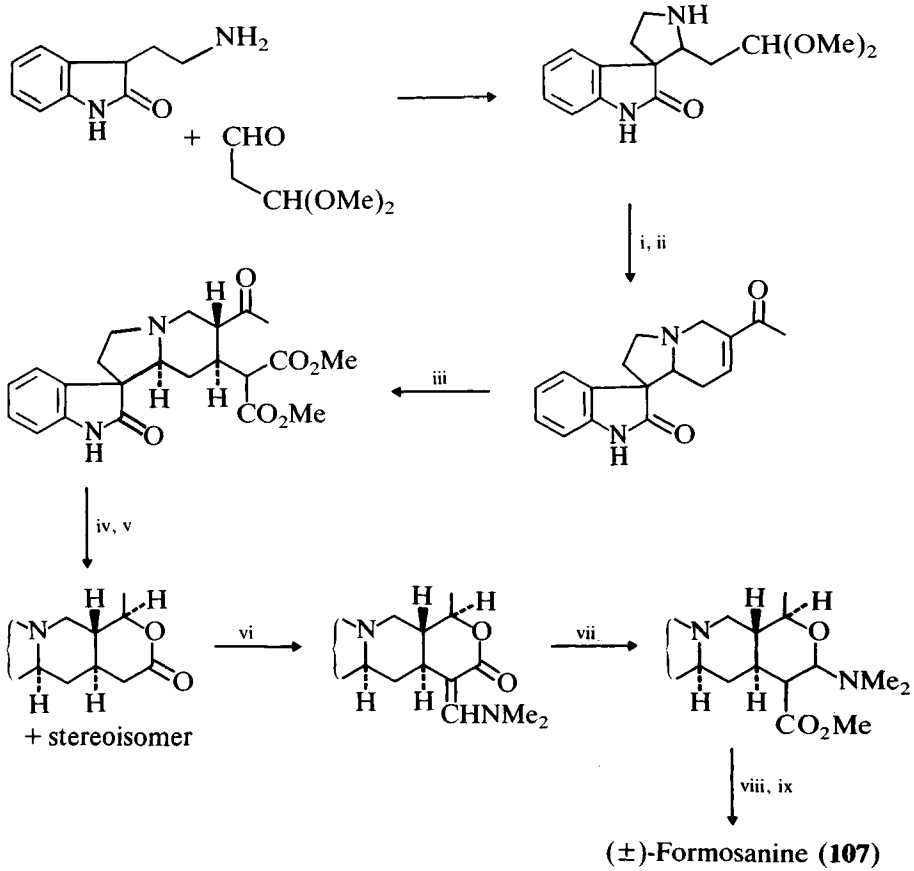


Scheme 39. Reagents: i, TsCl, py; ii, $KOBu^t$; iii, OH^-; iv, $p\text{-}O_2NC_6H_4OH$, DCC; v, tryptamine; vi, OsO_4; vii, $NaIO_4$; viii, HCl, Me_2CO; ix, $(CH_2OH)_2$, H^+; x, AlH_3; xi, H_3O^+; xii, Ag_2O; xiii, MeOH, H^+; xiv, $Hg(OAc)_2$; xv, Zn, AcOH; xvi, HCO_2Me, $LiNPr^i_2$; xvii, $NaBH_4$, AcOH; xviii, 2-pyridone, AcOH; xix, $POCl_3$; xx, $NaBH_4$; xxi, CF_3CO_2H; xxii, Ac_2O; xxiii, $Et_3O^+BF_4^-$; xxiv, HCO_2Et, NaH.

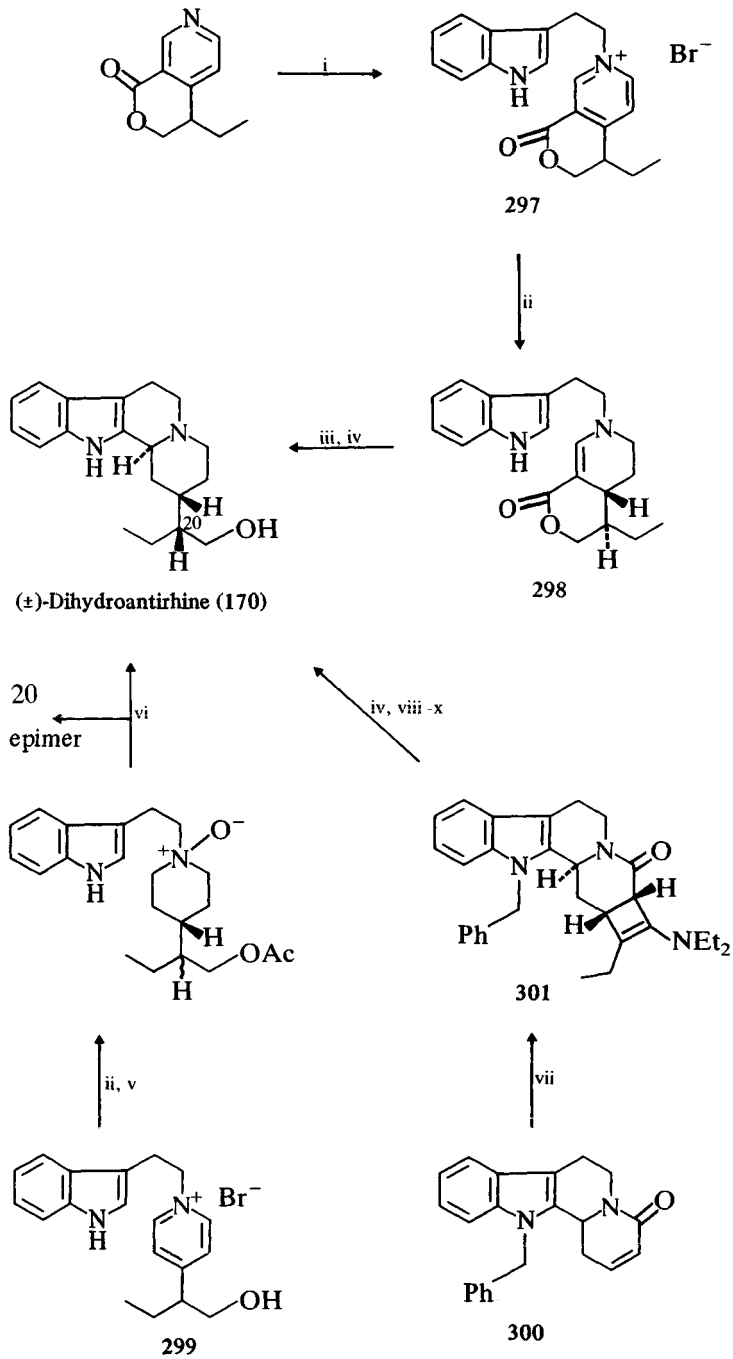


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As several previous examples have shown, oxindole alkaloids have generally been obtained by oxidation of the corresponding indoles, but some have been obtained by synthesis from 2-oxytryptamine. In addition to the short preparation[65] of isorhynchophylline (**84**) given above in Scheme 14, there is a synthesis of **83** and **84** by Ban and his collaborators.[132] This route has been recently extended to include the pentacyclic mitraphylline (**104/105**) and formosanine (**106/107**) isomers, and the synthesis of (±)-formosanine is given as an example in Scheme 40.[133]



Scheme 40. Reagents: i, $MeCOCH{=}CH_2$; ii, HCl, AcOH; iii, $CH_2(CO_2Me)_2$, NaOMe; iv, H_2, Pt; v, H_3O^+; vi $(Me_2N)_2CHOBu^t$, DMF, Δ; vii, HCl, MeOH; viii, aq. dioxane, Δ; ix, PPA.



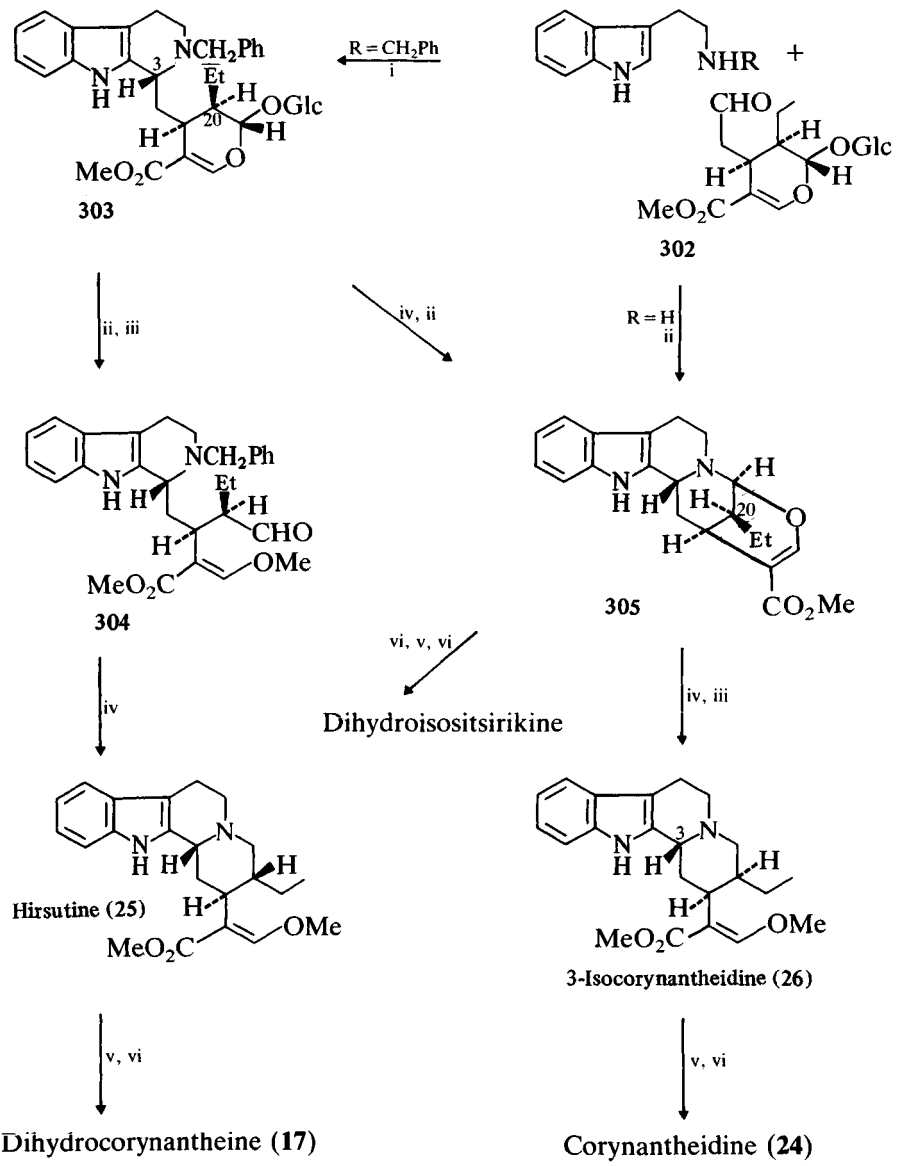
Scheme 41. Reagents: i, tryptophyl bromide; ii, H_2, Pd-C, Et_3N; iii, aq. KOH; iv, aq. HCl; v, H_2O_2; vi, $(CF_3CO)_2O$; vii, $Et_2NC{\equiv}CEt$, $MgBr_2$; viii, CH_2N_2; ix, $LiAlH_4$; x, Na, NH_3(liq).

18,19-Dihydroantirhine (**170**) has been prepared by three different groups (Scheme 41). As in several other syntheses, Wenkert et al. employed their method of decarboxylating β-aminoacrylic acids to generate an immonium ion under conditions that would lead to the desired trans relationship between C-3 and C-15 on cyclization to the indole ring. Furthermore, in producing the required tetrahydropyridine (**298**) by catalytic hydrogenation of **297**, the correct trans stereochemistry at positions 15 and 20 was apparently obtained.[142a] Another approach by Potier and co-workers from **299** made use of the modified Polonovski reaction to create the immonium ion and again achieved the correct 3,15-trans stereochemistry on closure of ring C, but the product was a mixture of C-20 epimers.[142b] Control over all three chiral centers was achieved in the novel process of Ficini and co-workers in which ynamine addition to an α,β-unsaturated lactam (**300**) gave the cyclobutene **301**; subsequent protonation of the enamine occurred stereoselectively from the β face, thus cleanly inducing the correct relative configuration at C-20.[142c] Recently antirhine (**216**) itself has been synthesized from norcamphor by Takano and co-workers.[142d]

B. Biomimetic Syntheses

An alternative "biomimetic" approach by Brown and co-workers to synthesis of these alkaloids has been to start from their natural precursors – tryptamine and secologanin – and attempt to reproduce in vitro the regio- and stereo-selectivity of the biogenetic sequence.[144] In this way an insight has been obtained into mechanistic details of the in vivo reactions that are not available from mere incorporations of labeled compounds. Condensation of N_b-benzyltryptamine and dihydrosecologanin (**302**) afforded only *N*-4-benzyl-18,19-dihydrovincoside (**303**) with no appreciable amount of its C-3 epimer, the purpose of the *N*-benzyl group being to block the ready formation of a lactam (N-4,C-22) or vallesiachotamine (N-4,C-17) type structures mentioned above (Scheme 42).[123] Glycolysis of **303** and methylation of the ring-opened form of the aglucone gave **304** which on catalytic hydrogenation was smoothly converted into hirsutine (**25**) by debenzylation and reductive amination. Epimerization of H-3 then afforded dihydrocorynantheine (**17**). During this sequence the configuration at C-20 had remained intact, but if glycolysis took place after debenzylation, then a pentacyclic base, dihydromancunine (**305**), was obtained, in which H-20 had been epimerized, presumably via intermediate formation of an enamine. Alternatively, dihydromancunine could be obtained in a "one-pot" glucolysis of **302** in presence of tryptamine.[143] Catalytic hydrogenation of **305** followed by methylation then provided a route to the 15,20 cis alkaloids 3-isocorynantheidine (**26**)[145] and corynantheidine (**24**).[123,144] Reduction of **305** with sodium borohydride yielded 20α isomers of dihydrositsirikine.

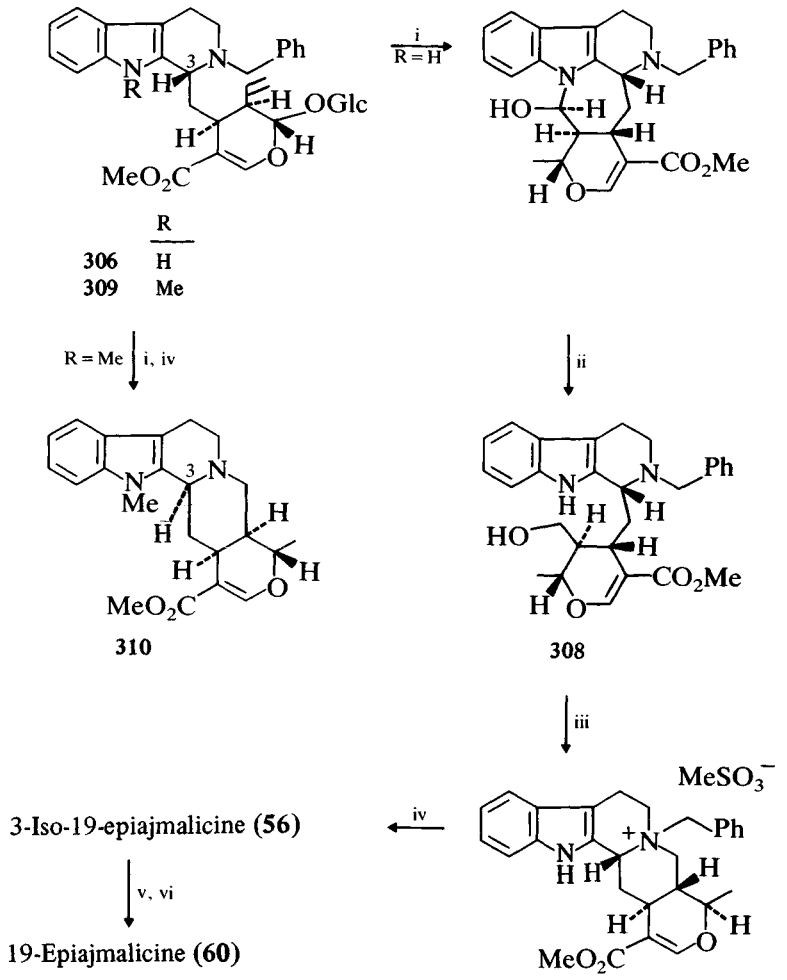
A corresponding synthetic sequence from *N*(4)-benzylvincoside (**306**) to heteroyohimbines was not immediately possible because, although the aglucone rearranged in the desired manner, on prolonged standing the C-21 aldehyde cyclized onto N-1 to give **307** as the major product (Scheme 43).[40] However, the last step



Scheme 42. Reagents: i, AcOH; ii, β-glucosidase, pH 5; iii, CH_2N_2; iv, H_2, Pd-C, MeOH, AcOH; v, $Pb(OAc)_4$; vi, $NaBH_4$.

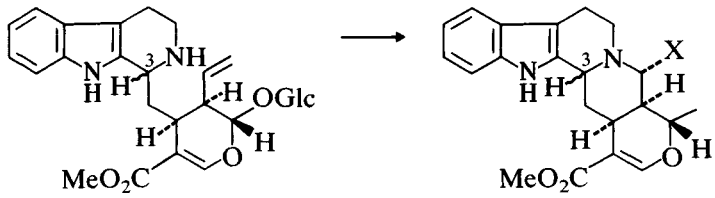
could be reversed in a basic medium, and reduction with sodium borohydride gave **308**, readily convertible into 3-iso-19-epiajmalicine (**56**) and 19-epiajmalicine (**60**). Interestingly, if cyclization to N-1 were prevented by methylation of the indolic nitrogen, as in **309**, then hydrogenolysis of the rearranged aglucone resulted in epimerization of H-3, giving *N*(1)-methyltetrahydroalstonine (**310**) as the major product.[130] The inversion of C-3 could be attributed to a reversible C-3,N-4 cleavage

in an intermediate immonium species, whereas the differences in 19 and 20 stereochemistry could be correlated with the short period allowed for aglucone rearrangement – a few hours rather than days, as in the former case.



Scheme 43. Reagents: i, β-glucosidase, pH 5; ii, $NaBH_4$, $HOPr^i$; iii, $MeSO_2Cl$; iv, H_2, Pd-C, AcOH, MeOH; v, $Pb(OAc)_4$; vi, $NaBH_4$.

Subsequently, it was considered that a blocking group on N-4 might not be essential; the desired N-4,C-21 cyclization in an aglucone might be occurring but was reversible, so that eventually the more stable N-4,C-17 β-aminoacrylate system of the vallesiachotamine type was formed. If such were the case, then the kinetically preferred carbinolamine or related immonium species might be trapped by reduction. In the event a "one-pot" glucolysis of strictosidine (**157**) at pH 5 in presence of sodium cyanoborohydride (Scheme 44) afforded tetrahydroalstonine



	H-3
157	α
158	β

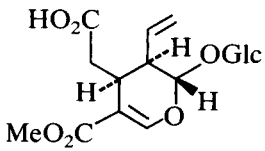
	H-3	X
55	α	H
311	α	CN
59	β	H
312	β	CN

Scheme 44. Reagents: β-glucosidase, pH 5, $NaCNBH_3$ (X=H) *or* NaCN(X=CN).

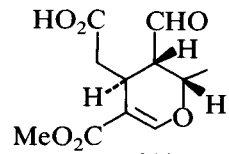
(**55**) as the only major product in 50–60% yield.[55] Minor amounts of ajmalicine (**54**) (~ 5%) and two C-16 epimers of sitsirikine isomers (**33**) (~ 8%)[25a] were also formed, and if a tenfold excess of reducing agent were used, then sitsirikine and its 16 epimer became the predominant products (Scheme 45).[39] Furthermore, if sodium cyanide replaced the reducing agent, the dehydro intermediate was trapped as 21-cyanotetrahydroalstonine (**311**), which could be reduced to **55**.[54] Vincoside (**158**) behaved in the same way to give the 3β isomers akuammigine (**59**) and its 21-cyano derivative (**312**), whereas the 2,3-seco analogues gave the corresponding 2,3-secoakuammigine.

The most striking feature of the heteroyohimbine products was the virtually stereospecific generation of 19β(*S*) chirality, which can be rationalized by the reaction sequence given above in Scheme 10 involving the intermediacy of an *E* alkene (**74**). Careful glucolysis of strictosidine allowed isolation of the labile dehydro intermediate cathenamine (**75**) which was found to equilibrate via the *Z*-alkene **77** with 19-epicathenamine (**78**), the requisite precursor for the 19α heteroyohimbine alkaloids.[54] Accordingly reduction of **78** with sodium borohydride in methanol gave 19-epiajmalicine (**60**), whereas sodium cyanoborohydride in pH6 buffer yielded the 20α isomer rauniticine (**61**). The major factor controlling stereochemistry in these cyclizations is the α(*S*) configuration of H-15, the nature or even presence of chirality at C-3 having no effect. Furthermore, the high degree of regioselectivity and stereoselectivity demonstrated by these latter in vitro reactions duplicates the biogenetic process in all essential details.[144]

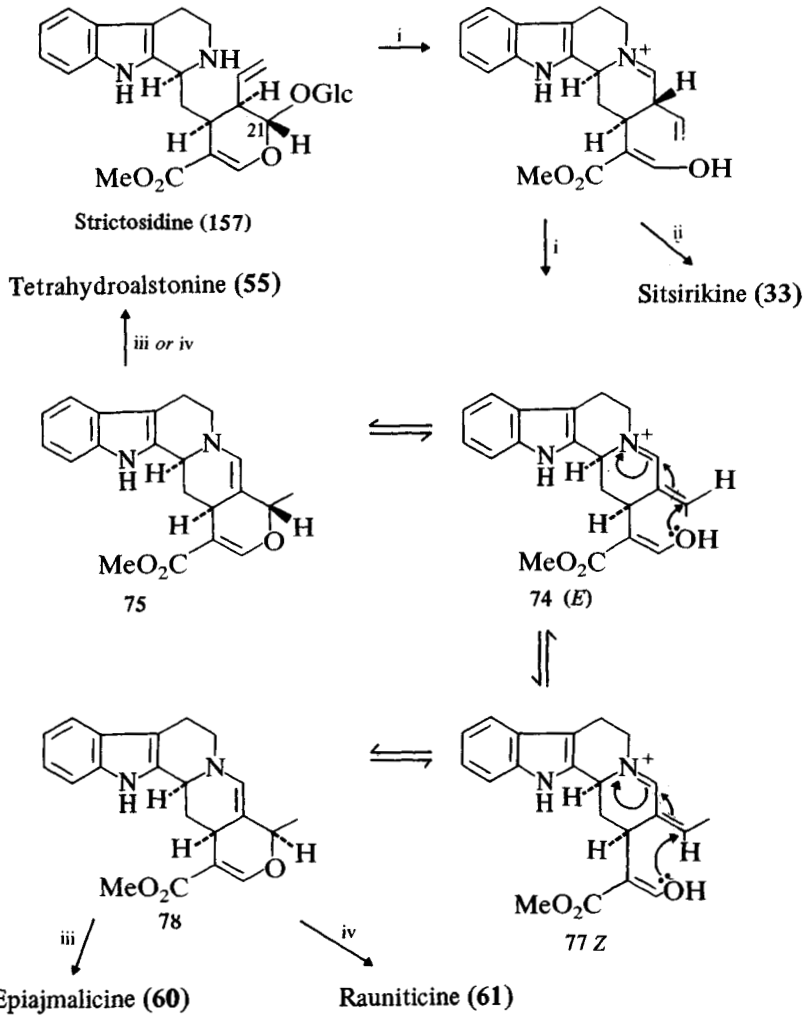
Glucolysis of secoxyloganin (**313**), prepared by oxidation of secologanin, resulted in a similar stereoselective rearrangement to elenolic acid (**314**) which has been converted into ajmalicine and other heteroyohimbine alkaloids essentially as in Woodward's reserpine synthesis (Chapter IV, Section VI. A).[129]



313



314



Scheme 45. Reagents: i, β-glucosidase, pH 5–7; ii, i + 10x excess $NaCNBH_3$; iii, $NaBH_4$; MeOH; iv, $NaCNBH_3$, pH 6.

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CHAPTER IV

The Yohimbine Group

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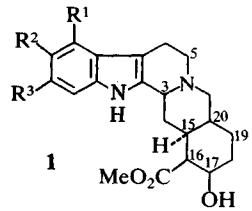
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I. INTRODUCTION

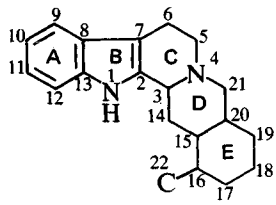
Yohimbine, its stereoisomers, and simple derivatives constitute a small group of indole alkaloids with the general structure **1** (Table I). The name is derived from the original source of yohimbine – commercial yohimbehe bark obtained from an African tree *Pausinystalia yohimba* Pierre (syn. *Corynanthe yohimbe* K. Schum) belonging to the Rubiaceae. However, the term "yohimbine alkaloid" is now generally extended to include all those which possess the common pentacyclic system of **2**, such as reserpine (**105**) and sempervirine (**125**), found in many different species of the Rubiaceae and Apocynaceae. The numbering system used throughout is indicated in **2**, together with the letter designation for rings.

TABLE I. YOHIMBINE STEREOISOMERS AND CONGENERS



1

Series	H-3	H-20	H-16	H-17	R^1	R^2	R^3	Name
Normal	α(*S*)	β(*R*)	β(*R*)	β(*S*)	H	H	H	Yohimbine (24)
	α	β	β	α	H	H	H	β-Yohimbine (40)
	α	β	α	β	H	H	H	Corynanthine (38)
								5α*H*-Carboxycorynanthine (78)
	α	β	α	β	H	OMe	H	Excelsinine (72)
	α	β	β	β	H	H	OMe	Poweridine (17-OAc) (74)
Pseudo	β	β	β	β	H	H	H	Pseudoyohimbine (48)
Allo	α	α	β	β	H	H	H	Alloyohimbine (58)
	α	α	α	β	H	H	H	α-Yohimbine (61)
	α	α	α	β	H	OMe	OMe	Seredine (69)
	α	α	α	α	OMe	H	H	Isovenenatine (71a)
Epiallo	β	α	α	β	H	H	H	3-Epi-α-yohimbine (65)
	β	α	α	β	H	H	OMe	Quaternatine (73)
	β	α	α	α	OMe	H	H	Venenatine (71b)
–	α	$\Delta^{19,20}$	β	β	H	H	H	19,20-Dehydroyohimbine (75)



2

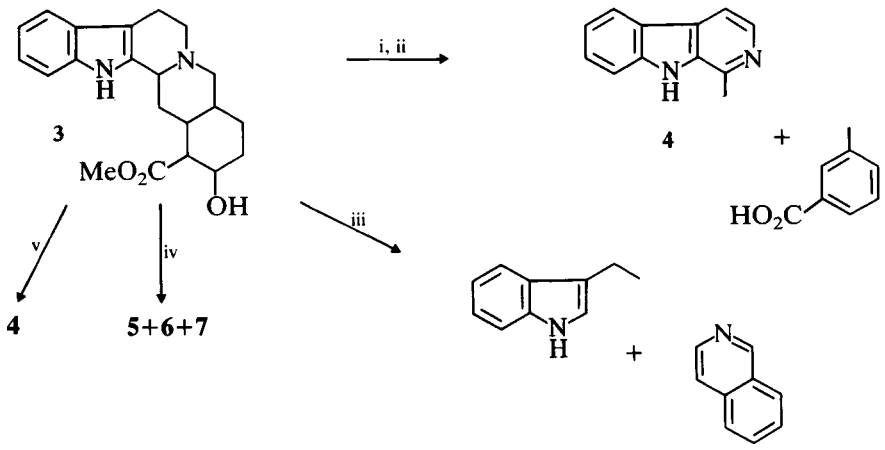
II. YOHIMBINE AND STEREOISOMERS

The stereoisomeric yohimbine alkaloids were originally isolated from *P. yohimba* bark in the late nineteenth century but have since been found to occur in a large number of plants, particularly rubiaceous and apocynaceous species.[1,2] Elucidation of the structure of the major alkaloid yohimbine was not completed until 1956 and was achieved essentially in the classical manner through interpretation of chemical reactions, degradations, and syntheses. The structures of the other stereoisomers were found either by correlation with yohimbine or by analogous methods. Eventually it was found that the absolute configuration at C-15 was invariably with the hydrogen $\alpha(S)$, and the alkaloids could be divided into four general stereochemical series according to the 3 and 20 configurations, namely, normal (3α, 20β), pseudo (3β, 20β), allo (3α, 20α), and epiallo (3β, 20α) (Table I).

A. Yohimbine

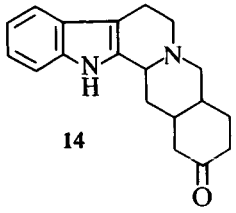
Yohimbine (**24**), $C_{21}H_{26}N_2O_3$, is a monoacidic tertiary base, reacting with only 1 mole of acid or methyl iodide. The presence of a carbomethoxy group was shown by hydrolysis to yohimbic acid, $C_{20}H_{24}N_2O_3$, which was reconverted into yohimbine with methanol and hydrogen chloride, and also by reduction to yohimbyl alcohol, $C_{20}H_{26}N_2O_2$, with sodium and ethanol. Acetylation under mild conditions gave a monoacetate in accordance with a hydroxyl group, although under forcing conditions a diacetyl derivative could be obtained. The latter was attributed to acylation of the second nonbasic nitrogen function, which therefore was secondary or primary. Consecutive treatment of yohimbine with sulfuric acid and alkali afforded apoyohimbine, $C_{21}H_{24}N_2O_2$, which could be hydrogenated to a dihydro derivative, deoxyyohimbine. Yohimbic acid behaved similarly and also could be decarboxylated by heating with soda lime to yohimbol, $C_{19}H_{24}N_2O$, together with a trace of a ketone yohimbone, $C_{19}H_{22}N_2O$. In a significant later development yohimbone was obtained by Oppenauer oxidation of yohimbine itself.[3]

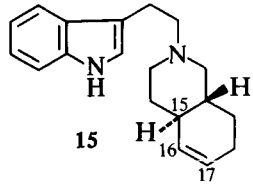
Information about the skeletal structure of yohimbine was obtained by drastic degradation to various recognizable heterocyclic and aromatic systems[4] (Scheme 1). Fusion with soda lime or potassium hydroxide afforded mixtures of indoles from which 3-ethylindole could be isolated, whereas with zinc dust or superheated steam some isoquinoline was also formed. Harman (**4**) was obtained by either simply heating yohimbine, or with *m*-toluic acid by oxidation with lead tetraacetate and cleavage with hot alkali, suggesting the likely relationship of the two nitrogen atoms.[4d] However, the most important reaction was dehydrogenation with selenium, which gave yobyrine, $C_{19}H_{16}N_2$; tetrahydroisoyobyrine (tetrabyrine), $C_{19}H_{20}N_2$; and ketoyobyrine, $C_{20}H_{16}N_2O$. Further reactions and degradation to known compounds, some of which are summarized in Scheme 2, led to the assignment of structures **5–7**, which were finally confirmed by synthesis.[5,6] The first two sufficed to establish the pentacyclic nuclear structure of yohimbine (**3**) since they had obviously been produced by alternative cleavages of the C-5 and C-21 bonds to N-4.



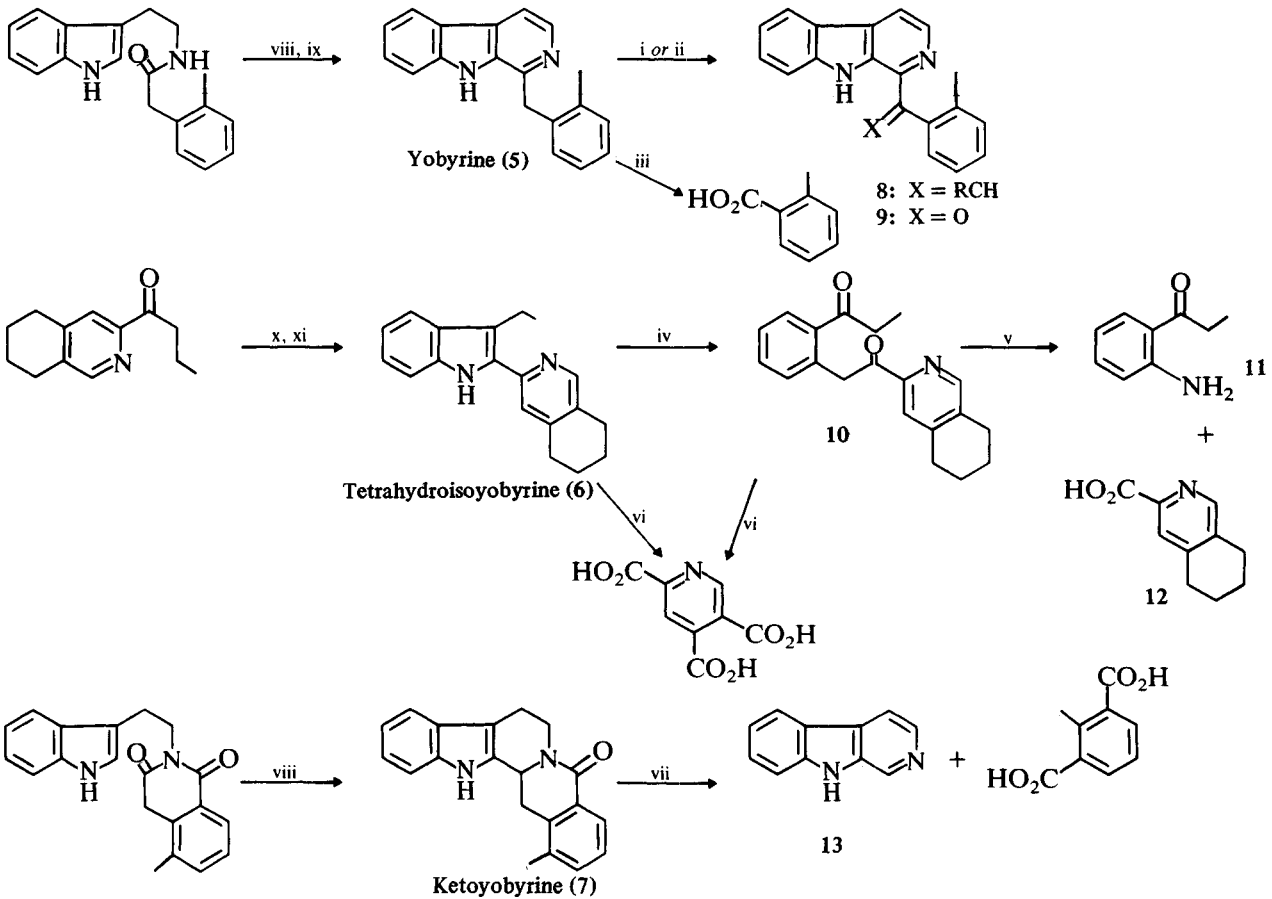
Scheme 1. Reagents: i, $Pb(OAc)_4$; ii, alc. KOH, Δ; iii, Zn, Δ; iv, Se, Δ; v, Δ.

Furthermore, formation of the lactam ring in ketoyobyrine (**7**) and the production of *m*-toluic acid and harman from tetradehydroyohimbine (Scheme 1) could be rationalized only if the carbomethoxy group were at C-16. Since Oppenauer oxidation of the hydroxyl group in yohimbine afforded a ketone, yohimbone, where the carbomethoxy group had been lost in a manner characteristic of a β-dicarbonyl system, the hydroxyl must be secondary and β to the carbomethoxy group, conditions that are met only by placing it at C-17. A direct proof of both the pentacyclic structure and the position of the oxygen in ring E was eventually afforded by the total synthesis of (−)-yohimbone (**14**) from *m*-methoxyphenylalanine.[7] Hence yohimbine has the gross structure **3**. Incidentally, because yohimbine was one of the first structures to be established, the numbering system indicated in **2** is now standard for all monoterpenoid indole alkaloids.



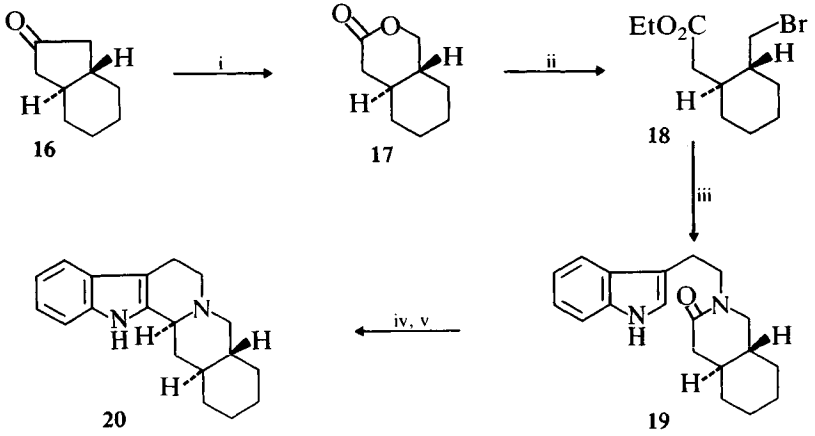


At this stage it was apparent that yohimbine possessed five chiral centers at C-3, 15, 16, 17, and 20, whose configurations remained to be determined. The first indication of stereochemistry was obtained from chanodeoxyyohimbol (**15**) derived by distillation of yohimbic acid from thallous oxide. Catalytic hydrogenation and Hofmann degradation of **15** afforded (+)-*N*-methyl-trans-decahydroisoquinoline, which suggested that the D/E ring junction in **15** and hence yohimbine was also trans.[8] However, the position of the double bond in chanodeoxyyohimbol was



Scheme 2. Degradations and syntheses of yobyrine, tetrahydroisoyobyrine, and ketoyobryine. Reagents: i, RCHO; ii, SeO_2; iii, $HCrO_4$; iv, O_3; v, H_2O; vi, HNO_3; vii, KOH; viii, $POCl_3$; ix, Pd, Δ; x, $PhNHNH_2$; xi, H^+, Δ.

uncertain and could conceivably have been between C-15 and C-16 rather than C-16 and C-17. In the former case an optically active trans product was also possible and hence the trans relationship could not be regarded as being rigorously established, although it was certainly much more likely. Eventually unequivocal proof of the D/E trans ring junction in yohimbine was provided by the synthesis of (±)-yohimbane from trans-hydrindan-2-one (**16**) (Scheme 3).[9] Baeyer-Villiger oxidation of **16** gave the δ-lactone (**17**) which was converted into the bromo ester (**18**), and subsequent reaction with tryptamine afforded the lactam (**19**). Bischler-Napieralski cyclization followed by reduction gave (±)-yohimbane (**20**) with an ir spectrum identical to that of authentic yohimbane prepared by Wolff-Kishner reduction of yohimbone (**14**).

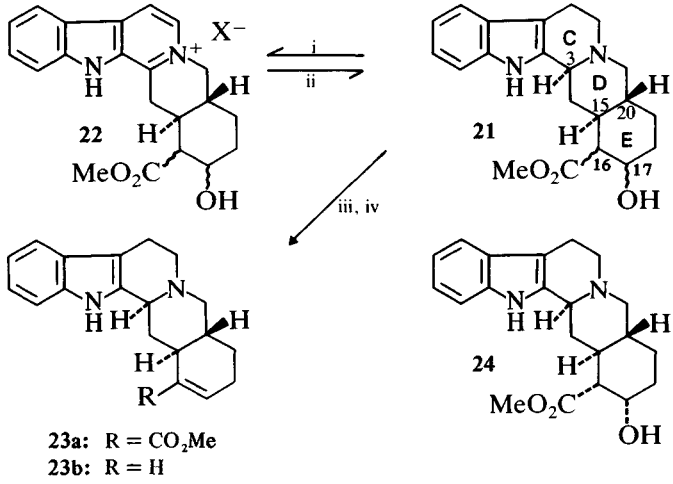


Scheme 3. Reagents: i, $PhCO_3H$; ii, EtOH, HBr; iii, tryptamine, K_2CO_3; iv, $POCl_3$; v, H_2, Pt.

Mild oxidation of ring C in both yohimbine and the isomeric pseudoyohimbine (Section II.D) with lead tetraacetate gave the same tetradehydroyohimbine (**22**) (Scheme 4), showing that they differ only in the C-3 configuration.[10] Catalytic hydrogenation of **22** in alkaline solution regenerated yohimbine, which was therefore presumed to be the more stable epimer with only equatorial substituents around a ring D chair conformation (**25**). Consequently 3-H, 15-H, and 20-H would all be axial in accordance with the relative 3α, 15α, 20β stereochemistry shown in **21**.*

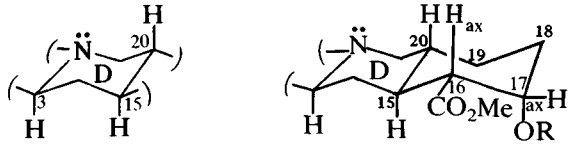
The remaining configurations at C-16 and C-17 were deduced from the production of apoyohimbine (**23a**) on treatment of the sulfate ester of yohimbine with alkali.[10] Ready elimination of sulfuric acid requires a trans diaxial arrangement of 16-H and the sulfate group on C-17 as in **26a**, which implies an analogous situation in yohimbine (**26b**) with the carbomethoxy group in the more stable equatorial orientation and hence α. Support for the latter assignment was obtained from the stereoisomer corynanthine (see Section II.B) (**21**), which differed only in the configuration of the carbomethoxy group since on saponification and reesterification

* The designations α (down) and β (up) have the same meaning as in the steroid convention.

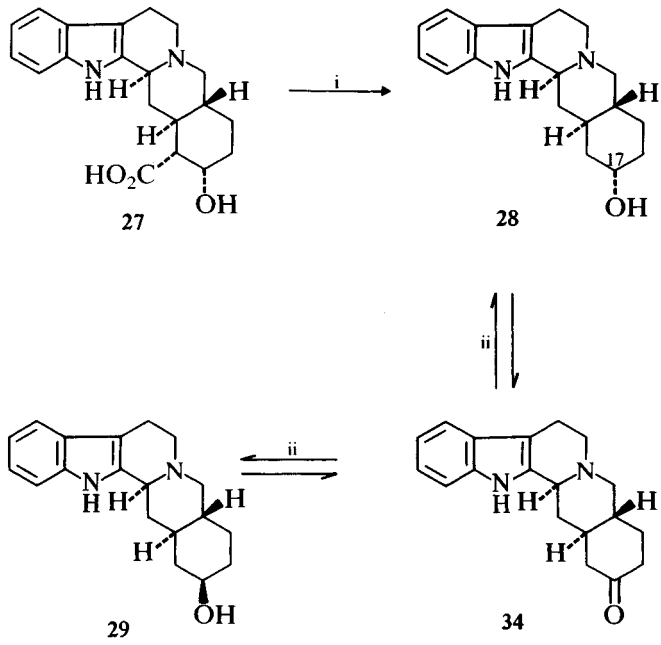


Scheme 4. Reagents: i, $Pb(OAc)_4$; ii, H_2, Pt, OH^-; iii, H_2SO_4; iv, OH^-.

C-16 was epimerized to afford yohimbine. The reverse process was not feasible and hence the carbomethoxy group in corynanthine must have the less stable axial orientation and be β. Two additional pieces of evidence for the α configuration of the hydroxyl group in yohimbine came from yohimbol (**28**) (Scheme 5), the decarboxylation product of yohimbic acid (**27**), and its 17 epimer. On prolonged reduction of yohimbone (**34**) under Meerwein-Ponndorf conditions an equilibrium is established between yohimbol and 17-epiyohimbol in favor of the latter, which consequently should have the hydroxyl group equatorial and β as in **29**.[10] Again, in their ir spectra yohimbol had a band at 1005 cm^{-1}, whereas the corresponding absorption for epiyohimbol was at 1020 cm^{-1}, a difference which by analogy with 3-hydroxy trans A/B steroids implied an axial hydroxyl group for the former and an equatorial for the latter.[11] All these deductions reinforced one another and left little doubt that the relative stereochemistry of yohimbine was given by structure **24**.

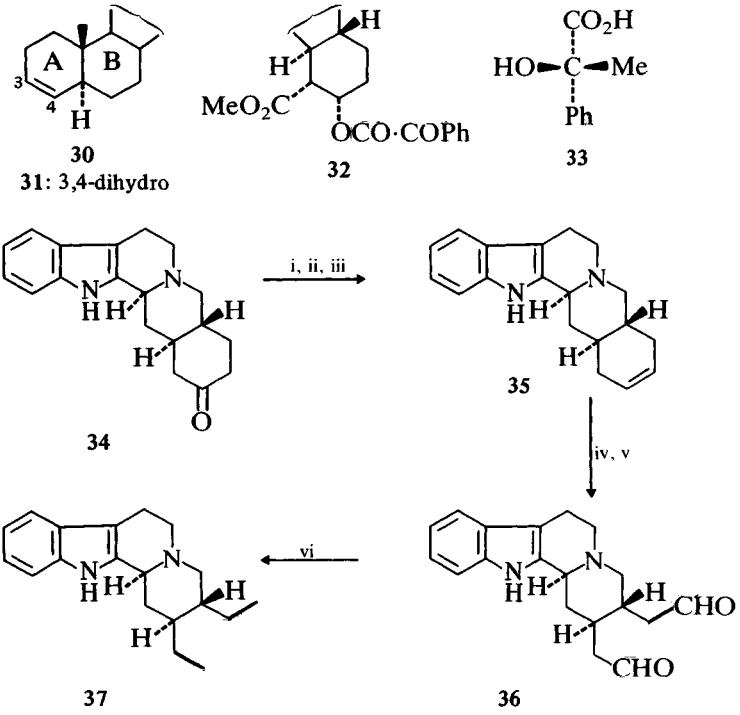


That **24** also represents the correct absolute configuration of the yohimbine molecule has been established by several different chemical and physical methods. The first assignment was by Klyne, who correlated the molecular rotation difference between Δ^{16}-yohimbene (**23b**) and yohimbane (**20**) with that between an analogous



Scheme 5. Reagents: i, soda lime, Δ; ii, Meerwein-Ponndorf reduction.

pair of trans A/B steroids of known absolute configuration (**30**, **31**).[12] In the former, the contribution of the double bond was large and negative ($\Delta[M]_D$ −292°) and in the latter large and positive, so that the ring junction configuration in Δ^{16}-yohimbene should be opposite to that in **30**. Thus Δ^{16}-yohimbene is correctly represented by **23b** rather than its enantiomer and hence yohimbine must be **24**, with H-3α(*S*), H-15α(*S*), H-16β(*R*), H-17β(*S*), and H-20β(*R*). A similar conclusion was drawn from comparing the molecular rotation contributions of the hydroxyl group in 16-methylyohimbol and cyclohexane derivatives. Further corroboration was provided by the ord curve of yohimbone (**34**), which suggested a trans D/E ring junction with H-15α.[13] Later, chemical methods were also applied.[14] Thus the absolute configuration of the alcohol at C-17 was confirmed by Prelog's method of asymmetric induction: treatment of the phenylglyoxalate ester (**32**) with methylmagnesium bromide and subsequent hydrolysis afforded (+)-atrolactic acid (**33**) in agreement with *S* chirality. Finally, a conversion of yohimbone (**34**) into dihydrocorynantheane (**37**) of previously established absolute configuration (see Chapter III, Section II.A) was achieved (Scheme 6). After reduction of **34** to the alcohol and conversion to the chloride, elimination of hydrogen chloride by heating with collidine proceeded in a selective manner to give Δ^{17}-yohimbene (**35**). Subsequent cleavage of ring E gave the dialdehyde **36**, which was reduced by the Wolff-Kishner method to dihydrocorynantheane. More recently an X-ray structure determination of yohimbine hydrochloride has given the expected confirmation of stereochemistry.[15]



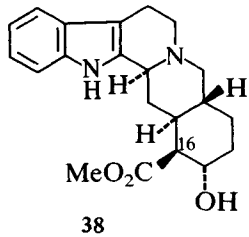
Scheme 6. Reagents: i, $NaBH_4$; ii, $POCl_3$, py; iii, collidine, Δ; iv, OsO_4; v, HIO_4; vi, N_2H_4, OH^-, Δ.

B. Corynanthine

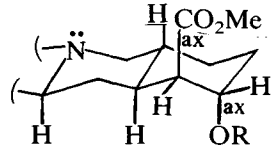
Corynanthine (rauhimbine) (**38**) was recognized at an early stage as a steroisomer of yohimbine, giving the same products with selenium and yohimbone on Oppenauer oxidation. It was converted into yohimbine by alkaline hydrolysis followed by reesterification, a process which was likely to affect only the configuration of H-16. Hence corynanthine must be the less stable 16 epimer (**38**) with an axial β-carbomethoxy group (**39a**), which accords with its lower rate of hydrolysis. Corroboration of the trans diaxial relationship of the 16 and 17 substituents was afforded by the production of Δ^{16}-yohimbene (**23b**) from corynanthine sulfate (**39b**): the steric requirements of elimination led to loss of the carbomethoxy group rather than the proton in conjunction with the sulfate group on treatment with alkali.[16]

C. β-Yohimbine

β-Yohimbine (amsonine) (**40**) gave the same products as yohimbine on selenium dehydrogenation and was yet another stereoisomer of yohimbine. It could only



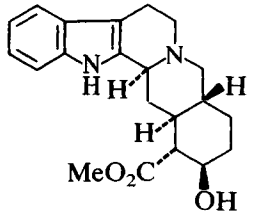
38



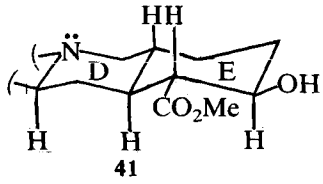
39a: R = H
39b: R = SO_3H

differ in the configuration at C-16 and/or C-17 since Oppenauer oxidation gave yohimbone. However, since the two C-16 epimers were known, and both had an α hydroxyl group, in β-yohimbine the hydroxyl group had to have the β configuration.

Again, like yohimbine and unlike corynanthine, H-16 in β-yohimbine was not epimerized by alkali and therefore the carbomethoxy group was equatorial and α.[17] Hence β-yohimbine corresponded to structure **40**, which would appear to be the most favored of the yohimbine stereoisomers with rings D and E in chair conformations and all substituent groups equatorial as in **41**. This greater stability is apparent from the isomerization of yohimbine to β-yohimbine by heating with potassium *t*-butoxide in benzene, presumably via elimination and addition of water, or by mild oxidation to yohimbinone (**42**) followed by stereoselective reduction with sodium borohydride (Scheme 7).[18,19] Likewise, the net hydration of apoyohimbine (**23a**) by base-catalyzed addition of methanol, demethylation of **43** with hydrobromic acid, and reesterification gave β-yohimbine.[20] Again, the β-lactone (**45**) obtained from yohimbic acid (**44**) underwent inversion at C-17 on treatment with lithium bromide in acetone to form the bromo acid (**46**).[18] Subsequent displacement of the bromide by acetate might have caused a second inversion but actually occurred with retention to give **47** and thence **40**. In all cases the outcome can be attributed to a preference for an equatorial hydroxyl group rather than an axial one as in yohimbine.



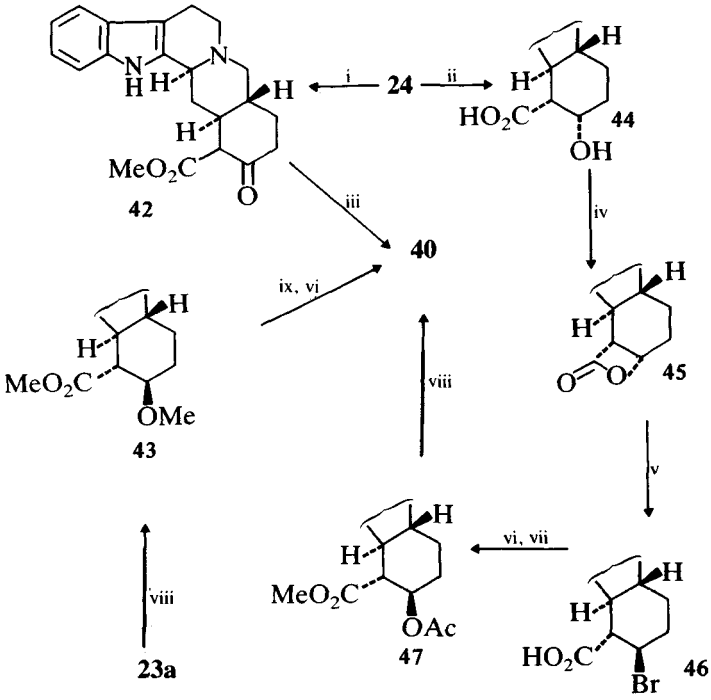
40



41

D. Pseudoyohimbine

Pseudoyohimbine (**48**) was originally isolated from *Pausinystalia yohimba* and has also been found in *Rauwolfia canescens* L. and *R. tetraphylla* L. It was isomeric

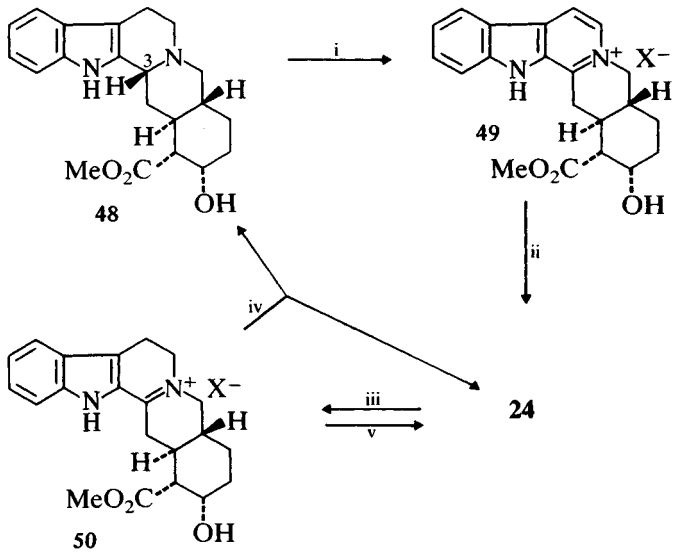


Scheme 7. Reagents: i, Oppenauer *or* CrO_3 *or* Me_2SO, Ac_2O; ii, H_2O; iii, $NaBH_4$; iv, $ClCO_2Et$; v, LiBr, Me_2CO; vi, CH_2N_2; vii, NaOAc; viii, NaOMe; ix, HBr.

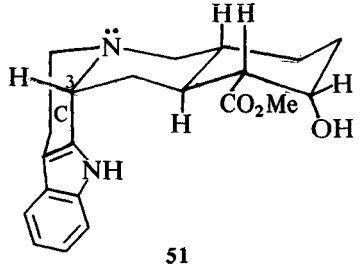
with yohimbine, had similar functional groups, and gave identical products on dehydrogenation with selenium, but Oppenauer oxidation gave pseudoyohimbone instead of yohimbone. Eventually treatment of pseudoyohimbine with lead tetraacetate gave a tetradehydro derivative (**49**) which was reduced to yohimbine (Scheme 8).[16] Hence the two bases are C-3 epimers and pseudoyohimbine has structure **48** with H-3 β and equatorial. As indicated in **51** the resulting 1,3 diaxial interactions of the indole moiety at C-3 make pseudoyohimbine less stable than yohimbine (**26b**). On prolonged heating of either in acetic acid C-3 is epimerized, the equilibrium largely (~85%) favoring yohimbine.[21] A rather better yield of pseudoyohimbine from yohimbine is obtained by oxidation with mercuric acetate to the 3-dehydroyohimbine (**50**) and reduction with zinc and acetic acid to a mixture of **48** and **24**. Reduction of **50** with sodium borohydride only regenerates yohimbine but catalytic hydrogenation under certain conditions can yield pseudoyohimbine.

E. Alloyohimbine

As with other isomers the relationship of alloyohimbine (**58**) to yohimbine was indicated by the formation of identical products on selenium dehydrogenation,[22]



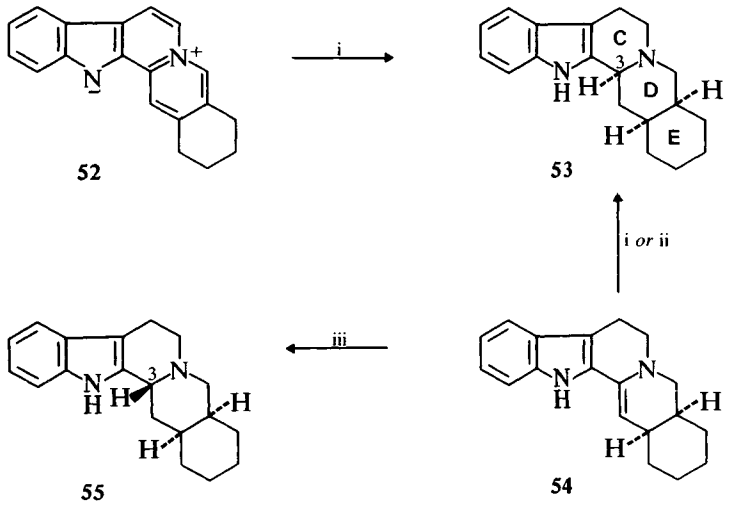
Scheme 8. Reagents: i, $Pb(OAc)_4$; ii, H_2, cat.; iii, $Hg(OAc)_2$; iv, Zn, AcOH; v, $NaBH_4$.



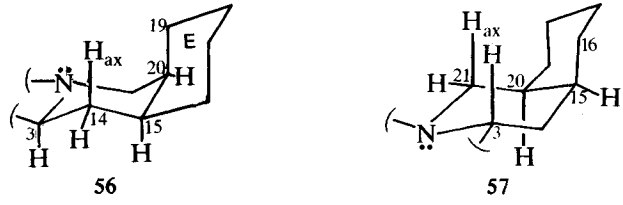
51

and the presence of carbomethoxy and hydroxyl groups was detected in a similar way. Oppenauer oxidation gave a stereoisomer of yohimbone, alloyohimbone, which was reduced by the Wolff-Kishner method to (−)-alloyohimbane. The latter was prepared by catalytic hydrogenation of sempervirine (**52**) (Scheme 9), whose structure had been established by synthesis, and resolution of the racemic product with (−)-tartaric acid.[23] Consequently, alloyohimbane was formulated as **53** with H-3, 15, and 20 all cis, since in catalytic hydrogenation all the hydrogen could be assumed to have added from the same side. This assignment was confirmed by a synthesis of alloyohimbane from cis-hydrindan-2-one via **54** by an analogous route to that of yohimbane from trans-hydrindan-2-one in Scheme 3.[24] Catalytic hydrogenation of the intermediate **54** can give only the H-3, 15 cis arrangement of **53**, and the product was found to be identical with alloyohimbane. However, reduction with sodium and liquid ammonia gave mainly 3-epialloyohimbane (**55**). Examination

of preferred conformations **56** and **57** for the two epimers shows that there is little difference between them in thermodynamic stability, unlike the corresponding yohimbane-pseudoyohimbane pair. Both have the indole group at C-3 equatorial and two sets of 1,3-diaxial interactions – between C-19, H-14 ax, and the nitrogen lone pair in **56** and between C-16, H-3, and H-21 ax in **57**. The cis α,α relationship between H-3 and H-15 was also confirmed by the presence of diagnostic ir bands in the 2700–2900 cm^{-1} region, which indicated a trans C/D ring junction with ring D in a chair conformation.[25]



Scheme 9. Reagents: i, H_2, cat.; ii, Sn, HCl; iii, Na, liq. NH_3.

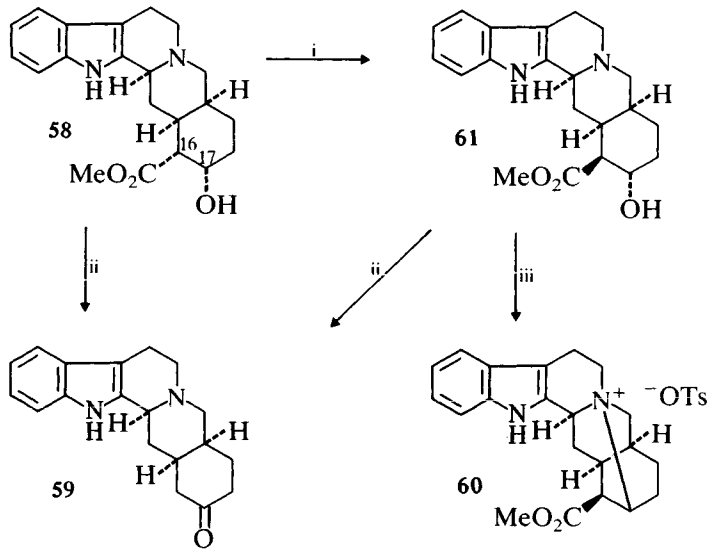


Initially it was thought that H-16 in alloyohimbine could not be epimerized by mild alkali treatment and hence that the ester group was in the more stable equatorial orientation, β and trans to H-15.[18b] Furthermore, the hydroxyl group was also deduced to have a β configuration from the transformation of alloyohimbine into α-yohimbine (**61**) with potassium *t*-butoxide in refluxing benzene[26] and from application of Klyne-Stokes generalizations on molecular rotation contributions.[27] It was not until 1973 that Töke and co-workers established the simple fact that alloyohimbine could be readily converted into α-yohimbine at room temperature with sodium methoxide.[28] Under such mild conditions only H-16 can be epimerized and hence the ester group in alloyohimbine must have the less stable α configuration.

Moreover, the hydroxyl must have the same α stereochemistry as that established for α-yohimbine (Section II.F) and hence alloyohimbine corresponds to structure **58** (Scheme 10).

F. α-Yohimbine

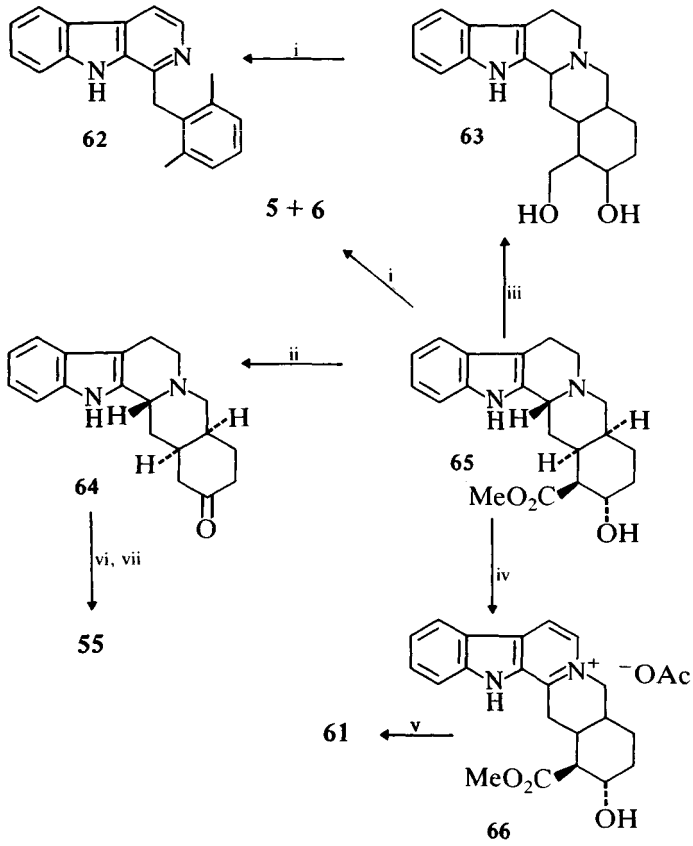
α-Yohimbine (corynanthidine) (**61**), originally isolated as a minor constituent of yohimbehe bark and from *Pseudocinchona africana*, was eventually found to be identical with rauwolscine, the major alkaloid of *R. canescens*. Its structure was established by chemical reactions including degradation with selenium in the same manner as other stereoisomers. In particular, Oppenauer oxidation (Scheme 10) afforded a ketone (corynanthidone, rauwolscone) identical with alloyohimbone (**59**), indicating that α-yohimbine and alloyohimbine differ only in their stereochemistry at C-16 and/or C-17.[18,22] Since α-yohimbine was not epimerized by alkali, its carbomethoxy group must be equatorial with a β configuration. The stereochemistry of the 17-hydroxyl group was assigned from the observation that mild treatment of α-yohimbine with *p*-tosyl chloride at 5° gave a quaternary tosylate (**60**). Because of the cis D/E ring junction, such a reaction could occur easily only via backside displacement of the tosylate group by the nitrogen lone pair approaching from the β face, resulting in inversion at C-17. Consequently, α-yohimbine must have an α hydroxyl group and is represented by structure **61**. The conversion of deserpidine into α-yohimbine (Scheme 19) was achieved with retention of configuration at C-15, 16, 17, and 20 and hence constituted further corroboration for structure and stereochemistry.



Scheme 10. Reagents: i, NaOMe; ii, Oppenauer oxidation; iii, *p*-TsCl, py.

G. 3-Epi-α-yohimbine

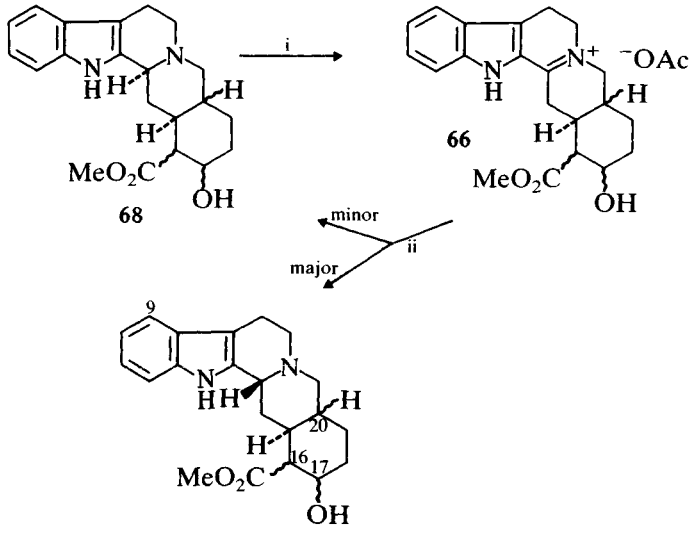
Unlike all the preceding analogues of yohimbine, 3-epi-α-yohimbine (isorauhimbine, 3-epirauwolsine, Alkaloid Su. 3078) (**65**) was not isolated from yohimbehe bark but from *Rauwolfia serpentina* Benth. ex. Kurz. Its identification as a yohimbine stereoisomer was achieved in the usual manner by the chemical reactions of the carbomethoxy, hydroxyl, and tertiary amine groups, and degradation with selenium to yobyrine (**5**) and tetrahydroisoyobyrine (**6**).[30] Reduction with lithium aluminum hydride to 3-epi-α-yohimbol (**63**) and heating with selenium afforded methylyobyrine (**62**) and indicated the position of the carbomethoxy group (Scheme 11). Oppenauer oxidation of the alkaloid gave 3-epialloyohimbone, whose ethylene thioketal was reduced with Raney nickel to 3-epialloyohimbane (**55**). Finally, its identity as the 3β epimer (**65**) of α-yohimbine was established by dehydrogenation with lead tetraacetate to a tetradehydro derivative which was subsequently reduced with sodium borohydride to α-yohimbine (**61**).



Scheme 11. Reagents: i, Se, Δ; ii, Oppenauer oxidation; iii, $LiAlH_4$; iv, $Pb(OAc)_4$; v, $NaBH_4$; vi, $(CH_2SH)_2$, H^+; vii, Raney Ni.

H. 3-Epicorynanthine, 3-Epi-β-yohimbine, and 3-Epialloyohimbine

The three 3β bases, 3-epicorynanthine (**67a**), 3-epi-β-yohimbine (**67b**), and 3-epialloyohimbine (**67c**), are not known as natural products but have been made by epimerizing the corresponding 3α isomers. The general procedure (Scheme 12) is analogous to that used above for producing pseudoyohimbine from yohimbine, that is, oxidation to a 3,4-dehydro derivative with mercuric acetate followed by reduction with zinc and acetic acid.[22b] There does not appear to be any reason for them not to be found eventually in vivo.



	H-16	H-17	H-20
67a	α	β	β
67b	β	α	β
67c	β	β	α

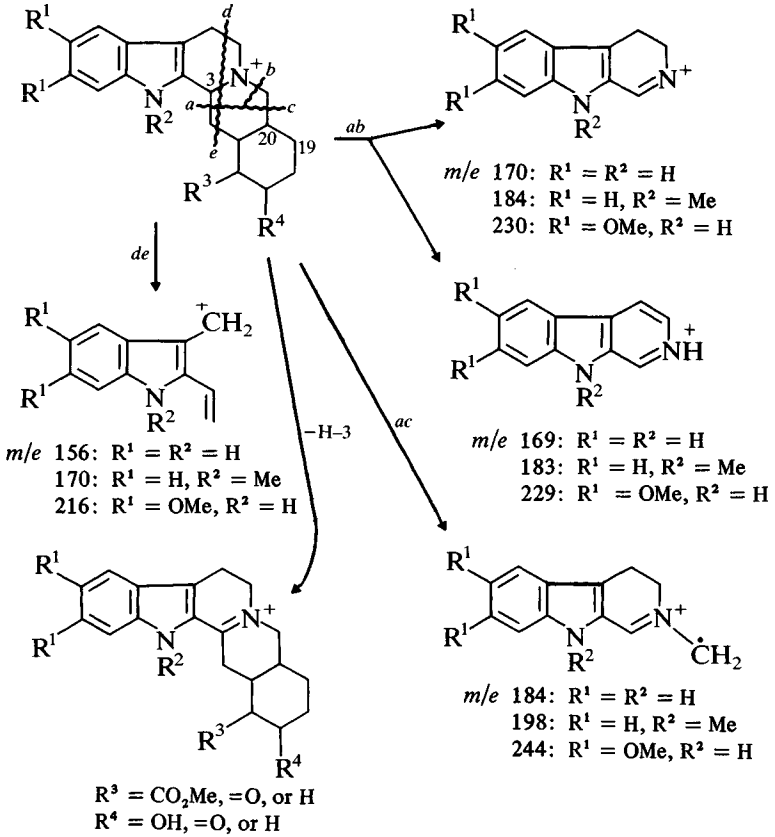
Scheme 12. Reagents: i, $Hg(OAc)_2$; ii, Zn, AcOH.

III. SUBSTITUTED AND UNSATURATED YOHIMBINES

A. Spectroscopic Methods

The structures of the above yohimbine stereoisomers had been elucidated by the mid 1950s, using essentially traditional chemical methods for analysis of functional groups, that is, degradation and interconversion, although uv and ir spectra were also used to some extent. The advent of unit resolution mass spectrometry about 1960 not only provided molecular masses but also largely replaced the drastic chemical degradations. In particular, comparing the major fragments in

the mass spectra of several yohimbine derivatives of known constitution established a common breakdown pattern which could then be used to identify structural features in related alkaloids (Scheme 13).[31] Thus the unsubstituted yohimbines and their derivatives ($R^1 = R^2 = H$) all invariably show a strong M-1 peak and four ions at *m/e* 184, 170, 169, and 156, no matter what the stereochemical differences or what groups (R^3, R^4) are attached to ring E. The M-1 fragment is largely due to loss of H-3, as shown by a substantial M-2 peak with 3-deuteroyohimbine. The other four ions all incorporate the indole residue, their formation being rationalized in terms of fragmentation *ab*, *ac*, and *de* triggered by the ready cleavage of the allylically activated 3,14 or 5,6 bonds. Importantly, when substituents are present in the indole nucleus (R^1 = OMe, or R^2 = Me) there is an appropriate increment in the mass of the corresponding fragments, for example, 14 m.u. for an N_a-methyl group or 60 m.u. for two methoxy substituents in the benzene ring. The consistent incremental shift in this group of ions is obviously of great value in structure determination of unknown yohimbinoid alkaloids, particularly now that provisional assignments can be corroborated by elemental analysis of the fragments by accurate mass measurement in high resolution mass spectrometers.



Scheme 13.

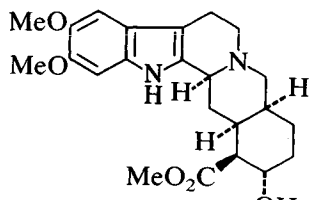
Proton nmr spectroscopy was another powerful technique for structure determination introduced in the late 1950s. Not only did it afford a rapid nondestructive method for identifying proton-containing functional groups from their chemical shifts but also enabled conformational and configurational assignments to be made. For example, in yohimbinoid compounds an axial H-3 is invariably found below δ 4 and an equatorial H-3 above δ 4, thus indicating whether the C/D ring junction is trans or cis, respectively, but further information is required before α or β configurational assignments can be made unambiguously. The same is true for the trans-quinolizidine bands in the 2700–2800 cm^{-1} region of the ir spectrum, the presence or absence of which was once erroneously used for deciding α or β stereochemistry at C-3, a correlation usually but not invariably valid.[25] Again, the magnitude of coupling constants between protons has been widely used to assign conformations and hence relative configurations for H-15, 16, and 17, for example. The more recent availability of ^{13}C nmr spectrometers has also been exploited increasingly for structural assignments in yohimbinoid compounds.[32]

As a result of a series of investigations it was found that ord or the related cd curves could be used to establish the absolute stereochemistry at C-3 in yohimbine and related alkaloids, a positive Cotton effect between 250 and 300 nm being correlated with an $\alpha(S)$ configuration and a negative effect with a $\beta(R)$ configuration.[33] Chiroptical properties have also proved useful for obtaining information about other chiral centers and conformations.[34]

The increasing and progressive use of these spectroscopic techniques from 1960 onward is well illustrated by the structure determinations of yohimbine derivatives given below.

B. Seredine

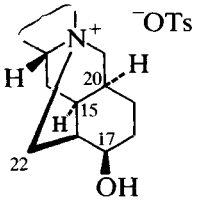
Seredine (**69**), $C_{23}H_{30}N_2O_5$, was isolated from *Rauwolfia vomitoria* Afzel and found to contain a basic nitrogen, a hydroxyl, and three methoxyl groups.[35] Its uv spectrum was that of a 5,6-dimethoxyindole and the ir spectrum showed a carbonyl group and other marked similarities to that of α-yohimbine. Accordingly, Oppenauer oxidation afforded seredone whose mass spectrum was identical with that of alloyohimbone (**59**) except for an increment of 60 m.u. corresponding to two methoxyl groups in characteristic fragments containing the indole nucleus (see Scheme 13).[31a] Furthermore, the ord curves of seredine and α-yohimbine were very similar, as were the changes in molecular rotation for two parallel series of derivatives, and hence seredine was considered to be 10,11-dimethoxy-α-yohimbine (**69**).



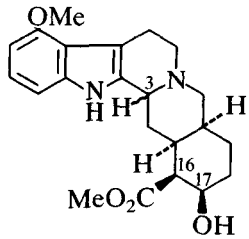
69

C. Venenatine and Isovenenatine (Alstovenine)

These alkaloids from *Alstonia venenata* R.Br. constituted a pair of 9-methoxyyohimbines epimeric at C-3.[36] Since venenatine showed no trans-quinolizidine bands in its ir spectrum and was unaffected by mercuric acetate, it was thought to have 3β chirality. However, it was oxidized by *t*-butyl hypochlorite to a 3-dehydro derivative which was reduced by sodium borohydride to isovenenatine, a procedure known to give 3α stereochemistry. These assignments were later confirmed by ord.[33] On reduction with lithium aluminum hydride to a diol and subsequent tosylation a quaternary salt was obtained. Consequently, H-15 and 20 were cis (and α) and C-22 was involved in bonding to N-4 and hence must be β as in **70**. Participation of the oxygen function on C-17 could be discounted because venenatine tosylate did not form a quaternary salt, this in itself indicating a β orientation for the hydroxyl group. On this basis venenatine was formulated as **71b** and isovenenatine as **71a**, that is, derivatives of the unknown 16*S*,17*R* yohimbines.



70

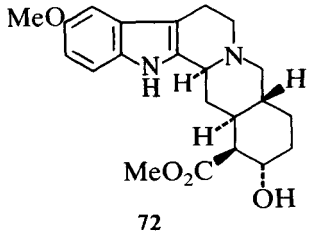


	3-H
71a:	α
71b:	β

D. Excelsinine

Excelsinine (**72**) (from *Aspidosperma excelsum* Benth.) was identified as a 10-methoxyyohimbine from its uv spectrum (λ_{max} 227, 282, 297 sh. nm) and its mass spectrum, which was analogous to that of yohimbine except for a characteristic shift of 30 m.u. (cf. Scheme 13). Its ir spectrum showed absorption for indolic NH and OH at 3380 cm^{-1}, the presence of both being confirmed by formation of a monoacetate. A methyl ester was indicated by an ir band at 1727 cm^{-1} and two methoxyl peaks at δ 3.84 and 3.58 in the nmr spectrum, and its relationship to the hydroxyl group was established in the usual way by Oppenauer oxidation to excelsinone. The stereochemistry at C-3 was α since trans-quinolizidine bands were evident in the ir spectrum and the positive ord curve of excelsinine was very similar to that of yohimbine but opposite to that of pseudoyohimbine. Furthermore, a close match between the ord curves of the corresponding ketones excelsinone and yohimbone indicated that the configurations at C-15 and C-20 were also the same. The 17 proton appearing at δ 5.22 in the nmr spectrum had

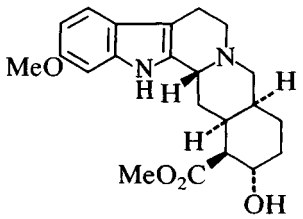
only very small couplings in accord with an equatorial and hence β orientation. Finally, on treatment with alkali H-16 was found to be epimerized, showing that the carbomethoxy group was in the less favorable axial β configuration and hence excelsinine corresponded to 10-methoxycorynanthine (**72**).[37]



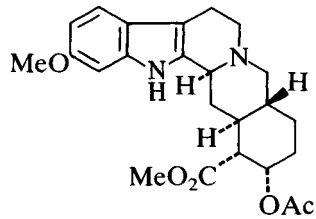
72

E. Quaternatine

The main structural features of this alkaloid from *Alstonia quaternata* Heurck et Muell. Arg. were revealed by uv, nmr, and mass spectra. In contrast to the preceding alkaloid, there were no trans-quinolizidine ir bands, and the nmr signal for H-3 occurred at δ 4.38, indicating an equatorial β orientation and a cis C/D ring junction. Confirmation of the C-3 configuration was afforded by a negative Cotton effect in the 295–275 nm region of the cd spectrum. Subsequent comparison of nmr and cd data for quaternatine and 3-epi-α-yohimbine showed identity of stereochemistry and the position of the methoxy group at C-11 was finally secured by ^{13}C nmr comparison with poweridine (**74**) and other methoxyyohimbines. Hence quaternatine is 11-methoxy-3-epi-α-yohimbine (**73**).[38]



73



74

F. Poweridine

Soon after poweridine (**74**) was isolated in 1962 from *Ochrosia poweri* Bail. it was recognized from its chemical and spectral behavior as an 11-methoxyyohimbine *O*-acetate derivative and some aspects of its stereochemistry were established.[39a] In particular the carbomethoxy and acetoxy groups had to have a 1,3-cis relationship, because they could be transformed into a β-lactone. In a later[39b] ^1H nmr study H-16 was located at δ 2.35 with a trans diaxial coupling of 11 Hz to H-15 and a

TABLE II. ^{13}C NMR CHEMICAL SHIFTS IN $CDCl_3$ (PPM RELATIVE TO TMS)

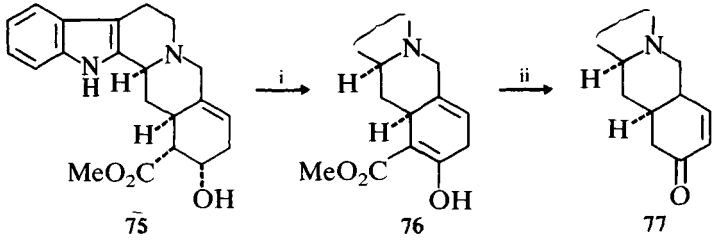
C	Poweridine	Yohimbine *O*-acetate	α-Yohimbine *O*-acetate	Reserpine
3	60.0	59.9	60.2	54.0
11	152.2	119.4	119.4	152
14	30.0	29.9	27.4	
15	37.0	36.9	36.6	
16	51.2	51.0	52.0	
17	69.7	69.7	69.2	
18	34.1	33.9	31.0	
20	40.2	39.9	38.4	

small axial-equatorial coupling of 2 Hz to H-17, thus establishing their relative configuration. All the remaining stereochemical features were revealed by a comparative analysis of the ^{13}C nmr spectra of poweridine, yohimbine *O*-acetate, and reserpine, the more important features of which are summarized in Table II. The most striking feature is the close correspondence (± 0.3 ppm) between the chemical shifts for poweridine and yohimbine *O*-acetate, apart from the expected difference in C-11. Assignments of C-3 stereochemistry to poweridine was straightforward from the chemical shift of 60 ppm for 3α alkaloids compared with 54 ppm for a 3β alkaloid. For the two alternative configurations of C-20 the difference of about 1.5 ppm was significant but less marked. However, corroborative evidence was provided by substantial differences between the shifts of the carbons at positions 14 (~ 2.5 ppm) and 18 (~ 3 ppm) which left no doubt that poweridine had 20β chirality and corresponded to 11-methoxyyohimbine *O*-acetate (**74**).[39b]

G. 19,20-Dehydroyohimbine

In addition to known yohimbine stereoisomers *Aspidosperma pyricollum* Muell. Arg. was found to contain a novel dehydro derivative. Although its uv and ir spectra were rather similar to those of yohimbine, in the mass spectrum the molecular ion appeared at *m/e* 352 rather than 354 in addition to standard indole-containing fragments at *m/e* 184, 170, 169, and 156. Formation of an *O*-acetate showed the presence of a hydroxyl group. The nmr spectrum had the appropriate signals for a yohimbine – δ 7.90 (NH), 7–7.5 (four aromatic H), 4.25 (H-C-O-), 3.80 (CO_2Me) – but also an olefinic proton at δ 5.55, indicating a trisubstituted double bond. On catalytic hydrogenation yohimbine was formed and thus the structure (**75**) and stereochemistry were determined, apart from the location of the double bond. Since the intensity of the *m/e* 156 peak was much higher and the *m/e* 184 lower than in yohimbine, it was suggested that the olefinic linkage was between C-19 and C-20, allylically assisting cleavage *e* and hindering *c* in Scheme 13. This location of the double bond was established by Moffatt oxidation to a β-keto ester (**76**) (M^+ 350, δ 5.55) which was hydrolyzed and decarboxylated with acid to an α,β-unsaturated ketone (**77**) (M^+ 292, ν_{max} 1672 cm^{-1}) (Scheme 14). Since the latter contained two olefinic protons (δ 5.92, 6.65; J = 10 Hz), the double bond could only be between

C-18 and C-19 and hence had migrated from the 19,20 position. The alkaloid must therefore be 19,20-dehydroyohimbine (**75**), related to the reserpine analogues raujemidine and deserpideine (Section IV.C).[40]



75 **76** **77**

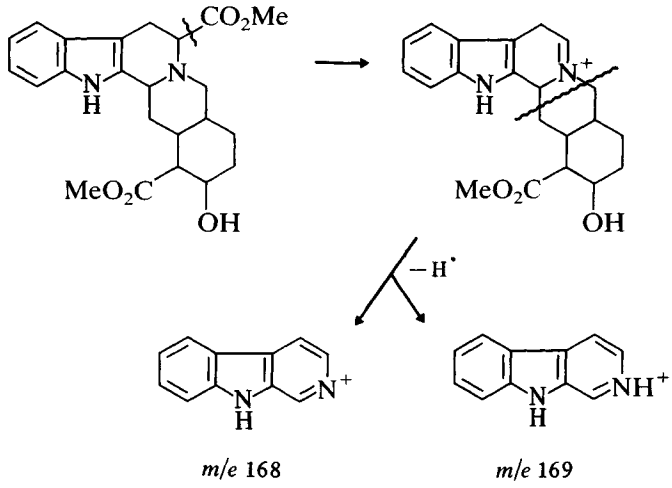
Scheme 14. Reagents: i, DCC, Me_2SO, pyH^+; ii, aq. HCl, Δ.

H. 5α*H*-Carboxycorynanthine

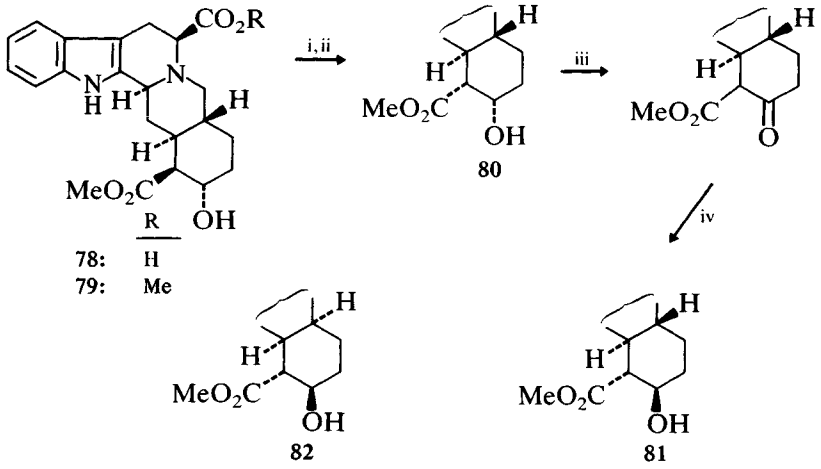
A so far unique yohimbine derivative is 5-carboxycorynanthine (**78**) inasmuch as it is derived from tryptophan rather than tryptamine. It was isolated from *Adina rubescens* Hemsl., after treatment with diazomethane, as the methyl ester, whose mass spectrum gave the first indication of its structure.[41] The molecular ion at *m/e* 412 ($C_{23}H_{28}N_2O_5$) gave a series of fragments analogous to those of yohimbine (Scheme 13) but shifted by 58 m.u. ($C_2H_2O_2$) and also a series of strong peaks attributable to loss of CO_2Me. In particular a pair of ions at *m/e* 169 and 168 rather than 170 and 169 indicated a facile cleavage α to N-4 of the carbomethoxy group and hence suggested a 5-carboxyyohimbine structure (Scheme 15). This provisional assignment was fully borne out by chemical reactions and spectra, from which the stereochemistry of **79** could also be deduced. The α configurations for C-3 and C-15 were evident from a positive Cotton effect in the cd spectrum, trans-quinolizidine ir bands, and the occurrence of H-3 below δ 4 in the nmr spectrum, whereas C-5 presumably retained the chirality of L-tryptophan with an equatorial carbomethoxy group. The stereochemistry at C-16, 17, and 20 was based on the analogy of its chemical behavior with corynanthine (**38**) (Scheme 16). Thus acetylation gave two monoacetates due to partial epimerization of C-16, which was completed on methanolysis to an isomer (**80**). Oxidation to a β-keto ester followed by reduction yielded yet another isomer which was considered to be a β-yohimbine derivative (**81**) since borohydride reduction was known to favor equatorial C-16 and C-17 substituents (cf. Scheme 7). This series of reactions was consistent with structure **79** for the isolated material and thus the natural base was presumably 5α*H*-carboxycorynanthine (**78**), although the alternative stereoisomer **82** (unknown in the tryptamine series) could not be definitely excluded.

IV. RESERPINE AND CONGENERS

For centuries extracts of the Indian shrub *Rauwolfia serpentina* Benth. ex Kurz (Apocynaceae) have been used in the Ayurvedic system of medicine as a specific



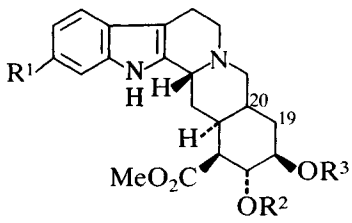
Scheme 15.

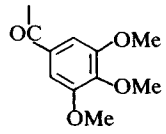


Scheme 16. Reagents: i, Ac_2O, py; ii, NaOMe; iii, Me_2SO, Ac_2O; iv, $NaBH_4$.

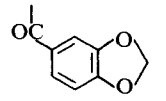
against various disorders. Although the hypotensive properties of the crude extract were reported in 1933 and it was increasingly used as a sedative,[42] not until 1952 did Müller and co-workers isolate the active principle, reserpine.[43] The therapeutic value of reserpine was soon evident and it was widely used, particularly in the treatment of mental disorders and high blood pressure. This provided the impetus for an intensive examination of several other *Rauwolfia* species as additional sources of reserpine and perhaps analogous compounds of potential therapeutic value. As a consequence reserpine was found to occur to a greater or lesser extent in more than 20 species and several congeners were isolated (Table III). Its structure was elucidated largely by classical chemical methods combined with conformational analysis and confirmed by a brilliant stereoselective total synthesis (Section VI.A).

TABLE III. RESERPINE AND CONGENERS

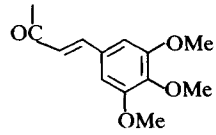




TMB



MYR

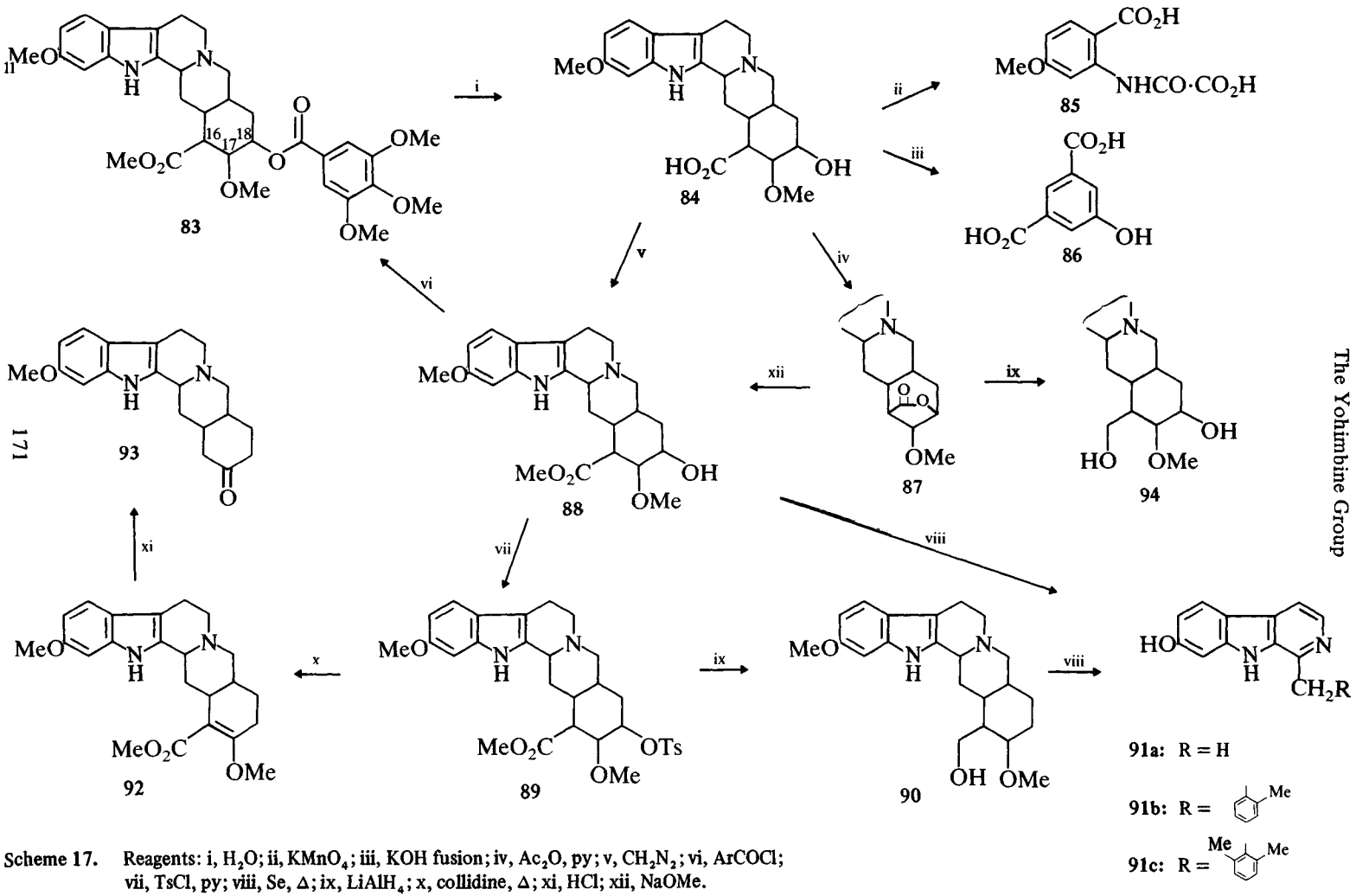


TMC

Name	Structure	H-20	R^1	R^2	R^3
Reserpine	**105**	α	OMe	Me	TMB
Rescinnamine	**115**	α	OMe	Me	TMC
Veneserpine	**116**	α	OMe	Me	MYR
Raujemidine	**122**	$\Delta^{19,20}$	OMe	Me	TMB
Pseudoreserpine	**118**	α	OMe	H	TMB
Rescidine	**117**	α	OMe	H	TMC
Raugustine	**119**	α	OMe	TMB	H
Deserpidine	**106**	α	H	Me	TMB
Deserpideine	**123**	$\Delta^{19,20}$	H	Me	TMB
Raunescine	**120**	α	H	H	TMB
Isoraunescine	**121**	α	H	TMB	H

A. Reserpine

Saponification of reserpine (**105**), $C_{33}H_{40}N_2O_9$, yielded methanol, 3,4,5-trimethoxybenzoic acid, and reserpic acid, $C_{22}H_{28}N_2O_5$, from which reserpine could be reconstituted by treatment with diazomethane to give methyl reserpate, $C_{23}H_{30}N_2O_5$, followed by acylation with trimethoxybenzoyl chloride. The two ester functions were confirmed by lithium aluminum hydride reduction of reserpine to a diol, $C_{22}H_{30}N_2O_4$, and 3,4,5-trimethoxybenzyl alcohol.[44,45] Reserpic acid (**84**) (Scheme 17) still contained two methoxyl groups, and since it was oxidized by permanganate to 4-methoxy-*N*-oxalylanthranilic acid (**85**) one must be attached to the equivalent of position 6 in the benzene ring of an indole. Accordingly the uv spectrum of 2,3-dimethyl-6-methoxyindole was close to that of methyl reserpate (λ_{max} 228, 270–272, 298 nm), and moreover, a summation spectrum with methyl 3,4,5-trimethoxybenzoate virtually reproduced that of resperine (λ_{max} 218, 268, 294–296 nm).[45] Extension of this part structure to a methoxytetrahydro-β-carboline was possible when selenium dehydrogenation of methyl reserpate gave a hydroxyyobyrine, $C_{19}H_{16}N_2O$, whose spectrum was very similar to that of harmol (**91a**), and hence was assigned structure **91b**. The constitution of **91b** was confirmed by reduction of its *p*-tosylate with Raney nickel to yobyrine, and by synthesis of its *O*-methyl derivative from harmine, the methyl ether of **91a**.[46]



Scheme 17. Reagents: i, H_2O; ii, $KMnO_4$; iii, KOH fusion; iv, Ac_2O, py; v, CH_2N_2; vi, ArCOCl; vii, TsCl, py; viii, Se, Δ; ix, $LiAlH_4$; x, collidine, Δ; xi, HCl; xii, NaOMe.

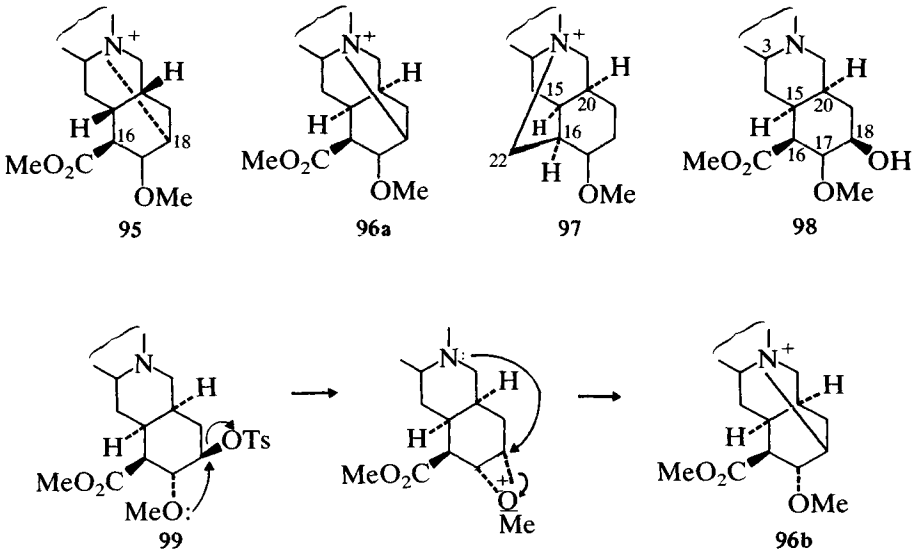
It was thus apparent that methyl reserpate was an 11-methoxyyohimbane derivative, and in all likelihood the carbomethoxy, hydroxyl, and methoxyl substituents were in ring E, but it remained to locate them unambiguously. Tosylation of methyl reserpate and subsequent treatment with lithium aluminum hydride removed the hydroxyl group and reduced the methyl ester to give reserpinol, $C_{22}H_{30}N_2O_3$. On dehydrogenation with selenium, reserpinol was degraded to the methylyobyrine derivative **91c**, whose structure was established by synthesis. The position of the second methyl group established unambiguously that the carbomethoxy substituent must be at C-16 as with other yohimbines.

One of the oxygen functions was located at C-18 since fusion of reserpic acid with potassium hydroxide yielded 5-hydroxyisophthalic acid (**86**), although such a drastic degradation did not permit a distinction between alcohol and ether groups. That it was actually the hydroxyl was demonstrated unequivocally by the formation of a γ-lactone (**87**) from reserpic acid on attempted acetylation. Finally the methoxyl group was proved to be attached to C-17 when methyl reserpate was converted into methyl anhydroreserpate (**92**) by treatment of the tosylate with collidine. The β-methoxyacrylate ester system in **92** was identified by characteristic uv and ir absorptions and by its ready, acid-catalyzed hydrolysis and decarboxylation to reserpone (**93**). Hence on the basis of the transformations summarized in Scheme 17, the gross structure of methyl reserpate could be formulated as **88**, and that of reserpine as **83**.[46]

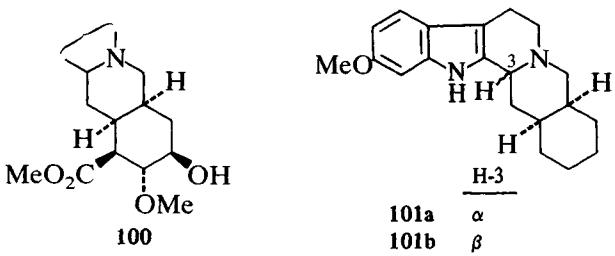
It remained to elucidate the stereochemistry of the six chiral centers at C-3, 15, 16, 17, 18, and 20, which proved to be by no means a straightforward task, in retrospect largely because of the conformational mobility of the molecule. Again, the ready epimerization of C-3 under acid or base catalysis to give 3-isoreserpine derivatives presented some difficulty. One definite stereochemical feature which had emerged from the previous work was the cis relationship of the C-16 and C-18 substituents established by the ready formation of a γ-lactone (**87**) from reserpic acid (**84**). Any possibility of concomitant epimerization at C-16 was discounted because the lactone gave only reserpine diol (**94**) on reduction with lithium aluminum hydride, and methyl reserpate (**88**) on ring opening with sodium methoxide. Furthermore, from the large positive change in molecular rotation on formation of the lactone ($[M]_D + 300°$) from reserpic acid ($[M]_D - 692°$) an absolute β(*R*) configuration for the hydroxyl group at C-18 was deduced from Klyne's extension of Hudson's lactone rule.[47]

Firm evidence about the relative stereochemistry of H-15 and H-20 was provided by the isolation of a quaternary salt in addition to methyl anhydroreserpate (**92**) after treatment of methyl reserpate 18-*O*-tosylate (**89**) with collidine.[47] Only if the D/E ring junction is cis can a bond be formed between the basic N-4 and C-18. However, an extension of the argument to the effect that this cyclization occurred to give part structure **95** with inversion of configuration at C-18, and hence implied a cis relationship between the C-18 oxygen function, H-15, and H-20 in reserpine, was proved to be erroneous.[48] Tosylation of reserpinol (**90**) afforded a quaternary salt which could be unequivocally formulated as **97** since C-22 was cis to the β hydroxyl group at C-18, and necessarily trans to H-15 and 20 to allow bond for-

mation to N-4. There was no likelihood of epimerization at C-16 at any stage, since this position in methyl reserpate was unaffected by alkali, confirming that the carbomethoxy group was already in the more stable equatorial orientation. Hence the former quaternary salt must be **96a** and thus **98** is a partial representation of the stereochemistry of methyl reserpate. Quaternization of the tosylate evidently proceeded with an overall *retention* of configuration, which was explicable by participation of the neighboring C-17 oxygen function in stabilization of the incipient carbonium ion at C-18, resulting in a double inversion as indicated in Scheme 18. However, this was likely to occur only if the methoxyl group was trans to the tosylate leaving group and hence had an α configuration as in **99**. On the basis of this argument it was possible to formulate methyl reserpate as **100**.



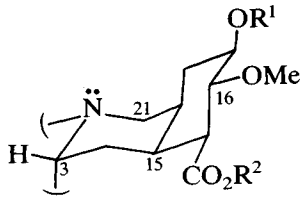
Scheme 18.



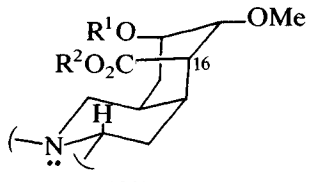
Assignment of the C-3 stereochemistry was not straightforward because of its relatively easy epimerization in acid. Thus reserpone (**93**), produced by acid hydrolysis of methyl anhydroreserpate, was found to be a 3:2 mixture of C-3 epimers. This was established by reduction to the reserpanes, 11-methoxyepialloyohimbane (**101b**) and 11-methoxyalloyohimbane (**101a**), which were synthesized in stereoselective routes from both 11-methoxysempervirine and cis-2-bromomethylcyclohexyl acetate.[49] In addition to further confirming the cis D/E ring junction, the ready interconversion of the reserpanes and reserpones to equilibrium mixtures containing comparable amounts of both epimers showed that there was little difference in stability between the allo and epiallo skeletons per se (cf. Section II.E). By way of contrast, epimerization of reserpine derivatives to the 3-iso series was about 85% on heating in acetic acid and virtually complete in acetic anhydride, a difference in stability attributed to steric interactions with the substituents in ring E. Under normal conditions the preferred conformations with the maximum number of equatorial substituents would be the C/D cis **102a** for the 3β and C/D trans **103a** for the 3α epimers. Furthermore, since the former has destabilizing 1,3-diaxial interactions between the indole residue at C-3 and hydrogens at C-15 and C-21 which are not present in the latter, the 3β epimer would be expected to be the less stable of the two, and hence correspond to reserpine. This assignment also afforded a satisfactory explanation for the experimental observations that reserpic acid readily formed a lactone configurationally stable at C-3, whereas 3-isoreserpic acid did so only under forcing conditions with epimerization to give the same lactone. The alternative C/D trans conformation **102b** ($R^1 = R^2 = H$) for the 3β acid has the axial orientations of the hydroxyl and carboxyl groups required for lactonization to **104**, while the indole residue is equatorial, reducing the energy difference between the two conformers, **102a** and **b**. Appropriate conformations in the 3α series (**103b, c**) are difficult to attain because of obvious steric interactions between the indole residue and the C-16 and 18 substituents. Even when 3-isoreserpic acid lactone was eventually obtained, it was found to isomerize readily with acid to reserpic acid lactone (**104**). On the basis of these considerations reserpine was allocated 3β stereochemistry, an assignment corroborated by other chemical and chiroptical results, and the complete structure of reserpine was thus formulated as **105**.[48,50] A final confirmation of the absolute stereochemistry was by use of Prelog's asymmetric induction method on methyl reserpate.[14]

B. Deserpidine

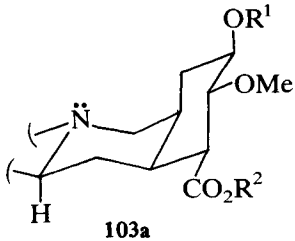
Deserpidine (canescine, recanescine, raunormine) (**106**), $C_{32}H_{38}N_2O_8$, was isolated from *R. canescens* and was found to have similar hypotensive and sedative activity to reserpine. Its chemical reactions were also analogous and together with the uv spectrum suggested an 11-desmethoxyreserpine structure (**106**) which was corroborated when methyl deserpidate *O*-tosylate (**107**) was converted into α-yohimbine (**61**) and α-yohimbyl alcohol (**108**) as outlined in Scheme 19, showing that the configurations at C-15, 16, 17, and 20 were the same. Epimerization to the



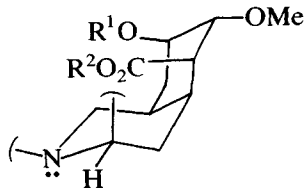
102a



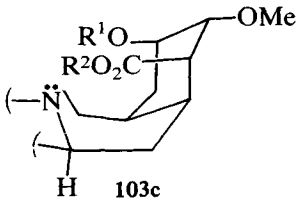
102b



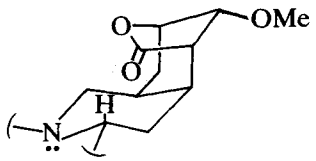
103a



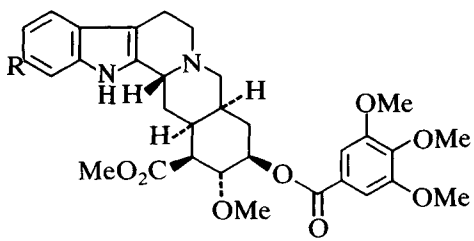
103b



103c



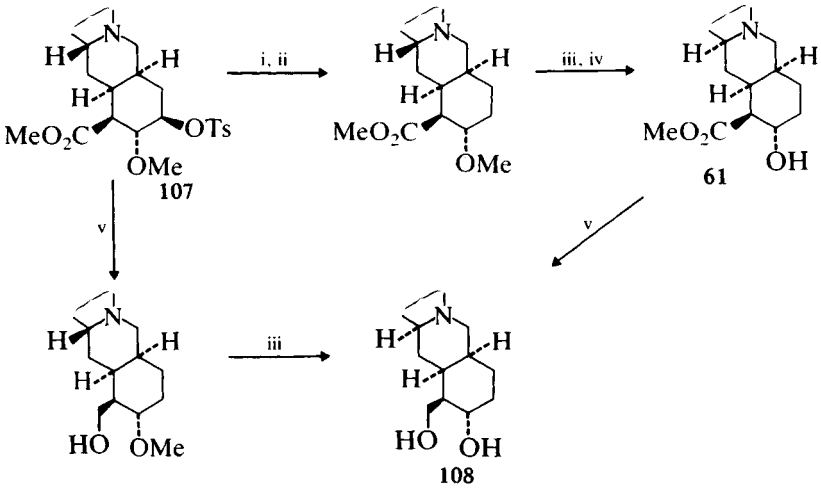
104



	R
105	OMe
106	H

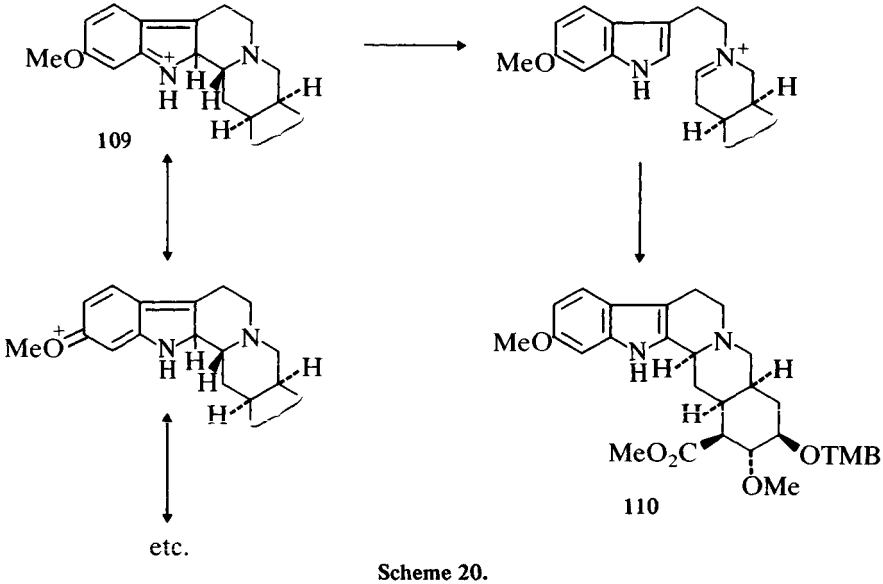
3α series was found to occur during cleavage of the methyl ether with hydrobromic acid, and hence deserpidine must be 3β. Since, like reserpine, a γ-lactone could be formed, the oxygen functions at C-18 must again be cis to the carbomethoxy group on C-16, and deserpidine was thus formulated as **106**.[50,51]

Interestingly, although the same destabilizing steric interactions with the C-16 and 18 substituents in rings D and E are involved, deserpidine is not isomerized at C-3 by acid nearly as readily as reserpine.[52] The difference in reactivity has been attributed to electron release from the 11-methoxy group in reserpine assisting protonation at C-2 to form **109**. Subsequently, epimerization to 3-isoreserpine (**110**) occurs via reversible C-2,C-3 cleavage, that is, a retro-Picter-Spengler reaction



Scheme 19. Reagents: i, NaI or LiBr; ii, Zn, AcOH; iii, HBr; iv, esterification; v, $LiAlH_4$.

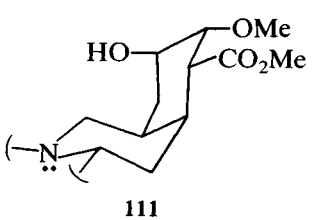
(Scheme 20). It is noteworthy that, although thermodynamically more stable than the 3β series, no 3α isomer has yet been recognized as a natural product and also that the 3-iso series is pharmacologically inactive.



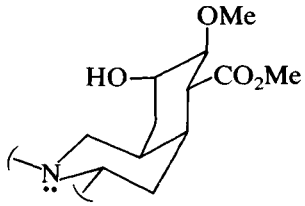
Scheme 20.

As an alternative to C-3 inversion, a C/D trans ring junction with an equatorial indole residue can be achieved by epimerization of C-16, placing the carbomethoxy group in an equatorial orientation and thus relieving some of the nonbonded interactions. Thus, in presence of base, methyl reserpate is converted to the 16-

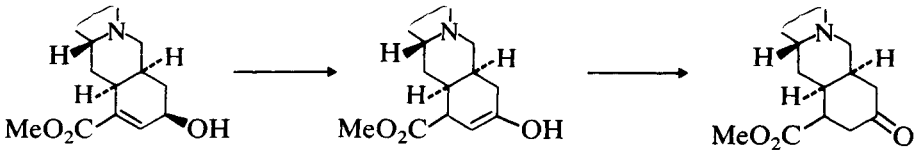
epireserpate (**111**), and also to the neoreserpate (**112**) by elimination and readdition of methanol to the α,β-unsaturated ester **113**. Eventually, under more vigorous conditions the intermediate **113** isomerizes to a γ-keto ester (**114**) via a β,γ-unsaturated ester (Scheme 21).[53]



111



112



113 **114**

Scheme 21.

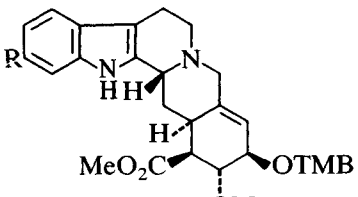
C. Other Reserpine Congeners

Other alkaloids related to reserpine and deserpidine are listed in Table III, and apart from the 19,20-dehydro derivatives, they differ only in minor variations on the oxygen substituents at C-17 and C-18. In most cases their structures have been determined simply by partial degradation or partial synthesis. Thus rescinnamine (**115**) and veneserpine (**116**) were hydrolyzed to reserpic acid and the corresponding aromatic acids;[54,55] in turn, rescidine (**117**) was correlated with **115** by methylation of the 17-hydroxyl function with diazomethane in presence of aluminum isopropoxide.[56] Pseudoreserpine (**118**) was methanolyzed to methyl 3,4,5-trimethoxybenzoate and the diol, methyl pseudoreserpate (**118**, R^3 = H), whose structure was established by 17-*O*-methylation to give methyl reserpate.[57] The benzoate ester was thought to be probably at C-18 as in reserpine since pseudoreserpine displayed similar pharmacological activity to reserpine, whereas its isomer raugustine (isopseudoreserpine) (**119**) did not. Hence the latter was allocated the alternative 17-*O*-trimethoxybenzoate structure.

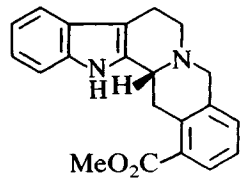
Raunescine (**120**) and isoraunescine (**121**) were shown by reduction to a common triol to be structural rather than configurational isomers, different hydroxyl groups being esterified by the trimethoxybenzoic acid. The structure and stereochemistry of their common debenzoylated derivative methyl raunescate were demonstrated by a series of chemical reactions and arguments essentially as with methyl deserpidate.[58] The free hydroxyl group was considered to be located probably at the more hindered C-17 in raunescine and at C-18 in isoraunescine since raunescine could not be tosylated under the same mild conditions as isoraunescine.

Again this assignment was supported by raunescine, but not isoraunescine, having reserpine-like activity.

The 19,20-unsaturated derivatives raujemedine (**122**) and deserpideine (**123**) had been thought to be stereoisomers of reserpine and deserpidine until nmr spectra revealed an olefinic proton at δ 5.6 in both.[59] Subsequent catalytic hydrogenation to **105** and **106** confirmed the relationship, the location of the double bond being indicated by the ready aromatization of ring E to form the dehydrogambirtannine structure (**124**) on treatment on deserpideine with sodium methoxide.



R	
122	OMe
123	H



124

V. AROMATIZED YOHIMBINES

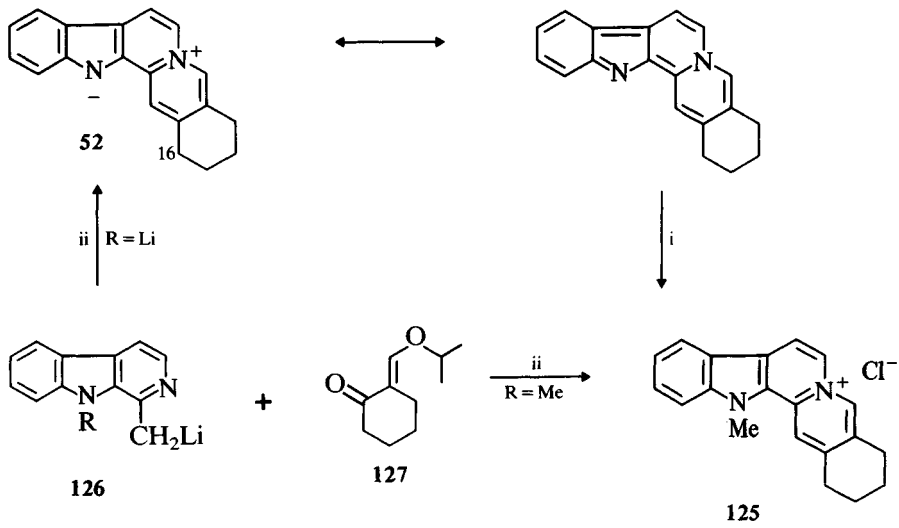
A. Sempervirine

Sempervirine (**52**), $C_{19}H_{16}N_2$, is an optically inactive, monacidic orange base obtained from *Gelsemium sempervirens* Ait. and *G. elegans* Benth. (Loganiaceae). The yohimbinoid nature of the ring system was revealed by the formation of yobyrine and tetrahydroisoyobyrine on heating with selenium and Raney nickel, respectively. To account for its color, intense uv absorption, and the absence of an NH band in its ir spectrum, the highly conjugated system **52** was eventually proposed.[60] Final proof of this structure was obtained by synthesis of the methochloride (**125**) from the lithium derivative of N_a-methylharman (**126**) and 2-isopropoxymethylenecyclohexanone (**127**) (Scheme 22).[61] Subsequently sempervirine itself has also been synthesized in an analogous fashion and also by other routes.[62]

On catalytic hydrogenation sempervirine gave alloyohimbane and, since the addition of hydrogen could be assumed to be all cis, provided an important clue in the early elucidation of the stereochemistry of the latter (Section II.E).

B. Alstoniline

Another optically inactive base, alstoniline (**128**), $C_{22}H_{18}N_2O_3$, was isolated from the bark of *Alstonia constricta* F. Muell as its red hydrochloride salt. Largely on the basis of uv and ir spectra and the degradations outlined in Scheme 23, structure **128** was suggested and confirmed by syntheses of tetrahydroalstonilinol



Scheme 22. Reagents: i, methylation; ii, acid.

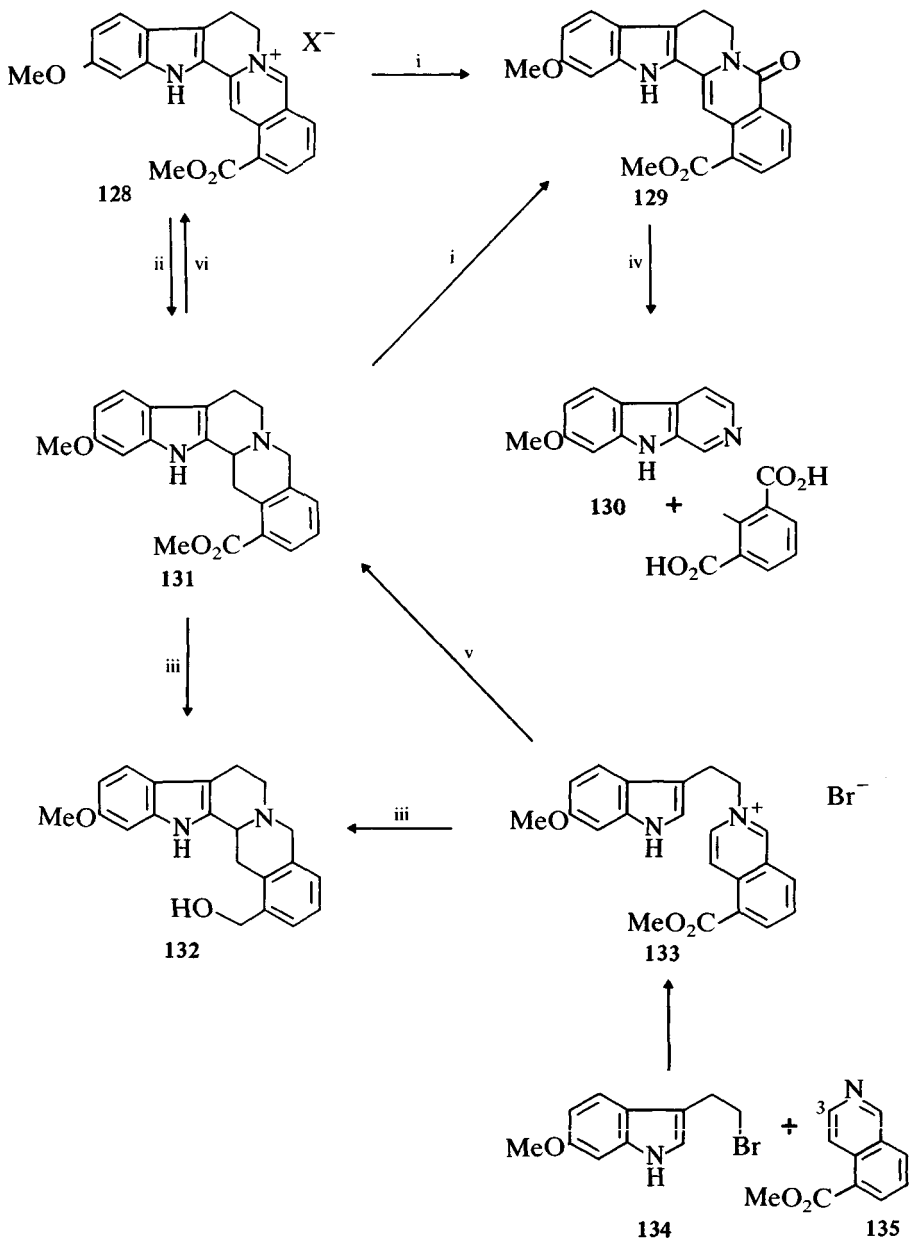
(**132**) from 6-methoxytryptophyl bromide (**134**) and 5-carbomethoxyisoquinoline (**135**), via **133**.[63] Alstoniline itself has been synthesized from **133** as indicated in Scheme 23 and also directly by heating **134** with the 3-bromo derivative of **135**.[64]

C. Alstonilidine

Another alkaloid from *A. constricta* is alstonilidine (**136**) which may be considered as derived from alstoniline via **129** by further oxidation and methanolysis. Its structure was assigned largely on the basis of spectral data. The ir spectrum showed two different unsaturated carbonyl functions and the mass spectrum had the losses of 59 m.u. from the molecular ion at *m/e* 418 corresponding to two carbomethoxy groups. In the nmr spectrum three methoxyl peaks were evident, but two were lost on hydrolysis of alstonilidine to the acid and hence one must be due to an aromatic methoxyl group. Analysis of the couplings of the eight aromatic protons was consistent with the harman and isophthalate moieties of **136**, which must be linked to each other at C-3 and C-15 via the other type of carbonyl group.[65]

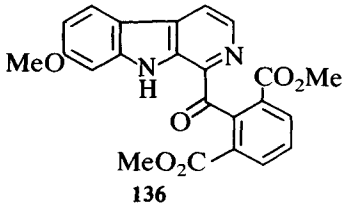
D. Gambirtannine and Related Alkaloids

Gambirtannine, (−)-dihydrogambirtannine, and oxogambirtannine were found as fluorescent constituents of gambir resin, a tanning material derived from *Uncaria gambir* Roxb. (*Ourouparia gambir* Baillon).[66] Their formulas were established by accurate mass measurement of the respective molecular ions and the presence of a methyl ester by appropriate losses in the mass spectrum and from ir and nmr spectra. Heating of gambirtannine with selenium afforded dehydroketoyobyrine

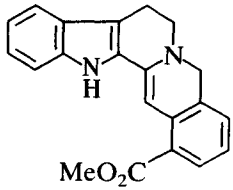


Scheme 23. Reagents: i, O_2; ii, H_2, PtO_2; iii, $LiAlH_4$; iv, NaOH, $C_5H_{11}OH$; v, $NaBH_4$; vi, I_2, KOAc.

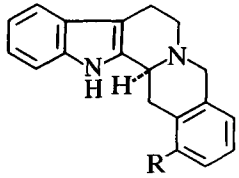
(141), which was also obtained from yohimbine under the same conditions and thus revealed the essential ring structure, whereas dehydrogenation of oxo-gambirtannine gave the nor compound **(142)**. The extended uv chromophore of



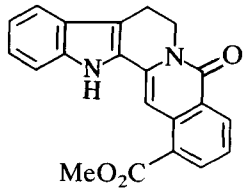
136



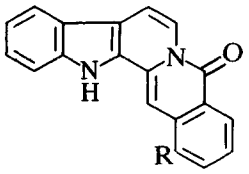
137



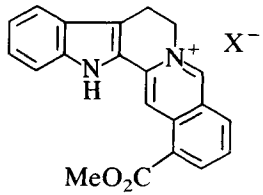
138: R = CO_2Me
139: R = H



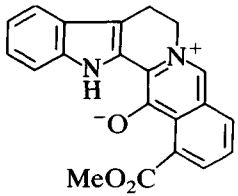
140



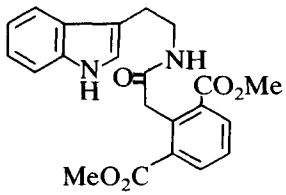
141: R = Me
142: R = H



143



144



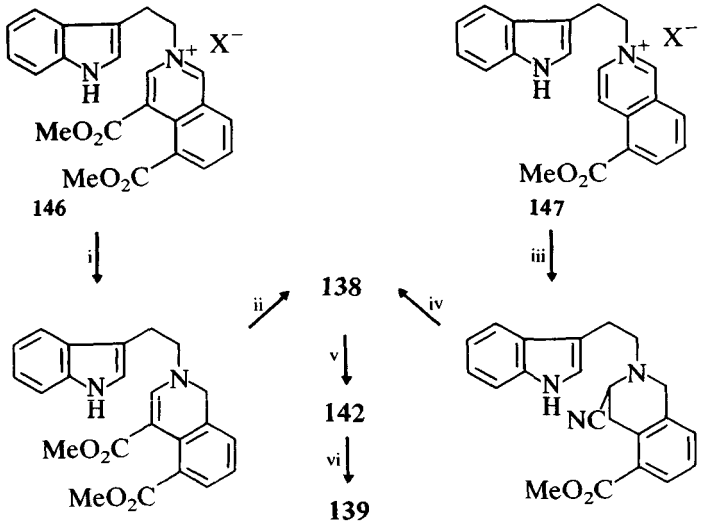
145

gambirtannine (λ_{max} 266, 314, 340, 410 nm) was changed to a simple indole absorption on catalytic hydrogenation to racemic dihydrogambirtannine, evidently by saturation of the 3,14 double bond. On the basis of this and other evidence gambirtannine and its dihydro derivative could be formulated as **137** and **138**, respectively, and oxogambirtannine as **140**, structures which were supported by analysis of their nmr spectra.[66] Furthermore, the known deserpideine had been degraded to the (+)-enantiomer (**124**) of the levorotatory dihydrogambirtannine and thus secured the chirality at C-3 as α in addition to corroborating the structure.

The related strong base ourouparine, isolated from the same source by Taylor and Raymond-Hamet, was assigned structure **143** because of its reduction to **138**.[67] Conversely oxidation of **138** with iodine and sodium acetate gave

ourouparine iodide.[67,68] With alkali ourouparine is readily transformed into a mixture of **137**, **140**, and neooxygambirtannine (**144**), yet another tannin constituent.

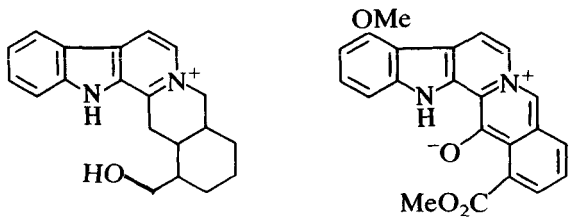
In addition to the interconversions within the series the structures have also been secured by total syntheses. Oxogambirtannine was obtained by Bischler-Napieralski cyclization with phosphorus oxychloride of the amide **145** prepared from tryptamine and 2,6-dicarboxyphenylacetic acid. Racemic dihydrogambirtannine has been made in two ways from isoquinolinium salts **146** and **147** and converted into oxogambirtannine via ourouparine (Scheme 24).[69]



Scheme 24. Reagents: i, H_2, Pd; ii, OH^-; iii, $NaBH_4$, NaCN; iv, H_3O^+; v, I_2, NaOAc; vi, H_2O_2, dioxane.

Decarbomethoxydihydrogambirtannine (**139**) occurs in the leaves of *Ochrosia lifuana* and *O. miana*.[70]

A β-carbolinium alkaloid from *Strychnos melinoniana*, melinonine E, has been formulated as **148**.[71a] Anhydroalstonatine, a bright red, zwitterionic alkaloid recently isolated from *Alstonia venenata* bark, has been tentatively assigned the structure **149**.[71b]



148 **149**

VI. SYNTHESES

In the preceding sections we have already mentioned several syntheses of degradation products with the pentacyclic yohimbane skeleton which were necessary to establish structural or stereochemical features during the structure elucidation of yohimbine and its analogues. Formally, the syntheses of the alkaloids themselves were required as classical final proofs of structure. Because of the presence of at least five chiral centers in yohimbine derivatives they have presented major, continuing challenges to the art and ingenuity of synthetic chemists over the past 25 years, and several different successful approaches have been devised. It is possible to discuss only a few in detail, but the majority of syntheses of various yohimbinoid skeletons are listed in Table IV.

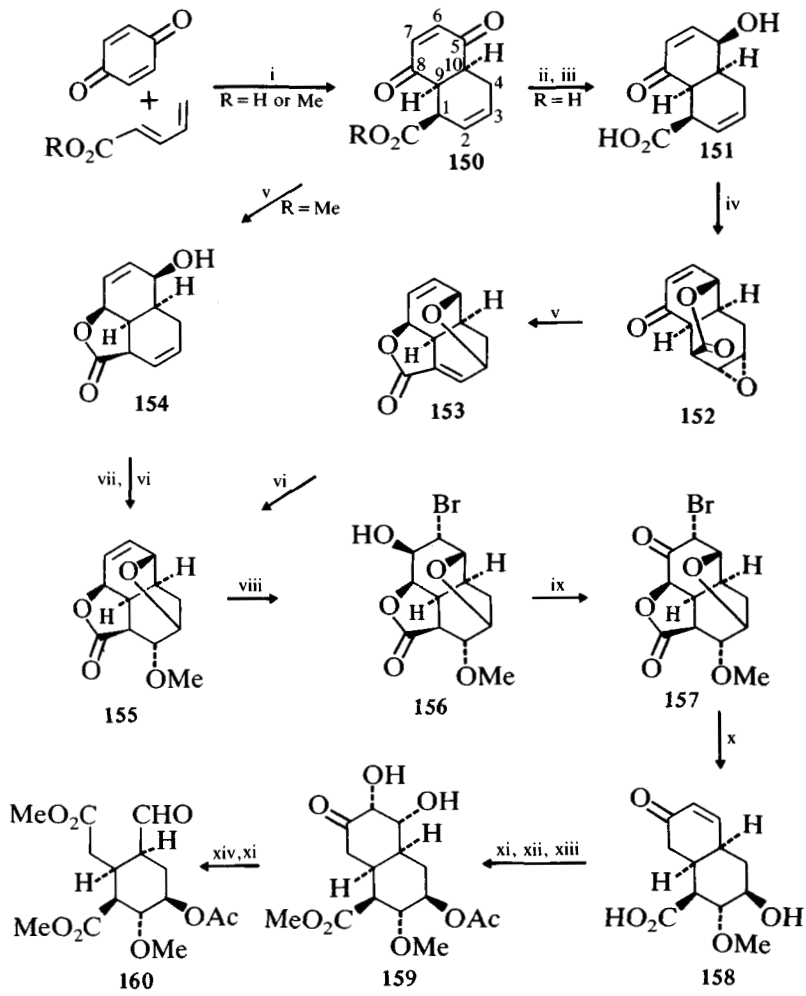
TABLE IV. SYNTHESES OF YOHIMBINOID SYSTEMS

Compound	Ref.
Dehydroyohimbanes	26, 61, 62, 72, 73, 74b, 90a
Gambirtannine, dihydrogambirtannine, and oxogambirtannine	68, 69, 83, 89
Alstoniline	64
Yohimbane	9, 26, 74, 90
Alloyohimbane and epialloyohimbane	24, 29, 75, 90c, d
Yohimbone and pseudoyohimbone	7, 76, 77, 79c, h, i
Apoyohimbine	78
Yohimbine, pseudoyohimbine, and β-yohimbine	72c, 79, 83
α-Yohimbine, 3-epi-α-yohimbine, alloyohimbine, and 3-epialloyohimbine	28, 79h, i
Reserpine and deserpidine	80–82
19,20-Dehydroyohimbine and 19,20-dehydro-β-yohimbine	83

A. Reserpine and Deserpidine

Since reserpine is perhaps the most complex of the yohimbine alkaloids, with no less than six chiral centers, it is somewhat surprising that this was actually the first yohimbine analogue to be synthesized (in 1956).[80] The outstanding feature of Woodward's brilliant synthesis was the highly stereoselective manner in which all five adjacent stereochemical centers in ring E were built into the crucial intermediate **160** as outlined in Scheme 25.

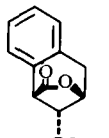
Diels-Alder reaction between *p*-benzoquinone and vinylacrylic acid occurred in the preferred endo mode to form an adduct (**150**, R = H) which already had the correct relative configuration at three centers. Subsequent reduction of **150** with sodium borohydride gave the keto alcohol **151** in a process which was both regio- and stereoselective. The former was attributed to interaction between the C-8 ketone and the carboxyl group preventing reduction, whereas the latter must be



Scheme 25. Reagents: i, PhH, Δ; ii, $NaBH_4$; iii, $PhCO_3H$; iv, Ac_2O, NaOAc; v, $Al(OPr^i)_3$, Pr^iOH; vi, NaOMe, MeOH; vii, Br_2; viii, NBS, H^+, 80°; ix, CrO_3, AcOH; x, Zn, AcOH; xi, CH_2N_2; xii, Ac_2O, py; xiii, OsO_4, $NaClO_4$; xiv, HIO_4.

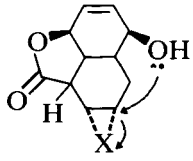
due to hydride addition to C-5 on the less hindered convex face of the cis-decalin derative **150**. Both features were confirmed by formation of a δ-lactone. Perbenzoic acid also approached from the convex face to afford an epoxide which was converted into the lactone **152**. Again in the Meerwein-Ponndorf reduction of the C-8 ketone the hydrogen was delivered from the less hindered side, the resulting hydroxyl forming a γ-lactone by displacement of the C-5 oxygen which in turn cleaved the epoxide ring by nucleophilic attack at C-3, as indicated in **162**; finally elimination of water led to the product of this complex sequence, **153**. Subsequent addition of methanol to **153** furnished the desired methyl ether **155**, the stereo-

chemistry at C-1, 2, and 3 being confirmed by transformation to the known compound **161**.

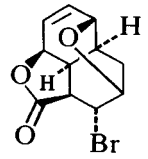


OMe

161



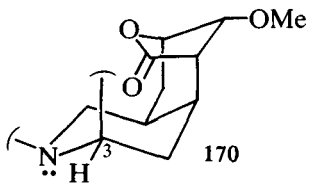
162: X = O
163: X = Br^+



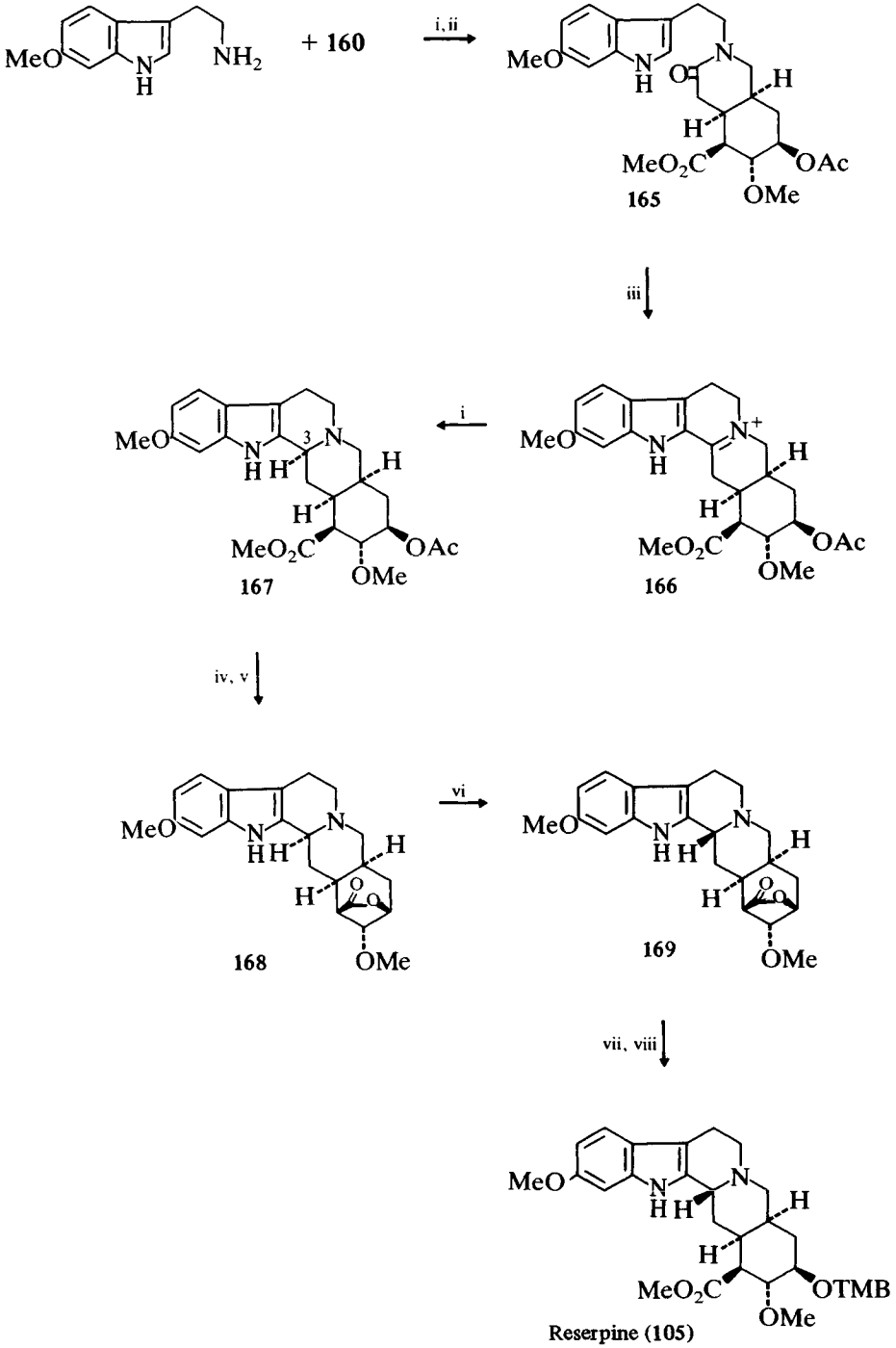
164

In a later development **155** was obtained in an even shorter stereoselective route from the methyl ester **150** via its Meerwein-Ponndorf reduction product **154**. The bromine ion preferentially attacked the 2,3-alkene with participation of the C-5 hydroxyl group from the opposite side as indicated in **163** to give the bromo ether **164**. Elimination of HBr then afforded **153** which added methanol as before to furnish **155**. Although it had not been affected by bromine, the less reactive double bond between C-6 and C-7 in **155** was subsequently converted with *N*-bromosuccinimide in sulfuric acid to the bromohydrin (**156**), which was oxidized to the α-bromoketone (**157**). When this was treated with zinc in acetic acid, two simultaneous reductive cleavages occurred and the unsaturated keto acid **158** was produced. After methylation and acetylation, hydroxylation of the double bond gave the diol **159**. Cleavage with periodic acid followed by methylation then yielded the desired aldehydo ester **160**, containing the five chiral centers present in ring E of reserpine.

The subsequent conversion of **160** into reserpine is summarized in Scheme 26. A major problem was that the configuration at C-3 in **167** corresponded to the generally more stable 3-iso series rather than reserpine. The ingenious solution was to hydrolyze the two ester groups and then force lactonization of 3-isoreserpic acid via the unfavorable conformation **103b** ($R^1 = R^2 = H$) to the previously unknown **168** by heating with *N,N'*-dicyclohexylcarbodiimide. As anticipated **168** was readily epimerized to reserpic acid lactone (**169**) since inversion of C-3 permits a conformation **104** in which severe nonbonded interactions between the indole and lactone rings in conformation **170** of the 3-isolactone are relieved. Subsequent opening of the lactone ring with methoxide and acylation afforded racemic reserpine which was resolved using camphor-10-sulfonic acid to give material identical with the natural alkaloid.



170



Scheme 26. Reagents: i, PhH; ii, $NaBH_4$; iii, $POCl_3$; iv, KOH; v, DCC/py; vi, Me_3CCO_2H, Δ; vii, NaOMe; viii, TMB chloride.

Modifications of Woodward's original synthesis subsequently led to commercial processes for the manufacture of reserpine and deserpidine.[81,84] The more important changes were resolution at an early stage to avoid waste of reagents and reduction of the 3-dehydro intermediate **166** or related compounds with zinc and perchloric acid directly to the 3β epimeric series. Various obvious analogues of reserpine have also been prepared by using substituted tryptamines and β-phenethylamines.[84]

After more than 20 years a second synthetic route to reserpine-type alkaloids was achieved by Szántay and co-workers[82a] employing a linear rather than a convergent approach, based upon their previous syntheses of yohimbine alkaloids.[79h] Starting from the readily available ketone **171**, regioselective alkylation and subsequent condensation with malononitrile resulted in inversion at the potential C-20 to **172** (Scheme 27). Stereoselective reduction then gave **173** with H-3, 15, 20 in cis configurations, which was converted into the diester **174** by standard reactions. Formation of ring E was achieved by a regioselective Dieckmann reaction involving preferential acylation of the C-16 carbanion rather than the sterically crowded C-18 alternative, and the resulting β-keto ester (**175**) was then transformed into deserpidine (**106**) by a series of well-established reactions.

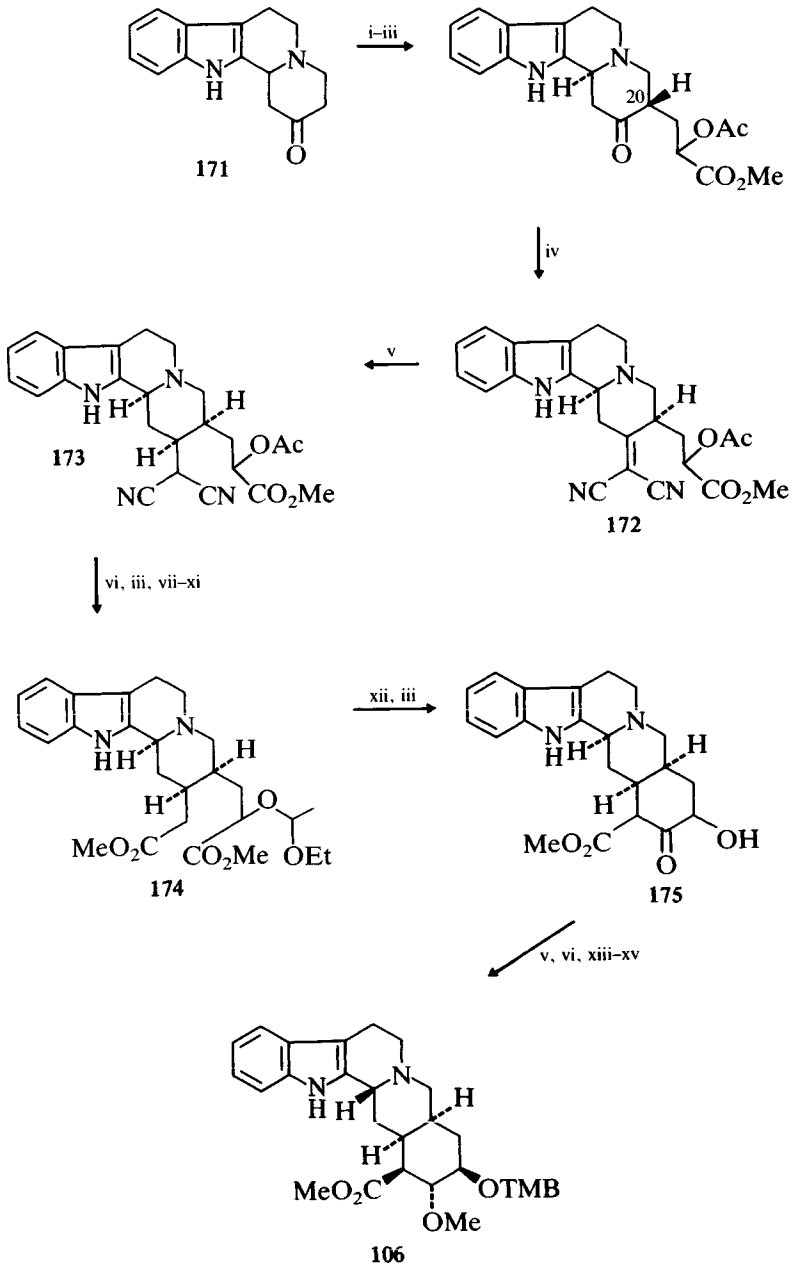
Recently the Woodward reserpine precursor **160** has been synthesized by Pearlman[82b] in a novel procedure starting from 1,4-dihydrobenzoic acid (Scheme 28). The regio- and stereoselective introduction of the vicinal aldehyde and acetic ester functions was achieved by intramolecular photoaddition of **176** to give a cyclobutane derivative (**177**) and subsequent conversion into the β-acetoxy ester **178**. In addition to opening the lactone, methanolysis of **178** cleaved the cyclobutane ring via a retro-aldol reaction, the resulting aldehyde being isolated as the acetal **179**. Acylation and hydrolysis then afforded the reserpine precursor **160**.

Yet another novel approach to reserpine has made use of a neat synthesis of a *cis*-hydroquinoline derivative (**180**) by means of a Cope rearrangement of a Diels-Alder adduct (Scheme 29).[82c] A multistage conversion of the intermediate **180** into 3-isoreserpine (**110**) was then achieved by unexceptional methods.

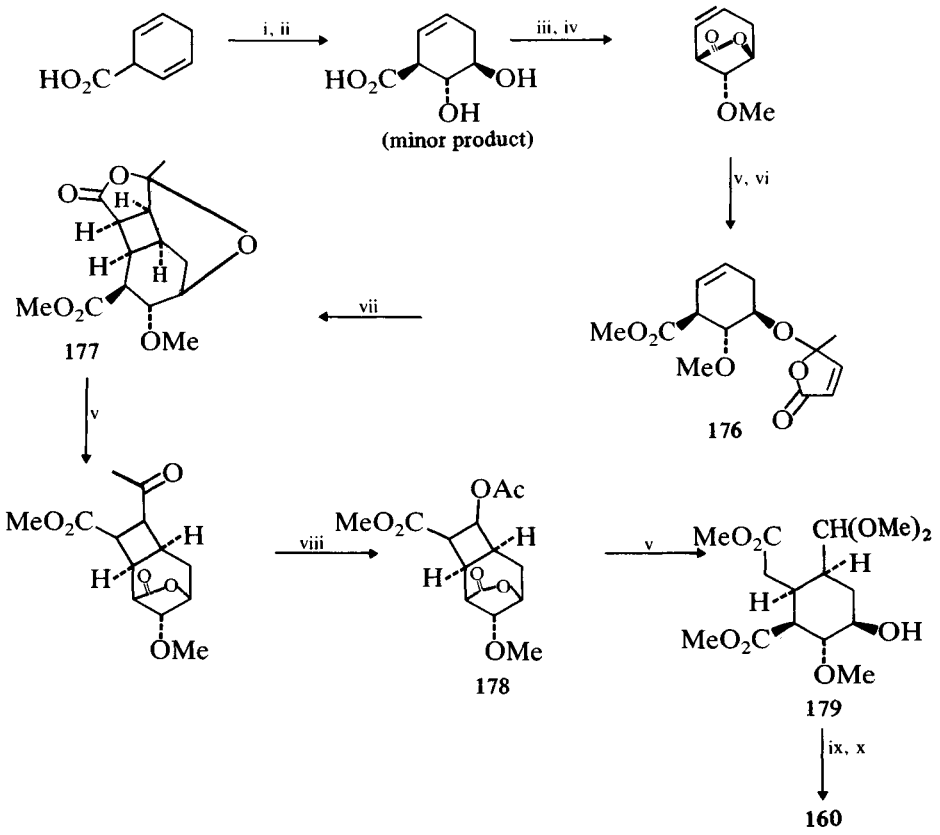
B. Yohimbines

The first total synthesis of yohimbine was by van Tamelen and co-workers in 1958 and, although lengthy, was remarkable in its introduction and control of stereochemistry.[79a] Four of the five chiral centers were created by taking skilful advantage of the preferred orientation of substituents in the series of trans-decalin derivatives **181** → **182** (Scheme 30).

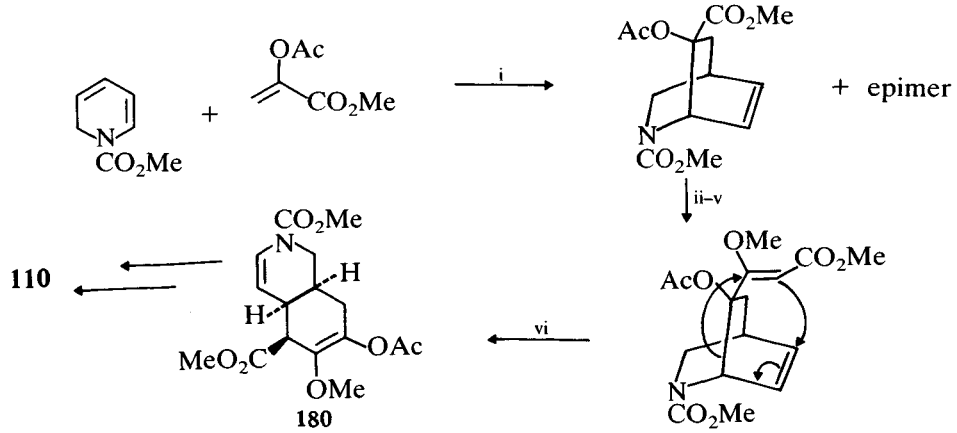
The rather unusual Picter-Spengler condensation of an amide nitrogen with one of the aldehyde groups formed by periodate cleavage of the diol (**182**) gave a β configuration at C-3 in **183**, but this center did not cause any problems since it could be readily epimerized. Another noteworthy feature was the use of the enol ether in **184** to provide ultimately the ester and hydroxyl functions in the final product (±)-pseudoyohimbine (**48**). Resolution afforded the (+)-enantiomer, identical with the natural product, and easily transformed into yohimbine (**24**).



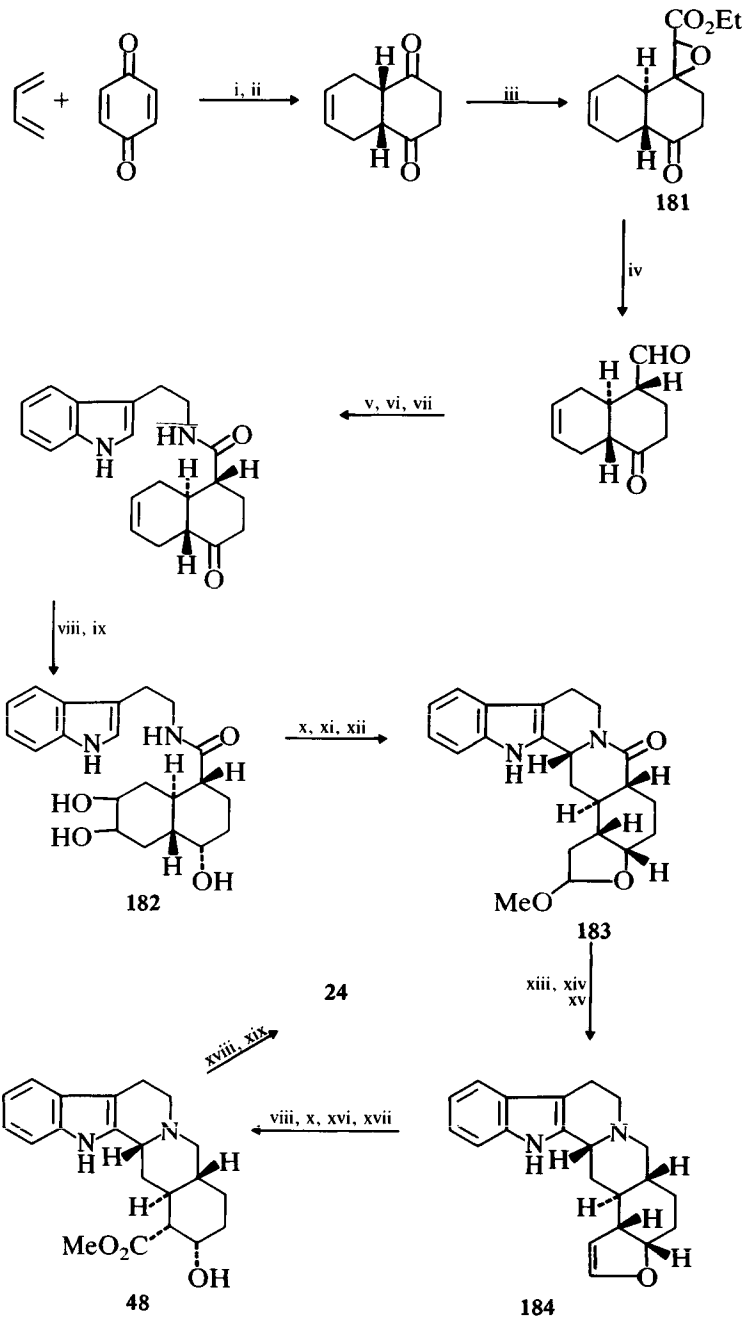
Scheme 27. Reagents: i, pyrrolidine, PhH, Δ; ii, CH_2=C(OAc)CO_2Me, Bu^tOH, PhH, 3 days, r.t.; iii, H_3O^+; iv, $CH_2(CN)_2$, P_2O_5, $Et_3N \cdot HOAc$; v, $NaBH_4$; vi, NaOMe, MeOH; vii, 5% aq. NaOH, 12 hr, r.t.; viii, NaCl, 120°, 0.5 hr; ix, 10% aq. NaOH, Δ, 3 hr; x, MeOH, H^+; xi, acetal; xii, Me_2SO, $KOBu^t$, 3 days, r.t.; xiii, $Pb(OAc)_4$; xiv, Zn, $HClO_4$; xv, TMB chloride.



Scheme 28. Reagents: i, 1 mole HCO_3H; ii, H_2O, Δ; iii, 180°; iv, Ag_2O, MeI; $CaSO_4$; v, MeOH, H^+; vi,  Ag_2O, $CaSO_4$; vii, *hν*; viii, CF_3CO_3H; ix, 3,4,5-trimethoxybenzoic anhydride, py; x, aq, AcOH.

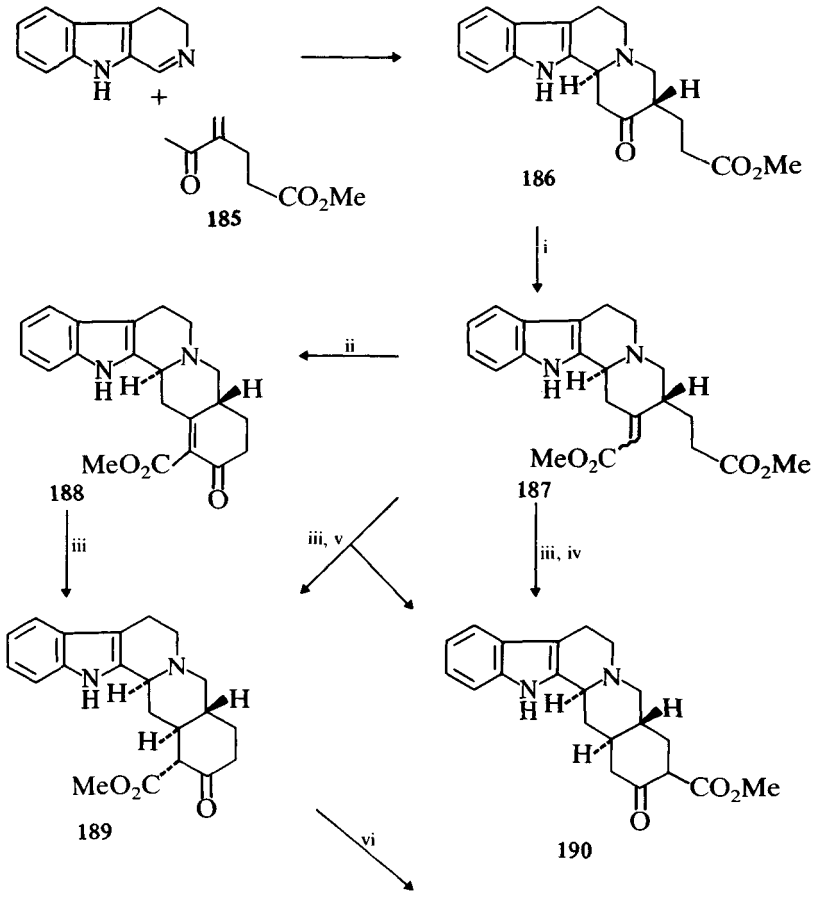


Scheme 29. Reagents: i, PhMe, Δ; ii, $LiCH_2CO_2Bu^t$, −78°; iii, Ac_2O, NEt_3; iv, CF_3CO_2H; v, CH_2N_2; vi, $C_6H_4Me_2$, Δ.



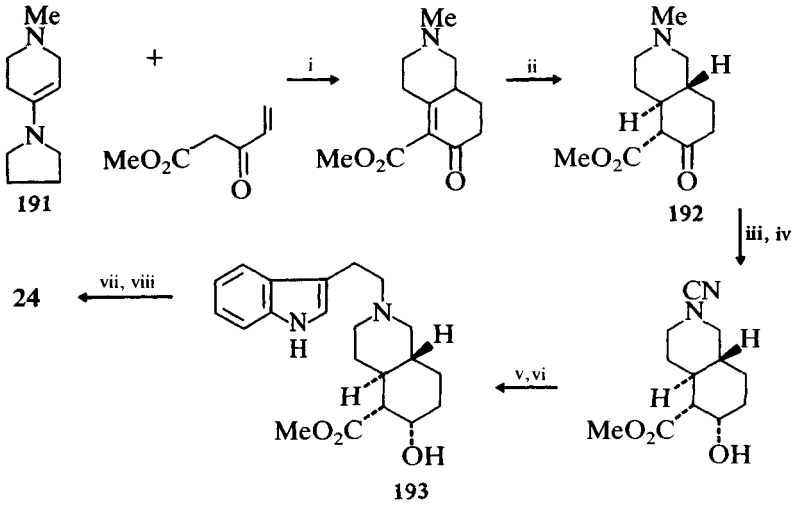
Scheme 30. Reagents: i, Diels-Alder; ii, Zn, AcOH; iii, Bu^tOK, $ClCH_2CO_2Et$; iv, OH^-; v, Ag_2O, OH^-; vi, $(COCl)_2$; vii, tryptamine; viii, OsO_4; ix, H_2, Pt; x, HIO_4; xi, H_3PO_4; xii, HCl, MeOH; xiii, $LiAlH_4$; xiv, H_3O^+; xv, $-H_2O$; xvi, CrO_3; xvii, methylation; xviii, $Pb(OAc)_4$; xix, $NaBH_4$.

In a series of papers from 1965 onwards Szántay and co-workers have reported a much shorter approach to yohimbine and its stereoisomers from the keto ester **186** prepared by condensation of dihydro-β-carboline with the α,β-unsaturated ketone **185** or its Mannich base equivalent (Scheme 31).[79b,c,h] Thus Wittig condensation of **186** afforded the unsaturated ester **187**, but hydrogenation and subsequent Dieckmann cyclization under a variety of conditions tended to give the unwanted β-keto ester **190** as the major product rather than **189**. Eventually, reversing the sequence by first cyclizing to **188** and then hydrogenating the alkene achieved the desired regioselectivity and gave yohimbinone (**189**).[79c] As anticipated **189** was reduced with sodium borohydride to give a 3 : 1 mixture of racemic yohimbine and β-yohimbine (**40**). The key pentacyclic intermediate **188** has also been synthesized in two different ways by Kametani and Szántay and their co-workers from the readily available ketone **171** and from 17-methoxy-3,14-dihydrogambirtannine.[79g,h]



Scheme 31. Reagents: i, $(EtO)_2POCH_2CO_2Me$; ii, NaH, THF; iii, H_2, Pd; iv, $MeSOCH_2Na$, Me_2SO; v, NaOMe, C_6H_6; vi, $NaBH_4$.

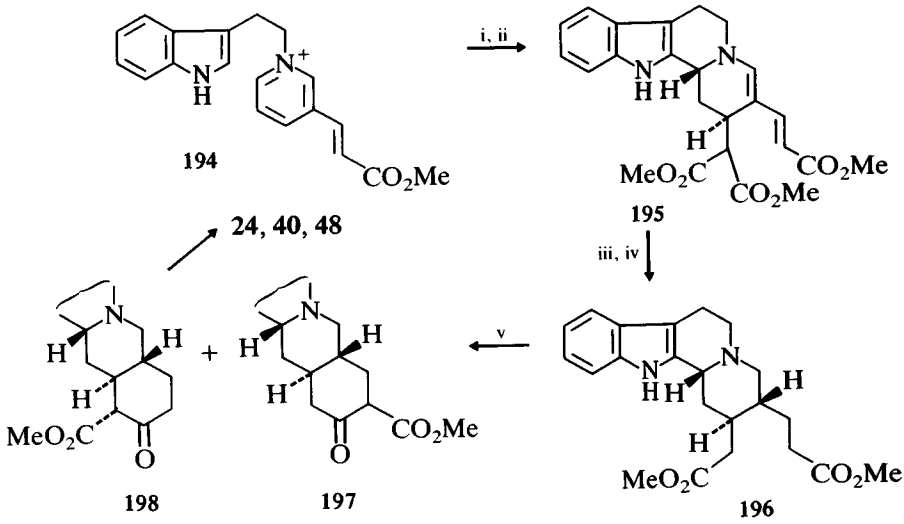
From the enamine derivative (**191**) of *N*-methyl-4-piperidone Stork and Nath Guthikonda have elaborated an intermediate (**192**) from which the 2,3-secoyohimbine **193** can be prepared (Scheme 32).[79d] Regioselective dehydrogenation of **193** with mercuric acetate in presence of ethylenediaminetetraacetic acid leads to cyclization in the correct mode and hence yohimbine. β-Yohimbine and pseudoyohimbine can also be obtained by slight modifications of the route.



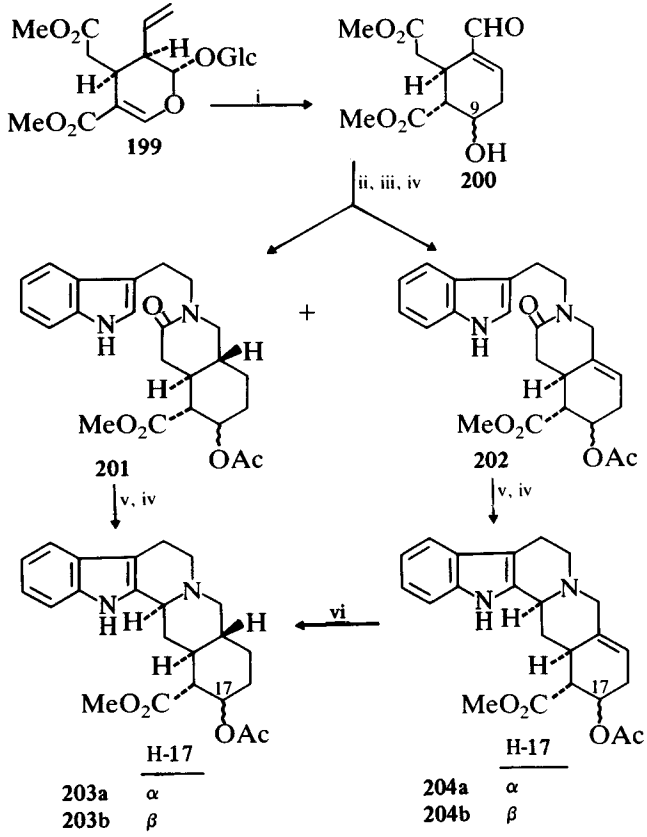
Scheme 32. Reagents: i, PhH, MeOH, Δ; ii, Li, liq. NH_3, Bu^tOH; iii, H_2, Pt, AcOH; iv, CNBr; v, Zn, AcOH; vi, tryptophyl bromide, K_2CO_3; vii, $Hg(OAc)_2$, EDTA; viii, $NaBH_4$.

Yet another approach to the yohimbine skeleton has been devised by Wenkert et al. in a development of their successful heteroyohimbine syntheses from *N*-alkylpyridinium salts (Scheme 33).[79i] Addition of malonate anion to **194** occurs at the γ position to give a 1,4-dihydropyridine which is cyclized to **195** with acid. Removal of a carbomethoxy group and stereoselective catalytic hydrogenation then affords **196**, but unfortunately the Dieckmann cyclization of this diester is not selective and yields a mixture of pseudoyohimbinone (**198**) and its unwanted isomer (**197**).

A partial synthesis of yohimbine alkaloids from the biological precursor secologanin has been reported by Brown and Pratt.[83] In addition to its brevity this route has the advantage of already being in the correct enantiomeric series (Scheme 34). At pH 7 the aglucone of diester **199**, obtained from secologanin by standard methods, underwent rearrangement specifically to a 3:1 epimeric mixture of aldehydo esters **200**, which were obvious analogues of Woodward's reserpine intermediate **160** and were converted to alkaloids in a similar manner. After acetylation, reductive amination with tryptamine afforded a 1:1 mixture of saturated (**201**) and unsaturated lactams (**202**). The former were cyclized and reduced to the acetates of β-yohimbine (**203a**) (major product) and yohimbine



Scheme 33. Reagents: i, $(MeO_2C)_2CHNa$; ii, HBr, C_6H_6; iii, LiI, Me_2SO, Δ; iv, H_2, Pt; v, NaH, THF.



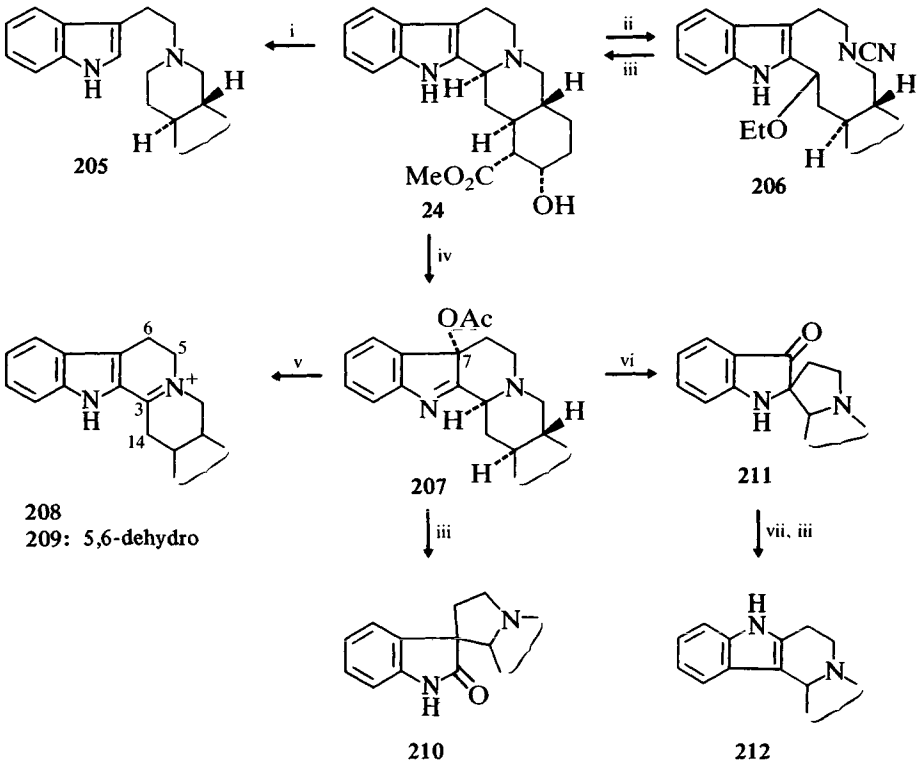
Scheme 34. Reagents: i, β-glucosidase, pH 7; ii, Ac_2O, py; iii, tryptamine; iv, $NaBH_4$; v, $POCl_3$; vi, H_2, Pd–C.

(**203b**) (minor product), whereas the latter yielded the acetates of 19,20-dehydroyohimbine (**204b**) and its previously unknown 17 epimer (**204a**).

C. Modified Yohimbines

In the search for potential therapeutic compounds a wide variety of modified derivatives of yohimbinoid alkaloids, particularly reserpine,[84] have been prepared, much of the work appearing in the patent literature. Some of the more interesting transformations are illustrated by those of yohimbine in Scheme 35, but involve reactions applicable to other alkaloids and tetrahydro-β-carboline systems in general. Thus, on heating with formic acid and formamide, yohimbine afforded the 2,3-seco derivative **205**, presumably by reduction of the C-3,N-4 immonium ion created by a retro-Pictet-Spengler reaction, whereas ethanolic cyanogen bromide cleaved the 3,4-bond to give **206**, a process that could be reversed with acid.[85,86]

When **24** was treated with lead tetraacetate, 7-acetoxy-7*H*-yohimbine (**207**) was obtained, electrophilic attack at the β-position of the indole having occurred from the α face, as established by X-ray analysis of the corresponding methiodide.[87a]



Scheme 35. Reagents: i, HCO_2H, $HCONH_2$, Δ; ii, CNBr, EtOH; iii, H^+; iv, $Pb(OAc)_4$, r.t.; v, AcOH; vi, alkali; vii, $NaBH_4$.

In glacial acetic acid **207** eliminated a molecule of acetic acid to give 3-dehydroyohimbine (**208**) which on heating with excess lead tetraacetate forms the tetradehydroyohimbine (**209**). However, in aqueous acid the β-acetoxyindolenine rearranged to an oxindole (**210**), or alternatively in alkali to an indolinone (**211**), the latter providing an interesting route to the inverted γ-carboline equivalents (**212**) of the natural alkaloids by reduction of the ketone and acid-catalyzed rearrangement.[87]

Various 3-substituted derivatives have been prepared from 3-dehydroyohimbane analogues of **208** by direct treatment with nucleophilic Grignard reagents or cyanide ion; alternatively, substitution of C-14 by the reactive electrophile ethyl bromoacetate was possible via the corresponding 3,14-enamine derivative of reserpine.[84,88]

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CHAPTER V

The Sarpagine-Ajmaline-Akuammiline Group

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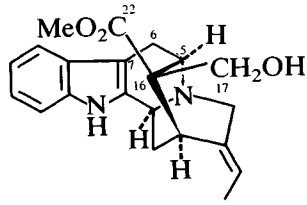
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The alkaloids belonging to this group are based on an unrearranged secologanin unit but have an additional bond between C-16 and either C-5 or C-7.

I. THE AKUAMMIDINE GROUP: ALKALOIDS WITH A 5,16 BOND

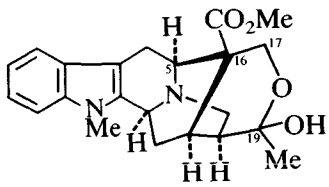
More than 70 indole alkaloids are known in which the carbon skeleton differs

from that in corynantheine by the introduction of one further carbon-carbon bond, between C-16 and C-5; not all of these can be mentioned specifically here. Akuammidine[1] (**1a**) serves as prototype for the simplest variation on this theme and indeed akuammidine types, including those which also lack either C-17 or C-22, make up the largest subgroup, numbering more than 30 bases. The representation for akuammidine (**1a**) serves to emphasize the structural relationship to the corynantheine types, and also to illustrate the conformation of such a skeletal system, which is an aza[2,2,2]bicyclooctane slightly twisted by the bridging indole C-6 unit. This representation also shows the closeness of C-7 to one of the C-16 substituents (C-22 in this case) (cf. Section III).

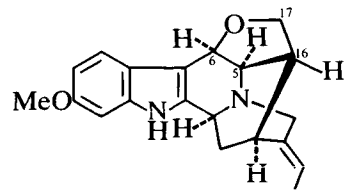


Akuammidine (**1a**)

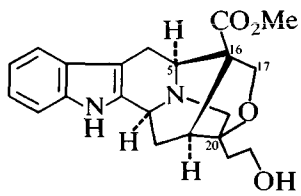
There are, as well as the straightforward akuammidine examples, seven alkaloids with the same C/N skeleton but having an additional cyclic ether or acetal ring, between C-17 and C-19, as in voacoline (**2**), from *Voacanga chalotiana* Pierre and Stapf.[2]; between C-17 and C-6, as in gardnutine (**3**)[3]; or between C-17 and C-20, as in the base eburnaphylline (**4**).[4] With rearrangement to an oxindole having C-3 now linked to C-7, one may add the voachalotine oxindole[5] (**5a**) type, also known in a cyclic imino ether form, containing an ether bridge between C-17 and C-2, as in gardneramine (**6a**).[6]



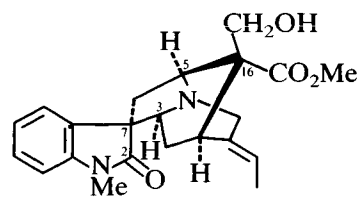
Voacoline (**2**)



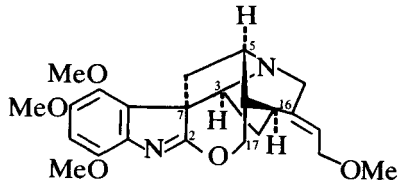
Gardnutine (**3**)



Eburnaphylline (**4**)

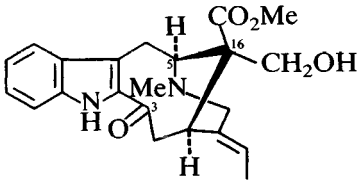


Voachalotine oxindole (**5a**)

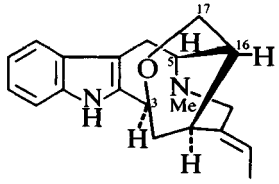


Gardneramine (6a)

Some 11 alkaloids are related to the akuammidine skeleton by the cleavage of the 3,N_b bond; vincadiffine (**7a**) (from *Vinca difformis* Pourr.)[7] is in fact the only one of these to retain both C-16 substituents. All the members of this subgroup have an oxygen function at C-3, usually a carbonyl group, as evidence of the postulated biosynthetic oxidative cleavage of the 3,N_b bond which led to them. Taberpsychine (**8**)[8] has an additional ether ring involving this C-3 oxygen.

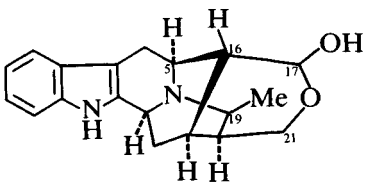


Vincadiffine (7a)

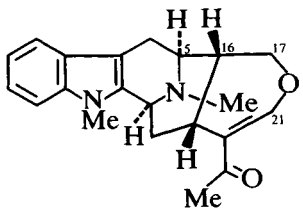


Taberpsychine (8)

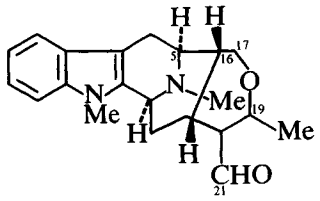
The variation present in the peraksine (**9**) type[9] involves a rearranged 18,19,20, 21,N_b unit; C-19, instead of C-21, is now attached to N_b. The C-17,O,C-21 link, as a hemiacetal, is present in each of the three examples of the next variation, which simply lacks the 21,N_b bond; alstonerine (**10a**) (*Alstonia muelleriana* Domin) is typical.[10] Talcarpine (**11**)[11] is a hybrid of these types; it lacks the 21,N_b bond but has an ether link between C-17 and C-19. Alstonisine (**12**), also from *A. muelleriana*, is the oxindole analogue of the alstonerine type; its structure was established by X-ray crystallography.[12] Suaveoline (**13a**) has the alstonerine carbon skeleton but in it an extra *nitrogen*, not oxygen, has been incorporated between C-17 and C-21 with aromatization of ring E.[13]



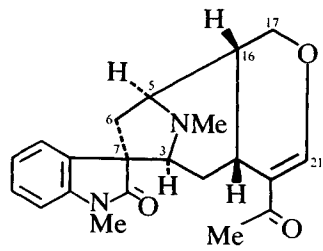
Peraksine (9)



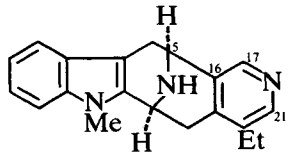
Alstonerine (10a)



Talcarpine (11)

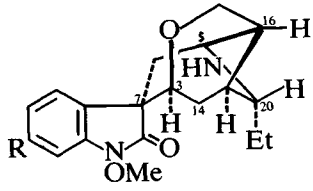


Alstonisine (12)



Suaveoline (13a)

Finally, three alkaloids from *Gelsemium sempervirens* Ait. and a fourth from *Mostuea brunonis* Didr. var. *brunonis forma augustifolia*[14d] must be included: these are gelsemicine (**14a**),[14a] gelsedine (**14b**),[14b] 14-hydroxygelsemicine,[14c] and *N*,20-dehydrogelsemicine.[14d] All are oxindoles with C-3 attached to C-7 and lacking a 3,N_b bond, but having a 5,16 bond. They also have a unique feature among all the indole alkaloids: C-21 is completely missing, and it is C-20 that is attached to the basic nitrogen atom. The structure of gelsemicine was established by X-ray analysis of its N_b-methyl hydriodide.[14a] Gelsedine was shown[14b] to be 11-demethoxygelsemicine by nmr spectral comparisons, and the likely structure[14c] of 14-hydroxygelsemicine was suggested by mass spectral comparison with gelsemicine.



	R
Gelsemicine (14a)	OMe
Gelsedine (14b)	H

A. Structural Studies

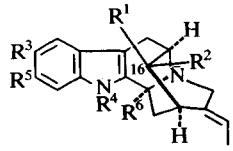
The structure and relative and absolute stereochemistry of akuammidine (**1a**) (from *Picralima nitida* Stapf.) were established by interrelationship with the ajmaline series (see Section IV.C) and by X-ray crystallographic analysis of its methiodide.[1b] Ord measurements can be used[15] to confirm the 3*S* absolute configuration in the akuammidine skeletal series (see Table I). Both akuammidine and polyneuridine[16] (**1b**) (from *Aspidosperma polyneuron* Müll. Arg.) gave the

same diol (**1c**) on lithium aluminum hydride reduction,[1c] showing polyneuridine to differ from akuammidine only in the stereochemistry at C-16. Of the naturally occurring[17a] N_b-metho salts of polyneuridine and akuammidine, named macusines-A and -C when isolated from *Strychnos toxifera* Schomb. ex Benth., the former was also subjected to the X-ray method.[17b] Both akuammidine and polyneuridine lose formaldehyde by a retro-aldol process on treatment with $KOBu^t$,[1c] giving an ester (**1d**) later isolated as a natural base,[18] pericyclivine (*Catharanthus lanceus* Boj. ex A.DC.), which in turn gives normacusine-B (**1e**) [= tombozine, from *Diplorrhynchus condylocarpon* (Mull. Arg.) Pichon ssp. *mossambicensis* Benth.[19]] on lithium aluminum hydride reduction.

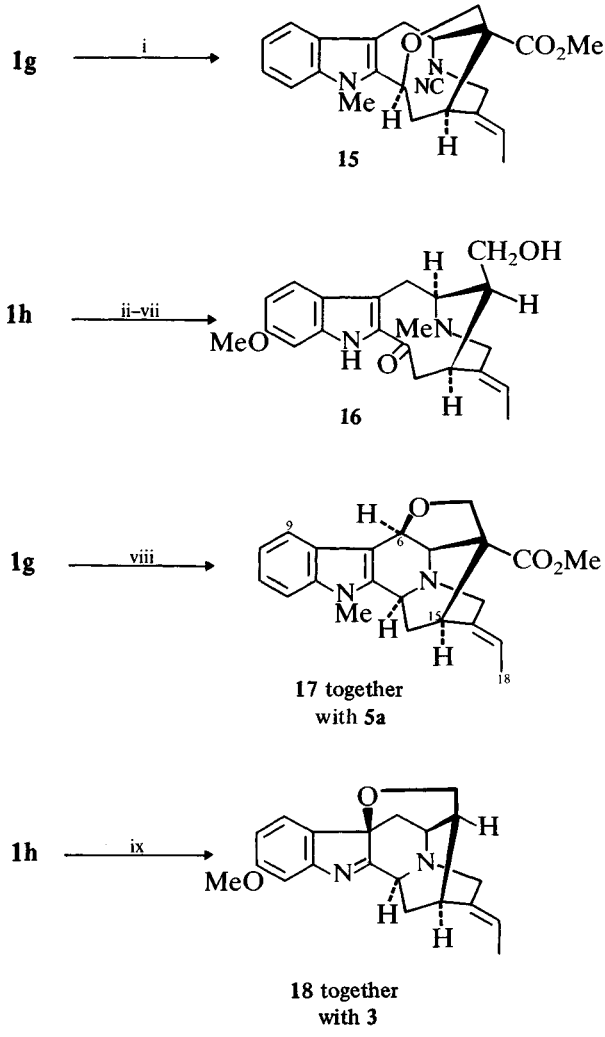
Historically, the ring-A oxygenated alkaloids sarpagine (**1f**) (from several *Rauwolfia* species[20a]) and lochnerine (= 10-*O*-methylsarpagine, from *Vinca rosea* var. *alba* Hubd.) were studied at an early stage and their correct structures were deduced[20a] and later proved by chemical correlation[20b] with the ajmaline series. Indeed, this strategy has been by far the most utilized in structural work on the alkaloids of this group, and a selection of typical examples of such interconversions is gathered in Section III.

Voachalotine (**1g**)[21a] undergoes von Braun degradation[21b] with cleavage of the 3,N_b bond to give an ether (**15**) of the taberpsychine (**8**)[8] type (Scheme 1). Following protection of the 17-hydroxyl group, treatment with cyanogen bromide can be

TABLE I. AKUAMMIDINE SERIES



Compound	Structure	R^1	R^2	R^3	R^4	R^5	R^6
Akuammidine	**1a**	CO_2Me	CH_2OH	H	H	H	H
Polyneuridine	**1b**	CH_2OH	CO_2Me	H	H	H	H
	1c	CH_2OH	CH_2OH	H	H	H	H
Pericyclivine	**1d**	H	CO_2Me	H	H	H	H
Normacusine B	**1e**	H	CH_2OH	H	H	H	H
Sarpagine	**1f**	H	CH_2OH	OH	H	H	H
Voachalotine	**1g**	CH_2OH	CO_2Me	H	Me	H	H
Gardnerine	**1h**	CH_2OH	H	H	H	OMe	H
Accedine	**1i**	H	CH_2OH	H	Me	H	OH
Voacarpine	**1j**	CO_2Me	CH_2OH	H	H	H	OH
Perivine	**1k**	CO_2Me	H	H	H	H	OH
	1l	CO_2Me	H	H	H	H	H
Lochnerine	**1m**	H	CH_2OH	H	H	H	H
Lochvinerine	**1n**	CH_2OH	H	H	H	H	H
Vellosimine	**1o**	H	CHO	H	H	H	H
	1p	CO_2Me	CH_2OAc	H	Me	H	H

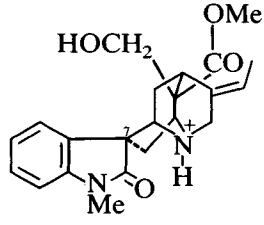


Scheme 1. Reagents: i, CNBr; ii, Ac_2O; iii, CNBr, MeOH, $CHCl_3$, Na_2CO_3; iv, Bu^tOCl, Et_3N; v, H_2O; vi, 5% aq. AcOH, NH_4OAc, Δ; vii, CH_2O, H_2, Pd/C; viii, $K_2Cr_2O_7$; ix, CrO_3, H_2SO_4.

made the means of conversion into the alkaloids lacking the $3,N_b$ bond but without concomitant ether formation; examples are the conversion[22a] of gardnerine (**1h**)[3] into **16** or, after transformation of hydroxymethyl into methoxycarbonyl, into ochropine (**7e**)[22b] (from *Ochrosia poweri* Bailey[22c]).

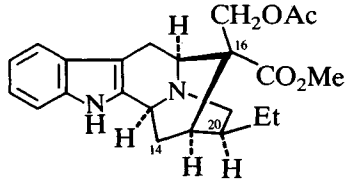
Voachalotine (**1g**)[21] is the major alkaloid of *Voacanga chalotiana* Pierre and Stapf; co-occurring with it is voachalotine oxindole (**5a**). The stereochemistry of the oxindole at C-7 was neatly deduced from the observation of a hydrogen-bonded oxindole carbonyl group absorption in the ir spectrum of the alkaloid

N_b-protonic salt but not in that of the free base; this is only possible for the C-7 configuration shown in **5b**. Interestingly, no epimerization at C-7 and/or C-3 was observed under the acidic conditions which normally effect such changes in the corynantheine/heteroyohimbine oxindoles (see Chapter III). In this case an analogous mechanism of epimerization would require the formation of a bridgehead immonium grouping at the $3,N_b$ position.

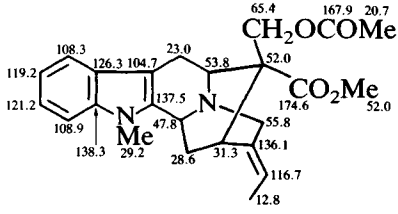


5b

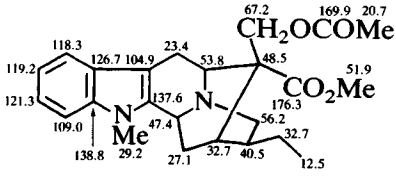
Voachalotine oxindole was one of several oxidation products obtained[5] by treatment of voachalotine with potassium dichromate, another being **17** (Scheme 1), having an ether linkage of the type present in gardnutine (**3**). Gardnerine (**1h**), first obtained[3a] from *Gardneria nutans* Sieb. and Zucc., was similarly oxidized[22] to gardnutine (**3**) itself, probably via **18**, since a mixture of gardnutine and **18** was obtained from the oxidation and **18** was rearranged by further acid treatment into gardnutine. In the rigid framework of **17** it was possible to observe[5b] nuclear Overhauser effects between the 15 and 18 hydrogen atoms and the 6 and 9 hydrogen atoms, respectively.



17-*O*-Acetyl-19,20-dihydrovoachalotine (19a)



1q (in $CDCl_3$)

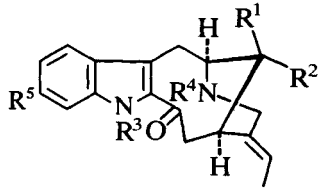


19b (in $CDCl_3$)

The stereochemistry at C-20 in 17-*O*-acetyl-19,20-dihydrovoachalotine (**19a**) (from *V. chalotiana*) was deduced[23] by noting that the difference (3.5 ppm) in the ^{13}C chemical shifts of the C-16 signals in **19a** (see **19b**) and 17-*O*-acetylvoachalotine

(see **1q**) was larger than that (1.5 ppm) for the C-14 signals in the same two bases. This small difference is considered sufficient to prove the proximity of the C-20 ethyl group to C-16 rather than to C-14.

In bases such as accedine[24] (**1i**) and voacarpine[25] (**1j**) (from *V. chalotiana*) the oxidation at C-3 postulated to lead biosynthetically to the alkaloids which lack the $3,N_b$ bond has occurred, but not the actual cleavage of the bond. From such a carbinolamine to a structure in which this cleavage has occurred is a simple step which can easily be achieved in the laboratory by N_b-alkylation or acylation. For example, accedine (from *Tabernaemontana accedens* Müll. Arg.) was converted into N_a-methyl-16-epiaffinine (**7b**), also isolated from *T. accedens*, by reaction with formaldehyde/hydrogen/palladium; perivine (**1k**) (from *Vinca rosea* L.) was converted into vobasine (**7c**) under the same conditions,[26a] and into periformyline (**7d**) (from *Catharanthus lanceus* Boj. ex A.DC. Pichon) with acetic anhydride/formic acid.[26b] Such a $3,N_b$-carbinolamine is easily reduced with sodium borohydride as in the transformation of perivine into **1l**.

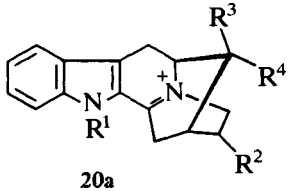


		R^1	R^2	R^3	R^4	R^5
Vincadiffine	(7a)	CO_2Me	CH_2OH	Me	Me	H
N_a-Methyl-16-epiaffinine	(7b)	H	CH_2OH	Me	Me	H
Vobasine	(7c)	CO_2Me	H	H	Me	H
Periformyline	(7d)	CO_2Me	H	H	CHO	H
Ochropine	(7e)	CO_2Me	H	Me	Me	OMe

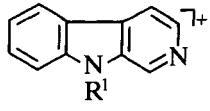
As already discussed, akuammidine and polyneuridine are epimeric at C-16. Of the bases having only one substituent at C-16, examples in both 16-epimeric series are also known, but only where the residual substituent is either methoxycarbonyl, for example, pericyclivine (**1d**)[18] and perivine (**1k**),[26] or hydroxymethyl, for example, lochnerine (**1m**)[20] and lochvinerine (**1n**) (from *Vinca major* L. var. *major*).[27] In the C-17 aldehyde series, only the stereochemistry exhibited by vellosimine (**1o**)[28] (from *Geissospermum vellosii* Allem), reducible by sodium borohydride to normacusine-B, has been encountered. The relative stereochemistry at C-16 can be established, where there is a residual ester group, from the ^1H nmr chemical shift of the ester methyl group, for example, δ 3.78 in pericyclivine (**1d**), but δ 3.05 in its 16 epimer.[26a]

Early systematic studies, independently by Biemann[29] and Djerassi et al.,[1c] of the mass spectral fragmentation of complex molecules concerned the akuammidine and yohimbine/heteroyohimbine alkaloid types. These studies showed the potential of the technique and the constancy of the fragmentation pathways within groups

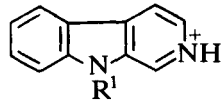
of skeletally related alkaloids. It proved possible, for example, to differentiate those skeletal types having a 5,16 bond from those without. Although both gave substantial M-1 peaks, owing largely to the loss of the C-3 hydrogen and the formation of stabilized ions (e.g., **20a**), the alternative 5,16 cleavage of the akuammidine types competes, leading to the structurally significant result that this type gives ions at *m/e* 168 and 169 (i.e., **20b**, R′ = H, and **20c**, R′ = H) compared with the pair at *m/e* 169 and 170 always associated with the spectra of yohimbine and heteroyohimbine types.



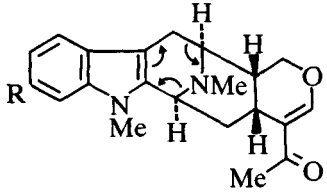
20a



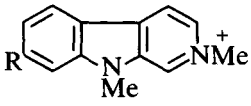
20b



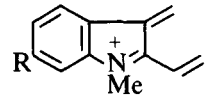
20c



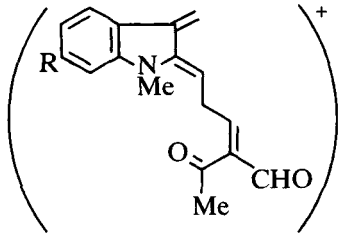
	R
Alstonerine (**10a**)	H
Alstophylline (**10b**)	MeO



10c



10d

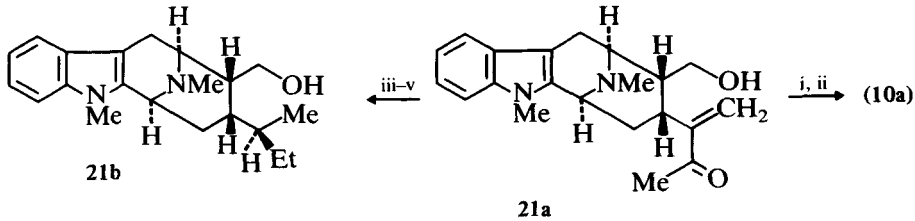


10e

The mass spectral fragmentation[30] of the alstophylline (**10b**) and alstonerine (**10a**) types[10] is also characteristic. The β-carbolinium fragment (**10c**) is by far the most abundant, but alternative fragmentation (arrows on **10a**) also gives rise to characteristic ions **10d** and **e**. The structure of alstonerine (**10a**) became clear

from this study, and was later confirmed[31a] by its preparation from macroline (**21a**), a degradation product of the dimeric alkaloid, villalstonine.

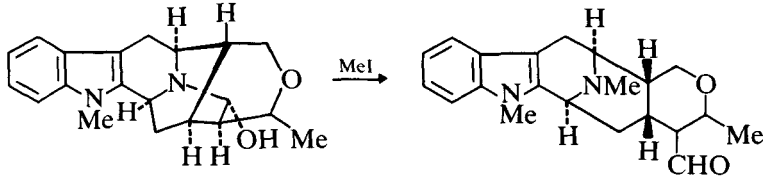
Macroline itself has been prepared[31b] from normacusine-B (**1e**) in nine steps in which, after conversion of the ethylidene unit into an acetyl group, ring D was opened by a simple Hofmann degradation (β-aminoketone metho-salt). The absolute configuration of **21a** was established[31c] by conversion into the alcohol (**21b**) (Scheme 2), which in turn was obtained from ajmaline (see below).



21b **21a**

Scheme 2. Reagents: i, Bu^tOOH, ii, PPA; iii, Ac_2O; iv, H_2, Pt; v, N_2H_4, KOH, $(HOCH_2CH_2)_2O$.

Talpinine (**22**), from *Pleiocarpa talbotii* Wernham,[11] with a carbinolamine group at the N_b,21 position, was converted (Scheme 3) with cleavage of the N_b,21 bond into talcarpine (**11**), isolated from the same plant. Close to the structure of talpinine is that of peraksine (**9**) (from *Rauwolfia perakensis* King and Gamble), determined[9] by X-ray crystallographic analysis of its methiodide.

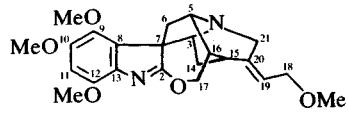


Talpinine (22) Talcarpine (11)

Scheme 3.

Several alkaloids (**6a–6f**) from various *Gardneria* species[6,32a,c] have a characteristic, cyclic iminoether link. The *Gardneria* alkaloids as a group, thoroughly studied by Sakai and co-workers,[32] have two other unique features. First, the 9,10,12-trioxygenation pattern has been found in no other indole alkaloid. Second, the exceptional geometry of the 18,19 double bond in gardneramine (**6a**) and several other *Gardneria* bases,[32a,d] for example, **23a–d**, is unique so far. The ^{13}C chemical shifts of C-15 and C-21 can be used[32b] to diagnose the geometry of the 18,19 double bond. The ^{13}C spectra of the *Gardneria* alkaloids have been studied[32b] in detail and assignments made: **6g** shows typical values (Table II).

TABLE II. CARBON-13 CHEMICAL SHIFTS (in $CDCl_3$)



6g

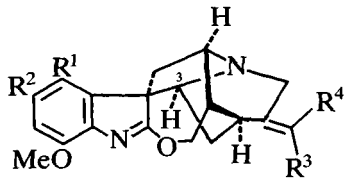
Carbon atom	δ
2	178.7
3	62.4
5	60.4
6	31.2
7	63.0
8, 9, 10	133.1
12, 13	134.1
	139.4
	145.7
	150.5
11	100.2
14	32.2
15	36.9
16	42.0
17	72.0
18	68.0
19	115.0
20	147.6
21	46.4
18-OMe	58.2
Ar-OMe	56.7, 57.6, 61.3

The alternative C-16 stereochemistry exhibited by Alkaloid J (**23b**) was confirmed[32d] by acid-catalyzed cyclic ether formation in the production of **24** by allylic displacement of the 18-methoxyl group (Scheme 4).

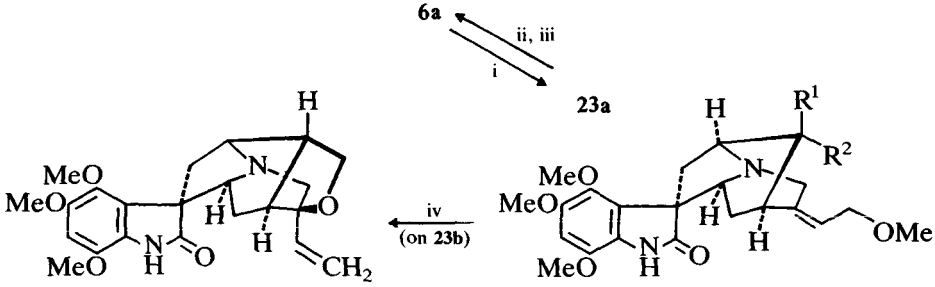
It was shown[6,32a] for gardneramine (**6a**) that the iminoether link could be cleaved (→ **23a**) with aqueous acid and remade by providing a leaving group at C-17. X-Ray analysis[6] of the 3,N_b-seco-3-bromo-N_b-cyano derivative of gardneramine first established the structure.

Vobasine[33] (**7c**) (*Voacanga africana* Stapf.) was hydrogenated mainly from the less hindered β face to give a mixture of dregamine[33] (**25a**) (major product) and tabernaemontanine[34] (**25b**), bases isolated from several plants including *Voacanga thouarsii* Roem. et Schult. var. *dregii* and *Tabernaemontana coronaria*, respectively. Some of the chemistry of these alkaloids is gathered in Scheme 5.

Hofmann degradation of dregamine methiodide gave the alkene (**26**) in which the initially formed double bond had migrated into conjugation with the aromatic system. Further lithium aluminum hydride reduction and acid-catalyzed cyclization gave **27**, which had also been obtained by Hofmann degradation of the methiodide



		R^1	R^2	R^3	R^4
Gardneramine	(6a)	MeO	MeO	H	CH_2OMe
19-(*E*)-18-Demethoxy-gardneramine	(6b)	MeO	MeO	Me	H
18-Demethylgardneramine	(6c)	MeO	MeO	H	CH_2OH
Gardfloramine	(6d)	OCH_2O		H/CH_2OMe	CH_2OMe/H
18-Demethylgardfloramine	(6e)	OCH_2O		H/CH_2OH	CH_2OH/H
Gardneramine N_b-oxide	(6f)	MeO	MeO	H	CH_2OMe



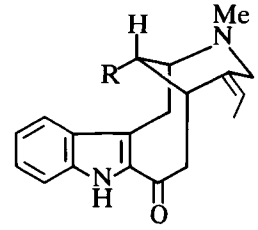
		R^1	R^2
Alkaloid I	(23a)	CH_2OH	H
Alkaloid J	(23b)	H	CH_2OH
Alkaloid N	(23c)	CH_2OH	OH
	(23d)	CH_2	

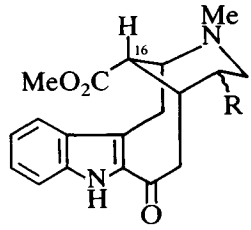
Scheme 4. Reagents: i, aq. HCO_2H, Δ; ii, TsCl; iii, KOH, EtOH; iv, 2 *M* HCl, Δ.

of the dihydro derivative of taberpsychine[8] (8) (*Tabernaemontana psychotrifolia* H.B.K.).

Vobasine and dregamine are epimerized at C-16 with sodium methoxide [16-epivobasinic acid is a natural product (*T. psychotrifolia*)].[33b] However, tabernaemontanine under the same conditions gave only a little of the 16 epimer and mainly the rearrangement product (28), resulting from Hofmann-type elimination and subsequent lactamization.

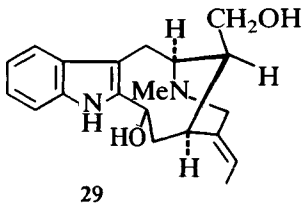
The lithium aluminum hydride reduction products of vobasine and affinine[35] (7e) (*Peschiera affinis* Miers) (Scheme 5) were shown to be identical; this diol (29) could be converted[36] into taberpsychine (8) by acid-catalyzed dehydrative cyclization.



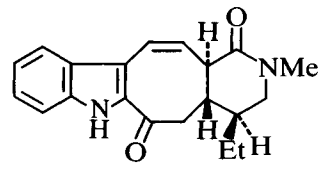


		R
Vobasine	(7c)	CO_2Me
Affinine	(7e)	CH_2OH

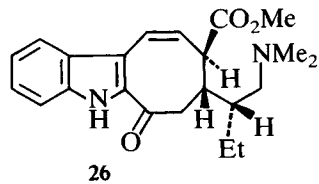
		R
Dregamine	(25a)	α-Et
Tabernaemontanine	(25b)	β-Et



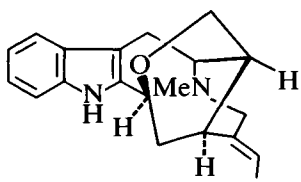
29



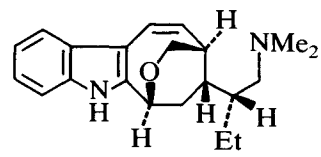
28



26

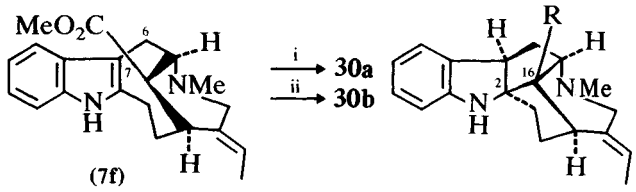


8 Taberpsychine



27

Scheme 5. Reagents: i, H_2, Pt; ii, $LiAlH_4$; iii, MeI; iv, NH_4OH; v, PhH, Δ; vi, NaOMe, MeOH; vii, 1 *M*, H_2SO_4, − 20°; viii, dil. HCl–MeOH; ix, $KOBu^t$, Bu^tOH, Δ.

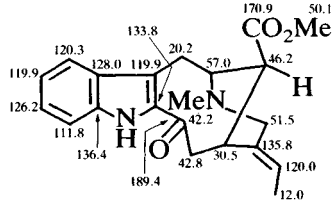


	R
30a	CO_2Me
30b	CHO

Scheme 6. Reagents: i, H_3PO_4; ii, $LiAlH_4$.

An unexpected cyclization (Scheme 6), involving a bonding between C-16 and C-2, was observed[37] when deoxyvobasine (**7f**), a degradation product of the bis-alkaloid voacamine, was treated with phosphoric acid (→ **30a**) or with lithium aluminum hydride (→ **30b**). Although it is relatively easy to envisage 7-protonation in strong acid being followed by attack by the potentially nucleophilic C-16 on the $2,N_a$-immonium group thus generated, giving rise to **30a**, the hydride sequence is less easy to rationalize.

Ord measurements[38] based on the chiral 2-acylindole uv chromophore have been utilized to confirm that these alkaloids, lacking the $3,N_b$ bond and having a carbonyl group at C-3, are all in the some absolute stereochemical series. The relative stereochemistry of the C-16 substituents in such alkaloids can be assigned by an examination[39] of the ^{13}C chemical shifts of the ester carbon but perhaps better on the ^1H shifts of ester methyl (δ 2.61 when shielded by the aromatic system as in[33c] vobasine, compared with δ 3.50 in its 16 epimer). The ^{13}C spectra of this indole alkaloid type have been studied:[39] **7g** gives typical values.

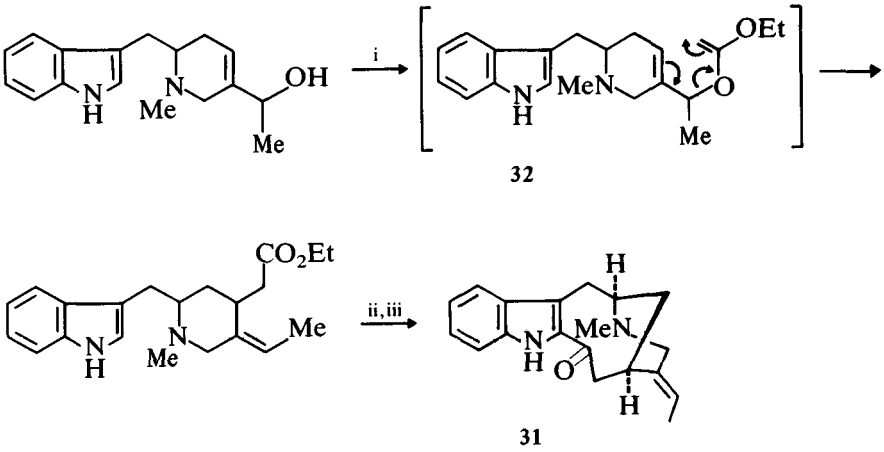


7g

B. Synthetic Studies

No synthesis of an alkaloid of this group either with both C-16 substituents present or with an ethylidene group has yet been reported. The ring skeleton of the vobasine type with no substituents at all was synthesized[40] and later a route[41a] (Scheme 7) was described to decarbomethoxyvobasine (**31**), the dihydro derivative

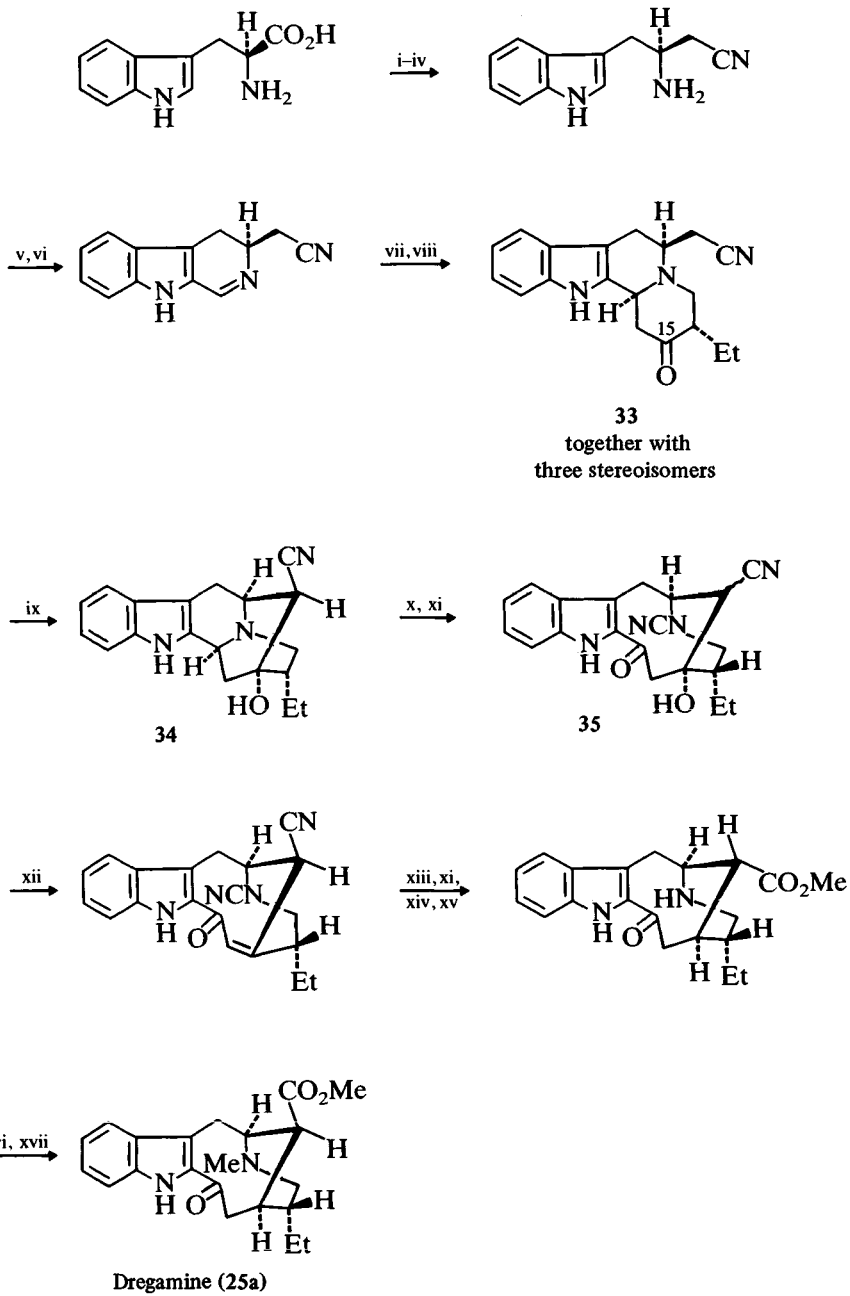
of which occurs[41b] in *Rauwolfia discolor* M. Pichon. This last required formation of the tricky ethylidene feature which was generated, concurrently with introduction of the required acetic acid residue at C-15, by a Claisen rearrangement (arrows on **32**). The eight-membered ring was then produced by an intramolecular acylation of the indole α position.



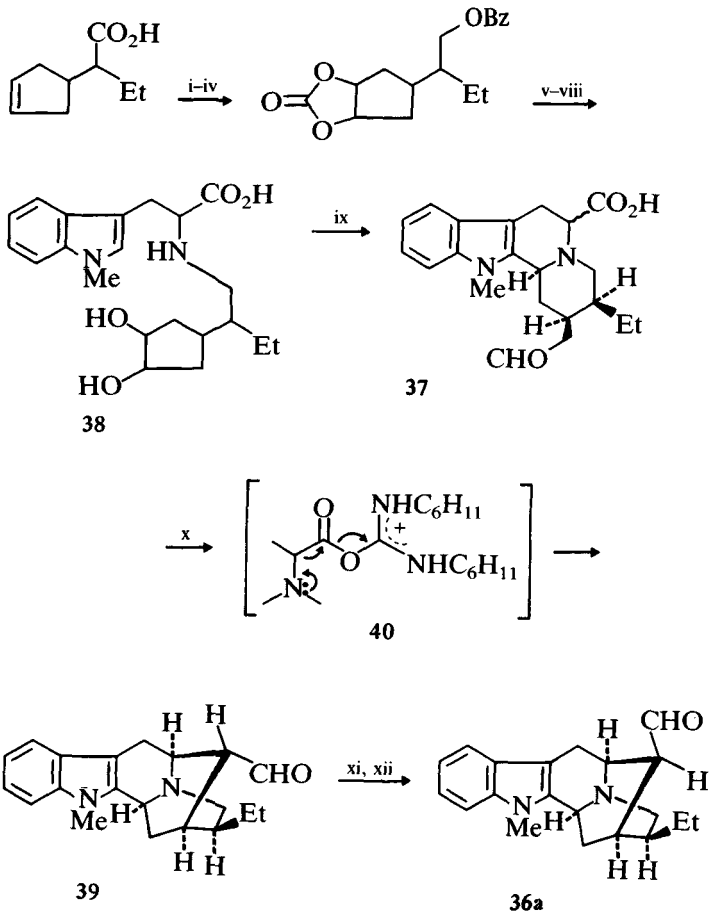
Scheme 7. Reagents: i, $MeC(OEt)_3$, $PrCO_2H$, diglyme; ii, $Ba(OH)_2$, dioxane; iii, PPA.

Dregamine (**25a**) itself has been made[42] by Kutney via a rather different synthetic strategy (Scheme 8); one disadvantage is that in forming the 15,16 bond by an intramolecular aldol condensation (**33** → **34**) in a precursor 15-ketone, it necessarily generated intermediates (e.g., **34**) which, although they possessed the akuammidine type pentacyclic skeleton, had an unwanted 15-hydroxyl group which had then to be eliminated. This necessitated cleavage of the $3,N_b$ bond (→ **35**) to allow dehydration and then reduction.

The formal total synthesis of ajmaline by van Tamelen and Oliver[43a] (see Section II.B) proceeded via (±)-21-deoxyajmalal-A (**36a**), which had previously been converted (see Section III) into ajmaline. Up to **37**, the synthesis (Scheme 9) followed principles previously exploited by van Tamelen and others in generating required 3- and 17-aldehyde functions by oxidative cleavage of a 1,2-dihydroxycyclopentane intermediate (**38**). The 5,16 bond was produced in an intriguing and elegant manner (**37** → **39**): oxidative decarboxylation (arrows on **40**) of the tryptophan carboxyl group produced an immonium function which was trapped by intramolecular condensation with the nucleophilic C-16. This process for the formation of the 5,16 bond may well mimic the natural generation of this bond in these alkaloids, although evidence[43b] for the nonincorporation of tryptophan into ajmaline has been reported.



Scheme 8. Reagents: i, $LiAlH_4$; ii, TsCl, py; iii, KCN; iv, Na, liq. NH_3; v, NaOMe, HCO_2Me; vi, PPE; vii, $MeCO.C(:CH_2)Et$, HCl, MeOH; viii, TsOH, Me_2CO, H_2O, Δ; ix, $LiNEt_2$, THF, 0°; x, CNBr; xi, MnO_2; xii, $SOCl_2$; xiii, $NaBH_4$; xiv, NaOH, H_2O; xv, MeOH, HCl; xvi, H_2, CH_2O, Pd; xvii, NaOMe, MeOH.

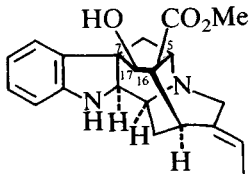


Scheme 9. Reagents: i, $LiAlH_4$; ii, $PhCH_2Cl$, KOH; iii, OsO_4, py; iv, $(MeO)_2CO$, MeONa; v, H_2, Pd; vi, CrO_3, py; vii, N_a-methyltryptophan, H_2, Pd/C; viii, KOH; ix, $NaIO_4$, NaOAc; x, DCC, TsOH; xi, resolution via D-camphor-10-sulfonate; xii, equilibration in AcOH, NaOAc.

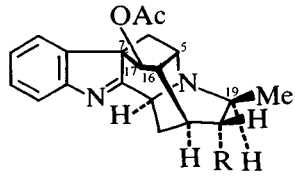
II. THE QUEBRACHIDINE GROUP: ALKALOIDS WITH A 5,16 BOND AND A 7,17 BOND

Nearly 40 bases make up the quebrachidine[44] **(41a)** group, only some typical members of which can be dealt with specifically here. All have two extra carbon-carbon bonds compared with the corynantheine type: one between C-5 and C-16 as in the akuammidine group, and *in addition* a further bond between C-7 and C-17. The rigid ring structure thus engendered leaves little scope for skeletal variation and only two of the group, perakine[45] **(42a)** and raucaffrinoline[46] **(42b)**, have any such variation, in the form of rearranged 18,19,20,21,N_b units, with C-19 now

attached to the basic nitrogen. In marked contrast with the akuammidine group, there are also *no* variations known in which there is an additional cyclic ether.

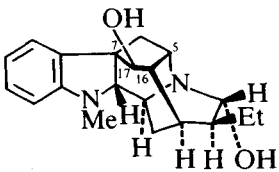


Quebrachidine (**41a**)

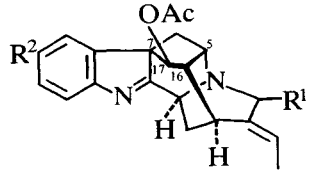


		R
Perakine	(**42a**)	CHO
Raucaffrinoline	(**42b**)	CH_2OH

Three-quarters of the group lack the C-22-ester carbon atom; ajmaline[47] (**43a**), around which centered all of the early chemical interest, is an example of such a base. The 21-hydroxyl group present in ajmaline is a feature of all the bases with a 20-ethyl group. All the members of this subgroup also lack the 22-ester group. The 21-hydroxyl group is encountered much less often in the alkaloids with an 18,19 double bond; an example which has both 21-hydroxyl and ethylidene groups is majorinine[48] (**44a**) (*Vinca major* Linn.). In fact half a dozen of the quebrachidine group have the indolenine oxidation level, as in **44a**; another, from *Vinca minor* L., is vinorine[49] (**44b**). This oxidation level witnesses the likely biogenetic derivation of the 7,17 bond by electrophilic attack of C-17 on C-7, the indole β position, a process that can be readily mimicked in the laboratory (see Section III). Indeed, all alkaloids in the entire group have oxygen at C-17, evidence for the aldehyde (or higher) oxidation level of C-17 when it attacks C-7 during biosynthesis.



Ajmaline (**43a**)

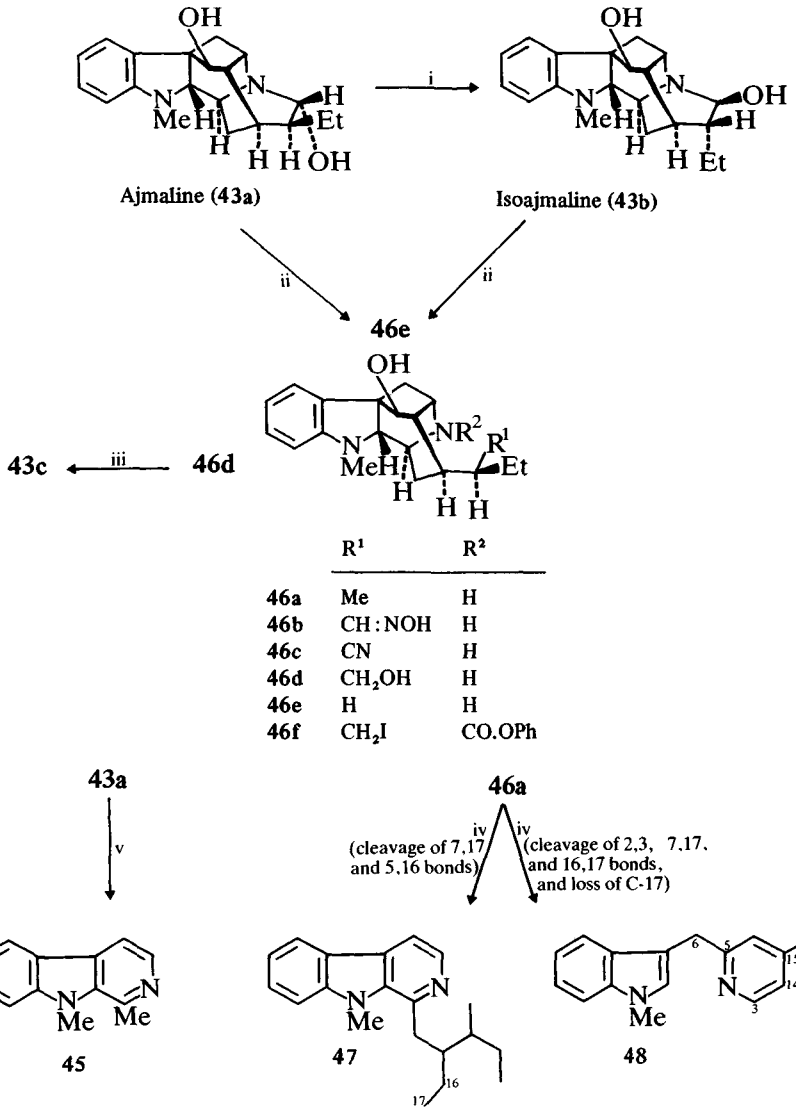


		R^1	R^2
Majorinine	(**44a**)	α-OH	OMe
Vinorine	(**44b**)	H	H

A. Structural Studies

The earliest structural work[47a] (Scheme 10) in this group was concerned with the indolines ajmaline (**43a**) [λ_{max} 250, 290 nm (log ϵ 3.9, 3.4)] and its stereoisomer isoajmaline (**43b**), bases that lack the 22-ester group; this was classical structure determination in a refined form, Robinson and Woodward making the major contributions. Only later were skeletally related bases with ethylidene

instead of ethyl groups and then the quebrachidine (**41a**) ester-containing alkaloids isolated and studied.



Scheme 10. Reagents: i, KOH, EtOH, Δ; ii, Raney Ni, xylene, Δ; iii, Δ, HBr salt; iv, Pd/C, 250°; v, soda lime, Δ.

Ajmaline[47] (**43a**) is the major alkaloid of *Rauwolfia serpentina* Benth. and a constituent of many other[47a] *Rauwolfia* species. The early work predated the general use of spectroscopy but much was learned from the most classical of degradative methods and is both historially and didactically interesting to recall.

For example, soda lime distillation gave N_a-methylharman (**45**), suggesting the presence of a reduced β-carboline unit and proving the location of the N-methyl group. Dehydrogenation of dihydro-21-deoxyajmaline (**46a**) (see below) with palladium/carbon at 250° gave aromatized derivatives, named ajarmine (**47**) and ajmyrine (**48**). The former contains all the carbon atoms of ajmaline in an unrearranged state and the latter has lost only one carbon, C-17. These three degradation products alone go a long way to establishing the skeleton of the alkaloid, excepting the 5,16 and 7,17 bonds.

Much effort[47b,c] went into elucidating the nature of the two hydroxyl groups in ajmaline; one was proved to be part of an N_b-carbinolamine unit. Thus in its aminocarbonyl form it reacted with hydroxylamine to give an oxime (**46b**) which could be dehydrated to a nitrile (**46c**). Similarly the open form could be reductively trapped by the Huang-Minlon procedure to give rise to dihydro-21-deoxyajmaline (**46a**) from which, after vigorous oxidation, butan-2-one could be isolated. Borohydride reduction of ajmaline gave dihydroajmaline (**46d**) by hydride attack on the open form. This alcohol could be recyclized by heating its hydrobromide at 300°C, giving rise to 21-deoxyajmaline (**43c**).

Thorough proof for the carbinolamine nature of the 21-hydroxyl group was deemed necessary, for it could not be made to undergo a number of reactions which are typical of simpler carbinolamines; for example, it is *not* reduced by zinc and hydrochloric acid and *is* reduced by sodium borohydride, but to an open alcohol. It was realized that all the failed reactions would have required the participation of a dehydrated, immonium form, and it was correctly deduced that formation of such an intermediate within the rigid framework of the hexacyclic system would have required violation of Bredt's rule.

21-Deoxyajmaline can be reoxidized[47c] to ajmaline, a process necessary to one total synthesis (see below), by a sequence involving, first, cleavage of the 21,N_b bond with phenyl chloroformate and lithium iodide to give **46f**. Oxidation at C-21 is then achieved by displacement of the 21-iodo group with acetate, alkaline hydrolysis, and oxidation with *N*-chlorosuccinimide; release of N_b from the amide with potassium *t*-butoxide then gives ajmaline.

Heating with alcoholic potassium hydroxide converts ajmaline into isoajmaline (**43b**), also isolated from *R. serpentina* as a natural base. It was early recognized that this change involves epimerization at C-20, for the isomerism persisted when the 21-hydroxyl group had been removed; for example, ajmaline oxime (**46b**) and isoajmaline oxime (**46b**, but epimeric at C-20) are different, but on the other hand *both* ajmaline and isoajmaline, on Raney nickel-catalyzed decarbonylation, gave **46e**. Only later was it realized that C-21 is also epimeric in the iso series. Conformational reasoning makes this readily understood in terms of setting the hydroxyl and ethyl substituents trans to each other in each compound. With the advent of ^{1}H nmr spectroscopy distinction between the normal and iso bases was rendered easy;[51] the angles in the slightly distorted azabicyclo[2,2,2] system are such that for the normal stereochemistry $J_{20,21}$ is less than 1 Hz and for the iso series it is about 6 Hz.

The secondary nature of the other hydroxyl group in ajmaline was proved[47d]

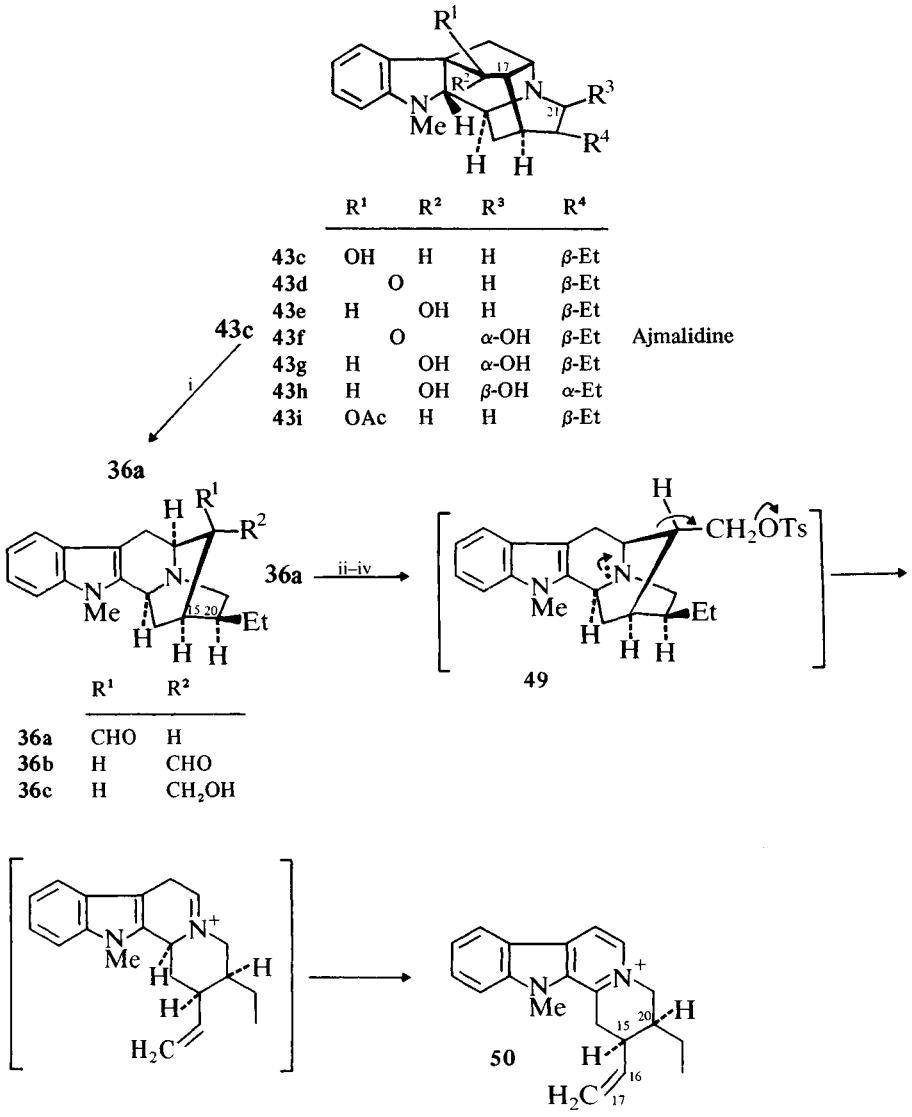
with difficulty, for although it is easily acetylated (the coacetylation of the carbinolamine hydroxyl group is another atypical carbinolamine reaction), prolonged treatment of 21-deoxyajmaline (**43c**) with potassium *t*-butoxide and benzophenone was necessary to effect oxidation to 21-deoxyajmalone (**43d**), which with a carbonyl absorption at 1742 cm^{-1} clearly contained a five-membered ring ketone. This meant that the two-carbon unit attached to C-15, and located by the dehydrogenation experiments, had to be attached not only to C-7, to account for the indoline uv absorption, but also to C-5.

Since 21-deoxyajmalone (**43d**) (Scheme 11) gave a 17 isomer (**43e**) of 21-deoxyajmaline on reduction and since from a study of molecular models it was clear that attack could occur only from the less hindered ("top") side of the molecule, this result provided convincing evidence for the stereochemistry of the 17-hydroxyl group in ajmaline. This assignment was confirmed by ^1H nmr spectroscopy,[47e] for $J_{16,17}$ is less than 2 Hz for ajmaline-type stereochemistry and about 9 Hz for 17-epi stereochemistry.

The naturally occurring 17-ketone ajmalidine[50] (**43f**) (*Rauwolfia sellowii* Muell. Arg.) gave sandwicine (**43g**) on reduction with sodium borohydride, and since sandwicine (**43g**) could be converted into isosandwicine (**43h**), both from *Rauwolfia sandwicensis* A. DC.,[51,54] by base-catalyzed epimerization at the 20 and 21 positions, the structures of these bases were similarly correlated.

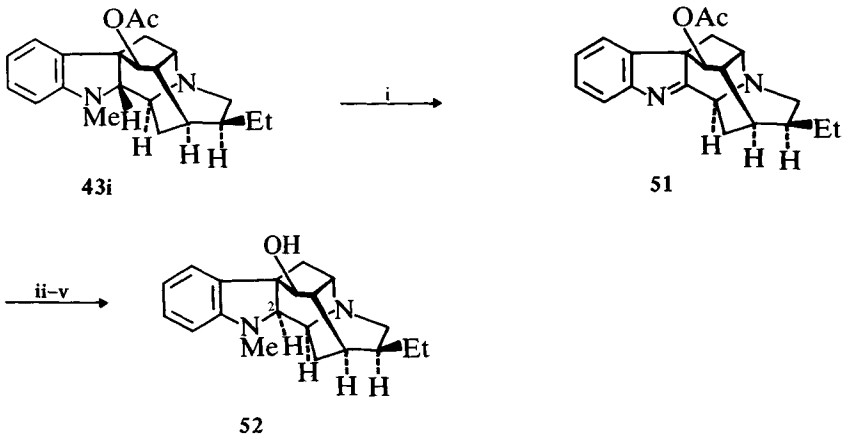
An elegant sequence[47e] (Scheme 11) interrelating ajmaline and the corynantheine alkaloids established the absolute configuration of ajmaline and related bases and represents one part of the significant contributions in this area by W. I. Taylor. In either the 21-deoxyajmaline or 21-deoxyisoajmaline series (shown for 21-deoxyajmaline in Scheme 11) lead tetraacetate effected an oxidative cleavage of the 7,17 bond and the formation of an indolic aldehyde, 21-deoxyajmalal-A (**36a**). Incidentally, that this cleavage of a bond to C-7 gives an aldehyde proves the 7,17 linkage as opposed to a 7,16 plus 5,17 combination. 21-Deoxyajmalal-A was epimerized by base to 21-deoxyajmalal-B (**36b**). Borohydride reduction of this aldehyde [→ 21-deoxyajmalol-B (**36c**)] and treatment with tosyl chloride and pyridine then effected *O*-tosylation which induced a fragmentation (arrows on **49**) which broke the 5,16 bond. Aromatization of ring C left only two asymmetric centers untouched, C-15 and C-20, in a salt (**50**) the 16,17-dihydro derivative of which was also derivable from corynantheine.

Oxidation of 21-deoxy-17-*O*-acetylajmaline (**43i**) with chromium trioxide and pyridine gave, among other products, an N_a-demethylated indolenine (**51**) (Scheme 12). Since this material, on catalytic reduction and reintroduction of an N_a-methyl group, gave a compound (**52**) stereoisomeric with 21-deoxyajmaline, necessarily epimeric only at C-2, it followed, making the reasonable assumption from a study of a molecular model that reduction would take place from the α face, that the original 21-deoxyajmaline, and therefore the alkaloid itself, had a β hydrogen at C-2. The two epimers, **43i** and **52**, had mirror image ord curves. Later it was discovered that the 2α and 2β series have distinctly different mass spectral fragmentation behavior.[50] Compounds in the normal series, with the C-2 hydrogen and 7,17 bridge cis, are believed to fragment by a pathway involving migration of the



Scheme 11. Reagents: i, $Pb(OAc)_4$; ii, MeONa; iii, $NaBH_4$; iv, TsCl, py.

apposite C-2 hydrogen onto C-17 and thus via 7,17-cleaved species following the pathway for the akuammidine types. At any rate the 2β hydrogen series gave major β-carbolinium ions at *m/e* 182 and 183 (**20b** and **c**, R = Me), which are very much less abundant in the spectra of compounds of the epimeric 2α-H series. The relative stereochemistry of ajmaline, in all the detail determined and described above, was confirmed[47f] by the X-ray method many years later.



43i 51 52

Scheme 12. Reagents: i, CrO_3, py; ii, H_2, Pt; iii, NaOH, MeOH; iv, MeI, 110°C; v, 330°C.

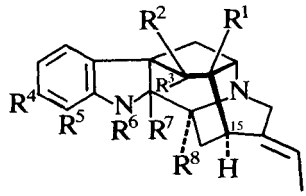


20b **20c**

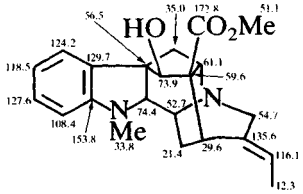
In recent work which has established the absolute configuration of macroline, it has been shown[31c] that the oxidative cleavage of the 7,17 bond can also be achieved *after* opening of ring D; thus dihydrodeoxyajmaline (**46a**) was N_b-methylated, then the 7,17 bond cleaved with lead tetraacetate, and after epimerization at C-16, the 17-aldehydo group reduced with sodium borohydride to furnish **21b**.

Among the first of this skeletal type found which had an ethylidene group rather than an ethyl group were tetraphyllicine (**41b**)[52] (*Rauwolfia tetraphylla* L.) and rauvomitine (**41c**) (*R. vomitoria* Afz.),[53] its 17-*O*-trimethoxybenzoyl ester. Catalytic reduction of tetraphyllicine gave 21-deoxyajmaline (**43c**), hydrogen having been added to the less hindered α face of the molecule.

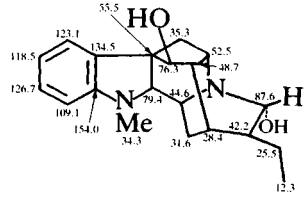
Oxidation of tetraphyllicine to tetraphyllicinone and then sodium borohydride reduction gave a 17 epimer of the alkaloid, which was shown to be identical with another natural base, mauiensine (**41d**) from *R. mauiensis* Shenff.[54] Seredamine (**41g**), mitoridine (**41h**), and purpeline (**41i**) are another set of similarly interrelated bases, all isolated from *R. vomitoria*[55] and having an oxygen function at C-12. Rauflexine (**41e**), reducible to reflexine (**41f**), both isolated from *R. reflexa* Teysm. et Binn., have an alternatively placed aromatic oxygen atom, at C-11. They were assigned their structures mainly as a result of a detailed examination[56] of the ^{13}C spectra of these hexacyclic ajmaline alkaloid types; typical values are cited for vincamajine (**41j**) and ajmaline (**43a**).



		R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
Quebrachidine	(41a)	CO_2Me	OH	H	H	H	H	α-H	H
Tetraphyllicine	(41b)	H	OH	H	H	H	Me	β-H	H
Rauvomitine	(41c)	H	$O.CO.C_6H_2(OMe)_3$	H	H	H	Me	β-H	H
Mauiensine	(41d)	H	H	OH	H	H	Me	β-H	H
Rauflexine	(41e)	H	O		OMe	H	Me	β-H	H
Reflexine	(41f)	H	H	OH	OMe	H	Me	β-H	H
Seredamine	(41g)	H	OH	H	H	OMe	Me	β-H	H
Mitoridine	(41h)	H	O		H	OH	Me	β-H	H
Purpeline	(41i)	H	O		H	OMe	Me	β-H	H
Vincamajine	(41j)	CO_2Me	OH	H	H	H	Me	α-H	H
Vincamedine	(41k)	CO_2Me	OAc	H	H	H	Me	α-H	H
	(41l)	CH_2OCMe_2O		H	H	H	H	α-H	H
	(41m)	CH_2OH	OH	H	H	H	H	α-H	H
Herbadine	(41n)	CO_2Me	OH	H	H	H	H	β-H	OH
Herbamine	(41o)	CO_2Me	OH	H	H	H	Me	β-H	OH



Vincamajine (41j) (in 5 : 1 $CDCl_3$: CD_3OD)



Ajmaline (43a) (in CD_3SOCD_3)

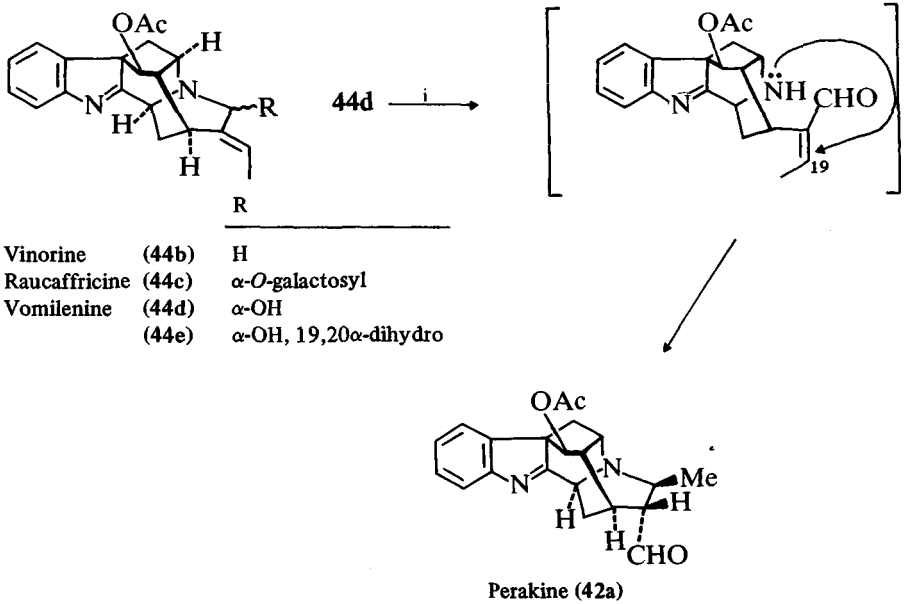
Quebrachidine (**41a**) (from *Aspidosperma quebrachoblanco* Schlecht),[44] vincamajine (**41j**) (from *Vinca major* L.),[57a,b] and its N_a-methyl analogue have α stereochemistry at C-2, the opposite of that prevailing in the ajmaline bases. The 17-*O*-trimethoxybenzoate of quebrachidine (from *Alstonia constricta* F. Müll.)[57b] and the 17-*O*-acetate (**41k**) and 17-*O*-trimethoxycinnamate esters of vincamajine also occur naturally; the acetate (= vincamedine, **41k**) occurs in *V. major*,[57c] and the trimethoxycinnamate in *A. constricta*.[57b] 10-Hydroxy and 10-methoxy derivatives of 17-*O*-trimethoxycinnamoylvincamajine occur in *V. major*.[57d]

The gross structures of these bases rest on interrelationships and conversions into compounds of the pentacyclic akuammidine type (see Section III), leaving the stereochemistry at C-2 and C-17 to be determined. How these questions were answered for quebrachidine is illustrative: the formation of an isopropylidene derivative (**41l**) from the lithium aluminum hydride reduction product (**41m**) of quebrachidine indicated the ajmaline-like stereochemistry at C-17, and the mass

spectral fragmentation, of the 2-epiajmaline type, settled the stereochemistry at C-2.[50]

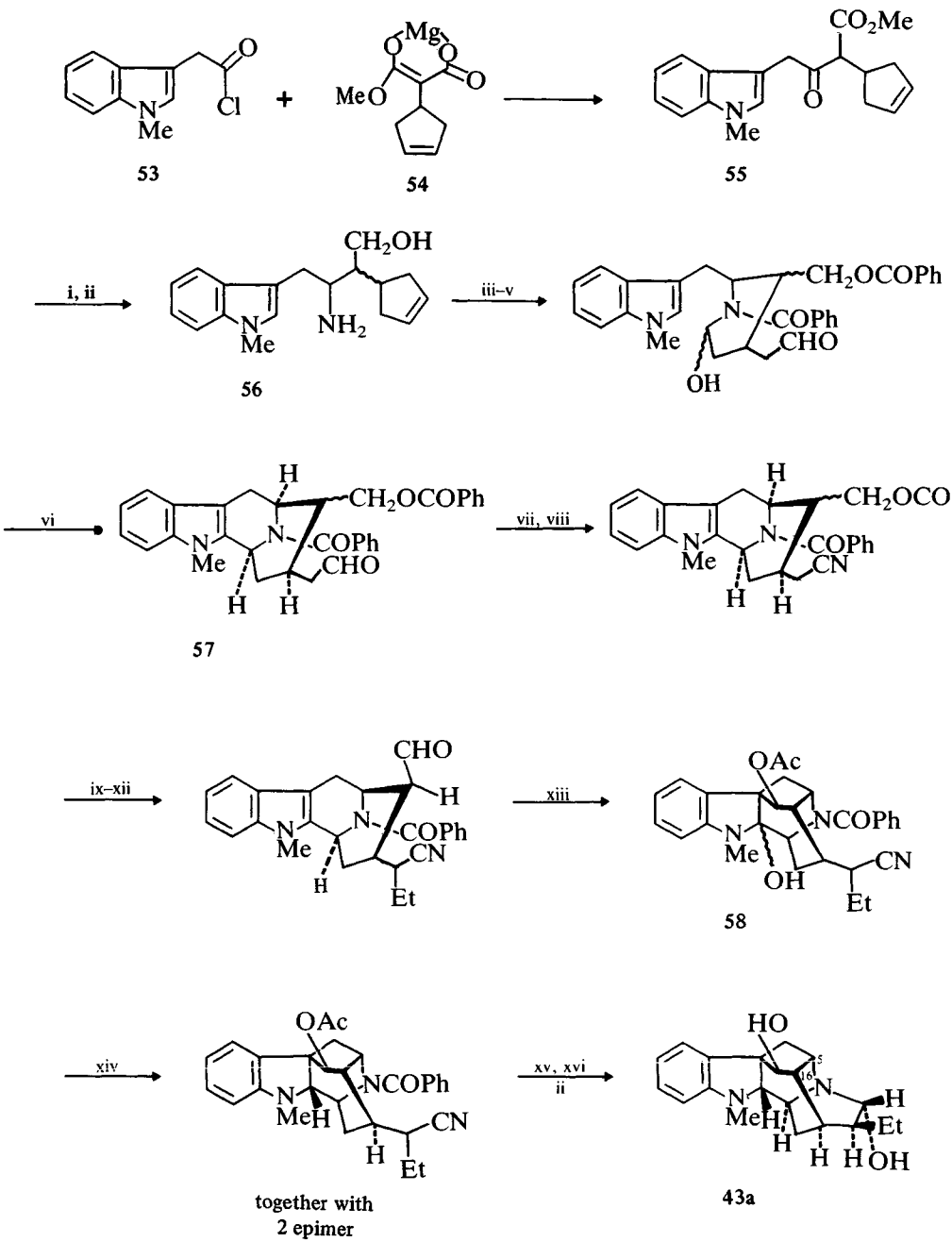
In the course of an nmr study[58] which corrected the structures of the *Vinca herbacea* alkaloids herbadine (**41n**) and herbamine (**41o**), two quebrachidine-type alkaloids but with the typical ajmaline β-H configuration at C-2, the diagnostically useful observation was made that in the 2-βH series the C-21 hydrogen atoms are magnetically nonequivalent, whereas in the 2-αH series the opposite is true. The location of the hydroxyl group in these two bases, unique for this hexacyclic group of alkaloids, was discerned from the singlet character of the C-2 hydrogen signal.

Raucaffricine (**44c**) (Scheme 13) (from *Rauwolfia caffra* Sonder)[59] is an example of the hexacyclic type at the indolenine oxidation level. The 7,17 bond in such a structure is particularly easily cleaved by very mild base treatment; indeed it seems likely that many more alkaloids of this type might have been isolated had the traditional alkaloid work-up with strong base to liberate the alkaloids from their salts not been in general use. Raucaffricine is also the only alkaloid in the group to have been isolated so far with a sugar molecule [D-(+)-galactose] attached. An indolenine 17-*O*-acetate (**44e**) with the ajmaline 19,20 oxidation level was isolated from various *Rauwolfia* species.[45a]



Scheme 13. Reagent i: aq. H^+, r.t.

Perakine (**42a**)[45b] (*R. perakensis* King et Gamble) was the first indolenine alkaloid to be recognized among this group; even 1 *M* sodium hydroxide at room temperature changes it instantly into a ring-opened indole. Since vomilenine (**44d**) (*R. vomitoria*)[45b] is transformed by dilute acid into perakine (**42a**) (Scheme 13) via carbinolamine cleavage and then cyclization involving Michael addition at

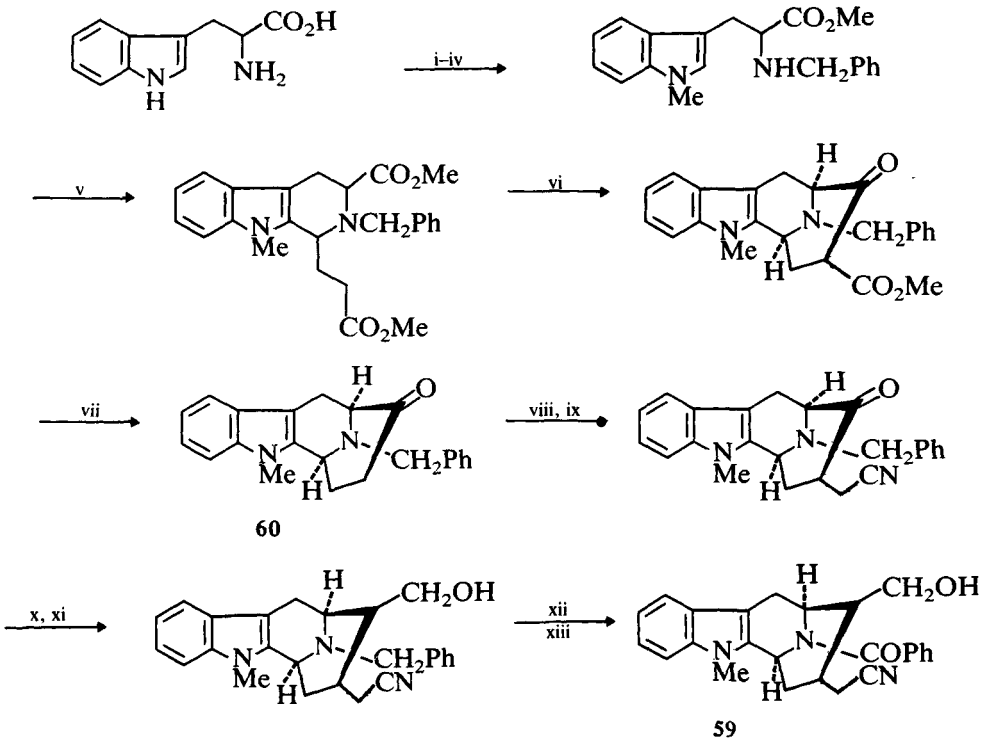


Scheme 14. Reagents: i, $MeONH_2$; ii, $LiAlH_4$; iii, PhCOCl; iv, OsO_4; v, HIO_4; vi, AcOH, 50°; vii, NH_2OH; viii, PhCOCl, py, warm; ix, Ph_3CNa, THF; x, EtI; xi, NaOMe; xii, DMSO, Ac_2O; xiii, HCl, Ac_2O, AcOH; xiv, H_2, Pt, 6*M* HCl; xv, $LiAl(OEt)_3H$; xvi, H_2, Pd/C.

C-19 in the α,β-unsaturated aldehyde thus generated, doubt was expressed as to the authenticity of perakine as a natural substance. However, since raucaffrinoline[46] **(42b)** with the alcohol oxidation level at C-21 is a natural base and is less likely to have arisen during the acidic processing of the plant material, it seems possible that neither base is an artifact.

B. Synthetic Studies

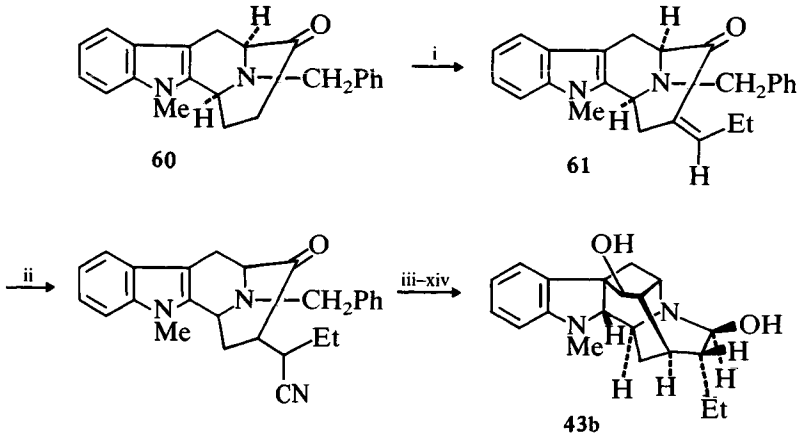
As yet no synthesis of a hexacyclic alkaloid of this group, either with an ethylidene function and/or with the C-22 ester group, has been described. However, ajmaline **(43a)** has been totally synthesized,[43,60] both in the sense that 21-deoxyajmalal-A has been prepared[43] (see Section I.B) and was known[47c] to be convertible into ajmaline (see Section II.A), and also by a route[60] which did not proceed via a pentacyclic akuammidine-type structure.



Scheme 15. Reagents: i, MeI, $NaNH_2$, liq. NH_3; ii, MeOH, HCl; iii, PhCHO; iv, $NaBH_4$; v, $MeO_2C.CH_2CH_2CHO$; vi, NaH, PhMe, MeOH; vii, AcOH, HCl; viii, pyrrolidine, TsOH; ix, $ClCH_2CN$, dioxane; x, $Me_2S^+(O)CH_2^-$, DMSO; xi, AlH_3; xii, H_2, Pd/C; xiii, PhCOCl, py.

The synthesis of Masamune et al.[60] (Scheme 14) was the first total synthesis of (±)-ajmaline. Proceeding from *N*-methylindol-3-ylacetyl chloride (**53**), all the necessary carbon atoms, except the ethyl group, were introduced by acylation of the magnesium chelate (**54**) of cyclopent-3-enyl monomethyl malonate, followed by decarboxylation (→ **55**). After introduction of N_b (→ diastereoisomers **56**) by use of methoxyamine, then reduction, ring E was formed when oxidative cleavage of the cyclopentene ring enabled one of the aldehyde groups so generated to interact with N_b. Intramolecular amidoalkylation at the indole α position (→ **57**) then allowed construction of ring C. After conversion of the remaining aldehyde function into a nitrile, the ethyl group was introduced by base-catalyzed α alkylation. Oxidation of the alcohol at the future C-17 then permitted electrophilic closure (→ **58**) to the indole β position and the completion of a fifth ring.

The nitrile (**59**) was synthesized by an alternative route[61] (Scheme 15) from tryptophan, the carboxyl of which was later utilized to allow Dieckmann cyclization to form the 15,16 bond and the E ring, the tryptophan carboxyl carbon becoming C-16. The side chain, C-20 and C-21, could be introduced[61b] via a pyrrolidine enamine of **60** in reaction with chloroacetonitrile. In a modification[61c] which led by a comparable sequence to isoajmaline, **60** was condensed with propanal (→ **61**) and then cyanide added to the conjugated ketone (Scheme 16).



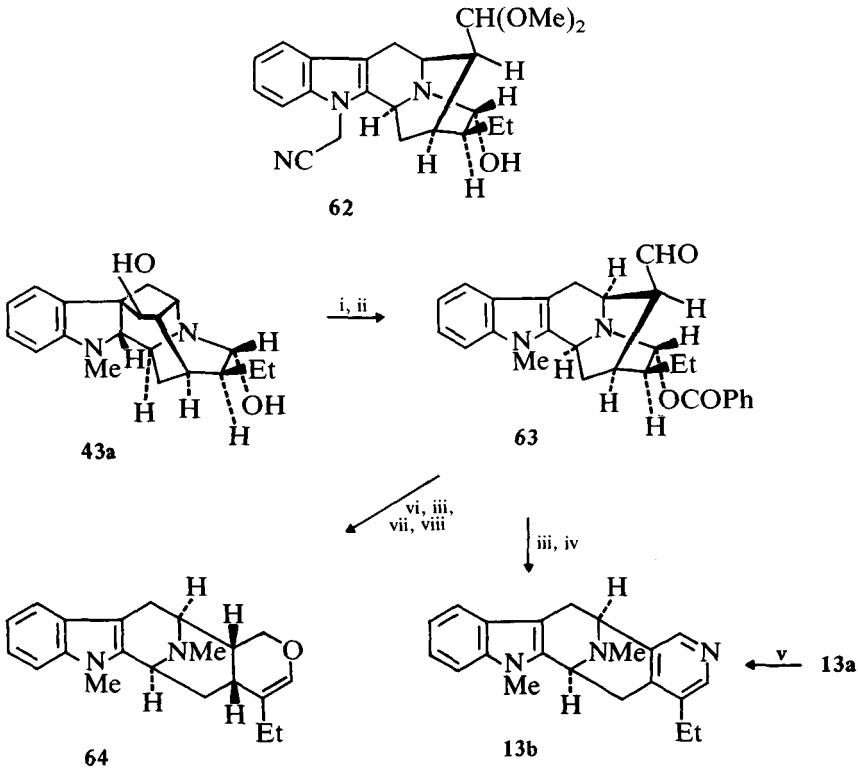
Scheme 16. Reagents: i, EtCHO, Triton B; ii, KCN, NH_4Cl; iii, $Me_2S^+(O)CH_2^-$, DMSO; iv, AlH_3; v, H_2, Pd/C; vi, PhCOCl, py; vii, 1% NaOH, MeOH (brief); viii, DMSO, Ac_2O; ix, Al_2O_3, PhH; x, Ac_2O, AcOH, HCl; xi, H_2, Pt, 6 *M* HCl; xii, $Et_3O^+BF_4^-$; xiii, $NaBH_4$; xiv, $LiAl(OEt)_3H$.

III. CHEMICAL INTERCONVERSIONS BETWEEN AKUAMMIDINE AND QUEBRACHIDINE SKELETAL TYPES

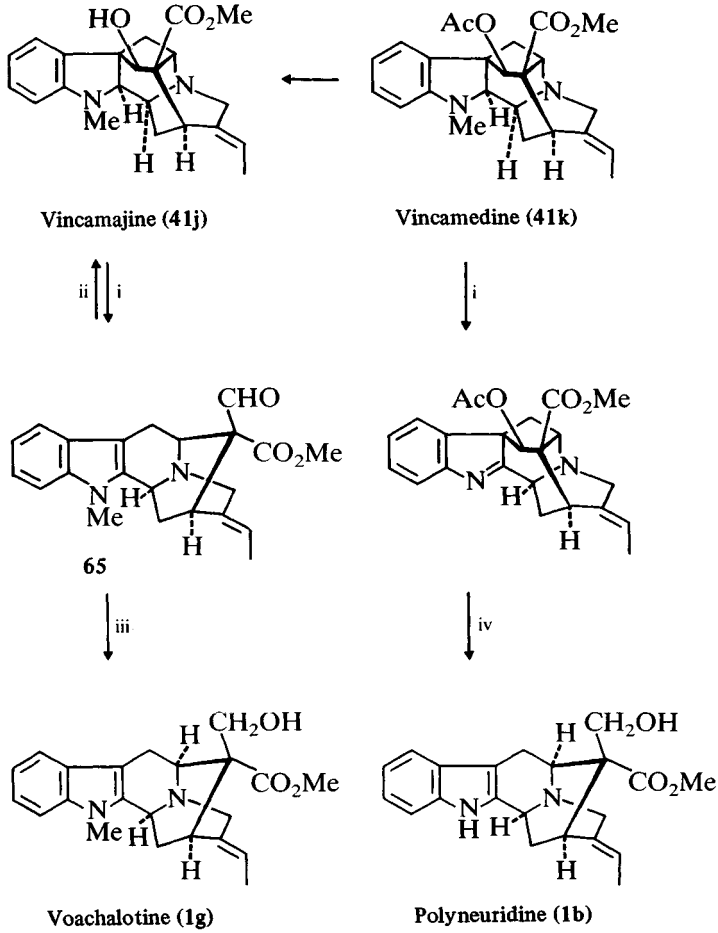
The key to interconversions between the hexacyclic quebrachidine types and pentacyclic akuammidine series lies, of course, in the making or breaking of the

7,17 bond. In proceeding *to* the quebrachidine types this has always involved making C-17 an electrophilic center to allow attack at C-7, the indole β position. In the reverse sense, the breaking of the 7,17 bond has usually been achieved by a chemical oxidation of a hexacyclic derivative in which C-17 carries an alcoholic oxygen function, to the indolenine oxidation level, which then permits a retro-indole-β-oxyalkylative cleavage. More recently it has been shown that this bond can also be cleaved via a photochemical oxidation;[62] for example, irradiation of ajmaline in methanol with eosin as sensitizer and in the presence of potassium cyanide gives the indolic nitrile (**62**) (Scheme 17). That the first step in this photochemical sequence is indeed oxidation at C-2 was shown by the failure of 17-*O*-acetylajmaline to undergo 7,17 cleavage: irradiation under the same conditions gave only the 2-α-cyano-derivative via, it was presumed, the indoleninium cation.

The N_a-methyl derivative (**13b**) of suaveoline (**13a**) (*Rauwolfia suaveolens* S. Moore) was synthesized[13] from ajmaline in four steps, of which the key oxidative cleavage (→ **63**) involved the use of lead tetraacetate (Scheme 17). Similarly ajmaline was degraded (Scheme 17) to **64**, for mass spectral comparison with alstophylline (**10b**) (*Alstonia macrophylla* Wall.), which has the same ring system.

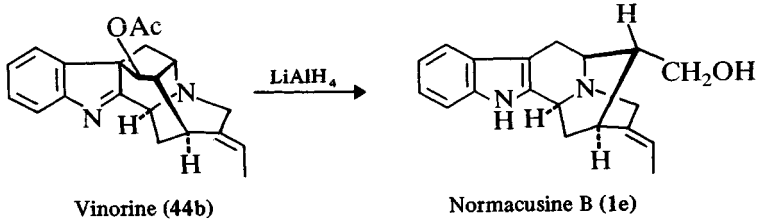


Scheme 17. Reagents: i, PhCOCl, PhH; ii, $Pb(OAc)_4$; iii, MeI; iv, NH_3, O_2; v, CH_2O, trace AcOH, $NaBH_4$; vi, $NaBH_4$; vii, NaOH; viii, $POCl_3$.



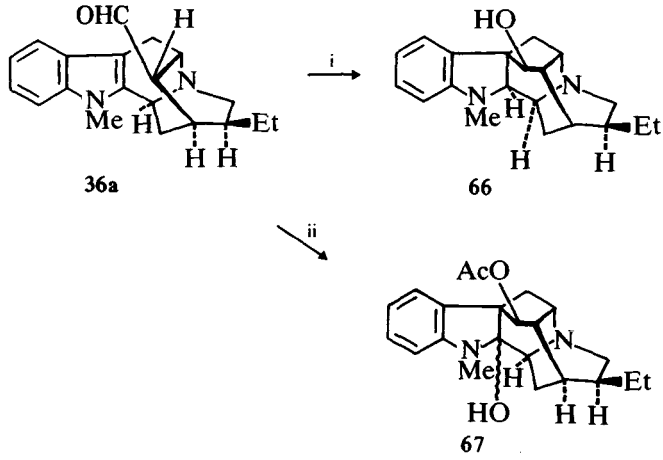
Scheme 18. Reagents: i, CrO_3, py; ii, H_2, Pt, AcOH; iii, $NaBH_4$; iv, KBH_4, NaOH.

Vincamedine (**41k**) and vincamajine (**41j**) were respectively degraded[1d] (Scheme 18) to polyneuridine (**1b**) and voachalotine (**1g**), chromium trioxide/pyridine being the oxidant employed. With the acetate (**41k**) this also brought about N_a-demethylation. These sequences also independently established the relative stereochemistry of these two pentacyclic bases at C-16.



Vinorine (**44b**), which is already at the indole oxidation level, gave[49] normacusine-B (**1e**) directly on treatment with lithium aluminum hydride; the reaction conditions presumably bring about epimerization at C-16.

Both normacusine-B (**1e**) and sarpagine (≡ 9-hydroxynormacusine-B) were converted[47b] into 21-deoxyajmalol-B (**36c**), a degradation product of ajmaline, the removal of the phenolic oxygen from sarpagine being achieved by treatment of its phenolic *O*-tosylate with hydrogen and Raney nickel. The comparable reductive cleavage necessary for conversion of gardnerine (**1h**) into 17,21-dideoxy-1-dimethyl-1,2-dihydroajmaline was achieved[3a] by hydrogenolysis of a 1-phenyltetrazol-2-yl ether.

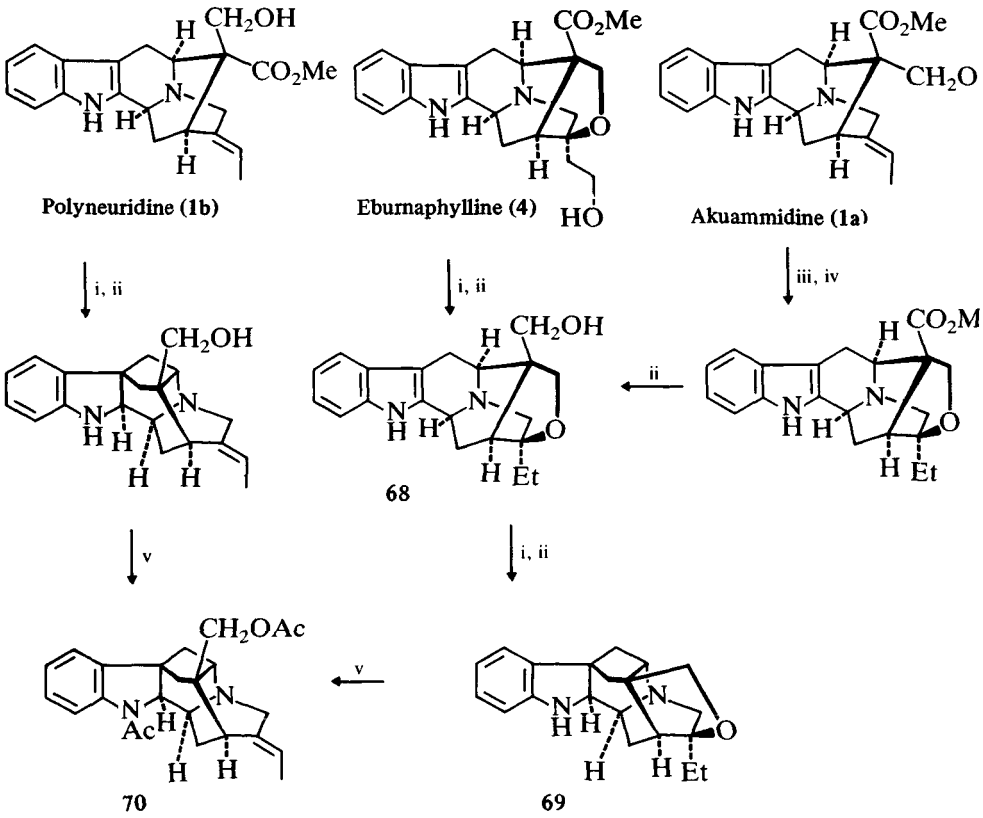


36a 66 67

Scheme 19. Reagents: i, H_2, Pt, AcOH; ii, Ac_2O, HCl.

In the opposite direction (Scheme 19), 17-aldehydes of the pentacyclic series have been cyclized by attack at the indole β position in several related ways; for example, catalytic hydrogenation of aldehyde (**65**) in acid solution re-formed vincamajine, the 17-hydroxyl *and* the 2-hydrogen taking up their natural configurations. This implies that reclosures of this type aimed at the ajmaline 2β-H stereochemistry fail; thus when 21-deoxyajmalal-A was subjected[63] to the same conditions a 2-epimer (**66**) of 21-deoxyajmaline was obtained. Without a reductant present, closure must lead to the indolenine oxidation level; thus acetic anhydride and hydrochloric acid converted[63] 21-deoxyajmalal-A into 2-hydroxy-21-deoxyajmaline (**67**), from which the 2-hydroxyl group could be removed with lithium aluminum hydride giving a product with an α-H at C-2. With C-17 at a lower oxidation level, the 17-*O*-tosylate of 21-deoxyajmalol-A also cyclized[63] easily, giving 2-hydroxy-17,21-dideoxyajmaline on treatment with pyridine.

Akuammidine (**1a**), polyneuridine (**1b**), and eburnaphylline (**4**) (*Hunteria eburnea* Pichon)[64a] were each converted into **70**, thus establishing the absolute stereochemistry of eburnaphylline. In this neat set of correlations (Scheme 20) by Le Men et al.[64b] the 7,17 bond was produced by treating a 17-*O*-tosylate



Scheme 20. Reagents: i, TsCl; ii, $LiAlH_4$; iii, $Hg(OAc)_2$; iv, $NaBH_4$; v, Ac_2O.

with lithium aluminum hydride, which must serve as a strong base to deprotonate the indolic *N*-hydrogen and thus promote attack at C-7. The 17,20 ether ring was introduced into akuammidine by intramolecular oxymercuration. This ether ring is stable to acetic anhydride in eburnaphylline itself and also, for example, in **68**, and can not be opened. However, when the 7,17 bond is formed, as in **69**, the ether ring becomes strained, and can now be cleaved, with formation of a degradation product (**70**) of polyneuridine.

IV. THE ERVATAMINE AND ERVITSINE GROUP. ALKALOIDS WITH (1) 5,16 AND 6,16 BONDS BUT NO 5,6 BOND AND (2) 5,16, 5,7, AND 6,16 BONDS BUT NO 5,6 BOND

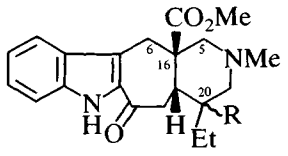
Nine alkaloids make up this group, the structures of the first three of which were disclosed[65a] in 1971. The structure of ervatamine (**71a**) is the prototype for eight of these bases. The ninth member of the group, ervitsine (**72**), has a different

skeleton.[66] That these bases are included in this chapter at all is based on a presumed biogenetic relationship to the dregamine/tabernaemontanine (**25a/b**) type; laboratory chemical transformations,[67a] exactly like those postulated for the biosynthetic conversion of one skeletal type into the other, have indeed been achieved (Scheme 21). Further, dregamine, for example, was converted into N_b-demethyldregamine (major product) and 20-epiervatamine (**71b**) by rat liver microsomes, NADPH, and oxygen (a combination believed to produce the in vivo equivalent of the modified Polonovski process). But however likely a candidate for the biogenesis these in vitro and in vivo transformations make this sequence, an alternative set of steps (Scheme 22) from a structure like **74**, reasonably derivable from a vallesiachotamine structural type (see Chapters I and III), cannot be ruled out. This alternative postulate would replace C-5 with C-17 (cf. **71c**). Indeed, this alternative view does seem to provide a rather simpler explanation for the biosynthesis of ervitsine, namely, that this base has lost C-6 (the N_b-methyl being C-5), and has a 7,17 bond (cf. **72b**); in this respect, ervitsine and ervatamine would parallel uleine and apparicine (see Chapter VI). The rationalization put forward[66] for ervitsine suggests its formation (Scheme 23) via the decarboxylation of an intermediate arising by 7-protonation of **75**, the analogue of **73** in Scheme 21, and thus predicts that both the tryptamine ethanamine carbon atoms, C-5 and C-6, would be present, though in a uniquely rearranged situation (**72a**), with C-5 now attached to C-7.

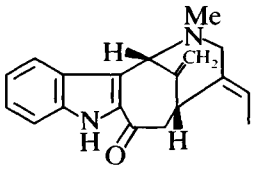
A. Structural Studies

The structures of 19,20-dehydroervatamine (**76a**) and of the ervatamines (**71a** and **b**) from *Ervatamia orientalis* (R. Br.) Turrell were demonstrated[65a,b] by combining classical degradation (Scheme 24) with spectroscopy. Thus the alkaloid (**76a**) was converted, by hydrogenation and then reoxidation at C-3, into ervatamine together with a minor amount of 20-epiervatamine. The quaternary environment of the ester function of 19,20-dehydroervatamine was demonstrated by lithium aluminum hydride reduction, mild reoxidation of only the benzylic C-3-hydroxyl group, and then *O*-acetylation to give **76b**, in the ^{1}H nmr spectrum of which there could be seen a clean AB quartet for the CH_2OAc.

One Hofmann cycle on the keto alcohol (**76c**) gave **77**, in which the conjugated diene unit could be easily recognized spectroscopically. A second cycle led to the loss of formaldehyde (no β-hydrogen; 1,3-hydroxyammonium system) and material (**78**) that must have arisen by conjugation, in the reaction medium, of the initially formed product. Of the two remaining carbon atoms one, a CH_2, was shown to be attached to C-3; borohydride reduction and dehydration gave an α-vinylindole (**79**), recognizable from its uv absorption, λ_{max} 237, 321 nm (log ϵ 4.5, 4.3) and having two cis-coupled olefinic hydrogen atom signals (δ 6.44 and 5.52, J 11 Hz) at C-3 and C-14. Since the typical 2-acylindole uv absorption of ervatamine specifies the position of the carbonyl group, the experiments described above lead[65] to part structure **80**, in which the missing carbon must necessarily be linked to each of

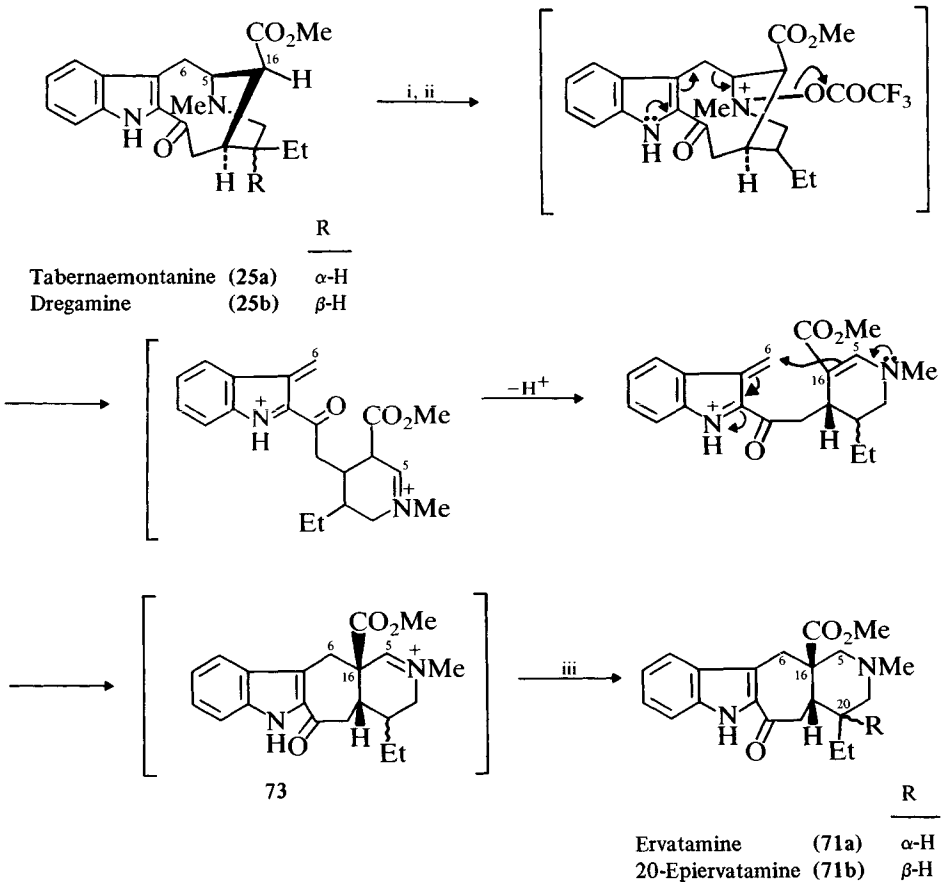


		R
Ervatamine	(71a)	α-H
20-Epiervatamine	(71b)	β-H



Ervitsine (72)

		R
Tabernaemontanine	(25a)	α-H
Dregamine	(25b)	β-H

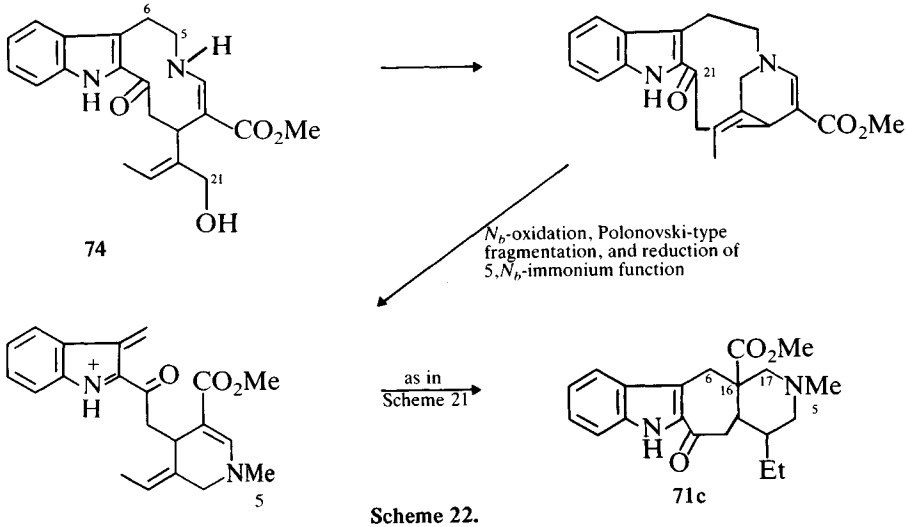


Ervatamine (71a) α-H
20-Epiervatamine (71b) β-H

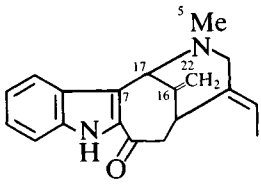
Scheme 21. Reagents: i, H_2O_2, $CHCl_3$, EtOH; ii, $(CF_3CO)_2O$, CH_2Cl_2, 0°; iii, $NaBH_4$.

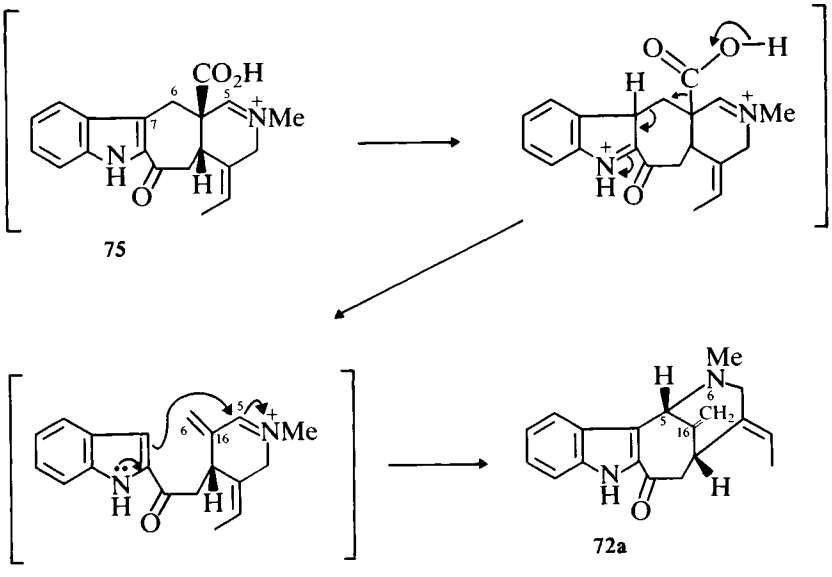
C-16, C-14, *and* C-20. The structure **(71a)** for ervatamine was confirmed[65c,67] and the stereochemistry established by X-ray analysis.

Of the alkaloids lacking the ester group the structure **(81a)** of decarbomethoxy-20-epiervatamine (*Pandaca caducifolia* Mgf.[68a]) (≡ silicine) was also established[68b] by the X-ray method. The structure of 6-oxosilicine **(81b)** was demonstrated by a

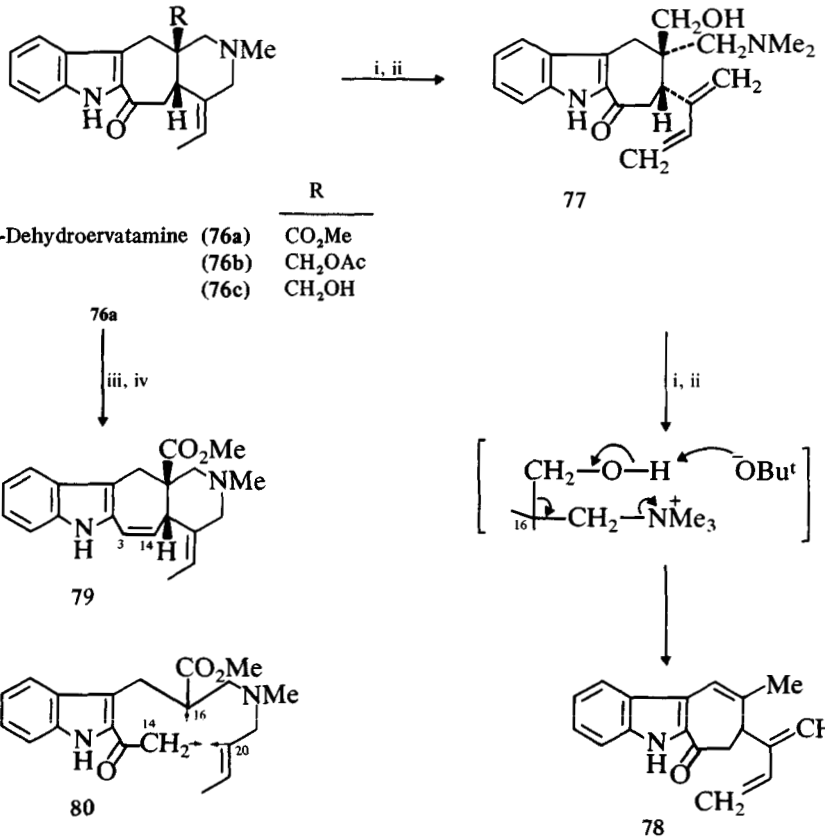


Scheme 22.



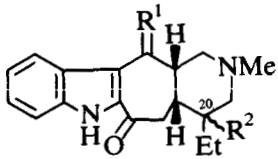


Scheme 23



Scheme 24. Reagents: i, MeI; ii, KOBu^t, Bu^{t}OH, Δ; iii, $NaBH_4$; iv, AcOH, Δ.

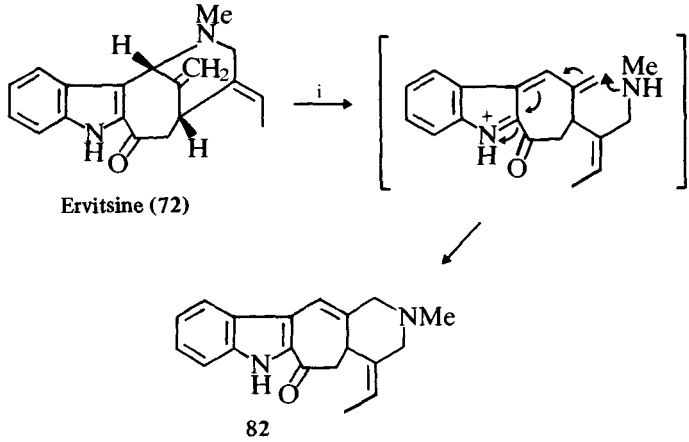
total synthesis[70] (see below). Methuenine and 6-oxomethuenine are the 19,20-dehydro versions of silicine and 6-oxosilicine; together with the 20-epimeric silicines they were obtained[69] from various *Hazunta* species.



		R^1	R^2
Silicine	(81a)	H_2	β-H
6-Oxosilicine	(81b)	O	β-H
20-Episilicine	(81c)	H_2	α-H

The structure of ervitsine[66] (72) (*Pandaca boiteaui*) was also established by X-ray crystallography; the structures of one-third of all the alkaloids in this small

group have been so determined! Ervitsine was converted into a compound of the silicine ring type by treatment with aqueous acetic acid (Scheme 25). Gramine-type cleavage and alternative reclosure gave **82**, catalytic reduction of which gave three stereoisomers, one of which was identical with a reduction product of methuenine.



Ervitsine (72)

82

Scheme 25. Reagent i: aq. AcOH, Δ.

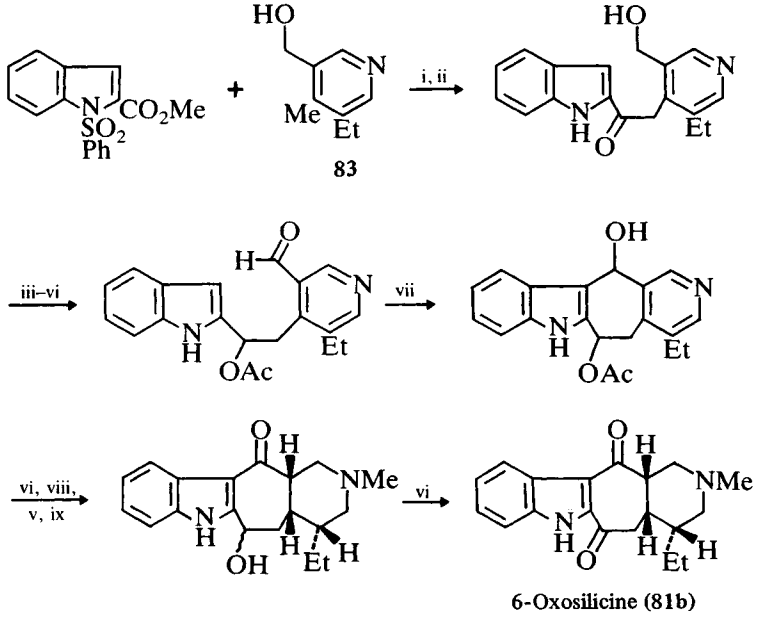
B. Synthetic Studies

All the reported synthetic work in this group so far has come from the Potier and Husson groups. The total synthesis[70] (Scheme 26) of (±)-6-oxosilicine (**81b**), which established the structure, is notable for the construction of the 3,14 bond using the *O,C*-dilithiated pyridine-alcohol (**83**) and of the 7,16 bond by alumina-catalyzed intramolecular oxyalkylation of the indole β position by the aldehyde function. The stereochemistry is controlled by the cis-catalytic reduction of a pyridinium salt intermediate.

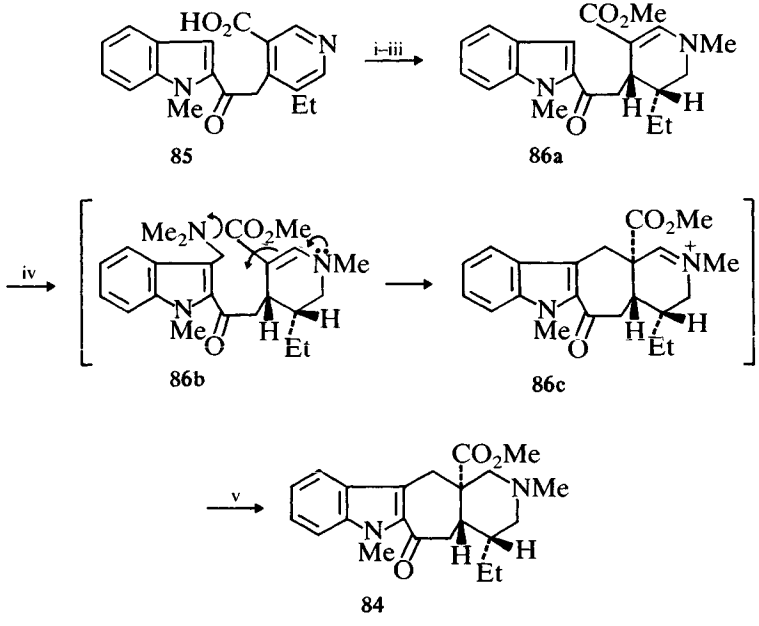
A rather similar approach (Scheme 27) was used[70b] to make N_a-methyl-16,20-epiervatamine (**84**). The carboxypyridylmethyl indolyl ketone (**85**) was transformed into the enamine (**86a**) and then the bridging carbon introduced by a Mannich reaction, presumably initially at the indole β position. Intramolecular enamine alkylation in the product (arrows on **86b**) achieved the formation of the cyclized immonium species **86c**, which was then trapped by reduction with sodium cyanoborohydride.

Earlier, a different synthetic strategy (Scheme 28) had produced[71a] 15,20-dehydroervatamine (**87**). In this approach the indole-β link was made early and the 3,14 bond by intramolecular aldol condensation with an indole-α-acetyl group introduced via the Friedel-Crafts reaction.

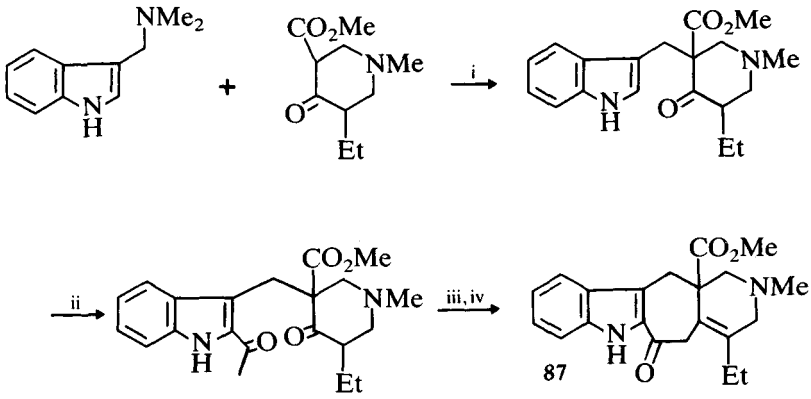
So far only the ring system of ervitsine has been synthesized;[71b] Scheme 29 shows how this was achieved, the key step being an S_N2' displacement of cyanide from a 2-cyano-3-piperideine derivative.



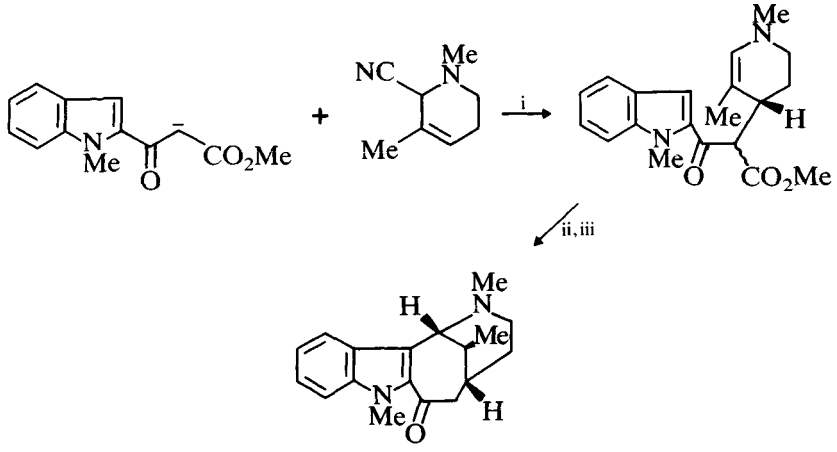
Scheme 26. Reagents: i, 2 × *n*-BuLi; ii, NaOH; iii, $NaBH_4$; iv, Ac_2O; v, $NaBH_4$; vi, MnO_2, THF; vii, Al_2O_3; viii, MeI; ix, H_2, Pt.



Scheme 27. Reagents: i, CH_2N_2; ii, MeI; iii, H_2, Pd/C; iv, $CH_2{=}\overset{+}{N}Me_2\ CF_3CO_2^-$; v, $NaB(CN)H_3$.



Scheme 28. Reagents: i, K_2CO_3, Me_2CO; ii, MeCO.Cl, $ZnCl_2$, $PhNO_2$; iii, $KOBu^t$, dioxane; iv, MeOH, HCl.

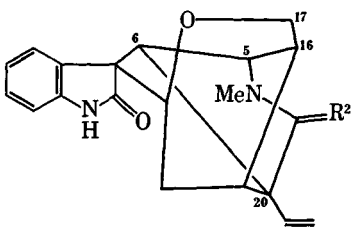


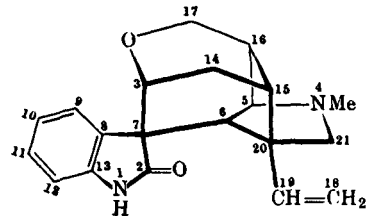
Scheme 29. Reagents: i, $AgBF_4$; ii, TsOH, PhMe, Δ; iii, AcOH, H_2O, H_2SO_4.

V. THE GELSEMINE AND KOUMINE GROUP: ALKALOIDS WITH A 5,16 BOND AND A 6,20 OR 7,20 BOND

Only three indole alkaloids are known which have a 6,20 bond; these are the oxindoles gelsemine (**88a**),[72] gelseverine (**88b**)[72c,73a] (= *Gelsemium* Alkaloid-A = N_a-methoxygelsemine), and 21-oxogelsemine (**88c**),[74a] each isolated from *Gelsemium sempervirens* Ait. Only one alkaloid is known with a 7,20 bond; this is koumine (**89a**), from *Gelsemium elegans* Benth.[74b,c]

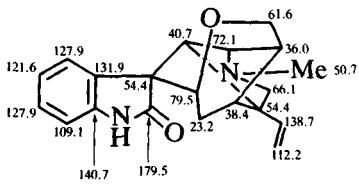
The representation (**88a**) for gelsemine aims to show its structural relationship to the akuammidine group in that the 5,16 bond typical of that group is present. However, there are several further modifications compared with the straightforward



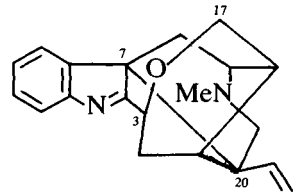


88d

		R^1	R^2
Gelsemine	(88a)	H	H_2
Gelseverine	(88b)	OMe	H_2
21-Oxogelsemine	(88c)	H	O



88e (in $CDCl_3$)



Koumine (89a)

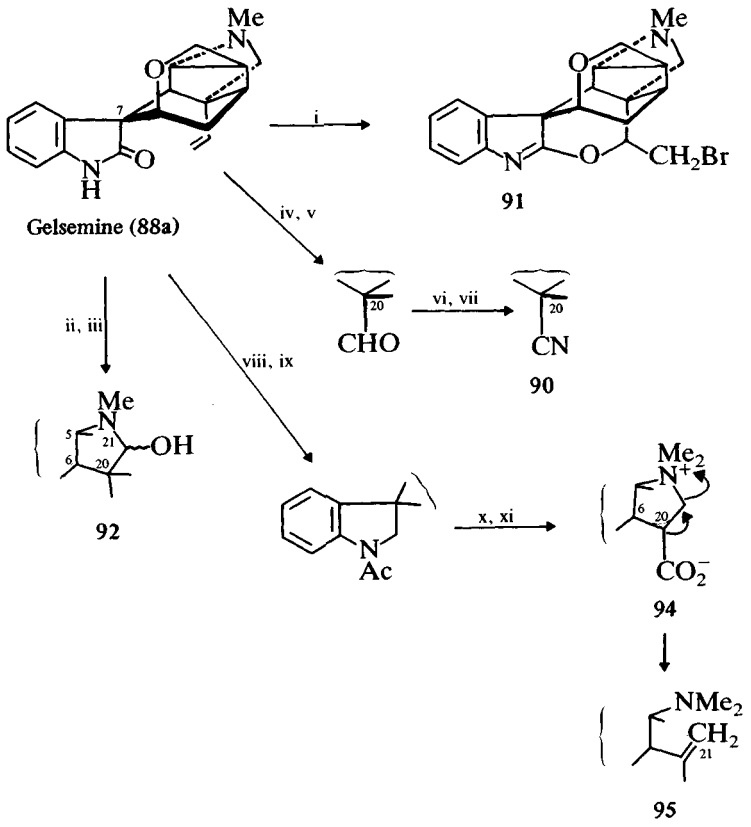
akuammidine type: the absence of a 3,N_b bond, the presence of a 3,7 rather than a 3,2 bond, and the C-3,O,C-17 ether link are all features encountered in various alkaloids in Section I.A. However, the 6,20 bond is unique to this trio of bases. It is not present, either, in the other three bases (Section I) isolated from *G. sempervirens*.[73] The structure of the gelsemine bases thus emerges as one of the most highly evolved of all the indole alkaloids.

The representation (**89a**) for koumine shows its relationship to the standard akuammidine type, from which it differs in the absence of a 3,N_b bond, the presence of the ether link between C-3 and C-17, and the unique 7,20 bond.

A. Structural Studies

The conformational representation **88d** shows the rigid cage structure of gelsemine, the main reason for the difficulties encountered by early workers in their attempts to elucidate the structure by classical degradative methods.

Gelsemine was the first complex alkaloid for which a complete assignment[72b] of the ^{13}C nmr signals was made (cf. **88e**); indeed, Wenkert has been by far the most active in this aspect of alkaloid spectroscopy. The 220 MHz ^1H nmr spectrum[72c] of gelsemine, which became available only after the structure had been determined, would no doubt have considerably facilitated the structural analysis, which had earlier been provided by an X-ray study[72d] of its hydrochloride and hydriodide, and independently[72e] by combining the interpretation of a partially resolved 60 MHz ^1H nmr spectrum with intuitive biogenetic argument.

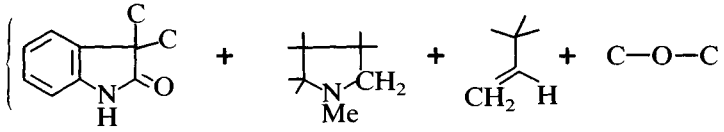


Scheme 30. Reagents: i, Br_2; ii, H_2, Pt; iii, $(EtO_2C.N:)_2$; iv, N_a-methylation; v, HIO_4, OsO_4; vi, H_2NOH; vii, Ac_2O; viii, $LiAlH_4$; ix, Ac_2O; x, MeI; xi, NaOH, $KMnO_4$.

Early chemical investigation (Scheme 30) of gelsemine had provided only peripheral information on the complex structure; little progress could be made in attempts to break it down, attempted[72f] Hofmann degradation, for example, simply leading to N_b-demethylation of gelsemine methohydroxide. The presence of a vinyl group was deduced by identification of formaldehyde from ozonolysis[72g] of gelsemine and by the periodic acid–osmium tetroxide cleavage[72h] of N_a-methylgelsemine to a carbonyl compound, shown to be an aldehyde by the dehydration of its oxime to a nitrile (**90**).

Reaction of gelsemine with bromine[72g] gave bromoallogelsemine (**91**) which, though demonstrating the steric proximity of oxindole oxygen and vinyl group, provided no direct skeletal information. Oxidation[72i] of 18,19-dihydrogelsemine with diethyl azodicarboxylate gave a carbinolamine (**92**), the lactam (CrO_3 on **92**) corresponding to which had carbonyl absorption typical of a five-membered lactam, thus providing evidence on the size of the smaller of the rings of which N_b forms a part.

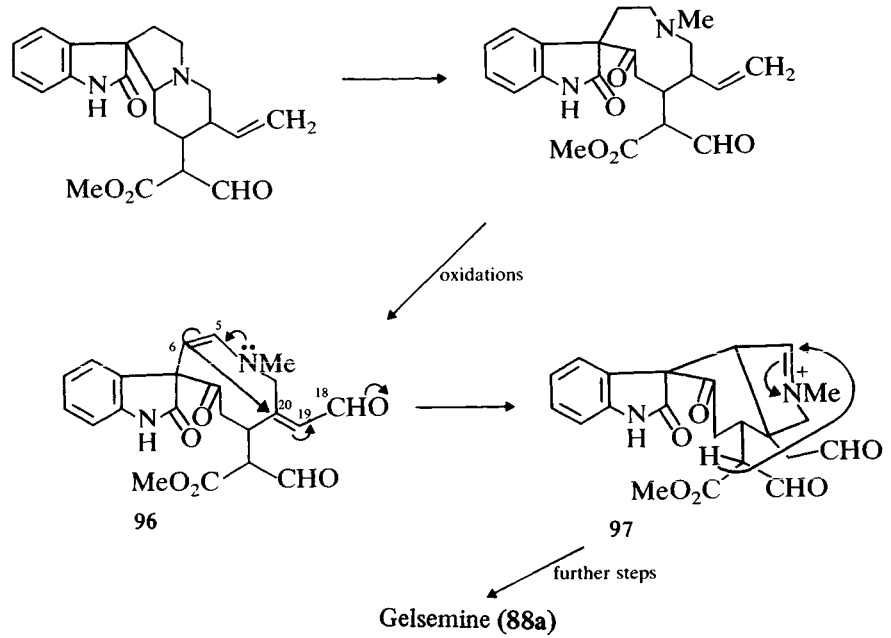
The overall, firm conclusions from these and other early chemical investigations, together with uv and ir measurements, amounted to no more than the expression **93**.



93

Proton nmr at 60 MHz was easily able to confirm[72e] the presence of a vinyl group and its location on a quaternary carbon, thus implying the novel fourth carbon bond at C-20. The geminally coupled 21-methylene adjacent to nitrogen and the groups OCH_2CH, $OCH(C)_2$, and $N_bCH(C)_2$ were also discernible from the 60 MHz spectrum. The relationship between the vinyl group and basic nitrogen atom, anticipated on biogenetic grounds, was confirmed[72e] by one of the few helpful chemical degradations, that is, **94** → **95**.

Armed with these data and a cleverly conceived, chemically rational modification of the standard biosynthetic pathway, the key steps of which are shown in Scheme 31, Conroy and Chakrabarti[72e] postulated the correct structure (**88a**). The keys to the formation of the novel 6,20 bond in their suggestion are the postulated oxidations at the 5,6 position, to give an enamine, and the 18, 19, and 20 positions, to give an unsaturated aldehyde, which changes then allow the required 6,20 bond formation, as shown in **96** → **97**.

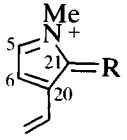


96 **97**

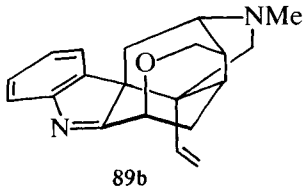
Scheme 31.

X-Ray analysis[72d] of the hydrochloride and hydriodide salts of gelsemine gave the relative, but only presumed absolute, stereochemistry shown in **88d**.

The mass spectrum[72c,j] of gelsemine is dominated by an ion at *m/e* 108, assigned structure **88f**; direct comparison with the fragmentation pattern of the minor base 21-oxogelsemine[74] (**88c**) was the main evidence for this last structure, the base peak now being seen at *m/e* 122 (**88g**). Mass spectral comparisons[72c,72j] were also adduced in support of **88b** for gelseverine, but more rigorously it was transformed[72c] into gelsemine by cleavage of the N_a-methoxyl group with lithium and liquid ammonia.

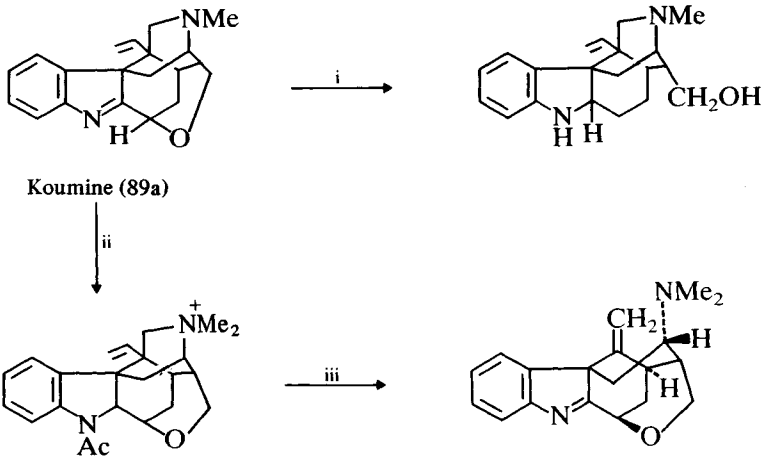


	R
88f	H_2
88g	O



89b

Representation **89b** shows the rigid structure of koumine in which all rings are boats except ring C, which is a chair; one consequence of this is that the alkaloid shows no significant mass spectral fragmentation! The structure was determined[74b,c] independently by two groups using the X-ray method, although considerable progress was made with spectral measurements and degradations, some of which are shown in Scheme 32.



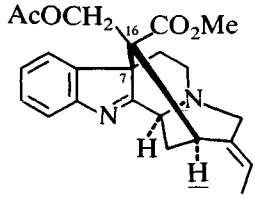
Scheme 32. Reagents: i, Na, EtOH; ii, unspecified; iii, aq. $KMnO_4$.

B. Synthetic Studies

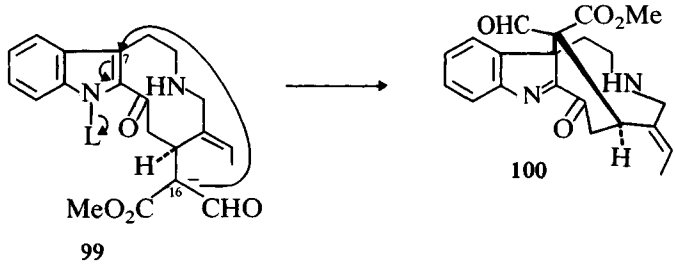
No synthesis, either partial or complete, of any of the alkaloids in this group, nor even of the ring systems, has been reported.

VI. THE AKUAMMILINE GROUP: ALKALOIDS WITH A 7,16 BOND

There are between 40 and 50 indole bases, not all of which can be dealt with specifically here, which have a common carbon skeleton formally derivable from the corynantheine type by the introduction of an extra carbon-carbon bond between C-7 and C-16. Akuammiline (**98a**)[75] represents the prototype in its skeletally most straightforward form. The mechanism of the biosynthetic formation of the 7,16 bond poses an intriguing question, for in a corynantheine-type precursor both C-7 as an indole β position *and* C-16 as a potential enol/enolate site are nucleophilic [the biosynthetic derivation of the 7,20 bond in koumine (Section V.A) presents a comparable problem]. In this connection it may be significant that more than 90% of the known bases in this group have a $2,N_a$ double bond, or its oxidation level equivalent, and that many also have a C-3 oxygen substituent. It may be that these alkaloids are produced by a nucleophilic attack (arrows on **99**)[76a,b] by C-16 on C-7, the latter rendered electrophilic by a conjugated indole α-carbonyl group[76a] and/or by the departure of a leaving group[76b] from N_a, with consequent unsaturation at the $2,N_a$ position (cf. **100**).



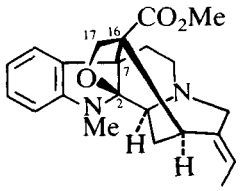
Akuammiline (98a)



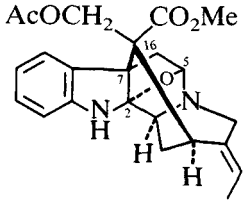
99 **100**

Besides the akuammiline type there are nine other variations in which, although the carbon skeleton remains unchanged (leaving aside the occasional absence of C-17 or C-22), additional ether links are present and/or bonds to N_a or N_b have been broken and/or made. Pseudoakuammigine (**101a**),[77] picraline (**102a**),[78] and quaternoline (**103**)[79a] (from *Alstonia quaternata* v. Heurck et Muell. Arg.) (probably identical with raucubaine, from *Rauwolfia salicifolia* Griseb.,[79b] structure by X-ray crystallography) exemplify structures that differ from akuammiline only in having an extra oxgen-containing ring, between C-2 and C-17, C-2 and C-5, and C-20 and C-22, respectively. In echitamine (**104a**)[80] a $2,N_b$ bond replaces the $3,N_b$ bond; the

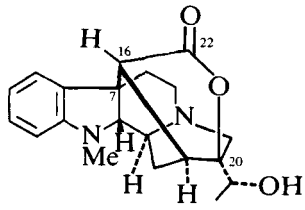
corymine (**105a**)[81] type is derivable from this by the formal introduction of a cyclic hemiacetal, formed from a hydroxyl group at C-3 and a C-17 aldehyde group. The absence of a 21,N_b bond characterizes the seventh and eighth variations, exemplified by eripine (**106**)[82,87b] and isocorymine (**107**),[81b,87b] represented in **106** and **107** in such a way as to emphasize their structural relationship to the other alkaloids in this group. Both alkaloids also have additional oxygen-containing rings, in which C-3 is attached via oxygen to C-22. Another variation on this carbon skeleton lacks a bond between C-5 and N_b. Aspidodasycarpine (**108a**)[83] is typical of this group; here the 2,N_a unsaturation is represented by a cyclic ether link between C-2 and C-5. The skeleton of lanceomigine (**109**) (from *Alstonia lanceolata* v. Heurck et Muell. Arg.),[77e,f] which represents the last variation recognized to date, is unique in having N_a attached to C-17 instead of to C-2.



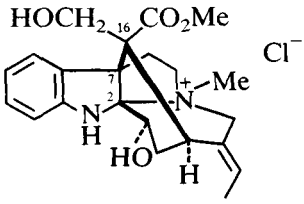
Pseudoakuammigine (**101a**)



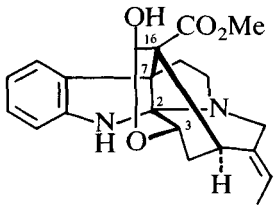
Picraline (**102a**)



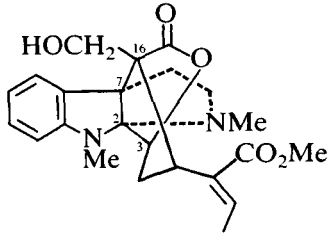
Quaternoline
(≡ Raucubaine) (**103**)



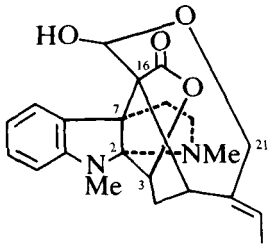
Echitamine chloride (**104a**)



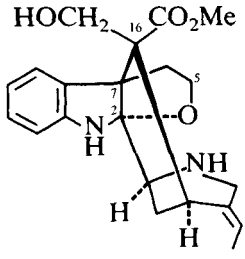
Corymine (**105a**)



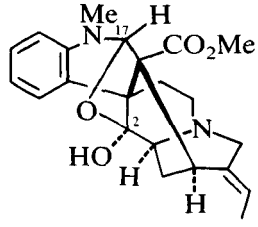
Eripine (**106**)



Isocorymine (**107**)

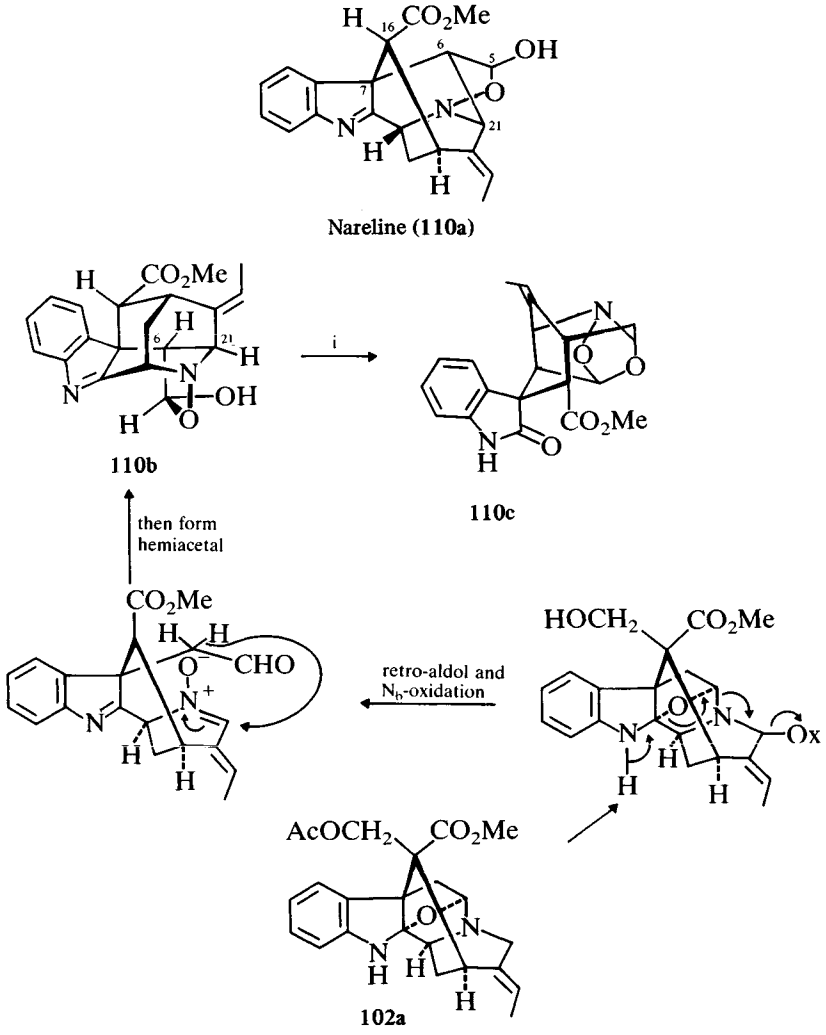


Aspidodasycarpine (**108a**)



Lanceomigine (**109**)

One further alkaloid containing a 7,16 bond may be conveniently added to this group; however, the convoluted structure (**110a**) of nareline[84] from *Alstonia scholaris* R. Br. lacks a 5,N_b bond but has a unique 6,21 bond and an N_b-hydroxylamine cyclic hemiacetal. The biogenetic formation of this structure (**110b**), which was determined by the X-ray method (one of the numerous contributions on indole alkaloids to emerge from the laboratory of Schmid and Hesse), has been rationalized, starting from picraline (**102a**), by the sequence shown in Scheme 33. Oxidation of picraline at C-21 followed by a fragmentation would lead to a species having a nucleophilic C-6 and an electrophilic C-21 so that the unique bond could be made. Laboratory oxidation of nareline with chromium trioxide and acetic acid results in cleavage of the 2,3 bond and the formation of the oxindole **110c**.



Scheme 33. Reagent i: CrO_3, AcOH.

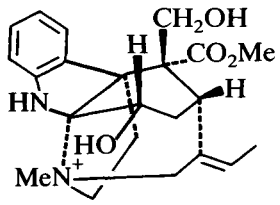
A. Structural Studies

Early efforts, the majority of which predated the use of nmr and mass spectrometry and which were aimed at the elucidation of the structure of alkaloids that are now known to fall into the 7,16 bonded group, were concerned with echitamine[80] and akuammine/pseudoakuammigine[77] and, later, picraline,[78] corymine,[81] and erinine/erinicine.[87] Although it is true to say that there was no difficulty in achieving chemical degradations of echitamine and pseudoakuammigine (contrast gelsemine, Section V.B), many of the changes involved confusing processes which led to a variety of speculative structural proposals, particularly for echitamine.[80a] The first structure to be firmly established was by X-ray crystallographic analysis[80b] of echitamine bromide methanol solvate, although the chemical work[80e–g] (Scheme 34), particularly by G. F. Smith and H. Conroy, on this alkaloid had produced evidence for the then-novel 7,16 bond and indeed for the entire structure, given the usual biosynthetic assumptions. Later, the X-ray analysis[80b] of echitamine iodide established the absolute configuration.

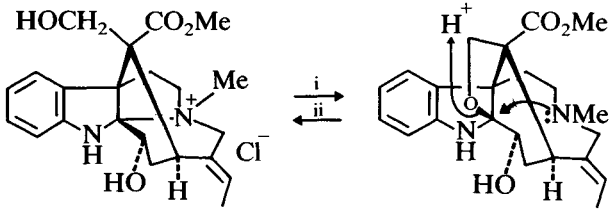
Echitamine (conformation shown in **104a**) was isolated[80d] from *Alstonia scholaris* as its chloride salt (**104b**). The treatment of **104b** with sodium hydroxide at room temperature liberates echitamine base (**111**), but this immediately reverts (arrows on **111**)[80e] to the quaternary form in hydroxylic solvents, giving a solution which exhibits the original indoline uv absorption, λ_{max} 235, 295 nm (log ϵ 3.9, 3.6). This phenomenon caused great confusion and controversy since it had been recognized[80f] that the failure of N_a in echitamine to protonate, and thus the failure of the indoline uv absorption to alter in acid solution (unlike that of normal indolines), was a result of the influence of a close, positively charged N_b. It was not until the uv absorption of echitamine base was recorded[80e] in aprotic petroleum ether solution, where no requaternization could occur, that a shift [to λ_{max} 227, 283 nm (log ϵ 4.0, 3.4)] with respect to echitamine chloride was observed.

The retro-aldol loss of formaldehyde on treatment of the alkaloid with potassium *t*-butoxide gave alloechitamine (**112**),[80g] an indoline, the uv absorption of which showed that it *did* protonate on N_a in dilute acid solution and thus could no longer have an $N_a.C.N_b$ system. This transformation thus gave evidence both for the presence of $HOCH_2.C.CO_2Me$ and also, importantly, that the secondary hydroxyl group which turns up in alloechitamine as a carbonyl group (in transannular interaction with N_b, since it exhibits ν_{max} 1689 cm^{-1}), is present in echitamine on a carbon (C-3) directly linked to C-2. Thus Hofmann elimination (arrows on **113**) of the positively charged N_b attached to C-2 gives an enol (**114**), ketonization of which then leads to the observed product.

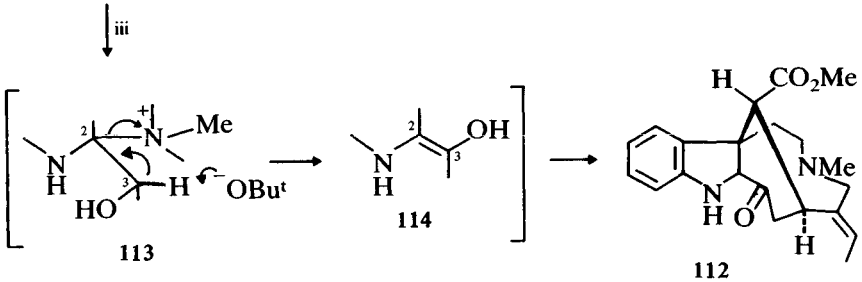
On treatment of echitamine with hydrogen/platinum, echitinolide (**115**), a δ-lactone,[80g] is produced in which hydrogenolysis of the allylic 21,N_b^+ bond has occurred, but not reduction of the hindered 19,20 double bond. Released from the constraints of the original ring system, the six-membered carbocyclic ring, in an alternative boat conformation, brings ester and C-3 hydroxyl groups close and lactonization occurs. It is the size of this lactone ring, established by the ir carbonyl frequency of 1742 cm^{-1}, taken with the location of the secondary hydroxyl group



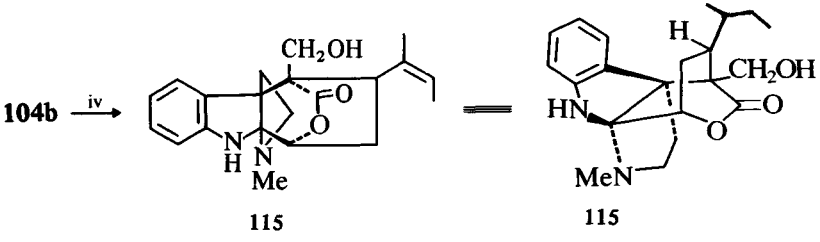
Echitamine (104a)



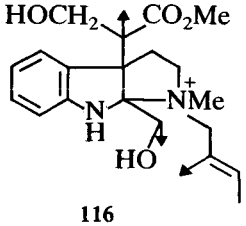
104b 111



113 114 112



115 115

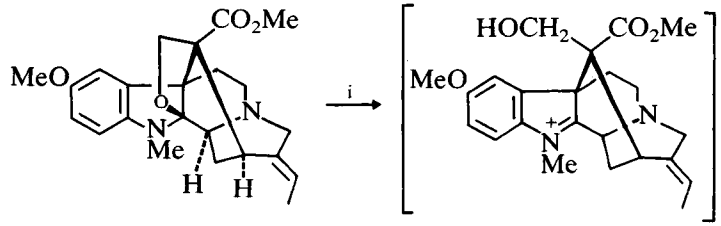


116

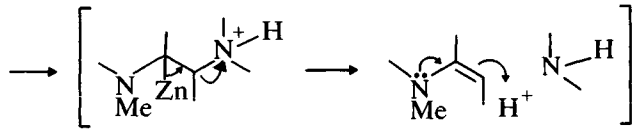
Scheme 34. Reagents: i, NaOH, r.t.; ii, protic solvents; iii, $KOBu^t$, Bu^tOH, Δ; iv, H_2, Pt, EtOH.

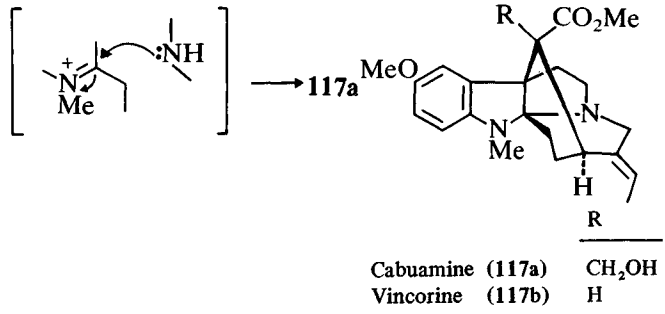
at C-3 (see above), that establishes the existence of the 7,16 bond. The hydrogenolytic cleavage of the 21,N_b^+ bond leaves behind an N_a.C.N_b unit now detectable by the hypsochromic shift in acid solution [λ_{max} 248, 309 nm (log ϵ 3.9, 3.6) → λ_{max} 238, 297 nm (log ϵ 3.9, 3.5)], first recognized[80h] in the eserine series.

The chemical evidence summarized above and an assumption of a tryptamine unit lead to a part structure (**116**) in which only C-14 and C-15 are missing. Incorporation of these carbon atoms into the formulation on the assumption that an unrearranged corynantheine carbon skeleton is present gives the complete structure.



O-Methylakuammine (**101b**)





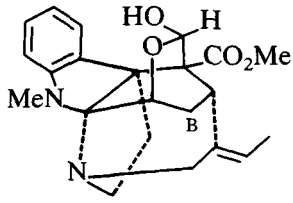
Cabuamine	(**117a**)	CH_2OH
Vincorine	(**117b**)	H

Scheme 35. Reagent i: Zn, AcOH.

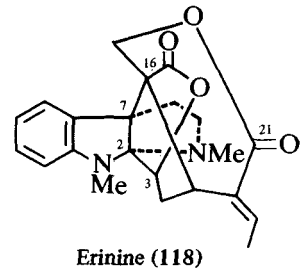
Structures of the echitamine type, with a 2,N_b bond, have been derived in the laboratory (Scheme 35) from bases with the akuammiline C/N ring skeleton and also having unsaturation at the 2,N_b position, by treatment with zinc amalgam and sulfuric acid,[77a] zinc-acetic acid,[85] or Raney nickel.[77b] A sequence (Scheme 35) involving reductive cleavage of the 3,N_b^+ link followed by N_b to C-2 bonding is envisaged, and illustrated for the conversion[85] of *O*-methylakuammine (**101b**) into cabuamine (**117a**) [from *Cabucala erythrocarpa* var. *erythrocarpa* (Vatke) Mgf.[85]].

Cabuamine was transformed in turn into vincorine (**117b**) [from *Vinca minor* L.[86a] (= vincovine[86b])] by base-catalyzed deformylation.[85]

Corymine and *O*-acetylcorymine from *Hunteria umbellata* (K. Schum.) Hall f. also contain the $N_a.C.N_b$ system. The former was shown by X-ray crystallographic analysis[81a] to have a structure (**105a** ≡ **105b**) closely related to that of echitamine, but one which also incorporates a cyclic hemiacetal, formed from the C-3 hydroxyl group and an aldehyde group attached to C-16.



Corymine (105b)

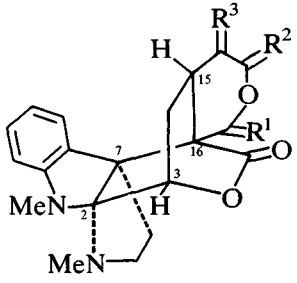


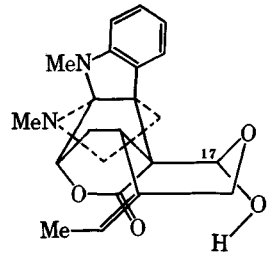
Erinine (118)

Erinine (**118**) and erinicine (= 19,20-dihydroerinine) are two further alkaloids of *H. umbellata*, which also incorporate $N_a.C.N_b$ units. Their structures were demonstrated[87] mainly by mass spectral comparisons with echitinolide (**115**) and derivatives. Eripine (**106**),[82] yet another base from this plant, could be thermally cyclized to a mixture of erinine and an unnatural 19,20 double bond isomer. Isocorymine (from *H. umbellata*) has a related structure (**107**).[81b]

Interestingly, while retaining the ubiquitous configuration at C-15, the complex ring system of erinine, erinicine, and isocorymine can be constructed in two ways, which differ in the configurations at the pair of centers, C-3 and C-16. A priori, all three alkaloids could have either stereochemistry, especially since in this subgroup alkaloids epimeric at C-16 have been isolated (see below). The conformation depicted in **119a–e** shows one of the two C-3/C-16 possibilities. That the relative stereochemistry shown in **119b** and **119c** represents erinine and erinicine was originally suggested[87a] simply on the basis of ir comparison with an echitinolide derivative. Later a detailed 300 MHz nmr study[87b] using decoupling experiments and transient nOe measurements confirmed the original assignments and proved all details as shown in **119a** and **119d** for isocorymine, **119b** for erinine, and **119c** and **119e** for erinicine. Conformation **119a–c** shows the configurations at C-3 and C-16, whereas **119d** emphasizes the configuration at C-17 and the geometry about the 18,19 double bond in isocorymine (erinine has the same configuration about the double bond), and **119e** illustrates the configuration at C-20 in erinicine. This study shows that three-dimensional detail, approaching that available from X-ray crystallographic studies in the solid state, can be achieved in suitable cases by nmr measurements in solution.

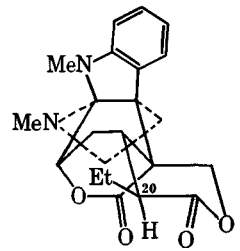
O-Methylakuammine (**101b**), isolated[88] as a natural product from *Cabucala fasciculata* Pichon, was first obtained[77b] by phenolic *O*-methylation of akuammine (**101c**) with diazomethane. It was hoped to demonstrate the suspected common skeleton of akuammine and pseudoakuammigine (**101a**), alkaloids from *Picralima*





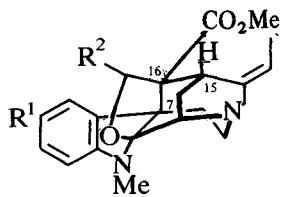
Isocorymine (119d)

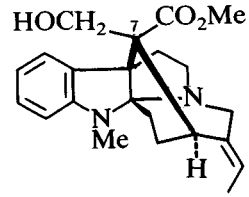
		R^1	R^2	R^3
Isocorymine	(119a)	H,OH	H_2	CHMe
Erinine	(119b)	H_2	O	CHMe
Erinicine	(119c)	H_2	O	H, Et



Erinicine (119e)

nitida Stapf,[77c] by removing the hydroxyl group from the former. However, when the phenolic *O*-tosylate **(101d)** of akuammine was treated with Raney nickel, not only did the desired oxygen removal take place, but the reductive rearrangement (see above) to an $N_a.C.N_b$ type also occurred and isodihydropseudoakuammigine **(117c)** resulted;[77b] this could also be obtained from pseudoakuammigine **(101a)** by similar treatment. Some other reactions of pseudoakuammigine are shown in Schemes 36 and 37.





117c

		R^1	R^2
Pseudoakuammigine	(101a)	H	H
O-Methylakuammine	(101b)	OMe	H
Akuammine	(101c)	OH	H
	(101d)	OTs	H
17-Hydroxypseudoakuammigine	(101e)	H	OH

The presence of an $N_a.C.O$ system in pseudoakuammigine **(101a)** (Scheme 36) was deduced[77a,b] by uv spectroscopy: the alkaloid shows indoline absorption [λ_{max} 245, 291 nm (log ϵ 4.0, 3.6)] in neutral solution, only slightly changed by

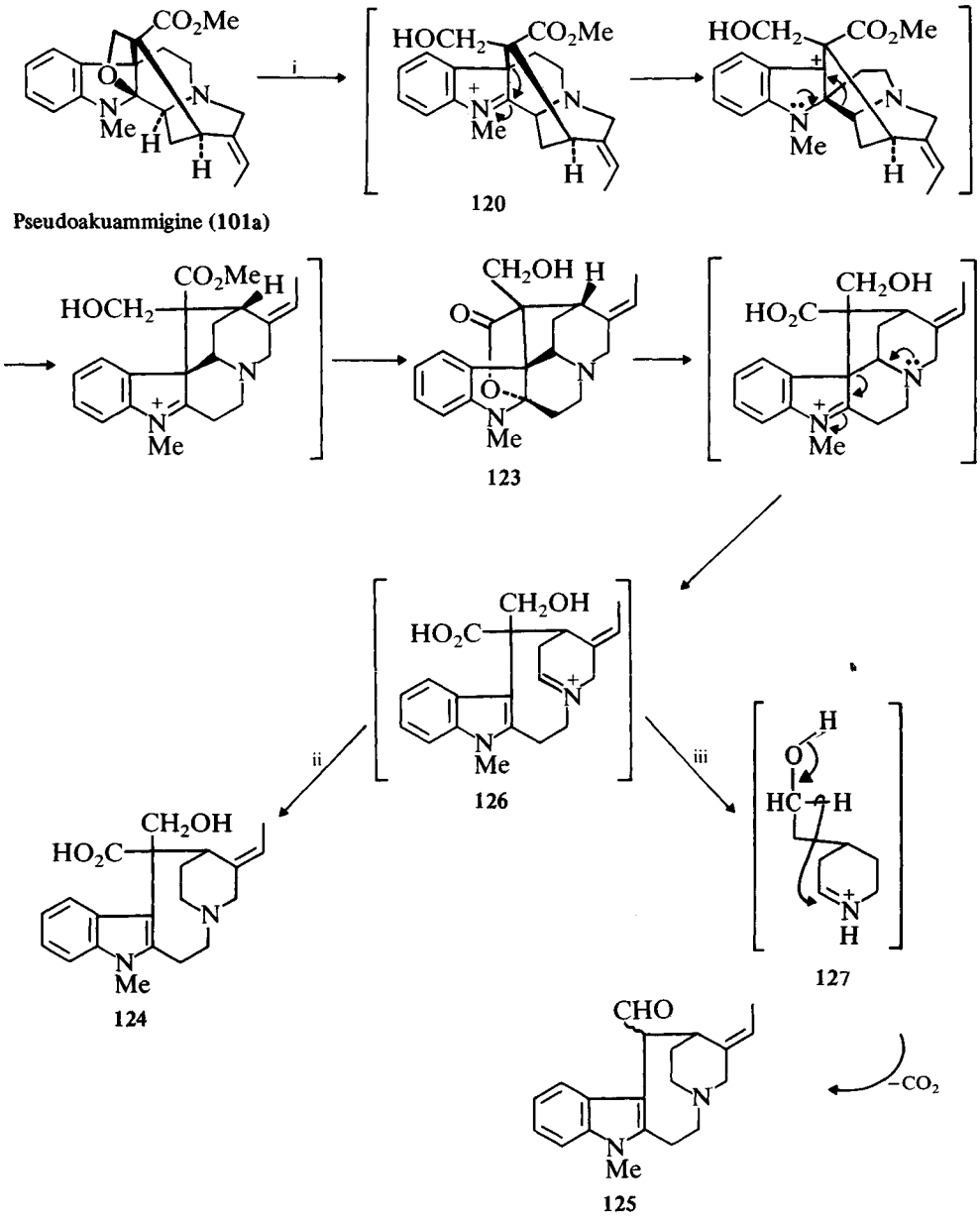
addition of dilute acid, but it exhibits a marked, reversible change in strong acid as a result of being converted into a ring-opened indoleninium cationic species (**120**) (Scheme 36), λ_{max} 241, 245, 306 nm (log ϵ 3.5, 3.6, 3.6). The carbinolamine ether was cleaved on lithium aluminum hydride reduction[77d] to pseudoakuammigol (**121a**) (Scheme 37), which, since it formed[77b] an isopropylidene derivative on reaction with acetone but was not cleaved by periodate, must be a 1,3-diol, thus establishing the 1,3 relationship between ether and ester carbon atoms. As with echitamine, the base-catalyzed loss of formaldehyde from isodihydropseudoakuammigine (**117c**) also showed[77a] the presence of the $HOCH_2.C.CO_2Me$ unit in **117c**, and therefore in the original alkaloid. The 19,20-double bond is hindered in this pentacyclic system; in neither pseudoakuammigine nor pseudoakuammigol, nor indeed in the hydrogenolysis product (**122**), where one ring has been cleaved, could the double bond be catalytically reduced.

The mass spectral fragmentation of pseudoakuammigol (**121a**) and picralinol (**121b**) (see below) was shown[78a] to be consistent with the proposed structures,[77a,78a,c] the fragmentation pattern being verified by a study of deuterated analogues where lithium aluminum deuteride was used to introduce the label variously at positions 2, 5, 17, and 22. The main peaks in the spectra result from fragmentations (→ **121c–e**) initiated by fission (arrows on **121a, b**) of the six-membered carbocyclic ring.

Although it has since proved most intriguing, the acid-promoted rearrangement[77b] of pseudoakuammigine into apopseudoakuammigine (**123**) (Scheme 36), a γ-lactone, was at the time confusing from the structural analysis viewpoint. The process was so efficient and clean that it was judged unlikely to have been the result of a deep-seated skeletal rearrangement (→ **120** → **123**), such as is now known to be the case. With the unexpected, easy formation of an *indolic* amino acid (**124**) by treatment of apopseudoakuammigine with potassium borohydride, the mystery deepened. In an analogous reaction apopseudoakuammigine reacted with hot sodium hydroxide (in pseudoakuammigine itself the hindered ester is completely resistant to such treatment) to give an indolic aldehyde (**125**). Both indole-forming sequences are explained[77b] as involving a retro-Mannich intermediate (**126**) which is then reductively trapped by borohydride (→ **124**) or by intramolecular hydride transfer (arrows on **127**) and decarboxylation, respectively.

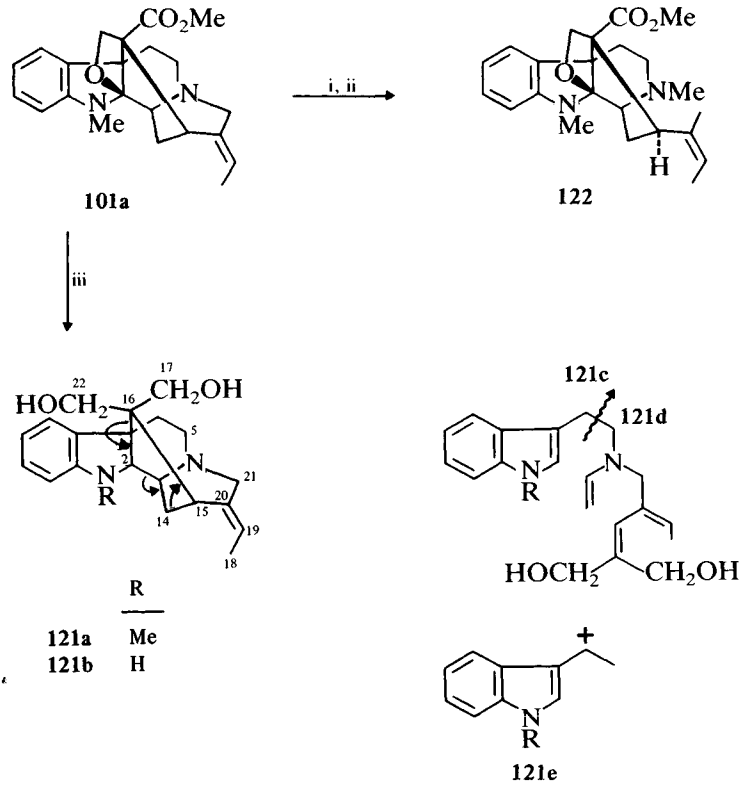
17-Hydroxypseudoakuammigine (**101e**), from *Hunteria congolana*, could be converted into pseudoakuammigine by reduction with triethylsilane and trifluoroacetic acid. Its isomer, lanceomigine (**109**) (from *Alstonia lanceolata* v. Heurck et Müll.-Arg.),[77e] co-occurs with **101e** in *H. congolana*, and was similarly reduced to a crystalline deoxyketone (**128**) (Scheme 38), the structure of which was determined by the X-ray method.[77f] Although 17-hydroxypseudoakuammigine is quantitatively converted into **109** by treatment with 3 *M* hydrochloric acid, the latter is not an artifact, since it was isolated from the plant material even when acid was not used.

Some of the chemistry of picraline (**102a**), another alkaloid from *P. nitida*,[78b] is shown in Schemes **39–41**. Thus it could be converted into pseudoakuammigol (**121a**) by successive reduction to picralinol (**121b**), then (to introduce a methyl group) *O*- and *N*-formylation, followed by lithium aluminum hydride reduction.[78a]



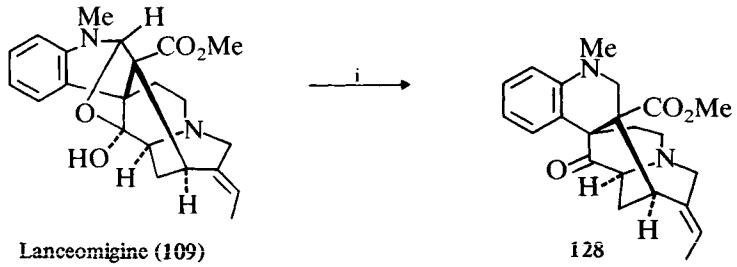
Scheme 36. Reagents: i, 3 *M* HCl, Δ; ii, $NaBH_4$, EtOH; iii, aq. NaOH, Δ.

This transformation established the common carbon skeleton for the two alkaloids and also that the cyclic ether in picraline is a double carbinolamine ether cleavable by lithium aluminum hydride. Since a shift of the uv spectrum in strong acid similar to that for pseudoakuammigine had been observed,[78d] it remained only to locate



R	
121a	Me
121b	H

Scheme 37. Reagents: i, MeI; ii, H_2, Pt, EtOH; iii, $LiAlH_4$.



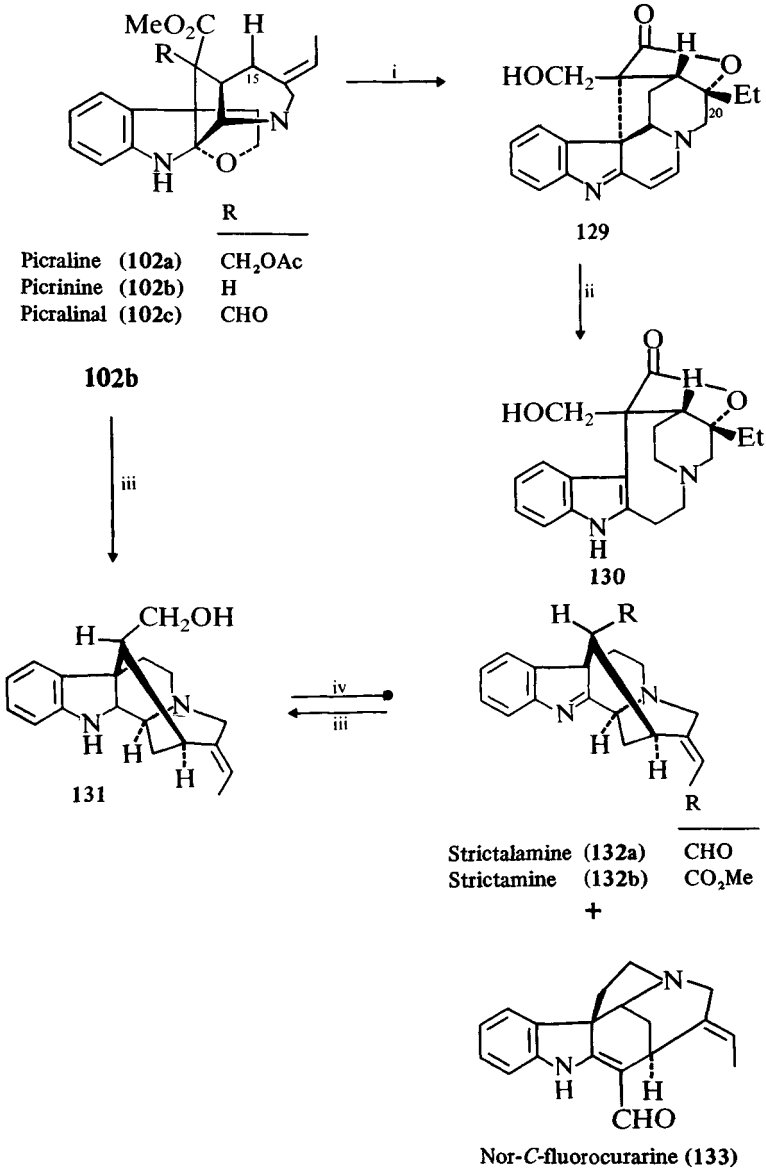
Scheme 38. Reagent i: Et_3SiH, CF_3CO_2H.

the other point of attachment of the ether bridge. Models indicated that this could be at C-5;[78d] confirmatory evidence was supplied by a ^1H nmr signal at δ 4.81, for the remaining C-5 proton.

Picraline undergoes a rearrangement[78c,d] involving a double Wagner-Meerwein shift, comparable to the formation of apopseuoakuammigine from pseudo-akuammigine, when heated in 3*M* hydrochloric acid (Scheme 39). The extra

oxygen is eliminated as water and lactonization takes place (→ **129**) at C-20 and not at C-2 as in the formation of apopseudoakuammigine. That lactonization *can* occur at C-20 is firm chemical evidence[78c] for the relative stereochemistry at C-16. The yellow product, flavopicraline (**129**), like apopseudoakuammigine, gave a ring-cleaved, colorless indole (**130**) on borohydride reduction.

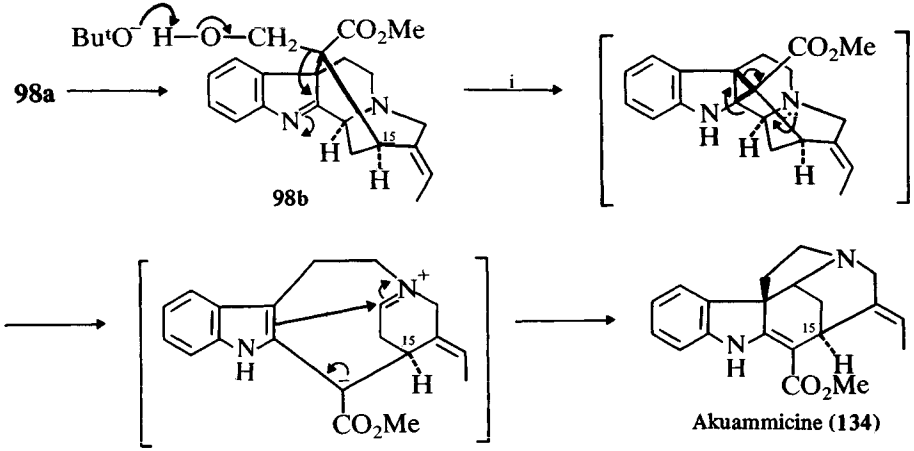
The absolute stereochemistry of picraline at C-15, and thus of the other centers



Scheme 39. Reagents: i, 3*M* HCl, Δ; ii, KBH_4; iii, $LiAlH_4$; iv, $KOBu^t$, fluorenone, PhH, Δ.

and of those bases interrelated with picraline, was unequivocally proved by transformation into nor-C-fluorocurarine (**133**), of known absolute configuration.[75c,91] Retro-aldol loss of formaldehyde from deacetylpicraline,[78d] or retro-Claisen fission of C-17 from picralinal (**102c**),[78d] affords picrinine (**102b**); both **102b** and **102c** are constituents of *Alstonia scholaris*.[89,90] Reduction of **102b** affords desformopicralinol (**131**) which, on Oppenauer oxidation, yields a mixture of the aldehyde (**132a**) and nor-C-fluorocurarine (**133**). Later the aldehyde (**132a**), named strictalamine, was isolated[91] from *Rhazya stricta* Decaisne. Co-occurring with it was strictamine (**132b**), the structure of which was determined by X-ray analysis.[91] Both the ester (**132b**) and the aldehyde (**132a**) were converted into desformopicralinol (**131**) by lithium aluminum hydride treatment. 16-Epipicrinine, named picralstonine, has also been isolated from natural sources[92] (*Alstonia macrophylla* Wall.); sodium methoxide equilibration of either **102b** or its 16-epimer favored picrinine by 9:1.

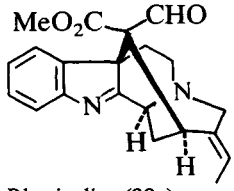
Strictamine was converted[91] into (−)-akuammicine by reaction with potassium *t*-butoxide, though not as efficiently as the transformation[75a] of akuammiline (from *P. nitida*)[75b] (**98a**), via deacetylakuammiline (**98b**). In the most reasonable mechanistic sequences for these processes producing akuamma skeletons, illustrated in Scheme 40 for akuammiline → (−)-akuammicine (**134**), it is clear that the absolute configuration at C-15 remains undisturbed.



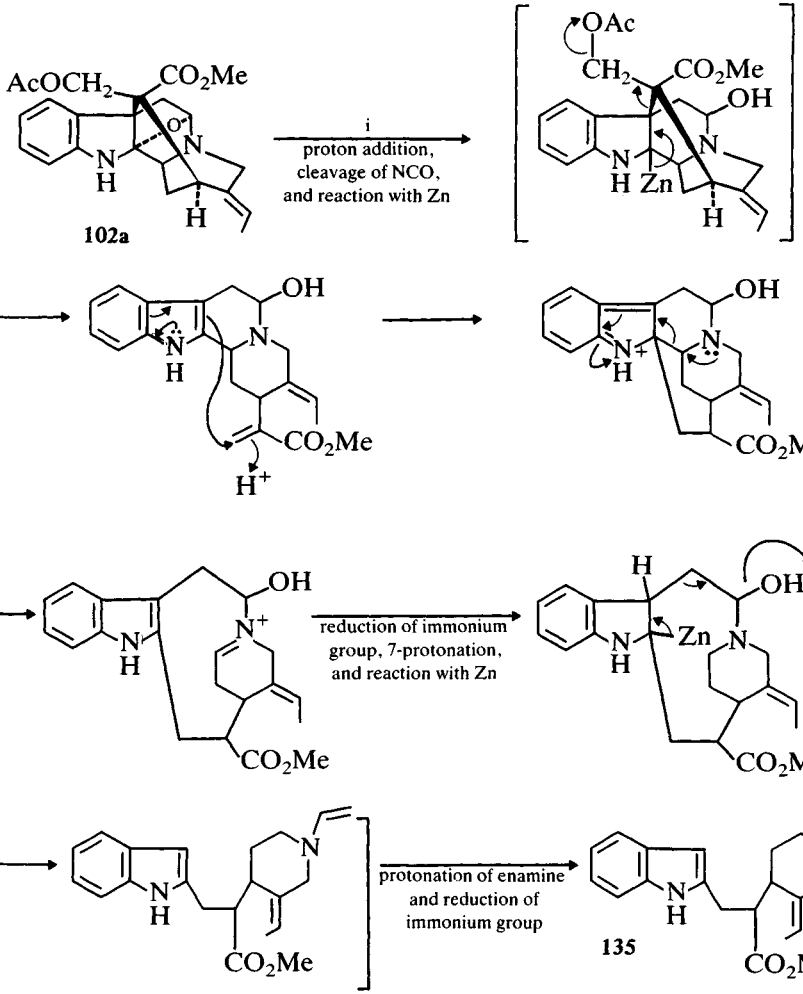
Scheme 40. Reagent i: KOBu^t, Δ.

The orientation of the C-16 substituents in akuammiline was supported[75b] by the signals for a relatively shielded acetyl methyl group (δ 1.55), and normal ester methyl group (δ 3.75), in its ^{1}H nmr spectrum. This shielding is attributed to the proximity of the acetate group and aromatic π system. Rhazinaline (**98c**), from *Rhazya stricta* Decaisne, has the opposite stereochemistry[93] at C-16, as evidenced by the relatively shielded ester methyl signal, at δ 3.16. Surprisingly, neither akuammiline nor rhazinaline could be converted,[75b] as was hoped, into

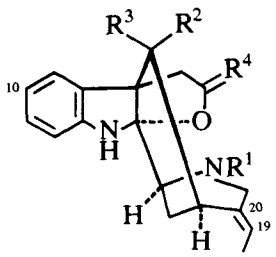
picralinol (**121b**) by lithium aluminum hydride treatment, the 2,N_a imine being so hindered as to be unreducible. Both reduction failures are in surprising contrast to the easy reduction of **132a** and **132b**, and of the C-2 carbinolamine ether function in picraline and pseudoakuammigine. Advantage could be taken of this inertness when picraline was transformed[75d] into akuammiline by vigorous reduction with sodium cyanoborohydride.

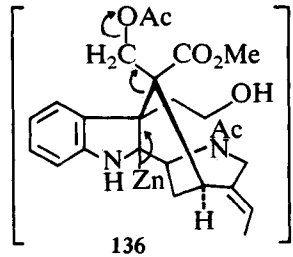


Rhazinaline (98c)



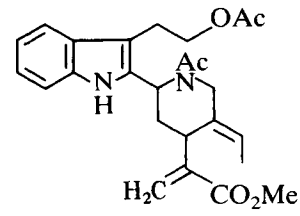
Scheme 41. Reagent i: Zn, conc. HCl.



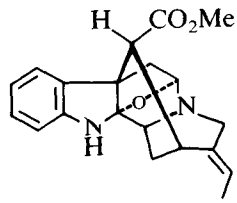


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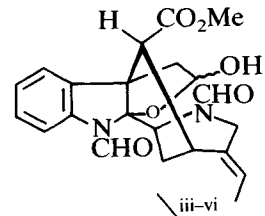
		R^1	R^2	R^3	R^4
Aspidodasycarpine	(108a)	H	CO_2Me	CH_2OH	H_2
	108b	Ac	CO_2Me	CH_2OAc	H_2
	108c	Me	CH_2OH	H	H_2
	108d	CH_2OH	CO_2Me	H	H_2
	108e	H	CO_2Me	H	H_2
Lonicerine	(108f)	H	CH_2OH	CO_2Me	H_2
				CH_2OCO	
Lanciferine	(108g)	Me	CO_2Me	PhCH=CH	O; 19,20-epoxy

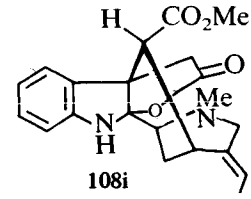


137



102b





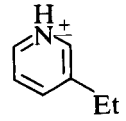
108i

Scheme 42. Reagents: i, Zn, HCl; ii, HCO_2H, Ac_2O; iii, CrO_3, H_2SO_4; iv, MeOH, NaOH; v, P_2S_5, PhH; vi, $NaBH_4$.

Perhaps the most extraordinary rearrangement (Scheme 41) discovered in investigations of picraline is the formation[78e] of the indole derivative **(135)** by reduction with zinc-concentrated hydrochloric acid; Scheme 41 provides a rationalization for this deep-seated change, which should be compared with the reductive cleavages of the $3,N_b$ bond and of diacetylaspidodasycarpine (see below).

A further base that has been interrelated with picraline is aspidodasycarpine (**108a**), from *Aspidosperma dasycarpon* A. DC.[84] This alkaloid was shown to be a secondary amine by acetylation to an amide (**108b**) and to be an N_a-carbinolamine ether by the lithium aluminum hydride reduction (→ **108c**) of the crystalline N_b-hydroxymethyl derivative (**108d**) of the amorphous base (**108e**) obtained by treatment of the alkaloid with sodium methoxide. Evidence[84] for the attachment of C-16 to C-7 was obtained in a most intriguing way: zinc-hydrochloric acid brought about a reductive fragmentation (Scheme 42), a process which may be visualized as the arrows on **136** indicate, with the formation of an indolic product (**137**). Reduction of picraline with potassium borohydride gave deformoaspidodasycarpine (**108e**).

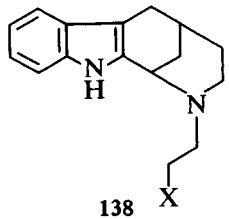
The C-16 epimer of aspidodasycarpine, named lonicerine (**108f**), was isolated from *Callichilia barteri* (Hook. f.) Stapf.[94] The mass spectra of the two alkaloids were almost identical, being dominated by a base peak at *m/e* 108 (**108h**). Deformylation of the N_b-acetyl derivatives of both aspidodasycarpine and lonicerine gave **108e**. Lanciferine (**108g**)[95] and its 10-methoxy and 10-hydroxy derivatives are more highly oxidized variations on the aspidodasycarpine theme; they were isolated from *Alstonia lanceolifera* S. Moore. Picrinine (**102b**) could be converted into a decinnamoyldeformolanciferine analogue by treatment with formic acid–acetic anhydride to cleave the N_b,C-5 bond (Scheme 42).



108h

B. Synthetic Studies

No synthesis, even of the pentacyclic skeleton of the akuammiline group nor of any of the variants discussed above, has been reported. Attempts to close the fifth ring in a model system (**138**) were unsuccessful.[96]



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CHAPTER VI

The Uleine-Ellipticine-Vallesamine Group

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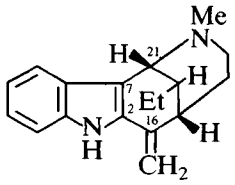
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These alkaloids are characterized by an unrearranged secologanin unit and the lack of one or both of the tryptamine bridge carbon atoms, C-5 and C-6.

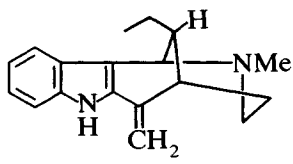
I. INTRODUCTION

A comparatively small group of indole alkaloids do not have a two-carbon link between the indole ring C-7 and the basic nitrogen atom; either one or both of the carbon atoms, C-5 and C-6, which in other indole alkaloids derive from the ethanamine unit of tryptamine or tryptophan, are absent. It has been shown,[1,2] in a couple of cases, that nonetheless these bases *are* biosynthesized from the usual precursors and thus that loss of one or both of these two carbon atoms occurs at a later stage. It seems very likely that this is true for all the alkaloids in this category and that earlier speculations[3,4a] that they are derived from a biosynthetic *precursor* of tryptophan should be set aside.

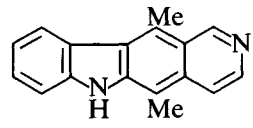
Four ring skeletal types are known, typified by the alkaloids uleine (**1a**), ellipticine (**2a**), vallesamine (**3**), and the quaternary salt (**4**). The only fundamental



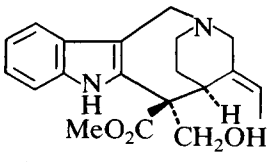
Uleine (1a)



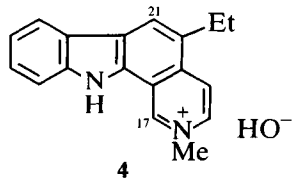
1b



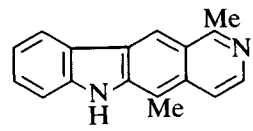
Ellipticine (2a)



Vallesamine (3)



4



Olivacine (5)

variation on any of these is exemplified by olivacine (**5**). One alkaloid in which C-5 and C-6 are also missing, but which is based on the *Aspidosperma* skeleton, is known[4b] (*Voacanga africana* Stapf.), but it does not fall within the scope of this chapter.

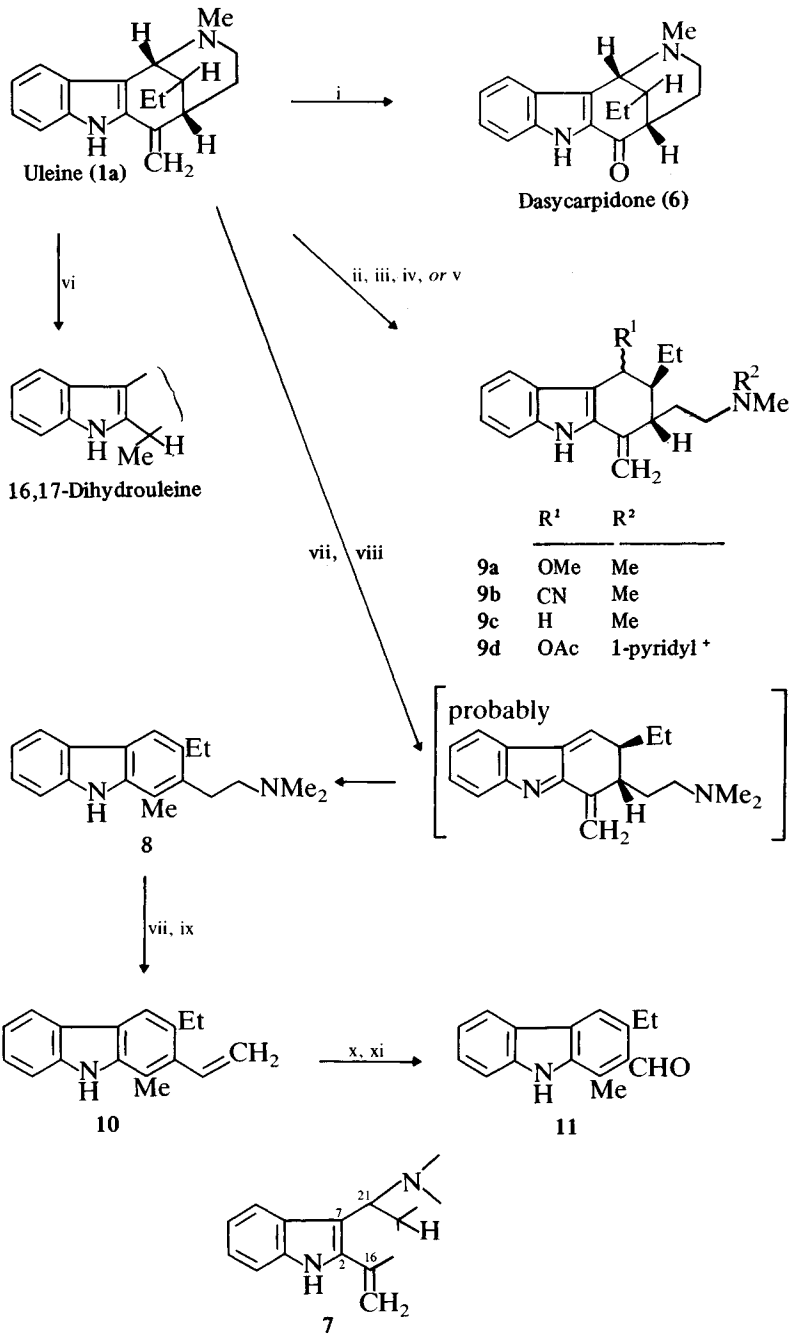
II. THE ULEINE GROUP: ALKALOIDS WITH 7,21 AND 2,16 BONDS BUT LACKING C-5 AND C-6

Several alkaloids, all from *Aspidosperma* species, have skeletons of the standard akuamma type, but without the ethanamine carbon atoms, C-5 and C-6. Of these the most widespread is uleine; it was also the first to be examined. In all the members of this subgroup the ester carbon (C-22) has been lost. In several, for example, dasycarpidone (**6**), C-17 has also been lost.

A. Structural Studies

The structure of uleine (**1a**), first obtained from *Aspidosperma ulei* Mgf., was determined[5b,6] at a time when the earliest impact of ^{1}H nmr spectroscopy on structure determination was being felt. The structure elucidation represents a didactically elegant example of the use of spectroscopy with degradation (Scheme 1), in particular, in this case, the Hofmann degradation, *the* classical degradative method of alkaloid chemistry.

The uv absorption of uleine, λ_{max} 309 (log ϵ 4.3), was recognized as clearly not that of a simple indole, but equally the absorption of 16,17-dihydrouleine, formed by reduction with hydrogen and platinum, *did* represent that of an unconjugated indole. The nature of the reducible, conjugated double bond was clarified by the observation of only two olefinic nmr signals (singlets at δ 4.98 and 5.27), replaced in the spectrum of the dihydro derivative by a methyl doublet, that is, $(C)_2C:CH_2 \rightarrow (C)_2CHMe$. The nmr spectrum had typical signals for indole *N*-



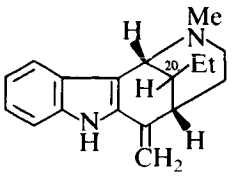
Scheme 1. Reagents: i, O_3, MeOH, $-70°C$; ii, MeI, then NaOMe; iii, MeI, then NaCN; iv, MeI, then $LiAlH_4$; v, Ac_2O, pyridine; vi, H_2, Pt; vii, MeI; viii, aq. NaOH, Δ; ix, KOH, $(CH_2OH)_2$, Δ; x, OsO_4; xi, HIO_4.

hydrogen and four aromatic protons, leaving a second hetero ring substituent to be identified. The link at the other pyrrole ring position was evidenced by a low-field doublet at δ 4.11 (*J* 2 Hz) in deuterochloroform, shifted[7] to δ 4.95 in acetic acid solution. These chemical shifts and the multiplicity showed the presence of basic nitrogen on an indolylic methine C-21 and thus the partial structure (**7**), in which the 7,21 and 2,16 linking (suggested by uv comparison with 2-vinylindoles), as opposed to the 7,16 and 2,21 alternative, remained to be finally confirmed. This confirmation came from a Hofmann degradation.

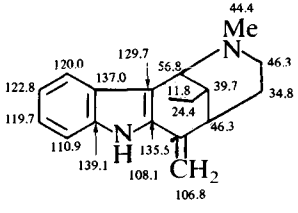
The presence of a gramine structural unit in uleine meant that its methiodide underwent a particularly easy Hofmann degradation when simply boiled in aqueous sodium hydroxide. The product was a carbazole (**8**), easily recognized by its distinctive uv absorption, in which the exocyclic double bond in uleine had migrated to generate the third aromatic ring. Thus in the Hofmann product nmr signals for an aromatic methyl and aromatic ethyl groups as well as for five aromatic protons could be seen, but no signals for olefinic hydrogen atoms. Later work[8] showed that it is possible to cleave the $21,N_b$ bond without migration of the exocyclic double bond; for example, by treatment of uleine methiodide at room temperature with sodium methoxide, sodium cyanide, or lithium aluminum hydride, or of uleine itself with acetic anhydride-pyridine, products **9a–d** could be obtained.

A second cycle of Hofmann degradation on **8** gave **10**, and osmium tetroxide then periodic acid cleavage of **10** gave the aldehydo-carbazole (**11**). Formation of a carbonyl-conjugated carbazole showed that the nitrogen had been attached to the carbazole nucleus via two carbon atoms. Ultraviolet comparisons with the four isomeric synthetic *C*-formylcarbazoles showed clearly that the degradation product was of the 2-formylcarbazole type. Thermal decarbonylation of **11** led to 3-ethyl-1-methylcarbazole, which was synthesized. The structure **1a**, apart from relative stereochemistry at C-20, was thus established.

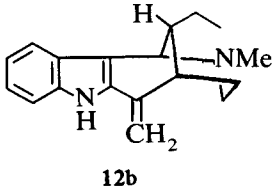
With the isolation[9] of 20-epiuleine (**12a**) from *Aspidosperma subincanum* Mart., comparisons allowed the assignment of the relative stereochemistry shown in **1b** to uleine: the ethyl methyl group, resonating at δ 0.82, is shielded by its proximity to the aromatic π-system (δ 1.08 in epiuleine), whereas the closeness of the ethyl group to the basic nitrogen (cf. **12b**) makes the rate of quaternization[10] of the epibase with methyl iodide 1/20 that for uleine. The absolute configuration of the uleines has not been established; that shown in **1a** and **12a** is the most likely on the basis of the common configuration at C-15 in other indole alkaloids. The ^{13}C shifts for uleine are shown in **1c**.



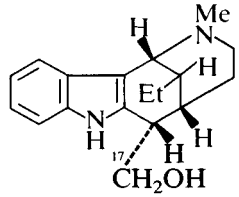
20-Epiuleine (**12a**)



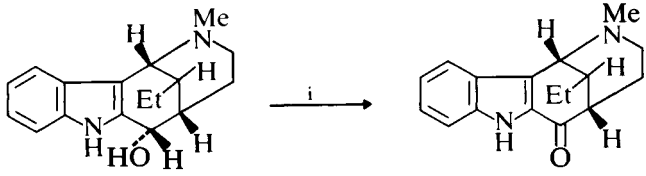
1c
(in $CDCl_3$)



12b



16,17-Dihydro-17-hydroxyuleine (13)



Dasycarpidol (14) 6

Scheme 2. Reagent i: CrO_3, py.

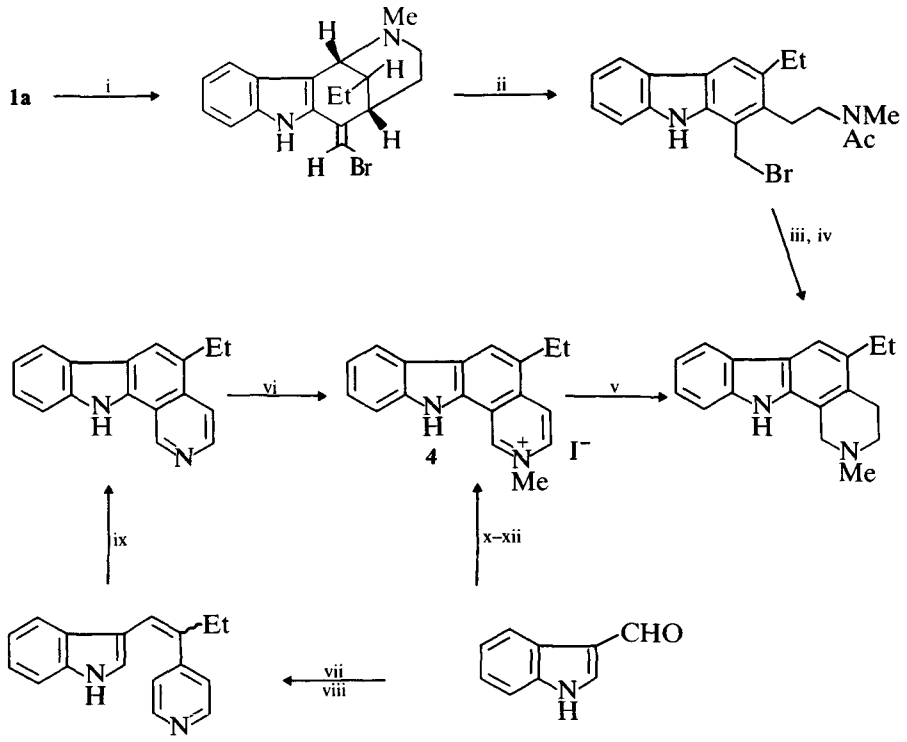
Dasycarpidone (**6**) (Scheme 2) was first obtained from *Aspidosperma dasycarpon* A. DC.; this base together with its 20 epimer were isolated[9] from *A. subincanum*. The 2-acylindole uv absorption [λ_{max} 316 nm (log ϵ 4.3)] and associated conjugated carbonyl absorption at 1640 cm^{-1} in the ir spectrum were clear guides to the structure. Taken together with the closely similar mass spectral fragmentation to that of uleine, which had previously been carefully studied,[8] and shown to be dominated by rearrangement to tricyclic carbazole species by cleavage of the 21,N_b bond, these data allowed the correct structure (**6**) to be postulated. The oxidative cleavage of C-17 that must occur during the biosynthesis of dasycarpidone was easily achieved in the laboratory by the ozonolysis of uleine, thus allowing the structure and relative stereochemistry of dasycarpidone and its 20 epimer to be confirmed.

Several variations on the uleine and dasycarpidone themes were also isolated[11a] from *A. dasycarpon*; these include N_b-demethyluleine and N_b-demethyldasycarpidone, a hydrated uleine, 16,17-dihydro-17-hydroxyuleine (**13**), synthezisable via hydroboration of uleine, and dasycarpidol (**14**), oxidizable to dasycarpidone with chromium trioxide and pyridine.

The salt **4**, from *A. gilbertii* A. P. Duarte,[11b] is structurally related to the uleine type, having N_b attached to C-17 and not to C-21. Indeed, this very change had been achieved[11c] in the laboratory before the salt (**4**) was isolated from natural sources. The salt was synthesized by a long conventional sequence[11c] from isoquinoline and by shorter sequences[11b,c] involving a photocyclization as a key step (Scheme 3).

B. Synthetic Studies

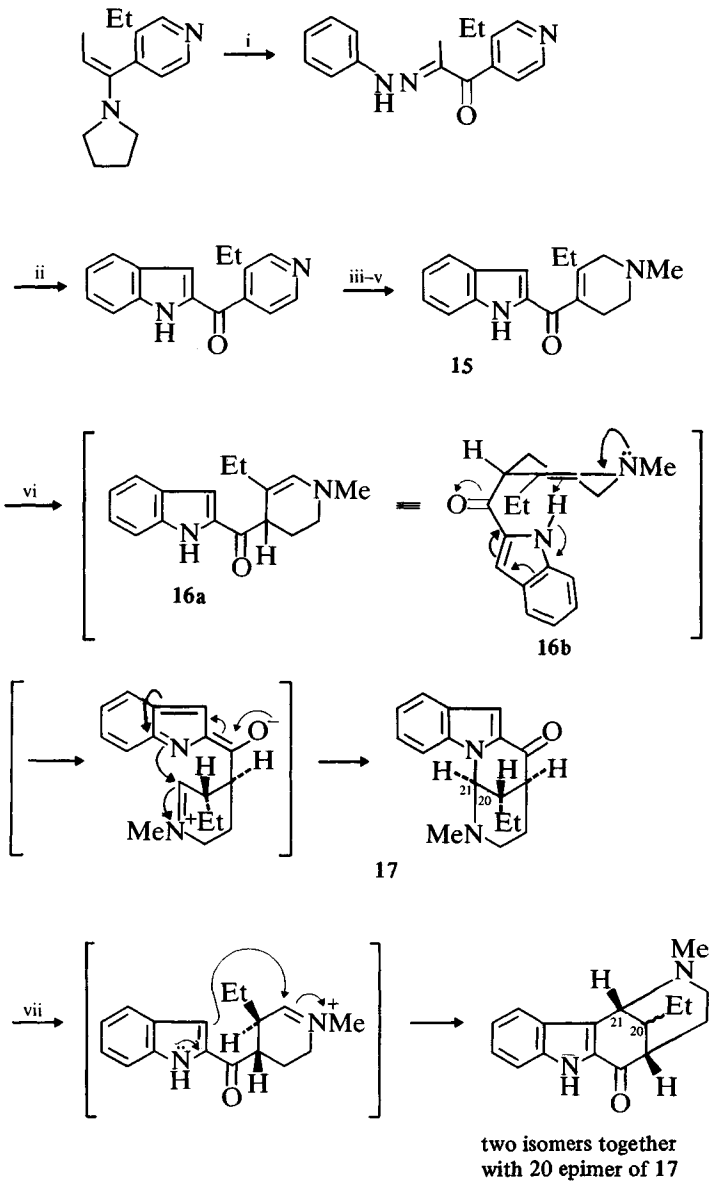
Several total syntheses[12–16] of (±)-uleine and (±)-dasycarpidone have been



Scheme 3. Reagents: i, Br_2, 0°; ii, AcCl, K_2CO_3; iii, NaOH, H_2O, MeOH, Δ; iv, AcOH, Δ; v, $NaBH_4$; vi, MeI; vii, 4-propylpyridine, Ac_2O, Δ; viii, NaOH; ix, EtOH, *hν*, O_2, I_2; x, 4-propylpyridine methiodide, piperidine; xi, *hν*, MeOH; xii, Al_2O_3.

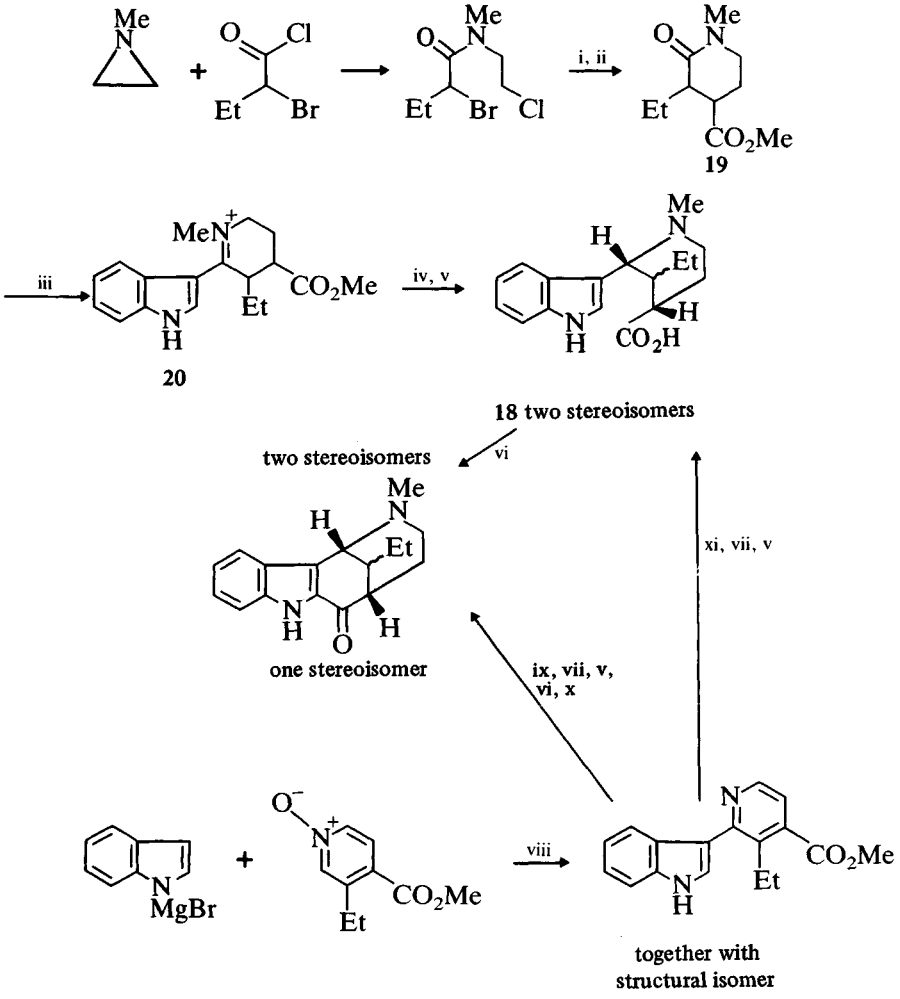
achieved, most of which employ a strategy of closing ring C from a β-substituted indole intermediate. The first synthesis,[12] however, utilized the opposite principle and as key intermediate, an α-substituted indole (**15**). At the heart of this first synthesis (Scheme 4) was the kinetically controlled deconjugation of the conjugated ketone (**15**), which thus forced the double bond into the cyclic enamine position (→ **16a**). This enamine could not be isolated as hoped, but proceeded via an intramolecular protonation (cf. **16b**) stereoselectively to **17**, in which an undesired 21,N_a bond had been made. However, acid treatment brought about ring opening, reversal of the 21,N_a bonding, and the build-up of 7,21 linked ketones via intramolecular Mannich attack at the indole β position. Unfortunately, a mixture of dasycarpidone and 20-epidasycarpidone was produced, together with some of the 20 epimer of **17**. It seems likely that the loss of stereochemical integrity involved equilibration to enamine **16a**. The synthetic dasycarpidone was converted into uleine by a Wittig reaction and the epiketone into the corresponding alkene using magnesium amalgam-diiodomethane; methyllithium addition and dehydration also effect[13b] the latter transformation.

Two of the successful approaches[13,14] (Scheme 5), which utilize a β-substituted indole intermediate (**18**), also had in common a PPA-induced intramolecular Friedel-



Scheme 4. Reagents: i, PhN_2^+; ii, PPA, Δ; iii, MeI; iv, $NaBH_4$; v, MnO_2; vi, $NaCH_2SO.Me$, DMSO, then H_2O; vii, 50% aq. AcOH, Δ.

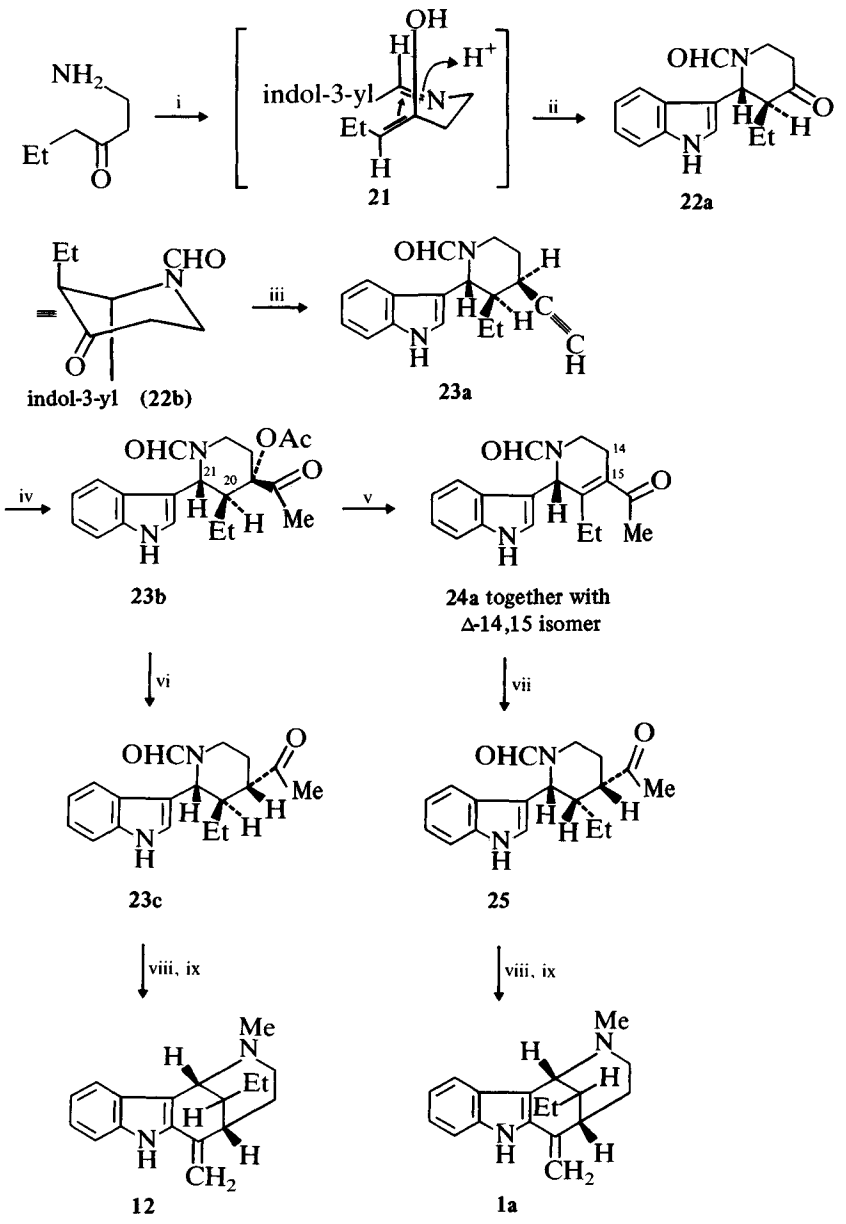
Crafts acylation of the indole α position to form ring C and provide the carbonyl group of the dasycarpidones. In the first[13] of these syntheses Dolby and Biere neatly introduced the piperidine fragment onto the indole β position by a Vilsmeier reaction with the cyclic amide **19**, followed by the borohydride reductive trapping of the immonium group in the intermediate **(20)** thus formed.



Scheme 5. Reagents: i, $CH_2(CO_2Me)_2$, NaOMe; ii, NaI, AcOH; iii, indole, $POCl_3$; iv, $NaBH_4$; v, aq. KOH; vi, PPA, Δ; vii, H_2, Pt; viii, PhCO.Cl; ix, HCl; x, HCHO, HCO_2H; xi, MeI.

The second method,[14] employed by Kametani and Suzuki to produce a stereoisomeric mixture of acids for cyclization, centered on the reaction of the indole Grignard reagent with a pyridine *N*-oxide in the presence of benzoyl chloride, but this reaction was not regioselective. Later it was shown[15] that by delaying the N_b-methylation to the final step nordasycarpidone and thence dasycarpidone could be produced selectively.

The synthesis[16a] with the most built-in stereochemical control is Büchi's sequence (Scheme 6), which again utilized a β-substituted indole intermediate, but which did not proceed via the dasycarpidones. The condensation of 3-formylindole with 1-aminohexan-3-one led to an imine, which on intramolecular Mannich reaction via a

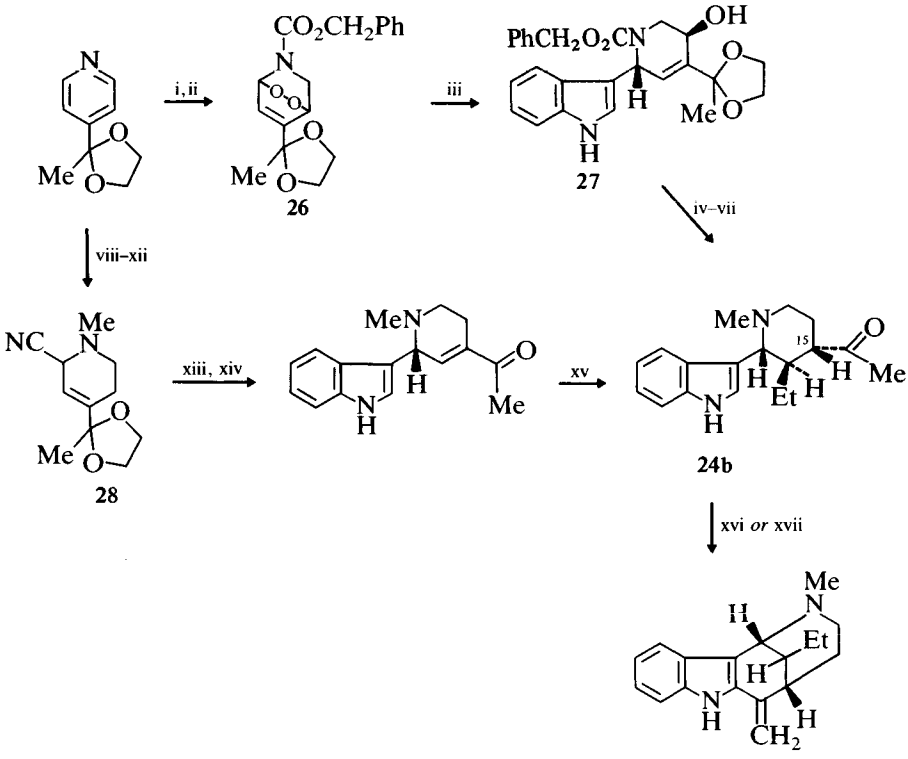


Scheme 6. Reagents: i, indol-3-yl.CHO, pH 9; ii, HCO_2H, Ac_2O; iii, HC:CK, Bu^tOH, THF; iv, $Hg(OAc)_2$, AcOH; v, 470°; vi, Li, liq. NH_3; vii, H_2, Pd, py; viii, BF_3; ix, $LiAlH_4$.

chair-like transition state (**21**) with the large substituents trans on the double bonds, gave a trans-piperidone. The N_b-formamide (**22a**) of this, employed rather than the methylated analogue for stability reasons, was shown to exist as a mixture of two chair conformations (**22b**), which differ in the orientation of the formyl

group (amide restricted rotation). Carbon atoms 16 and 17 were introduced by ethynylation in *t*-butyl alcohol-tetrahydrofuran, which generated **23a** by equatorial attack on **22b**. After reaction with mercuric acetate in acetic acid the acetoxy ketone (**23b**) was produced; reduction using lithium-ammonia then removed the acetoxy group and gave the thermodynamically stabler trans,trans ketone (**23c**). Cyclization and dehydration were induced by boron trifluoride, leading selectively to the epiuleine stereochemistry, requiring only lithium aluminum hydride reduction of the formyl group to complete the synthesis of 20-epiuleine.

In order to generate the uleine stereochemistry it was necessary to convert **23b** into a derivative containing cis hydrogens at positions 20 and 21 before closure of ring C. Pyrolytic elimination of acetic acid from **23b** gave **24a**, as well as some of the $\Delta^{14,15}$ isomer, and hydrogenation of **24a** then produced mainly the required cis,cis ketone (**25**) by cis addition of hydrogen from the side remote from the indole piperideine ring substituent. As before, boron trifluoride-catalyzed closure and lithium aluminum hydride reduction completed the sequence and gave uleine.

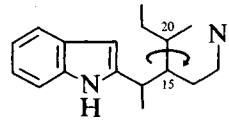


Scheme 7. Reagents: i, $ClCO_2CH_2Ph$, $NaBH_4$; ii, $^1O_2$; iii, indole, $SnCl_2$; iv, TsOH, Me_2CO; v, Et_2CuLi; vi, H_2, Pd/C, MeOH, CH_2O; vii, NaOMe, MeOH; viii, MeI; ix, $NaBH_4$, EtOH; x, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2; xi, $(CF_3CO)_2O$, CH_2Cl_2; xii, KCN, H_2O, pH 4; xiii, indole, AcOH, H_2O; xiv, 10% HCl–H_2O; xv, EtMgBr, CuCl, THF, 0°; xvi, TsOH, CH_2Cl_2; xvii, TsOH, $CHCl_3$.

More recently two syntheses[16b,c] (Scheme 7) of 20-epiuleine have proceeded via **24b**, the N_b-methyl analogue of Büchi's intermediate, which was cyclized with elimination of water by means of *p*-toluenesulfonic acid (surprisingly without gramine-type cleavage of ring D). In both syntheses conjugate addition to an enone was employed in the generation of **24b**, although in earlier stages the two approaches adopted quite different, elegant methods for the production of β-substituted indole intermediates. The endoperoxide (**26**), prepared by reaction of a precursor dihydropyridine urethane with singlet oxygen, reacted stereoselectively with indole in the presence of stannous chloride to generate **27**, which was converted into **24b** in three steps.[16b] Alternatively, the masked dihydropyridine (**28**), obtained by Polonovski oxidation of an appropriate tetrahydropyridine derivative, followed by trapping and stabilization of the resulting immonium ion as a cyanide adduct, reacted with indole to give, after deprotection, an enone, conjugate addition to which produced **24b** (or its C-15 epimer).[16c]

III. THE ELLIPTICINE-OLIVACINE GROUP: ALKALOIDS WITH 2,16, 7,19, AND 21,N_b BONDS OR 2,16, 7,21, AND 19,N_b BONDS BUT LACKING C-5 AND C-6

Including N_b-metho salts and N_b-oxides, there are more than a dozen alkaloids in this subgroup, based on two similar skeletons, and exemplified by ellipticine (**2a**) and olivacine (**5**). The numbering makes clear the common carbon skeleton of the two types. Since, apart from the 7,19 bond in the ellipticine system, the atoms are arranged as in a standard *Strychnos* alkaloid, it seems probable that the olivacine type is the more highly evolved and is biogenetically derived from an intermediate of the skeletal form **29**, which originates from an intermediate of the ellipticine skeletal type by obvious ring openings. Rotation about the 15,20 bond in **29**, followed by recyclization, then leads to the olivacine structural type.



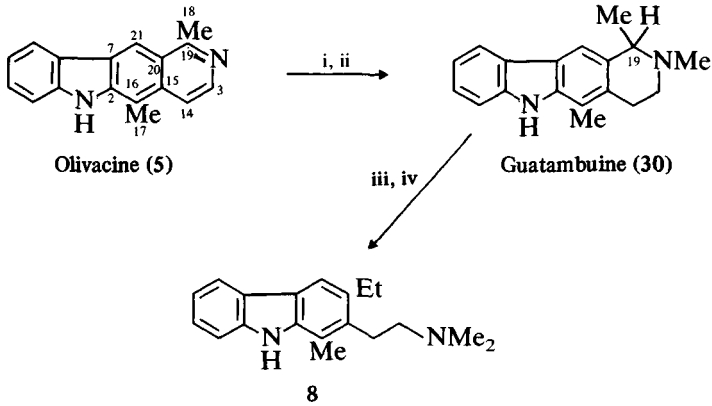
29

Note that the biogenetic numbering used here differs from the numbering system most often used for these alkaloids in the chemical literature, which is the systematic numbering of the pyrido[4,3-*b*]carbazole skeleton, as shown on **2b**.

A. Structural Studies

Ellipticine (**2a**) and olivacine (**5**) are high melting, pale yellow alkaloids originally isolated from *Ochrosia elliptica* Labill.[17a] and *Aspidosperma olivaceum* Muell-

Arg.,[17b] respectively. Ellipticine is a widely occurring base; recently, for example, it has been shown to be the major bark alkaloid of both *Strychnos dinklagei* Gilg.[18a] and *Ochrosia moorei* F. Muell.[18b]



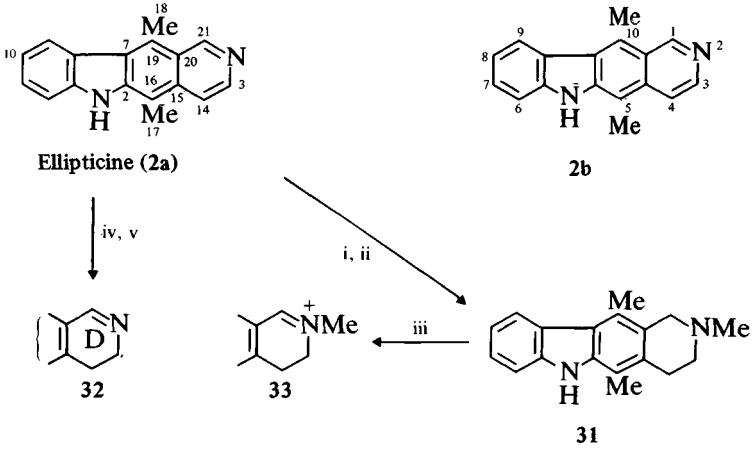
Scheme 8. Reagents: i, MeI; ii, $NaBH_4$; iii, Hofmann degradation; iv, H_2, Pt.

The evolution of the correct formulation for the tetracyclic ring systems of these alkaloids began with a comparison[19,20] of olivacine (**5**) with guatambuine (**30**), from *A. ulei*.[5b] Dehydrogenation of guatambuine gave olivacine; conversely, borohydride reduction of olivacine methiodide gave (±)-guatambuine, which is thus N_b-methyl-3,4,14,19-tetrahydroolivacine (Scheme 8).[19,20] In contrast to olivacine, guatambuine had a uv absorption which could be recognized as that of a straightforward carbazole, with which the basic nitrogen is not conjugated. However, that N_b *did* form part of the chromophore of olivacine itself was shown by the very characteristic uv spectrum, λ_{max} 224, 239, 269, 277, 288, 293, 315, 330, and 345 nm (log ϵ 4.3, 4.2, 4.7, 4.9, 3.6, 3.7, 3.5, and 3.6), which undergoes a bathochromic shift in acid solution [λ_{max} 242, 307, 351, and 412 nm (log ϵ 4.5, 4.9, 3.8, and 3.6)]. It could be concluded then that in olivacine a pyridine ring was fused to a carbazole nucleus, in one of the six possible orientations *not* having the basic nitrogen atom directly linked to the carbazole nucleus.

Hofmann degradation[21] of guatambuine methiodide led to the same dimethylaminoethylcarbazole (**8**) as had been obtained from uleine. Since two methyl groups had been identified in olivacine and since naturally occurring guatambuine is optically active, this degradation meant that N_b had to be attached to C-19, and not to C-17. Thus the pyrido[4,3-*b*]carbazole formulation, which had previously been assigned by a uv spectral comparison[19] with available, synthetic pyridocarbazoles, was unambiguously corroborated.

The related alkaloid ellipticine (**2a**) has uv absorption superimposable on that of olivacine in neutral and acid solution, and was also shown to have two *C*-methyl groups. It could be converted[17] into a naturally occurring[5b] N_b-methyltetrahydro derivative (**31**) (Scheme 9), an analogue of guatambuine, by reaction with methyl iodide and then sodium borohydride. Hence ellipticine has a structure (**2a**) isomeric

with that of olivacine; this was subsequently established by synthesis (see below), and much later confirmed by X-ray analysis.[22]

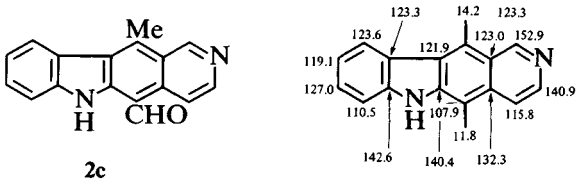


Scheme 9. Reagents: i, MeI; ii, $NaBH_4$; iii, $Hg(OAc)_2$; iv, H_2, Pt; v, 9,10-phenanthraquinone.

10-Methoxyellipticine occurs[23] as major base in *Excavatia coccinea* (Tejs et Bin) Mgf. The position of the oxygen function was indicated[23] by the nmr spectrum of its N_b-methyltetrahydro derivative and confirmed by a total synthesis[24e] starting from 5-methoxyindole. It is interesting that rats fed with ellipticine excrete[25a] mainly 10-hydroxyellipticine, together with a smaller quantity of the 12-hydroxy derivative, whereas the microbiological transformation[25b] by *Aspergillus alliaceus* gives, as well as the 10-hydroxy derivative, its 11-hydroxy isomer as minor product.

Both 3,14-dihydroolivacine[18] and 3,14-dihydroellipticine (**32**) are natural bases; synthesis[26] of the latter from the fully aromatic molecule was achieved by catalytic reduction to the tetrahydro derivative and then partial reoxidation using 9,10-phenanthraquinone (Scheme 9). The quaternary metho salt of 3,14-dihydroellipticine also occurs naturally.[26] This salt (**33**) was prepared[26] from **31** by oxidation with mercuric acetate. The *N*-oxides of ellipticine and olivacine have been isolated from *Ochrosia vieillardii* Guill.[27] and *Aspidosperma nigricans* Handro,[28a] respectively.

An aldehyde in which one of the two methyl groups of ellipticine is at a higher oxidation level was isolated[28b] from *Strychnos dinklagei*; this aldehyde could be produced by chromium trioxide-sulfuric acid oxidation of ellipticine and was assigned structure **2c**, which seems reasonable on biogenetic grounds.



An analysis[29] of the ^{13}C chemical shifts of the pyrido[4,3-*b*]carbazole alkaloids has been made; the figures on **2d** are typical values.

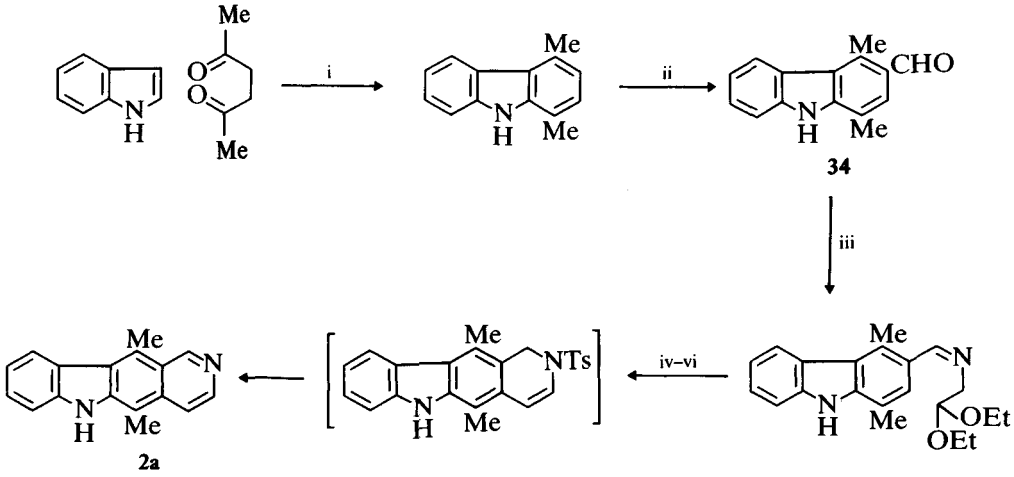
B. Synthetic Studies

A great deal of effort has been expended[24a–z] on the synthesis of the pyrido-[4,3-*b*]carbazole alkaloids. This large synthetic effort stems partly from biosynthetic interest in these bases, partly from the relative simplicity of the synthetic problem, since it has no stereochemical complications, and partly, and especially, from the later discovery of the anti-cancer activity[30] of ellipticine, 10-methoxyellipticine, olivacine, and their analogues. Some of the published syntheses are more efficient than others, some considerably longer, and some more easily modified for the synthesis of analogues for biological evaluation. Restrictions on space permit a detailed discussion of only some of the syntheses in the literature; the selection given below is thus somewhat arbitrary.

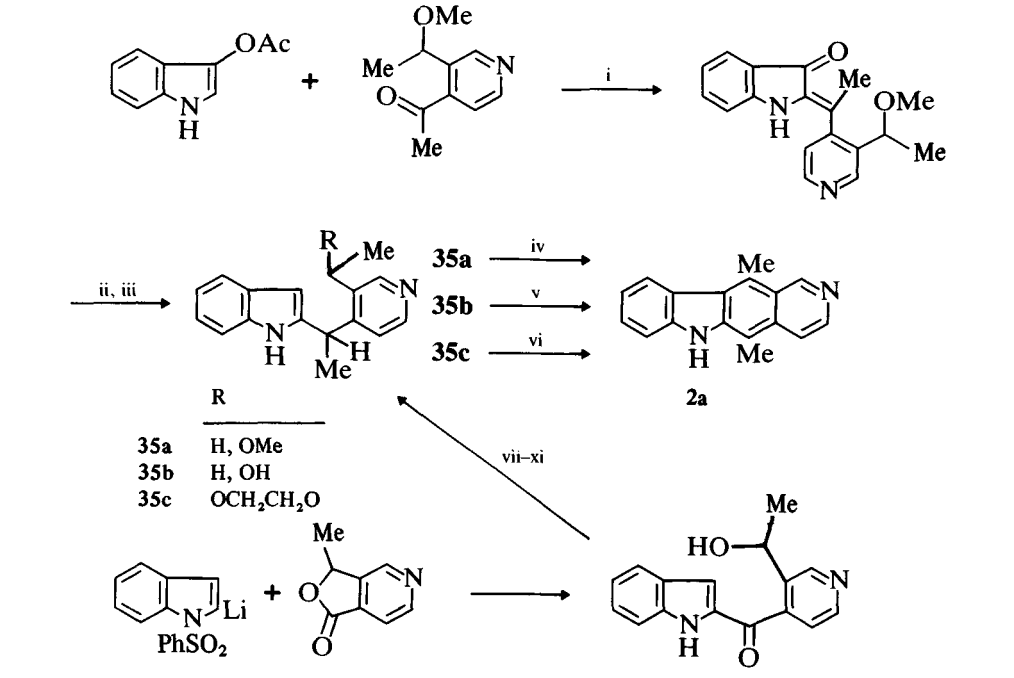
The first synthesis of ellipticine, although short, was very low yielding, but served to prove the structure of the alkaloid,[24a] although the more orthodox route of Cranwell and Saxton[24b] provided a thorough confirmation. This early route, especially as later improved,[24c,d] remains an efficient process (Scheme 10) compared with several that came later. 1,4-Dimethylcarbazole was subjected to Vilsmeier formylation, it being correctly predicted that electrophilic attack would occur in the more reactive dimethyl-substituted ring and also para to the nitrogen. Since the synthesis was originally intended as structure proof for the alkaloid, the position of the introduced formyl group was rigorously proved by reduction to the known 1,3,4-trimethylcarbazole. The pyridine ring was then constructed, as in a Pomeranz-Fritsch isoquinoline synthesis, by condensation of the aldehyde (**34**) with aminoacetal and cyclization. Although the imine condensation product can be cyclized using orthophosphoric acid,[24c] the most efficient sequence[24d] involves reduction, N_b-tosylation, closure, and elimination of *p*-toluenesulfinic acid. Ring A-substituted dimethylcarbazoles, for use in the Saxton route, are best prepared by the Borsche carbazole synthesis; 10-methoxyellipticine was synthesized[24e] in this manner.

Nearly all other approaches to ellipticine have utilized an intermediate in which the prospective ring D was linked through one carbon atom to indole at the α or β position and in which ring C was constructed at a late stage.

Sainsbury,[24f–h,v] Taylor and Joule,[24i] and Bergman and Carlsson[24k] have described sequences (Schemes 11 and 12) from either indole α- or indole β-substituted pyrid-3-yl or pyrid-4-yl ethanes. Condensation of 3-acetoxyindole with 3-(1-methoxyethyl)-4-pyridyl methyl ketone, followed by reduction and dehydration, afforded **35a**, which was cyclized and aerially oxidized to ellipticine.[24f] All three compounds, the ether (**35a**),[24g] alcohol (**35b**),[24h] and acetal (**35c**),[24i] have been converted directly into the alkaloid with, respectively, 60% hydrogen bromide, and aerial oxidation, acetic anhydride-dimethyl sulfoxide, and 0.2*M* hydrochloric acid (Scheme 11).

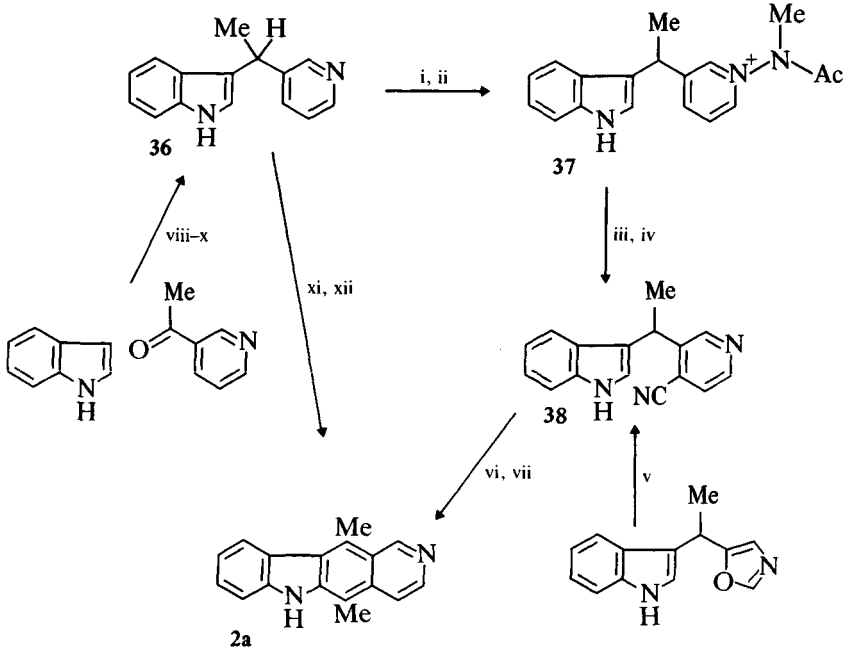


Scheme 10. Reagents: i, HCl; ii, $POCl_3$, PhN(Me)CHO; iii, $NH_2CH_2CH(OEt)_2$; iv, $NaBH_4$; v, TsCl; vi, dil. HCl, Δ.



Scheme 11. Reagents: i, aq. NaOH; ii, $NaBH_4$; iii, H^+; iv, 60% HBr, Δ; v, DMSO, Ac_2O; vi, 0.2*M* HCl, Δ; vii, MnO_2; viii, $(CH_2OH)_2$, TsOH; ix, NaOH; x, CH_2:PPh_3; xi, H_2, Pt.

The indolyl Grignard reagent could be β-alkylated with 3-(1-chloroethyl)pyridine to give the indol-3-ylpyrid-3-ylethane (**36**) (Scheme 12); a more efficient route[24v] was later developed in which 3-(pyrid-3-yl)butanal, prepared in three steps from 3-acetylpyridine, was used in a Fischer indole synthesis. A novel sequence involving an *N*-(*N*-methyl-*N*-acetylamino)pyridinium salt (**37**) was developed to allow introduction of C-16 as a cyano group (→ **38**); the nitrile was then transformed with methyllithium and then acid into ellipticine.[24f,g] The same nitrile has been prepared[24j] by reaction of 5-(1′-indol-3-ylethyl)oxazole with acrylonitrile. The intermediate (**36**) was later prepared by Bergman in an alternative way and neatly utilized in reaction with acetic anhydride-zinc to give ellipticine in one step.[24k]

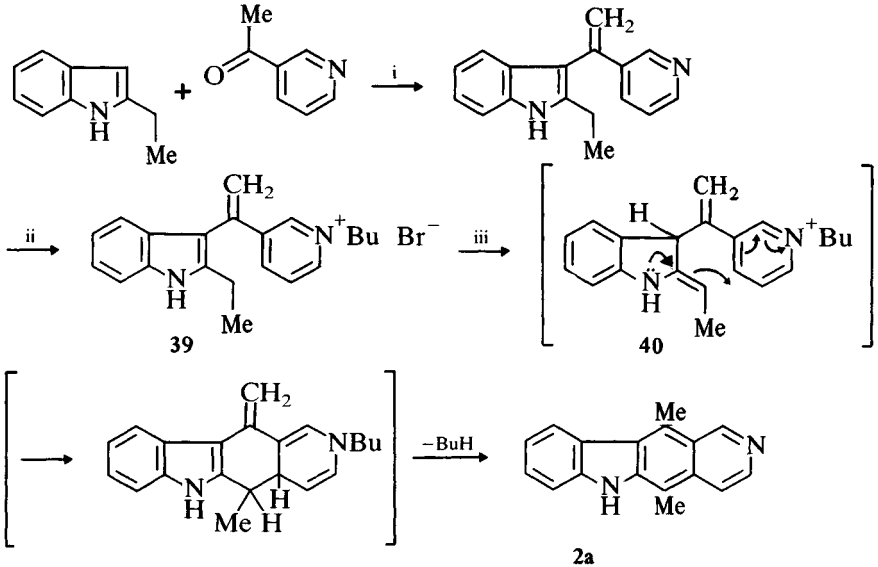


Scheme 12. Reagents: i, Ac_2O, NEt_3; ii, *O*-mesitylenesulfonylhydroxylamine, then Ac_2O, then MeI; iii, KCN, NH_4Cl; iv, $h\nu$, then Al_2O_3; v, CH_2:CH.CN, AcOH, Δ; vi, MeLi; vii, 20% AcOH; viii, HCl, EtOH; ix, Δ; x, H_2, Pd/C; xi, Zn, Ac_2O; xii, EtOH, Δ.

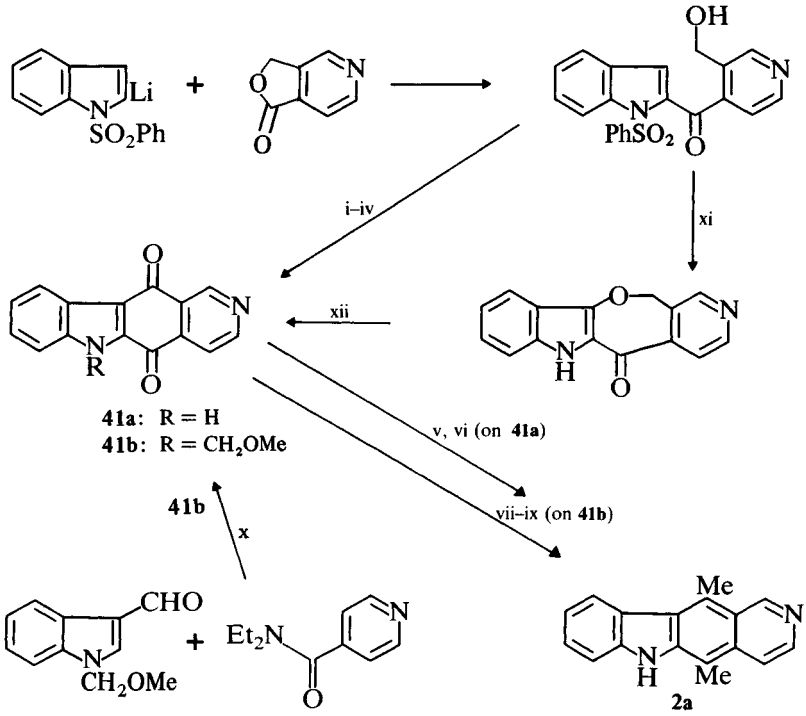
Another sequence by Bergman (Scheme 13)[24l] has the great advantage of a small number of steps; ring D was here again introduced at the required aromatic oxidation level. Thermolysis of salt (**39**) gave ellipticine via **40**, it is suggested, and thermal loss of butane.

The quinones **41a** and **41b**, independently prepared by Joule et al.[24m,w] and Watanabe and Snieckus[24n] as shown in Scheme 14, were both converted into ellipticine. Proceeding via the "ellipticine quinone," this route has potential for easily varying the alkyl side chains in the preparation of analogues of ellipticine.[24m]

Other workers have preferred to construct the skeleton of ellipticine using

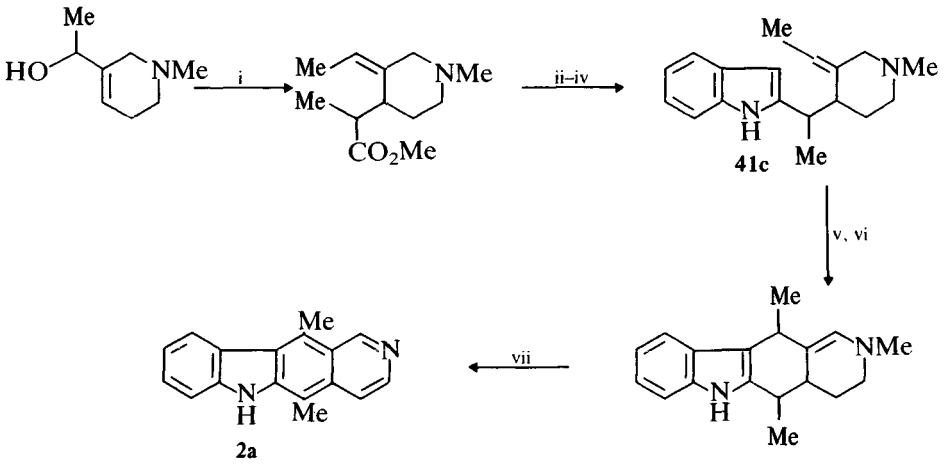


Scheme 13. Reagents: i, HBr, MeOH, Δ; ii, BuBr; iii, 350°+, 5 min.



Scheme 14. Reagents: i, MnO_2, ii, $(CH_2OH)_2$, TsOH; iii, NaOH, H_2O; iv, 1 *M* HCl, Δ; O_2; v, 3 × MeLi; vi, $NaBH_4$; vii, excess MeLi; viii, 47% HI, MeOH; ix, $SnCl_2$, AcOH, HCl, THF; x, 2 × *sec*-BuLi, then O_2; xi, 3 *M* NaOH, MeOH; xii, 3 *M* NaOH, MeOH, O_2, Δ.

intermediates with partially reduced D rings, leaving the task of providing the aromaticity in this ring to a late stage, there being no problem associated with a vigorous dehydrogenation step for the synthesis of the stable aromatic target molecule having no sensitive functional groups. It is extremely likely that biosynthetically the alkaloid is constructed with ring D at just such a lower oxidation level and, indeed, syntheses by Langlois and Potier[24o] and Besselièvre et al.[24p] were designed to mimic in part feasible biosynthetic steps. Intermediate **41c** was prepared by the route[24o] shown in Scheme 15. The desired electrophilic character at C-19 was then regioselectively introduced by partially oxidizing the piperidine ring using the modified Polonovski reaction.



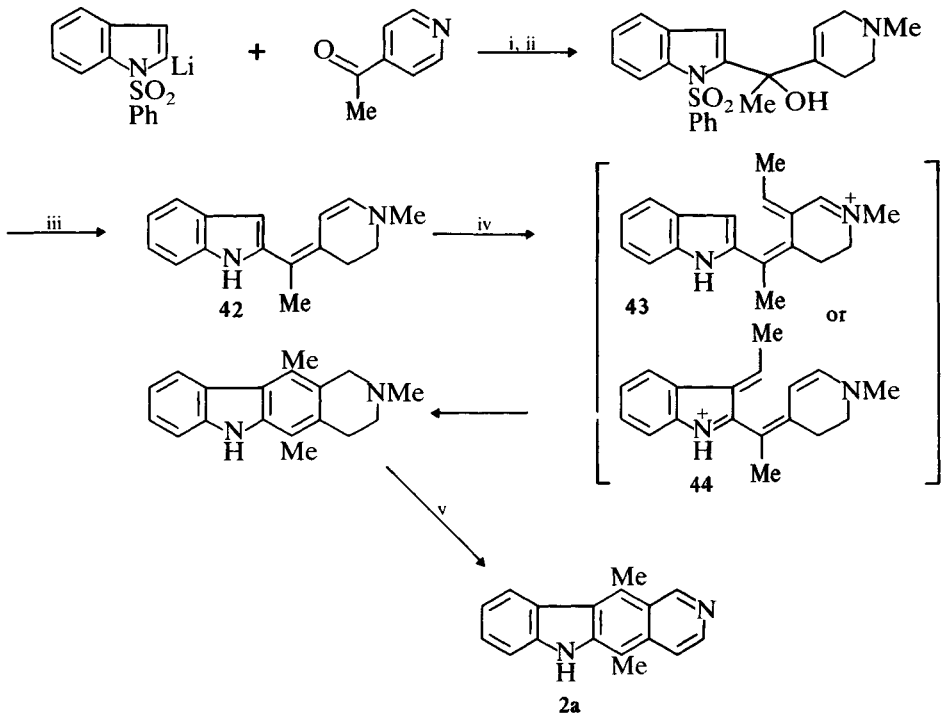
Scheme 15. Reagents: i, $EtC(OMe)_3$, $PrCO_2H$; ii, $Ba(OH)_2$; iii, MeLi; iv, $PhNHNH_2$, PPA; v, N_b oxidation; vi, $(CF_3CO)_2O$, 0°; vii, aromatization.

A related closure was effected[24p] (Scheme 16) by allowing the dienamine (**42**), generated by a sequence starting with the introduction of the indole α-substituent by reaction of α-lithiated 1-phenylsulfonylindole with 4-acetylpyridine, to react with the Mannich complex from acetaldehyde, dimethylamine, and acetic acid. Thus ring C was closed, via either **43** or **44**, or both, depending on which nucleophilic carbon the Mannich electrophile originally attacks.

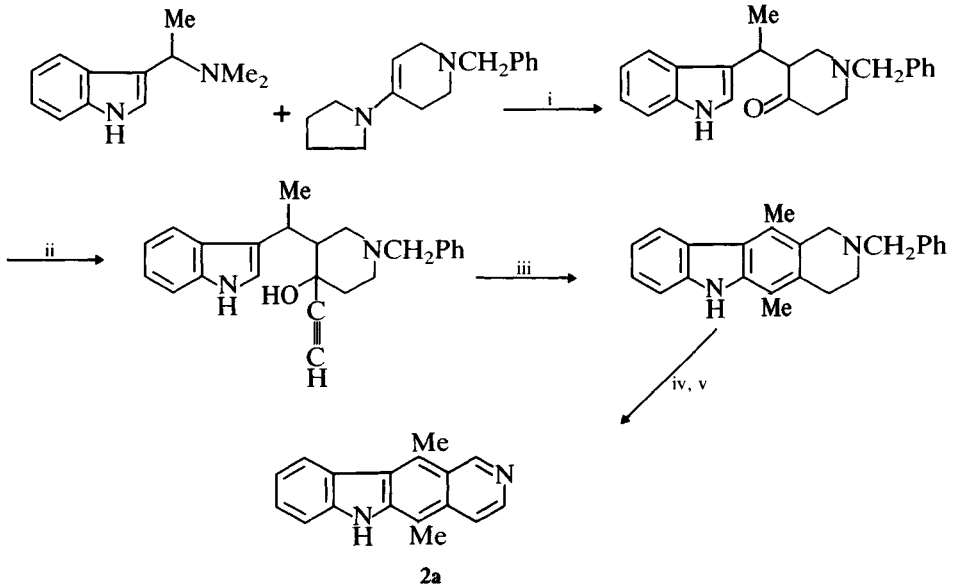
In Le Goffic's sequence[24q] also, ring D was introduced in a reduced form; 3-dimethylaminoethylindole was used to alkylate 1-benzyl-4-piperidone pyrrolidine enamine (Scheme 17); carbon atoms 16 and 17 were added by an alkyne addition, and ring C completed, at the correct oxidation level, by acid-catalyzed closure.

In a quite different synthesis[24x] of ellipticine the pyrrole ring was formed last. 2-Bromo-1,4-dimethylbenzene was converted in seven steps into 6-bromo-5,8-dimethylisoquinoline and then the halide displaced by the nitrogen atom of acetanilide with copper catalysis. The remaining carbon-carbon bond (C-7,C-8) was introduced using palladium acetate-trifluoroacetic acid-acetic acid.

One approach to a carbazole route to olivacine requires 2-formyl-1-methyl-

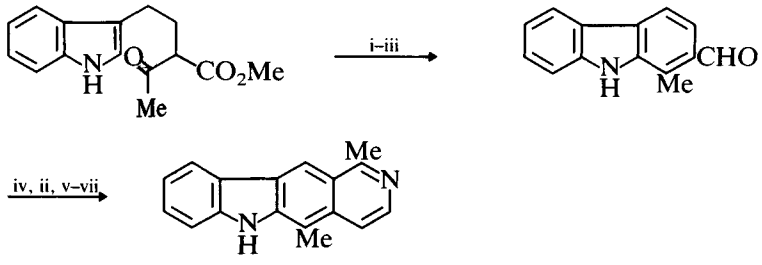


Scheme 16. Reagents: i, MeI; ii, $NaBH_4$; iii, $KOBu^t$, DMSO; iv, MeCHO, AcOH, Me_2NH; v, Pd/C, decalin, Δ.



Scheme 17. Reagents: i, dioxane, Δ; ii, HC≡CNa, liq. NH_3; iii, HCO_2H, Δ; iv, Na, liq. NH_3; v, Pd/C, Δ.

carbazole and the subsequent construction of ring D by elaboration into an ethanamine unit, then Bischler-Napieralski ring closure; an efficient synthesis (Scheme 18) of this aldehyde is available.[24r]



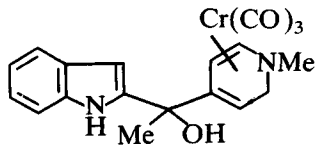
5

Scheme 18. Reagents: i, chloranil, 2% HCl, MeOH, PhH; ii, $LiAlH_4$; iii, CrO_3, H_2SO_4, Me_2CO; iv, $MeNO_2$; v, Ac_2O; vi, $POCl_3$; vii, Pd/C, Δ.

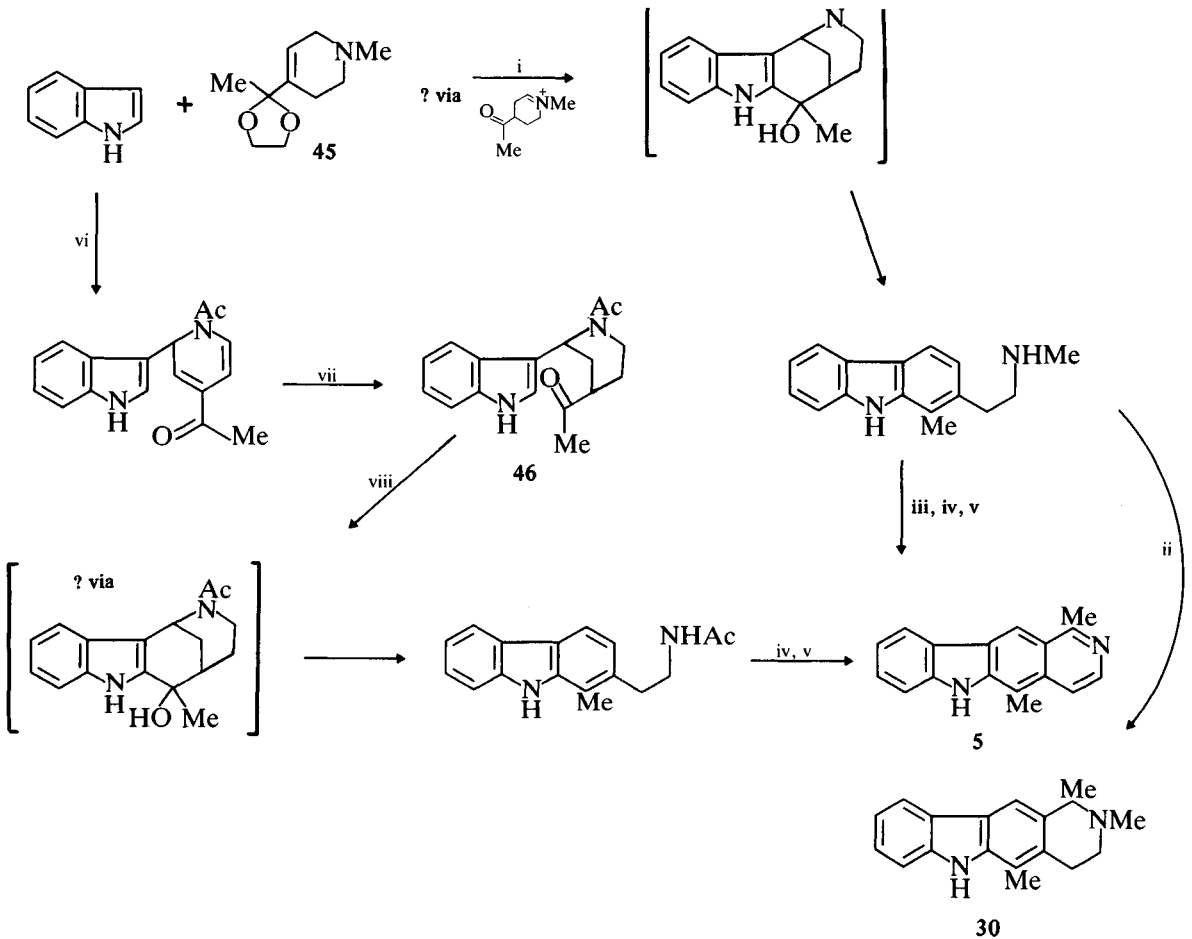
Two elegant, recent methods[24s,y] (Scheme 19) produce a suitable aminoethylcarbazole by the ring opening of a uleine derivative (not isolated). In the sequence of Besselièvre and Husson,[24s] reaction of indole with the 3-piperideine ketal (**45**) gave the desired carbazole directly; the mechanism indicated in Scheme 19 is believed to operate. Later, Naito et al.[24y] produced **46** by a slightly different route; acid treatment of **46** then gave an acetamidoethylcarbazole (Scheme 19) suitable for closure of ring D.

Bergman and Carlsson have also described a short synthesis[24t] of olivacine (Scheme 20), which parallels their pyrolytic method[24l] for ellipticine (Scheme 13), but no quaternization of N_b was employed; the ring closure (→ **47**) is presumably electrocyclic in character.

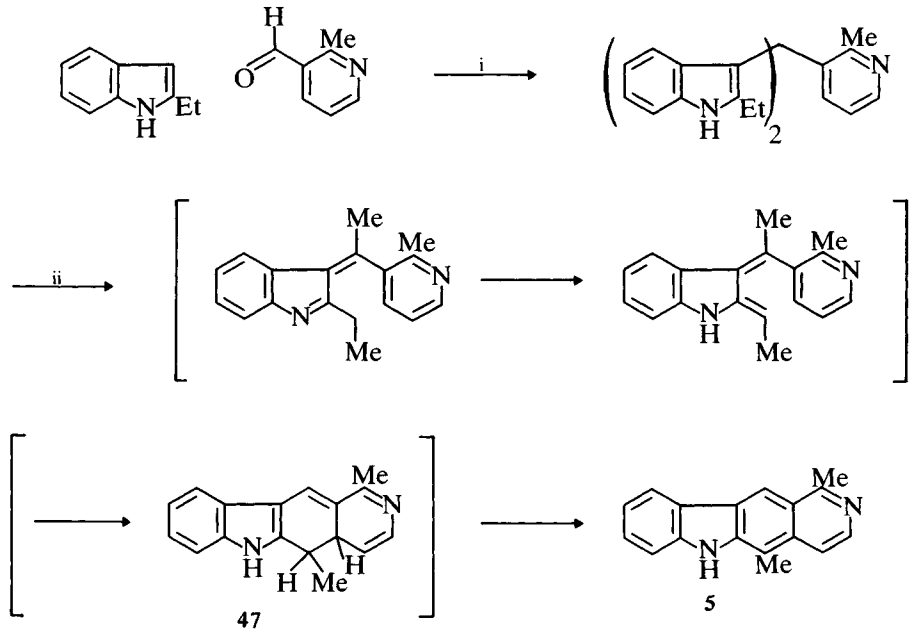
An intermediate (**48**), having a partially reduced pyridine ring stabilized by chromium tricarbonyl, and produced from indole in four steps, was converted[24z] into 19-norolivacine by Vilsmeier formylation, followed by cyclization with pyridine and vigorous dehydrogenation. The 19-methyl group was then introduced by means of methyllithium, and olivacine was finally obtained by dehydrogenation with iodine.



48



Scheme 19. Reagents: i, 50% AcOH–H_2O, Δ; ii, MeCHO; iii, Ac_2O; iv, $POCl_3$; v, Pd/C, Δ; vi, 4-acetylpyridine, CH_3COCl, CH_2Cl_2; vii, H_2, Pt; viii, TsOH, $CHCl_3$.



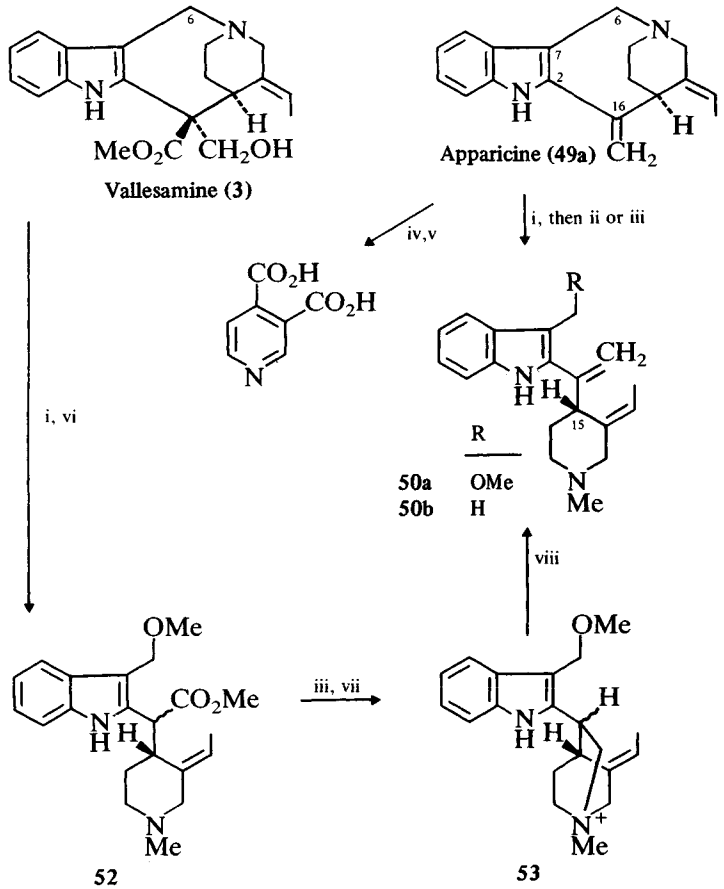
Scheme 20. Reagents: i, HCl, MeOH, Δ; ii, strong Δ.

IV. THE VALLESAMINE GROUP: ALKALOIDS WITH A 6,N_b BOND BUT LACKING C-5

Although vallesamine (**3**) has been chosen here as the skeletal prototype for this group of five alkaloids, the first member to be isolated and to have its structure determined was apparicine (**49a**) (Scheme 21), which lacks the C-22 ester carbon.[31] This structural modification is the only variation within this small group, the common feature of which is the 6,N_b bond.

A. Structural Studies

Apparicine was named in honor of the Brazilian botanist Apparicio Duarte to symbolize the great importance of his contribution to the onslaught on South American *Aspidosperma* species by Djerassi's group in the 1960s; from among these apparicine emerged, being isolated[28] from *A. dasycarpon, A. olivaceum, A. eburneum* Fr. All., *A. multiflorum* A. DC., and *A. gomezianum* A. DC. It proved to be a fairly widespread alkaloid,[32a] a factor that contributed to its also being named pericalline, tabernoschizine, and gomezine when isolated from *Catharanthus roseus* G. Don.,[32b] *Schizozygia caffaeoides* (Boj.) Baill.,[32c] and *A. gomezianum*, respectively. All reported isolations save that[28a] from *A. dasycarpon* have given the (−)-base.



Scheme 21. Reagents: i, MeI, ii, NaOMe; iii, $LiAlH_4$; iv, Pd/C, Δ; v, aq. $KMnO_4$; Δ; vi, NaOMe; vii, TsCl; viii, Δ.

The structure of apparicine (**49a**) was established[31] by a combination of chemical degradation (Scheme 21) and spectroscopy, a notable early example of the use of nmr decoupling experiments in this context. Despite the similarity of uv absorption and the still puzzling parallelism of the mass spectral fragmentation patterns of apparicine and uleine, it was easily recognized from the ^1H nmr spectrum that apparicine had a different skeleton; it lacked an *N*-methyl signal and had, as link between indole ring and basic nitrogen, a single, methylenic carbon (C-6), identified by the AB signals of its hydrogen atoms at δ 4.27 and 4.47 (*J* 18 Hz), shifted to δ 4.50 and 5.01 in acetic acid solution.[7]

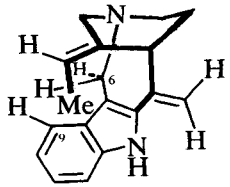
Biogenetic analogy suggested the location of the ethylidene group, which nmr showed to be present, on the piperidine ring and thus the structure **49a**. This was rigorously proved by a chemical degradation which exploited the gramine-type reactivity at C-6. Apparicine methiodide could be cleaved by attack at C-6 with either methoxide (→ **50a**) or lithium aluminum hydride (→ **50b**), the products

showing a quite different mass spectral fragmentation from the original alkaloid, which was totally dominated by the allylic fission between C-15 and C-16, giving rise to ions at *m/e* 122 and 124 corresponding to the aliphatic portion. After dehydrogenation of apparicine, vigorous permanganate oxidation gave pyridine-3,4-dicarboxylic acid, thus locating the two piperidine ring carbon substituents.

Recourse to a series of decoupling experiments on **50b** then established the sequences $CH_3CH{:}C(C)CH_2N$ and $CH_2{:}C(C)CH(C)CH_2CH_2N$ and thus the structures **50b** for the degradation product and **49a** for apparicine with two remaining uncertainties: the geometry of the ethylidene double bond and the biogenetically less likely possibility that the alkaloid has an "upside-down" structure with C-6 attached to C-2 and C-16 to C-7.

It was not till some years later, when the isolation[33] of 10-methoxy- and 10-hydroxyapparicines from *Ochrosia oppositifolia* allowed a comparison of the spectral characteristics of apparicine and the oxy derivatives that the geometry of the 19,20 double bond was established. It was shown to have the usual *E* configuration by the observation of a nuclear Overhauser enhancement of the C-15 hydrogen signal on irradiation of the C-18 methyl.

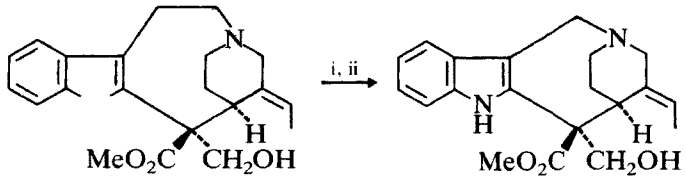
Measurements at 300 MHz also allowed a complete analysis of the ^1H nmr spectrum.[34] An extensive study of relaxation times led to the conclusion that the potentially flexible structure of apparicine spends most of its time in a conformation (**49b**) in which the two C-6 hydrogen atoms are equidistant from the aromatic proton at C-9. This corresponds to neither of the conformations that seem likely from molecular models; the extra conjugation between indole and double bond, possible in **49b**, must provide the energy necessary to overcome the angle strain indicated by models. The observation of a transient nOe between the C-6 protons and the C-9 hydrogen eliminated the "upside-down" possibility.



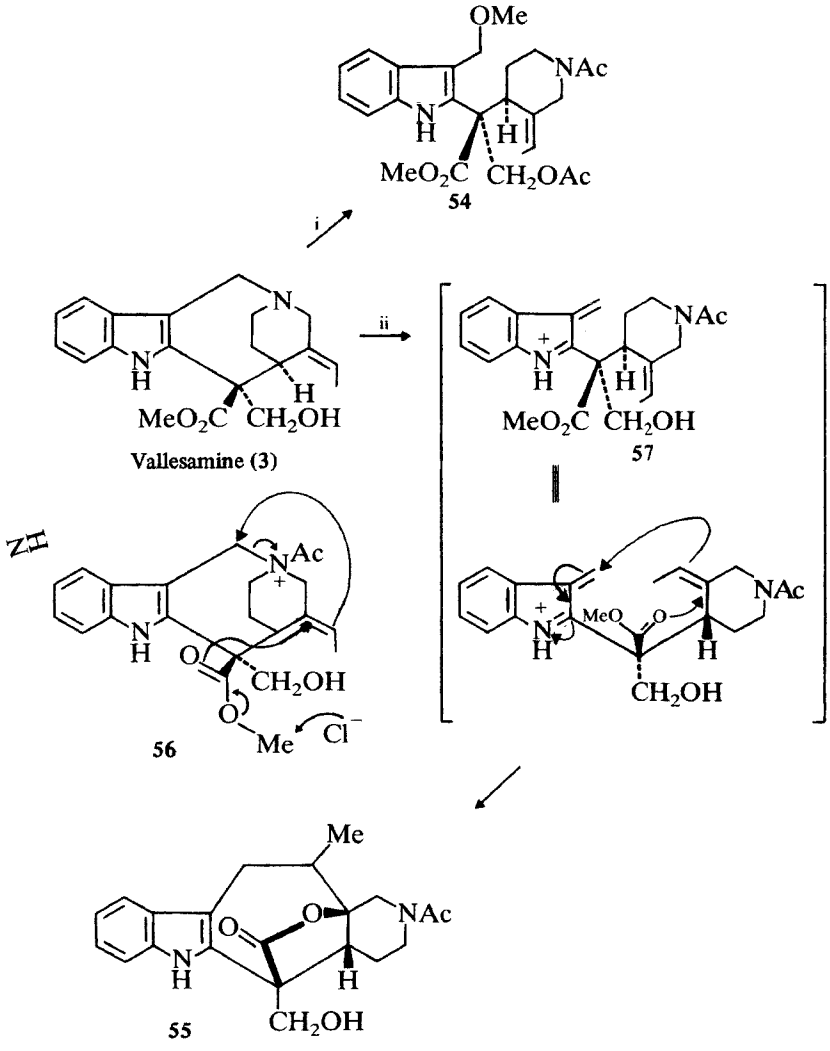
49b

The structure of vallesamine (**3**)[35] must represent a situation closer to the standard biosynthetic pathway than the apparicines, for in this base C-22 is still present. Indeed, stemmadenine (**51**) has been converted[36] into vallesamine (Scheme 22) by a modified Polonovski reaction, which type of process had been earlier suggested[37] as a rationalization for the loss, specifically, of the tryptamine bridge C-5 in the biosynthesis of apparicine from tryptophan and from stemmadenine in *A. pyricollum* Muell.-Arg.

During the chemical investigations (Schemes 21 and 23)[35] of vallesamine and its naturally occurring *O*-acetate, several intriguing transformations were achieved, including the preparation of **50b**, the degradation product previously obtained



ne 22. Reagents: i, H_2O_2; ii, $(CF_3CO)_2O$.



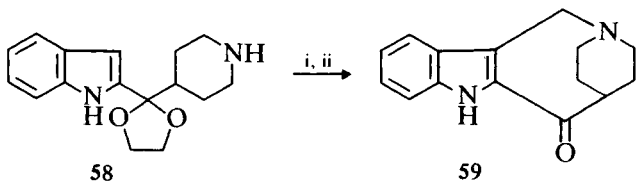
Scheme 23. Reagents: i, Ac_2O, MeOH; ii, AcCl.

from apparicine. This alkene was prepared by gramine-type opening of vallesamine methiodide accompanied by retro-aldol loss of formaldehyde to give **52** as a mixture of two stereoisomers. Without separation and following lithium aluminum hydride reduction, *O*-tosylation brought about intramolecular quaternization of N_b to give salts **53**. Hofmann degradation then eliminated the stereochemical difference in producing **50b**, shown to be identical with the apparicine degradation product in all respects. As well as verifying the structure this also showed both alkaloids to have the same absolute configuration at the one asymmetric center remaining in **50b**, that is, C-15. Later this was shown to be the usual configuration by the transformation[36] of stemmadenine (**51**) into vallesamine (Scheme 22). This last transformation also demonstrated that the absolute configuration of vallesamine at C-16 is the same as that of stemmadenine.

Acetylation of vallesamine (Scheme 23) in the presence of methanol led[35] to gramine-type cleavage, opening of ring C, and the formation of **54**. Acetyl chloride alone induced an extraordinary rearrangement in which **55** was formed. The arrows on **56** make clear which bonds are made and broken but study of a model shows clearly that it is impossible for the process to be synchronous; it may well proceed via **57**.

B. Synthetic Studies

No member of this group has yet been synthesized, although the ring system has been made[7] by a route which it was not possible to extrapolate for the synthesis of the alkaloid itself. The piperidine acetal (**58**) underwent intramolecular Mannich cyclization to give, after hydrolysis, the tetracyclic ketone (**59**).



58 59

Scheme 24. Reagents: i, CH_2O, AcOH, Me_2NH, high dilution; ii, aq. HCl.

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CHAPTER VII

The *Strychnos* Alkaloids

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I. INTRODUCTION

This chapter deals with those indole alkaloids that can be defined as being of the *Strychnos* type on the basis of their biogenesis, that is to say, those that are formed directly from preakuammicine, such as strychnine and its congeners, and those that are derived from the same precursor via the intermediacy of stemmadenine, such as condylocarpine, secodine, or andranginine. The principal structural characteristics of these alkaloids are the presence of an *unrearranged* monoterpenoid unit and the existence of a C-2,C-16 and a C-7,C-3 (or C-21) bond.

This biogenetic approach differs from that which has been most often employed hitherto, in which the alkaloids have been studied according to the genus in which they are found, for example, *Strychnos*.[1,2] Certain alkaloids biogenetically related to *Strychnos* have been reviewed together with alkaloids of other genera (e.g., *Aspidosperma*[3]); however, only in the second edition of Rodd's book[4] can there be found an excellent but short introduction to the chemistry of the *Strychnos* alkaloids following the definition that we have adopted. A complete review, though limited to the chemistry of strychnine and its immediate derivatives, has been published.[5]

The chemical and structural properties of the *Strychnos* alkaloids discovered or studied in the course of the past 10 years are examined in greater detail.

A list of *Strychnos* alkaloids with the most recent sources of extraction using the aforementioned classification is given below.

II. STRUCTURAL TYPES, OCCURRENCE, AND ISOLATION OF THE *STRYCHNOS* ALKALOIDS

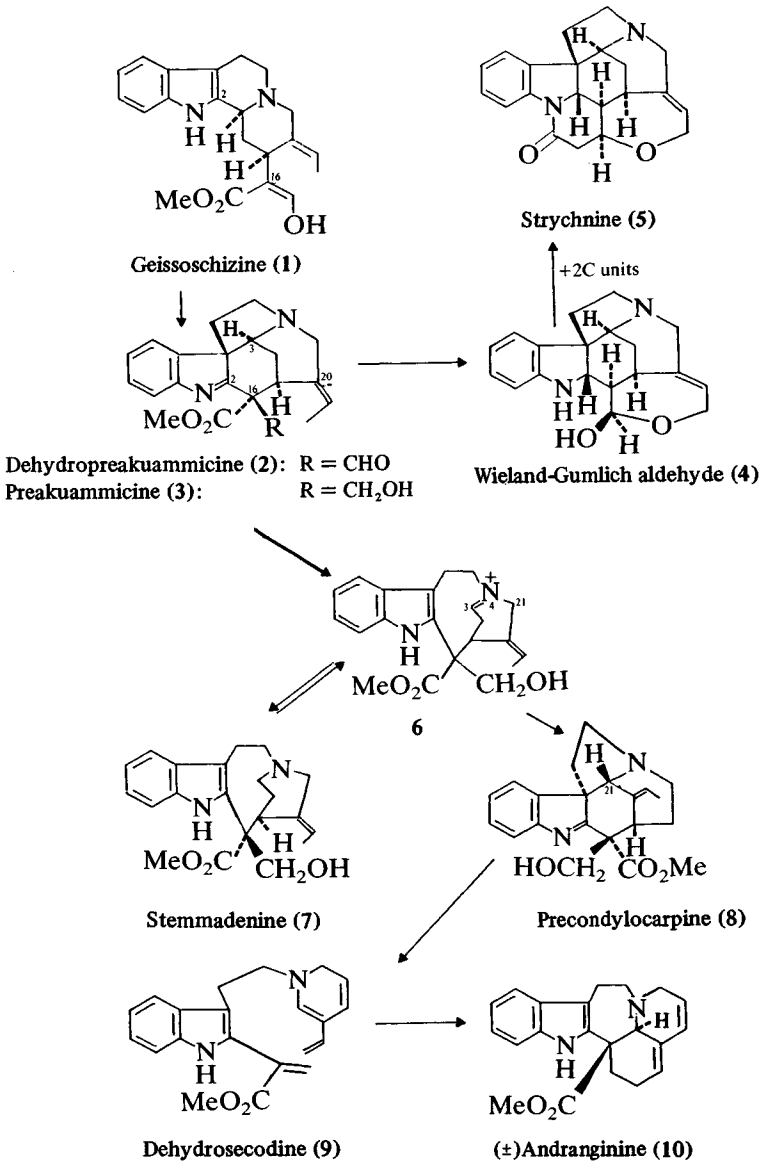
A. Structural Types

Geissoschizine (**1**) is an early transformation product of strictosidine, formed from the condensation of tryptamine with secologanin.

Although geissoschizine (**1**) is incorporated into strychnine (**5**)[6a] it has not yet been possible, in vitro, to compete with the natural process and accomplish the biomimetic oxidation leading from geissoschizine (**1**) to dehydropreakuammicine (**2**) and to preakuammicine (**3**) (Scheme 1).

Preakuammicine (**3**) is considered to be the biosynthetic precursor of the *Strychnos* alkaloids. All the alkaloids studied in this chapter can be biogenetically related to this key intermediate as shown in Scheme 1. Following this pathway we consider successively α-methyleneindoline (akuammicine, condylocarpine), indole (stemmadenine, secodine, andranginine), and finally indoline (dihydroindole) alkaloids of the strychnine type that contain two additional carbon units.

It is noteworthy that a great variety of aromatic substitution patterns is found in the last-mentioned group of alkaloids.



Scheme 1. Biogenetic relationship between the *Strychnos* alkaloids.

B. Occurrence and Isolation

The four botanical families containing the monoterpenoid indole alkaloids, or alkaloids that follow the same biogenetic pathway from strictosidine, are the Apocynaceae, Loganiaceae, Rubiaceae, and Nyssaceae. The exceptional presence of monoterpenoid indole alkaloids in other families should be considered with caution.[7]

The alkaloids that have been defined as being of the *Strychnos* type on the basis of their biogenesis are found in the Apocynaceae and the Loganiaceae. On consideration of the phylogenetic relationship between the four families it can be seen that there is a parallel between the evolution of the morphological character and the complexity of the alkaloids formed. The botanists who classified these plants largely agree that both the Rubiaceae and the Apocynaceae are derived from the old Loganiaceae.[8] This theory of the botanical evolution fits well with the alkaloid composition since the genus *Strychnos* (Loganiaceae) contains only alkaloids of the *Corynanthe-Strychnos* type which are almost exclusively dihydroindoles derived from the preakuammicine skeleton and which contain two supplementary carbon units. The passage to the precondylocarpine series, isomeric with preakuammicine, and other types of alkaloids via stemmadenine seems extremely rare in plants of this genus and has been mentioned in only two works.[83] The Apocynaceae, however, biosynthesize every type of indole alkaloid via preakuammicine. Thus the greater botanical evolution of the Apocynaceae results in their capacity to produce more complex alkaloids.

According to Markgraf and Boiteau,[9] the Apocynaceae comprise about 220 genera and 1300 species. According to Guédès,[10] 18 genera and 500 species are known for the Loganiaceae.

The Apocynaceae are most often trees, bushes, or creepers, chiefly of tropical origin, that are found in South America, Africa, and Australasia. Loganiaceae of the *Strychnos* genus are small trees or climbing shrubs which grow in South America, Africa, and Asia. Species rich in alkaloids are rarer in Africa than in Asia or South America. Extensive work has been carried out by Bisset and Phillipson,[11] who screened 36 out of 44 known species of Asian *Strychnos*.

In Tables I–III the *Strychnos* alkaloids are presented according to the listing employed for the chemical studies. The basic structures are given and compounds with substituents are regarded as their derivatives. Trivial names are given in brackets. The plant sources of more recent investigations are given with the appropriate references.

All genera mentioned belong to the Apocynaceae with the exception of *Strychnos*, which is in the Loganiaceae family.

TABLE I. α-METHYLENEINDOLINE AND RELATED ALKALOIDS

Compound	Plant source	Ref.
	Akuammicine derivatives	
Akuammicine	*Catharanthus trichophyllus* (Baker) Pichon	13
	Alstonia scholaris R. Br.	14
	Cabucala erythrocarpa (Vatke) Mgf. var. *erythrocarpa*	15
	Pandaca ochrascens (Pichon) Mgf.	16
	Alstonia lanceolata V. Heurck et Müll.	25b
N_b-Oxide	*Alstonia scholaris* R. Br.	14

TABLE I. CONTINUED

Compound	Plant source	Ref.
N_b-Metho salt (iodide)	*A. scholaris*	14
$\Delta^{18,19}$ (angustimycine)	*Amsonia angustifolia* Michx.	23
10-Hydroxy (sewarine)	*Rhazya stricta* Decne.	17
12-Hydroxy (vinervine)	*Vinca erecta* Regel et Schmalh.	19
11-Methoxy	*Alstonia muelleriana*	18
12-Methoxy (vinervinine)	*Vinca erecta* Regel et Schmalh.	19
19,20-Dihydroakuammicine		
(—)20β-Hydroxy (lochneridine)	*Ervatamia cumingiana* (A. DC.) Mgf. ex *Tabernaemontana pandacaqui* Poir.	22a
(+)20β-Hydroxy (epilochneridine)	*E. cumingiana*	22a
19-Hydroxy (echitamidine)	*Alstonia* sp.	22b
(±)-19-Hydroxy-12-methoxy (scholarine)	*A. scholaris*	22c
19,20-Dihydro-19,20-dihydroxy-akuammicine (compactinervine)	*Aspidosperma compactinervum* Kulmann	24
	Alstonia lanceolata	25b
10-Methoxy	*A. lanceolata*	25b
11-Methoxy (alstovine)	*Alstonia vitiensis* Seem.	25a
N_a-Methyl-2β,16β-dihydroakuammicine N_b-methochloride	*Vinca minor L.*	78b
(+)-N_a-Acetyl-2β,16α-dihydro-akuammicinal (isoretulinal)	*Strychnos variabilis* De Wild.	78a
(—)-2β,16β-Dihydroakuammicinol (desacetylretuline)	*S. variabilis*	77,78a
Preakuammicine	*Catharanthus roseus* (L.) G. Don	11
(±) Pseudoakuammicine	*Alstonia scholaris* R. Br.	14, 20
Vincanine [(—)-nor-C-fluorocurarine]	*Rhazya stricta* Decne.	26
N_b-Oxide	*Vinca erecta* Regel et Schmalh	27
12-Methoxy (vincanicine)	*V. erecta*	27
12-Hydroxy (vincanidine)	*Hazunta membranacea* (A. DC.) Pichon, *H. membranacea* for. *pilifera* Mgf.	28
Condylocarpine derivatives		
(+) Condylocarpine	*Craspidospermum verticillatum* Boj. ex A. DC.	36
	Pandaca minutiflora (Pichon) Mgf.	37a
19,20-Dihydro (Tubotaiwine)	*P. minutiflora*	37a
	Strychnos angolensis Gilg.	83
19,20-Epidihydro	*Pandaca eusepala* (A. DC.) Mgf.	37b
19,20-Dihydro *N*-oxide (Tubotaiwine *N*-Oxide)	*Conopharyngia johnstonii* Stapf	38
2,16-Dihydrodescarbomethoxy (aspidospermatidine)	*Aspidosperma quebrachoblanco* Schlecht.	39
Dichotine	*Vallesia dichotoma* Ruiz et Pav. = *V. cymbaefolia* Ontega	40
11-Methoxy	*V. dichotoma*	40
Geissovelline	*Geissospermum vellosii* Allem.	42

TABLE II. INDOLE ALKALOIDS AND RELATED ALKALOIDS

Compound	Plant Source	Ref.
Stemmadenine	*Pandaca minutiflora* Pichon Mgf.	37
	Craspidospermum verticillatum Boj. ex A. DC. var. *petiolare* A. DC.	36
Desformylstemmadenine	*C. verticillatum*	36
Hunteracine chloride	*Hunteria eburnea* Pichon	52
Secodine derivatives	*Rhazya* spp.	58, 59
(±)-Andranginine	*Craspidospermum verticillatum* Boj. ex A. DC. var. *petiolare* A. DC.	36, 69

TABLE III. INDOLINE ALKALOIDS

Compound	Plant source	Ref.
	Retuline derivatives	
Retuline	*Strychnos holstii* = *S. henningsii* Gilg.	74a
Retuline N_b-oxide	*S. camptoneura* Gilg. et Busse	74b
Desacetylretuline [= (—)-2β,16β-dihydroakuammicinol]	*S. variabilis* De Wild.	77, 78a
16-Epiretuline	*S. holstii*	74c
10-Methoxy	*S. holstii*	74c
Retulinal	*S. variabilis*	78c
12-Hydroxy	*S. variabilis*	78c
Isoretulinal	*S. variabilis*	78a, 78c
12-Hydroxy	*S. variabilis*	78c
16-Hydroxy	*S. variabilis*	78d
Strychnopivotine	*S. variabilis*	78d
Rosibiline	*S. variabilis*	78d
	Wieland-Gumlich aldehyde derivatives	
Wieland-Gumlich aldehyde (desacetyldiaboline)	*S. toxifera* Schomb. ex Benth.	81, 82
N_a-Acetyl Wieland-Gumlich aldehyde (diaboline)	*S. angolensis* Gilg.	83a
	S. jobertiana Baillon	83b
	S. rubiginosa A. DC.	83c
11-Methoxy-N_a-acetyl Wieland-Gumlich aldehyde (11-methoxydiaboline)	*S. angolensis*	83a
	S. gardneri A. DC.	83b
18-Deoxy Wieland-Gumlich aldehyde	*S. dolichothyrsa* Gilg ex Onochie et Hepper	84
	Strychnine derivatives	
Strychnine	*S. nux vomica* L.	96
N_b-Oxide	*S. nux vomica*	96
3-Hydroxy (pseudostrychnine)	*S. gaultheriana* Pierre	95
	S. icaja Baill.	102
	S. nux vomica	96
10-Methoxy (β colubrine)	*S. nux vomica*	96
11-Methoxy (α colubrine)	*S. nux vomica*	96
12-Hydroxy	*S. nux vomica*	96
10,11-Dimethoxy (brucine)	*S. nux vomica*	96

TABLE III. CONTINUED

Compound	Plant source	Ref.
3-Hydroxy-10,11-dimethoxy (pseudobrucine)	*S. nux vomica*	96
11-Methoxy-12-hydroxy	*S. wallichiana* Steud ex A. DC.	97
15α-Hydroxy	*S. nux vomica*	99
Isostrychnine	*S. nux vomica*	6a
17β,16α-Dihydro-17α-hydroxy-isostrychnine (protostrychnine)	*S. nux vomica*	6b
N_b-Methyl-*sec*-pseudostrychnine (icajine)	*S. icaja*	100
	S. wallichiana	103a
N_b-Oxide	*S. wallichiana*	103a
15-Hydroxy	*S. wallichiana*	103a
10-Methoxy (β-colubrine series)	*S. wallichiana*	103a
11-Methoxy	*S. nux vomica*	115
10,11-Dimethoxy (novacine)	*S. wallichiana*	103a
	S. icaja	105
10,11-Dimethoxy-15-hydroxy (15-hydroxynovacine)	*S. wallichiana*	103a
12-Hydroxy (vomicine)	*S. icaja*	100,105
N_b-Methyl-*sec*-pseudostrychnine, 19,20α epoxy		
12-Methoxy	*S. icaja*	105
10,11-Dimethoxy	*S. icaja*	104
11,12-Dimethoxy	*S. icaja*	105
15-Hydroxy-10,11-dimethoxy	*S. icaja*	105
12-Hydroxy	*S. icaja*	105
11-Methoxy-12-hydroxy	*S. icaja*	105
12,15-Dihydroxy	*S. icaja*	105
11-Methoxy-12,15-dihydroxy	*S. icaja*	105
12-Methoxy-15-hydroxy	*S. icaja*	105
N_b-Cyano-*sec*-pseudostrychnine	*S. ignatii* Berg.	103b
10-Methoxy (β-colubrine series)	*S. ignatii*	103b
10,11-Dimethoxy (brucine series)	*S. wallichiana*	103b
Spermostrychnine derivatives		
Spermostrychnine	*S. psilosperma* F. v. Muell.	107
11-Methoxy (strychnospermine)	*S. splendens* Gilg.	110
11-Methoxy-12-hydroxy	*S. brasiliensis* (Spreng.) Mart.	109
3-Hydroxy (N_a-acetyl-strychnosplendine)	*S. fendleri* Sprague et Sandwith	111
3-Hydroxy-11-methoxy-12-hydroxy (strychnosplendine series)	*S. fendleri*	111
Strychnobrasiline	*S. brasiliensis*	109
11-Methoxy-12-hydroxy	*S. brasiliensis*	109
10,11-Dimethoxy	*S. brasiliensis*	109
20α,21-Dihydro (isosplendine)	*S. splendens*	110
20α,21-Dihydro (strychno-fendlerine = 19-epi-isosplendine)	*S. fendleri*	111
11-Methoxy-12-hydroxy-20α,21-dihydro (strychno-fendlerine series)	*S. fendleri*	111
Strychnosilidine	*S. brasiliensis*	109

TABLE III. CONTINUED

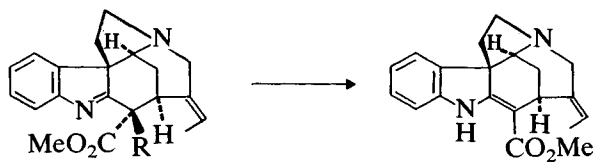
Compound P	Plant source	Ref.
Strychnosiline	*S. brasiliensis*	109
	Tsilanine derivatives	
Tsilanine	*S. henningsii* Gilg.	112
10-Methoxy	*S. henningsii*	112
23-*O*-Demethyl	*S. henningsii*	112
10-Methoxy-23-*O*-demethyl	*S. henningsii*	112
N_b-Methyl-*sec*-pseudotsilanine (holstiline)	*S. holstii* = *S. henningsii* Gilg.	114
23-*O*-Demethyl (holstiine)	*S. holstii*	114
10-Methoxy (rindline)	*S. holstii*	114

III. CHEMICAL AND PHYSICOCHEMICAL PROPERTIES OF THE *STRYCHNOS* ALKALOIDS

A. α-Methyleneindoline Alkaloids

1. *Akuammicine*

Dehydropreakuammicine (**2**) has not yet been isolated, probably because of its instability; however, there are good indications that it serves as a pivotal intermediate in the biosynthesis of both akuammicine (**11**) and strychnine (**5**).[6a] Preakuammicine (**3**) was obtained from 42–48 hour seedlings of *Catharanthus roseus* and then transformed into akuammicine (**11**) by base-promoted deformylation[12] (Scheme 2). Sodium borohydride reduction of **3** led to stemmadenine (**7**).



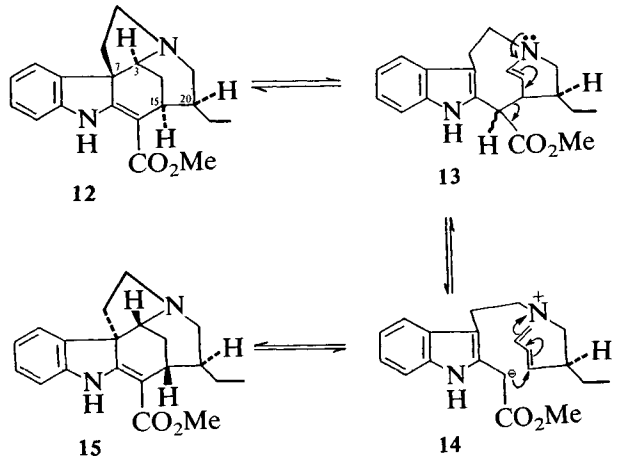
2: R = CHO
3: R = CH_2OH

Akuammicine (**11**)

Scheme 2.

Consequently, the configuration of preakuammicine (**3**) at C-16 can be inferred, given that the absolute configuration of stemmadenine (**7**) has been settled following the total synthesis of 16-epistemmadenine.[32] Akuammicine (**11**) and its derivatives have once more been found in various genera of Apocynaceae,[13–19] and it is noteworthy that **11** is present in *Picralima klaineana*[20] in the racemic form (pseudoakuammicine), meaning that C-15 can be epimerized. However, biosynthetic experiments showed that geissoschizine (**1**) is the precursor of (−)-akuammicine

(**11**) and strychnine (**5**), which have the same stereochemistry at C-15. A model reaction involving the transformation of (−)-19,20-dihydroakuammicine (**12**) into a single diastereoisomer (**15**) suggested a mechanism involving inversion of configuration at the conjugated iminium salt level (**14**) (Scheme 3).[21] Heating of (−)-19,20-dihydroakuammicine (**12**) in degassed absolute methanol gave a mixture of starting material and its diastereoisomer (**15**) in which C-3, C-7, and C-15 had epimerized.



Scheme 3. Proposed mechanism of epimerization at C-15 of 19,20-dihydroakuammicine (**12**).

These results also explain the occurrence in nature of the diastereoisomers (−)-lochneridine (20β-hydroxydihydroakuammicine) and (+)-20-epilochneridine.[22a]

Angustimycine, an isomer of akuammicine (**11**), may bear a vinyl (C-18,C-19) instead of an ethylidene double bond.[23] No definite correlation with akuammicine (**11**) is given.

19,20-Dihydroxydihydroakuammicine derivatives have also been isolated.[24,25]

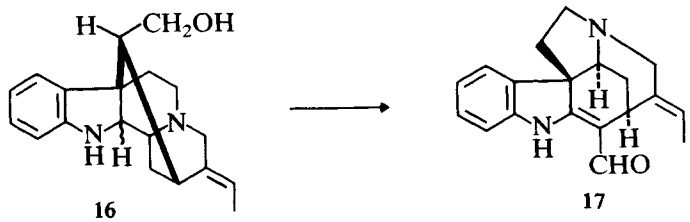
Vincanine [(−)-nor-C-fluorocurarine] (**17**)[26-28] represents the equivalent of akuammicine (**11**) having an aldehyde function instead of an ester. The corresponding N-CH_3 quaternary alkaloid, *C*-fluorocurarine, has been found in various *Strychnos* species.[29]

The assignment of the aromatic substitution of vinervine, vinervinine, vincanidine, and vincanicine has had to be revised on the basis of the 100 MHz nmr spectra; the substitution is at C-12 instead of C-11.[27]

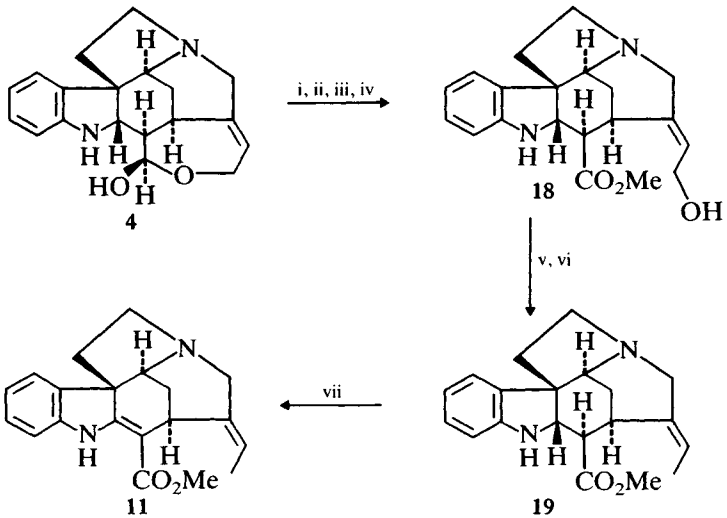
Vincanine (**17**) was formed as a by-product during the Oppenauer oxidation of the alcohol (**16**) (Scheme 4).

It is suggested[26] that this kind of reaction may represent an alternative to that previously proposed[30] for the formation of akuammicine and *Strychnos* alkaloids. Such a biomimetic reaction was first envisaged by Wenkert and Wickberg.[31]

The partial synthesis of akuammicine (**11**) by Kutney and Fuller,[32] employing the Wieland-Gumlich aldehyde (**4**) (a degradation product of strychnine) as starting material, represented the first synthesis of this alkaloid (Scheme 5).



Scheme 4.



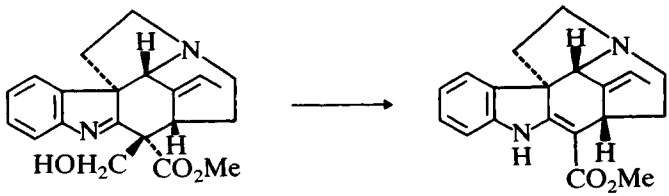
Scheme 5. Partial synthesis of akuammicine (11). Reagents: i, NH_2OH; ii, Ac_2O/py; iii, OH^-; iv, MeOH, HCl; v, HBr/HOAc; vi, Zn/HOAc; vii, $Pb(OAc)_4$.

The derivative **18**, successively treated with hydrogen bromide and zinc in acetic acid, yielded **19** (65%). Lead tetraacetate oxidation of the latter resulted in the formation of akuammicine (**11**). The crucial intermediate **19** was also used for the synthesis of 16-epistemmadenine (**34**) (see Section III.B.1).

2. *Condylocarpine*

The formation of precondylocarpine (**8**) can be explained by the cyclization of the N_b, C-21 iminium ion, isomeric with the N_b, C-3 iminium ion (**6**) formed in the fragmentation of preakuammicine (**3**) (Scheme 1). A deformylation of **8**, analogous to that of preakuammicine,[12] leads to condylocarpine (**20**), a positional isomer of akuammicine (**11**) (Scheme 6).

A chemical correlation between condylocarpine (**20**) and akuammicine (**11**) has been achieved, the two alkaloids having been transformed to the desformyl-descarbomethoxystemmadenine skeleton.[33] Furthermore, oxidation of stemmadenine (**7**) by means of oxygen with a platinum catalyst gave preakuammicine



8 Condylocarpine (20)

Scheme 6.

(3) and precondylocarpine (8).[30] These transformations proved the relationship between the two series and fixed the relative stereochemistry between C-7, C-15, and C-21 of condylocarpine (**20**), whose absolute stereochemistry has been related to that of strychnine (**5**).[34] The X-ray analysis of the borine adduct of condylocarpine, obtained by the action of mercuric acetate and sodium borohydride on stemmadenine (**7**), confirmed the already accepted structure and determined definitely the stereochemistry of the exocyclic double bond.[35] One must, however, note that the representation of the formula of condylocarpine given in the drawing in the aforementioned paper is wrong! The C-15 and C-21 hydrogens should be β instead of α. (+)-Condylocarpine (**20**) and its 19,20 and 19,20-epidihydro derivatives (tubotaiwines) have been identified in new plants.[36–38] The differentiation between the two isomers (tubotaiwine and 20-epitubotaiwine) has not been clearly settled.

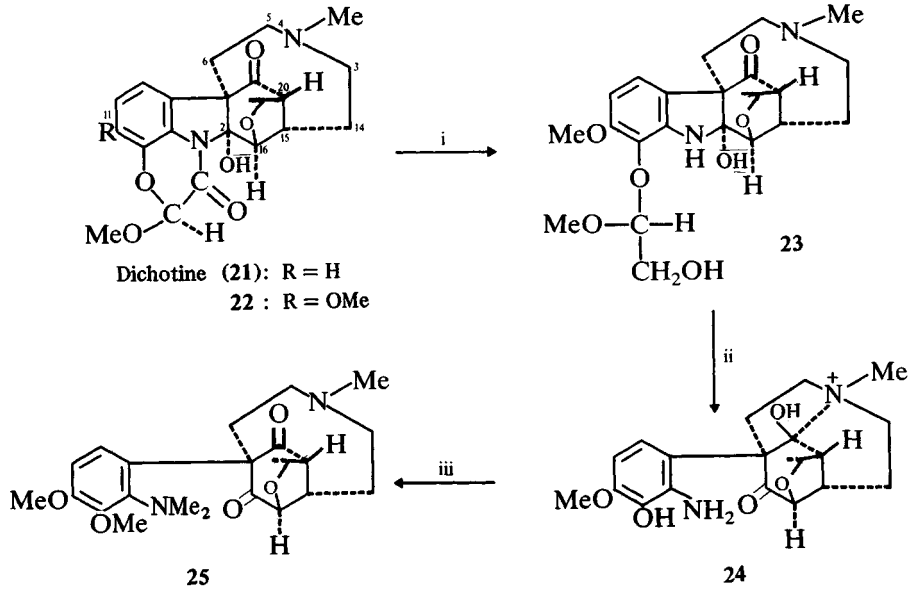
3. *Dichotine and Geissovelline*

Dichotine (**21**) and geissovelline (**26**) are two dihydroindole alkaloids of a closely related type which may be biogenetically derived from condylocarpine (**20**). They present very interesting structural features that result in an unexpected chemical reactivity.

Dichotine (**21**) and 11-methoxydichotine (**22**) were extracted from a Peruvian plant, *Vallesia dichotoma* Ruiz et Pav. (Apocynaceae). Their structures were investigated with the help of ir, uv, nmr, and mass spectroscopy by Ling and Djerassi.[40] A partial structural formulation, containing intriguing characteristics for the field of indole alkaloids, was proposed. The complete structure was determined by X-ray analysis of dichotine hydrobromide. The uv spectrum revealed an interaction between N_b and the ketone giving a zwitterion in neutral solution. This ionic form has precedence in the strychnine series with vomicine, novacine, and icajine (see Section III.C.3).[41]

Sodium borohydride reduction did not reduce the ketone at C-21 but opened the lactam to a primary alcohol and a carbinolamine giving **23**, which on treatment with methanolic acid gave a cleaved derivative (**24**) which was subsequently methylated to **25** (Scheme 7).

Treatment of the *O*-acetyl derivative of **22** with zinc in acetic acid plus ferrous sulfate yielded the 19-hydroxy compound via a free radical reaction. The resultant



Scheme 7. Reagents: i, $NaBH_4$, EtOH, H_2O; ii, MeOH, H^+; iii, $(CH_3)_2SO_4$, acetone, K_2CO_3.

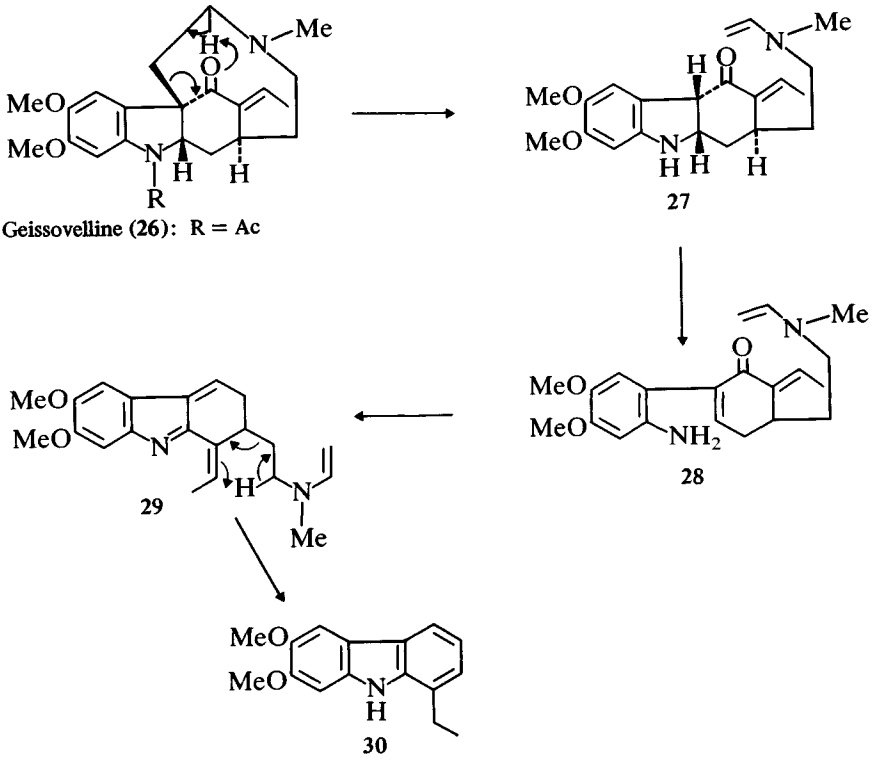
hemiketal was then deuterated at C-19 position. Dichotine was also deuterated at C-3 via the amide for the purposes of mass spectrometry. The numbering proposed by the authors should be slightly modified in accordance with the convention adopted throughout this book.

Proton nmr decoupling experiments were carried out on the alkaloid itself and on its derivatives.

A reasonable biogenetic hypothesis starting from condylocarpine (**20**) was proposed for dichotine involving the trans diaxial opening of a 2,16α epoxide by attack of the secondary C-19 alcohol, a transformation which would be responsible for one of the most unusual structural features of this alkaloid. This hypothesis and the chemical behavior of dichotine (N-1,C-2 bond cleavage) can be compared with the proposed biogenesis for the unusual structure of the alkaloid goniomine (see Chapter I).

Geissovelline (**26**), isolated by Moore and Rapoport[42] from the bark of the Brazilian *Geissospermum vellosii*, can also be related to condylocarpine (**20**). However, the absolute configuration depicted by the authors is that of the unknown enantiomeric series. This particular point is not discussed in the paper. As with dichotine (**21**), a transannular nitrogen-carbonyl interaction has been observed which explains an unusual carbon-carbon double bond reduction that occurs on treatment of **26** with sodium borohydride; the keto group remains unchanged.

Among the several complex molecular rearrangements whose rationalization led to the complete structure elucidation of deacetylgeissovelline, the result of its pyrolysis warrants a special mention (Scheme 8). A fragmentation process gave the ketone (**27**), which underwent retro-Michael reaction followed by 1,2 addition at



Scheme 8. Pyrolysis of deacetylgeissovelline.

the resultant α,β-unsaturated ketone (**28**). Finally, elimination of divinylmethylamine afforded the carbazole (**30**) (yield: 20%).

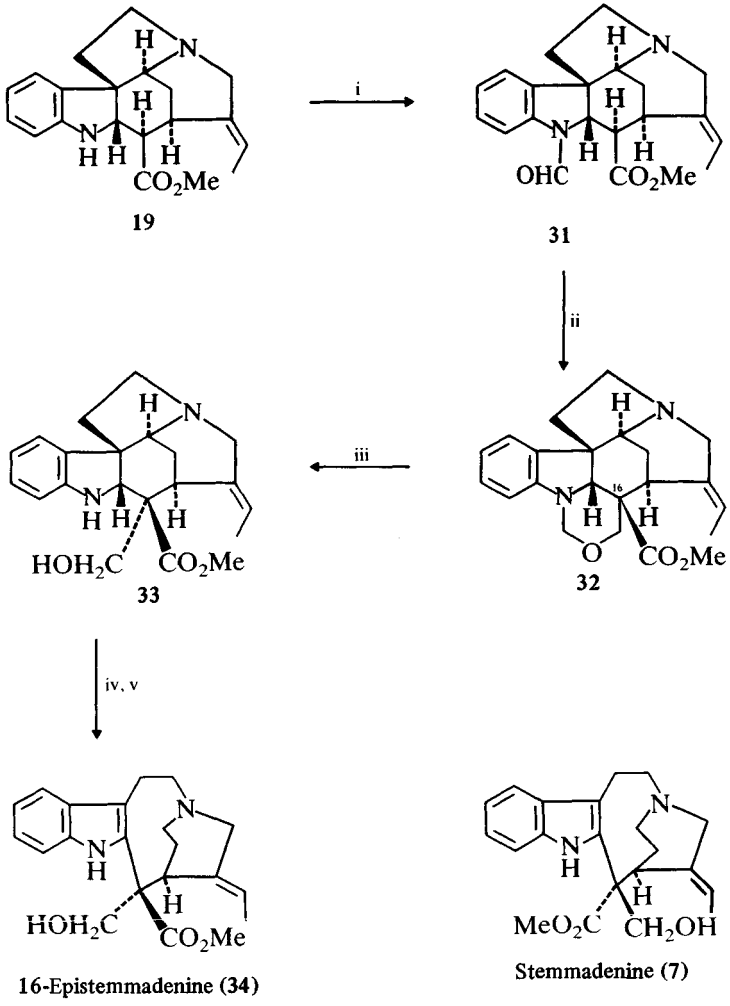
Along with the chemical degradation results a complete interpretation of the ^{13}C and 300 MHz ^{1}H nmr is provided.

B. Indole Alkaloids

1. *Stemmadenine and Hunteracine*

Stemmadenine (**7**) and its dehydro derivatives (iminium salts) play an important role in indole alkaloid biosynthesis as secodine precursors and as intermediates between the akuammicine and the condylocarpine series, as pointed out above. Only stemmadenine (**7**)[36,43] and desformylstemmadenine[36] have been isolated, the corresponding iminium salt or enamine being most likely too unstable. In spite of correlations with other *Strychnos* alkaloids the absolute configuration at C-16 remained unsettled until the partial synthesis of 16-epistemmadenine (**34**) by Kutney and Fuller[32] (Scheme 9).

Formylation of **19** (also used for a synthesis of akuammicine in the same work) with sodium hydride and methyl formate yielded **31**, which was treated with sodium hydride and formaldehyde in dimethyl sulfoxide to give the 1,3-tetrahydrooxazine **32**. Hydrolysis of **32** yielded the hydroxy ester **33**, which was transformed into the indole **34** in a classical manner (oxidation into indolenine followed by fragmentation and sodium borohydride reduction).

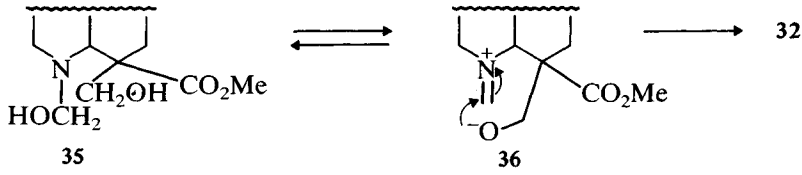


Scheme 9. Partial synthesis of 16-epistemmadenine (**34**). Reagents: i, NaH, HCO_2Me; ii, HCHO, NaH, DMSO; iii, MeOH, HCl; iv, $Pb(OAc)_4$; v, $NaBH_4$.

The product **34** was proved to be 16-epistemmadenine by examination of its physical data and by obtainment of the same diol on reduction of both natural stemmadenine (**7**) and the synthetic product (**34**) by means of sodium bis(methoxyethoxy)aluminum hydride.

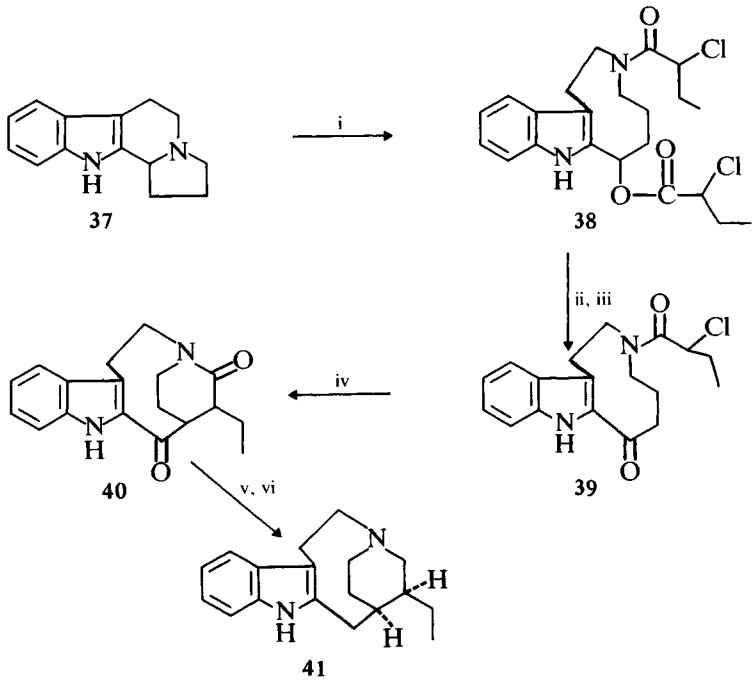
Essential to the attribution of the C-16 configuration in this synthesis is the fact that the starting material **31** was shown to be nonepimerizable.

No explanation is given concerning the formation of the unexpected reduced product **32**. Reduction of the intermediate carbinolamine is unlikely under the reaction conditions. Most probable is an *N*-deformylation followed by formation of the *N*-hydroxymethyl derivative **35** whose iminium form is attacked by the intermediate primary alcohol **36**. Such a cyclization has precedent[44] (Scheme 10).



Scheme 10.

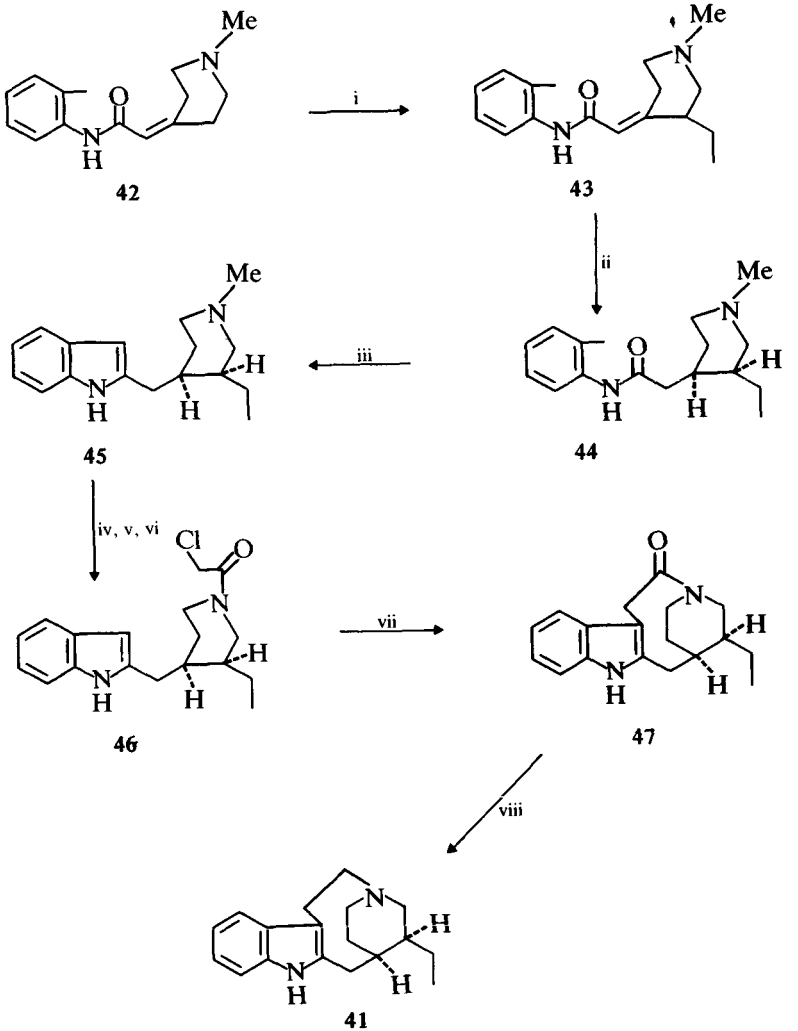
An ingenious ring expansion reaction allowed the first total synthesis of the (±)-stemmadenine skeleton by Dadson et al.[45] Treatment of the tetrahydroindoloindolizine **37** with α,α'-dichlorobutyric anhydride gave the *N,O*-dichlorobutyryl compound **38** (Scheme 11).



Scheme 11. Synthesis of a stemmadenine model (**41**). Reagents: i, α,α'-dichlorobutyric anhydride; ii, NaOH; iii, MnO_2; iv, sodium 1,1-dimethylpropoxide; v, Wolff-Kishner reduction; vi, $LiAlH_4$.

Ester hydrolysis, followed by manganese dioxide oxidation, yielded the ketone **39**, which was cyclized to **40** on base treatment. Wolff-Kishner reaction followed by lithium aluminum hydride reduction gave the tetracyclic indole **41**, whose structure was proved by direct comparison with a degradation product of akuammicine (**11**).

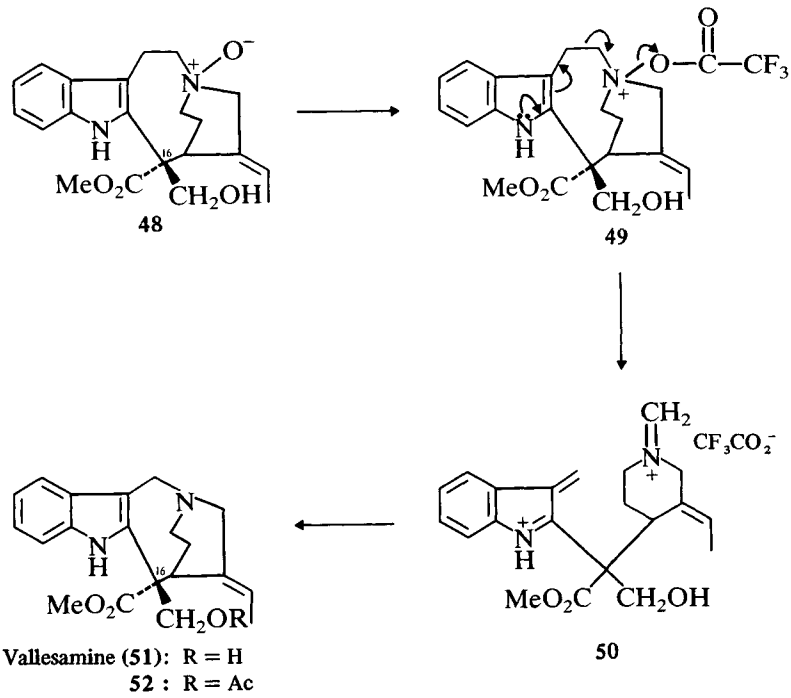
More recently **41** has been synthesized according to a scheme based on two original key steps.[46] A new stereoselective γ-alkylation of an α,β-unsaturated amide **42** via a dianion enabled the introduction of the ethyl chain on the piperidine ring. Finally the nine-membered ring (Scheme 12) was constructed in a photocyclization to give **47**.



Scheme 12. Another synthesis of the stemmadenine model (**41**). Reagents: i, *n*-BuLi, TMEDA, Et_2O, EtBr; ii, H_2, Pd/C, EtOH; iii, Bu^tOK, 340°; iv, $ClCOCH_2CCl_3$; PhH; v, Zn, HOAc, MeOH; vi, $ClCOCH_2Cl$, NaOH; vii, $h\nu$; viii, $LiAlH_4$.

The indole nucleus was formed from **44** in a Madelung reaction. The lactam **47** was subjected to lithium aluminum hydride reduction to give **41**.

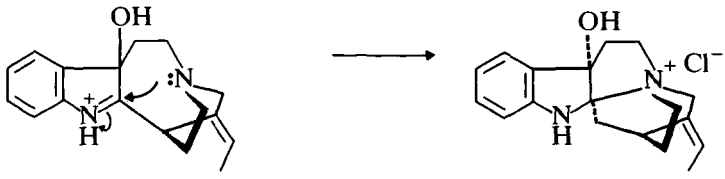
The modified Polonovski reaction[47] has provided several unprecedented biomimetic syntheses.[48] An obvious application of this reaction was the transformation of stemmadenine *N*-oxide (**48**) to vallesamine (**51**) (see Chapter VI) and this has recently been described.[49] Treatment of stemmadenine (**7**) or its acetate with hydrogen peroxide gave the *N*-oxides, which were reacted with trifluoroacetic anhydride followed by mild hydrolysis and acidification. Fragmentation of the tryptamine system, as previously encountered,[50,51] gave a conjugated iminium ion **50** which, after the loss of formaldehyde from N_b, led to vallesamine (**51**) by intramolecular nucleophilic attack. Vallesamine (**51**) and vallesamine acetate (**52**) were obtained in 25 and 12% yields, respectively (Scheme 13).



Scheme 13. Biomimetic transformation of stemmadenine into vallesamine.

This correlation establishes the configuration at C-16 for vallesamine given that of stemmadenine has been settled.[32] (It would be the opposite of that drawn in the paper.)

Hunteracine (**54**), isolated from the bark of *Hunteria eburnea* Pichon (Apocynaceae),[52] is a quaternary base (chloride) whose structure was determined by X-ray diffraction (Scheme 14).



53 Hunteracine (54)

Scheme 14.

A plausible biogenetic origin for **54** has been suggested from the hydroxyindolenine **53** derived from stemmadenine. After decarboxylation and desformylation of stemmadenine, an oxidative process could lead to **53**, which may then afford hunteracine (**54**) by transannular attack of the lone pair of N_b.

2. *Secodine*

The role of compounds of the dehydrosecodine type (**56**) as intermediates in indole alkaloid biosynthesis (*Corynanthe-Strychnos* → *Aspidosperma* and *Iboga*) was postulated by Wenkert[53] as early as 1962. Later Kutney et al.[54] and Qureshi and Scott[55] postulated the rearrangement of a stemmadenine derivative **55** to dehydrosecodine (**56**) and did radiochemical experiments with *Catharanthus roseus* plants and germinated *C. roseus* seedlings that supported this hypothesis.

One of the first pieces of evidence for the occurrence of secodine type derivatives in indole biogenesis appeared with the isolation of the secodine dimers: secamine (**60**),[56] from *Rhazya* species, and later its precursor presecamine (**59**).[57]

Eventually three monomers derived from secodine itself were discovered in the same plants: 15,16,17,20-tetrahydrosecodine (**62**), 16,17-dihydrosecodine,[58] and the alcohol (**58**).[59]

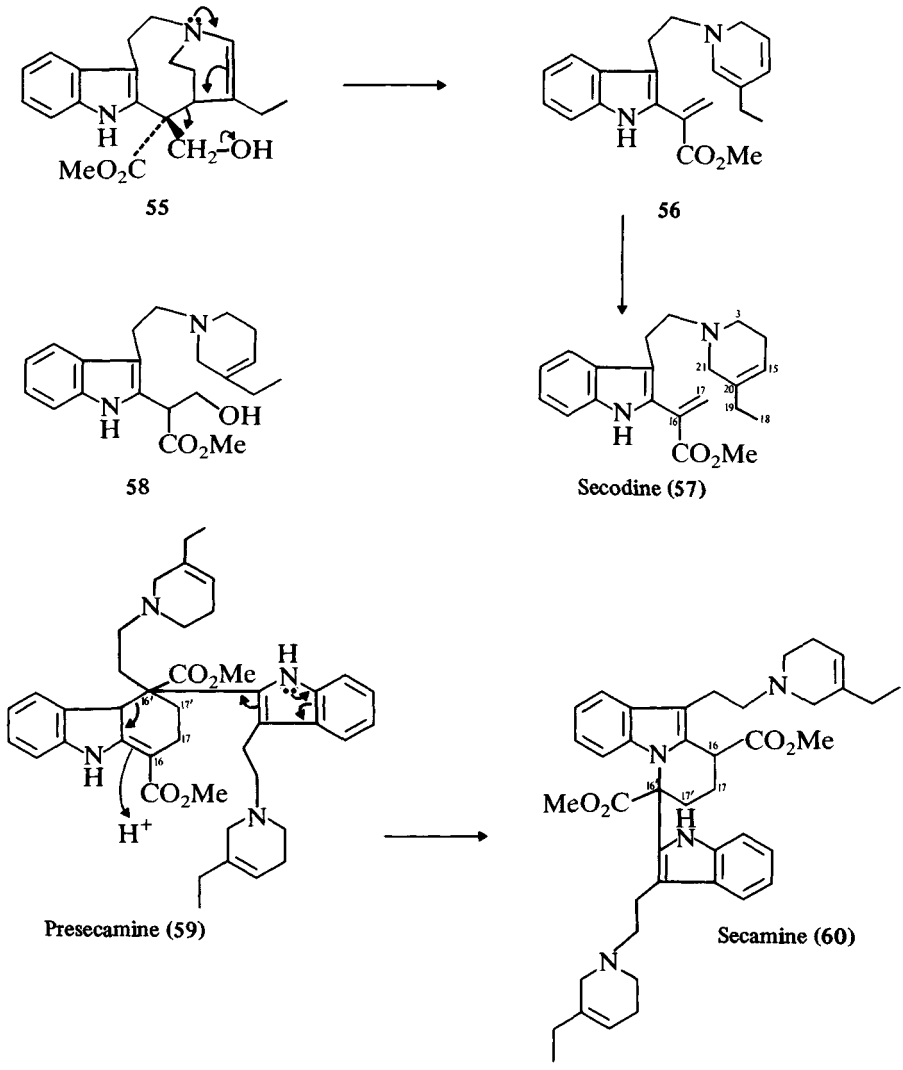
Secodine derivatives dimerize easily owing to the acrylic ester system; indeed it was shown that tetrahydropresecamine was a Diels-Alder type dimer of 15,20-dihydrosecodine.[57] Thus two structures are possible for this compound. The formulation **59** is the most probable because it quantitatively rearranges at room temperature in 2*M* aqueous hydrochloric acid to secamine (**60**), according to the mechanism depicted in Scheme 15.

The question of whether presecamine and secamine are artifacts still remains.

The first synthesis of a secodine derivative[60] (Scheme 16) has been achieved via the condensation of 1-methyl-1,2,3,4-tetrahydro-β-carboline and 1,5-diiodo-2-ethylpentane which afforded the spiroammonium salt **61**. The latter, without isolation, was reacted with potassium cyanide to give a nitrile which was methanolized to the ester **62**, identical with natural tetrahydrosecodine as shown by isotopic dilution analysis in *Rhazya orientalis*.

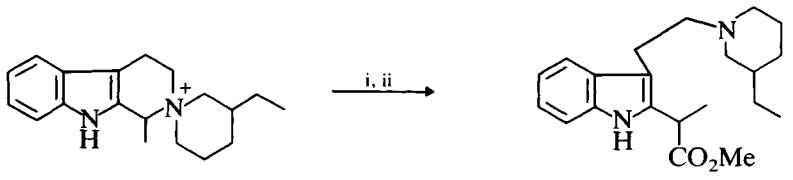
A recent elegant biomimetic preparation of vincadifformine via the intermediacy of secodine is reminiscent of this efficient synthesis (see below).[68]

The alcohol (**58**), called 16,17-dihydrosecodin-17-ol and shown by Battersby



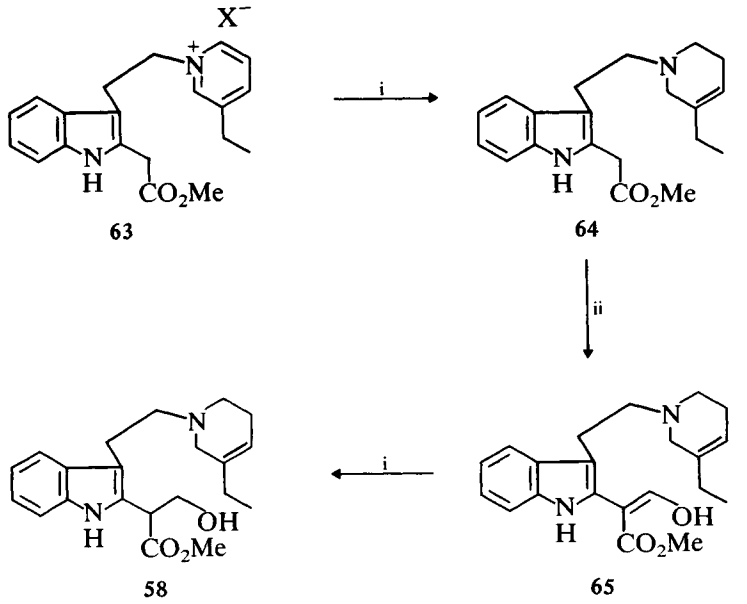
Scheme 15. Secodine derivatives.

and Bhatnagar[59] to be present in *Rhazya orientalis*, could be considered as a potential form of the secodine derivatives. It has been synthesized[59] (Scheme 17) from the pyridinium salt **63** which gave, after sodium borohydride reduction, the tetrahydropyridine (**64**). The latter was formylated to **65** and then reduced with sodium borohydride to yield the alcohol (**58**). A synthesis of **58** using the same strategy has recently been reported;[61] the attempted dehydration of the primary alcohol led to the unstable secodine (**57**) (not isolated) which then gave presecamine and secamine as previously demonstrated.



61 62

Scheme 16. Reagents: i, KCN, DMF, 100°; ii, CH_3OH, H^+.



63 64 58 65

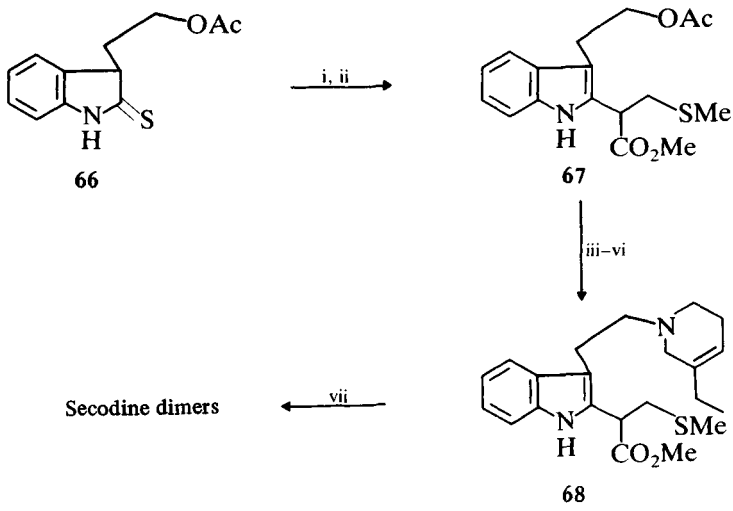
Scheme 17. Synthesis of 16,17-dihydrosecodin-17-ol. Reagents: i, $NaBH_4$; ii, tritylsodium, methyl formate.

Two approaches have been made that came very close to achieving a total synthesis of secodine itself.[62,63]

The first one involved the photoinduced addition of thiones to electron-deficient olefins. Irradiation of **66** in dichloromethane solution in the presence of methyl acrylate yielded **67** after methylation (MeI, K_2CO_3, in acetone). De-*O*-acetylation of **67** followed by bromination, condensation with 3-ethylpyridine, and sodium borohydride reduction of the resultant pyridinium salt afforded **68** (Scheme 18).

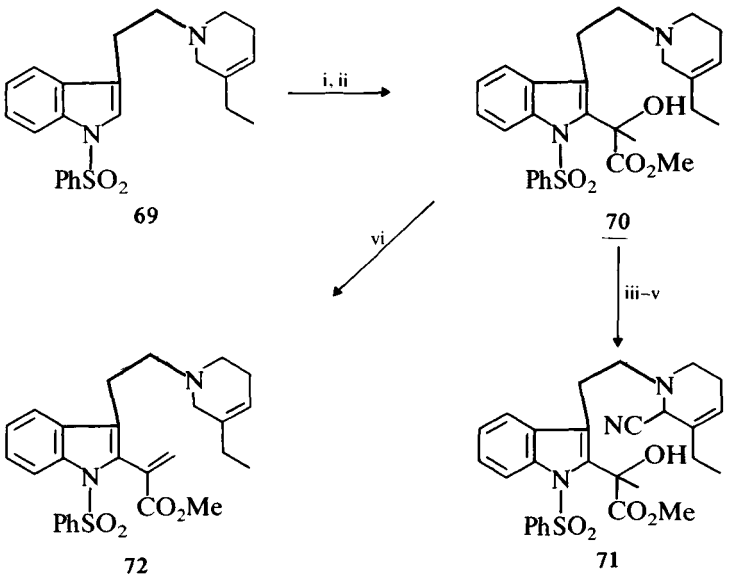
The thio derivative **68**, a potential form of secodine (**57**), was oxidized with *m*-chloroperbenzoic acid to give a mixture of secodine dimers.

The second route[63] took advantage of the condensation of 1-benzenesulfonyl-2-lithioindole (**69**) with methyl pyruvate[64] to introduce the acrylic system, and of the modified Polonovski reaction[47] to generate a potential form (**71**)[65] of the dehydrosecodine system (Scheme 19).



Scheme 18. Synthesis of secodine type alkaloids. Reagents: i, methyl acrylate, *hν*; ii, MeI, K_2CO_3, acetone; iii, OH^-; iv, PBr_3; v, 3-ethylpyridine; vi, $NaBH_4$; vii, *m*-chloroperbenzoic acid.

Phosphorus oxychloride-pyridine dehydration of **70** yielded the expected *N*-benzenesulfonylsecodine **(72)** as a stable, easily characterizable compound. Modified Polonovski reaction on the *N*-oxide of **70** followed by cyanide trapping of the conjugated iminium salt gave **71**.



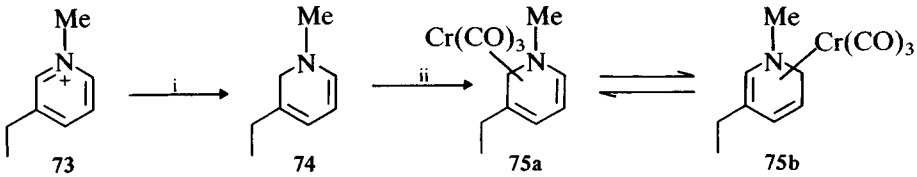
Scheme 19. Syntheses of *N*-benzenesulfonylsecodine derivatives. Reagents: i, Bu^tLi, THF, $-10°$; ii, methyl pyruvate, THF, $-78°$; iii, mCPBA, CH_2Cl_2; iv, $(CF_3CO)_2O$; v, KCN, pH 4; vi, $POCl_3$, py.

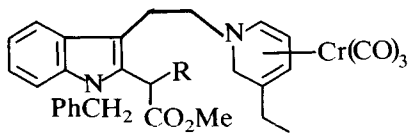
The total synthesis of secodine itself has at last been achieved by careful deprotection of a N_a-substituted derivative;[121] for details, see Chapter VIII, Section IV.F.

These results open the way for the biomimetic synthesis of *Iboga* and *Aspidosperma* type alkaloids.

Two different routes[66,67] are available to create the dihydropyridine system of dehydrosecodine; however, these model reactions have not yet been extended to the synthesis of dehydrosecodine itself.

In order to stabilize the dihydropyridine **74** coming from sodium borohydride reduction of the model pyridinium salt **73**, it was reacted with trisacetonitriletricarbonylchromium(0) (Scheme 20).[66]





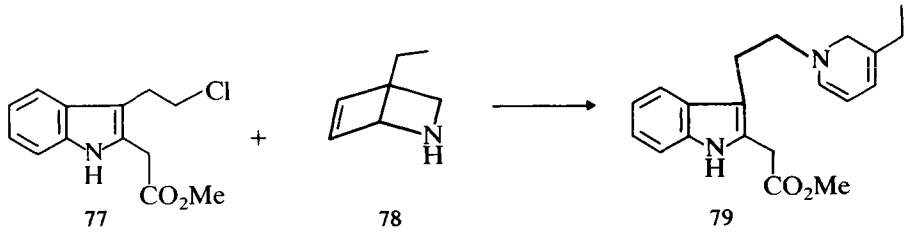
76a R = H
76b R = Me

Scheme 20. Reagents: i, 2.1 *M* NaOH, CH_3OH, ether, $NaBH_4$; ii, trisacetonitriletricarbonylchromium in dry ether.

The stable mixture of isomeric complexes **75a** and **75b** are interrelated by thermal equilibration. In an extension of this work the tryptamine derivatives **76a** and **76b** were prepared by an analogous route.[66]

The tricarbonylchromium(0) complex of a dehydrosecodine and the regeneration and reactivity of the dihydropyridine are announced for publication at a later date.

The other way to prepare the 1,2-dihydropyridine system involves the thermal ring opening of the *N*-substituted 2-azabicyclo[2.2.0]hex-5-ene (**78**)[67] (Scheme 21).

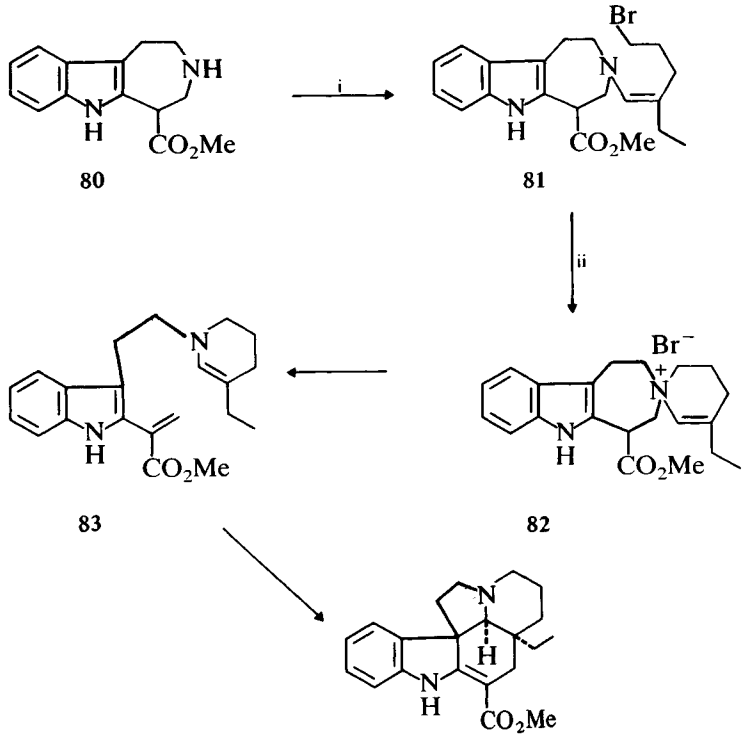


Scheme 21. Synthesis of a secodine model.

The unstable 1,2-dihydropyridine (**79**) may be useful for the biomimetic synthesis of *Strychnos* alkaloids as depicted earlier in the mechanism of the in vitro antipodal interconversion of dihydroakuammicine.

A very ingenious and efficient total synthesis of vincadifformine (**84**) by Kuehne et al.[68a] involved the preparation of an intermediate secodine derivative **83** which cyclized in a biomimetic manner. Using the enamine (**83**) derived from secodine, in the Diels-Alder type of reaction, the dimerization previously encountered in the secodine series was avoided. The key step was the opening of the quaternary salt **82**, which is reminiscent of a reaction used for the first synthesis in the secodine series.[60]

The required bromoaldehyde was condensed in methanol with the indoloazepine (**80**). Subsequent addition of triethylamine gave (±)-vincadifformine (**84**) in a one-pot reaction (Scheme 22).



80 81 82 83

(±)-Vincadifformine (84)

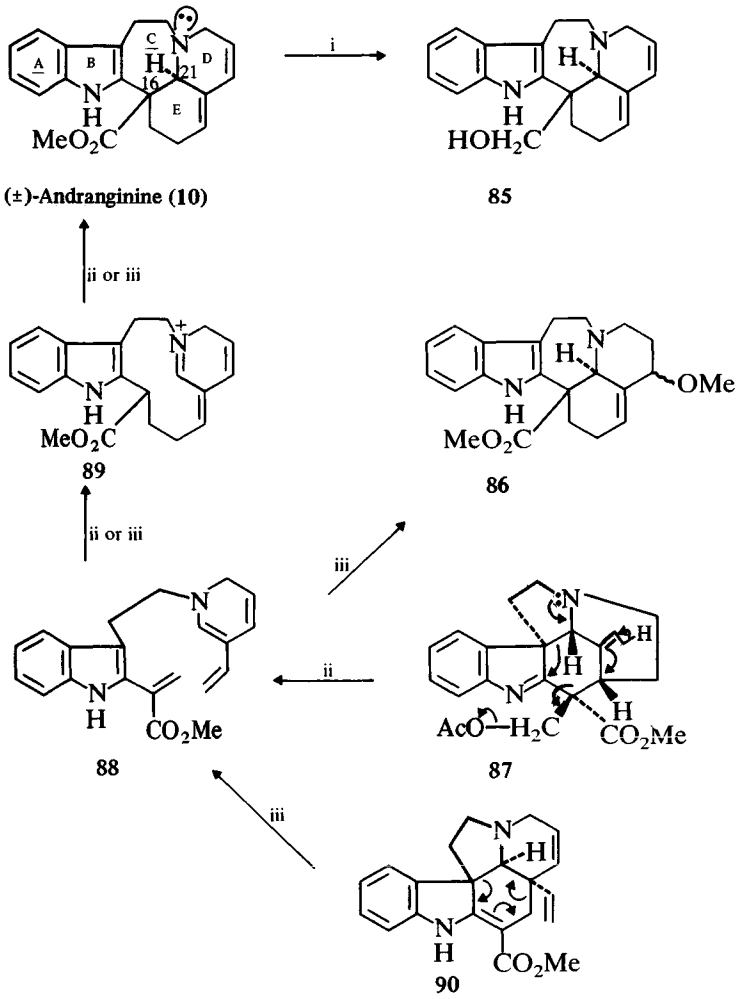
Scheme 22. Total synthesis of (±)-vincadifformine (84). Reagents: i, 5-bromo-2-ethylpentanal, CH_3OH; ii, $N(C_2H_5)_3$.

Kuehne and Bohnert[68b] have used a similar strategy for the syntheses of other indole alkaloids; for further details see Chapter VIII, Section. IV.F.

Recently the synthesis of a stabilized dehydrosecodine analogue bearing electron-withdrawing substituents on the pyridine ring has been reported.[68c] However, this compound did not undergo the Diels-Alder reaction.

3. (±)-*Andranginine*

(±)-Andranginine (**10**), an indole alkaloid of a new type, was isolated from *Craspidospermum verticillatum* Boj. var. *petiolare*.[36,69] The ^{13}C nmr assignments of the natural product and ^{1}H nmr data for the corresponding lithium aluminum hydride reduction product **85** were consistent with a proposed structure based on a biogenetic hypothesis and a partial synthesis. Indeed, andranginine (**10**) proved to be identical with a product synthesized independently during studies on the transformation of secodine derivatives formed from precondylocarpine acetate (**87**). Thermolysis of the latter at 100° in ethyl acetate solution afforded andranginine (**10**) in 28% yield (Scheme 23).



Scheme 23. Partial synthesis of andranginine (**10**). Reagents: i, $LiAlH_4$; ii, EtOAc, Δ; iii, MeOH, Δ.

The nmr difference spectrum technique confirmed the structure, allowing the identification of all the protons of andrangininol (**85**).[70] X-Ray analysis[71] has proved the correctness of this structure and established the stereochemistry of the C, D, E ring junctions as trans trans. Without direct evidence for the assignment of the configurations at C-16 and C-21 the cis stereochemistry had been previously proposed on the base of a concerted cycloaddition mechanism.

A Mannich type reaction could rationalize the obtainment of **10** from **88**.[72] This hypothesis is supported by the obtainment of, besides (±)-andranginine (**10**) (yield 16%), (±)-21-epiandranginine (yield 1.5%) in another experiment where **88** was generated by thermolysis of Δ^{18}-tabersonine (**90**).[73]

When the thermolysis of **87** was carried out in methanol, the racemic compound **86** was obtained as a result of the trapping of the intermediate iminium species derived from **88**.

The lack of optical activity in both the natural and synthetic products suggests that the achiral secodine type precursor **88** could be transformed into andranginine in a nonenzymatic process.

The discovery of andranginine (**10**) is interesting and again shows the pivotal position of dehydrosecodine type compounds in indole alkaloid formation.

C. Indoline Alkaloids

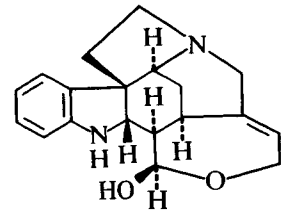
This group of dihydroindole alkaloids is found in the genus *Strychnos* (Loganiaceae) and has been reviewed in detail in the past as "the *Strychnos* alkaloids".[1,5]

Strychnine and its congeners have been the subject of a lot of work owing to the fascinating challenge offered by the structure elucidation and the total synthesis of these complicated molecules at a time when the facilities of present physical methods did not exist. The amount of chemistry in this field in the past 10 years has decreased, most of the work being directed toward the structural elucidation of minor alkaloids from new species of *Strychnos*.

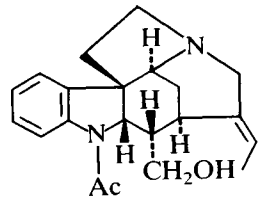
The different kinds of structures in this series are considered as derivatives of the basic ring systems depicted in Scheme 24: retuline (**91**), Wieland-Gumlich aldehyde (**4**), strychnine (**5**), spermostrychnine (**93**), and tsilanine (**95**).

1. *Retuline*

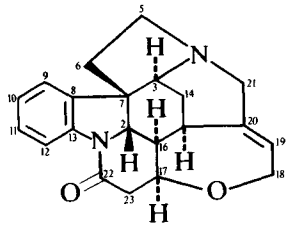
Retuline (**91**) occupies a special place in the 2,16-dihydroindole series since the proton at C-16 is β instead of α as in the rest of the series, Retuline (**91**) was isolated for the first time from the African *S. holstii* var. *reticulata* in 1951.[74a] Proton and mass spectroscopy studies led to the proposition of the structure **98** where H-16 was α. Finally, partial syntheses by Wenkert and Sklar[75] established the stereochemistry of retuline (**91**). The first synthesis (Scheme 25), starting from the Wieland-Gumlich aldehyde (**4**), which bears a 16α-H, gave the alcohol (**98**), which



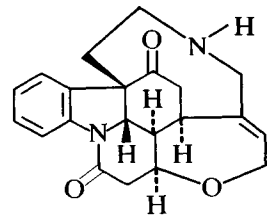
Wieland-Gumlich aldehyde (4)



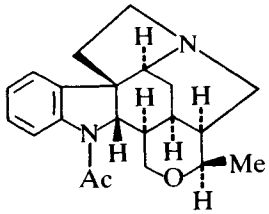
Retuline (91)



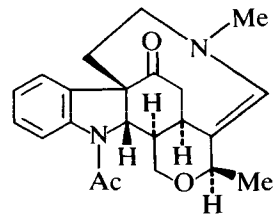
Strychnine (5)



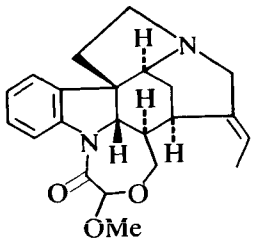
N-sec-Pseudostrychnine (92)



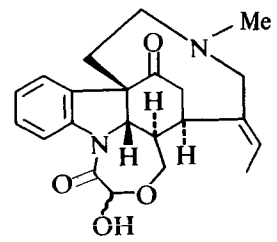
Spermostrychnine (93)



Strychnobrasiline (94)



Tsilanine (95)

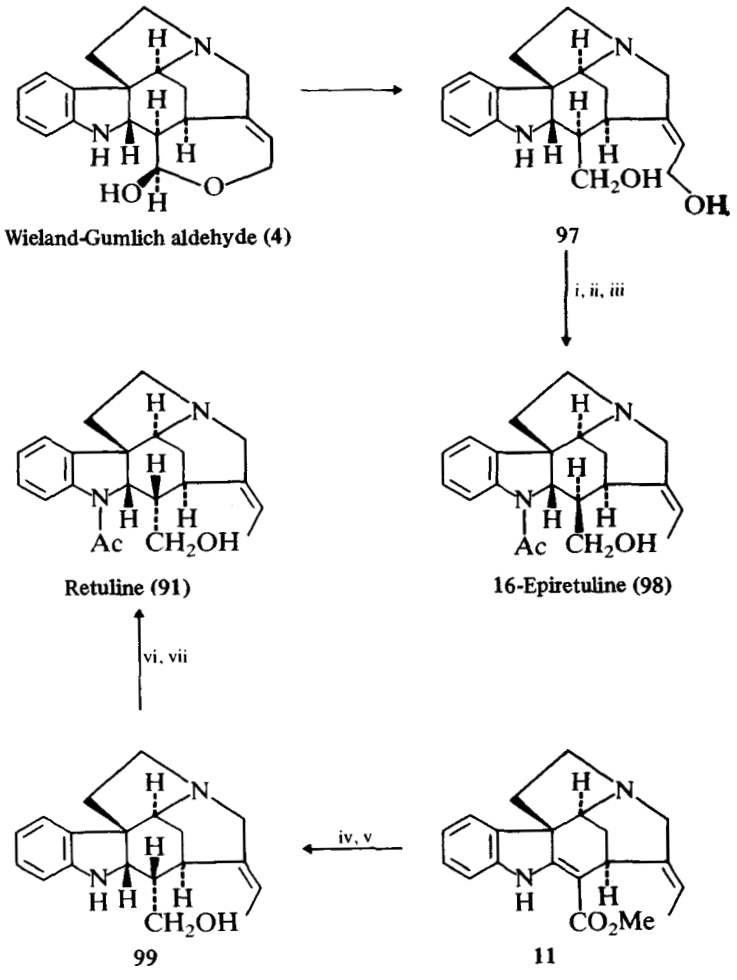


Holstiine (96)

Scheme 24. Indoline alkaloids: structural types.

proved to be different from retuline **(91)**. Consequently, it was thought that retuline might be the 16-epimeric compound.

The latter was prepared from akuammicine **(11)** by zinc-acid reduction of the anilinoacrylic double bond followed by lithium aluminum hydride reduction of the ester function to **99**. Complete acetylation of **99** and ensuing partial hydrolysis afforded **91**, identical in all respects with retuline.



Scheme 25. Syntheses of retuline (**91**) and 16-epiretuline (**98**). Reagents: i, Ac_2O/py; ii, Pd/C, H_2; iii, 10% NaOH; iv, Zn-acid; v, $LiAlH_4$; vi, Ac_2O/py; vii, 10% NaOH.

Independently, Hymon and Schmid[76] reported the synthesis of retuline (**91**) via an intermediate prepared from the Wieland-Gumlich aldehyde which had been epimerized at C-16.

More recently, desacetylretuline (**99**) [(−)-2β,16β-dihydroakuammicinol] has been found as a natural product in *Strychnos variabilis* De Wild.[77,78a] as well as retulinal and isoretulinal,[78a,c] the epimeric aldehydes corresponding to retuline (**91**) and 16-epiretuline (**98**).

Three other retuline derivatives have been isolated from the same plant: strychnopivotine (16-keto derivative lacking C-17), 16-hydroxyisoretulinal, and rosibiline, the latter being a derivative of *N*-desacetylretuline with an extra oxazine ring between N_a and C-16.[78d]

The ^{13}C nmr spectrum of *N,O*-diacetylgeissoschizoline (19,20-dihydroretuline series), a derived moiety of the dimer geissospermine, has been analyzed.[79]

2. *Wieland-Gumlich Aldehyde*

The Wieland-Gumlich aldehyde (**4**) (Scheme 25) was first isolated in the course of chemical investigations of strychnine (**5**).[80] This alkaloid, lacking an acetate unit with respect to strychnine, has been shown by Heimberger and Scott[6a] to be a precursor of strychnine in *Strychnos nux vomica* as well as geissoschizine.

The Wieland-Gumlich aldehyde is identical with caracurine VII,[81] which has been isolated from the Venezuelan *S. toxifera*.[82] The Wieland-Gumlich aldehyde played an important role in the structural determination of the curare alkaloids.

As previously mentioned, this alkaloid has been used as the starting material for the partial synthesis of alkaloids of unknown stereochemistry[75] or configuration.[32]

The classic reaction of strychnine degradation to the Wieland-Gumlich aldehyde has been reinvestigated using modern chemical techniques. 23-Isonitrosostrychnine was polymer-attached by quaternization with chloroacetylated styrene-divinylbenze copolymer and then treated with thionyl chloride (Beckmann rearrangement), hydrolyzed, and cleaved from the polymer to yield the Wieland-Gumlich aldehyde.[85]

3. *Strychnine and its Derivatives*

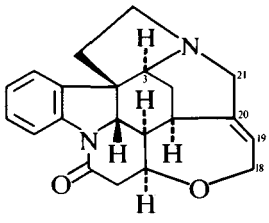
a. STRYCHNINE. It took no less than 60 years of intensive efforts to elucidate the structure of this notorious alkaloid, known since 1818.[86] The structure (**5**) (Scheme 26) was elucidated in 1947 owing to the major contributions of H. Leuchs and of Sir Robert Robinson, and the strychnine story culminated with Woodward's famous total synthesis (Scheme 27).[87] An exhaustive and excellent review on the chemistry of strychnine covering a century and a half is available.[5]

Recent works on strychnine and its derivatives deal mainly with spectral properties. Ultraviolet absorption and circular dichroism spectra of strychnine, β-colubrine, brucine, dihydrostrychnine, dihydro-β-colubrine, and dihydrobrucine (see Table III) have been studied[88] under various conditions. Spectroscopic properties of these compounds, above 190 nm, are associated with at least five electronic transitions. The chromophores involved are those of the dihydroindole and the ethylenic group. The cd spectra showed significant differences between the series of alkaloids.

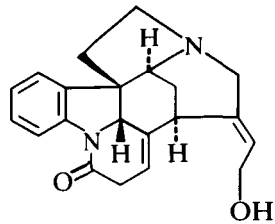
Several ^{1}H and ^{13}C nmr studies[78,89–93] in the dihydroindole base series, depicted in Scheme 24, led to the complete assignment of the protons and of the carbons and to the solution of conformational problems.[92]

The structures of the products of Leuchs reaction (sulfur dioxide-manganese dioxide) on strychnine have recently been determined.[118]

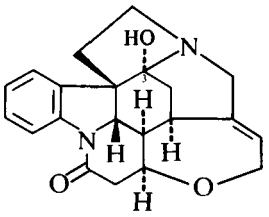
Some aromatic ring-substituted derivatives of strychnine have been synthesized for biological testing. They were prepared by electrophilic substitutions at C-10[117,120] or C-12[116] or by heteroannulation between C-10 and C-11.[119]



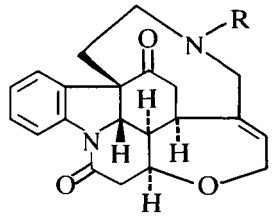
Strychnine (5)



Isostrychnine (100)



Pseudostrychnine (101)



N_b-*sec*-Pseudostrychnine **101**: R = H
Icajine (**102**): R = Me
103: R = CN

Scheme 26.

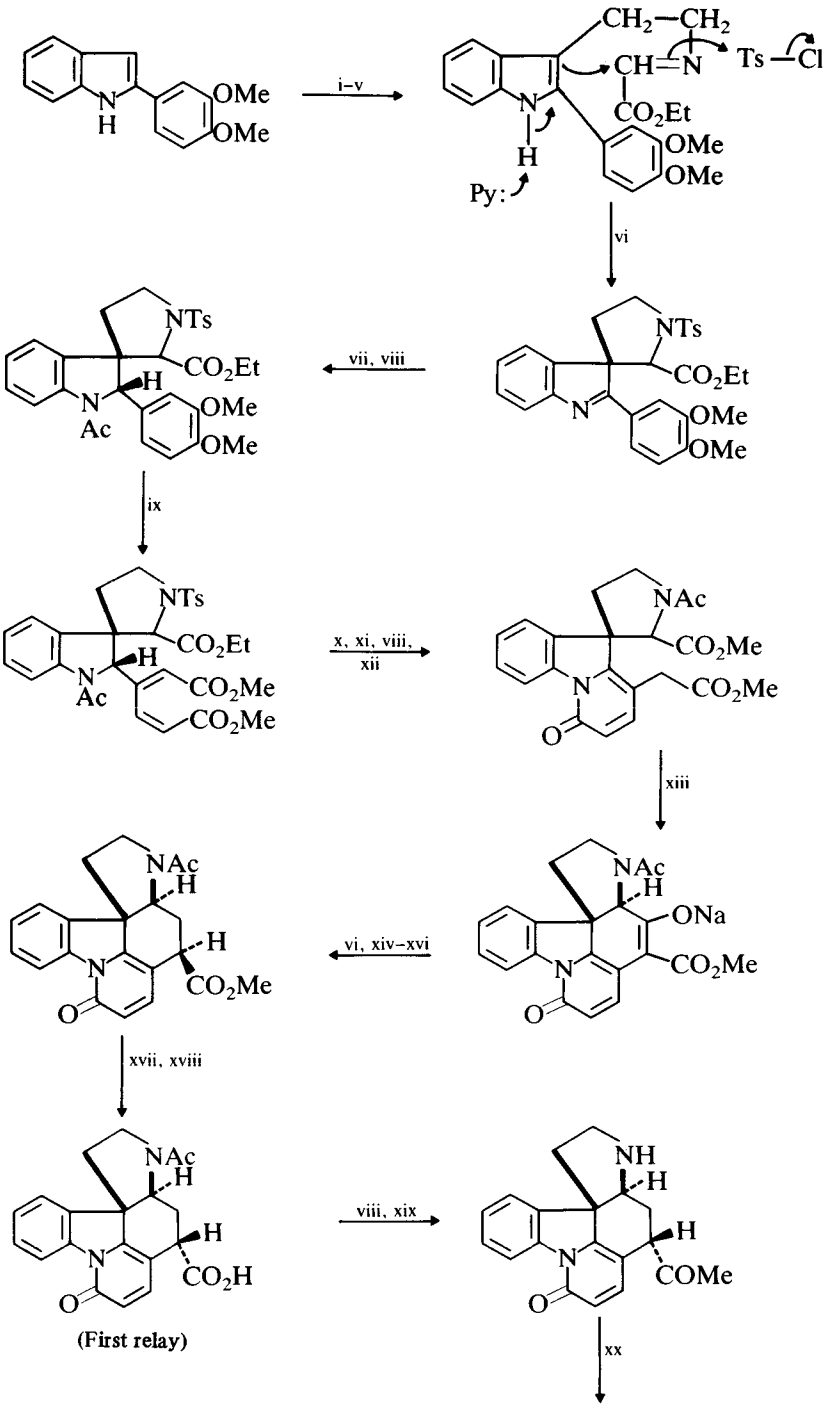
b. ISOSTRYCHNINE. Isostrychnine (**100**) is the product of a retro-Michael addition with double bond migration obtained from strychnine (**5**) by base or acid treatment;[94] it was isolated from the roots of young seedlings of *S. nux vomica*.[6a]

Protostrychnine, recently found in the root bark of *S. nux vomica*,[6b] is 17β,16α-dihydro-17α-hydroxyisostrychnine. These two alkaloids are thought to play a role in the last stages of strychnine biosynthesis.

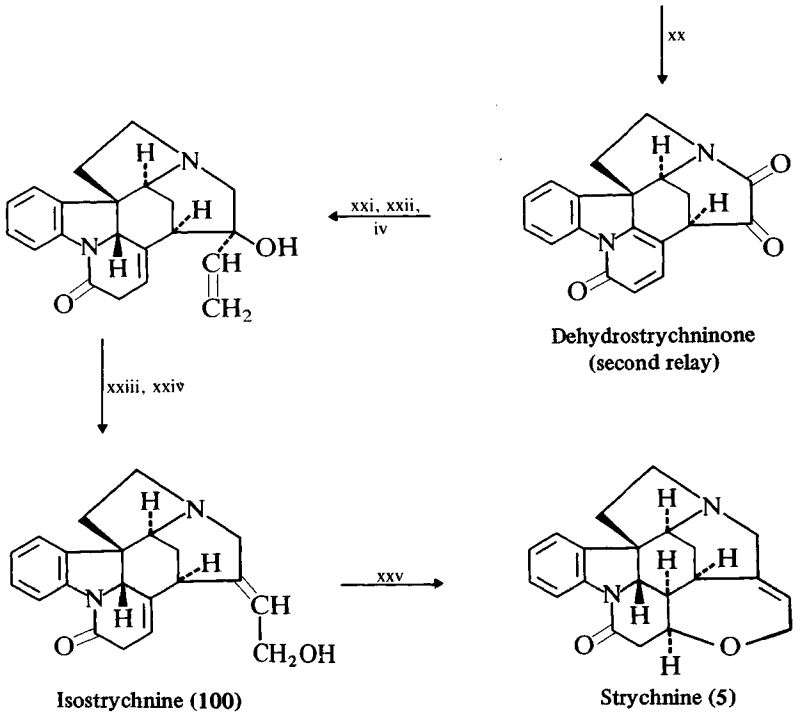
c. PSEUDOSTRYCHNINE. Pseudostrychnine (3-hydroxystrychnine) (**101**) was found in different species of *Strychnos*,[95] especially *S. nux vomica*,[96] along with many strychnine derivatives.[99] This alkaloid can be obtained by the sodium dichromate-catalyzed rearrangement of strychnine N_b-oxide in boiling water.[98] It exists almost entirely in the carbinolamine form as drawn in Scheme 26. The possible equilibration with the carbonyl form could proceed via protonation of the nitrogen and ring opening. An extension of this, in which the equilibrium is displaced toward the right, is the treatment of **101** with methyl iodide which affords N_b-methyl-*sec*-pseudostrychnine (**102**).

d. N_b-*sec*-PSEUDOSTRYCHNINE DERIVATIVES. N_b-Methyl-*sec*-pseudostrychnine (icajine) (**102**) was isolated later as a natural product by Bisset.[100] The interaction between the tertiary nitrogen and the carbonyl lowering the carbonyl stretching frequency[101] has been found again more recently in dichotine (**21**) and geissovelline (**26**) (see Section III.A.3).

An important contribution to the structure determination of the pseudo and N_b-*sec*-pseudostrychnine alkaloids has been provided by Bisset et al.,[102] who have discussed the diagnostic features of the ^{1}H nmr and mass spectra of these series.


OMe
OMe
i–v
CH2—CH2
CH=N
Ts—Cl
CO2Et
OMe
OMe
Py:
vi
NTs
CO2Et
OMe
OMe
vii, viii
NTs
CO2Et
Ac
OMe
OMe
ix
NTs
CO2Et
Ac
CO2Me
CO2Me
x, xi, viii, xii
NAc
CO2Me
CO2Me
xiii
NAc
ONa
CO2Me
vi, xiv–xvi
NAc
CO2Me
xvii, xviii
NAc
CO2H
(First relay)
viii, xix
NH
COMe
xx

Scheme 27.



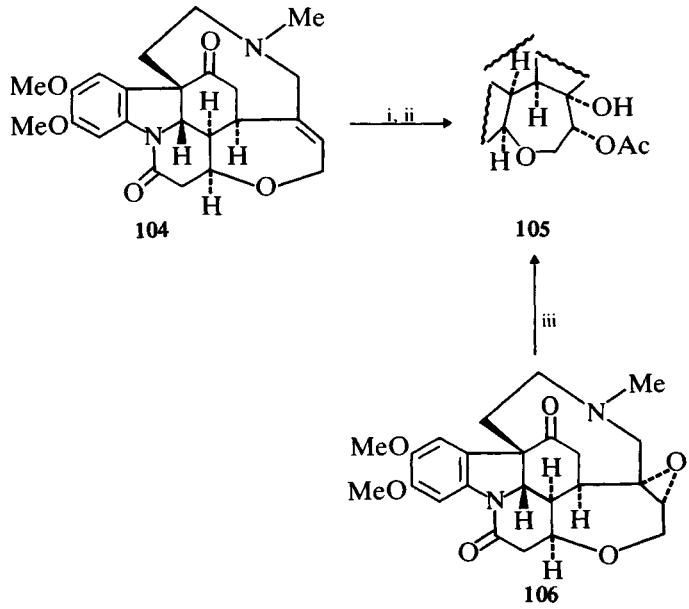
Scheme 27. Synthesis of strychnine.[87] Reagents: CH_2O, $HNMe_2$; ii, MeI; iii, NaCN, DMF; iv, $LiAlH_4$; v, $OHC.CO_2Et$, C_6H_6; vi, TsCl, py; vii, $NaBH_4$; viii, Ac_2O, py; ix, O_3; x, MeOH, HCl; xi, P, HI; xii, MeOH, CH_2N_2; xiii, MeONa, MeOH; xiv, $NaSCH_2Ph$; xv, Raney Ni; xvi, H_2, Pd/C; xvii, KOH, H_2O, MeOH; xviii, resolution with quinidine; xix, HCl, AcOH, H_2O, Δ; xx, SeO_2, EtOH: xxi, NaC≡CH; xxii, H_2, Pd (Lindlar); xxiii, HBr, AcOH; xxiv, H_2O, H_2SO_4, Δ; xxv, EtOH, KOH.

N_b-Cyano-*sec*-pseudostrychnine (**103**) has quite recently been discovered in an Asian *Strychnos* species.[103b] This is the first example of a natural compound containing an *N*-cyano function. It was thought that these compounds were artifacts formed by the action of hydrogen cyanide, which is sometimes used to fumigate plant materials before exportation; however, enquiries about this treatment were negative. Hydrogen cyanide could be generated from cyanogenetic compounds in the plant during drying. No definite evidence is available.

A series of aromatic ring-substituted 19,20α-epoxy-N_b-methyl-*sec*-pseudostrychnines (**106**) has been found in *S. icaja* Baill.[104,105] Structural elucidation was based on spectral properties and a correlation between the osmium tetroxide hydroxylation product and the product of the opening of the epoxide (Scheme 28).

The unusual cis opening of the epoxide ring was attributed to hindrance of the approach of the acetate nucleophile.

The N_b-methyl-*sec* system is found in other series of strychnine type alkaloids: strychnobrasiline (**94**) and holstiine (**96**) (Scheme 24).



Scheme 28. Reagents: i, OsO_4, py; ii, AcCl, THF; iii, AcOH, Δ.

4. *Spermostrychnine, Strychnosilidine, and Related Alkaloids*

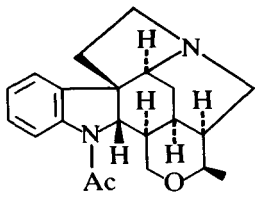
a. SPERMOSTRYCHINE. Spermostrychnine **(93)** theoretically might come from 1,4 addition of a C-17 primary alcohol onto a C-19/C-20, C-21/N_b conjugated iminium ion. This kind of reaction has previously been invoked in indole alkaloid biosynthesis.[106]

The absolute configuration of spermostrychnine, apart from the configuration at C-19, was established by correlation with strychnine.[107] Proton nmr experiments at 220 MHz demonstrated[108] that in this series Me-18 is equatorial (β), or axial (α) in the iso derivatives.

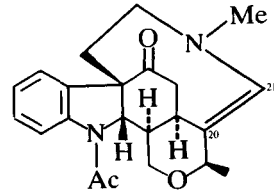
Related alkaloids, called strychnobrasiline **(94)**, strychnosiline **(109)**, and strychnosilidine **(108)**, were found in *S. brasiliensis* Spreng. along with spermostrychnine **(93)**.

Ord curves, nmr, and mass spectroscopy were studied in detail and allowed the complete structural determinations of these alkaloids.[109]

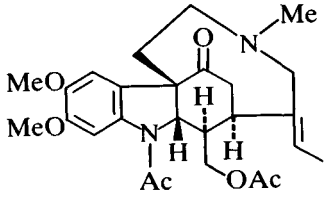
b. STRYCHNOSILIDINE. Strychnosilidine **(108)** is the N_b-methyl-*sec* derivative corresponding to 16-epiretuline **(98)** (Scheme 25). However, the ethylidene chain is represented with a configuration opposite to that generally found in the dihydroindoles of the *Strychnos* series (this feature is not discussed[109]). This alkaloid could be regarded as the precursor of the strychnosilidine series **(109)**, which after protonation and cyclization would lead to the strychnobrasiline ring system **(94)**.



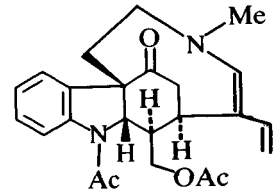
Spermostrychine (93)



Strychnobrasiline (94)
Strychnofendlerine(20α,21-dihydro) (107)



Strychnosilidine (108)



Strychnosiline (109)

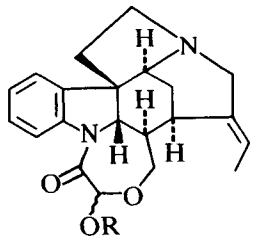
c. STRYCHNOSILINE. The C-20,C-21 enamine double bond of strychnosiline (**109**) as well as that of **94** are particularly unreactive. This interesting observation is probably due to a low π electron density (demonstrated by the deshielded H-21 signal in the nmr) resulting from a double interaction of the C-3 carbonyl with the double bond and the N_b lone pair.[109]

d. STRYCHNOBRASILINE. Strychnobrasiline (**94**) possesses the same tetrahydropyran ring system as spermostrychnine with the same configuration at C-19. The mass spectrum of **94** has been fully interpreted and compared with that of isosplendine,[110] the C-19 epimer of strychnofendlerine (20α,21-dihydrostrychnobrasiline) (**107**),[111] recently discovered in *S. fendleri* Sprague et Sandwith. This interpretation is in agreement with the proposed structure.

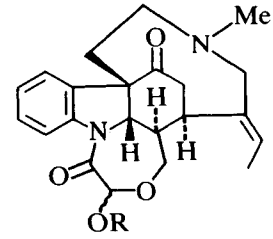
5. *Tsilanine and Holstiline*

a. TSILANINE. Tsilanine (**95**),[112] isolated from *S. henningsii*, has a novel seven-membered lactam ring (glyoxamide acetal). Its relative and absolute configurations have been determined by a correlation with 16-epiretuline (**98**) (Scheme 25). Treatment of **95** in methanolic hydrochloric acid followed by acetylation and partial hydrolysis led to **98**.

b. HOLSTILINE. The structures previously proposed[113] for the holstiline series have been reconsidered[114] after the isolation of tsilanine (**95**)[112] from the same *Strychnos* species (*S. holstii* is identical with *S. henningsii*). Comparison with tsilanine suggested a related structure for **111**. Nmr and mass spectroscopy led to the formulation of the N_b-methyl-*sec*-pseudotsilanine structure for this series.



Tsilanine (95): R = Me
110: R = H



Holstiline (111): R = Me
Holstiine (96): R = H

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CHAPTER VIII

The Aspidospermine Group

J. EDWIN SAXTON

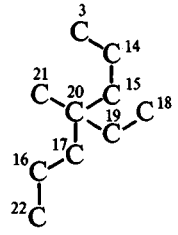
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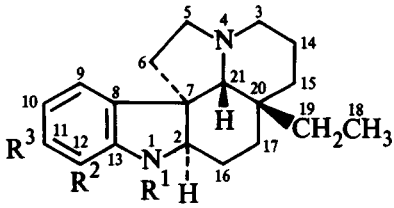
I. INTRODUCTION

A. Survey of Structural Types

The *Aspidosperma* alkaloids are based on the C_{19} or C_{20} skeleton formed by condensation of tryptamine with the rearranged secologanin-derived C_9 or C_{10} unit (**1**). Two important groups of alkaloids result from this condensation. Attachment of C-21 to N_b and the β position of the tryptamine nucleus (the so-called[2] β con-



1



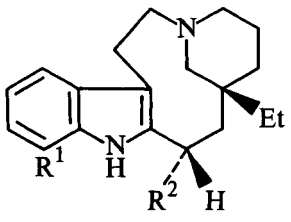
		R^1	R^2	R^3
Aspidospermidine	(2)	H	H	H
Aspidospermine	(7)	Ac	OMe	H
Vallesine	(8)	CHO	OMe	H
Palosine	(9)	COEt	OMe	H
Aspidocarpine	(10)	Ac	OH	OMe
(−)-Pyrifolidine	(11)	Ac	OMe	OMe
(+)-Deacetylaspidospermine	(54)	H	OMe	H

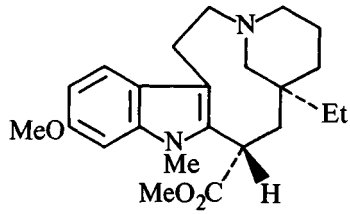
densation), followed by further cyclization between C-16 and C-2, leads to the aspidospermidine (2) skeleton, from which all the *Aspidosperma* alkaloids can in principle be derived by appropriate transformations. Alternatively, attachment of C-21 to N_b and C-2 (α condensation[2]), followed by cyclization between C-16 and N_a, leads to the eburnamine-vincamine group, which is discussed in Chapter IX.

The *Aspidosperma* group constitutes the largest group of indole alkaloids, and presently numbers approximately 220 alkaloids, which may be divided into several structurally distinct subgroups. The simplest group is exemplified by quebrachamine (3) and its derivatives, which lack the 7,21 bond. (−)-Quebrachamine itself occurs* in *Aspidosperma quebrachoblanco* Schlecht., and was isolated, with aspidospermine, in the pioneering investigations in this area.[3] Comparatively little structural variation occurs in this small subgroup of 18 alkaloids, but the retention of the ester group attached to C-16, as well as N_a-methylation and *ar*-methoxylation, and the presence of a 14,15 double bond, have all been encountered; these are exemplified in vincaminoridine (4), a constituent[4] of *Vinca minor* L., dehydrovincadine (5) from *Amsonia tabernaemontana* Walt.,[5] and 12-methoxyvoaphylline (6) from *Crioceras dipladeniiflorus* (Stapf) K. Schum.[6]

The largest group of *Aspidosperma* alkaloids, with approximately 140 members, is based on aspidospermidine, and includes aspidospermine (7), the principal alkaloid of *Aspidosperma quebrachoblanco*, the first alkaloid of this group to be isolated,[3] and the best known. The N_a-formyl analogue, vallesine (8), from *Vallesia glabra* (Cav.) Link,[7] and the N_a-propionyl analogue, palosine (9), from *A. polyneuron* Muell-Arg., are also known.[8] Other positions in the aspidospermidine nucleus in which substitution is often encountered include positions 10, 11, 16, 17, and 18, and double bonds or epoxide functions are occasionally observed at the 14,15 position. Substitution at positions 11 and 12 is exemplified by aspidocarpine (10), from *A. megalocarpon* Muell-Arg.,[9] and (−)-pyrifolidine (11), from *A. quebrachoblanco*,[10] and an additional aromatic substituent is present in aspido-

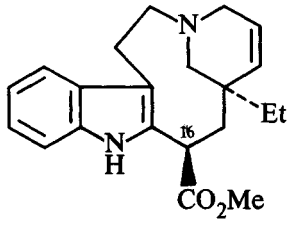
* The occurrences cited are representative, and are not intended to be complete; generally, but not necessarily, the first reported isolation is quoted. For a complete listing of occurrences Ref. 1 should be consulted.



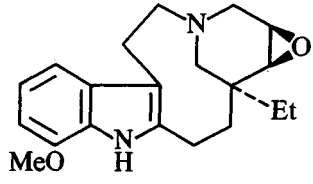


		R^1	R^2
(−)-Quebrachamine	(3)	H	H
12-Methoxyquebrachamine	(53)	OMe	H
(−)-Vincadine	(45)	H	CO_2Me

Vincaminoridine (4)



(+)-14,15-Dehydrovincadine (5)



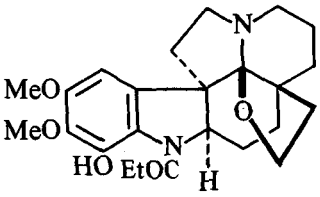
12-Methoxyvoaphylline (6)

albine (12), from *A. album* (Vahl) R. Benth.,[11] an alkaloid in which further oxidation at C-18 and C-21 has resulted in formation of a carbinolamine ether function. Introduction of an oxygen atom at position 9 of the aspidospermidine skeleton appears not to have been observed yet. The functionalization of C-18 is also a feature of several alkaloids of *A. cylindrocarpon* Muell-Arg. and *A. limae* Woodson, which include cylindrocarpine (13)[12] and limapodine (14).[13] Oxidation at C-16 is a characteristic feature of the alkaloids of *A. chakensis* Speg., for example, spegazzinine (15)[14] and spegazzinidine (16).

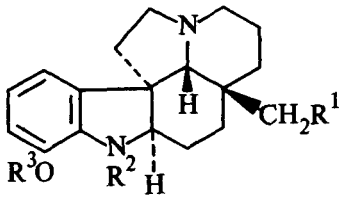
Of the alkaloids based on the simple aspidospermidine skeleton the most highly functionalized are represented by vindorosine (17) and vindoline (18), which occur in *Catharanthus roseus* G. Don.[15]

Alkaloids in which changes to the aspidospermidine skeleton are involved include the obscurinervine (19, 20) group of alkaloids, from *A. obscurinervium* Azambuja,[16] in which a three- or four-carbon unit has been attached to N_a, and aspidodispermine (21), and its deoxy derivative (22), from *A. dispermum* Muell-Arg.,[17] in which the angular group attached to C-20 has been eliminated.

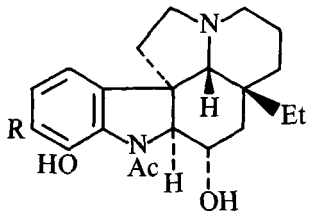
The alkaloids containing a β-anilinoacrylate chromophore, that is, those in which C-22 has been retained and a double bond has been introduced into the 2,16 position, form a large subgroup which it is convenient to discuss separately. Vincadifformine (23), the racemic form of which occurs[18] in *Vinca difformis* Pourr., and tabersonine (24), from *Amsonia tabernaemontana*,[19] are the parent members of this group. Several derivatives of 11-methoxyvincadifformine, a constituent[20] of *V. minor* L., are known; these include bases in which functionalization of C-19 is observed, and/or an epoxide group has been introduced into ring D, for example, echitoserpine (25b)



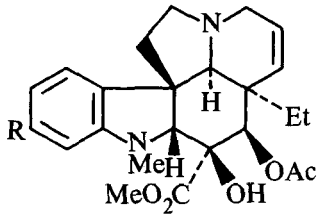
Aspidoalbine (12)



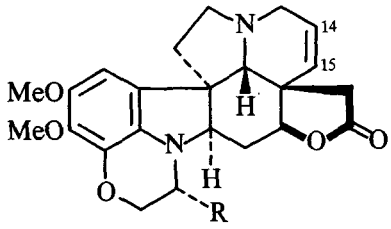
		R^1	R^2	R^3
Cylindrocarpine	(13)	CO_2Me	COCH=CHPh	Me
Limapodine	(14)	CH_2OH	Ac	H



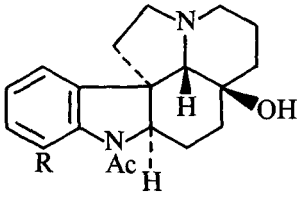
Spegazzinine (15): R = H
Spegazzinidine (16): R = OH



Vindorosine (17): R = H
Vindoline (18): R = OMe



Obscurinervidine (19): R = Me
Obscurinervine (20): R = Et

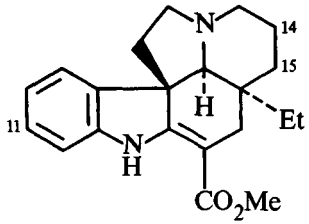


Aspidodispermine (21): R = OH
Deoxyaspidodispermine (22): R = H

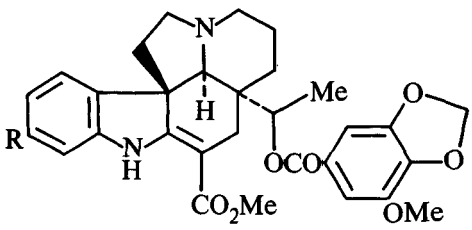
from *Alstonia venenata* R. Br.,[21] and lochnerinine (26) and hörhammerinine (27) from *Catharanthus lanceus* Boj. ex A. DC.[22] Polysubstitution in the aromatic ring is rare in this subgroup of alkaloids, but occurs in hazuntinine (28), from *Hazunta velutina* Pichon.[23] This and cathovalinine (29), from *C. ovalis* Mgf.,[24] are the only two alkaloids for which the configuration of the epoxide function has been rigorously established.

A small group of hexacyclic alkaloids results from attachment of C-19 to C-2; hence the additional ring is five membered. At present nine such alkaloids are known; these may be exemplified by tuboxenine (30) from *Pleiocarpa tubicina* Stapf,[25] vindolinine (31) from *Catharanthus roseus*,[16,26] and pseudokopsinine (32) from *Vinca erecta* Rgl. et Schmalh.[27]

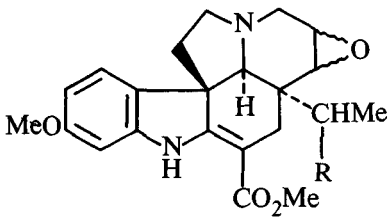
Enlargement of ring B at the expense of ring C leads to quinolone derivatives,



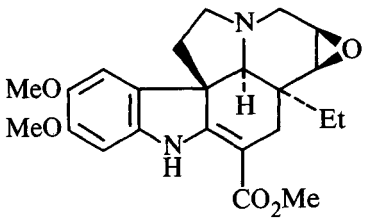
(−)-Vincadifformine (23)
(−)-Tabersonine (24) $\Delta^{14,15}$



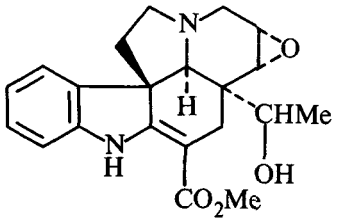
Echitoserpidine (25a): R = H
Echitoserpine (25b): R = OMe



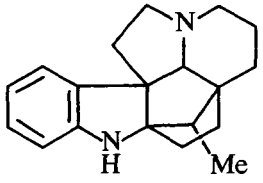
Lochnerinine (26): R = H
Hörhammerinine (27): R = OH



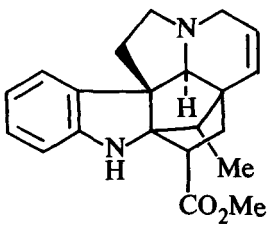
Hazuntinine (28)



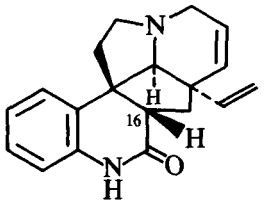
Cathovalinine (29)



Tuboxenine (30)



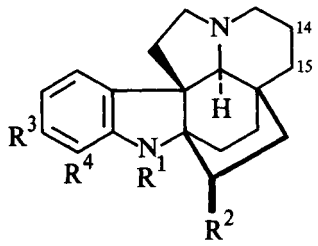
Vindolinine (31)
Pseudokopsinine (32): 14,15-dihydro



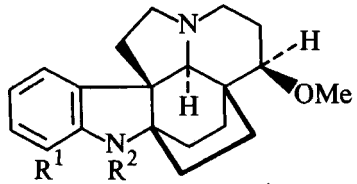
Meloscine (33)

for example, the meloscine (33) group of alkaloids, which are characteristic bases of *Melodinus scandens* Forst.[28]

A further variation in the *Aspidosperma* alkaloid skeleton includes a major hexacyclic group of some 36 members in which C-18 is attached to C-2. The parent base of this group is aspidofractinine (34) which occurs, together with aspidofractine (35), in *Aspidosperma refractum* Mart.[29] Substitution in the aromatic



		R^1	R^2	R^3	R^4
Aspidofractinine	(34)	H	H	H	H
Aspidofractine	(35)	CHO	CO_2Me	H	H
Dimethoxyaspidofractinine	(36)	H	H	OMe	OMe
Venalstonidine	(37)	H	CO_2Me	H	H; 14,15-α-epoxide
Venalstonine	(38)	H	CO_2Me	H	H; $\Delta^{14,15}$

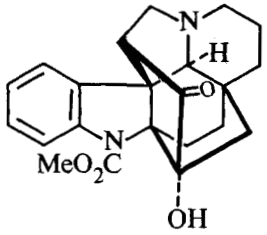


		R^1	R^2
Pyrifoline	(39)	OMe	Ac
Refractidine	(40)	H	CHO

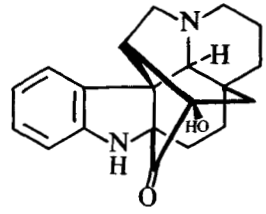
ring is seen in 11,12-dimethoxyaspidofractinine (**36**), an alkaloid of *A. populifolium* A. DC.,[30] and the epoxide base venalstonidine (**37**) and the related unsaturated base, venalstonine (**38**), occur together in *Melodinus australis* (F. Muell.) Pierre[31] and other *Melodinus* species. Methoxyl substitution at C-15, a rare phenomenon, is present in pyrifoline (**39**) and refractidine (**40**) obtained, respectively, from *A. pyrifolium* Mart. and *A. refractum*.[12,32]

The remaining alkaloids, 13 in number, include the *Kopsia* bases, in which an additional bond in the aspidofractine skeleton is formed by attachment of C-22 to C-6, as in kopsine (**41**), the principal base of *K. fruticosa* A. DC.[33] It is of interest to note that kopsine was probably isolated as early as 1890, and thus qualifies as the first *Aspidosperma* alkaloid to be isolated. Variations on the kopsine skeleton include decarbomethoxyisokopsine (**42**), the acyloin rearrangement product of decarbomethoxykopsine, which also occurs in *K. fruticosa*,[34] and fruticosamine (**43**),[34,35] from the same plant, in which C-22 in the kopsine skeleton has migrated to C-17.

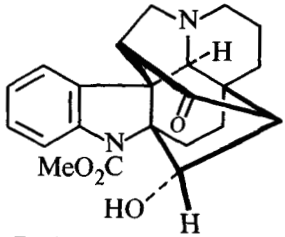
Finally, mention may be made of the indolic alkaloid (**44a**), which has recently been isolated from *Voacanga africana* Stapf.[36a] This base, so far unnamed, clearly belongs to this group, but is unique to date in that it lacks C-5 and C-6 of the ethanamine chain of the original tryptamine; at which stage in the biosynthesis this is lost is at present a matter for speculation.



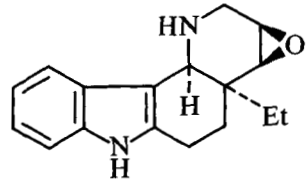
Kopsine (41)



Decarbomethoxyisokopsine (42)



Fruticosamine (43)



44a

B. Occurrence

In spite of the very large number of known *Aspidosperma* alkaloids, and the wide variations in molecular structure encountered, as illustrated above, this group of alkaloids appears to occur naturally in only a very restricted number of plant genera. To date they have been isolated only from plants belonging to the subfamily Plumerioideae, one of the three subfamilies of the Apocynaceae family. For this reason these alkaloids have been designated[36b] the plumerane alkaloids. The subfamily Plumerioideae consists of 94 genera in seven tribes; so far *Aspidosperma*

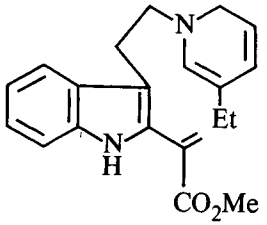
TABLE I. PLANT GENERA OF THE FAMILY APOCYNACEAE, SUBFAMILY PLUMERIOIDEAE, CONTAINING ASPIDOSPERMA ALKALOIDS

Tribe	Genera	Tribe	Genera
Carisseae	*Hunteria*	Alstonieae	*Alstonia*
	Melodinus		*Amsonia*
	Pleiocarpa		*Aspidosperma*
			Catharanthus
Tabernaemontaneae	*Conopharyngia*		*Craspidospermum*
	Crioceras		*Gonioma*
	Ervatamia		*Haplophyton*
	Hazunta		*Rhazya*
	Hedranthera		*Vinca*
	Pagiantha	Rauwolfieae	*Cabucala*
	Pandaca		*Kopsia*
	Stemmadenia		*Vallesia*
	Tabernaemontana		
	Tabernanthe		
	Voacanga		

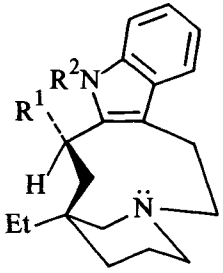
alkaloids have been isolated from 25 genera belonging to the four largest tribes, that is, the Carisseae, Tabernaemontaneae, Alstonieae, and the Rauwolfieae (see Table I). Nineteen other genera have been shown to contain indole alkaloids belonging to other groups, but only two of these (*Callichilia* and *Rejoua*) contain alkaloids possessing a ring system closely related to aspidospermine; these alkaloids are bisindole alkaloids in which one component has a modified aspidospermidine skeleton. It is of interest to note that such a restricted occurrence of such a large group of alkaloids is not matched by any other group of indole alkaloids.

C. Stereochemistry

Stereochemical constancy at any one asymmetric center is not observed among the *Aspidosperma* alkaloids, in sharp contrast to the almost universal constancy of configuration at C-15 in the yohimbine, heteroyohimbine, corynantheine, and strychnine groups, in which the secologanin-derived terpenoid unit is incorporated into the alkaloids without skeletal rearrangement. This lack of constancy is, perhaps, not surprising if the biochemical equivalent of an achiral intermediate such as the secodine derivative (**44b**) is implicated in the biosynthesis of these alkaloids. Accordingly, quebrachamine occurs in both enantiomeric forms, the levorotatory enantiomer (**3**) occurring in *A. quebrachoblanco*, as noted above, and (+)-quebrachamine (**3a**) in *Stemmadenia donnell-smithii* (Rose) Woodson.[37] Vincadine occurs in both levorotatory (**45**) and racemic forms, and so does its 16 epimer, in *Amsonia tabernaemontana*.[38]

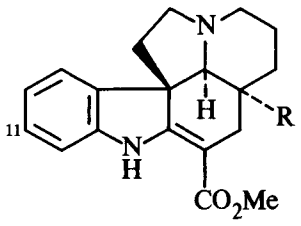


44b



	R^1	R^2
(+)-Quebrachamine (**3a**)	H	H
(+)-Vincadine (**45a**)	CO_2Me	H

In the pentacyclic series the vast majority of alkaloids belong to the two enantiomeric series which exhibit the *relative* stereochemistry at positions 2, 7, 20, and 21 shown in structure **2**. The larger group has the same absolute configuration as (−)-aspidospermine (**7**); that is, they are related to (−)-quebrachamine (**3**). This also applies to the carbinolamine ether group exemplified by aspidoalbine (**12**), and those alkaloids (**21** and **22**) in which C-18 and C-19 have been lost. The



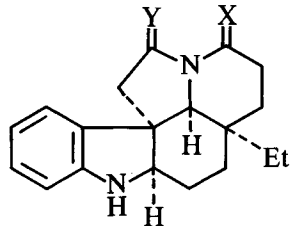
		R
(−)-Minovincine	**(46)**	COMe
(−)-Minovincinine	**(47)**	CH(OH)Me; 19*R*
(−)-Echitovenine	**(48)**	CH(OAc)Me
(−)-19-Epiminovincinine	**(143a)**	CH(OH)Me; 19*S*

enantiomeric series is represented by (+)-pyrifolidine (enantiomer of **11**), which occurs in *Aspidosperma pyrifolium*[39a] and, notably, vindorosine (**17**) and vindoline (**18**).[15] Pyrifolidine is thus one of the few bases in this group known to occur in both enantiomeric forms. Another is 1,2-dehydroaspidospermidine, the (+) enantiomer of which has been frequently encountered, for example, in *Rhazya stricta* Decaisne[39b] and *Amonsia tabernaemontana*[38]; the levororatory enantiomer has been reported to be present in *Vinca erecta* Rgl. et Schmalh.[39c]

This stereochemical series, related to (+)-quebrachamine, is more commonly encountered in the anilinoacrylate (vincadifformine) group, as indicated in structures **23–29**. In this group also some bases occur in both enantiomeric forms; thus (−)-vincadifformine (**23**) occurs in *Vinca minor*, and the dextrorotatory enantiomer in *Amsonia tabernaemontana*.[40] Both enantiomeric forms of minovincine (**46**), minovincinine (**47**), and echitovenine (**48**) also occur naturally.[41] The levorotatory forms of **46** and **47** were originally isolated from *V. minor*,[40a] and (−)-echitovenine has been found in *Catharanthus trichophyllus* (Bak.) Pichon.[41a] (+)-Minovincine occurs in *Tabernaemontana riedelii*,[41b] and (+)-**47** and (+)-**48** in *C. longifolius* Pichon.[41c]

The relative stereochemistry depicted in **2** and **23** is the preferred stereochemistry of these pentacyclic systems, at least in those compounds that contain a sterically undemanding substituent attached to C-20, and this appears to be the stereochemistry exhibited by all the bases mentioned so far. However, four bases isolated[42] from *Melodinus celastroides* H. Baillon, namely, **49–52**, appear to have the less stable stereochemistry in which the ring fusions B/C, C/D, and C/E are all cis; however, the evidence on which these structures rest is almost entirely physical, and to that extent the stereochemical deductions are not completely rigorous and definitive.

Without exception all the hexacyclic and heptacyclic alkaloids of the aspidofractinine, vindolinine, and kopsine groups belong to the same stereochemical series, in which the hydrogen at C-21 has the α configuration. These bases are thus related to (+)-pyrifolidine, rather than the aspidospermine/(−)-pyrifolidine series. Not surprisingly, the biosynthetic processes have become more highly stereospecific with increasing complexity of the alkaloid end product.



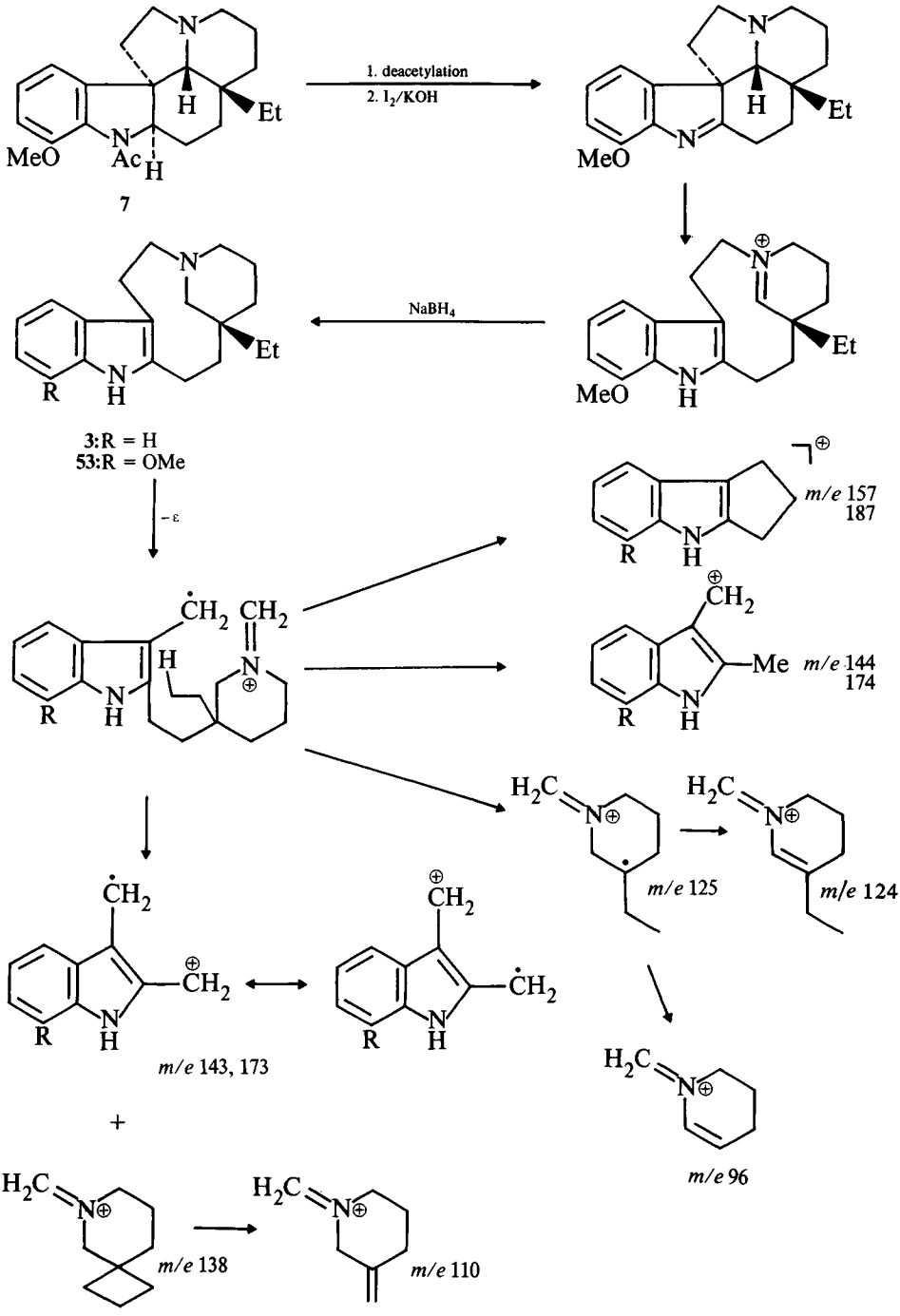
		X	Y
(+)-20,21-Epiaspidospermidine	(49)	H_2	H_2
20,21-Epiaspidospermidine N_b-oxide	(50)	H_2	H_2; N_b-oxide
Melocelinine	(51)	O	H_2
Meloceline	(52)	H_2	O

II. ELUCIDATION OF STRUCTURE AND STEREOCHEMISTRY

A. The Quebrachamine Group

The elucidation of the structure of quebrachamine closely followed that of aspidospermine. The main structural features of the molecule had been defined earlier, mainly by Witkop and co-workers,[43] but the complete structure (3) was finally established by comparison of the mass spectra of quebrachamine and 12-methoxyquebrachamine (53), prepared from aspidospermine (7) (Scheme 1). As expected, the two molecules exhibited identical fragmentation patterns, those fragments derived from 53 which still contained the methoxyl group appearing 30 m.u. higher than the corresponding fragments from quebrachamine.[44] Conversely, oxidative cyclization of (−)-quebrachamine (3), followed by reduction, affords (+)-aspidospermidine (2) (Scheme 2).[45] The close similarity of the ord curves of (−)-quebrachamine (3) and (−)-12-methoxyquebrachamine[44] derived from (−)-aspidospermine (7), as well as those of (+)-aspidospermidine (2), prepared from (−)-quebrachamine, and (+)-deacetylaspidospermine (54), leaves no doubt that the absolute configuration of C-20 in (−)-quebrachamine is as expressed in 3. More recently, the structure of (+)-quebrachamine has been verified by X-ray crystal structure analysis,[46] which reveals that the preferred conformation of the molecule in the crystal is as shown in 3a. If this conformation predominates in solution, the reluctance of quebrachamine to form quaternary salts is understandable.

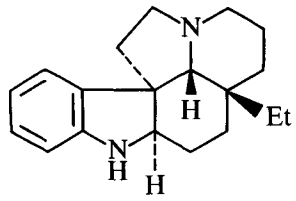
Aside from *ar*-methoxyl derivatives of quebrachamine the most important derivatives are those containing an ester group attached to C-16, which occur in *Vinca minor* and *Amsonia tabernaemontana*. (+)-Vincaminorine has its C-16 proton strongly deshielded by N_b, as shown in 55; the proximity of this proton to N_b also results in a lower basicity of vincaminorine, compared with its C-16 epimer, vincaminoreine. The vincaminorine conformation is also adopted by its 11-methoxy derivative, vincaminoridine (28a), and by 16-epivincadine (56) and its derivatives.



Scheme 1. R = H or OMe.

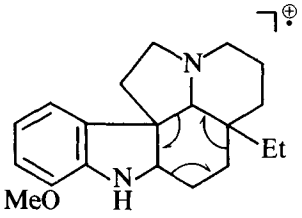
(−)-Quebrachamine (3)

1. $Hg(OAc)_2$/AcOH or $KMnO_4$
2. $LiAlH_4$

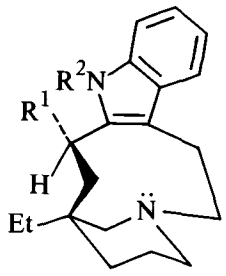


2

Scheme 2.

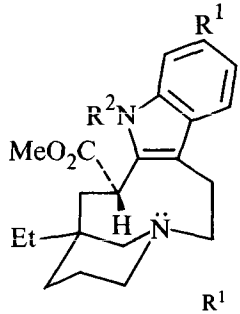


54

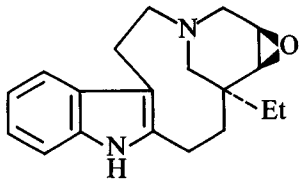


	R^1	R^2
(+)-Quebrachamine (3a)	H	H
(+)-Vincadine (45a)	CO_2Me	H
(+)-Vincaminoreine (57)	CO_2Me	Me

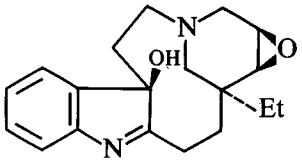
In contrast, (+)-vincadine (**45a**) and its derivatives and (+)-vincaminoreine (**57**) cannot adopt this conformation, owing to steric crowding, and instead adopt[47] the alternative (quebrachamine) conformation of the nine-membered ring. Equilibration experiments show that of the C-16 epimeric pair, vincaminorine and vincaminoreine, the latter is the more stable thermodynamically.[48]



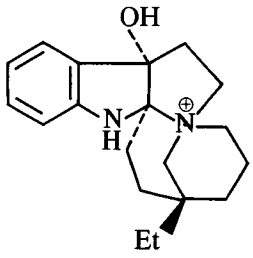
	R^1	R^2
(+)-Vincaminorine (55)	H	Me
Vincaminoridine (4)	OMe	Me
16-Epivincadine (56)	H	H



Voaphylline (**58**)



Voaphylline hydroxyindolenine (**59**)



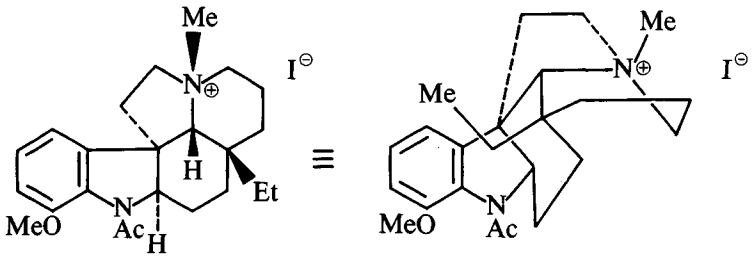
Rhazidine (**60**)

Of the other alkaloids in this group voaphylline (**58**) has been interrelated[49] with (+)-quebrachamine and this, together with the relative configuration of voaphylline hydroxyindolenine (**59**) deduced by the X-ray method,[50] gives the absolute stereochemistry of both bases, since borohydride reduction of **59** affords voaphylline (**58**).

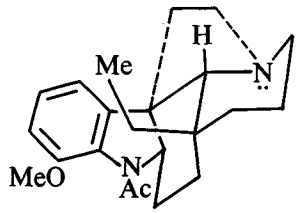
A closely related alkaloid, rhazidine (**60**), has been correlated with (−)-quebrachamine, and consequently belongs to the opposite stereochemical series.[51]

B. The Aspidospermine Group

Initial work on the structure of aspidospermine was mainly concerned with determination of the ring system by means of destructive dehydrogenation reactions, pK_a measurements of aspidospermine and several of its derivatives, and the identification of the chromophore by uv spectral comparison. On the basis of the slender meaningful evidence gleaned from these experiments a structure was proposed[52] which was remarkable in that it was only incorrect in the placing of the ethyl group – understandable in view of the misleading dehydrogenation evidence. The structure and relative configuration were eventually established[53] by the X-ray crystal structure determination of aspidospermine N_b-methiodide (**61**), in which the piperidine ring has the boat conformation shown. Simultaneously some further chemical degradations, largely concerned with the environment of N_b, were published, which also pointed to the same structure.[54] Later refinement of the X-ray data revealed that **61** also represents the absolute configuration of aspidospermine N_b-methiodide.[55] In aspidospermine free base, however, it seems likely that the piperidine ring adopts a chair conformation, as expressed in **7a**; such a conformation would explain the reluctance of aspidospermine to form quaternary salts.

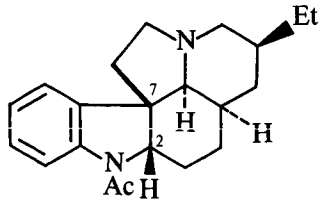


Aspidospermine N_b-methiodide (**61**)

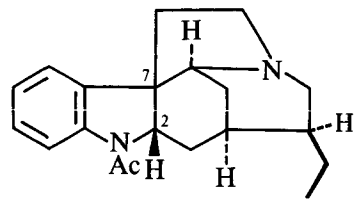


Aspidospermine (**7a**)

The initial determination of the absolute configuration of aspidospermine was based on a comparison of the ord spectra of aspidospermine and its derivatives with those of N_a-acetyl-14-ethyl-20-desethylaspidospermidine (**62**) and N_a-acetyltubifolidine (**63**) of known absolute configuration.[56] In general these ord curves exhibit extrema at 262–278 and 225–247 nm, owing to the N_a-acylindoline chromophore, the signs of the extrema obviously depending on the absolute configuration at C-2 and C-7. A positive Cotton effect is characteristic of compounds related to **62** and **63**, in which C-6 is β. Aspidospermine itself consequently exhibits a negative Cotton effect. In derivatives of aspidospermine a carbonyl group at C-16 appears not to interfere, but the spectra of compounds containing an unsubstituted N_a, or an N_a-carbomethoxy group, may be misleading.[57]

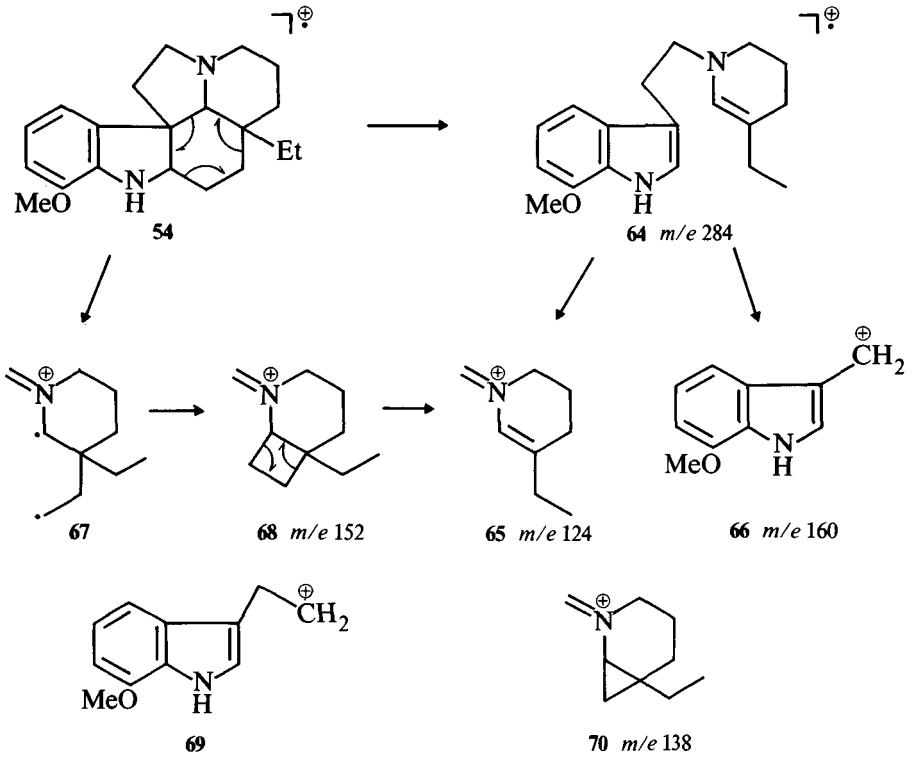


N_a-Acetyl-14-ethyl-20-desethylaspidospermidine (**62**)



N_a-Acetyltubifolidine (**63**)

Knowledge of the structure of aspidospermine provided the basis for the elucidation of the structures of all the other alkaloids in this series, which can be correlated with aspidospermine by chemical or spectroscopic methods. The nature of the aromatic chromophore can usually be established by examination of the nmr and uv spectra, and the substitution in the hydroaromatic portion of the molecule can



Scheme 3.

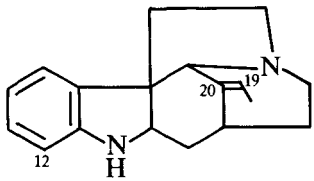
in part be derived from the nmr spectrum. Aside from the obvious diagnosis of terminal methyl groups, N_a-acetyl and other N_a-acyl groups, carbomethoxy groups, and methoxy groups, the signals owing to protons on carbon atoms adjacent to N_a and N_b can often be identified. The C-2 proton, for example, gives rise to a quartet centered around δ 4.25–4.5 ppm; this proton is obviously not present in the hexacyclic alkaloids of the aspidofractinine group, and is also indicative of the cis stereochemistry of the C/D ring junction.[58] In the trans C/D series, so far only known in synthetic compounds,[59,60] the C-2 proton appears at lower field, for example, around δ 4.8–4.9 ppm. The methylene protons on positions 3 and 5, adjacent to N_b, absorb at δ 2.9–3.3, and are not usually obscured by other absorptions, in contrast to the signal owing to the C-21 proton (singlet ~ δ 2.3), which may be superimposed on the N_a-acetyl absorption.

However, it is in the area of mass spectroscopy that physical methods have made their greatest contribution to the elucidation of the structures of the *Aspidosperma* alkaloids. The behavior of the aspidospermine skeleton may be illustrated (Scheme 3) by deacetylaspidospermine (**54**).[10,61] On electron impact ring C suffers a reverse Diels-Alder fission with expulsion of C-16 and C-17 to give a fragment of mass *m/e* 284, which can conveniently break at the benzylic position to give the piperidine fragment **65** (*m/e* 124), which is usually the base peak in the spectrum, or the indole fragment **66**. Incomplete Diels-Alder fission of ring C affords a radical-

ion **67**, which possibly cyclizes to **68**; loss of ethylene then provides another route to the base peak (**65**). Alternative fragmentations of **54** lead to the ions **69** and **70**. In the mass spectrum of aspidospermine itself the ion (**64**) responsible for the peak at *m/e* 284 is accompanied by its N_a-acetyl derivative.

Evidently, this mode of fragmentation can be used to determine in large measure the pattern of substitution in derivatives of aspidospermidine. The presence of substituents in the aromatic ring leads to appropriate displacement of the peaks owing to fragments **64**, **66**, and **69**, whereas substitution at positions 16 and 17 results in loss, during the primary fragmentation, of a substituted ethylene, rather than ethylene itself. Substitution in ring D, or at positions 18 and 19, leads to displacements, to appropriate *m/e* values, of the base peak **65**. Occasionally, confirmatory evidence for these various fragmentations can be derived from deuteration experiments and the identification of metastable peaks.

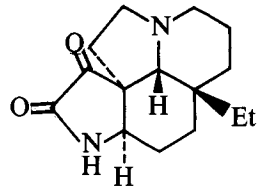
The value of mass spectrometry in this area was impressively well demonstrated at an early stage by Biemann and co-workers,[10,62] who isolated more than 20 minor alkaloids of *Aspidosperma quebrachoblanco* by alumina and gas-liquid chromatography, and completed the structure determination of 15 of them. These included four known aspidospermidine derivatives, namely, aspidospermine (**7**), deacetylaspidospermine (**54**) and its N_a-methyl derivative, and (−)-pyrifolidine (**11**), only the first of which had previously been isolated from a natural source. Two new compounds were shown to be aspidospermidine (**2**) and its N_a-methyl derivative. Six other alkaloids belonged to the aspidospermatidine (**71**) group, namely, aspidospermatidine (**71**) itself, N_a-methylaspidospermatidine, 12-methoxyaspidospermatidine, N_a-acetylaspidospermatidine, N_a-acetyl-12-methoxyaspidospermatidine (aspidospermatine), and 19,20-dihydroaspidospermatine. The structures of the simple aspidospermidine derivatives were elucidated from their nmr and mass spectra as described above, and (−)-pyrifolidine was identified as *O*-methylaspidocarpine.



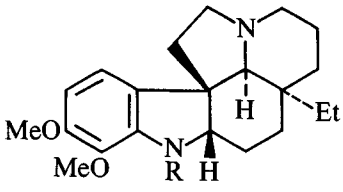
Aspidospermatidine (**71**)

The molecule of aspidocarpine (**10**) contains one oxygen atom more than aspidospermine, and behaves as a 12-hydroxy-*N*-acetylaspidospermidine derivative, since the hydroxyl group is cryptophenolic; that is, it resists methylation, even with diazomethane, although its uv spectrum displays a bathochromic shift in alkali, and the N_a-carbonyl group absorbs at a distinctly lower frequency than in *O*-methylaspidocarpine. A methoxyl group is situated at C-11, since its nmr spectrum discloses the presence of two ortho-coupled aromatic protons, and demethylation of aspidocarpine affords a catechol derivative. The nmr spectrum of the nonaromatic part of the molecule closely resembles that of aspidospermine, and the

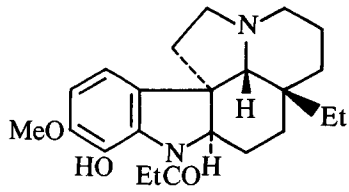
Aspidocarpine (**10**) ⟶ ⟵ Aspidospermine (**7**)



72



(+)-Pyrifolidine (**73**): R = Ac
(+)-Deacetylpyrifolidine (**74**): R = H



Aspidolimine (**75**)

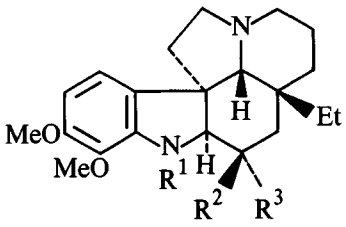
complete structure and absolute stereochemistry were finally established by a process rare in this series, that is, by chromic acid oxidation of aspidocarpine to the α-ketoamide (**72**), also obtainable by similar oxidation of aspidospermine.[9,58b]

(+)-Pyrifolidine (**73**) and its deacetyl derivative (**74**) occur in *A. pyrifolium*[12] and has been isolated before the enantiomeric series was encountered. The nmr spectrum of (+)-pyrifolidine indicated the presence of two methyl groups, an N_a-acetyl group, two ortho-coupled aromatic protons, and an aliphatic portion resembling that of aspidospermine; its complete structure as an *ar*-dimethoxy-N_a-acetylaspidospermidine was confirmed by comparison of the mass spectrum of (+)-deacetylpyrifolidine with that of deacetylaspidospermine. This limits the structure of pyrifolidine to three possibilities, depending on the positions of the methoxyl groups, although preference was given to **73**. This structure was finally established when (+)-pyrifolidine was shown conclusively to be the enantiomer of (−)-*O*-methylaspidocarpine.

Aspidolimine (**75**), one of the principal alkaloids of *A. limae* Woodson[63] and a constituent of *A. triternatum* Rojas Acosta,[64] is simply the N_a-propionyl analogue of aspidocarpine. This was shown by examination of its mass spectrum,[63b] and proved unequivocally by chemical correlation.

Spegazzinine (**15**) and spegazzinidine (**16**) are two phenolic alkaloids of *A. chakensis*,[14] which have suffered oxidation at C-16. Spegazzinidine contains two oxygen atoms more than aspidospermine and on methylation gives a dimethyl ether whose nmr spectrum shows a striking similarity to that of pyrifolidine, with the exception of the signal owing to the C-2 proton. In the spectrum of spegazzinidine dimethyl ether (**76**) this proton appears as a doublet, indicating that the alcoholic group is secondary and situated at position 16, probably in the equatorial configuration since $J_{2,16} = 8$ Hz, consistent with a trans diaxial arrangement of protons at these positions. In consonance with this oxidation of spegazzinidine dimethyl ether affords a ketone (**77**) which on deuteration in presence of base incorporates six deuterium atoms, three in the N_a-acetyl group, and three on the carbon atoms

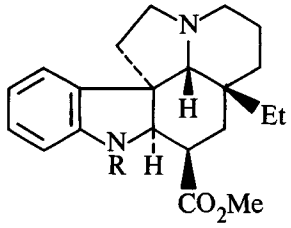
adjacent to the carbonyl group. Only two positions, 16 and 19, are thus possible for the carbonyl group in this ketone, and of these the latter is excluded by the nmr spectrum.[14] The structure (**76**) thus deduced for spegazzinidine dimethyl ether was confirmed by its mass spectrum, which is exactly that expected of an *ar*-methoxylated 16-hydroxyaspidospermine. Thus the alcoholic hydroxyl group does not appear in any of the principal fragments, and is presumably lost in the initial fragmentation of **76**, as "vinyl alcohol." This evidence is consistent only with structure **76**, which was conclusively proved by reduction of its tosylate by means of lithium aluminum hydride, which afforded (−)-N_a-deacetyl-N_a-ethylpyrifolidine (**78**), enantiomeric with the similar reduction product of (+)-pyrifolidine. Spegazzinidine is thus **16**, and comparison of the chemical and spectroscopic properties of spegazzinine establish[14] that it has the constitution **15**.



Spegazzinidine dimethyl ether (**76**): R^1 = Ac, R^2 = H, R^3 = OH

77: R^1 = Ac, R^2, R^3 = O

78: R^1 = Et, R^2 = R^3 = H

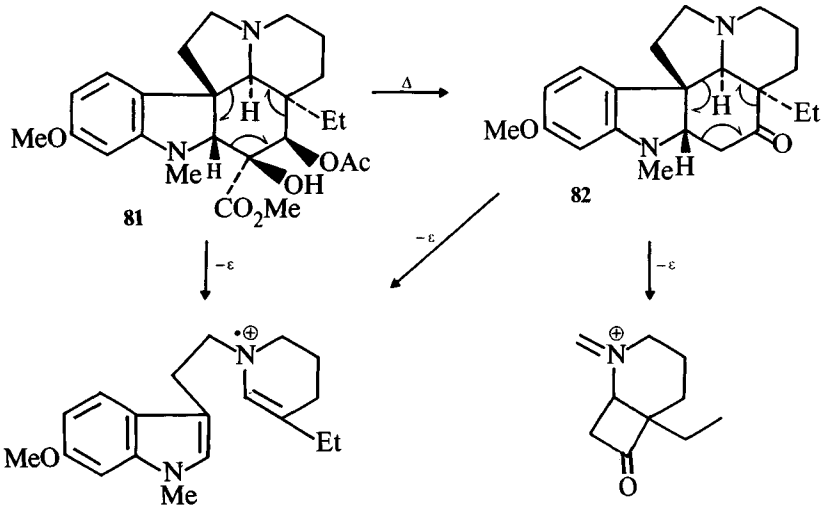


Eburine (**79**): R = H

Eburcine (**80**): R = CO_2Me

Other alkaloids which contain a substituent at C-16 include eburine (**79**) and its N_a-carbomethoxy derivative, eburcine (**80**), which occur in the seeds of *Hunteria eburnea* Pichon.[65] As expected from this formulation the mass spectrum of eburine is very similar to that of aspidospermidine, the initial fission of ring C resulting in the elimination of methyl acrylate, and the formation of a fragment identical with that obtained from aspidospermidine.

The best known alkaloids containing substituents at C-16 and C-17 are vindorosine (**17**) and vindoline (**18**)[15]; these alkaloids, particularly the latter, have been intensively studied owing to the fact that vindoline is one of the constituent bases of the important oncolytic bisindole alkaloid vinblastine. Vindoline[66] is a 6-methoxydihydroindole derivative which, in addition to the aromatic methoxyl group, contains carbomethoxy, *N*-methyl, and secondary acetate groups, as well as two cis-coupled olefinic protons, one of which is further coupled to two non-equivalent methylene protons. A tertiary hydroxyl group is also present. The structure of vindoline becomes clear from the mass spectra of dihydrovindoline (**81**) and the ketone (**82**) obtained by pyrolysis of dihydrovindoline (Scheme 4). Both spectra contain peaks owing to the ion (**83**), derived by fission of ring C, and its further fragmentation products. The spectrum of **82** also contains a peak at *m/e* 166, corresponding to the ion **84**, which is shifted to *m/e* 168 in the spectrum of the dideutero derivative of **82**. These data prove that all the oxygen functions in vindoline, except the 11-methoxy group, are attached to C-16 and C-17 and,

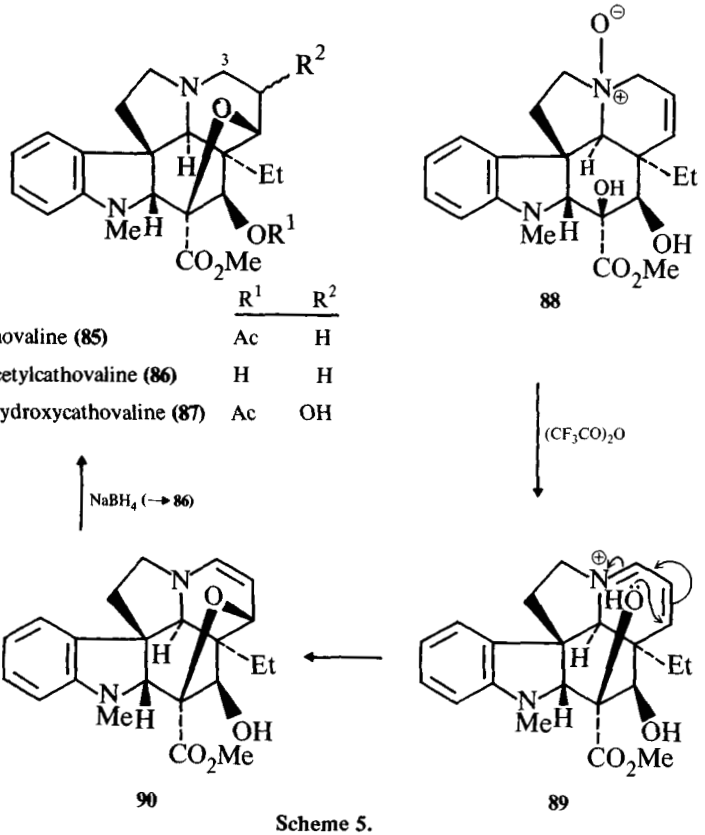


Scheme 4.

when taken into account with the fact that the signals owing to the protons at positions 2 and 17 are singlets, allow only one structure (**81**) for dihydrovindoline.[66] Since vindoline is not an enamine, and the methylene group coupled with one of the olefinic protons is attached to nitrogen (chemical shift evidence), vindoline must have the structure (**18**). The stereochemistry of the ring system in vindoline follows from the chemical shift of the C-18 methyl group (0.48 ppm); no other stereochemistry can account for the strong shielding of this methyl group by the aromatic ring. The complete stereochemistry of vindoline (**18**) follows from the X-ray crystal structure determination[67] of vincristine methiodide (see Chapter XI, Section XXII.A), which has been correlated with vindoline via vinblastine.

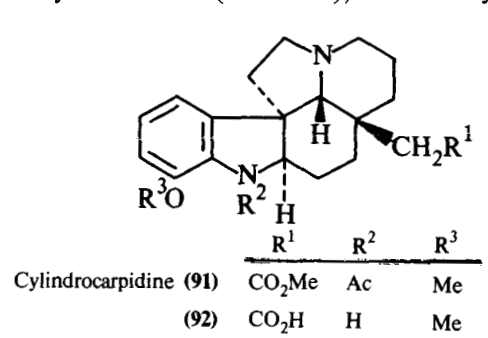
On the basis of its spectroscopic properties, including its ord spectrum, vindorosine has been proved to be demethoxyvindoline, and hence has the structure **17**, including absolute configuration.[15a]

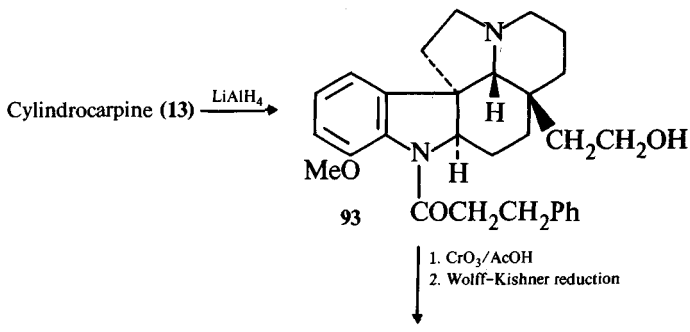
Cathovaline (cathanneine) (**85**), from *Catharanthus ovalis* and *C. lanceus*,[68] is simply the internal ether derived by addition of the C-16 hydroxyl group in vindorosine to the ring D double bond. Deacetylcathovaline (**86**) and 14-hydroxycathovaline (**87**) also occur in *C. ovalis*.[69] Correlation of cathovaline with vindorosine was achieved by two methods. The first of these involved the oxidation of vindorosine by means of chromic acid in pyridine, which gave two major products, one of which was identified as 3-oxocathovaline.[70] The second route (Scheme 5) proceeded via the Polonovski reaction on deacetylvindorosine N_b-oxide (**88**), prepared by oxidation of *O*-acetylvindorosine followed by deacetylation with sodium methoxide. Reaction of **88** with trifluoroacetic anhydride gave an intermediate immonium ion (**89**) in which the C-16 hydroxyl group was conveniently situated for cyclization on to the electrophilic C-15; reduction ($NaBH_4$) of the enamine (**90**) thus formed afforded deacetylcathovaline (**86**).[69a]



Scheme 5.

Several alkaloids are known in which C-18 has suffered oxidation, and has been converted into an ester or primary hydroxyl group. The first of these alkaloids to be encountered[12] were cylindrocarpine (**13**) and its N_a-acetyl analogue cylindrocarpidine (**91**). The unusual uv spectrum of cylindrocarpine was explained when it was shown that acid hydrolysis yields cinnamic acid and cylindrocarpinic acid (**92**), whose uv spectrum is almost identical with that of deacetylaspidospermine. The structure (**13**) of cylindrocarpine was finally demonstrated[58a] by reduction ($LiAlH_4$) to the primary alcohol **93** (Scheme 6), followed by oxidation to the

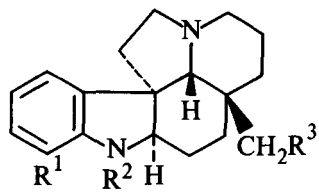




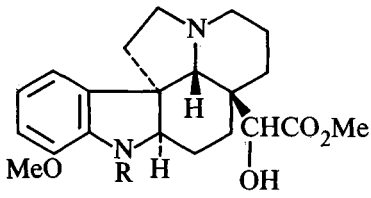
Scheme 6.

corresponding aldehyde, and Wolff-Kishner reduction, which gave deacetylaspidospermine (**54**). The structure of cylindrocarpidine follows from its hydrolysis to cylindrocarpinic acid (**92**), methanol, and acetic acid.

Later extractions of *A. cylindrocarpon* resulted in the isolation of cylindrocarine (**94**) and several new derivatives (**95–99**), two derivatives (**100, 101**) of cylindrocarpinol, and six new bases (**102–107**) in which C-19 has also been oxidized.[71] These new 19-hydroxylated bases belong to the same stereochemical series as (−)-aspidospermine (ord evidence). The configuration at C-19 was deduced by comparison of the cd spectrum of the xanthate of *N*-acetyl-19-hydroxycylindrocarine (**104**) with that of the xanthate of *R*-(−)-lactic acid; a negative Cotton effect at ~ 350 nm exhibited by both compounds, but absent in the spectrum of **104** itself, indicated the *R* configuration of C-19 in **104**, and presumably also in **102**, **103**, and **105–107**.

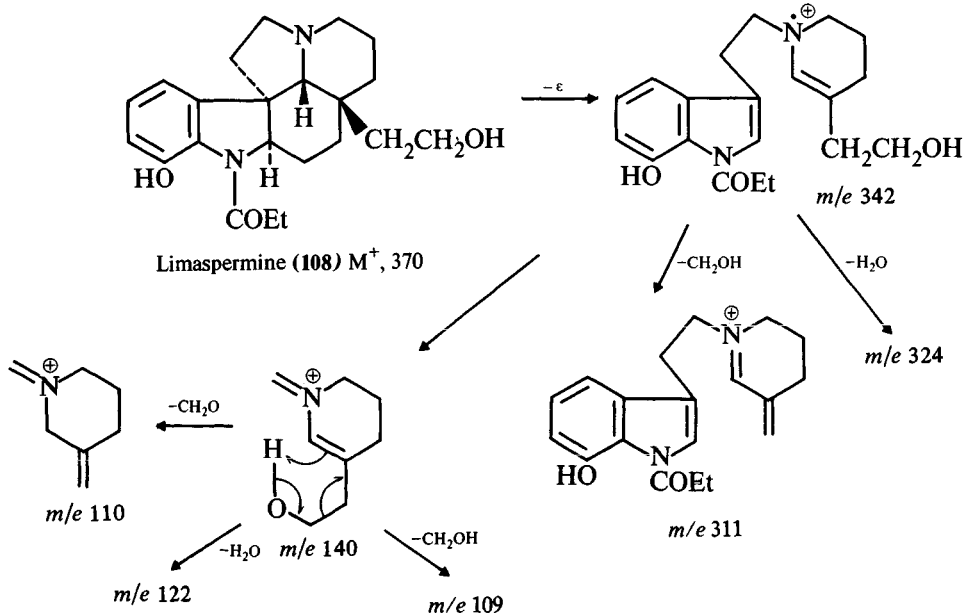


	R^1	R^2	R^3
Cylindrocarine (**94**)	MeO	H	CO_2Me
N-Formylcylindrocarine (**95**)	MeO	CHO	CO_2Me
N-Methylcylindrocarine (**96**)	MeO	Me	CO_2Me
12-Demethoxy-*N*-acetylcylindrocarine (**97**)	H	Ac	CO_2Me
N-Benzoylcylindrocarine (**98**)	MeO	COPh	CO_2Me
Homocylindrocarpidine (**99**)	MeO	COEt	CO_2Me
N-Formylcylindrocarpinol (**100**)	MeO	CHO	CH_2OH
N-Acetylcylindrocarpinol (**101**)	MeO	Ac	CH_2OH
Cylindrocarpinol (**112**)	MeO	H	CH_2OH

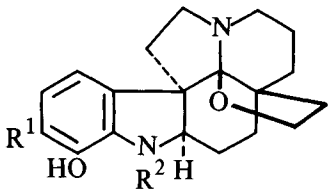


	R
19-Hydroxycylindrocarine (**102**)	H
N-Formyl-19-hydroxycylindrocarine (**103**)	CHO
N-Acetyl-19-hydroxycylindrocarine (**104**)	Ac
N-Benzoyl-19-hydroxycylindrocarine (**105**)	COPh
N-Cinnamoyl-19-hydroxycylindrocarine (**106**)	COCH = CHPh
N-Dihydrocinnamoyl-19-hydroxycylindrocarine (**107**)	$COCH_2CH_2Ph$

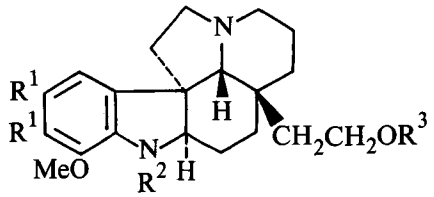
A primary alcohol group at C-18 is also a feature of the structure of limaspermine (**108**), an alkaloid from *A. limae* whose phenolic hydroxyl group is strongly hydrogen bonded to an N_a-propionyl group.[72] The absence of a terminal methyl signal in the nmr spectrum, and the presence of a triplet at 3.25 ppm, shifted downfield to δ 4.0 in the spectrum of the acetate, provide clear evidence for the gross structure (**108**), which is amply confirmed by its mass spectrum. The expected peaks arising from the normal fragmentation of the ring system in **108** are accompanied by others resulting from the presence of the primary hydroxyl group; these include peaks at *m/e* 324, 311, 122, 109, and a particularly revealing one at *m/e* 110 (Scheme 7).



Scheme 7.



	R^1	R^2
Haplocine (**109**)	H	COEt
Haplocidine (**110**)	H	COMe
Aspidolimidine (**113**)	MeO	COMe



	R^1	R^2	R^3
111	H	COEt	H
114	MeO	H	H
115	MeO	COMe	COMe
116	MeO	Et	H
117	H	COMe	COMe
118	H	Et	H

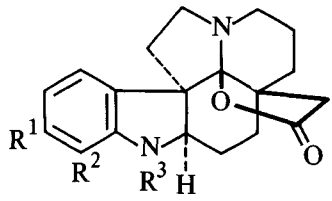
Close relatives of limaspermine found in *A. limae* include 11-methoxylimaspermine,[72] limapodine (**14**), and 11-methoxylimapodine.[13]

Oxidation at C-21 of alkaloids such as limaspermine and closure of the carbinolamine ether ring between positions 18 and 21 affords the aspidoalbine (**12**) group of alkaloids, exemplified also by haplocine (**109**) and haplocidine (**110**), from *Haplophyton cimicidum* A. DC.[73] The structure of haplocine was deduced by methylation to *O*-methylhaplocine, followed by hydrogenation to the primary alcohol (**111**) and removal of the primary hydroxyl group, which gave palosine (**9**). Hence the absolute configuration of haplocine is as shown in **109**, and since hydrogenation gives limaspermine (**108**), the absolute configuration of the latter is also established.

The constitution of haplocidine (**110**), which is also found in *Vallesia dichotoma*, becomes clear from its conversion into a mixture of cylindrocarpinol (**112**) and its C-21 epimer, by methylation, hydrolysis, and reduction by means of lithium aluminum hydride.[74] Other bases in this group include aspidolimidine (**113**), from *A. limae*,[63b] and aspidoalbine (**12**), from *A. album*,[11] whose structures were deduced mainly from nmr and mass spectral data. Comparison[11,16] of the mass spectra of the aspidoalbine derivatives **114–116** with those of cylindrocarpinol (**112**) and the corresponding derivatives **117** and **118** left little doubt that the structure of aspidoalbine is **12**, and comparison of the mass spectra of aspidoalbine and aspidolimidine (**113**) similarly confirmed the structure of aspidolimidine.[63b]

Oxidation of haplocine by means of chromium trioxide in pyridine yields the lactonic alkaloid cimicine (**119**), which occurs in *H. cimicidum*, together with cimicidine (**120**), its 11-methoxy derivative.[75] Dichotamine, a constituent of *Vallesia dichotoma*, has the structure **121**, since its deformyl derivative can be reduced ($LiAlH_4$) to a mixture of cylindrocarpinol (**112**) and its C-21 epimer.[74,76]

The alkaloids obscurinervine (**20**), obscurinervidine (**19**), and their 14,15-dihydro derivatives (from *A. obscurinervium*) and neblinine (**122**) (from *A. neblinae* Monachino)[16] are unusual in that they contain an additional six-membered ring



	R^1	R^2	R^3
Cimicine (**119**)	H	OH	COEt
Cimicidine (**120**)	MeO	OH	COEt
Dichotamine (**121**)	H	MeO	CHO

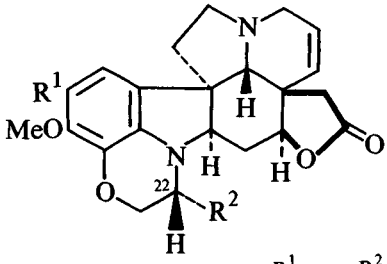
incorporating N_a and an oxygen atom attached to C-12. The mass spectra of these alkaloids are comparatively simple, the main fragments involving loss of carbon monoxide and a methyl or ethyl group, as appropriate. In contrast, the mass spectra of the products (**123, 124**) obtained by reduction ($LiAlH_4$) of obscurinervine and obscurinervidine were extremely revealing, and exhibited the typical fragmentation pattern of an aspidospermidine derivative containing a hydroxyethyl group at position 20 (Scheme 8). Acetylation of the primary alcohol function in the 14,15-dihydro derivatives of **123** and **124** gave acetates whose mass spectra showed prominent peaks owing to the ions **125** and **126**, as did the mass spectra of the 17-ketones obtained by oxidation. In all these spectra the positions of the appropriate indole ions **127–130** were unchanged.

The complete structure and relative configuration of dihydroobscurinervidinol (**132**), obtained by standard procedures from dihydroobscurinervidine (**131**) (Scheme 9), were established[16a] by an independent preparation from depropionyl-aspidoalbine (**133**). Alkylation of N_a by means of 2-iodo-1-propanol, followed by cyclization of the monobrosylate and reduction of the carbinolamine ether linkage, afforded dihydroobscurinervidinol (**132**). Subsequently neblinine (**122**), which was shown structurally and stereochemically to be demethoxyobscurinervidine, was converted into dihydroneblininane (**134**) via dihydroneblininol (**135**), which was prepared from deacetyl-(+)-aspidocarpine (**136**) by a process analogous to the conversion of **133** into **132**. Since obscurinervine (**20**), obscurinervidine (**19**), and neblinine (**122**) have the same absolute configuration (ord evidence) these correlations prove that these three alkaloids, *and also aspidoalbine*, have the same absolute configuration as aspidocarpine (**10**).

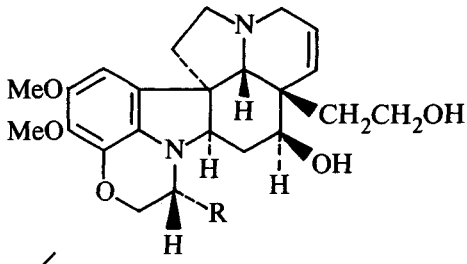
The stereochemistry at the remaining asymmetric centers (C-17 and C-22) in obscurinervine (**20**) and its relatives (**19** and **122**) was initially deduced[16a] on the basis of the nmr evidence, and subsequently confirmed[16b] by the X-ray crystal structure determination of obscurinervine hydrobromide.

Recently a new variant of this structural type has been encountered in alalakine (**137**), an alkaloid of the seeds of *A. album*.[77]

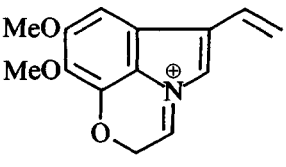
Aspidodispermine (**21**) and deoxyaspidodispermine (**22**) are two constituents of *A. dispermum*[17] which differ from all other *Aspidosperma* alkaloids known at present in lacking a two-carbon unit at C-20. Both alkaloids contain an *N*-



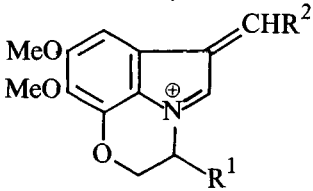
	R^1	R^2
Obscurinervidine (19)	MeO	Me
Obscurinervine (20)	MeO	Et
Neblinine (122)	H	Me



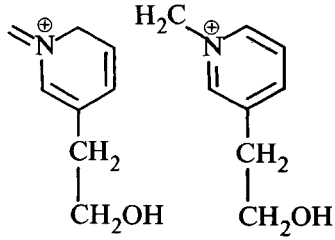
123:R = Et
124:R = Me



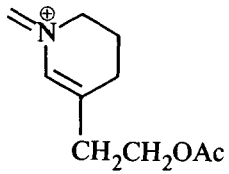
m/e 244



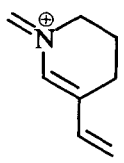
	m/e	R^1	R^2
127	246	Me	H
128	260	Et	H
129	260	Me	Me
130	274	Et	Me



m/e 138 *m/e* 137



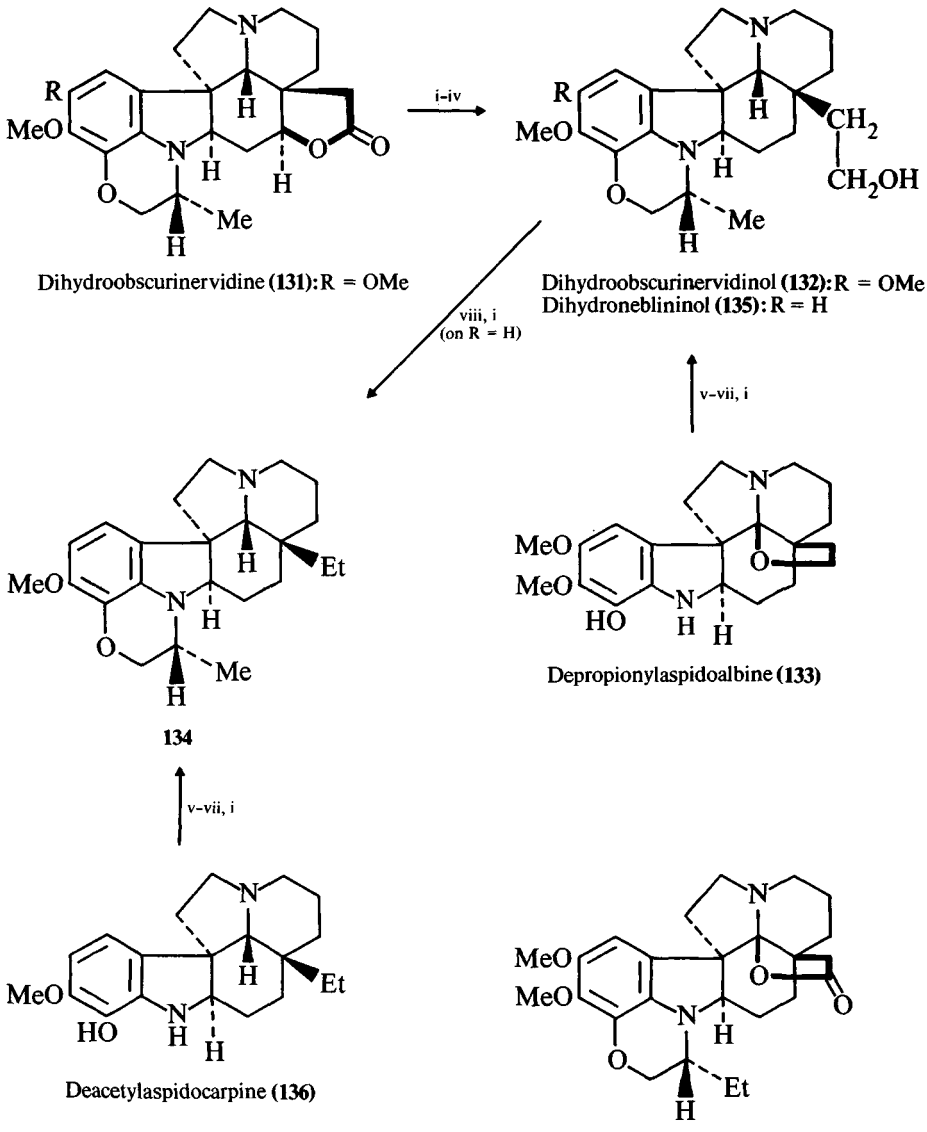
125 *m/e* 182



126 *m/e* 122

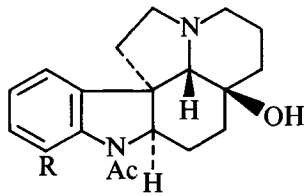
Scheme 8.

acetyldihydroindole part structure, the additional oxygen atom in aspidodispermine being contained in a hydroxyl group attached to C-12. The remaining oxygen atom is present as an alcohol function (ir spectrum), which must be tertiary since the nmr spectrum of its acetate does not show the absorption of a C*H*OAc proton. The mass spectra contain peaks at $M^+ - 18$, and also at *m/e* 112 and 140, owing to the ions **138** and **139**. Since aspidodispermine and deoxyaspidodispermine are not carbinolamines, and since their nmr spectra contain the aspidospermine "finger-

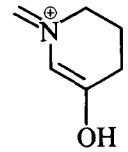


Scheme 9. Reagents: i, $LiAlH_4$; ii, MeCOCl, K_2CO_3, C_6H_6; iii, DCC, H_3PO_4, DMSO; iv, Wolff-Kishner reduction; v, $MeCHICH_2OH$; vi, $BrC_6H_4SO_2Cl$, py; vii, NaOH, MeOH; viii, $MeC_6H_4SO_2Cl$, py.

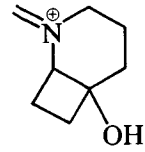
print" quartet owing to the C-2 proton, positions 2 and 21 are eliminated, and the only possible position for a tertiary hydroxyl group is C-20. The structures **21** and **22** thus deduced were subsequently[78] confirmed by the X-ray crystal structure determination of 12-*O*-methylaspidodispermine N_b-hydrobromide, the absolute configuration being established by ord comparison with (−)-aspidospermine.



21: R = OH
22: R = H



138

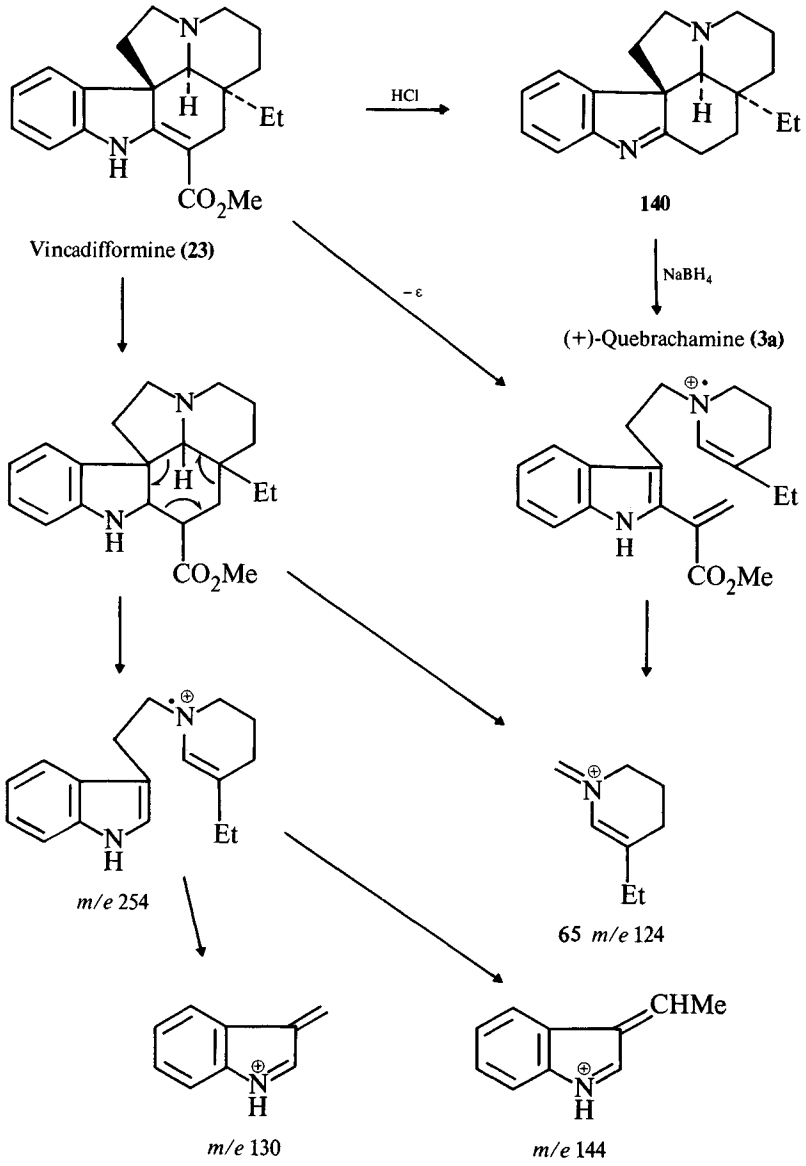


139

C. The Vincadifformine Group

The alkaloids of this group, which currently numbers around 50 bases, are derived from the parent alkaloid (−)-vincadifformine (**23**) or its enantiomer. (±)-Vincadifformine occurs in *Vinca difformis*,[18] and the dextrorotatory form occurs, among other sources, in *Amsonia tabernaemontana*, together with (−)-tabersonine.[38] (−)-Vincadifformine is a constituent of *V. minor*.[40] A characteristic feature of all the alkaloids in this group is the extremely high optical rotatory power; pure (+)-vincadifformine, from *A. tabernaemontana*,[40b] has $[\alpha]_D + 600°$, consistent with a rotation of $-600°$ for (−)-vincadifformine synthesized[79] from (−)-tabersonine. (−)-Tabersonine[19] itself has $[\alpha]_D - 310°$. The few apparent exceptions to this rule concern alkaloids of uncertain structure or purity, or they may even be partly racemic. Other characteristic features exhibited by these bases include the uv spectrum (λ_{max} 225, 300, 328 nm) and ir spectrum (ν_{max} 1660 and 1610 cm^{-1}), which are indicative of the β-anilinoacrylate chromophore. The chemical behavior includes a resistance to *N*-acylation and hydrogenation; however, the double bond can be reduced by metal-acid reagents (e.g., $Zn\text{-}H_2SO_4$). Hydrolysis of the ester group is slow and, except under mild conditions, is accompanied by decarboxylation, with formation of the related indolenines. In the case of (±)-vincadifformine [(±)-**23**] this reaction (Scheme 10) gives (±)-1,2-dehydroaspidospermidine [(±)-**140**], which on reduction affords (±)-quebrachamine [(±)-**3**]. In consonance with this, the mass spectrum of vincadifformine contains an important peak at *m/e* 124, owing to the ion **65** produced by fission of ring C and the 5,6-bond. As expected, the mass spectrum of 2,16-dihydrovincadifformine exhibits the typical aspidospermidine fragmentation pattern, the initial reverse Diels-Alder fission of ring C involving loss of methyl acrylate; the ion at *m/e* 124 is now responsible for the base peak in the spectrum.[18b]

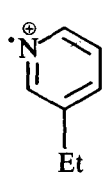
The ir, uv, nmr, and mass spectra of 14,15-dihydrotabersonine are superimposable on those of vincadifformine; hence this molecule also has the gross structure **23**. However, acid hydrolysis of dihydrotabersonine affords (−)-1,2-dehydroaspidospermidine (**140**), which on reduction (KBH_4) gives (+)-quebrachamine (**3a**).[80] Hence (+)-vincadifformine belongs to the aspidospermine group, whereas (−)-vincadifformine and tabersonine have the opposite stereochemical configuration. The double bond in tabersonine must be in the 14,15 position, since the molecule contains two olefinic protons, but it is not an enamine since it is unaffected by



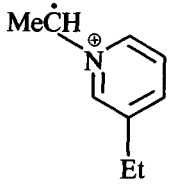
Scheme 10.

chemical reducing agents (e.g., KBH_4 or Zn/H_2SO_4). The mass spectrum supports[80] the inclusion of a double bond in ring D, the peaks at *m/e* 107 and 135, for example, being due to the ions **141** and **142**.

Related alkaloids include several in which C-19 carries an oxygen function. (−)-Minovincine, from *V. minor*, is a methyl ketone of structure and absolute configuration (**46**), since Wolff-Kishner reduction gives (−)-vincadifformine.[40a] Related lactams are also known; (+)-3-oxominovincine, obtainable with (+)-5-



141
m/e 107

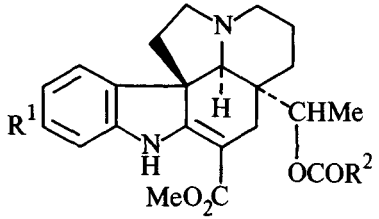


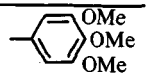
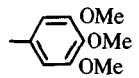
142
m/e 135

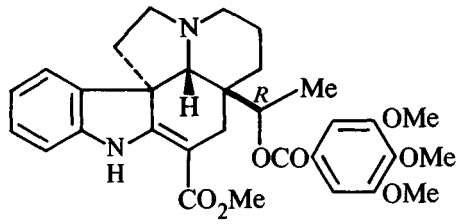
oxominovincine by oxidation of (+)-minovincine, is a constituent of *Tabernaemontana riedelii*,[41b] while (−)-5-oxominovincine, which belongs to the enantiomeric series, has been found in *V. minor*.[81]

The related C-19 epimeric secondary alcohols are also known. (−)-Minovincinine (**47**) is an amorphous base, $[\alpha]_D - 418°$, isolated from *V. minor*,[40a] but it has also been prepared by reduction of (−)-minovincine,[82] as a crystalline product, mp 135°, $[\alpha]_D - 580°$, together with (−)-19-epiminovincinine (**143a**), mp 155°, $[\alpha]_D - 510°$, which has also been isolated from *V. minor*.[82] The configuration at C-19 in these epimers was determined by the application of Horeau's rule following esterification with phenylbutyric anhydride, from which it was concluded that in (−)-minovincinine C-19 has the *R* configuration, and in the epimer of mp 155° [(−)-19-epiminovincinine] it has the *S* configuration.[82] 11-Methoxyminovincine, which occurs in *V. minor*,[40b] also affords two epimeric alcohols on reduction; of these 11-methoxy-19-epiminovincinine, a minor base of *V. minor*, has the 19*R* configuration.[83]

The ester alkaloids in this group include echitoserpidine (**25a**) and (−)-echitovenine (**48**), mentioned earlier. The 11-methoxy derivatives of these bases, echitoserpine (**25b**) and (−)-echitovenaldine, occur also in *Alstonia venenata*, together with (−)-echitoveniline (**143b**) and (−)-11-methoxyechitoveniline (**143c**), which are the trimethoxybenzoyl analogues of echitoserpidine and echitoserpine, and echitovenidine (**143d**) and 11-methoxyechitovenidine (**143e**), the corresponding dimethylacryloyl esters.[84a–d]



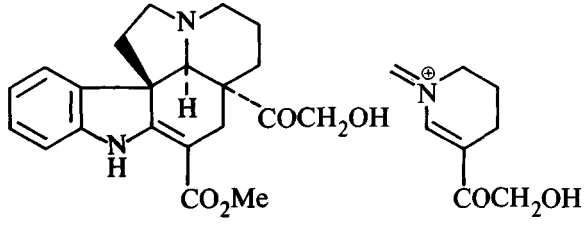
		R^1	R^2
Echitoveniline	(**143b**)	H	
11-Methoxyechitoveniline	(**143c**)	MeO	
Echitovenidine	(**143d**)	H	$-CH=CMe_2$
11-Methoxyechitovenidine	(**143e**)	MeO	$-CH=CMe_2$



19-Epi-(+)-echitoveniline (**143f**)

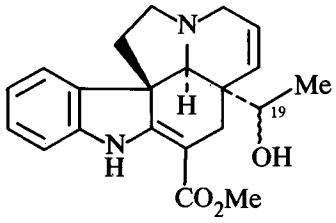
Whereas (−)-echitoveniline (**143b**) occurs in the fruits of *A. venenata*, a member of the opposite stereochemical series occurs in the leaves.[84e] This is not the enantiomer of **143b**, since it possesses the same configuration at C-19; it is therefore 19-epi-(+)-echitoveniline (**143f**).

Cathaphylline, a constituent of the roots of *Catharanthus trichophyllus*,[41a] differs from all other known alkaloids of this subgroup in being functionalized at both C-18 and C-19. The constitution **144** follows from its mass spectrum, which contains peaks at *m/e* 337 ($M^+ - CH_2OH$), 309 ($M^+ - COCH_2OH$), *m/e* 59 ($\overset{+}{C}OCH_2OH$), and *m/e* 154, the last of which is presumably due to the ion **145**; the nmr spectra of the base and its *O*-acetate are consistent with this formulation. The absolute configuration **144** follows from the high negative rotation ($[\alpha]_D - 438°$).

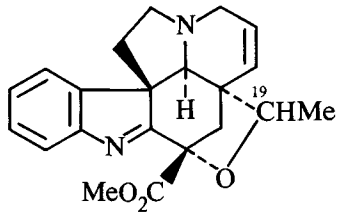


Cathaphylline (**144**) **145** *m/e* 154

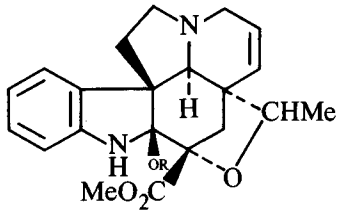
In the tabersonine group, both 11-hydroxytabersonine and 11-methoxytabersonine occur naturally, for example, in *Craspidospermum verticillatum* Boj. var. *petiolare* A. D.C.[85] The 19-hydroxy epimers (**146** and **147**) are apparently among the constituents of the aerial parts of *Catharanthus ovalis*;[86a,b] of these the 19*S* epimer is presumably identical with an alkaloid of *C. lanceus* which is reported[87] to give (−)-19-epiminovincinine (**143a**) on hydrogenation. These epimers (**146** and **147**) were independently prepared from vindolinine (**31**) by reaction with iodine, which gave the epimeric 19-iodotabersonines; hydrolysis then gave **146** and **147**. Oxidation by means of lead tetraacetate afforded two indolenines **148** and **149**, which were converted by sodium methoxide into the epimeric bases kitramine (**150**) and kitraline (**151**). One of these bases contains a methyl group which is strongly shielded, presumably by the aromatic ring[86b]; molecule models indicate that this should be the 19*S* epimer **151**. These two carbinolamine ethers have also been shown to occur in *C. ovalis*, and in the course of studying them it was noted that their mass spectra show a clear resemblance to the mass spectrum of vincoline,



146 19*R*
147 19*S*



148 19*R*
149 19*S*



Kitramine (**150**): R = Me 19*R*
Kitraline (**151**): R = Me 19*S*
Melobaline (**152a**): R = H 19*R*
Vincoline (**152b**): R = H 19*S*

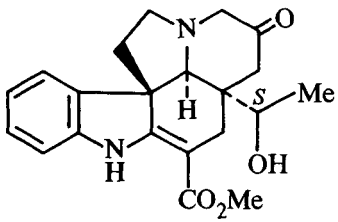
an alkaloid first isolated from *C. lanceus*,[22a,88] except that the fragments containing the indole unit are displaced by 14 mass units. In fact vincoline is the 19*S*-carbinolamine **152b** corresponding to **151**, and was prepared from the indolenine **149** by hydration in the presence of silica.[86]

Subsequently these conclusions were confirmed by the determination of the absolute configuration at C-19 in **146** and **147** by application of Horeau's method.[86c] Since hydrogenation of 19*R*-hydroxytabersonine (**146**) gave (−)-minovincinine (**47**), this also confirms the stereochemistry of **47** deduced by Meisel and Döpke.[82]

Melobaline, an alkaloid of *Melodinus balansae* Baill.,[89a,b] shows a striking resemblance to vincoline in chemical and spectroscopic properties. Examination of its ^{13}C nmr spectrum showed that C-2 carries both nitrogen and oxygen substituents, and the hydroxyl group must therefore be situated at C-2 (previously it had been placed at C-6); melobaline (**152a**) is consequently the C-19 epimer of vincoline.[89c]

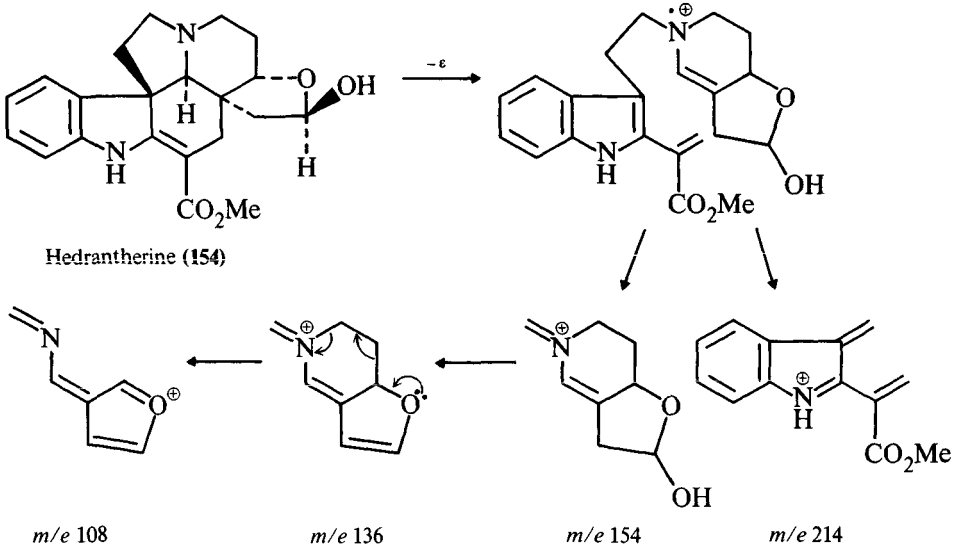
19*S*-Hydroxytabersonine (**147**) has also been used[90] in the confirmation of the structure (**153**) deduced for baloxine, another alkaloid of the leaves of *Melodinus balansae*.[89a,b] Protection of the hydroxyl group in **147** as its tetrahydropyranyl ether, followed by regiospecific hydroboration-oxidation, gave a mixture of diastereoisomeric C-14 alcohols which, on oxidation and removal of the tetrahydropyranyl group, gave 19*S*-hydroxy-14-oxovincadifformine, identical with baloxine (**153**).[90]

Hedrantherine, from *Hedranthera barteri* (Hook. f.) Pichon,[91] is one of a small group of alkaloids in which an additional five-membered ring has been formed



Baloxine (153)

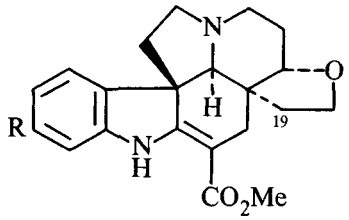
between oxygen functions attached to positions 15 and 18. Although it has not yet been rigorously purified owing to possible contamination by a 12(?)-methoxy derivative, hedrantherine appears to have the constitution **154**, since its mass spectrum indicates a vincadifformine-type structure in which two additional oxygen atoms are present in ring D or the angular side chain (Scheme 11). As a hemiacetal hedrantherine gives rise to C-18 epimeric acetates and methyl ethers, and can be reduced ($NaBH_4$) to a diol. The optical rotation ($[\alpha]_D - 459°$) indicates that **154** is also the absolute configuration. Related bases include 12-hydroxyhedrantherine[91] and vandrikine (**155**), from an unspecified *Aspidosperma* species[92a]; the latter has not yet been fully described, although its structure has been elucidated by complete analysis of its ^{13}C nmr spectrum. Deoxoapodine (**156**) is formulated (without stereochemistry but almost certainly belongs to the same configurational series) as a demethoxyvandrikine, and occurs,[93] together with the related lactone apodine (C=O at C-18) in *Tabernaemontana armeniaca*. Alkaloid M, a constituent of *Craspidospermum verticillatum*,[92b] proves from an examination of its 400 Hz ^1H nmr spectrum to be 19-hydroxyvandrikine.



Hedrantherine (154)

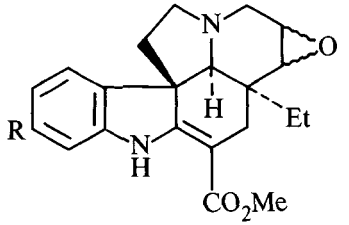
m/e 108 *m/e* 136 *m/e* 154 *m/e* 214

Scheme 11.

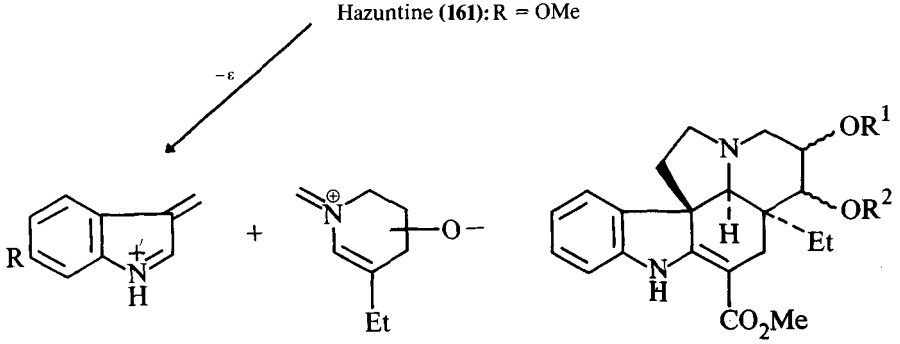


Vandrikine (**155**): R = OMe
Deoxoapodine (**156**): R = H
(no stereochemistry postulated)

As well as tabersonine and several of its derivatives this group of alkaloids includes a number of related epoxides. Lochnericine (**157**) and its 11-methoxy derivative, lochnerinine (**26**), which occurs[15b,94] in *C. roseus*, were among the first to be isolated. The uv spectrum of lochnericine clearly indicates a β-anilinoacrylate chromophore, and since the remaining oxygen is not contained in a hydroxyl or lactone group it must be present as an ether or epoxide. The mass spectrum confirms the vincadifformine-type structure, and also indicates that the unidentified oxygen is present in ring D, since the ring D fragment (**158**) appears at *m/e* 138. Lochnericine contains a *C*-ethyl group (nmr spectrum) and a trans-quinolizidine ring system containing hydrogen at C-21 (ir spectrum), and shows no absorption owing to an –N–CH–O proton. The epoxide function is therefore limited to the 14,15 position. In accordance with this conclusion lochnericine gives a hydroxyacetate (**159**) with glacial acetic acid, and the corresponding 2,16-dihydro derivative



Lochnericine (**157**): R = H
Pachysiphine (**160**): R = H
Lochnerinine (**26**): R = OMe
Hazuntine (**161**): R = OMe

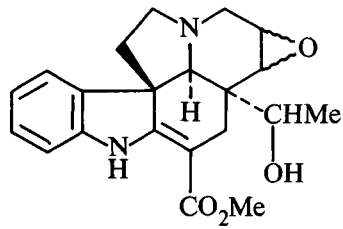


158 *m/e* 138

159: R^1 = H or Ac; R^2 = Ac or H

with zinc and acetic acid.[15a,95] The mass spectrum of lochnerinine (**26**) indicates it to be an *ar*-methoxylochnericine which, from the uv spectrum of 2,16-dihydrolochnerinine, is concluded to be the 11-methoxy derivative; hence lochnerinine is the epoxide of 11-methoxytabersonine,[15a,95] with which it occurs in *Vinca herbacea* Waldst. et Kit.[96]

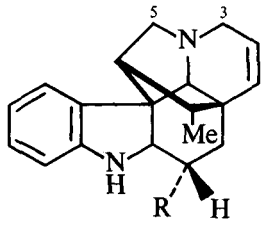
The complete stereochemistry of these alkaloids has still not been completely defined, in view of the uncertain configuration of the epoxide group. Lochnericine, $[\alpha]_D - 432°$, and pachysiphine (**160**) (B.HCl has $[\alpha]_D - 455°$) from *Tabernaemontana pachysiphon* var. *cumminsii* (Stapf) H. Huber and *Pandaca retusa* (Lam.) Mgf.,[97] clearly have the same absolute configuration at C-7, 20, and 21, and are presumably epimeric epoxides;[23,97a] lochnerinine (**26**) and hazuntine (**161**), from *Hazunta velutina*, form a similar epimeric pair.[23] The ^{13}C nmr spectrum of hazuntinine (**28**) has been discussed in some detail,[92a,b] and the complete stereochemistry implied has been assigned to it. If this conclusion is correct, it is possible that hazuntine is also a β-epoxide, in which case lochnerinine and lochnericine may be α-epoxides, and pachysiphine a β-epoxide. Hörhammericine (**162**) and its 11-methoxy derivative, hörhammerinine (**27**), from *Catharanthus lanceus*,[22b,98] contain both epoxide and C-19 hydroxyl functions, but the stereochemistry is unknown beyond the fact that they belong to the (−)-vincadifformine group. However, hörhammericine is stated[24] to be different from cathovalinine (**29**), whose complete relative stereochemistry has been deduced by the X-ray method; the absolute configuration follows from the optical rotation, $[\alpha]_D - 492°$.



Hörhammericine (**162**)

D. The Vindolinine Group

Tuboxenine (**30**) and vindolinine (**31**) are the parent members of a small group of (currently) eight alkaloids which contain a 2,19 bond in an aspidospermine ring system. The structure (**163**) initially proposed for vindolinine, which was incorrect in containing a 6,19 rather than a 2,19 bond, was largely deduced from its spectroscopic properties, in particular the mass spectra of the alkaloid and a number of transformation products, including deuterated derivatives. The presence of an indoline ring system, carbomethoxy group, disubstituted double bond, and a methyl group attached to a methine carbon were easily diagnosed. N_b is situated at the junction of five- and six-membered rings, since permanganate oxidation of N_a-formyldihydrovindolinine gives five-membered (5-oxo) and six-membered (3-oxo)



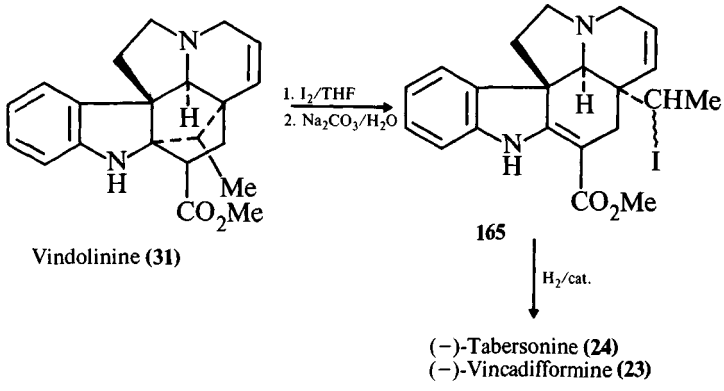
163: R = CO_2Me

164: R = H; 14,15-dihydro

lactams without rearrangement. The double bond is present at position 14,15 since hydrogenolysis of the allylic 3,N_b bond gives a product containing a new methyl group. The other attachment of the double bond is to a quaternary center (C-20), since the olefinic protons are coupled to only two allylic protons. The ester group is attached to a methine carbon, since vindolinine can be epimerized by base.

The general properties of vindolinine and its derivatives, and in particular the mass spectral data, indicate a modified 2,16-dihydrotabersonine type of structure in which an additional ring is present. Since C-19 carries only one hydrogen atom (nmr evidence) this carbon atom must be involved in the sixth ring, and on the basis of all the available evidence the structure **163** was proposed.[99] By detailed comparison of the mass spectra of tuboxenine and dihydrovindolinine it was also concluded[25] that tuboxenine is **164**.

Subsequently[26] the ^{13}C nmr spectrum of vindolinine revealed the presence in the molecule of one more quaternary, nonaromatic carbon atom than is contained in **163**, and further that it had a chemical shift appropriate to a carbon atom, that is, C-2, attached to nitrogen. The remaining signal, owing to a methylene carbon, was appropriate to C-6. The correct structure for vindolinine is thus **31**, which was subsequently proved[100] by reaction with iodine and sodium carbonate (Scheme 12), which afforded 19-iodotabersonine (**165**); hydrogenation then gave a mixture of (−)-tabersonine (**24**) and (−)-vincadifformine (**23**).



Vindolinine (**31**)

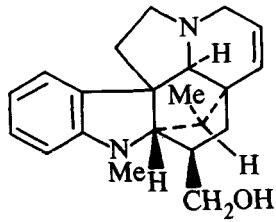
165

(−)-Tabersonine (**24**)
(−)-Vincadifformine (**23**)

Scheme 12.

Independently and simultaneously the same structure for vindolinine was deduced following an examination of its 300 MHz ^{1}H nmr spectrum.[101] On the basis of the chemical shift of the C-18 methyl protons vindolinine is concluded to have the 19*R* configuration; this, together with the configuration at C-16 and the absolute configuration, has been confirmed by X-ray crystal structure analysis.[102]

N_a-Methylation of vindolinine, followed by reduction ($LiAlH_4$), affords N_a-methylvindolininol, which epimerizes at C-19 in the presence of trifluoroacetic acid, by a mechanism that is still obscure. This same product, N_a-methyl-19-epivindolininol (**166**), can be obtained by N_a-methylation and reduction of 19-epivindolinine, which also occurs in *M. balansae*.[89a] The structure and stereochemistry of **166** have been confirmed by the X-ray method; this also serves to confirm the structure of 19-epivindolinine.[103]



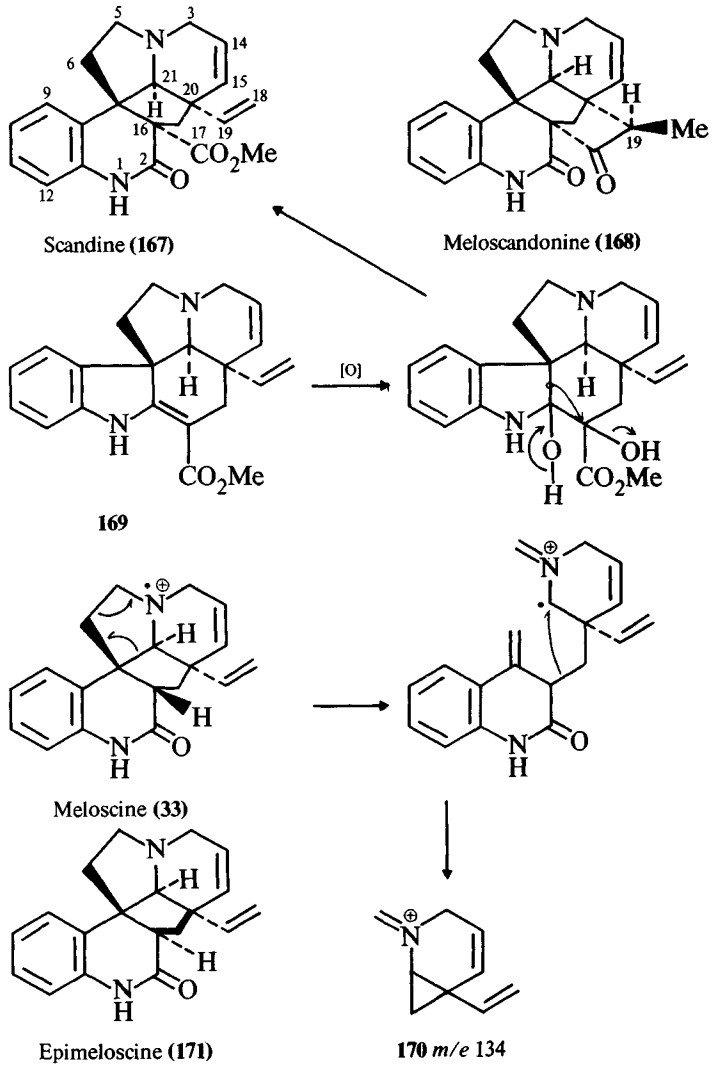
166

On the basis of these results tuboxenine is **30**, and pseudokopsinine is **32**; this latter conclusion has also been confirmed by X-ray crystal structure analysis.[104] The structures of all the other alkaloids in this group also follow; these include vindolinine N_b-oxide and its C-19 epimer,[89a] and pseudokopsinine N_b-oxide and N_b-methylpseudokopsininium chloride, which have been isolated from *Vinca erecta*.[104]

E. The Meloscine Group

The aerial parts of *Melodinus scandens* Forst. contain[28,105] several related alkaloids, namely, (+)-meloscine (**33**), (+)-16-epimeloscine and its N_b-oxide, (+)-scandine (**167**), and meloscandonine (**168**), which, although they are 2-quinolone derivatives, are clearly derived by oxidative rearrangement of a molecule of the tabersonine type, for example, **169** (Scheme 13). In this connection it is relevant to note that both tabersonine and (+)-vincadifformine occur in the same plant.[105]

Meloscine exhibits an acylaniline uv spectrum, which becomes an alkylaniline spectrum following reduction ($LiAlH_4$). Two easily hydrogenated double bonds are present, one as a terminal vinyl group attached to quaternary carbon; the other is disubstituted and is situated between a fully substituted carbon atom and a methylene group which is in turn attached to N_b (nmr evidence from the base and its N_b-methiodide). N_b is tertiary, and is enclosed in an indolizidine system since



Scheme 13.

oxidation ($KMnO_4$) of tetrahydromeloscine gives a mixture of δ (3-oxo) and γ (5-oxo) lactams. The latter contains a methylene group situated between the newly introduced carbonyl group and a quaternary carbon atom, from which it would appear that in meloscine the tryptamine ethanamine chain is intact.[28]

The alkylamine system deduced for meloscine is confirmed by Emde reduction of meloscine N_b-metho salt in alkaline solution, which gives three Emde bases by fission of the 3,N_b bond, followed by partial or complete hydrogenation of the double bonds.

The nmr spectrum of meloscine also reveals the presence of an *o*-disubstituted aromatic ring, an exchangeable hydrogen on the acylaniline nitrogen atom, and an

uncoupled proton, which is responsible for a singlet at 3.53 ppm, appropriate to a C-21 proton adjacent to N_b.

Only three protons remain to be accounted for; these are contained in an ABX system in which the X proton may be replaced by deuterium in alkaline medium. The methylene group in the deuterated compound gives rise to a clean AB quartet centered on 2.15 ppm; this methylene group must therefore be attached to quaternary carbon.[28] The mass spectrum of meloscine contains a significant peak at *m/e* 134, unchanged in the spectrum of deuterated meloscine, which is presumably due to the ion **170**; accordingly, in the spectrum of tetrahydromeloscine the corresponding peak occurs at *m/e* 138.

These data are consistent only with the structure **33** for meloscine,[28] which was subsequently confirmed by the X-ray crystal structure analysis of meloscine N_b-methobromide.[106] This investigation also defined the absolute configuration of meloscine, in agreement with the conclusions reached earlier[28] on the basis of ord spectra.

Epimeloscine **(171)** epimerizes to meloscine in the presence of strong base, and hence contains the less stable trans B/C ring junction.

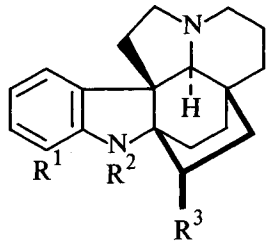
The constitution of scandine **(167)** follows from its conversion into meloscine by hydrolysis and decarboxylation; the configuration at C-16 follows from the nmr spectrum, which discloses shielding of the C-21 proton by the ester grouping.[28]

Meloscandonine **(168)** contains a carbonyl group in a five-membered ring (ir spectrum) and a methyl group attached to a methine carbon atom (MeCH signals in nmr spectrum in place of $CH{=}CH_2$ signals in spectrum of epimeloscine); this methine carbon atom must be situated α to the carbonyl group since the doublet owing to the methyl group moves to higher field when the solvent is changed from deuterochloroform to deuterobenzene. The structure deduced for meloscandonine is thus **168**, the endo configuration of hydrogen at C-19 being deduced from the nmr spectra of the epimeric alcohols produced by reduction of **168** and their acetates. This structure has subsequently[107] been confirmed by X-ray crystal structure analysis. The absolute configuration rests on ord comparison with epimeloscine **(171)**.[107]

F. The Aspidofractinine Group

The structures of the aspidofractinine group of alkaloids, which number approximately 40 alkaloids at the present time, were largely deduced by extensive application of physical methods, and in particular mass spectrometry, to the alkaloids and numerous transformation products, coupled with chemical correlation. The hexacyclic ring system, which contains three quaternary carbon atoms (C-2, C-7, and C-20), and the lack of appropriate functional groups in many instances result in a molecular framework that is not susceptible to degradation by familiar chemical methods.

The first alkaloids in this group to be studied were pyrifoline **(39)** and refractidine **(40)**,[32a] refractine **(172)** and aspidofractine **(35)**,[29b] aspidofiline **(173)**,[108]

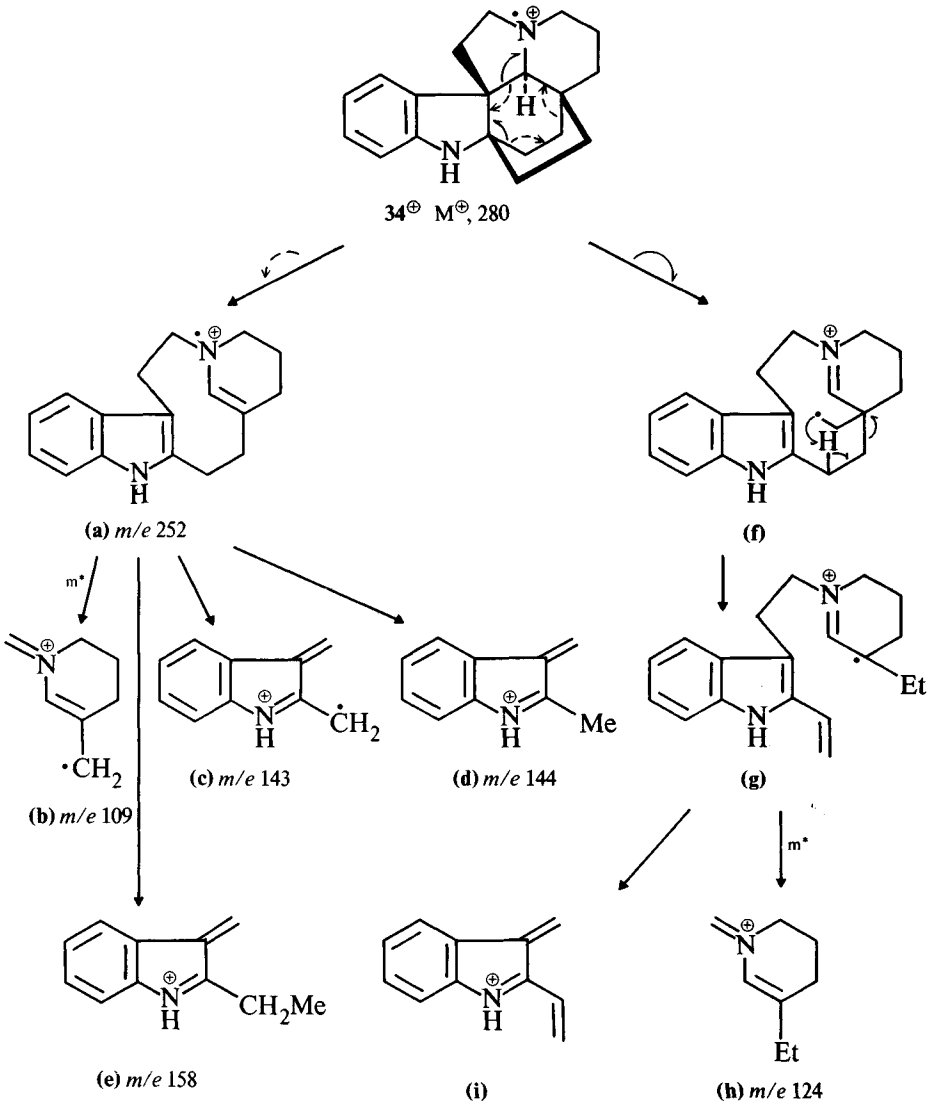


		R^1	R^2	R^3
Refractine	(172)	MeO	CHO	CO_2Me
Aspidofiline	(173)	OH	Ac	H
Pleiocarpine	(174)	H	CO_2Me	CO_2Me
Pleiocarpinine	(175)	H	Me	CO_2Me
Kopsinine	(176)	H	H	CO_2Me
N-Methylkopsinyl alcohol	(184)	H	Me	CH_2OH
Pleiocarpinilam	(185)	H	Me	CO_2Me; C=O at C−5
Kopsinilam	(186)	H	H	CO_2Me; C=O at C−5
	183	MeO	H	H

pleiocarpine (**174**), pleiocarpinine (**175**), and kopsinine (**176**)[109] and the parent base of the series, aspidofractinine (**34**).[29a]

The hexacyclic nature of these alkaloids became clear from the fact that aside from the substituted dihydroindole component and, in most examples, an acyl and ester grouping, no unsaturation was present in the molecule. Further important features that emerged from a study of the nmr spectra were the notable absence of the signal owing to C-2, the aspidospermine "fingerprint," which normally appears near 4.5 ppm, and the absence of a terminal methyl group. If a close biogenetic relationship with the aspidospermine group is assumed, these facts are consistent with a hexacyclic skeleton such as **34**, although other ring systems are possible. However, a detailed analysis of the mass spectral data proved that this is indeed the parent skeleton of these alkaloids.

The initial fragmentation of the aspidofractinine molecule (Scheme 14) involves fission of ring C, with expulsion of ethylene and the formation of an ion at $M^+ - 28$, that is, *m/e* 252 (**a**), as in the aspidospermidine fragmentation. The driving force for this fragmentation is presumably the aromatization of the indole ring and the relief of ring strain in the fused hexacyclic system. Further fission at the benzylic positions gives the piperidine-derived fragment **b**, and the aromatic ions **c–e**. Rupture of rings C and E without loss of C-18 and C-19 gives an ion **f**, which can fragment to give ions **g–i**. In some cases, for example, **a** → **b** and **g** → **h**, metastable ions can be observed at appropriate *m/e* values. Evidently the precise *m/e* values of the principal peaks in the spectra of these alkaloids, coupled with the spectra of appropriate transformation products, including deuterated products, and the other spectroscopic data, can be used to deduce the structures of many of these alkaloids with a fair degree of certainty.

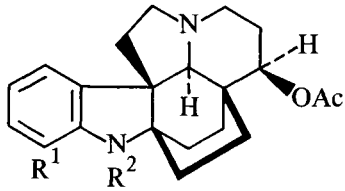


Scheme 14.

Pyrifoline, for example, is readily shown to be a derivative of 7-methoxy-*N*-acetyldihydroindole; a second methoxyl group is, however, present in the aliphatic part of the molecule, probably in the piperidine ring, since ions **b** and **h** appear 30 m.u. higher, at *m/e* 139 and 154. A peak at *m/e* 109 is attributed to an ion obtained by loss of CH_2O from the methoxy derivative of **b**, with rearrangement. The methoxyl group in pyrifoline was placed at C-15 since demethylation gave a secondary alcohol whose acetate (**177**) was shown to have only two nonequivalent hydrogen atoms on carbon adjacent to the oxygen-containing carbon (−C*H*OAc, q 4.45–4.8 ppm). Since the related ketone showed ir absorption corresponding to a

six-membered ketone and exchanged only two hydrogen atoms for deuterium in the presence of base, the only possible position for the ketone group, and therefore the aliphatic methoxyl group in pyrifoline (**39**), is at C-15.[32a]

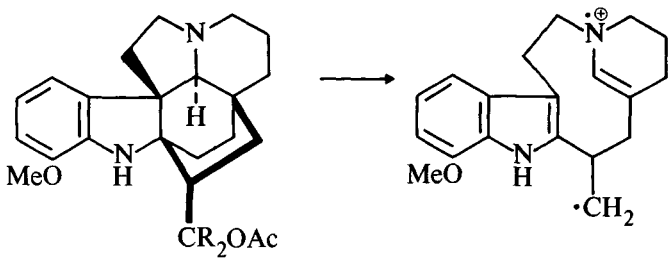
The close similarity between pyrifoline and refractidine was apparent from their spectra and chemical properties, and a particularly close resemblance was noted between deacetylpyrifoline and deformylrefractidine. The structure (**40**) for refractidine was placed beyond doubt by mass spectral comparison of these and other appropriate pairs of derivatives.[32a]



	R^1	R^2
177	MeO	Ac
178	H	CHO

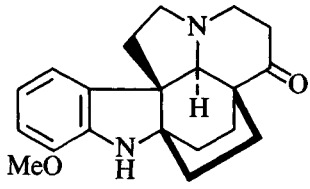
The coupling constants for the quartet owing to the C-15 hydrogen in the acetates **177** and **178** are 5 and 10.5 Hz, appropriate to an axial proton at this position.[32b] The complete stereochemistry of pyrifoline and refractidine is therefore as given in **39** and **40**.

A similar study enabled the structures of refractine (**172**) and aspidofractine (**35**), from *Aspidosperma refractum*, to be established.[29b] In addition to a 7-methoxy-*N*-formyldihydroindole component refractine contains a carbomethoxy group, which is attached to a methine carbon atom, since deformylrefractine gives an isomeric ester on equilibration with base; formylation then affords isorefractine. In the mass spectra of refractine and a number of derivatives an ion at $M^+ - 28$ indicates loss of ethylene, while ions at *m/e* 109 and 124 indicate that the ester group cannot be situated in the piperidine ring. In fact, the formation of these ions indicates that only positions 6 and 16 are possible for the ester group, and of these the latter is preferred on biogenetic grounds. Confirmation of this was derived from the mass spectrum of the primary acetate **179**, which contained a prominent ion at *m/e* 295, resulting from loss of ethylene from the molecular ion, followed by loss of an acetoxyl group, to give the ion **181**. In the spectrum of the dideutero analogue



179: R = H
180: R = D

181 *m/e* 295



182

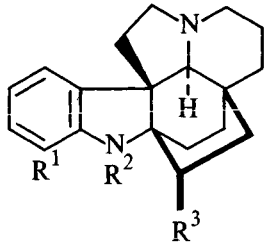
180 this ion appeared at *m/e* 297, but the ion at *m/e* 109 remained unchanged; refractine therefore has the structure **172**.

The structure of aspidofractine (**35**) became clear from mass spectral comparison of deformylisoaspidofractine and deformylisorefractine.[29]

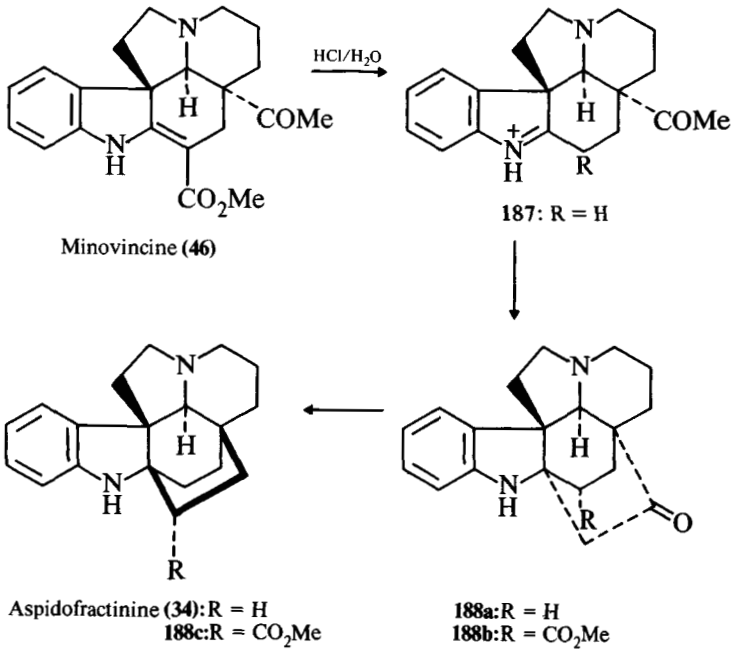
The salient features of the mass spectrum of aspidofiline (**173**), from *A. pyrifolium*, suggested that it belonged to the aspidofractinine group, and since it was shown to be a 7-hydroxydihydroindole derivative, chemical correlation with pyrifoline (**39**) suggested itself. In fact, deacetylation of pyrifoline and preferential demethylation of the aliphatic methoxyl group with acid gave an alcohol which could be oxidized (Oppenauer) to the 15-ketone (**182**). Removal of the carbonyl group by Clemmensen reduction followed by hydrogenation then gave *O*-methyldeacetylaspidofiline (**183**).[108]

Further chemical correlation demonstrated that kopsinine (**176**) is deformyl-aspidofractine,[109] while reduction of pleiocarpine (**174**) by means of lithium aluminum hydride gave N_a-methylkopsinyl alcohol (**184**), also obtainable by the reduction of pleiocarpinine (**175**).[110] Pleiocarpinilam, a γ-lactam from *Pleiocarpa tubicina* Stapf, can also be reduced to N_a-methylkopsinyl alcohol (**184**), and hence has structure **185**; its congener and close relative kopsinilam (**186**) is likewise reduced to kopsinyl alcohol.[111]

These deductions based on physical data and chemical correlation provided a convincing and completely self-consistent structural picture of this group of alkaloids; nevertheless, an independent proof of skeletal structure was desirable,



		R^1	R^2	R^3
N-Methylkopsinyl alcohol	**(184)**	H	Me	CH_2OH
Pleiocarpinilam	**(185)**	H	Me	CO_2Me; C=O at C−5
Kopsinilam	**(186)**	H	H	CO_2Me; C=O at C−5
	183	MeO	H	H



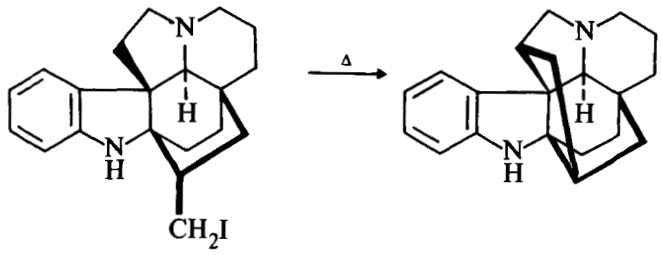
Scheme 15.

and this was provided by the preparation of (−)-aspidofractinine (**34**) from (−)-minovincine (**46**). Hydrolysis and decarboxylation of **46** gave an indolenine (**187**, not isolated), which suffered cyclization by an internal Mannich reaction to give 17-oxoaspidofractinine (**188a**), subsequently reduced to (−)-aspidofractinine (**34**).[112,113]

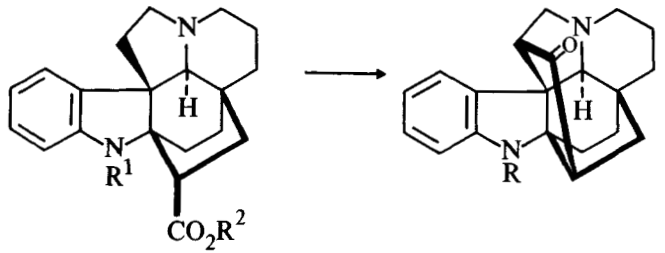
Under anhydrous and carefully controlled acidic conditions the ester group is retained, and the internal Mannich reaction following protonation at C-16 in minovincine (**46**) results in the formation of 16-epi-19-oxokopsinine (**188b**) (Scheme 15); removal of the C-19 carbonyl group then gives 16-epikopsinine (**188c**), also obtainable from venalstonine (**38**) by hydrogenation of the 14,15 double bond, followed by epimerization at C-16.[86c]

In the aspidofractinine ring system the D/E ring junction must be cis, and hence the only doubts in the stereochemistry of kopsinine and related molecules concern the configuration of the ester function. However, reaction of kopsinyl alcohol with phosphorus and hydriodic acid gives[109] the related iodide (**189**), which on pyrolysis gives a surprisingly high yield (60%) of kopsane (**190**).[33b,114] Provided that no inversions have occurred during this sequence of reactions the relative configuration of kopsinine (**176**) follows.

The remarkable cyclization which occurs in the conversion of **189** into **190** has its parallel in the pyrolysis of kopsininic acid (**191**), which gives a moderate yield of kopsanone (**192**). An even better yield of N_a-methylkopsanone (**193**) was obtained[115] by prolonged heating of pleiocarpinine (**175**) in methanol solution at 200°.



189 Kopsane (190)



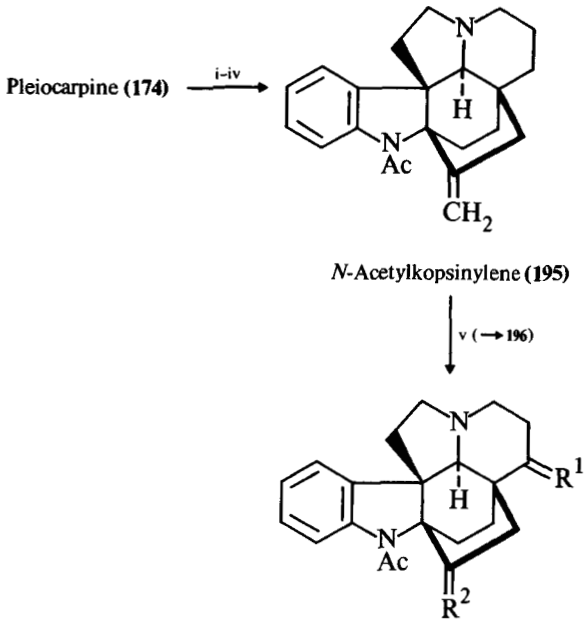
	R^1	R^2
191	H	H
Pleiocarpinine (175)	Me	Me

Kopsanone (192): R = H
N-Methylkopsanone (193): R = Me

The absolute configuration of (−)-aspidofractinine (**34**) follows from its preparation from (−)-minovincine, and is confirmed by the ord evidence, which indicates[57,113] that N_a-acetylaspidofractinine and N_a-acetyl-15-oxoaspidofractinine (**194**), prepared from refractidine (**40**), have the opposite configuration to aspidospermine at C-7.

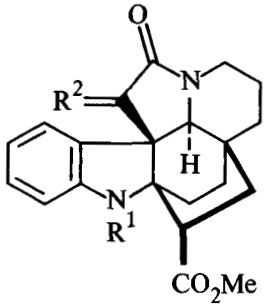
A further correlation brings (−)-pleiocarpine into this same stereochemical group. Standard procedures were used to convert pleiocarpine (**174**) into *N*-acetylkopsinylene (**195**) (Scheme 16), which on oxidative fission gave *N*-acetyl-16-oxoaspidofractinine (**196**), convertible into (−)-aspidofractinine.[109,113]

The ord spectrum of (−)-kopsinine (**176**) proves that the alkaloid belongs to the same configurational series, as do kopsinilam (**186**) and pleiocarpinilam (**185**), two γ-lactams which occur with pleiocarpine, pleiocarpinine, and kopsinine in *Pleiocarpa mutica* Benth. and *P. tubicina*.[111] The structures of these lactam alkaloids were established by chemical correlation; oxidation ($KMnO_4$) of pleiocarpinine in acetone gave pleiocarpinilam, and similar oxidation of *N*-acetylkopsinine, followed by hydrolysis of the *N*-acetyl group, gave kopsinilam. Other oxidation products of these three alkaloids have been encountered in pleiocarpoline, pleiocarpolinine, and kopsinoline, which occur, for example, in *P. mutica*[116]; these are simply the N_b-oxides of pleiocarpine, pleiocarpinine, and kopsinine, and can be readily reduced to the tertiary basic alkaloids.[117] 5,6-Dioxopleiocarpine (**197**), yet another oxidation product of pleiocarpine, also occurs in *P. mutica*; its structure and absolute configuration follow from its preparation by the chromic acid oxidation of pleiocarpine.[118]

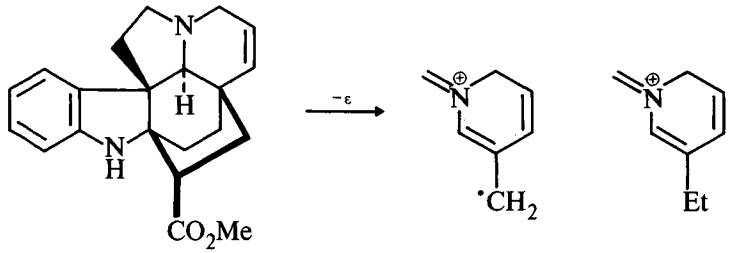


Scheme 16. Reagents: i, $LiAlH_4$; ii, P/HI; iii, KOH; iv, acetylation; v, $NaIO_4$, OsO_4, MeOH. H_2O.

Venalstonine (**38**), from *Alstonia venenata* and *Melodinus australis* (F. Muell.) Pierre, is Δ^{14}-dehydrokopsinine, since hydrogenation gives kopsinine.[31,119] The double bond is placed in position 14,15 since the mass spectrum exhibits strong peaks at *m/e* 107 (**198a**) and 122 (**198b**) (Scheme 17), among others; these are also present in the mass spectrum of venalstonyl alcohol (**38**; $CO_2Me \rightarrow CH_2OH$). The nmr signal owing to the C-3 methylene group also appears downfield (3.5 ppm),



		R^1	R^2
Pleiocarpinilam	(**185**)	Me	H_2
Kopsinilam	(**186**)	H	H_2
5,6-Dioxopleiocarpine	(**197**)	CO_2Me	O

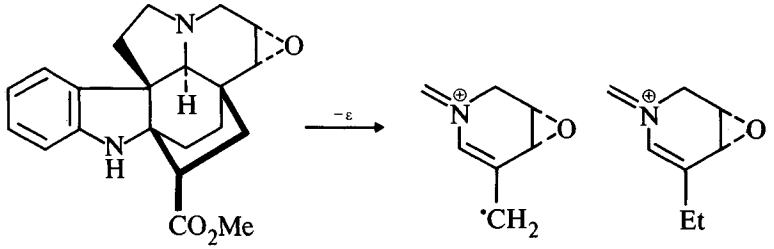


Venalstonine (**38**) **198a** *m/e* 107 **198b** *m/e* 122

Scheme 17.

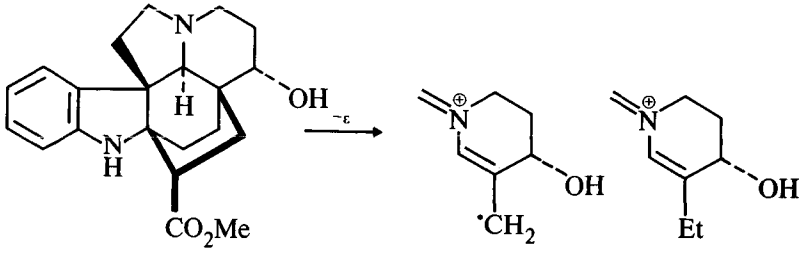
the protons at this position being deshielded by the double bond.[119] Venalstonidine (**37**) is 14,15-epoxyvenalstonine[31]; its mass spectrum is of the kopsinine type, but the molecule obviously contains an additional oxygen atom in the piperidine ring, since prominent peaks at *m/e* 123 and 138 (**199a** and **199b**) are observed (Scheme 18). The molecule does not contain a ketone carbonyl group, but since reduction by means of lithium aluminum hydride gives a diol, this additional oxygen atom must be present as an epoxide function, which conclusion is confirmed by the nmr spectrum.

Two other constituents of *M. australis* are hydroxykopsinines. One of these gave ions at *m/e* 125 and 140, owing to **201a** and **201b** (Scheme 19), and therefore contains a hydroxyl group in the piperidine ring.[31] The position and configuration of this hydroxyl group became clear from the nmr spectrum of its acetate, which



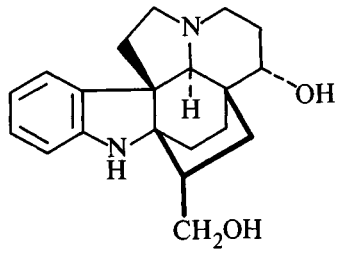
Venalstonidine (**37**) **199a** *m/e* 123 **199b** *m/e* 138

Scheme 18.



15α-Hydroxykopsinine (**200**) **201a** *m/e* 125 **201b** *m/e* 140

Scheme 19.



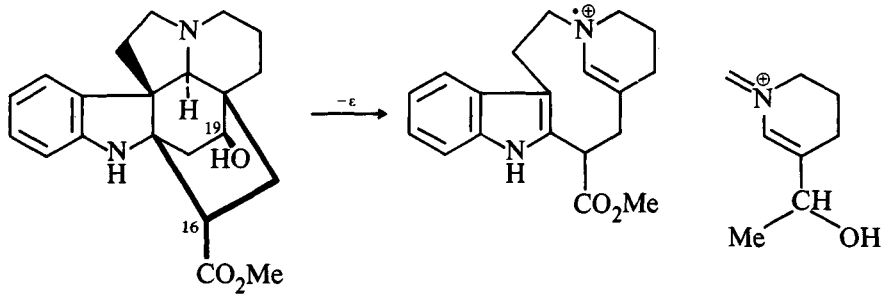
202

exhibits a rather ill-resolved, one-proton triplet at δ 4.88 (C*H*OAc). Hence this proton is coupled to only two other protons and must be situated at C-15. The width (7 Hz) at half-height of this triplet is consistent with an equatorial proton in a chair-shaped ring. Boat conformations of ring D can be ignored, owing to the serious eclipsing interactions which result between the hydroxyl group and C-17 or C-19. Hence the C-15 hydroxyl group is axial, and the alkaloid is 15α-hydroxykopsinine (**200**). Since reduction of **200** and venalstonidine (**37**) gives the same diol (**202**), venalstonidine must be the 14,15-α epoxide (**37**).[32b]

The other hydroxykopsinine has the structure (**203**), since its mass spectrum shows prominent ions at *m/e* 310 ($M^+ - 44$) (**204a**) and 140 (**204b**) (Scheme 20). The initial fragmentation thus involves loss of "vinyl alcohol," which limits the hydroxyl group to positions 18 and 19. The former is not favored, since the fragment of *m/e* 140 produced on fragmentation would certainly lose formaldehyde [cf. spectrum of limaspermine (**108**)], but only a very weak ion is observed at *m/e* 110. The alkaloid is thus 19-hydroxykopsinine, and gives on equilibration with sodium methoxide a C-16 epimer, which exhibits intramolecular, concentration-independent hydrogen bonding (ir spectrum). This is possible in the ring system depicted in **203** only if the hydroxyl group has the β configuration.[32b]

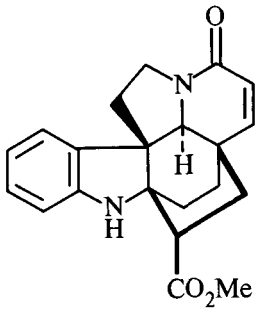
Co-occurring with these bases in *M. australis* is 3-oxovenalstonine (**205**), the structure of which becomes clear from its reduction to 3-oxokopsinine.[31]

Of the other well-defined alkaloids of this group 12-methoxyaspidofractinine (**206**), 11,12-dimethoxyaspidofractinine (**36**), and their *N*-formyl derivatives occur

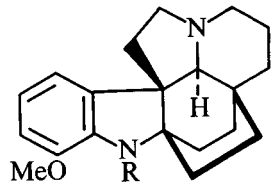


19β-Hydroxykopsinine (203) **204a** *m/e* 310 **204b** *m/e* 140

Scheme 20.



(205)



206: R = H
208: R = Me

in *Aspidosperma populifolium*.[30] The absolute configurations of these bases appear not to have been rigidly established, but since they occur in the same plant as kopsinine and aspidofractine it seems more than probable that they have the same absolute configuration as all the other hexacyclic bases.

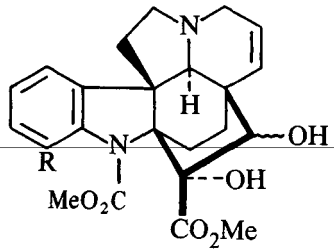
Three *Kopsia* bases, isolated[120] from *K. singapurensis*, contain a more complex pattern of substitution, one that is reminiscent of vindoline in the aspidospermine group. Kopsingine (**207**) contains aromatic methoxyl, urethane, methyl ester, and two hydroxyl groups, as well as a double bond in the 14,15 position. The unfamiliar features in the molecule are the ester and hydroxyl groups but because of the striking similarity of the nmr data for kopsingine and vindoline the structure **207** was proposed (Scheme 21). This was confirmed by the conversion of dihydrokopsingine into 12-methoxy-*N*-methylaspidofractinine, whose structure was deduced by mass spectral comparison with 12-methoxyaspidofractinine (**206**).

The position of the carbonyl group in the intermediate ketone (**209**), and hence the position of the ester group and one hydroxyl group in kopsingine, was also determined by mass spectrometry. The most abundant ion in the spectrum of **209** occurred at *m/e* 215, attributed to the fragment **210a** which might cyclize to **210b**.

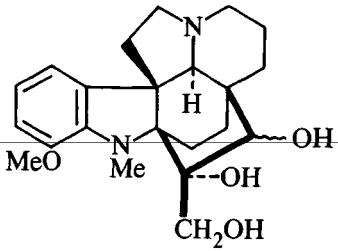
The remaining hydroxyl group was located at C-17 by periodate oxidation of the triol **211**. In this reaction the primary hydroxyl group was readily lost, but the 16,17 bond remained intact, and the three products obtained were the α-diketone **212a**, the ketol **212b**, and the enediol **212c**. The formation of these compounds requires the secondary hydroxyl group to be situated at C-17.

Two final stereochemical points deserve comment. In kopsingine the substituents are placed on C-16 and C-17 rather than C-18 and C-19 since its mass spectrum indicates initial loss of ethylene. Since in aspidofractinine derivatives the bridge trans with respect to the ethanamine bridge (C-5 and C-6) is generally lost, the stereochemistry of the kopsingine skeleton follows. The configuration at C-16 depicted in **207** is the only one that can explain the observed hydrogen bonding of the hydroxyl group to the urethane carbonyl group.

On the basis of mass spectral data kopsaporine (**213**) is almost certainly demethoxykopsingine, and on the basis of ir and uv data kopsingarine is tentatively regarded as 12-hydroxykopsaporine (**214**).[120]



1. H_2/PtO_2
2. TsCl/py
3. $LiAlH_4$



Kopsingine (**207**): R = OMe

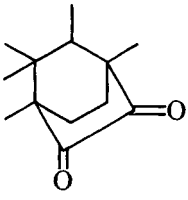
Kopsaporine (**213**): R = H

Kopsingarine (**214**): R = OH

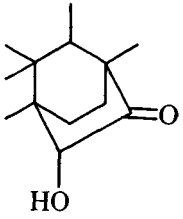
211

$NaIO_4$

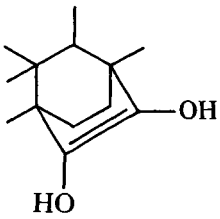
1. H_2/PtO_2
2. TsCl/py
3. $LiAlH_4$
(on **207**)



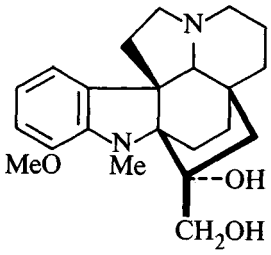
212a



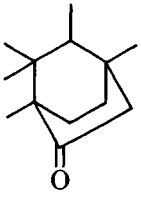
212b



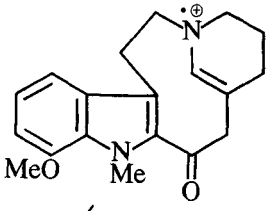
212c



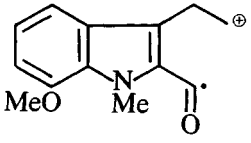
$NaIO_4$



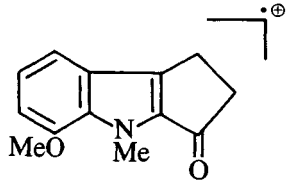
209



208



210a



210b

Scheme 21.

G. The Heptacyclic Kopsine Group

The most complex ring system encountered among the *Aspidosperma* alkaloids is that which occurs in kopsine (**41**) and its congeners, which are characteristic bases of *Kopsia fruticosa*.[121] Kopsine, $C_{22}H_{24}N_2O_4$, is a dihydroindole base in which the nitrogen atom carries a methoxycarbonyl group; the molecule also contains a carbonyl group in a five-membered ring, and a hydrogen-bonded hydroxyl group which is probably tertiary, since kopsine and its decarbomethoxy derivative resist acetylation.[122,133] Since kopsine reacts with sodium periodate the ketone and hydroxyl groups are presumably vicinal.[124]

Oxidation of kopsine (CrO_3-pyridine) gives a five-membered lactam (**215**) whose nmr spectrum contains a singlet at 2.82 ppm, which becomes a doublet with a very small coupling constant in the spectrum of its C-22 dihydro derivative. This signal is attributed to hydrogen at C-6 in a β-keto lactam system (reduced to a β-hydroxylactam in the dihydro derivative) in which the α-carbon atom carries only one hydrogen. A similar conclusion emerges from the Hofmann degradation of kopsine methiodide, which gave an α,β-unsaturated ketone (**216**) containing a terminal methylene group, and which was reducible to a vicinal diol (**217**) (Scheme 22).[33b,114] These results establish the relationship of the α-ketol system to N_b in kopsine, and prove the presence of two five-membered rings in addition to the indoline system. If a structural relationship with aspidospermidine and its derivatives is assumed (kopsine, like aspidospermine, gives 3,5-diethylpyridine on zinc dust distillation and loses ethylene in the initial fragmentation in the mass spectrometer)[123] a considerable part structure for kopsine can be constructed. On the basis of this and other evidence the structure (**41**) was proposed for kopsine. This structure received firm support from the conversion of pleiocarpine (**174**) into kopsane (**190**), which was also prepared from kopsine (**41**) by reaction with phosphorus and hydrogen iodide.[33b,114] The additional ring introduced during the pyrolysis of kopsinyl iodide does not involve N_a, since the product can be acetylated. A cyclopropane ring is not present (nmr evidence), and position 5 is not involved, since oxidation gives a five-membered lactam. From a study of models C-6 appears to be the most probable site of ring closure; hence kopsane is **190** and kopsine is **41**.[33b,114]

As an acyloin kopsine (**41**) undergoes reversible rearrangement when heated in tetralin solution to give isokopsine (**218**),[125] in which the tertiary hydroxyl group is no longer hydrogen bonded to the urethane carbonyl group. Similarly, hydrolysis of kopsine by means of dilute alkali gives a mixture of decarbomethoxykopsine (**219**) and decarbomethoxyisokopsine (**42**); these two isomers, which also occur in the leaves of *Kopsia fruticosa*,[34] rapidly equilibrate at room temperature even in 0.01 *M* alkali.[125]

The above evidence provides convincing support for the structure (**41**) of kopsine, even if it falls short of a completely unequivocal proof. Subsequently a definitive proof was provided by the correlation of kopsine with (−)-minovincine (**46**) via (−)-aspidofractinine.[113] This sequence of reactions, set out in Scheme 22, started with the periodate oxidation of kopsine in acid solution, which gave a keto acid,

isolated as the lactol (**220**). Esterification gave a keto ester (**221a**), epimerizable at C-6 by base; both epimers **221a** and **b** could then be oxidized to the enamine (**222**), which on hydrolysis and decarboxylation gave an unstable enamine, reducible to the keto urethane (**223**). Obvious stages then completed the conversion into (−)-aspidofractinine. Since this has been correlated with (−)-minovincine (**46**), this completes the elucidation of the structure and absolute configuration of kopsine.[113]

Three bases which occur in *Pleiocarpa mutica* prove to be ketolactams derived from kopsane.[126] The structures **224–226** of these bases were derived from spectroscopic data, particularly the mass spectrometric data, and by comparison with the known lactam, decarbomethoxy-5-oxokopsine (**227**). Confirmation of the structures was obtained by alkaline cleavage of the β-ketolactam system in **224**, which gave pleiocarpinilam (**185**). Correlation of the three bases was then achieved by reduction with lithium aluminum hydride; **224** gave N_a-methylkopsanol (**228a**), **226** gave kopsanol (**228**), and **225** gave a mixture of these two alcohols.[126]

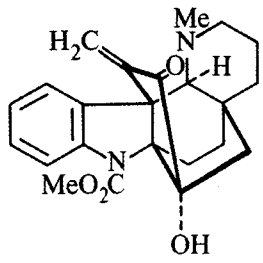
The C-22 epimeric kopsanols of structure **228b** and **c** occur in *Aspidosperma duckei* Hub., *A. macrocarpon* Mart.,[127] *A. cuspa* Blake,[128] and *A. verbascifolium* Muell-Arg.[129] together with kopsanone (**192**). 5-Oxoepikopsanol also occurs in *A. duckei*[127] and *A. verbascifolium*;[129] in the latter species it is accompanied by N_a-formylkopsanol. The configuration at C-22 in the epimers **228b** and **c** was determined by an examination of the nmr spectra of their acetates.

In epikopsanol (**228c**) the C-22 proton is almost perpendicular to the protons at C-6 and C-16, and hence no coupling is observed; in kopsanol (**228b**), on the other hand, the dihedral angles between the bonds are such that substantial coupling would be expected, as observed ($J = 4.5$, 9 Hz).[127]

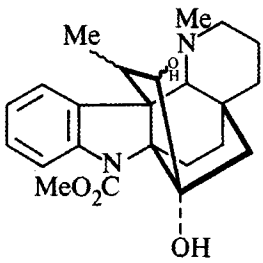
(−)-Fruticosine (**229**) and (+)-fruticosamine (**43**) are two further isomers of kopsine which occur in *K. fruticosa*.[34,122] Both bases contain an *N*-carbomethoxydihydroindole system, a ketone group in a six-membered (or larger) ring, and a secondary alcohol group. The two bases can be interconverted by the action of ammonia or dilute sodium hydroxide (cf. kopsine ⇄ isokopsine).[34]

The nmr spectra of fruticosine (**229**) and fruticosamine (**43**) do not contain an absorption owing to a C-2 proton; hence this position must be fully substituted as in the kopsine-aspidofractinine nucleus. Normally the C-12 proton in this nucleus is deshielded by an N_a-carbomethoxy group; this is observed in fruticosine but not in its isomer fruticosamine, presumably owing to hydrogen bonding of the urethane carbonyl group with the hydroxyl group, which must therefore be attached to C-16. The hydrogen atom at C-16 is coupled to one other proton, attached to C-17; the position of this latter signal (δ 2.55 ppm) is consistent with proximity to the ketone carbonyl group. C-17 must also be attached to a quaternary center, obviously C-20. Fruticosine therefore contains a β-ketol system, and the easy interconversion into fruticosamine is readily explained; fruticosine undergoes a reversible aldol cleavage in alkali, with formation of its C-16 epimer fruticosamine, via the intermediate aldehyde (**229**) (Scheme 23).[35,130]

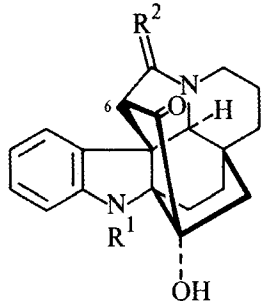
Fruticosine (**229**) methiodide undergoes a very facile Hofmann degradation; hence the alkaloid is very probably a β-amino ketone. The methine base **231** is a



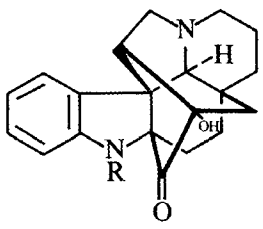
216



217

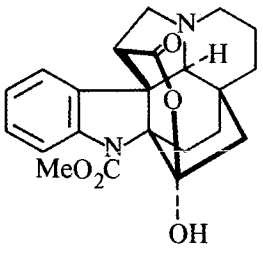


		R^1	R^2
Kopsine	**(41)**	CO_2Me	H_2
	215	CO_2Me	O
	219	H	H_2
	227	H	O



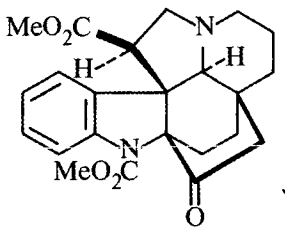
Isokopsine **(218)** R = CO_2Me
42 R = H

H_2SO_4
$NaIO_4$
(on **41**)



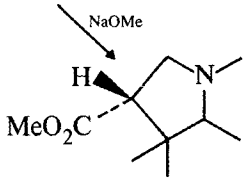
Kopsine pseudoacid **(220)**

HCl
MeOH



221a

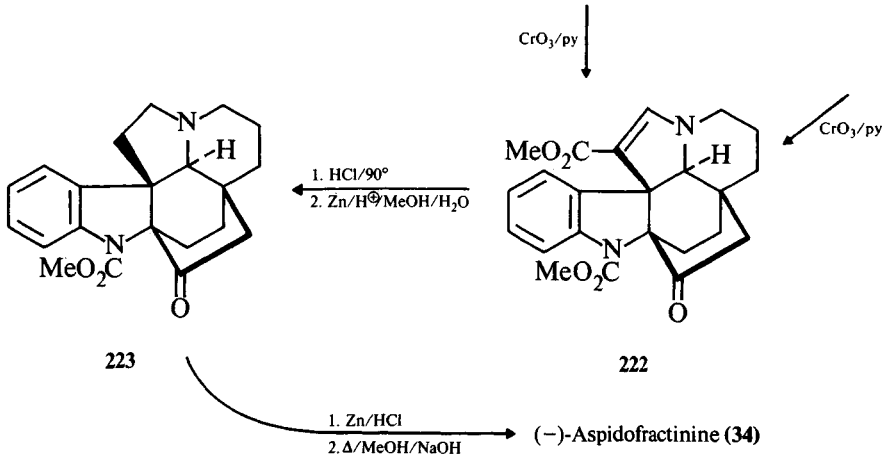
NaOMe



221b

CrO_3/py

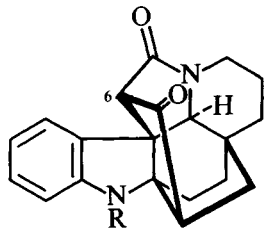
CrO_3/py



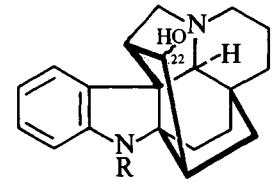
Scheme 22.

methylenecyclohexanone derivative which on hydrogenation gives a dihydro derivative (**232**). In this product C-6 gives rise to a quartet owing to coupling with the methyl group; no other coupling is observed. Hence the adjacent carbon atom is probably contained in the carbonyl group, and this is consistent with the chemical shift of the C-6 proton (δ 3.09 ppm). The five-membered ring is severed during the Hofmann degradation, since oxidation of **232** affords a six-membered lactam; in contrast fruticosine gives a five-membered lactam. This evidence formally places N_b in an indolizidine system, which may be extended by addition of the interrelated β-ketol system and the N_a-carbomethoxyindoline unit. The proton at C-21 appears in all derivatives as a singlet, and the three surviving protons in the tryptamine ethanamine chain absorb as an AMX system. Taken in conjunction with other nmr evidence and the mass spectral evidence, this allows structures **229** and **43** to be proposed for fruticosine and fruticosamine.[35,130] Proof of these structures was provided by the correlation of fruticosine with kopsine (**41**).[35] Oxidation of either epimer (**43** or **229**) gave a β-diketone **233**, which on acid fission followed by esterification gave the chano ester **234**, also obtainable by the periodate fission of isokopsine (**218**), followed by esterification.[35]

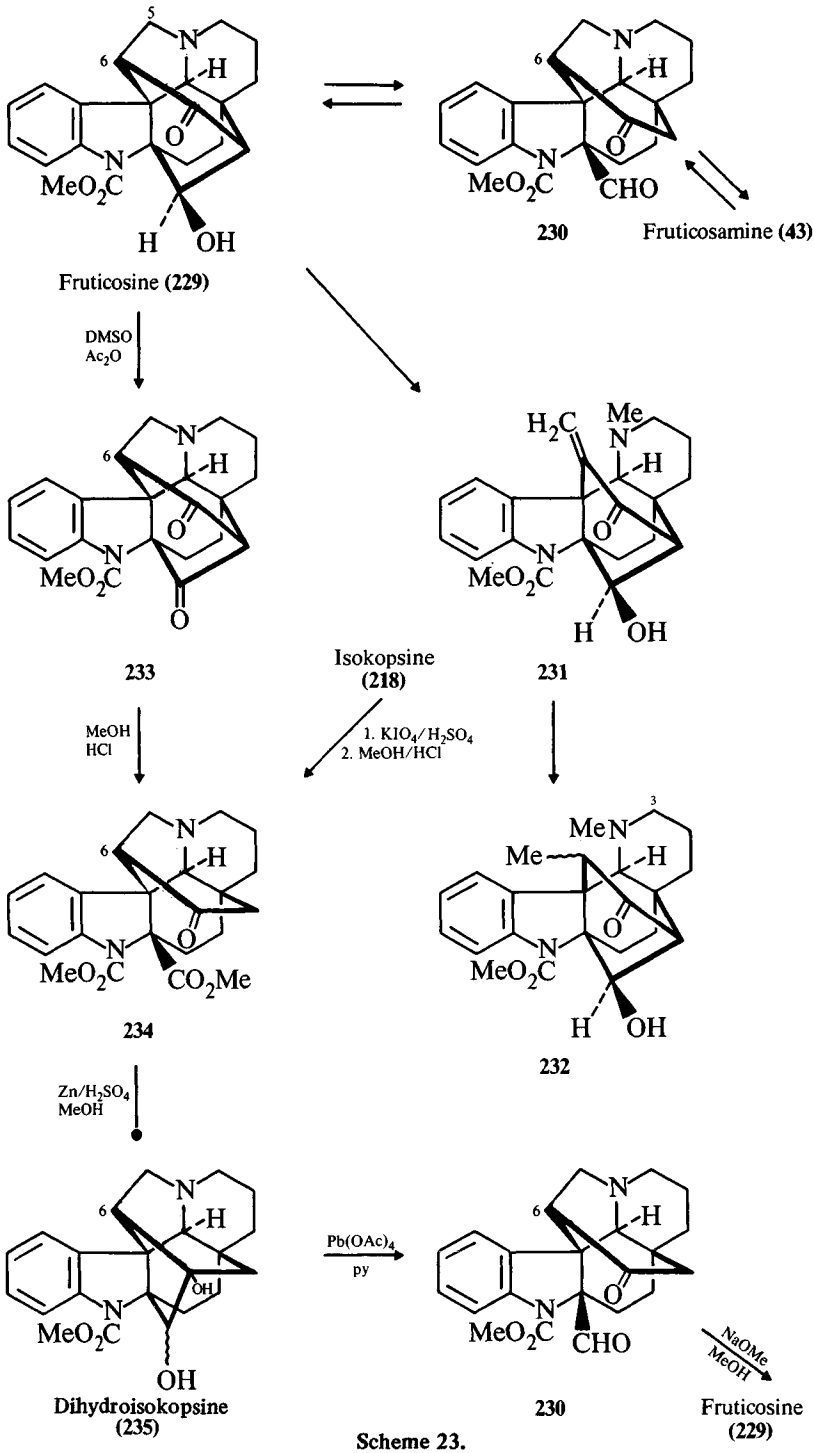
Partial synthesis of fruticosine and fruticosamine has also been achieved.[35]



224: R = Me
225: R = CO_2Me
226: R = H



N-Methylkopsanol (**228a**): R = Me
Kopsanol (**228b**): R = H; α-H at C-22
Epikopsanol (**228c**): R = H; β-H at C-22


Fruticosine (229)
230
Fruticosamine (43)
DMSO
Ac2O
233
Isokopsine
(218)
231
MeOH
HCl
1. KIO4/H2SO4
2. MeOH/HCl
234
232
Zn/H2SO4
MeOH
Pb(OAc)4
py
NaOMe
MeOH
Dihydroisokopsine
(235)
230
Fruticosine
(229)

Scheme 23.

Reduction ($NaBH_4$) of isokopsine gave the known dihydroisokopsine (**235**), which on fission by means of lead tetraacetate gave the ketoaldehyde (**230**). An aldol condensation between C-16 and C-17 then gave a very high yield of fruticosine (**229**). The chano ester **234** was also directly converted into dihydroisokopsine (**235**) by reaction with zinc and acid, which resulted in acyloin condensation followed by reduction.

These interconversions establish not only the structure and relative stereochemistry of fruticosine and fruticosamine, but also the absolute configuration, which receives final confirmation from the ord evidence.[57]

III. TRANSFORMATIONS AND REARRANGEMENTS OF *ASPIDOSPERMA* ALKALOIDS

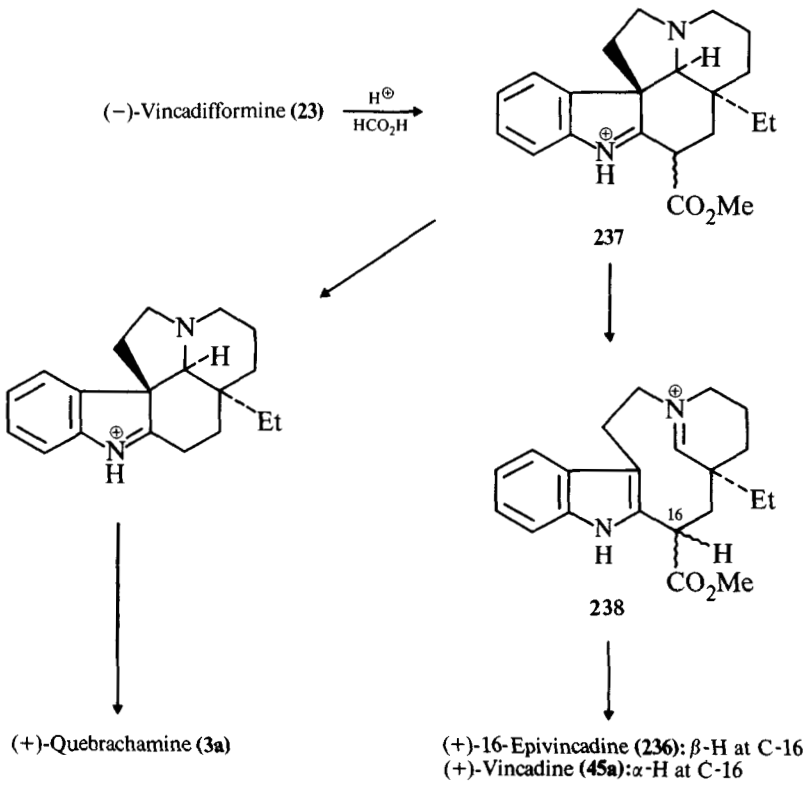
The chemistry of the *Aspidosperma* alkaloids has been enriched by the discovery of a number of fascinating rearrangements which, together with appropriate transformations, have resulted in the clarification of the structures of several alkaloids containing rearranged ring systems, and have provided a number of partial syntheses of other alkaloids.

Prior to their isolation from *Amsonia tabernaemontana* (+)-vincadine (**45a**) and (+)-16-epivincadine (**236**) had been prepared by partial synthesis from (−)-vincadifformine (**23**), simply by heating the alkaloid in a mixture of formic acid and formamide, which caused Mannich fission of the 7,21 bond in **237**, followed by reduction of the N_b,21 double bond in **238** (Scheme 24). Loss of the ester function before Mannich fission of the 7,21 bond gave (+)-quebrachamine (**3a**), the third product obtained.[131] (−)-Tabersonine behaves similarly.

(+)-1,2-Dehydroaspidospermidine (**239**), when oxidized with *m*-chloroperbenzoic acid, then treated with aqueous iron(II) sulfate, affords[132] (−)-rhazinilam (**240**) (Scheme 25),[133a] which has been isolated from a number of plant species, for example, *Rhazya stricta* Decaisne[133b] and *Melodinus australis*.[31] In view of its comparatively easy formation rhazinilam is almost certainly an artifact; it is presumably formed in the above reaction by fragmentation of the intermediate (**241**), or its carbinolamine equivalent, generated from the N_b-oxide (**242**) by a Polonovski reaction. The final stage then involves dehydrogenation. The structure **240** has been unequivocally confirmed by synthesis.[132]

Alternatively, the intermediate (**243**) can yield an immonium ion by protonation at C-7, which can then cyclize to form a pentacyclic lactam. Such a reaction has been observed by Hugel et al.,[134] working in the enantiomeric series; only one of the C-7 epimers can cyclize, so the product almost certainly has the stereochemistry shown in **244**.

The lactam base (**244**) was first encountered as a by-product in the oxidation of (−)-1,2-dehydroaspidospermidine with *p*-nitroperbenzoic acid, followed by reaction with acetic acid and triphenylphosphine (Scheme 26). The major product of the oxidation step is (−)-16-hydroxy-1,2-dehydroaspidospermidine N_b-oxide (**245**), which on N_b-deoxygenation with triphenylphosphine, and rearrangement



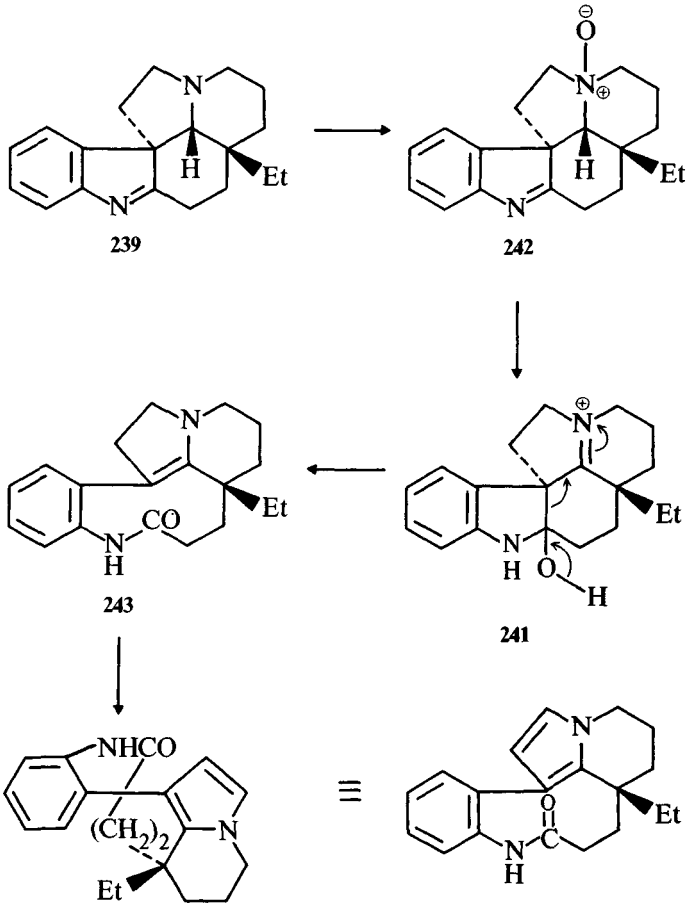
Scheme 24.

of the product **246** with acetic acid, affords a mixture of (+)-eburnamine [(+)-vincanol, **247**] and (−)-eburnamenine (**248**), the latter presumably arising by dehydration of isoeburnamine.[135a]

16-Oxoaspidospermidine (**249a**), prepared from (−)-vincadifformine (**23**) by oxidation to the hydroxyindolenine *N*-oxide (**250a**), followed by hydrolysis, decarboxylation, and selective removal of the N_b-oxide group, is at the same oxidation level as **246**, and can similarly be converted into (−)-eburnamenine (**248**), presumably via **246**. An alternative rearrangement of **250a**, analogous to the formation of **244** from (−)-1,2-dehydroaspidospermidine, affords oxymetavincadifformine (**250b**).[135b]

Attempted Beckmann rearrangement of the oxime (**249b**) of the ketone (**249a**) gives the nitrile **251**, which rearranges to the epimeric tetracyclic nitriles **252a/b** (Scheme 27); since, in contrast to the rearrangement of **246**, the reaction is non-stereospecific, it presumably proceeds via fission of the 7,21 bond in **251** followed by Mannich cyclization of the intermediate. Hydrolysis and cyclization of **252a/b** gives (−)-eburnamonine (**253a**) [(−)-vincamone] and (+)-21-epivincamone (**253b**).[135a]

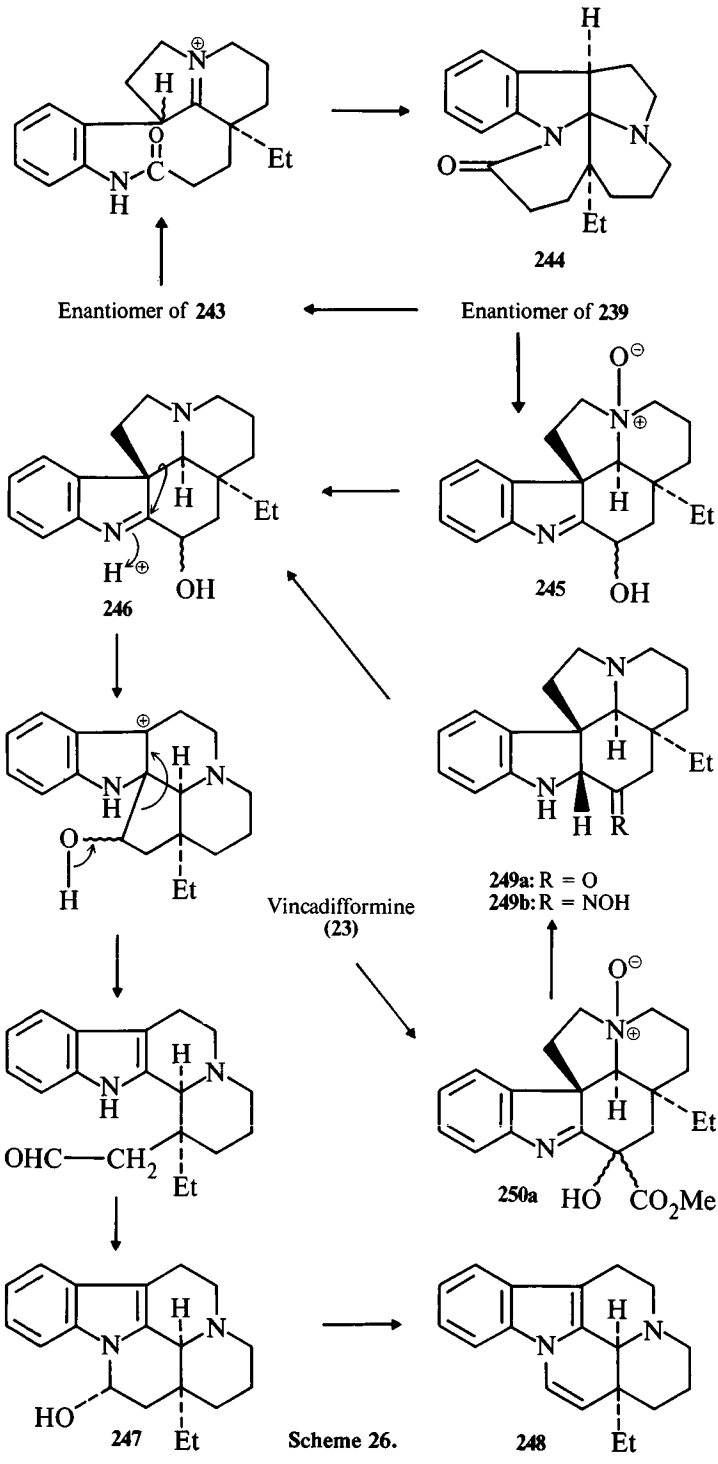
Vincadifformine and tabersonine have been particularly extensively studied in recent years; these somewhat strained molecules undergo a variety of rearrange-



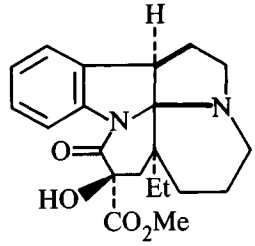
Scheme 25.

ments under oxidizing or reducing (metal-acid) conditions, under the influence of acid catalysts, or even on simple thermolysis, to give products that occasionally contain apparently unrelated ring systems. The rearrangements include indirect, but possibly useful, syntheses of vincamine and its derivatives; other rearrangements, for example, of tabersonine, are of vital importance in connection with in vivo processes, and have thus been the subject of considerable study. The complex behavior of this molecule has led to divergent results by different investigators, and the ensuing controversy has resulted in an even closer examination of the chemistry of tabersonine.

Reduction of tabersonine (**24**) by means of zinc and sulfuric acid affords principally 2β,16β-dihydrotabersonine; in acetic acid solution, however, in the presence of pulverized zinc and copper sulfate the major products are the indole derivative (**255a**) (16%) and the indoline, vincamsonine (**256a**) (53%) (Scheme 28).[136] Hydro-


Enantiomer of 243
Enantiomer of 239
244
245
246
249a: R = O
249b: R = NOH
Vincadifformine
(23)
250a
247
248

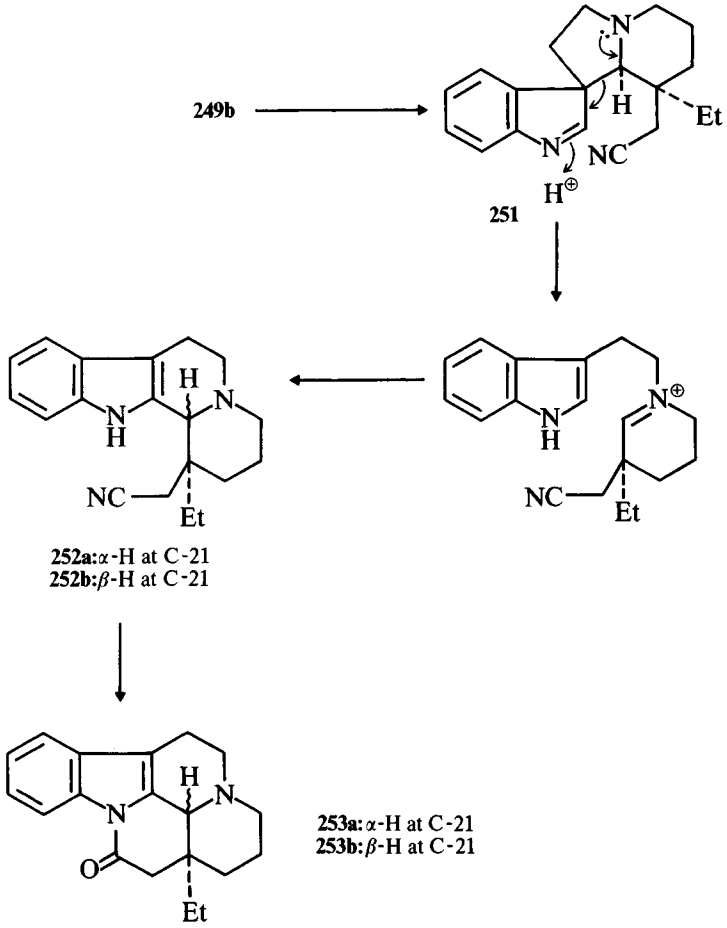
Scheme 26.



Oxymetavincadifformine (**250b**)

genation of **255a** affords a dihydro derivative (**255b**), identical with a racemic intermediate prepared by Kuehne[137] in the first total synthesis of vincamine. This proves that during the formation of **255a** from tabersonine inversion occurs at C-21.

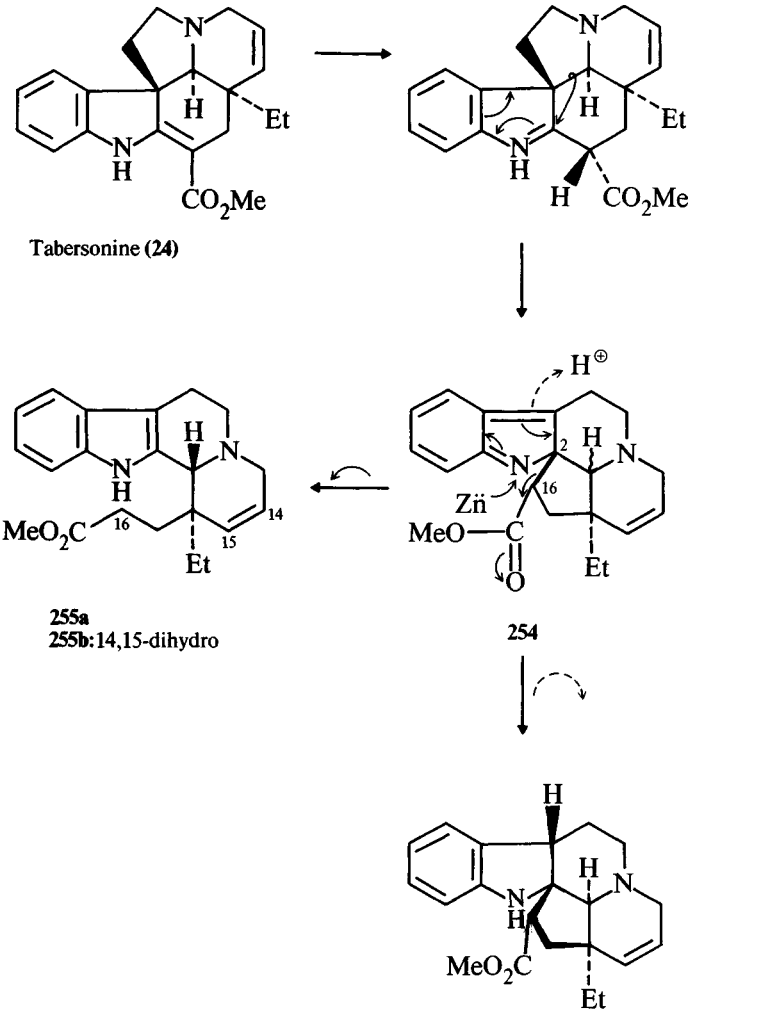
As expected, dihydrovincamsonine (**256b**) can be prepared by the analogous zinc-acetic acid reduction of (—)-vincadifformine.



252a:α-H at C-21
252b:β-H at C-21

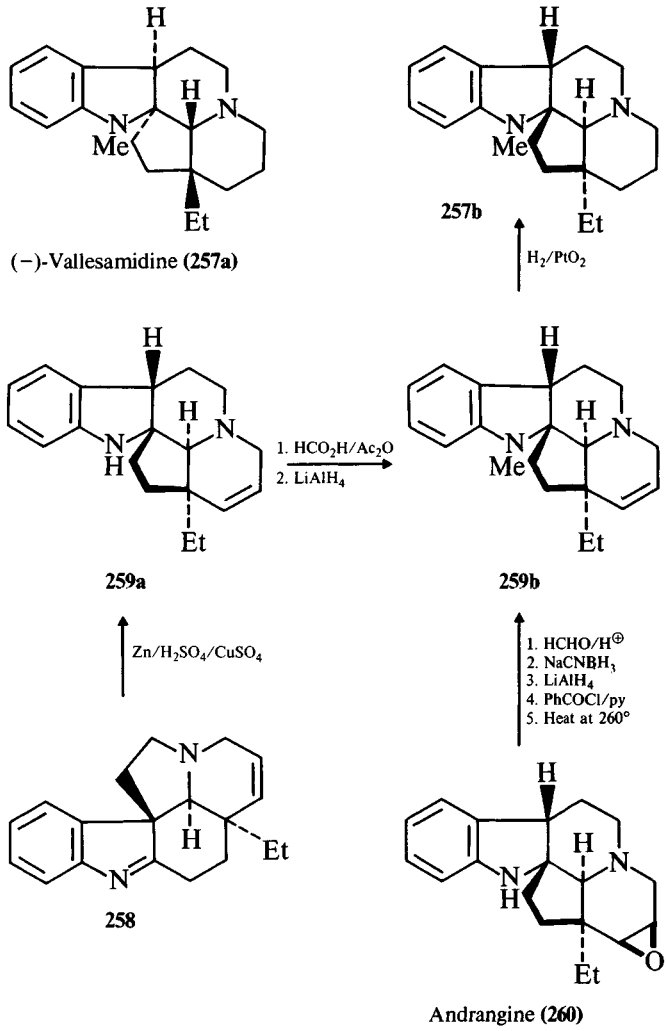
253a: α-H at C-21
253b: β-H at C-21

Scheme 27.



Scheme 28.

The indoline esters (**256a**) and (**256b**) possess the vallesamidine (**257**) skeleton, and it would therefore be expected that rearrangement of a vincadifformine derivative lacking the ester group would give as end product a pentacyclic base related to vallesamidine, since in the absence of an ester group no mechanism is available for the fission of the 2,16 bond (arrows in **254**). In fact, 1,2,14,15-tetradehydroaspidospermidine (**258**), prepared by hydrolysis and decarboxylation of tabersonine (**24**), when reduced by means of pulverized zinc and acetic acid, gave rise to 14,15-dehydroaspidospermidine (6%) and an indoline base of structure **259a** (Scheme 29), which on *N*-methylation and hydrogenation gave (+)-vallesamidine (**257b**),[138] the

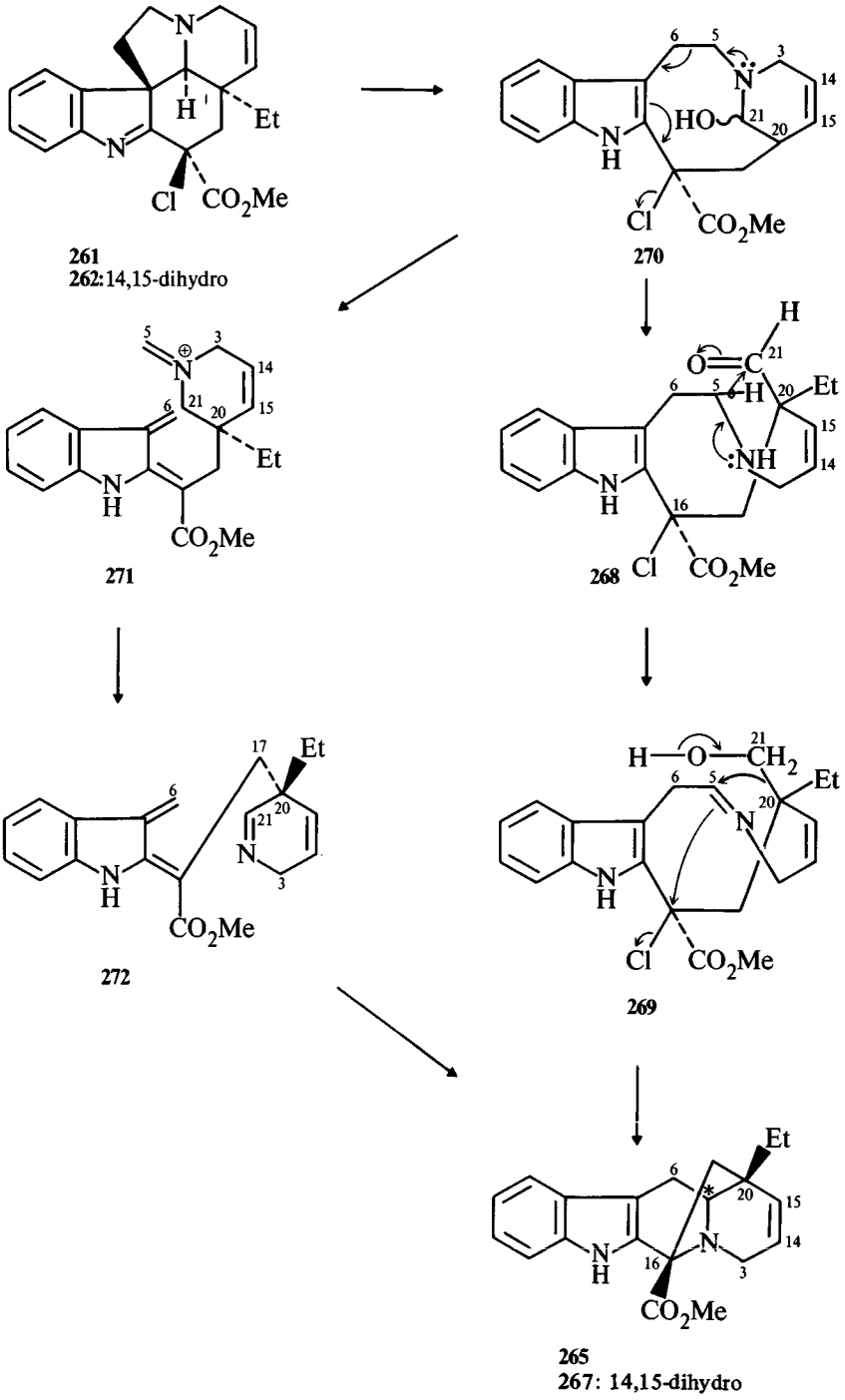


Scheme 29.

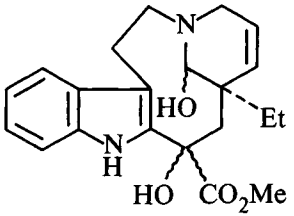
enantiomer of (−)-vallesamidine (**257a**), from *Vallesia dichotoma*.[139] Since the structure and absolute configuration of (−)-vallesamidine have been established by the X-ray crystal structure determination of its N_b-methiodide,[140] the structures **256a**, **256b**, and **257b** in the enantiomeric series are confirmed.

The unsaturated base **259b** was also obtained by a simple sequence of reactions which served to confirm the structure of andrangine (**260**), an alkaloid of *Craspidospermum verticillatum* var. *petiolare* Mgf.[151] and *Crioceras dipladeniiflorus*.[6]

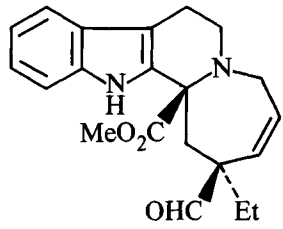
An entirely different series of rearrangements has been observed in the solvolysis of 16-chlorotabersonine (**261**) and its dihydro derivative (**262**), prepared from the parent alkaloids by reaction with *t*-butyl hypochlorite (Scheme 30). With the intention of preparing a derivative of 14,15-dehydrovincadine (**5**) Lévy et al. heated



Scheme 30. C* = C-5 or C-21.



263



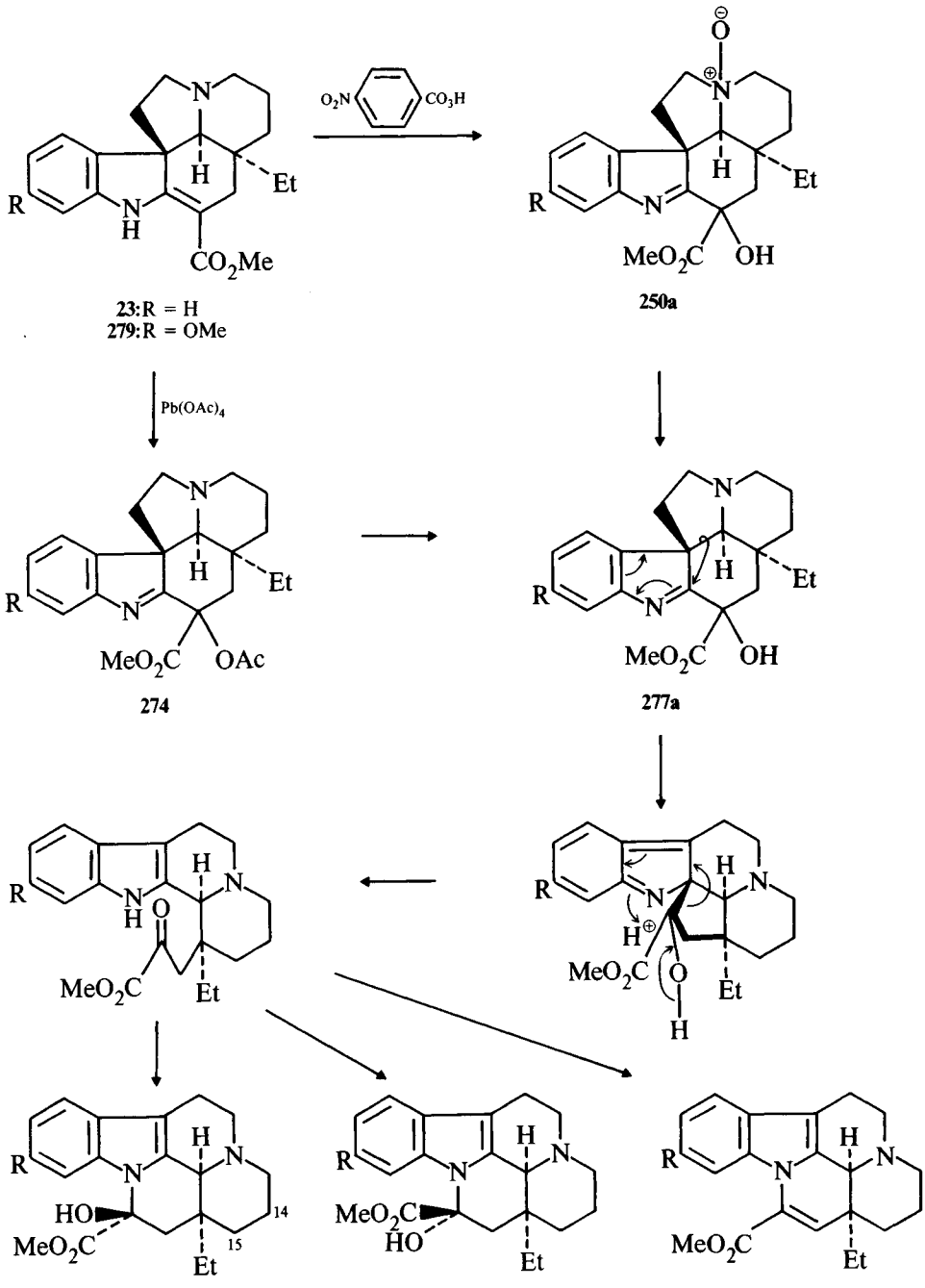
264
266: 14,15-dihydro

16-chlorotabersonine in a mixture of water and tetrahydrofuran. The expected product (**263**) was not obtained, however; instead, the products isolated were the aldehyde **264** and a new tetrahydro-β-carboline derivative of structure **265**.[142] Similarly, 16-chlorovincadifformine (**262**) gave the dihydro analogues **266** and **267**. The base **265** was also obtained in an independent investigation in which an attempt was made to convert tabersonine into a compound containing the meloscine ring system (cf. **33**) by solvolysis of 16-chlorotabersonine (**261**) in the presence of silver perchlorate.[143]

The mechanism by which **265** is formed is not at present clear. The proposal of Lévy et al.[142] involves all the asymmetric centers in the molecule, and requires an intramolecular hydride transfer in the aminoaldehyde (**268**) to give the imino alcohol **269** which, by loss of formaldehyde, cyclization, and elimination of chloride ion, gives the final product (**265**). Since **265** is optically active this last, unorthodox stage must be presumed to be stereospecific, with C-20 retaining its original configuration.

The mechanism of Hofheinz et al.[143] postulates the fragmentation of a vinylogous γ-chloroamine (**270**) to give an immonium ion (**271**) which, by hydrolysis and dehydration, affords a highly reactive entity **272**; a $4\pi + 2\pi$ cyclization then affords the final product. Since at no time is C-20 implicated in this mechanism the isolation of an optically active product is to be expected.

The rearrangement of vincadifformine following reduction by zinc and acetic acid affords the tetracyclic ester (**255b**), from which vincamine (**273**) can be prepared in very low yield; this last step obviously requires oxidation at C-16. By inserting an oxidation stage before the rearrangement a vastly improved partial synthesis of vincamine can be achieved.[144a] Thus oxidation of (−)-vincadifformine by means of lead tetraacetate gives a C-16 acetoxyindolenine (**274**) which, on treatment with trifluoroacetic acid in chloroform at room temperature, or on heating with acetic acid and sodium acetate, is transformed into a mixture of (+)-vincamine (**273**), (−)-16-epivincamine (**275**), and (+)-apovincamine (**276**) (Scheme 31). The overall yield of vincamine from vincadifformine was 36%; however, an even more efficient route was found in the oxidation of vincadifformine by means of two equivalents of *p*-nitroperbenzoic acid, which gave the 16-hydroxyindolenine N_b-oxide (**250a**). In the presence of triphenylphosphine and acetic



23:R = H
279:R = OMe

250a

274

277a

Vincamine (273): R = H
Vincine (280): R = OMe
14,15-Dehydrovincamine (278): $\Delta^{14,15}$

16-Epivincamine (275): R = H
16-Epivincine (281): R = OMe

Apovincamine (276): R = H
Apovincine (282): R = OMe

Scheme 31.

acid the *N*-oxide function in **250a** was reduced, and the resulting hydroxyindolenine **277a** rearranged to a mixture of vincamine (**273**) and 16-epivincamine (**275**).[144a]

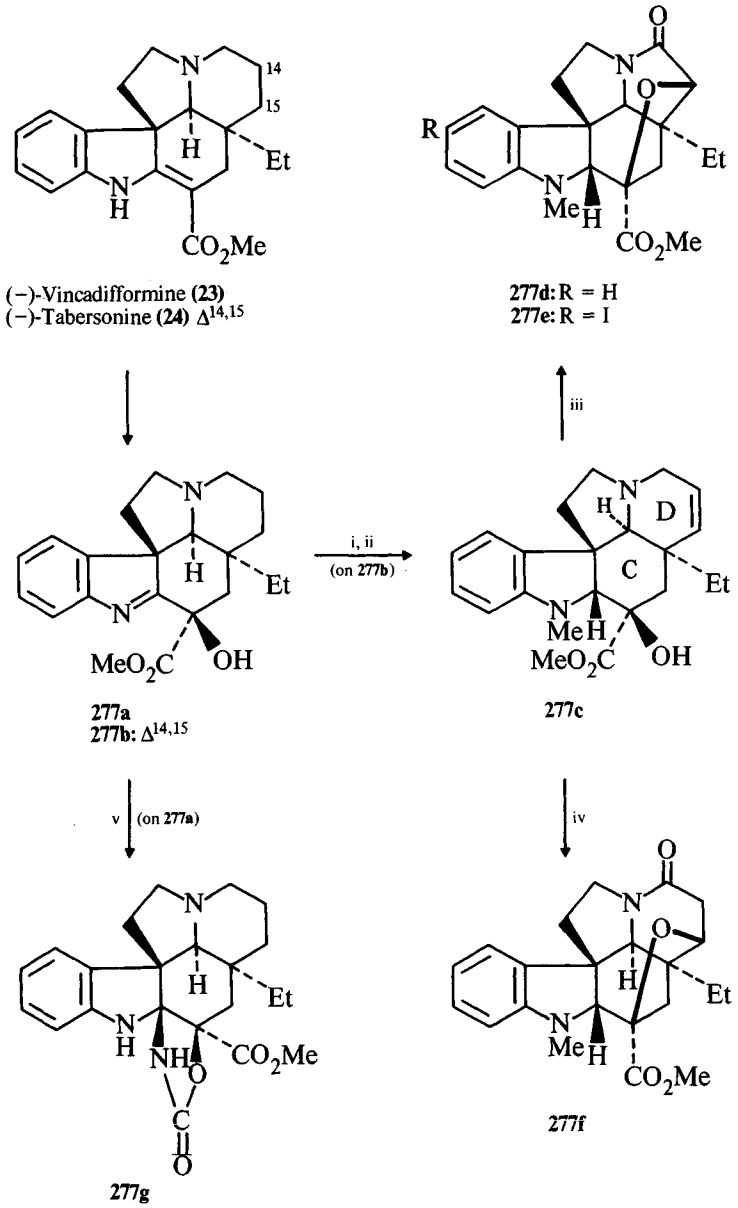
Analogous processes have allowed the conversion of tabersonine (**24**) into 14,15-dehydrovincamine (**278**) and its C-16 epimer, and of (−)-11-methoxyvincadifformine (**279**), obtained by hydrogenation of 11-methoxytabersonine, into vincine (**280**), 16-epivincine (**281**), and apovincine (**282**).[144b] Proof of the intermediacy of the 16-hydroxyindolenine derivatives such as **277a** and **277b** and the configuration at C-16 in these compounds comes from a study of the rearrangement of tabersonine (**24**) into 14,15-dehydrovincamine (**278**).[144c] The intermediate (**277b**), proved by simple correlation to have the same stereochemistry as **277a**, can be converted by methylation and reduction into the C-16 hydroxy-N_a-methylindoline derivative (**277c**) (Scheme 32), in which the ring D double bond is retained. Reaction of **277c** with iodine and potassium iodate gives a lactam (**277d**), together with an aromatic iodo derivative (**277e**), on prolonged reaction. Alternatively, oxidation of **277c** by means of chromium trioxide in pyridine affords a small yield of the lactam ether **277f**, which still contains the six-membered ring D. Obviously the products **277d–f** can be obtained only if the C-16 hydroxyl group is trans with respect to the C/D ring junction substituents.

The same overall transformation of vincadifformine into vincamine can also be achieved under milder oxidative conditions which avoid the formation of the N_b-oxide. Of the various methods developed the best involves ozonization of vincadifformine in 0.43 *M* sulfuric acid in methanol at 60°C, which gives a 74% yield of a 7:3 mixture of vincamine and 16-epivincamine in a one-pot oxidation rearrangement.[145a] Here again the 16-hydroxyindolenine derivative (**277a**) is an intermediate, since it can be isolated if the ozonization reaction is conducted at 20°C; its stereochemistry follows from its reaction with potassium cyanate in dicyclohexyl-18-crown-6 and methylene chloride, which affords the hexacyclic urethane (**277g**). Similarly the ozonization of tabersonine at 65°C affords a 71% yield of a mixture of Δ^{14}-vincamine (**278**) and its 16 epimer.

An independent method[145b] involves passing oxygen through a solution of vincadifformine and copper sulfate in aqueous hydrochloric acid at 50°C for 8 days; vincamine is thus obtained in 20% yield and 16-epivincamine in 15% yield.

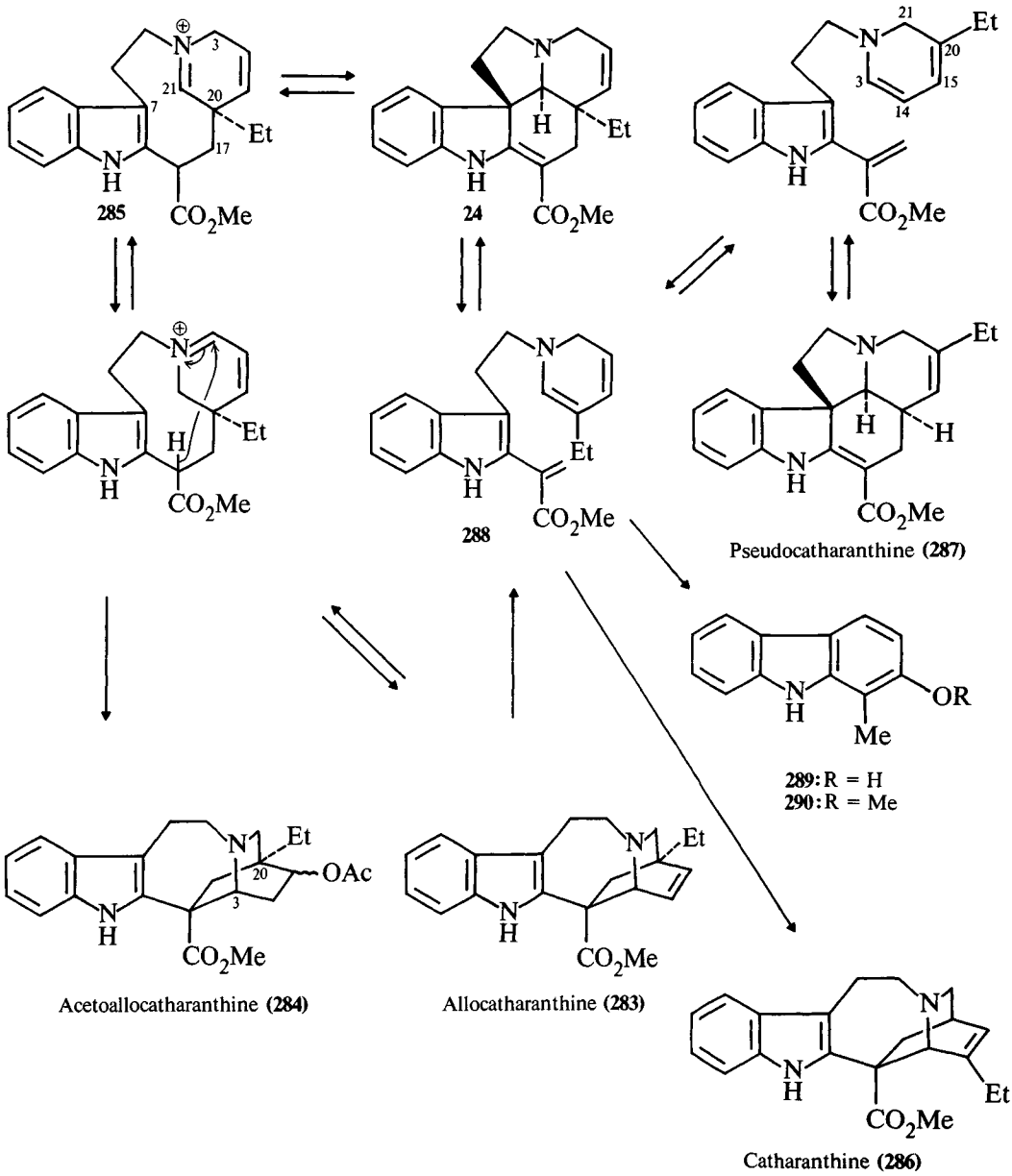
The thermal behavior of tabersonine (**24**) under various conditions has been extensively investigated, and its rearrangement to several related alkaloids has been reported, as well as degradation to simple carbazole derivatives. The reactions are complex, the yields of rearrangement products are low and variable, and it would seem that they depend critically on factors such as temperature and surface effects. Before these factors were appreciated and defined the experiments were found, not surprisingly, to be difficult to reproduce, and divergent results were reported in the literature. Space permits only a brief outline of the numerous investigations reported in this area.

Tabersonine (**24**), when heated in refluxing acetic acid (bath temperature 130°, or 190–205°), affords a new base, (+)-allocatharanthine (**283**) (17%), together with (+)-dihydroallocatharanthine (15%), (+)-acetoallocatharanthine (**284**) (6%), vincadifformine (14%), and some unchanged tabersonine (Scheme 33).[146] These



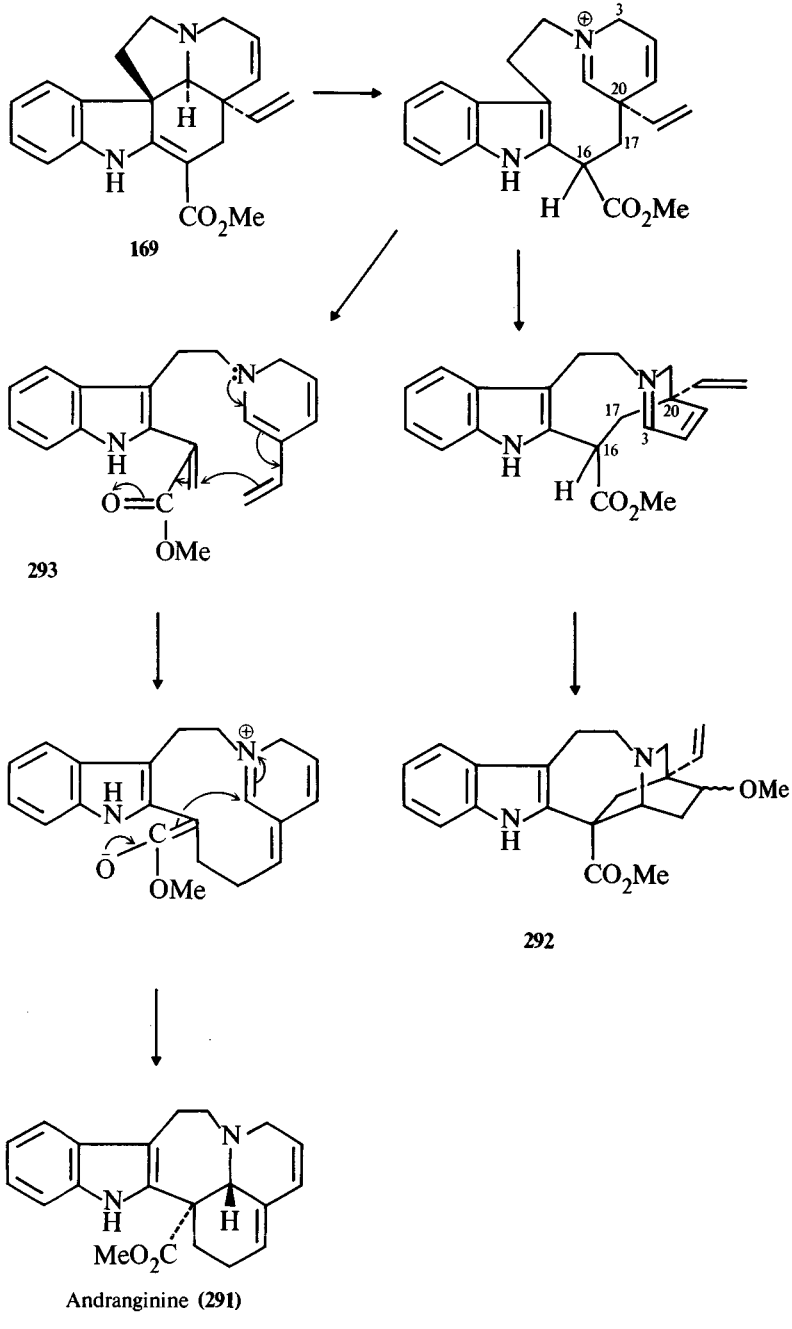
Scheme 32. Reagents: i, Methylation; ii, reduction; iii, I_2, KIO_3; iv, CrO_3, py; v, KCNO, dicyclohexyl-18-crown-6, CH_2Cl_2, r.t.

products are simply the result of a reverse Mannich fission of the 7,21-bond in protonated tabersonine followed by a prototropic shift in the intermediate (**285**), and recyclization; some disproportionation also occurs. Since C-20 is not involved the recyclization is stereocontrolled.



Scheme 33.

Under other conditions, for example, vigorous and prolonged refluxing in acetic acid (external oil bath temperature 210°) in the presence of alundum, tabersonine is stated to be converted into (±)-catharanthine (3–5%) (**286**), (±)-pseudocatharanthine (**287**) (15–20%), and unchanged (−)-tabersonine.[147] This reaction can best be explained by the reverse Diels-Alder fission of both the 7,21 and 17,20



Scheme 34.

bonds in tabersonine to give the achiral dehydrosecodine derivative (**288**), which can then cyclize in alternative ways to give *racemic* catharanthine and pseudocatharanthine. This process provides the much-desired laboratory analogy for the *Aspidosperma-Iboga* biochemical interrelationship, but unfortunately it is admitted[148] that it is not a consistently reproducible experiment, and others have been unable to reproduce it.

When heated at 190° without solvent in evacuated sealed tubes,[146] or when heated in xylene in sealed tubes at 175°,[149] tabersonine breaks down to 2-hydroxy-1-methylcarbazole (**289**) and 2-methoxy-1-methylcarbazole (**290**); some 3-ethylpyridine is also formed.[149] The formation of these products obviously implies the fission of the 7,21 and 17,20 bonds in tabersonine, but the conditions used are sufficiently vigorous to result in further degradation of the dehydrosecodine derivative (**288**).

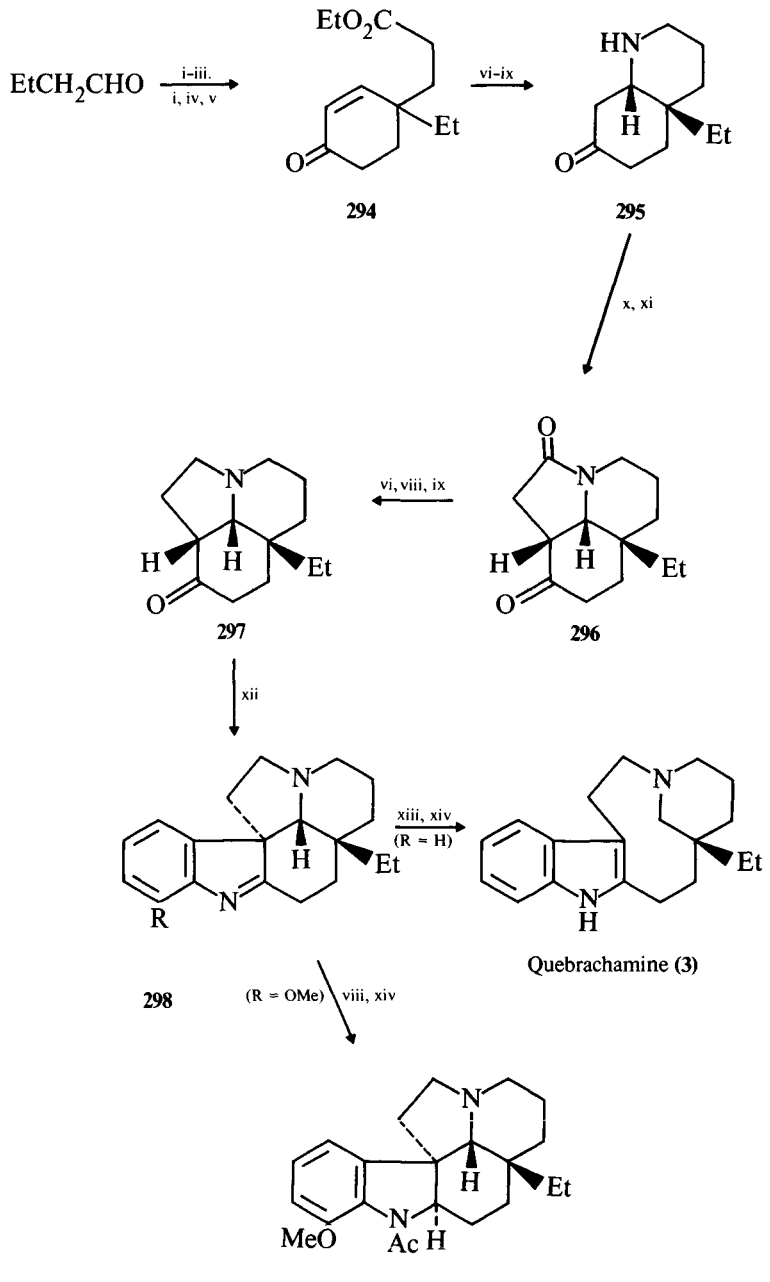
One further thermal rearrangement may be mentioned here. Δ^{18}-Tabersonine (**169**), prepared from vindolinine (**31**) via 19-iodotabersonine (**165**), when heated in methanol at 145°, gives a 16% yield of racemic andranginine (**291**) (Scheme 34),[150] identical with the alkaloid (also racemic) isolated recently[151] from *Craspidospermum verticillatum*. Other products obtained in the same reaction were (+)-15-methoxy-14,15-dihydro-Δ^{18}-allocatharanthine (**292**), 2-hydroxy-1-methylcarbazole (**289**), and a very small amount of (±)-epiandranginine; some tabersonine was also recovered. The formation of **289** and andranginine provides evidence for the intermediate formation of the dehydrosecodine derivative **293**, and the formation of some epiandranginine provides evidence for the two-stage recyclization of **293** via an intramolecular Michael reaction, rather than a concerted $2\pi + 4\pi$ stereospecific cycloaddition.

IV. TOTAL SYNTHESIS OF *ASPIDOSPERMA* ALKALOIDS

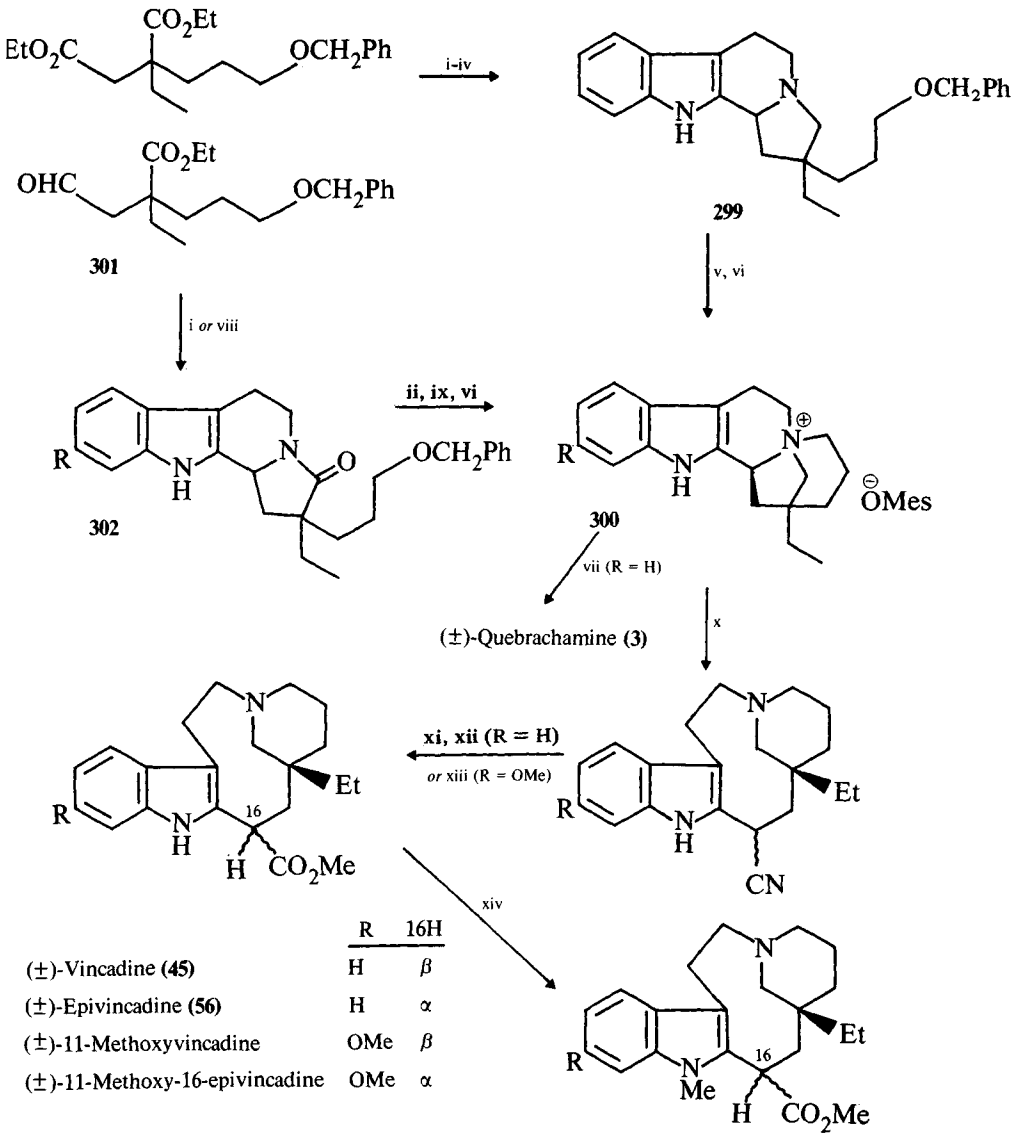
A considerable amount of effort has been expended on the synthesis of *Aspidosperma* alkaloids in recent years. The intellectual challenge offered by these alkaloids has provided the principal motivation, rather than the desire to achieve a commercially viable synthesis. Aside from vindoline, which constitutes one component of the important antileukemic bisindole alkaloids vinblastine, few, if any, of the *Aspidosperma* bases show any useful pharmacological activity.

A. The Quebrachamine Group

The first synthesis of quebrachamine involved a simple adaptation of Stork's celebrated aspidospermine synthesis.[152] Alkylation of butyraldehyde by the enamine method, first with ethyl acrylate and then with methyl vinyl ketone gave, after cyclization, the cyclohexenone **294** (Scheme 35). The ketone group in **294** was protected by ketalization, the ester group converted into the corresponding primary amine, and the ketone group released by hydrolysis; internal Michael addition of



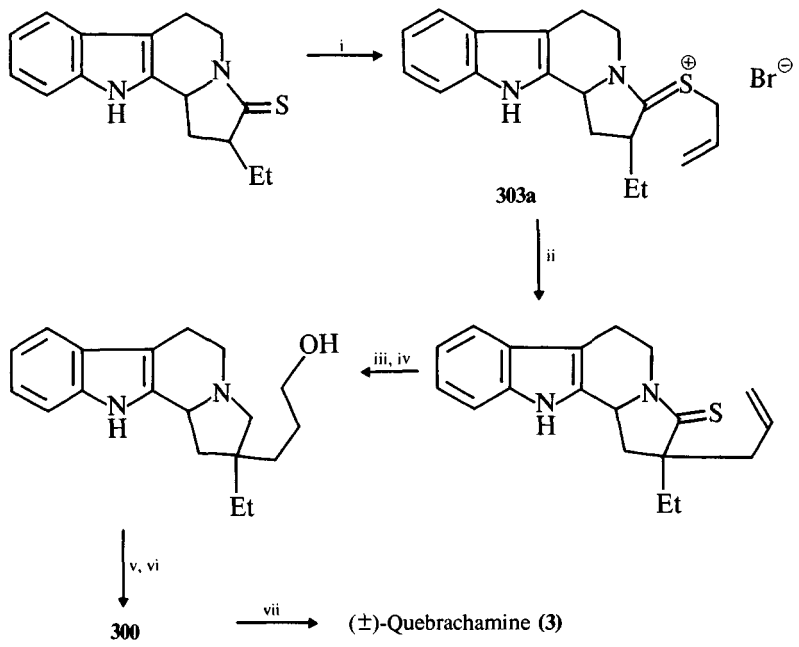
Scheme 35. Reagents: i, Pyrrolidine; ii, CH_2=$CH.CO_2Et$; iii, H_2O, AcOH; iv, $MeCOCH{=}CH_2$; v, AcOH; vi, $(CH_2OH)_2$, H^+; vii, NH_3, H_2O; viii, $LiAlH_4$; ix, H_2O, H^+; x, $ClCH_2COCl$; xi, $KOBu^t$, C_6H_6; xii, $RC_6H_4NHNH_2$, AcOH, Δ; xiii, KBH_4; xiv, Ac_2O, py.



	R	16H
(±)-Vincadine (**45**)	H	β
(±)-Epivincadine (**56**)	H	α
(±)-11-Methoxyvincadine	OMe	β
(±)-11-Methoxy-16-epivincadine	OMe	α

	R	16H
(±)-*N*-Methyl-11-methoxyvincadine	OMe	β
(±)-Vincaminoridine (**4**)	OMe	α
(±)-Vincaminoreine (**57**)	H	β
(±)-Vincaminorine (**55**)	H	α

Scheme 36. Reagents: i, Tryptamine; ii, $LiAlH_4$; iii, $Hg(OAc)_2$, MeOH, AcOH; iv, $NaBH_4$; v, BBr_3, CH_2Cl_2; vi, $MeSO_2Cl$, base; vii, Na, NH_3; viii, 6-methoxytryptamine; ix, Pd/C, H_2, AcOH: x, KCN, DMF; xi, OH^-, H_2O; xii, CH_2N_2; xiii, MeOH, HCl; xiv, $NaNH_2$, MeI, NH_3; xv, NaOMe.



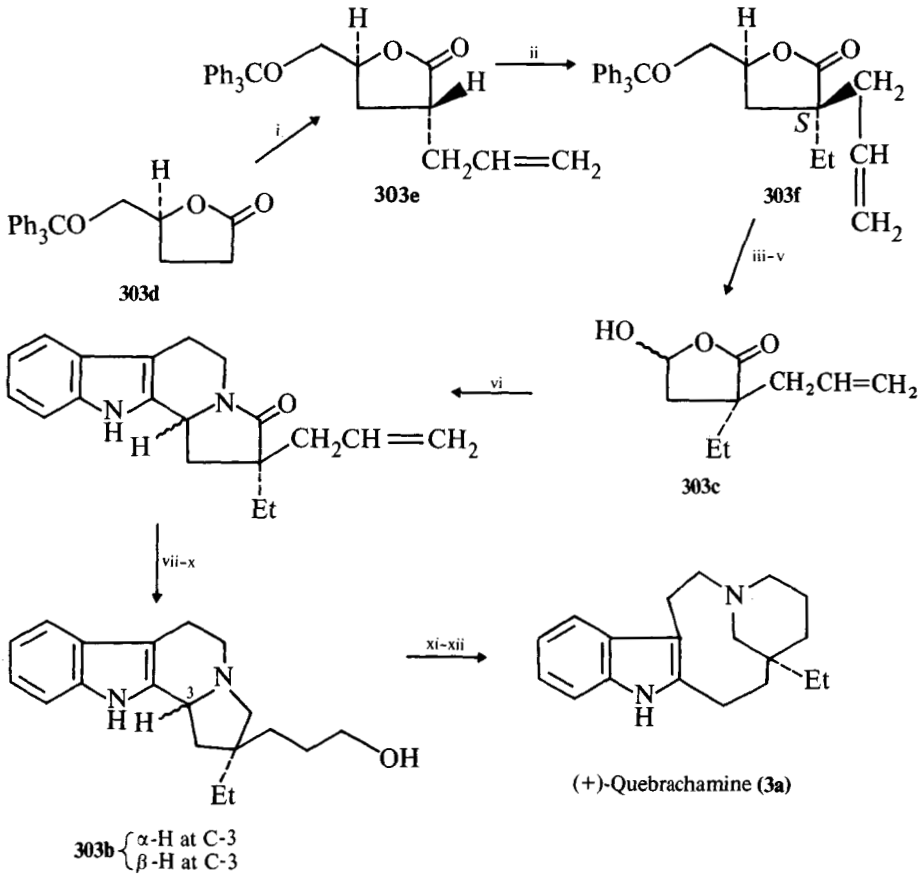
Scheme 37. Reagents: i, CH_2=$CHCH_2Br$, EtOH; ii, $KOBu^t$, THF; iii, B_2H_6, THF, Δ; iv, H_2O_2, NaOH; v, $MeSO_2Cl$, py; vi, $CHCl_3$, 60°, 3 hr; vii, Na, NH_3.

the amino group to the enone system then gave the bicyclic aminoketone **295** which was converted, via the tricyclic ketolactam (**296**), into the tricyclic amino ketone (**297**), as shown in Scheme 35. Fischer indolization of **296** gave the undesired linear indole derivative, but the amino ketone **297** gave mainly the desired pentacyclic indolenine (**298**), which gave (±)-quebrachamine [(±)-**3**] on reduction.

Subsequently, Kutney and his collaborators contributed a second synthesis.[153] In essence this involved the construction, by conventional means, of the tetracyclic β-carboline derivative (**299**). Debenzylation of **299**, followed by internal quaternization of the mesylate of the resulting alcohol, gave **300**, which on reductive fission of the benzylic bond to the quaternary N_b afforded (±)-quebrachamine (Scheme 36).

Kutney's improved route[154] to quebrachamine involves a second synthesis of the versatile quaternary mesylate **300**, via the intermediates **301** and **302**, which, as well as affording a much more efficient preparation of quebrachamine than the earlier synthesis, provided a route to the vincadine group of alkaloids. The completed project embraced the synthesis of the racemic alkaloids vincadine (**45**), 16-epivincadine (**56**), vincaminoreine (**57**), and vincaminorine (**55**), as well as their 11-methoxy derivatives. Of these, vincaminoridine (**4**) is a known alkaloid, but the other bases have not yet been encountered in nature.

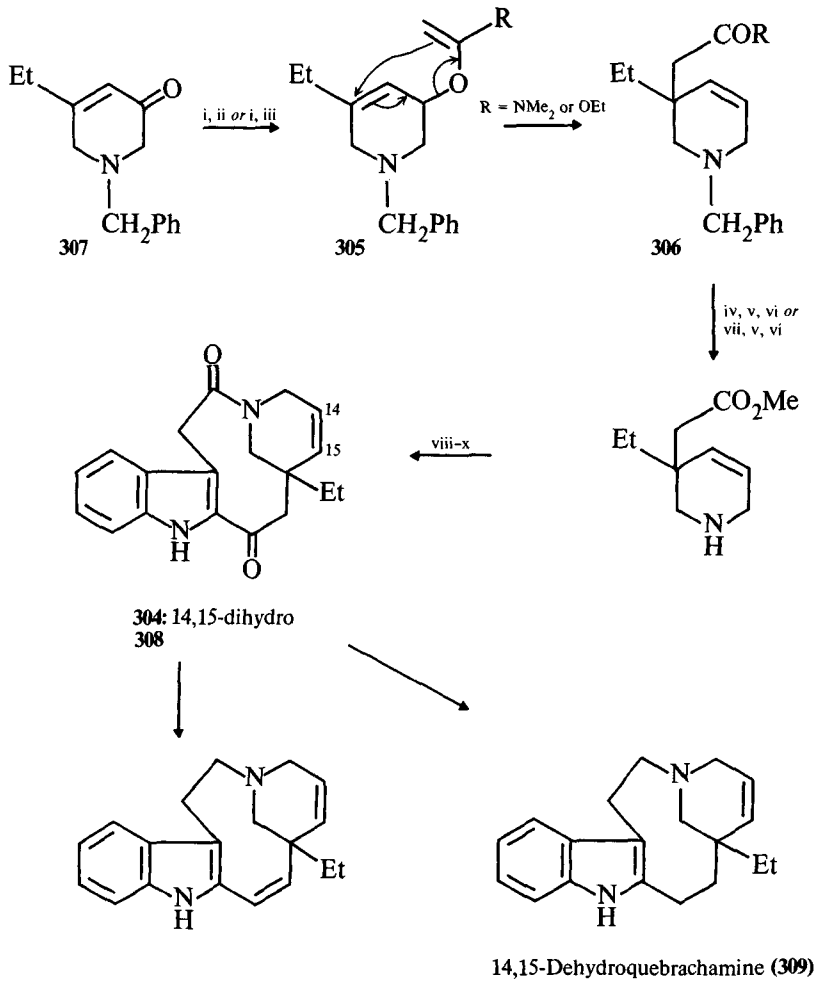
Two further syntheses of quebrachamine, which essentially afford alternative routes to the quaternary mesylate (**300**), have been reported recently by Takano



Scheme 38. Reagents: i, $LiNPr^i_2$, CH_2=CH.CH_2Br, THF, −78°; ii, $LiNPr^i_2$, EtBr, THF, −78°; iii, HCl, EtOH; iv, NaOH, H_2O, MeOH; v, $NaIO_4$; vi, tryptamine, AcOH, Δ; vii, B_2H_6, DMS, THF; viii, NaOH, H_2O_2, H_2O; ix, $LiAlH_4$; x, separation of diastereoisomers, xi, MsCl; xii, Na, NH_3, EtOH.

et al.[155a,b] In the second of these the three-carbon unit required for completion of the piperidine ring was introduced via an ingenious application of the thio-Claisen rearrangement on the thio ether derived by abstraction of a proton from the sulfonium salt **303a** (Scheme 37).

The first enantioselective synthesis of (+)-quebrachamine is the subject of yet another contribution from Takano et al[155c]; in principle this constitutes an elegant preparation of the amino alcohol **303b**, the required aldehydo acid **303c**, with *S* configuration at the future C-20, being prepared from the lactone **303d**, itself obtained from L-glutamic acid. Alkylation of the anions from both **303d** and **303e** proceeded preferentially at the less hindered side, with stereoselective formation of **303e** and **303f**. The subsequent stages were conventional, and allowed the construction of **303b**, both epimers of which were transformed into (+)-quebrachamine (**3a**) (Scheme 38).[155c]



Scheme 39. Reagents: i, $LiAlH_4$; ii, $MeC(OMe)_2NMe_2$, diglyme, Δ; iii, $MeC(OEt)_3$, Me_3CCO_2H, 140°; iv, $ClCO_2Ph$, CH_2Cl_2; v, KOH, $MeOCH_2CH_2OH$; vi, MeOH, HCl; vii, $ClCO_2Et$, C_6H_6, 80°; viii, β-indolylacetyl chloride; ix, saponification; x, polyphosphoric acid, 85°.

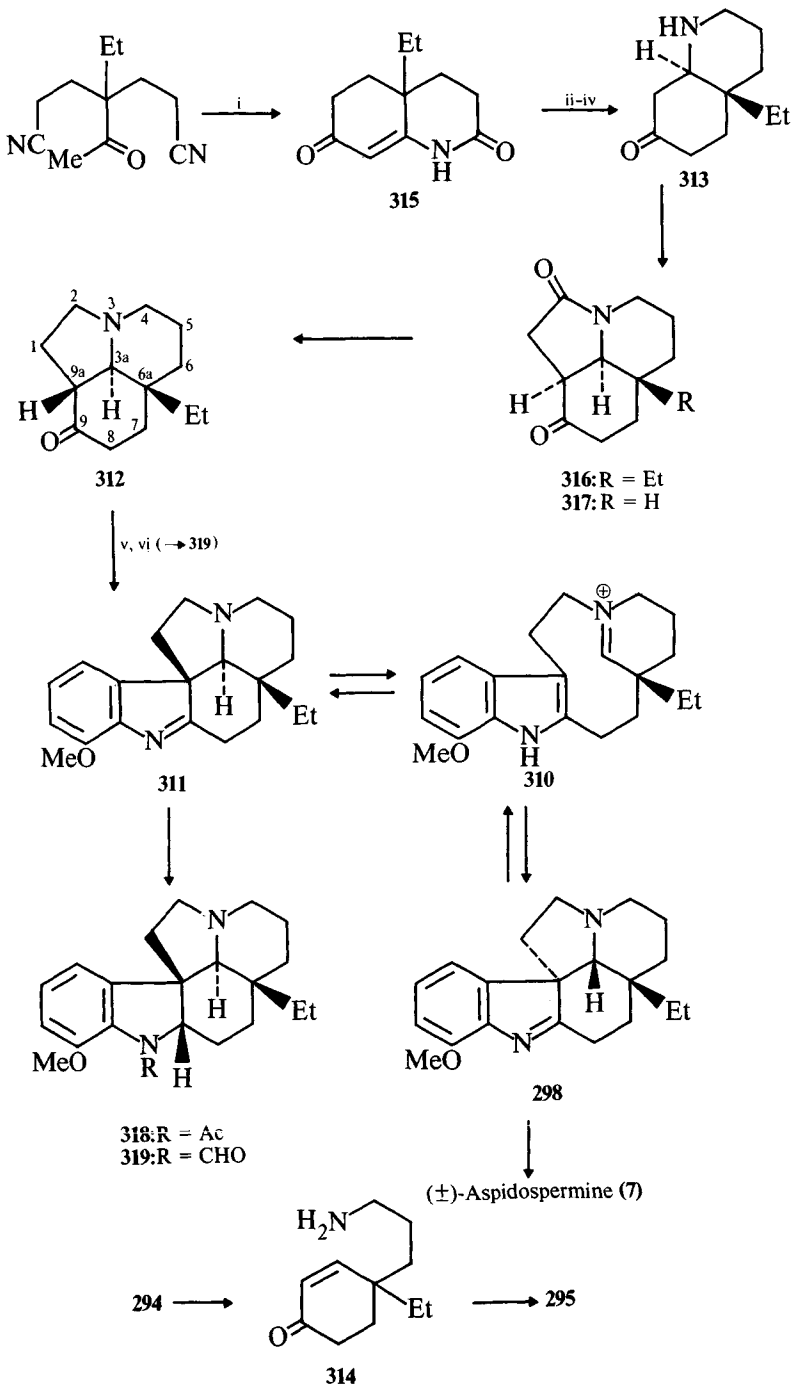
Ziegler has completed two routes to quebrachamine. The first of these gave only a low yield in the final stage, mainly owing to the difficulty of reducing the keto-lactam (**304**) efficiently.[156] In the second approach the acetic ester residue, the double bond, and the quaternary center (C-20) were neatly introduced via a Claisen rearrangement (**305** → **306**) on a derivative of the allylic alcohol obtained by reduction of the enone **307**. The mixture of bases produced by reduction of the cyclization product **308** included 14,15-dehydroquebrachamine (**309**) (41% yield), hydrogenation of which afforded an independent synthesis of (±)-quebrachamine (Scheme 39).[157]

B. Aspidospermine

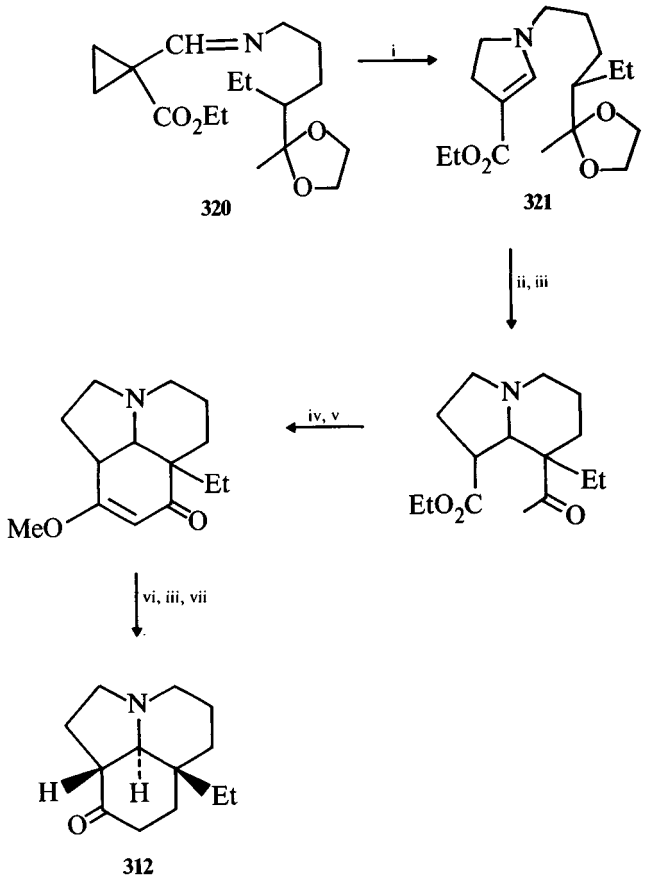
In the first contribution to synthesis in this group of alkaloids Stork and Dolfini synthesized aspidospermine itself.[152a] Fischer indolization of the tricyclic amino ketone (**297**) with *o*-methoxyphenylhydrazine gave the pentacyclic indolenine (**298**; R = OMe), which on reduction and acetylation gave (±)-aspidospermine [(±)-**7**]. This elegant route to aspidospermine does not depend critically on the stereochemistry of the amino ketone (**297**), since it was realized that under the acidic conditions of the Fischer indole reaction the initially formed indolenine could equilibrate with its C/D stereoisomer via the immonium salt (**310**) obtained by reversible Mannich fission of the 7,21 bond; that is, **298** ⇄ **310** ⇄ **311** (Scheme 40). Equilibration thus ensures that the thermodynamically preferred isomer (**298** or **311**) is obtained, regardless of the stereochemistry of the initial tricyclic ketone; in the aspidospermine series the cis C/D stereoisomers are preferred.

Somewhat later Ban and his collaborators[158] corroborated Stork's proposal in an independent synthesis of aspidospermine, which proceeded via a tricyclic amino ketone (**312**), stereoisomeric with Stork's amino ketone (**297**) (Scheme 40). In essence this synthesis involved a different approach from that of Stork as far as the bicyclic amino ketone (**313**), but the stages from this point onwards were similar to those developed by Stork. The preparation of the common pentacyclic indolenine **298** from the two tricyclic ketones **297** and **312** is ample evidence for the equilibration postulated.

Initially Stork had assumed[152b] that his tricyclic ketone had a trans C/D ring junction, and Ban et al. therefore provisionally concluded that their ketone had a cis ring junction. These proposals are perhaps contradictory to what might have been predicted, since cyclization of the unsaturated amino ketone **314** presumably proceeds preferentially by axial approach of the amino group to the enone system, which must necessarily result in a cis hydroquinoline product (**295**). Equally, it would be expected that hydrogenation of **315** would result in delivery of hydrogen to the less hindered side of the molecule, with formation of a trans amino ketone (**313**). Subsequently a comprehensive and rigorous conformational analysis of the amido ketones **296** and **316**, the amino ketones **297** and **312** and the related amino alcohols, together with an amido ketone **317** lacking the angular ethyl group and of undisputed trans stereochemistry at positions 3a and 6a, resulted in unequivocal proof[159] that Stork's amido ketone had the complete stereochemistry shown in **296**, whereas that of Ban et al. was **316**. The related amino ketones have the stereochemistry shown in **297** and **312**, the latter being the result of epimerization at position 9a to relieve nonbonded interactions which are more serious in the amino ketone than in the amido ketone **316**. The conclusion concerning **312** was further confirmed by its conversion into the trans C/D aspidospermine isomer **318**. Fischer indolization of the *o*-methoxyphenylhydrazone of the ketone **312** by means of formic acid resulted in the formation of an indolenine **311** which suffered reduction and formylation before equilibration to the cis C/D isomer **298** could supervene; the product was therefore the *N*-formyl derivative **319**, which gave the trans C/D aspidospermine isomer **318** on replacement of the formyl group by an acetyl group.[160]



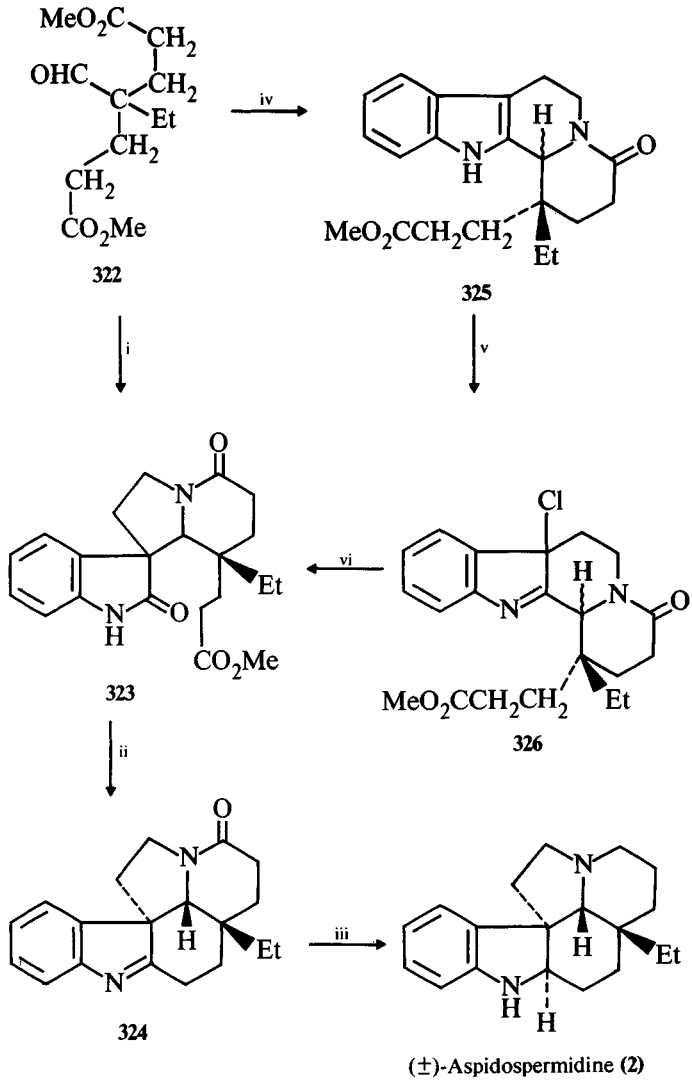
Scheme 40. Reagents: i, 80% H_2SO_4, 150°; ii, H_2, Pd, OH^-; iii, $LiAlH_4$, THF; iv, Oppenauer oxidation; v, *o*-$MeOC_6H_4NHNH_2$; vi, HCO_2H, Δ.



Scheme 41. Reagents: i, NH_4Cl, 160°; ii, HCl, Et_2O; iii, H_3O^+; iv, NaOMe, MeOH; v, MeOH, HCl; vi, $LiAlH_4$; vii, H_2, Pd/C.

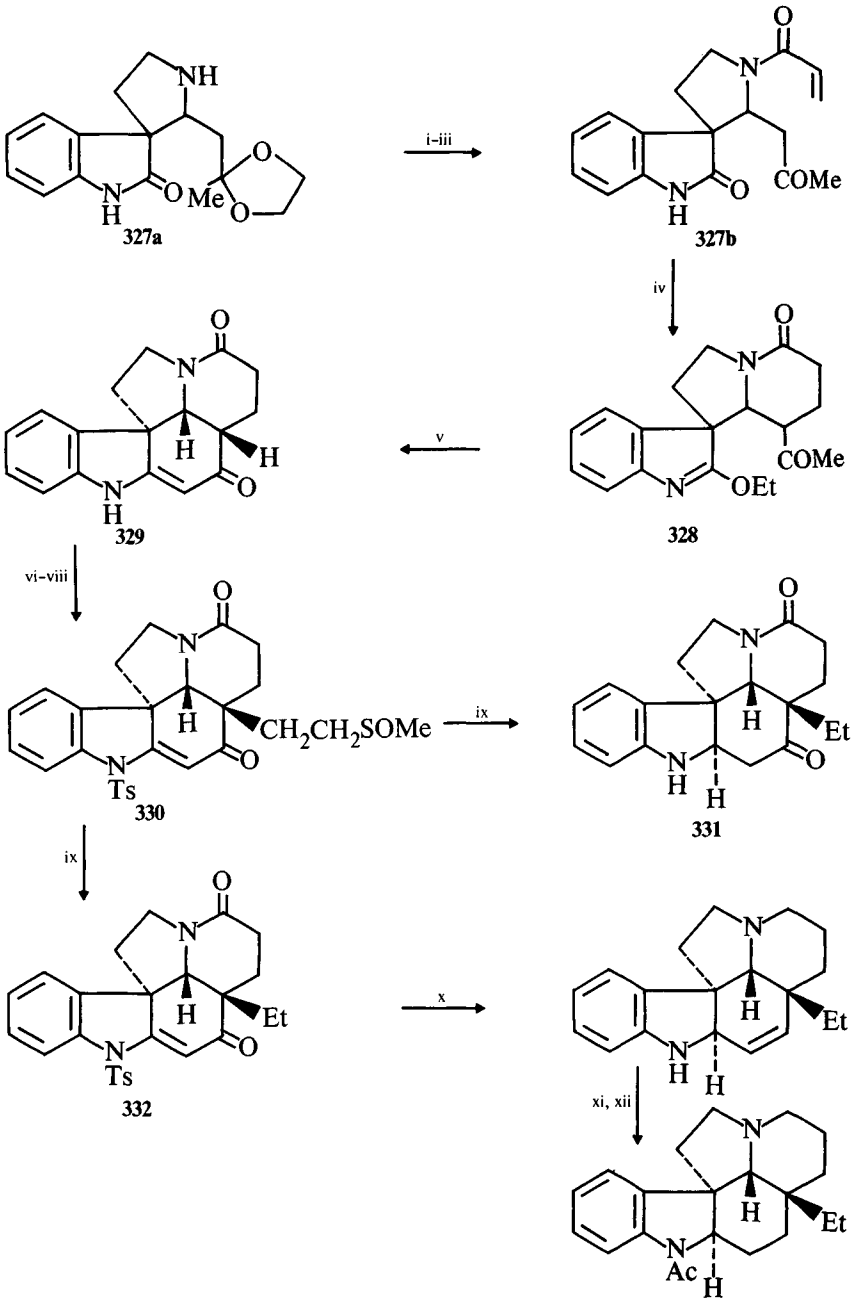
Two bicyclic amino ketones having the same plane formula as **297** and **312** have been synthesized by Kuehne and Bayha,[161] and have been converted into aspidospermine by the method adopted by Stork and Ban et al. The stereochemistry of these amino ketones has not been rigorously deduced and, in fact, complete stereochemical purity is not claimed for them.

The route adopted by Stevens and his collaborators in their formal synthesis of aspidospermine involves a new preparation of the tricyclic amino ketone **312** (Scheme 41).[162] This approach differs from previous ones in that the five-membered ring is formed first, the vital stage being an ingenious, thermal, acid-catalyzed rearrangement of the imine **(320)** of a cyclopropyl aldehyde to give a Δ^2-pyrroline **(321)**. Whereas Stork's synthesis must give a cis-coupled decahydroquinoline derivative as kinetically favored product by virtue of the cyclization processes involved, the cyclization of **321** and subsequent transformations result in the preferential formation of the all-trans amino ketone **312**.



Scheme 42. Reagents: i, 3-(2-Aminoethyl)oxindole; ii, polyphosphoric acid, 125°, N_2; iii, $LiAlH_4$; iv, tryptamine; v, Bu^tOCl; vi, MeOH, H_2O.

The shortest synthesis of (±)-aspidospermidine reported to date[163] simply involves the condensation of aminoethyloxindole with the aldehyde diester (**322**) to give two stereoisomeric oxindoles (**323**), one of which, when heated with polyphosphoric acid, suffered cyclization, hydrolysis, and decarboxylation, with formation of 3-oxo-1,2-dehydroaspidospermidine (**324**). Reduction of **324** by means of lithium aluminum hydride then gave (±)-aspidospermidine [(±)-**2**]. An alternative preparation of the stereoisomers of **323** is afforded by the rearrangement of the lactam esters **325** via the chloroindolenines **326** (Scheme 42).[163]



(±)-*N*-Acetylaspidospermidine (333)

Scheme 43. Reagents: i, $ClCH_2CH_2COCl$; ii, H^+; iii, EtOH, CH_2Cl_2, NaOH; iv, $Et_3O^+BF_4^-$, $ClCH_2CH_2Cl$, 65–70°, 20 hr; v, NaH/DMSO, Δ, 60 hr; vi, NaH/monoglyme, Δ; vii, TsCl, Δ, 5 hr; viii, CH_2=CHSOMe, $LiNPr^i_2$, THF; ix, Ni, 60°, 2.5 hr; x, $LiAlH_4$, DMF; xi, MeCOCl, CH_2Cl_2, K_2CO_3; xii, H_2, PtO_2, EtOH, HCl, 4 atm.

The second synthetic route of Ban et al.[164] to aspidospermine derivatives utilizes as initial stage the condensation of aminoethyloxindole with the ketal of 3-oxobutanal (Scheme 43). Acylation of the product (**327a**) with β-chloropropionyl chloride, followed by ketal hydrolysis and elimination of hydrogen chloride, then gave the tricyclic amido ketone **327b** as a mixture of two racemates, which were separately cyclized by Meerwein's reagent to three tetracyclic amido ketones **328**. Further cyclization of **328** (NaH in DMSO) gave mainly (31–50%) the pentacyclic product **329**, together with a very small amount of stereoisomer.

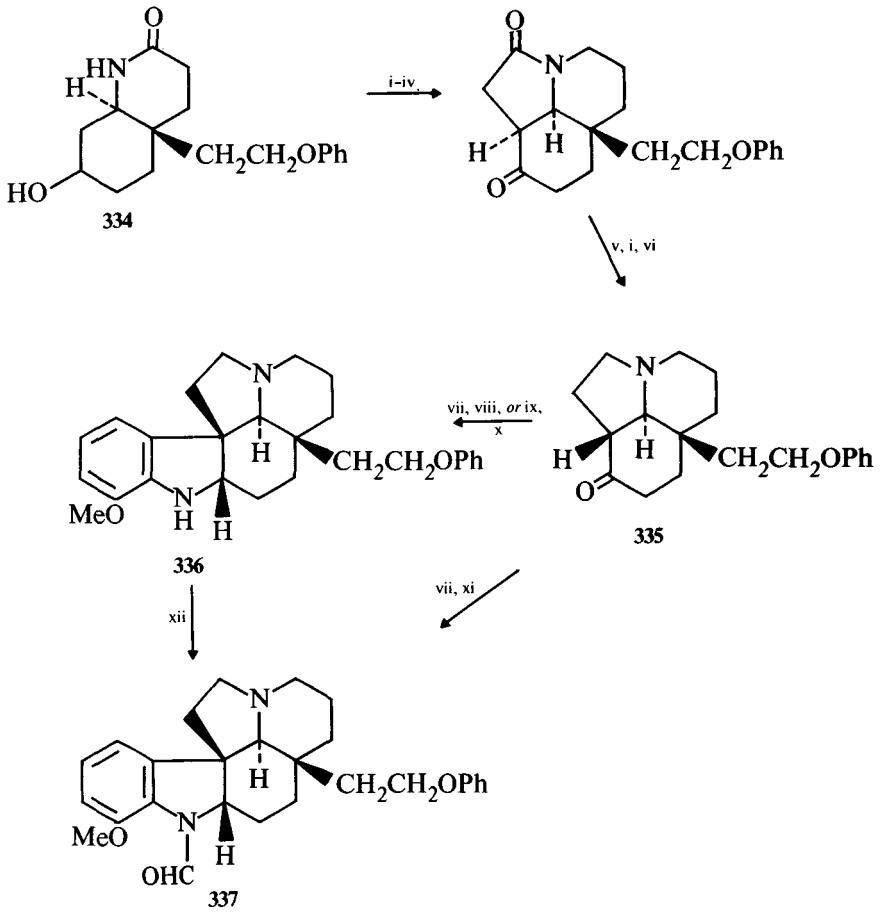
This compound (**329**) has proved to be a very versatile intermediate, and has been used in a number of syntheses of aspidospermine derivatives. The first application[165] led to a synthesis of (±)-*N*-acetylaspidospermidine. The secondary nitrogen was first protected by tosylation[166] and the product then alkylated stereospecifically at C-20 by means of methyl vinyl sulfoxide and lithium diisopropylamide. Desulfurization of the product (**330**) gave a mixture of **331** and **332**, the latter of which was reduced, acetylated, and hydrogenated to (±)-*N*-acetylaspidospermidine (**333**) (Scheme 43).

C. Deoxylimapodine, Fendleridine, and the Cylindrocarpine Group

The first attempt to prepare an alkaloid containing a functionalized two-carbon substituent at position 20 was made by Inoue and Ban,[60] who attempted the synthesis of compounds related to 18-hydroxyaspidospermidine or limaspermine (**108**) by a route based on the earlier synthesis of aspidospermine. The synthesis was carried through using the more abundant trans isomer **334** of the two hydroxylactams obtained in the early stages of the sequence, the further elaboration of **334** again being based on the Stork synthesis. However, although a mechanism was available for the isomerization of the C/D ring junction during the Fischer cyclization of the arylhydrazone of the amino ketone **335** both the products obtained (**336** and **337**) (Scheme 44) contained a trans C/D ring junction, and no trace of an isomer containing the aspidospermine stereochemistry could be detected.

For the first successful synthesis of an alkaloid of this group Ban and co-workers returned to a study of the reactions of the tetracyclic intermediate (**338**), prepared by *N*-tosylation of (**329**). A stereospecific Michael reaction at C-20 with ketene thioacetal monoxide gave the adduct **339** as a mixture of two diastereoisomers epimeric at C-18, since acid hydrolysis gave a single aldehyde (**340**) (Scheme 45), reduction and detosylation of which gave the primary alcohol (**341**). Acetylation and reduction of **341** then gave (±)-deoxylimapodine (**342**), which on oxidation with mercuric acetate afforded (±)-*N*-acetylaspidoalbidine (**343**). Alternatively, reduction of **341** gave a base which, when oxidized by means of mercuric acetate, yielded (±)-fendleridine (**344**).[167,168]

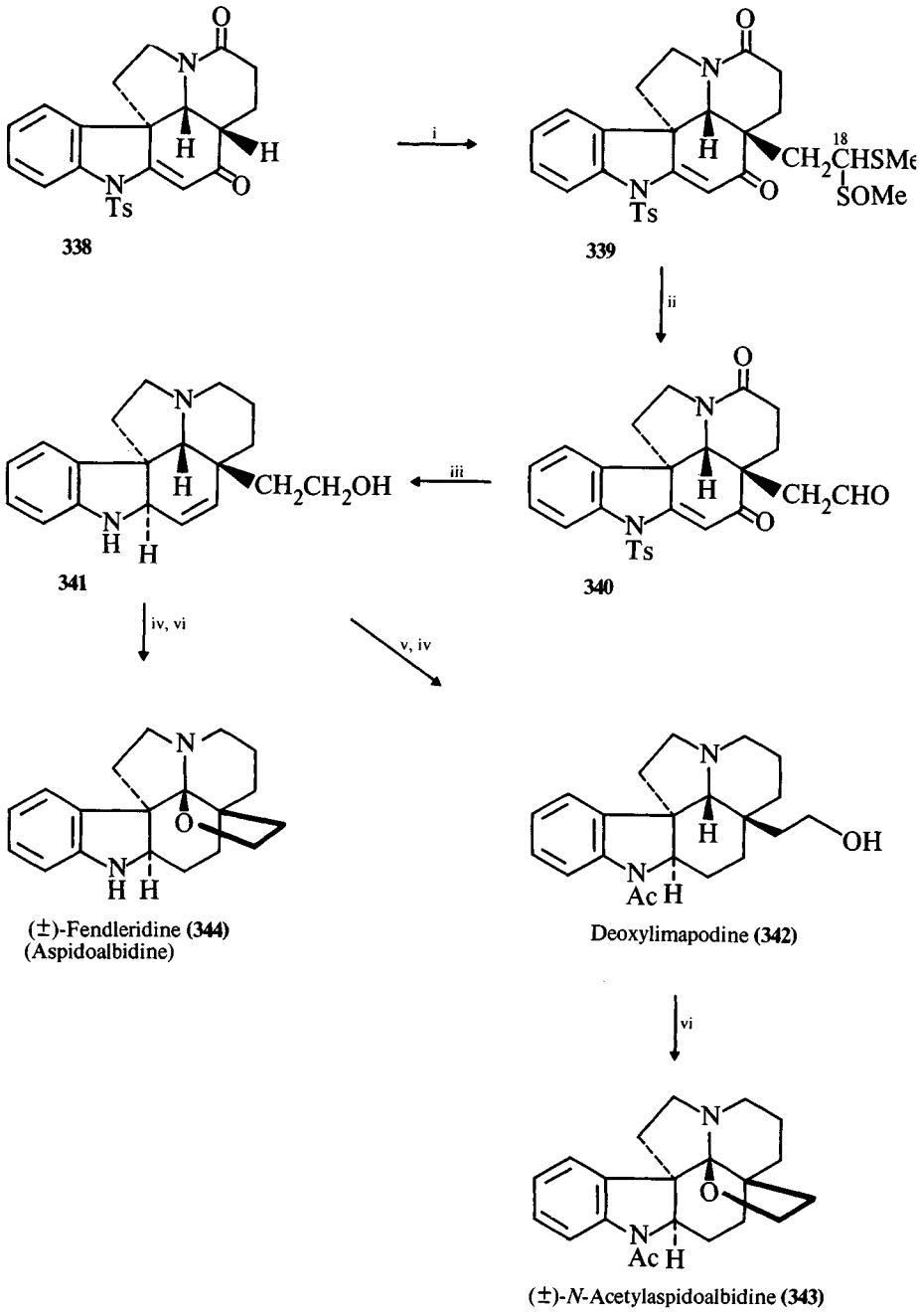
Contemporaneously Saxton et al. were also investigating the synthesis of C-18 functionalized bases.[59] Their approach was based on the Stork synthesis and involved the construction of a pentacyclic system bearing at C-20 a sterically undemanding substituent, but one that could subsequently be converted into the



Scheme 44. Reagents: i, $LiAl(OMe)_2H_2$, THF; ii, $ClCH_2COCl$, $CHCl_3$, NaOH, H_2O; iii, CrO_3, acetone; iv, $KOBu^t$, Bu^tOH, C_6H_6; v, $HOCH_2CH_2OH$, TsOH, C_6H_6; vi, HCl, H_2O; vii, *o*-$MeOC_6H_4NHNH_2$; viii, AcOH, 90°, 30 min; ix, polyphosphate ester, $CHCl_3$, Δ; x, $LiAlH_4$; xi, HCO_2H, 120°, 20 min; xii, HCO_2H, Ac_2O.

hydroxyethyl group, as in cylindrocarpinol, or an acetic ester residue, as in cyclindrocarpidine. The synthesis therefore proceeded via the pentacyclic base **345**, which was successfully converted into (±)-*N*-acetylcylindrocarpinol (**101**), (±)-cylindrocarine (**94**), (±)-cylindrocarpine (**13**), and (±)-cylindrocarpidine (**91**), as outlined in Scheme 46.

For comparison purposes a member of the trans C/D series, (±)-20-allyl-20-desethyl-20-epiaspidospermine (**346**) was also synthesized, utilising the trans isomer of the amidoketal (**347**). During the course of this work a new route to the cis bicyclic amino ketone (**349**) was developed. This involved cyanoethylation of the enol ether (**348**), initially prepared by Stork and Danheiser,[169] followed by reduction, acid hydrolysis, and cyclization. The cyclization stage presumably



Scheme 45. Reagents: i, CH_2=C(SMe)SOMe, $LiNPr^i_2$, DME; ii, MeCN, $HClO_4$ (trace), Δ, 1.5 hr; iii, $LiAlH_4$, DME; iv, H_2, PtO_2; v, AcCl, CH_2Cl_2, NaOH, H_2O; vi, $Hg(OAc)_2$, AcOH, H_2O, 70°.

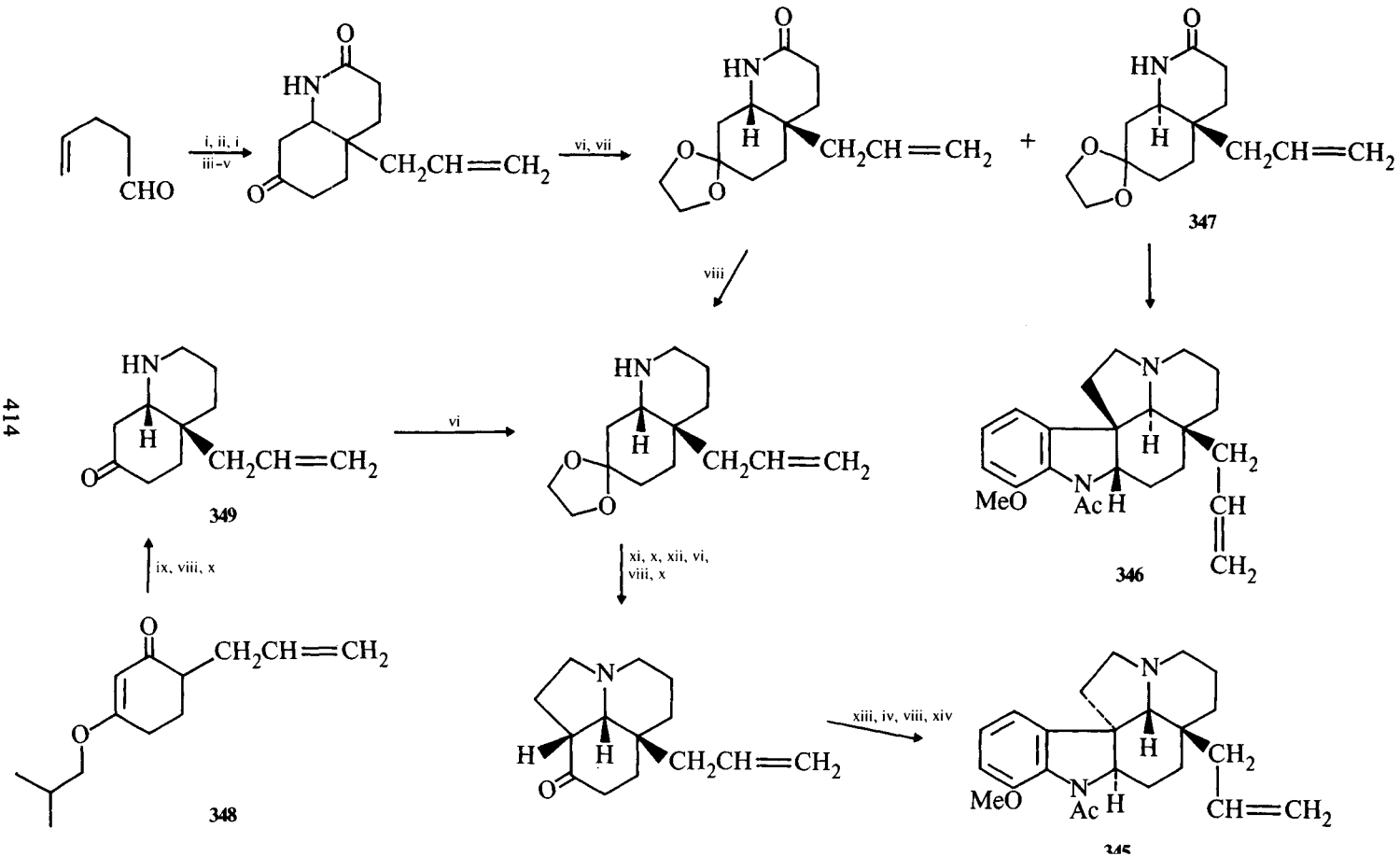
proceeds preferentially by axial approach of the amino group to the enone system with initial formation of a cis ring junction. In accord with this view the only product obtained was the cis amino ketone (**349**); it was further observed that both **349** and its diastereoisomer containing a trans ring junction, prepared independently, were not isomerized by aqueous acid or base under moderate conditions; hence the possibility of equilibration of the cis and trans amino ketones via β elimination of the amino group and Michael readdition does not arise.[59]

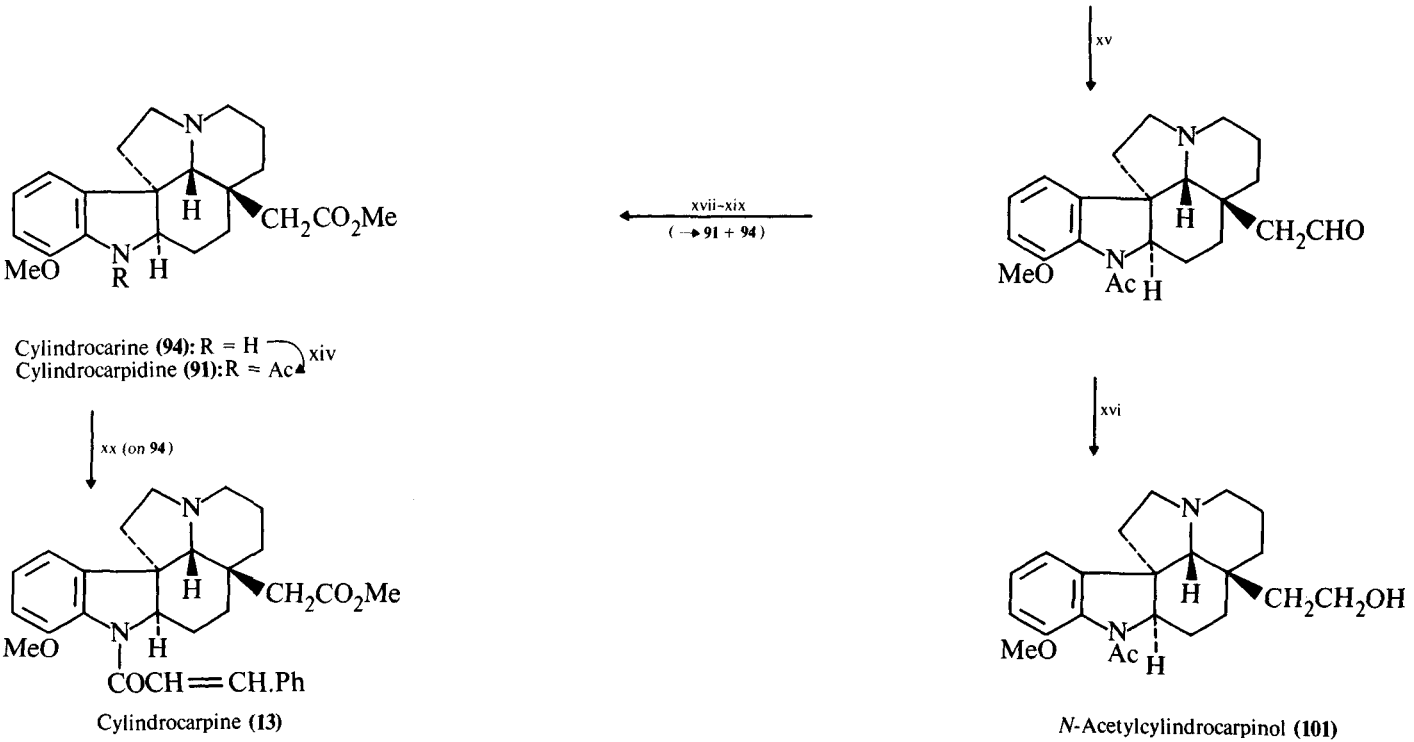
D. Vindorosine and Vindoline

The extremely elegant syntheses of vindorosine (**17**) and vindoline (**18**), achieved by Büchi and his collaborators,[170] are outlined in Scheme 47. The crucial cyclization which results in formation of the weakly basic tetracyclic amino ketone **350** involves the cycloaddition of an enone to a 1,3-dialkylindole via the enol of **351** and is reminiscent of the acid-catalyzed condensation of 1,3-dimethylindole with mesityl oxide.[171] N_b appears not to be involved in the formation of **350**; in fact, conjugation of a basic N_b with the enone system inhibits the reaction, hence the necessity for acetylation of N_b. Inevitably some tetrahydro-β-carboline derivative (**352**) is also formed, but this is not the principal product when R = H; neither is it an intermediate in the major route by which **350** is produced, since **352** could be isomerized to **350** in only 8% maximum yield.

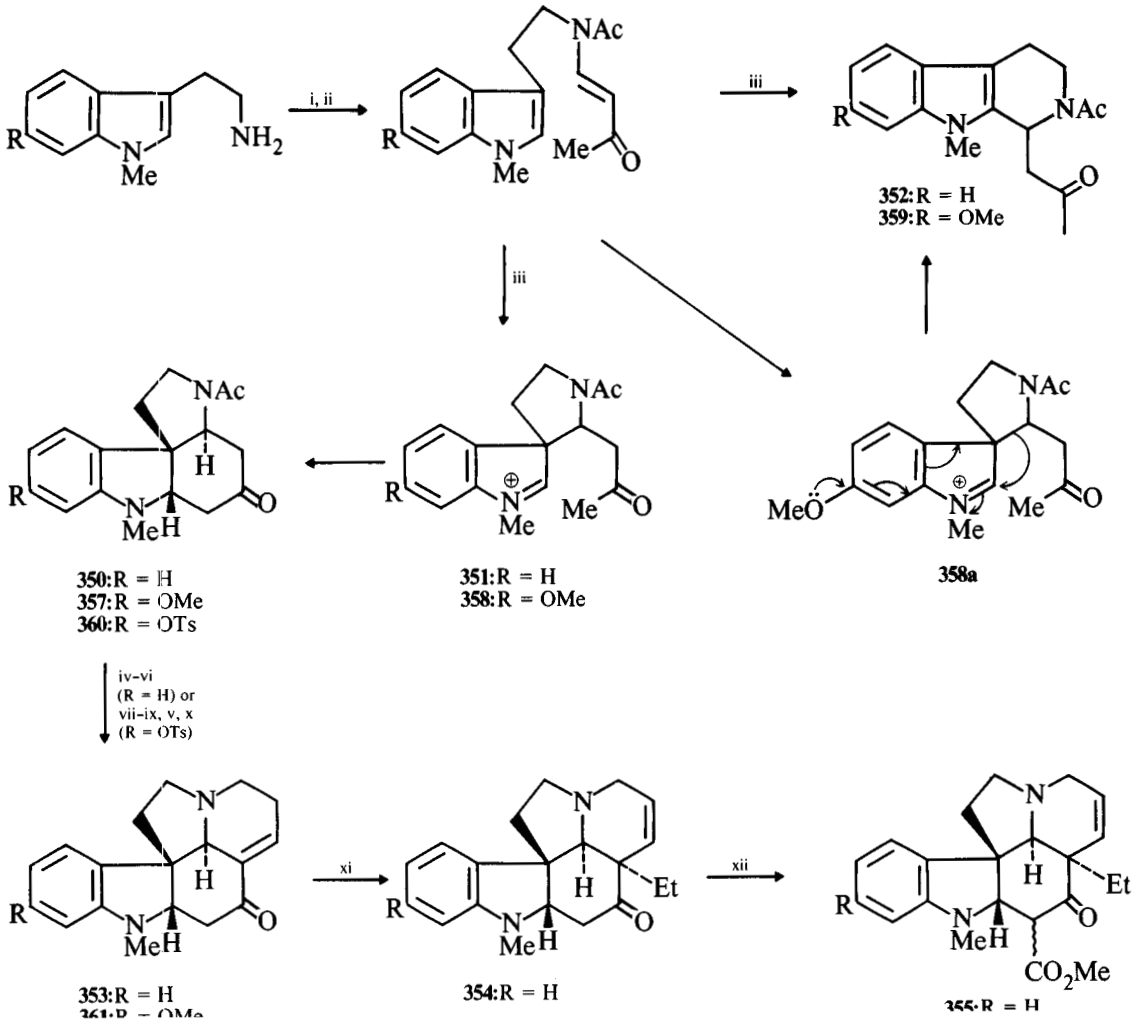
Ring D was introduced via Michael addition of acrolein to the secondary base corresponding to **350**, followed by ketol formation and dehydration. This afforded an enone **353** whose conjugated enolate anion could be neatly alkylated, regiospecifically and stereospecifically, at C-20, since the incoming ethyl group avoids that face of the anion sterically shielded by the ethanamine bridge. The product **354** contains the desired 14,15 double bond, and an active methylene group into which the C-16 ester function was introduced. Oxidation of the resulting keto ester **355** by means of hydrogen peroxide in the presence of strong base presumably proceeds by the mechanism shown (**355** → **356**), in which stereospecific delivery of hydroperoxide anion to C-17 is the result of hydrogen bonding of the reagent to N_b in the cis-fused C/D system. Reduction of **356**, followed by acetylation, then completed the synthesis of (±)-vindorosine (**17**).[170]

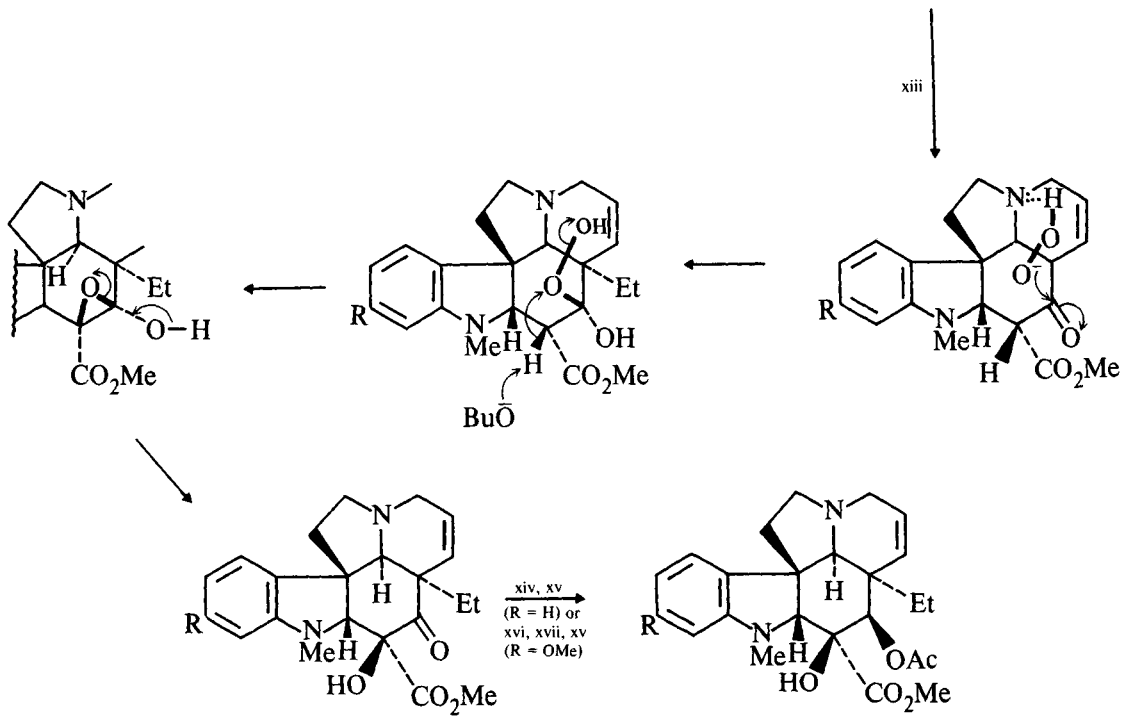
In the analogous synthesis of vindoline (**18**) difficulties were encountered in the formation of the tetracyclic amino ketone (**357**), since the electron-donating methoxyl group encouraged the rearrangement of the intermediate **358** (cf. arrows on **358a**), and the major product was therefore the tetrahydrocarboline derivative **359**; only 9% of **357** was obtained. The difficulty was circumvented by synthesizing the analogue **360** containing an electron-withdrawing tosyloxy group at the future C-11; the tosyloxy group was subsequently replaced by a methoxyl group, ring D was added to form the unsaturated amino ketone **361**, and the synthesis was then completed by a route which followed, in principle, the later stages of the vindorosine synthesis. A refinement in the penultimate stage of the synthesis ensured the stereospecific formation of deacetylvindoline uncontaminated with its C-17 epimer.


CHO
i, ii, i
iii–v
HN
O
CH2CH=CH2
vi, vii
H
O
+
347
viii
vi
349
ix, viii, x
xi, x, xii, vi,
viii, x
MeO
N
Ac
346
348
xiii, iv, viii, xiv
CH=CH2



Scheme 46. Reagents: i, Pyrrolidine, C_6H_6; ii, $CH_2{=}CHCO_2Me$; iii, $CH_2{=}CHCOMe$, iv, AcOH; v, NH_3, EtOH; vi, $HOCH_2CH_2OH$, TsOH, C_6H_6; vii, separation of isomers, viii, $LiAlH_4$; ix, $CH_2{=}CHCN$, Bu^tOH, Triton B; x, H^+, H_2O; xi, $ClCH_2COCl$, NaOH; xii, $KOBu^t$, Bu^tOH; xiii, *o*-$MeOC_6H_4NHNH_2$; xiv, Ac_2O, py; xv, OsO_4, $Na_2H_3IO_6$; xvi, $NaBH_4$; xvii, $NH_2OH \cdot HCl$, NaOAc; xviii, Ac_2O; xix, MeOH, H_2SO_4; xx, $C_6H_5CH{=}CHCOCl$, py.


R
N
Me
NH2
i, ii
NAc
Me
O
iii
352: R = H
359: R = OMe
350: R = H
357: R = OMe
360: R = OTs
351: R = H
358: R = OMe
MeO
358a
iv–vi
(R = H) or
vii–ix, v, x
(R = OTs)
353: R = H
xi
354: R = H
Et
xii
CO2Me
355: R = H



Scheme 47. Reagents: i, ClCH=CHCOMe, NEt_3, EtOH, ii, Ac_2O, NEt_3, C_6H_6, Δ; iii, $BF_3.Et_2O$, 90°, iv, 10% HCl, H_2O, Δ; v, CH_2=CHCHO, NaOMe, MeOH; vi, BF_3, AcOH; vii, 20% KOH, MeOH, H_2O, Δ; viii, Me_2SO_4, acetone, K_2CO_3, ix, $Et_3O^+BF_4^-$, CH_2Cl_2, $NaHCO_3$, then H_2O, x, $MeSO_2Cl$, py; xi, Bu^tOK, Bu^tOH, EtI; xii, $(MeO)_2CO$, NaH; xiii, H_2O_2, Bu^tOK, Bu^tOH, DME; xiv, $LiAlH_4$, THF, −70°; xv, Ac_2O, NaOAc; xvi, $AlCl_3$, THF, at −25°; xvii, $NaAl(OCH_2CH_2OMe)_2H_2$ at −20°.

Addition of a Lewis acid (aluminum chloride) to **362** presumably resulted in the formation of a complex involving both N_b and the C-16 hydroxyl group; reduction by a very bulky substituted aluminohydride anion then ensured stereospecific delivery of hydride to the opposite face of the molecule, with formation of deacetylvindoline, acetylation of which gave (±)-vindoline (**18**).[170]

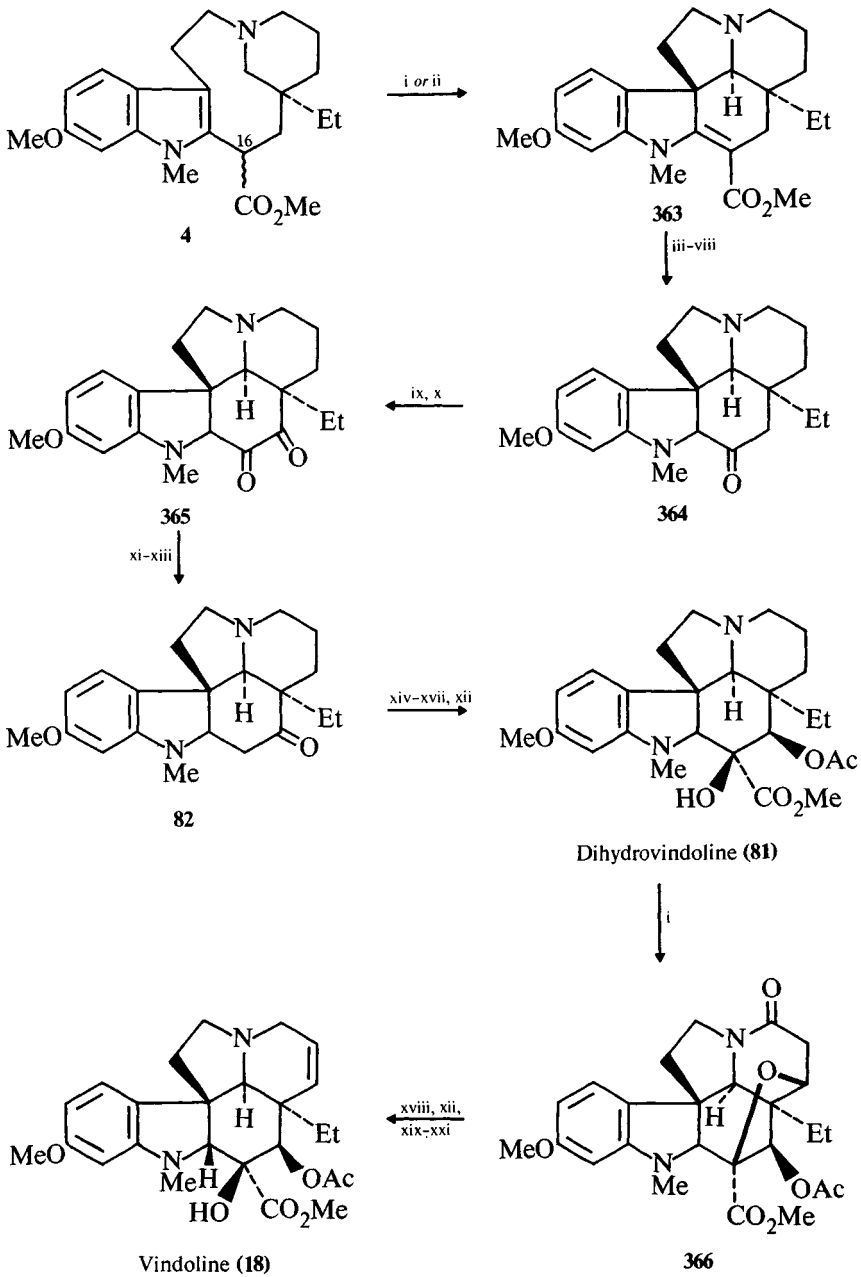
The amino ketone **357** is obviously a crucial intermediate in this synthesis. Its preparation has therefore attracted attention from other investigators, and recently three independent syntheses have been reported.[172]

Kutney's conversion of (±)-vincaminoridine (**4**) and its C-16 epimer into vindoline (**18**) constitutes a formal total synthesis of vindoline, and involves neat applications of functional group transposition in the aspidospermidine nucleus.[173] Oxidative cyclization of vincaminoridine gave 11-methoxy-*N*-methylvincadifformine (**363**) (Scheme 48), the structure of which was confirmed by its preparation from vindoline. It was then converted into the 16-ketone **364** by conventional methods, and then subjected to functional group transposition, via the α-diketone **365** to give the 17-ketone **82**. Functionalization of C-16 and C-17 by Büchi's method (see above) gave dihydrovindoline (**81**), which on mercuric acetate oxidation resulted in the formation of the ether-lactam **366**, together with 3-oxovindoline and 5-oxodihydrovindoline. Fission of the ether bridge in **366** by means of trityllithium, and trapping of the resulting anion by acetylation, gave *O*-acetyl-3-oxovindoline, which on reduction by the Borch method and deacetylation on moist silica gel gave vindoline (**18**) (Scheme 48).[173]

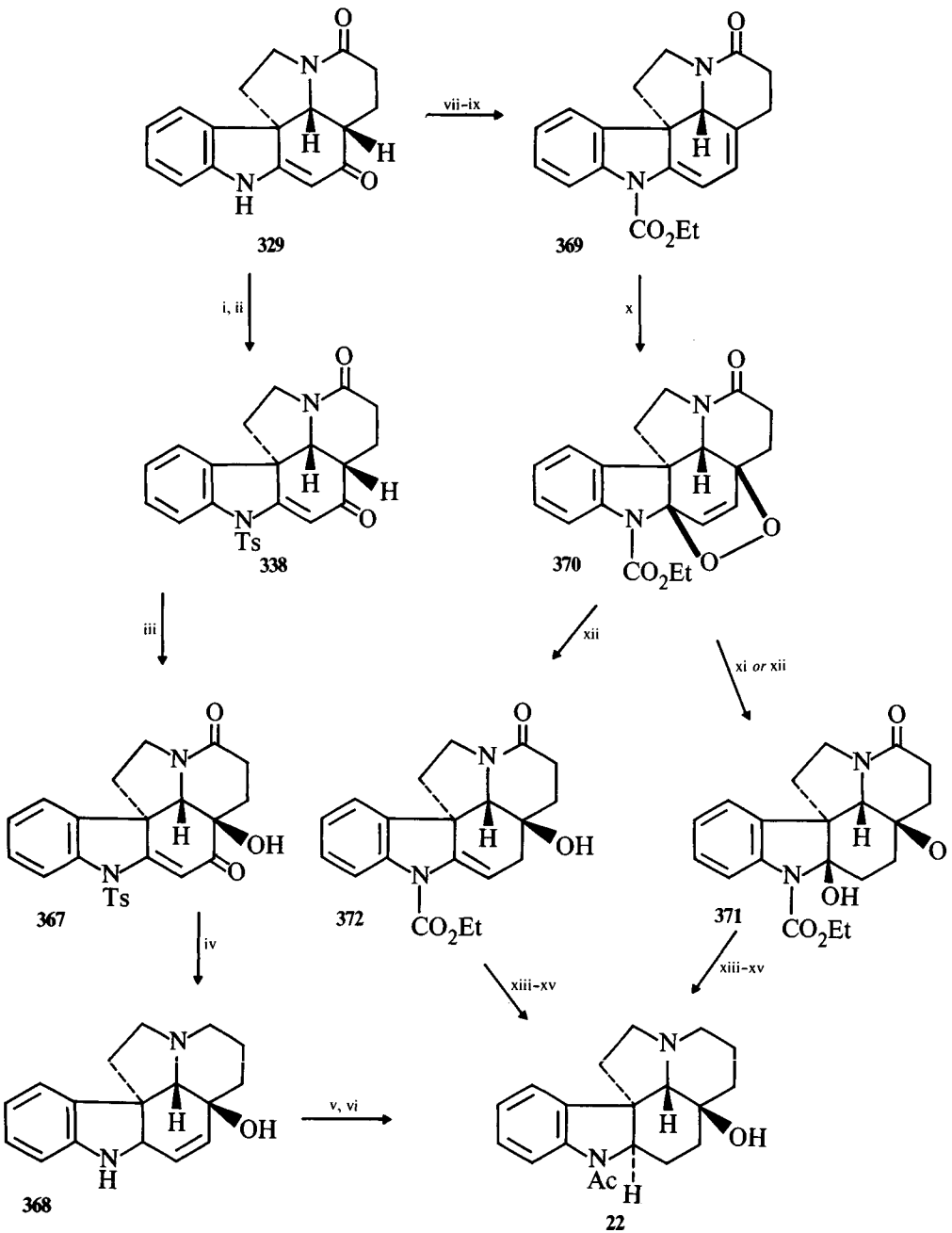
E. Deoxyaspidodispermine

The synthesis[174] of deoxyaspidodispermine involved yet another application of Ban's pentacyclic intermediate (**338**), into which the angular oxygen was introduced by treatment with oxygen at $-78°$ in the presence of sodium *t*-butoxide and triethyl phosphite in dimethylformamide. Some of the C-20 epimer of the major product **367** was also produced. Reduction of **367** by means of lithium aluminum hydride gave a base (**368**) which, on acetylation followed by hydrogenation, gave (±)-deoxyaspidodispermine (**22**) (Scheme 49).[174]

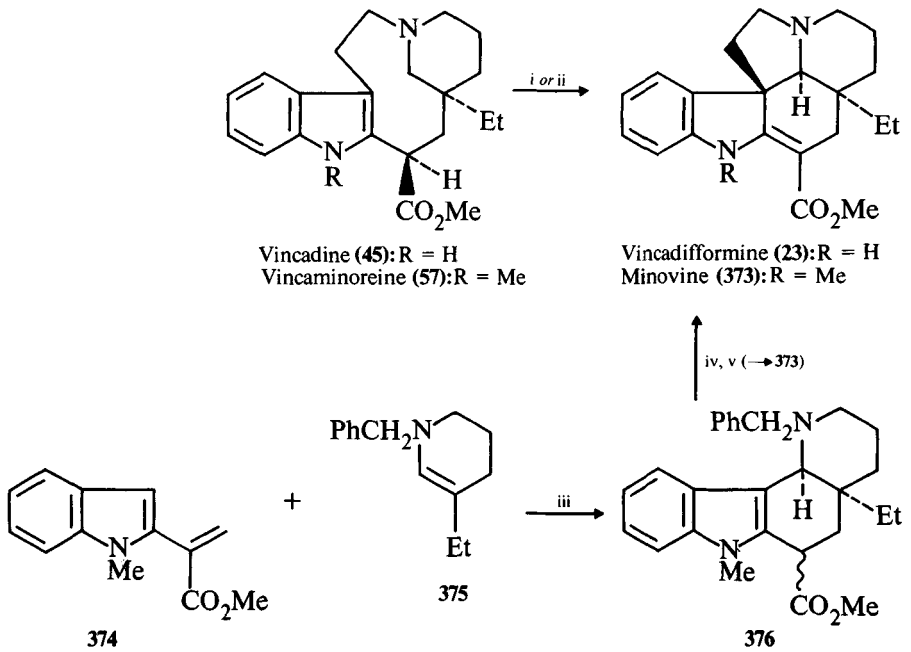
Subsequently a second synthesis was developed which followed more closely the presumed biosynthetic route to this alkaloid.[175] In this sequence the indole nitrogen in the intermediate **329** was protected by formation of a urethane, which was converted into the diene **369** by conventional steps. A photosensitized oxygenation of this diene gave a cyclic peroxide (**370**) in which the peroxide bridge was trans with respect to the ethanamine bridge (C-5 and C-6). Hydrogenation stages then gave the diol **371** or a mixture of **371** and **372** which on saponification, further reduction, and acetylation, gave (±)-deoxyaspidodispermine (**22**) (Scheme 49).



Scheme 48. Reagents: i, $Hg(OAc)_2$; ii, Pt, O_2; iii, Zn, H_2SO_4; iv, AlH_3; v, PhNCO; vi, pyrolysis; vii, OsO_4; viii, $NaIO_4$; ix, molybdenum peroxide, OH^-; x, $Cu(OAc)_2$; xi, $TiCl_3$, MeOH; xii, Ac_2O, py; xiii, Zn, HI; xiv, Me_2CO_3, NaH; xv, H_2O_2, $KOBu^t$; xvi, $AlCl_3$; xvii, Red-Al, THF; xviii, Ph_3CLi; xix, $Et_3O^+BF_4^-$; xx, $NaBH_4$; xxi, moist silica gel.



Scheme 49. Reagents: i, NaH, monoglyme, Δ; ii, TsCl, Δ; iii, O_2, NaH, Bu^tOH, Et_3PO_3, DMF, −78°; iv, $LiAlH_4$, DME; v, AcCl, NaOH; vi, H_2, PtO_2, EtOH, HCl; vii, NaH, $ClCO_2Et$, DMF; viii, $NaBH_4$, EtOH, THF; ix, PBr_3, py; x, O_2, EtOH, eosin, *hν*; xi, H_2, PtO_2, EtOH; xii, H_2, PtO_2, EtOAc; xiii, NaOH, H_2O, MeOH; xiv, $LiAlH_4$, THF; xv, Ac_2O, py.

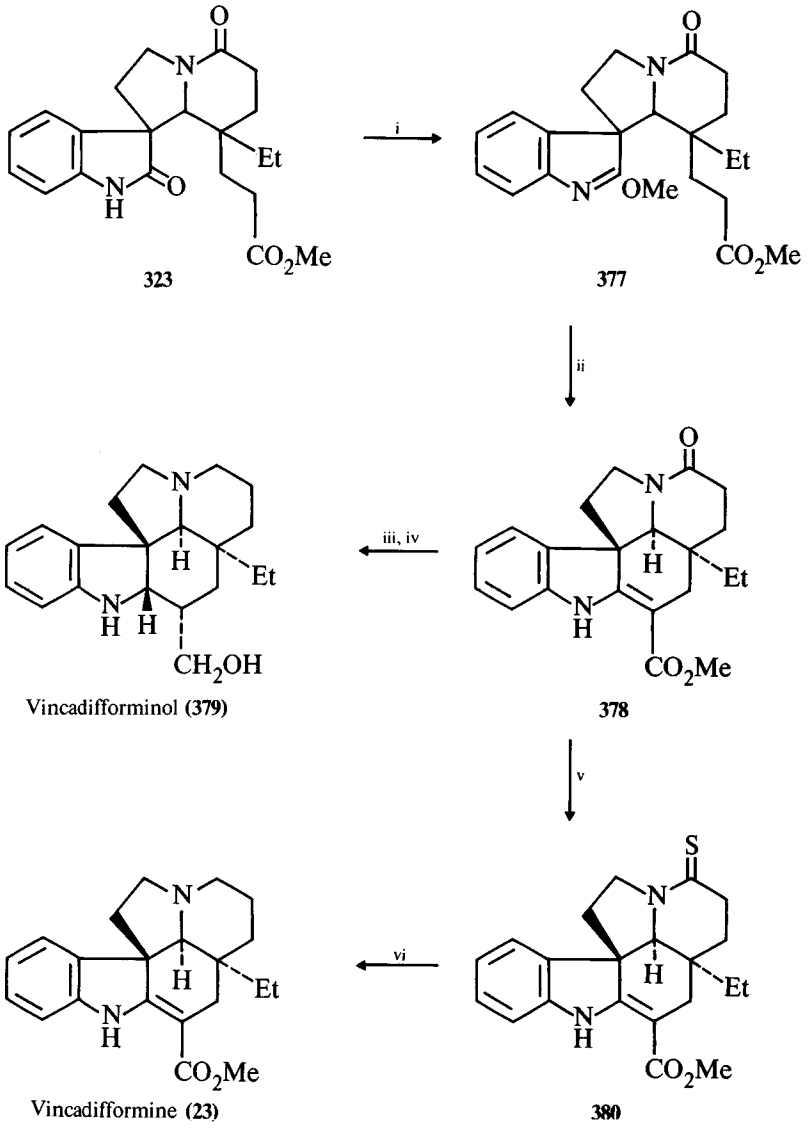


Scheme 50. Reagents: i, $Hg(OAc)_2$, AcOH; ii, Pt, O_2; iii, MeOH, Δ; iv, H_2, Pd/C, MeOH, HCl; v, $BrCH_2CH_2Br$, Na_2CO_3, DMF, N_2, Δ.

F. The Vincadifformine-Tabersonine Group

The first synthesis of (±)-vincadifformine was achieved as an extension of the synthesis of (±)-vincadine (± **45**), discussed earlier.[154] Reaction of vincadine with either mercuric acetate, or with oxygen in the presence of a platinum catalyst, provided (±)-vincadifformine [(±)-**23**]; similarly, the oxidation of vincaminoreine [(±)-**57**] led to the first total synthesis of (±)-minovine (**373**) (Scheme 50).

The second synthesis of (±)-minovine is an elegant, direct synthesis by Ziegler and Spitzner (Scheme 50).[176] The indole acrylic ester (**374**) was condensed with the enamine **375** to give a mixture of C-16 epimeric esters (**376**) interconvertible by equilibration with sodium methoxide. Since one of the primary alcohols obtained by reduction ($LiAlH_4$) of the esters exhibited concentration-independent intramolecular hydrogen bonding (ir spectrum), the C/D ring junction in these compounds must be cis, a conclusion that was reinforced by an examination of the nmr spectra of the hydrochlorides of the esters (**376**). Completion of the synthesis of (±)-minovine involved debenzylation and introduction of carbon atoms 5 and 6 by alkylation with 1,2-dibromoethane; either epimer of **376** could be used for this purpose. Since these final stages did not affect the stereochemistry at positions 20 and 21, this synthesis constitutes the first rigorous demonstration of the cis disposition of the ethyl group and hydrogen atom at these positions in minovine (**373**).[176]



Scheme 51. Reagents: i, $Me_3O^+BF_4^-$; ii, NaH, DMSO, 115°; iii, $NaBH_3CN$, AcOH; iv, $LiAlH_4$; v, P_2S_5, THF; vi, Raney Ni, THF.

Lévy's brief, five-stage synthesis of (±)-vincadifformine proceeds via the mixture of tetracyclic lactam-esters (**323**), prepared by condensation of aminoethyloxindole with the aldehyde **322** (Scheme 51).[163] Conversion of **323** into the imino ether **377** by means of Meerwein's reagent (trimethyloxonium fluoroborate), followed by base-catalyzed cyclization (NaH/DMSO/115°/2 hours), gave the ester (**378**) having the vincadifformine stereochemistry. Apparently at lower temperatures stereoisomers of **378** are formed, but the stereochemistry of these products has not so far

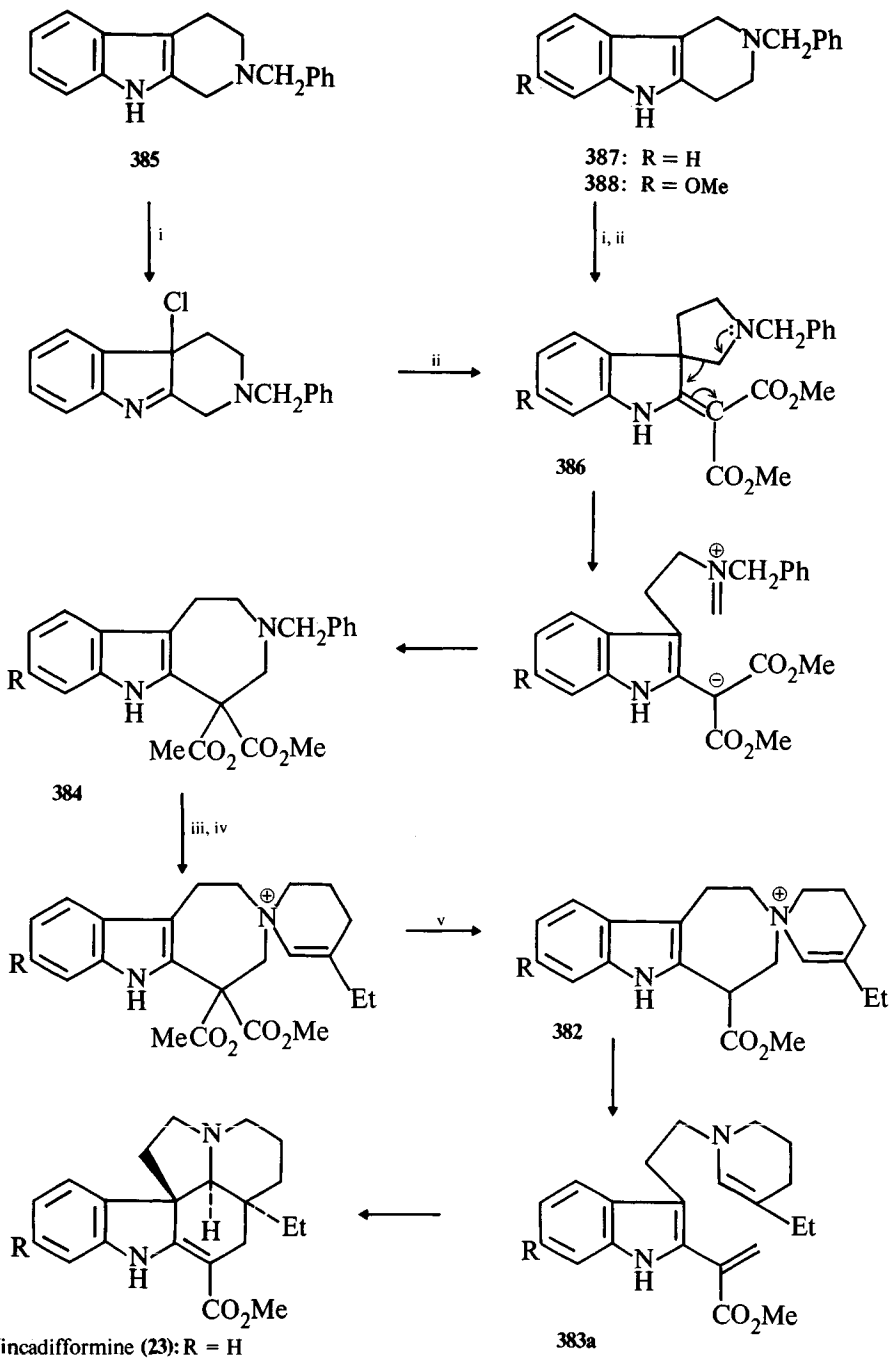
been discussed. Reduction of the 2,16 double bond in the ester **378**, followed by reduction ($LiAlH_4$) of the lactam and ester functions, gave a single product, identified as (±)-vincadifforminol (**379**). The synthesis of (±)-vincadifformine (**23**) was then completed by reaction of **378** with phosphorus pentasulfide, followed by desulfurization of the thiolactam (**380**) obtained.[163,177]

The basic strategy adopted by Kuehne and his collaborators[178] in their synthesis of vincadifformine and 11-methoxyvincadifformine (ervinceine, **381**) involved the construction of a spirocyclic quaternary ammonium ion (**382**) which, on fragmentation, was expected to yield the fugitive isosecodine (**383a**) (Scheme 52); spontaneous biomimetic cyclization of **383a** should then yield (±)-vincadifformine (**23**). This approach was elegantly executed and high yields of vincadifformine were obtained from the intermediate indolazepine dicarboxylic ester (**384**). The preparation of **384** from *N*-benzyltetrahydro-β-carboline (**385**) was itself an ingenious process which presumably involved the spiropyrrolidino derivative (**386**) (not isolated). Evidence that **386** was involved was obtained from an alternative preparation of **384** from the γ-carboline derivative **387**; the two conversions **385** → **384** and **387** → **384** must proceed via a common intermediate, which can only be the spirocyclic compound **386** (Scheme 52).

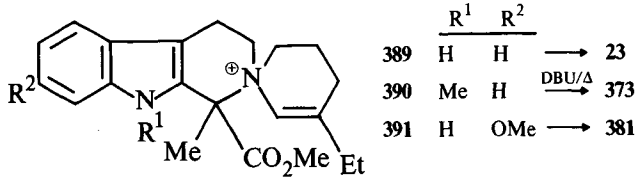
Extension to the synthesis of ervinceine (**381**) involved as starting material the methoxytetrahydro-γ-carboline derivative (**388**), which is more accessible, by synthesis from *N*-benzyl-4-piperidone, than the isomeric β-carboline derivative.[178]

Subsequently,[179] a much improved modification of this synthesis was reported, in which the important secodine precursor is a spirocyclic tetrahydro-β-carbolinium salt (e.g., **389–391**) rather than an indolazepine derivative, as in **382**. This leads to a much simpler synthesis, the tetrahydro-β-carbolines required for the preparation of **389–391** being obtained directly from the appropriate tryptamine and pyruvic ester. By this route (±)-vincadifformine (**23**), (±)-minovine (**373**), and (±)-ervinceine (**381**) were synthesized in comparatively high yield, in essentially two stages from the starting tryptamine. This work also encompasses a formal total synthesis of vindoline (**18**), which has already been prepared from the natural enantiomer of N_a-methylervinceine (**363**) (see Scheme 48).

An indolazepine ester, for example, **392**, can also react with aldehydes at N_b and the β position of the indole ring, to give a bridged azepine, and in a further extension of his synthesis Kuehne et al. have applied this concept to a new synthesis of 3-oxovincadifformine (**378**).[180] Condensation of **392** with methyl 4-formylhexanoate in refluxing toluene gave a mixture of the epimeric bridged azepines **393**, which spontaneously fragmented and recyclized, to give 3-oxovincadifformine (**378**) directly, in 85% yield (based on **392**), presumably via the oxosecodine **394** (Scheme 53). These preparations emphasize the reactivity of the secodines (e.g., **383a**, R = H) and underline the difficulties inherent in their synthesis. However, the synthesis of secodine itself (**383b**) has recently been achieved,[181] by a route which involves as critical stage an ingenious application of the Claisen ortho ester rearrangement, in which the ortho ester derived from the benzylic-type alcohol (**395**) and trimethyl β-methoxyorthopropionate (an acrylic ester equivalent), undergoes simultaneous rearrangement and elimination of methanol, to give the

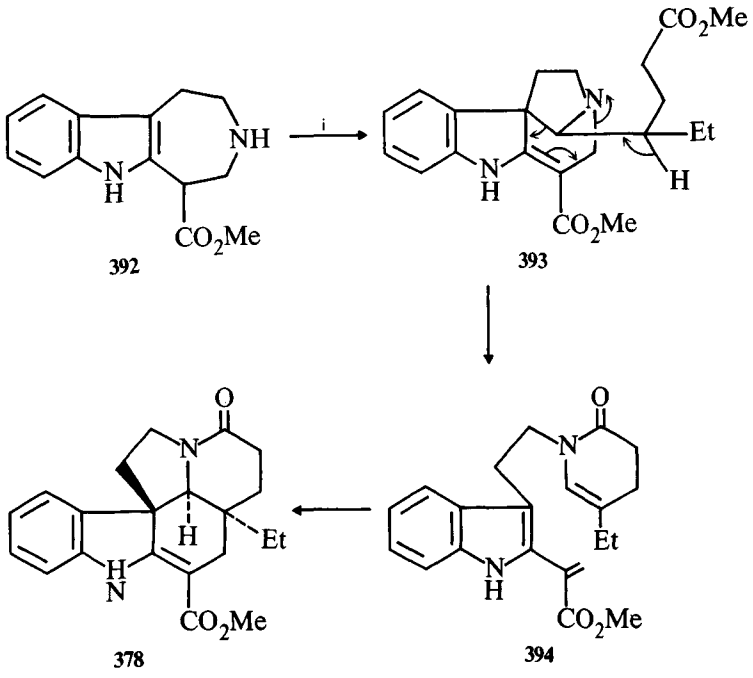


Scheme 52. Reagents: i, Bu^tOCl, C_6H_6, NEt_3; ii, $TlCH(CO_2Me)_2$, C_6H_6; iii, H_2, Pd/C, AcOH; iv, $Br(CH_2)_3CHEtCHO$, TsOH, MeOH, N_2, 40°; v, NEt_3, MeOH, 60°.

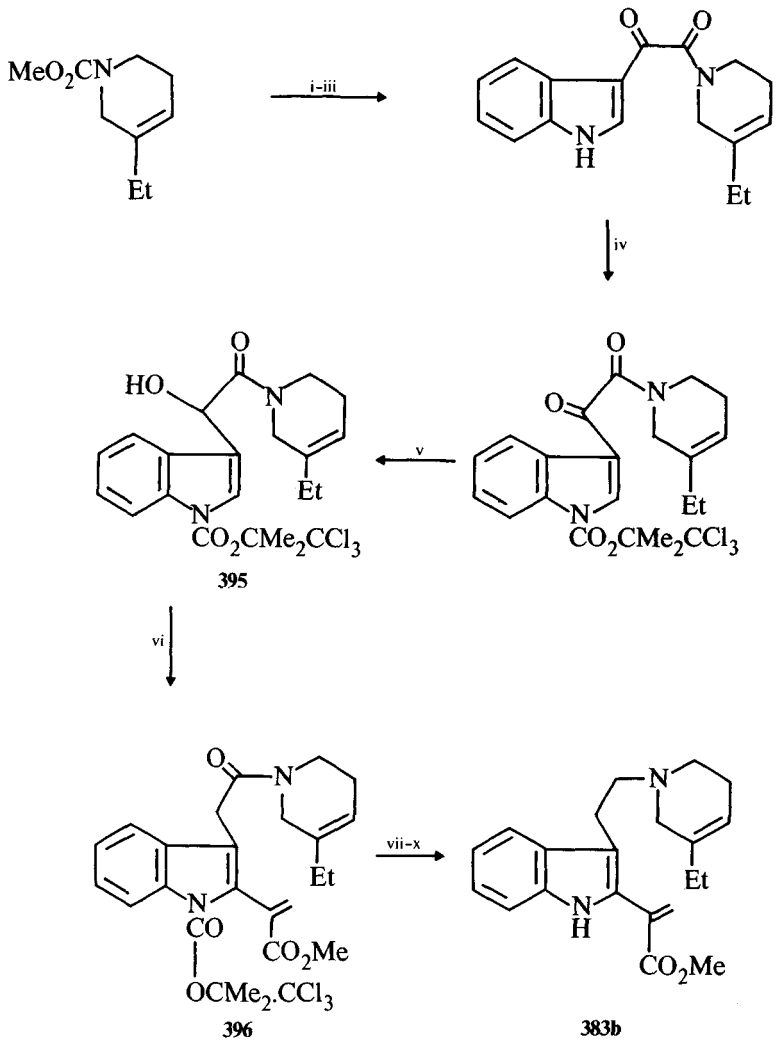


desired product (**396**) in one step (Scheme 54). Removal of the amide carbonyl group and the protecting group from the indole nitrogen atom then completes the synthesis.

The total synthesis of (±)-tabersonine [(±)-**24**] requires provision to be made for the introduction of a double bond into the vincadifformine skeleton, and hence inevitably results in a considerably longer synthesis. The problem, however, has been elegantly solved by Ziegler and Bennett,[157,182] who introduced the quaternary center (C-20) and the ring D double bond by the Claisen rearrangement of an enol ester, **305** → **306**, generated from the enone **307**; the further elaboration of the product of this reaction as far as the tetracycle **308** was carried out as outlined in Scheme 39. Reduction ($LiAlH_4$) of the ketolactam **308** followed by reaction with methanesulfonyl chloride in pyridine gave a quaternary salt (**397**), which on reaction with potassium cyanide gave two C-16 epimeric nitriles **398**. Saponification and subsequent esterification of these nitriles afforded the corresponding esters, one of which proved to be 14,15-dehydro-16-epivincadine (**399**), subsequently isolated[24]



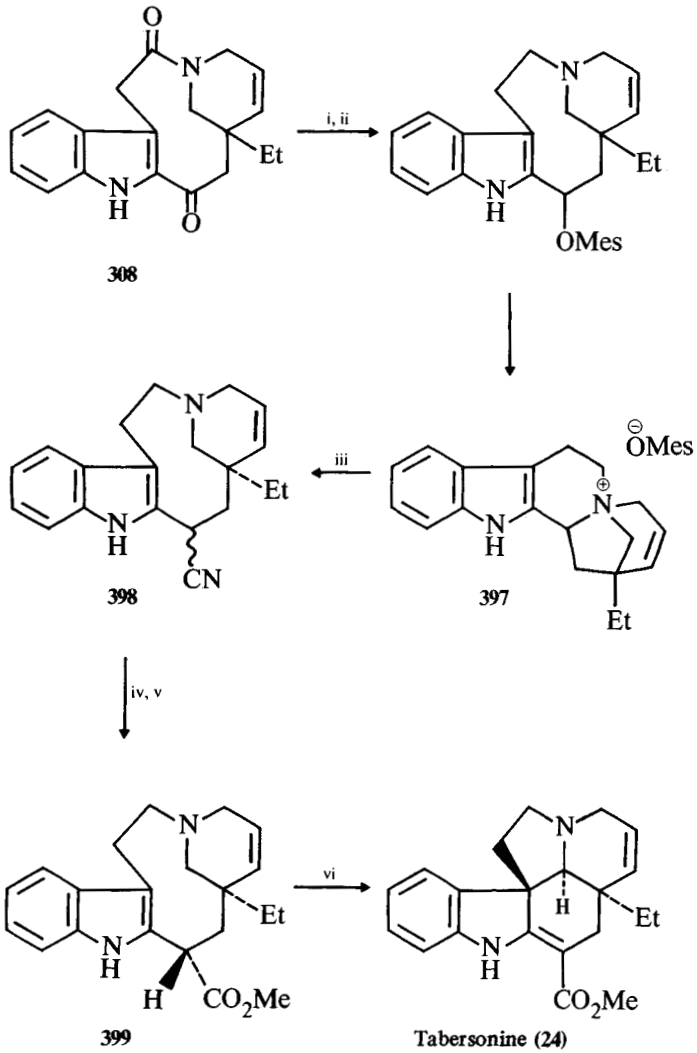
Scheme 53. Reagent i: $OHCCHEtCH_2CH_2CO_2Me$, PhMe, N_2, 4A mol. sieves, Δ.



Scheme 54. Reagents: i, MeLi; ii, HCl; iii, indole β-glyoxylyl chloride, NEt_3; iv, $ClCO_2CMe_2CCl_3$, NEt_3, CH_2Cl_2; v, $NaBH_4$, MeOH; vi, $MeOCH_2CH_2C(OMe)_3$, mesitoic acid, argon, Δ; vii, $(MeOC_6H_4)_2P_2S_4$; viii, $Et_3\overset{+}{O}\overline{B}F_4$; ix, $NaBH_4$, MeOH, AcOH; x, Zn, MeOH, AcOH.

from *Amsonia tabernaemontana*. Finally, oxidation of **399** with oxygen in the presence of freshly reduced platinum gave (±)-tabersonine [(±)-**24**]. It is of interest to note that in this last stage no allocatharanthine (**283**) was formed; hence immonium salt formation occurs preferentially in the N_b,21 position, rather than the conjugated N_b,3 position (Scheme 55).[157,182]

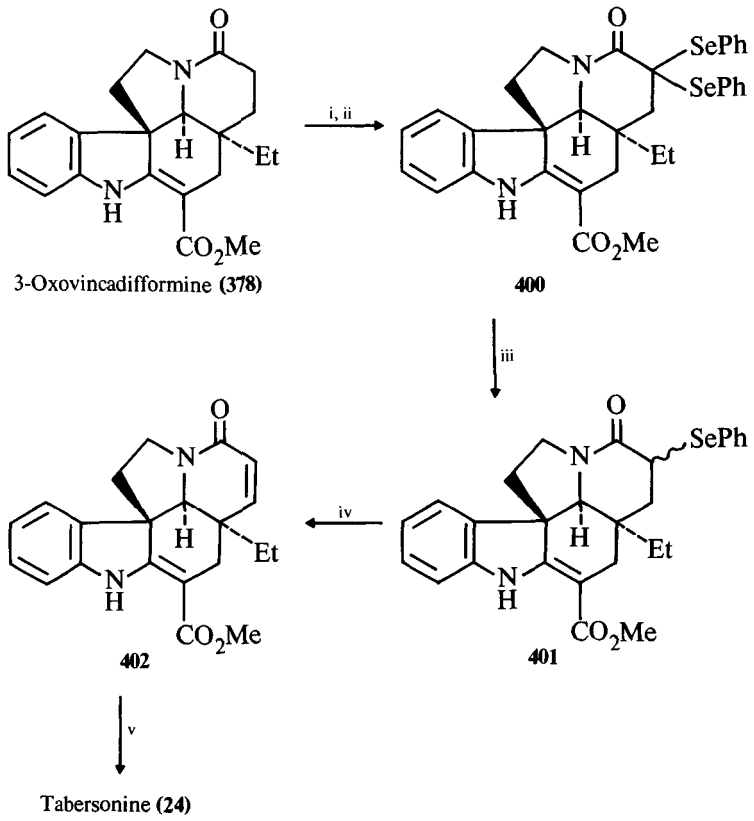
An independent synthesis of the quaternary mesylate **397** constitutes a second formal synthesis of (±)-tabersonine.[155] The most recent, and most direct, synthesis[183] of tabersonine (**24**) simply involves the introduction of the 14,15 double



Scheme 55. Reagents: i, $LiAlH_4$, THF; ii, $MeSO_2Cl$, py, 0°; iii, KCN, DMF; iv, KOH, $HOCH_2CH_2OH$; v, CH_2N_2; vi, Pt, O_2, EtOAc.

bond into 3-oxovincadifformine (**378**) by an ingenious process in which the dianion from **378** was reacted with phenylselenyl chloride to give the disubstituted derivative (**400**) (Scheme 56). Reductive removal of one phenylselenyl group gave a mixture of epimeric monophenylselenyl derivatives (**401**), which on oxidation and fragmentation gave 3-oxotabersonine (**402**). Carefully controlled reduction of **402** finally yielded (±)-tabersonine (**24**) (Scheme 56).[180]

A similar approach has been used in a recent synthesis[184] of Δ^{18}-tabersonine (**169**), which thus constitutes also a formal total synthesis of andranginine (**291**).

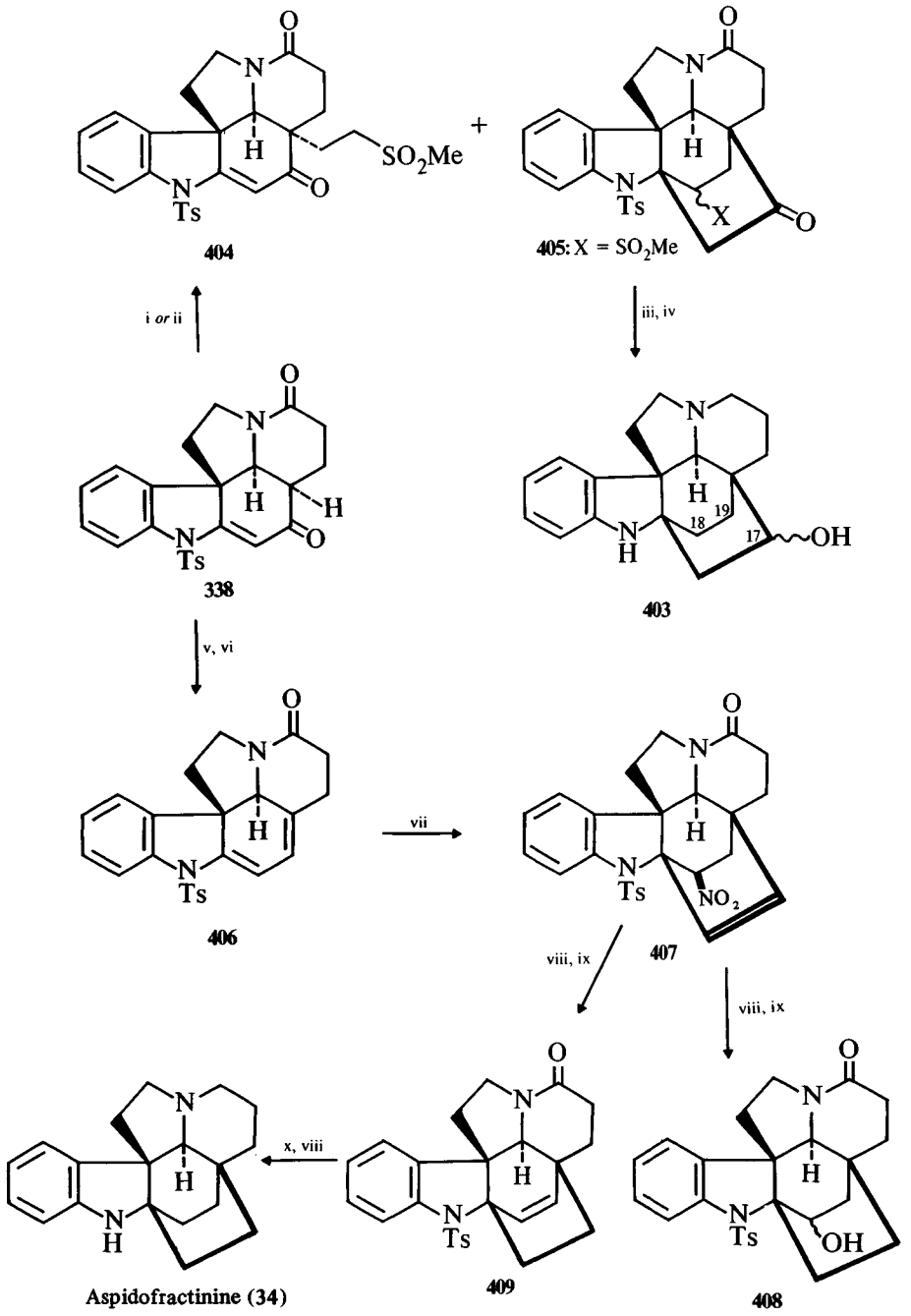


Scheme 56. Reagents: i, $LiNPr^i_2$, HMPA, THF, −78°; ii, PhSeCl; iii, PhS^-; iv, *m*-$ClC_6H_4CO_3H$; v, $LiAlH_4$, THF, 4 hr, 0°.

G. Aspidofractinine

The first total synthesis of the aspidofractinine ring system gave, as end product, (±)-17-hydroxyaspidofractinine (**403**) (Scheme 57).[166] A Michael reaction with methyl vinyl sulfone on Ban's intermediate (**338**) gave a mixture of the pentacyclic enone **404** and the two C-18 epimeric sulfones **405**, one of which was the exclusive product of base-catalyzed cyclization of **404**. Reduction and desulfurization of the mixture of hexacyclic sulfones **405** then gave (±)-17-hydroxyaspidofractinine (**403**), of undetermined configuration at C-17.[166]

Unfortunately, the hydroxyl group in **403** could not be removed, and consequently an alternative method was adopted for the synthesis of (±)-aspidofractinine itself.[185] The crucial intermediate was again the pentacyclic enone **338**, which was converted into the diene **406** by conventional methods. A stereospecific and regiospecific Diels-Alder addition of nitroethylene to **406** gave the hexacyclic nitro compound **407**, in which the newly formed two-carbon bridge was trans



Scheme 57. Reagents: i, CH_2=CHCN, Bu^tOH, Bu^tOK, DMSO; ii, $MeSO_2CH$=CH_2, Bu^tOH, Bu^tOK, DMSO; iii, $NaAlH_2(OCH_2CH_2OMe)_2$, dioxane; iv, Ni, EtOH; v, $NaBH_4$, EtOH, THF; vi, PBr_3, py, C_6H_6; vii, CH_2=$CHNO_2$, CH_2Cl_2, N_2; viii, H_2, PtO_2; ix, $NaNO_2$, H_2O, AcOH; x, $LiAlH_4$, DME.

with respect to the ethanamine bridge. Since the nitro group in **407** could not be converted directly into a carbonyl group it was reduced and deaminated, to give a mixture of the epimeric alcohols (**408**) and the related unsaturated lactam **409**. Reduction and hydrogenation steps on **409** then completed the synthesis of (±)-aspidofractinine (**34**).

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CHAPTER IX

The Eburnamine-Vincamine Group

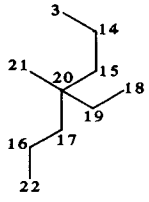
J. EDWIN SAXTON

Department of Organic Chemistry, The University of Leeds, Leeds, United Kingdom

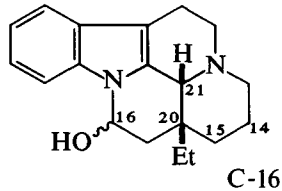
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I. STRUCTURE AND STEREOCHEMISTRY

This group of approximately 35 bases may be divided into three subgroups. Two of these subgroups, exemplified by eburnamine and vincamine, originate from the α condensation of tryptamine with the rearranged secologanin skeleton (**1**) followed by cyclization onto N_a. In the eburnamine (**2**) group C-22 is lost, but in the vincamine (**3**) group it is retained. The third group, represented by the alkaloids of *Schizozygia caffaeoides*, could conceivably be formed by rearrangement of an intermediate (e.g., **4**) containing the aspidospermidine ring system with retention of the 2,16 bond; cyclization of the intermediate (**5**) would then give a product (**6**) containing the schizogaline-isoschizogaline ring system (Scheme 1).

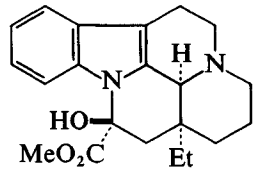


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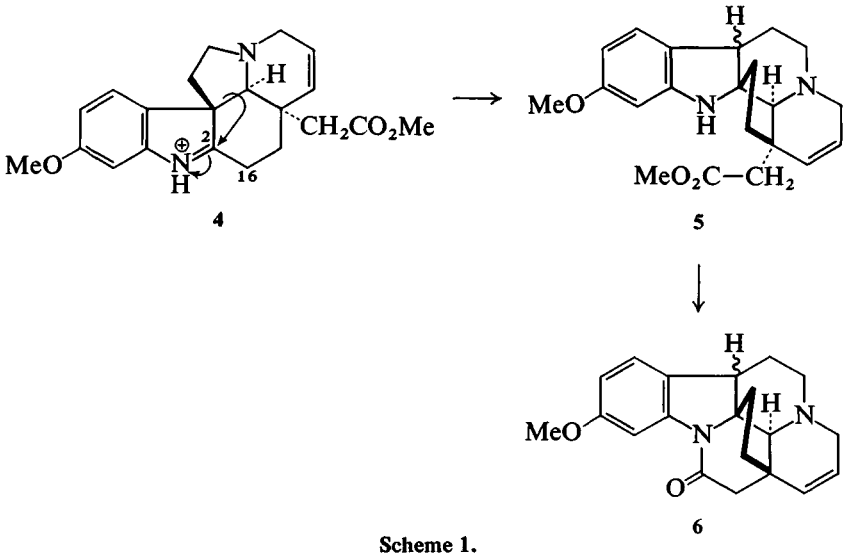
C-16

(–)-Eburnamine (**2**): β-OH
(+)-Isoeburnamine (**7**): α-OH



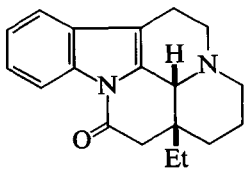
(+)-Vincamine (**3**)

(–)-Eburnamine (**2**), its C-16 epimer (+)-isoeburnamine (**7**), (+)-eburnamonine (**8**), and (+)-eburnamenine (**9**) were first isolated[1] from *Hunteria eburnea* Pichon, and were subsequently found in *Vinca minor* L.[2] Other sources of these alkaloids

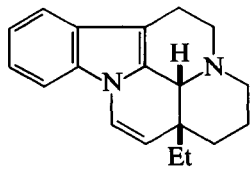


Scheme 1.

include *Rhazya stricta* Decaisne (2, 8, and 9),[3] *Pleiocarpa mutica* Benth. (2 and 9),[4] and *Amsonia tabernaemontana* Walt. (2, 7, and 8).[5] Both enantiomers of eburnamonine (8) (vincanorine) occur in *V. minor*,[2] and the levorotatory enantiomer of eburnamenine is said to be present in *A. angustifolia* Michx.[6]



(+)-Eburnamonine (8)

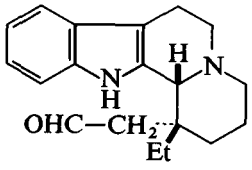


(+)-Eburnamenine (9)

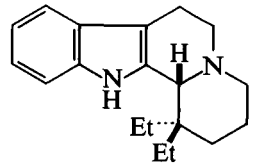
Eburnamine and isoeburnamine are diastereoisomeric bases which can be equilibrated in dilute acid; in the presence of more concentrated acid or on warming the solution eburnamenine (9) is formed.

Oxidation of either eburnamine or isoeburnamine gives eburnamonine (8) which, on reduction with lithium aluminum hydride, regenerates eburnamine and isoeburnamine. The six-membered ring containing N_a in these alkaloids shows unusual stability; thus eburnamonine can be hydrolyzed to an amino acid which recyclizes readily. Eburnamine and isoeburnamine are unaffected by sodium borohydride, and are only slowly reduced by lithium aluminum hydride, which affords dihydroeburnamenine; this last base, however, is best produced by hydrogenation of eburnamenine. The only reaction that indicates the alkaloids may be in equilibrium with the tetracyclic aldehyde (10) is the Wolff-Kishner reduction, which gives the tetrahydro-β-carboline derivative (11), the racemic form of which was subsequently synthesized.[1,7] This behavior indicates rather the preference of eburnamine and

isoeburnamine to react via the immonium ion (**12**) (Scheme 2), in which the six-membered ring is preserved, in all conditions except the most strongly basic. The reactivity of this ion is presumably the result of disruption of the indole aromaticity by participation of the lone electrons on N_a in the immonium ion. In accordance with this both alcohols **2** and **7** readily give the same *O*-ethyl derivative (**13**) in ethanolic picric acid.

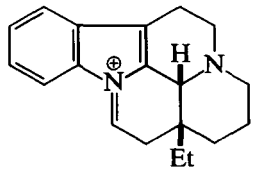


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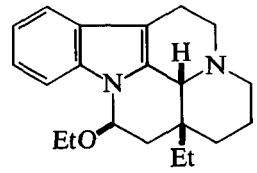
(+)-**11**

2 or 7 ⟶



12

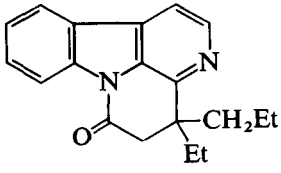
$\xrightarrow[EtOH]{H^+}$



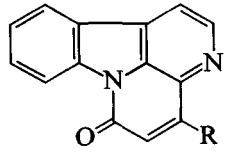
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Scheme 2.

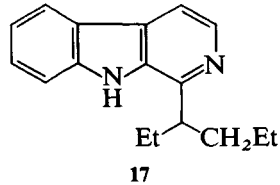
The key to the structures of these alkaloids was provided by the degradation of eburnamonine. Brief treatment at 360° with selenium gave in high yield the tetracyclic base (**14**), which on more prolonged treatment gave the two canthin-6-one derivatives **15** and **16**. Prolonged heating of **14** with sodium hydride in toluene gave the β-carboline derivative (**17**) by elimination of the acetic acid unit. The structures of all four products, **14–17**, have been confirmed by synthesis.[1,7,8]



14

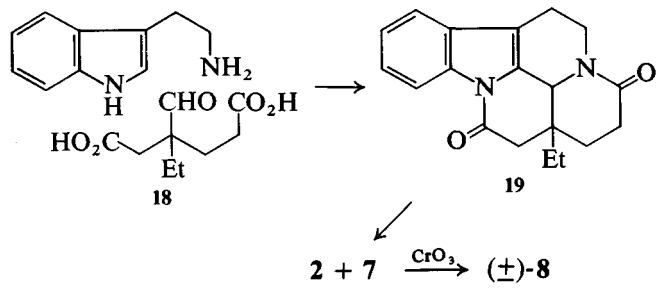


15: R = Et
16: R = CH_2Et



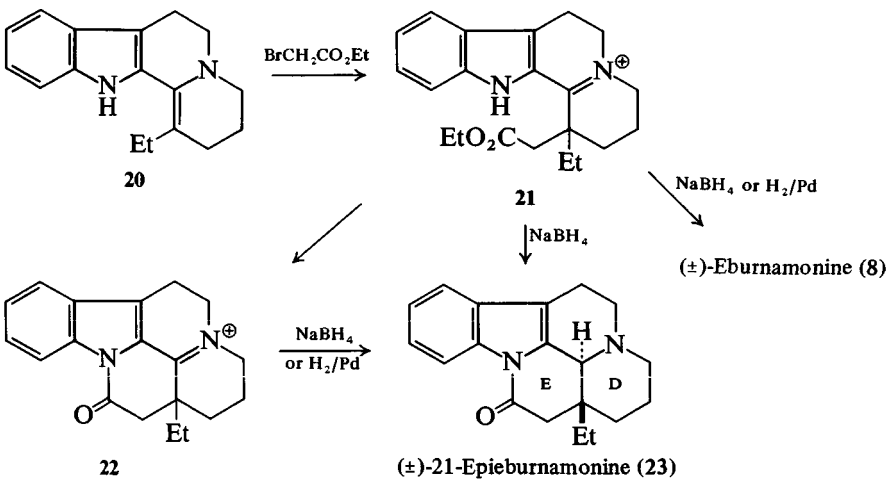
17

The structure (**8**) deduced for eburnamonine on the basis of these results was confirmed by a neat synthesis.[7,9] The aldehydodicarboxylic acid (**18**), prepared in four stages from *p*-ethylphenol, condensed with tryptamine to give the pentacyclic lactam **19**, which on reduction ($LiAlH_4$) gave (±)-eburnamine [(±)-**2**] and (±)-isoeburnamine [(±)-**7**]; oxidation then gave (±)-eburnamonine (**8**) (Scheme 3).



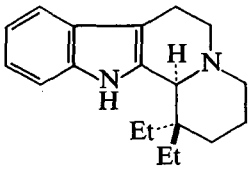
Scheme 3.

A second synthesis of (±)-eburnamonine[10] gives a clue to the relative configuration at C-20 and C-21. Alkylation of the enamine **20** by means of bromoacetic ester gave an immonium salt (**21**) which on cyclization gave the pentacyclic ion **22** (Scheme 4). Reduction (chemical or catalytic) of **22** would be expected to yield an aminolactam (**23**) containing a trans D/E ring junction by delivery of hydrogen to the less hindered side of the 21,N_b double bond. The product, in fact, proved to be 21-epieburnamonine. In contrast, chemical reduction ($NaBH_4$) of **21** gave an approximately equimolecular mixture of esters, which cyclized to 21-epieburnamonine (**23**) and eburnamonine, whereas hydrogenation followed by cyclization gave predominantly eburnamonine. The balance of evidence thus indicates that eburnamonine contains a cis D/E ring junction.

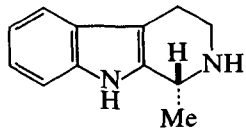


Scheme 4.

The absolute configuration of eburnamonine follows from a comparison of the ord spectra of (−)-**11** [obtained by Wolff-Kishner reduction of (−)-eburnamonine] and (+)-tetrahydroharman (**24**), of known absolute configuration.[11] Since the ord curves were enantiomeric, (+)-eburnamonine (**8**) has the same absolute configuration at C-21 as **24**.



(−)-11



24

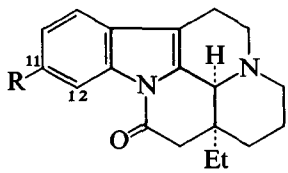
The absolute configurations of all the other alkaloids of the eburnamine and vincamine subgroups rest on correlation with (+)- or (−)-eburnamonine.

The predominance of eburnamine in the eburnamine-isoeburnamine equilibrium indicates that eburnamine contains an equatorial hydroxyl group[7]; this is confirmed by the nmr spectrum, which indicates a larger chemical shift (δ 6.0 ppm) for the equatorial proton at C-16 in isoeburnamine than for the corresponding axial proton (δ 5.48 ppm) in eburnamine.[12] The coupling constants (J = 5, 10 Hz) of the double doublet owing to the C-16 proton in eburnamine are also consistent with an axial configuration.[13] The remaining point to be established concerns the *relative* stereochemistry at C-16 and C-21; although eburnamine has been frequently represented as 7, the evidence from ord studies indicates[14] that the C-21 hydrogen is β, and the hydroxyl group is situated virtually in the plane of the indole ring system, and is similarly β, as shown in 2.

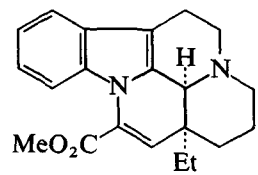
Related compounds which occur naturally are 14,15-dehydroeburnamine, from *Melodinus celastroides* H. Baillon,[15] (−)-11-methoxyeburnamonine (25), and 11,12-dimethoxyeburnamonine (rotation not specified), which occur in *V. minor*.[16]

Vincamine, the major alkaloid of *V. minor*,[17] also occurs in other *Vinca* species, for example, *V. major* L.,[18] *V. difformis* Pourr.,[19] and *V. erecta* Rgl. et Schmalh.,[20] and it has also been detected in *Amsonia tabernaemontana*.[21] Racemic vincamine is apparently present in *Tabernaemontana rigida* Miers.[22]

Vincamine is an indole derivative containing tertiary amino, hydroxyl, and methyl ester groups. Its overall structure (3) becomes apparent from the formation of (−)-eburnamonine (26) on treatment of vincamine with acid.[23] Alternatively, eburnamonine may be obtained by the oxidation of vincamine with ammoniacal silver nitrate, or by oxidation of vincaminol (3; $CO_2Me \rightarrow CH_2OH$) with periodic acid,[24] and it has even been isolated following an attempt[25] to reduce vincamine to vincaminol by means of lithium aluminum hydride, when acid conditions were used during the work-up procedure.



25: R = OMe
26: R = H

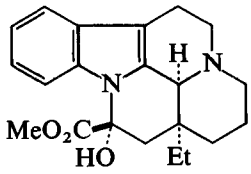


Apovincamine (27)

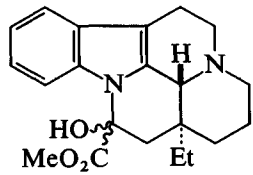
Attempts to acetylate the hydroxyl group in vincamine result in dehydration, with formation of apovincamine (27); this is consistent with the presence of a

tertiary, axial hydroxyl group at C-16.[25] The configuration of C-16 may also be inferred from a comparison of the nmr spectra of vincamine and 16-epivincamine (**28**), which occurs in *V. minor*.[12,26] In vincamine, the methyl protons of the equatorial ester group absorb at lower field than those of the axial ester group in 16-epivincamine.[12]

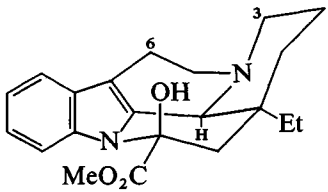
The C/D ring junction in **3** is also cis, since the ir spectrum does not exhibit Bohlmann bands, and the proton at C-21 absorbs in the relatively downfield position expected (δ 3.92 ppm) for such a proton in a cis-fused quinolizidine system.[27] These conclusions have been confirmed and extended by a thorough examination[28,29] of the proton, ^{13}C nmr, and cd spectra of vincamine (**3**), 16-epivincamine (**28**), and their C-21 epimers (**29**, **30**) prepared by the oxidation of the alkaloids to the 21,N_b-dehydro derivatives, followed by hydrogenation.[28] In particular, the signal owing to C-3 occurs at considerably higher field than the corresponding signal in the spectra of the trans isomers **29** and **30**, owing to interaction of C-3 with C-6 in the cis series.[28] All the evidence thus points to the conformation **3a** for vincamine.



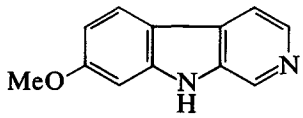
16-Epivincamine (**28**)



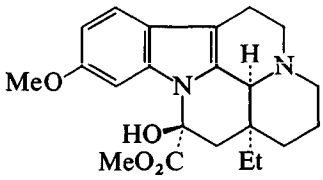
C-16	
29	α-CO_2Me
30	β-CO_2Me



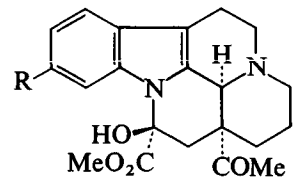
Vincamine (**3a**)



32



Vincine (**31**)

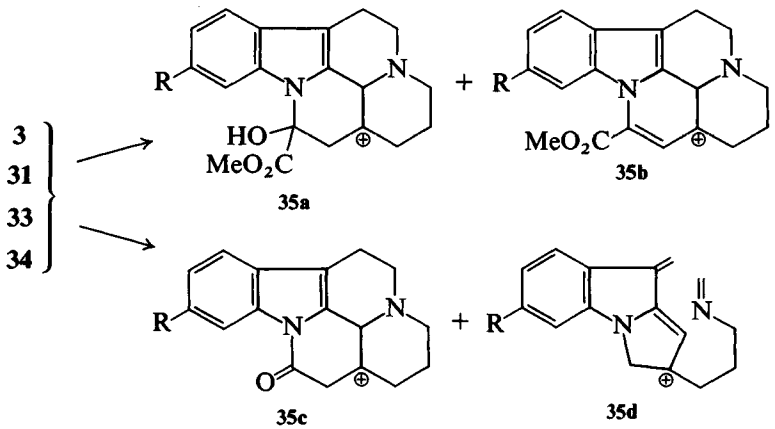


Vincaminine (**33**): R = H
Vincinine (**34**): R = OMe

11-Methoxyvincamine (vincine, **31**) occurs in both *V. major*[18] and *V. minor*.[30] The presence of a methoxyl group at position **11** was deduced spectroscopically, and proved by degradation to norharmine[31] (**32**). In its chemical properties vincine

behaves in a closely analogous fashion to vincamine, being readily dehydrated to an apo base, and readily degraded to (—)-11-methoxyeburnamonine (**25**). Its formulation as an *ar*-methoxyvincamine also follows from mass spectral comparison with vincamine.[25] The optical rotation evidence indicates that **31** is also its absolute configuration.[31]

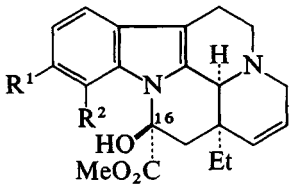
Vincaminine (vincareine, **33**)[32,33] and vincinine (**34**)[32] form a similarly related pair of alkaloids, vincinine simply being 11-methoxyvincaminine.[34] Found among the minor alkaloids of *V. minor*, these alkaloids contain a methyl ketone grouping (iodoform reaction, nmr spectrum), and exhibit nmr and mass spectra very similar to those of vincamine and vincine, when allowance is made for the presence of an angular acetyl group in **33** and **34** rather than an ethyl group. In particular the fragments **35a–d** arising from loss of the angular group result in peaks at identical *m/e* values in the spectra of **3** and **33**, and in the spectra of **31** and **34** (Scheme 5).



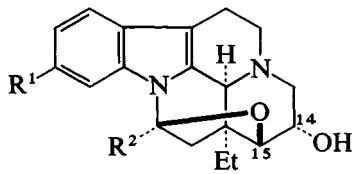
Scheme 5. From **3** and **33**, R = H; from **31** and **34**, R = OMe.

Of rather more widespread occurrence are the 14,15-dehydro derivatives of vincamine and vincine. 14,15-Dehydrovincamine (**36**) and its C-16 epimer, for example, occur in *Crioceras longiflorus* Pierre [*C. dipladeniiflorus* (Stapf) K. Schum.][35a,b] and *Amsonia elliptica* Roem. et Schult.,[36] dehydrovincamine also in *Voacanga chalotiana* Pierre ex Stapf,[37] and its epimer in *Pandaca ochrascens* Mgf.[38] The C-16 epimeric 14,15-dehydrovincines (**37** and C-16 epimer) have been isolated from *Craspidospermum verticillatum* Boj. ex A. DC.[39] 12-Methoxy-14,15-dehydrovincamine (**38**) has been identified among the constituents of *Crioceras dipladeniiflorus*[35b,c] and *Hunteria elliottii* (Stapf) Pichon,[40] and 14,15-dehydroapovincamine in *C. dipladeniiflorus*.[35b]

Oxidation of the double bond in 14,15-dehydrovincine (**37**) followed by internal ether formation can in principle lead to **39a**, which is the structure and relative stereochemistry deduced for vincarodine, a constituent of *Catharanthus roseus* G. Don.[41] Its demethoxy relative, vincapusine (**39b**) occurs in the leaves and roots of *Vinca pusilla*,[41b] and an unnamed alkaloid (**39c**), isolated[41c] from *Voacanga*



	R^1	R^2
36	H	H
37	OMe	H
38	H	OMe



	R^1	R^2
Vincarodine (**39a**)	OMe	CO_2Me
Vincapusine (**39b**)	H	CO_2Me
39c	H	H

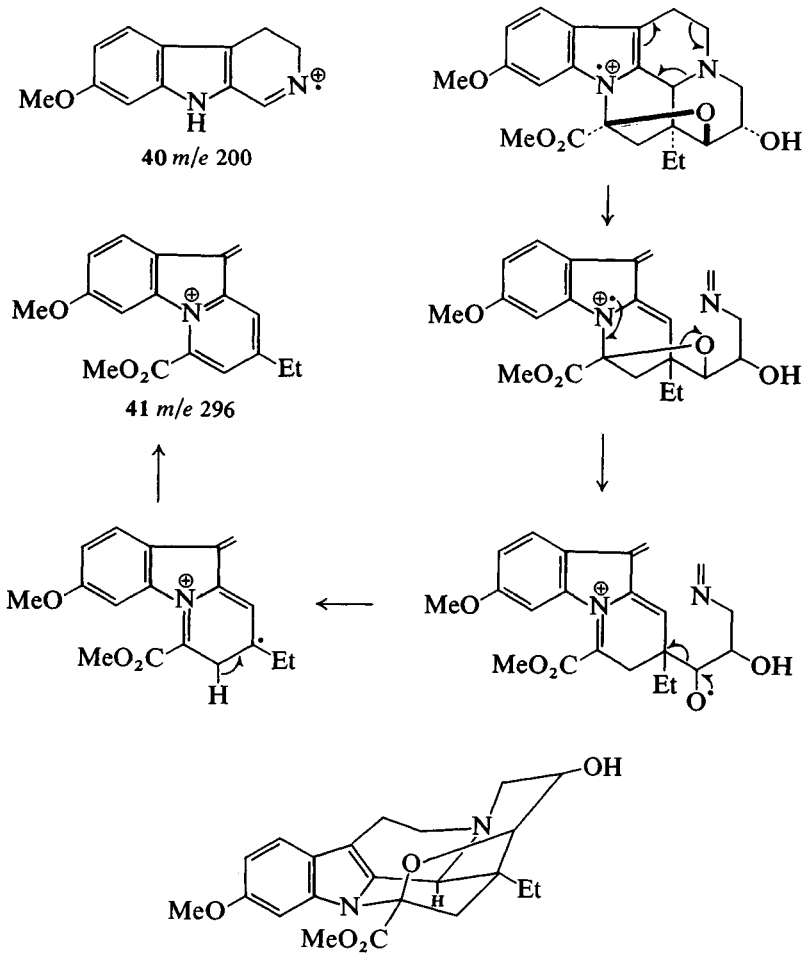
africana Stapf., lacks both the methoxy and the methoxycarbonyl groups of vincarodine.

The ir and uv spectra of vincarodine show a close similarity to those of vincine (**36**). Its nmr spectrum reveals the presence of methyl ester and secondary hydroxyl groups, confirmed by the formation of a monoacetate from vincarodine, and a diacetate from vincarodinol, the product of reduction by lithium aluminum hydride. The remaining oxygen atom must be contained in an ether linkage, since vincarodine is neither a tertiary alcohol nor an acetal. The position of this ether bridge became clear from a detailed examination of the nmr and mass spectral data (Scheme 6). In particular the mass spectrum exhibits a base peak at *m/e* 200, owing to the ion **40**, a small peak at *m/e* 380 resulting from dehydration of vincarodine, and an important peak at *m/e* 296, attributed to the ion **41**, also observed in the mass spectrum of vincine. The proton at C-14 is coupled to a methylene group attached to N_b, and a methine hydrogen whose carbon atom (C-15) carries oxygen, presumably the ether oxygen. These data allow only one structure[29,42] for vincarodine (**39a**), which is amply confirmed by the ^{13}C nmr spectrum,[29] and by X-ray crystal structure analysis.[43] The absolute configuration is not yet certain, but it is formulated as **39** by analogy with vincamine and vincine.[29]

The unsaturated base (**42**) related to vincarodine is the alkaloid, craspidospermine, which occurs in *Craspidospermum verticillatum*[44]; its demethoxy analogue, criocerine (**43**), has been isolated from *Crioceras dipladeniiflorus*.[35d] The structures of both alkaloids were confirmed by partial synthesis (Scheme 7); thus a Polonovski reaction on the N_b-oxide (**44**) of 14,15-dehydrovincine gave an intermediate salt (**45a**) which spontaneously cyclized to craspidospermine (**42**).[45] In an exactly similar manner, 14,15-dehydrovincamine N_b-oxide (**46**) gave criocerine (**43**), via the salt **45b**.[35d]

Alternatively, the photooxidation of 14,15-dehydrovincine (**37**) in acetone solution affords[46a] craspidospermine (**42**), and similar photooxidation of vincamine (**3**) gives criocerine (**43**); necessarily, this latter conversion involves a double oxidation of the starting alkaloid. These conversions presumably also proceed via the unsaturated immonium ions **45a** and **45b**.

The conversion of 14,15-dehydrovincamine (**36**) into criocerine (**43**) has also been achieved by iodination of **36** with iodine and potassium iodate, which results in the formation of the unsaturated iodo ether (**47**). Since **47** is also an iodo-

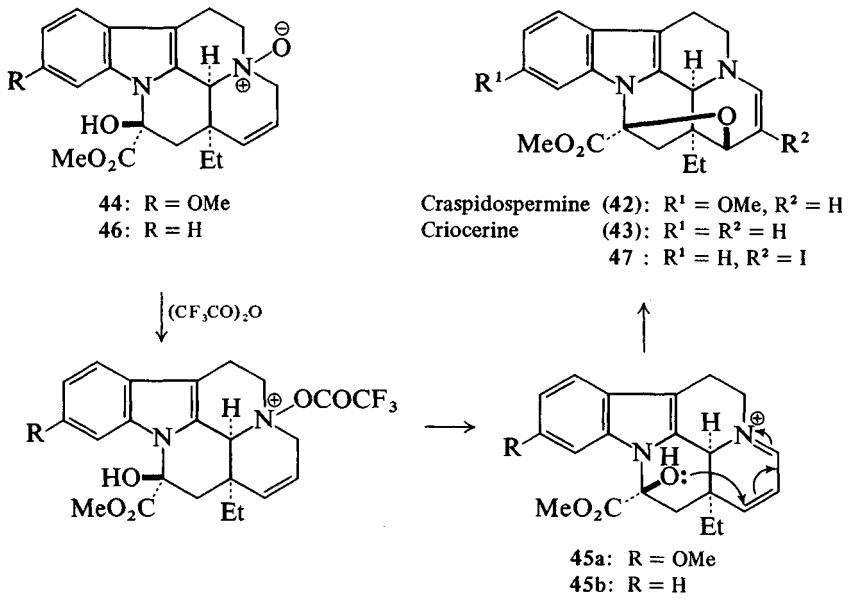


Vincarodine (39a)

Scheme 6.

enamine, it loses iodine when treated with acid, and the product is criocerine (43).[46b]

The two remaining alkaloids of this subgroup, cuanzine (48) and decarbomethoxyapocuanzine (49) (Scheme 8), occur in *Voacanga chalotiana*.[37,47] The general spectroscopic properties of cuanzine suggest a structure akin to 12-methoxyvincamine, the fifth (ethereal) oxygen atom in the molecule probably being attached to C-18, since cuanzine does not contain a *C*-methyl group. The other terminus of the ether bridge is not at C-17, since there are two protons at this position which give rise to a clear AB system in the nmr spectrum. An oxymethine proton which is responsible for a double doublet at δ 4.72 is coupled to a methylene group whose complex signal shows that in turn it is attached to another (downfield) methylene group, attached to N_b. These data allow only one possible point of



Scheme 7.

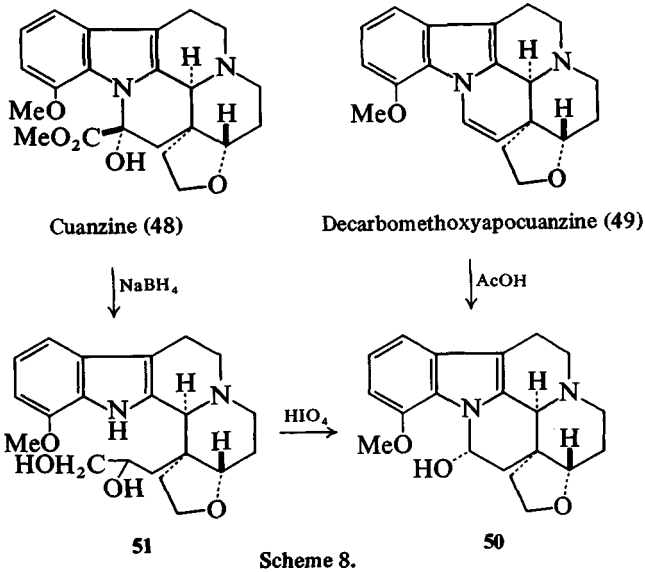
attachment of this ether linkage, that is, C-15, as shown in **48**. This structure for cuanzine is convincingly supported by a comparison of its ^{13}C nmr spectrum with those of vincamine and 16-epivincamine, which shows that C-15 and C-18 in cuanzine carry oxygen substituents; C-17 appears at higher field than in vincamine and 16-epivincamine, as a result of the presence of a β oxygen atom.

The absolute configuration follows from comparison of the cd spectra of cuanzine and 16-epivincamine; this also reveals the configuration at C-16, since the spectrum shows a greater similarity to that of 16-epivincamine than to that of vincamine, particularly in the region 230–250 nm.[28b,47]

Decarbomethoxyapocuanzine (**49**) exhibits an nmr spectrum similar to that of cuanzine, but lacking the ester and hydroxyl groups and the C-17 AB system; instead an AB system owing to two olefinic protons is present. The structure **49** follows from these observations, and is proved by the conversion of cuanzine into the eburnamine analogue **50** by reduction ($NaBH_4$) followed by oxidation (HIO_4) of the diol (**51**) so produced; alternatively, **50** could be obtained by hydration with acetic acid of the double bond in decarbomethoxyapocuanzine (**49**) (Scheme 8).[48]

The third subgroup of alkaloids have so far been isolated from only two plant sources, *Schizozygia caffaeoides* (Boj.) Baill.[49a] and *Strempeliopsis strempelioides* K. Schum.[49b] The principal alkaloid is schizozygine (**52**), which is one of only three indole alkaloids known to date that contain a methylenedioxy group; the presence of hydrogen at C-7 in a dihydroindole structural unit is also unusual.

The presence of a methylenedioxy group was readily diagnosed from the nmr spectrum and color reactions; its position in an *N*-acylindoline part structure was deduced from the similarity of its uv spectrum to that of brucine, and from its nmr

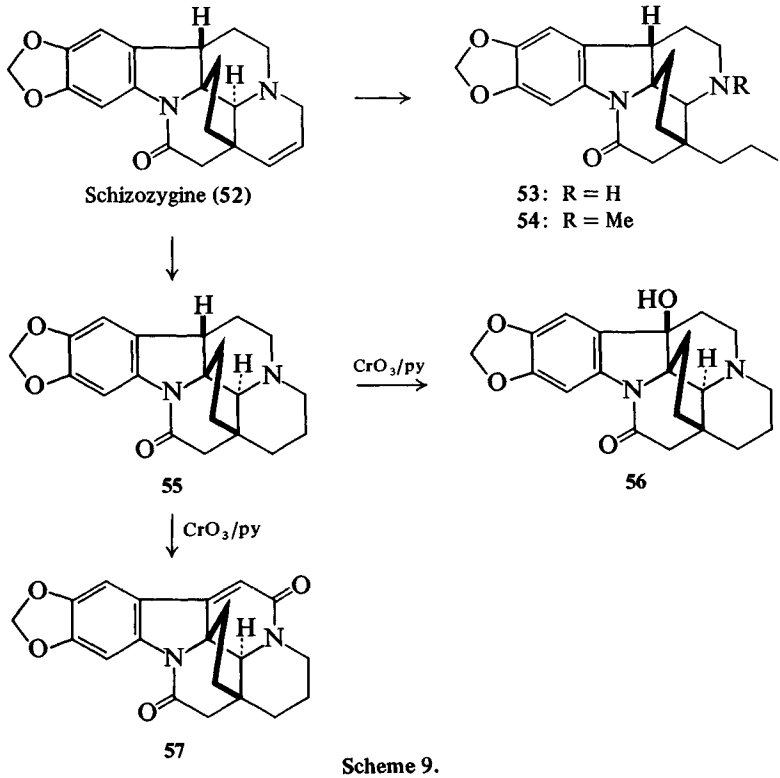


Scheme 8.

spectrum. The amide group is contained in a six-membered lactam ring (ir spectrum), which can be hydrolyzed to an easily recyclized amino acid. A cis-disubstituted double bond contained in an allylamine system is also present. This is responsible for an ABXY pattern of signals in the nmr spectrum, indicating that the other terminus of the double bond is attached to a quaternary center. Hydrogenation of the double bond is accompanied by some fission of the allylic carbon-nitrogen bond, with formation of a secondary amine (**53**) containing a propyl group (modified Kuhn-Roth determination) (Scheme 9).[50] In analogous fashion the Emde hydrogenation of schizozygine methochloride leads to the related tertiary amine **54**. The presence of a propyl group in **53** and **54** reveals that dihydroschizozygine contains a chain of three methylene groups attached to N_b, a characteristic shared only by the aspidospermine and eburnamine groups among the indole alkaloids.

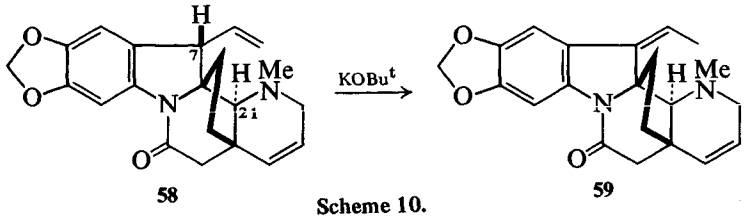
Oxidation (CrO_3/pyridine) of dihydroschizozygine (**55**) gives a hydroxy derivative (**56**), which on further oxidation gives a product (**57**) containing an *o*-acylaminocinnamic acid amide chromophore. Consequently the tertiary hydroxyl group in the oxidation product must be situated at C-7, and the tryptamine unit in schizozygine must be intact, provided that rearrangement of the carbon skeleton has not occurred.[50]

Hofmann degradation of schizozygine methiodide gives a methine base (**58**) containing a vinyl group, which on treatment with strong base isomerizes to a compound (**59**) containing an ethylidene group conjugated with the aromatic ring (Scheme 10). Since this double bond shows no tendency to isomerize into the indole position the indole α position must be fully substituted. This is consistent with the observation that the C-7 proton in **58** is coupled only with the C-6 proton. Further, the proton at C-21 in **58** occurs as a *singlet* (at δ 2.72); hence both C-2 and C-20 must be fully



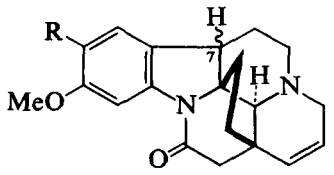
Scheme 9.

substituted. That C-20 is quaternary is confirmed by that fact that the C-17 protons show no vicinal coupling. On the basis of this evidence schizozygine has the structure **52**. In contrast to the eburnamine-vincamine group the D/E ring junction must be trans and, of the two possibilities, the one with a cis B/C junction is the less highly strained, as in **52**.

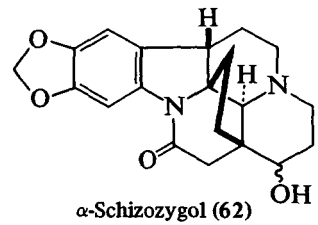


Scheme 10.

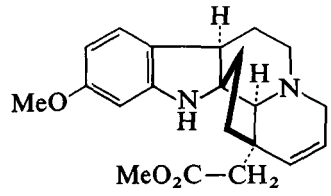
Of the minor alkaloids[51] schizogaline (**60**) contains one methoxyl group at position 11, and schizogamine (**61**) is the analogue of schizozygine with methoxyl groups at positions 10 and 11. α-Schizozygol is a secondary alcohol which on tosylation and elimination affords schizozygine. Since the oxymethine proton appeared to be coupled to only two neighboring protons the hydroxyl group is assumed to be at C-15, and α-schizozygol is therefore formulated as **62**.



		R	7H
Schizogaline	(60)	H	β
Schizogamine	(61)	OMe	β
Isoschizogaline	(63)	H	α
Isoschizogamine	(64)	OMe	α



α-Schizozygol (62)



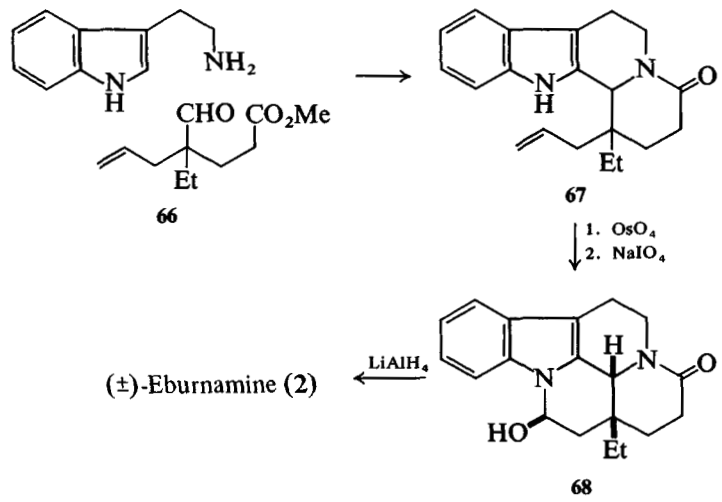
Schizophylline (65)

Isoschizogaline (**63**) and isoschizogamine (**64**) are two bases which contain a rather more strained ring system than their isomers **60** and **61**. In accordance with this the corresponding amino acids do not cyclize as readily as the acids from **60** and **61**, and they can be esterified with diazomethane without cyclization (attempts to esterify the amino acids derived from **60** and **61** result in regeneration of the alkaloids themselves). This additional strain in **63** and **64** is also reflected in anomalous Hofmann degradations, which give products of unknown structure. On the basis of the available evidence isoschizogaline (**63**) and isoschizogamine (**64**) are formulated as the C-7 epimers of schizogaline and schizogamine. Schizophylline, an ester alkaloid, is presumably **65**, since on chromatography on alumina, it is converted into isoschizogaline (**63**).[51]

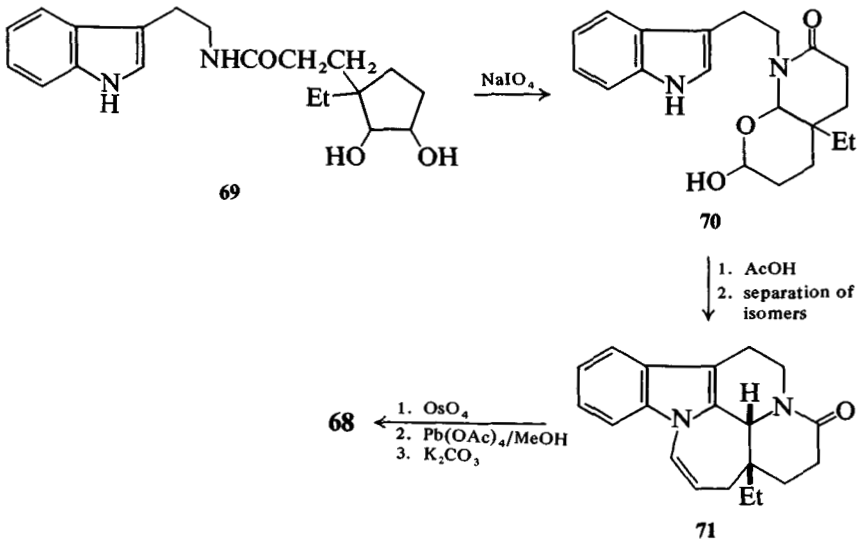
II. SYNTHESIS OF THE EBURNAMINE-VINCAMINE ALKALOIDS

The potentially useful pharmacological properties of eburnamine and (particularly) vincamine have stimulated considerable synthetic effort, and several syntheses of both alkaloids have been developed. The first two syntheses of eburnamine were mentioned earlier, in connection with the proof of structure and stereochemistry; the third synthesis, reported by Harley-Mason and co-workers,[52] was essentially a variant of the first route, and involved condensation of tryptamine with the unsaturated aldehydo ester (**66**). Oxidative fission of the terminal double bond in the product (**67**) provided a means for the introduction of the C-16 aldehyde function (→ **68**); reduction then gave (±)-eburnamine (Scheme 11).

The approach adopted by Gibson and Saxton[53] proceeded via the construction of an acyltryptamine derivative (**69**), which on periodate fission gave the carbinolamide-lactol (**70**) (Scheme 12). Cyclization of **70** by means of acetic acid afforded the C-21 epimeric 3-oxohomoeburnamenines, the cis isomer (**71**) of which was hydroxylated with osmium tetroxide. Cleavage of the resulting diol with lead tetraacetate followed



Scheme 11.

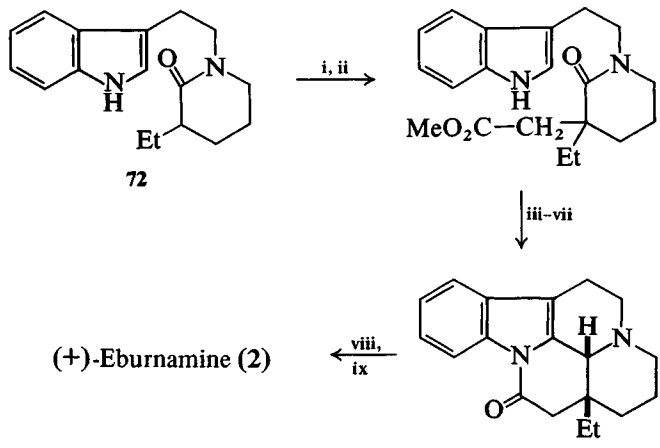


Scheme 12.

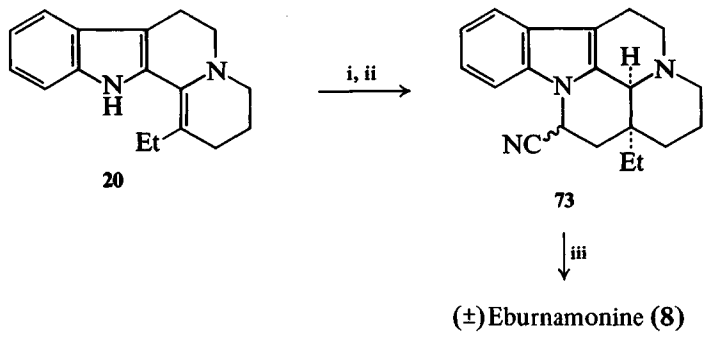
by hydrolytic removal of the *N*-formyl group gave (±)-3-oxoeburnamine (**68**), which was reduced to (±)-eburnamine.[53]

Schlessinger's synthesis[54] employed the known lactam **72**, the dianion from which was alkylated with methyl bromoacetate in order to complete the carbon skeleton; Bischler-Napieralski cyclization, followed by several unexceptional stages, then gave (±)-eburnamine (**2**) (Scheme 13).

Wenkert's enamine (**20**) also figures in a recent synthesis[55] of eburnamonine (Scheme 14). In what was presumably an attempt to synthesise vincamine the carbon skeleton was completed by alkylation of **20** with 2-chloroacrylonitrile,



Scheme 13. Reagents: i, $LiNPr^i_2$, THF, −78°; ii, $BrCH_2CO_2Me$, −78°; iii, $POCl_3$, MeCN; iv, $LiClO_4$; v, H_2, Pd/C; vi, NaOMe, MeOH; vii, separation of isomers; viii, $LiAlH_4$, THF; ix, NaOMe, MeOH, 70°, 12 hr (epimerization at C-16).

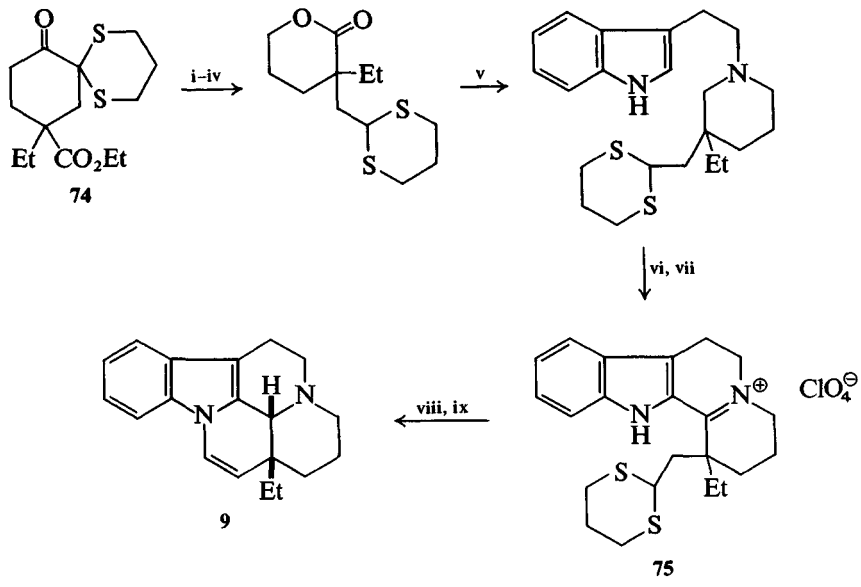


Scheme 14. Reagents: i, CH_2=CCl.CN, CH_2Cl_2; ii, Zn, HCl, EtOH; iii, $LiNC_6H_{11}Pr^i$, THF, HMPA, O_2, −78°.

followed by reduction. However, the introduction of oxygen into C-16 in the epimer **73** gave a fragile derivative of vincaminic acid, which lost HCN to give eburnamonine [(±)-**8**]. Similarly the C-20 epimer of **73** gave 20-epieburnamonine (**23**).

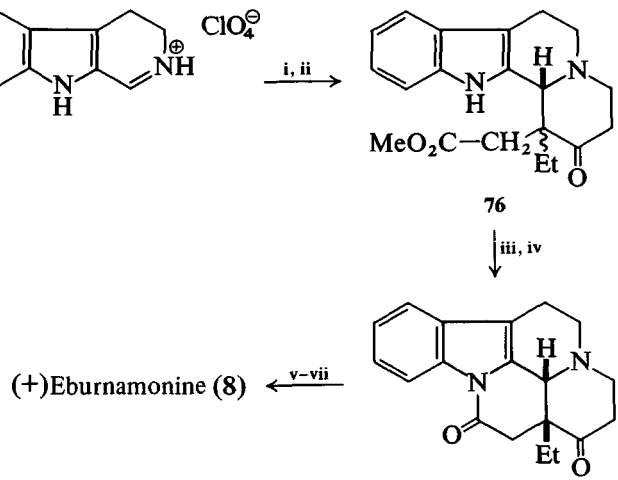
In their synthesis of eburnamenine (Scheme 15) Takano et al.[56] make further use of the thioacetal keto ester **74**, prepared earlier during the synthesis of quebrachamine. Reduction of the dehydro salt **75** followed by thioacetal hydrolysis gave a good yield of (±)-eburnamenine [(±)-**9**]; however, if the last two stages were reversed, and the final stage carried out by means of $NaBH_4$, a good yield of 20-epieburnamenine was obtained.

Novák and his collaborators[57] adopted the annulation reaction between 3,4-dihydro-β-carboline and an appropriate enone for the purpose of constructing the



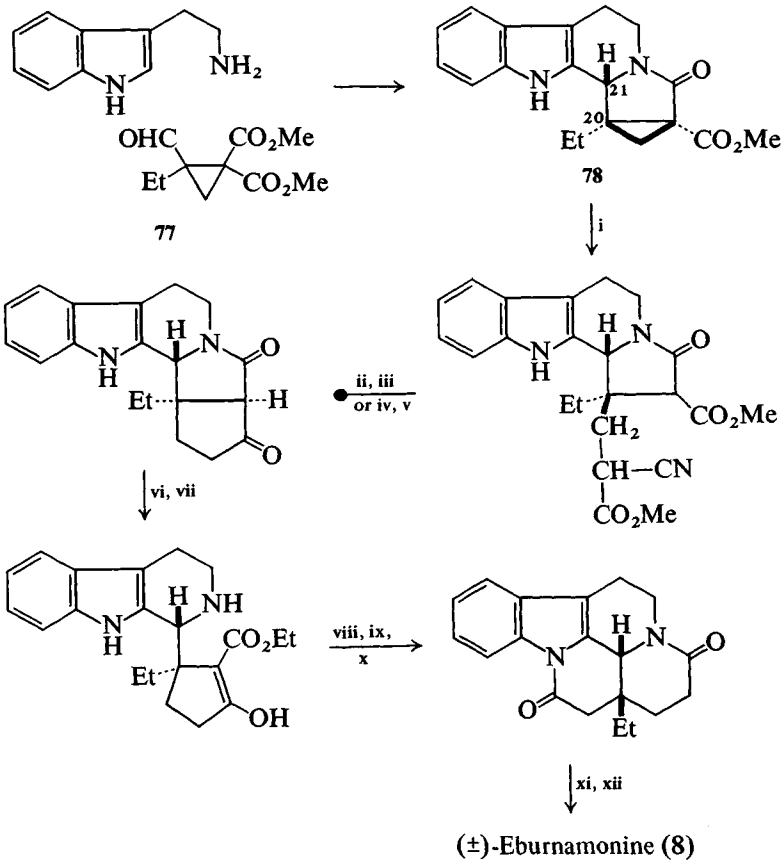
Scheme 15. Reagents: i, NaH, Et_2O, H_2O; ii, $ClCO_2Et$, NEt_3; iii, $NaBH_4$, THF; iv, H_3O^+; v, tryptamine, 160°; vi, MeCN, $POCl_3$; vii, $LiClO_4$; viii, $LiAlH(OBu^t)_3$, THF; ix, MeI, MeCN, H_2O.

tetracyclic intermediate (**76**). This was cyclized, the resulting epimers were separated, and the desired epimer reduced and resolved, to give (+)-eburnamonine (**8**) (Scheme 16).



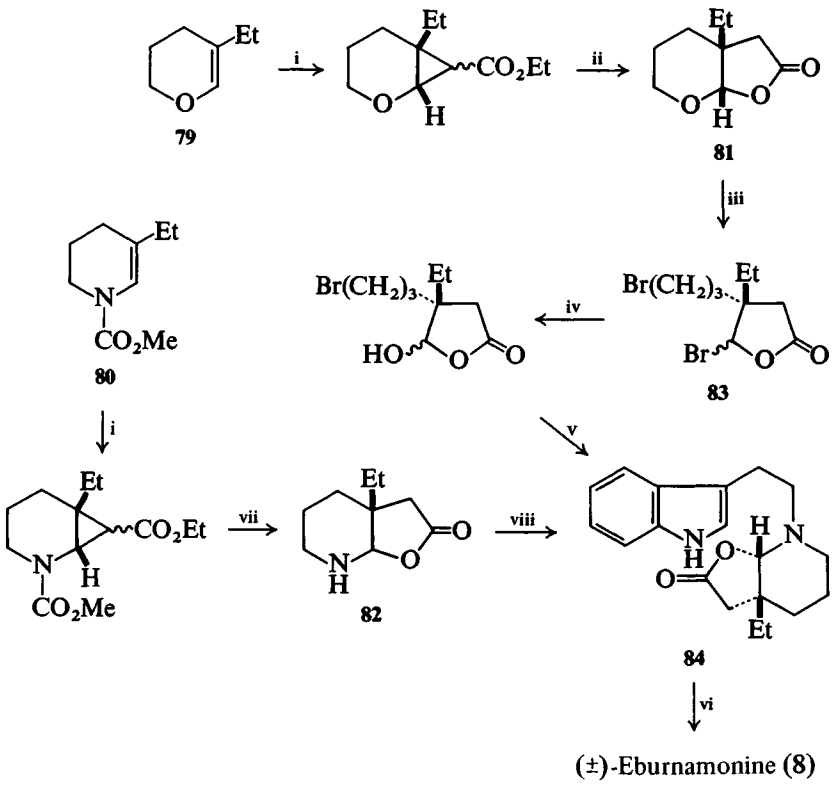
Scheme 16. Reagents: i, $MeO_2CCH_2CHEtCOCH{=}CH_2$; ii, NEt_3, MeOH, r.t., 4 days; iii, $NaOBu^t$, PhMe; iv, *separation of epimers*; v, *p*-$MeC_6H_4SO_2NHNH_2.HCl$; vi, $NaBH_3CN$, DMF, sulfolane, TsOH, 110°; vii, (+)-*O,O*-dibenzoyltartaric acid.

The ingenuity that has been applied to the synthesis of these alkaloids, sometimes at the expense of brevity, is well exemplified by the recent contributions of Klatte et al.[58] and Wenkert et al.[59] The former approach follows quite different lines from any other synthesis, and leads to eburnamonine with a very high degree of stereoselectivity (Scheme 17). The initial stage, which involved the condensation of tryptamine with the cyclopropyl aldehydo ester (**77**), gave 85% of pentacyclic lactam ester (**78**); only 15% of the epimer of **78** was obtained. The correct stereochemical relationship between C-20 and C-21 was thus assured, and this remained undisturbed during the later stages of the synthesis.[58]



Scheme 17. Reagents: i, $LiCH(CN)CO_2Me$; ii, LiI, DMF; iii, KF, AcOH; iv, RO^-; v, H^+; vi, $Et_3O^+PF_6^-$; vii, hydrolysis; viii, MeO^-; ix, reesterification; x, CF_3CO_2H; xi, $Et_3O^+BF_4^-$; xii, $NaBH_4$.

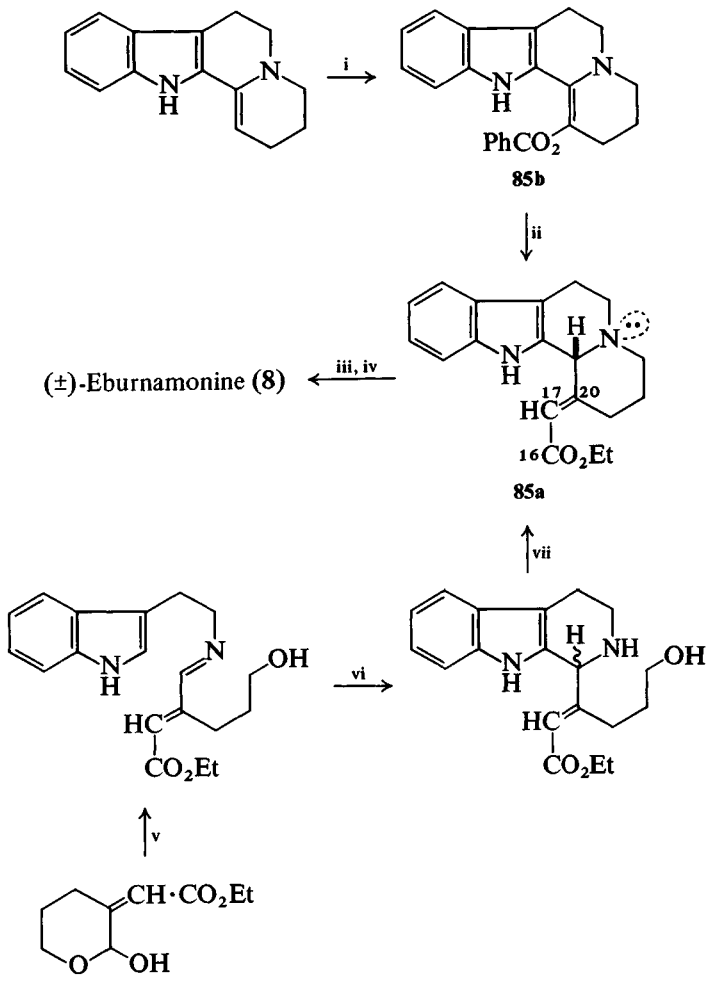
Wenkert's second route[59a] to eburnamonine (Scheme 18) involves a neat extension of the preparation of 1,4-diketones via cyclopropanoid intermediates which allows the formation of γ-imino or γ-keto acids. Two variations of this approach were reported, all the stages in which were very high yielding, given the



Scheme 18. Reagents: i, N_2CHCO_2Et, Cu; ii, H^+, H_2O; iii, BBr_3, CH_2Cl_2; iv, 1% HCl, dioxane, Δ; v, tryptamine. HCl, DMSO, 3A mol. sieves, 55°; vi, 250°, 0.01 mm; vii, KOH, H_2O, $HOCH_2CH_2OCH_2CH_2OH$, 100°; viii, tryptophyl bromide, NaOH, $Et_3^+NCH_2PhCl^-$, C_6H_6, 35°.

essential starting materials, **79** and **80**. In both variations the intermediate γ-substituted acid was stabilized by cyclization, either as a hemiacetal lactone (**81**) or as its aza analogue, the carbinolamine lactone (**82**). The lactone (**81**) was manipulated via the epimeric dibromides (**83**) to the carbinolamine lactone (**84**), thermolysis of which gave (±)-eburnamonine (**8**). Alternatively, in a much more direct synthesis, **84** was obtained by alkylation of **82** with tryptophyl bromide; this route, however, suffers from a low yield in the initial sequence leading to the urethane (**80**).

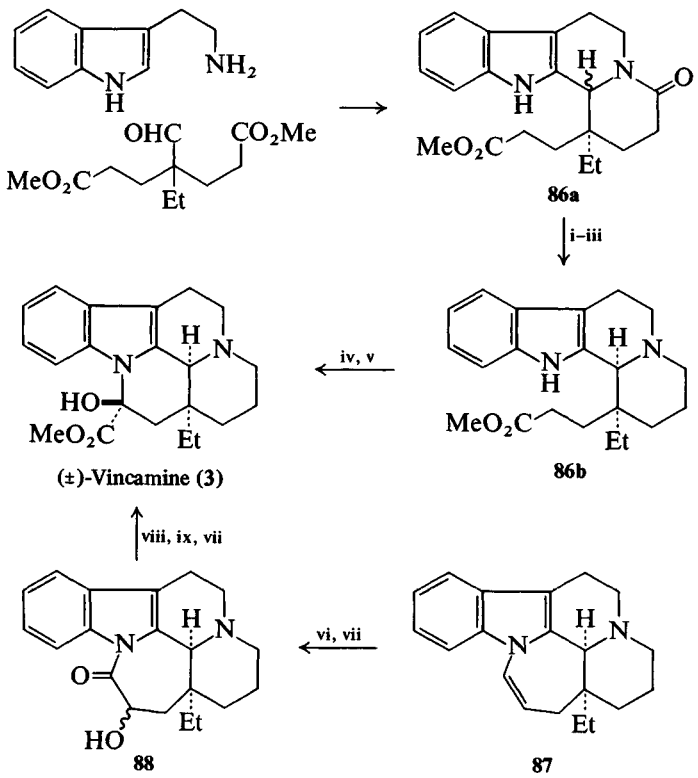
Yet another synthesis[59b] of (±)-eburnamonine employs two routes to the preparation of the tetracyclic unsaturated ester (**85a**), one of which involved the first application of the Wadsworth-Emmons reaction to an enol ester (**85b**). This neatly introduced the future C-16 and C-17 to give a trans-quinolizidine derivative which on 1,4-addition of ethylmagnesium bromide completed the carbon skeleton with formation of the desired cis C/D quinolizidine ester; cyclization onto the indole nitrogen then gave (±)-eburnamonine (**8**) (Scheme 19).



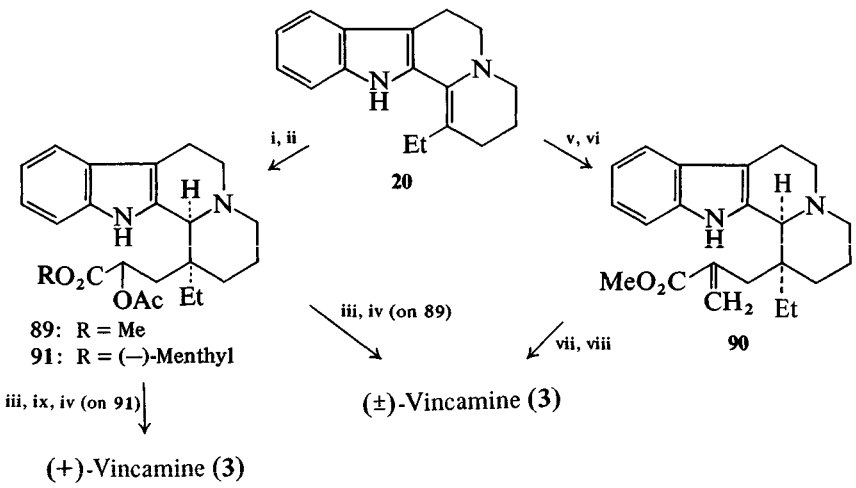
Scheme 19. Reagents: i, $(PhCO_2)_2$, hydroquinone, dioxane, 25°, then NH_4OH; ii, $(EtO)_2POCH_2CO_2Et$, NaH, DME, N_2; iii, EtMgBr, $CuCl_2$, THF, Et_2O, N_2; iv, NH_4Cl, H_2O; v, tryptamine, C_6H_6, N_2; vi, EtOH, HCl; vii, $SOCl_2$, py, C_6H_6.

Similar ingenuity has been applied to the synthesis of vincamine. Indirect routes via vincadifformine derivatives have already been described (see Chapter VIII). Of the direct syntheses the first two[60,61] are now mainly of historical interest. Kuehne's initial synthesis (Scheme 20) is based on the Bartlett-Taylor method for the construction of the tetracyclic intermediate **86a**, and has the advantage of brevity. However, both epimers of **86a** were naturally obtained, and the functionalization of C-16 in the ester **86b** was accomplished in only 3% yield.[60]

In the second synthesis advantage was taken of the fact that homoeburnamenine (**87**), prepared by reduction ($LiAlH_4$) of (±)-3-oxohomoeburnamenine (**71**), contains the complete vincamine carbon skeleton, and has an appropriately placed



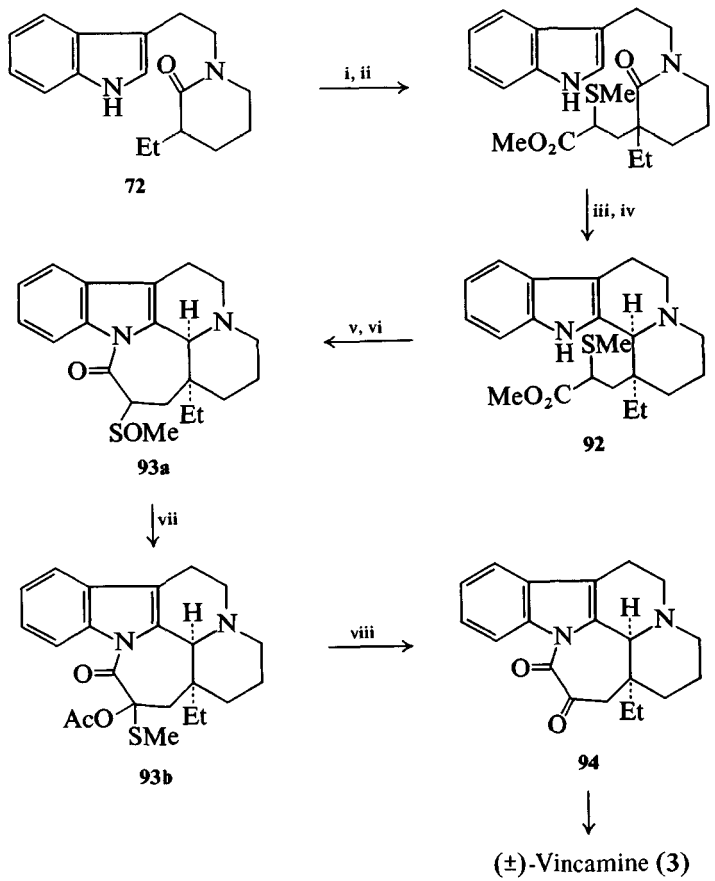
Scheme 20. Reagents: i, P_2S_5; ii, separation of epimers; iii, Raney Ni; iv, *p*-$Me_2NC_6H_4NO$, $NaCPh_3$; v, H^+, H_2O; vi, OsO_4; vii, DMSO, NEt_3, py, SO_3, H_2O; viii, NaOH; ix, CH_2N_2.



Scheme 21. Reagents: i, $CH_2=C(OAc)CO_2R$; ii, H_2, Pd, MeOH; iii, NaOMe, MeOH; iv, Ag_2CO_3, celite, C_6H_6; v, $BrCH_2C(=CH_2)CO_2Me$; vi, $NaBH_4$; vii, OsO_4; viii, HIO_4; ix, dibenzoyltartaric acid.

double bond that can easily be functionalized.[61] Hydroxylation of **87**, followed by oxidation, gave a hydroxylactam (**88**), which on hydrolysis, esterification, and oxidation, gave (±)-vincamine [(±)-**3**] (Scheme 20).

The availability of the enamine (**20**) suggests an obvious, direct preparation of vincamine by reaction of **20** with bromopyruvic ester followed by reduction; unfortunately, attempts to achieve this process have met with failure.[62] The difficulty, however, has been elegantly circumvented by alkylation of **20** with 2-acetoxyacrylic ester[63] or 2-(bromomethyl)acrylic ester,[64] followed in each case by reduction; the intermediates thus obtained (**89** and **90**, respectively) were then converted into vincamine by standard methods. A significant stereoselectivity was introduced into the synthesis of Novák et al.[57] by a modification in which the enamine (**20**) was alkylated by means of the (−)-menthyl ester of α-acetoxyacrylic acid. Methanolysis of the product (**91**) then gave an intermediate ester with ~ 40%



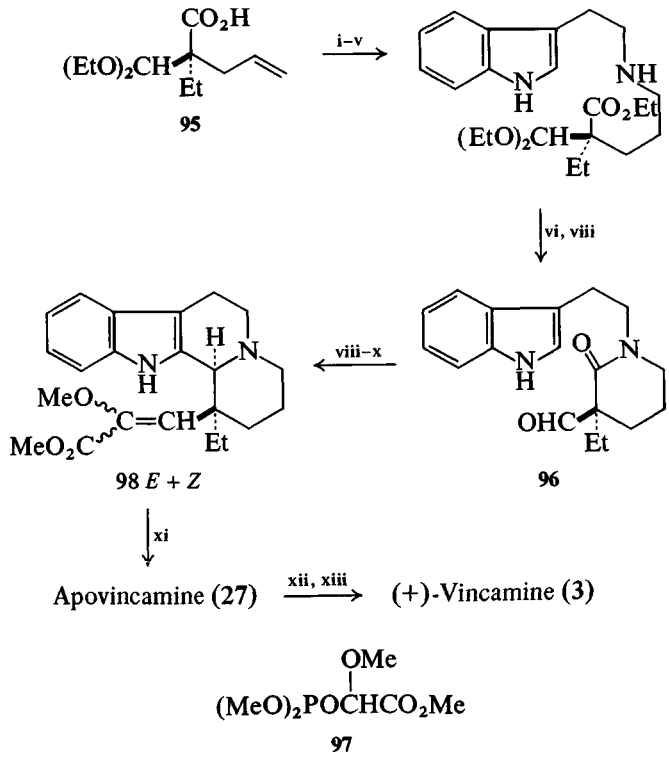
Scheme 22. Reagents: i, $LiNPr_2$, −78°; ii, CH_2=C(SMe)CO_2Me; iii, $POCl_3$, MeCN; iv, $LiAl(OBu^t)_3H$; v, *m*-$ClC_6H_4CO_3H$; vi, NaH, THF; vii, AcCl, 0°; viii, NaOMe, MeOH.

optical purity; resolution was completed via the dibenzoyltartrate salt, and the synthesis finished as before (Scheme 21).

Appropriate modification of the original version of this synthesis resulted in the preparation of 10-methoxyvincamine (isovincine), which is not known as a natural product, but is of obvious pharmacological interest.[65]

In the synthesis by Herrmann and his collaborators[54b,66] the carbon skeleton was completed by alkylation of the dianion of the lactam **72** before cyclization by the Bischler-Napieralski method; reduction of the product then gave predominantly the desired epimer (**92**), as expected. Following closure of the fifth ring and oxidation of the thioether group, the oxygen functionality was introduced into the sulfoxide (**93a**) so obtained by an ingenious application of the Pummerer rearrangement, which presumably gave the acetoxy thio ether (**93b**) (not isolated); treatment with sodium methoxide then gave (±)-vincamine, via the α-ketolactam (**94**) (Scheme 22).

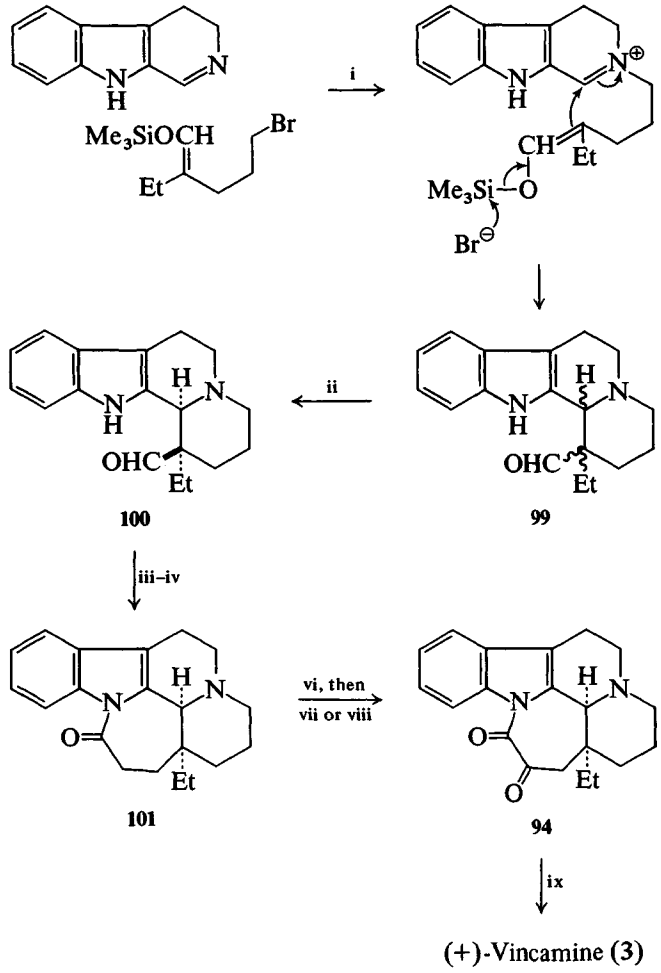
The two most recent syntheses of vincamine have been contributed by Oppolzer's group.[67,68] In the first of these the correct absolute configuration at C-20 was



Scheme 23. Reagents: i, Et_2SO_4, K_2CO_3; ii, BH_3, THF; iii, H_2O_2, KOH; iv, TsCl, py; v, tryptamine; vi, imidazole, 130°; vii, AcOH, H_2O; viii, $(MeO)_2POCH(OMe)CO_2Me$ (97), NaH, THF; ix, $POCl_3$; x, H_2, Pd/C, NEt_3; xi, HBr, AcOH; xii, HBr, − 78°; xiii, 10 *M* KOH, H_2O, hexane, − 50°, then $(NH_4)_2SO_4$, − 40° to 5°.

ensured by use of the appropriate enantiomer of the carboxylic ester (**95**). Again the carbon skeleton was completed, in this synthesis by a Wadsworth-Emmons condensation of the aldehyde **96** with the phosphonate ester **97**, before Bischler-Napieralski cyclization (Scheme 23). Stereoselective reduction of the dihydro-β-carboline so obtained then gave the enol ester **98**. Unfortunately **98** proved unexpectedly resistant to hydrolysis, and the vigorous conditions required resulted in concomitant dehydration of the cyclized material, with formation of apovincamine **27**, which therefore had to be reconverted to vincamine, a difficult stage that had not previously been achieved.[67,69]

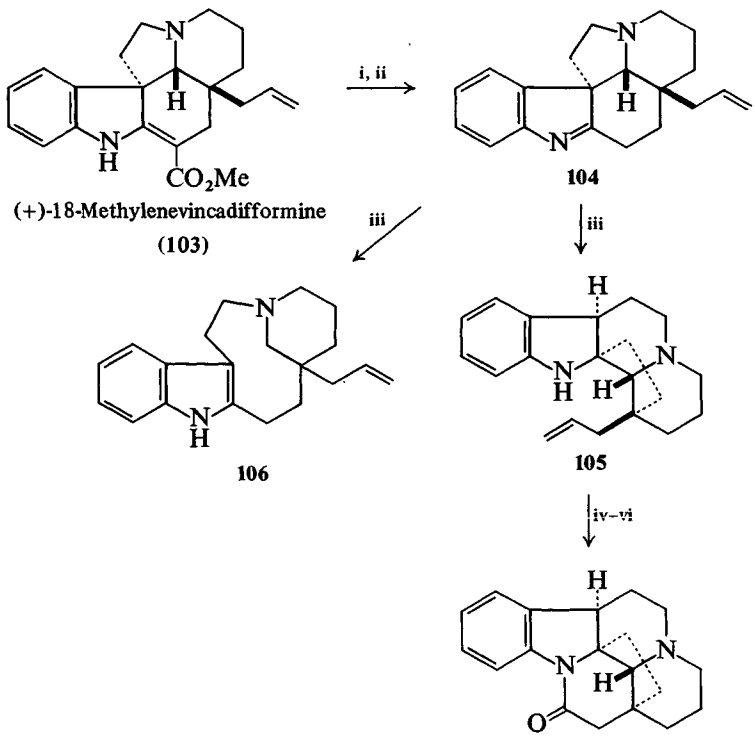
The second synthesis of Oppolzer et al.[68] proceeds via the aminoaldehyde **99**, the final stage in the preparation of which involves an ingenious new modification



Scheme 24. Reagents: i, $EtNPr^i_2$, DMF, 70°; ii, (+)-malic acid; iii, $(EtO)_2POCH_2CO_2Et$, NaH, DMF; iv, H_2, Pd; v, $(Me_3Si)_2NNa$; vi, BuONO, $(Me_3Si)_2NNa$, PhMe; vii, CH_2O, H_2O, HCl; viii, ceric ammonium nitrate, MeOH, − 30°; ix, NaOMe, MeOH.

of the Mannich reaction. This stage is also remarkable in that the cis racemate of **99** could be separated and resolved, and the unwanted cis enantiomer and (±)-trans epimer could be reequilibrated with the desired cis enantiomer (**100**) by reversible Mannich fission on the tosylate of **99** (Scheme 24). In this way virtually all the aminoaldehyde **99** could be utilized. The carbon skeleton was completed by a phosphonate ester condensation on the cis aldehyde (**100**). Reduction and cyclization gave homoeburnamonine (**101**), which was raised to the vincamine oxidation level by nitrosation at C-16. Removal of the oximino function then gave the ketolactam **94**, which on methanolysis afforded (+)-vincamine (**3**).

(−)-Strempeliopine (**102**), an alkaloid recently isolated[49b] from Cuban *Strempeliopsis strempelioides*, may be regarded as the parent base of this series. Its structure was very neatly established[49b] by synthesis of the racemic form from (±)-18-methylenevincadifformine (**103**), itself prepared[70] by appropriate modification of Kuehne's synthesis of vincadifformine (see Chapter VIII). Hydrolysis and decarboxylation of **103** gave (±)-18-methylene-1,2-dehydroaspidospermidine (**104**), which on reaction with zinc and hydrated copper sulfate in acetic acid gave a mixture of the rearranged base (**105**) and 18-methylenequebrachamine (**106**) (Scheme 25). Formylation of **105**, followed by separation from **106**, oxidative



Scheme 25. Reagents: i, OH^-, H_2O; ii, C_6H_6, Δ; iii, Zn, $CuSO_4.5H_2O$, AcOH, 103°; iv, HCO_2H, Ac_2O; v, O_3, HCl, MeOH; vi, H_2O_2.

ozonolysis, and removal of the *N*-formyl group, then gave (±)-strempeliopine **(102)**.[49b]

Subsequently,[71] the synthetic (±)-18-methylenevincadifformine **(103)** was resolved, and the dextrorotatory enantiomer shown to have the absolute configuration depicted in **103** by comparison of the cd spectra of **103** and its 18,19-dihydro derivative with those of (−)-vincadifformine and (−)-tabersonine, which are known to belong to the enantiomeric series (see Chapter VIII).

The absolute configuration of (−)-strempeliopine **(102)** was then finally established by its preparation from (+)-**103**, by the route shown in Scheme 25.

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CHAPTER X

The Ibogamine-Catharanthine Group

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I. INTRODUCTION

In the middle part of the nineteenth century, French and Belgian explorers of the Gabon and Congo regions of West Africa brought back to Europe reports of a remarkable shrub. Natives of the region claimed that the root bark was an aphrodisiac, a powerful stimulant, and that it increased their strength and endurance. Other tribes reported that larger doses of the roots would produce fantastic images. du Bellay in 1864 indicated that iboga is "an aphrodisiac and a stimulant of the nervous system; warriors and hunters use it constantly to keep themselves awake during night watches . . . ."[1]

In 1892 the plant was described botanically by Baillon[2] and named *Tabernanthe iboga* Baill. The genus was stabilized by Stapf, who subsequently described several other species.

Chemical work began in the latter part of the nineteenth century and in 1901 the principal alkaloid, ibogaine, was isolated.[3,4] The root bark typically contains 5–6% of alkaloids (35–85% ibogaine) with the root itself having a somewhat lower (1.0–2.6%) alkaloid content. As chemical work continued, additional alkaloids were isolated from this and other apocynaceous sources, and it became clear that ibogaine was merely one member of a series of alkaloids having the same skeleton. In deference to the original plant source these alkaloids are described as having the "iboga" skeleton. It is one of the fundamental skeletons of the monoterpenoid indole alkaloids.

Several reviews of iboga alkaloids have appeared[5–8] and are readily available; other reviews are less comprehensive.[9–11]

II. CHEMOTAXONOMY

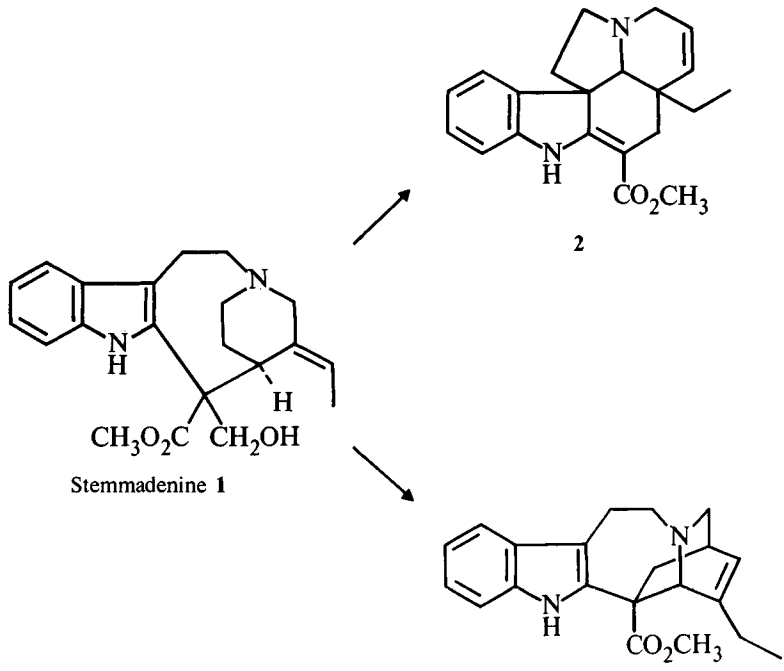
Since the isolation of ibogaine from *Tabernanthe iboga*, related alkaloids have been found in the genera *Anartia, Catharanthus, Conopharyngia, Daturicarpa, Ervatamia, Gabunia, Hazunta, Malouetia, Melodinus, Muntafara, Pagiantha, Pandaca, Peschiera, Rejoua, Stemmadenia, Tabernaemontana*, and *Voacanga*. All these genera belong to the family Apocynaceae. There are no reports of an iboga alkaloid isolation from any other family.

From a chemotaxonomic and biogenetic point of view, the iboga alkaloids seem to occur infrequently with alkaloids of the *Aspidosperma* type; indeed no examples have been isolated from the genus *Aspidosperma*. The significance of this may well lie in the nature of the enzymes required to take stemmadenine (**1**) through to the *Aspidosperma* (e.g., **2**) and iboga (e.g., **3**) alkaloid types.

III. STRUCTURE ELUCIDATION AND SPECTROSCOPIC PROPERTIES

A. Fundamental Chemistry

It was mentioned previously that ibogaine was first isolated at the turn of the century.[3,4] Work on its structure, however, did not begin until the 1950s. Color reactions[13,14] and analysis of the uv spectrum[15,16] suggested an indole nucleus, and degradation[17] indicated a methoxyindole to be present. The complete structure **4** was deduced[18] from an analysis of its potassium hydroxide fusion products,[19,20] 1,2-dimethyl-3-ethyl-5-hydroxyindole (**5**) and 3-ethyl-5-methylpyridine (**6**), and its selenium dehydrogenation products **7** and **8** (Scheme 1).[21,22] The stereochemistry of the ethyl side chain and an independent proof of the structure came from an X-ray analysis of the hydrobromide salt.[23]



Alkaloids possessing a carbomethoxy group at C-16 could be related to the "parent" compound in any of several ways, including hydrolysis followed by decarboxylation,[24] refluxing with hydrazine,[25] or elimination of formaldehyde on heating the lithium aluminum hydride reduction product.[26] Facilitation of these reactions is considered to occur because of the near planarity of the indole ring, C_{16}, and its substituent, and typically involves the 7*H*-indolenine tautomer.[22,25,26] The techniques are shown in Scheme 2 as they apply to a correlation of voacangine (**9**) with ibogaine (**4**).

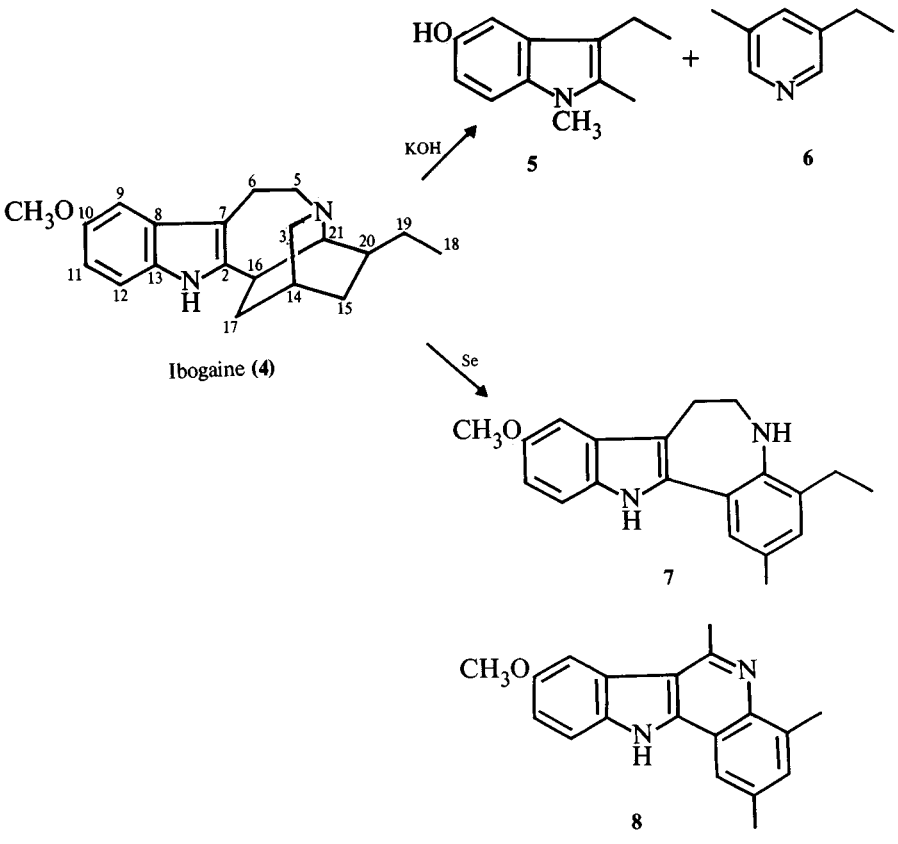
B. Spectroscopic Properties

1. *Ultraviolet Spectroscopy*

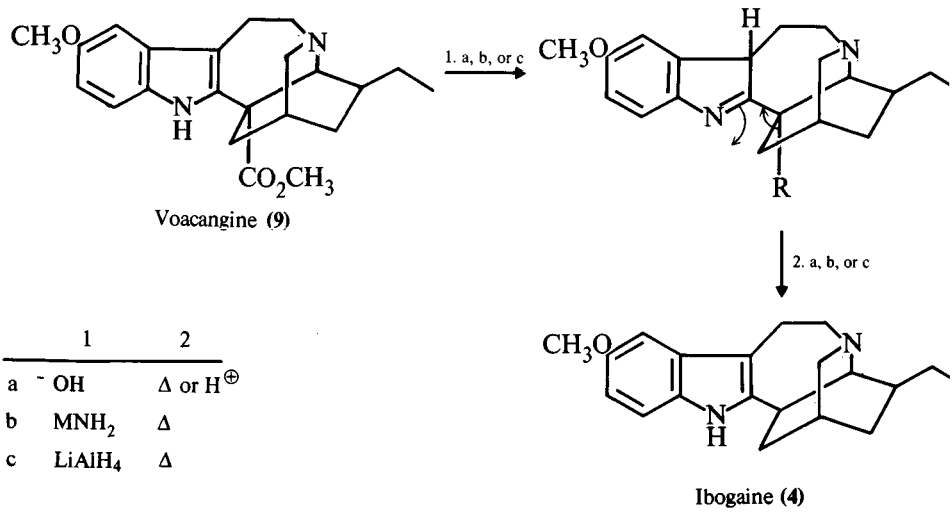
The uv spectra of the iboga alkaloids fall into three broad categories, the indoles, the hydroxyindolenines, and the oxindoles, the spectrum of each parent compound being modified by further substitution in the benzenoid ring as shown in Table I.

2. *Proton Nuclear Magnetic Resonance Spectroscopy*

Key proton nmr spectral assignments of several iboga alkaloids are given in Figure 1. Most of the assignments are based on chemical shift theory considerations,



Scheme 1.



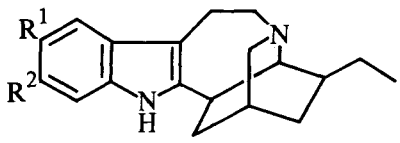
	1	2
a	$^-$OH	Δ or $H^{\oplus}$
b	MNH_2	Δ
c	$LiAlH_4$	Δ

Scheme 2. Correlation of voacangine (9) and ibogaine (4).[22,25,26]

TABLE I. REPRESENTATIVE UV SPECTRA OF THE IBOGA ALKALOIDS[a]

Uv spectral type	Example	λ_{max}	ϵ
Indole	Ibogamine (10)	225, 283, 291	4.56, 3.96, 3.94
10-Methoxyindole	Ibogaine (4)	226, 298	4.39, 3.93
11-Methoxyindole	Tabernanthine (11)	228, 271, 299	4.53, 3.64, 3.77
10,11-Dimethoxyindole	Ibogaline (12)	227, 302	4.40, 3.92
7-Hydroxyindolenine	Ibogamine hydroxyindolenine (13)	218, 222, 228(sh) 253, 281, 292(sh)	4.27, 4.30, 4.14 3.59, 3.50, 3.48
7-Hydroxy-10-methoxyindolenine	Ibogaine hydroxyindolenine (14)	223, 260(sh), 280 290(sh), 312	4.14, –, 3.77, –, 3.55
7-Hydroxy-10,11-dimethoxyindolenine	Jollyanine (15)	217, 238, 300	4.14, 4.12, 3.67
Oxindole	Demethoxyiboluteine (16)	228, 407	4.46, 3.56
10-Methoxyoxindole	Iboluteine (17)	227, 245, 420	4.44, 4.20, 3.45

[a] Data are from Refs. 27 and 28.

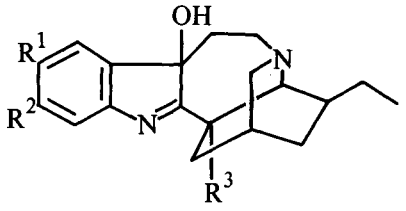


Ibogamine (**10**): $R^1 = R^2 = H$

Ibogaine (**4**): $R^1 = OCH_3$, $R^2 = H$

Tabernanthine (**11**): $R^1 = H$, $R^2 = OCH_3$

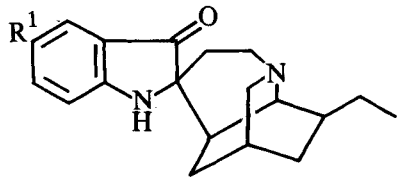
Ibogaline (**12**): $R^1 = R^2 = OCH_3$



Ibogamine hydroxyindolenine (**13**): $R^1 = R^2 = R^3 = H$

Ibogaine hydroxyindolenine (**14**): $R^1 = OCH_3$, $R^2 = R^3 =$

Jollyanine (**15**): $R^1 = R^2 = OCH_3$, $R^3 = CO_2CH_3$



Demethoxyiboluteine (**16**): $R^1 = H$

Iboluteine (**17**): $R^1 = OCH_3$

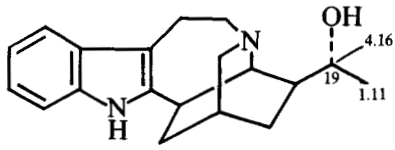
but one important stereochemical assignment is possible if a 19-hydroxy group is present. For example, in 19-epiheyneanine (19*R*) (**21**) where hydrogen bonding occurs between N-4 and the hydroxy group, the methyl group is brought into a deshielding region of the lone pair and is observed at 1.28 ppm. In the 19*S* configuration, it is the 19-H that is deshielded to 4.13 ppm versus 3.88 in the 19*R* isomer **23**.[29,32,33] The proton nmr assignments for coronaridine are shown in **20a**. Some interesting long-range couplings were also observed,[36a] for example, $J_{3A,17A}$ = 2.3 Hz, $J_{3B,15B}$ = 1.8 Hz, and $J_{15A,17A}$ = 4.1 Hz.

3. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*

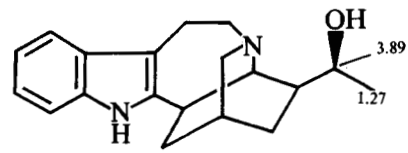
Wenkert and co-workers have established the ^{13}C nmr parameters for alkaloids in the iboga series[37] and for derivatives in the cleavamine series[38]; and data for representative compounds are shown in Tables II and III, respectively.

Aromatic carbon shifts were based on established[39,40] data, the major problem being the assignment of C-11 and C-12 in voacangine (**9**) (and ibogaine) as a result of the unequal shielding of ortho carbons by the 10-methoxy group.

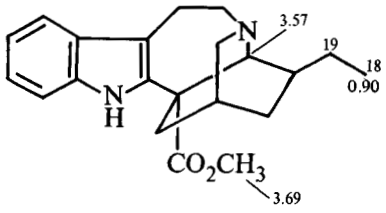
Aliphatic carbon shifts in catharanthine (**28**) could also be readily assigned except for the five methylene groups. The rigidity of the ring system suggested two conformations **35** and **36**, and in the former C-6 and C-3 are placed into a gauche nonbonded interaction which leads to γ effects. In the latter conformation, C-6 receives an additional γ effect from C-21 and thus conformation **37** has been



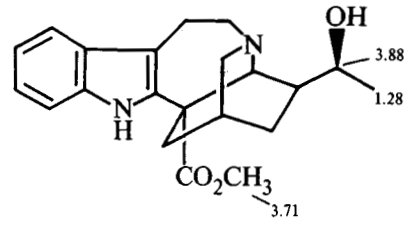
Decarbomethoxyheyneanine (**18**)[29]



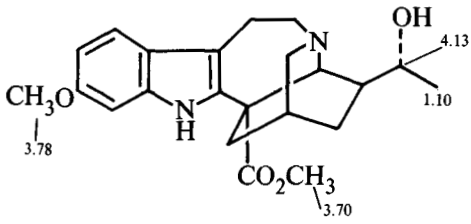
Decarbomethoxy-19-epiheyneanine (**19**)[29]



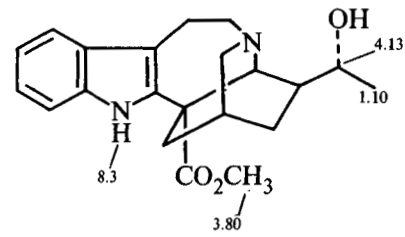
(−)-Coronaridine (**20**)[30]



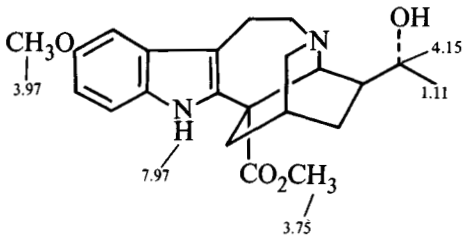
19-Epiheyneanine (**21**)[29]



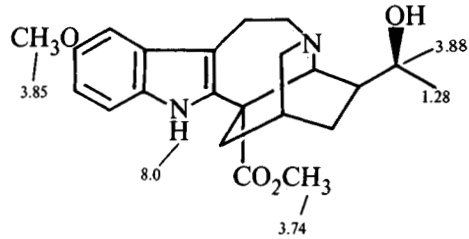
Isovoacristine (**22**)[31]



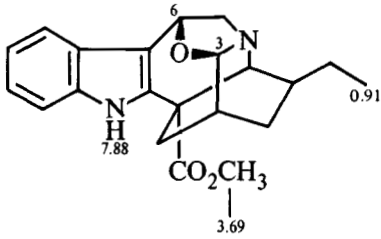
Heyneanine (**23**)[29,32,33]



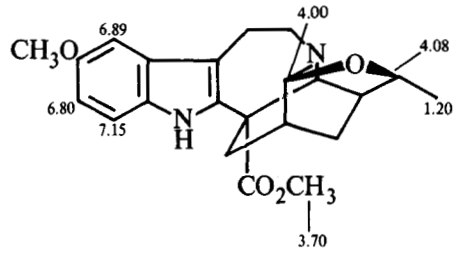
Voacristine (**24**)[34]



19-Epivoacristine (**25**)[34]

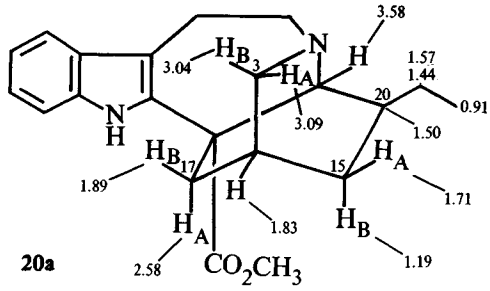


Eglandine (**26**)[35]



Heyneatine (**27**)[36]

Fig. 1. Representative proton nmr spectral data for the iboga alkaloids.



20a

suggested to explain the dramatically different chemical shifts associated with dihydrocatharanthine (**29**). These differences between dihydrocatharanthine (**29**) and coronaridine (**20**) permit ready determination of the configuration at C-20 in heyneanine (**23**) and 19-epiheyneanine (**21**), which, except for the vicinity of C-19, indicates a similar configuration to coronaridine. An interesting deshielding effect is observed for C-21 compared with coronaridine, suggesting a hydrogen bond between N-4 and the C-19 hydroxy group. The γ effect of the methyl group in coronaridine is removed in both heyneanine (**23**) and 19-epiheyneanine (**21**), which becomes oriented toward C-15 as shown in **38**. In contrast, C-15 in 19-epiheyneanine (**21**) is not shielded, indicating that C-21 and C-18 have a gauche butane relationship as shown in configuration **39**.[37]

The chemical shifts of the cleavamine derivatives were assigned in characteristic fashion.[38] Thus nonaromatic methine protons (C-14, C-16, and C-20) were differentiated by their residual one-bond coupling in the SFORD spectra, and the aminomethylene groups by comparison with related and model compounds. As expected, major changes are observed only for C-16 and C-17 on removing the carbomethoxy group of **31** or **34**. Introducing a C-20 hydroxy group into **32** causes predictable α, β, and γ effects.

Except for cleavamine (**30**), the compounds show a C-6 methylene resonance at 22.0 ± 0.7 ppm, indicating that they adopt the same conformation for the azacyclononane ring shown in **40**. On the other hand, cleavamine (**30**) shows C-6 at 26.1 ppm, indicating it to exist in the conformation **41**. In the proton spectrum this leads to anisotropic shielding by N-4 of H-16β which appears at 3.60 ppm. Another guide to the conformation of the azacyclononane system is the multiplicity, in the SFORD spectrum, of C-21 and C-3. Compounds in the 16β-series appear as doublets, but as triplets in the 16α-series.[38] Carbon-13 nmr data for several other iboga alkaloids have been reported.[36,40a,40b]

4. *Mass Spectrometry*

As with other groups of monoterpenoid indole alkaloids the mass spectral fragmentation of the iboga alkaloids has been well studied and consequently can be highly diagnostic of functional group substitution.[41,42]

Two series of ions are typically observed, one due to the aliphatic moiety and

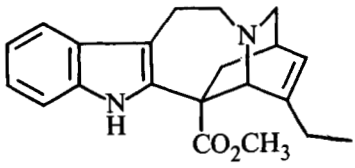
TABLE II. ^{13}C-SHIFTS OF IBOGA ALKALOIDS AND DERIVATIVES[37]

Carbon	Catharanthine (28)	Coronaridine (20)	Dihydrocatharanthine (29)	Voacangine (9)	Heyneanine (23)	19-Epiheyneanine (21)
2	136.0	136.5[a]	135.6[a]	137.3	136.5[a]	135.9[a]
3	52.9	53.1	56.1	53.0	52.1[b]	52.0[b]
5	49.3	51.5	53.5	51.5	51.1[b]	50.9[b]
6	21.0	22.2	17.9	22.0	21.3	21.6
7	110.2	110.3	108.8	109.7	110.7	109.6
8	128.4	128.8	126.5	128.7	129.5	128.4
9	117.7	118.3	117.8	100.4	119.3	118.3
10	118.9	119.0	118.6	153.6	119.3	120.3
11	121.3	121.8	121.4	111.4	123.2	122.1
12	110.2	110.3	111.3	110.9	111.4	110.4
13	131.7	135.6[a]	135.1[a]	130.5	136.3[a]	135.6[a]
14	30.4	27.2	24.4	27.2	26.7	26.0
15	123.4	32.0	28.2	31.9	22.9	28.6
16	55.0	55.1	47.1	55.0	56.8	54.1
17	38.0	36.3	34.4	36.2	36.8	36.5
18	10.5	11.6	12.0	11.5	20.2	22.1
19	25.9	26.6	25.6	26.6	72.3	70.7
20	148.5	38.9	37.1	38.9	39.5	40.2
21	61.5	57.2	55.4	57.2	59.7	54.7
C=O	173.6	175.9	171.7	175.4	175.7	174.8
OCH_3	52.0	52.4	52.7	52.2	52.8	52.6
$ArOCH_3$				55.7		

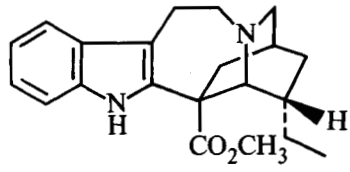
Note: The assignments of signals denoted by superscripts *a* or *b* in any spectrum may be reversed.

TABLE III. ^{13}C-SHIFTS OF CLEAVAMINE DERIVATIVES[38]

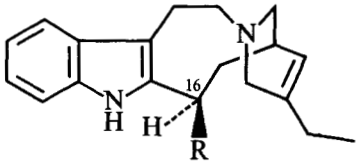
Carbon	Cleavamine (30)	16β-Carbomethoxy-cleavamine (31)	16β-Carbomethoxydihydro-cleavamine (32)	Velbanamine (33)	16β-Carbomethoxyvelbanamine (34)
2	139.2	138.4	135.0	138.5	N/O
3	53.5	47.0	50.6	50.6	50.9
5	53.8	51.2	52.5	52.3	52.0
6	26.1	21.7	22.1	22.7	22.4
7	109.5	109.5	109.5	108.0	109.2
8	128.5	127.9	127.8	127.4	127.7
9	117.6	117.5	117.4	116.8	117.5
10	118.5	118.6	118.6	118.4	119.0
11	120.3	120.9	120.7	120.4	121.4
12	109.8	110.6	110.5	110.8	111.1
13	135.2	135.0	135.0	135.2	134.0
14	35.3	34.1	32.8	30.1	30.5
15	122.3	124.0	36.7	40.4	39.5
16	22.4	39.3	39.0	22.7	39.3
17	34.1	39.1	36.3	31.5	36.1
18	12.6	12.3	11.3	6.9	6.9
19	27.6	27.3	27.3	32.3	32.6
20	140.4	138.4	33.1	71.6	71.2
21	55.1	57.5	61.3	65.8	66.1
C=O		175.8	176.1		175.2
OCH_3		52.2	52.1		52.2



Catharanthine (**28**)



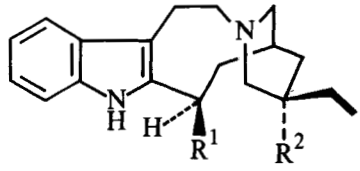
Dihydrocatharanthine (**29**)



Cleavamine (**30**): R = H

16β-Carbomethoxycleavamine (**31**):

R = CO_2CH_3



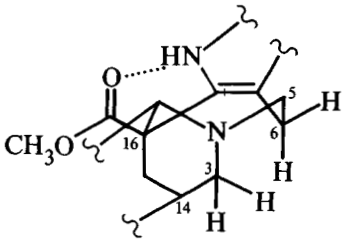
16β-Carbomethoxydihydrocleavamine (32):

$R^1 = CO_2CH_3$, $R^2 = H$

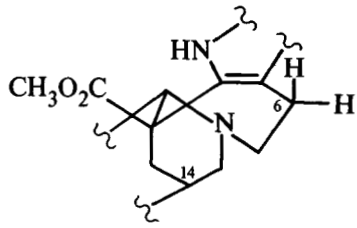
Velbanamine (**33**): $R^1 = H$, $R^2 = OH$

16β-Carbomethoxyvelbanamine (**34**):

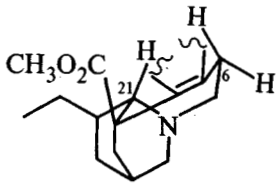
$R^1 = CO_2CH_3$, $R^2 = OH$



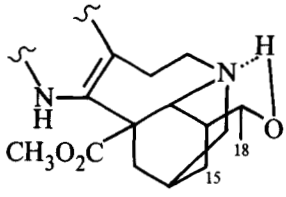
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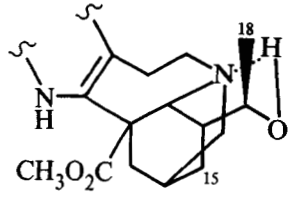
36



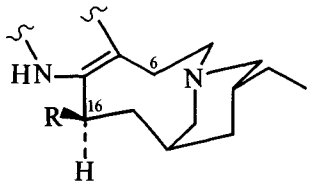
37



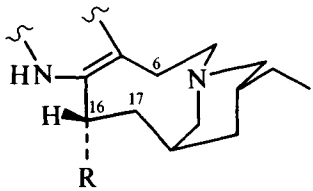
38



39



40



41

the second due to the aromatic moiety. In the case of ibogamine (**10**) these ions are at *m/e* 122, 124, 135, and 149 for one series and at *m/e* 156, 175, 251, and 266 for the second series. A rationalization of the formation of these fragments is shown in Scheme 3 as implied by deuterium labeling studies.[41]

5. *Absolute Configuration*

For many years it was thought that the iboga alkaloids existed in only one enantiomeric form; subsequently, however, this was shown not to be the case, which raises a biogenetically highly significant point.

The first evidence for an absolute configuration came from the X-ray determination of cleavamine,[43,44] which indicated the stereochemistry **30**. Since cleavamine (**30**) may be derived from catharanthine, and 16β-carbomethoxycleavamine (**31**) regenerates catharanthine (**28**), this establishes the absolute configuration of catharanthine.[45]

A serious error was made at this point, for it was assumed that since catharanthine (**28**) and ibogamine (**10**) could be interrelated they had the same absolute configuration, although no optical rotations of the corresponding derivatives were apparently made. The assignment of the cleavamine absolute stereochemistry could also be deduced from the X-ray structure analysis of leurocristine methiodide.[46]

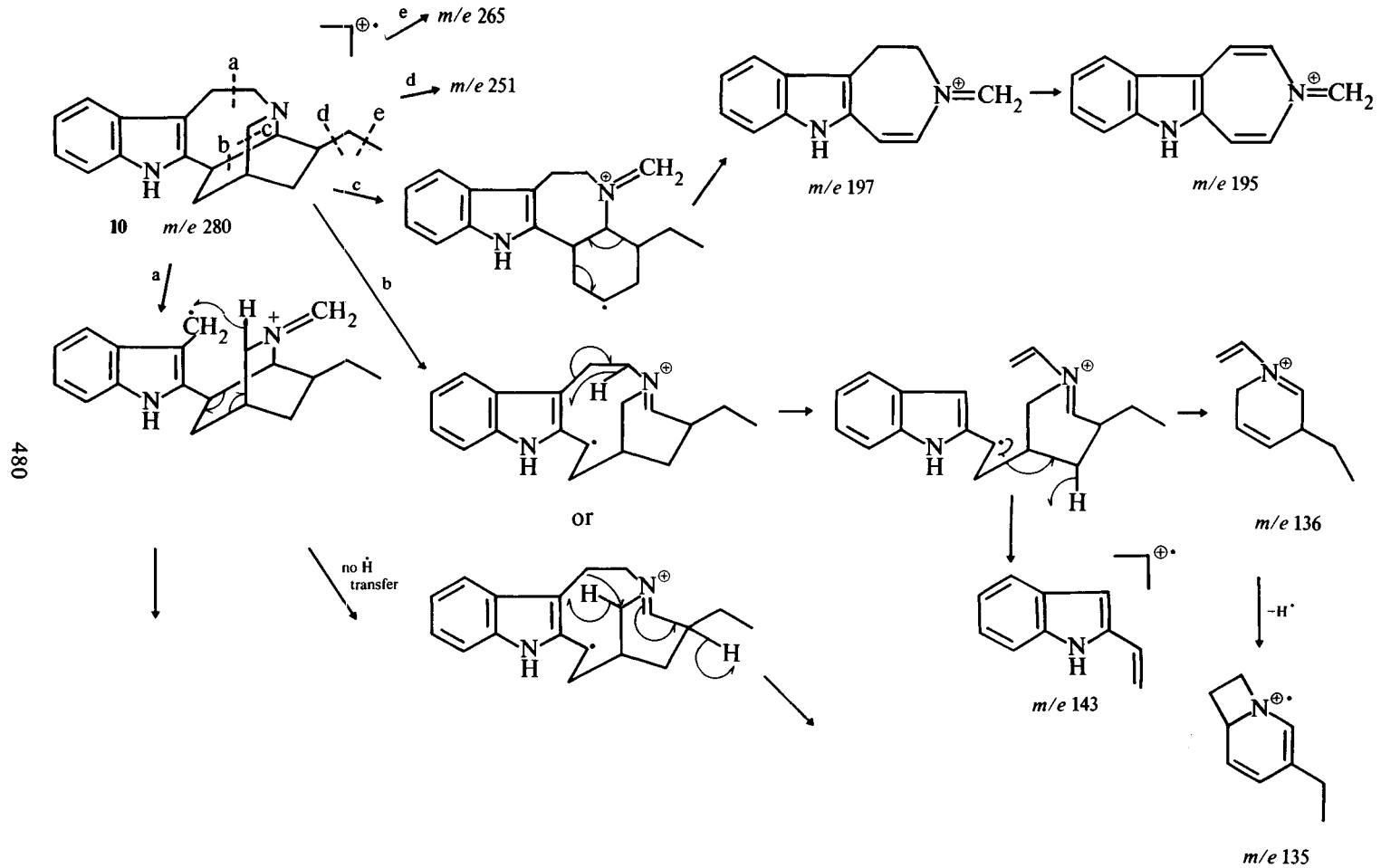
This situation was changed dramatically when Bláha and co-workers[47] examined the cd curves of a number of iboga alkaloids, for it was found that dihydrocatharanthine (**29**) and (−)-coronaridine (**20**) showed similar Cotton effects but of *opposite* sign. Further, when the other natural iboga alkaloids were examined they were found to be in the same antipodal series as (−)-coronaridine (Table IV). Since the absolute configuration of catharanthine had been established as **28**, (−)-coronaridine must be represented by **20**.

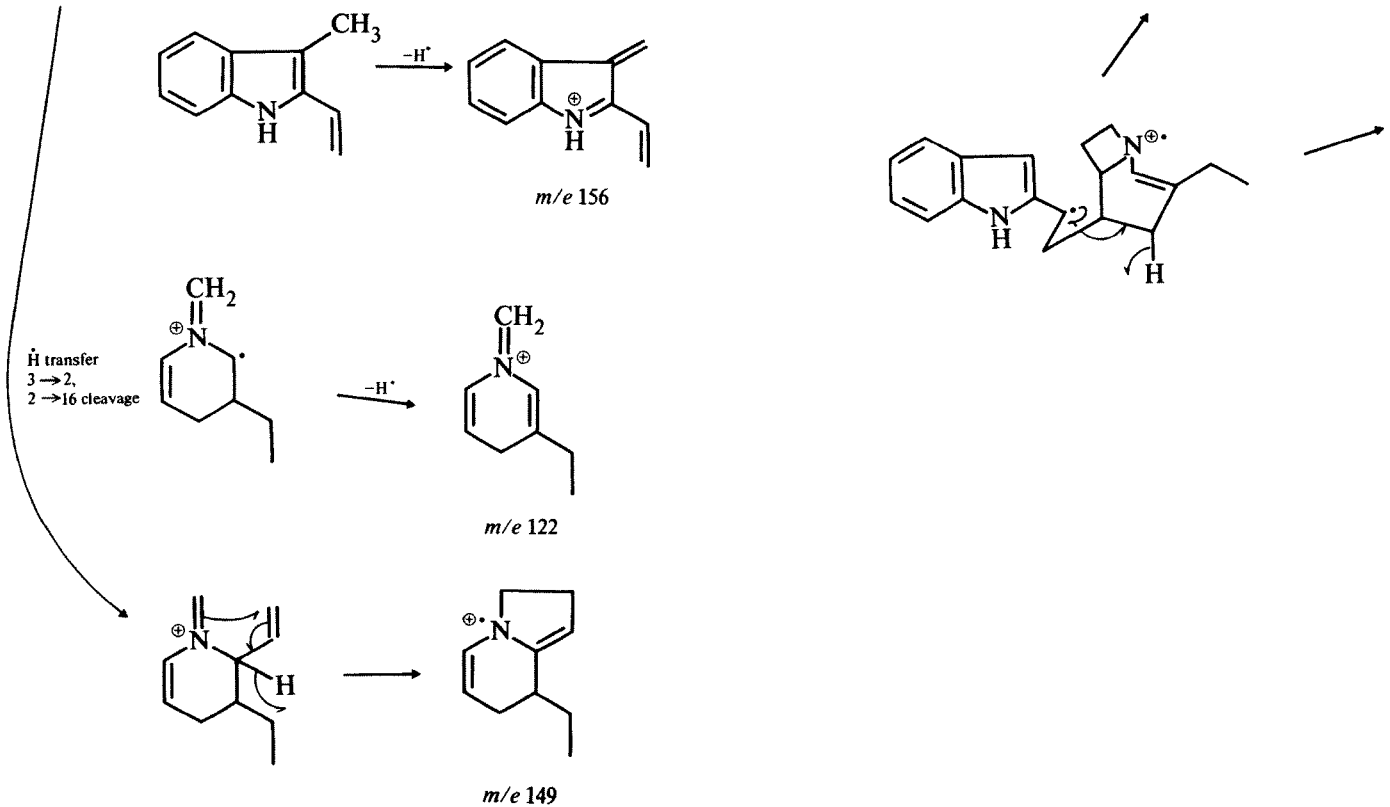
Subsequently, Kutney et al.[48] determined the absolute configuration of coronaridine hydrobromide to be the same as that deduced by Bláha et al. Furthermore, they showed that ord could also be used to distinguish between the antipodal series as shown in Table V. In determining the absolute configuration of any new iboga alkaloid it is recommended that both ord and cd measurements be considered.

The importance of these findings is biogenetic, for a rather special situation is evident with *Catharanthus roseus* which produces both (+)-catharanthine and (−)-coronaridine in the mature plant and in the late and early stages of germination.[48]

TABLE IV. CIRCULAR DICHROISM DATA FOR SOME REPRESENTATIVE IBOGA ALKALOIDS[47]

Alkaloid	λ_{max} $\Delta\epsilon$				
(—)-Ibogamine (10)	218	238	288		
	−8.9	+7.5	−0.4		
(—)-Coronaridine (20)	215	227, 231, 242	272, 277, 288, 296		
	−2.6	+3.3 +2.4 +5.0	−9.3 −8.1 −5.6 −2.1		
Voacangine (9)	225	251	281	312	
	−1.5	+2.5	−5.0	+0.7	
Isovoacangine (42)	217	239 250	277, 286, 301	307, 316	
	−1.5	+5.7 +4.5	−2.9 −2.5 −4.4	−3.7 −1.2	
Catharanthine (28)	219	242	270, 278, 286, 293		
	+3.3	−0.25	+3.2 +2.8 +1.9 +0.8		
Dihydrocatharanthine (29)	217	221, 229, 240	275, 281, 295		
	+1.5	−0.7 −2.9 −1.6	+3.7 +3.5 +2.5		


e
m/e 265
d
m/e 251
a
b
c
d
e
10 m/e 280
c
m/e 197
m/e 195
a
b
or
no Ḣ transfer
m/e 136
-Ḣ·
m/e 143
m/e 135



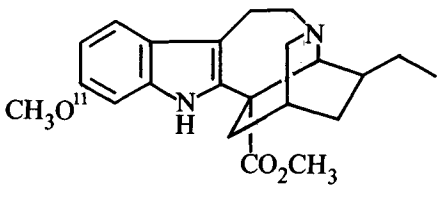
Scheme 3. Mass spectral fragmentation of ibogamine (10).[41]

IV. CHEMISTRY

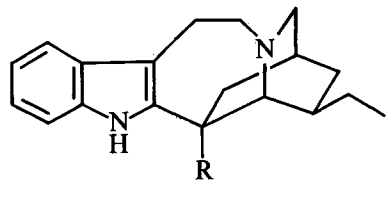
A. Normal Iboga Alkaloids

The chemistry of the iboga alkaloids is a rich and complex one[7,8] and no attempt will be made to discuss this area exhaustively. All the iboga alkaloids, with the exception of catharanthine (**28**), have a saturated 15,20 bond. However, the presence of a double bond at this position leads to a fascinating chemistry independent of that of the other alkaloids and consequently catharanthine (**28**) is the subject of a separate section.

Carbon atoms 3 and 7 of the iboga nucleus are particularly susceptible to oxidation and agents such as iodine/sodium bicarbonate,[22,49] platinum/oxygen,[49] chromium trioxide in pyridine,[22] or photosensitized oxidation in the presence of Rose Bengal or benzophenone[49] predominantly give the 3-oxo derivative, such as **45** [from ibogaine (**4**)] or **46** [from voacangine (**9**)]. Under mild conditions



Isovoacangine (**42**)



(+)-Coronaridine (**43**): R = CO_2CH_3

(+)-Ibogamine (**44**): R = H

TABLE V. OPTICAL ROTATORY DISPERSION DATA FOR SOME REPRESENTATIVE IBOGA ALKALOIDS AND DERIVATIVES[48]

Alkaloid (or derivative)	λ (nm) Φ			
	300	275	260	250
(+)-Catharanthine (**28**)	+7,892	−6,070	−11,537	−13,962
(+)-Coronaridine[a] (**43**)	+5,859	−6,348	−11,232	−6,103
(+)-Ibogamine[a] (**44**)	+1,200 (298)	−6,600 (270)		−1,800 (257)
(−)-Coronaridine (**20**)	−8,150 (304)	+15,400 (265)		
(−)-Ibogamine (**10**)	−1,460 (298)	+2,080 (270)		+2,500 (257)

[a] Semisynthetic derivatives from natural catharanthine.

($I_2/C_6H_6/H_2O$ overnight) voacangine (**9**) afforded the 3-hydroxy derivative **47** as a mixture of stereoisomers.[50]

Overoxidation with chromium trioxide may lead to a ketolactam such as **48**, or a hydroxyquinoline lactam **49** with oxygen followed by acid rearrangement (Scheme 4).[22] The latter reaction is quite characteristic of iboga alkaloids and may

occur in air with or without a catalyst.[21,22] The initial intermediate from **4** is a 7-hydroperoxy-7*H*-indolenine **50**, which can undergo acid rearrangement to iboquine (**51**) or be reduced to a 7-hydroxyindolenine derivative **14**. Alternative routes to the 7-hydroxyindolenine series have included aeration of a chloroform solution of the alkaloid,[51] as a by-product in the iodine/sodium bicarbonate reaction at 0°,[50] photosensitized oxidation,[49] oxygenation of the Grignard derivative of the alkaloid at 0°,[49] or most effectively (55% yield from **9**) with trifluoroperacetic acid.[51a]

Abstraction of the hydroxy proton of **14** with base leads to concomitant C-6 → C-2 migration and the formation of a 3-oxoindoline, for example, iboluteine (**17**).[22,49] An attempt to carry out a similar reaction with the hydroxyindolenine **52** from voacangine (**9**) was unsuccessful, but rearrangement to voaluteine (**53**) was effected with warm concentrated hydrochloric acid (Scheme 5).[49] In the presence of hydrogen peroxide and exposure to light, catharanthine (**28**) affords the pseudoindoxyl **54** directly.[52]

Reduction of the hydroperoxy derivative **50**[22] or the hydroxyindolenine **52**[49] with sodium borohydride or zinc and hydrochloric acid,[50] or the lactams **45** or **46** with lithium aluminum hydride,[22,49] regenerates the parent nucleus. But when iboluteine (**17**) is reduced with sodium borohydride, the intermediate alcohol **55** rearranges in acid by migration of C-16 to C-3 to afford a product **56** in which the indole nucleus is inverted.[53]

Iboluteine (**17**) is a ketone, and its *O*-tosyl oxime derivative **57** undergoes an interesting Beckmann fragmentation in refluxing pyridine to provide an anthranilonitrile **58** and an amino ketone **59**.[22]

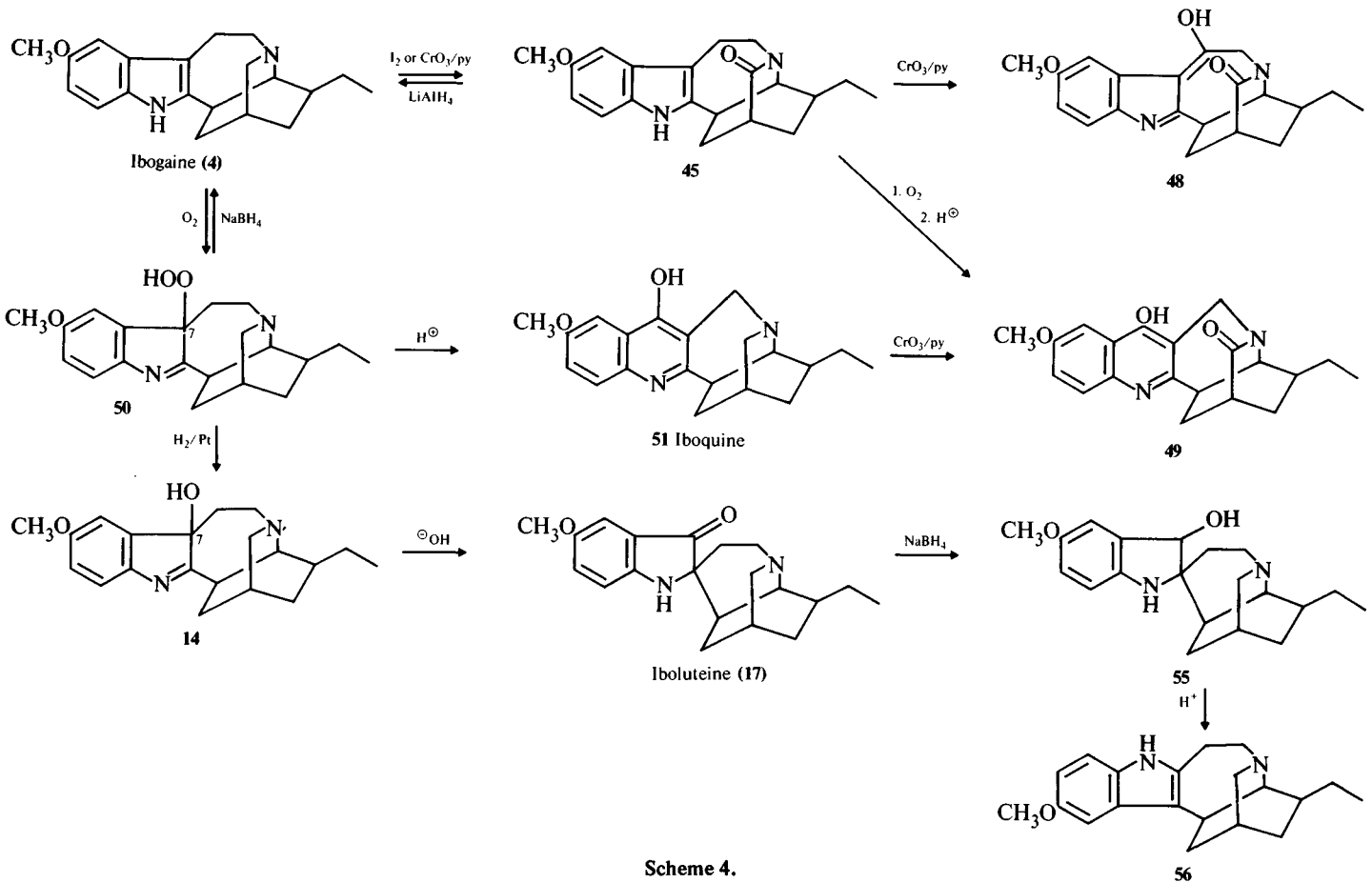
Iboxygaine (19-hydroxyibogaine) (**60**) contains a C-19 hydroxy group and the stereochemistry at C-20 can be determined using this functionality. Thus treatment with tosyl chloride in pyridine afforded a quaternary base **61**,[54] which could be reconverted into iboxygaine (**60**) with aqueous sodium hydroxide,[55] or into ibogaine (**4**) through lithium aluminum hydride reduction (Scheme 6).[56,57]

The facile loss of a carboxylic acid, amide, or hydroxymethyl group at C-16 of the iboga alkaloids has already been mentioned. As confirmation of the planarity of the system, voacanginol (**62**) forms an acetonide derivative **63** with acetone and dry hydrogen chloride (Scheme 7),[58] and a similar reaction was observed with catharanthine.[59]

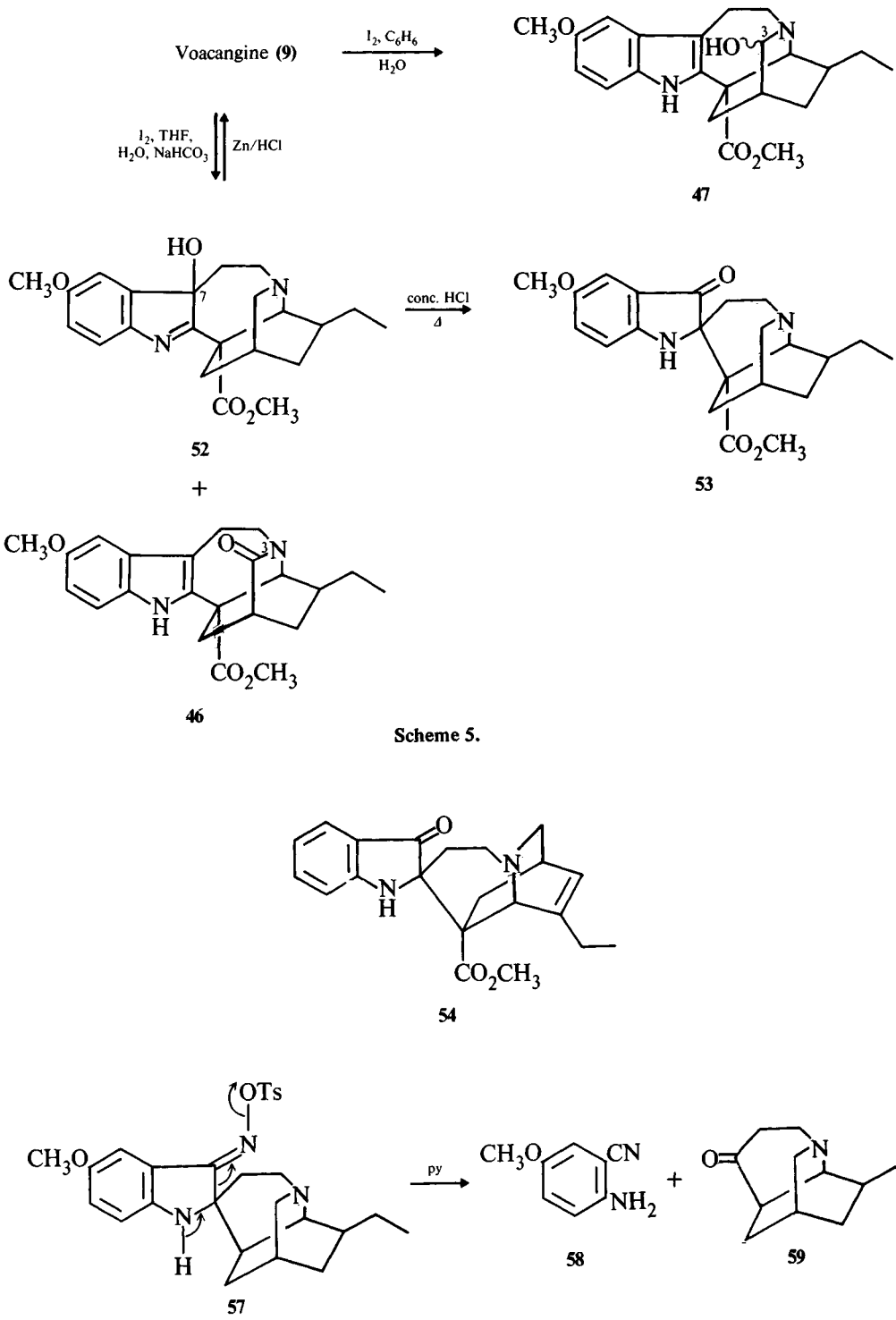
The tosylate of voacanginol (**64**) on treatment with triethylamine in warm benzene, however, affords a 16,21-secodiene **65**, which being an enamine can be reduced with sodium borohydride to the 2-vinylindole **66**.[60,61] Again this is a reflection of the coplanarity of the system and should be contrasted with the fragmentation of the tosylate of iboxygaine mentioned previously.

Alternatively, treatment of the tosylate of voacanginol (**64**) with methanolic pyridine in the presence of air for 48 hr afforded the β-carboline derivative voaketone (**67**) in about 25% yield. The same compound could also be obtained through oxidation of the enamine **65**.[62] The mechanism proposed for this remarkable transformation of **65** is shown in Scheme 8.

Yet another dramatic rearrangement occurred when the 7-chloro-7*H*-indolenine


CH3O
N
H
Ibogaine (4)
I2 or CrO3/py
LiAlH4
O2
NaBH4
HOO
7
50
H⊕
H2/Pt
HO
14
⊖OH
O
45
CrO3/py
OH
48
1. O2
2. H⊕
51 Iboquine
49
Iboluteine (17)
NaBH4
55
H+
56

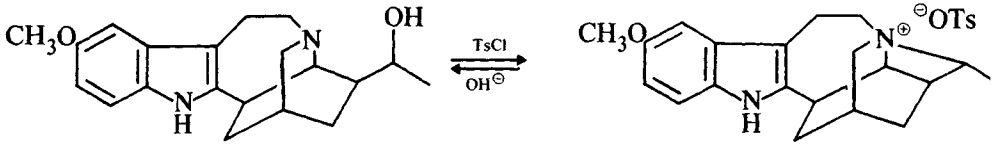
Scheme 4.


Voacangine (9)
I2, C6H6
H2O
I2, THF,
H2O, NaHCO3
Zn/HCl
47
52
conc. HCl
Δ
53
+
46

Scheme 5.

54

py
57
58
59

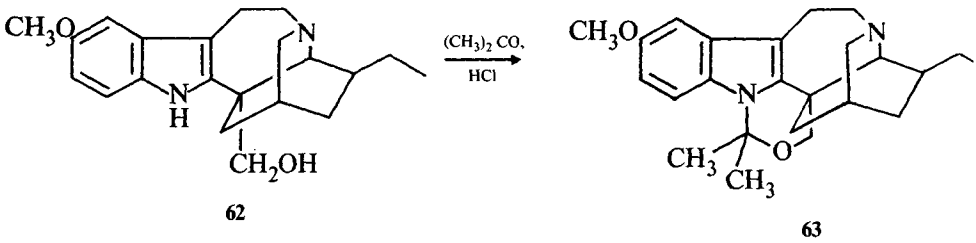


Iboxygaine (**60**) **61**



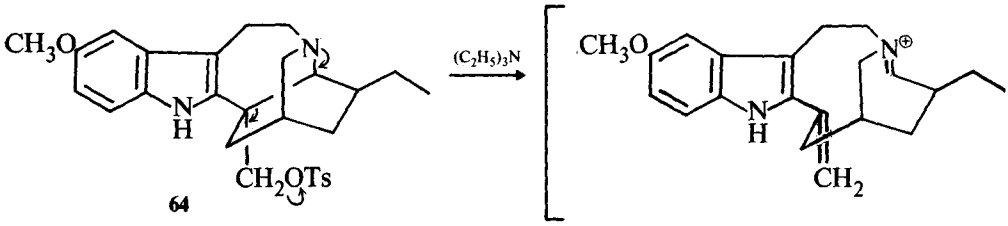
Ibogaine (**4**)

Scheme 6.

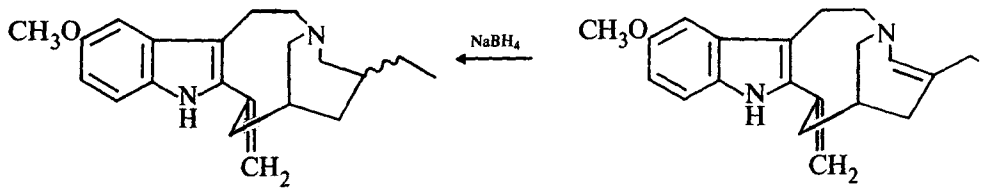


62 **63**



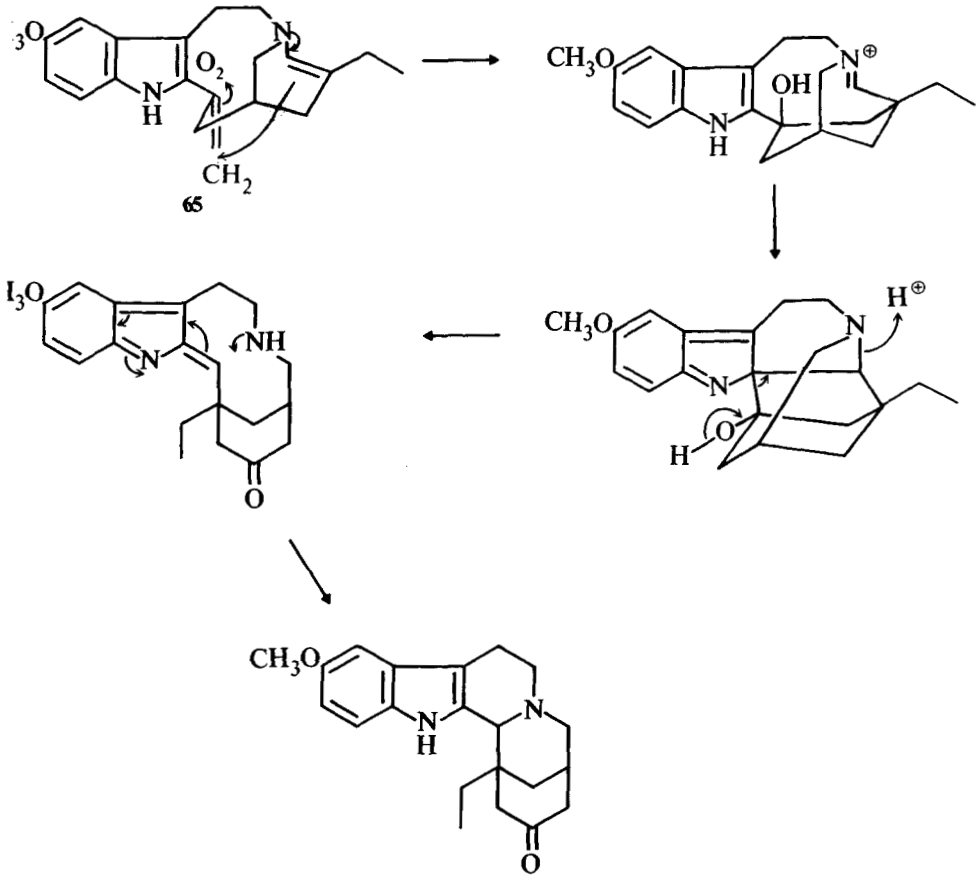


64



66 **65**

Scheme 7.

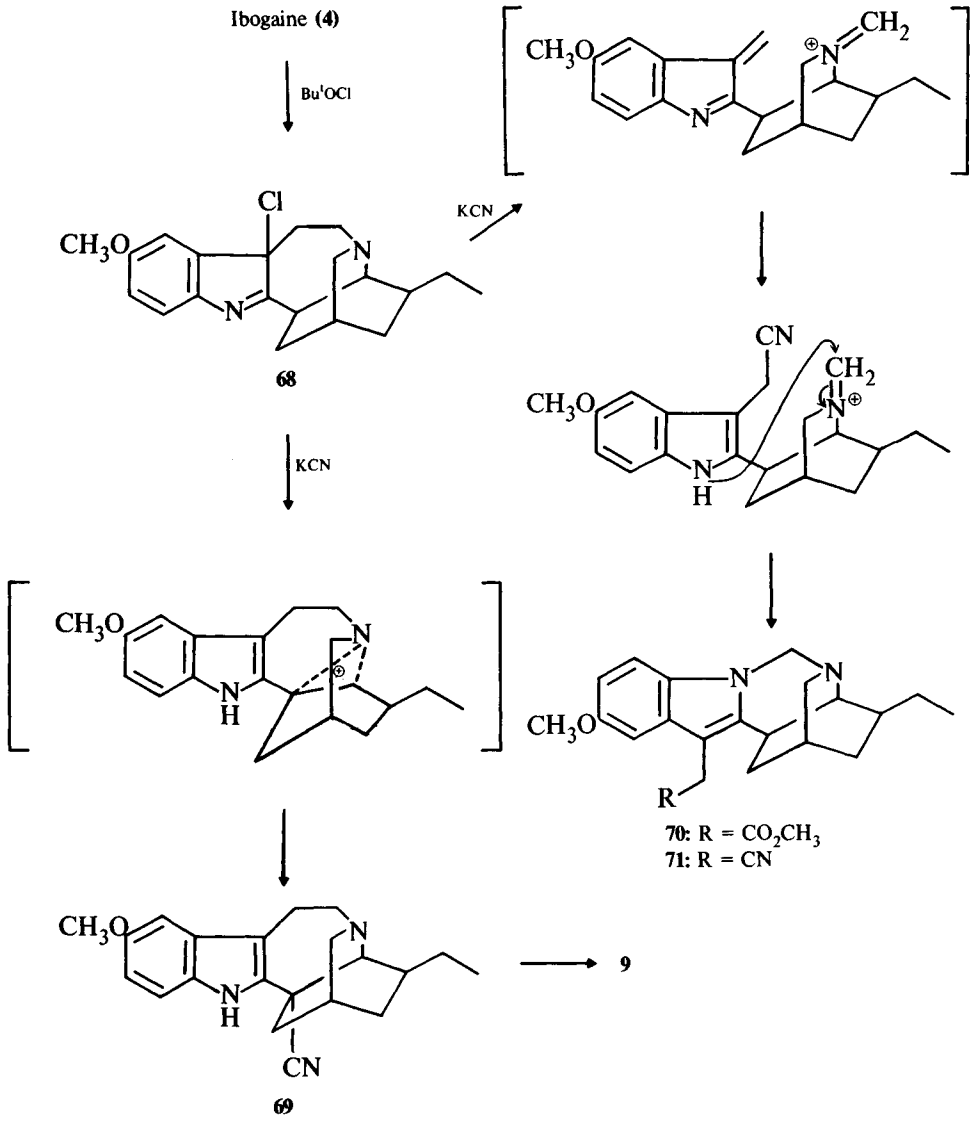


Voaketone (67)

Scheme 8. Formation of voaketone (67).[62]

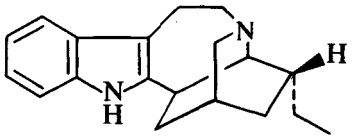
68, produced from ibogaine (4) with *t*-butyl hypochlorite, was treated with potassium cyanide to give 16-cyanoibogaine (69). A minor product, 70, was obtained after working up the mother liquors from 71 with methanolic hydrogen chloride followed by methanolic hydroxide.[63,64] Methanolysis of 69 permitted conversion to voacangine (9), thereby completing the reaction cycle (Scheme 9).

Formation of an internal quaternary salt was previously indicated to be one way to deduce the stereochemistry at C-20 if C-19 is substituted. If this is not the case the stereochemistry of the ethyl group may be determined by the rate of methylation of the basic nitrogen. Thus ibogamine (10) shows a rate of methylation of 0.23×10^4 per second whereas 20-epi-ibogamine (72) has a rate of methylation of 132×10^4 per second.[65]

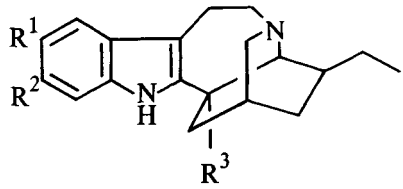


Scheme 9. Conversion of ibogaine (4) to voacangine (9).[63,64]

One of the new, structurally modified, iboga alkaloids to be obtained is eglandine (**26**) having an ether bridge between C-3 and C-6.[35] Sodium borohydride reduced the termini of the ether linkage to afford (−)-coronaridine (**20**), whereas lithium aluminum hydride gave coronaridinol (**73**). Similar reductions of 10-methoxy-eglandine (**74**) afforded voacangine (**9**) and voacanginol (**62**),[36] and 11-methoxy-eglandine (3,6-oxidoisovoacangine) (**75**) gave isovoacanginol (**76**).[66]



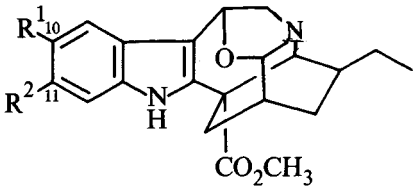
72



76: $R^1 = H, R^2 = OCH_3, R^3 = CH_2OH$

62: $R^1 = OCH_3, R^2 = H, R^3 = CH_2OH$

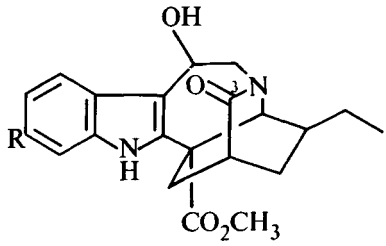
73: $R^1 = R^2 = H, R^3 = CH_2OH$



Eglandine (26): $R^1 = R^2 = H$

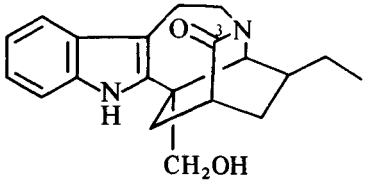
10-Methoxyeglandine (74): $R^2 = H, R^1 = OCH_3$

11-Methoxyeglandine (75): $R^2 = OCH_3, R^1 = H$

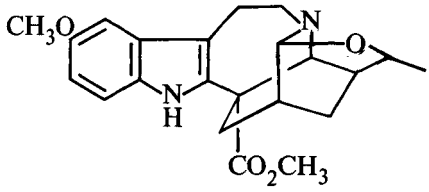


Eglandulosine (77): R = H

79: $R = OCH_3$



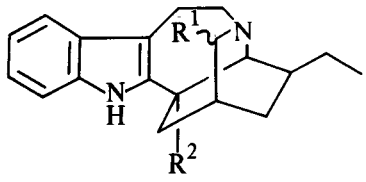
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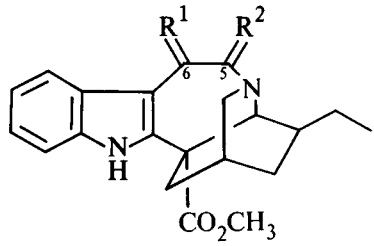
Heyneatine (27)

Co-occurring with eglandine (**26**) in *Gabunia eglandulosa* Stapf was eglandulosine (**77**) which could be reduced with lithium aluminum hydride to a mixture of **73** and 3-oxocoronaridinol (**78**); 6-hydroxy-3-oxoisovoacangine (**79**) afforded corresponding products.[66] Oxidation of coronaridine (**20**) with chromium trioxide-pyridine afforded eglandulosine (**77**) in 70% yield, and eglandine (**26**) was obtained (58% yield) by oxidation of **20** in basic ($NaHCO_3$) aqueous tetrahydrofuran in the presence of iodine.[35,37] The corresponding 3,6-oxidoibogaine and iboxygaine derivatives are also known.[67a]

Tabernaemontana glandulosa Stapf has yielded 3-oxygenated derivatives including 3-hydroxy-[67b] and 3-ethoxycoronaridines (**79a** and **79b**)[67c] and 3-hydroxyibogamine (**79c**).[67b] The stereochemistry at C-3 in **79b** was deduced to



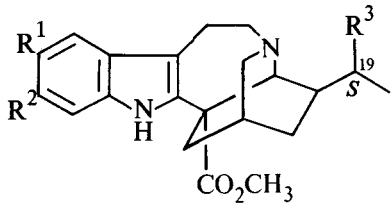
	R^1	R^2
79a	OH	CO_2CH_3
79b	OC_2H_5	CO_2CH_3
79c	OH	H



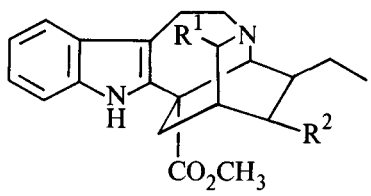
	R^1	R^2
79d	H_2	O
79e	O	H_2
79f	O	H,OH

be a 17:3 mixture. 5-Oxo- and 6-oxo-coronaridines (**79d** and **79e**) were recently isolated from *T. divaricata* R. Br. ex Roem. et Schult.[67d] A pair of doublets centered at 3.91 ppm were observed for the C-6 methylene in **79d**, whereas in **79e** the C-5 protons appeared at 3.33 and 1.80 ppm. 5-Hydroxy-6-oxocoronaridine (**79f**) was also isolated[67d] where H-9 appeared at 8.77 ppm. Oxidation of coronaridine with potassium permanganate in acetone gave **79d** and **79e**, each in 5% yield.

A different ether linkage is present in heyneatine (**27**), from *Ervatamia heyneana* (Wall.) T. Cooke, where the structure and stereochemistry were determined by sodium borohyride reduction to voacristine (**24**).[36] Three phenolic alkaloids, the 10- and 11-hydroxyheyneanines (**79g** and **79h**) and 11-hydroxycoronaridine (**79i**), have been isolated from an *Anartia* species,[40b] and **80** has been obtained from *Tabernanthe pubescens*[67a] and *E. heyneana*.[36]



	R^1	R^2	R^3
79g	OH	H	OH
79h	H	OH	OH
79i	H	OH	H
80	OH	H	H



	R^1	R^2
81	=O	H
82	=O	OH
83	H_2	OH

There have been few studies of the microbial transformation of any iboga alkaloids, but Garnier[68] has examined the action of the organism *Sporotrichum sulfurescens* V. Beyma and *Cunninghamella blackesleana* Lendner on coronaridine (**20**). The former produced 10-hydroxycoronaridine (**80**), 3-oxocoronaridine (**81**),

and its corresponding 15-hydroxy derivative **82**. *C. blackesleana* afforded a mixture from which 15-hydroxycoronaridine (**83**) was obtained.

B. Catharanthine

Catharanthine is the only iboga alkaloid containing an olefinic bond; this functionality leads to some interesting chemistry.

Hydrogenation of catharanthine (**28**) led to a single isomer, dihydrocatharanthine (**29**), in which the 20-ethyl group is α.[69] Like voacangine (**9**), **29** could be readily decarbomethoxylated to 20-epi-ibogamine (**72**).[59]

The fragile nature of the 16,21 bond in catharanthine (**28**), which is key to so much of its chemistry, was first demonstrated in 1963 when Kutney et al.[43] and Neuss and co-workers[9,70,71] described the formation of cleavamine (**30**)[44] by treatment with concentrated hydrochloric acid, preferably with added stannous chloride.

At that time cleavamine had previously been obtained through the acid-catalyzed cleavage of vincaleukoblastine and leurosine,[70] and therefore this reaction of catharanthine constituted interesting evidence for the indole "half" of the dimers.

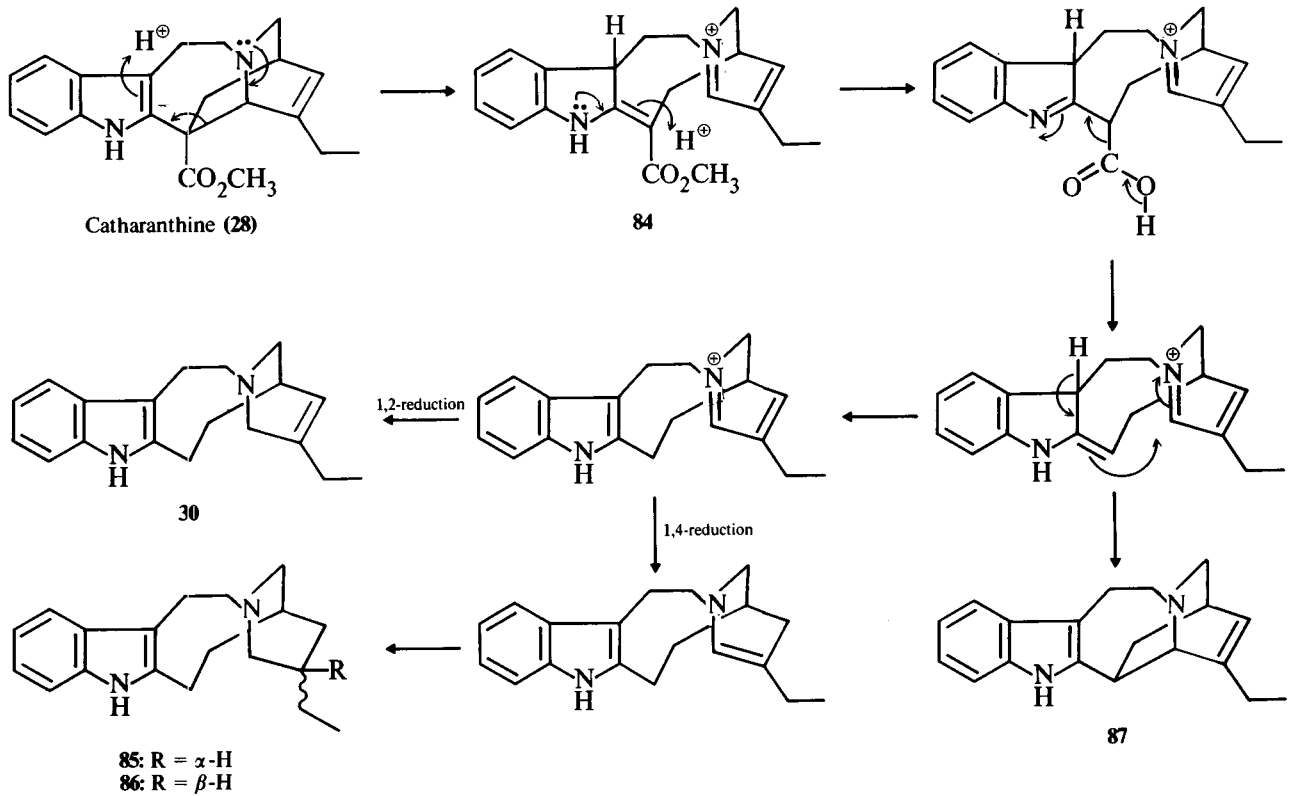
This reaction is regarded as proceeding by way of the retro-Mannich product **84**, which may be decarbomethoxylated and reduced to cleavamine (**30**) and the 20-epimeric dihydrocleavamines **85** and **86**, or recycled with concomitant decarboxylation to **87** (Scheme 10).[9,17,72]

Of great similarity to the unit present in the dimers were the 16β-carbomethoxydihydrocleavamines (**32**), formed by treatment of **28** with zinc and acetic acid,[71,73] or 16β-carbomethoxycleavamine (**31**) with sodium borohydride in acetic acid. A preferred route to **32** is reaction of catharanthine (**28**) with trifluoroacetic acid at 60° followed by reduction[73a]; the 16*S* isomer predominates (3:1) in an almost quantitative reaction.

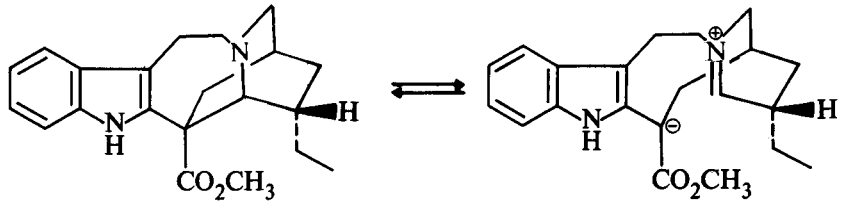
Closely related immonium species have also been proposed to explain (1) the formation of 20-epi-ibogamine (**72**) (no absolute stereochemistry implied) when either coronaridine (**20**) or dihydrocatharanthine (**29**) is refluxed in concentrated hydrochloric acid,[74] and (2) the epimerization of dihydrocatharanthine (**29**) to (+)-coronaridine (**43**) on prolonged reflux (72 h or more) in glacial acetic acid (Scheme 11).[71]

Perhaps the most interesting reaction reported, somewhat innocuously, by Gorman et al.[71] was that refluxing catharanthine (**28**) in glacial acetic acid afforded racemic pseudotabersonine* (**88**) in 45% yield after only 2½ hours. Subsequently, the survival of catharanthine in refluxing glacial acetic acid became a matter of some controversy.[12] It is now firmly established[75–77] that refluxing tabersonine (**89**) in glacial acetic acid does not give catharanthine (**28**) or pseudocatharanthine (**88**), but rather the three compounds allocatharanthine (**90**), dihydroallocatharanthine (**91**), and acetoallocatharanthine (**92**) (Scheme 12). These compounds are members of a new series of compounds which are structurally isomeric with the iboga alkaloids.

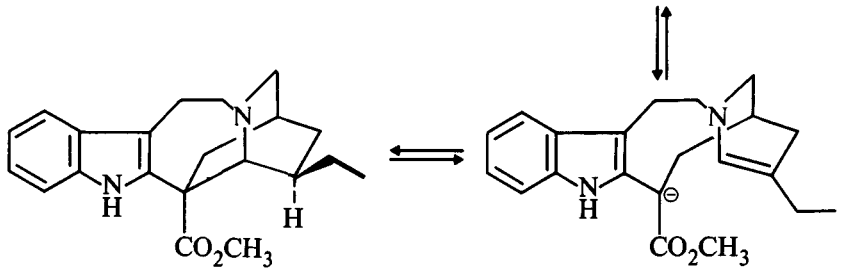
* This compound is also known as pseudocatharanthine.



Scheme 10. Formation of cleavamine (30) and the dihydrocleavamines (85/86) from catharanthine (28).[9,71,72]

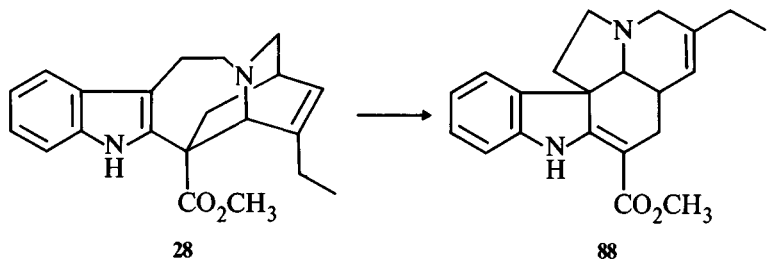


Dihydrocatharanthine (29)

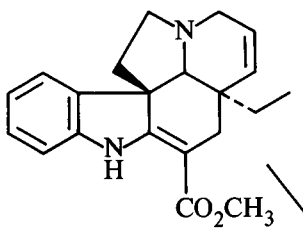


(+)-Coronaridine (43)

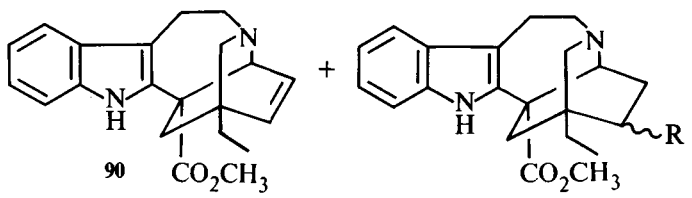
Scheme 11. Equilibration of dihydrocatharanthine (29) and (+)-coronaridine (43).[71]



28 88



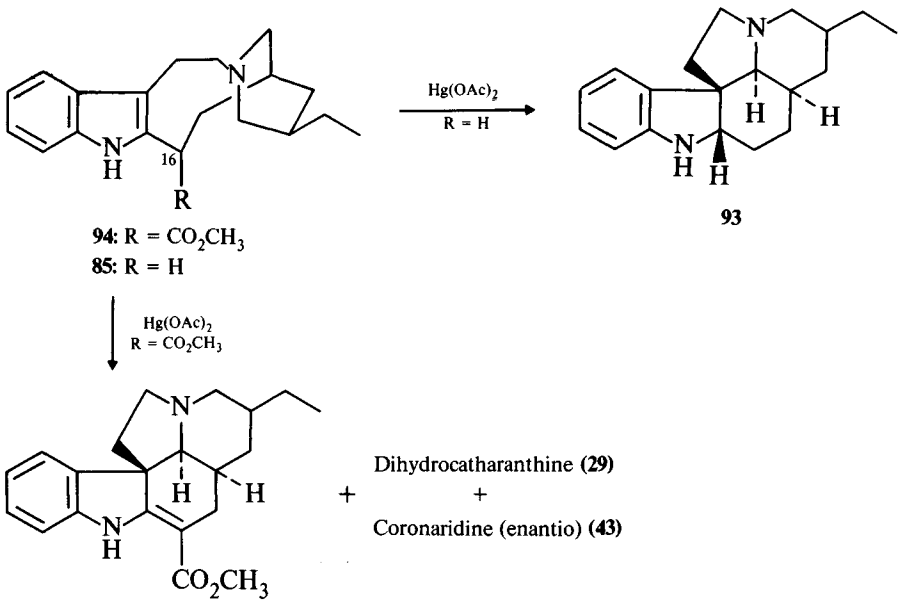
Tabersonine (89)



90 91: R = H
92: R = OAc

Scheme 12.

The availability of the cleavamines led Kutney and co-workers[78–83] to investigate their oxidative cyclization products which could potentially yield the pseudo-*Aspidosperma* skeleton (oxidation at N-4, C-3) or the iboga skeleton (oxidation at N-4,C-21). Thus mercuric acetate oxidation of dihydrocleavamine (**85**) gave pseudoaspidospermidine (**93**), whose structure was determined by X-ray analysis (Scheme 13).[84] Similarly, 16α-carbomethoxy-20α-dihydrocleavamine (**94**)[73] afforded pseudovincadifformine (**95**) and the two C-20 epimeric dihydrocatharanthines **29** and **43**,[78,80,81,83] and oxidation of 16β-carbomethoxycleavamine (**31**) [$Hg(OAc)_2$, HOAc, r.t.] gave pseudotabersonine (**88**) (29% yield) and catharanthine (**28**) (5% yield).[78,83] Such processes are necessarily stereospecific.

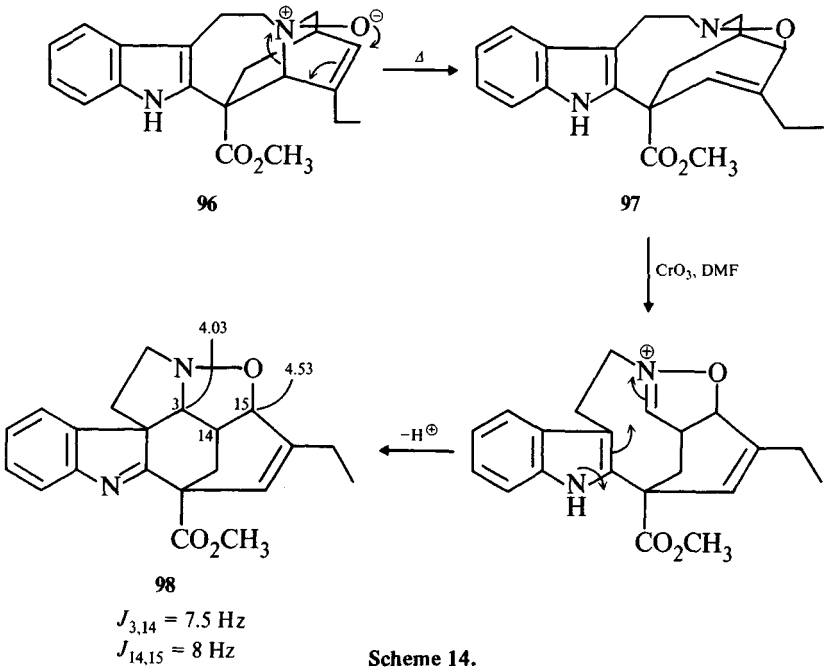


Scheme 13.

Langlois and co-workers[85,86] have described two novel rearrangements of catharanthine *N*-oxide (**96**) (Scheme 14). In one of these,[86] **96** is refluxed in chloroform for 3 hours, whereupon the isoxazolidine **97** is produced quantitatively. This reaction, which is remarkable for its ease, is thought to occur by way of a [2,3]-sigmatropic rearrangement as shown. The structure was established through spectral studies and X-ray analysis.

Chromic acid oxidation of **97** afforded the internally cyclized derivative **98**, which showed some stereochemically very informative coupling constants for $J_{3,14}$ and $J_{14,15}$.[86]

Hydrogenolysis of **97** afforded the allylic alcohol **99** which on oxidation[87,87a] underwent internal Michael addition (Scheme 15). Epimerization with trifluoroacetic acid gave 15-oxo-15,20-dihydrocatharanthine (**100**) exclusively, which could be reduced with L-selectride to 15*R*-hydroxy-15,20*S*-dihydrocatharanthine



Scheme 14.

(**100a**).[87a] Attempts to recyclize **99** directly to **28** failed, but the corresponding 15-acetate afforded **28** in 40% yield with $Pd(PC_6H_5)_4$ as a catalyst.[87b]

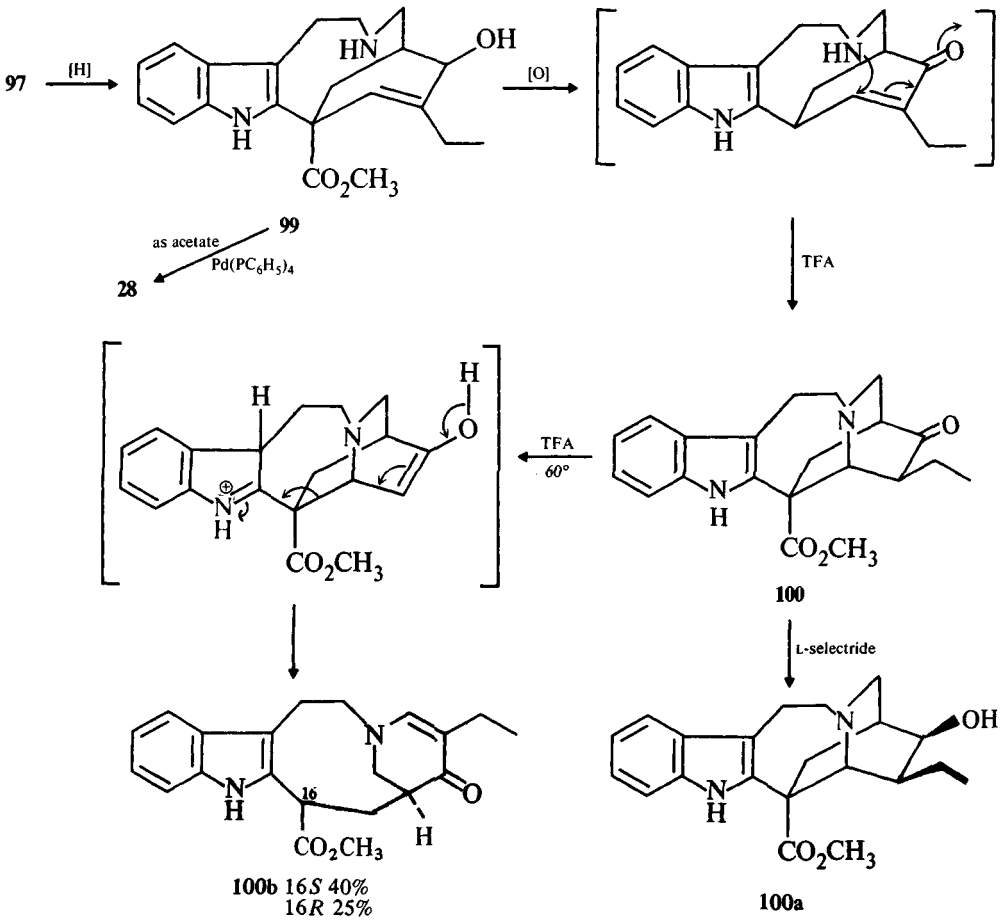
The second rearrangement is the result of a fragmentation of the 5,6 bond of **96** under Polonovski conditions (Scheme 16). The intermediate **101** is similar to one observed previously by Büchi et al. in the ibogaine series,[63,64] but in this instance it is trapped by a nucleophilic acetate anion to yield **102** in up to 40% yield. Further reaction of **100** with trifluoroacetic acid at 60° led to 16,21 cleavage possibly by way of the enol form to afford **100b**.[73a]

Kutney et al.[88,89] have further developed the chemistry of catharanthine (**28**) with a view to providing new monomer units to couple with vindoline.

Electrophilic additions to the olefinic linkage of catharanthine (**28**) are inevitably made more complex by the basic nitrogen and the indole nucleus. Kutney found that protection of either group was preferable and N_a-carbomethoxy-3-oxocatharanthine (**103**) was used for much of the chemistry.

Deprotection, hydrolysis, and iodolactonization of **103** gave **104**, which is a useful compound because it can be reduced and esterified to 20α-hydroxy-3-oxodihydrocatharanthine (**105**) or methanolized to the epoxide **106** (Scheme 17).[88,89]

Epoxidation of **103** followed by diborane reduction and removal of the protecting group gave 15β,20β-epoxydihydrocatharanthine (**107**). Osmylation of **103** introduced two β hydroxy groups at C-15 and C-20, and the initial product **108** could be converted into **109**, which is of potential use in the synthesis of the

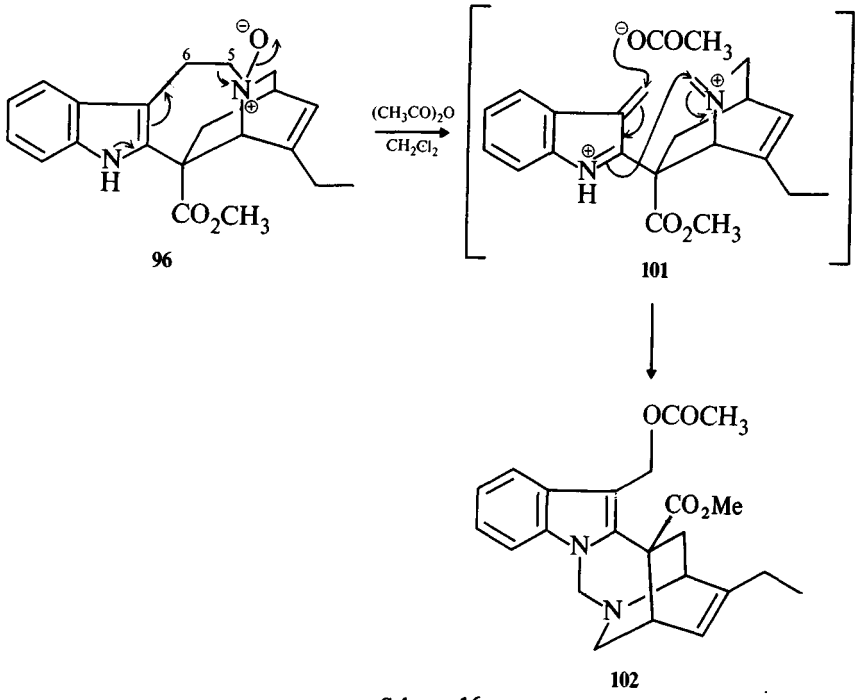


Scheme 15.

bisindole vincadioline.[88,89] The conversion into **107** could also be carried out through reduction of the thiolactam corresponding to **110**.[89]

Potier has also investigated the formation of catharanthine lactone (**111**) by an alternative route involving saponification of the ester with barium hydroxide, cyclization with mercuric chloride to **112**, and demercuration with basic sodium borohydride (Scheme 18).[90]

Honma and Ban[91] have also developed syntheses of the lactones and epoxides reported by Kutney and Potier, although certain steps utilized different reagents and no nitrogen protection was afforded. Thus catharanthine (**28**) was oxidized with mercuric acetate directly to the lactam **110a** (42% yield), which on hydrolysis and iodolactonization afforded **104** (60% yield) (Scheme 19). Reductive elimination of iodine and diborane reduction of the lactam afforded catharanthine lactone (**111**). Hydrolysis of **111** gave an intermediate hydroxy acid (**113**) which could not be esterified with diazomethane (cf. Kutney et al.[88,89]).



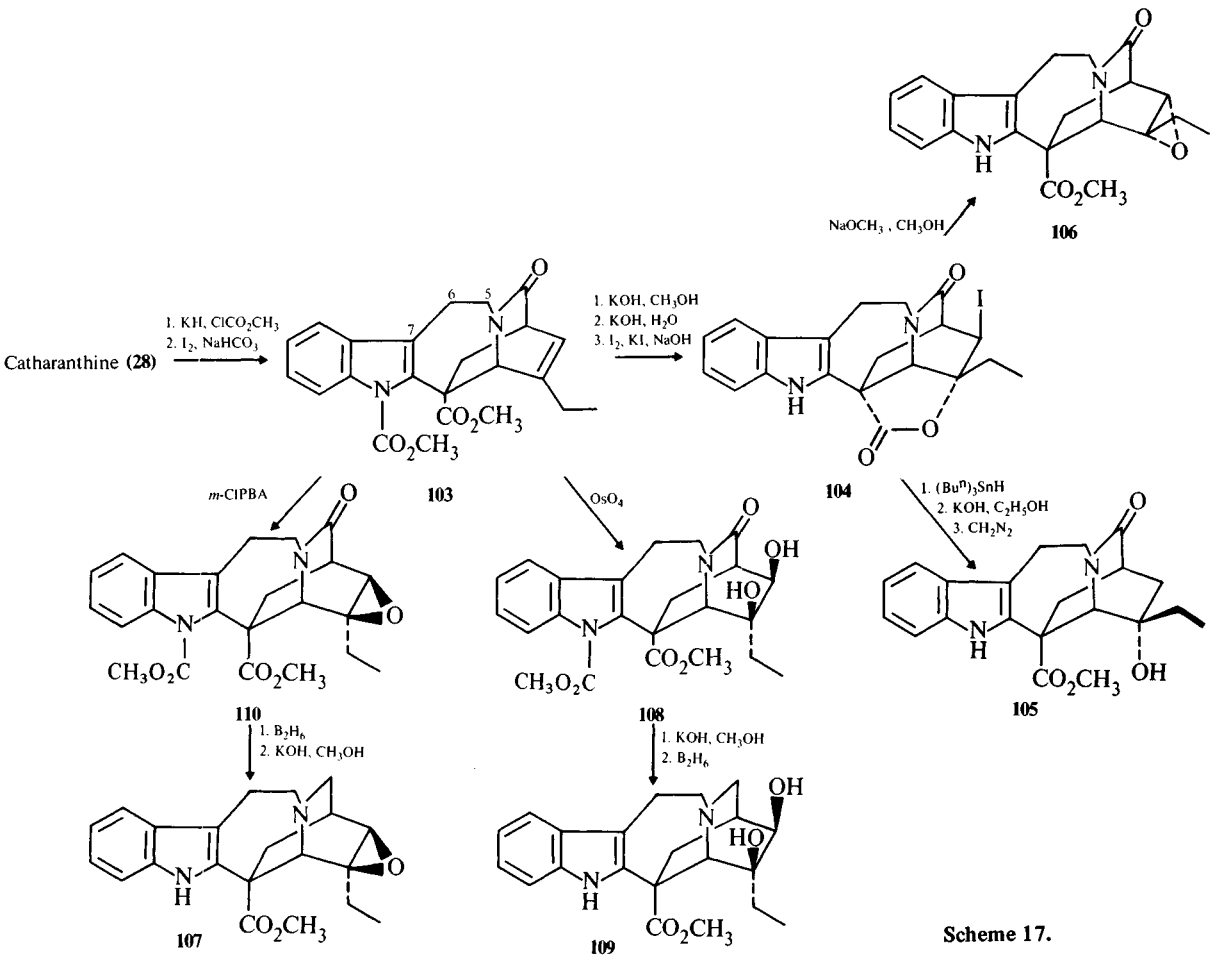
Scheme 16.

The epoxide **106** was obtained from the iodolactone **104** with methoxide anion. Selective reduction of the lactam carbonyl with diborane was not possible (cf. reaction on **108** by Kutney et al.[88,89]), but immonium ion formation with Meerwein's reagent followed by sodium borohydride reduction afforded the α-epoxide derivative **114**.[91]

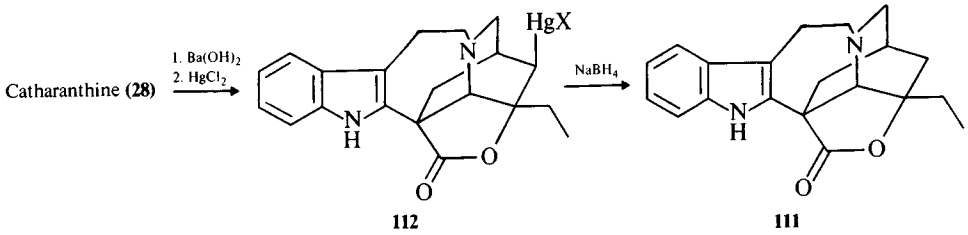
Mangeney and Langlois[92] have reported an alternative synthesis of catharanthine lactone (**111**) involving reaction of the mercurilactone derivative **112** with sodium amalgam or tetrabutyl ammonium borohydride in 1:1 methanol:carbon tetrachloride (Scheme 20). A slightly different solvent composition for the borohydride reduction, however, afforded a mixture of the 15-hydroxy epimers of catharanthine lactone (**115** and **116**).[92]

Under the normal conditions [$MeOH/H_2O/Hg(OAc)_2$] of oxymercuration, catharanthine carboxylic acid (**117**) underwent another rearrangement to afford **118**,[92] and the mechanism shown in Scheme 21 has been proposed.

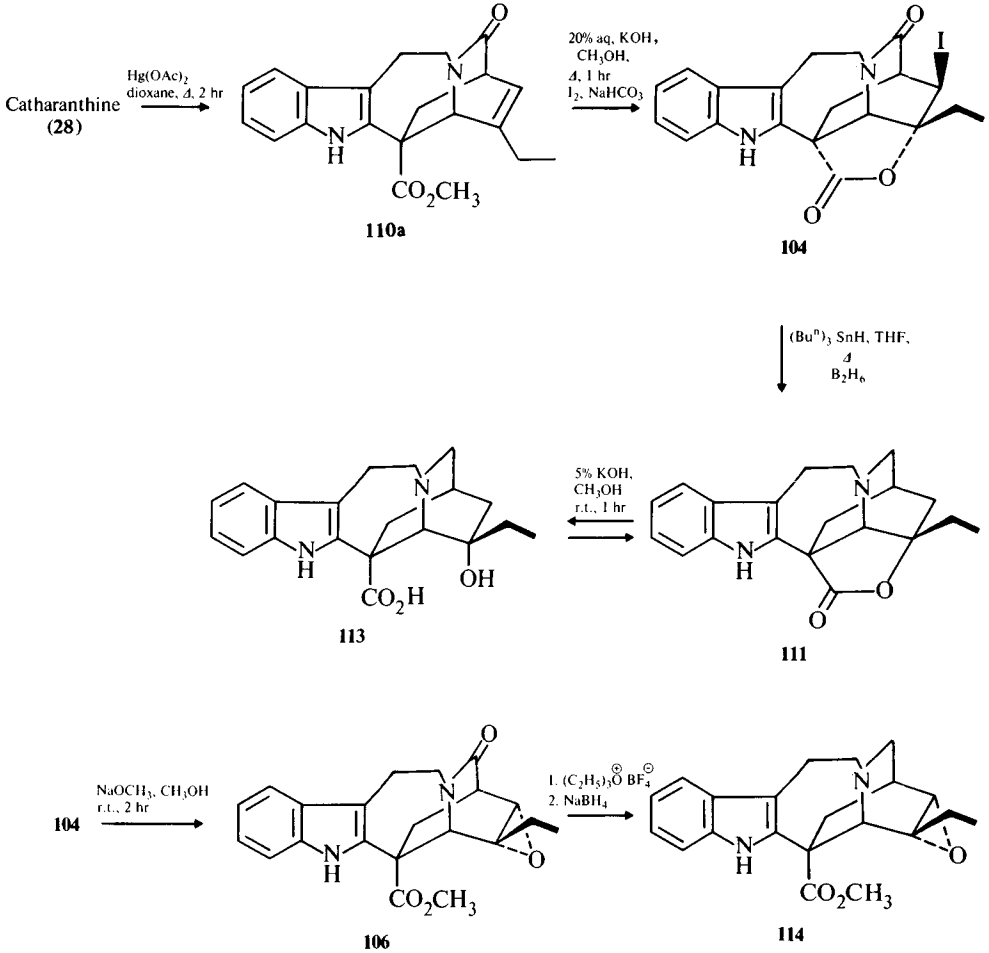
The structure of **118** was confirmed by an alternative synthesis from **28** involving von Braun degradation, hydrolysis, lithium aluminum hydride reduction, and mercuric ion assisted methanolysis of the intermediate diene **119** (Scheme 22).[92] Methanolysis of the diene nitrile **120** gave the methoxyimine **121**, which, on attempted acid hydrolysis, afforded decarbomethoxycatharanthine (**87**) rather than the expected diene **119**.[92]


Catharanthine (28)
1. KH, ClCO2CH3
2. I2, NaHCO3
1. KOH, CH3OH
2. KOH, H2O
3. I2, KI, NaOH
NaOCH3, CH3OH
106
103
104
m-ClPBA
OsO4
1. (Bu^n)3SnH
2. KOH, C2H5OH
3. CH2N2
110
108
105
1. B2H6
2. KOH, CH3OH
1. KOH, CH3OH
2. B2H6
107
109

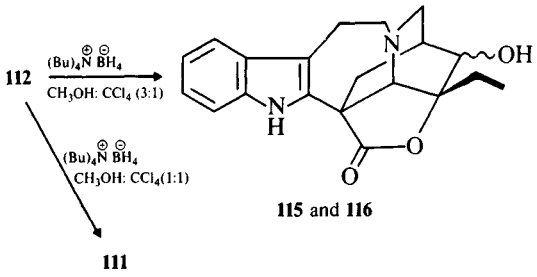
Scheme 17.



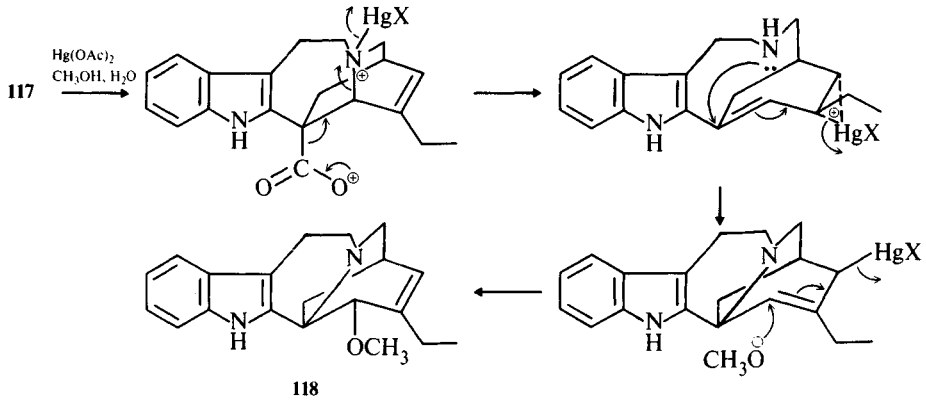
Scheme 18.



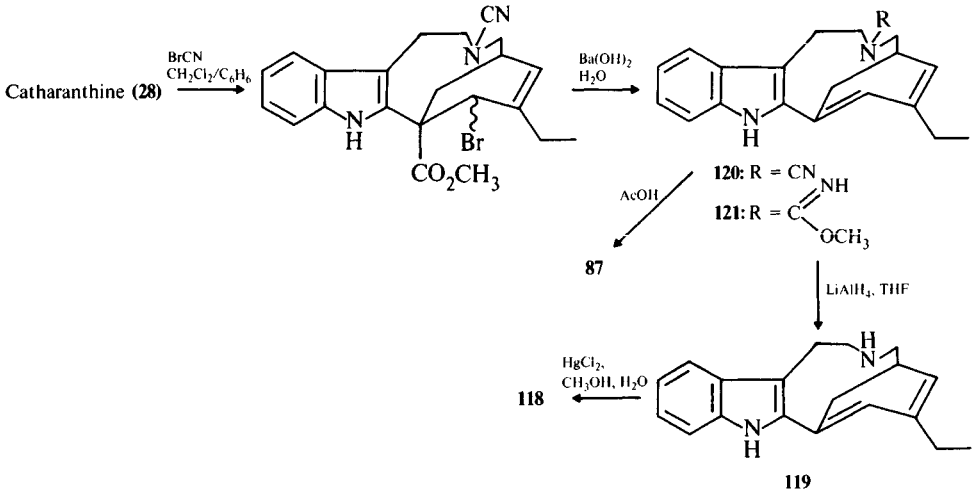
Scheme 19.



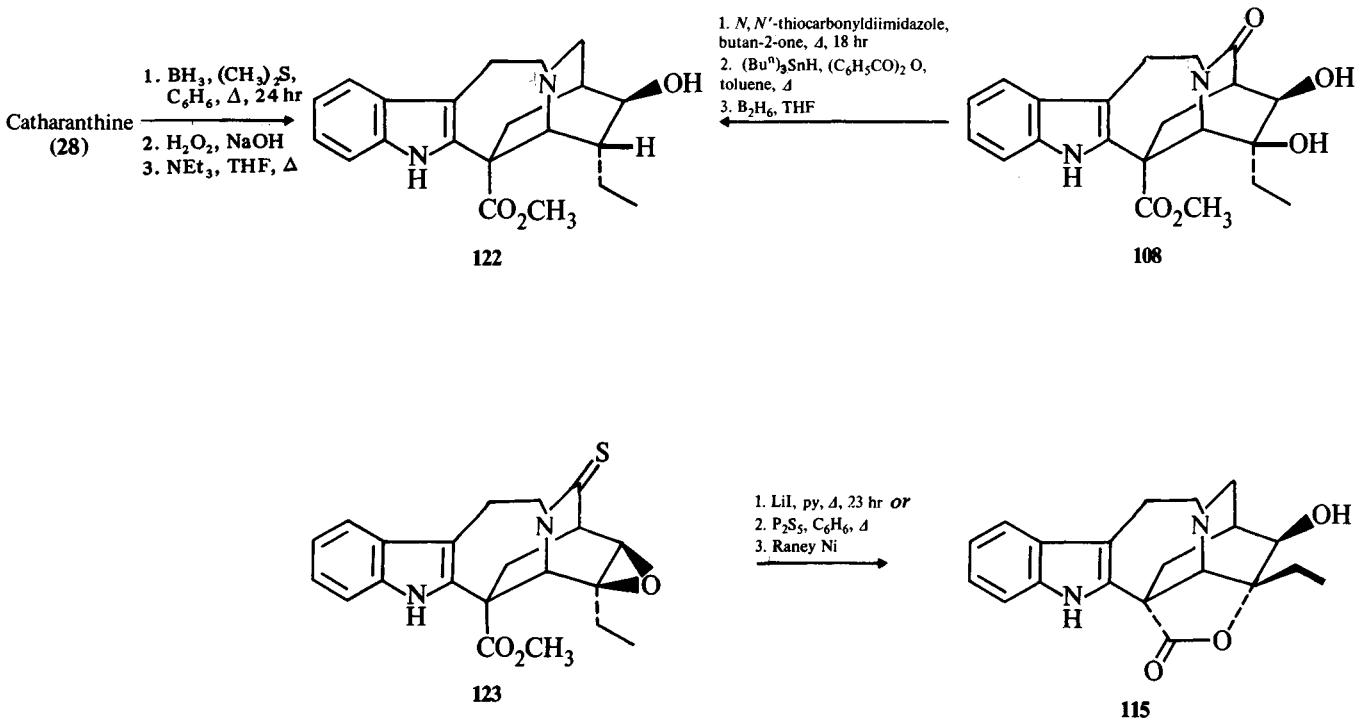
Scheme 20.



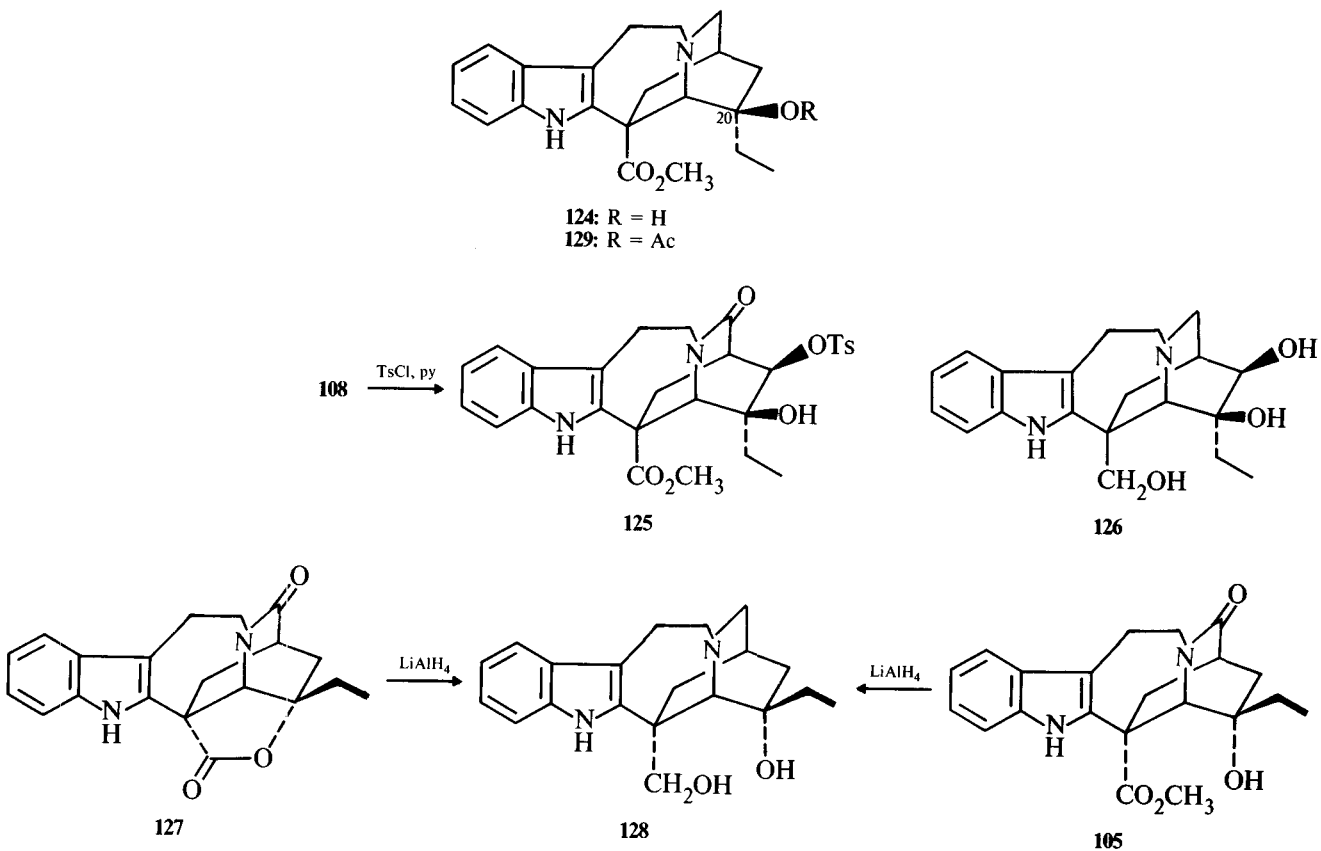
Scheme 21.



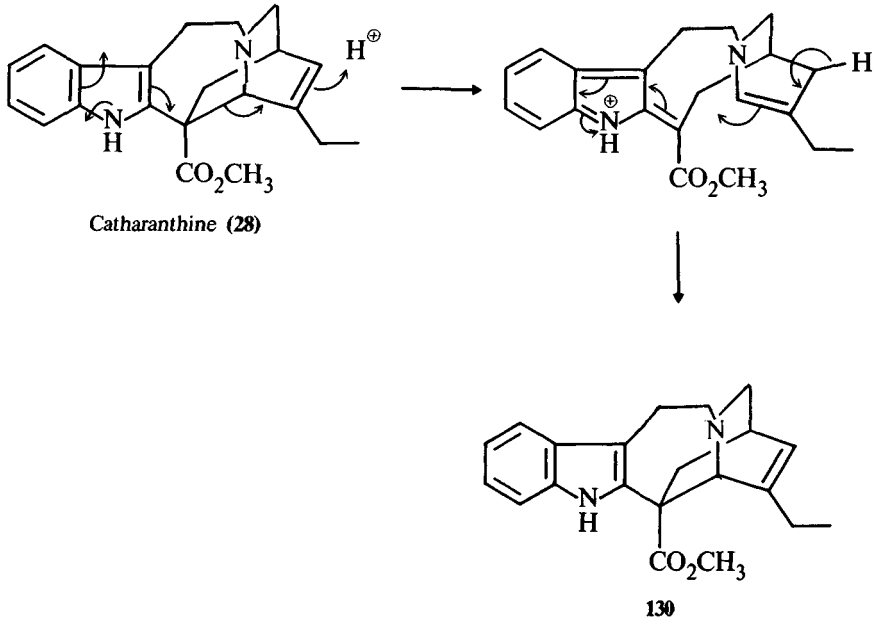
Scheme 22.


Catharanthine
(28)
1. BH_3, $(CH_3)_2S$, C_6H_6, Δ, 24 hr
2. H_2O_2, NaOH
3. NEt_3, THF, Δ
OH
H
N
H
CO_2CH_3
122
1. N, N'-thiocarbonyldiimidazole, butan-2-one, Δ, 18 hr
2. $(Bu^n)_3SnH$, $(C_6H_5CO)_2O$, toluene, Δ
3. B_2H_6, THF
O
OH
OH
108
S
O
123
1. LiI, py, Δ, 23 hr *or*
2. P_2S_5, C_6H_6, Δ
3. Raney Ni
115

Scheme 23.


N
H
20
OR
CO2CH3
124: R = H
129: R = Ac
108
TsCl, py
O
OTs
OH
125
CH2OH
126
LiAlH4
127
128
105

Scheme 24.



Catharanthine (28)

130

Scheme 25.

Reaction of catharanthine (**28**) with borane-methyl sulfide followed by oxidation and equilibration gave an alcohol (**122**) (Scheme 23). This alcohol was correlated with the diol **108**, prepared previously,[88,89] by way of the thionocarbonate, deoxygenation, and borane reduction.[93] The stereochemistry at C-20 in **122** (and **108**) was confirmed by deoxygenation to yield dihydrocatharanthine (**29**).[93]

The previously prepared[89] epoxythiolactam **123** has been converted into the 15β-hydroxylactone **115** through cyclization, reaction with phosphorus pentasulfide, and desulfurization with Raney nickel.[93]

The preparation of catharanthine lactone (**111**) has been discussed[34] and Kutney et al. have attempted the synthesis of the epimeric ester (**124**)[93] from the glycol **108**. Tosylation or mesylation with a view to reductive displacement of the leaving group at C-15 was unsuccessful. Borane reduction of the monotosylate **125** reduced only the lactam carbonyl and lithium aluminum hydride reduction afforded a triol **126** (not a diol) (Scheme 24).[93] Similar problems had been encountered previously in the reduction of **127** and **105** which could only be reduced to the diol **128**.

Kutney's experience therefore indicates that displacement of a functionality at C-14 or C-15 is quite difficult and that the nucleophilic displacement from the α face at C-15 impossible. Attempts[93,95] to reproduce the formation of 20β-acetoxydihydrocatharanthine (**129**) by the procedure of Atta-ur-Rahman[96] failed.

Atta-ur-Rahman et al. have recently[97] made the extraordinary claim that catharanthine (**28**) is converted into "21-epicatharanthine" (**130**) by treatment with sodium borohydride in methylene chloride at room temperature (Scheme 25).

No reaction was observed with sodamide or sodium hydride. The correct explanation of this reaction has not yet been published.

As mentioned previously, Neuss et al. could not decarboxylate catharanthine (**28**) directly, but it has now been shown[97] that **87** can be produced in greater than 90% yield by reaction with hydrogen sulfide in acidified dioxane at room temperature.

An alternative route to decarbomethoxycatharanthine (**87**) involves reaction of the mercurilactone derivative **112** with trifluoroacetic acid.[92]

V. SYNTHESIS

Because of the importance of ibogamine and catharanthine (through involvement in the bisindole alkaloids) it is not surprising to find that this has been a very active synthetic area. These efforts are summarized in Table VI and have been previously reviewed.[126,129]

The first total synthesis of an alkaloid in this series was that of ibogamine (**10**) by Büchi and co-workers[105,109] and is summarized in Scheme 26. Crucial steps are the Diels-Alder reaction of the dihydropyridine **134** with methyl vinyl ketone, the acid cyclization of the ketoamide **135**, and the rearrangement of **136** to the required isoquinuclidine skeleton of **137**. Ibogaine (**4**) was synthesized by an analogous route.[109]

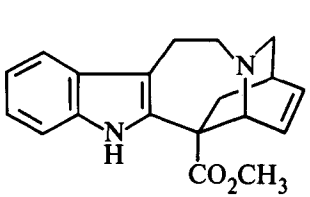
Formation of **138** has been explained[109] as occurring by way of the aziridinium ion **139** (Scheme 27) and the rearrangement of **136** during zinc-acetic acid reduction through an intermediate **140** (Scheme 28) analogous to that discussed in the formation of **100**.[87]

The strategy of Kutney et al. was based on the cyclization of cleavamine derivatives discussed previously and centers on the synthesis of a quaternary ammonium species such as **141** which can be easily cleaved and oxidatively cyclized (Scheme 29). Synthesis of ibogamine was therefore achieved through the formation of the appropriate dihydrocleavamine **85/86** (Scheme 30),[102] and in the case of coronaridine (**20**) by way of the corresponding 16-carbomethoxydihydrocleavamine (**94**) (Scheme 31).[102] Introduction of the 16-carbomethoxy group was achieved from dihydrocleavamine (**86**) by way of the chloroindolenine **142**, which, when treated with sodium acetate in glacial acetic acid followed by potassium cyanide, gave the 16β-cyano derivative **143**. Hydrolysis and methylation then yielded **94**. A somewhat similar strategic approach to the dihydrocleavamines was described by Harley-Mason.[120–123,123b] The stereochemistry of indolenine derivatives has been deduced to be 7β through ^{13}C nmr measurements,[123c] in agreement with earlier X-ray studies[123d] of the hydroxyindolenine of voaphylline.

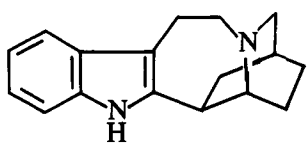
Takano and co-workers have refined this approach through the stereospecific synthesis of 20α-dihydrocleavamine (**85**) (Scheme 32).[130] Thus Claisen rearrangement of the sulfinium species **144** with potassium t-butoxide gave a separable mixture of diastereoisomers. Hydroboration and alkaline oxidation of each diastereoisomer

TABLE VI. SUMMARY OF THE SYNTHESIS OF THE IBOGA AND CLEAVAMINE SKELETONS

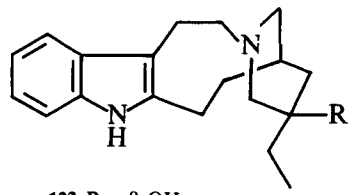
Compound synthesized	Investigators	Ref.
Alkaloid		
Catharanthine (28)	Büchi et al.	98
	Kutney and Bylsma	99, 100
	Trost et al.	101
Coronaridine (20)	Kutney et al.	102
	Hirai et al.	103
Epi-ibogamine (72)	Ban et al.	104
	Büchi et al.	105
	Nagata et al.	106
	Rosenmund et al.	107, 108
Ibogaine (4)	Büchi et al.	109
	Rosenmund et al.	108
Ibogamine (10)	Ikezaki et al.	110
	Büchi et al.	105, 109
	Kutney et al.	102
	Hirai et al.	103
	Nagata et al.	106, 111
	Ikezaki et al.	110
	Rosenmund et al.	108
	Sallay	112
	Trost et al.	113
Derivatives		
Desethylcatharanthine (131)	Sundberg and Bloom	114
Dihydrocatharanthine (29)	Kutney et al.	102
Desethylibogamine (132)	Augustine and Pierson	115
	Huffman et al.	116
	Nagata et al.	117
	Rosenmund et al.	118
	Trost and Genêt	119
16β-Carbomethoxycleavamine (31)	Kutney and Bylsma	99, 100
Cleavamine (30)	Kutney and Bylsma	99, 100
16β-Carbomethoxydihydrocleavamine (94)	Kutney et al.	102
Dihydrocleavamine (85)	Harley-Mason et al.	120–123
	Kutney et al.	102
Isovelbanamine (133)	Kutney and Bylsma	99, 100
Velbanamine (33)	Büchi et al.	98, 124
	Kutney and Bylsma	99, 100
	Narisada et al.	125



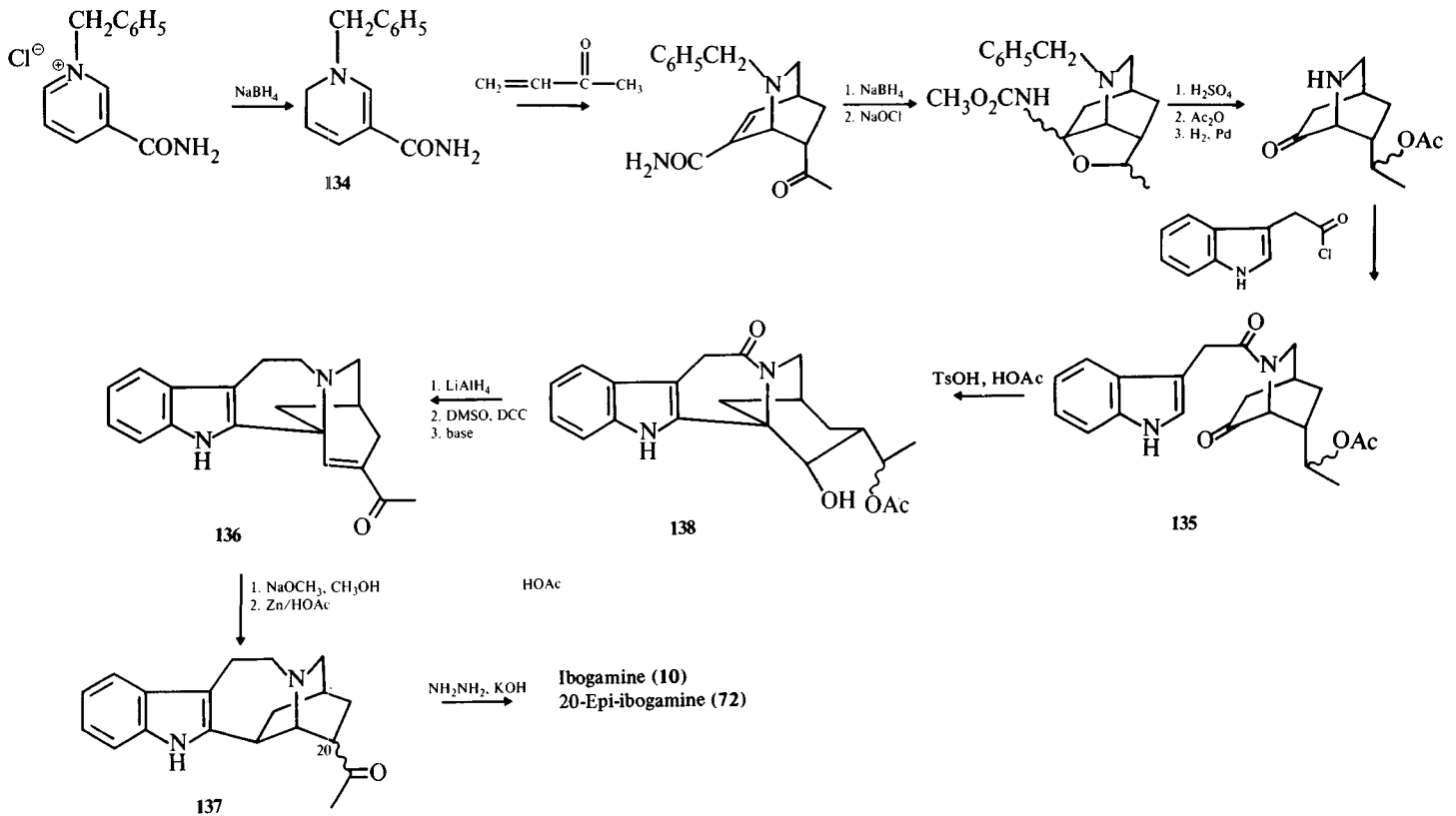
131



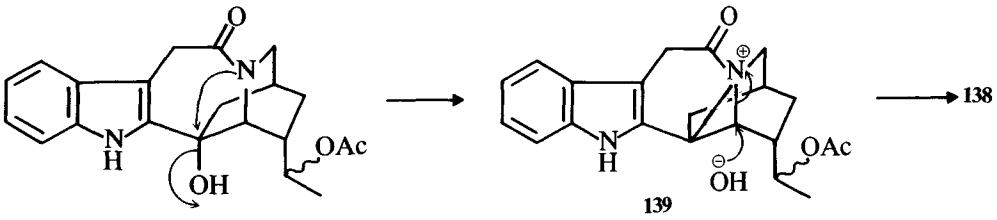
132



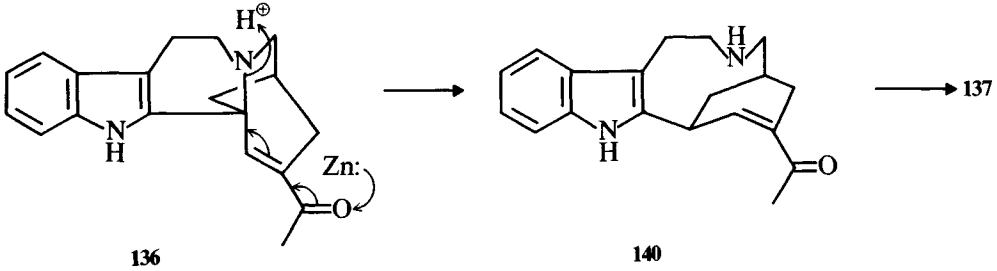
133: R = β-OH
33: R = α-OH



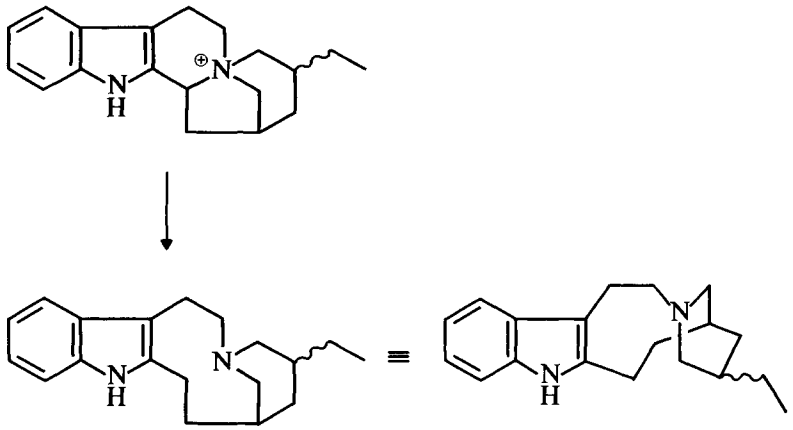
Scheme 26. Büchi synthesis of ibogamine (10) and 20-epi-ibogamine (72).[105,109]



Scheme 27.



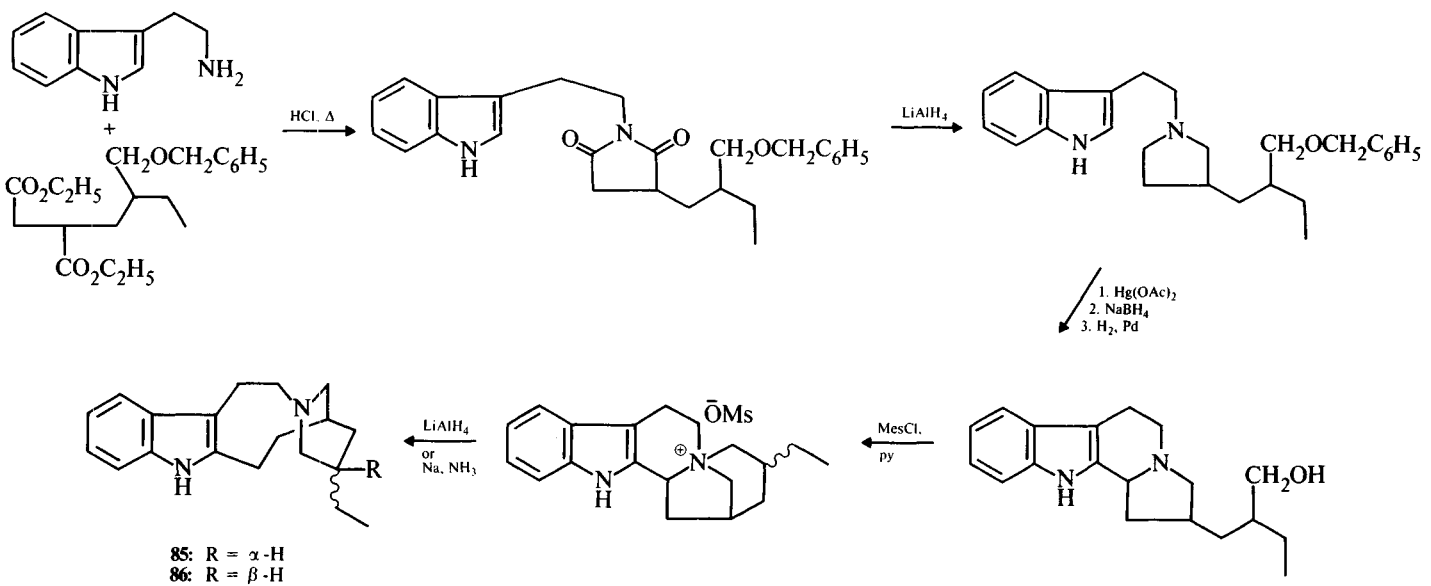
Scheme 28.



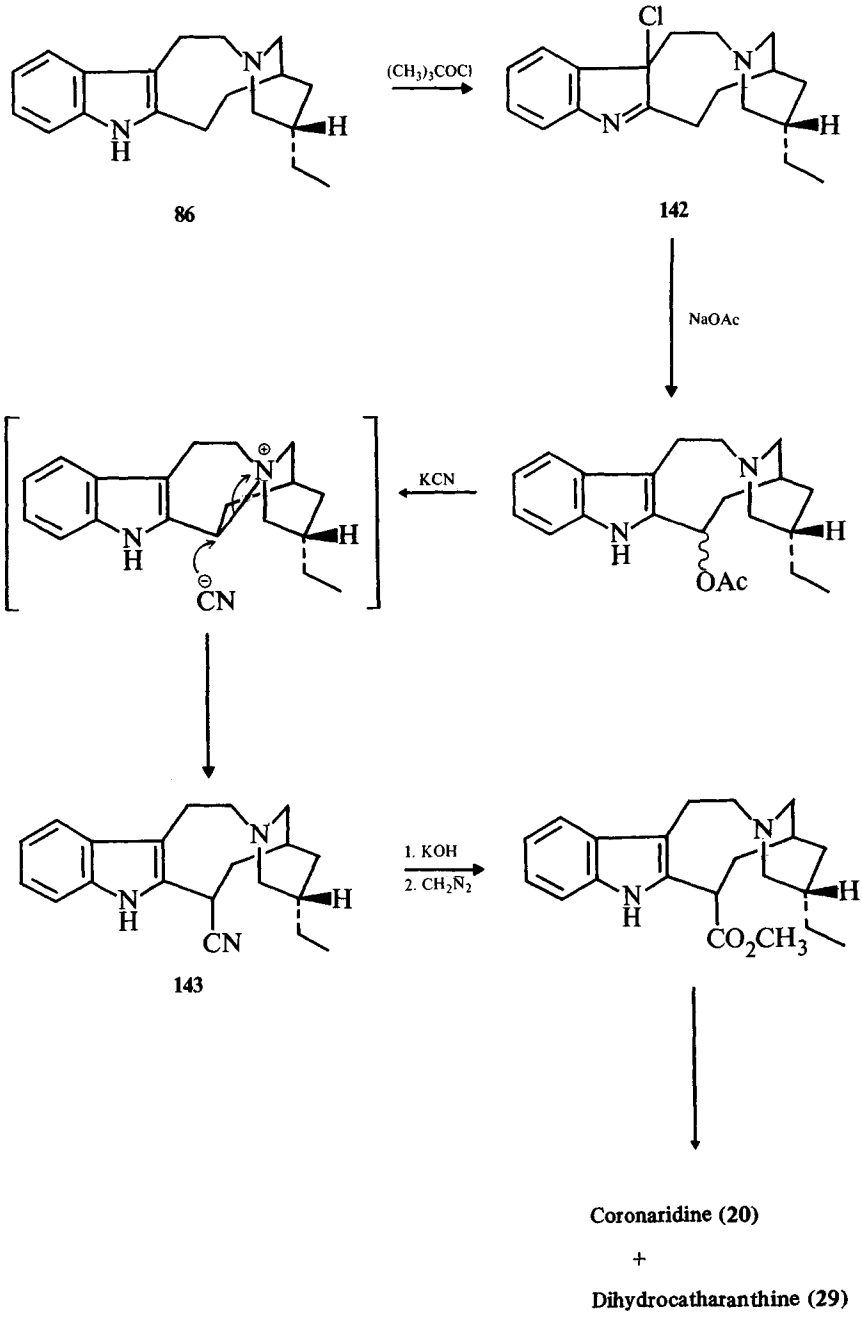
Scheme 29.

gave single products, one of which (**145**), by desulfurization, mesylation, heating and reduction, was converted into **85**. Stereospecific hydroboration is rationalized as occurring through a nine-membered boron-sulfur complex which then cyclizes from the most thermodynamically stable conformation.[130]

Cleavage of an aziridine species has also been used by Nagata and co-workers as a point of entry for the isoquinuclidine system. Typically the crucial steps are



Scheme 30. Synthesis by Kutney et al. of the dihydrocleavamines (85/86).[102]



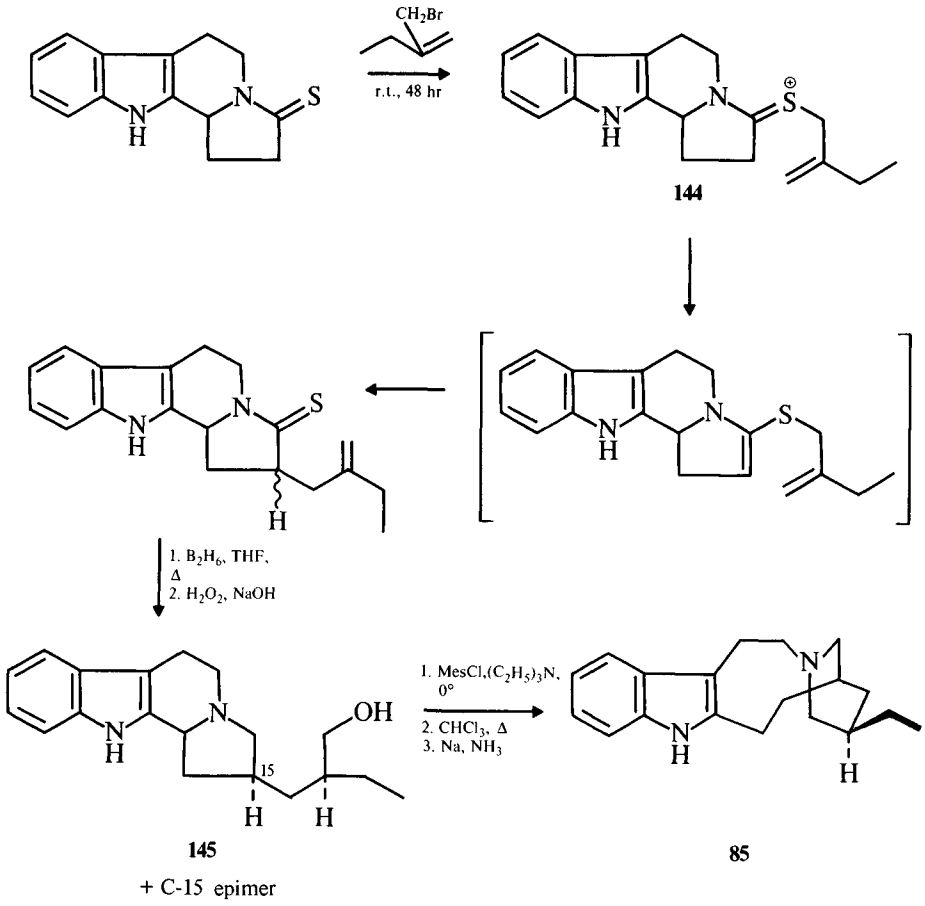
86 142 143

Coronaridine (20)

+

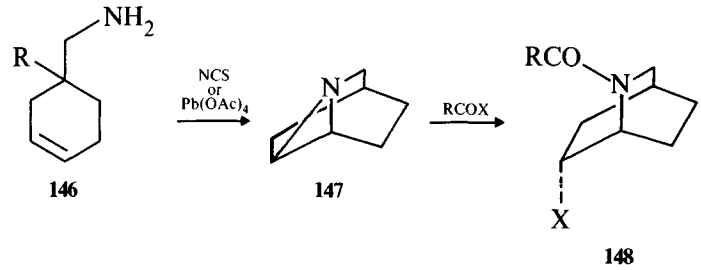
Dihydrocatharanthine (29)

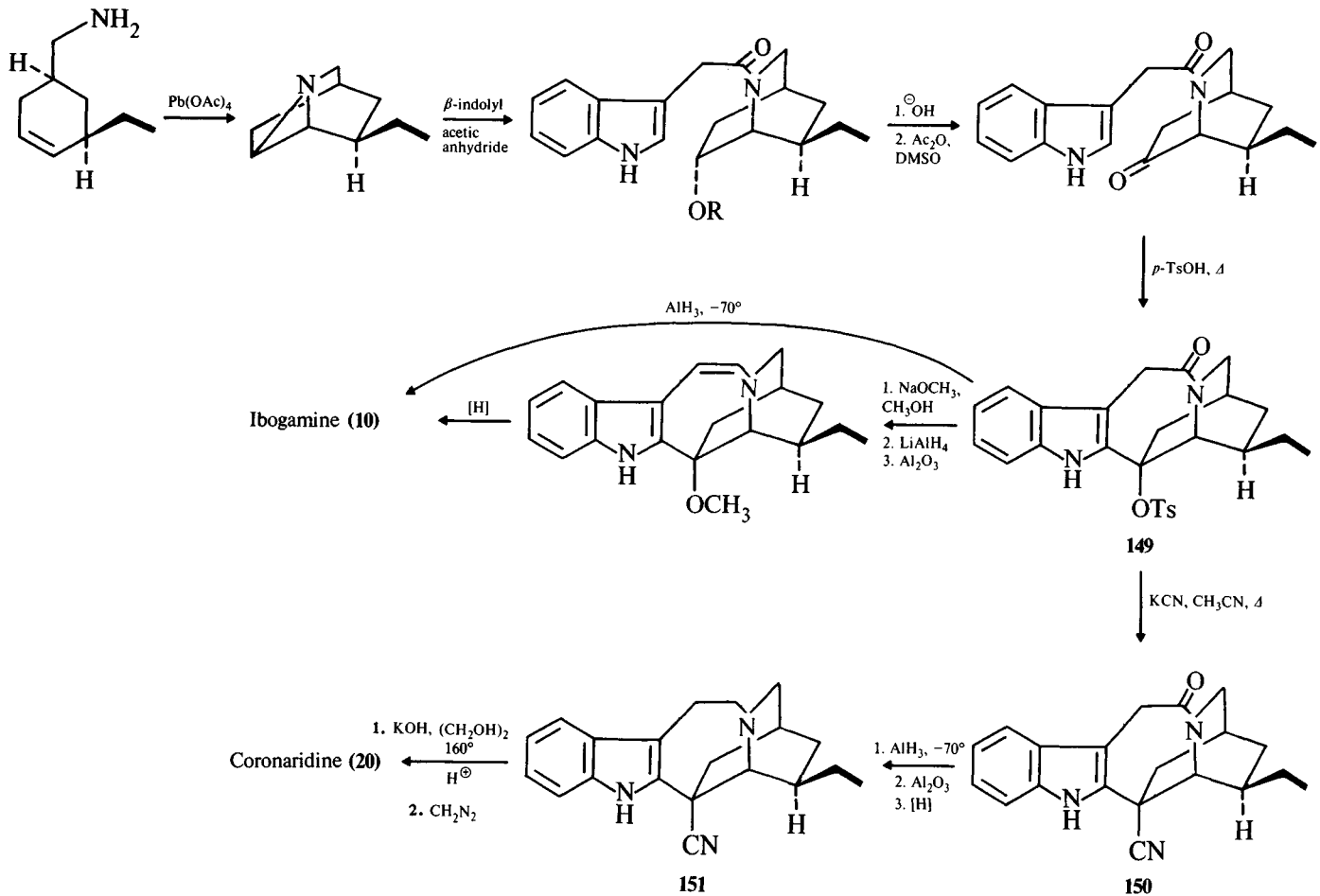
Scheme 31. Kutney synthesis of coronaridine (20).[102]



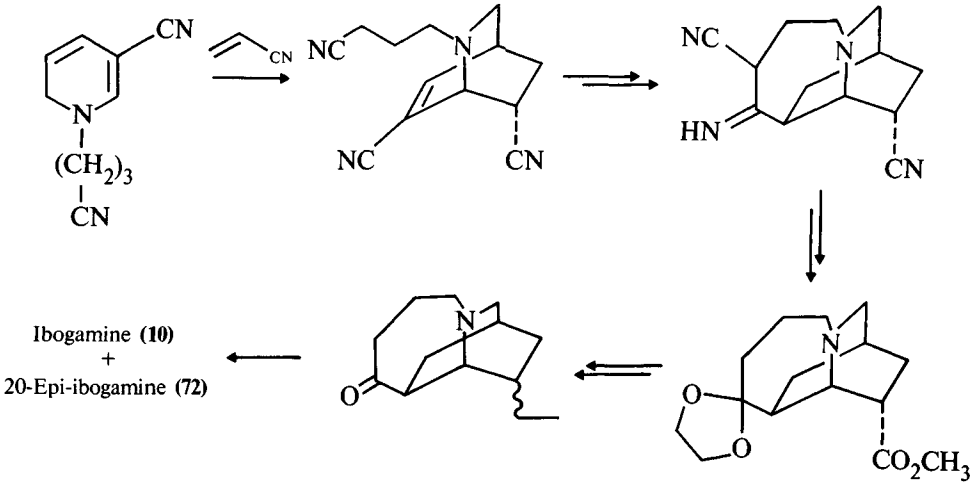
Scheme 32. Synthesis by Takano et al. of 20α-dihydrocleavamine (85).[130]

oxidation of a δ,ε-unsaturated primary amine such as **146** with either *N*-chlorosuccinimide in methylene chloride or lead tetraacetate in benzene.[131] Acylation of the aziridine **147** results in cleavage to afford the required nucleus **(148)**. Such a sequence was successfully applied to the synthesis of desethylibogamine **(132)**[117] and ibogamine **(10)** (Scheme 33) and epi-ibogamine **(72)**.[106] This synthesis was





Scheme 33. Nagata et al. synthesis of ibogamine (10)[106] and coronaridine (20).[103]



Scheme 34. Ban et al. synthesis of ibogamine (**10**)[110] and epi-ibogamine (**72**).[104]

improved[103] by reducing the 5-oxo-tosyloxyibogamine (**149**) intermediate with aluminum hydride to afford **10** directly in up to 45% yield, and extended by treating **149** with potassium cyanide in refluxing acetonitrile to give the lactam nitrile **150**. Reduction, dehydration, and catalytic hydrogenation afforded 16-cyanoibogamine (**151**) which, on hydrolysis, acidification, and methylation gave racemic coronaridine (**20**) (Scheme 33).[103]

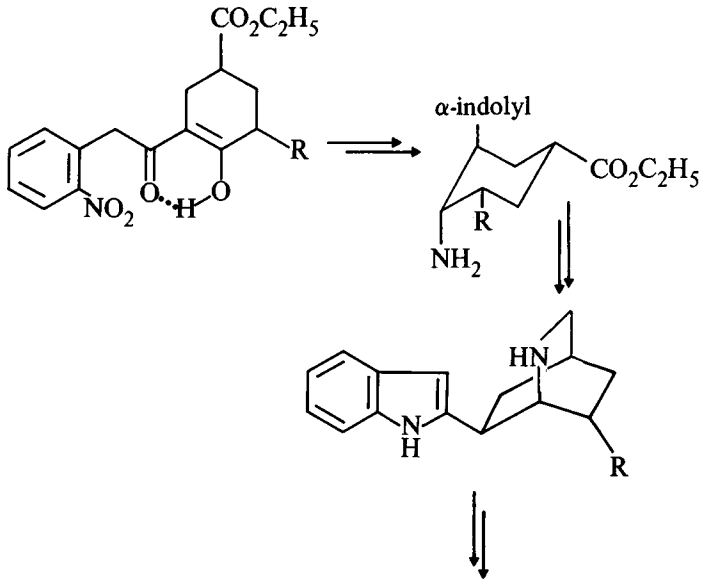
There have been several other approaches to the iboga skeleton (Table VI); the principal steps in these reactions are summarized in Schemes 34–38.

Of greater significance as far as the structures of the bisindole alkaloids vinblastine and vincristine are concerned is the synthesis of velbanamine (**33**), where the groups of Büchi et al.,[98,124] Kutney and Bylsma,[99,100] Narisada et al.[125] and Takano et al.[125d,125f] have all been successful.

In the first described route[98,124] (Scheme 39) the isoquinuclidine **152**, used previously, was elaborated to the isoquinuclidone **153** which was condensed with the sodium salt of indolyl-3-acetic acid to yield the amide **154**. One of the key subsequent steps is the retro-aldol reaction of **155** to generate an unstable diketoamide **156**.

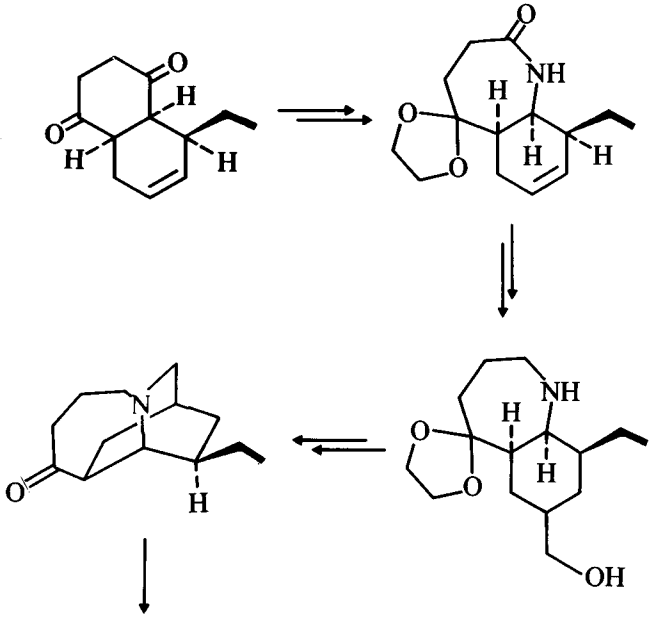
The approach of Kutney and Bylsma[99,100] is degradative in that it proceeds from dihydrocatharanthine (**29**) through 16,21 cleavage to an enamine **157**. Double 1,2-hydroxylation followed by reduction of the carbinolamine and the acylindole generated isovelbanamine (**133**). Inversion at C-20 with aqueous sulfuric acid afforded velbanamine (**33**) (Scheme 40).

The route developed by Narisada et al.[125] (Scheme 41) utilizes an oxidative cleavage of C-16,C-21 with lead acetate and elimination of methanol to yield an enamide **158**. Oxygenation at C-20 was again achieved through a cis-diol followed by complete reduction with lithium aluminum hydride. Oxidation and reaction with ethyl Grignard gave, in poor yield, the 20-epimeric velbanamines **33/133** in



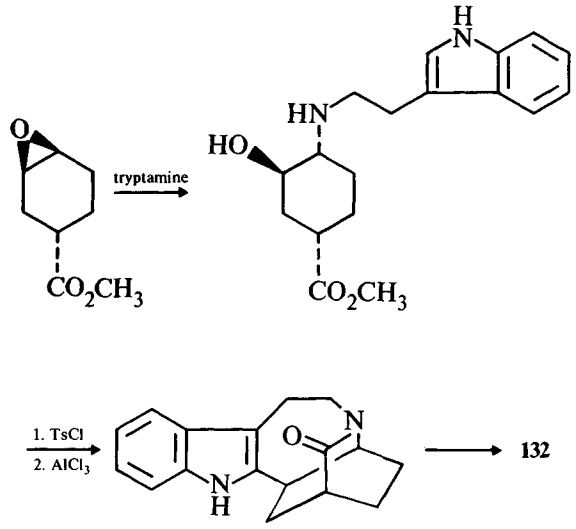
Desethylibogamine (132): R = H
Ibogamine/20-epi-ibogamine (10/72): R = C_2H_5

Scheme 35. Rosenmund et al. synthesis of ibogamine (10),[108] 20-epi-ibogamine (72),[107,108] and desethylibogamine (132).[118]

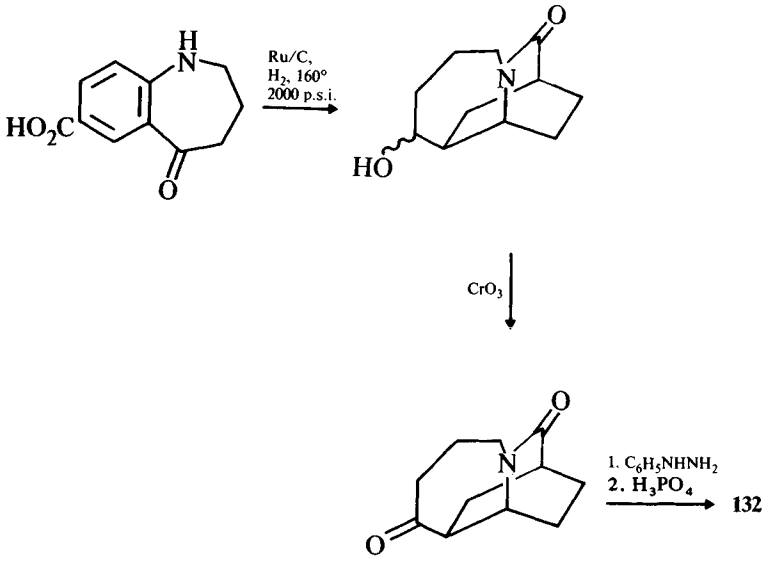


Ibogamine (10)

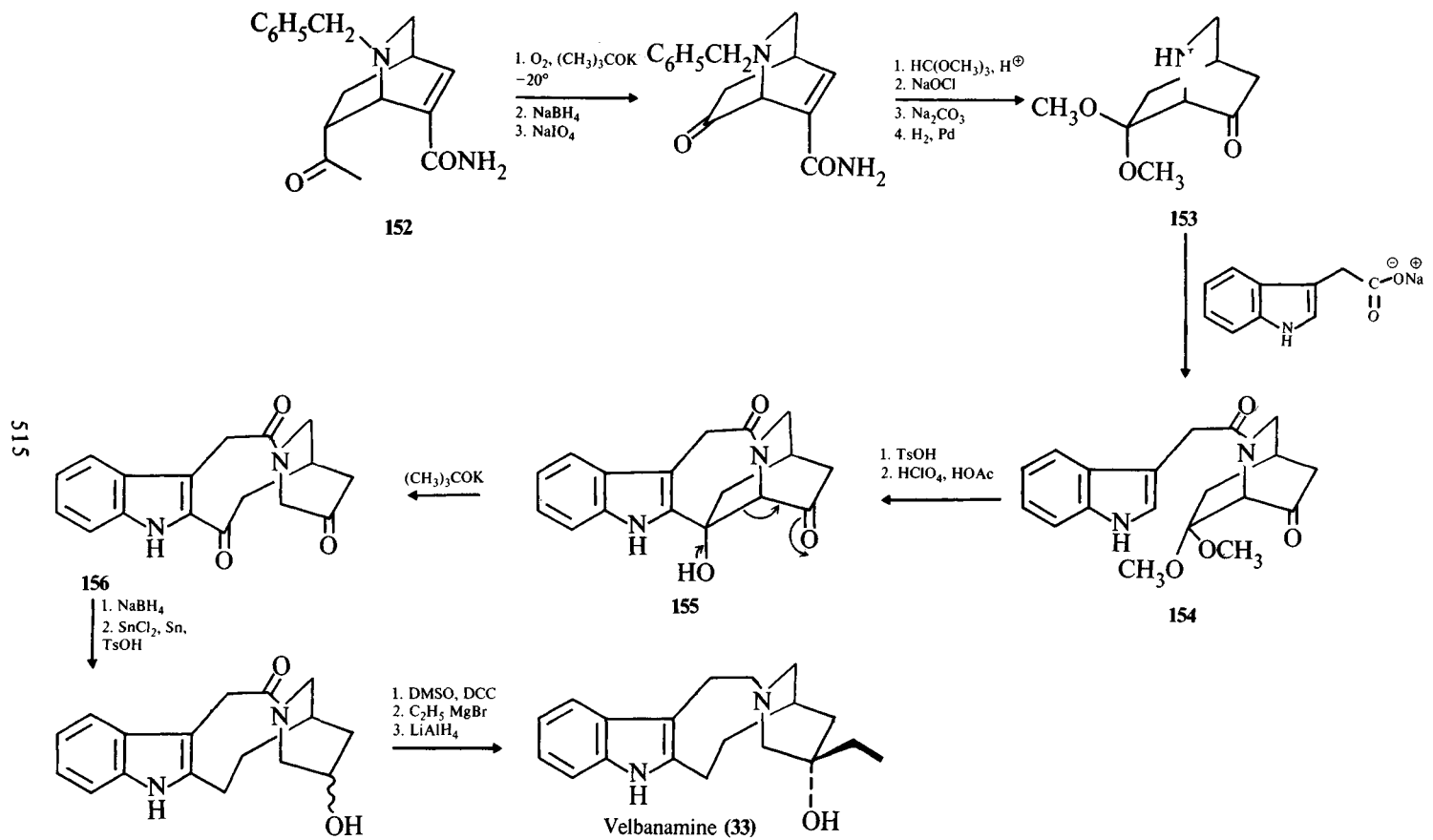
Scheme 36. Sallay synthesis of ibogamine (10).[112]



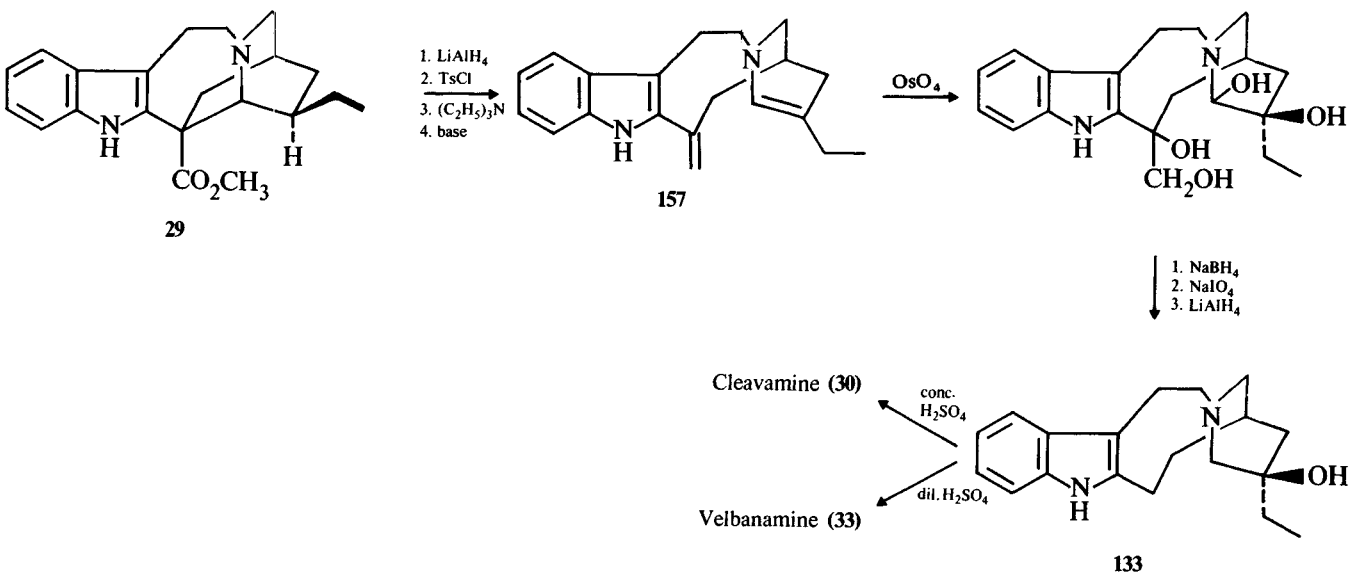
Scheme 37. Huffman synthesis of desethylibogamine (132).[116]



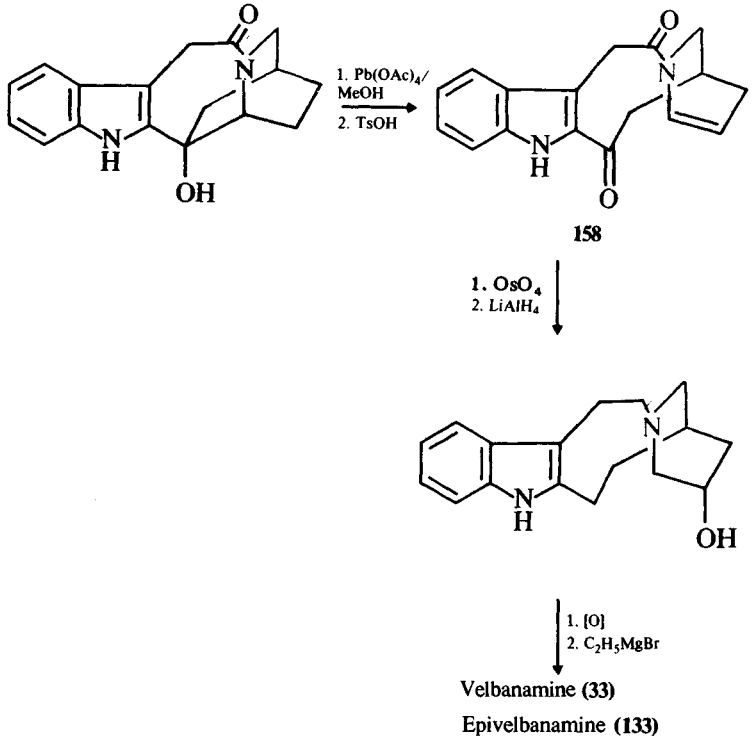
Scheme 38. Augustine and Pierson synthesis of desethylibogamine (132).[115]



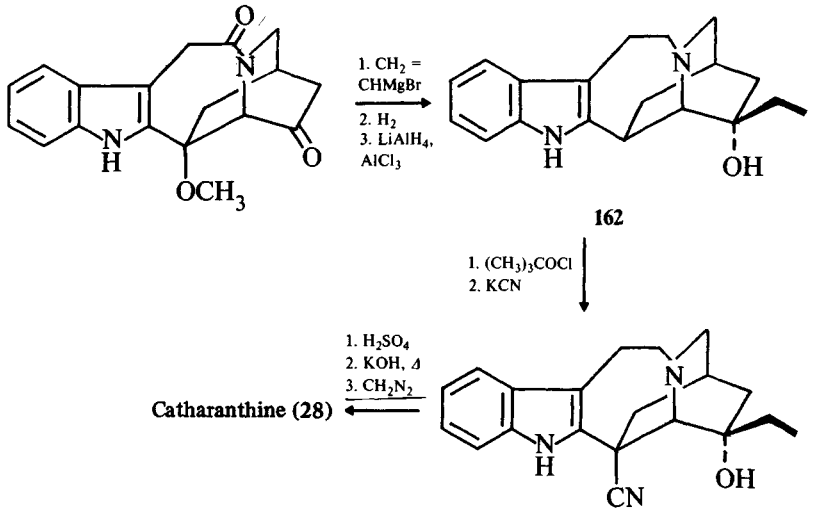
Scheme 39. Büchi et al. synthesis of velbanamine (33).[98,124]



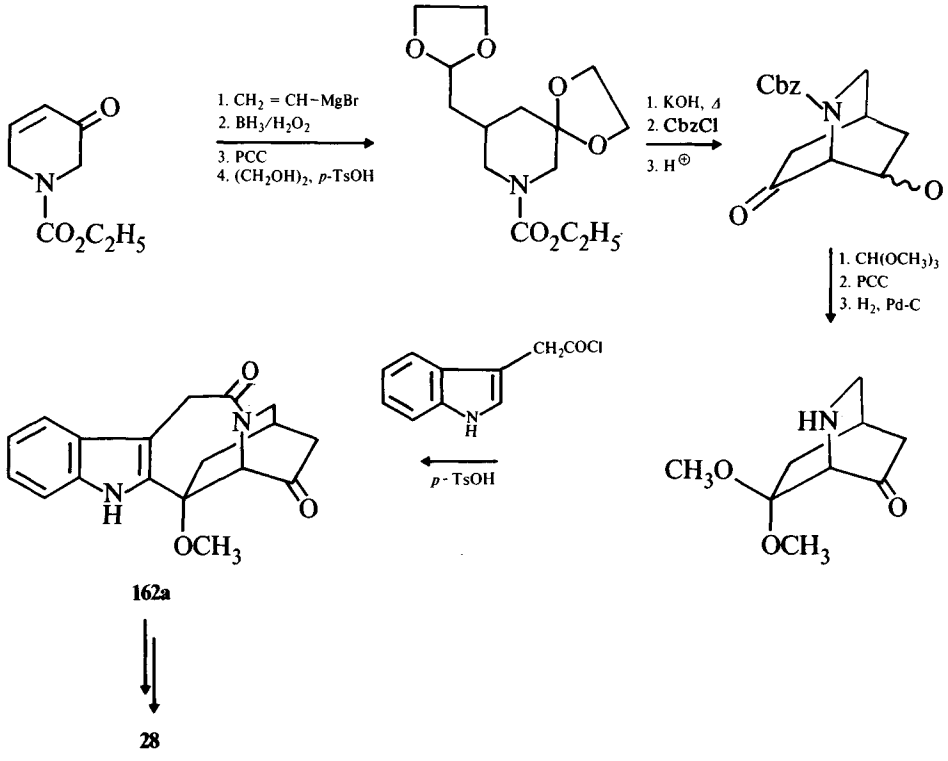
Scheme 40. Kutney and Bylsma synthesis of velbanamine (33).[99,100]



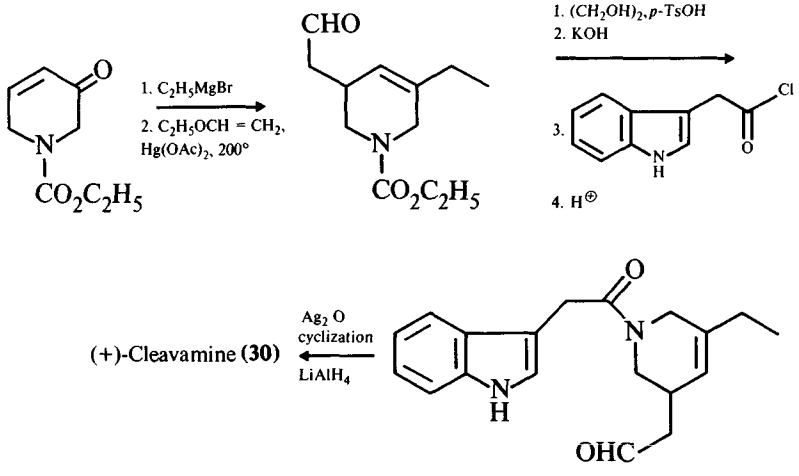
Scheme 41. Narisada et al. synthesis of velbanamine (133).[125]



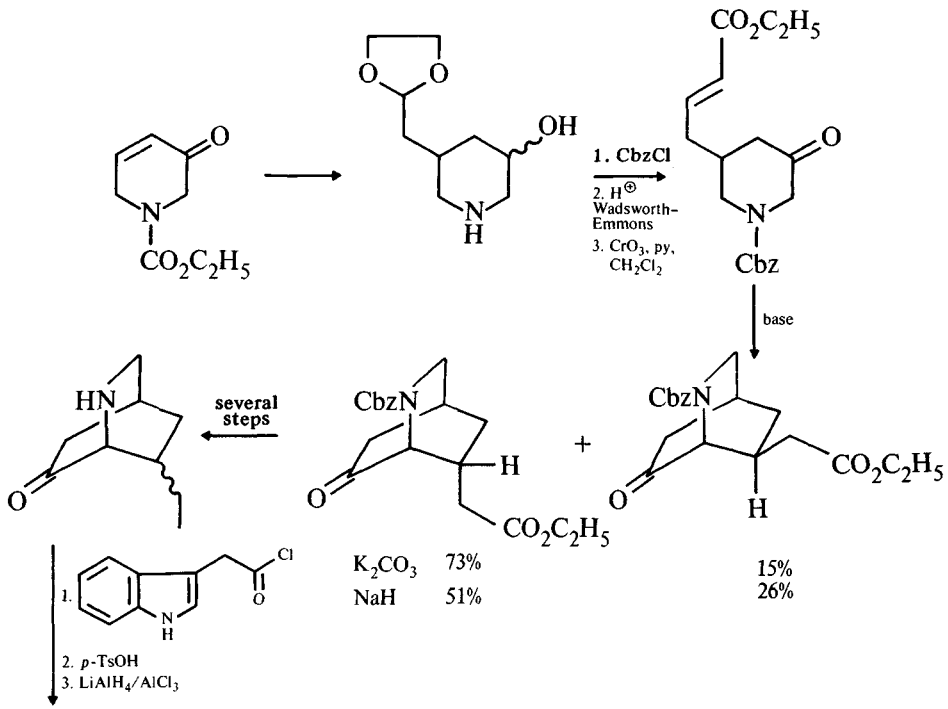
Scheme 42. Büchi et al. synthesis of catharanthine (28).[98]



Scheme 43. Hanaoka and co-workers' synthesis of (±)-catharanthine (28).[98a]



Scheme 44. Hanaoka and co-workers' synthesis of (±)-cleavamine (30).[98b]

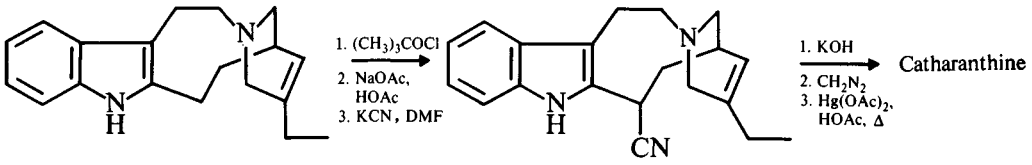


Scheme 45. Hanaoka and co-workers' synthesis of (±)-ibogamine (10) and (±)-20-epi-ibogamine (72).[98c]

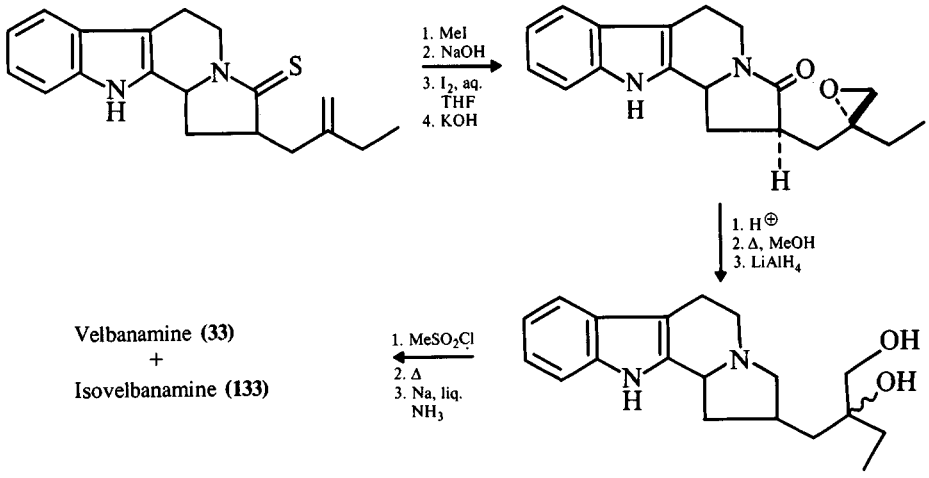
which the correct isomer predominated (5:4).[125] An extension of Büchi's procedure led to catharanthine (**28**), in which C-17 was introduced by way of an intermediate chloroindolenine (Scheme 42).[98] The Büchi intermediate **162a** has been synthesized by an alternative route (Scheme 43).[125a] Subsequent studies have led to the synthesis of (±)-cleavamine (**30**) (Scheme 44),[125b] (±)-ibogamine (**10**), and (±)-20-epi-ibogamine (**72**) (Scheme 45).[125c]

The route of Kutney and Bylsma could also be extended[99,100] to yield successively cleavamine (**30**), 16β-carbomethoxycleavamine (**31**) by the chloroindolenine approach, and catharanthine (**28**) through oxidative cyclization (Scheme 46). The group of Takano and Ogasawara have recently reported four routes to this framework,[125d–125g] including the first chiral synthesis of (−)-velbanamine (**177**).[125f] Scheme 47 shows the synthesis of velbanamine (**33**)/isovelbanamine (**133**) and Scheme 48 the chiral synthesis of **177**, in which **158a** is a intermediate.

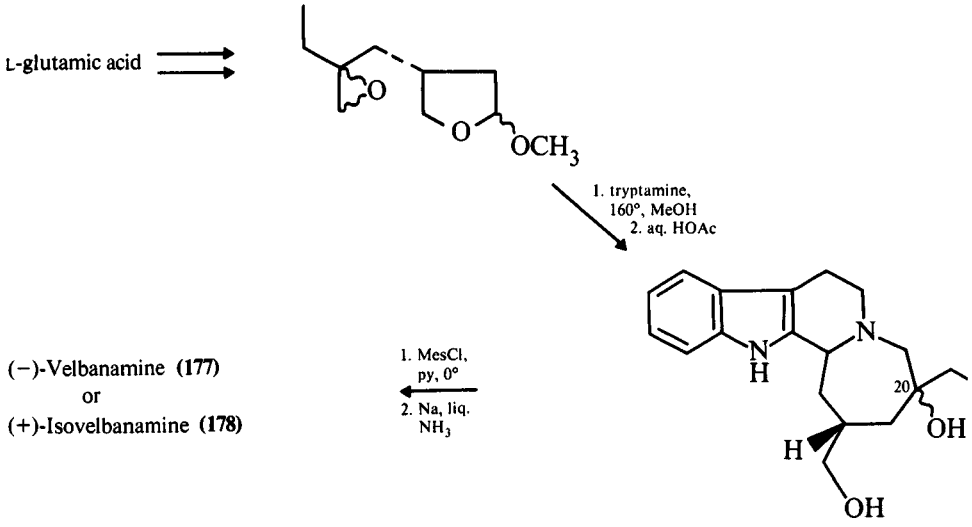
The third route[125e] has afforded the potentially versatile nine-membered ring intermediate **158b** (Scheme 49), whereas a fourth synthetic procedure[125g] (Scheme 50) has afforded the epimeric dihydrocleavamines (**85** and **86**).



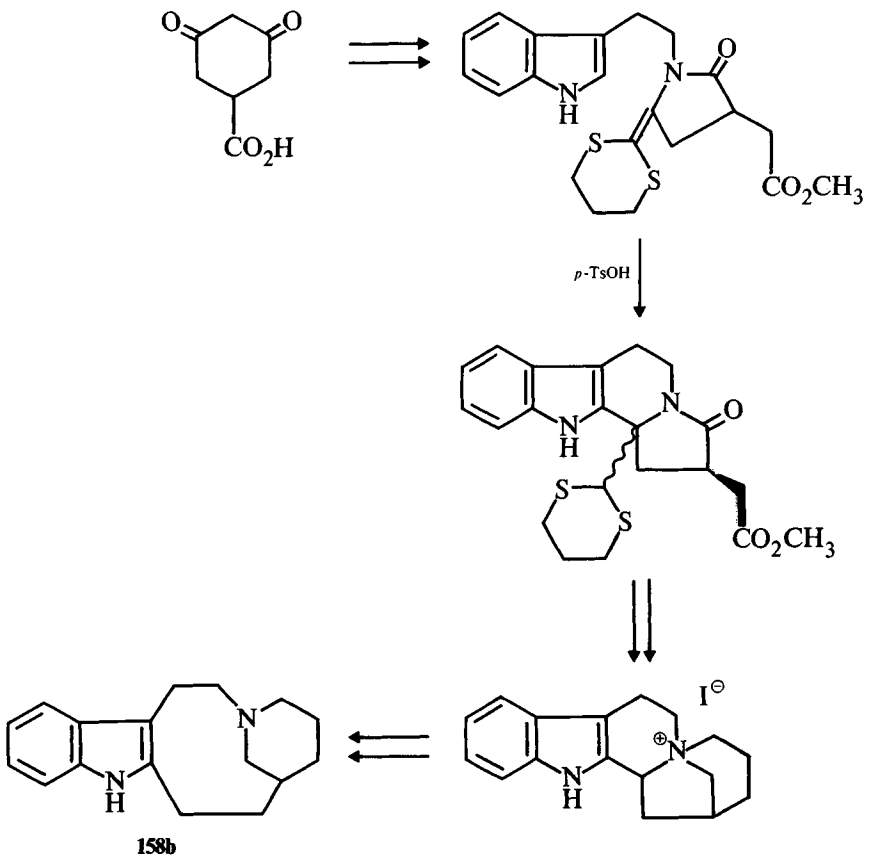
Scheme 46. Kutney and Bylsma synthesis of catharanthine (28).[99,100]



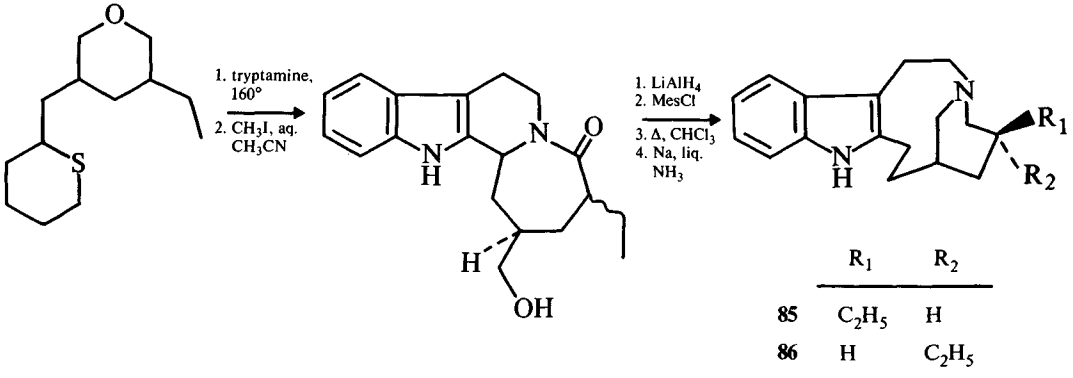
Scheme 47. Takano-Ogasawara group's synthesis of velbanamine (33) and isovelbanamine (133).[125d]



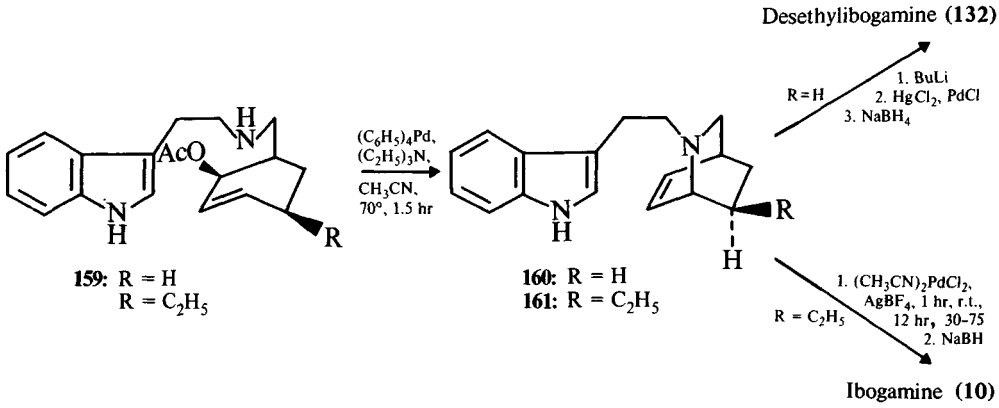
Scheme 48. Takano-Ogasawara group's synthesis of (−)-velbanamine (177) and (+)-isovelbanamine (178).[125f]



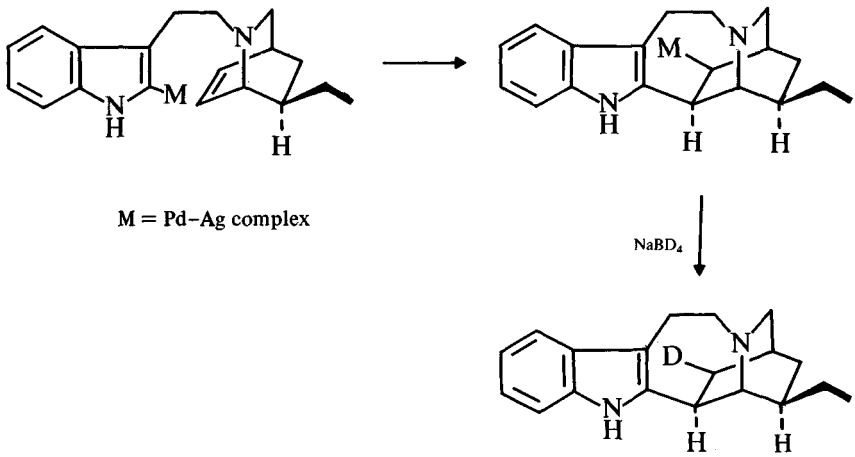
Scheme 49.



Scheme 50. Takano-Ogasawara group's synthesis of 20α-H- and 20β-H-dihydrocleavamines (85 and 86).[125g]



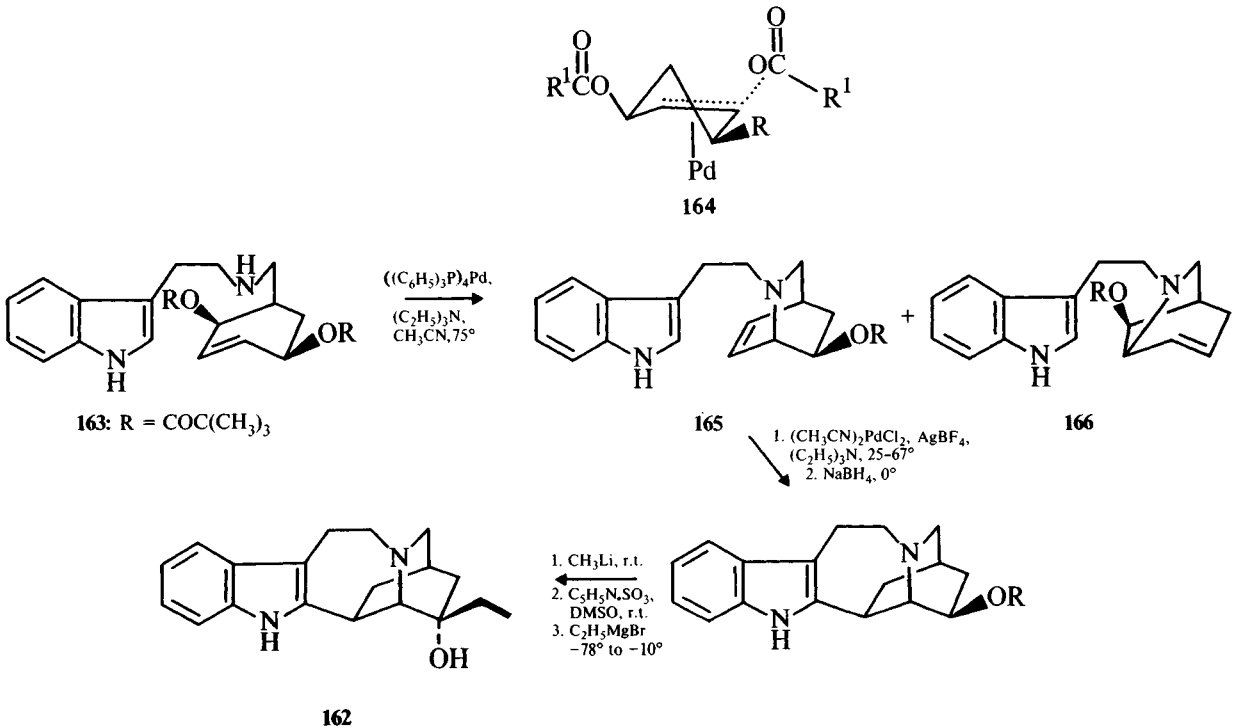
Scheme 51. Trost and Genêt synthesis of desethylibogamine (132)[119] and ibogamine (10).[113]



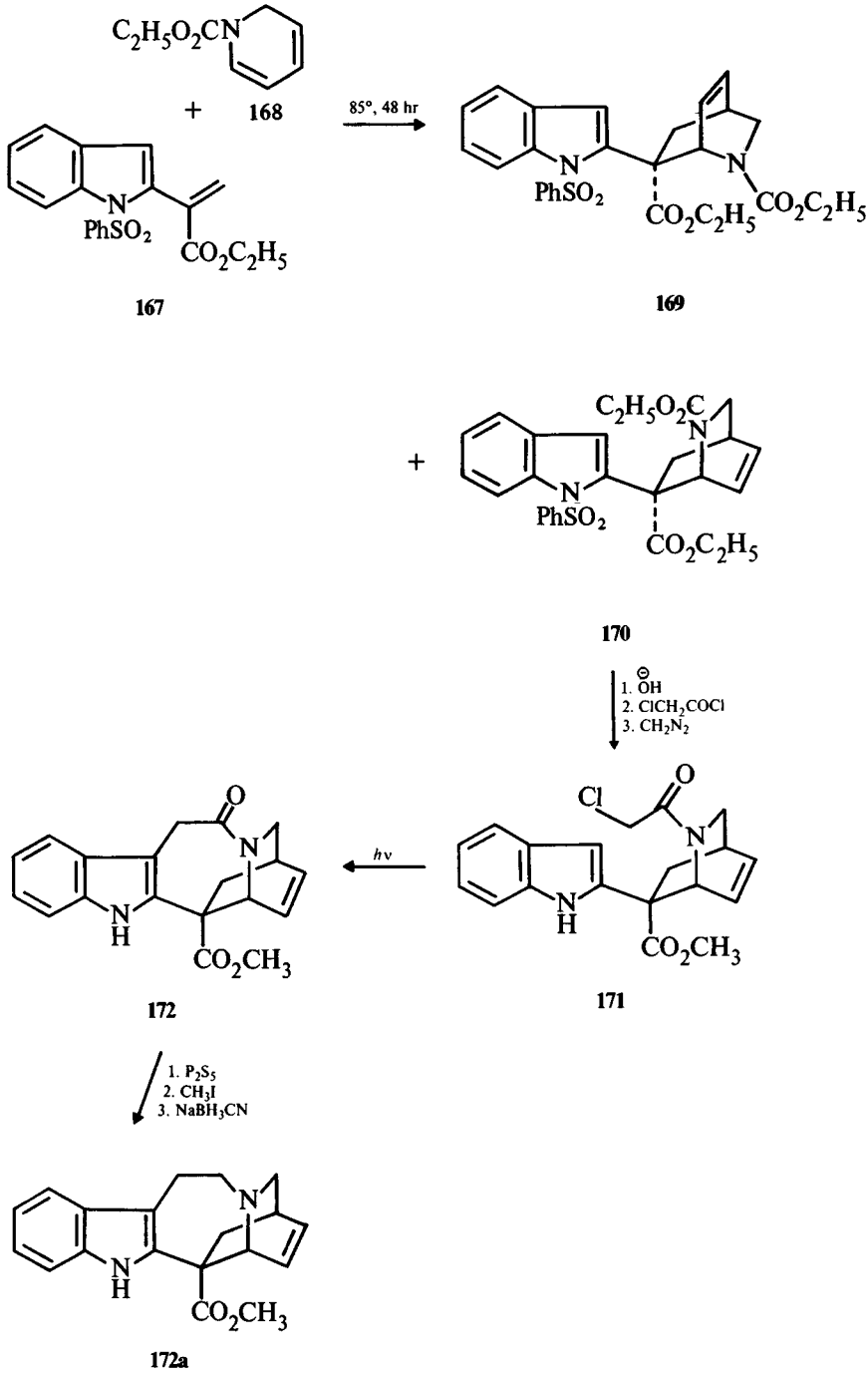
Scheme 52.

One of the most novel approaches to the iboga skeleton was described recently by Trost and Genêt[119] and involves a regiospecific palladium-catalyzed intramolecular alkylation, for example, **159** to **160**. Subsequent treatment of the lithio derivative of **160** with mercuric chloride, followed by treatment with palladium chloride and sodium borohydride reduction, afforded desethylibogamine (**132**) (Scheme 51).[119]

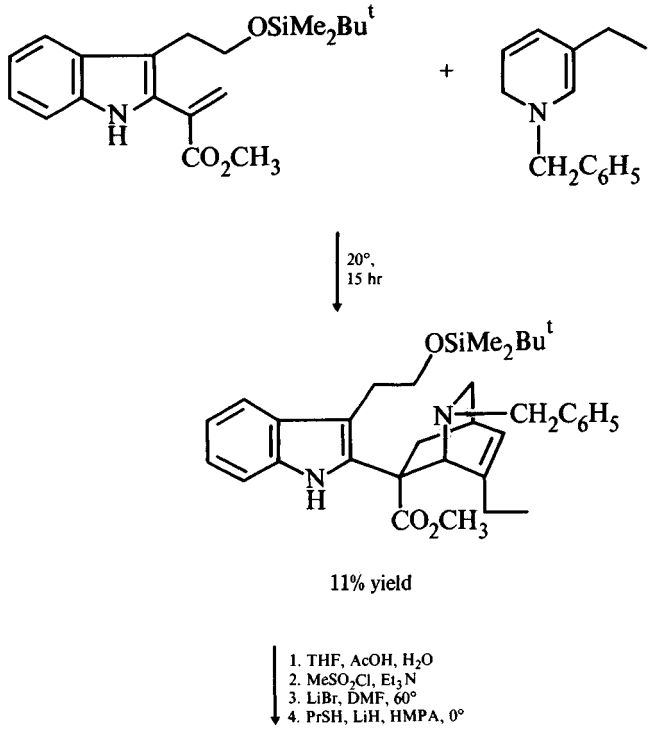
When the reaction was extended to the ethyl series, cyclization of the intermediate **161** was effected with bisacetonitrile-palladium chloride, silver tetrafluoroborate, and triethylamine, followed by sodium borohydride reduction to give ibogamine (**10**) in 45% yield.[113] Replacing the sodium borohydride with sodium borodeuteride afforded [17β-^{2}H]-ibogamine, suggesting the mechanism shown (Scheme 52) for the arylation reaction. The overall yield was 17%.


O
R1CO
OC
R1
R
Pd
164
RO
N
H
OR
((C6H5)3P)4Pd,
(C2H5)3N,
CH3CN, 75°
163: R = COC(CH3)3
165
166
1. (CH3CN)2PdCl2, AgBF4,
(C2H5)3N, 25-67°
2. NaBH4, 0°
OH
1. CH3Li, r.t.
2. C5H5N.SO3,
DMSO, r.t.
3. C2H5MgBr
-78° to -10°
162

Scheme 53.


C2H5O2CN
+ 168
85°, 48 hr
N
PhSO2
CO2C2H5
167
169
C2H5O2C
170
1. ⊖OH
2. ClCH2COCl
3. CH2N2
Cl
O
hν
H
CO2CH3
171
172
1. P2S5
2. CH3I
3. NaBH3CN
172a

Scheme 54.



Scheme 55. Das and co-workers' synthesis of (±)-catharanthine (28).[114c]

The next target molecule of Trost and co-workers was the alcohol **162**,[101] previously synthesized by Büchi et al.,[98] which was envisaged as being produced by cyclization and arylation of a 3,6-dioxygenated cyclohexene, for example, **163**. The theory was that of the two possible isoquinuclidines that could be produced, one would be preferred from a less-crowded transition state such as **164**. In practice, variable yields of each structural isomer (**165** and **166**) were produced, the isoquinuclidine **165** being carried through an arylation, hydrolysis, oxidation, and Grignard reaction sequence to afford the desired alcohol **162** (Scheme 53).[101]

A different approach (Scheme 54) to the problem of a 15,20-dehydro compound such as catharanthine (**28**) has been developed by Sundberg and Bloom.[114,114a] Diels-Alder addition of the indolyl acrylic ester derivative **167** with the tetrahydropyridine **168** gave a mixture of the two addition products **169** and **170**, one of which was carried through to the corresponding chloroacetamide **171**. Photolysis then yielded 5-oxodesethylcatharanthine (**172**) in 55% yield, which could be carried through to 20-desethylcatharanthine (**172a**).[114b] A group at Gif has offered another approach utilizing a dihydropyridine intermediate and leading to the synthesis of catharanthine (**28**) (Scheme 55).[114c]

VI. PANDOLINE AND RELATED ALKALOIDS

In the discussion of the chemistry of catharanthine (**28**) mention was made of the partial synthesis of a skeleton isomeric with the *Aspidosperma* skeleton, but having an ethyl group apparently shifted from C-20 to C-14. It was not until 1974 that compounds of this structural type were obtained from natural sources. Subsequently several alkaloids have been isolated, particularly from *Pandaca* and *Capuronetta* species.

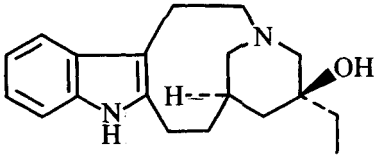
The first alkaloid to be obtained was pandoline (**173**) from *Pandaca* species[132,133] and the structure was determined on the basis of chemical and spectroscopic evidence. Although the cis C/D stereochemistry was deduced from a broad singlet for H-3 at 2.86 ppm, the stereochemistry of the C-20 hydroxy group in pandoline and epipandoline was deduced subsequently.[134,135]

Reduction of pandoline with sodium borohydride/glacial acetic acid at 90° for 30 minutes afforded the 3,7-secopandolines A (**174**) and B (**175**), whereas epipandoline gave only the isomer **176**. Comparison with (+)-velbanamine (**33**) by ^{13}C nmr conclusively showed that in pandoline the C-20 ethyl group is β.[135]

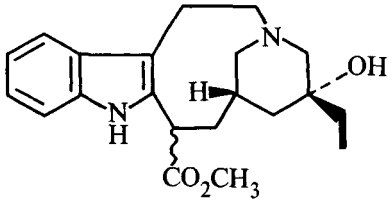
Alternatively, catalytic hydrogenation of pandoline followed by acid-catalyzed decarboxylation gave (−)-velbanamine (**177**), whereas epipandoline afforded (−)-isovelbanamine (**178**).[134] Thus pandoline (**173**) has the 20*R* configuration (α-OH) and epipandoline (**179**) the 20*S* configuration (β-OH).

Previously,[133] pandoline (**173**) had been correlated with (+)-catharanthine (**28**) by two separate routes (Scheme 56). One of these involved the optical antipodes of pseudotabersonine (**88** and **180**), and a second the antipodes of 15,20-dehydropseudoaspidospermidine (**181**) and (**182**).

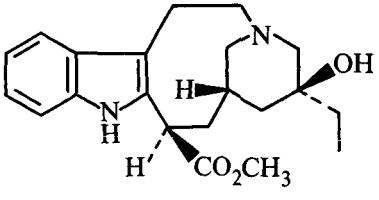
This work with pandoline (**173**) opened up a new area of indole alkaloid chemis-



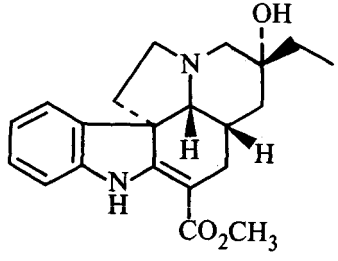
33



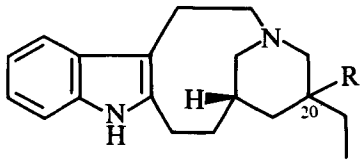
174/175



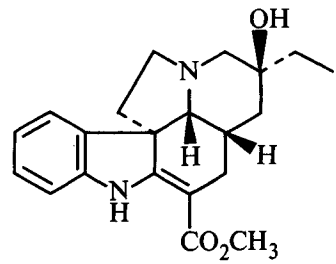
176



Pandoline (173)



177: R = α-OH
178: R = β-OH



179

try, and the next interesting alkaloid to be obtained was pandine.[132,136] Although like many *Aspidosperma* alkaloids it displayed a β-anilinoacrylate chromophore, no retro-Diels-Alder reaction following fission of the 5,6 bond was observed in the mass spectrum.

From the ^{13}C nmr spectrum, pandine contained a tertiary alcohol (quaternary carbon at 80.3 ppm) and by comparison with pandoline it was shown that a new bond was present between C-21 (77.0 ppm) and C-17 (40.8 ppm), each carbon being shifted downfield by about 15 ppm. Pandine was therefore suggested to have the structure **183**,[136] the C-20*R* configuration being established subsequently by single crystal X-ray analysis.[137]

Alkaline hydrolysis of pandine, followed by heating in acid and reduction with sodium cyanoborohydride gave the indoline **184**, and as in the case of akuammicine (Chapter VII) lithium aluminum hydride reduction gave the exomethylene derivative **185**.[136]

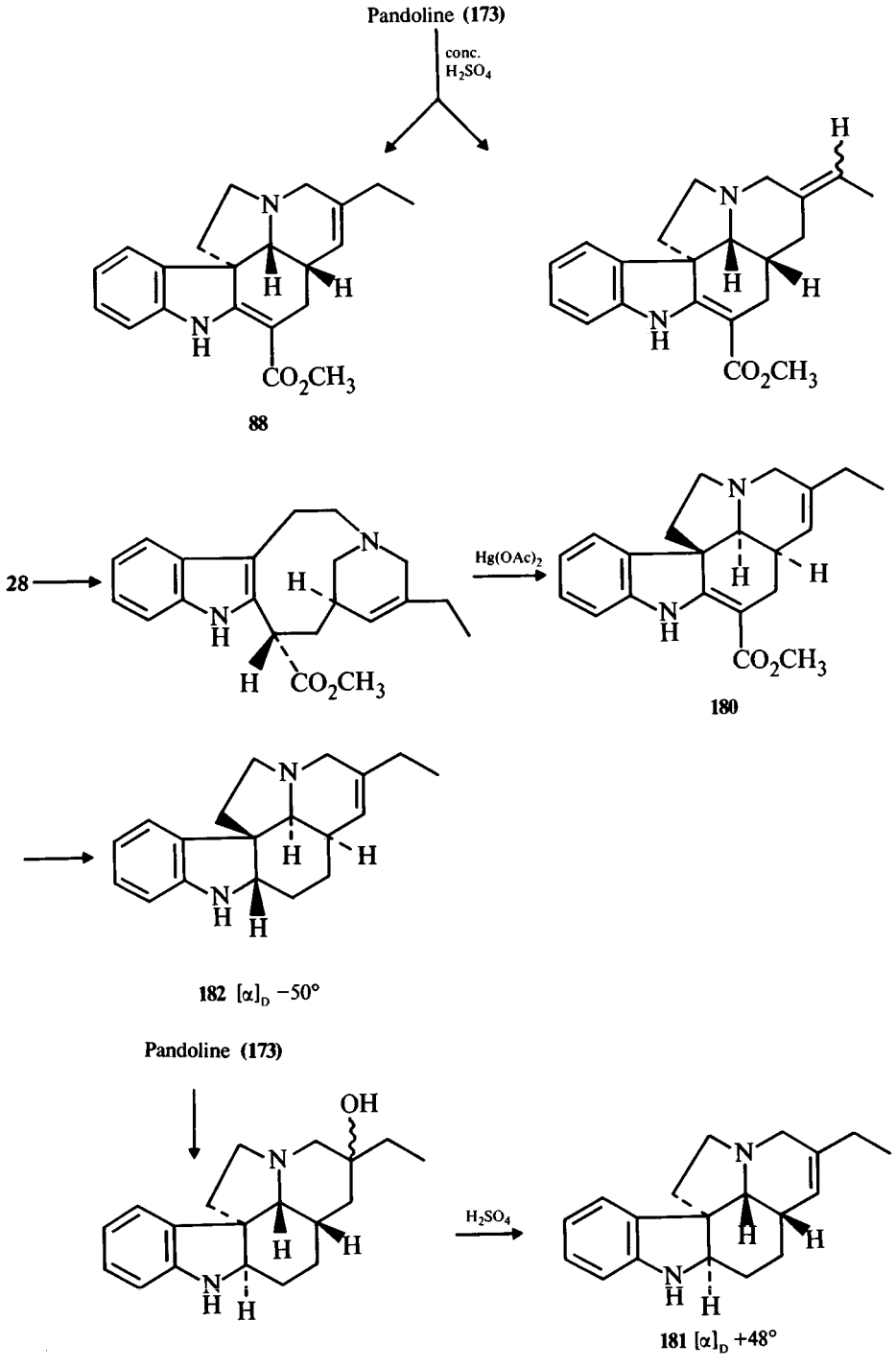
Capuronidine (**186**) and capuronine (**187**) were obtained from *Capuronetta elegans* Mgf.[138] and could be interrelated through reduction and decyclization.

Oxidation and base-catalyzed deuteration of the ketone **188** from capuronine located the secondary hydroxy group at C-15 and the relative stereochemistry of the hydroxy and ethyl groups could be determined through hydroboration of (+)-cleavamine (**30**). The two cis products proved to be diastereoisomers of capuronine and the structure **187** was eventually deduced by X-ray analysis of the acetate derivative **189**. Dehydration of (+)-capuronine (**187**) with sulfuric acid gave (−)-cleavamine (**190**), thereby establishing the absolute configuration.[138]

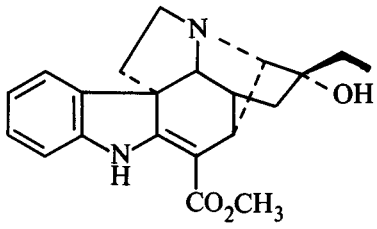
14,15-Anhydrocapuronidine (**191**) and its dihydroderivative **192** were also isolated from *C. elegans*.[139] In **191** H-3 appeared as a singlet at 3.62 ppm with an olefinic proton at 5.45 ppm. The remaining structural aspects of the piperidine ring were deduced through extensive decoupling experiments.

Tabernanthe iboga and *T. subsessilis* Stapf have also yielded alkaloids belonging to this series but with a modified piperidine ring.[140]

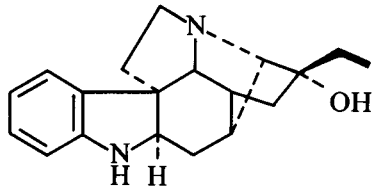
Ibophyllidine ($C_{20}H_{24}N_2O_2$) showed an ethyl group in the ^1H nmr spectrum but a base peak at *m/e* 110 (**193**) 14 mass units less than for the typical aspidospermine skeleton. In the ^{13}C nmr spectrum, C-7 (55.8 ppm) was the only aliphatic quaternary carbon, and three methine carbons were observed at 37.8 (C-14), 65.7 (C-3), and 75.6 (C-20), thereby placing the ethyl group on the carbon adjacent to nitrogen.



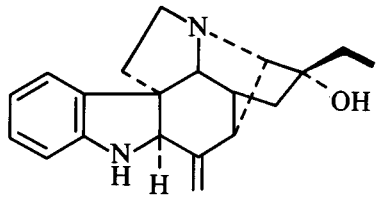
Scheme 56. Correlation of pandoline (173) with catharanthine (28).[133]



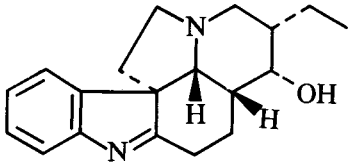
Pandine (183)



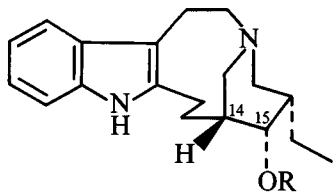
184



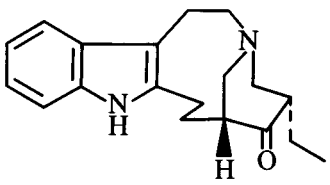
185



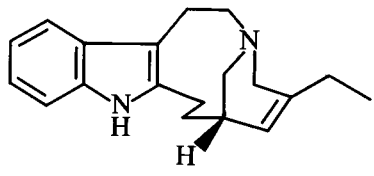
Capuronidine (186)



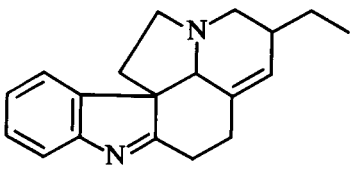
Capuronine (187): R = H
189: R = Ac



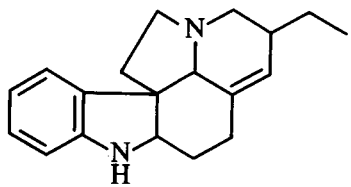
188



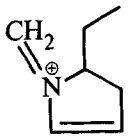
190



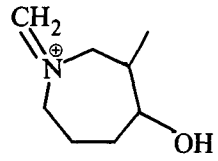
191



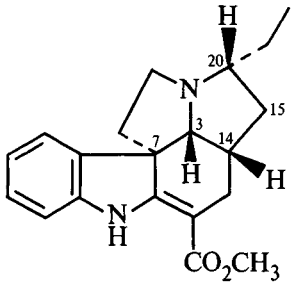
192



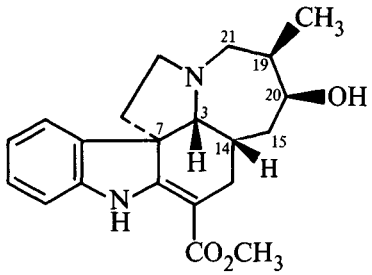
193 *m/e* 110



195 *m/e* 140



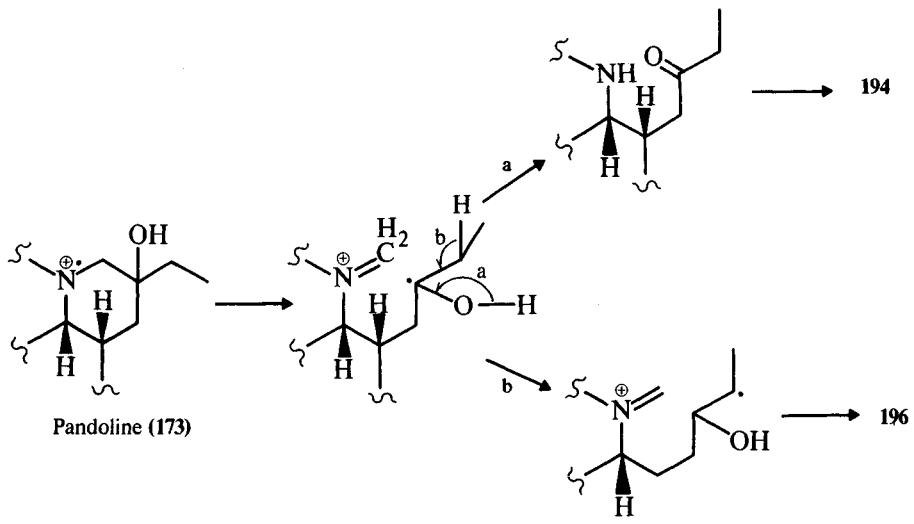
Ibophyllidine (194)



Iboxyphylline (196)

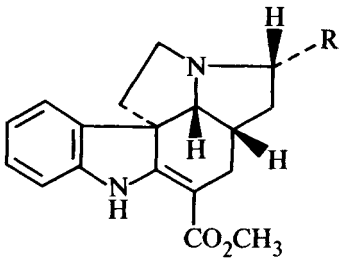
Since H-3 was a narrow doublet ($J = 3$ Hz) it must be cis to H-14. The multiplicity of H-20 and restricted rotation of the 19,20 bond then led to a complete structure **194** for ibophyllidine.[140]

Iboxyphylline ($C_{21}H_{26}N_2O_3$) also showed an anilinoacrylate chromophore, with secondary alcohol (multiplet at 3.95 ppm) located in the base peak at *m/e* 140 (**195**). A methyl group was observed at 0.93 ppm (doublet) with a methine carbon resonance at 41.1 ppm for C-19. Three other secondary carbons were observed at 70.3 (C-13), 37.6 (C-14), and 73.1 ppm (C-20). The structure **196** and stereochemistry were eventually deduced by X-ray analysis.[140]

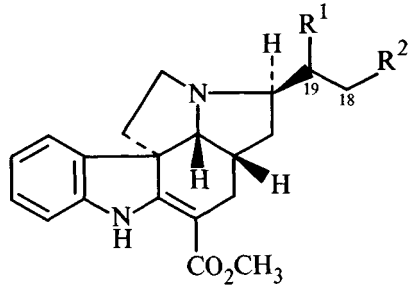


Pandoline (173)

Scheme 57.

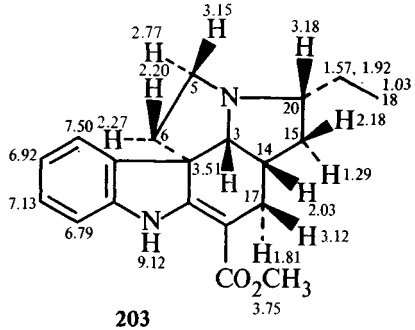


	R
Ibophyllidine (**194**)	C_2H_5
Desethylibophyllidine (**197**)	H
19-Hydroxyibophyllidine (**198**)	$CH(OH)CH_3$

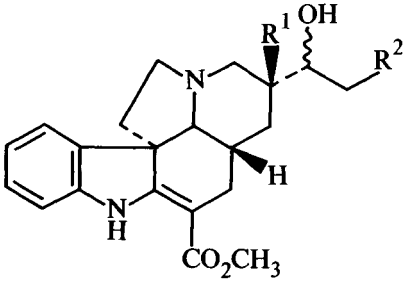


	R^1	R^2
20-Epi-ibophyllidine (**199**)	H	H
19*R*-Hydroxy-20-epi-ibophyllidine (**200**)	OH	H
19*S*-Hydroxy-20-epi-ibophyllidine (**201**)	OH	H
18-Hydroxy-20-epi-ibophyllidine (**202**)	H	OH

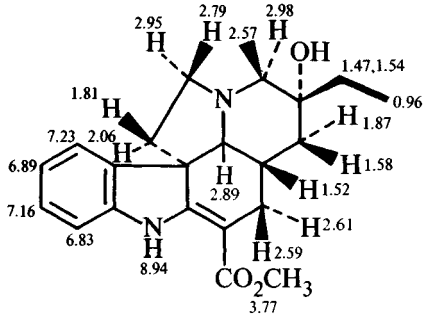
Coupling Constants (H)	
3,14	7.5
5α,5β	10
5α,6α	7
5α,6β	7
14,15α	6
14,17α	11
14,17β	6.5
15α,15β	12.5
15α,20β	12.5
17α, 17β	15
18,19	7
18,19′	7
19,19′	14
19,20β	7
19′,20β	7



203



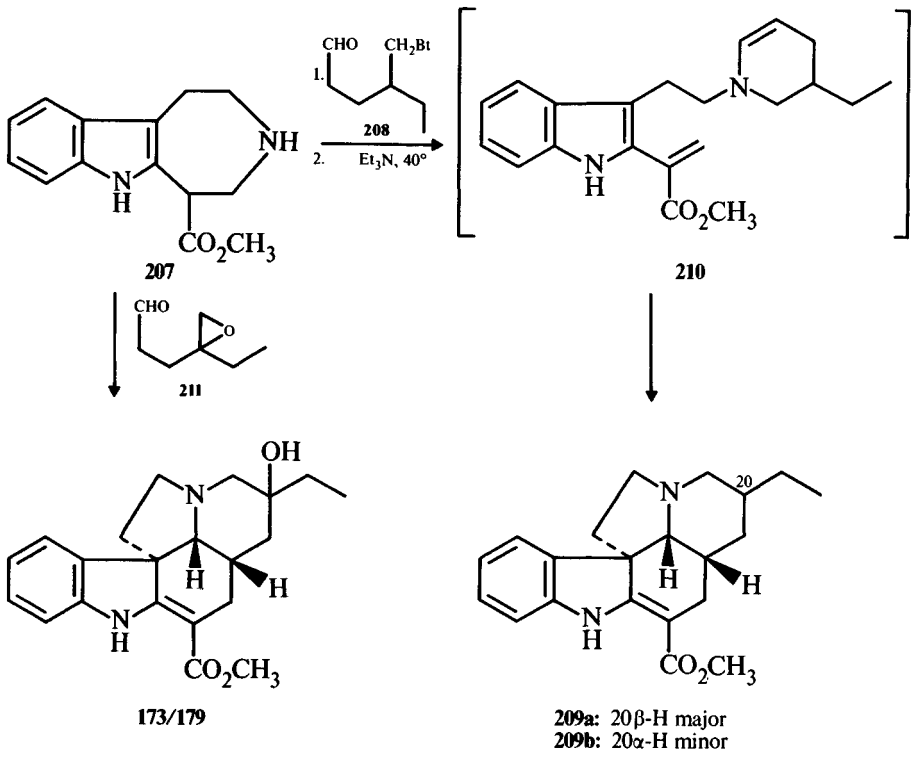
	R^1	R^2
204	OH	H
205	H	OH



206

These isolates were suggested to have a novel biogenesis in which pandoline (**173**) is a key intermediate (Scheme 57).[140] Several simple members of this series have been isolated from *Pandaca boiteau* Mgf.[141]

Tabernaemontana albiflora Miq. has also recently yielded alkaloids of the pandoline[142] and norpandoline types[143,144] including the ibophyllidine type alkaloids **197–202**. Two protons appear to characterize the stereochemistry at C-20 in



these compounds; in the ibophyllidine series H-3 and H-20 appear at 3.51 and 3.18 ppm, respectively, whereas in the 20-epi series these signals are at 3.89 and 2.78 ppm. Thus even in **198** and **202** where the respective H-20's appear at 3.34 and 3.30 ppm, the chemical shifts of H-3 are characteristically different (3.61 and 3.86 ppm, respectively).[144] The complete ^{1}H nmr assignments for ibophyllidine are shown in **203**.[143]

The high-field ^{1}H nmr spectra of two new pandoline alkaloids, 19-hydroxy-20-epipandoline (**204**) and 20*R*-18,19-dihydroxypseudovincadifformine (**205**), together with pandoline (**173**) and 20-epipandoline (**179**), have also been examined.[142] Data are shown in **206** for pandoline itself.

Some progress has also been made on the synthesis of alkaloids in the pandoline series[145] utilizing a secodine intermediate in the cyclization step. Thus treatment of the indoloazepine ester **207** with 4-(bromomethyl)hexanal (**208**), with subsequent addition of base (Et_3N) and slight warming, afforded a 4:1 mixture of the C-20 epimers of pseudovincadifformine **209a** and **209b** in 40% yield. Analysis of the natural product indicated the same ratio of C-20 epimers, suggesting that possibly the same secodine intermediate **210** is involved in this reaction.

Condensation of the amino ester **207** with the epoxyaldehyde **211** afforded a 1:1 mixture of pandoline (**173**) and 20-epipandoline (**179**) in 64% yield identical with the natural products.[145]

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CHAPTER XI

The Bisindole Alkaloids

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I. INTRODUCTION

Previous discussions of the bisindole alkaloids have usually been involved with a description of the corresponding monomeric species,[1–14] and with one important exception,[15] until quite recently[16] no unification of this diverse group of alkaloids had been attempted, although a French group did make some progress in systematizing this area in 1969.[17]

Fundamentally, this chapter deals with those alkaloids derived from tryptamine/tryptophan and at least one monoterpenoid unit. In addition, it is organized approximately along the lines of a progressing biosynthetic pathway, even though little experimental work has been conducted in this area.

It is rare that these alkaloids contain two identical monomeric units. Indeed frequently, widely different carbon skeletons are involved in the two "halves." Consequently, it is more correct to refer to them as "bisindoles" rather than "dimers."

There are manifold problems in deducing molecular structures of this complexity, and the area was virtually unexplored until the structures of vincaleukoblastine[18] and voacamine[19] were deduced. Currently, there are more than 175 characterized alkaloids in this series, and these have been reviewed annually[15,20–26] and according to their various groups.[19,27–35]

II. BORREVERINE AND RELATED ALKALOIDS

In 1973, Pousset and co-workers isolated a novel monomeric alkaloid borrerine (1) from *Borreria verticillata* G.F.W. Mey (Rubiaceae).[36] More recently, additional

alkaloids including borreverine (**2**),[37,38,40] isoborreverine (**3**),[38,40] and several derivatives of these have been obtained.[41]

Borreverine showed a uv spectrum typical of the indole-dihydroindole system (λ_{max} 225, 285, and 295 nm) and the ^{1}H nmr spectrum indicated the presence of two quaternary methyls (0.32 and 0.90 ppm), a vinyl methyl (1.70 ppm), two *N*-methyls (2.53 and 2.56 ppm), and an olefinic proton (5.60 ppm).

Acetylation gave a diacetate whose structure was deduced to be **4** by X-ray crystallography.[37] However, this is a bis*indole* alkaloid and consequently borreverine must have rearranged on acetylation. Examination of the highly unstable crystals of a methanol-water solvate gave the structure **2** for borreverine,[37] and it was suggested that rearrangement to diacetylborreverine (**4**) may occur by fragmentation to **5** with participation from the indoline nitrogen, followed by rotation about the 2,12 bond and recyclization.

A biogenetically modeled synthesis of borreverine (**2**) and isoborreverine (**3**) was achieved when borrerine (**1**) was heated in TFA/benzene for 30 minutes[39] (Scheme 1). This led to a search for natural isoborreverine (**3**), which was subsequently isolated from *B. verticillata*[38] and *Flindersia fournieri* Pauch. et Sieb. (Flindersiaceae).[40] Acetylation of **3** gave a diacetyl derivative **4** identical to that obtained from borreverine (**2**).[39]

III. *CORYNANTHE*-TRYPTAMINE TYPE

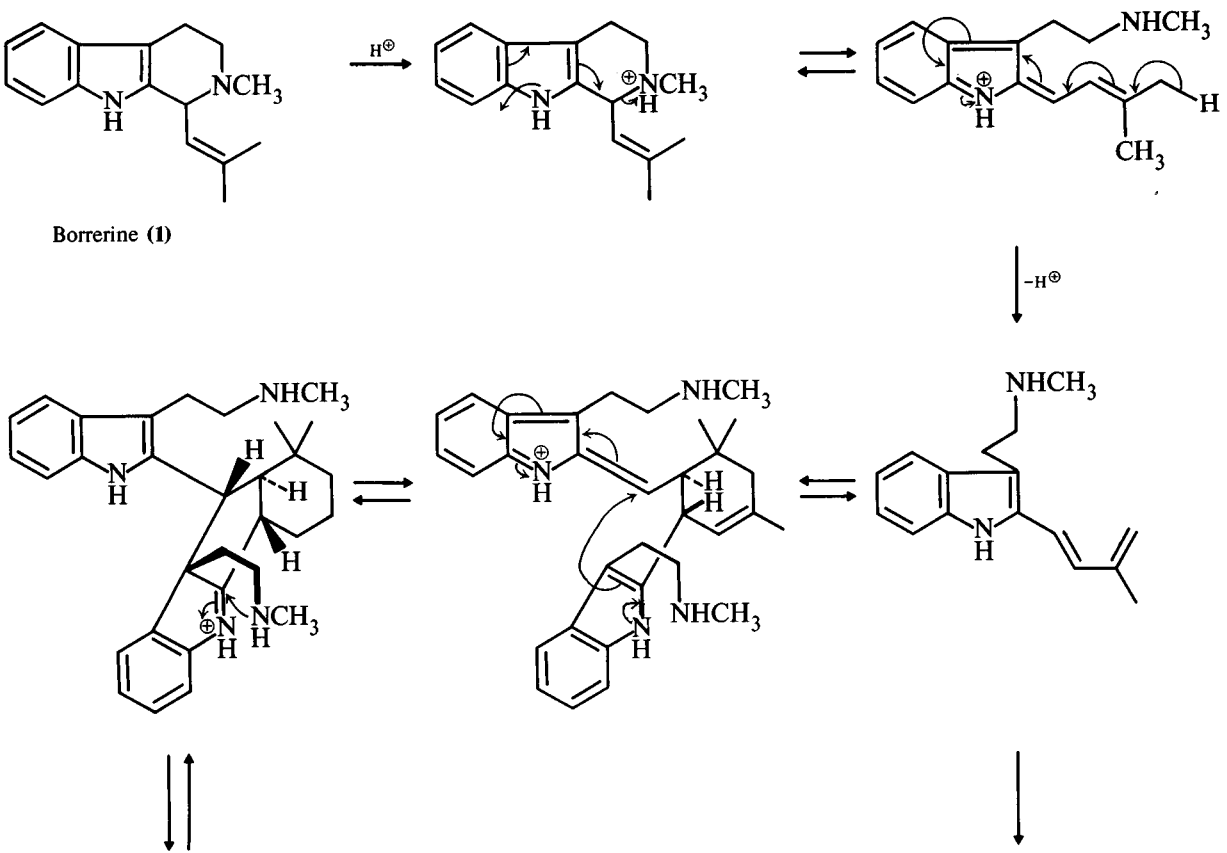
A. The Ochrolifuanines, the Usambarines, and Related Alkaloids

The ochrolifuanines and the usambarines are derived from a *Corynanthe* moiety and an additional tryptamine unit. This series of alkaloids has been obtained from plants in the Loganiaceae (*Strychnos* spp.), Rubiaceae (*Cinchona ledgeriana*), and Apocynaceae (*Ochrosia* and *Rauwolfia* spp.) and is typified by the alkaloid usambarine I (**6**) (no stereochemistry).[16] The major structural problems to be solved therefore involve the stereochemistry at C-3, C-17, and C-20 if an ethyl group is present, and the nature and location of any substituents on the indole nuclei. Formerly, mass spectral and ^{1}H nmr information were critical in structure elucidation, but more recently partial synthesis and ^{13}C nmr have been used successfully in this area.

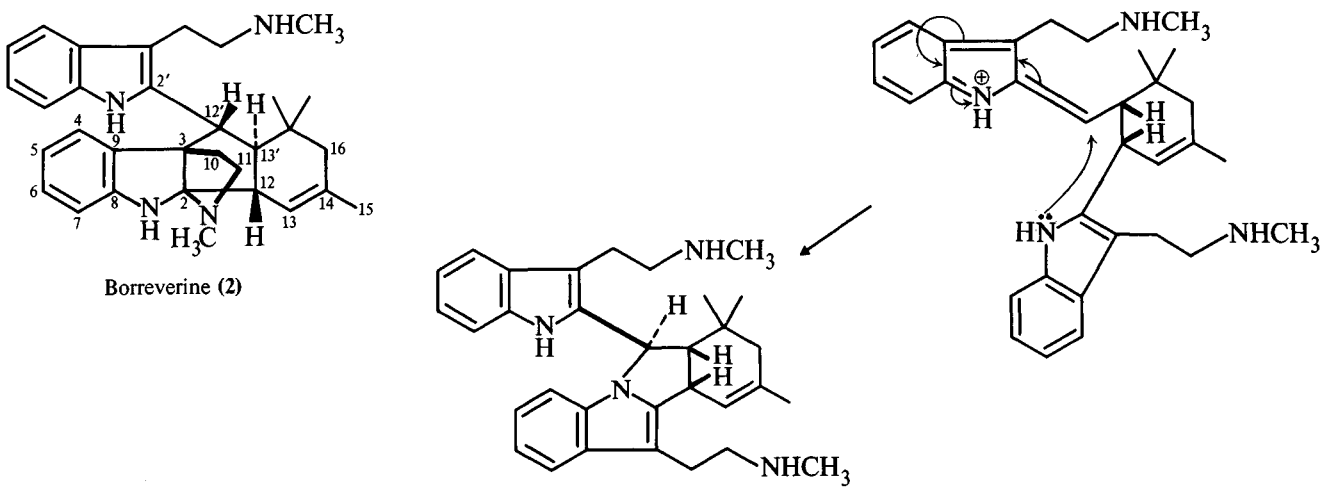
Considerable information can frequently be gained from the mass spectrum of these alkaloids, which typically cleave at the C-16,C-17 bond. Thus, although the molecular ion (*m/e* 450) in usambarine I (**6**) is quite intense (77%), the base peak appears at *m/e* 185 (**7**) with a corresponding fragment at *m/e* 265 (**8**). A competing fragmentation involves cleavage of the C-15,C-16 bond.

The chemical shift of H-3 (3.7 ppm for H-3β, 4.1 ppm for H-3α) and its multiplicity are often preliminary indications of the C-3 stereochemistry, but determination of the C-20 stereochemistry in a dihydro derivative is a more difficult problem.

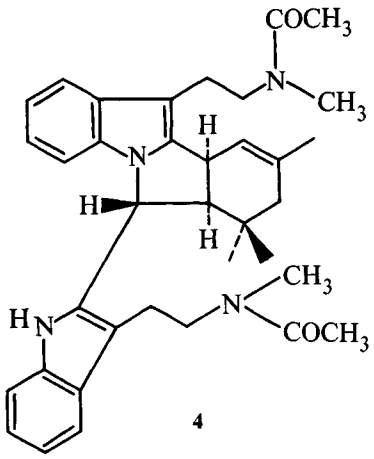
Although the *N*-methyl group appears at a typical chemical shift (2.44 ppm),



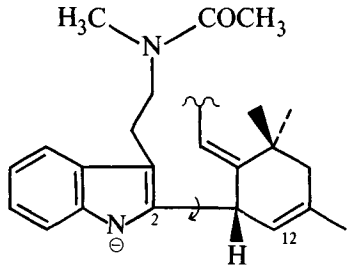
Borrerine (1)



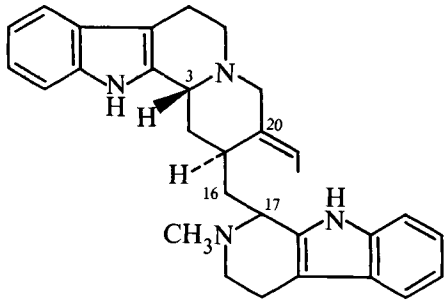
Scheme 1. Mechanism of formation of borreverine (2) and isoborreverine (3) from borrerine (1).



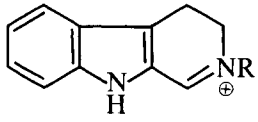
4



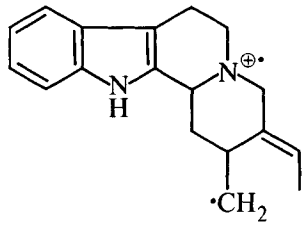
5



Usambarine I (**6**)

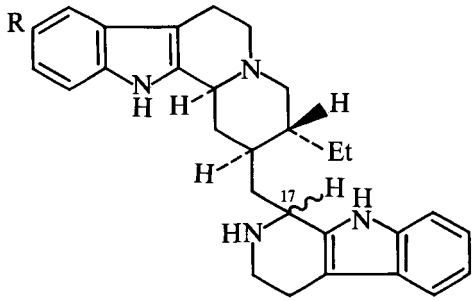


7: R = CH_3, *m/e* 185
15: R = H, *m/e* 171

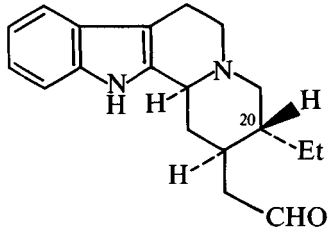


8 *m/e* 265

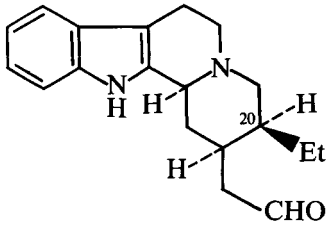
the methyl doublet of the ethylidene side chain is somewhat shielded at 1.22 ppm, presumably by the second indole nucleus. This effect is even more pronounced in ochrolifuanines A (**9**) and B (**10**). In ochrolifuanine A, a triplet for the methyl group is observed at 0.73 ppm, but in ochrolifuanine B this signal is observed at 0.20 ppm.[42,43] Initially, this was thought to be due to isomerization at C-20, but semisynthesis has indicated that this is not the case.



Ochrolifuanine A (**9**): H-17β R = H
Ochrolifuanine B (**10**): H-17α, R = H
13/14: R = OH

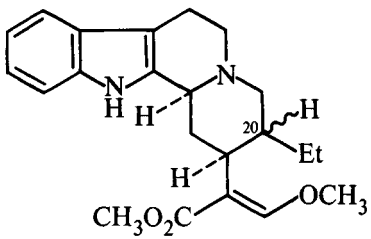


11



12

Condensation of the dihydrocorynantheals **11** (20H-β) and **12** (20H-α) with tryptamine under Pictet-Spengler conditions gave in each instance a mixture of C-17 stereoisomers.[44] Thus, in the four compounds, H-3 and H-15 are both α, leaving the configurations at C-17 and C-20 as either α or β. Determination of the C-17 stereochemistry could be made from the cd spectrum and in this way ochrolifuanine A was assigned the stereochemistry in which H-17 and H-20 are β (**9**), and ochrolifuanine B that in which H-17 is α whereas H-20 is β (**10**).[44] Besides *Ochrosia lifuana* Guill.[42,43] these alkaloids have also been isolated from *Ochrosia miana* H. Bn. ex Guill.,[45] and **10** from *Ochrosia confusa* Pichon.[46] Co-occurring with **9** and **10** in *O. miana*[45] were two hydroxy derivatives **13** and **14** where the uv spectrum and bathochromic shift in alkali indicated the presence of a phenolic group at C-10. An alternative site (C-6′) could be eliminated from the observation of an important fragment ion at *m/e* 171 (**15**). No C-17 stereochemical assignments were made.



16: H-20β
17: H-20α

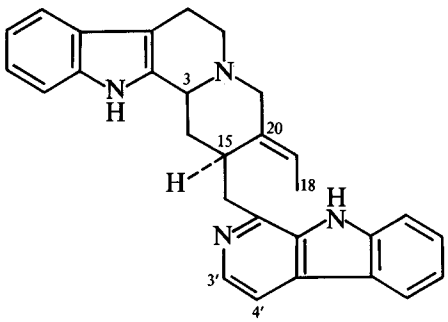
TABLE I. ^{13}C NMR DATA OF PERTINENT CARBONS IN THE OCHROLIFUANINES AND RELATED COMPOUNDS

Compound	Chemical shift, δ (ppm)									
	C-3	C-14	C-15	C-16	C-17	C-18	C-19	C-20	C-21	Ref.
Ochrolifuanine A (9)	59.3	34.3	35.8	38.1	48.8	11.0	23.2	42.2	59.9	47
Ochrolifuanine B (10)	59.5	36.4	37.8	38.4	51.9	11.2	23.8	42.5	60.1	47
(16)	60.2	33.8	38.7			11.3	24.4	39.3	61.3	47
Ochrolifuanine C (40)	60.3	32.4	36.1	37.8	50.9	12.4	17.5	38.3	57.5	47
Ochrolifuanine D (41)	59.4	31.1	35.1	38.4	49.8	12.5	18.6	41.3	57.3	47
(17)	61.3	29.8	40.8			12.8	19.1	40.0	57.9	47
Tchibangensine (42)	53.2	29.0	31.3	36.4	160.9	12.6	119.7	134.9	52.1	57
Ochrolifuanine C (40)	60.5	32.6	36.2	38.3	50.0	12.6	17.7	38.5	57.7	57
Ochrolifuanine D (41)	59.7	31.1	35.3	38.5	49.8	12.6	18.7	41.6	57.7	57

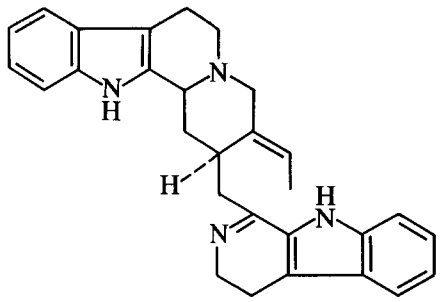
The ^{13}C nmr data for this group of alkaloids[47] (Table I) also support some of the key stereochemical assignments. For example, in comparison with the two dihydrocorynantheine derivatives **16** and **17**, the C-3 chemical shift confirms the trans nature of the C/D ring junction, and the shifts of C-18, C-19, and C-21 distinguish the two alternative stereochemistries at C-20.

The root bark of *Strychnos usambarensis* Gilg. has been used by the Banyambo hunters in Rwanda in arrow poisons, and the Liège group has successfully investigated the alkaloids from both their chemical and pharmacological aspects.[48-52] Besides a number of alkaloids in the curarine series, four ochrolifuanine-type bases were obtained, namely, usambarensine (**18**) and 3′,4′-dihydrousambarensine (**19**) and their corresponding N_b-methyl salts **20** and **21**.

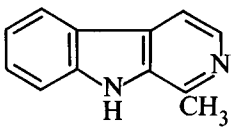
The uv spectrum of usambarensine showed λ_{max} 233, 291, 337, and 349 nm for the presence of both harman (**22**) and indole nuclei. This was supported by the mass spectrum where an ion at *m/e* 182 (**23**) would be derived from the harman moiety, and the ions at *m/e* 251 (**24**, base peak) and 249 (**25**) from the tetrahydro-β-carboline nucleus.



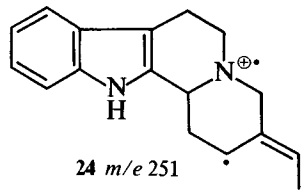
Usambarensine (**18**)
N_b-Methyl-**18** (**20**)



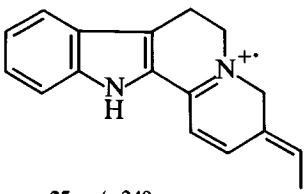
3′,4′-Dihydrousambarensine (**19**)
N_b-Methyl-**19** (**21**)



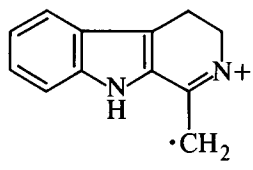
22
23 *m/e* 182



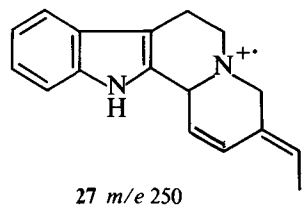
24 *m/e* 251



25 *m/e* 249



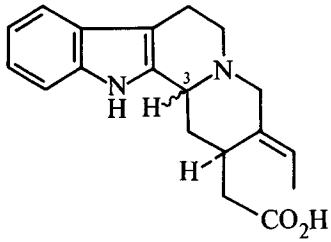
26 *m/e* 183



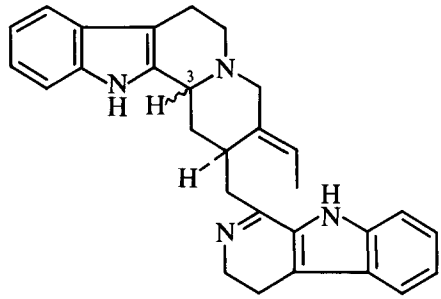
27 *m/e* 250

Doublets ($J = 5$ Hz) at 8.52 and 7.86 ppm for the 3′ and 4′ protons also support a harman moiety, but besides typical signals for the aromatic protons, the NH protons (8.09 and 10.8 ppm), and an ethylidene group (methyl doublet now at 1.67 ppm), little additional information was available.[48] Oxidation [$Hg(OAc)_2$] and reduction (Zn/HCl) afforded a product different from the starting material, suggesting an H-3β stereochemistry for usambarensine.[48]

The second alkaloid isolated was a dihydrousambarensine and from the uv spectrum (λ_{max} 229, 284, 291, and 318 nm) the isolate was comprised of indole and harmalane nuclei. Mass spectrally, major fragment ions were observed at *m/e* 183 (**26**) and 250 (**27**, base peak). No deshielded aromatic protons were observed (for H-3′ and H-4′), but the aliphatic proton region was more complex and consequently the structure 3′,4′-dihydrousambarensine (**19**) was assigned.[48]

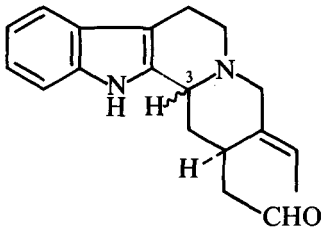


28: H-3α
31: H-3β

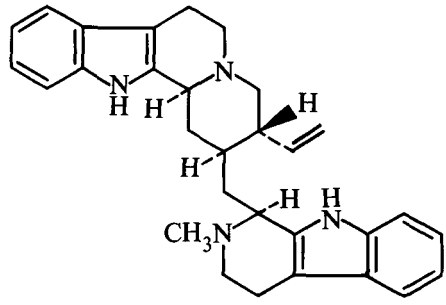


3′,4′-Dihydrousambarensine (**29**): H-3α
30: H-3β

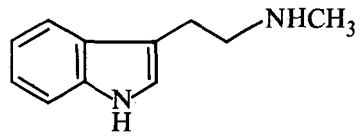
Condensation of geissoschizoic acid (**28**) with tryptamine in the presence of dicyclohexylcarbodiimide followed by cyclization of the intermediate amide with phosphorus oxychloride gave 3′,4′-dihydrousambarensine (**29**),[53] and analogously 3-epi-3′,4′-dihydrousambarensine (**30**) was prepared from 3-epigeissoschizoic acid (**31**). Unfortunately the structure of usambarensine itself was not confirmed at this time. However, when attention was refocused on usambarine,[54] which had been assigned the structure **6**,[55] some quite fundamental problems were illuminated. Thus condensation of geissoschizal (**32**) or 3-epigeissoschizal (**33**) with *N*-methyltryptamine (**34**) in 0.3 *M* sulfuric acid at 103° did not yield usambarine.[54] And when usambarine was reisolated from the leaves of *S. usambarensis*, it was found that the ^{1}H nmr spectrum showed a three-proton multiplet for a vinyl group in the region 4.95–5.46 ppm. The stereochemistry at C-15 was assumed on biogenetic grounds,[56] and since usambarine showed a Cotton effect analogous to that observed for ochrolifuanine B,[54] the structure **35** was proposed although no definitive evidence for the stereochemistry of C-20 was presented. However, condensation of corynantheal and *N*-methyltryptamine did afford **35**.[54a] Usambarine has also been isolated from *S. nigritana* Bak.[54b,54c]



Geissoschizal (**32**): C-3Hα
3-Epigeissoschizal (**33**): c-3Hβ

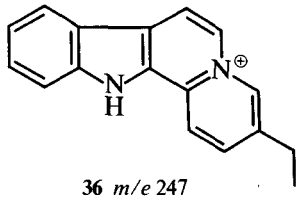


Usambarine (**35**)

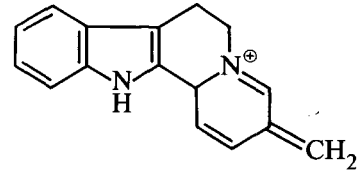


34

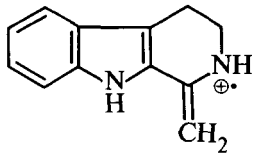
The major alkaloid of the root and stem bark of *Strychnos tchibangensis* Pellgr. was tchibangensine,[57] displaying a uv spectrum (λ_{max} 227, 286, 293, and 319 nm) for the summation of indole and harmalane chromophores. In the mass spectrum important ions were observed at *m/e* 250, 249, 247, 235, 184, and 183, respectively assigned the structures **26**, **25**, and **36–39**. An ethylidene group, two indolic NH groups, and eight aromatic protons were the principal features of the nmr spectrum, and when catalytic reduction yielded a mixture of ochrolifuanine C (**40**) and ochrolifuanine D (**41**) identical with the synthetic products,[44] tchibangensine was assigned the structure **42**.[57]



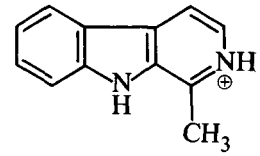
36 *m/e* 247



37 *m/e* 235



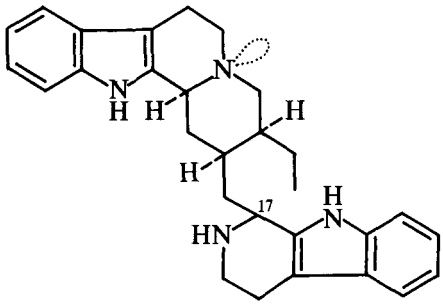
38 *m/e* 184



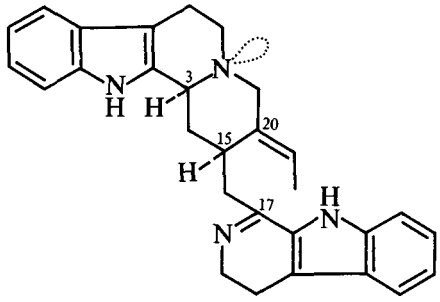
39 *m/e* 183

A cis C/D ring junction was substantiated by the lack of Bohlmann bands and the similar carbon chemical shift of C-3 (53.2 ppm) to that in geissoschizine (53.6 ppm) (Table I). Oxidation of tchibangensine (**42**) with cuprous chloride

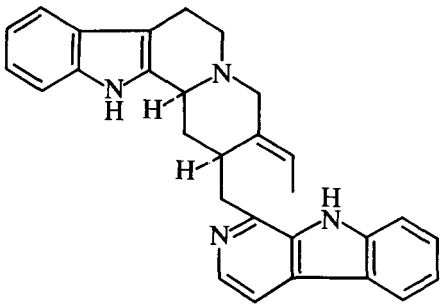
afforded usambarensine (1.7% yield), thereby establishing the structure of this alkaloid to be **43**.[57] Whether tchibangensine (**42**) and 3′,4′-dihydrousambarensine (**29**) are identical is unclear, for there is some confusion[48,49,51] concerning the C-3 stereochemistry of **29**.



Ochrolifuanine C (**40**):H-17α
Ochrolifuanine D (**41**):H-17β



Tchibangensine (**42**)

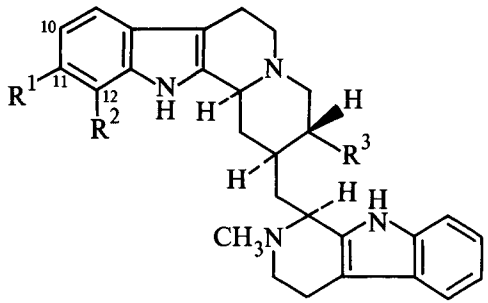


Usambarensine (**43**)

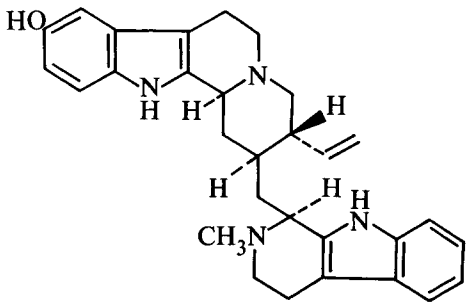
Angenot and co-workers have made substantial studies of *S. usambarensis*[52,54,58] and have reported the isolation of 18,19-dihydrousambarine (**44**).[52] A characteristic base peak at *m/e* 185 (**7**) indicated the two mass units to be in the corynane unit, and Bohlmann bands in the ir spectrum and a strong positive Cotton effect indicated 3*S*, 4*R*, and 17*S* configurations. The 15*S* configuration was assigned on biogenetic grounds and the 20*R* configuration from the asymmetric nature of the methyl triplet at 0.82 ppm.[52] The isolate was not correlated with usambarine (**35**) and the relationship to nigritanin from *S. nigritana*[54b,54c] is unknown.

A number of phenolic alkaloids have also been isolated from *S. usambarensis*. "Usambaridine" was the first of these,[59] but its structure was not fully elucidated. The Belgian group separated "usambaridine" into two components,[52] each having the molecular formula $C_{30}H_{34}N_4O$, where the additional oxygen atom was traced to a phenol. Typical proton nmr absorptions were observed for a vinyl group and an *N*-methyl group in each compound, and a base peak at *m/e* 185 (**7**) limited the phenolic substitution to ring A. In one alkaloid, a doublet ($J = 2$ Hz) at 6.22 ppm and a doublet of doublets ($J = 8$, 2 Hz) at 6.45 ppm indicated the phenolic group

to be at C-11. In contrast, the other alkaloid showed two doublets ($J = 9$ Hz) at 6.58 and 6.87 ppm for H-9 and H-11, placing the phenolic group at C-12. The Cotton effects of these alkaloids were similar to usambarine (**35**) and consequently the structures 11-hydroxyusambarine (**45**) and 12-hydroxyusambarine (**46**) were assigned.[52] Also isolated were the corresponding 18,19-dihydro derivatives **47** and **48**.[52] Strychnobaridine is a member of this series containing two phenolic groups,[52] but it could well be a mixture.[16]



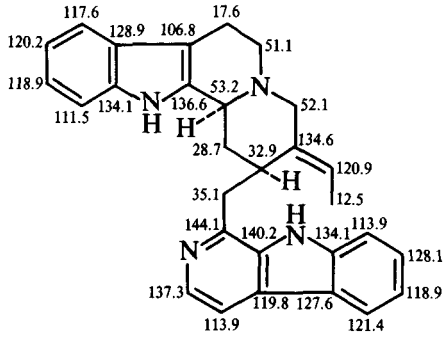
	R^1	R^2	R^3
18,19-Dihydrousambarine (**44**)	H	H	$-CH_2CH_3$
11-Hydroxyusambarine (**45**)	OH	H	$-CH=CH_2$
12-Hydroxyusambarine (**46**)	H	OH	$-CH=CH_2$
18,19-Dihydro-12-hydroxyusambarine (**47**)	H	OH	$-CH_2CH_3$
18,19-Dihydro-11-hydroxyusambarine (**48**)	OH	H	$-CH_2CH_3$



10-Hydroxyusambarine (**49**)

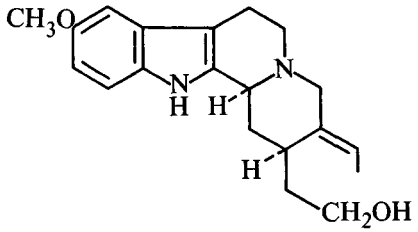
More recently the structure of 12-hydroxyusambarine has been revised to 10-hydroxyusambarine (**49**).[60] Important factors were a reevaluation of the uv spectrum and of the aromatic region in the ^{1}H nmr spectrum in $CDCl_3/CD_3OD$ (1 : 1) which showed H-9 as a doublet ($J = 2$ Hz) at 6.78 ppm, H-11 as a doublet of doublets ($J = 2$, 8.5 Hz) at 6.67 ppm, and H-12 as a doublet ($J = 8.5$ Hz) at

7.04 ppm. This compound may be the same as the nigritanin derivative described by Oguakwa and co-workers.[54b,54c] This group has also described preliminary details of the ^{13}C nmr spectrum of nigritanin,[54d] but more definitive data for compounds in the usambarensine series are available from Coune and co-workers,[54e] and the data for usambarensine itself are shown in **49a**.

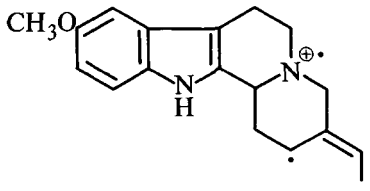


49a

Although the roots of *Rauwolfia obscura* K. Schum. had been investigated, a quite different spectrum of alkaloids was observed when the leaves were examined[61]; one of the monomeric alkaloids obtained was 10-methoxygeissoschizol (**50**), together with four bisindole alkaloids B_1, C_2, D_1, and D_2. Structural information is available only for B_1, which differed from the other members of the series by lacking an *N*-methyl group and possessing an aromatic methoxy group (singlet at 3.80 ppm), suggested to be at C-10. Important fragment ions were observed at *m/e* 281 (**51**) and *m/e* 185 (**52**, base peak). On the basis of this similarity of the ir spectra of **50** and alkaloid B_1, the latter alkaloid was assigned the structure **53**,[61] although the C-3 stereochemistry was not proved.

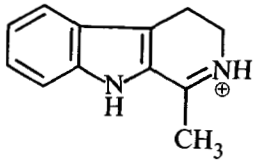


10-Methoxygeissoschizol (**50**)

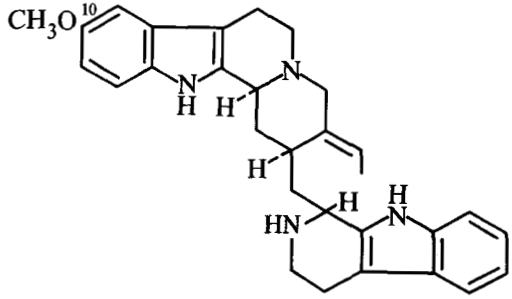


51 *m/e* 281

Cinchophyllamine and isocinchophyllamine from *Cinchona ledgeriana* Moens leaves were actually the first alkaloids[62] to be obtained in this series. Early structural work[63] had indicated that cinchophyllamine had either the gross structure **54** or **55**, of which the latter was preferred on mass spectral grounds. Isocinchophyllamine

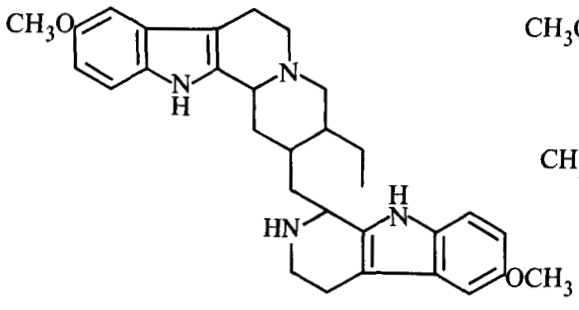


52 *m/e* 185

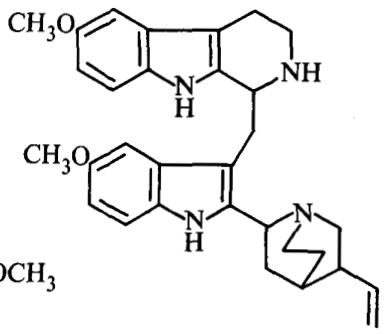


Alkaloid B_1 (**53**)

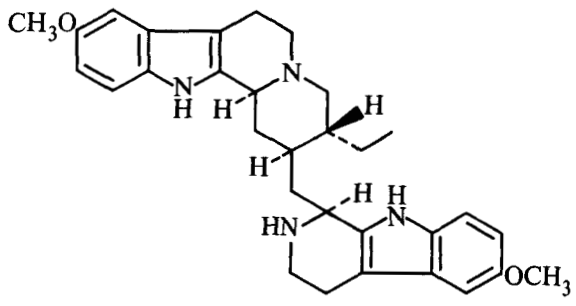
was thought to be a stereoisomer, but when this alkaloid was submitted to single crystal X-ray crystallography[64] it was found that it has the structure **56**. Reexamination of the leaves of *Cinchona ledgeriana* led to the isolation of seven bisindole alkaloids,[65,65a] including cinchophyllamine (**56a**), 3-epicinchophyllamine (**56b**), and 17-epicinchophyllamine (**56c**) as the major compounds. Together with isocinchophyllamine, which was reestablished as 3-epi-17-epicinchophyllamine (**56**), these compounds represent the four stereoisomers of this system.



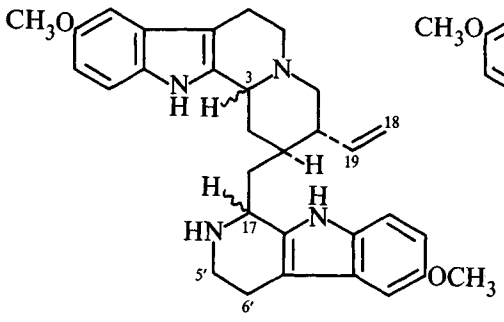
54



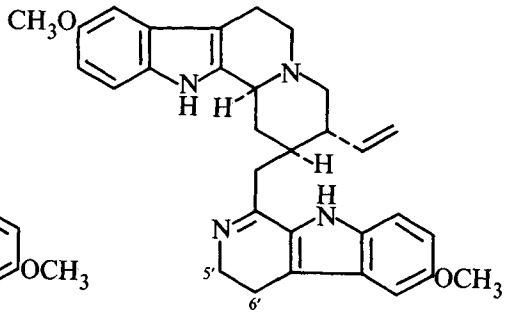
55



56

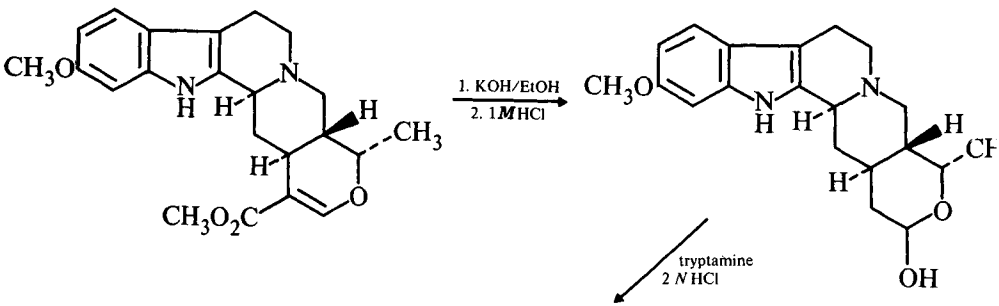


	3-H	17-H
56	α	α
56a	β	β
56b	α	β
56c	α	β
56f	β	β, 18,19-H_2



56d $\Delta^{5',6'}$

56e



	3-H	17-H
56i	α	α
56j	α	β
56k	β	α
56l	β	β

Three interlocking parameters could be used to determine the C-3 and C-17 stereochemistries in these compounds; the presence or absence of Bohlmann bands, the number of protons between 4 and 4.5 ppm, indicative of a C/D *cis*-quinolizidine, and the Cotton effect observed at 280 nm. Carbon-13 nmr spectral parameters were obtained for all four compounds.[65a] As expected, C-6, C-15, C-20, and C-21 show distinct upfield shifts on changing from an α to a β stereochemistry at C-3 due to increased steric interactions. But less definitive information was obtained for deducing the C-17 stereochemistry although upfield shifts in the 17β-H series for C-14, C-15, C-16, and C-17 may be diagnostic.

The three minor bisindole alkaloids[65] **56d**, **56e**, and **56f** are close relatives in this series; their structures were determined from their spectral properties and chemical correlations.

A new synthesis of this skeletal type involves condensation of the hemiacetal **56g**, derived from tetraphylline (**56h**), with tryptamine under acidic conditions, to afford a mixture of **56i** (58% yield), **56j** (30%), **56k** (6.78%), and **56l** (4.9%).[65a]

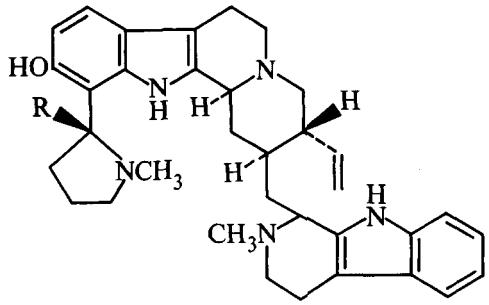
The most novel alkaloid in this series is strychnopentamine from *S. usambarensis*.[52,58] Analysis of the molecular ion (*m/e* 549) indicated a molecular formula $C_{35}H_{43}N_5O$ and the oxygen function was traced to a phenolic group even though it showed no bathochromic shift on addition of base. Although the mass spectrum, with a base peak at *m/e* 185, indicated the lower unit to be unsubstituted, a unique structure was only obtained by X-ray crystallography.[58] Strychnopentamine having the structure **57**, therefore, joins a select group of alkaloids including nicotine, brevicolline, ficine, and macrostomine, which contain an *N*-methylpyrrolidine unit attached to an aromatic ring. Two isomers were also isolated[52] but their structures, subsequently suggested[16] to be **58** and **59**, remain to be proved.

B. The Roxburghines

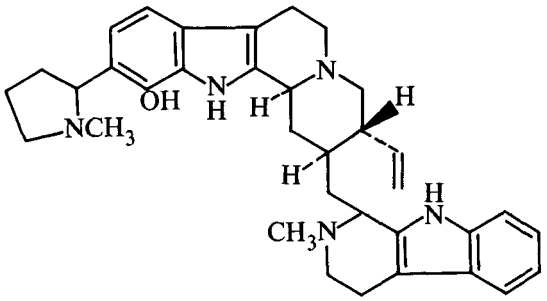
The leaves and stems of *Uncaria gambier* Roxb. (Rubiaceae) have yielded a rather interesting group of five alkaloids, the roxburghines A–E, which are isomers of the molecular formula $C_{31}H_{32}N_4O_2$.[66] Two indolic NH groups were observed in the nmr spectrum together with a single, deshielded, olefinic proton (7.53 ppm), a carbomethoxy group (3.64 ppm), and a tertiary methyl (1.21 ppm). Because it was the major alkaloid isolated, most of the chemistry was carried out on roxburghine D.

From catalytic reduction, which yielded a dihydro derivative, it was deduced that a vinylogous urethane was present. Partial dehydrogenation of roxburghine D afforded a pyridinium species showing two low-field ortho-related aromatic protons at 8.43 and 8.78 ppm and a deshielded olefinic proton at 8.76 ppm. On the basis of elegant decoupling experiments two alternative structures **60** and **61** were suggested for roxburghine D, of which **60** would be favored biogenetically.[66]

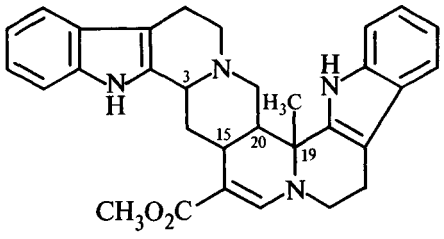
The series of alkaloids could be interrelated chemically, for dehydroroxburghines B and E were identical as were dehydroxburghines C and D. These two dehydroroxburghines must therefore differ in the stereochemistry of the 19-methyl group.[66]



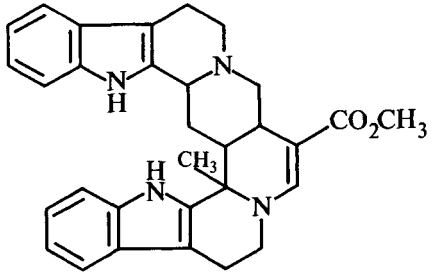
Strychnopentamine (**57**): R = β-H
Isostrychnopentamine A (proposed) (**58**): R = α-H



Isostrychnopentamine B (proposed) (**59**)



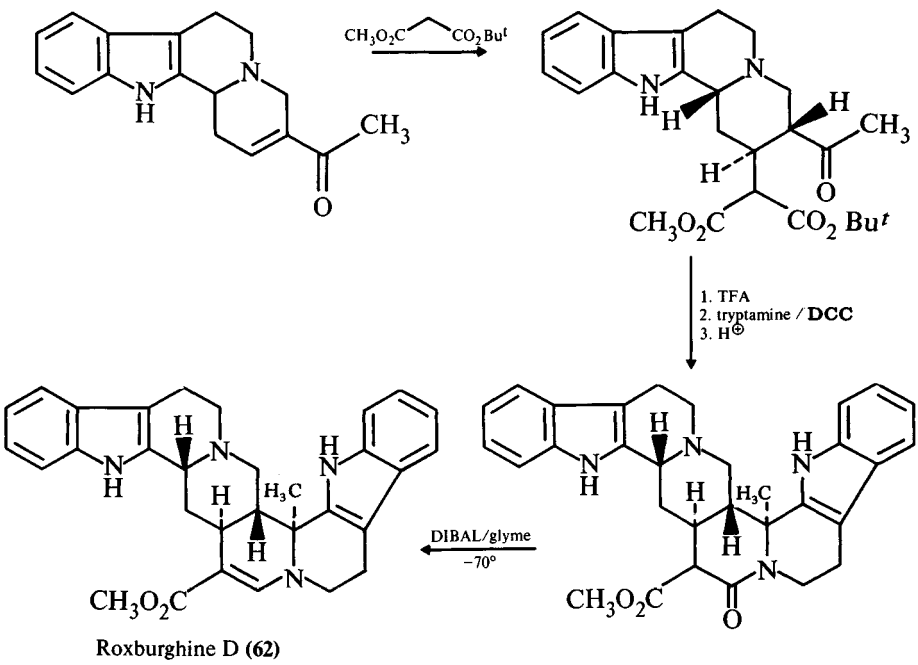
60



61

Heating roxburghine E in zinc and acetic acid afforded roxburghine B, suggesting that these alkaloids differed only in configuration at C-3, being α in roxburghine B[66,67] (this was subsequently revised). From the ^{1}H nmr spectrum of roxburghine E it was deduced that these alkaloids differed only in configuration of C-19.[68,69]

Since in all indole alkaloids having a 15-H, this proton is α, based on a biosynthesis from loganin,[56] the two possibilities for the configurations of roxburghine D (and E) are 3β, 15α, 19α, 20β and 3β, 15α, 19β, 20β.[66] A distinction was made through Winterfeldt's elegant total synthesis (Scheme 2),[70] which indicated a 19α-CH_3 and the complete structure **62**.



Roxburghine D (62)

Scheme 2. Winterfeldt synthesis of roxburghine D (62).[70]

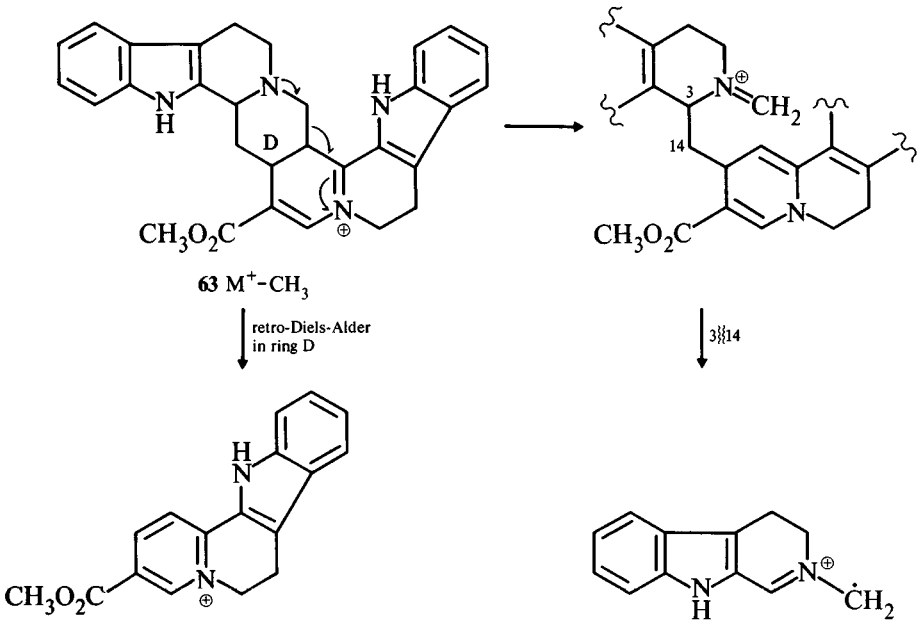
Additional ^{1}H nmr data[69] then permitted complete stereochemical assignments to be made for roxburghines B–E as follows:

	C-3	C-19
Roxburghine B	α	β
Roxburghine C	α	α
Roxburghine D	β	α
Roxburghine E	β	β

The mass spectra of these alkaloids indicated some interesting fragmentation schemes.[66] Reactions from the M^+—CH_3 ion **63** were suggested (Scheme 3) to account for the important fragment ions at *m/e* 184 (**64**) and 279 (**65**). In the case of roxburghine D (**62**) the ion at *m/e* 321 (**66**) depends on the presence of the 16,17-double bond as shown in Scheme 4.

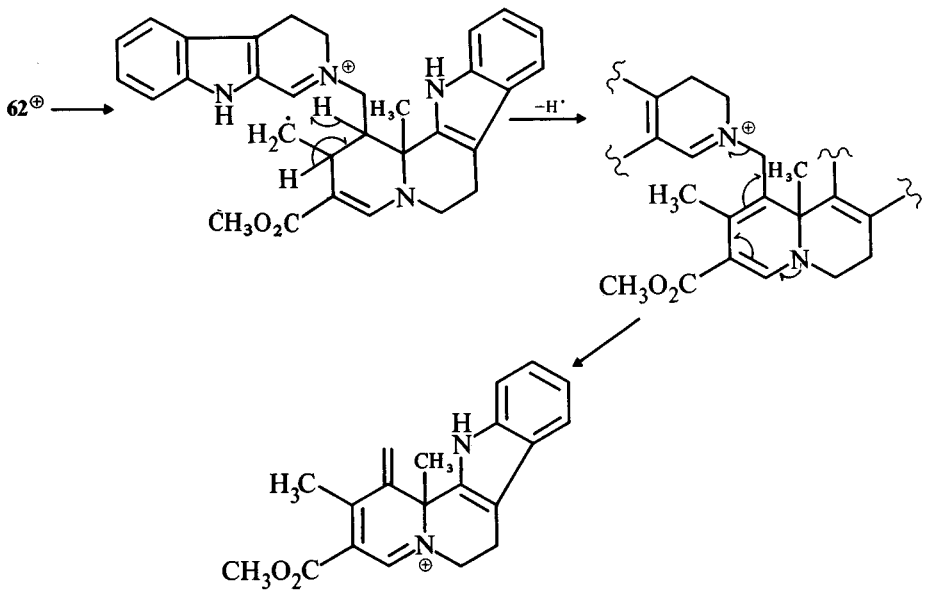
Subsequently it became necessary to revise the C-3 stereochemistry of H-3 in roxburghine B from α to β. Thus analysis of the 300 MHz nmr spectrum by the INDOR technique indicated the chemical shifts and coupling constants for the aliphatic protons as summarized in Table II.

The coupling constants of H-15 and H-20 indicated that the former is equatorial and the latter axial. Since H-3 couples with H-14 axial to the extent of 11.5 Hz, this proton should also be axial and β-oriented. Roxburghine B therefore has the struc-



63 M^+-CH_3 **65** *m/e* 279 **64** *m/e* 184

Scheme 3.



66 *m/e* 321

Scheme 4.

TABLE II. PROTON NMR DATA FOR ROXBURGHINE B (67)[a]

Signal	Chemical shift		Coupling constants, J (Hz)			
	Acetone	BPA[b]				
H-3	3.19	3.73	3,14ax	11.5;	3,14eq	2.5
H-14ax	1.49	1.66	14ax,14eq	−13.0;	14ax,15	2.5
H-14eq	3.31	3.47	14eq,15	2.5		
H-15	2.74	~3	15,20	⩽2;	15,17	2.0
H-20	2.90	~3	20,21eq	5.0;	20,21ax	11.0
H-21eq	3.10	3.17	21ax,21eq	−10.5		
H-21ax	2.60	2.67				
H-5'ax	3.75	3.58	5'ax,5'eq	−13.5;	5'ax,6'ax	11.0
H-5'eq	3.61	3.37	5'eq,6'ax	6.5;	5'eq,6'eq	⩽1
H-6'ax	2.86	2.82	6'ax,6'eq	−15.0		
H-6'eq	2.71	2.62	5'ax,6'eq	5.0		
H-17	7.42	–	5'eq,17	⩽1		

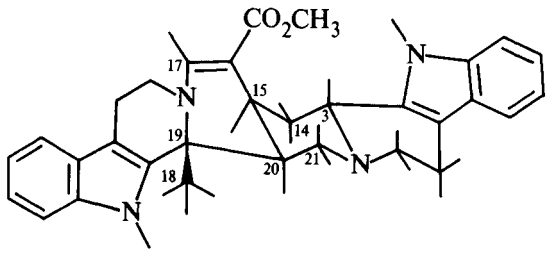
[a] Data are from Ref. 71.
[b] Benzene/pyridine/acetone 30:65:5 (v/v).

TABLE III. ^{13}C NMR DATA FOR THE ROXBURGHINES

Carbon	Chemical shift, δ (ppm)			
	Roxburghine D (62)	Roxburghine E (70)	Roxburghine C (71)	Roxburghine B (67)
C-2	132.9	132.3	136.5[a]	136.5
C-3	54.0	55.1	60.6	56.0
C-5	51.4	52.1	54.0	54.2
C-6	17.6	17.5	22.7[b]	22.7[b]
C-7	108.1	109.7	109.9	108.1
C-14	32.9	32.8	35.3	32.0
C-15	30.6	29.5	36.1	30.3
C-16	95.1	105.7	96.2	102.3
C-17	144.8	149.1	146.9	149.0
C-18	18.1	26.9	18.7	26.6
C-19	57.7	58.1	58.5	57.7
C-20	49.4	49.3	50.0	42.7
C-21	48.1	48.6	57.9	52.9
CO_2CH_3	49.4	50.8	50.1	50.8
CO_2CH_3	165.4	167.8	167.7	168.2
C-2'	135.3	137.2[a]	137.2[a]	137.0[a]
C-5'	49.9	47.4	50.7	46.6
C-6'	23.0	23.0	23.3[b]	23.0[b]
C-7'	106.0	107.6	107.7	106.8
C-8,C-8'	125.5, 126.8	127.7, 128.7	127.3, 128.1	128.2
C-9,C-9'	116.4, 117.0	118.7, 118.8	118.1, 118.8	118.2, 118.5
C-10,C-10'	117.5, 118.0	119.8, 120.0	119.2, 119.7	119.3, 119.6
C-11,C-11'	119.5, 120.4	122.1, 122.4	121.1, 122.2	121.2, 121.9
C-12,C-12'	110.2, 110.4	112.2, 112.4	111.7, 111.9	111.8, 112.0
C-13-C-13'	135.3	137.4[a], 137.7[a]	137.3[a], 137.4[a]	137.5[a], 139.4[a]

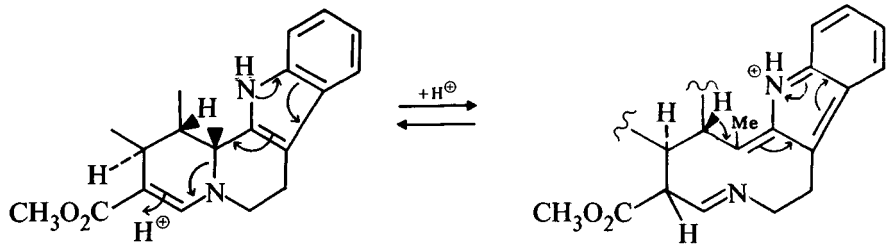
[a,b] Signals may be interchanged.

ture **67**, where it is shown in its preferred conformation.[71] It had been found previously that roxburghine E could be converted to roxburghine B with zinc-acetic acid[42] and this now must be interpreted in terms of an inversion of C-20[73] for which the mechanism shown in Scheme 5 can be proposed.

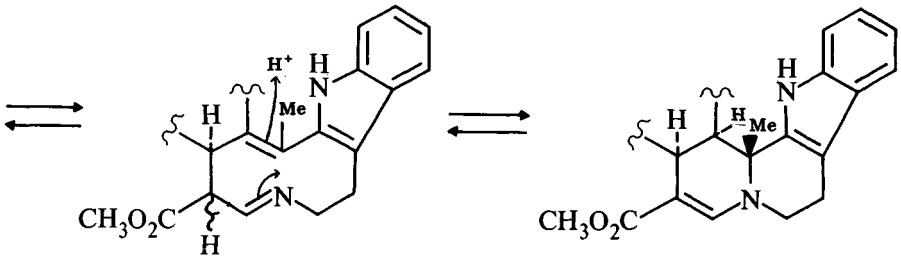


Preferred conformation of roxburghine B (**67**)

The reassignment of the C-3 stereochemistry of roxburghine B was substantiated when the ^{13}C nmr spectra of the roxburghines were examined.[72] These data are shown in Table III, and crucial in establishing the carbon shifts was the availability[73] of data on the ajmalicinoid systems, particularly ajmalicine (**68**) and 3-epi-19-epiajmalicine (**69**).

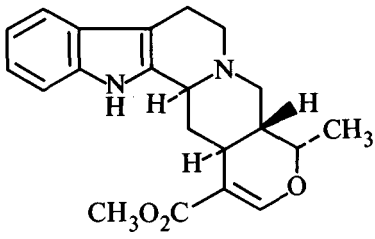


Roxburghine E (**70**)

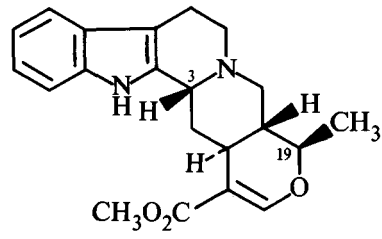


Roxburghine B (**67**)

Scheme 5.



Ajmalicine (**68**)



3-Iso-19-epiajmalicine (**69**)

Roxburghines D (**62**) and E (**70**) belong to the pseudo ajamalicinoid series having characteristic shifts of C-3 (54 ppm) and C-6 (17 ppm), and are distinguished by the chemical shift for C-18. For when C-18 is β, the γ effects of C-15 and C-17 are greatly reduced and this carbon is therefore deshielded to 26.9 ppm.

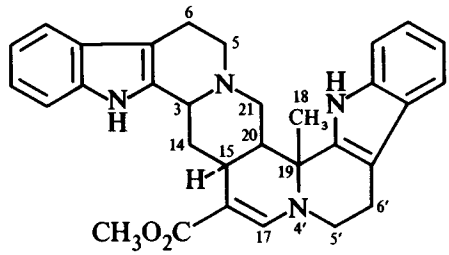
Roxburghine C (**71**) has the normal ajmalicinoid system displaying C-3 in the region of 60 ppm and C-6 at 21.5 ± 0.5 ppm. Roxburghine B (**67**), on the other hand, is a member of the C/D trans epiallo series where C-3 and C-6 appear in the ranges 54.5 ± 0.5 and 21.5 ± 0.5 ppm, respectively. Clearly the chemical shift of C-18 in **67** and **70** indicates that they have similar spatial environments (i.e., that C-18 is β), in agreement with the revised structure of roxburghine B.[72]

IV. *CORYNANTHE-CORYNANTHE* TYPE

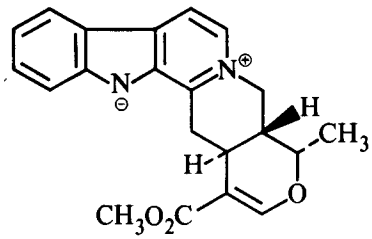
Only one alkaloid is known which is formed by the joining of two *Corynanthe* units, namely, serpentinine, obtained by Djerassi and co-workers from *Rauwolfia serpentina* Benth. ex Kurz (Apocynaceae).[74]

The uv spectrum was the sum of serpentine (**72**) and tetrahydro-β-carboline chromophores and consequently serpentinine exhibits two pK_a values (6.0 and 10.6). In the ir spectrum saturated ester (1730 cm^{-1}) and β-alkoxy-α,β-unsaturated ester (1705 and 1616 cm^{-1}) units were substantiated by the nmr spectrum (singlets at 3.45 and 3.75 ppm). Two three-proton doublets at 1.23 and 1.90 ppm were originally assigned to secondary methyl groups adjacent to oxygen. From these data and some chemical degradative evidence the structure **73** was proposed for serpentinine.[75]

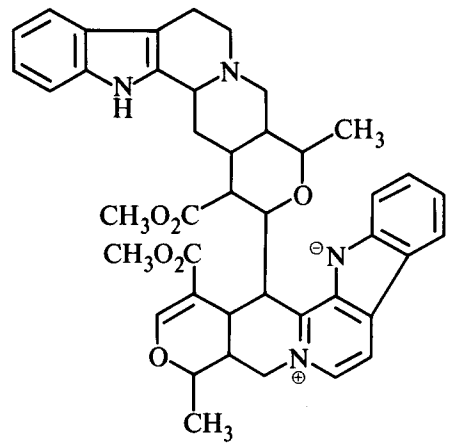
Subsequently,[76] sodium borohydride reduction afforded two tetrahydro-serpentinines having molecular ions at *m/e* 704, and an important fragment ion at *m/e* 438 ($C_{25}H_{30}N_2O$) shifted to *m/e* 441 when sodium borodeuteride was used, and to *m/e* 439 when the tetrahydroserpentinine was treated with sodium methoxide–sodium deuteroxide. The fragment ions at *m/e* 351 and 352 were shifted to *m/e* 354 and 355 in the borodeuteride product and *m/e* 352 and 353 in the deuterium exchange product. The ion at *m/e* 352 therefore involves transfer of the α proton to the lower "half" of the molecule which is bound to C-17 of the upper "half." This limits the linkage points to C-5′, C-6′, C-15′, or C-21′.



	H-3	H-20	C-18
Roxburghine D (62)	β	β	α
Roxburghine B (67)	β	α	β
Roxburghine E (70)	β	β	β
Roxburghine C (71)	α	β	α



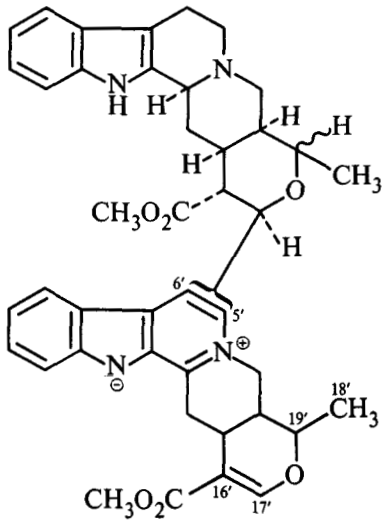
Serpentine (72)



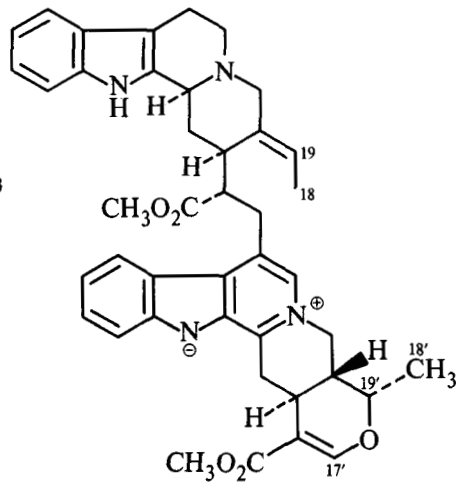
73

The 220 MHz nmr spectrum, with singlets at 7.6 and 7.3 ppm (one of these is H-17) indicated the linkage to be either at C-5 or C-6. A "quartet" at 5.85 was found to be H-19 or H-19′ and a two-proton multiplet at 4.55 ppm contained H-19′ or H-19. Being adjacent to a quaternary nitrogen, the equatorial H-21′ appeared as a doublet of doublets ($J = 4.5$ and 18.5 Hz) at 4.75 ppm. The structure **74** was then assigned to serpentinine with the linking point of the lower unit left undefined. But the deshielding of the proton at 4.45 ppm (shifted to 4.3 ppm in the tetrahydro derivative) suggested that there were still problems to be resolved.[15]

X-ray crystallographic analysis of the dihydrobromide dihydrate[77] established the structure **75** ($C_{42}H_{44}N_2O_5$). The mass spectral studies discussed above remain to be presented in terms of the revised structure.



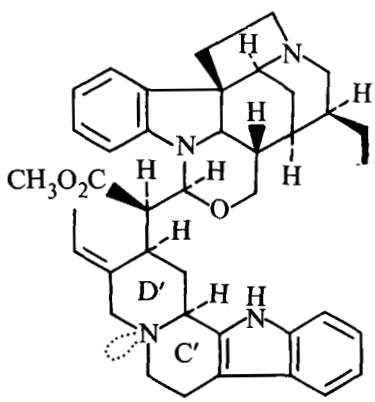
74



Serpentinine (75)

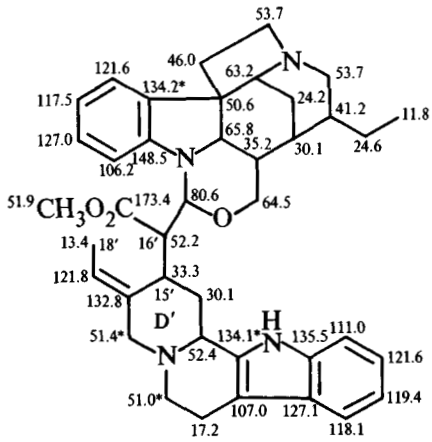
V. *CORYNANTHE-STRYCHNOS* TYPE

Geissospermine from the Brazilian tree *Geissospermum laeve* (Vellozo) Baillon was first isolated in 1877[78] and the structure **76** was deduced in 1959.[79] The stereochemistry of the 16′-17′ linkage and of the C′/D′ ring junction were established by X-ray analysis.[80,80a] It was surprising to find the N-4′ lone pair and the C-3′ proton to be cis and the conformation of ring D′ to be such that the 15′-16′ bond is axially oriented.



Geissospermine (76)

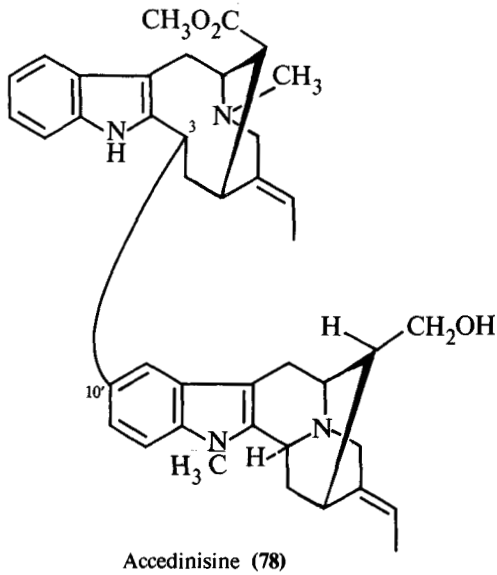
The ^{13}C nmr spectrum of geissospermine is shown in **77**.[81] The C-3′ and C-6′ shifts confirm the *cis*-quinolizidine unit in solution and the C-18′ and C-15′ chemical shifts indicate a δ interaction between C-15′ and C-18′, confirming C-16′ to be axial with respect to ring D′.[81]



77 (*denotes that assignments may be reversed)

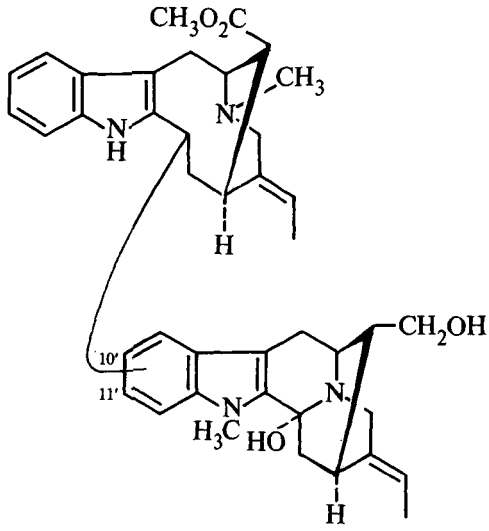
VI. VOBASINE-VOBASINE TYPE

There are three alkaloids in this group; accedinisine (**78**) and accedinine (**79**) from *Tabernaemontana accedens* Muell.-Arg. (Apocynaceae),[82] and gardmultine (**80**) from *Gardneria multiflora* Makino (Loganiaceae).[83,84]

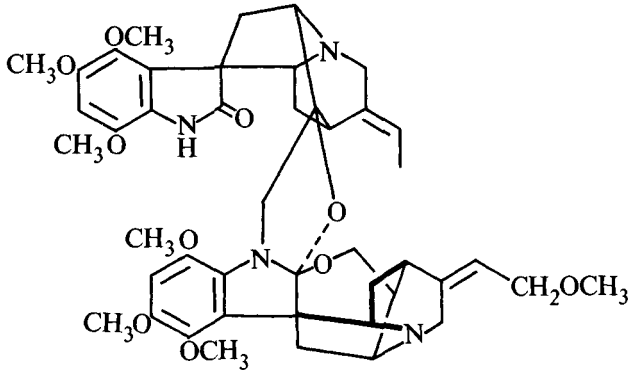


Accedinisine (**78**)

Accedinisine, with an indolic uv chromophore, afforded cycloaffinisine (**81**) on acid hydrolysis. Two ethylidene groups were indicated from the ^{1}H nmr spectrum, together with an aliphatic *N*-methyl group at 2.58 ppm and an indolic



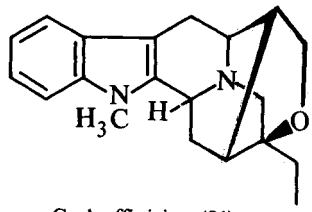
Accedinine (79)



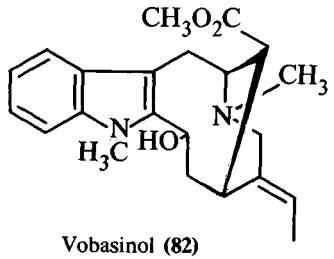
Gardmultine (80)

N-methyl group at 3.54 ppm. A highly shielded carbomethoxy group at 2.36 ppm is typical of a vobasinol (82) unit, and a doublet ($J = 10$ Hz) at 4.64 ppm for H-3 with a C-9 proton at 7.20 ppm indicated the structure 78. Condensation of vobasinol (82) with affinisine (83) in 3 *M* aqueous methanolic acid under reflux afforded a low yield of 78.[82]

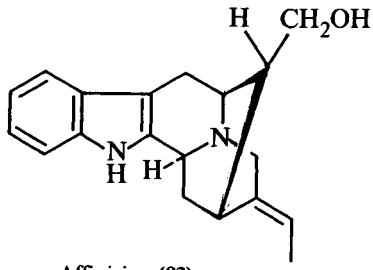
Accedinine ($C_{41}H_{48}N_4O_4$) also afforded cycloaccedine (84) on acid hydrolysis but yielded an *N,O*-diacetate (λ_{max} 320 nm) on acetylation. Similar proton absorptions were observed for ethylidene, indolic *N*-methyl, aliphatic *N*-methyl, and carbomethoxy groups. A doublet ($J = 15$ Hz) was observed at 4.28 ppm and assigned to the C-21 α-H of the accedine (85) unit. Accedinine was assigned the partial structure 79.[82]



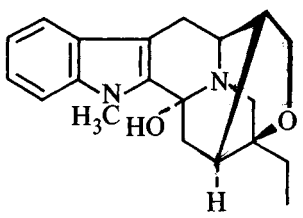
Cycloaffinisine (**81**)



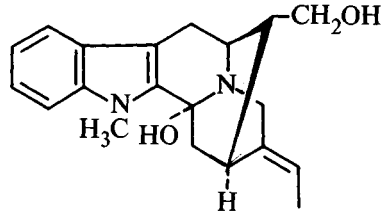
Vobasinol (**82**)



Affinisine (**83**)

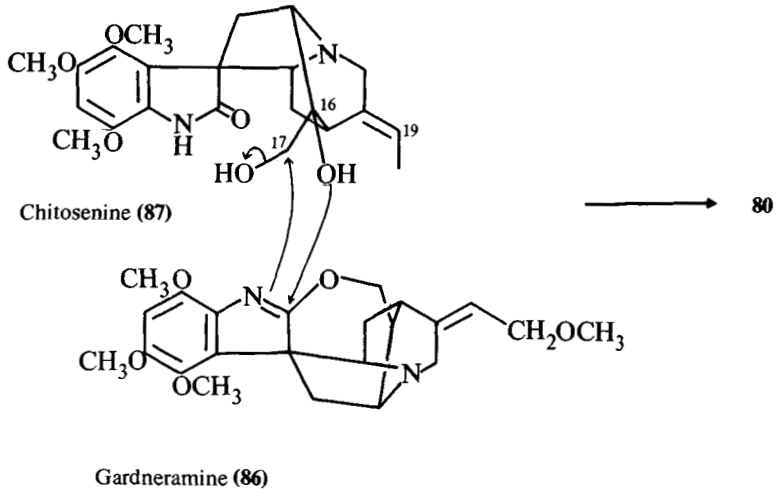


Cycloaccedine (**84**)



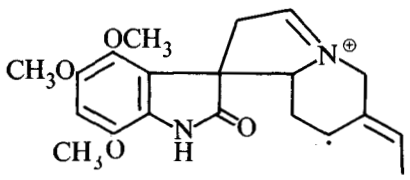
Accedine (**85**)

The nmr spectrum of gardmultine ($C_{45}H_{54}N_4O_{10}$) (**80**) showed seven methoxyl groups, six aromatic and one aliphatic, an ethylidene group with a shielded methyl doublet at 0.88 ppm, and an olefinic proton (5.26 ppm) coupled to a methylene at 3.84 ppm. The unusual uv spectrum (λ_{max} 213, 247, and 305 nm) was traced to a summation of 4,5,7-trimethoxyindoline and 4,5,7-trimethoxyoxindole chromophores. These data suggested that the two monomer units (Scheme 6) could be gardneramine (**86**)[85] and chitosenine (**87**)[86] which co-occur with gardmultine.

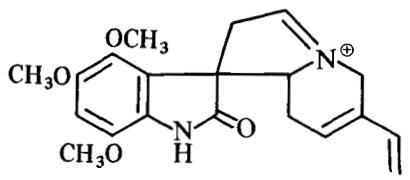


Scheme 6.

Prominent ions at *m/e* 412 and 398 were ascribed to gardneramine (**86**) and dehydrochitosenine, and ions at *m/e* 356 and 355 were assigned the structures **88** and **89**, respectively.[86]



88 *m/e* 356



89 *m/e* 355

Acid (HCl) cleavage of gardmultine gave an oxindole product where the olefinic methyl group now appeared at 1.43 ppm, indicating that an ether linkage between C-2 and C-17 is vital for inducing shielding of the olefinic methyl.

The remaining linkage was resistant to both acid and base cleavage and was envisaged as being between N_a of gardneramine and C-17 of chitosenine. The acid-susceptible linkage must therefore be between the C-16 hydroxy group of **86** and C-2 of **87** and gardmultine has the structure **80**. Biogenetically, gardmultine (**80**) may be derived from **86** and **87** according to Scheme 6.

The stereochemistry at C-19 of chitosenine remained uncertain for several years, but when ^{13}C nmr was applied to the monomeric alkaloids it was found[87] that the chemical shifts of C-21 and C-15 were diagnostic of the C-19 configuration. In compounds where the double bond is *Z*, that is, C-18 is cis to C-21, the C-15

resonance appears at lower field than in a compound with an *E* configuration (30 vs. 37 ppm). In this way the configuration of the double bond in chitosenine (and by inference gardmultine) was established to be *E*.

VII. BISINDOLE ALKALOIDS OF *ALSTONIA* SPECIES

A. Pleiocarpamine-Macroline Type

1. *Structure Elucidation*

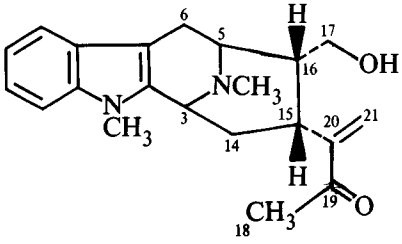
Alstonia species in the family Apocynaceae are the source of several bisindoles which are typically derived from a macroline (**90**) unit and a pleiocarpamine (**91**) unit; these alkaloids have been reviewed.[2,13,15,88]

The structure of villalstonine, the principal alkaloid of *Alstonia macrophylla* Wall.,[89-92] was deduced by the Swiss group[89,90] and confirmed by X-ray analysis.[93] In cold 70% perchloric acid (+)-pleiocarpamine (**91**) is the only isolated product, but in trifluoroacetic acid–trifluoroacetic anhydride the isomer villamine (**92**) is produced, which unlike villalstonine contains an acetylatable hydroxy group.

The mass spectrum of villamine (M^+ 660) was found to be a summation of the mass spectra of pleiocarpamine (M^+ 322) and macroline (M^+ 338), and this reaction could be reproduced at 250° in vacuo, suggesting that it is a retro-Diels-Alder reaction. An α,β-unsaturated ketone was absent from villamine and the uv spectrum was the sum of indoline and indole chromophores. Characteristic nmr signals were observed for 2,7-dihydropleiocarpamine (**93**), together with an *N*-methylindole.

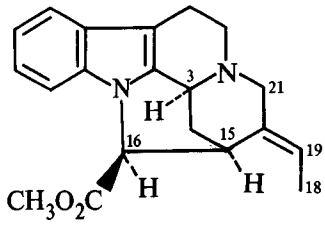
Since villalstonine contains no hydroxy groups or enol ether grouping (villamine does), it should have a six-membered ether ring formed by addition of a hydroxy group to the enol ether double bond; this is supported by a singlet for C-18′ H_3 at 1.31 ppm. Two structures could be proposed for villalstonine and **94** was suggested on biogenetic, chemical, and spectral grounds.[89,90] The alkaloid has also been isolated from *Alstonia glabrifolia* Mgf.,[94] *A. muelleriana* Domin.,[93,95,96] and *A. spectabilis*.[91,94] Macralstonine ($C_{43}H_{52}N_4O_5$) has been isolated from *A. macrophylla* Wall.,[91,97-99] *A. muelleriana*,[95,96,100] and *A. glabrifolia*.[94] Acid (2*M* HCl) cleavage afforded macroline (**90**) and alstophylline (**95**), and when heated at 300–350°C anhydromacralstonine (**96**) is produced, whose uv spectrum is the sum of alstophylline (**95**) and the ketone **97**. This latter compound is also produced on acid cleavage of macralstonine, which therefore must undergo cleavage by two different routes.

The ^1H nmr spectrum of anhydromacralstonine (**96**), with six aromatic protons, shows a doublet at 7.30 ppm for H-9 and singlets at 6.69 and 6.31 ppm for H-9′ and H-12′, indicating C-10′ as the point of attachment to the macroline component. Two singlet methyl groups are also observed, and since the deuterated ketone d_9-**97** (obtained with d_6-alstophylline on cleavage of anhydromacralstonine under deuterating conditions) only contains deuterium at C-18 and C-20 in the aliphatic

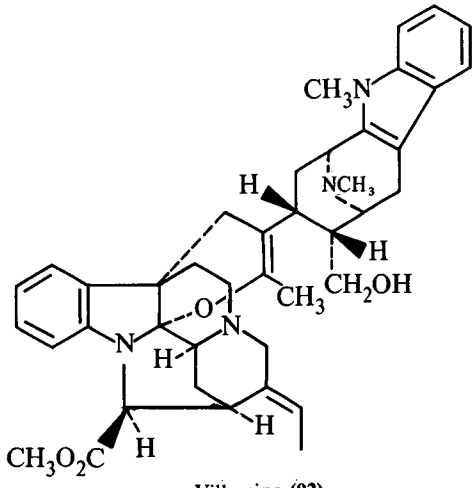


Macroline (**90**)

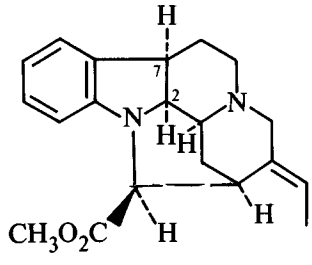
+



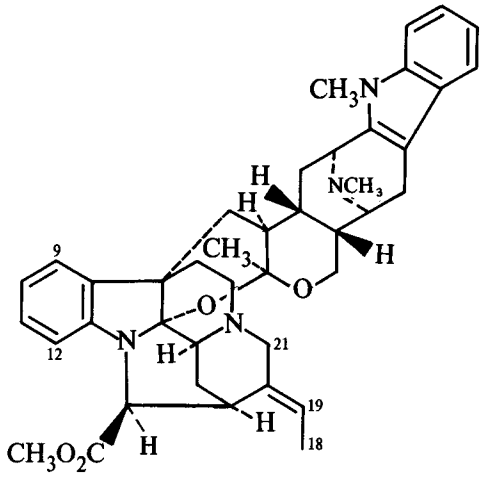
Pleiocarpamine (**91**)



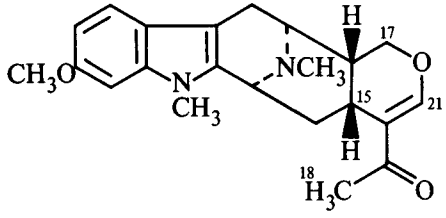
Villamine (**92**)



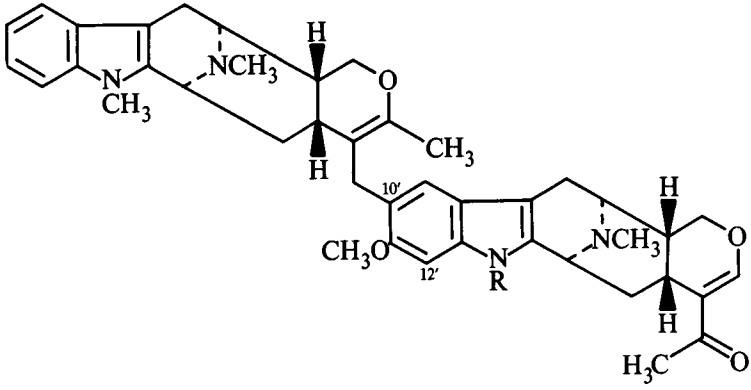
2,7-Dihydropleiocarpamine (**93**)



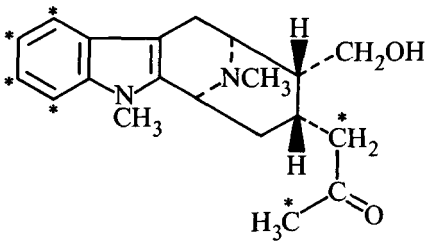
Villalstonine (**94**)



Alstophylline (**95**)

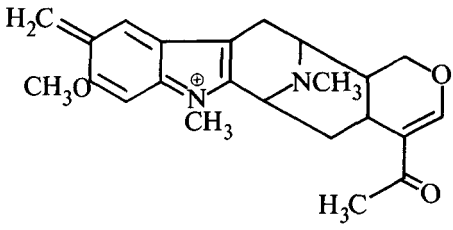


Anhydromacralstonine (**96**): R = CH_3
Des-N_a'-methylanhydromacralstonine (**104**): R = H

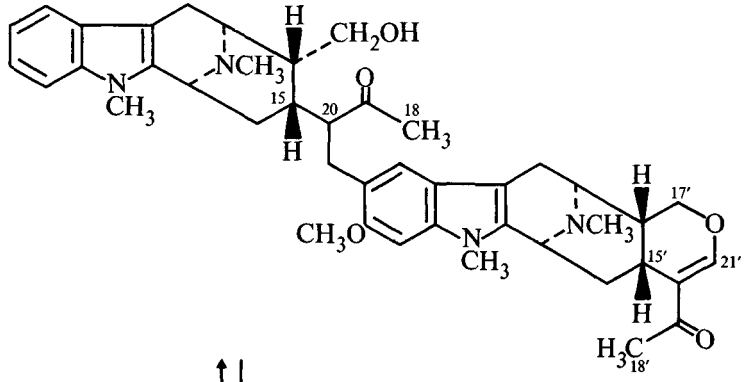


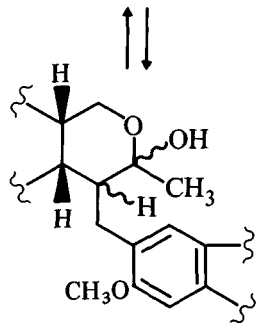
97

d_9-97; D at asterisked positions



98 *m/e* 379





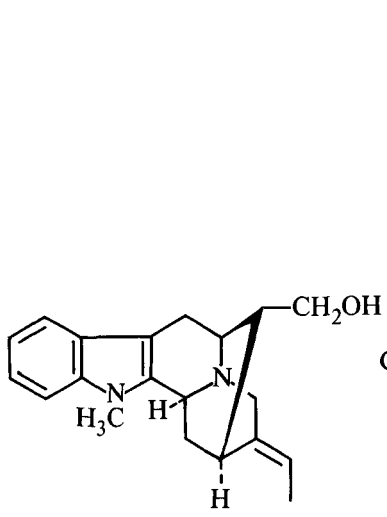
Macralstonine (**99**)

part of the molecule, C-21 of the macroline unit (**90**) must be coupled at C-10′ of the alstophylline unit, as shown in **96**. An ion at *m/e* 379 (**98**), confirms this coupling mode.

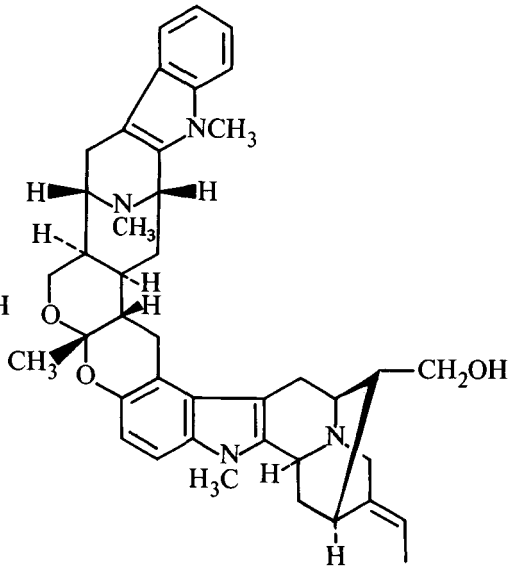
Hydration of **96** must be at the double bond of the macroline unit since macralstonine and anhydromacralstonine show the same uv spectra and low-field C-21 proton. This leads to the structure **99** for macralstonine.[98]

Macralstonidine from *A. macrophylla*[91,99] and *A. spectabilis*[91,94] has a molecular formula $C_{41}H_{48}N_4O_3$ and also yields the ketone **97** together with N_a-methylsarpagine (**100**) and formaldehyde on hydrolysis with concentrated hydrochloric acid. This led to the suggestion of **101** for macralstonidine which is supported by the

absence of a phenolic group (uv spectrum), the presence of a primary hydroxy group (aldehyde and acetate formation), and the absence of the ketonic groups of macroline (**90**) and **97**. In addition, six aromatic protons (two are ortho coupled), an ethylidene, three *N*-methyl groups, and a tertiary methyl group were observed.



N-Methylsarpagine (**100**)



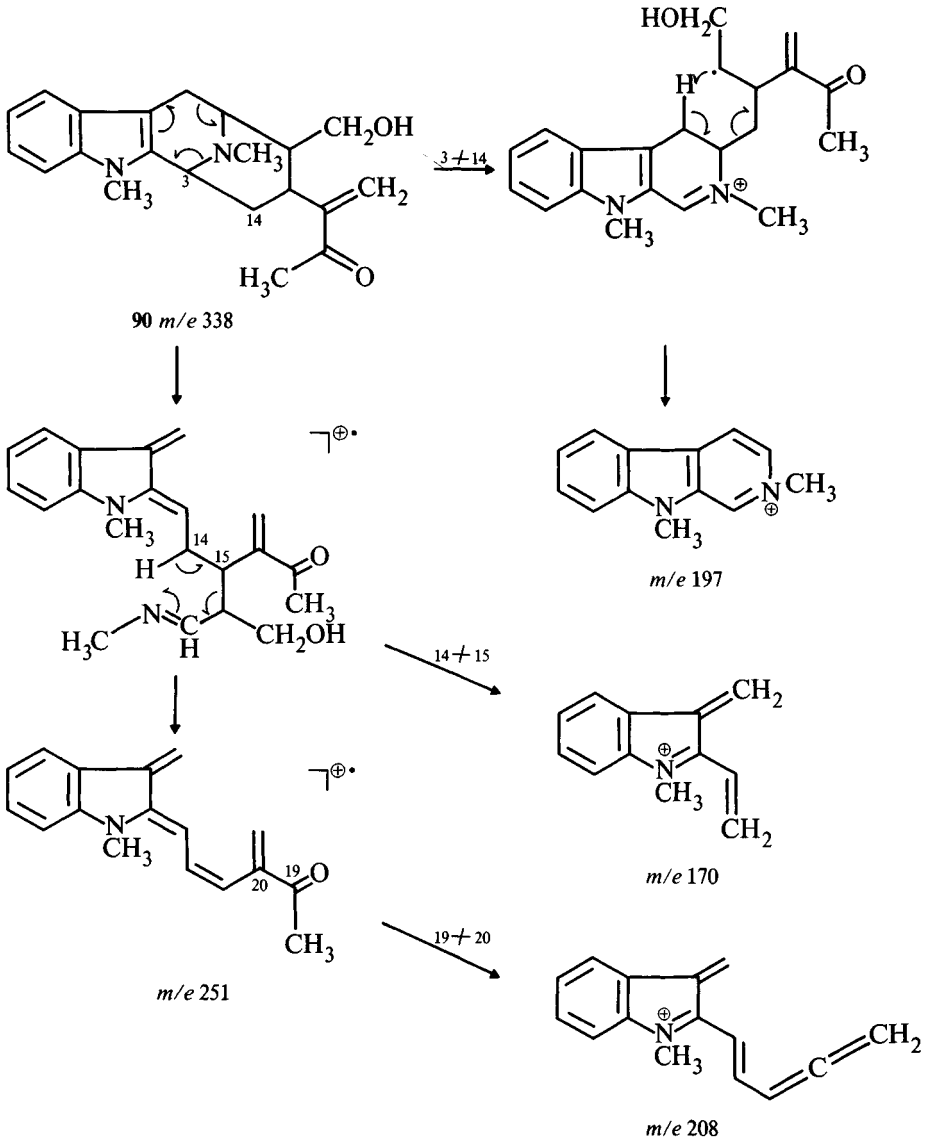
Macralstonidine (**101**)

Additional evidence for the structure was obtained through deuterium labeling studies and analysis of the mass spectrum. Typical macroline (**90**) ions were observed at *m/e* 251, 197, and 170 (Scheme 7). Important ions at *m/e* 375 and 211 are rationalized as shown in Schemes 8 and 9, and retro-Diels-Alder reaction in ring F leads to *m/e* 308 (**102**) and *m/e* 336 (**103**) depending on charge location.[99]

Continuing work[96] on the bark of *A. muelleriana* has yielded a new alkaloid identified as des-N_a-methylanhydromacralstonine (**104**). The uv spectrum was the summation of indole and 10-methoxyindole chromophores (λ_{max} 230, 285, 305, and 318 nm) and substantial similarities to the ^{1}H nmr spectrum of anhydromacralstonine were observed, the major difference being the presence of only one indolic *N*-methyl group at 3.58 ppm.

The *m/e* 379 ion (**105a**) of macralstonine (**99**), missing in the mass spectrum, was replaced by an ion at *m/e* 365 (**105b**), indicating that this unit lacks the N_a-methyl group. A base peak at *m/e* 197 ($C_{13}H_{13}N_2$) (**106**) was considered to be derived from the fragmentation at *m/e* 307, confirming the location of the single *N*-methyl group.[96] The biogenetically interesting 2,7-dihydropleiocarpamine (**93**) was also isolated at this time.

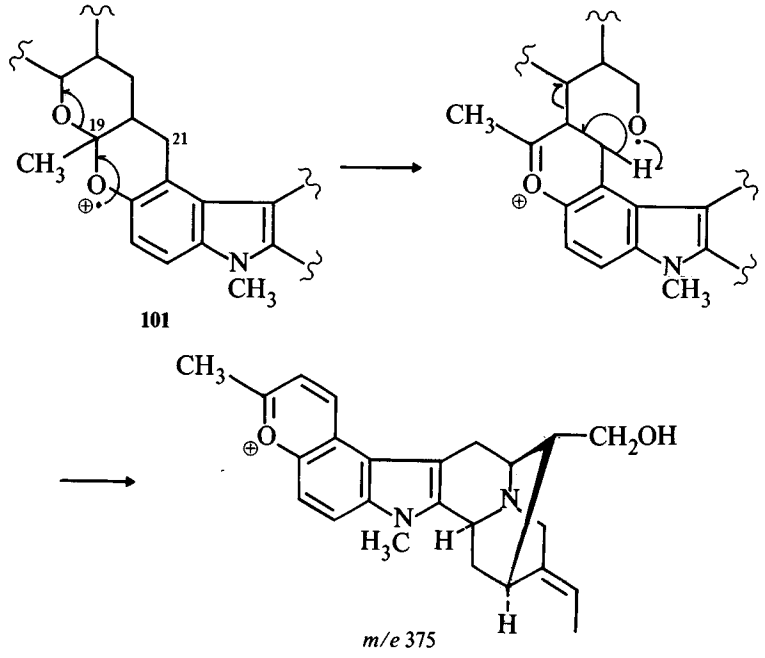
In addition to the alkaloids discussed previously, *A. macrophylla* has yielded another bisindole alkaloid, macrocarpamine (**107**)[101] having the molecular formula



Scheme 7.

$C_{41}H_{46}N_4O_3$. Indoline and indole units were deduced from the uv spectrum and a carbomethoxy group (1735 and 1765 cm^{-1}) and an enol ether (1645 cm^{-1}) from the ir spectrum, which also showed an absence of NH and OH absorption.

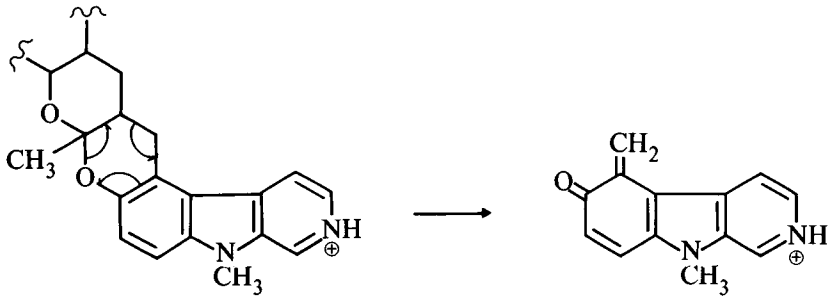
Acid cleavage (trifluoroacetic acid–trifluoroacetic anhydride, 10 minutes) afforded (+)-pleiocarpamine (**91**) as one of the units, and this unit together with (−)-anhydromacrosalhine methine (**108**) was produced on pyrolysis (280°, 0.01 mm). These units sum to the molecular weight of macrocarpamine.



101

m/e 375

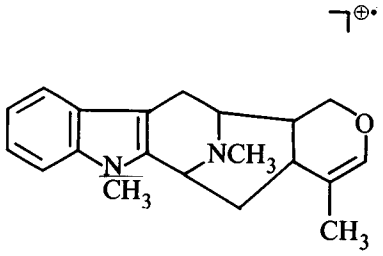
Scheme 8.



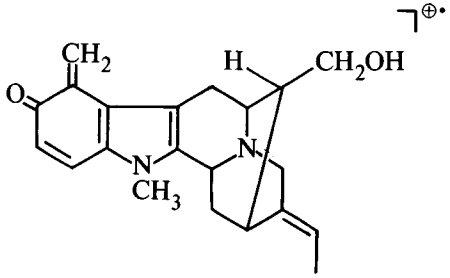
m/e 519

m/e 211

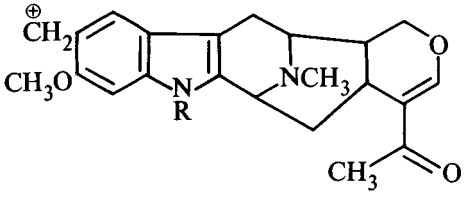
Scheme 9.



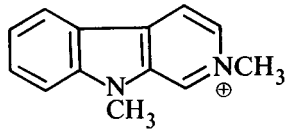
102 *m/e* 308



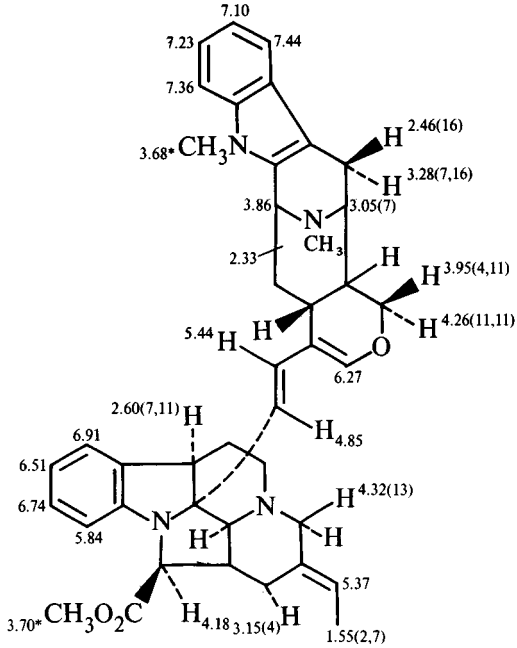
103 *m/e* 336



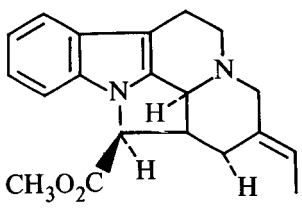
105a: R = CH_3, *m/e* 379
105b: R = H, *m/e* 365



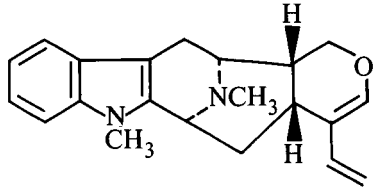
106 *m/e* 197



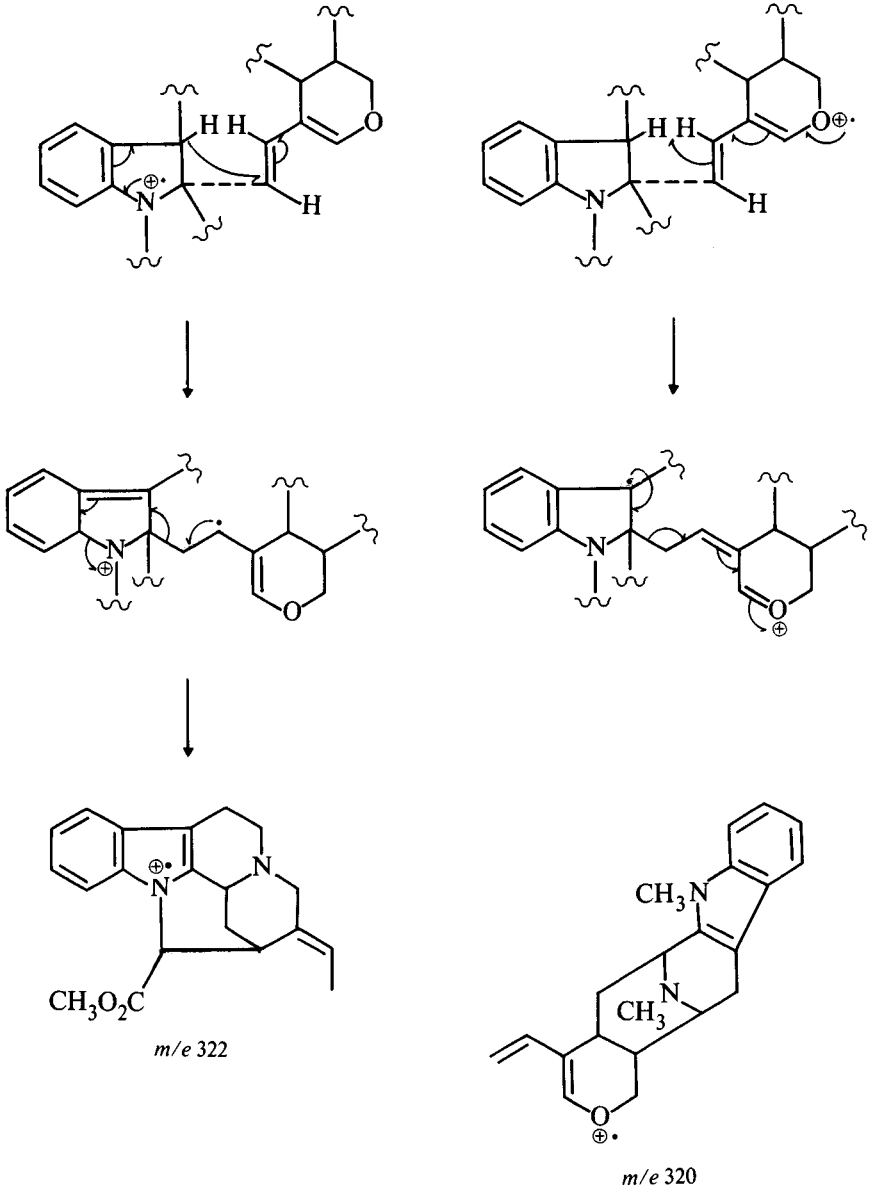
107 (*denotes that assignments may be reversed)



91



Anhydromacrosalhine methine **(108)**



Scheme 10. Formation of the ions *m/e* 320 and 322 in the mass spectrum of macrocarpamine (**107**).

Two important electron impact fragment ions at *m/e* 322 and *m/e* 320 gave rise to series of ions derived from each of them (Scheme 10). In both dihydro- and tetrahydromacrocarpamine (10% $Pd/C/H_2$), *m/e* 322 was still the base peak, suggesting that C-18 of **108** should be linked to C-2 of **91**.

In the nmr spectrum of macrocarpamine the C-21′ proton was observed as a singlet at 6.27 ppm with doublets (J = 16 Hz) at 5.44 and 4.58 ppm for the trans related C-19′ and C-18′ protons, respectively. A doublet of doublets (J = 4 Hz) at 3.15 ppm was assigned to the C-15H on the basis of double resonance studies which also confirmed the deshielding of the C-21β-H to 4.32 ppm. A doublet of doublets (J = 7 and 11 Hz) was ascribed to H-7 in the pleiocarpamine unit and established[101] macrocarpamine (**107**) to have the linkage between C-2 and C-18′.

2. *Biogenetically Modeled Synthesis*

Recent efforts in this area have concentrated on biomimetic synthesis from the monomeric units with some surprising results.[102–105]

Although macroline (**90**) is not a natural product, it is a proposed biogenetic intermediate and condensation of pleiocarpamine (**91**) and macroline (**90**) in 0.2 *M* hydrochloric acid at room temperature afforded villalstonine (**94**) in 38% yield (Scheme 11).[102,106] A similar reaction of **90** and alstophylline (**95**) yielded "macralstonine" (**99**) in 40% yield[104] as a mixture of C-20 and (C-19?) epimers.

Model reactions with 4-methoxy-2-tosyloxybutane (**109**) and indoline (**110**) afforded 4-methyllilolidine (**111**), whereas methyl vinyl ketone yielded the 6-methyl derivative **112** (Scheme 12),[105] suggesting that the product of condensation of macroline (**90**) and quebrachidine (**113**) could have the opposite orientation to that predicted previously.[107]

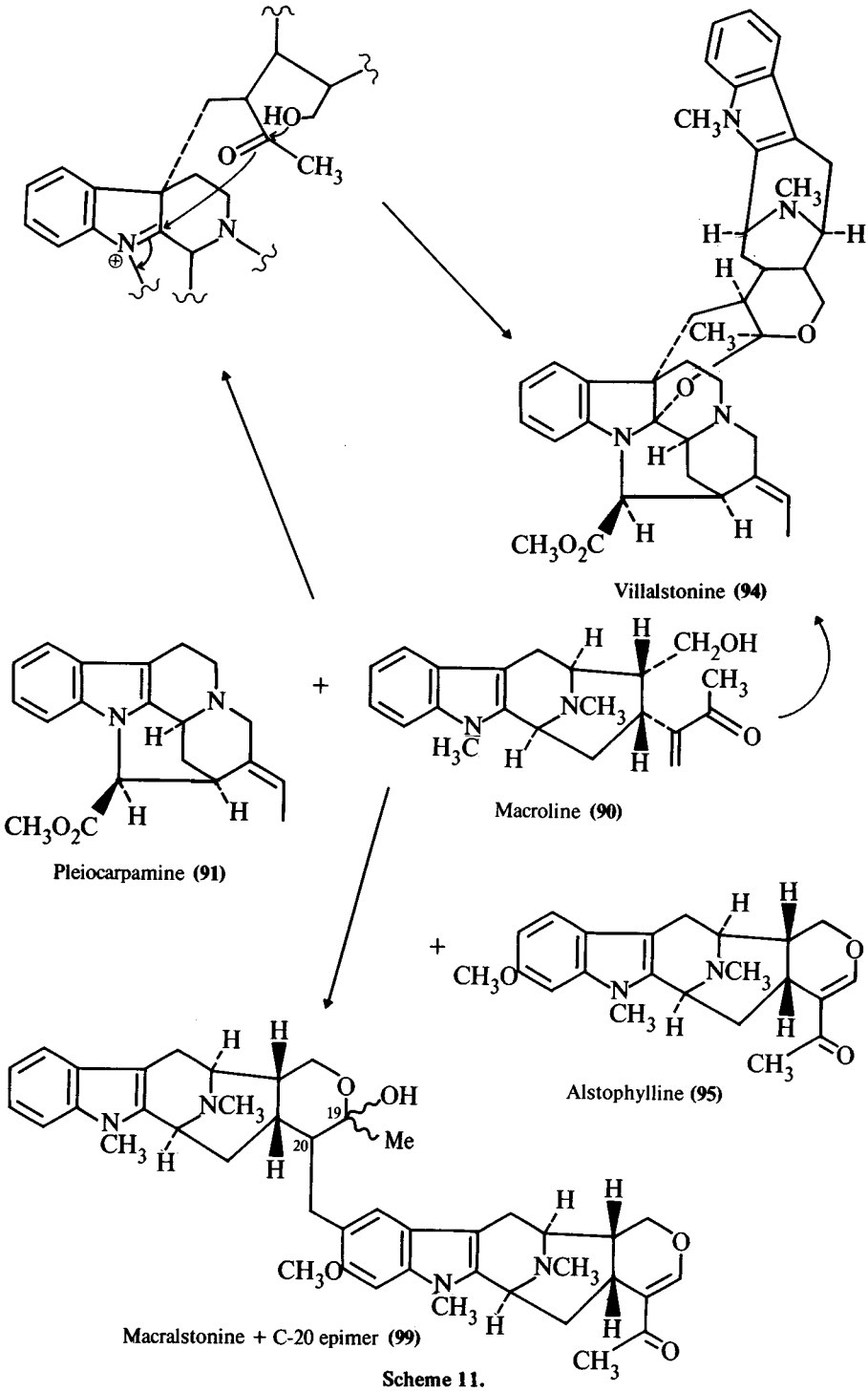
Condensation of **90** and **113** in 0.2 *M* hydrochloric acid afforded a labile intermediate **114**, which on further treatment with boron trifluoride etherate at 0° yielded alstonisidine (**115**) (Scheme 13).[103,105] The stereochemistry at the ring junction remains to be deduced.

3. *Biogenesis and Absolute Configuration of Macroline*

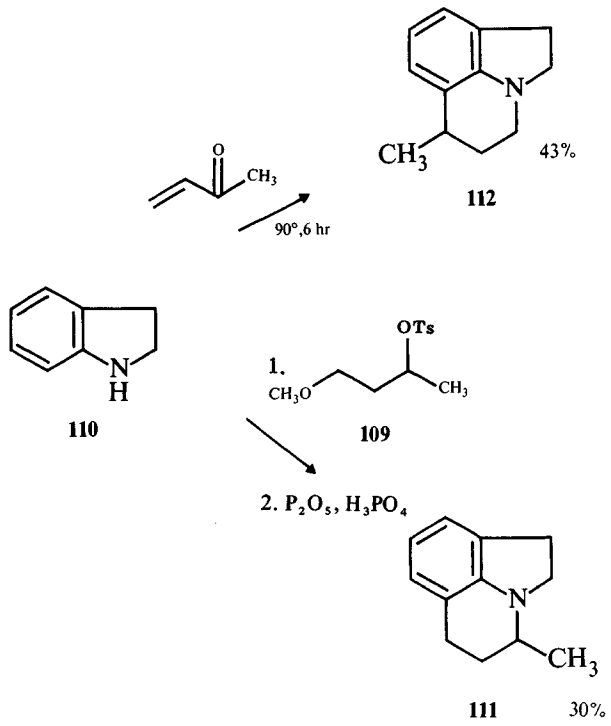
Normacusine B (**115a**) has been converted to macroline (**90**)[107a] by way of tetra-*n*-butylammonium fluoride-induced rearrangement of the N_b-methyl salt of ketone **115b** (Scheme 14). This gives strong support to an earlier[107b] biogenetic proposal for the formation of macroline (**90**). The absolute configuration of **90** was determined[107c] through chemical correlation with ajmaline (**115c**) and isoajmaline (**115d**) (separately) by way of the epimers **115e** and **115f** (Scheme 15).[107c] Since the relative configuration of villalstonine (**94**) had been determined previously,[90] this allowed the absolute configuration of **94** and the (+)-pleiocarpamine (**91**) unit to be determined, and permitted assignments in the *Aspidosperma-Pleiocarpa* series (Section XVII) to be made.[107c]

B. Pleiocarpamine-Vincorine and Pleiocarpamine-Akuammiline Types

Besides the pleiocarpamine-containing bisindole alkaloids from *Alstonia* species discussed previously, there are two other pleiocarpamine-containing bisindoles


Villalstonine (94)
Pleiocarpamine (91)
Macroline (90)
Alstophylline (95)
Macralstonine + C-20 epimer (99)

Scheme 11.



Scheme 12.

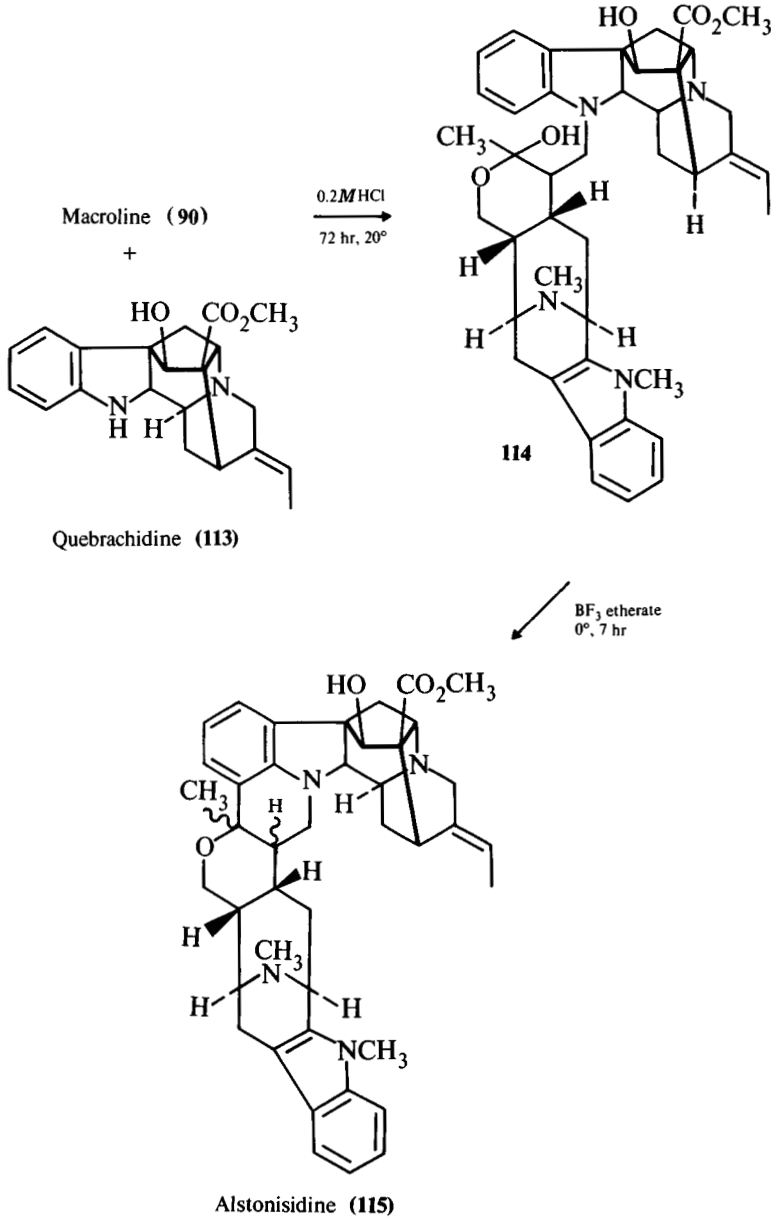
pleiocorine (**116**)[108] and pleiocraline (**117**),[109] both of which were isolated from *Alstonia deplanchei* Van Heurck et Muell-Arg. (Apocynaceae).

The uv spectrum (λ_{max} 244, 297, and 344 nm) of pleiocorine ($C_{41}H_{46}N_4O_5$) was of an unknown type, but the ir spectrum indicated two different carbomethoxy functions and no NH or OH groups. Singlets at 3.65 and 3.72 ppm confirmed two carbomethoxy groups and also indicated two ethylidene side chains, an *N*-methyl group, and six aromatic protons, two of which were para related.[108]

Structure elucidation was made possible through ^{13}C nmr analysis of a number of alkaloids in this series which defined the carbons attributable to a 2,7-disubstituted pleiocarpamine moiety (Table IV). Analysis established the presence of this unit in the molecule, but indicated additional chemical shift factors for C-2 and C-7.

The remaining signals, obtained by subtraction, revealed a highly deshielded (97.5 ppm) quaternary carbon analogous to that found in the co-occurring alkaloid vincorine (**118**). Detailed comparison (Table IV) indicated that indeed vincorine was the second unit and that substitution was through C-10 and C-11. Since it is C-2 (103.2 ppm) of pleiocorine which is necessarily substituted by both nitrogen and oxygen, the alkaloid has the structure **116**.[108]

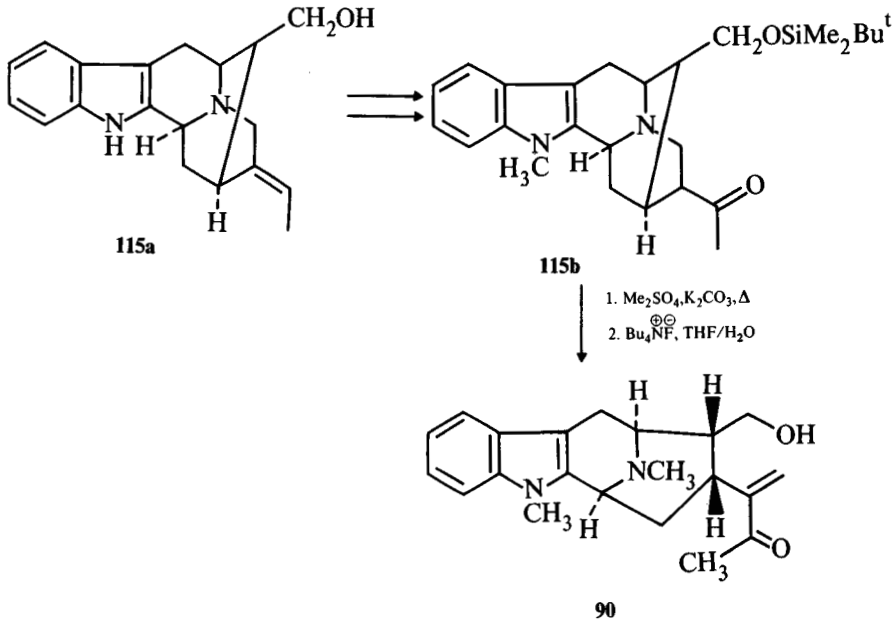
Pleiocraline ($C_{41}H_{46}N_4O_5$) showed a uv spectrum analogous to pleiocorine and again two ester groups and no NH or OH functions were indicated by the ir



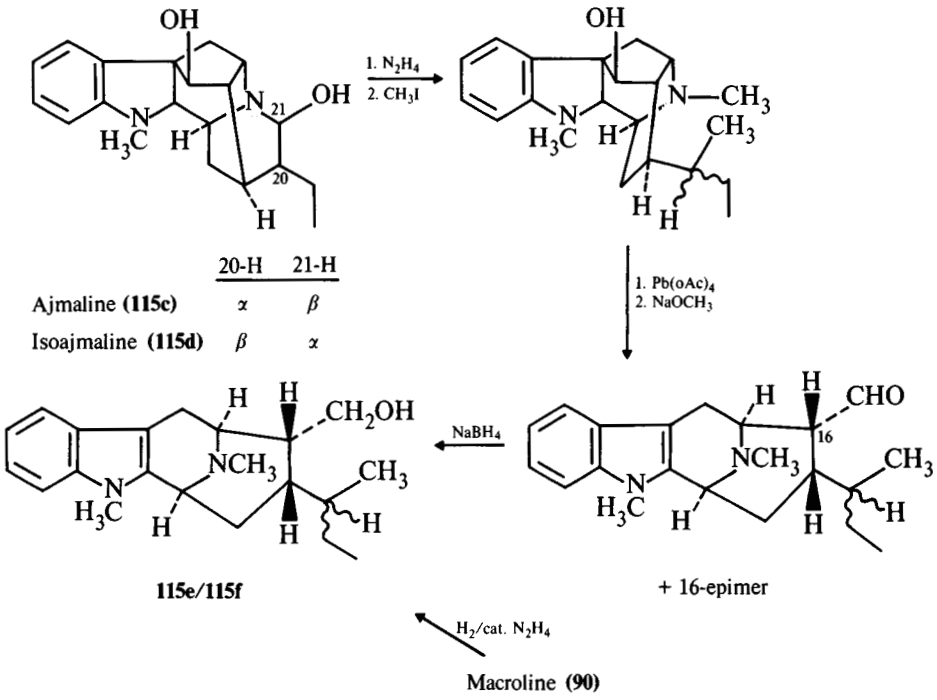
Scheme 13.

spectrum. Two ethylidene groups, two carbomethoxy groups, an *N*-methyl group, and six aromatic protons were indicated, and it was the characteristic doublet ($J = 4$ Hz) at 4.68 ppm which suggested the presence of a **93** unit.[109]

Indeed the ^{13}C nmr spectrum once again substantiated this (Table IV) and



Scheme 14.



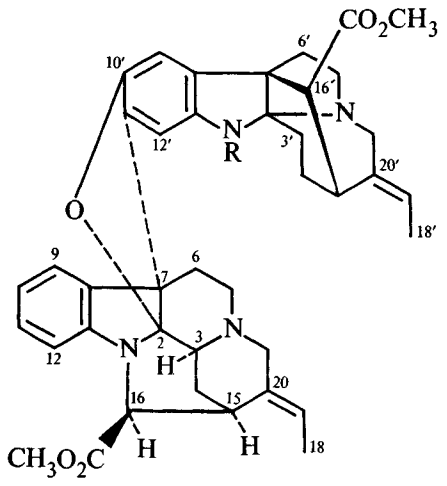
Scheme 15. Hesse and co-workers' correlation of macroline (90) and ajmaline (115c).[107c]

TABLE IV. ^{13}C NMR DATA OF PLEIOCORINE (116) AND PLEIOCRALINE (117)

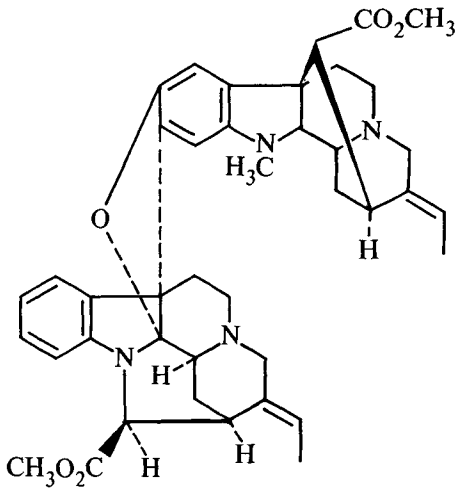
Carbon	Pleiocarpamine part of			Carbon	Vincorine part of Pleiocorine (116)	Vincorine (118)	Substituted akuammiline part of Pleiocraline (117)	N_a-Methyl-deacetyldeformyl-1,2-dihydro-akuammiline (119)
	Villalstonine (94)	Pleiocorine (116)	Pleiocraline (117)					
C-2	92.2	103.2	104.3	C-2′	97.5	97.9	80.3	79.1
C-3	51.5	51.3	51.8	C-3′	40.6	40.6	53.0	52.8
C-5	53.1	52.0	52.1[d]	C-5′	55.0[a]	56.1[g]	55.0	54.7
C-6	28.6[a]	24.6	24.7	C-6′	20.2	20.4	31.5	31.1
C-7	44.2	54.0	54.1	C-7′	56.9	57.3	43.2	43.0
C-8	132.9	134.4	134.7	C-8′	134.8	138.2	140.3	*i*
C-9	120.9	121.6	122.8	C-9′	106.1	105.5	104.8	120.5
C-10	118.1[b]	119.2[c]	118.5[e]	C-10′	151.1	152.3	153.4	119.0
C-11	126.5	126.3	126.9	C-11′	127.4	111.7[h]	127.8	126.7
C-12	109.3	108.9	109.5	C-12′	100.1	112.1[h]	104.3	109.0
C-13	147.0	144.4	144.9	C-13′	143.6	143.6	148.2	*i*
C-14	28.9[a]	28.1	27.9	C-14′	26.3	26.3	34.2	33.9
C-15	31.9	32.2	32.2	C-15′	34.7	34.8	34.5	34.4
C-16	57.8	58.1	58.3	C-16′	50.9	50.7	47.5	47.3
C-17	170.8	169.3	169.9	C-17′	173.1	173.5	172.9	172.2
C-18	12.2	12.3	12.3	C-18′	13.4	13.6	12.9	13.0
C-19	118.4[b]	119.5[c]	119.9[e]	C-19′	122.5	123.2	120.1	118.7
C-20	136.4	136.1	135.2	C-20′	138.8	138.2	140.3	*i*
C-21	47.5	48.2	48.2[e]	C-21′	58.1[f]	58.1[g]	50.8	50.6
CO_2CH_3	51.9	50.6	51.0	CO_2CH_3	51.6	51.7	51.3	51.3
				N_aCH_3	28.1	28.3	35.2	33.9

[a–h] Assignments may be reversed.

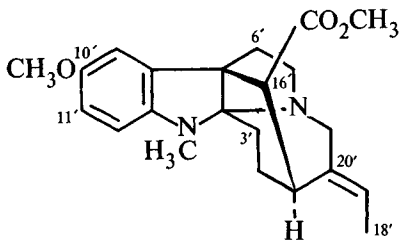
[i] Quaternary carbon signals not observed.



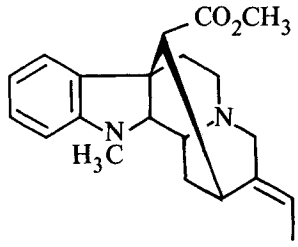
Pleiocorine (**116**): R = CH_3
120: R = H



(**117**) Pleiocraline



Vincorine (**118**)



119

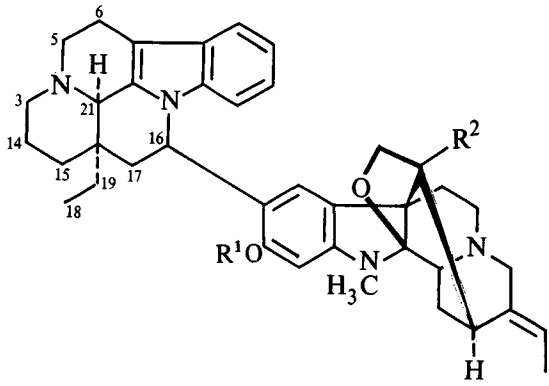
showed that C-2 (104.3 ppm) was again substituted by both oxygen and nitrogen. The data also established that the second unit was not of a similar skeleton to that in pleiocorine, but indicated C-2′ and C-3′ to be methine carbons, that is, an akuammiline skeleton. Comparison with **119** indicated C-2′ has the β configuration (2α-H configuration shows C-2 at 70.6 ppm) and consequently pleiocraline has the structure and stereochemistry shown in **118**.[109]

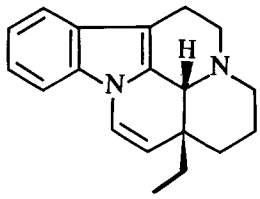
Pleiocorine (**116**) and pleiocraline (**117**) have also been isolated[110] from the leaves of *Alstonia odontophora* Boiteau together with a new alkaloid des-N_a'-methylpleiocorine (**120**), which lacked the *N*-methyl singlet at 2.70 ppm but which did show a characteristic doublet ($J = 4$ Hz) at 4.63 ppm. Treatment of **120** with formaldehyde under reducing conditions afforded **116**.[110]

VIII. PSEUDOAKUAMMIGINE-*EBURNEA* TYPE

Umbellamine (**121**) from the root bark of *Hunteria umbellata* (K. Schum.) Hall. F. is the only member of this series.[111] Eburnamenine (**122**) was one of the fragments observed in the mass spectrum and could be obtained from umbellamine (M^+, $C_{41}H_{48}N_4O_4$) preparatively. Carbomethoxy, *N*-methyl (2.78 and 2.83 ppm), and ethylidene (methyl doublet at 1.37 ppm) groups were located in the other "half" from the ^1H nmr spectrum. A bathochromic (295 to 309 nm) shift on the addition of alkali indicated a phenolic group to be present.

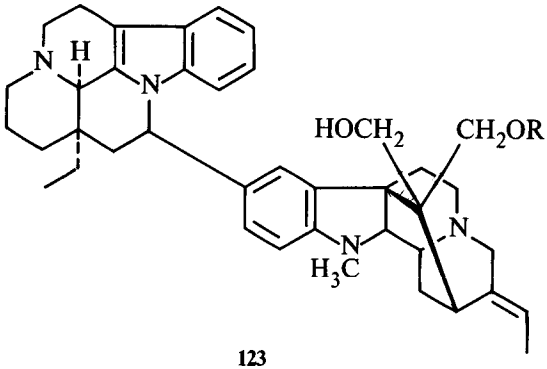
Lithium aluminum hydride reduction under vigorous conditions yielded **123**, and under mild conditions **124** showing that the fourth oxygen atom was present as a carbinolamine ether. Mass spectral analysis of **123** and its trideuterio derivative indicated a set of peaks at *m/e* 196 (**125**), 178, and 166 for pseudoakuammigol



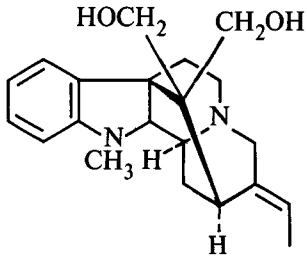


(+) – Eburnamenine (**122**)

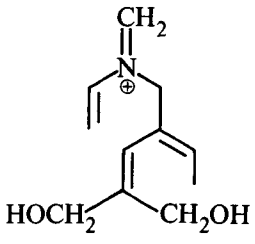
Umbellamine (121): $R^1 = H$, $R^2 = CO_2CH_3$
124: $R^1 = CH_3$, $R^2 = CH_2OH$



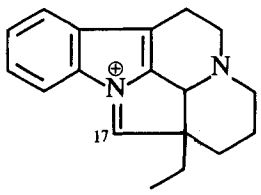
123



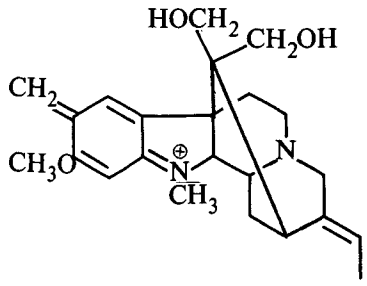
Pseudoakuammigol (**126**)



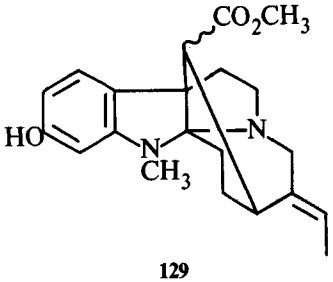
125 *m/e* 196



127 *m/e* 265



128 *m/e* 383



129

(126)[111] and the *m/e* 196 ion was shifted by 2 m.u. in the trideuterio derivative, indicating the carbinolamine ether to be attached at C-2′. An ion at *m/e* 265 in **123** was suggested to have the structure **127**, which indicates the union of the pseudoakuammigine unit to be through C-16. The other "half" of the molecule appeared as a fragment at *m/e* 383 formulated at **128**.[111]

Six aromatic protons were indicated in the nmr spectrum, two of which were para related. A distinction between C-10′ and C-11′ for the linkage of the eburnamenine unit was made through reductive cleavage (Zn or Sn/HCl), affording **129**, whose uv spectrum corresponded to an 11-hydroxy derivative. Umbellamine was therefore suggested to have the structure **121**,[111] with the stereochemistry at C-16 to be determined.

IX. *STRYCHNOS-STRYCHNOS* TYPE

Only two groups of bisindole alkaloids have been isolated as a result of searching for compounds based on the biological activity of a plant extract; one of these is the *Aspidosperma*-cleavamine type (Section XXII), and the second is the *Strychnos-Strychnos* type.[1,5,11,15,27-31]

There are two main types of South American curare,[112] named after the mode of carrying the dart or arrow poison. One is the tubocurare derived from the liana *Chondodendron tomentosum* Ruiz et Pav. (Menispermaceae), and the second is the calabash curare, which is carried in a gourd, and is derived from various *Strychnos* species. In each instance bisalkaloids are the active principles. Tubocurare yields

alkaloids in the bisbenzylisoquinoline series, whereas calabash curare yields the bis-*Strychnos* alkaloids. The common denominator between these two series is that pronounced activity is observed only for certain members in the N_b,N_b'-dimetho salt series.

The *Strychnos-Strychnos* alkaloids are typically derived by the dimerization of Wieland-Gumlich aldehyde (**130**). Modifications involve N_b-oxide formation, loss of the C-18 oxygen atom, or reduction of the 19,20 double bond. Twenty alkaloids are known,[16] of which C-curarine I (**131**) is the most widely distributed.

Wieland-Gumlich aldehyde (**130**) was obtained in 1933 as a degradation product of strychnine,[113–115] and was subsequently[116] shown to be identical with caracurine VII from *Strychnos toxifera* F. Schomb.[117]

C-Toxiferine (**132**), from curare,[118,119] *Strychnos froesii* Ducke,[120] and *S. toxifera*,[121,122] is a product of the direct condensation of the metho salt **133** in either acetic acid-*p*-toluenesulfonic acid[123] or pivalic acid,[124] through double deprotonation of the intermediate **134**. Further cyclization of the 18- and 18′-hydroxy groups then leads to caracurine V dimetho salt (**135**), which, in the nonquaternary form **136**, occurs in *Strychnos dolichothyrsa* Gilg. ex Onochie et Hepper.[125] and *S. toxifera*.[117] In the presence of mild acid, an equilibrium is produced between *C*-toxiferine (**132**) and **136**, which depends on both temperature and pH.

Caracurine V (**136**) is a product of the self-condensation of **130**, with little bisnortoxiferine (**137**) being formed. However, the equilibrium shifts to favor **137** when the dihydrochloride of **136** is heated in water at pH 6.7,[127] and this reaction is reversible in methanolic hydrochloric acid.

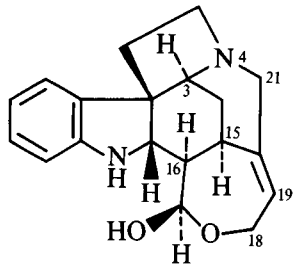
If N_b of Wieland-Gumlich aldehyde is alkylated with alkyl halides other than methyl iodide, a range of *C*-toxiferine derivatives is produced of which alloferine (**138**) is the most important.

C-Dihydrotoxiferine (**139**), a constituent of calabash curare,[121,128,129] *S. froesii*,[120] and *Strychnos trinervis* (Vell.) Mart.,[130] may be prepared from caracurine V (**136**). With hydrogen bromide, **136** affords the allylic dibromide **140**, which may be reduced with zinc-acetic acid to bisnordihydrotoxiferine (**141**); *N,N*-dimethylation then affords **139**. The intermediate **141** is a constituent of *S. dolichothyrsa*[132] and *S. toxifera*,[131] and the *N*-oxide[132] and the *N,N′*-dioxides[132] also occur naturally.

Some alkaloids such as *C*-alkaloid H (**142**) and *C*-dihydrotoxiferine (**139**) are the fundamental structures of the "families" of curare alkaloids, and the relationships within these "families" have been elegantly summarized by Gorman et al.[15] as shown in Figure 1. Many of the structures of these products remain unknown, however, and there is considerable further work to be done in this area.

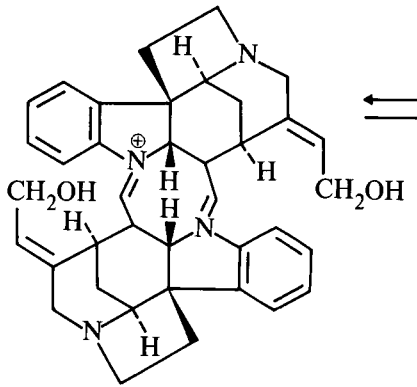
These relationships are shown diagrammatically in Scheme 16, in which one of the interesting reactions is the oxidation of *C*-toxiferine (**132**) to *C*-alkaloid E (**143**), containing a C-2-C-2′ ether bridge, the same linkage as is present in *C*-curarine (**131**).

Fritz and co-workers[133–135] have made some strides in developing the synthesis of model compounds in this series. Thus condensation of **144** and **145** in ether

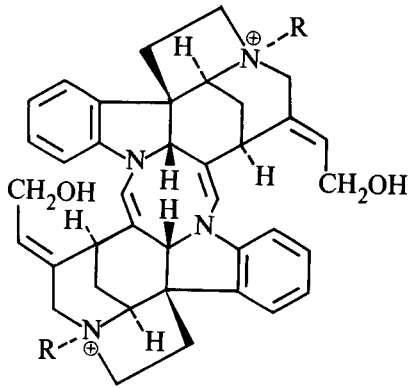


Wieland-Gumlich aldehyde (**130**)

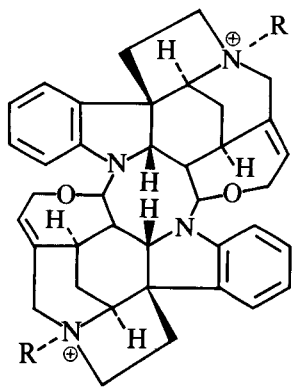
133; $\overset{\oplus}{N}(4)-CH_3$



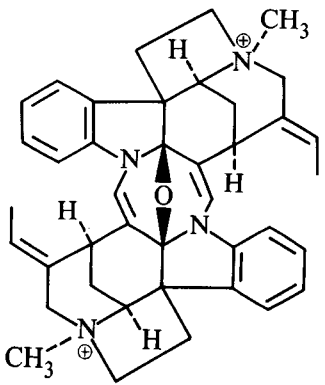
134



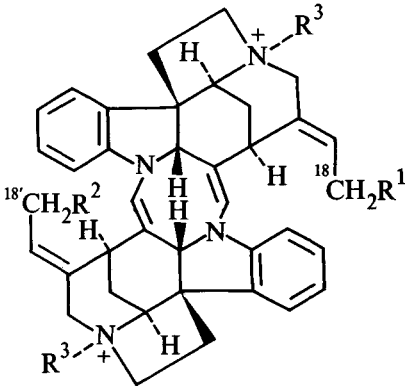
C-Toxiferine (**132**): R = CH_3
Bisnortoxiferine (**137**): no R
Alloferine (**138**): R = $CH_2CH{=}CH_2$



135: R = CH_3
136: Caracurine V, no R



C-Curarine I (**131**):



C-Dihydrotoxiferine (**139**): $R^1 = R^2 = H$, $R^3 = CH_3$

140: $R^1 = R^2 = Br$, R^3 not present

C-Bisnordihydrotoxiferine (**141**): $R^1 = R^2 = H$, R^3 not present

C-Alkaloid H (**142**): $R^1 = H$, $R^2 = OH$, $R^3 = CH_3$

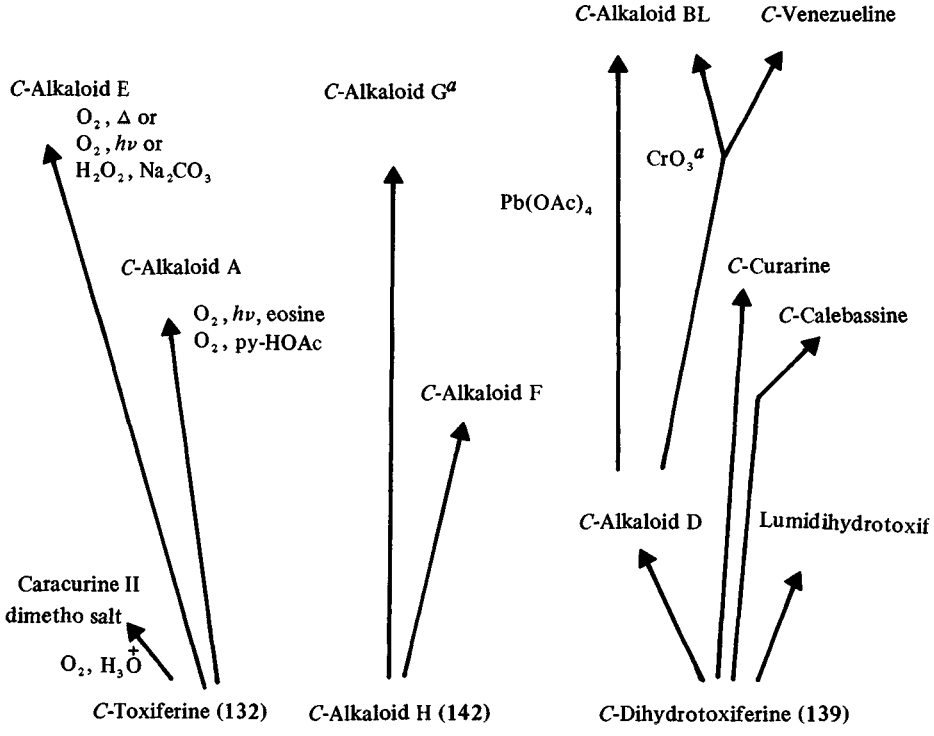
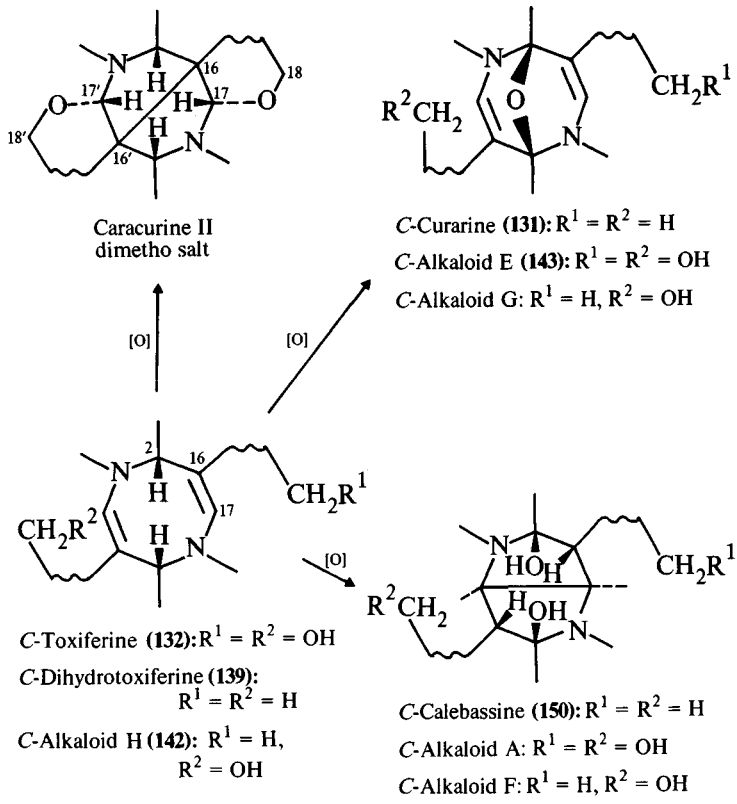


Fig. 1. Alkaloid families of the *Strychnos-Strychnos* group. [a]H. D. Schroeder, unpublished results; see M. Hesse, Dissertation, Universität Zurich, 1964.



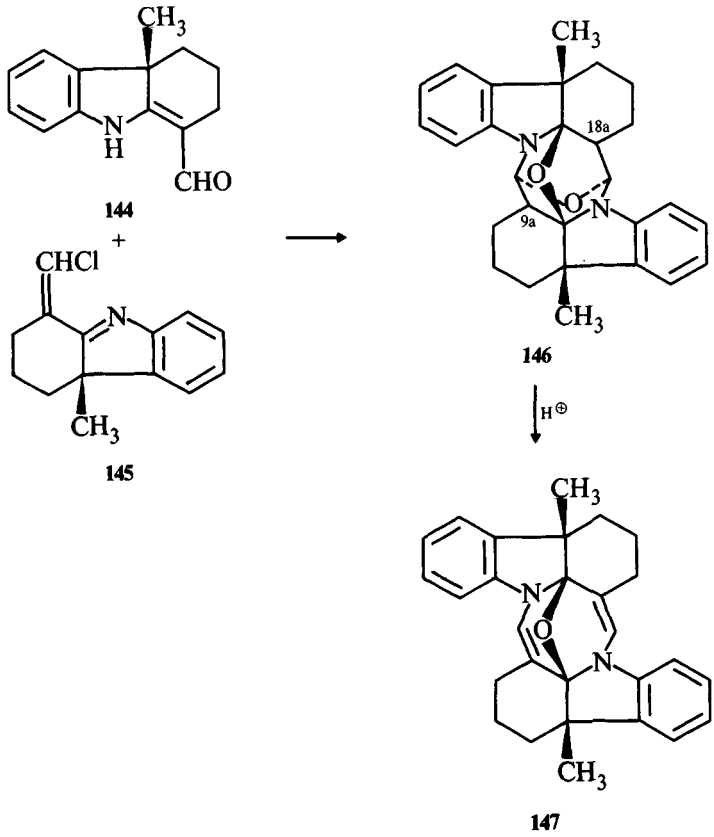
Scheme 16.

yielded the dioxadiazaadamantane derivative **146**, which could be equilibrated in methanolic hydrochloric acid with the dehydration product **147** (Scheme 17). Because this compound has the same central ring system as *C*-curarine (**131**), it is not surprising to find that it gives the same color reaction with cerium(IV) and a similar uv spectrum.[136] After these reactions had been extended[133,134] to other series of compounds, attention was turned to the stereochemistry of C-9a and C-18a.

With concentrated sulfuric acid **146** gave the bis salt **148** which was rehydrated with base to **149**, a compound stereoisomeric at C-9 and C-18 with **146** (Scheme 18).[135] This relationship was confirmed when the aminoacetal protons at C-9 and C-18 appeared as a singlet at 5.37 ppm in **146**, but as a two-proton doublet ($J = 3$ Hz) at 5.24 ppm in **149**.

Relative to the configuration of the natural dimers, however, examination of the ord and cd spectra of the corresponding compounds in the optically active series was important. Indeed, optically active **146** displayed characteristic positive maxima at 248 nm (cd) and 252 nm (ord).[135]

The acid-catalyzed cleavage of alkaloids such as *C*-toxiferine (**132**) does not take place with the highly oxidized dimers such as *C*-curarine (**131**) or *C*-calebassine

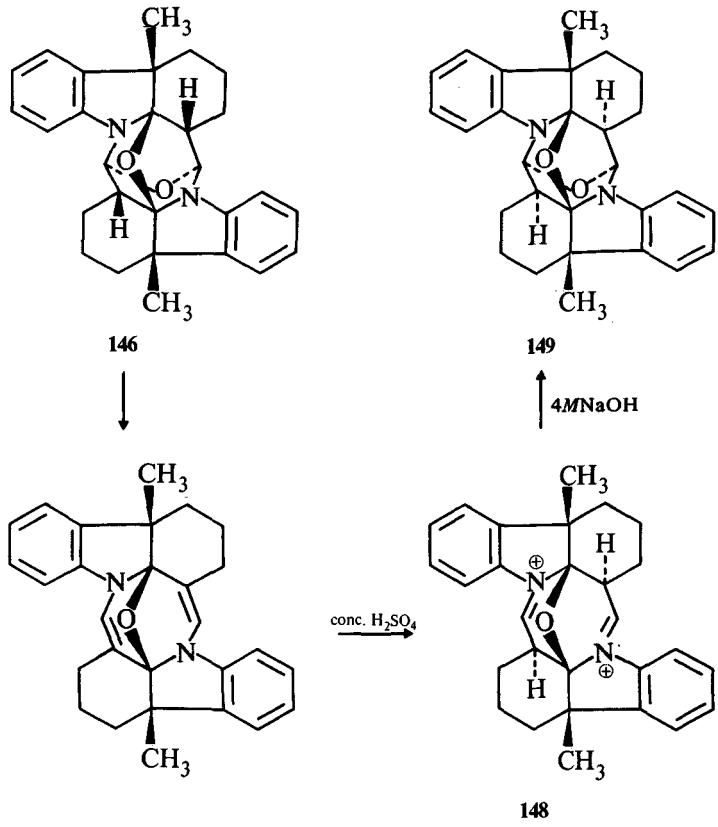


Scheme 17.

(150). For example, *C*-calebassine salts, when heated in strong mineral acid, afford a yellow (λ_{max} 450 nm) anhydroisocalebassine **(151)**,[137] a compound, which at pH 4–7 is very oxygen sensitive, affording a merocyanin derivative of possible structure **152** (Scheme 19).[138] In 0.1 *M* alkali **151** shows a hypsochromic shift (to λ_{max} 432 nm) formulated as the cyanin **153**.

C-Curarine **(131)**, on the other hand, affords ultracurine A **(154)** as one of the products on treatment with hot (60°) concentrated hydrochloric acid.[15,139] Evidence for this structure comes from several sources, principally chemical,[15] and its mode of formation is shown in Scheme 20.

The ^{1}H nmr spectrum served to distinguish between the partial structures **155** and **156** for calebassine, an alkaloid of curare,[121,140,141] and several *Strychnos* species.[130,142,143] A two-proton singlet observed at 4.92 ppm was assigned[144] and confirmed by deuterium labeling[145] to be due to the C-17 and C-17′ protons. The absence of coupling between H-17 and H-16, which are trans disposed, is frequently observed in the spectra of pyrrolidine and tetrahydrofuran systems. In *C*-toxiferine **(132)** H-17 and H-17′ appear at 7.07 ppm.[145] The structure of calebassine was confirmed through X-ray analysis of diiodide derivative.[146]

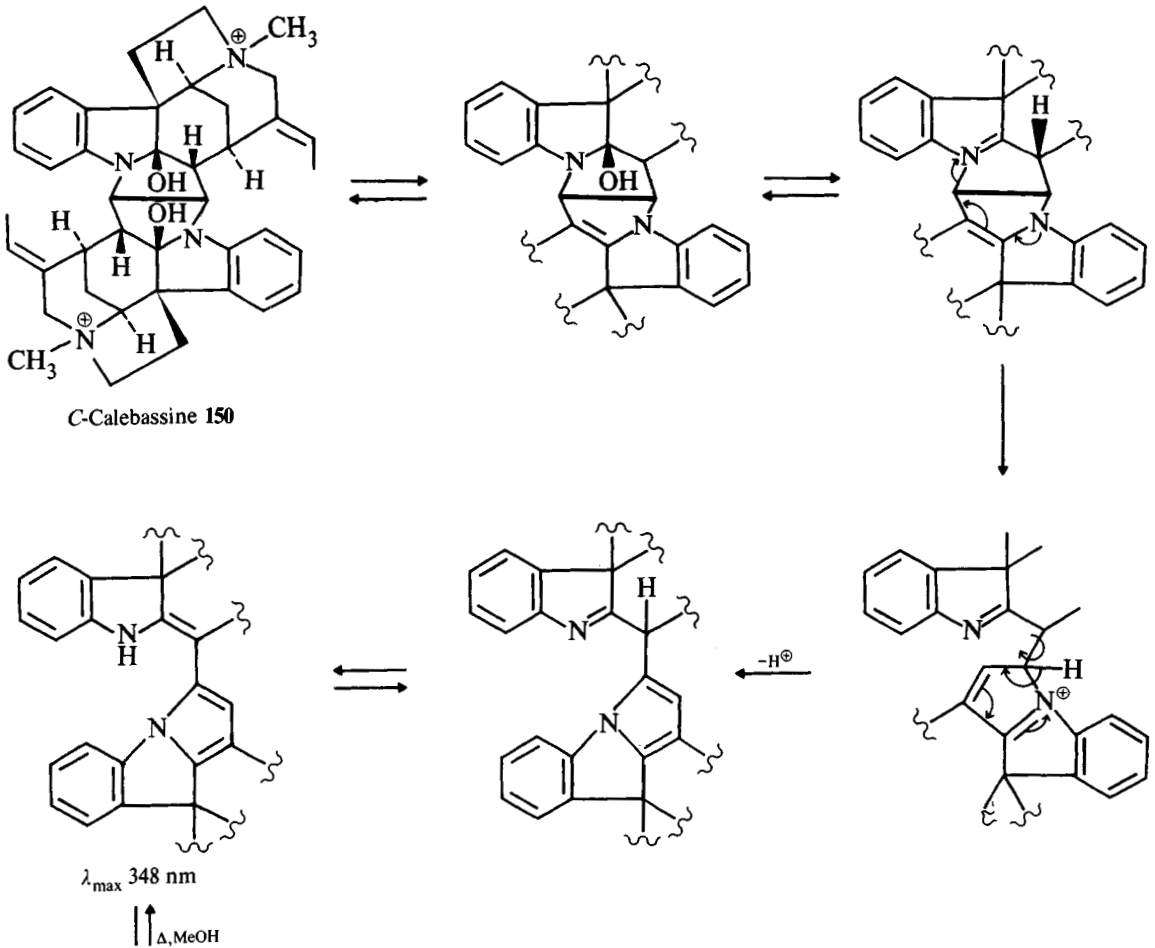


Scheme 18.

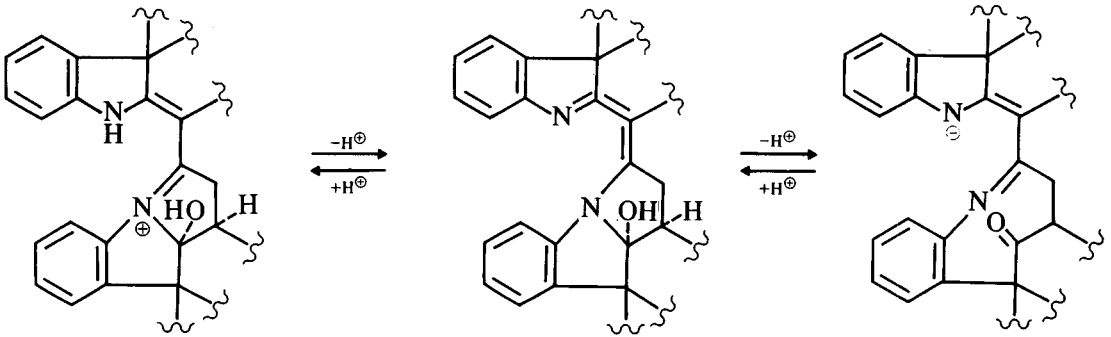
In the course of structure determination of several alkaloids from *S. dolichothyrsa*,[125] the ^{13}C nmr spectra of this series were examined and comparison was made with strychnine and its *N*-oxide. As expected, the aminomethylene carbons adjacent to the *N*-oxide are substantially shifted, C-3 by 22.6, C-5 by 12.5, and C-21 by 17.8 ppm. In caracurine V values for the same carbons on *N*-oxidation were 22.7, 17.4, and 17.2 ppm, respectively. Two carbons C-8 and C-20 were shifted upfield on *N*-oxidation, by 2.7 and 4.7 ppm in the case of caracurine V (**136**), and by 3.3 and 5.2 ppm for strychnine (Table V).[125]

A new and quite different series of *Strychnos-Strychnos* alkaloids has been isolated from the roots of *S. variabilis* Wild.[147,148] Two of the isolates, strychnobiline (**159**) and isostrychnobiline (**160**), are isomers, whereas the third compound is the 12′-hydroxy derivative **161**, showing a strongly hydrogen-bonded phenolic group.

A crucial signal in assigning the gross structure was a doublet at 5.25 ppm assigned to a methine proton at C-17′.[147] The stereochemical assignments in **160** and **161** were deduced[148] from the 300 MHz nmr spectrum where a large (10.2 Hz) coupling of H-2′ and H-16′ indicated these protons to be trans disposed, and from

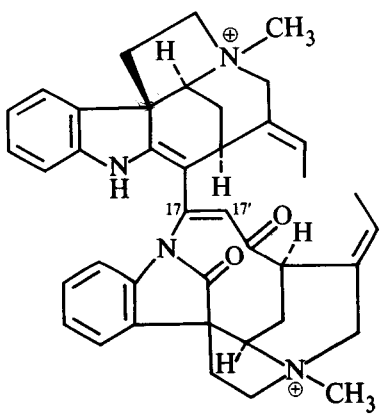


C-Calebassine **150**



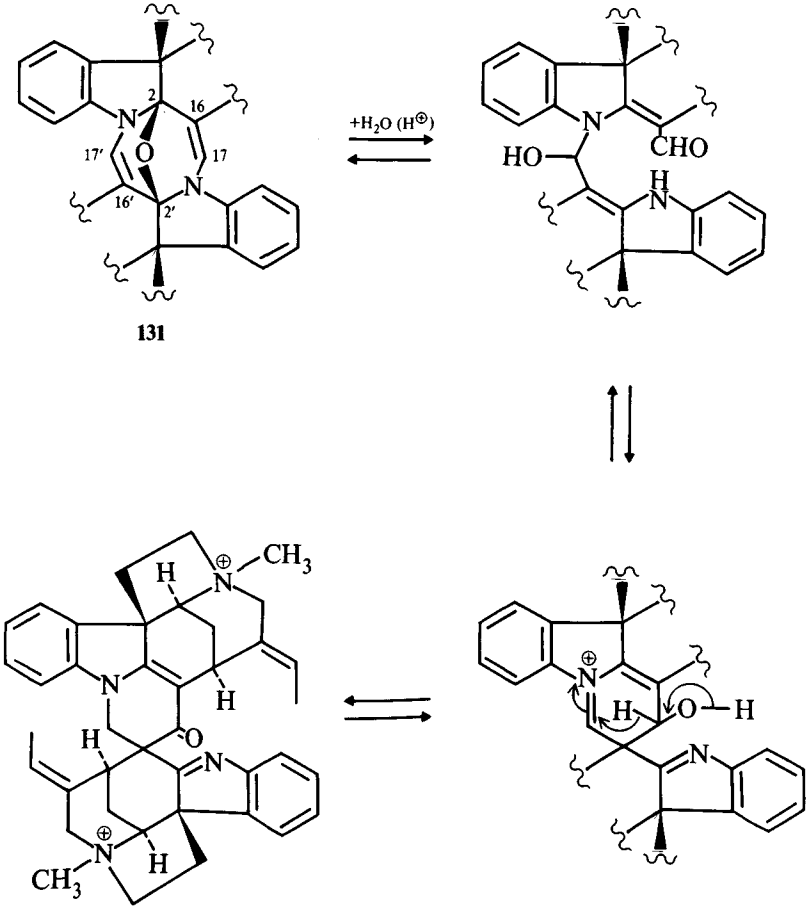
151 λ_{max} 450 nm

153 λ_{max} 432 nm



152

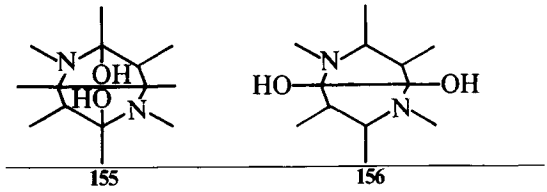
Scheme 19.



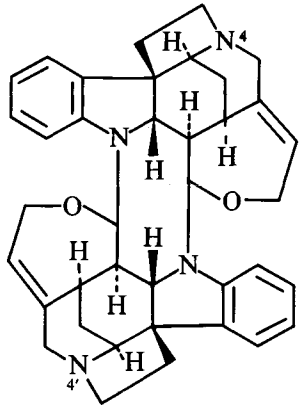
Scheme 20.

the H-2 to H-16 coupling a cis configuration was assigned. Two rotamers were observed for isostrychnobiline in which the major rotamer showed a coupling constant of 9.5 Hz for H-16′ with H-17′, suggesting the stereochemistry shown. A positive cd curve indicated the configurations at H-2 and H-2′. All the isolates displayed a based peak at *m/e* 307 attributed to the ion **162.**

An even more unusual *Strychnos-Strychnos* alkaloid has been isolated in high (2%) yield from the root bark of *Strychnos icaja* Baill.[149] This is sungucine **(163)**, which contains a novel C-23,C-5′ bond and whose structure was solved by X-ray crystallography. The chromophore showed λ_{max} 218 (4.87), 265 (3.84), 292 (4.02), and 305 (4.01) and the nmr spectrum (250 MHz) displayed H-23′ as a doublet ($J = 10$ Hz) at 6.02 ppm and H-19 and H-19′ as quartets at 5.24 and 5.47 ppm.[149]



155 156



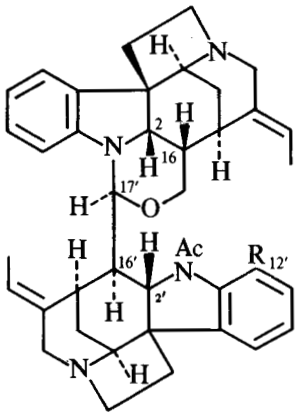
Caracurine V (136)

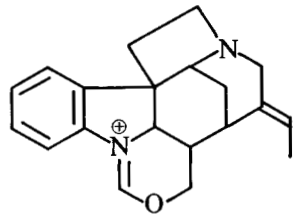
157: $N_4^{\oplus}-O^{\ominus}$

158: $N_4^{\oplus}-O^{\ominus}$, $N_{4'}^{\oplus}-O^{\ominus}$

TABLE V. ^{13}C NMR SPECTRAL DATA OF CARACURINE V AND RELATED ALKALOIDS

Carbon	Chemical Shift, δ (ppm)			
	Caracurine V (136)	Caracurine V *N*-oxide (157)		Caracurine V *N,N'*-dioxide (158)
		a	b	
C-2	56.8	56.9	55.8	55.8
C-3	59.9	59.9	82.6	82.6
C-5	51.2	51.3	68.7	68.7
C-6	40.8	40.7	37.2	37.2
C-7	55.5	55.8	56.9	56.9
C-8	133.6	133.3	130.6	130.7
C-9	119.5	120.3	120.7	121.2
C-10	121.7	121.8	121.8	121.9
C-11	128.2	128.6	129.6	129.6
C-12	110.2	110.7	111.5	111.6
C-13	152.3	152.1	152.0	151.6
C-14	26.1	25.9	24.5	24.4
C-15	34.0	33.8	32.5	32.4
C-16	52.5	52.4	52.1	52.0
C-17	98.9	98.9	98.5	98.6
C-18	66.5	66.4	65.9	65.9
C-19	127.3	128.1	133.8	133.8
C-20	141.2	140.7	136.0	136.2
C-21	53.3	53.3	70.5	70.5



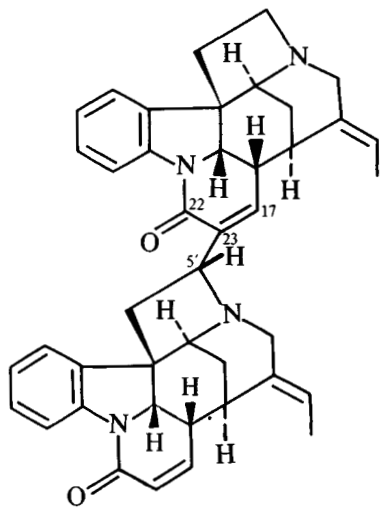


162

Strychnobiline **(159)**:R = H,
H-16′ and H-17′ stereochemistry
not defined

Isostrychnobiline **(160)**:R = H

12′-Hydroxyisostrychnobiline **(161)**:R = OH



Sungucine **(163)**

X. SECODINE-CONTAINING DIMERS

The small genus *Rhazya* has been investigated by several groups[150] over the years and has provided two groups of dimeric indole alkaloids, the secamines[151,152] and the presecamines[153,154] (Table VI). In each instance three isolates were

obtained, the parent compound, a mixture of dihydro species, and a tetrahydro compound. The secamines all displayed indolic uv spectra and the ir spectra indicated NH, saturated ester, and disubstituted benzene nuclei. The mass spectrum of tetrahydrosecamine (THS) with a molecular ion at 680 m.u. showed an extremely intense ion at *m/e* 126 having the structure **164**.

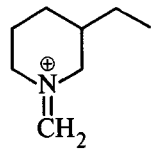
TABLE VI. ISOLATION OF SECAMINES AND PRESECAMINES

Compound	Source	Ref.
Presecamine	*Rhazya stricta* Decsne	154, 155
Dihydropresecamine	*R. stricta*	154, 155
Tetrahydropresecamine	*Amsonia tabernaemontana* Walt.	156
	Pandaca minutiflora Mgf.	157
	R. orientalis A.DC.	154, 155
	R. stricta	154, 155
Decarbomethoxytetrahydrosecamine	*A. tabernaemontana*	156
Secamine	*R. stricta*	151, 155
Dihydrosecamine	*R. stricta*	151, 155
Tetrahydrosecamine	*A. elliptica* Roem. et Schult.	158, 159
	A. tabernaemontana	152, 155
	R. stricta	151, 155

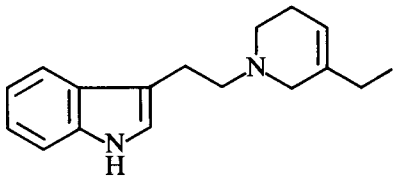
Two carbomethoxy groups were observed in the ^{1}H nmr spectrum together with eight aromatic protons, a very broad NH, and a broad six-proton triplet at 1.0 ppm, indicating the presence of two ethyl groups. A one-proton multiplet at 4.3 ppm was exchanged with sodium methoxide–deuteromethanol at 100° and assigned to an α-indolylacetic ester proton. In secamine, two broad olefinic signals at 5.5 and 5.36 ppm were assigned to the olefinic protons of an ethylpiperideine unit such as **165**, and this was confirmed by Hofmann degradation.[151] Reductive didecarbomethoxylation of tetrahydrosecamine with stannous chloride-hydrochloric acid afforded **166** whose structure was confirmed by synthesis. This led to two structures being considered for THS, namely, **167** and **168**.[151]

Many of the fractions of THS, although homogeneous by tlc, exhibited complex carbomethoxyl regions with one sample displaying singlets at 3.78, 3.77, 3.74, and 3.65 ppm in the ratio 2:3:2:3, but this ratio varied in other samples. This complexity was shown to be due to diastereoisomerism at C-16 (as opposed to structural isomerism) when a THS mixture was heated with methoxide/methanol at room temperature to yield "wide" THS showing singlets at 3.77 and 3.65 ppm.

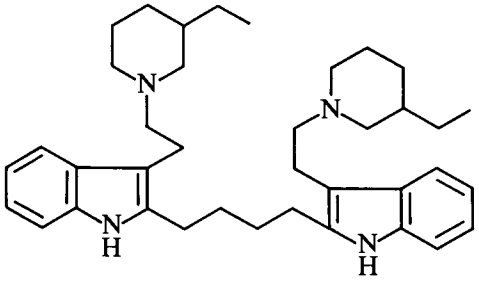
The presecamines were isolated when alkaloid fractions of *Rhazya orientalis* and *R. stricta* were examined by mass spectrometry for intense ions at *m/e* 124 (**169**) and 126 (**164**).[154] One fraction from *R. orientalis* displayed both indole and β-anilinoacrylic ester (**170**) chromophores, but in the mass spectrum essentially only two ions at *m/e* 340 ($C_{21}H_{28}NO_2$) and 126 appeared even at low probe temperatures, suggesting a thermal retro-Diels-Alder reaction. Based on the known[160] mass spectral reactions of β-anilinoacrylates it was surmised that the simplicity of the mass spectrum was due to one monomer unit constituting each "half" of the dimer.



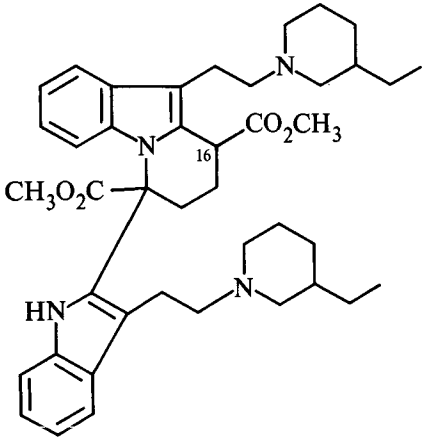
164 *m/e* 126



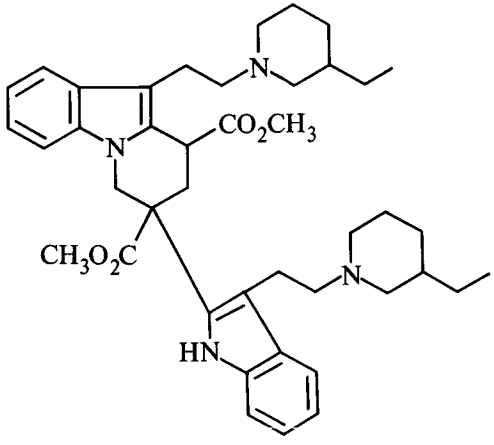
165



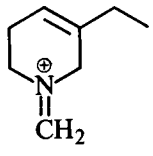
166



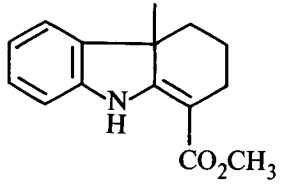
167



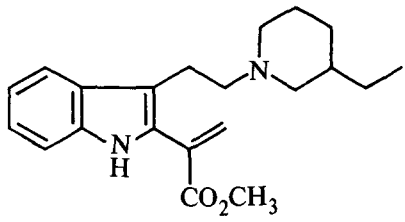
168



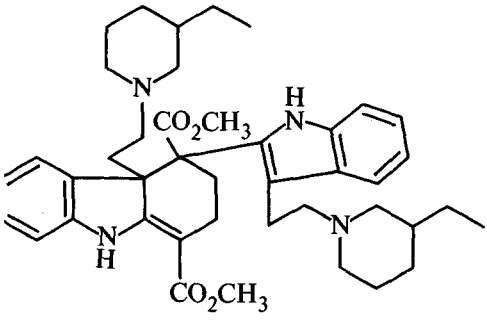
169 *m/e* 124



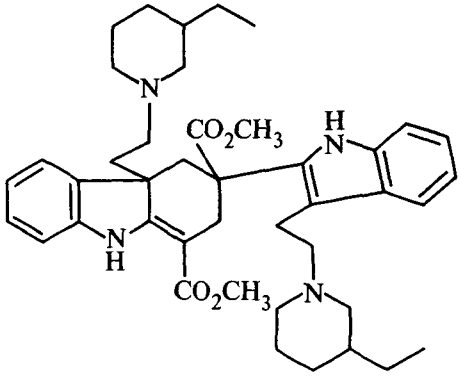
170



171



172



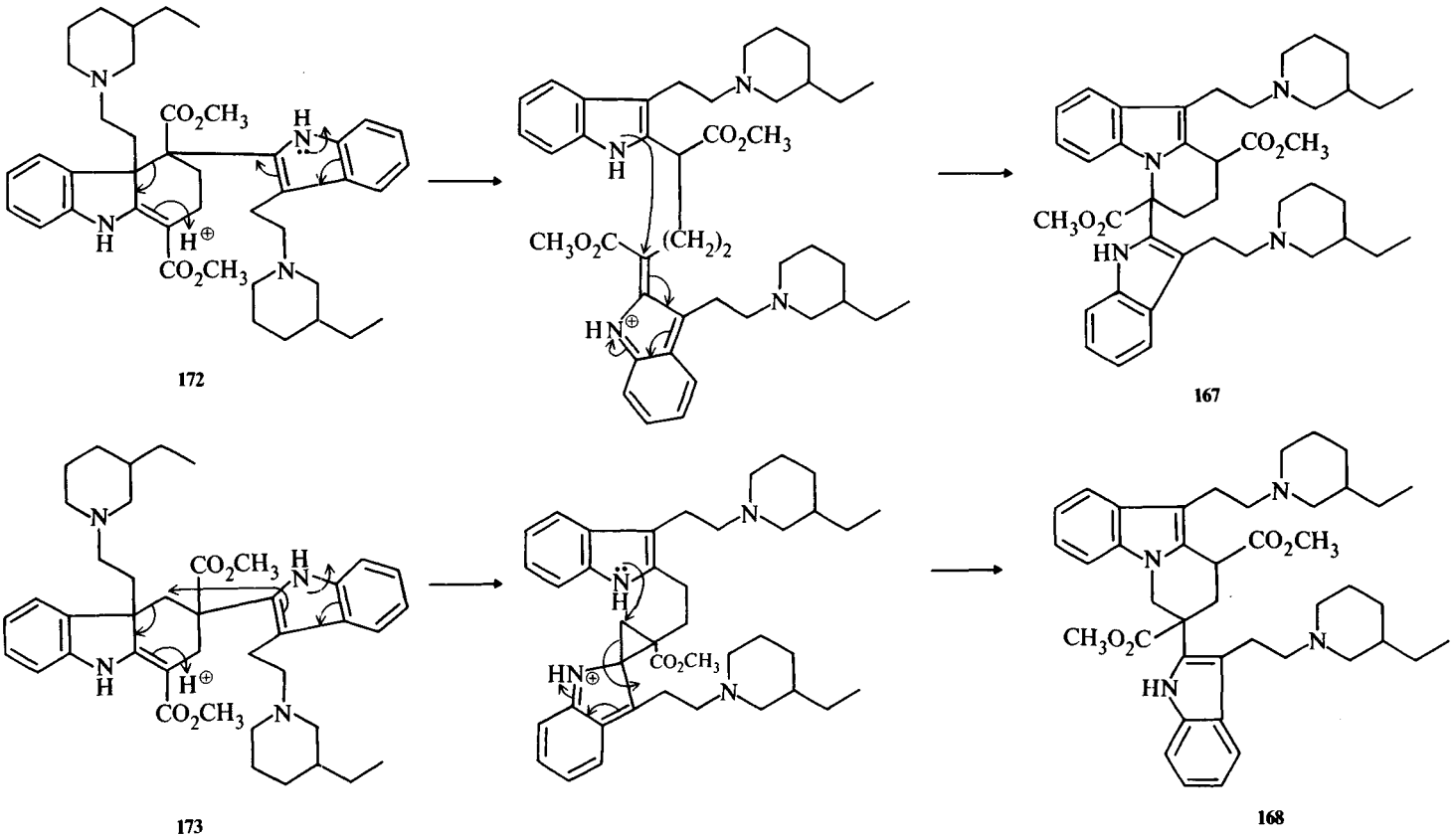
173

Biogenetically,[56] the acrylic ester **171** was considered for this monomer unit. Since, from the uv spectrum, it is the acrylic ester portion of this unit which is the ethylenic product in the reverse Diels-Alder reaction, two gross structures, **172** and **173**, were suggested for tetrahydroprescamine (THPS).[154]

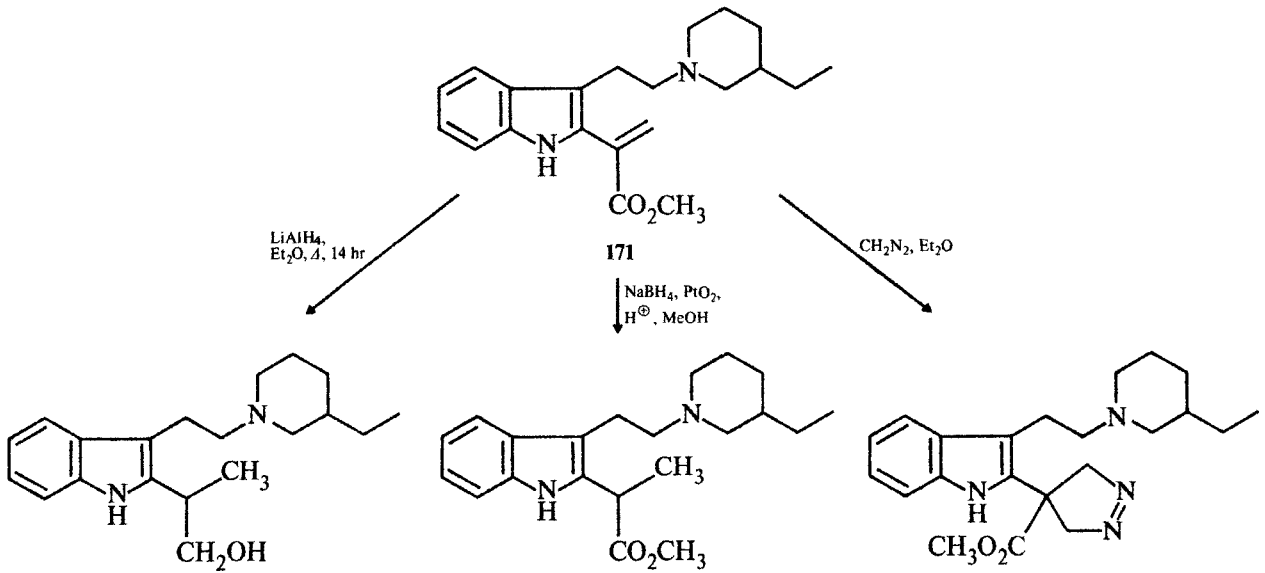
In support of this, saturated ester (1730 cm^{-1}) and β-anilinoacrylic ester (1675 and 1610 cm^{-1}) units were observed in the ir spectrum, together with NH absorptions at 3420 and 3360 cm^{-1}. Confirmation came from the nmr spectrum which showed two exchangeable NH protons and carbomethoxy singlets at 3.56 and 3.76 ppm.

When THPS was treated with formic acid at room temperature for 4 minutes or 2*M* hydrochloric acid for 15 minutes, a single product, having a pure indolic uv spectrum, was obtained that was identical with THS by tlc and mass spectral fragmentation. Unfortunately the mechanisms that explain this rearrangement (Scheme 21) do not distinguish between the two possible skeletons.[154] When the nmr spectrum of the product was examined it was found to be the pure "narrow" THS with singlets at 3.75 and 3.72 ppm, indicating acid-catalyzed rearrangement to the kinetically controlled product.

The product from the thermal decomposition of THPS was also examined spectrally and chemically (Scheme 22). The uv spectrum in ether exhibited λ_{max} 278(sh) and 312 nm and the nmr spectrum displayed characteristic doublets



Scheme 21.

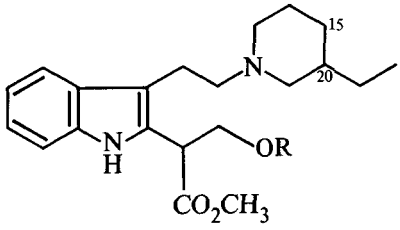


Scheme 22.

($J = 1.2$ Hz) and 6.46 and 5.49 ppm for the C-17 protons, in agreement with the structure 15,20-dihydrosecodine (**171**).[154]

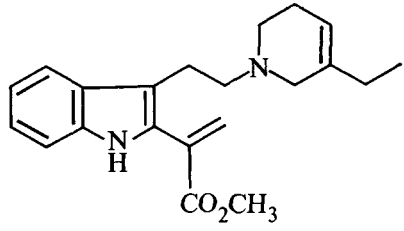
At 0° in the condensed phase the acrylic ester **171** underwent a Diels-Alder reaction to afford THPS as a mixture of isomers displaying carbomethoxy singlets at 3.79, 3.76, 3.69, and 3.56 ppm in the ratio 2:9:2:9 and separable by tlc. The major product ("major" THPS) was identical with the natural product. Acid rearrangement of "minor" THPS gave "narrow" THS, indicating the former to be the diastereoisomer at C-16′ of the natural THPS from *R. orientalis*.[154] However, evidence was still lacking which would firmly settle the skeletons of the secamines and the presecamines, and it became necessary to synthesize analogues which possessed simpler ^{1}H nmr spectra. One important reaction remains to be discussed, however.

When an attempt was made to acetylate the alcohol ester **174**, which had also been isolated from *R. orientalis*,[153] a product was obtained identical with THPS. Thus, in one step, acetylation, elimination, *and* Diels-Alder dimerization had occurred. In a similar way, the presecamines themselves were prepared from the alcohol ester **175** by way of secodine (**176**).[154]



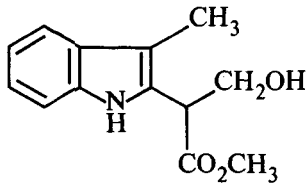
174: R = H

175: R = H, $\Delta^{15,20}$

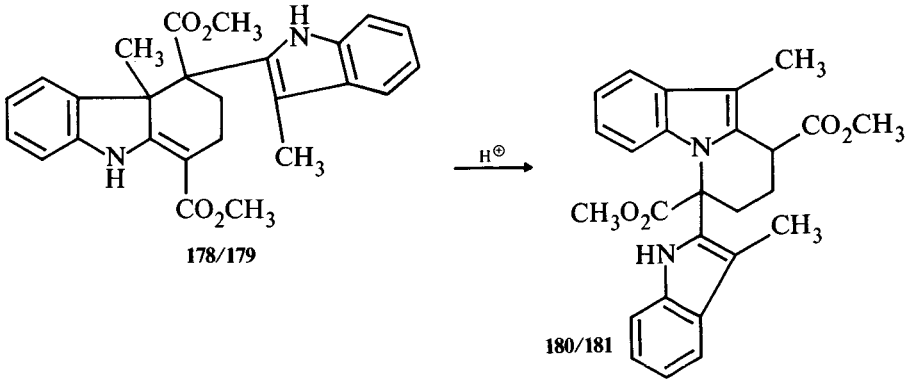


Secodine (**176**)

Compounds (monomers, presecamines, and secamines) were synthesized in the *N,N*-dimethyltryptamine series to try to deduce the ring substitution, but it was only when the skatolyl series was studied that definitive evidence was obtained. Thus acetylation-elimination of the alcohol ester **177**[155] with acetic anhydride/pyridine/triethylamine gave the skatolyl presecamine isomers **178** and **179** which could be rearranged to the skatolyl secamine isomers **180** and **181**, whose nmr spectra established the substitution pattern.



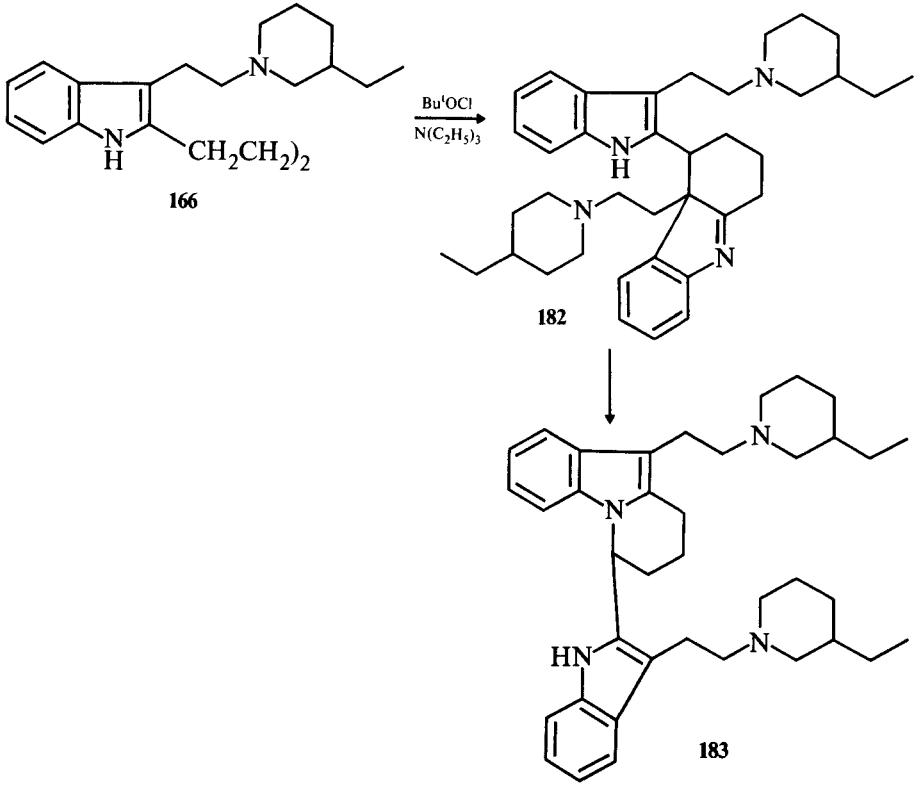
177



178/179

180/181

Sakai and co-workers[158,159] subsequently confirmed these results when oxidation of **166** with *t*-butyl hypochlorite/triethylamine gave the indolenine **182**. Acid rearrangement then afforded didecarbomethoxytetrahydrosecamine **(183)** (Scheme 23).

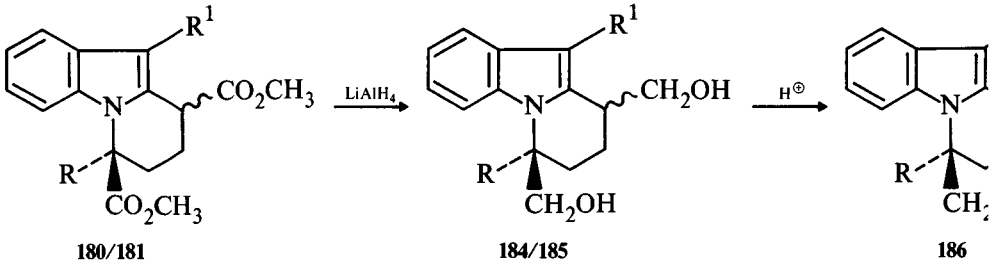


166

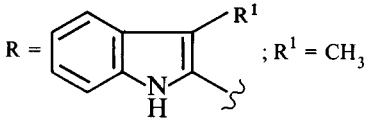
182

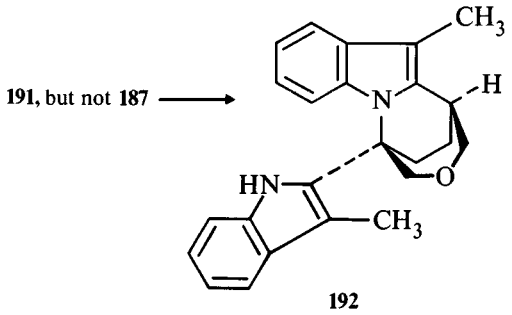
183

Scheme 23.

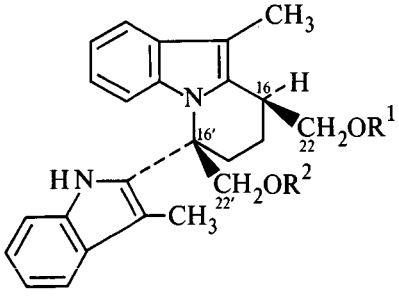


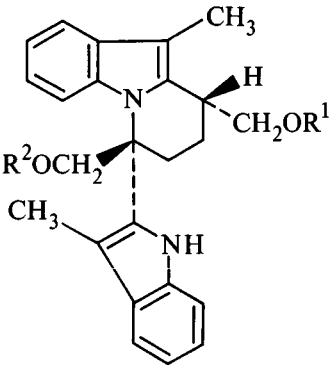
180/181 **184/185** **186**





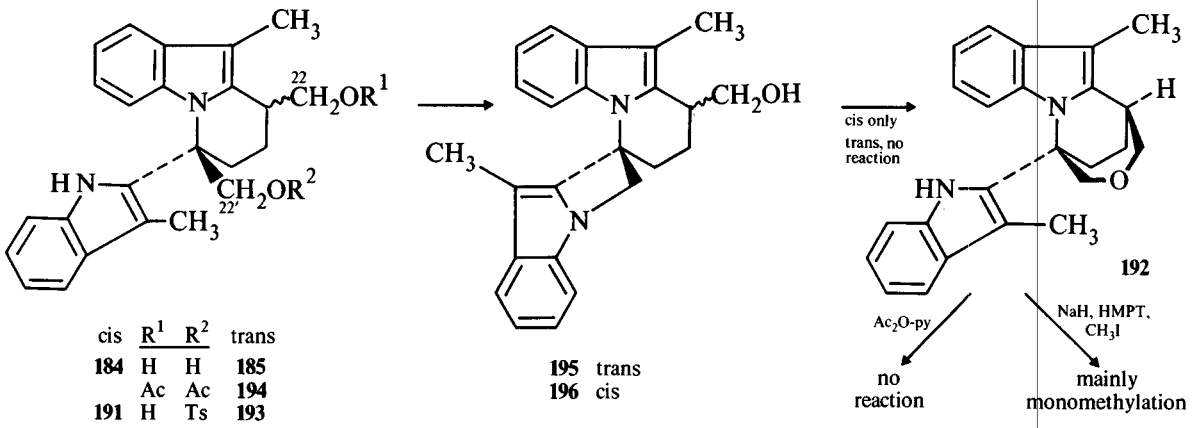
192





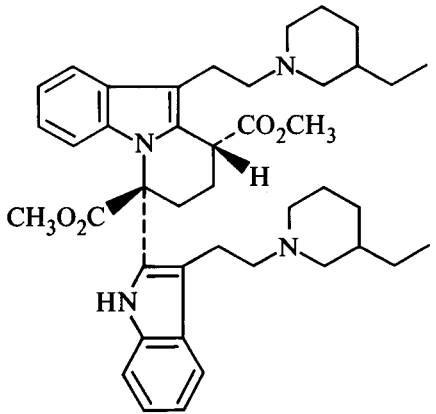
cis ("narrow")	R^1	R^2	trans ("wide")
184	H	H	**185**
187	Ts	H	**188**
189	Ts	Ts	**190**
191	H	Ts	**193**

Scheme 24.

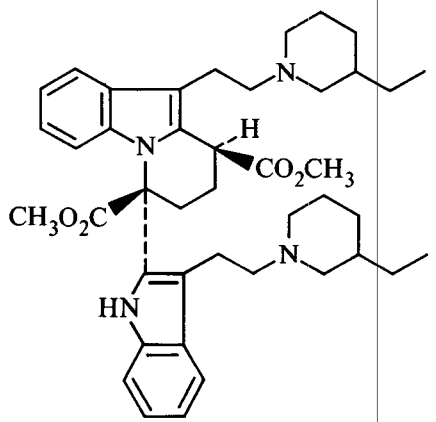


cis	R^1	R^2	trans
184	H	H	**185**
	Ac	Ac	**194**
191	H	Ts	**193**

195 trans
196 cis

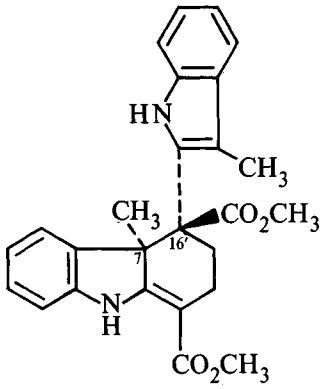


"Wide" tetrahydrosecamine (**197**)

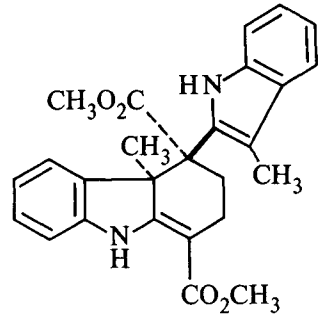


"narrow" tetrahydrosecamine (**198**)

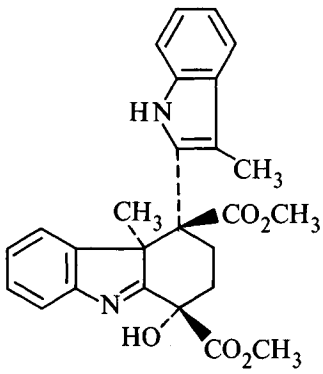
Scheme 25.



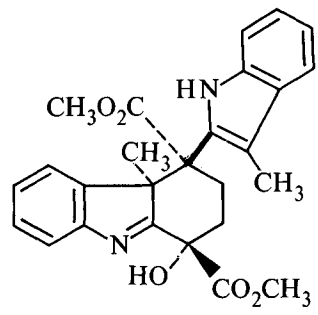
"Minor" isomer (178)



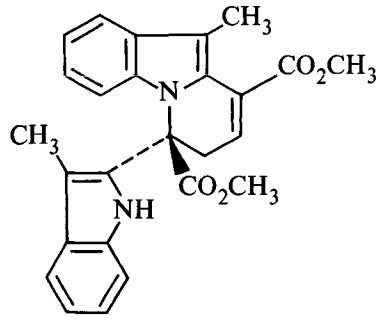
"Major" isomer (179)



199

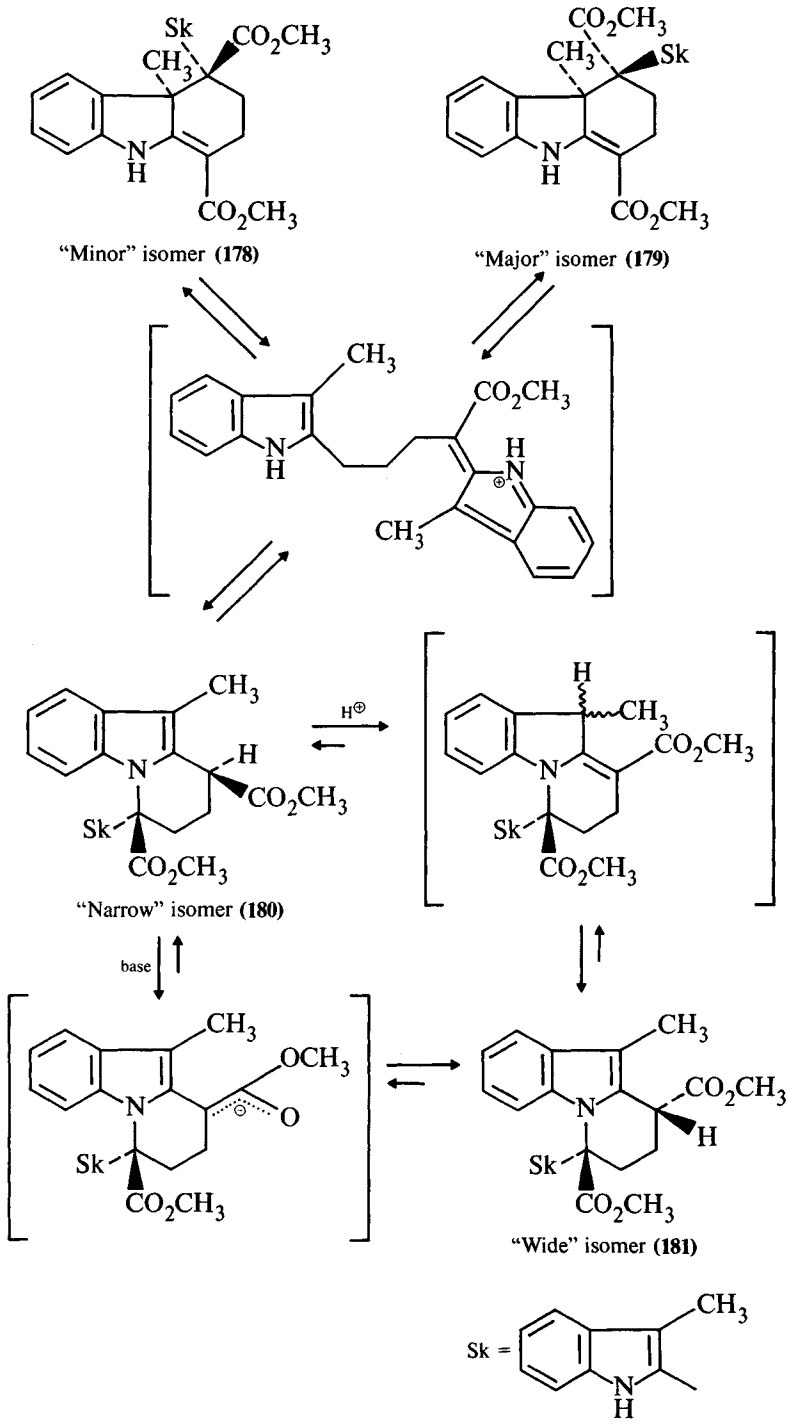


200



201

Scheme 26.



Scheme 27. Presecamine-secamine interconversions in the skatolyl series.

TABLE VII. CORRELATION OF THE PRESECAMINES AND SECAMINES

	Tetrahydropresecamines		Dimethylaminoethylpresecamines		Skatolylpresecamines	
	"Major"	"Minor"	"Major"	"Minor"	"Major"	"Minor"
Relative amounts formed in dimerization of secodine monomer (%)	82	18	70	30	70	30
Ester CH_3 (ppm)	2.76, 2.56	3.79, 3.69	3.76, 3.56	3.80, 3.71	3.76, 3.57	3.84, 3.66
	Tetrahydrosecamines		Dimethylaminoethylsecamines		Skatolylsecamines	
	"Narrow"	"Wide"	"Narrow"	"Wide"	"Narrow"	"Wide"
Relative amounts formed in acid rearrangement (%)	> 95	< 5	95–98	2–5	60	40
Relative amounts in NaOMe equil. (%)	< 5	> 95	7	93	25	75
Ester CH_3 (ppm)	3.75, 3.72	3.76, 3.63	3.77, 3.73	3.77, 3.63	3.76, 3.72, 3.62	

The synthetic work on the secamines and the presecamines and their analogues had established the ring substitution, but although each diastereoisomer in each series was available, stereochemical conclusions[155] were tentative. Table VII summarizes the similarities of corresponding isomers in each series chemically and spectrally, and it was therefore reasoned that deduction of the stereochemistry in one series would permit correlation with each of the other series.

In the secamine series it was hoped that an appropriate cyclization involving C-22 and C-22′ could distinguish the diastereoisomers. Anhydride formation was unsuccessful, as was direct ketal formation from the skatolyl secamine diols **184** and **185** (elimination to **186** occurred) (Scheme 24). Similar problems were also encountered with the C-22 monotosylates **187** or **188** and the ditosylates **189** and **190**. Treatment of the C-22′ monotosylate **191** with sodium hydride in hexamethylphosphoramide gave the ether **192** in high yield.[161]

The trans C-22′ tosylate **193** (prepared indirectly from the diacetate **194**) with sodium hydride-hexamethylphosphoramide afforded a stable indolic product, assigned the structure **195**, and when the reaction in the cis series was reinvestigated, a corresponding intermediate **196** was obtained, which could be transformed to **192** (Scheme 25).[161]

In this way it was established that the "wide" isomer in the secamine series corresponds to a trans stereochemistry of the ester groups. "Wide" tetrahydrosecamine has the structure **197** and "narrow" tetrahydrosecamine is **198**.[161]

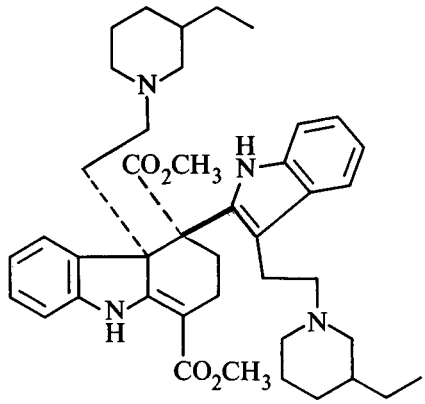
The skatolyl presecamines **178** and **179** on reflux in dioxane in the presence of air afforded, stereospecifically, an oxidation product from each isomer. Molecular models established the location of the C-7 angular methyl group to be the least hindered side, and therefore the products were formulated as **199** and **200**, respectively. Acid rearrangement of either isomer afforded the same unsaturated secamine derivative **201** (Scheme 26).[161]

In the mass spectrum the oxidation product **199** from the minor skatolyl presecamine eliminated dimethyl ether, which is possible only when the carbomethoxy groups are cis to each other. The other isomer preferentially lost methanol in the mass spectrum. Through the correlations discussed previously, natural tetrahydropresecamine has the structure **202**.[161]

The explanation of how the two presecamines could afford a single secamine isomer was determined when the acid rearrangement was studied by hplc. The "major" skatolyl presecamine (**179**) was transformed directly to the "narrow" skatolyl secamine (**180**). The "minor" isomer **178**, however, was rapidly transformed into the "major" isomer **179** and *then* to **180**. These results were interpreted in terms of the mechanism shown in Scheme 27.[161]

XI. *IBOGA*-CANTHINONE TYPE

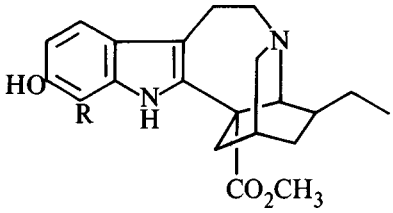
Bonafousine (**203**), from the leaves of *Bonafousia tetrastachya* (Humboldt, Bonpl. & Kunth) Mgf. (Apocynaceae), is the only member of this series.[162] Three oxygen atoms deduced from the molecular formula ($C_{35}H_{40}N_4O_3$) were traced

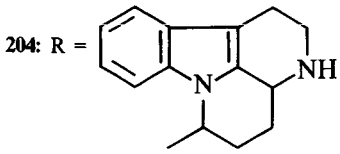


Natural tetrahydropresecamine (**202**)

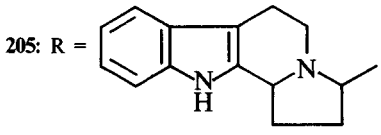
to a carbomethoxy group (ν_{max} 1715 cm^{-1}, δ 3.54 ppm) and a hydroxy group (ν_{max} 3600 cm^{-1}). In alkali the uv spectrum (λ_{max} 228, 286, 294 sh, and 300 nm) was shifted to λ_{max} 228, 286, 294, and 320 nm, suggesting the presence of indole and 11-hydroxyindole moieties. From the nmr spectrum the latter unit was 11,12-disubstituted (ortho protons at 7.09 and 7.51 ppm).

In the mass spectrum the two "halves" were observed at *m/e* 353 and 211, the former showing an iboga alkaloid fragmentation, the latter being a β-carboline. A distinction between the two possibilities **204** and **205** was made through X-ray crystallography of the dihydrochloride trihydrate, which indicated the structure

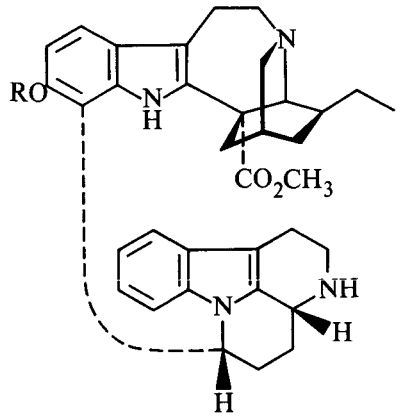




204: R =



205: R =



Bonafousine (**203**): R = H
206: R = CH_3

203. Circular dichrosim of 11-*O*-methylbonafousine (**206**) established the iboga unit to have the absolute stereochemistry shown.[162]

XII. *IBOGA*-VOBASINE TYPE

The largest group of bisindole alkaloids are those derived from an iboga and a vobasine unit and they frequently occur with their corresponding monomers in the genera *Conopharyngia*, *Gabunia*, *Tabernaemontana*, and *Voacanga*, all in the family Apocynaceae.[15,16,19]

Voacamine ($C_{43}H_{52}N_4O_5$) was the first alkaloid in this series to be characterized. From the uv spectrum indole and 5-methoxyindole chromophores were deduced, and the nmr spectrum revealed an *N*-methyl group, two carbomethoxy groups, an aromatic methoxy group, six aromatic protons, two indolic NH groups, and ethylidene and ethyl side chains.

Acid hydrolysis afforded voacangine from one "half," and the other "half" was thought to be a member of the vobasine series since sodium methoxide shifted one of the carbomethoxy groups from 2.44 to 3.57 ppm.[163] The linkage between the two units should be between an aromatic carbon of voacangine and an electrophilic center in the vobasine unit. Indeed, heating vobasinol (**82**) and voacangine (**207**) afforded voacamine (**208**),[164,165] probably via the less thermodynamically stable isomer voacamidine (**209**), for voacamidine (**209**) had previously been shown to yield voacamine (**208**) on heating in 2 *M* hydrochloric acid.[164]

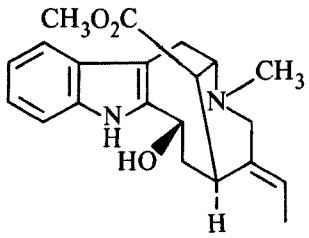
In the condensation reaction it is suggested that voacangine (**207**) attacks the immonium species **210** from the α face, giving voacamine with a 3β-H configuration; this is supported by the shift of this proton on epimerizing C-16.

Hydrolysis of the ester functionalities of voacamine (**208**) and decarboxylation in methanolic hydrochloric acid gave 16′-decarbomethoxy-16-epivoacamine (**211**);[165] the epimer **212** was obtained as a natural product from *Voacanga africana* Stapf,[166,167] several other sources,[167,168-171] and by partial synthesis from vobasinol (**82**) and ibogaine (**213**).[172]

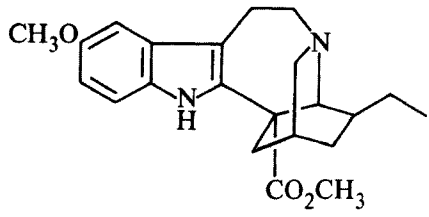
Also isolated from *V. africana* was voacamine *N*-oxide (**214**), which on acid hydrolysis yielded voacangine (**207**).[173] From the nmr spectrum which showed the *N*-methyl singlet shifted downfield by 0.7 ppm the *N*-oxide group was assigned to the vobasinyl unit. Confirmation of this came[173] through the condensation of voacangine (**207**) and vobasinol *N*-oxide (**215**).

Closely related to voacamine was an alkaloid obtained from the root bark of *Tabernaemontana accedens*,[82] the nmr spectrum of which lacked the *N*-methyl singlet at 2.69 ppm in **208**. In agreement with the *N*-demethylvoacamine structure (**216**), the molecular ion appeared at 14 m.u. less than in **208** and the NH group could be methylated to yield **208**.[82]

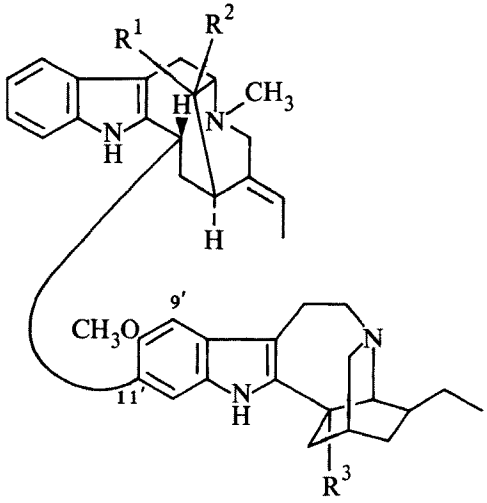
Voacamidine (**209**) from *V. africana*[164,174] and *Conopharyngia durissima* Stapf[169] on acid treatment yields a mixture containing both voacangine (**207**) and voacamine (**208**).[164] It is readily distinguished from voacamine (**208**) by the two ortho doublets at 7.05 and 6.70 ppm and from the shielded nature of the aromatic methoxy group (3.08 ppm).



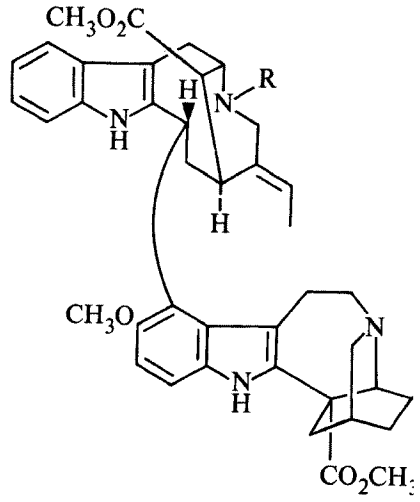
Vobasinol (82)
N(4)-Oxide (215)



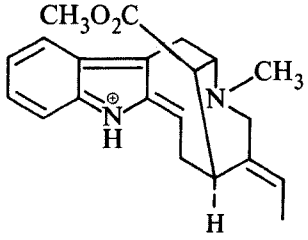
Voacangine (207)



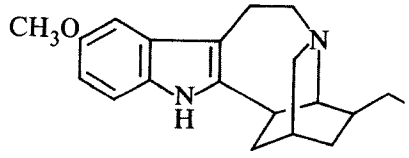
Voacamine (208) $R^1 = R^3 = CO_2CH_3$, $R^2 = H$
211: $R^1 = R^3 = H$, $R^2 = CO_2CH_3$
212: $R^2 = R^3 = H$, $R^1 = CO_2CH_3$
214: $R^1 = R^3 = CO_2CH_3$, $R^2 = H$, *N*(4)-oxide



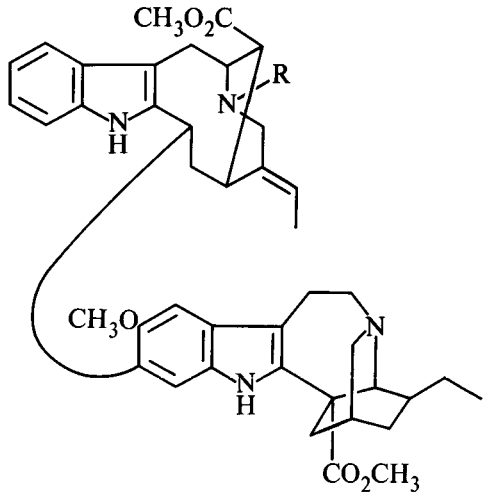
Voacamidine (209) R = CH_3
209a: R = H



210



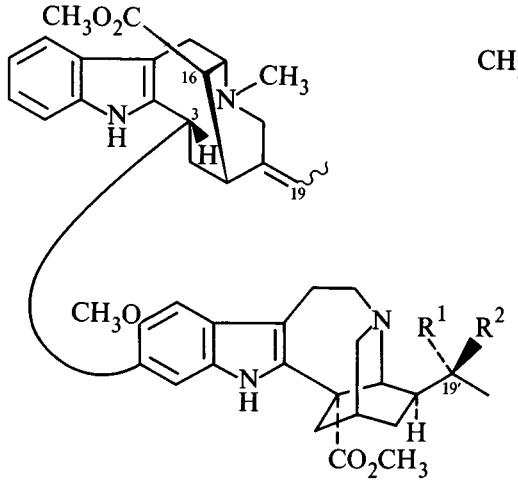
Ibogaine (213)



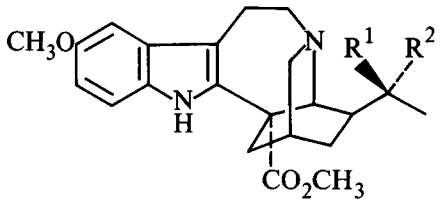
N-Demethylvoacamine **(216)**: R = H
Voacamine **(208)**: R = CH_3

Voacorine **(217)**, from several *Conopharyngia*[168,175] and *Voacanga* species,[163,165,168,172,176-181] co-occurs with its C-19′ epimer **(218)** in *Voacanga bracteata* Stapf,[181] and with its 19 isomer **(219)** in *Tabernaemontana brachyantha* Stapf.[182]

The carbomethoxy group appeared in the "normal" position (3.68 ppm) in voacorine together with a methyl doublet at 0.95 ppm for C-18′H_3, and the stereo-



Voacorine **(217)**: R^1 = H, R^2 = OH
19′-Epivoacorine **(218)**: R^1 = OH, R^2 = H
19-Epivoacorine **(219)**: R^1 = H, R^2 = OH



Voacristine **(220)**: R^1 = OH, R^2 = H
19-Epivoacristine **(221)**: R^1 = H, R^2 = OH

chemistry at C-19′ was deduced by acid hydrolysis to voacristine (**220**)[183] and synthesis from **220** and vobasinol (**82**).[165]

Acid hydrolysis of 19′-epivoacorine (**218**) afforded 19-epivoacristine (**221**)[184] which assisted in determination of the structure. Comparison of the nmr spectra of voacorine (**217**), 19′-epivoacorine (**218**), and the isolate from *T. brachyantha*[182] (Table VIII) indicated that the C-19 proton was now somewhat deshielded, although the chemical shift of C-18′H_3 indicated it to belong to the same stereochemical series at C-19′ as voacorine (**217**).

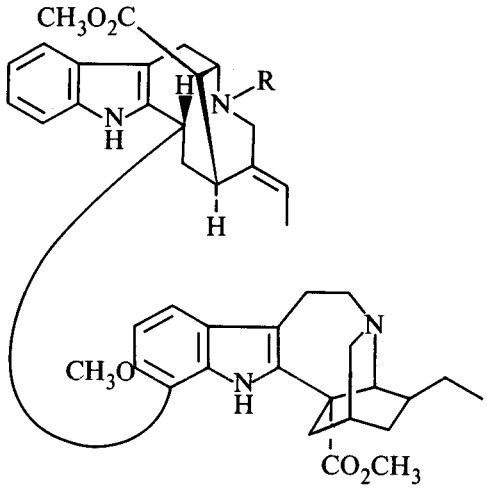
TABLE VIII. COMPARISON OF THE PRINCIPAL ^{1}H NMR DATA OF VOACORINE (**217**), 19′-EPIVOACORINE (**218**), AND THE ALKALOID FROM *T. BRACHYANTHA* (**219**).[182]

	Voacorine (217)	19′-Epivoacorine (218)	Alkaloid from *T. brachyantha* (219)
$\underline{CH_3}^{19'}CH$ (OH)	1.07	1.22	1.0
$\underline{CH_3}^{19}CH{=}C$	1.67	1.66	1.67
$-{}^{16}CO_2\underline{CH_3}$	2.48	2.47	2.55
$-{}^{16'}CO_2\underline{CH_3}$	3.68	3.63	3.74
$-N\underline{CH_3}$	2.60	2.58	2.64
$ArO\underline{CH_3}$	3.99	3.98	4.00
$\underline{CH_3}^{19}CH{=}C$	5.15	5.15	5.35

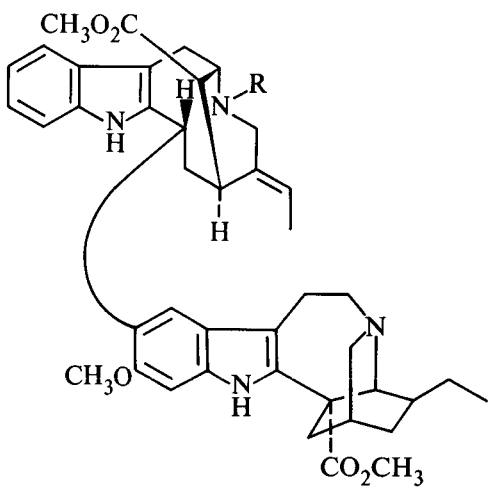
The mass spectra of voacamine and related alkaloids frequently show ions in the *m/e* 100–200 range of diagnostic significance, normally in two groups, for example, *m/e* 122, 124, 136, and 148 and *m/e* 122, 180, 181, 182, and 194 from the voacangine (**207**) and vobasinol (**82**) units, respectively. Like the bisindole alkaloids from *Catharanthus* (Section XXII), this is another group of alkaloids where the molecular ion is frequently accompanied by a transmethylation ion at 14 m.u. to higher mass. But the intensity of this ion apparently depends on the point of attachment, since only 3,10′-linked isomers permit transfer of a methyl from the iboga carbomethoxyl group to the basic vobasinyl nitrogen.[185]

Gabunine (**222**), conodurine (**223**), and conoduramine (**224**) bear a similar relationship to each other in the isovoacangine (**225**) series as do *N*-demethyl voacamidine, voacamidine, and voacamine in the voacangine series.

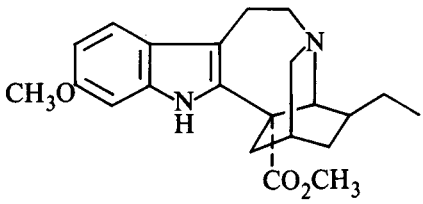
Gabunine (**222**), from *Gabunia odoratissima* Stapf (Apocynaceae),[186] contained no *N*-methyl group from its ^{1}H nmr spectrum and methylation (formaldehyde-Pd/H_2) afforded conodurine (**223**), which co-occurs with **222** in *G. odoratissima*. Conodurine (**223**) and its isomer conoduramine (**224**) also co-occur in *G. odoratissima*[186,187] and *Tabernaemontana johnstonii*.[188]



Gabunine (222): R = H
Conodurine (223): R = CH_3



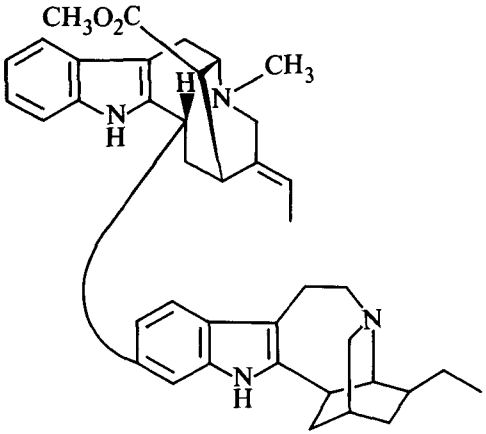
Conoduramine (224): R = Me
Gabunamine (229): R = H



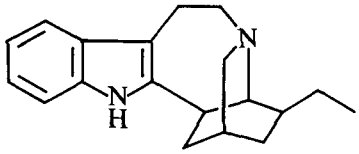
Isovoacangine (225)

Acid cleavage of conodurine (223) yielded isovoacangine (225) and condensation of 225 with vobasinol afforded both conodurine (223) and conoduramine (224) in the ratio 1:2.[164] Again these compounds are readily distinguished by the aromatic region of their ^1H nmr spectra, where conoduramine (224) shows an AB pattern at 6.90 and 7.24 ppm and a carbomethoxy singlet in a "normal" position at 3.66 ppm.[188]

Tabernamine (226) is one of the cytotoxic constituents of *Tabernaemontana johnstonii* Pichon (Apocynaceae) obtained by Kingston and co-workers.[189] The molecular ion at *m/e* 616 indicated the compound to be isomeric with 16′-decarbomethoxyvoacamine (212) and indeed only one carbomethoxyl group, that in the vobasine unit (ν_{max} 1720 cm^{-1}, 2.56 or 2.50 ppm), was observed. Nuclear magnetic resonance signals for the ethylidene (doublet at 1.68 ppm, multiplet at 5.38 ppm), ethyl (triplet at 0.90 ppm), and *N*-methyl (singlet at 2.50 or 2.56 ppm) groups confirmed these ideas.



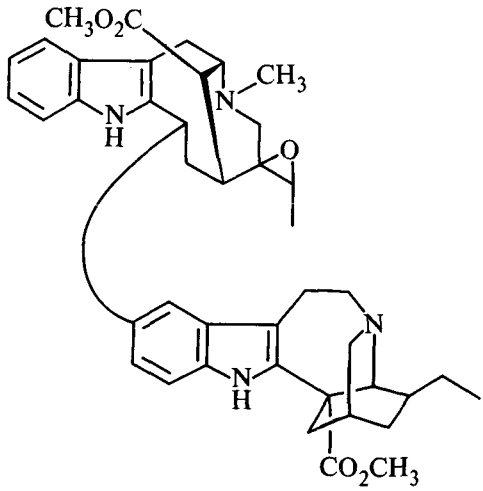
Tabernamine (226)



Ibogamine (227)

Acid hydrolysis afforded ibogamine (227), and condensation of this alkaloid with vobasinol (82) afforded tabernamine (226). This site of attack was deduced from the multiplicity of the 9′-proton which appeared as a doublet ($J = 8$ Hz) at 7.45 ppm. Tabernamine therefore has the structure **226**.[189]

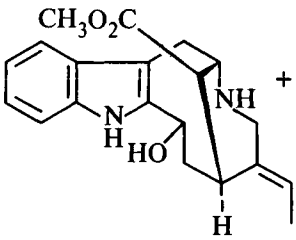
Also obtained from *T. johnstonii* was an alkaloid having a molecular ion at *m/e* 720, 16 m.u. higher than in conoduramine (224), and although ions typical of the iboga unit were observed, those of the vobasine moiety were shifted by 16 m.u. (i.e., to *m/e* 196, 198, and 210). Typical three-proton singlets were observed at 2.42, 2.60, 3.66, and 3.92 ppm for an *N*-methyl, two carbomethoxy groups, and an aromatic methoxy group. The aromatic region indicated that the iboga unit was linked to the vobasine moiety the same way as in **224**. The key to the structure, however, was a three-proton singlet at 1.34 ppm, which was assigned to a C-18 H_3 with a 19,20 epoxy group as shown in **228**.[188]



19,20-Epoxyconoduramine (228)

Gabunamine (**229**) was also isolated from *T. johnstonii*[188] as a cytotoxic constituent and it too displayed spectral properties very similar to those of conoduramine (**224**), but the *N*-methyl group was missing as shown from the nmr spectrum and the base peak (*m/e* 166) in the mass spectrum. Methylation of gabunamine afforded **224**, and acid hydrolysis yielded isovoacangine (**225**).

Condensation of perivinol (**230**) with isovoacangine (**225**) in 1.5% methanolic hydrogen chloride afforded gabunamine (**229**) and gabunine (**222**) identical with the natural products (Scheme 28).[188]



Perivinol (**230**)

+ Isovoacangine ⟶ Gabunamine (**229**) + Gabunine (**222**)

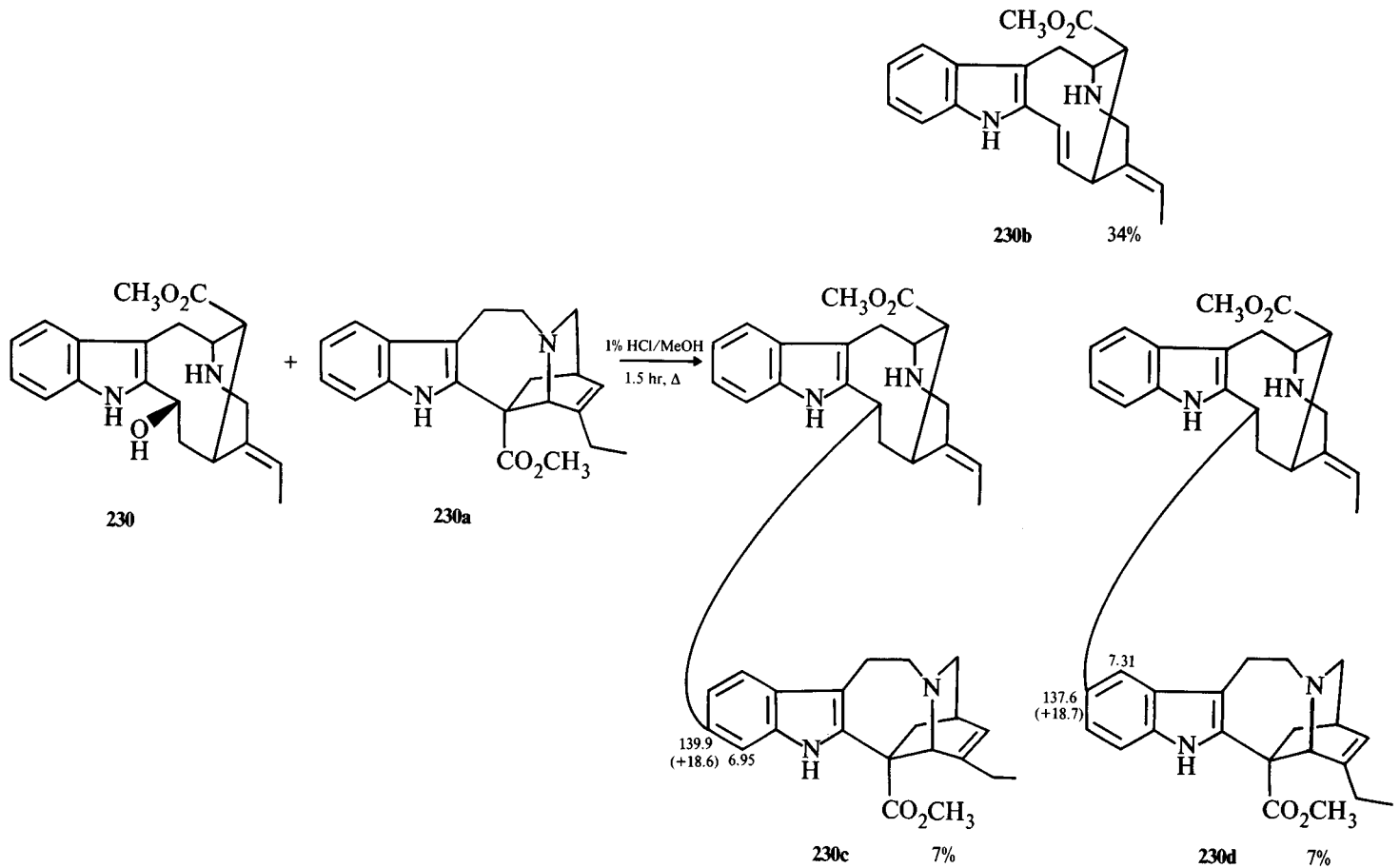
Scheme 28.

Similarly, condensation of perivinol (**230**) and voacangine (**207**) afforded *N*-demethylvoacamine (**216**) and *N*-demethylvoacamidine (**209a**).[188a] On the other hand, reaction of catharanthine (**230a**) with perivinol (**230**) afforded three products, the major being 3,14-dehydroperivinol (**230b**)[188b] and the minor, the isomers **230c** and **230d**. Similar products were derived from the reaction of dregaminol (**233**) and catharanthine (**230a**).[188a]

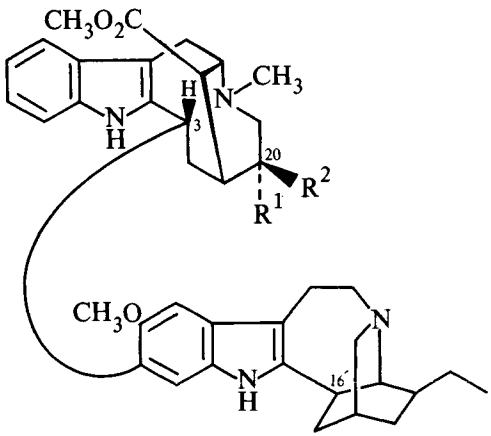
Two further alkaloids in the voacamine series have been isolated from the bark of *Ervatamia orientalis* and were shown to be the C-20 epimers of 16′-decarbomethoxy-19,20-dihydrovoacamine, namely, **231** and **232**.[171] Ibogaine (**213**) was produced from each compound on acid hydrolysis, and the structures were confirmed and distinguished by synthesis from **213** and the corresponding vobasinol systems, dregaminol (**233**) and tabernaemontaninol (**234**).[171]

The root bark of *Tabernaemontana elegans* Stapf has yielded seven alkaloids in this series,[185,190] namely, tabernaelegantines A-D, tabernaelegantinines A-B, and tabernaelegantinidine.

Tabernaelegantines A-D were isomers of the molecular formula $C_{43}H_{54}N_4O_5$ displaying similar uv, ir, and mass spectral data including ions at *m/e* 196, 182 (**235**), and 124 for a 19,20-dihydrovobasinol unit and at *m/e* 136 and 122 (**236**) for the iboga unit. The nmr spectra were also quite similar showing the characteristic singlets for aromatic methoxy, iboga carbomethoxy, vobasine *N*-methyl, and vobasine carbomethoxy groups. Differences were observed in the aromatic region, however, where tabernaelegantines A and C showed the presence of ortho-related protons, whereas compounds B and D, like voacamine (**208**), showed a singlet for para-related protons. Their interrelationship was established through acid-catalyzed

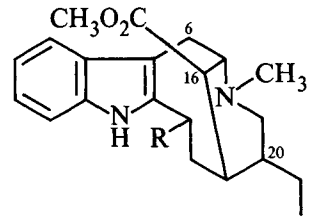


Scheme 29. Values in parentheses are shifts on comparison with corresponding carbons in 230a.



231: $R^1 = C_2H_5$, $R^2 = H$

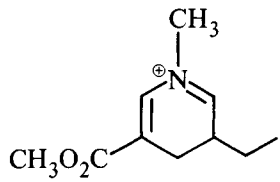
232: $R^1 = H$, $R^2 = C_2H_5$



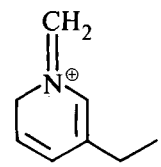
233: R = β-OH, 20β-H

234: R = β-OH, 20α-H

isomerization of tabernaelegantines A and C to isomers B and D, respectively. On this basis each group of isomers was regarded as being epimeric at C-20 in the dihydro series and a clear distinction was made with the aid of the ^{13}C nmr spectra of dregaminol (**233**) and tabernaemontaninol (**234**) (Table IX), particularly the shifts of C-16 and C-14, which are deshielded if the C-20 ethyl group is axial or equatorial, respectively.



235 *m/e* 182



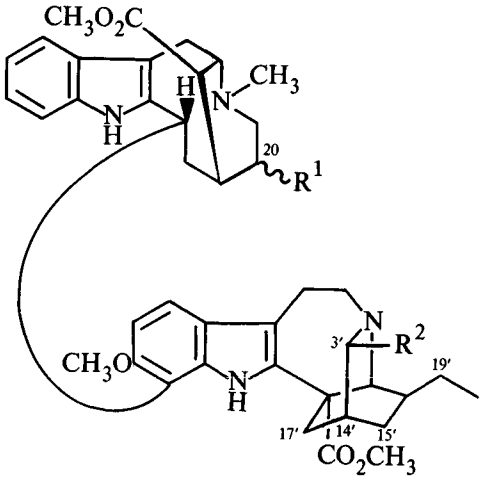
236 *m/e* 122

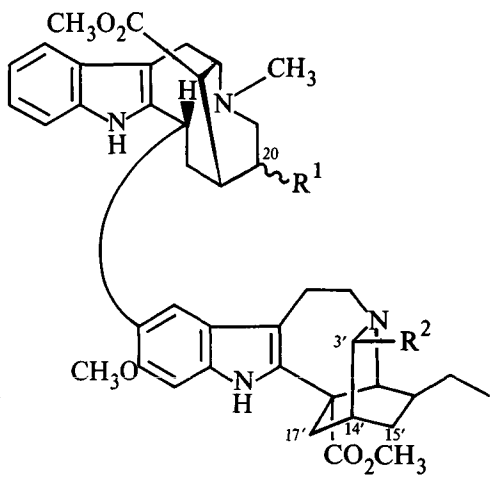
After assignment of the iboga resonances and from the chemical shifts of C-14 and C-16, tabernaelegantines A and B were assigned the C-20β configuration and tabernaelegantines C and D the C-20α configuration for the ethyl side chain.

Substitution of the aromatic nuclei in these compounds was also confirmed by the ^{13}C nmr spectra, where C-10′ and C-12′ in particular display characteristic shifts depending on the point of attachment. Thus tabernaelegantines B and D, which are C-10′,C-11′ substituted, displayed (in the SFORD spectrum) a singlet for C-10′ at 127 ppm and a doublet for C-12′ at 93 ppm. On the other hand, tabernaelegantines A and C, which are C-11′,C-12′ substituted, displayed a doublet for C-10′ at 105 ppm and a singlet for C-12′ at 115 ppm. The tabernaelegantines A-D can be represented by structures **237–240**, respectively.[185]

TABLE IX. SELECTED ^{13}C NMR DATA OF *TABERNAEMONTANA* ALKALOIDS[185]

Carbon	Dregaminol (318)	Tabernaemontaninol (321)	Tabernaelegantine A(328)	Tabernaelegantine B(329)	Tabernaelegantine C(330)	Tabernaelegantine D(331)
C-6	19.3	17.7	17.9	17.6	19.5	19.9
C-14	30.6	38.2	36.9	37.1	29.2	31.5
C-16	50.3	44.2	44.0	44.1	49.9	49.8
C-18	11.6	42.8	12.9	13.0	11.4	10.7
C-19	23.6	25.6	25.7	25.8	23.5	22.9
C-20	43.8	42.9	43.1	43.2	43.9	41.6
C-21	49.3	47.1	47.0	47.2	49.5	48.4





237: $R^1 = \beta\text{-}C_2H_5$, $R^2 = H$

238: $R^1 = \beta\text{-}C_2H_5$, $R^2 = H$

239: $R^1 = \alpha\text{-}C_2H_5$, $R^2 = H$

240: $R^1 = \alpha\text{-}C_2H_5$, $R^2 = H$

241: $R^1 = \beta\text{-}C_2H_5$, $R^2 = CH_2COCH_3$

242: $R^1 = \beta\text{-}C_2H_5$, $R^2 = CH_2COCH_3$

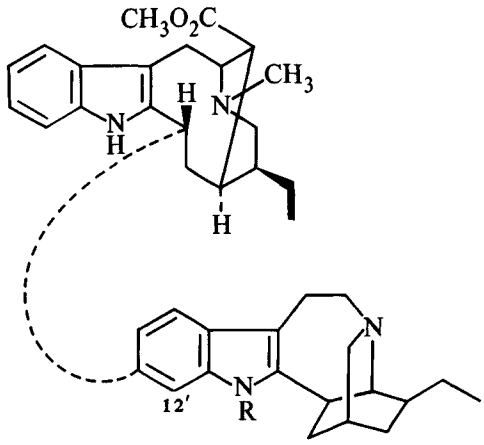
241a: $R^1 = \alpha\text{-}C_2H_5$, $R^2 = CN$

242a: $R^1 = \alpha\text{-}C_2H_5$, $R^2 = CN$

The isomeric tabernaelegantinines A and B ($C_{46}H_{58}N_4O_6$) displayed aromatic regions of their ^{13}C nmr spectra essentially identical with those of **237** and **238**, respectively. Based on the ^1H and ^{13}C nmr spectra an additional $-CH_2COCH_3$ unit was located in the isovoacangine part and its location at C-3′ was deduced from the shifts observed for C-3′, C-5′, C-14′, and C-15′. Also determined from the ^{13}C nmr spectra were the stereochemistries at C-3 and C-20 which permitted assignment of the structures **241** and **242** to tabernaelegantinines A and B.[185]

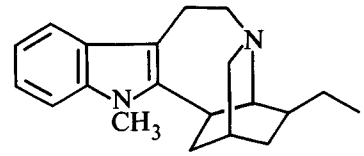
T. elegans has also yielded two nitrile-containing bisindole alkaloids tabernaelegantinines C (**241a**) and D (**242a**)[185] where the 3′-nitrile carbon appeared at ~ 120 ppm in the ^{13}C nmr spectra of the isolates. Tabernaelegantine A (**237**) has also been isolated from *Hazunta castata* together with its 19′*R*-hydroxy derivative, and another species, *H. modesta* var. *methuenii* subvar. *methuenii*, has afforded 19,20*S*-dihydrotabernamine (**242b**).[185b] The decision between a C-3-C-10′ or C-3-C-11′ linkage could not be achieved directly through ^1H or ^{13}C spectroscopy. The problem was resolved through a partial synthesis of the N_a-methyl derivative **242c** from tabernaemontaninol (**234**) and N_a-methylibogamine (**242d**) followed by an nOe experiment in which enhancement of broadened singlet at 7.01 ppm permitted this proton to be assigned to H-12′.[185b]

Quite closely related to the tabernaelegantinines is 3′-(2-oxopropyl)conodurine (**243**) which was isolated together with 3′-oxoconodurine (**244**) from the roots of *Tabernaemontana holstii* K. Schum.[191] 3′-Oxoconodurine (**244**) displayed an abundant ion at *m/e* 523 (**245**) shifted by 14 m.u. from the typical ion observed at *m/e* 509 (**246**) in the voacamine series.[166] A complex multiplet at 4.30 ppm was

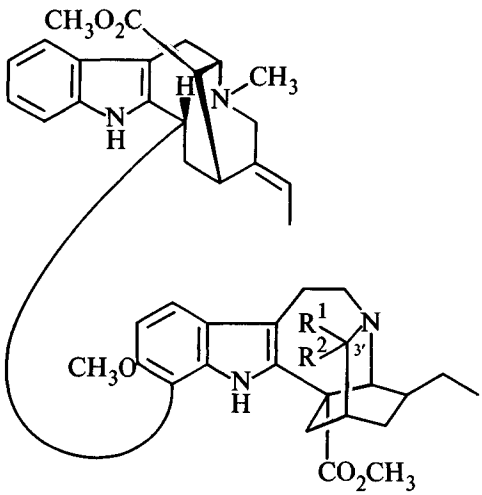


242b: R = H

242c: R = CH_3



242d

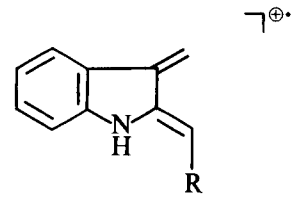


Conodurine (**223**): $R^1 = R^2 = H$

3′-(2-Oxopropyl)conodurine (**243**):

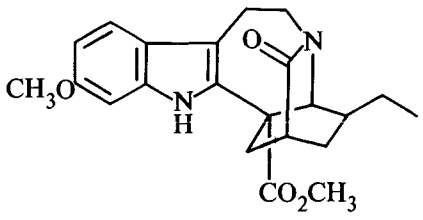
$R^1 = CH_2COCH_3$, $R^2 = H$

3′-Oxoconodurine (**244**): R^1, $R^2 = =O$



245: R = Oxovoacangine or oxoisovoacangine, *m/e* 523

246: R = Voacangine or isovoacangine, *m/e* 509



247

attributed to protons at C-14 and C-21, similarly to 3-oxovoacangine (**247**), and the structure 3′-oxoconodurine (**244**) was assigned on this basis.[191]

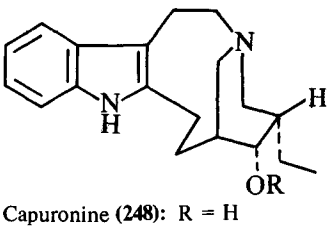
The second isolate showed a molecular ion 50 m.u. higher than **244**, suggesting a $-CH_2COCH_3$ unit which was confirmed by a two-proton doublet at 3.04 ppm and a three-proton singlet at 2.16 ppm. A doublet at 7.02 ppm and a carbomethoxy

singlet at 3.84 ppm indicated the alkaloid to be in the conodurine series. In view of the preferred sites of oxidation of iboga alkaloids (Chapter X), the isolate was suggested to be 3′-(2-oxopropyl)conodurine (**243**).[191]

XIII. CLEAVAMINE-VOBASINE TYPE

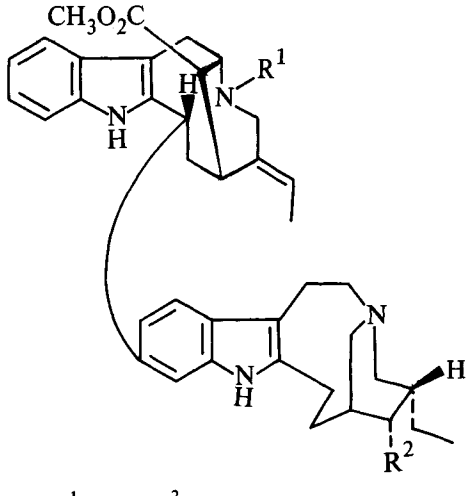
This is a relatively new combination of monomer units obtained from the leaves of *Capuronetta elegans* Mgf.[192–194] and from *Pandaca boiteau*.[194]

Capuvosine ($C_{40}H_{50}N_4O_3$) displayed an indolic uv spectrum, and both the mass and ^1H nmr spectra suggested the possible presence of a vobasinol (**82**) unit. Acid hydrolysis afforded (+)-capuronine (**248**), which had been isolated by the same group.[192] Condensation of vobasinol (**82**) and capuronine acetate (**249**) in methanolic hydrochloric acid afforded a mixture containing capuvosine acetate (**250**), and the structure **251** was proposed for capuvosine, although the linkage between C-3′ and C-11 was not firmly established.[192]



Capuronine (**248**): R = H

249: R = $COCH_3$



250: $R^1 = CH_3$, $R^2 = OCOCH_3$

Capuvosine (**251**): $R^1 = CH_3$, $R^2 = OH$

Dehydroxycapuvosine (**252**): $R^1 = CH_3$, $R^2 = H$

Demethylcapuvosine (**253**): $R^1 = H$, $R^2 = OH$

A continuing study led to the isolation of two closely related alkaloids.[193] Dehydroxycapuvosine ($C_{40}H_{50}N_4O_2$) again demonstrated the presence of unsubstituted indole nuclei, but unlike **251**, no hydroxyl absorption was observed in the ir spectrum. The ^1H nmr spectrum showed a methyl triplet at 0.87 ppm, an ethylidene group (doublet at 1.67 ppm), an *N*-methyl group (2.57 ppm), and the carbomethoxyl group was typically shielded at 2.44 ppm. A one-proton multiplet for the C-3′ proton was found at 4.55 ppm. The base peak appeared at *m/e* 138,

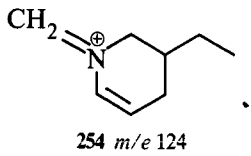
16 m.u. less than in capuvosine, suggesting that the C-15 hydroxy group was absent and that the alkaloid had the structure **252**.[193]

Demethylcapuvosine ($C_{39}H_{48}N_4O_3$) had spectral properties very similar to those of capuvosine (**251**) including NH, OH, ethyl, shielded carbomethoxy, ethylidene, and deshielded C-3′ proton groups. The *N*-methyl singlet, however, was lacking, and in support of the assignment of demethylcapuvosine (**253**) to this isolate, fragments containing the vobasine moiety were all shifted by 14 m.u.[193]

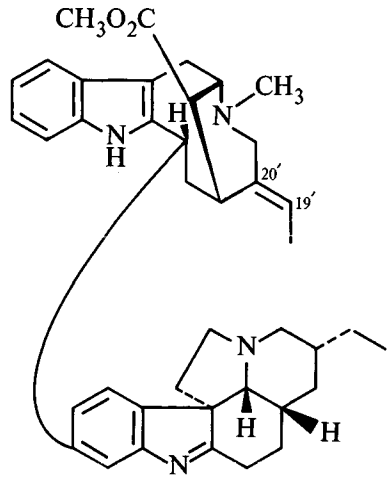
XIV. PSEUDO-*ASPIDOSPERMA*-VOBASINE TYPE

Capuvosidine ($C_{40}H_{48}N_4O_2$) was also obtained from the leaves of *Capuronetta elegans*.[193,194] A vobasine unit was deduced from the ir and uv spectra, and confirmed from the ^{1}H nmr spectrum which displayed an ethylidene group (doublet at 1.75 ppm), a shielded carbomethoxy group (2.45 ppm), and an *N*-methyl group (2.55 ppm).

The second unit contained an ethyl group (triplet at 1.0 ppm) but no indole NH or additional olefinic bonds. An indolenine (ν_{max} 280 nm) unit indicated this to be a member of the *Aspidosperma* or pseudo-*Aspidosperma* series. Sodium borohydride reduction yielded a dihydro product showing fragment ions at *m/e* 124 (**254**) and *m/e* 190, characteristic of the pseudoaspidospermane nucleus. By analogy with the co-occurring alkaloids, one linkage in capuvosidine was thought to be at C-11 whereas the second point of attachment was C-3′ (multiplet at 4.65 ppm), and therefore the structure **255a** was proposed.[193,194] Dihydrocapuvosidine (**255b**) has been obtained from *C. elegans* and *P. boiteau*.[194]



254 *m/e* 124



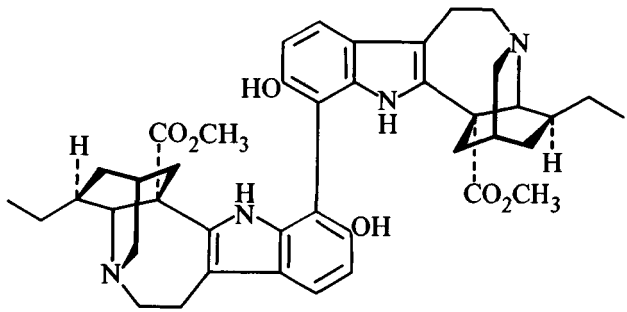
Capuvosidine (**255a**)
19′,20′-Dihydrocapuvosidine (**255b**)

XV. *IBOGA-IBOGA* TYPE

Damak and co-workers[195] recently reported the first member of this new series obtained from *Bonafousia tetrastachya* (Humboldt, Bonpland & Kunth) Mgf. (Apocynaceae).

The alkaloid ($C_{42}H_{50}N_4O_6$) displayed an almost typical hydroxyindole chromophore and significant fragment ions at *m/e* 353 ($M^+/2$), 136, and 122. In the ^1H nmr spectrum the equivalency of the two monomer units became evident, for a single carbomethoxyl resonance at 3.66 ppm, exchangeable NH and OH protons, and a pair of ortho-related protons at 6.90 and 7.41 ppm were observed.

The ^{13}C nmr spectrum confirmed the coronaridine skeleton, the 11,12 substitution in each "half," and from the pronounced downfield shift, the hydroxy group was placed at C-11. The alkaloid is therefore a true dimeric alkaloid having the structure **256**.[195]



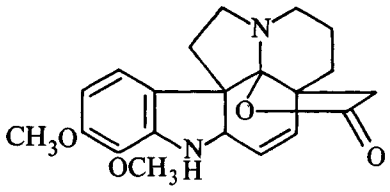
256

XVI. *ASPIDOSPERMA*-CANTHINONE TYPE

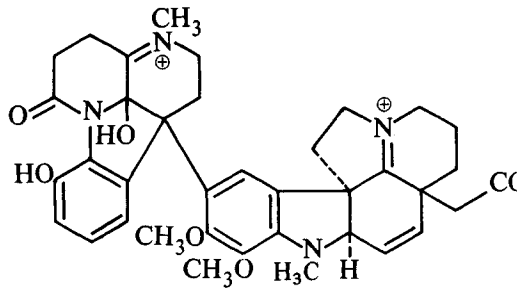
Haplophytine is the major alkaloid of *Haplophytum cimicidum* A. DC. (Apocynaceae) and is formed by the union of *Aspidosperma* and canthinone units. Acid-catalyzed cleavage afforded the base **257** and the structure **258** was deduced for the hydrobromide salt. However, the alkaloid is a ditertiary base, and it was initially proposed[196] that the parent alkaloid possessed the structure **259**. Subsequently,[197] this structure was revised to the spiro ketoamide form **260**.

Two alkaloids, cimiciphytine (**261**) and norcimiciphytine (**262**), have recently been added to this group.[198] Thus cimiciphytine showed two carbonyl groups at 1755 and 1630 cm^{-1}, two *N*-methyl functions (2.4 and 3.6 ppm), two methoxy groups (3.18 and 3.57 ppm), two cis olefinic protons (5.54 and 5.86 ppm), and four aromatic protons, including a one-proton singlet at 7.21 ppm assigned to H-9. The structure **261** was established by reduction (Zn–HOAc) of haplophytine.

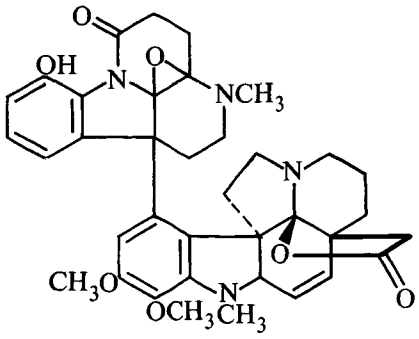
Norcimiciphytine (**262**) was very similar to **261**, but displayed only one aromatic methoxy group (3.67 ppm). A pronounced bathochromic shift (λ_{max} 265 to



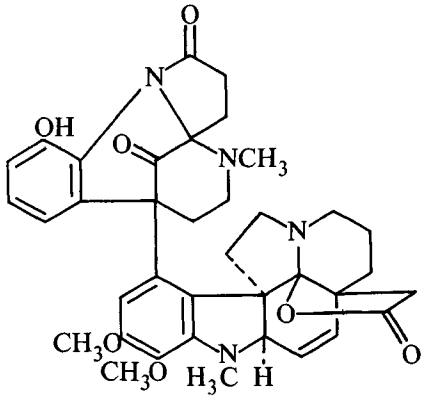
257



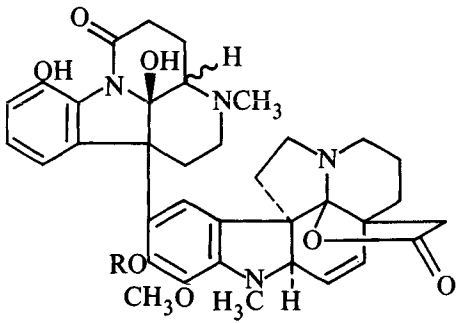
Haplophytine hydrobromide (258)



Haplophytine (original) (259)



Haplophytine (revised) (260)



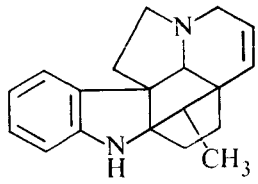
Cimiciphytine (261): R = CH_3

Norcimiciphytine (262): R = H

300 nm) was observed in the base, and *O*-methylation with diazomethane afforded cimiciphytine (**261**).[198]

XVII. *ASPIDOSPERMA-PLEIOCARPA* TYPE

There are three alkaloids in this group, pycnanthine, 14′,15′-dihydropycnanthine (pleiomutinine), and pycnanthinine, and they are derived from decarbomethoxyvindolinine (**263**) and pleiocarpamine (**91**).



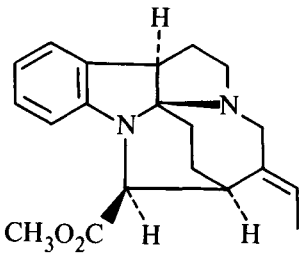
263

Pycnanthine was an important constituent of the root bark of *Pleiocarpa pycnantha* (K. Schum.) Stapf var. *pycnantha* M. Pichon[199] and pycnanthinine was a minor constituent.[200] Pleiomutinine was a minor alkaloid of *P. mutica* Benth.[201] and subsequently[199] shown to be 14′,15′-dihydropycnanthine.

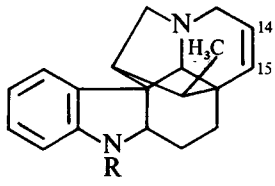
The complex uv spectrum (λ_{max} 267, 309, 325 nm) did not correspond to the summation of two recognizable chromophores, but is due to the interaction of two indoline chromophores and is characteristic of this alkaloid group.

Pycnanthine showed no hydroxyl or amino groups, but the two bands at 1754 and 1724 cm^{-1} for a pleiocarpamine unit[202] were found. Hydrogenation gave a 14′,15′-dihydro derivative identical to pleiomutinine, in which the ethylidene group and the uv spectrum remained. Treatment of either pycnanthine or pleiomutinine with 11 *M* methanolic hydrochloric acid at 120° gave formaldehyde and (+)-pleiocarpamine (**91**).

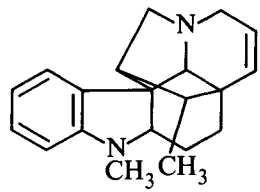
Cleavage of either alkaloid with zinc and acid afforded 2,7-dihydropleiocarpamine (**93**) and isodihydropleiocarpamine (**264**) from the lower half and



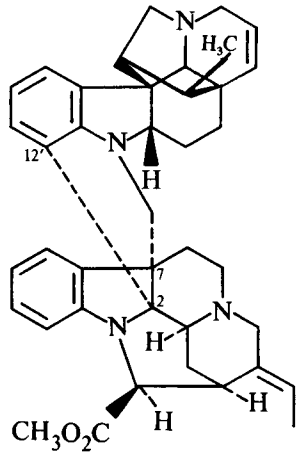
264



265: R = H , 14,15-dihydro-
266: R = CH_3, 14,15-dihydro-
267: R = CH_3



268



Pycnanthine (**269**)

isotuboxenine (**265**) and N_a-methylisotuboxenine (**266**) (from pleiomutinine) and **267** and **268** from pycnanthine. The formaldehyde produced on acid hydrolysis therefore is the bridging unit and becomes the N_a-methyl under reducing conditions.

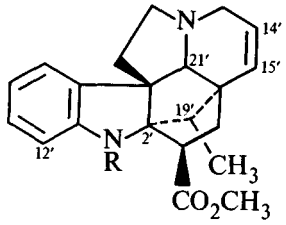
Besides a methyl doublet at 0.56 ppm, the ^1H nmr spectrum indicated seven aromatic protons with the C-12′ proton on the isotuboxenine unit missing. This led to a structure proposal for pycnanthine in which C-2 is linked to C-12′, that is, **269**.[199]

Gonioma malagasy Mgf. et P. Bt. (Apocynaceae) has also afforded 14′,15′-dihydropycnanthine, but in the intervening period the structure of vindolinine was revised based on a ^{13}C nmr analysis,[203] and consequently reexamination of the structure of the dimers became necessary. The 2,7-dihydropleiocarpamine unit was confirmed by the ^{13}C nmr spectrum with C-2 appearing at 67.6 ppm, and subtraction then gave the carbon resonances of the dihydrovindolinine unit. In vindolinine (**270**), a quaternary carbon resonance at 81.4 ppm assigned to C-2 was critical in revising the linkage of C-19 from C-6 to C-2. In 14′,15′-dihydropycnanthine a quaternary carbon resonance was observed at 80.1 ppm and with the similar

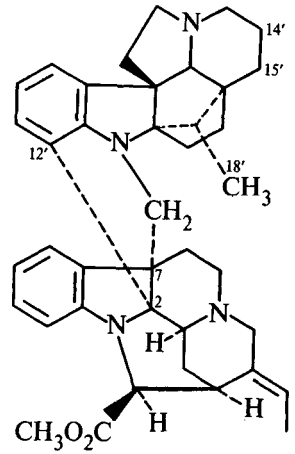
chemical shifts of C-6′ and C-7′ to those carbons in **270**, the revised dihydrovindolinine skeleton was established.

In *N*-methylvindolinine (**271**), the NCH_3 was observed at 30.0 ppm, and was deshielded to 41.4 ppm (as a methylene) in 14′,15′-dihydropycnanthine, and C-12′ was shifted from 105.6 ppm in **271** to 120.6 ppm in the dimer. Because C-7 in villalstonine (**94**) and 14′,15′-dihydropycnanthine were very close (44.2 and 46.3 ppm, respectively) C-12′ was thought to be linked to C-2 and not to C-7.

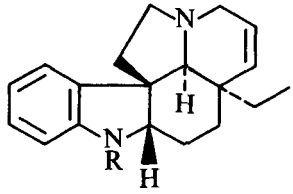
In 19*S*-vindolinine (**272**) C-18 appeared at 10.1 ppm and C-21 at 74.2 ppm, but at 7.4 and 78.4 ppm, respectively, in the 19*R* isomer **270**. Because these resonances were observed at 11.0 and 74.5 ppm, the 19*S* stereochemistry was assigned for the dimer, and is supported by the chemical shift of the C-18 H_3 doublet (0.56 ppm



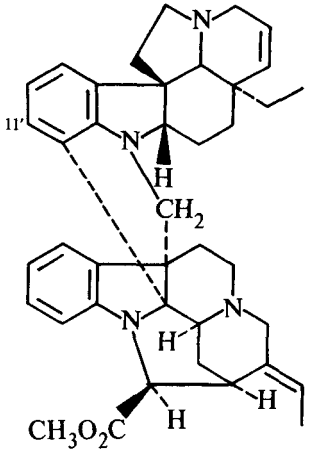
270: R = H
271: R = CH_3
272: 19′-epi, R = H
278: 14′,15′-dihydro, R = H



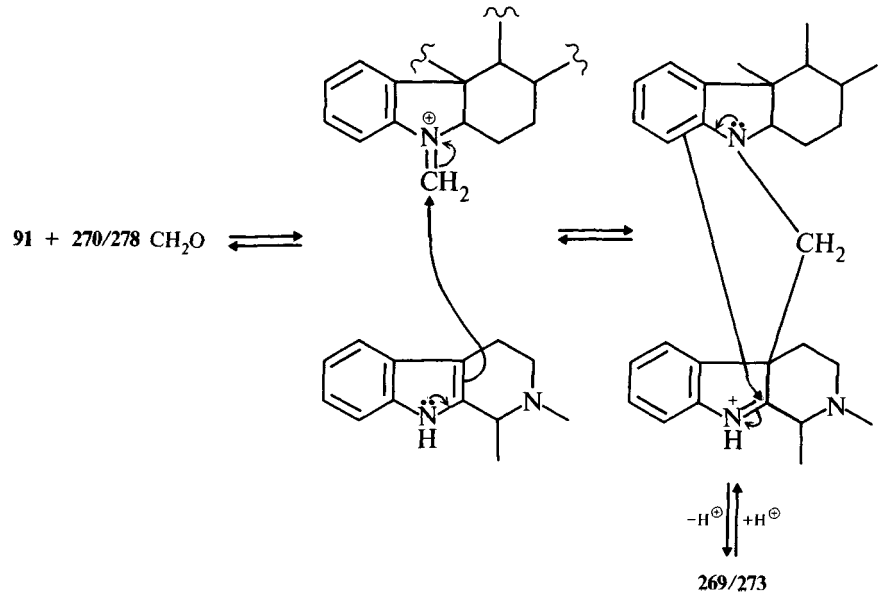
273: 14′,15′-Dihydropycnanthine
274: Pycnanthine, $\Delta^{14',15'}$



275: R = H
276: R = CH_3



Pycnanthinine (**277**)



Scheme 30.

in dimer, 0.55 ppm in the 19*S* series, 0.90 ppm in the 19*R* series). 14′,15′-Dihydropycnanthine has the structure **273** and pycnanthine the structure **274**.

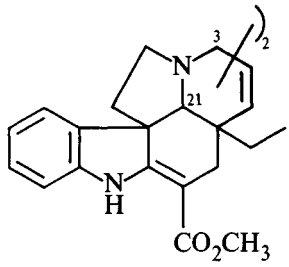
Pycnanthinine ($C_{40}H_{46}N_4O_2$)[200] was isomeric with 14′,15′-dihydropycnanthine and substantial similarities were observed between their uv and mass spectra. Acid hydrolysis gave **91**, formaldehyde, and 14,15-dehydroaspidospermidine (**275**), and under reducing conditions **93**, **264**, **275**, and its *N*-methyl derivative **276** were produced. Again the C-12′ aromatic proton was missing and this evidence was taken to indicate structure **277** for pycnanthinine.[200] The biogenesis of these alkaloids is shown in Scheme 30.

XVIII. *ASPIDOSPERMA-ASPIDOSPERMA* TYPE

This is a very substantial group of bisindole alkaloids and has been the subject of intense investigation, particularly by French and Swiss groups. Of all the bisindole groups, members of this group appear to occur in the highest concentration in certain plants. For example, vobtusine has been obtained in 0.75% yield from the root bark of *Voacanga chalotiana*.[39]

A. Dimeric Alkaloids

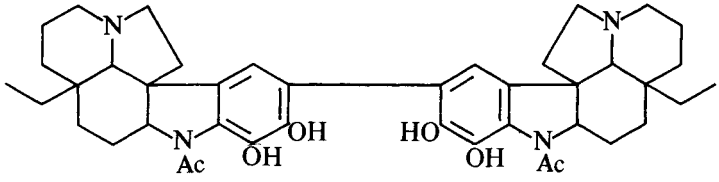
Perhaps the simplest member of this series is bistabersonine (**279**) from *Crioceras*



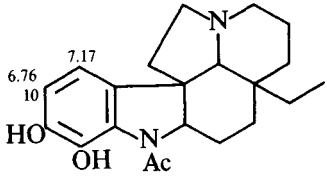
Bistabersonine (**279**)

dipladeniiflorus (Stapf) K. Schum.[205] The uv and ^{1}H nmr spectra established the aromatic unit and the olefinic and ethyl side chain units to be unsubstituted. From the molecular ion, the two units are joined by a bond, possibly between the C-3 carbons of each unit.[205]

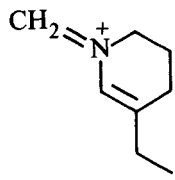
Miranda and Gilbert[206] have isolated a novel bisindole from the *Aspidosperma melanocalyx* Muell-Arg. and shown it to be 10,10′-bis(*N*-acetyl-11,12-dihydroxy-aspidospermidine) (**280**). The uv spectrum was similar to that of **281** (λ_{max} 236, 297 nm) shifting in base to λ_{max} 243, 302, and 335 nm, and the molecular ion at *m/e* 710 analyzed for $C_{42}H_{54}N_4O_6$. Acetylation yielded a tetraacetate, M^+ 878, showing four successive losses of ketene, and a base peak at *m/e* 124 (**282**). An ion at *m/e* 516 (**283**) was present in the spectrum of the tetraacetate.



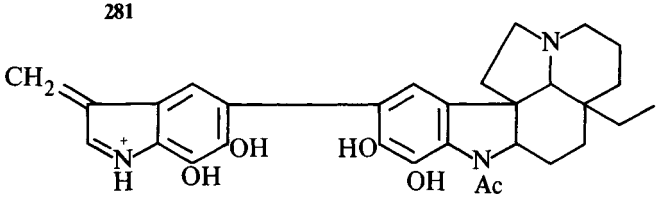
280



281



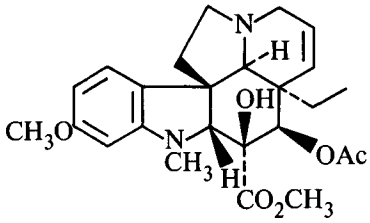
282 *m/e* 124



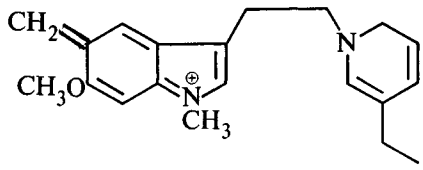
283 *m/e* 516

From the doubling of peaks in the nmr spectrum it was clear that the two units were equivalent. By comparison with the spectrum of the monomer **281**, which showed two doublets at 6.76 and 7.17 ppm for the C-10 and C-9 protons, respectively, the singlet at 7.11 ppm in the dimer was regarded as indicative of a linkage between the two C-10 positions and the structure **280**.[206]

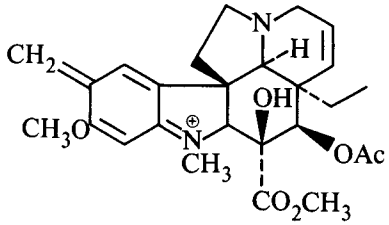
Most of the bisindole alkaloids from *Catharanthus* spp. are of the *Aspidosperma*-cleavamine type (see Section XXII), but *C. roseus* (L.) G. Don[207,208] and *C. longifolius* (Pichon) Pich.[209] have yielded an *Aspidosperma-Aspidosperma* dimer, vindolicine, where the two units are joined by a methylene bridge. The structure was initially based principally on mass spectral evidence,[209] particularly a series of ions characteristic of a vindoline (**284**) unit (e.g., *m/e* 121, 122, 135, and 282) and two ions at *m/e* 308 and *m/e* 469, suggested to be **285** and **286**, respectively. The structure **287** was therefore proposed,[209] and this has been substantiated by a recent[208] ^{1}H and ^{13}C nmr examination of vindolicine which confirmed the linkage as shown and further demonstrated that the two units are not equivalent, and that due to overlap of the units, certain carbons exhibit chemical shift differences.



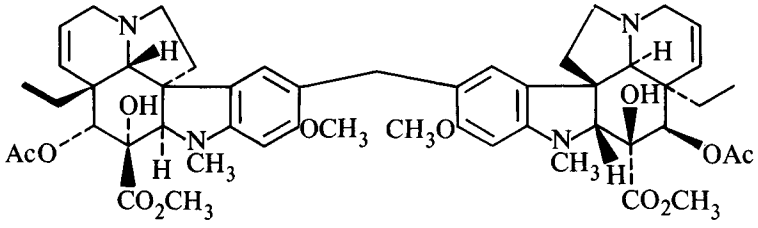
Vindoline (**284**)



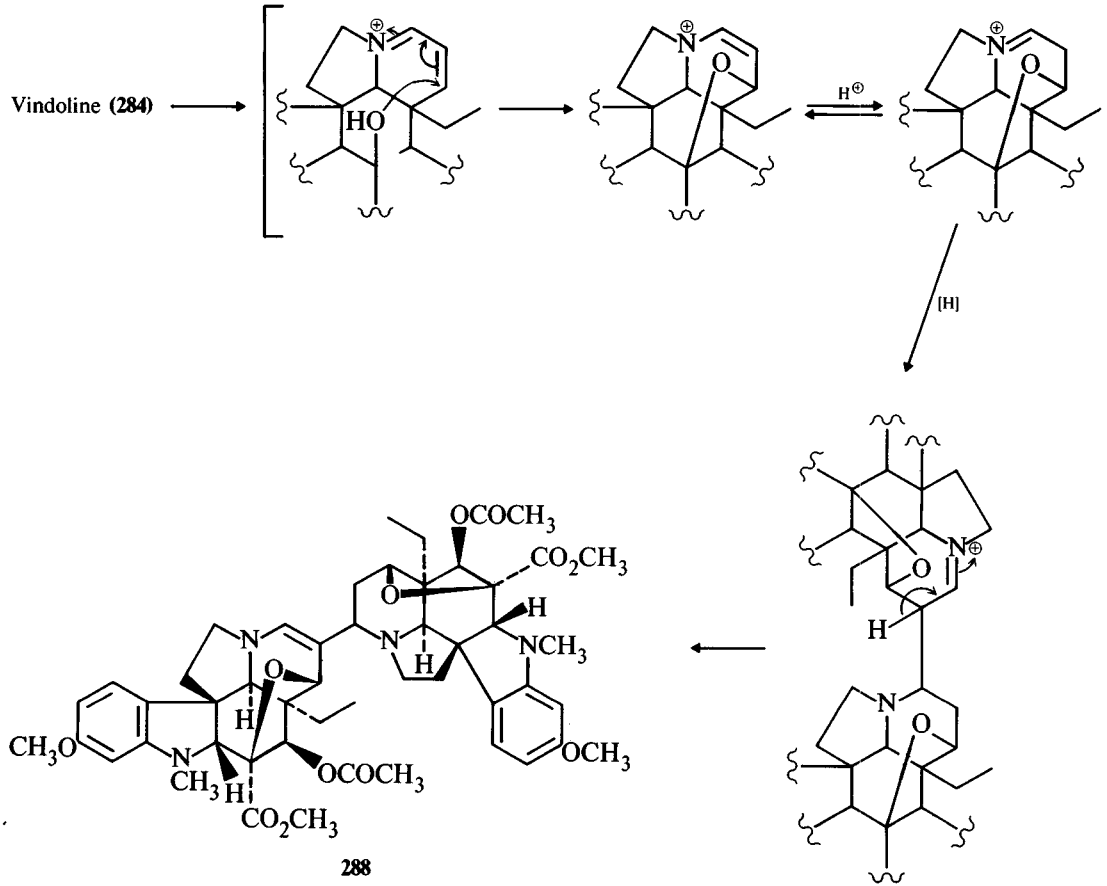
285 *m/e* 308



286 *m/e* 469



Vindolicine (**287**)



288

Scheme 31.

It is also worth mentioning a novel dimer produced through the microbial transformation of vindoline (**284**) by *Streptomyces griseus*.[210] Critical in the structure elucidation was an interpretation of the ^{13}C nmr spectrum, which showed 26 of the 49 observed carbons as 13 distinct pairs. Particularly significant was the presence of an enamine double bond at C-3,14 in one unit (reduced by $NaBH_4$) and the coupling of C-15′, which suggested that the correct structure, without C-3′ stereochemistry, was **288**. The proposed mechanism of formation is shown in Scheme 31.

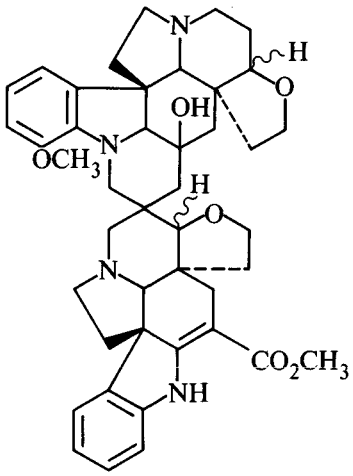
B. Vobtusine and Related Alkaloids

Vobtusine is probably the most widespread of any bisindole alkaloid (Table X), yet structurally it has been one of the most problematic. A partial structure for vobtusine was proposed by Poisson et al.,[218] and this was followed by a proposal for the complete structure **289** by Gorman et al.[214] Since these data were initially summarized[12] two major developments have occurred. First, a substantial number of closely related alkaloids have been isolated, and second, the structure of vobtusine has been revised based on X-ray crystallographic data of the 10,10′-dibromo derivative **290**.[229] The correct structure **291** differs from the earlier structure **289** by virtue of shifting the tertiary hydroxy group from C-16 to C-2. Almost as important, the X-ray data also yielded the stereochemistries at the spiro carbon C-14′ and at C-15 and C-15′.

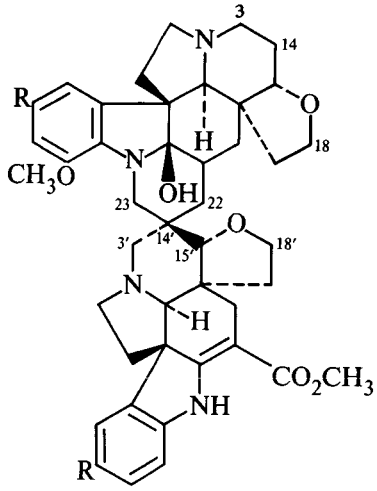
But how had Gorman et al. been misled? Heating vobtusine in acid yielded anhydrovobtusine (**292**) by trans elimination of water and the resistance of a potential carbinolamine at C-2 to lithium aluminum hydride reduction was initial evidence in placing the hydroxy group at C-16 originally. In addition, the formation of ions at *m/e* 174 (**293**) and 188 (**294**) was thought to parallel the formation of

TABLE X. SUMMARY OF THE ISOLATION OF VOBTUSINE (291)

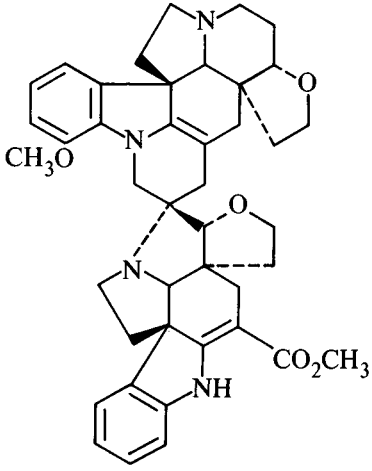
Source	Ref.
Callichilia subsessilis	211
C. stenosepala Stapf	212
Conopharyngia longiflora	168
Crioceras dipladeniiflorus (Stapf) K. Schum.	205
Hedranthera barteri	170, 212–215
Rejoua aurantiaca Gaudich	216
Voacanga africana	172, 214, 217–219
V. chalotiana	218, 220
V. dregei E. Mey	181, 221
V. globosa	222
V. grandifolia	223, 224
V. megacarpa	225
V. papuana	216
V. schweinfurthii	226, 227
V. thouarsii	168, 170, 228



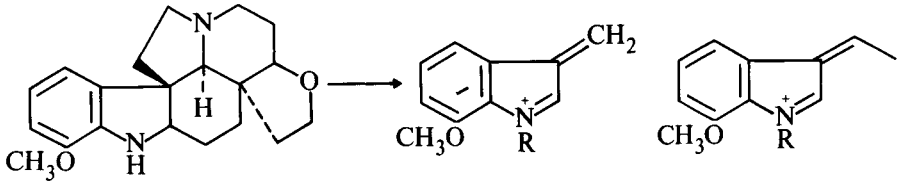
Vobtusine (original structure) **(289)**



290: R = Br
Vobtusine (revised structure) **(291):** R = H



Anhydrovobtusine **(292)**

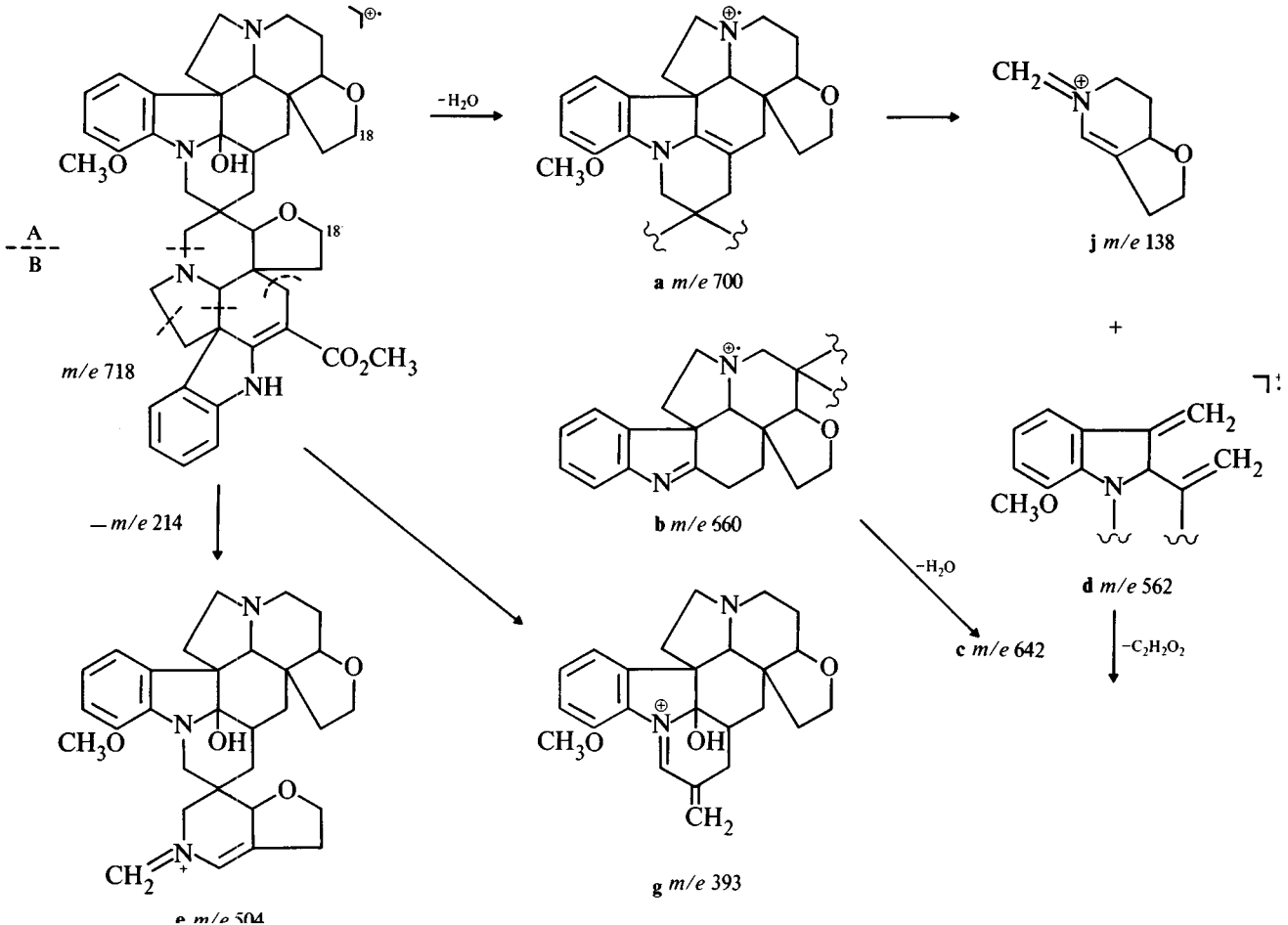


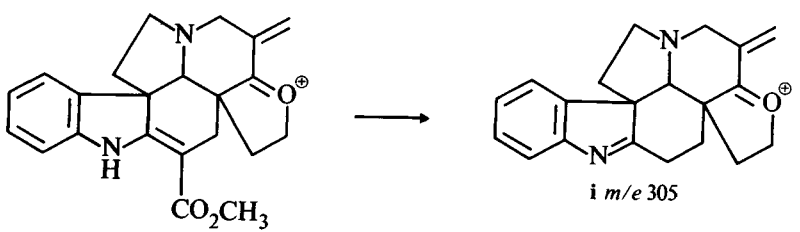
Beninine **(297)**

293: R = CH_3, *m/e* 174
295: R = H, *m/e* 160

294: R = CH_3, *m/e* 188
296: R = H, *m/e* 174

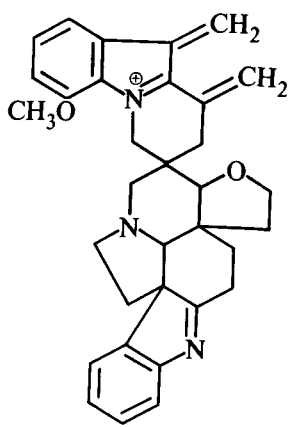
Scheme 32.


-H2O
A
B
m/e 718
— m/e 214
a m/e 700
b m/e 660
c m/e 642
d m/e 562
-C2H2O2
j m/e 138
g m/e 393
e m/e 504



h *m/e* 363

i *m/e* 305



f *m/e* 504

Scheme 33. Summary of the mass spectrum of vobtusine (291).

TABLE XI. PRINCIPAL MASS SPECTRAL FRAGMENTS OF VOBTUSINE AND RELATED ALKALOIDS

Compound	Ion (m.u.)										
	M^+	a	b	c	d	e	f	g	h	i	j
Vobtusine (291)	718	700	660	642	562	504	504	393	363	305	138
12-Demethylvobtusine (302)	704	686	646	628	548	490	490	379			138
2-Deoxyvobtusine (303)	702						488	377	363		138
18-Oxovobtusine (305)	732	719	674	656	562	518	504	407	363	305	152
2-Deoxy-18-oxovobtusine (306)	716		658			502		391	363	305	152
3′-Oxovobtusine (311)	732	714	674		576	518	518				138
3′-Oxovobtusine *N*-oxide (312)	748	730	674	656	576	518	518				138
2-Deoxy-3′-oxovobtusine (313)	716		658					391	377		138
2,16-Anhydrovobtusine (292)	700			642	562		504	375	363	302	138
2,16-Anhydrodihydroamataine (owerreine) (315)	700			642	562		504	375	363	305	138
Quimbeline (316)	716					502		391	363	305	138
Amataine (321)	716				578	502		391	363	305	138
18-Oxoamataine (323)	730					516			363		152

m/e 160 (**295**) and 174 (**296**) in beninine (**297**) (Scheme 32). Little has been done in reformulating the structures of these ions in terms of the revised vobtusine structure. However, the mass spectra of alkaloids in this series display some highly diagnostic similarities, which are formalized in Scheme 33 and summarized in Table XI.

It is worth analyzing some of the evidence that led to the original structure proposal for vobtusine. The molecular formula was deduced to be $C_{43}H_{50}N_4O_6$ and both β-anilinoacrylate and the *N*-alkyl-7-methoxyindoline chromophores were deduced from the uv spectra. The complex ^1H nmr spectrum showed an NH, two methoxy singlets, and seven aromatic protons, but no *C*-methyl or *N*-methyl groups. Anhydrovobtusine displays no olefinic protons. In the absence of acetate formation and additional carbonyl groups, the two remaining oxygen functions must be present in the form of ether groups, which are resistant to both lithium aluminum hydride and zinc/sulfuric acid reduction.

Analysis of the mass spectra of vobtusine and derivatives, particularly the presence of ions at $M^+ - 138$ and $M^+ - 214$ (*m/e* 138 and *m/e* 214 are **298** and **299**, respectively), led to a partial structure **300**.

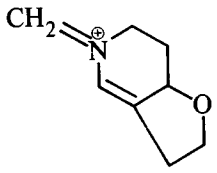
One of the critical proton signals in vobtusine and related signals is a one-proton doublet at 5.13 ppm ($J = 14$ Hz) coupled to a second doublet at 3.09 ppm,[218] suggesting an AB system involving $\begin{matrix} C \\ C \end{matrix}\!\!>\!C\text{–}CH_2\text{–}X$ (X = N or O). In anhydrovobtusine this signal is shifted to 4.38 ppm. This must be the C-3′, C-18′, or C-23 protons. Two structures were then proposed, of which **289** was favored, and this was supported by ord data which showed a close similarity to that of (−)-vincadifformine (**301**), indicating this indoline unit to have little effect, as expected. In an alternative structure in which C-22 and C-23 are linked to C-19′, the indoline unit was expected to contribute to the ord spectrum.

This is but one of the many variations in the fundamental vobtusine nucleus. Others include loss of the 2-oxygen, oxidation at either C-3′ or C-18, formation of an ether linkage between C-2 and C-3′, and inversion of the stereochemistry of C-14′. Unfortunately, only a brief discussion of some of these compounds is possible, but a fuller account of their chemistry is available.[16]

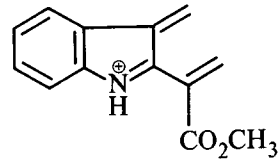
One of the simplest derivatives of vobtusine to be obtained is 12-demethylvobtusine (**302**), which was obtained initially from *Hedranthera barteri*[230] and subsequently from *Voacanga thouarsii*.[228] The absorption spectra (uv and ord) were similar to vobtusine (λ_{max} 263, 300, and 326 nm) but on addition of base the 263 nm band was shifted bathochromically and on acetylation an aryl acetate (ν_{max} 1760 cm^{-1}) was produced and an exchangeable proton at 8.62 ppm disappeared. Methylation of the sodium salt afforded vobtusine (**291**), indicating that demethylvobtusine therefore has the structure **302**.[230,231]

2-Deoxyvobtusine from *Voacanga africana*[232] and *V. grandifolia*[224] showed a molecular ion at *m/e* 702 ($C_{43}H_{50}N_4O_5$) and both the uv and ir spectra were similar to those of vobtusine. But it was the mass spectrum, through comparison of the ions **e**, **g**, and **h** (Scheme 33), which indicated the structure **303**.[232]

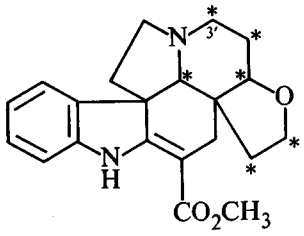
An alkaloid goziline had been obtained from the root bark[215] and leaves[230]

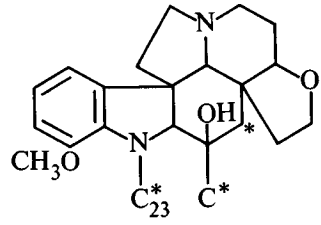


298 *m/e* 138



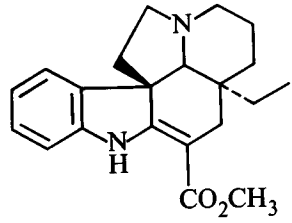
299 *m/e* 214



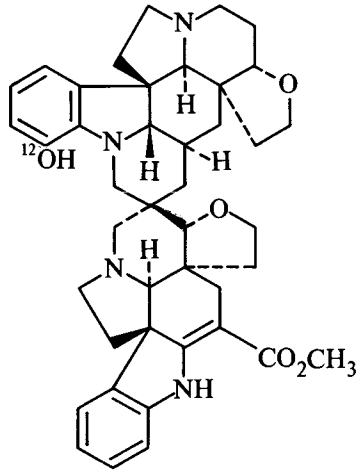


+ 1 ring

300



301



12-Demethylvobtusine (302)

of *Hedranthera barteri* and it too was deduced to be 2-deoxyvobtusine (**303**) on the basis of uv, ir, and mass spectral data. When a larger quantity was obtained,[230] the nmr spectral features confirmed the assignment, and the doublet for one of the C-3′ protons was observed at 5.36 ppm (but see below).

Catalytic reduction of anhydrovobtusine (**292**) gave 2-deoxy-16-epivobtusine (cis-2,16-dihydroanhydrovobtusine) (**304**) which, although similar to 2-deoxyvobtusine and goziline, had a number of distinctly different properties including melting point, $[\alpha]_D$, and mass spectra which were all quantitatively different.

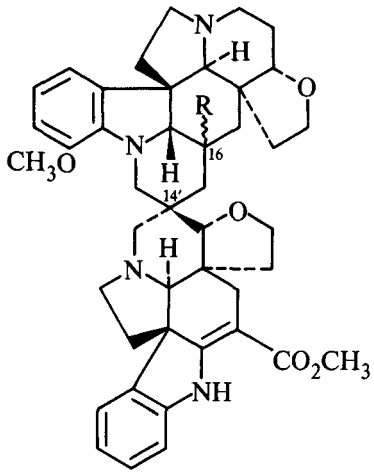
The similar color reaction with the ceric reagent and mass spectra of 2-deoxyvobtusine (obtained by Majumder et al.[224]) and **304** suggest that these could be similar. Identity of the C-14′ stereochemistry was deduced from the similar ord spectra, but the relationship of goziline,[215,230] the deoxyvobtusine from *V. africana*,[232] and the alkaloid from *V. grandifolia*[224] to 2-deoxy-16-epivobtusine (**304**) is presently unclear.

18-Oxovobtusine (**305**) and 2-deoxy-18-oxovobtusine (**306**) have thus far been obtained only from *Voacanga* species.[219,223,224,228,232,233] 18-Oxovobtusine (M^+ *m/e* 732, $C_{43}H_{48}N_4O_7$) displayed ^1H nmr and uv spectral data similar to vobtusine, but the ir spectrum showed a new carbonyl band at 1795 cm^{-1} typical of a γ-lactone moiety which could be either at C-18 and C-18′. Since ions **a**, **b**, **c** (**b**-H_2O), **e**, **g**, and **j** (Scheme 33) were all shifted by 14 m.u. (+ O − 2H), but not those lacking the piperidine moiety of unit A (e.g., **d**, **f**, **h**, and **i**), the lactone was assigned to C-18, and 18-oxovobtusine was assigned the structure **305**.[233] In a similar way the structure of 2-deoxy-18-oxovobtusine (**306**), also from *V. africana*,[219] was assigned.[233]

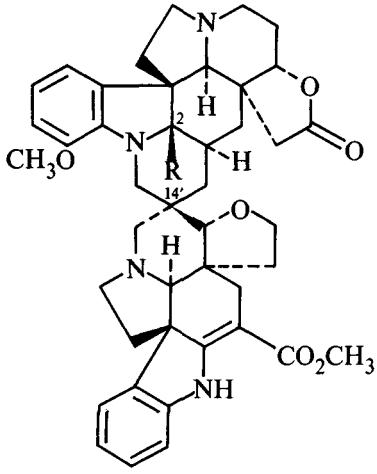
When chemical correlation was obtained some problems were encountered, however. Thus dehydration of 18-oxovobtusine followed by decarbomethoxylation gave the bisindole lactone **307** having the 2β,16β-stereochemistry. Lithium aluminum hydride reduction and recyclization with hydrogen bromide then yielded a bisindoline bisether **308** identical with a compound obtained from vobtusine (**291**). However, the corresponding compound **309** from 2-deoxy-18-oxovobtusine (**306**) was not identical in terms of $[\alpha]_D$ and melting point; hence the C-16 and C-14′ stereochemistries cannot be rigidly assigned at this point, although in a subsequent paper[234] the structure was given as **310** without comment.

Voacanga thouarsii Roem. et Schult. has been a substantial source of bisindole alkaloids in this series,[228] and three of these were closely related compounds, namely, 3′-oxovobtusine (**311**), 3′-oxovobtusine *N*-oxide (**312**), and 2-deoxy-3′-oxovobtusine (**313**) (Scheme 34).[231]

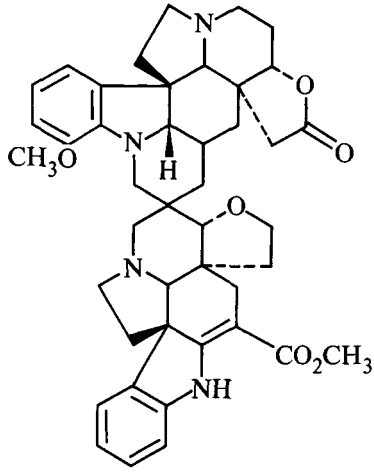
3′-Oxovobtusine (M^+ *m/e* 732, $C_{43}H_{48}N_4O_7$) was isomeric with **305** and displayed similar uv and chemical shift data to vobtusine. But the ir spectrum indicated an additional carbonyl band at 1650 cm^{-1} for an amide moiety which could potentially be placed at either C-3, C-3′, or C-23. A ready distinction was made from the mass spectral ions **d** (*m/e* 576) and **j** (*m/e* 138), which indicated the lactone to be located at C-3′. Chemical correlation was made through sodium cyanoborohydride followed by lithium aluminum hydride reduction to the alcohol **314**, which could also be obtained from vobtusine (**291**).[231]



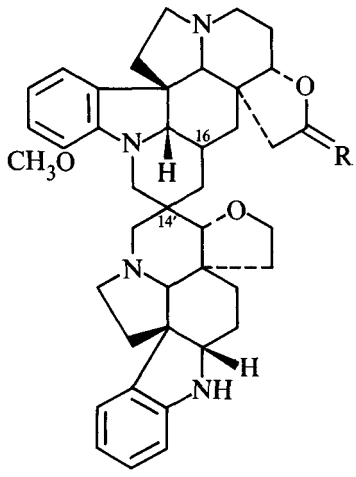
2-Deoxyvobtusine (**303**): R = α-H
304: R = β-H



18-Oxovobtusine (**305**): R = OH
310: R = H



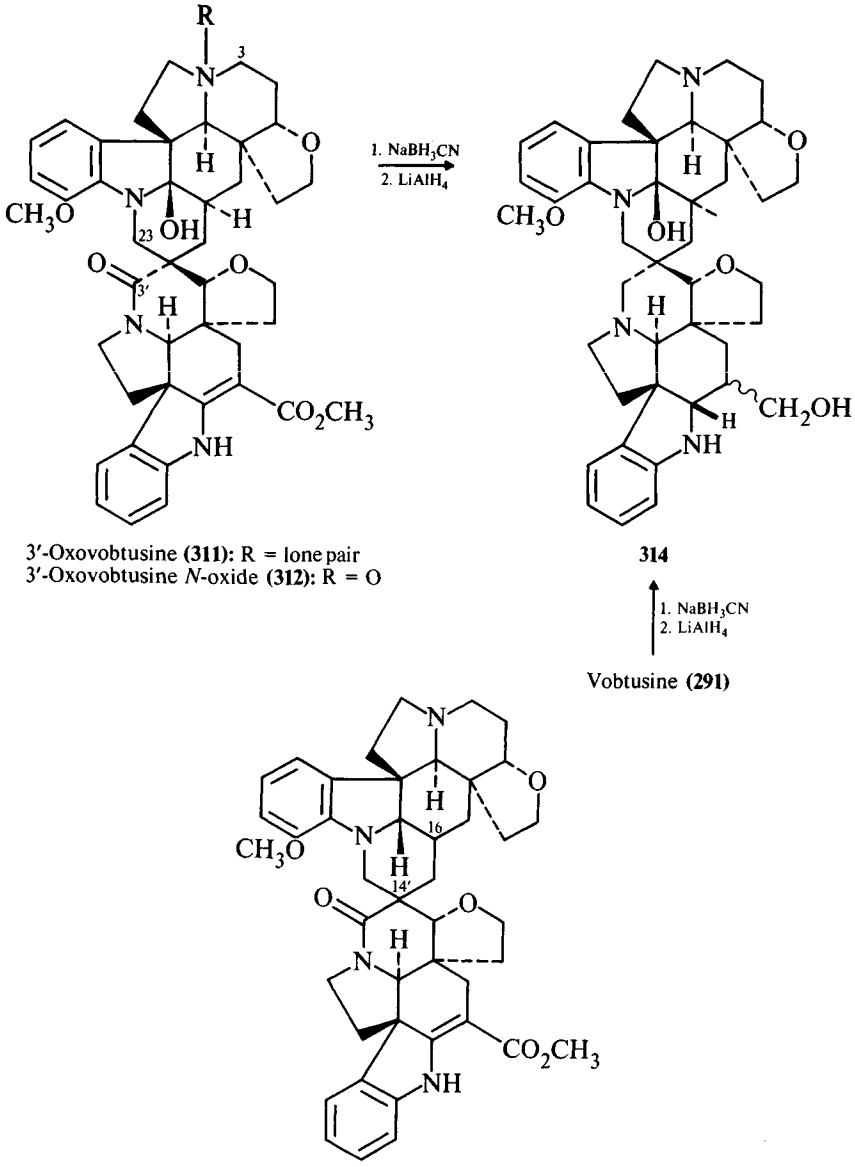
2-Deoxy-18-oxovobtusine (**306**)



307: 14's, 16β-H, R = O
308: 14's, 16β-H, R = H_2
309: R = H_2

In the mass spectrum of 2-deoxy-3′-oxovobtusine (**313**) no $M^+ - 18$ ion was observed and the ions **b**, **g**, and **h** were all shifted by 14 m.u. in comparison with 2-deoxyvobtusine. The stereochemistry of C-16 and C-14′ remains unknown.[231]

A trace alkaloid (M^+ *m/e* 700, $C_{43}H_{48}N_4O_5$) from the root bark of *Hedranthera barteri*[215] was given the name owerreine. From the uv (λ_{max} 272sh, 298 and 327 nm) and ir (ν_{max} 1721 cm^{-1}) spectra owerreine was deduced to contain an enamine. Similarities to 2,16-anhydrovobtusine (**292**) were found in the mass spectrum where ion **g** was observed at 18 m.u. less than in vobtusine, and ions **c**, **d**,



3'-Oxovobtusine (**311**): R = lone pair
3'-Oxovobtusine *N*-oxide (**312**): R = O

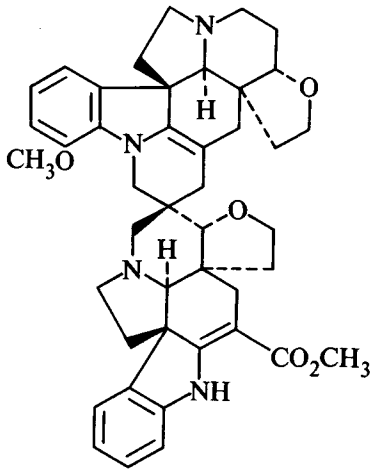
314

Vobtusine (**291**)

2-Deoxy-3'-oxovobtusine (**313**)

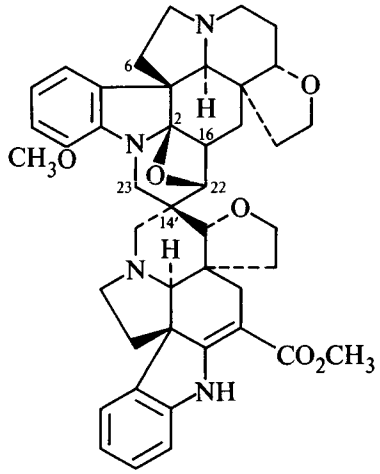
Scheme 34.

f, **h**, and **i** remained at the same mass. However, some differences (color reaction with Ce(IV), uv, ir, and $[\alpha]_D$) in physical properties were observed. The mass spectra were also quantitatively different, for *m/e* 138 is the base peak in owerreine, but M^+-138 is the base peak in the spectrum of **292**. Most probably owerreine is the C-14′ diastereoisomer, **315**, of 2,16-anhydrovobtusine.[215]



Owerreine (**315**)

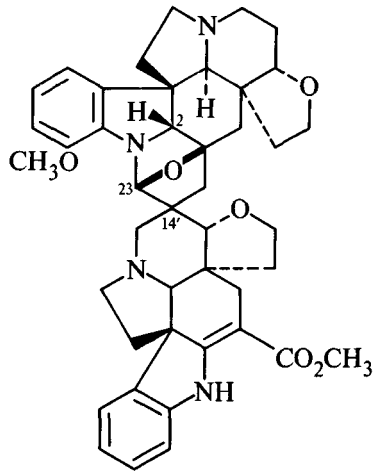
The root bark of *Voacanga chalotiana* Pierre ex Stapf yielded the alkaloid quimbeline (**316**)[220] whose structure was deduced[235] through interpretation of spectral data. A typical vobtusine uv spectrum was observed together with analogous ir and nmr data. In the mass spectrum the ions **e** and **g** were shifted 2 m.u., but ions **h**, **i**, and **j** were not, on comparison with vobtusine. Two hydrogens are therefore lost from the ring linking the two units, and since no olefinic protons or additional carbonyl groups were observed, an ether linkage was deduced. Hydrogenolysis afforded vobtusine, thereby fixing one end of the ether linkage, and the ^{13}C nmr spectrum suggested (oxymethine carbon at 82.0 ppm) that quimbeline had the novel oxetane structure **316**.[235]



Quimbeline (**316**)

Amataine was obtained as grandifoline from *Voacanga grandifolia* (Miq.) Rolfe, as subsessiline from *Callichilia subsessilis* Stapf[232] and as amataine from *Hedranthera barteri* (Hook. f.) Pichon[215] and *Voacanga chalotiana*.[220] The uv, ir, and nmr spectral data confirmed it to be a member of the vobtusine series, but instead of a doublet in the region 4.8–5.2 ppm, two singlets were observed at 4.75 and 4.18 ppm.[215] A molecular ion at *m/e* 716 ($C_{43}H_{48}N_4O_6$) showed fragment ions **e** and **g** shifted by 2 m.u. suggesting that the ring joining the two units to **g** contained an ether linkage.[215]

Reduction with potassium borohydride afforded a dihydro derivative (named isovobtusine) and with potassium borodeuteride ions **h** and **i** were increased by 1 m.u. On this basis the alkaloid was suggested to have the structure **317** with C-14′ having the opposite configuration to vobtusine.[232] But when the structure of vobtusine was revised, a proposal for an ether linkage between either C-2 and C-23 or C-2 and C-3′ was made.[220] Additional work has established the latter hypothesis to be correct.[210,238,239]

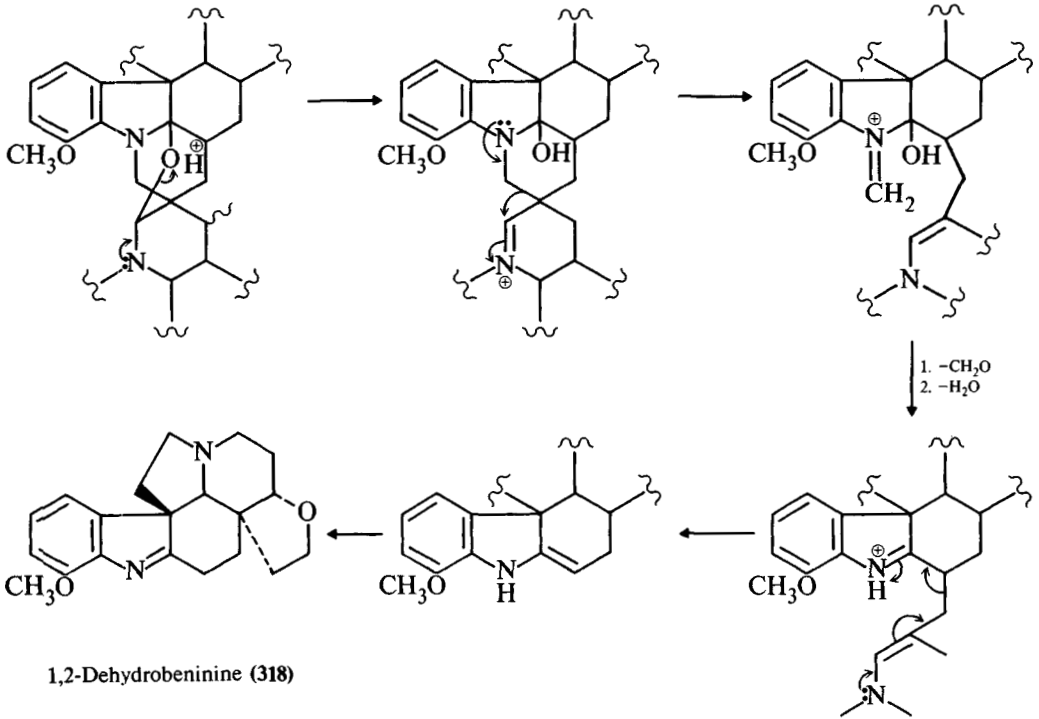


Amataine (original) (**317**)

Amataine is the only alkaloid in this series to undergo acid (70% H_3PO_4) cleavage, in this case to give formaldehyde and 1,2-dehydrobeninine (**318**)[238]; the mechanism shown in Scheme 35 has been proposed.

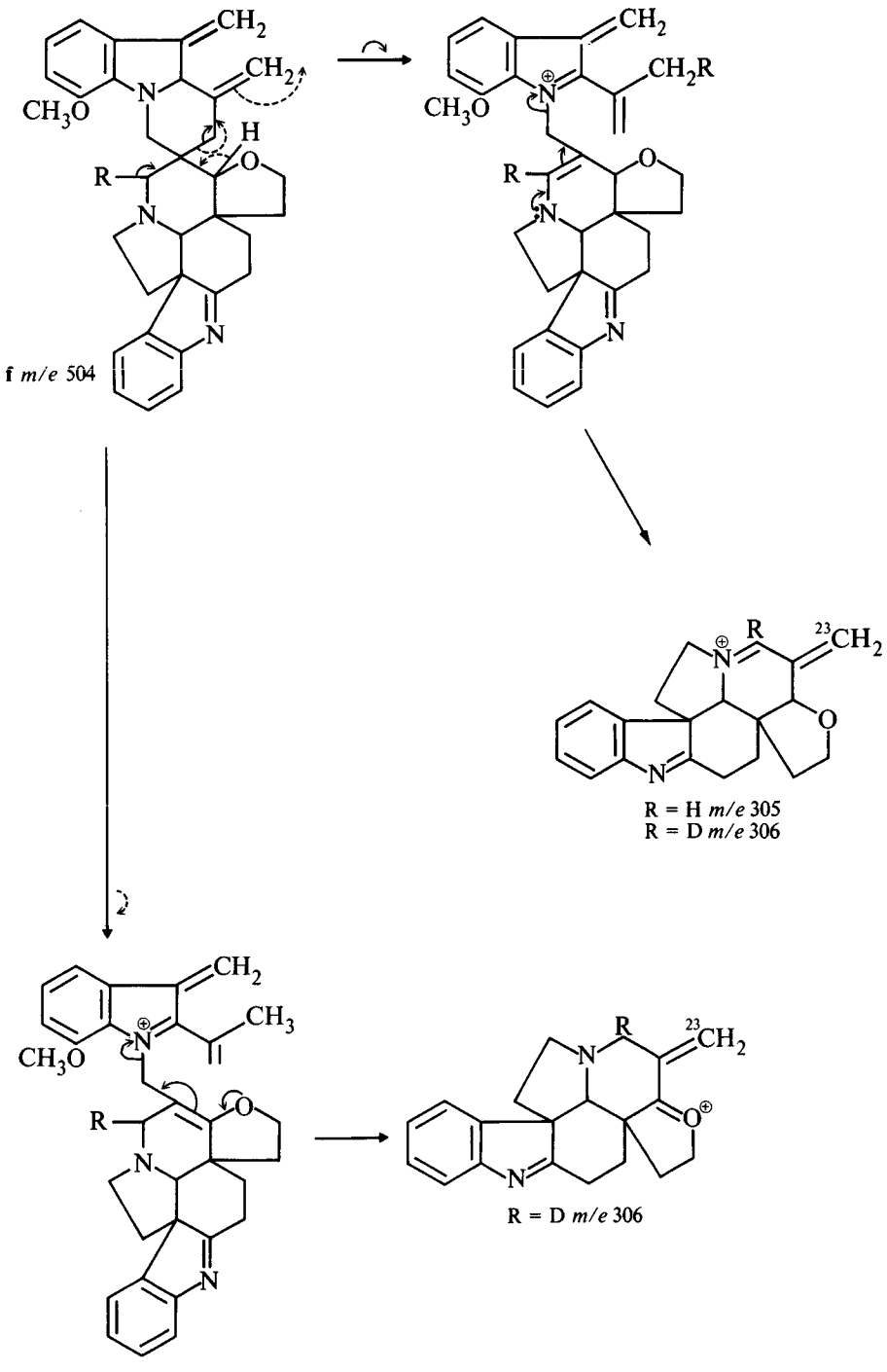
Catalytic[238] or sodium borohydride[238,239] reduction afforded dihydroamataine (isovobtusine) giving a reddish-blue color with cerium(IV) (vobtusine gives blue), and in which the vobtusine doublet has reappeared at 4.70 ppm ($J = 14$ Hz) in the nmr spectrum. Although the mass spectrum was similar to that of vobtusine a new ion at *m/e* 305 was observed, possibly derived by one of the pathways shown in Scheme 36.[238] Note that C-23 is present in this species.

When dihydroamataine (isovobtusine) (**319**) was treated with hydrochloric acid (6 *M*) at 25° for 15 hours anhydrodihydroamataine (**315**) was produced [blue-violet color with cerium(IV)][238] and both the ir and uv spectra were similar to anhydro-

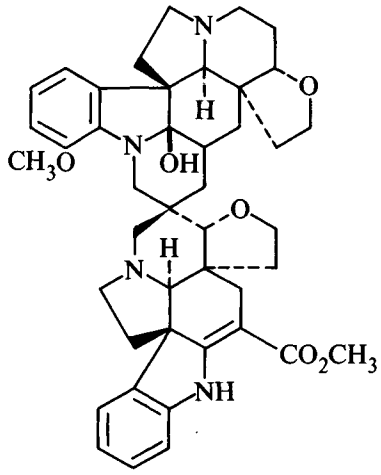


1,2-Dehydrobeninine (**318**)

Scheme 35.



Scheme 36. Formation of ion i in the mass spectrum of vobtusine derivatives.



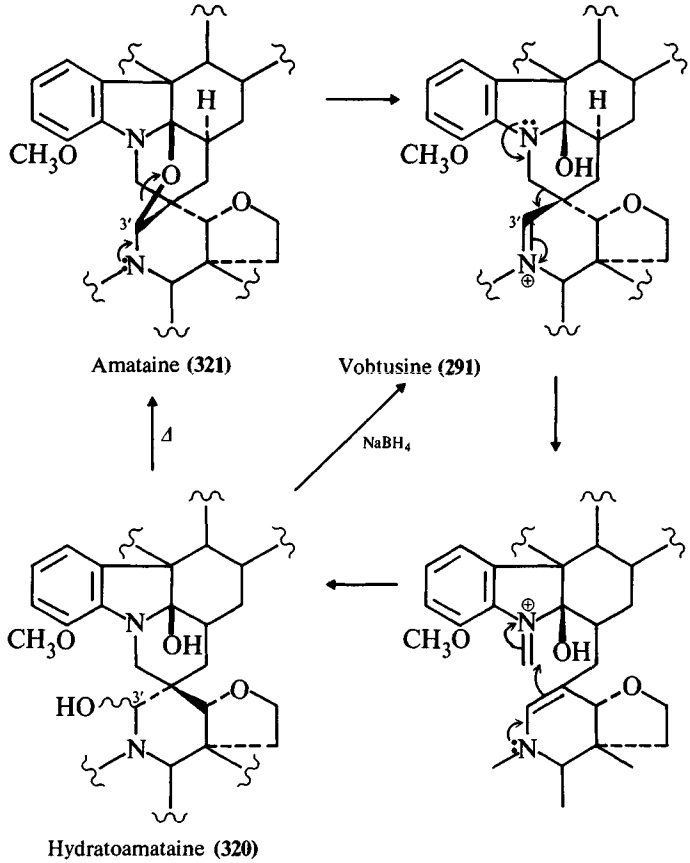
Dihydroamataine (isovobtusine) (**319**)

vobtusine (**292**). The nmr spectrum was also quite similar except that the "vobtusine doublet" was observed at 4.55 ppm ($J = 12$ Hz) coupled to a proton at 2.63 ppm. A second doublet at 3.24 ppm ($J = 11$ Hz) was assigned to H-3′ and a singlet at 3.27 ppm to H-15′, H-21, or H-21′. It was suggested[238] that anhydrodihydroamataine (**315**) and owerreine were identical.

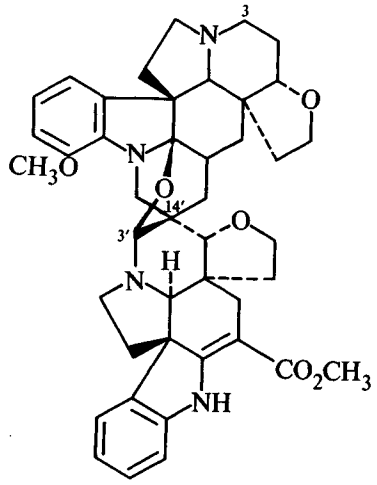
Hydrolysis of amataine with 0.01 *M* hydrochloric acid in 50% aqueous dioxane at 80° for 2 hours afforded hydratoamataine (3′-hydroxyvobtusine) (**320**) showing doublets in the nmr spectrum at 5.07 ppm ($J = 14$ Hz) and 4.53 ppm ($J = 10$ Hz), the latter signal being ascribed to H-3′. Reduction of **320** then yielded vobtusine (**291**), whereas pyrolysis at 340° for 2 seconds yielded amataine (**321**) (Scheme 37).[238] The facile interconversion between the *R* and *S* stereochemistries at C-14′ is particularly interesting.

18-Oxoamataine (subsessiline lactone) ($C_{43}H_{46}N_4O_7$) was first obtained as alkaloid H from *Voacanga thouarsii* and displayed characteristic spectral properties similar to amataine (**321**) but with an additional carbonyl moiety at 1780 cm^{-1} (γ-lactone). Fragmentations at *m/e* 516 (ion **e**), *m/e* 363 (ion **h**), and *m/e* 152 (ion **j**) suggested that the carbonyl was located at C-18 as in 18-oxovobtusine (**305**).[239] Sodium borohydride reduction afforded 18-oxoisovobtusine (**322**), indicating 18-oxoamataine to have the structure **323**. Subsequently this structure was supported[234] by ^{13}C nmr evidence (see below), although the stereochemistry at C-3′ was reversed.

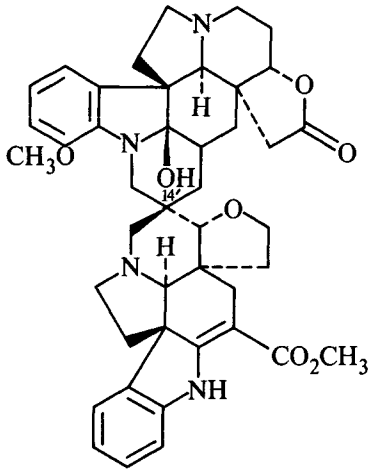
Callichiline ($C_{42}H_{48}N_4O_5$) co-occurs with vobtusine in *Callichilia subsessilis*[211] and *H. barteri*,[213,215,240,241] but in spite of considerable effort its structure has remained an enigma. It does not undergo acid cleavage and cannot be formylated, acetylated, or hydrogenated. The methoxyindoline unit was determined by nitration and the carbomethoxy group through its spectral and chemical properties. From the absence of any olefinic protons or additional carbonyl carbons and resistance to chemical reduction the remaining two oxygen atoms were deduced to be ether linkages.



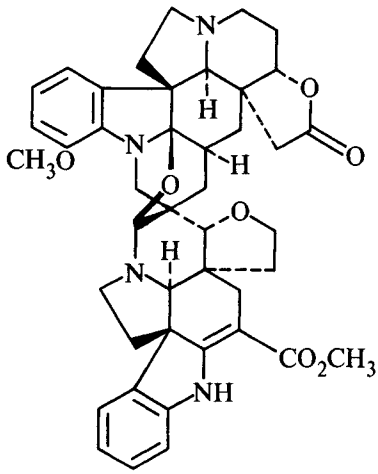
Scheme 37.



Amataine (321)

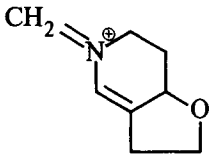


18-Oxoisovobtusine (322)

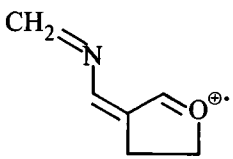


18-Oxoamataine (323)

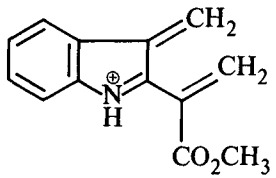
Callichiline, like vobtusine, shows fragment ions at *m/e* 138 (**298**), *m/e* 110 (**324**), and *m/e* 214 (**299**), and from the nmr spectrum (two NH protons), C-23 of vobtusine is missing, and the aromatic nucleus is not further substituted. This led to a structure proposal of **325** for callichiline, and subsequent arguments rest mainly on mass spectral interpretation.[240]



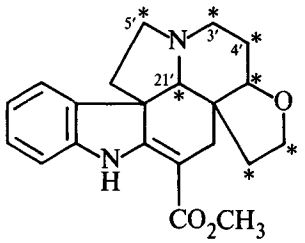
298 *m/e* 138



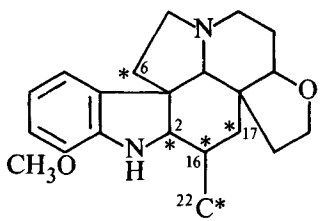
324 *m/e* 110



299 *m/e* 214



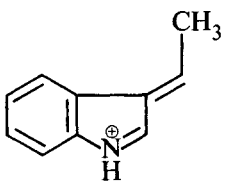
Unit A



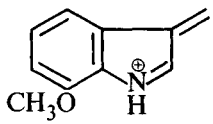
Unit B

325

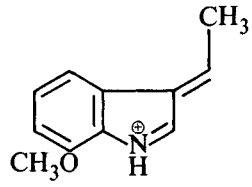
An ion at *m/e* 144 (**326**) eliminates C-5′ as a linking point, and the absence of an M^+-28 ion or ions such as **295** and **296** indicates that C-2 or C-6 and C-16, 17, or 22 in unit B are linked to unit A.



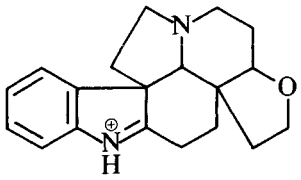
326 *m/e* 144



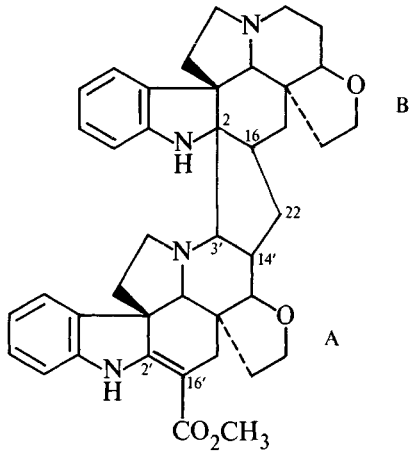
295 *m/e* 160



296 *m/e* 174



327 *m/e* 324



Callichiline (**328**)

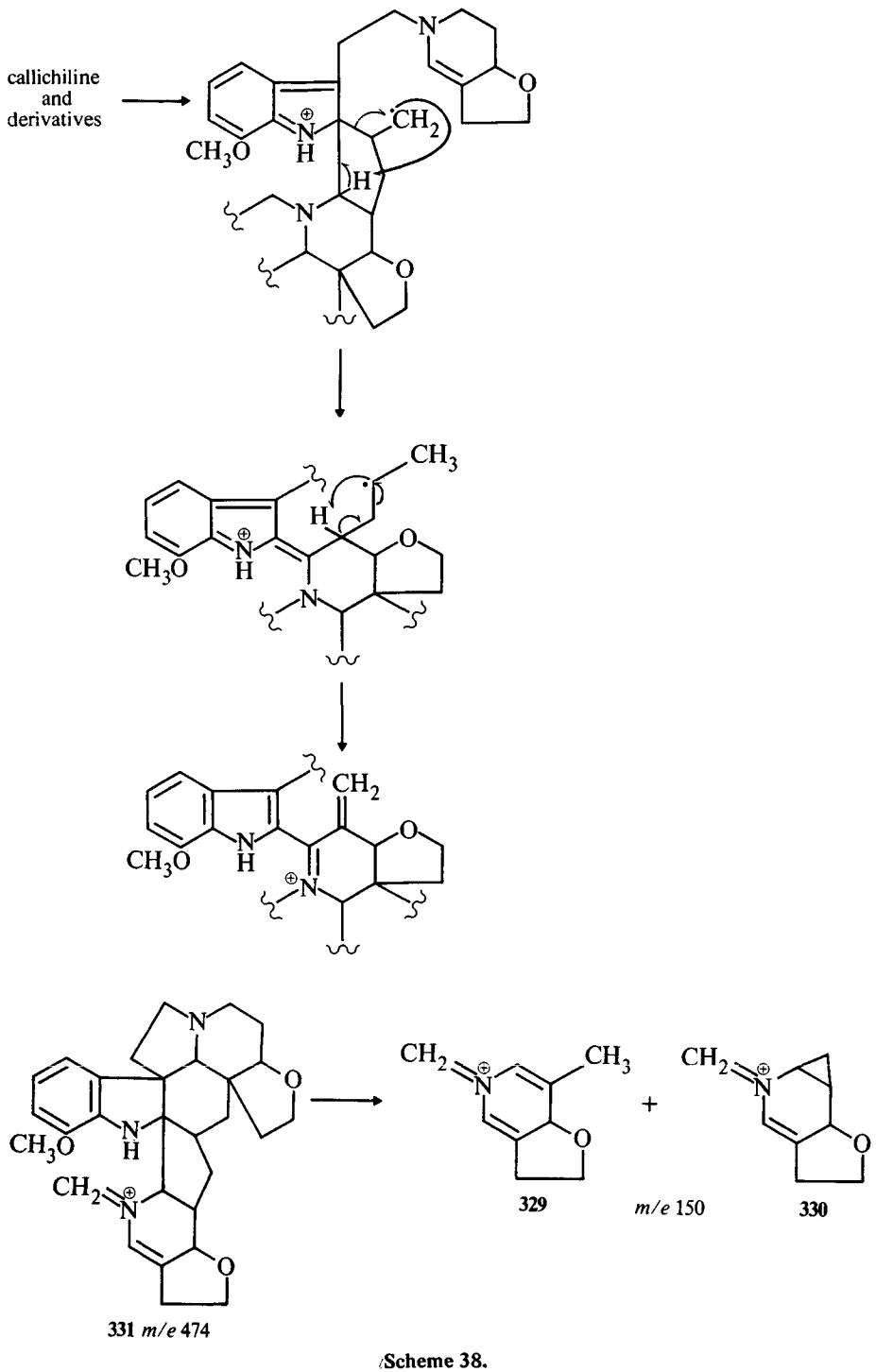
An important ion at *m/e* 324 (**327**) is present in callichiline and several of its derivatives, and the easy loss of C-22 and resistance (steric hindrance?) to formylation suggests that C-2 and C-22 are the key linking points with unit A. Three structures were proposed, and of these **328** was favored.

This structure was also used to explain (Scheme 38) the loss of an *ethyl* radical in the spectra of callichiline and its derivatives, and to provide evidence for the formation of an ion at *m/e* 150 (**329** or **330**) directly from *m/e* 474 (**331**).[240] A further important fragment at *m/e* 349 (**332**), shifting to *m/e* 265 (**333**) in the spectrum of 2′,16′-dihydrocallichiline, has been rationalized in terms of Scheme 39, and supports the presence of a tetrahydrofuran moiety in the A unit rather than elsewhere. Definitive proof of the structure **328** is lacking, however.

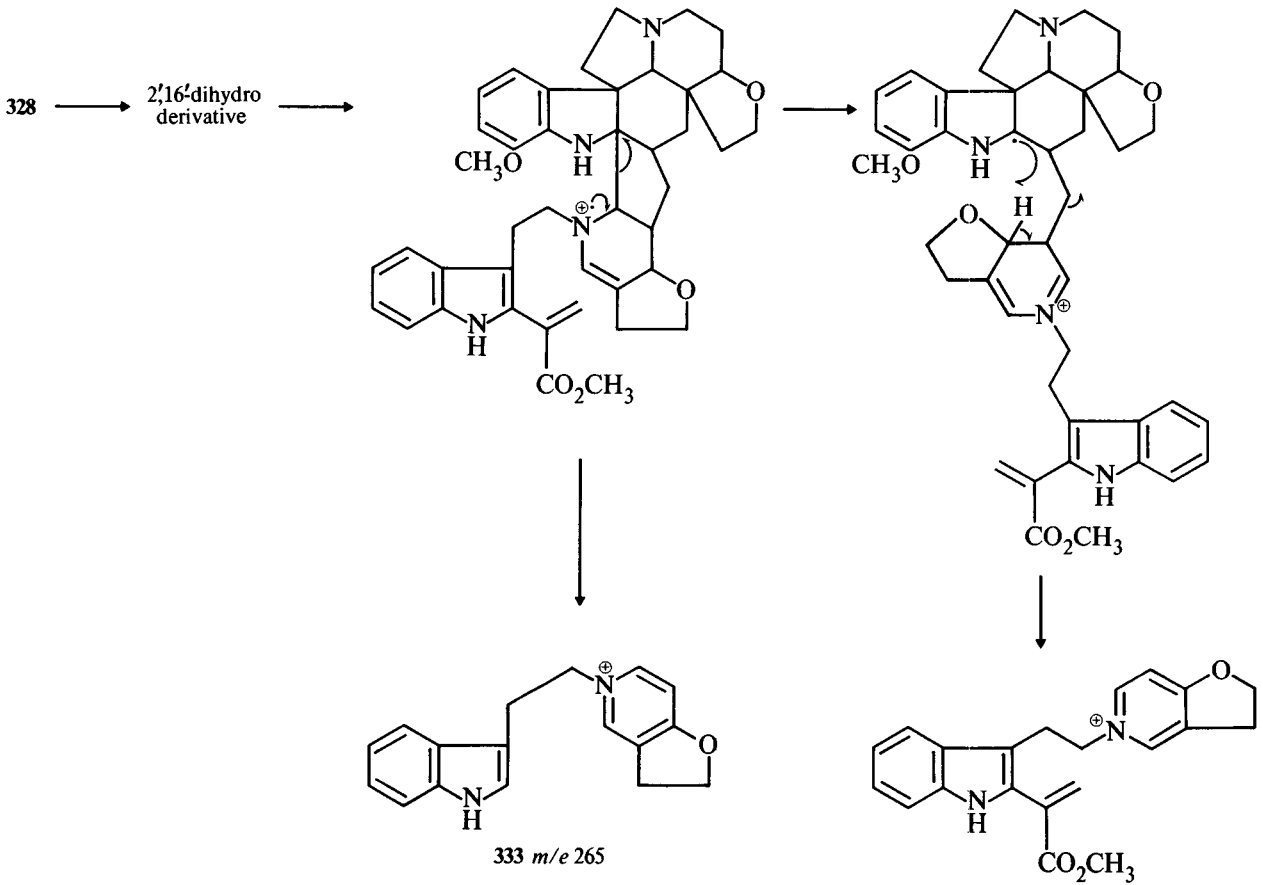
C. Voafolidine and Related Alkaloids

Voacanga africana leaves, besides being a source of bisindoles in the vobtusine series, also produce another series of closely related alkaloids[219] of which voafolidine may be regarded as the parent compound.

Although the uv spectrum (λ_{max} 260, 300, and 325 nm) was similar to vobtusine,


callichiline
and
derivatives
CH3O
CH2
CH3
329
m/e 150
330
331 m/e 474

Scheme 38.


328
2′,16′-dihydro derivative
CH3O
N
H
O
CO2CH3
333 m/e 265
332 m/e 349

Scheme 39.

TABLE XII. PRINCIPAL MASS SPECTRAL FRAGMENTS OF VOAFOLIDINE AND RELATED ALKALOIDS

Compound	Ion (m.u.)										
	M^+	a′	b′	c′	d′	e′	f′	g′	h′	i′	j′
Voafolidine (337)	688	670	630	612	532	474	474	363	363	305	138
Voafoline (341)	672	–	–	–	–	458	–	347	363	–	138
Isovoafoline (342)	672	–	614	–	–	458	–	347	363	305	138
Folicangine (357)	686	–	628	–	–	472	–	–	363	305	138

no aromatic methoxy group and eight aromatic protons were observed in the ^1H nmr spectrum. A suggestion of the structure class was a doublet ($J = 13$ Hz) at 4.4 ppm analogous to the "vobtusine doublet." In the aliphatic region a triplet ($J = 7$ Hz) at 0.88 ppm indicated the presence of an ethyl side chain.

Analogous mass fragmentation ions were observed from a molecular ion at *m/e* 688 ($C_{42}H_{48}N_4O_5$) with the ions **b'**, **c'**, **e'**, and **g'**, shifted by 30 m.u. (loss of OCH_2), whereas the ions **h'**, **i'**, and **j'** were not shifted (Table XII) (Scheme 40). The co-occurrence with voaphylline (**334**) suggested that **j'** might have the structure **335**. On this basis, together with evidence of an acid cleavage of the epoxide, the structure **336** was proposed,[232] which was subsequently[234] revised to that shown in **337**.

Voafoline and isovoafoline were also obtained from *V. africana*.[232] Their uv and ir spectra established the basic nucleus and their nmr spectra indicated the presence of an ethyl side chain and "vobtusine doublets" ($J = 14$ Hz) at 4.60 and 4.15 ppm, respectively. Their mass spectra were very similar, displaying a molecular ion at *m/e* 672 ($C_{42}H_{48}N_4O_4$) and with ions **h'**, **i'**, and **j'** at the same mass as in voafolidine. However, no $M^+ - 18$ ion was observed and the ions **e'** and **g'** were shifted by 16 m.u., and structure **338** was proposed for isovoafoline.[232] Only ion **e'** was substantially more intense in the spectrum of isovoafoline than in voafoline.

The epoxide groups in these alkaloids could be cleaved with acetic acid under reflux, but none of the isomers (e.g., **339/340** from isovoafoline) was identical and consequently voafoline was also assigned the structure **338** without stereochemistry. Their structures were established[234] as **341** and **342** when ^{13}C nmr spectroscopy was applied to this problem.

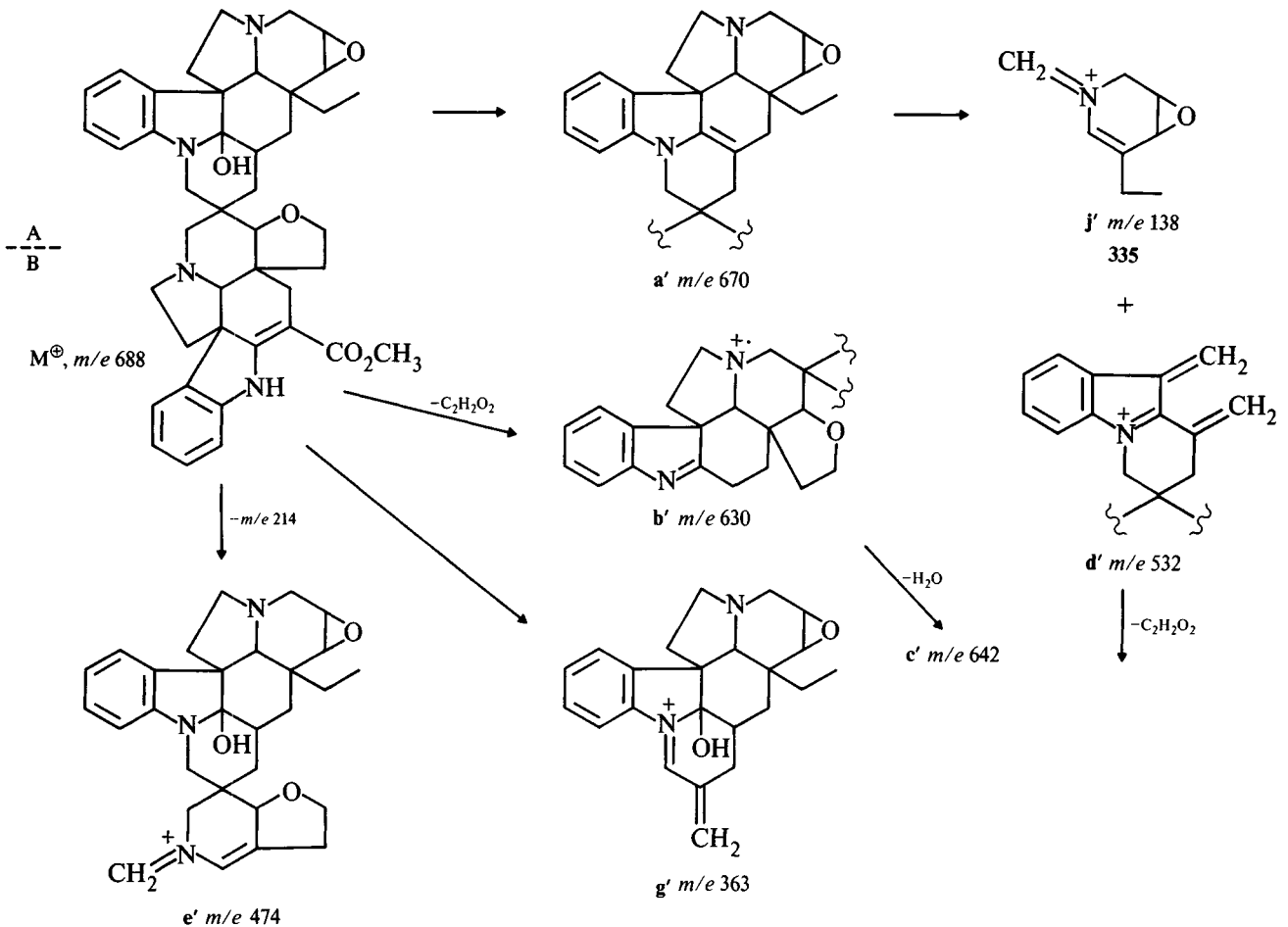
The final member of this series is folicangine, also from the leaves of *V. africana*.[219] Characteristic signals for the β-anilinoacrylate unit were observed, but the indoline band in the uv spectrum was hypsochromically shifted from 260 nm to 255 nm. Eight aromatic protons were observed together with a triplet for the C-18' protons at 0.82 ppm. Two one-proton singlets were observed at 3.96 and 4.60 ppm, but no "vobtusine doublet"[219,232] (see also amataine).

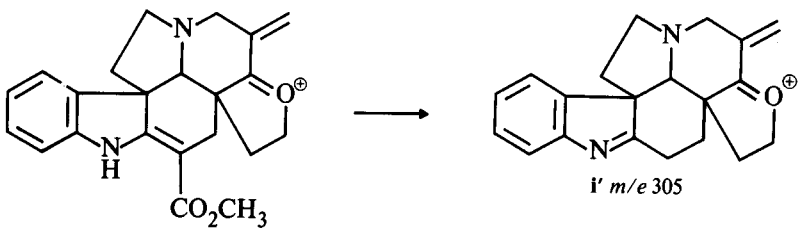
The molecular ion (*m/e* 686, $C_{42}H_{46}N_4O_5$) indicated the presence of two hydrogen atoms fewer than in voafolidine. The absence of additional carbonyl groups or double bonds and the absence of an $M^+ - 18$ peak suggested the presence of an ether linkage. Ions **b'** and **e'** were shifted by 2 m.u. to lower mass, but ions **h'** and **i'** remained at the same mass, suggesting[232] that folicangine had the structure **343**.

Treatment with potassium borohydride gave a product isomeric with voafolidine and having similar uv and mass spectral properties, although in their mass spectra the intensities of the ions at *m/e* 474 and 363 were reversed. The characteristic doublet ($J = 14$ Hz) had also returned in isovoafolidine (**344**) at 3.96 ppm, substantially (0.4 ppm) shifted upfield compared with its frequency in voafolidine.[232]

Before the structures of voafoline, etc., are corrected, it is worth mentioning that mass spectrometry also apparently distinguishes between the vobtusine and voafolidine series. In the voafolidine series a prominent ion is observed at *m/e* 108 (**345**) but in the vobtusine series this ion is apparent at *m/e* 110 (**346**).

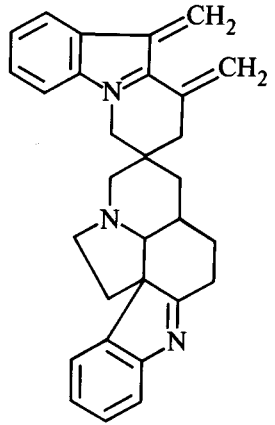
After the structure of vobtusine was revised, attention naturally turned to the


A
B
M⊕, m/e 688
CO2CH3
NH
OH
O
N
−C2H2O2
−m/e 214
−H2O
a′ m/e 670
b′ m/e 630
c′ m/e 642
d′ m/e 532
e′ m/e 474
g′ m/e 363
j′ m/e 138
335
+
CH2
−C2H2O2



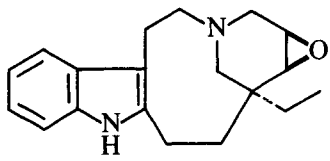
h' *m/e* 363

i' *m/e* 305

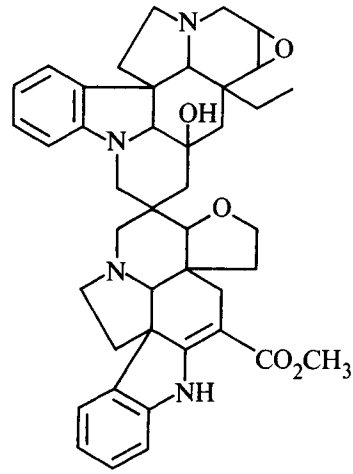


f' *m/e* 474

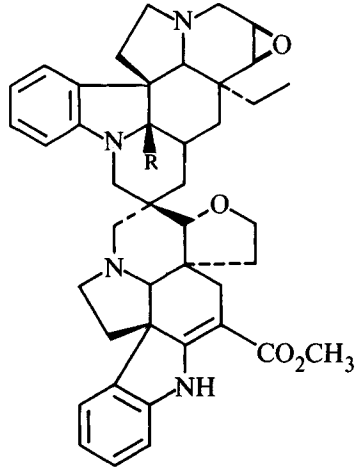
Scheme 40. Summary of the mass spectrum of voafolidine (337).



Voaphylline (**334**)

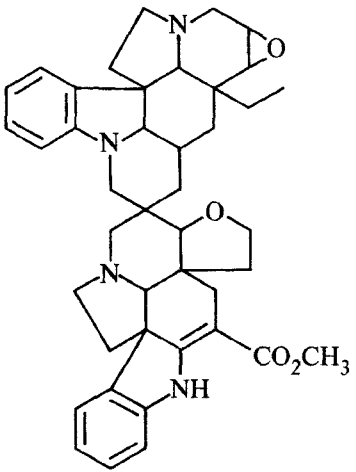


Voafolidine (original structure) (**336**)

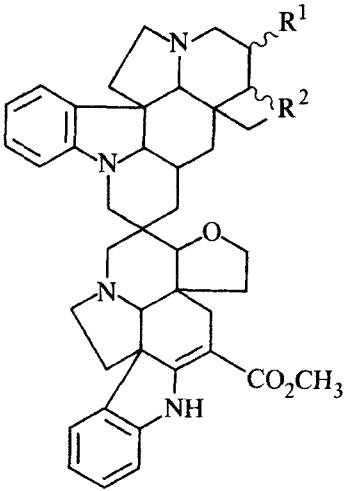


Voafolidine (revised) (**337**): R = OH
Voafoline (revised) (**341**): R = H

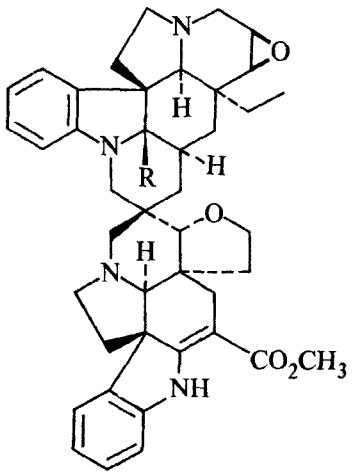
related alkaloids including folicangine[239] and consideration was given to the possibility of an ether linkage between C-2 and positions 3′, 5′, or 21′. Molecular models indicated that if the C-2-O bond is β, the configuration at C-14′ must be *R* and then only C-3′ is proximate, suggesting that folicangine has the structure **347**.[239] The singlet proton at 4.60 ppm can now be attributed to H-3′α analogous to the corresponding protons at 4.75 and 4.78 ppm in amataine (**321**) and 18-oxoamataine (**323**), respectively.[239]



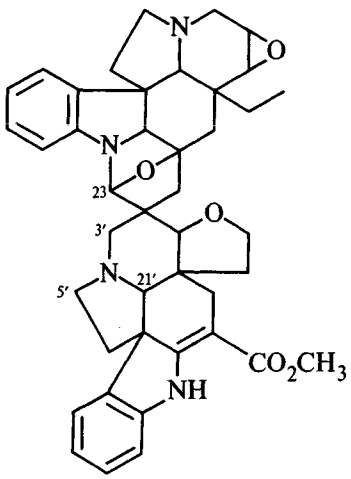
Voafoline (original structure) **(338)**
Isovoafoline (original structure) **(338)**



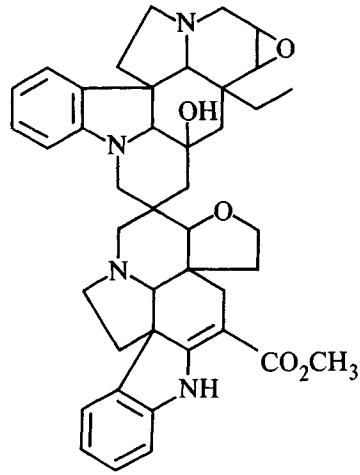
339: $R^1 = OCOCH_3$, $R^2 = OH$
340: $R^1 = OH$, $R^2 = OCOCH_3$



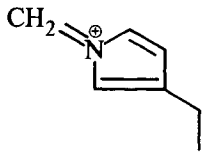
Isovoafoline (revised) **(342):** R = H
Isovoafolidine (revised) **(354):** R = OH



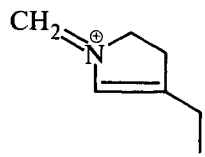
Folicangine (original) **(343)**



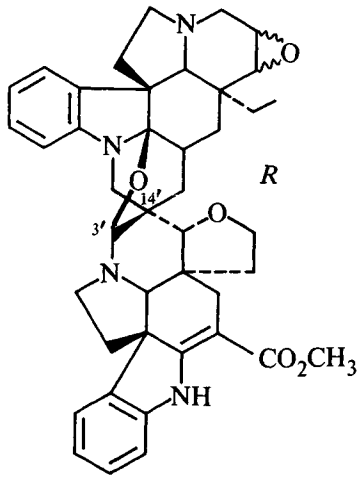
Voafolidine (original) **(336)**
Isovoafolidine (original) **(344)**



345 *m/e* 108



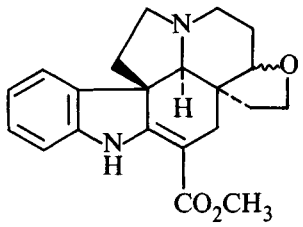
346 *m/e* 110



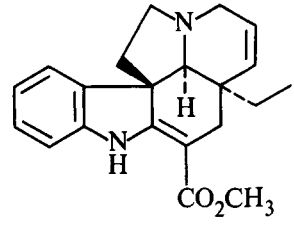
Folicangine (revised) **(347)**

D. Carbon-13 Nmr Spectra of the Spiro *Aspidosperma-Aspidosperma* Alkaloids

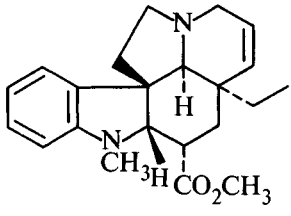
Wenkert and Poisson and their respective co-workers have made a significant contribution to the ^{13}C nmr spectroscopy of this group of alkaloids (Table XIII)[234] in which the assignment of the spectra of vandrikine (**348**), tabersonine (**349**), N_a-methyl-2β,16β-dihydrotabersonine (**350**), and pachysiphine (**351**) was important. As expected, major problems were encountered in assigning the methylene carbons, and, for example, a distinction between C-6 and C-22 could be made only when 3′-oxovobtusine (**311**) and 3′-oxovobtusine *N*-oxide (**312**) were examined, where in the latter compound C-6 is substantially deshielded.



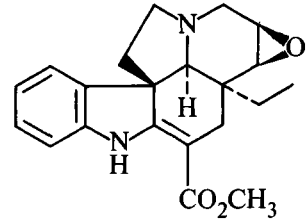
Vandrikine (**348**)



Tabersonine (**349**)



350



Pachysiphine (**351**)

The stereochemistry of the epxoide function in voafolidine was deduced by comparison with C-14 and C-15 of pachysiphine (**351**) and from the shielding of C-17 in voafolidine (**337**) compared with vobtusine (**291**). Carbon-23 is also shielded in voafolidine with respect to C-23 in vobtusine (**291**) owing to the absence of the 12-methoxy group.

Carbon-2 in voafolidine bears the hydroxy group since this signal is shifted from about 94 ppm to 76.0 ppm in voafoline, which agrees well with the corresponding data in the vobtusine series.

Comparison of the spectra of voafoline and isovoafoline indicated the isomerism to be at the C-14′ spiran center, indicating isovoafoline to have the structure **342**.[234] The major shifts on changing the C-14′ stereochemistry are a shielding of C-15′ of about 6 ppm and a deshielding effect on C-3′ of about 4.3 ppm. Carbon-3′ in voafoline (**352**) suffers 1,3-diaxial interactions with N_a and C-16, but in isovoafoline (**353**) it is C-15′ that experiences these effects, and this may be used

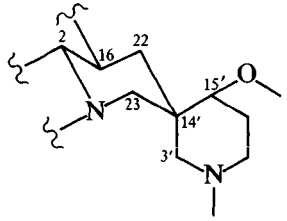
TABLE XIII. ^{13}C NMR CHEMICAL SHIFTS OF TABERSONINE (349), VOBTUSINE (291), VOBTUSINE LACTONE (305), 2'-DEOXYVOBTUSINE LACTONE (310), AND VANDRIKINE (348)[a]

	349	291	305	310		348[b]	291	305	310
C-2	166.7	166.6	166.6	166.7	C-2′		93.7	93.3	75.6
C-3		53.7	53.8	53.8	C-3′	45.7	48.7	48.0	47.8
C-5		50.9	50.9	51.2	C-5′	51.2	51.9	51.8	52.7
C-6		44.9	44.9	45.0	C-6′	45.1	31.1	30.8	37.7
C-7		54.8	54.8	55.0	C-7′	54.2	55.9	55.8	51.0
C-8	137.8	137.6	137.5	137.5	C-8′		134.2	133.0	135.6
C-9	121.4	121.2	121.2	121.4	C-9′		114.5	114.6	114.8
C-10	120.5	120.4	120.4	120.5	C-10′		118.1	118.8	118.3
C-11	127.6	127.4	127.5	127.6	C-11′		110.8	111.1	110.9
C-12	109.2	109.1	109.1	109.2	C-12′		144.9	144.9	145.1
C-13	143.1	142.8	142.8	142.9	C-13′		137.2	136.9	137.9
C-14		39.6	39.5	40.0	C-14′	26.6	25.7	24.7	25.3
C-15		87.4	87.3	87.5	C-15′	79.8	80.3	81.4	82.0
C-16	92.2	94.3	94.2	94.1	C-16′		31.5	31.1	29.4
C-17		27.3	27.3	27.5	C-17′	27.4	32.4	31.7	33.7
C-18		64.2	64.2	64.3	C-18′	64.7	65.1	175.3	175.5
C-19		34.8	34.8	34.8	C-19′	34.6	36.6	41.4	41.5
C-20		47.6	47.6	47.8	C-20′	46.4	44.1	43.4	44.0
C-21		68.9	68.8	68.8	C-21′	68.7	63.6	63.9	65.3
C=O	168.8	168.3	168.3	168.4	C-22′		34.1	33.5	39.0
OMe	50.8	50.9	50.9	51.0	C-23′		46.1	46.0	52.7
					OMe		55.0	55.0	54.9

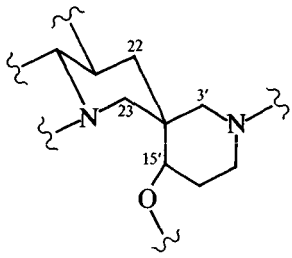
[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm.

[b] The previously undifferentiated C-14′ and C-17′ shifts are resolved by the present study.

(Table XIV) to assign the 14*R* and 14*S* stereochemistries in this series. In this way the structure of voafolidine (**337**) was confirmed and that of 14′-isovoafolidine (**354**), from the borohydride reduction of folicangine, was deduced. Comparison of the chemical shift data for folicangine, amataine, and 18-oxoamataine, particularly with respect to C-3′ and C-15′, indicated these alkaloids to have the same C-14′ and C-3′ stereochemistry (Table XV).



Voafoline (**352**)



Isovoafoline (**353**)

TABLE XIV. CHEMICAL SHIFT DIFFERENCES FOR C-3′ AND C-15′ IN THE 14*R* AND 14*S* SPIRO-*ASPIDOSPERMA-ASPIDOSPERMA* ALKALOIDS

14′*R*	14′*S*	Δδ C-3′	Δδ C-15′
14′-Isovobtusine-vobtusine		4.3	−5.9
18-Oxo-14′-isovobtusine-18-oxovobtusine		4.5	−5.8
14′-Isovoafoline-voafoline		4.3	−6.4
14′-Isovoafolidine-voafolidine		4.3	−7.1

If the C-3′ proton is α (as in **355**) ring D′ exists in a chair conformation where only the shifts of C-3′, C-15′, C-14′, C-5′, and C-21′ should be affected. However, because C-6′, C-7′, C-17′, and C-19′ are also affected, Rolland et al.[234] have suggested that this requires H-3′ to be β as in **356**. The required inversion of the N'_b lone pair then accounts for the many shift changes produced when the C-2-C-3′ ether linkage is present. Folicangine was therefore assigned the structure **357** and amataine and 18-oxoamataine the structures **358** and **359**, respectively.[234]

E. Other Physical Data of Spiro *Aspidosperma-Aspidosperma* Alkaloids

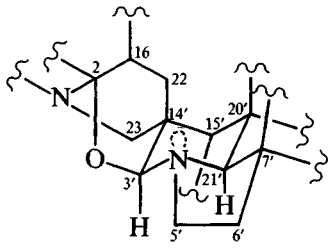
Almost all the ^{1}H nmr spectra of these alkaloids display a doublet (J = 12–14 Hz) in the region 4–5.4 ppm (Table XVI) which had previously been assigned to one of the C-3′ protons. Spin decoupling[202,238] and INDOR[238] experiments on vobtusine (**291**) indicated that the proton at 5.13 ppm was coupled to another proton at 3.10 ppm, and these protons could be on either C-3′ or C-23. The former possibility is eliminated since 3′-oxovobtusine (**311**) shows this signal, indicating it to be one

TABLE XV. ^{13}C NMR CHEMICAL SHIFTS OF FOLICANGINE (357), AMATAINE (358), AND 18-OXOAMATAINE (359)[a,b]

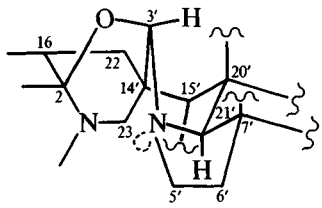
Carbon	357	358	359	Carbon	357	358	359
C-2	93.9[c]	94.6[e]	93.9[g]	C-2′	165.8	165.9	165.7
C-3	53.7[d]	49.0	48.4	C-3′	91.8	91.9	91.9
C-5	53.3[d]	53.2	52.9	C-7′	59.1	59.1	*i*
C-6	30.5	31.1	31.5	C-8′	136.1	137.1	*i*
C-7	53.7	54.4	54.4	C-9′	121.4	122.4	122.3
C-8	135.9	136.0	135.8	C-10′	121.0	120.9	120.9
C-9	122.2	114.6	114.6	C-11′	127.8	127.7	127.8
C-10	118.1	118.8	119.1	C-12′	109.1	109.0	109.1
C-11	127.8	111.1	111.6	C-13′	142.9	142.9	142.8
C-12	106.9	145.8	145.9	C-14′	38.1	38.1	38.2
C-13	147.8	136.2	136.0	C-15′	87.5	87.6	87.5
C-14	52.9	26.1	25.2	C-16′	93.0[c]	92.8[e]	92.7[g]
C-15	56.5	80.9	81.9	C-18′	67.3	67.3	67.3
C-16	32.2	32.8	32.2	C-20′	49.9	49.9	50.0
C-17	29.6	34.4[f]	33.7[h]	C-21′	70.6	70.6	70.7
C-18	7.6	65.0	175.2	C=O	168.1	168.1	168.0
C-19	28.0	35.8	40.6	OMe	51.0	50.9	51.0
C-20	35.5	44.1	43.4				
C-21	67.7	65.8	65.9				
OMe		55.6	55.6				

	357	358	359
NCH_2	47.5, 51.2	49.0, 50.9	48.9, 50.8
CH_2	33.9, 38.0, 38.6	34.0,[f] 38.1, 38.6	34.0,[h] 37.7, 38.6
	41.6	41.5	41.4

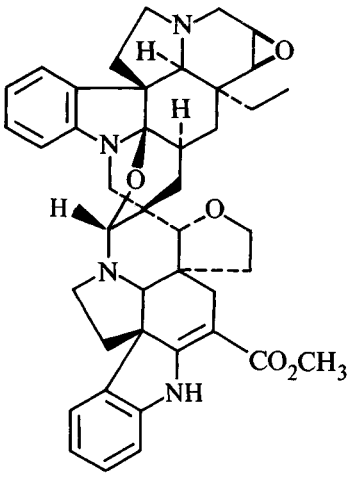
[a] Data are from Ref. 234.
[b] δ ppm TMS = δ($CDCl_3$ + 76.9 ppm).
[c–h] Indicates assigment may be reversed.
[i] Indicates signal not observed.



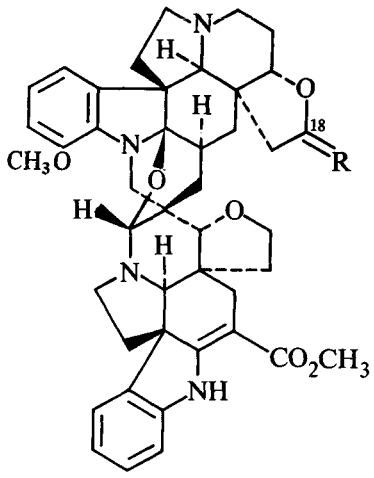
355 H-3′α



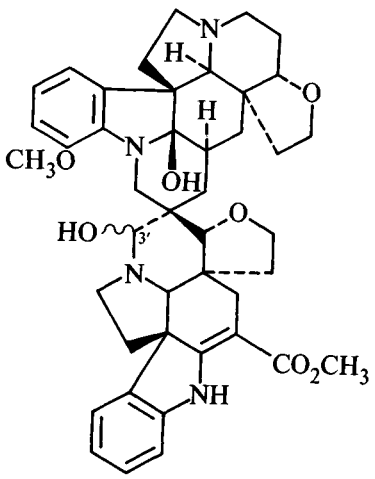
356 H-3′β



Folicangine (**357**)



Amataine (**358**): R = H_2
18-Oxoamataine (**359**): R = O



358a

of the C-23 protons. Interesting shifts are observed in this signal when the 14′ stereochemistry or when the 12-methoxy group is absent.[238] Compounds in the series having a C-2-C-3′ ether bridge do not show this signal.

TABLE XVI. CHEMICAL SHIFT DATA FOR AN H-23 PROTON IN THE SPIRO-*ASPIDOSPERMA-ASPIDOSPERMA* SERIES

Compound	δ (ppm)	*J* (Hz)	14′	Ref.
Vobtusine	5.13	14	*S*	220, 230, 238
Vobtusine *N*-oxide	5.13	14	*S*	238
Vobtusine *N,N′*-dioxide	–	–	*S*	238
Anhydrovobtusine	4.38	12	*S*	238
Anhydrotetrahydrovobtusine	5.11	12	*S*	238
12-Demethylvobtusine	4.83	14		230
2-Deoxyvobtusine (goziline)	5.37	14	*S*	224, 230, 232, 238
2-Deoxy-3′-oxovobtusine	4.8	13	*S*	228
3′-Oxovobtusine	4.55	14	*S*	228
3′-Oxovobtusine *N*-oxide	4.75	14	*S*	228
Amataine (subsessiline)	4.75[a]	–	*R*	215, 220, 238
Dihydroamataine (isovobtusine)	4.69	14	*R*	238
18-Oxoamataine (subsessiline lactone)	4.78[a]	–	*R*	228, 239
Hydratoamataine	5.07	14	*S*	238
Anhydrodihydroamataine (owerreine)	4.55	12	*R*	238
Quimbeline	4.95	14	*S*	235
Voafolidine	4.4	13	*S*	232, 238
Isovoafolidine	3.96	14	*R*	232, 238
Voafoline	4.60	14	*S*	232, 238
Isovoafoline	4.15	14	*R*	232, 238
Folicangine	4.6[a]	–	*S*	232

[a] Tentatively assigned to H-3′.

Also useful in determining the 14′-stereochemistry are the molecular rotation values $(M)_D$ (Table XVII). Although the data are somewhat limited, −2500° is apparently a lower limit for the 14′*S* stereochemistry, and about −3500° is an upper limit for the 14′*R* series of alkaloids.

Voacanga chalotiana has yielded 3′-hydroxyvobtusine (**358a**),[241a] which is of interest as a possible link between vobtusine (**291**) and amataine (**358**).

XIX. BISINDOLE ALKALOIDS FROM *MELODINUS* SPECIES

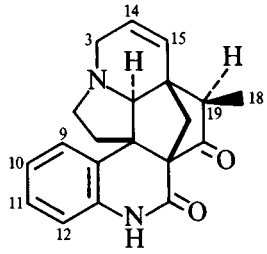
Melodinus scandens Forst. produces a number of interesting monomeric alkaloids and further fractionation afforded two pairs of closely related derivatives.[242]

Scandomelonine and episcandomelonine were isomers ($C_{41}H_{42}N_4O_5$) having NH, carbonyl, and β-anilinoacrylate moieties, and besides confirming the latter unit, the uv spectrum indicated a meloscandonine type chromophore. Methyl doublets at 1.21

TABLE XVII. MOLECULAR ROTATION DATA FOR SOME SPIRO *ASPIDOSPERMA-ASPIDOSPERMA* ALKALOIDS

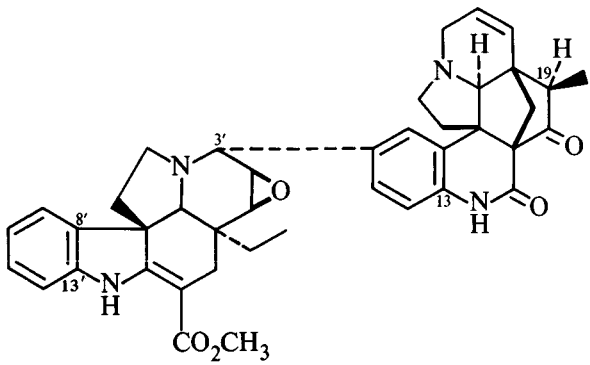
Compound	Stereochemistry	$[M]_D$	Compound	Stereochemistry	$[M]_D$
Vobtusine	14′*S*	−2527°	Isovobtusine	14′*R*	−3619°
2-Deoxyvobtusine	14′*S*	−2359°			
Voafolidine	14′*S*	−2064°	Isovoafolidine	14′*R*	−4417°
Voafoline	14′*S*	−2083°	Isovoafoline	14′*R*	−3810°

and 0.93 ppm in the epimers corresponded to the C-18 protons of meloscandonine (**360**) and its 19 epimer (**361**).[243,244] A loss of the unit *m/e* 214 (**299**) from the molecular ion suggested the junction to involve the aliphatic (3, 5, 14, and 15) carbons of the anilinoacrylate unit.



Meloscandonine (360)
19-Epimeloscandonine (361)

From the ^{13}C nmr spectra the meloscandonine unit (**360**) was clearly present with only C-10 showing a major shift (123.4 to 129.1 ppm), indicating it to be one point of attachment (Table XVIII). The second unit was shown to contain an epoxide and comparison with pachysiphine (14β,15β-oxidovincadifformine) (**351**) suggested that attachment was to C-3, indicating scandomelonine to have the structure **362**. Notable shifts were observed for C-3 and C-14 from 49.4 and 52.0 ppm in **351** to 57.4 and 56.2 ppm in **362**, respectively. The α stereochemistry was deduced from the small shift on C-5 and C-6, and more substantial γ shift of C-21 from 70.9 in **351** to 61.5 ppm in **362**.[242] Episcandomelonine, differing only in the stereochemistry of C-19, was assigned the structure **363** by analogy.[242]



Scandomelonine (362)
19-Episcandomelonine (363)

Scandomeline and 19-episcandomeline were also found to be isomers ($C_{42}H_{46}N_4O_6$) containing OH, NH, saturated ester, and β-anilinoacrylate units and the uv spectrum (λ_{max} 214, 257, 300, and 325 nm), besides confirming the latter functionality, indicated an *o*-toluidine unit in the second moiety.

TABLE XVIII. ^{13}C NMR DATA OF THE *MELODINUS* BISINDOLE ALKALOIDS (Ref. 242)[a,b]

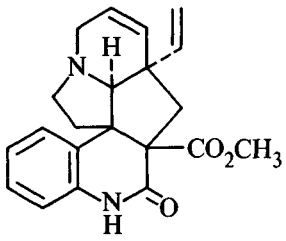
Carbon	360	361	363	Carbon	361	363	351	365	366	Carbon	365	366
C-3	47.2	47.3	47.0	C-2′	164.6	164.7	164.9	164.9	164.9	C-3	49.2	49.4
C-5	54.8	54.7	54.9	C-3′	57.4	57.6	49.4	58.2	58.2	C-5	52.7	52.9
C-6	38.1	37.9	38.0	C-5′	47.8	47.5	51.0	48.2	47.8	C-6	38.1	36.7
C-7	54.8	54.7	56.7	C-6′	42.1	42.3	43.9	42.4	42.5	C-7	50.9[e]	51.4
C-8	130.5	130.7	130.3	C-7′	53.8	53.6	54.7	54.1	53.8	C-8	124.5	124.6
C-9	123.5[c]	124.7	125.0	C-8′	137.2	137.1	137.5	137.8	137.7	C-9	127.7[d]	127.4[f]
C-10	123.4[c]	129.1	128.6	C-9′	121.2	121.6	121.3	121.6	121.2	C-10	123.5	123.2
C-11	127.6	127.1	126.8	C-10′	120.8	121.1	120.3	120.4	120.2	C-11	127.1[d]	127.3[f]
C-12	116.3	116.0	115.8	C-11′	127.3	127.2	127.6	127.4	127.3	C-12	114.6	112.8
C-13	136.5	136.3	136.3	C-12′	108.9	108.7	109.2	109.0	108.9	C-13	139.8	140.8
C-14	124.0	123.9	125.5	C-13′	142.5	142.3	142.9	142.8	142.7	C-14	125.8[d]	127.4
C-15	127.4	127.7	128.0	C-14′	56.2	56.2	52.0	56.4	56.3	C-15	129.4	129.9
C-16	67.7	67.6	67.6	C-15′	53.5	53.5	56.2	54.1	54.0	C-16	59.1	59.0
C-17	36.0	36.0	40.0	C-16′	90.2	90.1	90.4	90.6	90.5	C-17	40.3	41.9
C-18	11.0	11.1	8.6	C-17′	23.6	23.2	23.5	23.5	23.2	C-18	10.5	8.9
C-19	50.7	50.8	52.6	C-18′	7.3	7.2	7.1	7.4	7.2	C-19	49.8[e]	51.4
C-20	44.3	44.5	45.4	C-19′	26.6	26.3	26.5	26.9	26.7	C-20	46.5	47.6
C-21	69.9	70.4	61.5	C-20′	36.5	36.7	37.0	36.6	36.7	C-21	82.0	74.6
NC=O	169.0	169.0	168.7	C-21′	61.5	61.5	70.9	62.2	62.0	OCN	88.1	88.4
C=O	210.0	209.8	208.4	C=O	168.4	168.4	168.6	168.6	168.6	C=O	171.9	171.9
				OMe	50.8	50.8	50.8	50.9	50.9	OMe	51.9	51.7

[a] Chemical shift in ppm from TMS.

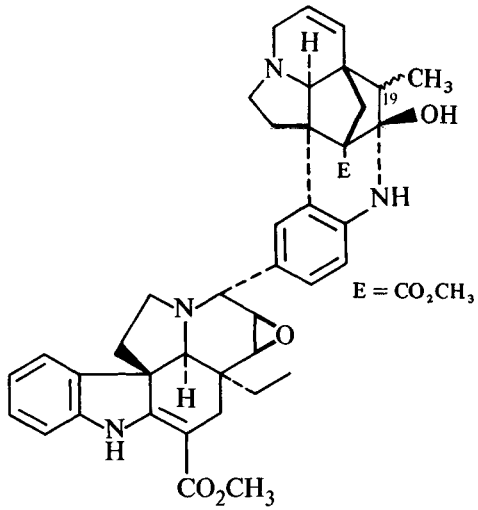
[b] **360** = Meloscandonine; **361** = scandomelonine; **363** = episcandomelonine; **351** = pachysiphine; **365** = scandomeline; **366** = episcandomeline.

[c–f] Signals may be reversed.

A 3′α-pachysiphinyl unit was again deduced from the ^{13}C nmr spectrum with attachment to C-10 of a second unit having a novel skeleton. Some similarities were noted with scandine (**364**), but except for the carbomethoxy group, no other carbonyl carbons were observed and the vinyl group of **364** was replaced by a methyl and a methine. A new quaternary carbon was observed at 88.1 ppm indicating attachment to both nitrogen and oxygen. On this evidence scandomeline was given the structure **365** and episcandomeline the structure **366**.[242]



364



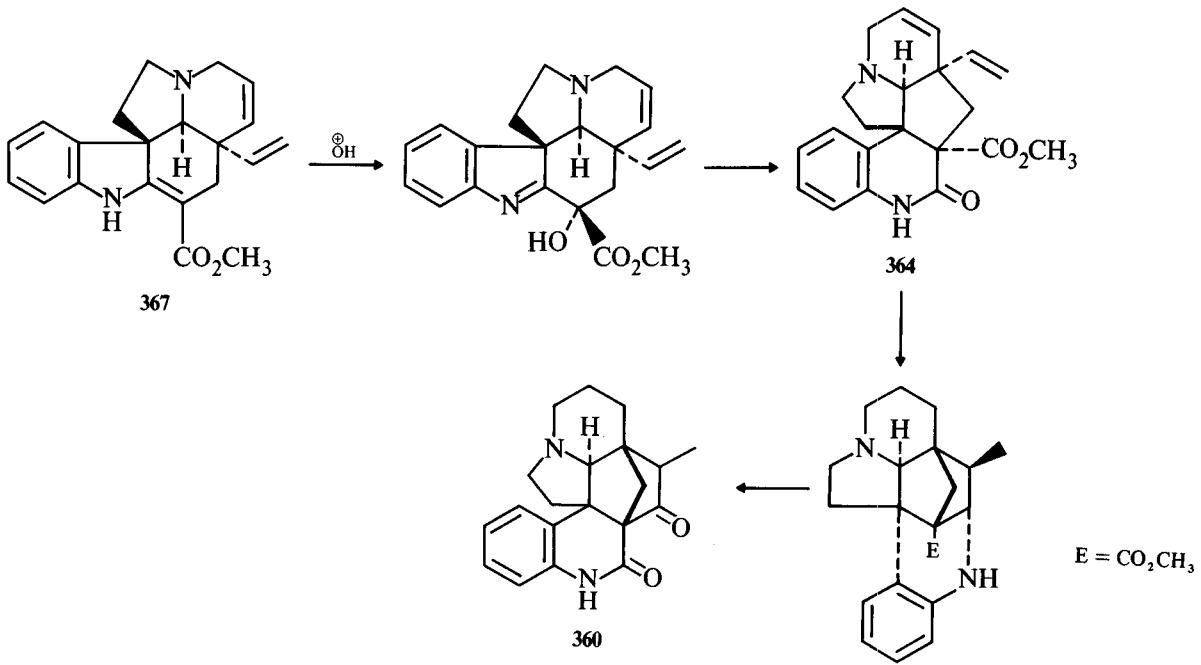
Scandomeline (**365**)
19-Episcandomeline (**366**)

It has been suggested[242] that 18,19-dehydrotabersonine (**367**) is a crucial biogenetic intermediate as shown in Scheme 41. Evidence for the last rearrangement step came when scandomeline (**365**), on heating with acetic anhydride at 100°, afforded scandomelonine (**362**) in 15% yield.

XX. *ASPIDOSPERMA-EBURNEA* TYPE

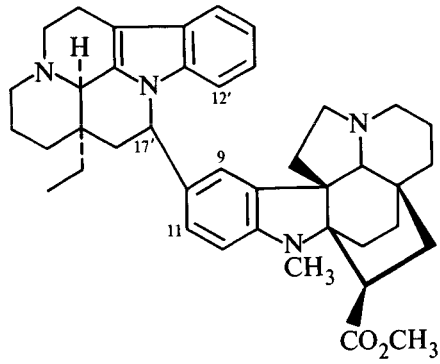
There are three alkaloids in this series, pleiomutine (**368**) from *Pleiocarpa mutica* Benth.,[201,245,246] criophylline (**369**) from *Crioceras dipladeniiflorus* (Stapf) K. Schum.,[247,248] and paucivenine (**370**) from *Melodinus balansae* Baillon var. *paucivenosus* (S. Moore) Boiteau.[249] Interestingly, in each compound the linkage between the two units is quite different.

Pleiomutine, $C_{41}H_{50}N_4O_2$, contained *N*-methyl, carbomethoxyl, and ethyl groups, and the chemical shift of the methyl triplet suggested that the alkaloid might contain an eburnamine (**371**) unit. Similarly, the ions at *m/e* 124 (**282**) and 109 (**372**) with the *N*-methyl and carbomethoxy groups indicated the second component to be pleiocarpinine (**373**), which together with **371** occurs with **368**

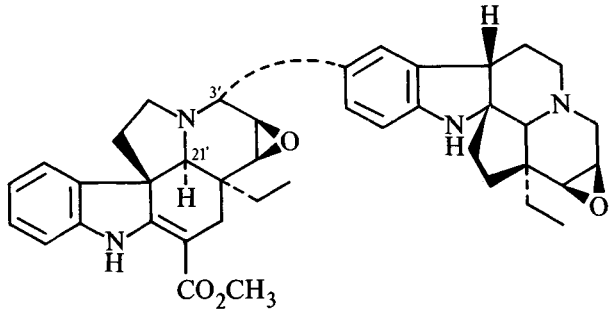


367 364 360

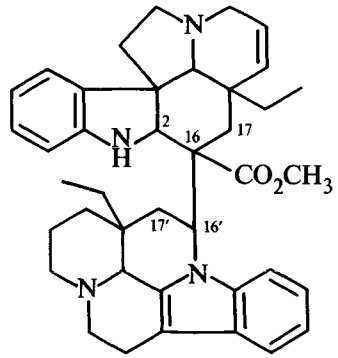
Scheme 41.



Pleiomutine (**368**)



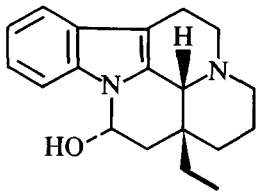
Criophylline (**369**)



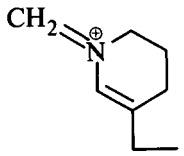
Paucivenine (**370**)

in *P. mutica*. Acid hydrolysis (4*M* HCl at 90°) confirmed the presence of the **373** unit, and in the presence of zinc, 16,17-dihydroeburnamenine (**374**) was obtained.

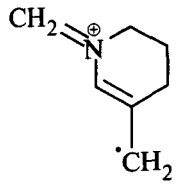
The structural units were firmly established through biomimetic synthesis from (−)-pleiocarpinine (**373**) and (−)-eburnamine (**371**) in cold 1*M* hydrochloric acid.[246] Eburnamenine (**122**) did not react under these conditions, suggesting that



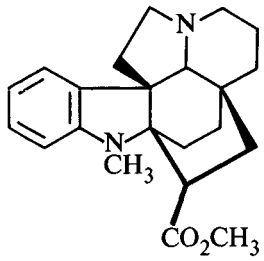
Eburnamine (371)



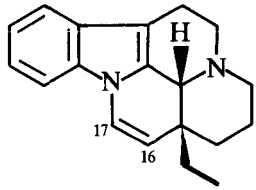
282 *m/e* 124



372 *m/e* 109



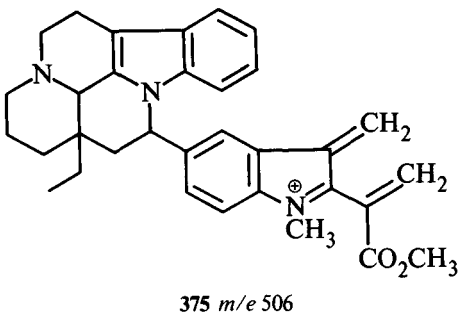
Pleiocarpinine (373)



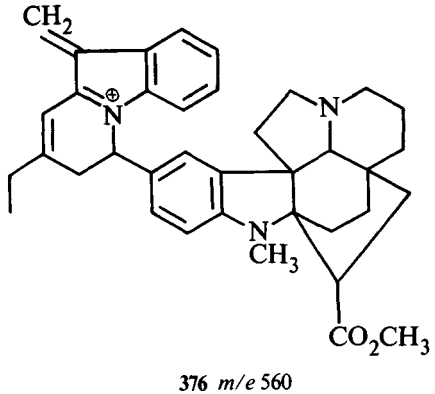
Eburnamenine (122)
16,17-Dihydro- (374)

the linkage of the two units was between C-17 of **371** and either C-10 or C-12 of **373**. Seven aromatic protons were apparent and at 6.27 ppm two overlapping ortho doublets were observed corresponding to the C-12 and C-12′ protons. The linkage is therefore C-10,C-17′ with H-17′ in an axial configuration ($J = 5$, 12 Hz) and pleiomutine has the structure **368**.

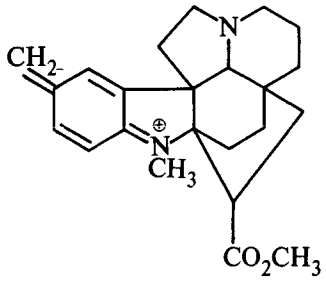
Typical mass fragments were observed at *m/e* 278, 249, and 208 for an eburnamenine unit together with ions at *m/e* 109, 124, and $M^+ - 28$ of the pleiocarpinine moiety. Other important ions are produced by established retro-Diels-Alder reactions in either the *Aspidosperma* unit (ion **375** at *m/e* 506) or *Eburnea* unit (ion **376** at *m/e* 560). Ions at *m/e* 365 (**377**) and 265 (**378**) also substantiate the nature of the linkage.



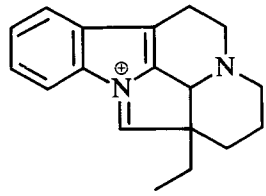
375 *m/e* 506



376 *m/e* 560



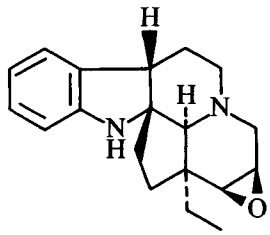
377 *m/e* 365



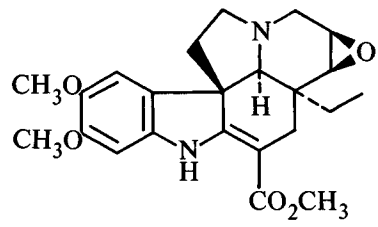
378 *m/e* 265

Criophylline displayed a uv spectrum for the summation of a dihydroindole and a β-anilinoacrylate and the molecular ion at *m/e* 646 ($C_{40}H_{46}N_4O_4$) gave an important ion at *m/e* 436 derived by loss of the unit **299**.[160]

The structure was deduced mainly through interpretation of the ^{13}C nmr spectrum which indicated, in the aliphatic region, two ethyl groups and a carbomethoxy methyl together with eight other methylenes, eight methines, and four quaternary carbons. No olefinic protons were observed and consequently the seven methine protons above 80 ppm should be aromatic in nature. From the large number of aliphatic methines, it appeared that the two remaining oxygen atoms were epoxides. Comparison with the ^{13}C nmr spectra of andrangine (**379**) and hazuntinine (**380**) indicated that similar units were present in criophylline.



Andrangine (**379**)



Hazuntinine (**380**)

Since the aliphatic carbon resonated at the same frequency in andrangine and criophylline, this unit is linked through an aromatic carbon to the aliphatic part of the second unit. In the SFORD spectrum of criophylline, only the methylene groups adjacent to nitrogen were observed and the substantial shift of C-21′ from 70.8 ppm in hazuntinine to 62.0 ppm in criophylline indicated a γ effect due to substitution at either C-3′α or C-5′α. A choice between these two possibilities was made from the downfield shift (β effect) of C-14′ [hazuntinine (51.8 ppm), criophylline (56.8 ppm)], whereas C-6′ was shifted only slightly. Criophylline was therefore suggested to have the structure **369**.[247]

Paucivenine, with a molecular ion at *m/e* 616 ($C_{40}H_{48}N_4O_2$), gave fragment ions at *m/e* 336 and 280, ions at M^+-70 suggested an eburnane skeleton, and at

m/e 109, 121, and 122, an *Aspidosperma* nucleus having a 14,15 double bond.

The uv spectrum indicated both indole and indoline nuclei and therefore the ion at *m/e* 336, thought to be tabersonine (**349**), should involve H migration to the *Eburnea* unit. The absence of an ion derived by loss of C-16 and C-1 from the dihydroindole unit suggested that C-16 or C-17 was involved in the bond between the two units.

The $M^+ - 70$ ion suggests loss of the methylenes 3′, 5′, 14′, and 15′ and the observation of an indolic uv spectrum implies union of the *Eburnea* unit through C-16 or C-17, and the structure **370**, involving a linkage between C-16 and C-16′, was proposed.[249]

XXI. *ASPIDOSPERMA*-PSEUDO-*ASPIDOSPERMA* TYPE

Ervafoline (**381**) is the first member of a new group of bisindole alkaloids from *Ervatamia pandacaqui*[250] and *Stenosolen heterophyllus* (Vahl) Mgf. (Apocynaceae).[251] The structure was deduced by X-ray analysis[251] and substantiated by the ^{13}C nmr spectrum which showed a low-field N-C-O quaternary carbon (C-2) at 103.4 ppm and a deshielded quaternary ether carbon (C-20′) at 87.7 ppm. In the ^1H nmr spectrum, a particularly shielded (to 5.65 ppm) aromatic proton was assigned to H-12 from selective decoupling studies.

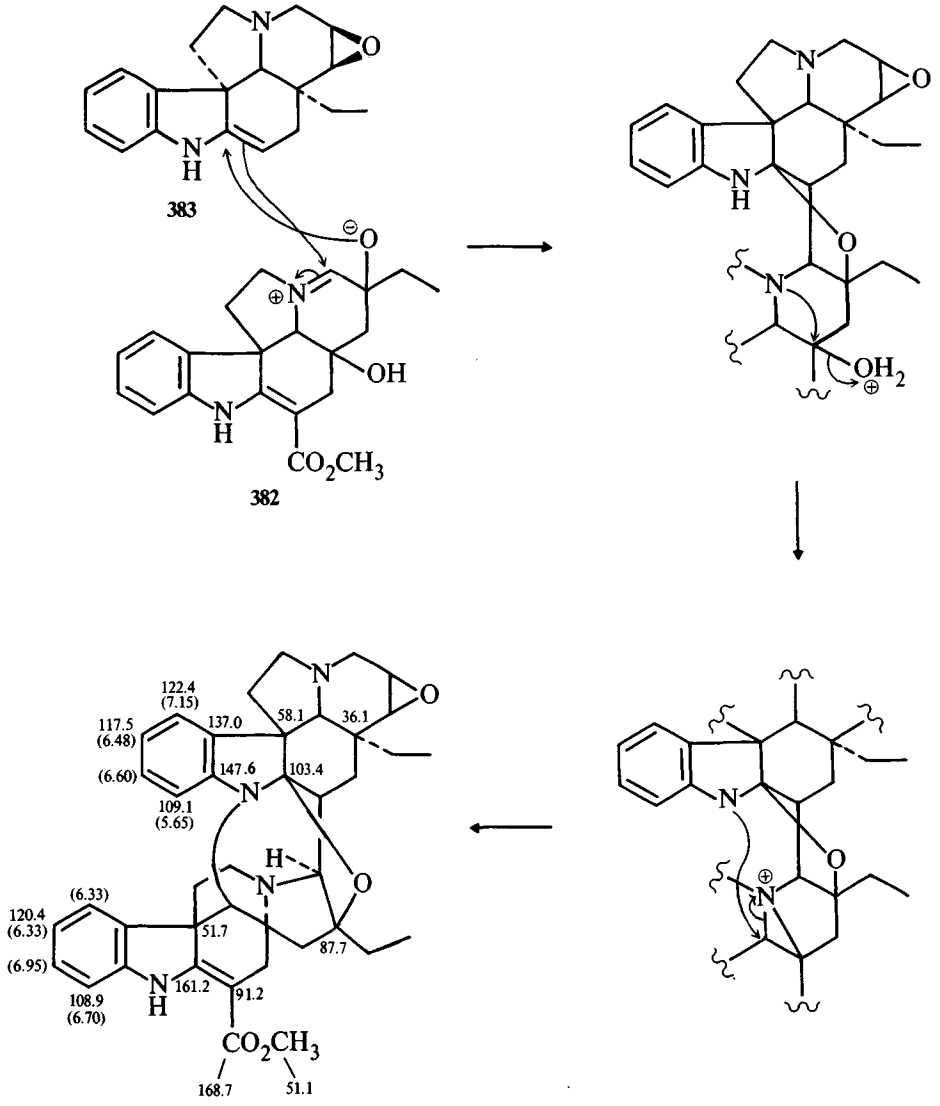
Biogenetically, the alkaloid has been proposed[251] to be derived by the coupling and rearrangement of hydroxypandoline (**382**) and decarbomethoxylochnericine (**383**) units (Scheme 42). This is the only bisindole alkaloid with three bonds between the two units.

Attempts to synthesize this skeleton biomimetically have also begun,[251a] and partial success has been achieved. Condensation of the enamine **383a**, derived from tabersonine (**349**), with the 21-cyano-20-epipandoline (**382a**) gave, in 20% yield, a bisindole suggested to have the structure **381a**. In the ^{13}C nmr spectrum of **381a**, C-2′ appeared at 104.1 ppm.

XXII. *ASPIDOSPERMA*-CLEAVAMINE TYPE

Clinically and commercially, the most important bisindole alkaloids are the antitumor agents vincaleukoblastine (**384**) and leurocristine (**385**) isolated from the leaves of the Madagascan periwinkle, *Catharanthus roseus* (L.) G. Don.* This area of alkaloid chemistry is an extensive one and has been reviewed on many occasions.[15,16,30,254–272a] More alkaloids (over 90) have been isolated from *C. roseus* than any other plant, and it has been the prime focus of biosynthetic studies of the monoterpenoid indole alkaloids.[56] Simultaneously, strenuous efforts have been devoted toward the synthesis of the two component "halves" of the bisindole alkaloids. These massive efforts have now come to a meaningful point from which many new developments may be expected.

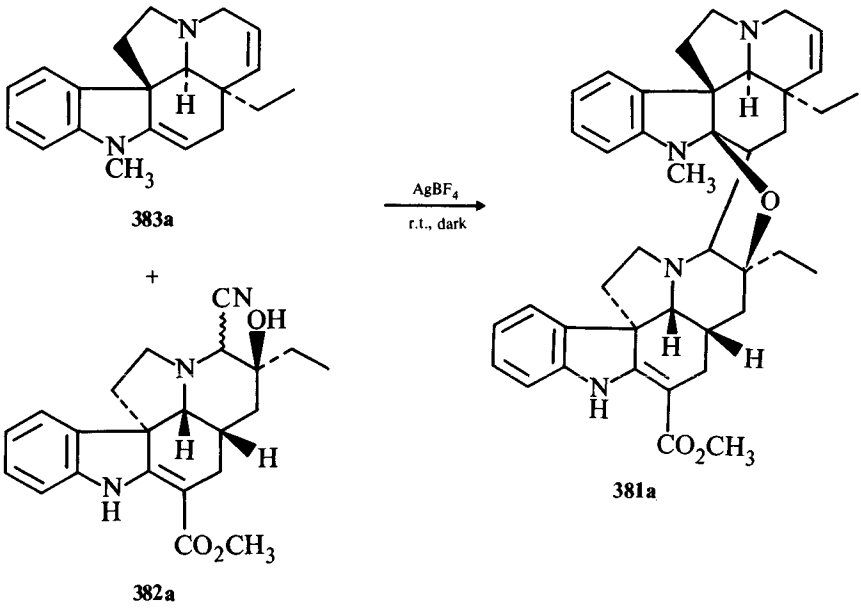
* This plant is occasionally referred to as *Vinca rosea* L. This is erroneous, as Stearn has conclusively demonstrated,[252] for the genera *Vinca* and *Catharanthus* are botanically and chemically quite distinct.[30,253]

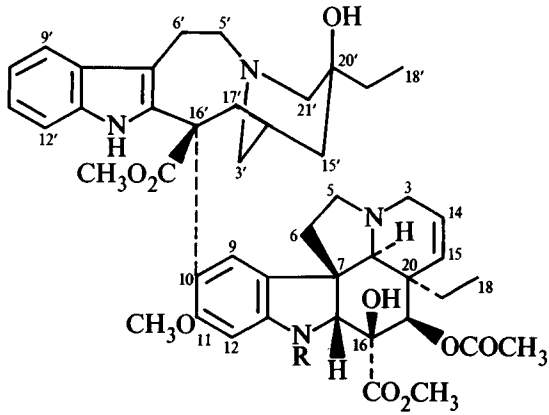


Ervafoline (**381**)

Scheme 42. Biogenesis of ervafoline.

The almost simultaneous discovery of vincaleukoblastine by Noble et al.[273] and by Svoboda and co-workers[274] is now legendary, and has been described succinctly elsewhere.[254,257,269] Continued work by Svoboda led to the isolation of leurocristine[275] and a number of other bisindole alkaloids.[276–280] Table XIX summarizes the isolation of some of the characterized alkaloids.





Vincaleukoblastine (**384**): R = CH_3
(Vinblastine, VLB)

Leurocristine (**385**): R = CHO
(Vincristine, VCR)

Demethylvinblastine (**414**): R = H

B. Structure Elucidation

1. *Vincaleukoblastine and Leurocristine*

Vincaleukoblastine (vinblastine, VLB, $C_{46}H_{58}N_4O_9$) displays, in the uv spectrum, the summation of indole and 6-methoxyindoline chromophores, and its ir spectrum

TABLE XIX. ISOLATION OF BISINDOLE ALKALOIDS OF THE *ASPIDOSPERMA*-CLEAVAMINE TYPE

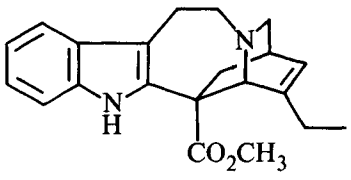
Alkaloid	Source	Ref.
Vincaleukoblastine (384)	*Catharanthus roseus*	273,281–283
	C. ovalis Mgf.	284
	C. longifolius Pich.	285
Leurocristine (385)	*C. roseus*	282
Leurosidine (462)	*C. roseus*	275
Deacetoxyvinblastine (468)	*C. roseus*	286, 287
Leurosine (395)	*C. roseus*	281, 282, 288
	C. ovalis	284
	C. longifolius	285
	C. lanceus (Boj. ex A. DC.) Pich.	289
	C. pusillus (Murr.) G. Don.	290
20′-Deoxyleurosidine, "isoleurosine" (393)	*C. roseus*	291
Pleurosine (396)	*C. roseus*	208, 292
21′-Oxoleurosine (401)	*C. roseus*	293
De-*N*-methylvinblastine (414)	*C. roseus*	294–297
Catharine (402)	*C. roseus*	207, 298
	C. ovalis	284
	C. longifolius	285
Vincathicine (404)	*C. roseus*	299
Vinamidine (406)	*C. roseus*	300
	C. ovalis	301
Leurocolombine (408)	*C. roseus*	300
Pseudovinblastinediol (409)	*C. roseus*	300
Vincadioline (411)	*C. roseus*	302
Vincovaline (413)	*C. ovalis*	303

was found to correspond* closely with the addition of catharanthine (386) and vindoline (284).[257,304] Leurocristine (vincristine, VCR, $C_{46}H_{50}N_4O_{10}$) possessed an indole plus *N*-formyl-6-methoxyindoline chromophore and could be correlated with VLB because their pentahydroxy lithium aluminum hydride reduction products were identical.[305]

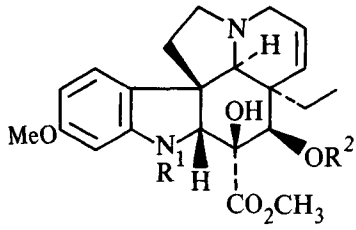
Reductive cleavage (Sn-$SnCl_2$-conc. HCl) afforded the same indolic "half," velbanamine (387), and the indoline "halves" desacetylvindoline (388) and des-*N*-methyldesacetylvindoline (389) from VLB and VCR, respectively.[305] But it was a careful evaluation of the spectroscopic data which led to partial structure proposals for VLB and VCR,[305] taking into account the spectral properties of vindoline and catharanthine.*

Thus the features of aromatic methoxy, indolic NH, two carbomethoxy, two olefinic protons, two methyl triplets, and one acetyl group were present in the spectra of both VLB and VCR. The principal difference was the absence of an *N*-methyl singlet (2.73 ppm) in the nmr spectrum of VCR with an additional low-field *N*-formyl proton at 8.9 ppm.

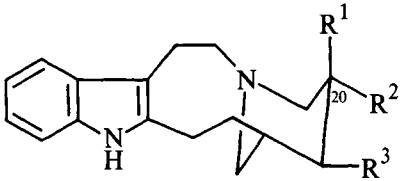
* The structures of these monomeric bases were unknown at this time.



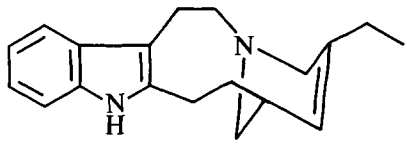
Catharanthine (386)



Vindoline (284): $R^1 = CH_3$, $R^2 = COCH_3$
388: $R^1 = R^2 = H$
389: $R^1 = R^2 = H$



	R^1	R^2	R^3
Velbanamine (387)	OH	C_2H_5	H
Vinrosamine (391)	H	C_2H_5	OH
20α-Dihydrocleavamine (398)	H	C_2H_5	H
20β-Dihydrocleavamine (394)	C_2H_5	H	H



Cleavamine (390)

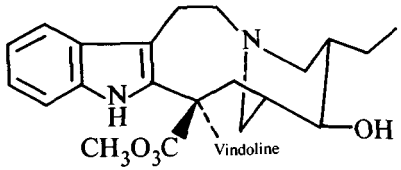
When mass spectrometry was applied to these alkaloids it became apparent that the skeleton of velbanamine, rather than being produced during cleavage from a pentacyclic indole moiety, was actually present in the parent alkaloid. Cleavamine (**390**) is produced in the reductive cleavage of VLB, VCR, and catharanthine.[305]

The nature of the linkage and the linkage to velbanamine were deduced, through deuterium labeling studies, to be between C-16′ and C-10 of the indole and dihydroindole units, respectively.[306] These interpretations were placed on a firm footing when the structure **385** was deduced for leurocristine through X-ray analysis of its methiodide derivative.[307]

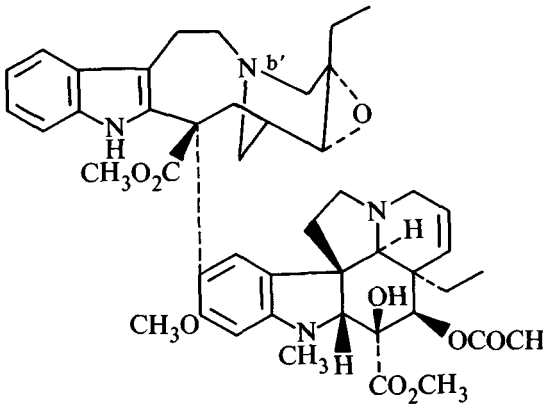
2. *Leurosidine and Leurosine*

Leurosidine ($C_{46}H_{58}N_4O_9$) was found to be an isomer of VLB and reductive cleavage afforded desacetylvindoline (**388**) and cleavamine (**390**) together with vinrosamine (**391**), which was deduced to be an isomer of velbanamine.[308] Leurosidine was therefore assigned the structure **392**, which was subsequently[309] revised.

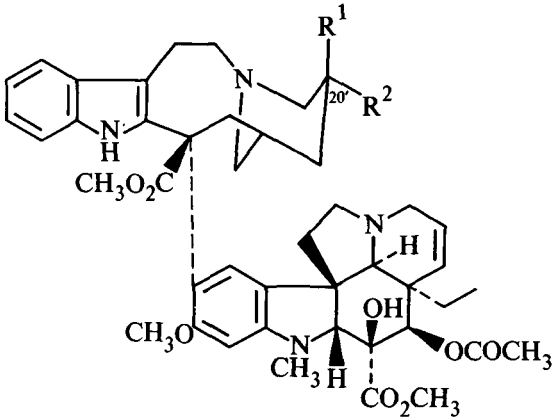
Leurosine as the free base ($C_{46}H_{56}N_4O_9$) is probably the most unstable of these alkaloids. It contains an ether linkage (no additional hydroxy or carbonyl group) and on treatment with Raney nickel it afforded 20′-deoxyvinblastine B (20′-deoxyleurosidine) (**393**).[291] Cleavage of the deacetylhydrazide derivative of this base then yielded 20β-dihydrocleavamine (**394**).[291]



Leurosidine (incorrect) (**392**)



Leurosine (**395**)
Pleurosine $N_{b'}$-oxide (**396**)



20′-Deoxyvinblastine B (**393**): $R^1 = C_2H_5$, $R^2 = H$
Isoleurosine (**399**): $R^1 = H$, $R^2 = C_2H_5$
Leurosidine (**462**): $R^1 = C_2H_5$, $R^2 = OH$

The ^1H nmr data firmly established the vindoline unit and the nature of the linkage and an ion at *m/e* 152 ($C_9H_{14}NO$) was suggested[310] to have an epoxy group. This possibility was substantiated by a doublet ($J = 4.1$ Hz) at 3.1 ppm attributed to H-15′ coupling with H-14′.

Although leurosine was assigned a partial structure by Neuss et al.,[291] Abraham and Farnsworth,[310] through an extensive examination of the fragment ions, refined the structure to **395**. Pleurosine, which afforded leurosine on zinc-acetic acid[208,291] reduction, is leurosine N_b'-oxide (**396**).

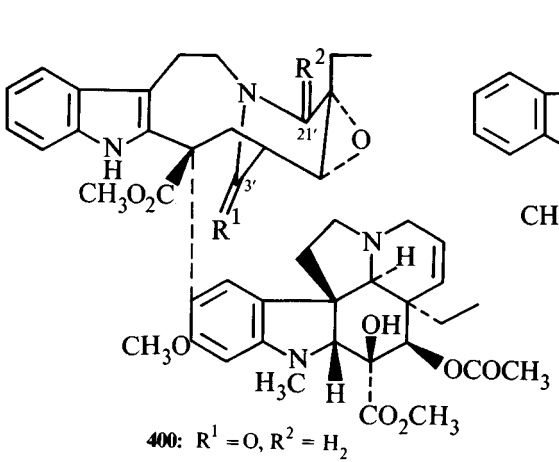
Confirmation of these structural assignments came from the ^{13}C nmr spectrum of leurosine[309,311] (Table XX, below) and from the structure* of **397**, an acid rearrangement product,[309] and an isolate from *C. roseus* alkaloid fractions.[312] The mechanism postulated for the formation of this compound (Scheme 43) would not be expected if the 15′,20′-epoxide had the opposite configuration.

"Isoleurosine" ($C_{46}H_{58}N_4O_8$) was obtained as a contaminant of leurosine, and the structure was apparent from the characteristic vindoline proton singlets and from reductive cleavage of the hydrazide, which gave 20α-dihydrocleavamine (**398**). The compound is therefore 20′-deoxyvinblastine (**399**).[291]

Oxidation of leurosine with iodine/sodium bicarbonate affords the 3′-lactam (**400**)[313] and it was originally thought that oxidation with oxygen/trifluoroacetic anhydride afforded the 21′-lactam (**401**). This product was subsequently[298] identified with catharine (**402**), also obtained from *Catharanthus*,[207,284,285,314,315] whose structure had been established through X-ray analysis.[316,317] In trifluoroacetic anhydride catharine undergoes fragmentation to yield vindoline and the pentacyclic product **403** after reduction[317] (Scheme 44). More recently[293] the 21′-lactam (**401**) has been obtained from alkaloid fractions of *C. roseus*.

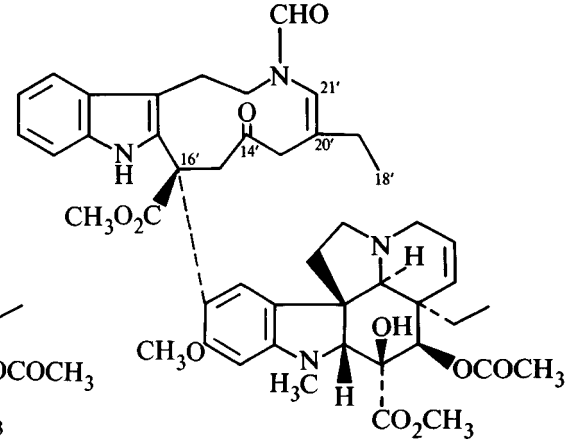
3. *Other Alkaloids*

Vincathicine ($C_{46}H_{56}N_4O_9$) from *C. roseus*[299] is also a product of the acid treatment of leurosine (**395**) and on the basis of spectral evidence was assigned the structure **404**,[318,319] in which the epoxide has been attacked by the nucleophilic C-7′ center, and the intermediate deprotonated (Scheme 43). Of the two possible structures, due to attack at either C-15′ or C-20′, the former was chosen,[318] mainly on the basis of the ^{13}C nmr shifts of these carbon atoms.



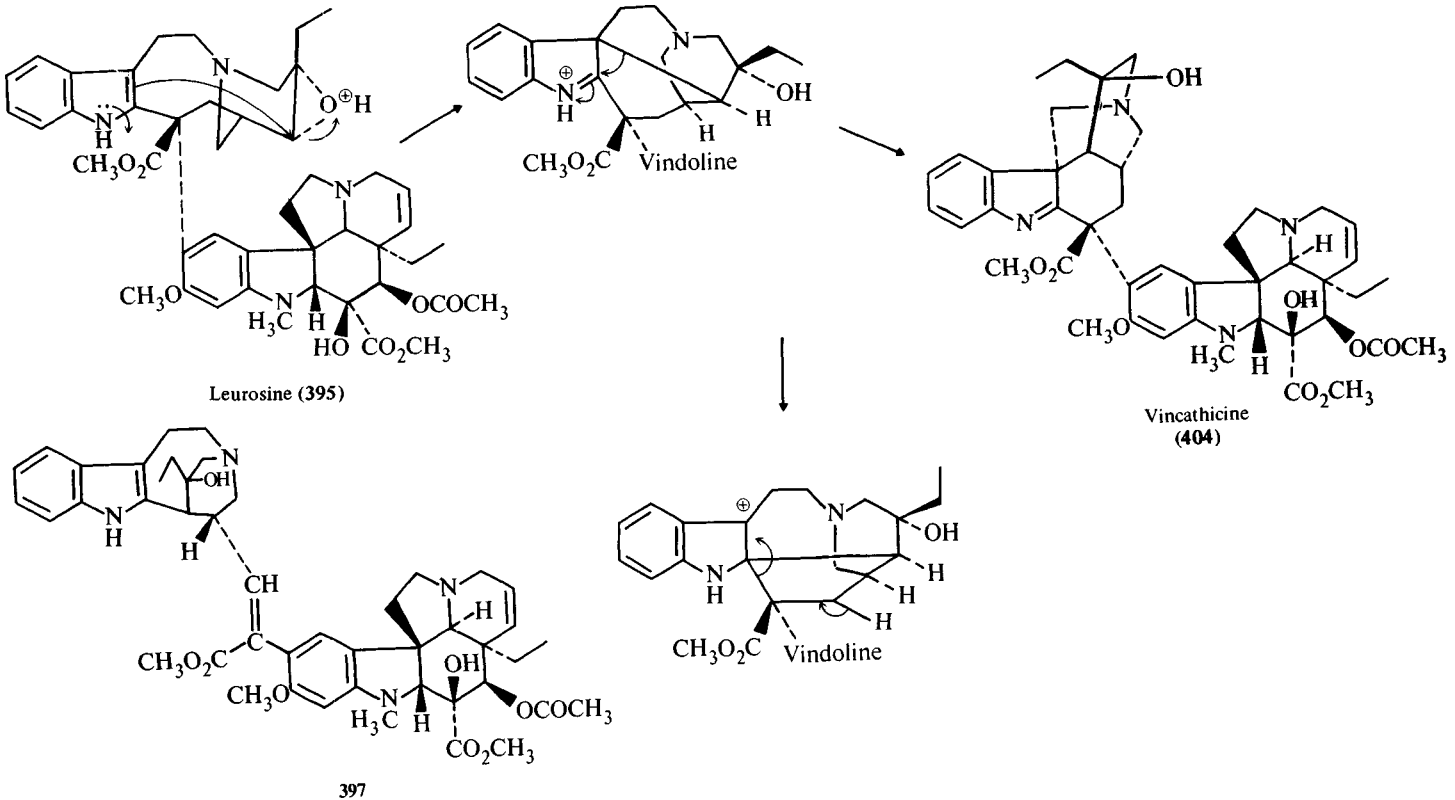
400: $R^1 = O$, $R^2 = H_2$

401: $R^1 = H_2$, $R^2 = O$

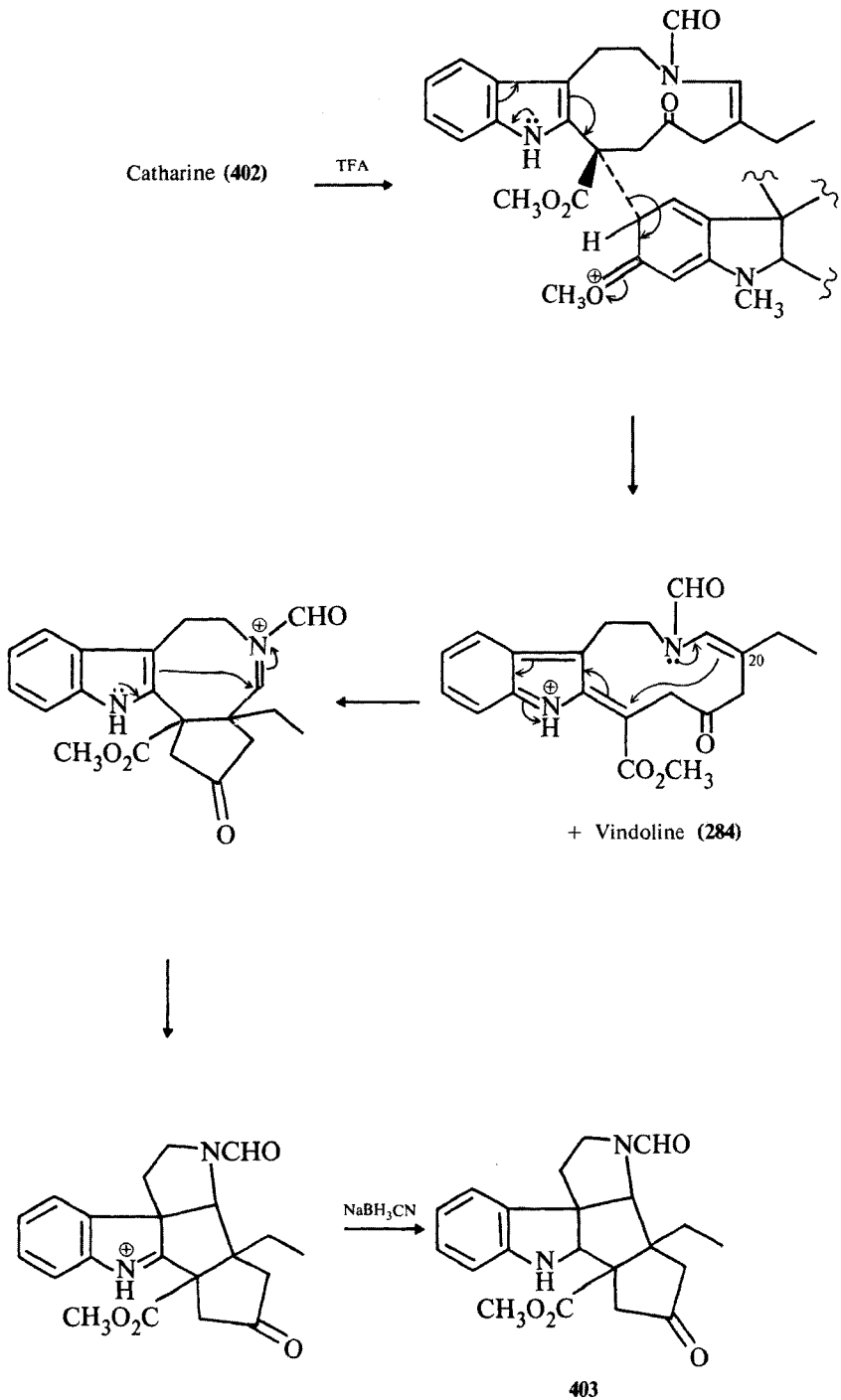


Catharine (**402**)

* The methyl group in the indole "half" is exceptionally shielded to −0.16 ppm[309,312] owing to proximity with the indole nucleus.

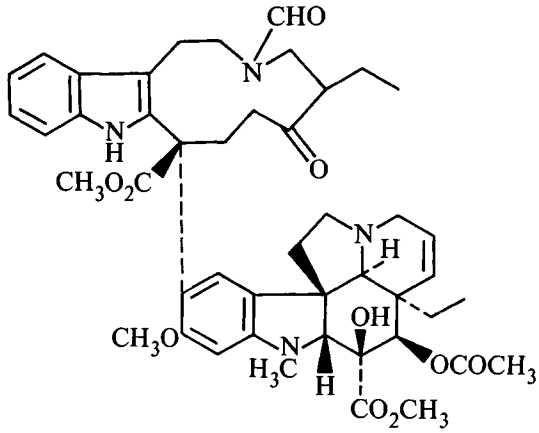


Scheme 43.

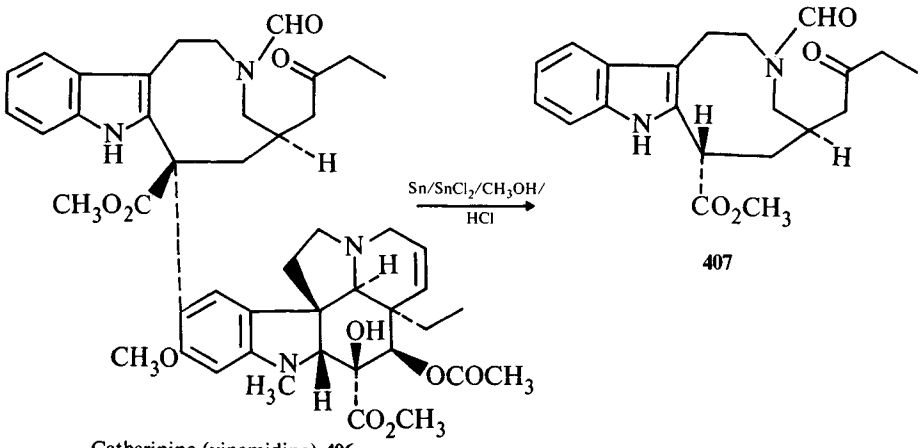

Catharine (402)
TFA
CHO
N
O
N
H
CH3O2C
H
CH3O
N
CH3
CHO
N
20
N
H
O
CO2CH3
+ Vindoline (284)
CHO
N
N
H
CH3O2C
O
NCHO
NaBH3CN
N
H
CH3O2C
O
403

Scheme 44.

Vinamidine ($C_{46}H_{56}N_4O_{10}$) was originally obtained from *C. roseus*, and subsequently as catharinine from *C. longifolius*[320] and *C. ovalis*.[301] Initially, the alkaloid was assigned the structure **405**,[300] but this was recently revised to **406**.[301] Structure **405** is the equivalent of a dihydrocatharine, but authentic dihydrocatharine on sodium borohydride reduction lactonized, whereas catharinine under similar conditions did not. Of the potential schemes available, the favored route of formation is thought to be that shown in Scheme 45, based on a reductive ($Sn/SnCl_2$/MeOH/HCl) cleavage and X-ray analysis of the indole derivative **407**.[301]



405

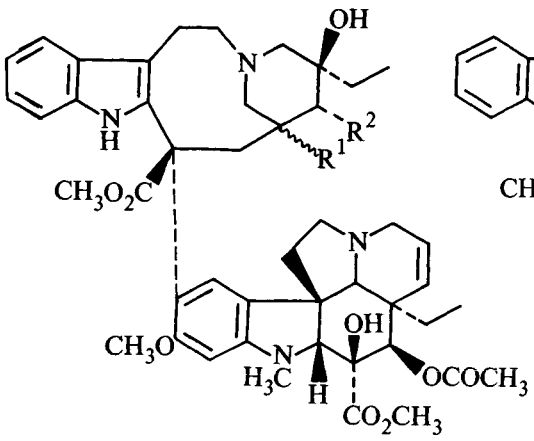


407

Catharinine (vinamidine) **406**

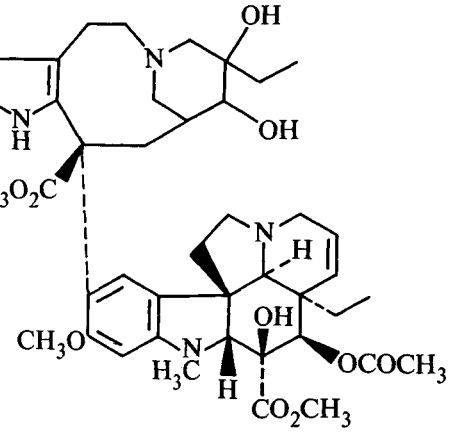
Scheme 45.

Leurocolombine, pseudovinblastinediol, and vincadioline contain an additional hydroxy group in the velbanamine moiety. The structure of leurocolombine (**408**, $C_{46}H_{58}N_4O_{10}$) from *C. roseus* was established mainly on the basis of mass and ^{13}C nmr spectral evidence.[300] All the characteristic peaks were observed for a 10-substituted vindoline fragment and the indole nucleus. The aliphatic unit of the

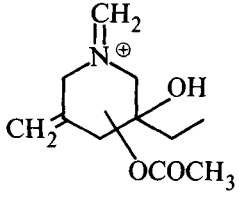


Leurocolombine (**408**): R^1 = OH, R^2 = H

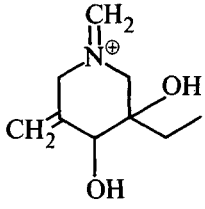
Vincadioline (**411**): R^1 = H, R^2 = OH



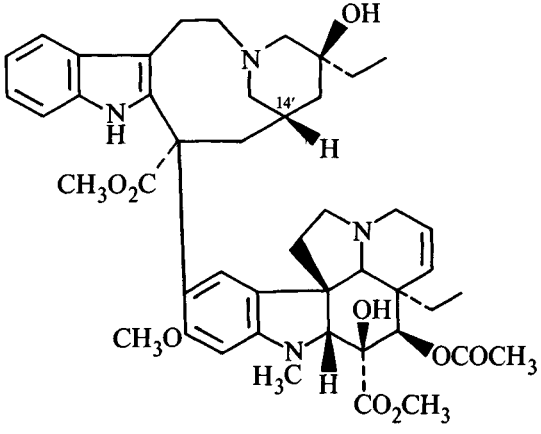
409



410 *m/e* 212



412 *m/e* 170



Vincovaline (**413**)

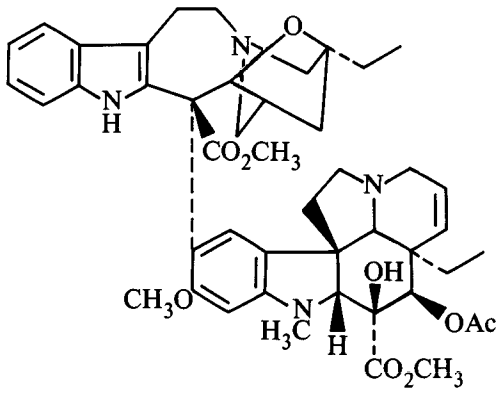
velbanamine moiety indicated three quaternary carbons, two of which could be readily assigned (by similarity to VLB) to C-16′ and C-20′. Because a methine doublet for C-14′ was absent, it was considered that the additional oxgyen was located at this position.

Pseudovinblastine diol (**409**, $C_{44}H_{56}N_4O_8$) is isomeric with deacetylvinblastine, but the characteristic vindoline ions at *m/e* 282 and 469 are shifted by 58 m.u. On the other hand, the velbanamine unit ions at *m/e* 154 and 355 are shifted by 16 m.u. to *m/e* 170 and 371, and *m/e* 212 (**410**) and 413 in the acetate derivative. Note that the ion *m/e* 212 offers direct proof of the location of the hydroxy group at either C-3′ or C-15′.

Vincadioline (**411**) is 15′α-hydroxy VLB displaying an important ion at *m/e* 170 (**412**) and a hydroxymethine proton at 3.84 ppm, shifting to 4.48 ppm on acetylation. The rationale for the stereochemistry at C-15′ is less clear.[302]

Vincovaline (**413**) from *C. ovalis*[303] is an isomer of vinblastine, and the ^{1}H nmr spectrum indicates that one of the C-18 methyl groups is substantially shifted. Only a monoacetate (at C-16) is produced, suggesting that C-20′ has the same configuration as in VLB. When the cd spectrum was compared with synthetic bisindoles epimeric at carbons 14′ and 16′, it became apparent that vincovaline has the 16′*R*/14′*S* configuration. Vincovalinine ($C_{44}H_{54}N_4O_7$) and vincovalicine ($C_{44}H_{54}N_4O_{10}$) are related alkaloids in this series, whose structures remain to be firmly established.[303]

Catharanthamine (**413a**) from *C. roseus*[303a] apparently possesses a novel ether linkage between C-17′ and C-20′, as evidenced by the ^{13}C nmr spectrum.



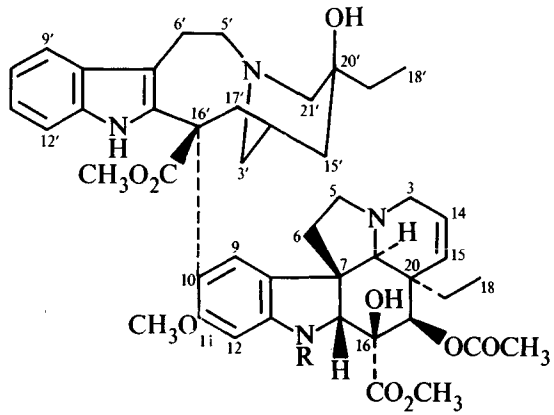
Catharanthamine (**413a**)

B. Synthesis

1. *Partial Synthesis*

The higher yield of VLB from the plant has led to the development of methods to convert VLB to VCR[321-323] where chromic acid at low temperature (−60°) is

the reagent of choice. Because some demethylation also occurs, formylation of the crude reaction product improves the yield. An alternative chemical method[324] involves oxidation of VLB sulfate in formic acid with molecular oxygen in the presence of palladized carbon.

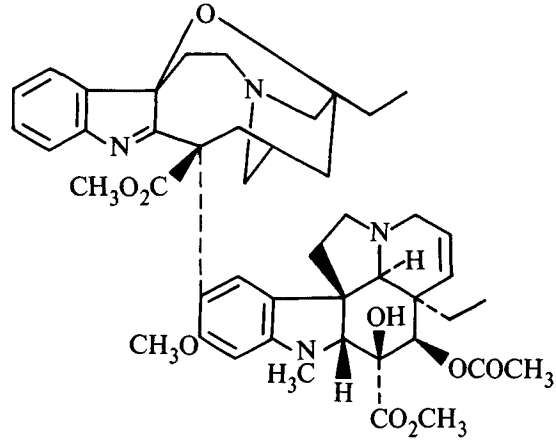


Vincaleukoblastine (**384**): R = CH_3
(Vinblastine, VLB)

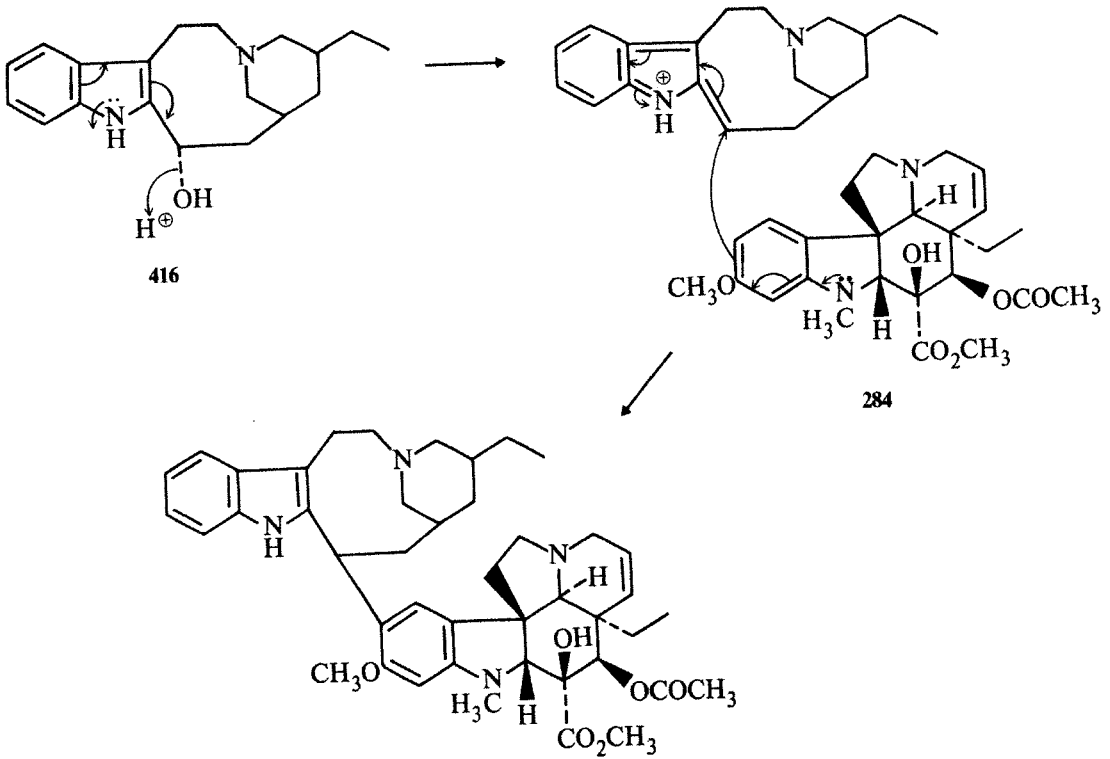
Leurocristine (**385**): R = CHO
(Vincristine, VCR)

Demethylvinblastine (**414**): R = H

Microbial transformation has also been used to remove the N_a-methyl group of VLB, subsequent to success being achieved with vindoline (**284**).[325] After 6 days of fermentation with *Streptomyces albogriseolus* (A17178), one of the products was N_a-demethylvinblastine (**414**),[326] a natural product,[294,296] together with several other metabolites including the indolenine-ether **415**. *Streptomyces panipalus* (A36120) afforded only a 10′-hydroxylated product,[326] and a similar observation was made by Schaumberg and Rosazza,[326a] who studied the microbial transformation of leurosine (**395**) by *Streptomyces griseus* (UI 1158).



415



416 284 417

Scheme 46.

2. *Total Synthesis*

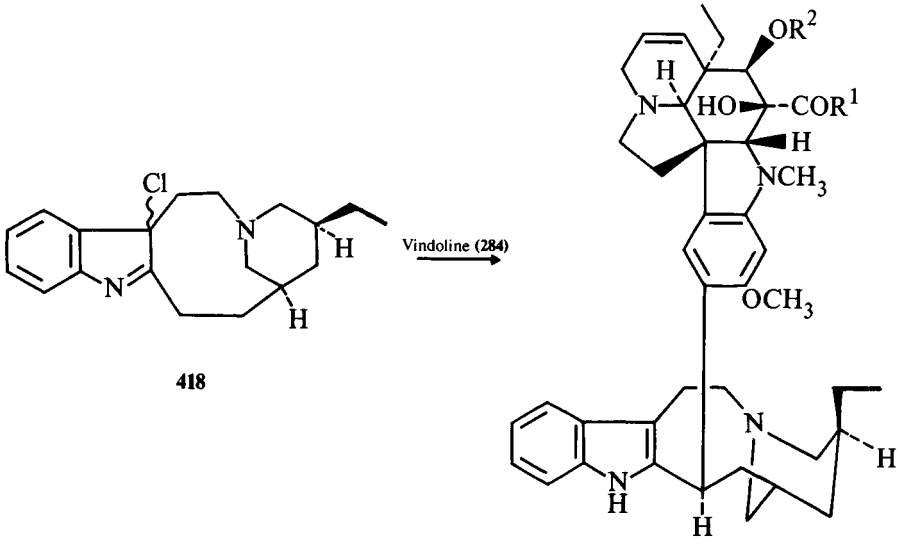
Since the early 1960s intensive efforts have been made to synthesize the most important members of this series, with the clear aim being to link the 10-position of vindoline with an appropriate indole component stereospecifically at the C-16 position.

Two approaches to this condensation have been generally successful, the chloroindolenine approach and the modified Polonovski reaction. As it transpired, carefully controlled conditions were required for obtaining a stereoselective reaction at C-16′.

The first report of a method to link C-10 with C-16′ came in 1967,[327] through the reaction of 16-hydroxydihydrocleavamine (**416**) with vindoline (**284**) in cold 1% methanolic hydrogen chloride to afford 16′-decarbomethoxy-20′-deoxyvinblastine (**417**) as a mixture of the diastereoisomers (Scheme 46).[327a] This was followed[291] by a successful application of the chloroindolenine approach when **418** was condensed in acid with desacetylvindoline hydrazide to afford **419**, having the unnatural configuration at C-16′ (Scheme 47). A similar result was obtained by Kutney et al.,[328] who reported the synthesis of the hydrazide **419** and the related derivative **420**. Condensation of **421** from 16-carbomethoxy-20β-dihydrocleavamine (**422**) with a variety of vindoline derivatives afforded **423**, **424**, and **425** (Scheme 48). The structures of these compounds were established by the ir and nmr spectra and degradation,[328,329] and X-ray analysis revealed the 16′-epimeric nature of **423**.[320] Extensive experimentation with the chloroindolenine approach failed to yield compounds in the C-16′ natural series, but conditions were found which afforded **423** in almost quantitative yield.[329]

The C-16′ epimer of anhydrovinblastine, that is, **426**, was also synthesized by this approach[331] and its stereochemistry established[330] by correlation with **423**. Coupling of the chloroindolenine from cleavamine (**390**) with vindoline (**284**) afforded the 16′-decarbomethoxy compound **427**,[332] where the characteristic chemical shifts were observed for C-3′ and C-6′ corresponding to the 16α-substituted cleavamine series (Scheme 49).

In summary, the chloroindolenine approach, like acid catalysis, leads to coupling between a cleavamine derivative and vindoline, but unfortunately the C-16′ stereochemistry is *invariably* the unnatural one unless C-14′ is inverted. A different approach was therefore required, and it was Potier and co-workers who first reported[333,334] success in this area with the modified Polonovski reaction.[335] Soon afterward, Kutney et al. reported[336,337] their results using a very similar approach. The concept is to provide a leaving group at N_b' in a *catharanthine* derivative which will induce nucleophilic attack at C-16 with fragmentation of the 16,21 bond. Indeed, treatment of catharanthine *N*-oxide (**428**) with vindoline in the presence of trifluoroacetic anhydride, followed by sodium borohydride reduction, afforded anhydrovinblastine as a mixture of 16′ epimers,[332–334] in which as much as 50% of the natural epimer **429** was produced under optimum conditions (Scheme 50).[334] The configuration was established through dehydration of vinblastine (**384**) with sulfuric acid to give **431** and by the cd spectrum of the synthetic product. It is



418

419: $R^1 = NHNH_2$, $R^2 = H$

420: $R^1 = OCH_3$, $R^2 = COCH_3$

Scheme 47.

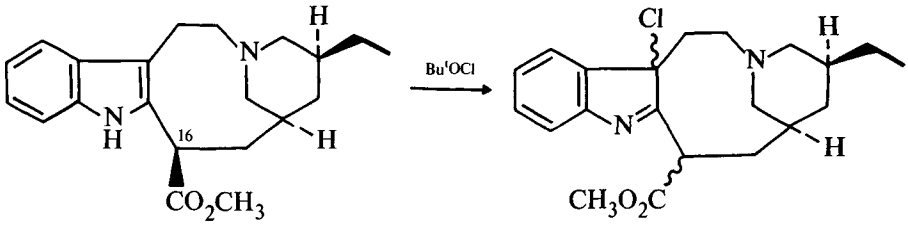
pertinent to note that C-14′ epimerization does not take place in the postulated intermediate immonium ion **430**.

The yields and relative proportions of the two epimers **426** and **429** depend on the precise experimental conditions and indicate that two mechanisms may be in operation, one in which **429** may be the result of a concerted fragmentation coupling process, whereas **426** may result from a nonconcerted process. Although initially portrayed as relatively clear-cut reactions, it has become apparent that they are in fact complex, and a variety of other products may also be formed.

In the discussion of the chemistry of catharanthine (Chapter X), it was described how the 5,6 bond is also antiparallel to the N_b-oxygen bond in catharanthine *N*-oxide, and that fragmentation of this bond leads to an intermediate ion which may suffer nucleophilic attack at either C-6 or C-5. When vindoline is the nucleophile the compound **432** results (Scheme 51).[334]

At −50° Kutney et al. did not observe the formation of the C-16′ epimer in the condensation of catharanthine *N*-oxide (**428**) and vindoline (**284**), but in refluxing dichloromethane (61°) **426** was obtained in 34% yield. This may be explained either in terms of an initial immonium species "frozen" in its initial conformation or as a concerted attack at C-16′. At higher temperatures **430** may undergo a conformational change, such that **433**, in which the α face is more accessible, has the higher conformer population.[337] Exclusion of air is important, for in its presence the carbinolamine **434** is produced, from which anhydrovinblastine (**429**) could be obtained through mild reduction (Sn/HCl).

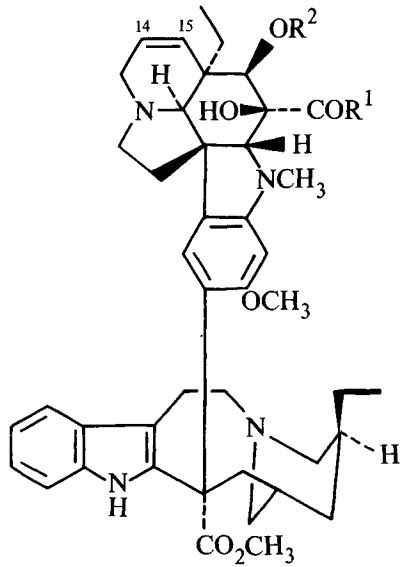
Additional evidence for at least the partial involvement of a concerted mechanism



16β-Carbomethoxy-
20β-dihydrocleavamine (**422**)

421

Vindoline (**284**)



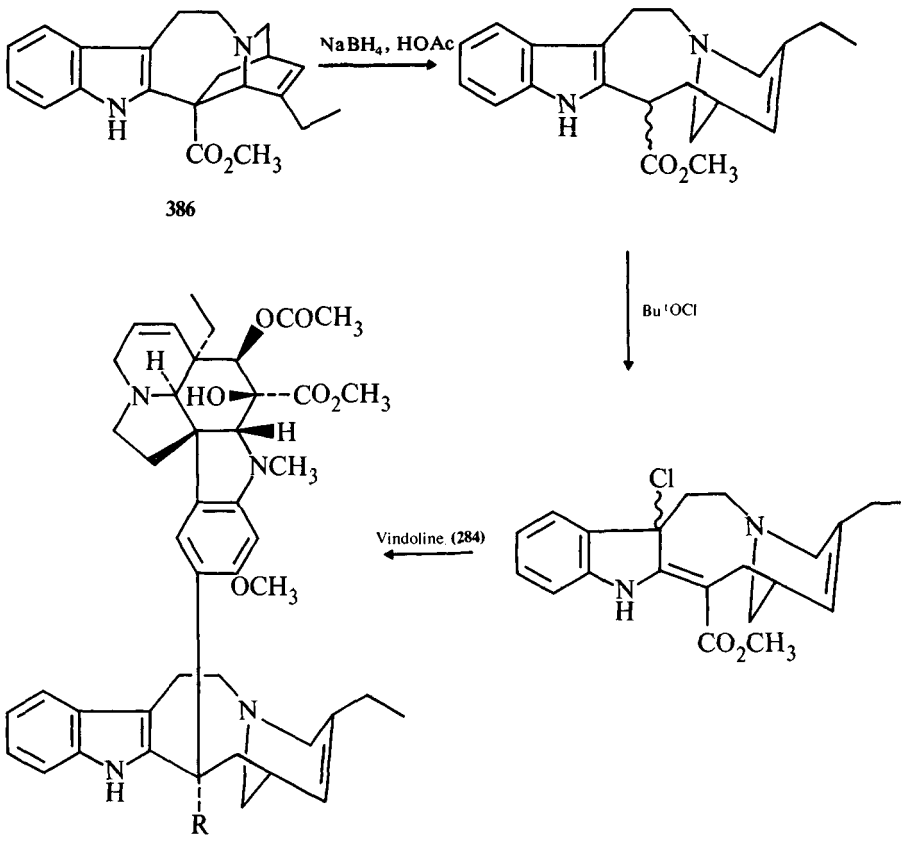
423: $R^1 = OCH_3$, $R^2 = COCH_3$

424: $R^1 = OCH_3$, $R^2 = COCH_3$, 14,15-dihydro-

425: $R^1 = NHNH_2$, $R^2 = H$

Scheme 48.

may come from the coupling of vindoline (**284**) and 15,20*S*-dihydrocatharanthine *N*-oxide (**435**), for Potier et al. obtained only three deoxyvinblastine isomers, **393**, **436**, and **437**, but none of the remaining isomer **399** in the natural series (Scheme 52). The formation of both **436** and **437** with the 16′*R* configuration requires the intermediacy of the immonium ion **438** which can epimerize at C-20 via the enamine **440**.[334] On the other hand, at −10°, Kutney et al. observed all four stereoisomers (**393**, **399**, **436**, and **437**), but at −50° only the two natural (from cd data) epimers (**393** and **399**) were obtained, although the stereochemistry at C-20′ in **399** is somewhat uncertain.[337]



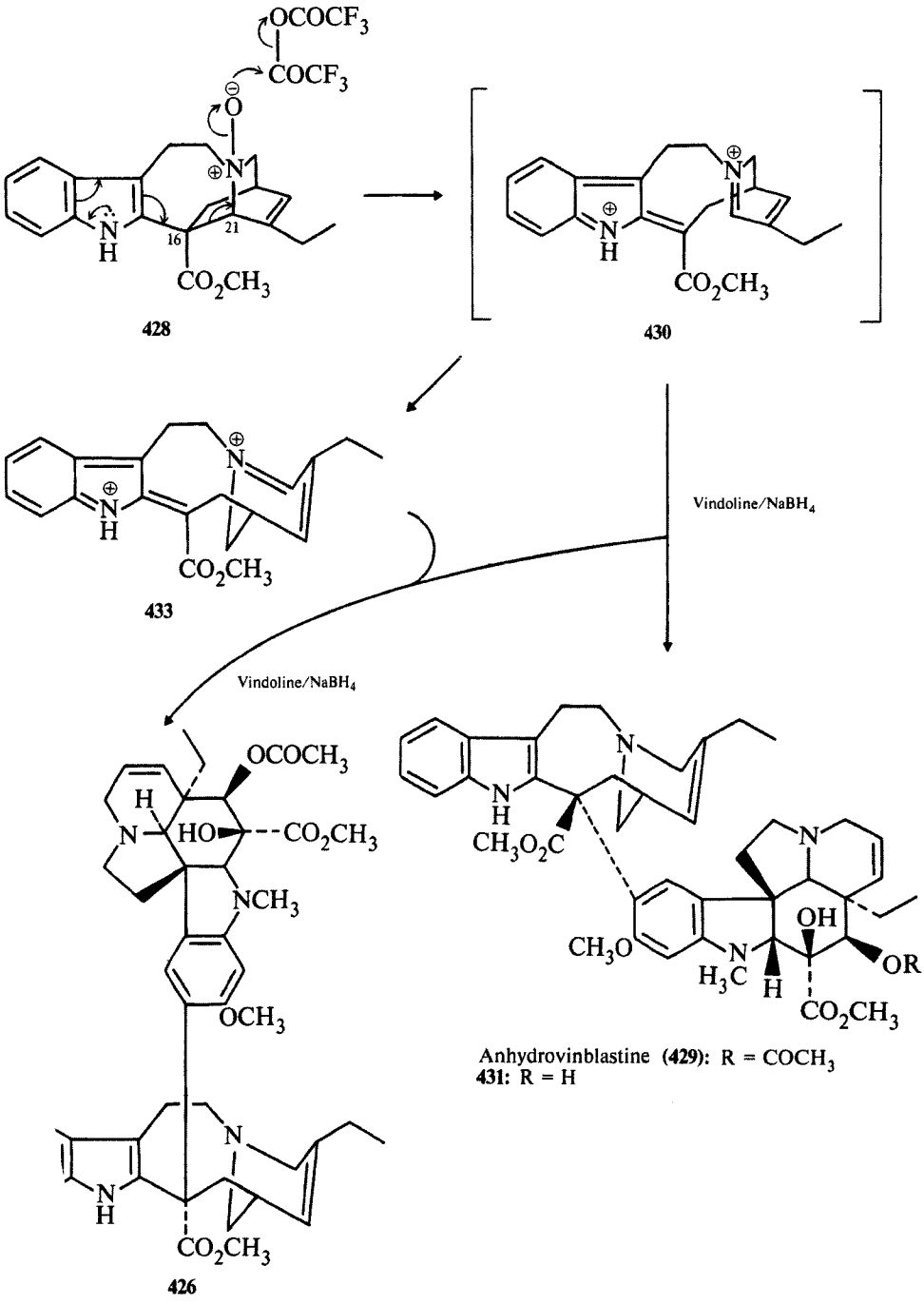
386

426: R = CO_2CH_3
427: R = H

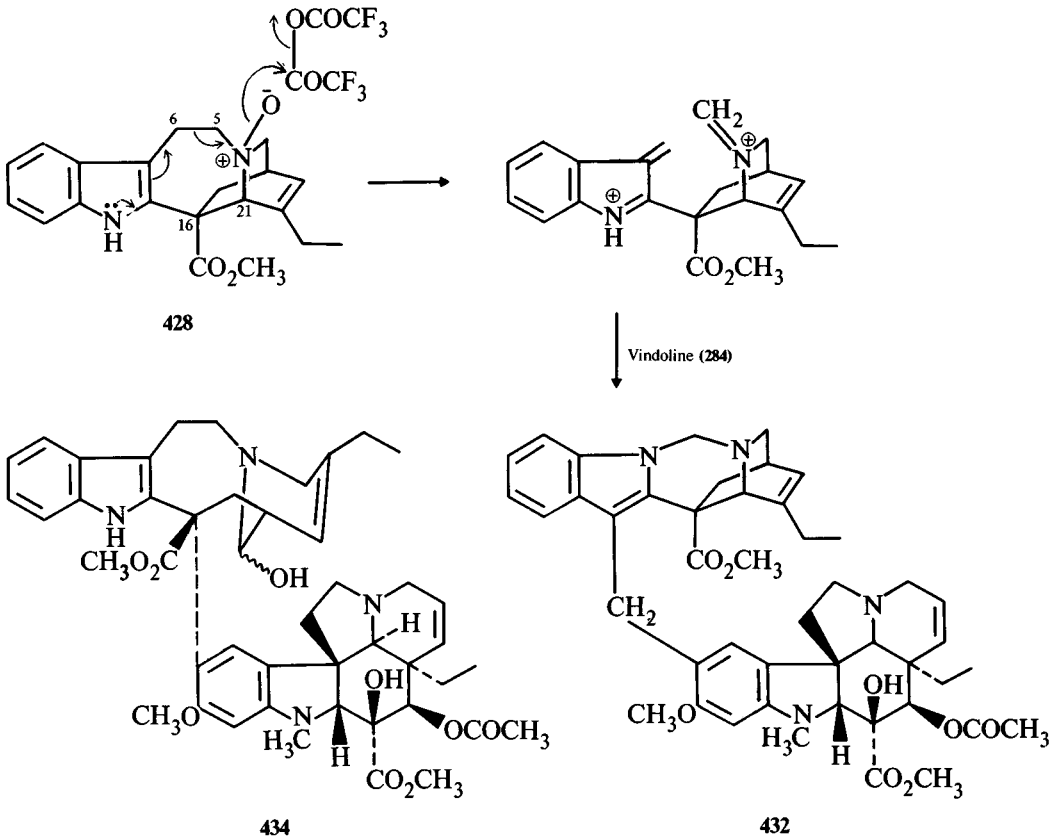
Scheme 49.

Coupling of decarbomethoxycatharanthine *N*-oxide (**441**) with vindoline (**284**) gave **442** as the major product,[338] and the expected products **443** and **444** only in low yield (Scheme 53).[337] A new synthesis of 15′,20′-anhydrovinblastine (**429**) involves a coupling of the N_b-oxide of 15*R*-acetoxy-15,20*S*-dihydrocatharanthine (**444a**) with vindoline (**284**),[338a] in which there is a loss of acetate from the intermediate **444b** (Scheme 54).

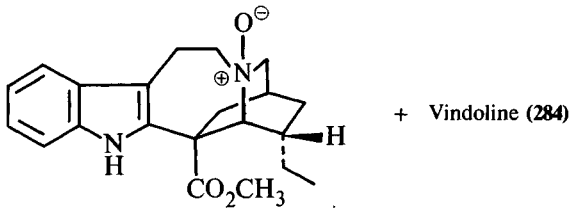
After the establishment of the basic coupling reaction through the modified Polonovski reaction, additional ingenious modifications have succeeded in producing many of the previously discussed natural products. When 15′,20′-anhydro vinblastine (**429**) became available, attempts were made to transform this to leurosine (**395**). Several methods are now available for carrying out this reaction, including *t*-butyl hydroperoxide/trifluoroacetic acid (58%),[339,340] mercuric acetate followed by sodium borohydride (62%),[339] *p*-nitroperbenzoic acid/HMPA followed by zinc/acetic acid (27%),[340] and lead tetraacetate.[341] Aerial oxygen is also suf-


OCOCF3
COCF3
O
N
H
16
21
CO2CH3
428
430
433
Vindoline/NaBH4
Vindoline/NaBH4
OCOCH3
HO
CO2CH3
NCH3
OCH3
426
CH3O2C
CH3O
H3C
OH
OR
Anhydrovinblastine (429): R = COCH3
431: R = H

Scheme 50.


OCOCF3
COCF3
O
6
5
N
H
16
21
CO2CH3
428
CH2
N
H
CO2CH3
Vindoline (284)
CH3O2C
OH
N
H
CH3O
N
H3C
H
OCOCH3
CO2CH3
434
CH2
432

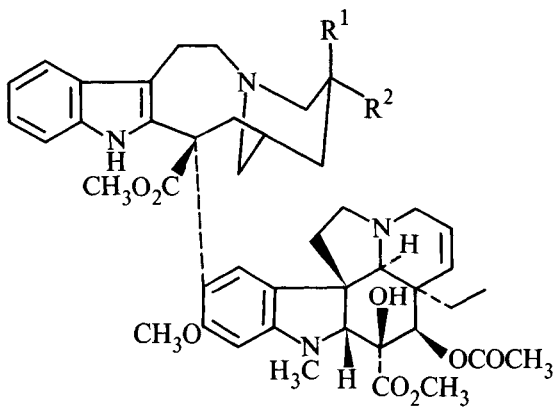
Scheme 51.



435

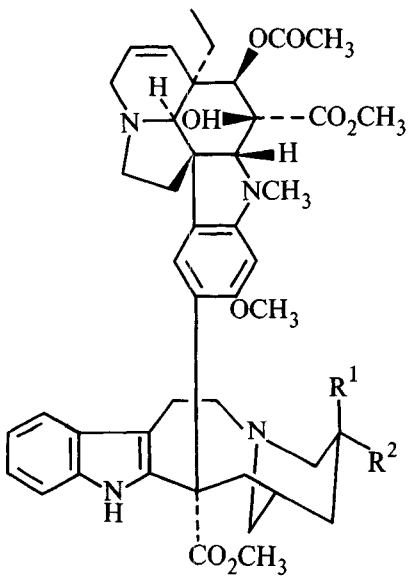
+ Vindoline (**284**)

1. $(CF_3CO)_2O$
2. $NaBH_4$



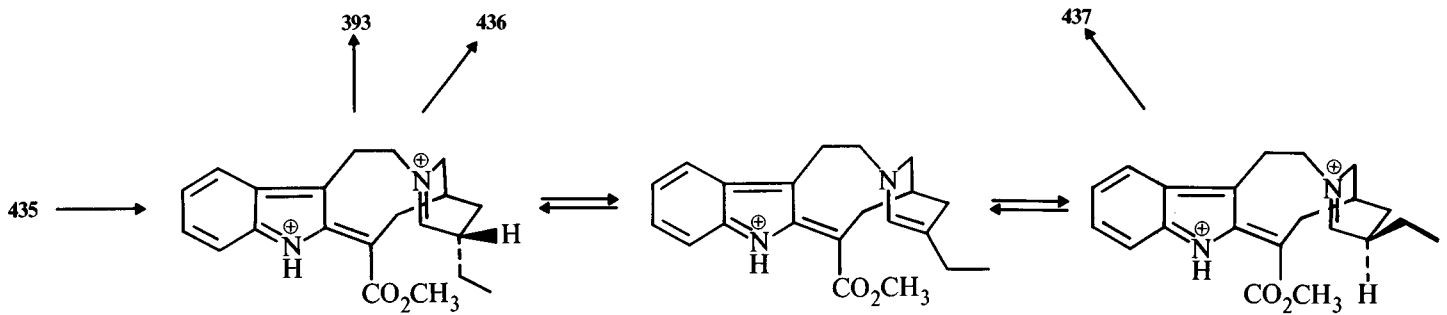
20′-Deoxyvinblastine B (**393**): $R^1 = C_2H_5$, $R^2 = H$

Isoleurosine (**399**): $R^1 = H$, $R^2 = C_2H_5$

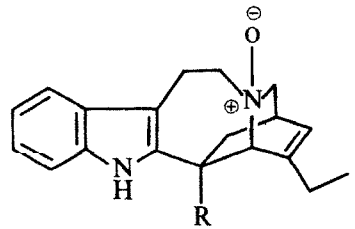


436: $R^1 = C_2H_5$, $R^2 = H$

437: $R^1 = H$, $R^2 = C_2H_5$



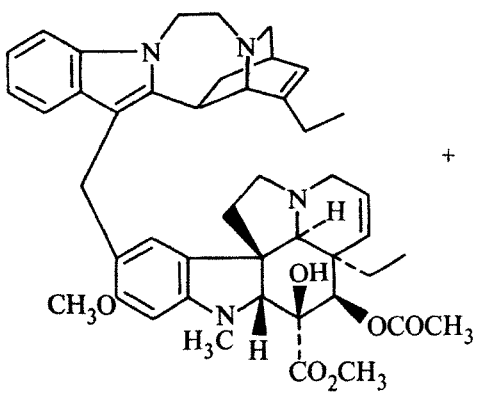
Scheme 52.



428: R = CO_2CH_3

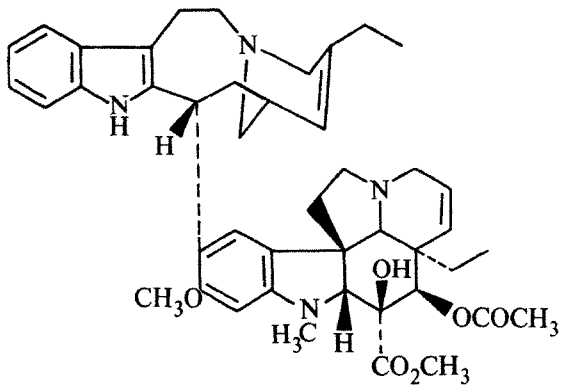
441: R = H

Vindoline (**284**)



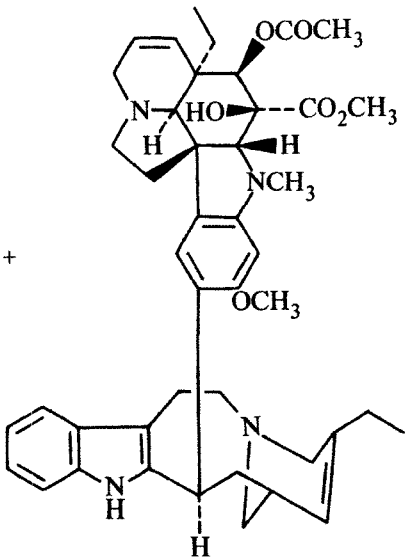
442

+



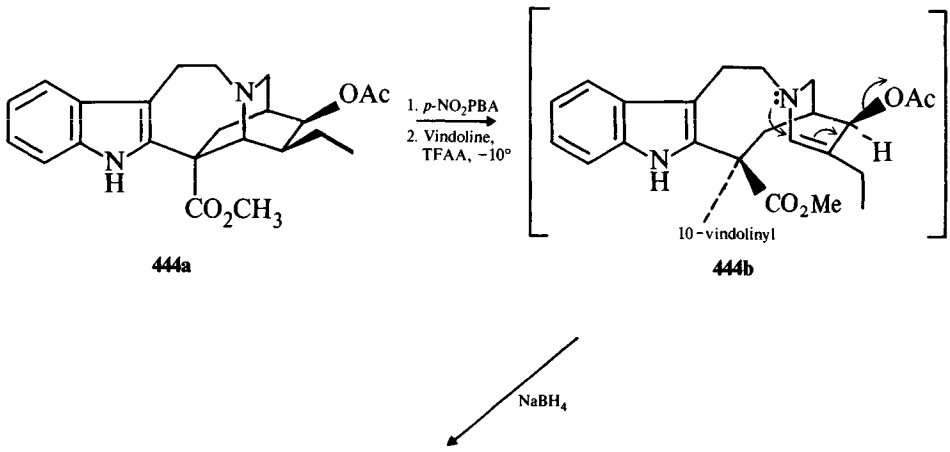
443

+



444

Scheme 53.



444a 444b

15′,20′-Anhydrovinblastine (429)

Scheme 54.

ficient to convert **429** to **395**,[342] and under controlled conditions yields may be as high as 40% (see below). However, overoxidation of **429**[313,340] or treatment of leurosine (**395**) with *t*-butyl hydroperoxide in dichloromethane[298] leads to catharine (**402**).

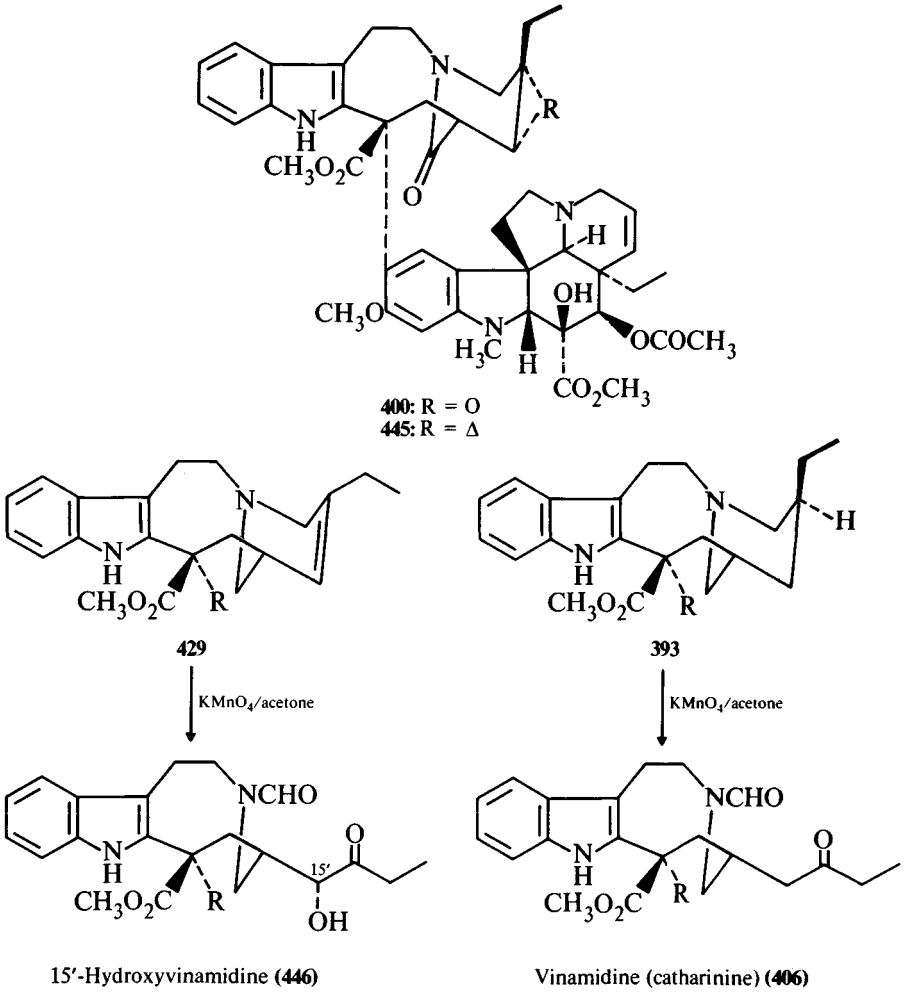
Oxidation of either anhydrovinblastine (**429**) or leurosine (**395**) with potassium permanganate afforded the 3′-lactams **400** and **445** together with a ketol, identified as 15′-hydroxyvinamidine (**446**).[343] Oxidation of 20′-deoxyleurosidine (**393**) afforded vinamidine (**406**)[343] directly in 25% yield (Scheme 55).

Independent proof of the stereochemistry of the epoxide in leurosine (**395**) was also obtained by synthesis,[344,345] for condensation of the *N*′-oxide epoxide (**447**) with vindoline (**284**) at −50° in the presence of trifluoroacetic acid and followed by reduction gave leurosine (**395**) (Scheme 56). Coupling of 15β-acetoxy-20β-dihydrocatharanthine *N*-oxide (**448**) and vindoline (**284**) afforded 15′α-acetoxy-20′-deoxyleurosidine (**449**) and 15′α-acetoxy-20′-deoxyvinblastine (**450**). Honma and Ban[347] obtained **429** (22%) and the base **451** (32%) from the same reaction (Scheme 57).

When the coupling of 20α-hydroxydihydrocatharanthinic acid lactone *N*-oxide (**452**), with vindoline (**284**) was studied,[345,348–350] all three groups obtained the product **453**, derived by fission of the 5,6 bond in **452**, condensation with vindoline, and recyclization (Scheme 58).

The 15′,20′ double bond of anhydrovinblastine (**429**) can also be functionalized directly. For example, hydroboration and oxidation gave 15′β-hydroxy-20′-deoxyvinblastine (**454**) as one of the products (Scheme 59),[346] a reaction that contrasts, stereochemically, with the synthesis of leurosine discussed previously. It is thought that this might indicate coordination of N_b and boron to direct attack from the β face.

The first synthesis of vincaleukoblastine (**384**) has been claimed,[351] through the

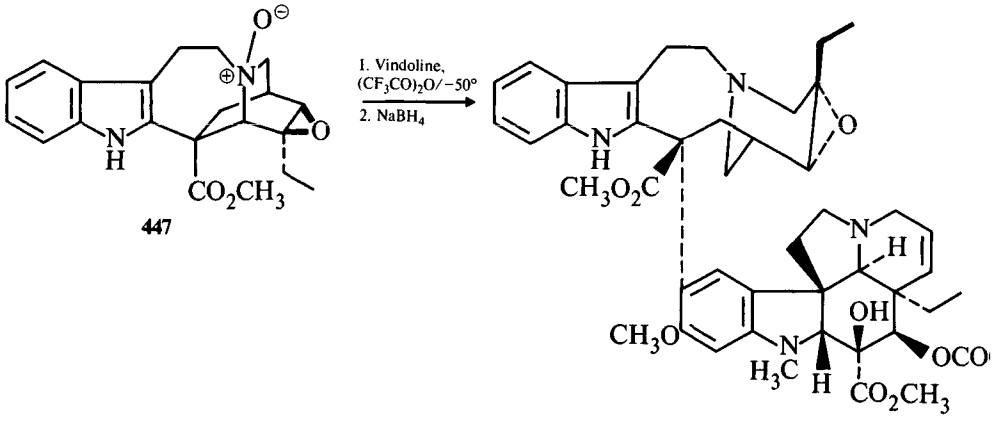


Scheme 55. R = 10-vindolinyl.

coupling of the *N*-oxide of 20-acetoxy-15,20-dihydrocatharanthine (**455**)[352] with vindoline to afford 20′-acetylvinblastine (**456**). Alkaline hydrolysis then yielded deacetylvinblastine (**457**), which could be acetylated to afford vinblastine (**384**).[352a]

Clearly this synthesis depends critically on the stereochemistry of the catharanthine derivative, which should be 20α-acetoxy-15,20-dihydrocatharanthine *N*-oxide (**458**). Neither Kutney's not Potier's groups have been able to repeat this α-functionalization at C-20 in the catharanthine series.[353,354]

The successful route to vincaleukoblastine (Scheme 60) involves an elaboration of 15′,20′-anhydrovinblastine (**429**) in a rather interesting manner, which began as an outgrowth of a synthesis of the wrong C-20′ diastereoisomer, leurosidine.[355]



447

Leurosine (395)

Scheme 56.

In the coupling of 15,20*S*-dihydrocatharanthine *N*-oxide (**435**) with vindoline (**284**), the initially formed immonium ion **459** is in equilibrium with the enamine **460**. This compound could be trapped through reaction with osmium tetroxide which stereospecifically yields an intermediate diol **461**, where attack has occurred from the α face. Reduction ($NaBH_4$) of the C-21′ carbinolamine unit then afforded leurosidine (**462**).[355] Kutney and Bylsma had previously[356,357] used a similar strategy in the synthesis of velbanamine (**387**).

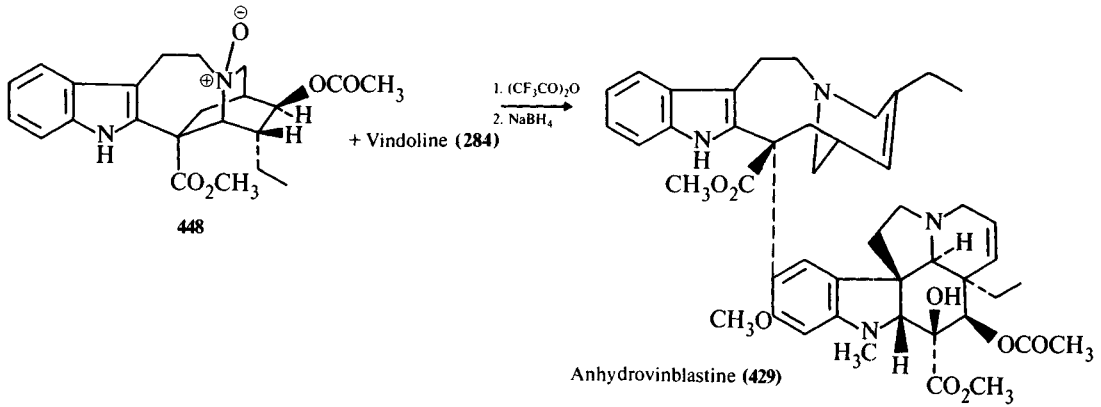
The unstable enamine **460** could also be obtained through hydrogenation (attack from the α face) of anhydrovinblastine (**429**) followed by oxidation (*m*-ClPBA) to the N_b'-oxide **463** and elimination ($TFAA/CH_2Cl_2$).[354,358] An oxidation-reduction sequence then afforded leurosidine (**462**) as above. But oxidation with thallium acetate resulted in attack from the β face and consequently reduction of the intermediate carbinolamine with sodium borohydride afforded vincaleukoblastine (**384**), in 30% yield from the N_b'-oxide (**463**).[354,358,358a] The difference in stereochemical attack between the two oxidizing reagents has been postulated to involve coordination of thallium with the nitrogen lone pair.

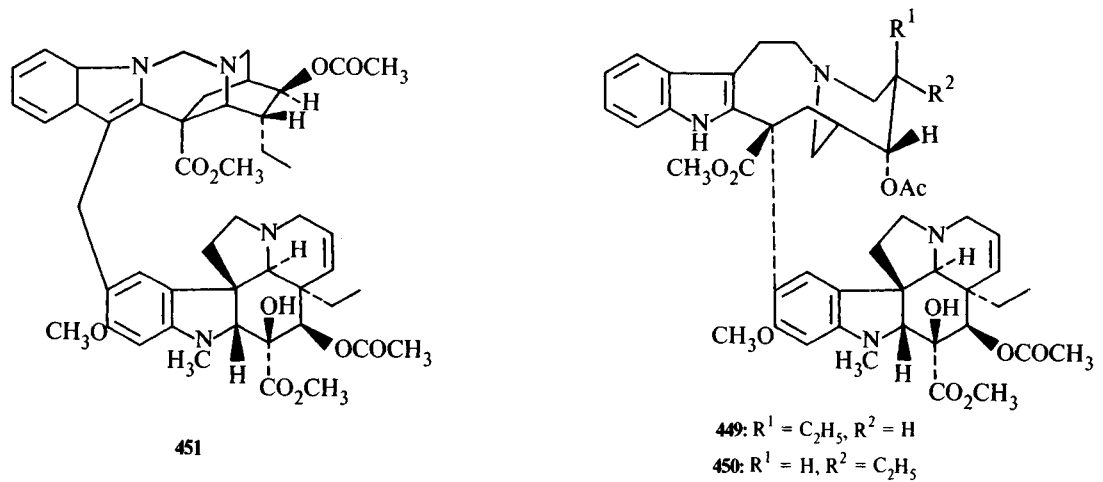
Both Potier[358b,358c] and Kutney[358d] have reviewed their respective efforts on the synthesis of the bisindole alkaloids.

3. *Synthesis of Isomers and Analogues*

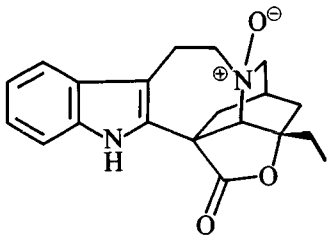
Most of the recent synthetic efforts have been directed toward the synthesis of isomers and analogues of vinblastine.

Kutney and co-workers[358e] have described the synthesis of the glycols **463a** and **463b**, the latter through an oxidation-reduction sequence on the former, as well as the four 15′-acetoxy compounds (**463c–463f**) in the 20′-deoxyvinblastine/

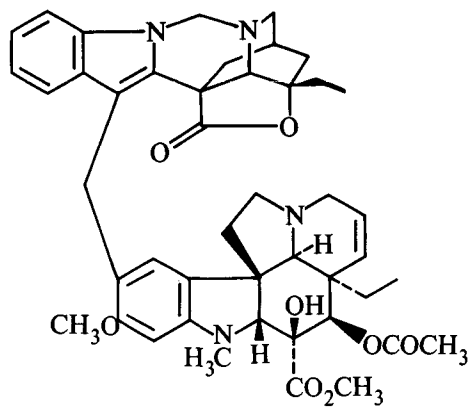

1. $(CF_3CO)_2O$
2. $NaBH_4$
+ Vindoline (284)
448
Anhydrovinblastine (429)


451
449: $R^1 = C_2H_5$, $R^2 = H$
450: $R^1 = H$, $R^2 = C_2H_5$

Scheme 57.

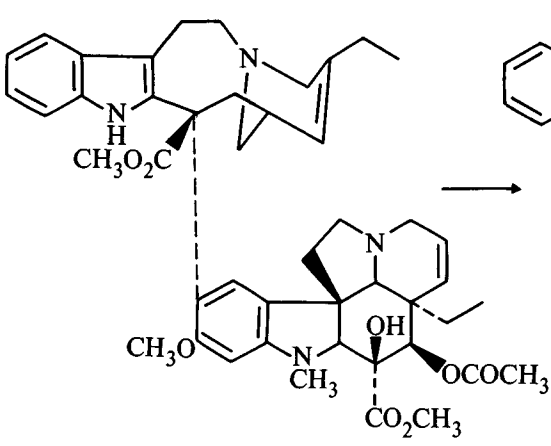


452

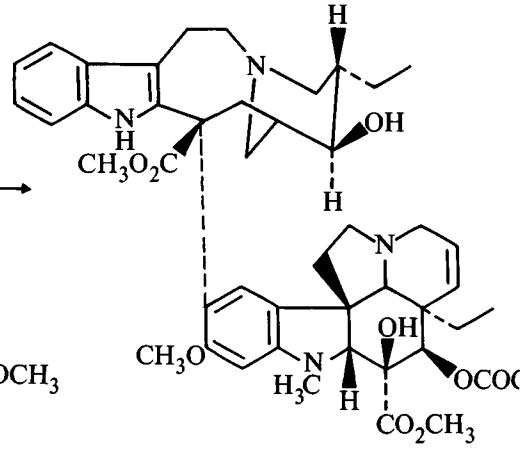


453

Scheme 58.



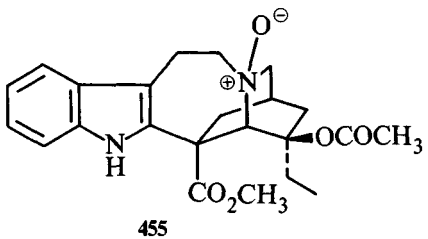
Anhydrovinblastine (429)



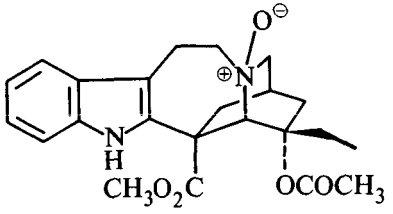
454

Scheme 59.

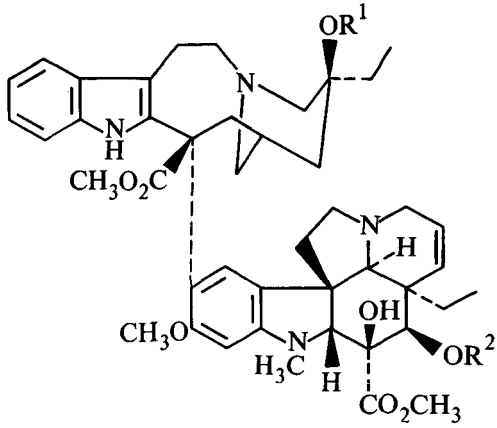
20′-deoxyleurosidine series. For example, hydroboration/oxidation of 15′,20′-anhydrovinblastine (**429**) followed by acetylation gave an acetate, originally[346] thought to be **463e**, but subsequently shown to be **463c** through correlation with 20′-deoxyleurosidine (**393**). The ketone **463g**, an intermediate in the synthesis of **463d**, was epimerized with dimethylamine in a sealed tube to afford a 1 : 1 mixture of **463g** and **463h**. Reduction of **463h** followed by acetylation gave **463e**. In the latter compound H-15′ appeared at 4.39 ppm as a doublet of doublets



455



458



456: $R^1 = R^2 = COCH_3$

457: $R^1 = R^2 = H$

384: $R^1 = H$, $R^2 = COCH_3$

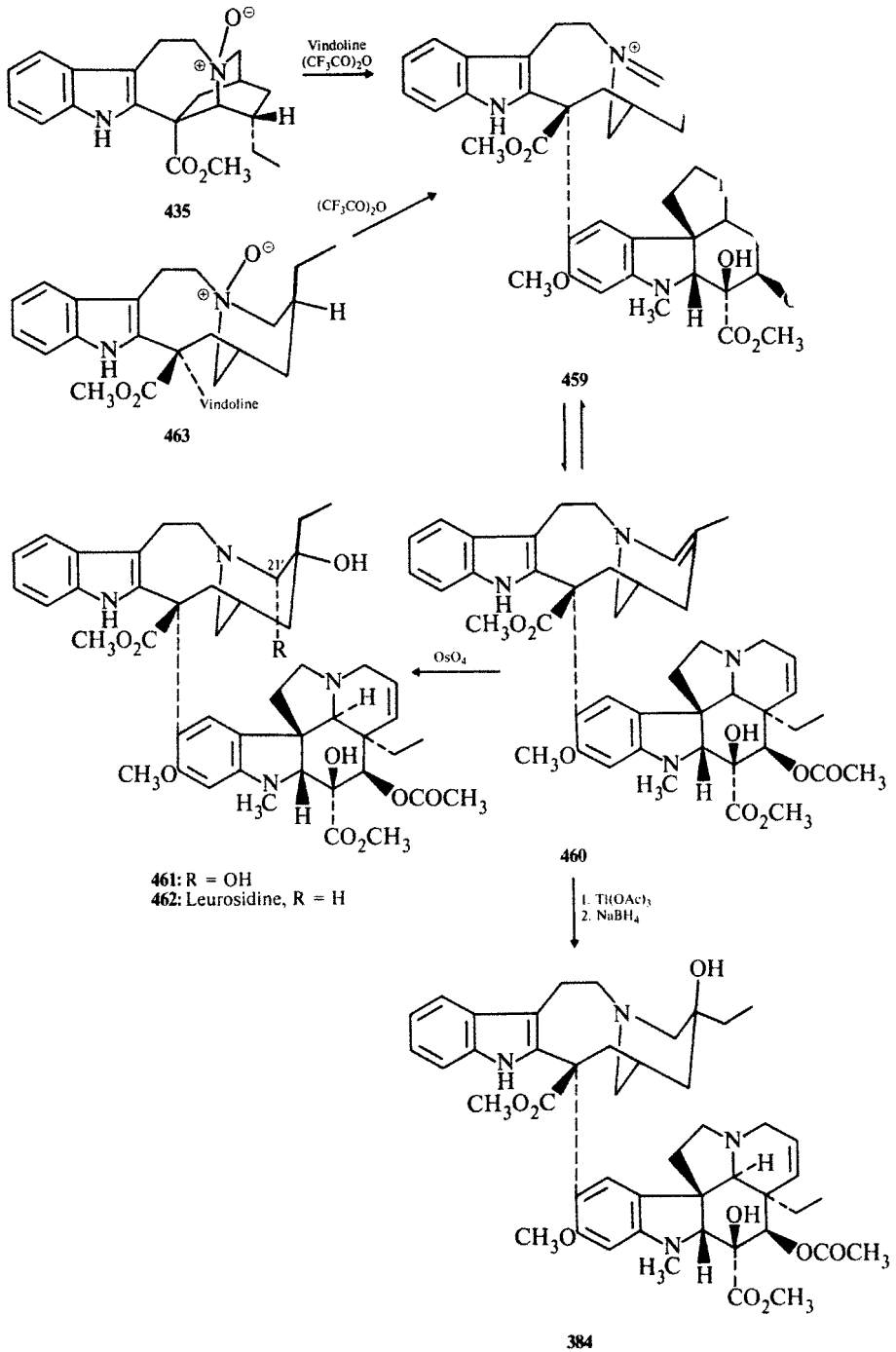
($J = 5$ and 11 Hz), indicating the piperidine ring to exist in a chair conformation. However, in **463d** this signal appears at 5.10 ppm as a broad signal, and the piperidine is regarded as having a half-chair conformation.[358e]

A new isomer of vinblastine was made available by Kunesch and co-workers[358f] through the condensation of the chloroindolenine derived from secopandoline (**463i**) with vindoline (**284**). Since **463i** is epimeric at C-14 and C-20 compared with velbanamine (**382**), the product was 14′,20′-epivinblastine (**463j**). The configuration at C-16′ was *S*, the same as that in the natural series, indicating that C-14′ is a controlling factor in the orientation of the approaching vindoline (**284**), and the reason the chloroindolenine approach had not previously yielded compounds in the natural series.

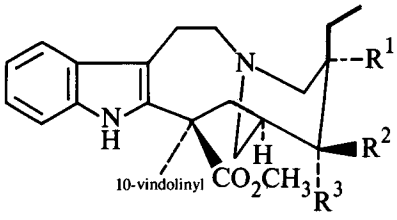
As a further example, when the chloroindolenine of 15-oxo-16-methoxycarbonyl-15,20-dihydrocleavamine (**463k**) was coupled with vindoline (**284**), **463l** was produced in 55% yield, together with its deacetyl derivative **463m**. The configurations are 16′*R* and 14′*S* as expected, but the potential exists to invert C-14′ through epimerization and thus reach a vinblastine derivative in which the whole cleavamine unit is enantiomeric with that in the natural alkaloids.

When the modified Polonovski reaction was applied to anhydrovinblastine N_b'-oxide (**464**), the only product obtained (27% yield) was 5′-noranhydrovinblastine (**465**). When the reaction mixture was reduced with sodium cyanoborohydride, some anhydrovinblastine (**429**) was recovered together with 20′-deoxyleurosidine (**393**). The formation of **393** and **465** is shown in Scheme 61.[359,359a] The C-6 methylene group in **465** was observed at 53.6 ppm.

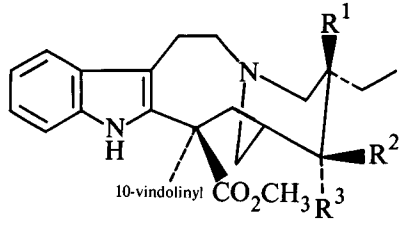
A modified Polonovski reaction on leurosine *N*′-oxide (**396**) afforded a small quantity of 5′-norleurosine (**465a**) with 21′-oxoleurosine (**401**) and 21′-hydroxyleurosine (**465b**) as the major products[359b]; 5′,6′-seco derivatives may be found in the presence of a nucleophile.[359c] 5′-Norcatharanthine (**465c**), available


Vindoline
(CF3CO)2O
435
(CF3CO)2O
Vindoline
463
459
OsO4
461: R = OH
462: Leurosidine, R = H
460
1. Tl(OAc)3
2. NaBH4
384

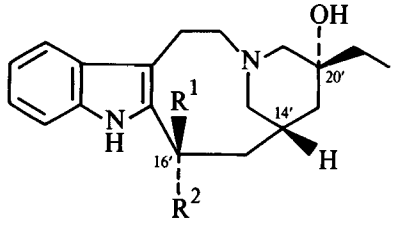
Scheme 60.



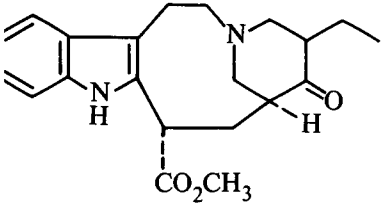
	R^1	R^2	R^3
463a	OH	H	OH
463b	OH	OH	H
463c	H	H	OAc
463d	H	OAc	H
463g	H	=O	



	R^1	R^2	R^3
463e	H	OAc	H
463f	H	H	OAc
463h	H	=O	

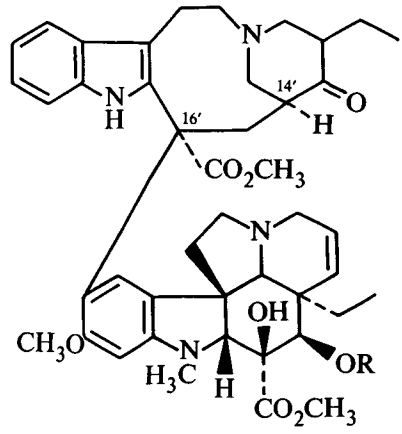


	R^1	R^2
463i	H	CO_2CH_3
463j	CO_2CH_3	10-vindolinyl

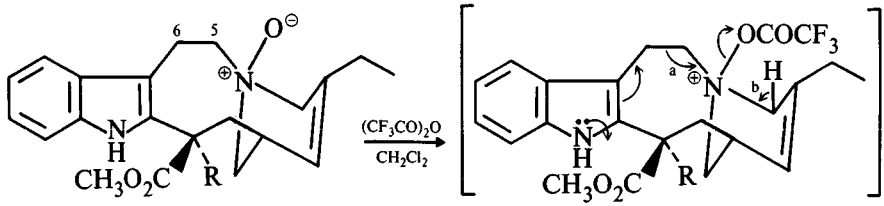


463k

N-chlorobenzotriazole
vindoline, HCl/MeOH



463l: R = Ac
463m: R = H

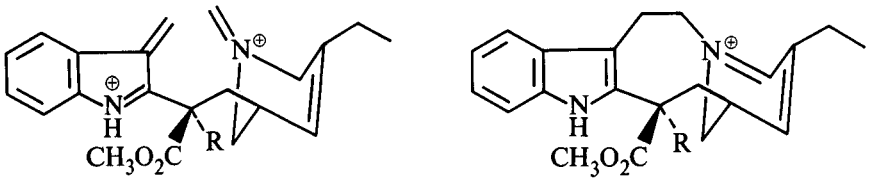


464

R = 10-vindolinyl

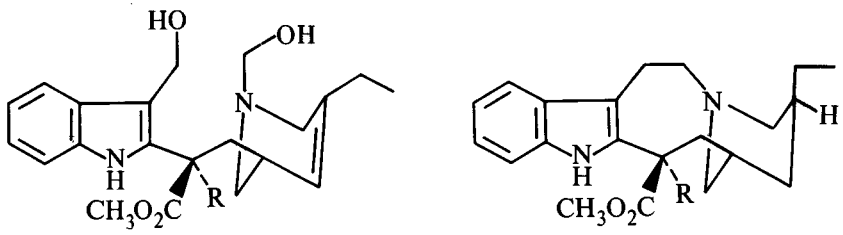
a

b

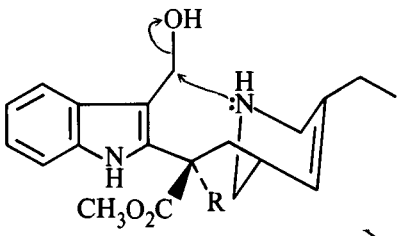


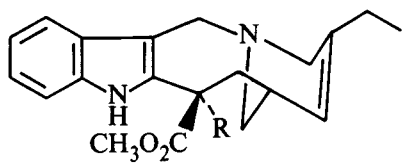
H_2O, THF

$NaBH_4$



20′-Deoxyleurosidine (393)
+
Anhydrovinblastine **(429)**





5′-Noranhydrovinblastine (465)

Scheme 61.

from the N_b-oxide,[428] afforded two bisindole derivatives on condensation (as the N_b-oxide) with vindoline (**284**).[359d]

One of these was 3′-(10-vindolinyl)-5′-norcatharanthine (**465d**, 28% yield) and the other (23% yield) was 6′-(10-vindolinyl)-5′-norcatharanthine (**465e**), in which nucleophilic attack by vindoline (**284**) occurs on either of the two immonium species generated by loss of the 3′ or 6′ protons, respectively. No products were obtained in which 16′,21′ cleavage had occurred. A different approach to derivatives in the 5′-norvinblastine series involves[359b] reaction of the corresponding 7′-chloroindolenine with silver borofluoride. Thus anhydrovinblastine (**429**), anhydrovincristine (**465f**), leurosine (**395**), and leuroformine (**465g**) were transformed into the corresponding 5′-nor compounds **465h**, **465i**, **465a**, and **465j** in 15–53% overall yield. However, when the chloroindolenine of **465k** was treated with silver borofluoride in the 5′,6′-seco compound, **465l** was the product (31% yield). It was hypothesized that reclosure of C-6′ to N_b' is sterically hindered by the β-ethyl group at C-20′.[359b]

C. Physical Properties

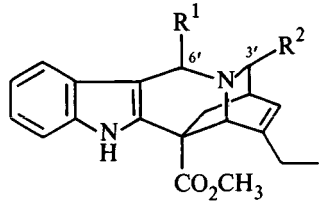
Probably more than for any other group of alkaloids, structure elucidation of the bisindole alkaloids of *Catharanthus* depends utterly on the successful integration of as many spectroscopic methods as can possibly be applied.

The characteristic indole plus dihydroindole uv spectrum (λ_{max} 270, 291, and 320 nm) and additional carbonyl groups in the molecule may be deduced from the ir spectrum. But it is the cd, ^{1}H nmr, ^{13}C nmr, and mass spectra that are most critical in structure determination.

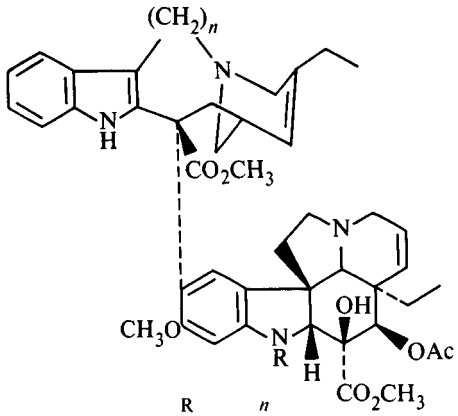
The chiral center C-16′ controls not only the relative geometry of the indole and dihydroindole components but also the antitumor activity, for compounds in the "unnatural" series do not display activity. Thus as an adjunct to the development of synthetic methods, attention was turned to determining the configuration of this center through optical methods. Indeed Langlois et al.,[334] and subsequently Kutney et al.,[360] reported a procedure based on circular dichroism for determining the configuration at C-16′, for the natural dimers show a positive Cotton effect [e.g., at 224 nm ($\Delta\epsilon$, + 30) for VLB], whereas the unnatural series display a negative Cotton effect at a slightly lower length (210 nm). There is also some evidence that where similar compounds are being compared, the chemical shifts of the C-18 protons and the C-16′ carbomethoxy group may be significant.[361]

In the mass spectra of alkaloids in this series transmethylation ions are frequently observed, which may lead to an erroneous molecular ion being assigned unless the fragmentation pathway is evaluated.

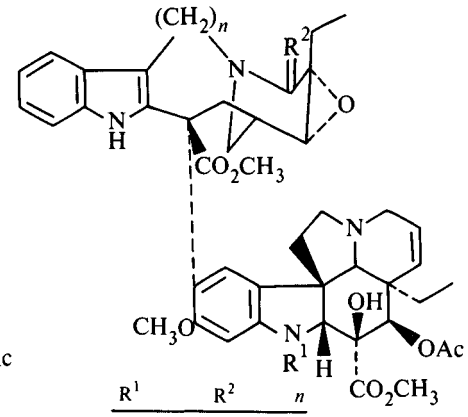
Abraham and Farnsworth[310] have studied the electron-impact induced degradation of leurosine which is typical of this group of alkaloids. Recognition of the fragmentation of vindoline (**284**) (Scheme 62), and the two pathways which dominate the fragmentation of the indole moiety (Schemes 63 and 64) indicates that one series of ions should be derived by the addition of 156 m.u. to the ions



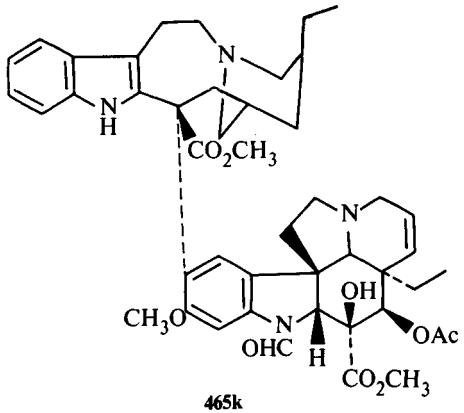
	R^1	R^2
465c	H	H
465d	H	10-vindolinyl
465e	10-vindolinyl	H



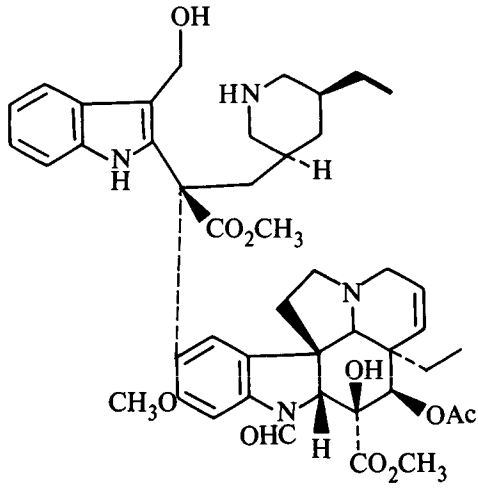
	R	*n*
429	CH_3	2
465f	CHO	2
465h	CH_3	1
465i	CHO	1



	R^1	R^2	*n*
395	CH_3	H_2	2
401	CH_3	O	2
465a	CH_3	H_2	1
465b	CH_3	H,OH	2
465g	CHO	H_2	2
465j	CHO	H_2	1

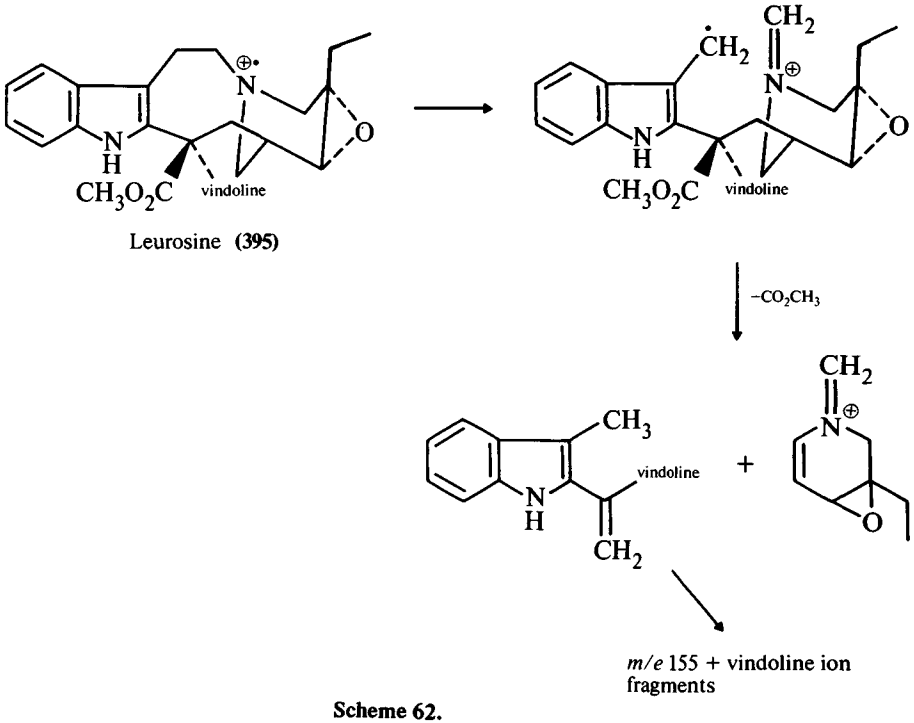


465k

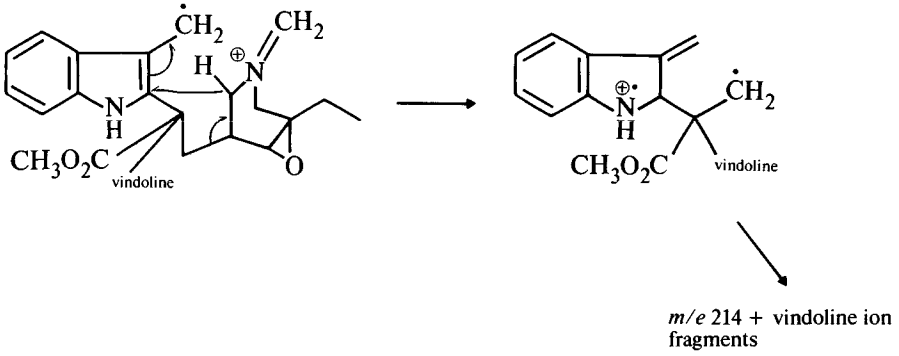


465 I

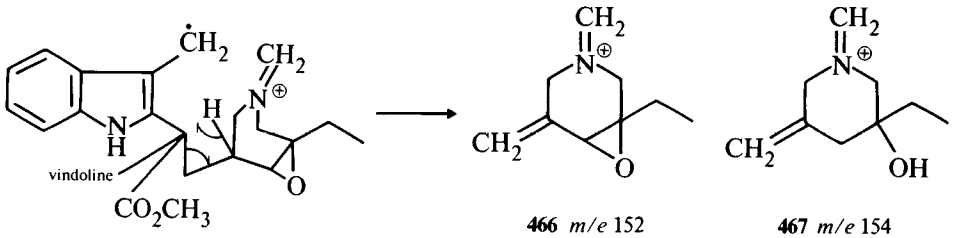
455, 396, 395, 295, and 173, and a second series of ions by the addition of 215 m.u. to the same ions. Indeed all these ions were observed and high resolution mass measurements confirmed the proposed molecular formulas. Beta-cleavage with γ-hydrogen transfer leads to the ion *m/e* 152 (**466**) in the case of leurosine (**395**) (Scheme 64) and *m/e* 154 (**467**) in the mass spectrum of VLB.



Scheme 62.

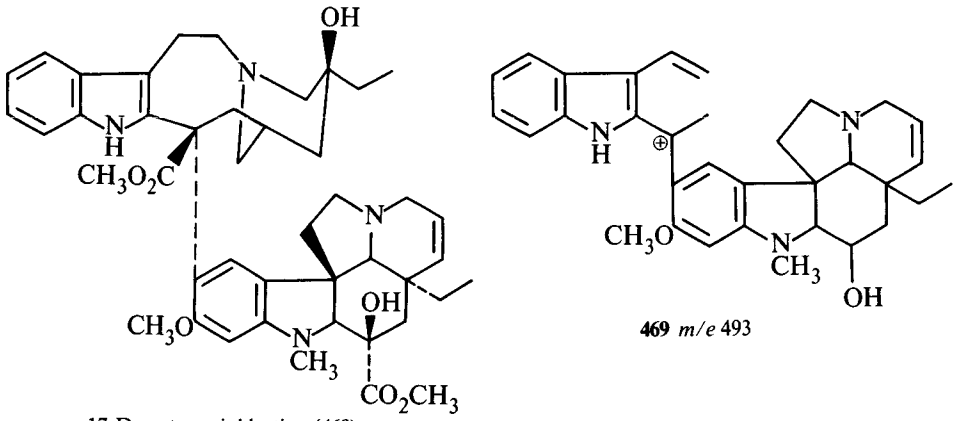


Scheme 63.

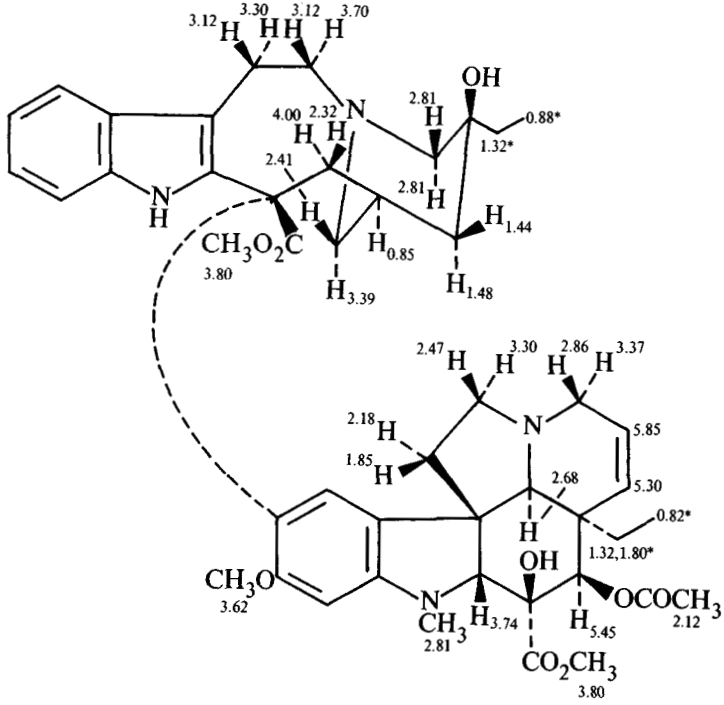


Scheme 64.

The structure of 17-deacetoxyvinblastine (**468**, $C_{44}H_{56}N_4O_7$) was determined[286] through a combination of ^1H nmr and mass spectrometry, for the acetyl methyl signal was missing and the acetylated derivative displayed a singlet at 1.90 ppm, characteristic of a C-16 acetyl group. The mass spectrum of the hydrazide of **468** gave a prominent ion at *m/e* 493 which was rationalized to have the structure **469**.



The ^1H nmr spectrum of an alkaloid in this series offers a wealth of information and is used initially to establish the presence of the 10-vindolinyl moiety. The high-field ^1H nmr spectra of leurosine (**395**)[361a] and vinblastine (**384**)[361b] have been reported, in which essentially all the protons have been assigned; the data for vinblastine are shown in **470**. In leurosine, the epoxypiperidine ring apparently exists in the half-chair conformation, whereas in vinblastine (**384**) it exists in a full-chair conformation. A substantial chemical shift difference was observed for H-3′α and H-3′β in **384** and a moderate one in **395**.



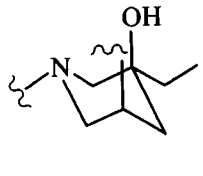
470 (*denotes that assignments may be reversed)

Probably the most important current technique for structure elucidation in this area is ^{13}C nmr spectroscopy,[309,311,362] which has yielded assignments for all the carbons. These data are summarized for some of the principal alkaloids in Table XX.

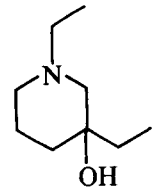
In the case of VLB, the data suggest the conformation shown in **471** for the velbanamine component, for the chemical shifts of C-18′, 19′, 20′, and 21′ correspond closely with those of the model compound, 1,3-diethylpiperidin-3-ol (**472**)[309] where the hydroxy group is axial. The configuration and conformation also permit N–H–O hydrogen bonding, which might account for the reduced basicity of this nitrogen in VLB (pK_a 7.4).

TABLE XX. ^{13}C NMR DATA OF THE VINBLASTINE GROUP OF ALKALOIDS

Carbon	Vinblastine (384)[362]	Deacetyl-vinblastine (457)[362]	De-*N*-Methyl-vinblastine (414)[362]	Deacetoxy-vinblastine (468)[362]	Leurocolombine (408)[362]	Vincadioline (411)[362]	Leurosidine (462)[309]	Leurosine (395)[309]	Vincathicine (404)[318]	21'-Oxoleurosine (401)[293]
2	83.8	82.8	74.2	81.8	83.3	83.4	83.1	83.1	83.0	83.2
3	50.2	50.4[a]	50.5	50.1	50.5	50.4	50.2	50.2	50.6[d]	50.3
5	50.2	49.8[a]	51.1	50.1	50.5	50.4	50.2	50.2	50.9[d]	50.3
6	44.6	44.7	42.9	44.7	44.4	44.6	44.5	44.5	43.6	44.6
7	53.2	53.2	53.2	53.8	53.2	53.3	53.1	53.1	53.0	53.1
8	122.6	122.8	122.7	121.8	124.0	123.0	123.0	123.0	122.8	123.4
9	123.5	123.9[b]	124.2[c]	123.7[d]	123.7[f]	123.6[g]	123.4	123.4	123.6	122.7
10	121.1	120.9	120.7	120.4	120.0	120.6	120.4	120.4	120.6	120.0
11	158.0	158.0	157.9	157.8	158.7	158.1	157.6	157.6	159.1	157.8
12	94.2	93.9	93.9	93.5	94.6	94.2	94.0	94.0	94.3	94.3
13	152.5	152.5	149.1	152.8	153.7	152.7	152.8	152.8	152.8	153.2
14	124.4	124.2[b]	124.5[c]	124.0[d]	124.5[f]	124.5[g]	124.3	124.3	124.6	124.4
15	129.9	130.0	129.9	135.9	129.9	130.0	129.7	129.7	130.5	129.8
16	79.7	80.7	79.7	77.1	79.5	79.6	79.5	79.5	79.6	79.4
17	76.4	74.1	76.5	38.1	76.3	76.5	76.2	76.2	76.3	76.1
18	8.3	8.6	8.3	8.6	8.4	8.4	8.3	8.3	7.6	8.4
19	30.8	32.9	31.2	34.3	30.9	30.9	30.7	30.7	30.6	30.7
20	42.7	42.4	43.4	37.2	42.7	42.7	42.6	42.6	42.8	42.5
21	65.5	66.4	66.7	65.5	65.8	65.7	65.5	65.5	65.7	65.8
CO_2CH_3	170.8	173.1	170.8	173.6	170.9	170.9	170.7	170.7	170.7	170.8
CO_2CH_3	52.1	52.3	52.7	52.4	52.3	52.2	51.9	52.1	52.2	52.1
C_{11}-OCH_3	55.8	55.8	55.7	55.7	55.4	55.8	55.7	55.7	55.4	55.8
N_a-CH_3	38.3	38.6	-	38.1	38.2	38.3	38.2	38.2	38.4	38.0
$OCOCH_3$	171.6	-	172.7	-	171.6	171.7	171.4	171.4	171.7	171.5
$OCOCH_3$	21.1	-	21.0	-	21.1	21.1	21.0	21.0	21.1	20.9
2'	131.4	131.3	131.7	131.6	130.4	131.6	130.2	130.7	187.0	131.1
3'	48.0	48.1	48.4	48.4	56.0	43.2	43.9	42.3	52.6[l]	44.0
5'	55.8	55.8	55.7	55.7	56.0	55.6	53.9[i]	49.6	55.0[l]	46.6
6'	28.2	28.7	28.8	28.8	27.3	28.5	21.4	24.6	32.2[m]	23.4
7'	117.0	117.0	116.9	116.8	117.2	116.9	116.8	116.7	57.1[n]	115.3
8'	129.5	129.4	129.5	129.5	129.3	129.4	128.9	129.1	144.2	128.9
9'	118.4	118.4	118.5	118.4	118.5	118.5	117.9	118.1	124.69[o]	118.1
10'	122.1	122.2	122.2	122.1	122.4	122.3	122.0	122.2	127.79[o]	123.2
11'	118.7	118.7	118.8	118.7	119.0	118.9	118.6	118.4	124.19[o]	119.3
12'	110.4	110.4	110.3	110.3	110.6	110.5	110.2	110.3	121.39[o]	110.5
13'	135.0	134.9	135.0	134.9	135.1	134.9	134.5	134.6	134.0	134.6
14'	30.1	30.2	30.4	30.3	71.3	39.2	29.8	33.5	28.9	31.9
15'	41.4	41.4	41.6	41.6	50.5	75.2	40.4[j]	60.3	49.2	61.4
16'	55.8	55.8	55.9	55.7	54.3	55.8	55.4	55.3	63.1[n]	55.1
17'	34.4	34.3	34.5	34.5[e]	40.7	32.8[h]	35.1[j]	30.7	38.7[m]	29.4
18'	6.9	6.9	6.9	6.9	6.9	6.2	7.1	8.6	7.0	8.7
19'	34.4	34.3	34.3	34.7[e]	34.0	29.2[h]	38.5[j]	28.0	34.4[m]	29.4
20'	69.4	69.5	69.8	69.7	69.9	71.3	71.8	59.9	75.8	59.5
21'	64.2	64.3	64.5	64.5	63.6	60.3	55.5[i]	54.0	63.1[l]	167.8
CO_2CH_3	174.9	175.1	175.0	175.2	174.4	174.8	173.9	174.1	174.8	173.4
CO_4CH_3	52.3	52.3	52.4	52.4	52.6	52.4	52.1	52.3	52.6	52.1



471

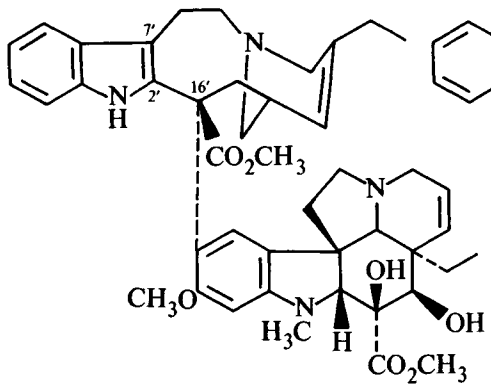


472

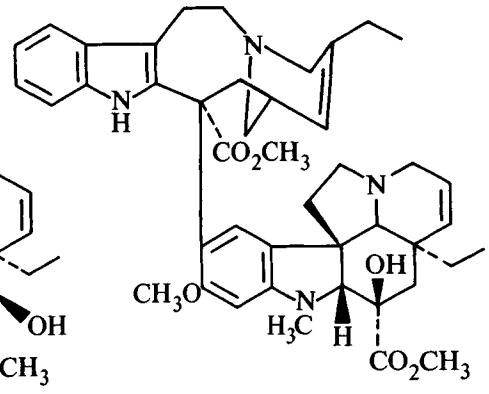
Leurosidine had been suggested to have a secondary hydroxy group (at C-15′) because of its ease of acetylation.[308] However, when the ^{13}C nmr spectrum of leurosidine was examined, revision of the structure became necessary. A quaternary carbon was observed at 71.8 ppm for a C-20′ and a methylene at 40.4 ppm for C-15′, and this led to the designation of leurosidine as 20′-epivinblastine (**462**).[309] Vincaleukoblastine (**384**) can be epimerized to leurosidine (**462**),[363] but the reported[308] oxidation of leurosidine to afford a ketone requires reinvestigation.

The ^{13}C nmr data may also be useful in deducing the configuration at C-16′ in the vinblastine-type alkaloids.[363a] Only a small shift was observed for C-16′ itself, but more substantial shifts (> 3.5 ppm) were observed for C-9, C-10, C-2′, and C-7′, the immediate aromatic neighbors of C-16′. In the compounds studied, 15′,20′-anhydrodeacetylvinblastine (**473**) and 15′,20′-anhydro-16′-isovinblastine (**474**), a substantial shift (4.4 ppm) was also measured for C-17′, although this was not commented on. Comparison with data for vinblastine (**384**), leurosidine (**462**), leurosine (**395**), and **474** confirmed the initial finding that C-2′ and C-10 shift downfield and C-9 and C-7′ shift upfield on changing from the 16′*R* (natural) to the 16′*S* stereochemistry.

An evaluation of ^{13}C data in the vinblastine and voacamine series indicated that the attacking aromatic carbon is shifted downfield 15.7–20.8 ppm in the bisindole derivatives compared with the corresponding monomers.[188a]



473



474

D. Natural Occurrence

The question of the natural occurrence of these bisindole alkaloids is a profound one which is not simply answered. The facile air oxidation of leurosine, discussed previously, supports the contention that leurosine may not occur naturally but rather is produced during plant processing.[342] But other evidence supports the idea that leurosine *is* a constituent of *C. roseus*.[364] In the presence of hydrogen peroxide and horseradish peroxidase, anhydrovinblastine (**429**) was converted to leurosine (**395**) in 65% yield in only 1.5 hours, and *C. roseus* cellfree extracts and added hydrogen peroxide also carried out this conversion at a rate five times more rapidly than in the absence of the *C. roseus* enzymes.

Langlois and Potier[365] have recently examined the transformations of anhydrovinblastine (**429**) in acetonitrile solution, and have rationalized the observed formation of several of the natural alkaloids by postulating a series of oxidation and reduction reactions; for details see Chapter I. Scott and co-workers have established[366] that **429** occurs naturally in *C. roseus*, and Stuart and co-workers[367] have shown that catharine (**402**) is probably also a bona fide alkaloid. The same group has also shown[368] that their cell line "916" of *C. roseus* has the ability to transform 15′,20′-anhydrovinblastine (**429**), the major products being leurosine (**395**, 31% yield) and catharine (**402**, 9% yield).

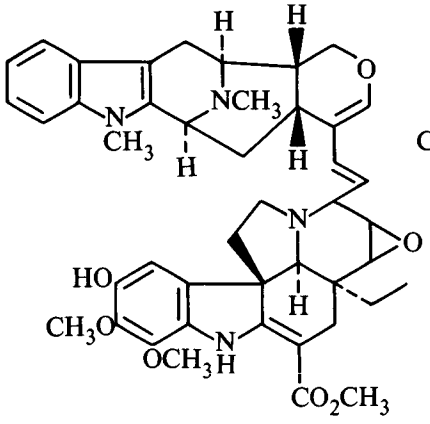
The situation is clearly a complex one and it may well be that at least some of the bisindole alkaloids of *Catharanthus* spp. are produced during work-up. However, the dramatic difference between the bisindole alkaloids of *C. roseus* and *C. lanceus* or *C. trichophyllus* indicates that Mother Nature may not be so easily fooled.

XXIII. *ASPIDOSPERMA*-MACROLINE TYPE

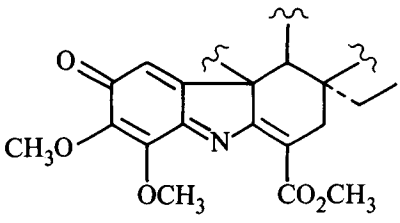
Pandacastrum saccharatum Pich. (Apocynaceae) has yielded a bisindole alkaloid, pandicine (**475**), in which a macroline (**90**) unit and a polyoxygenated tabersonine unit are constituents.[369] The alkaloid was quite unstable in organic solvents giving rise to the iminoquinone **476**, showing λ_{max} 233, 260, and 396 nm. Characteristic retro-Diels-Alder fragmentation of ring C followed by C-5,C-6 cleavage led to an ion (*m/e* 456) formulated as **477**, which was crucial in initially defining the point of attachment of the second unit. Analysis of the ^{13}C nmr spectrum on comparison with those of criophylline (**369**) and villalstonine (**94**) facilitated the assignment of most of the carbons in both units.

XXIV. BISINDOLE ALKALOIDS FROM *PETCHIA CEYLANICA*

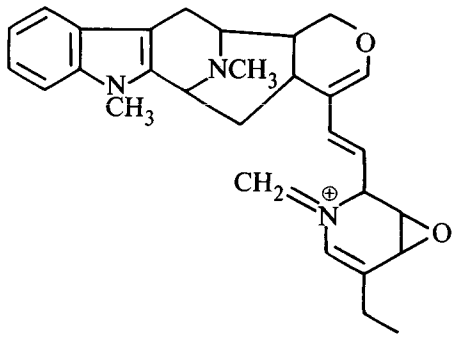
Three new bisindoline alkaloids based on the vincorine system have been isolated from *Petchia ceylanica* Wight; these are peceyline (**478**), peceylanine (**479**), and pelankine (**480**).[370] The structures were deduced principally by interpretation of ^{13}C nmr data, and the chemical shifts of C-2 (97.5, 97.2 ppm) and C-2′ (96.3 ppm) in **478** and **479** are noteworthy.



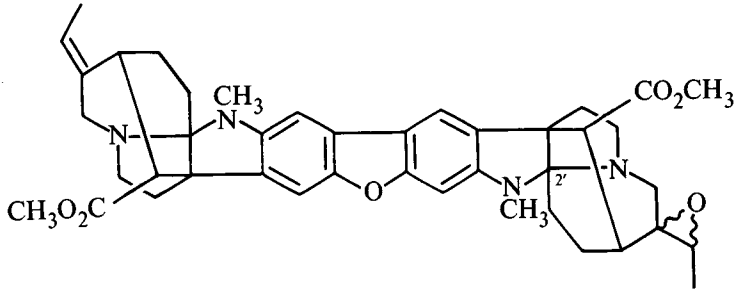
Pandicine (475)



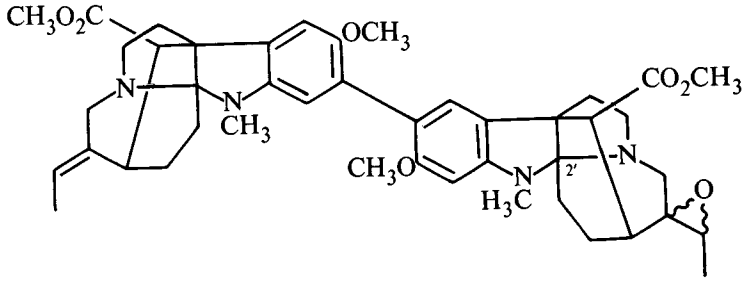
476



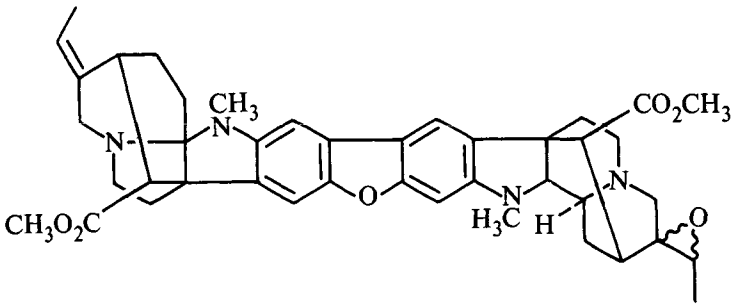
477



Peceyline (478)



Peceylanine (479)



Pelankine (480)

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CHAPTER XII

The *Cinchona* Group

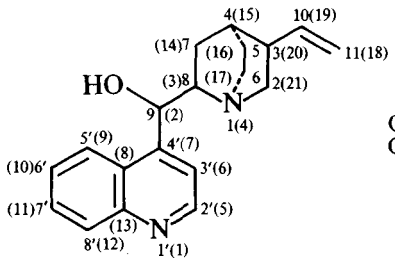
GUENTER GRETHE and MILAN R. USKOKOVIĆ

Research Laboratories, Hoffmann-La Roche Inc. Nutley, New Jersey

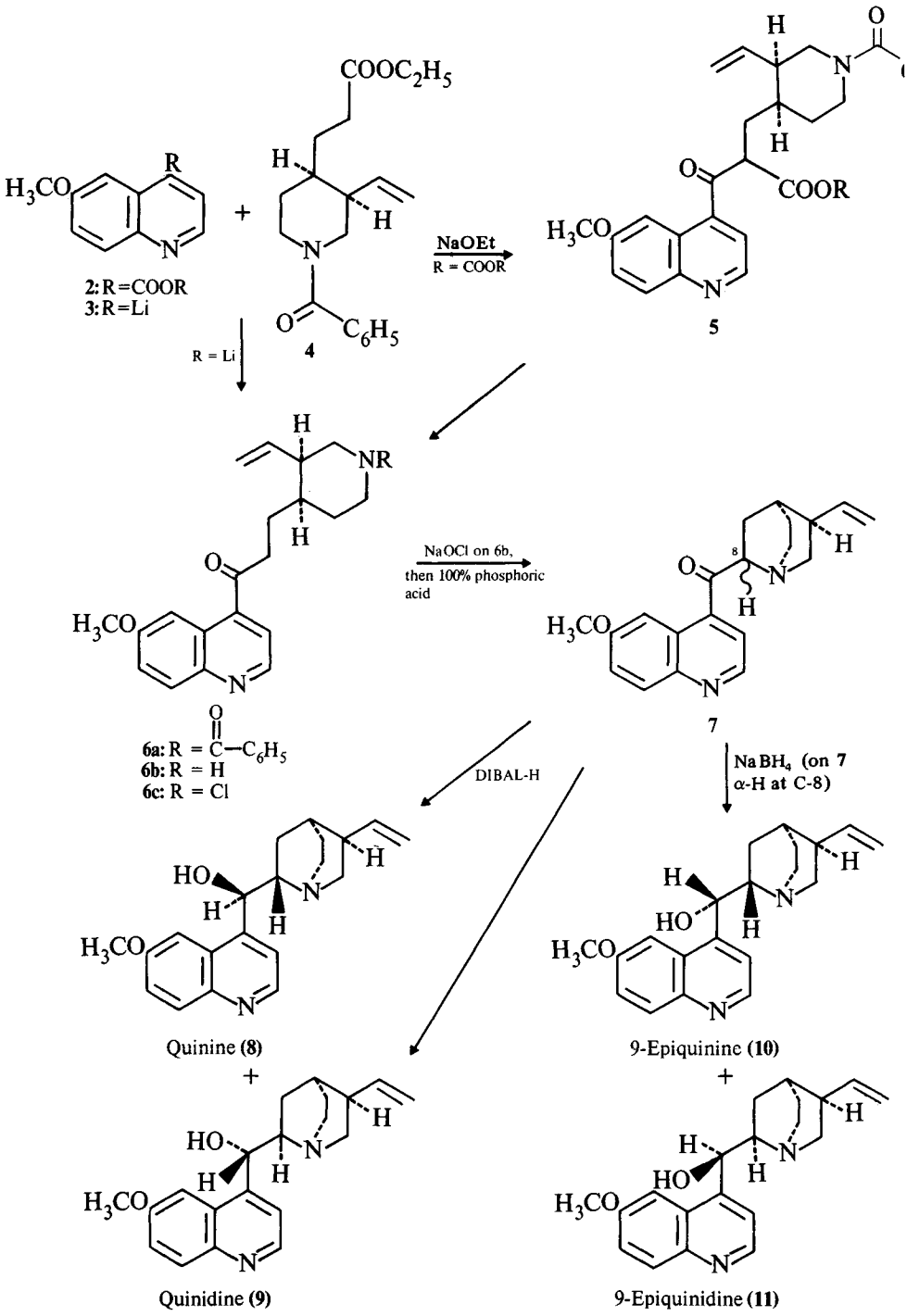
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I. INTRODUCTION

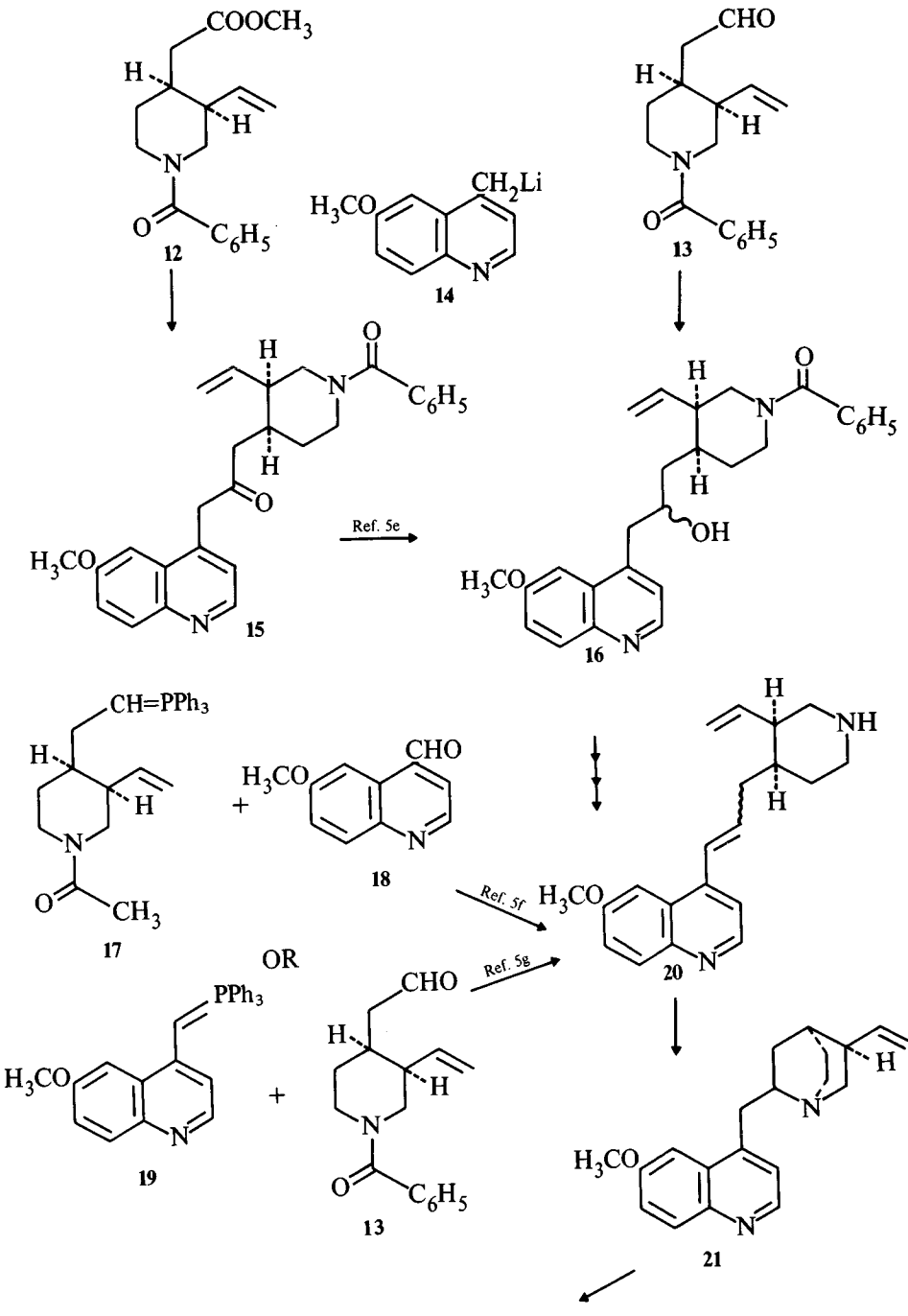
After a period of intensive synthetic work in the 1970s, the interest in *Cinchona* alkaloids has now shifted to a study of their biological activities and of their use in asymmetric synthesis. Therefore, this chapter schematically summarizes previously reviewed[1,2] synthetic accomplishments and focuses attention on new developments in metabolite work and asymmetric synthesis. The numbering used throughout the chapter is the more familiar one indicated in formula **1**, as compared to the biogenetic numbering (numbers in parentheses).



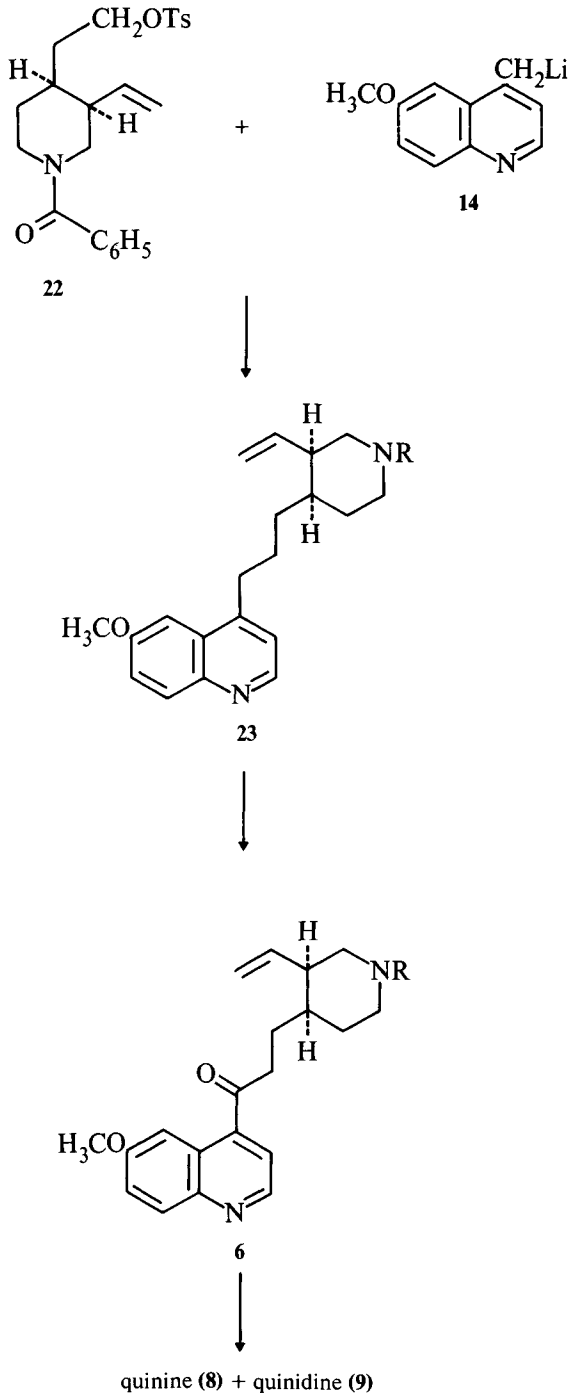
Quinine, Cinchonidine (**1**): 8 (*S*) 9 (*R*)
Quinidine, Cinchonine (**1**): 8 (*R*) 9 (*S*)



Scheme 1. Rabe-Woodward synthesis and modifications.[5a–d]



Scheme 2. Synthesis via vinylquinoline intermediates.[5e-g]



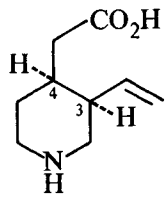
Scheme 3. Synthesis from meroquinene alcohol.[1,2]

II. SYNTHESIS OF *CINCHONA* ALKALOIDS

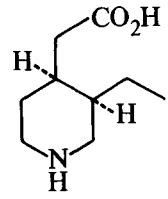
Despite the discoveries of many new antimalarial and antiarrhythmic drugs, quinine and quinidine, alkaloids isolated primarily from the bark and leaves of *Cinchona* and *Remijia* species,[3] are still widely used for control of these diseases.[4] It is therefore not surprising that nearly 50 years after Rabe's classical synthesis of dihydroquinine[5a] an upsurge in interest resulted in several new and efficient syntheses of these alkaloids and their derivatives. These new syntheses have been the subject of two previous detailed reviews,[1,2] and the important features are shown in Schemes 1–5.

III. SYNTHESIS OF THE QUINUCLIDINE SYNTHON

The successful completion of the syntheses of *Cinchona* alkaloids depended very much on the availability of the quinuclidine synthon. The precursor most frequently used was meroquinene (**36**), which contained the right number of carbon atoms and the correct chirality at C-3 and C-4. A recent review[2] describes methods for the preparation of meroquinene (**36**) and its dihydro analogue cincholoipon (**37**); they are summarized in Schemes 6 and 7.



36

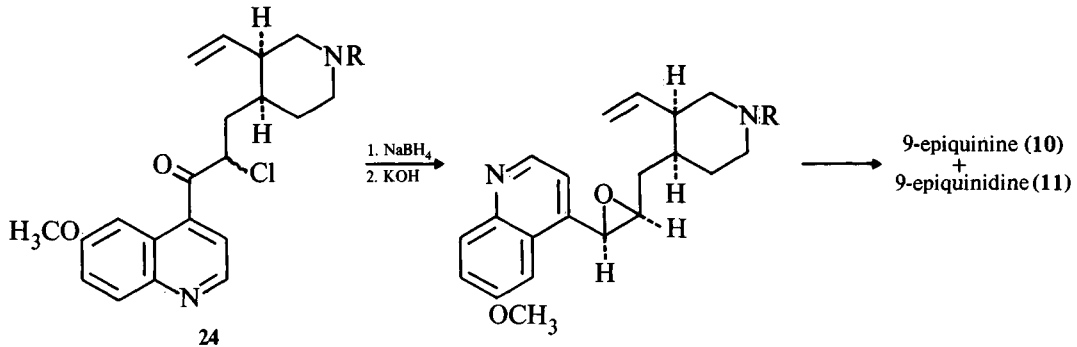


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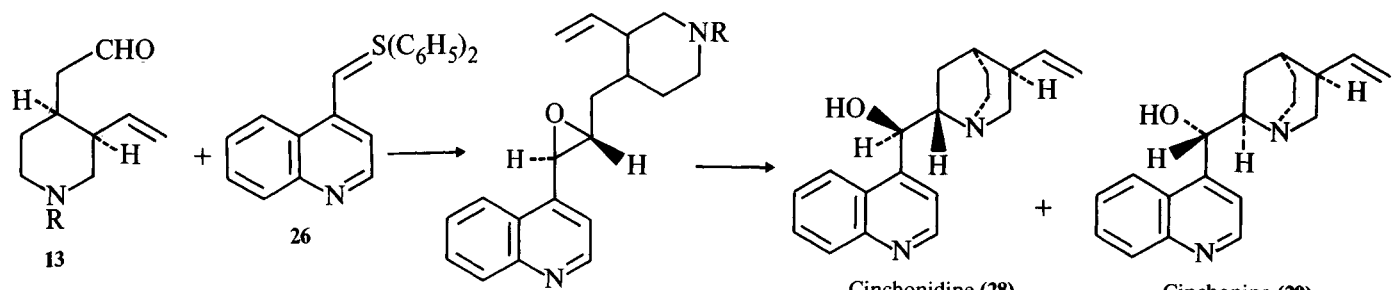
Recently, Brown and Leonard[6] reported the synthesis of meroquinene and cincholoipon from secologanin (**52**), the biogenetic terpenoid precursor[7] of the *Cinchona* alkaloids. This approach has the advantage that the chiral centers at C-3 and C-4 are already present in the starting material with the correct configurations. The preparation of meroquinene methyl ester (**56**)[6b] is shown in Scheme 8 and that of cincholoipon (**37**)[6a] in Scheme 9. The key step in both sequences is the reductive amination of the dihydropyran derivative (**54** or **60**) to the corresponding tetrahydropyridine derivatives (**55** or **61**). The use of sodium cyanotrihydridoborate under controlled pH conditions resulted in good yields of desired products without disturbing the chiral centers.

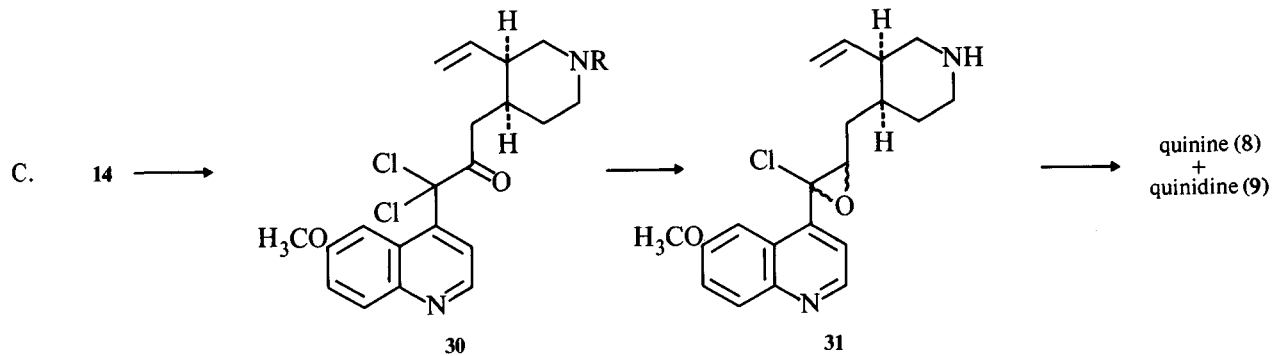
Takano and co-workers[8] described the synthesis of racemic *N*-benzoylmeroquinene aldehyde (**13**) from racemic norcamphor. This lengthy approach suffers from loss of stereospecificity and from excessive use of protecting groups.

A. **6a** → **24** → (1. $NaBH_4$, 2. KOH) → **25** (erythro) diastereomeric pair → 9-epiquinine (**10**) + 9-epiquinidine (**11**)

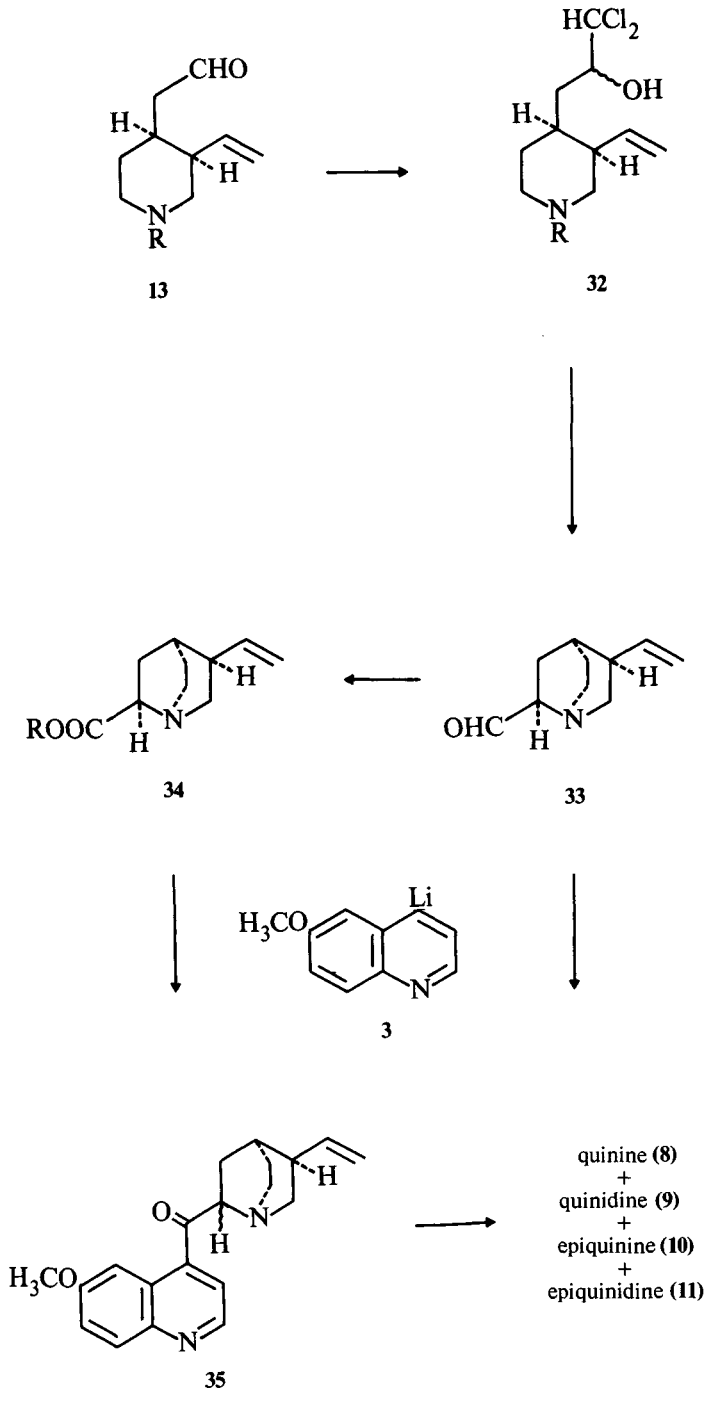


B. **13** + **26** → **27** (threo) diastereomeric pair → Cinchonidine (**28**) + Cinchonine (**29**)

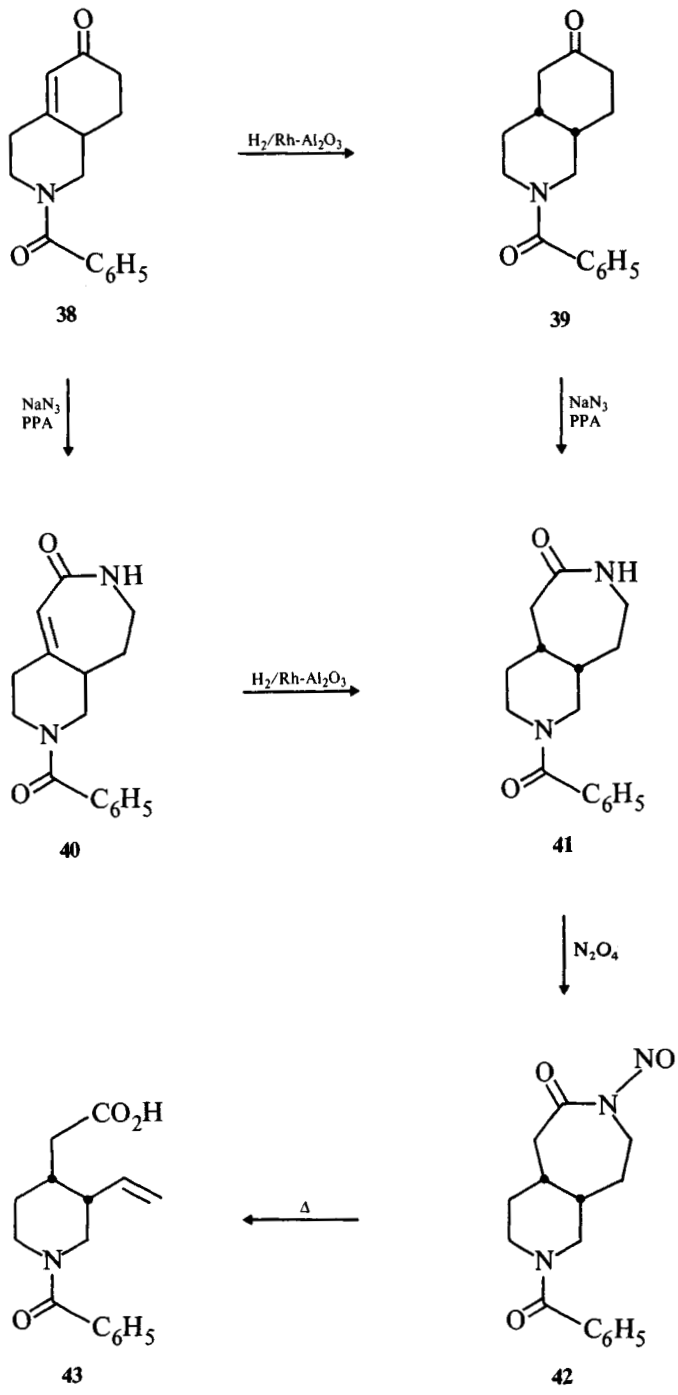




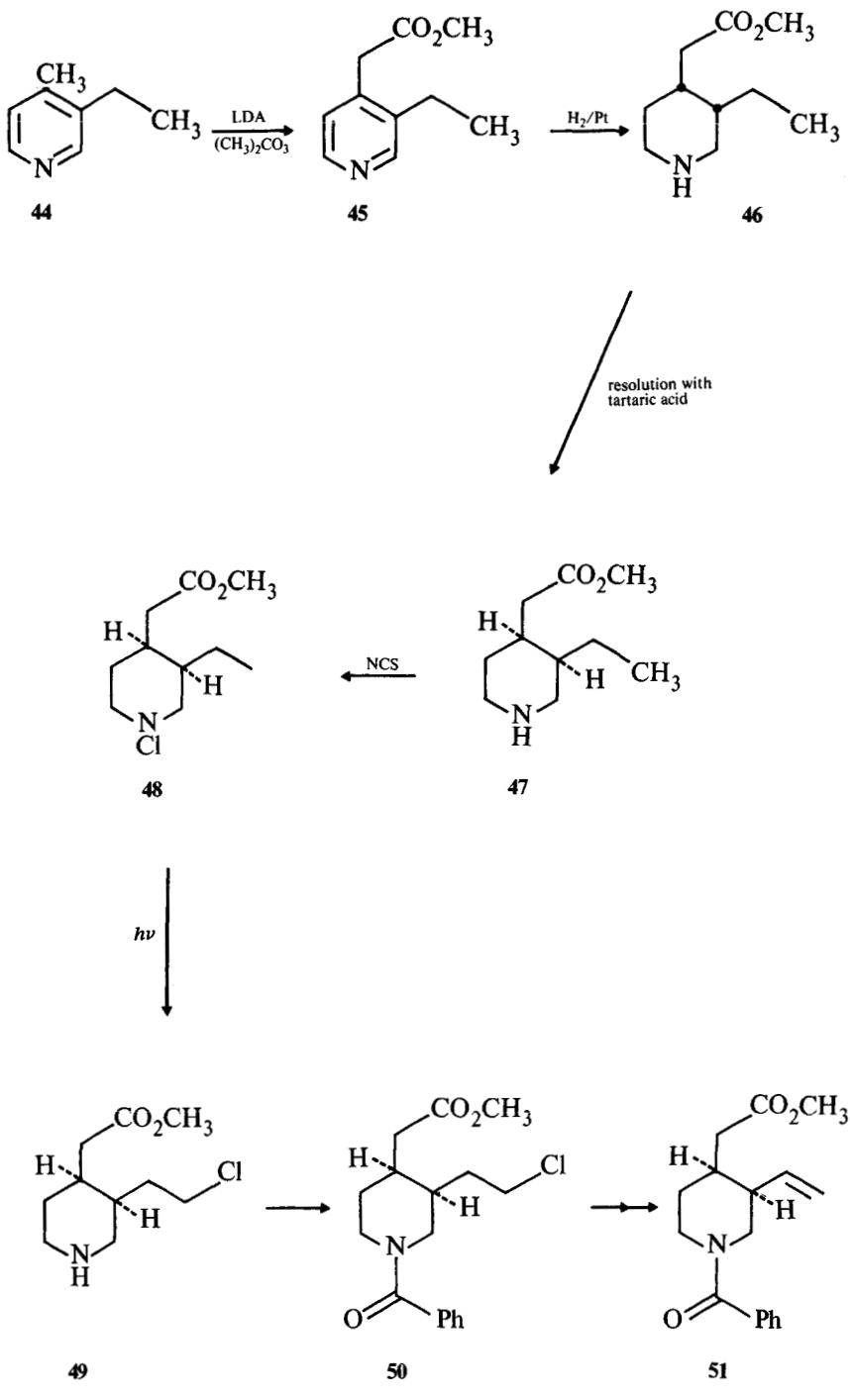
Scheme 4. Syntheses from aminoepoxides.[5c,g,l]



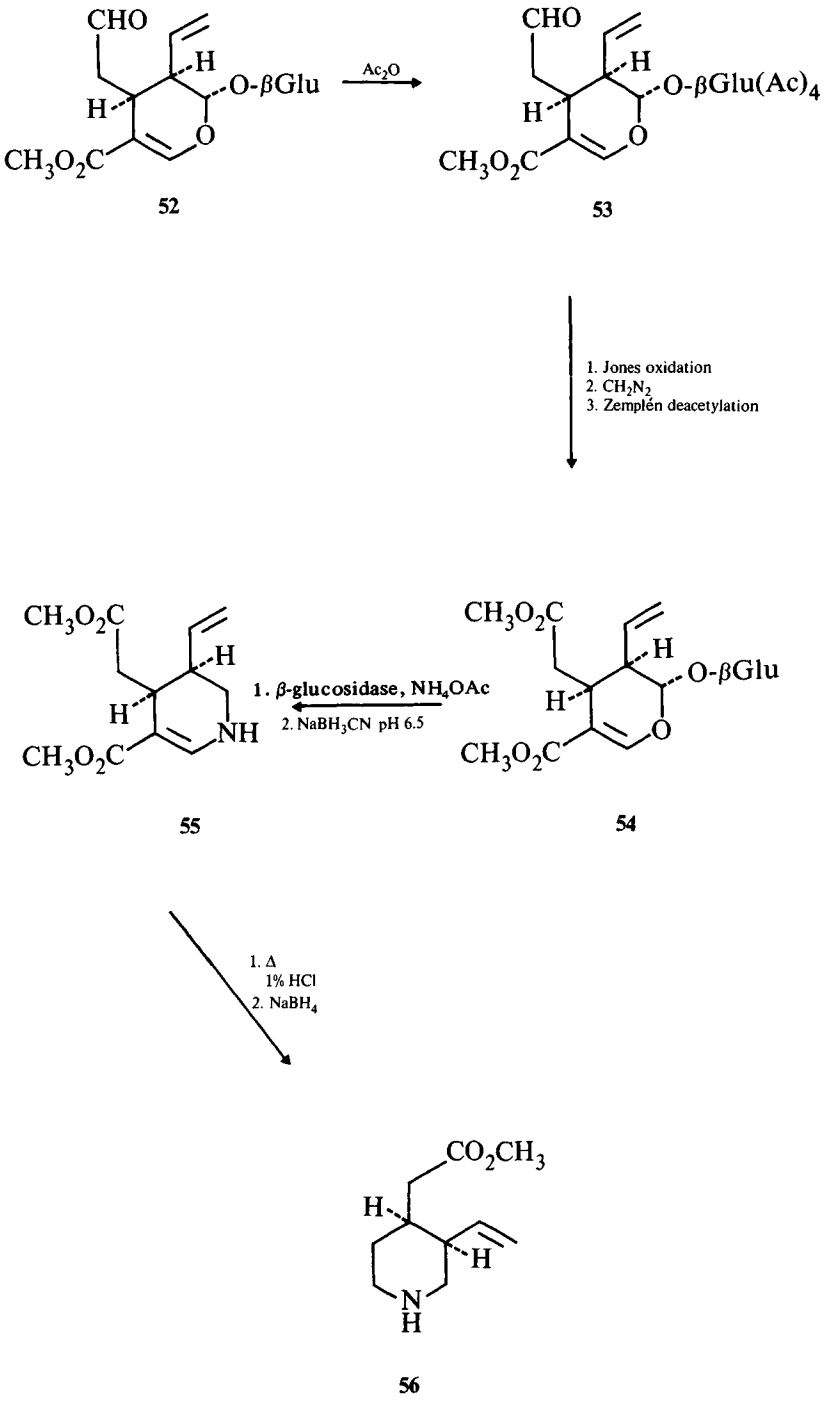
Scheme 5. Synthesis from quinuclidine derivatives.[5h]



Scheme 6. Synthesis of racemic *N*-benzoylmeroquinene.[5i]

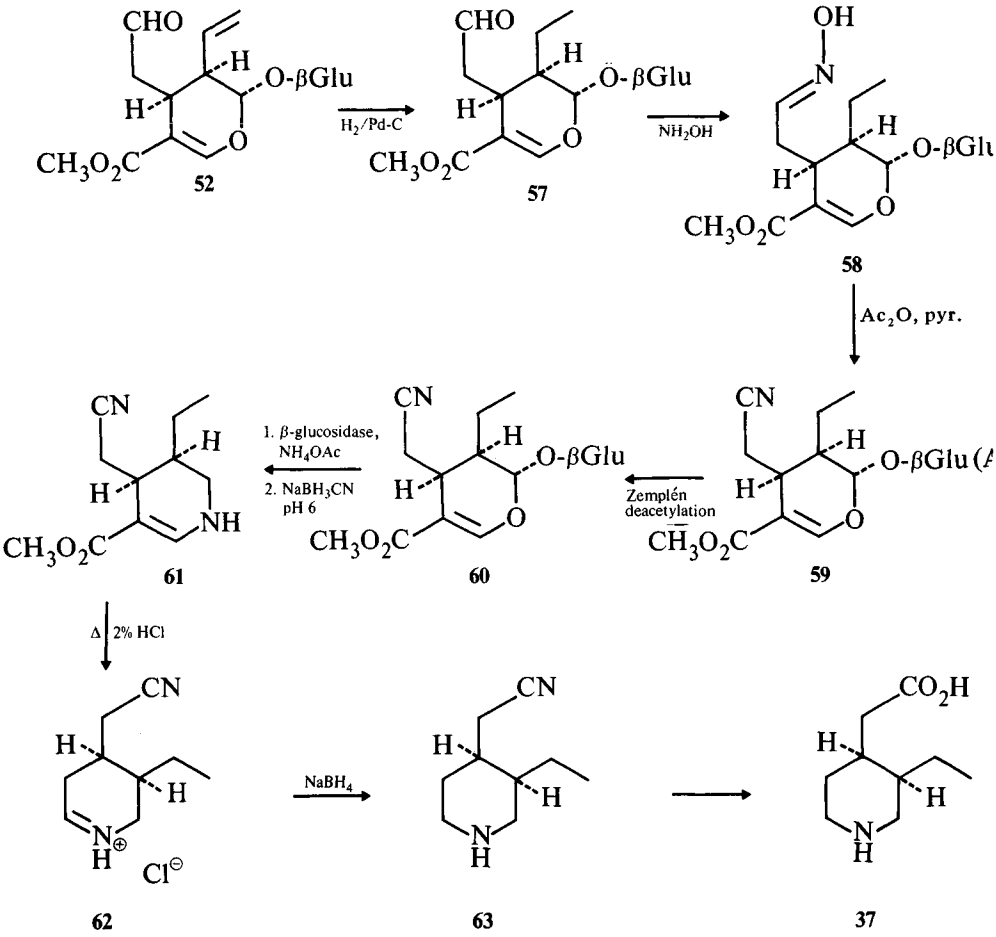


Scheme 7. Synthesis of cincholoipon methyl ester and *N*-benzoylmeroquinene methyl ester.[5j]



52 53 55 54 56

Scheme 8. Synthesis of meroquinene methyl ester from secologanin.



Scheme 9. Synthesis of cincholoipon from secologanin.

IV. METABOLISM

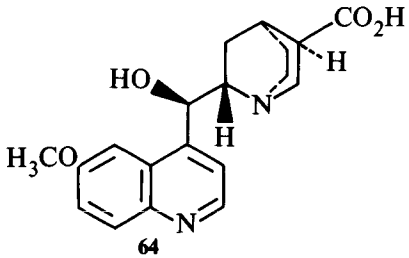
A. Isolation of Metabolites

The continued use of *Cinchona* alkaloids in medicine brings with it an intense investigation of the modes of their pharmacological actions. One aspect of these investigations is the metabolism of these drugs under in vivo and in vitro conditions.

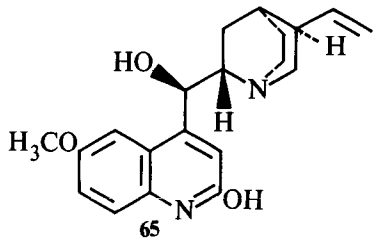
The metabolism of quinine has been under investigation since 1869 when Kerner[9] isolated quinetine (**64**) from human urine. In this metabolite, the vinyl side chain is oxidized to a carboxyl group. Hemoquinic acid – 6-methoxyquinoline 4-ketocarboxylic acid – was isolated by Nierenstein[10] in 1918 from the urine of

subjects with blackwater fever. More than 30 years later, Brodie and co-workers[11] isolated 2′-hydroxyquinine (**65**), which was also obtained in vitro when rabbit liver preparations were incubated with quinine.[12]

Investigation of the quinine metabolism in rabbits by Watabe and Kiyonaga[13] led to the isolation and characterization of two additional metabolites, 2′,3-

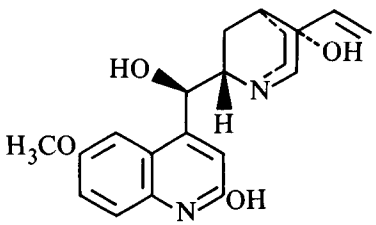


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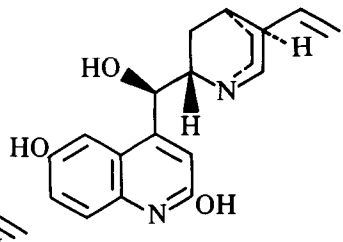


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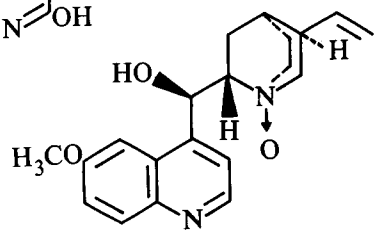
dihydroxyquinine (**66**) and 2′,6′-dihydroxycinchonidine (**67**). Most recently, Jovanovic and co-workers[14] showed quinine *N*-oxide (**68**) to be a human metabolite isolated from urine.



66

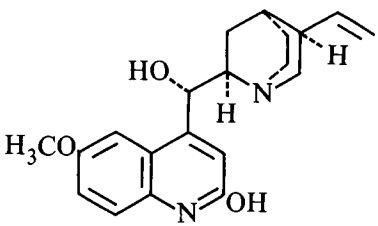


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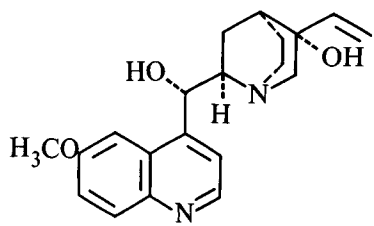


68

Similarly to quinine, the human metabolites of quinidine (**9**) are 2′-hydroxyquinidine (**69**), 3-hydroxyquinidine (**70**), and quinidine *N*-oxide (**71**). They were isolated from urine samples after oral administration of quinidine.[11,15–17] Metabolites **69** and **70** were found to have essentially the same ED_{50} as quinidine for protection against chloroform-hypoxia induced ventricular fibrillation in mice.[18]

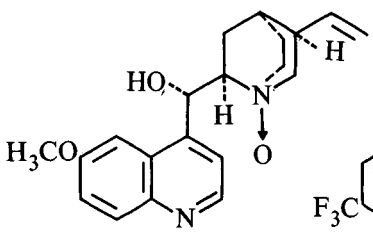


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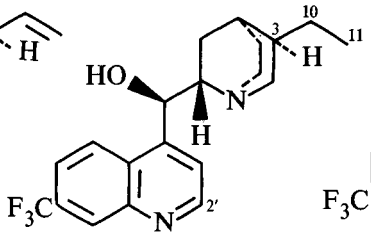


70

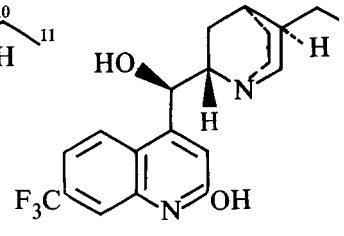
Derivatives of quinine and quinidine were expected to show the same metabolic pattern. 7′-Trifluoromethyldihydrocinchonidine (**72**), a specific supraventricular antiarrhythmic agent, is one compound of a large number of derivatives prepared by total synthesis.[19] In vitro metabolism of **72** by rat liver supernate produced six metabolites. In addition to the expected products **73–75**, the side chain-hydroxylated metabolites **76–78** were isolated. The structures of these compounds were confirmed by ^{13}C nmr, ^{1}H nmr, and mass spectroscopy.[20]



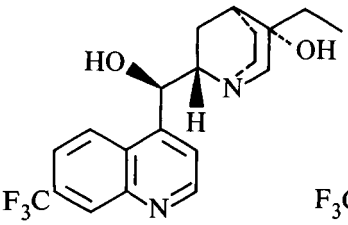
71



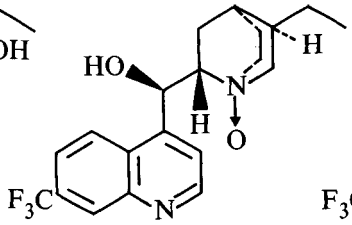
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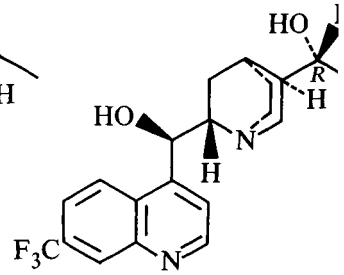
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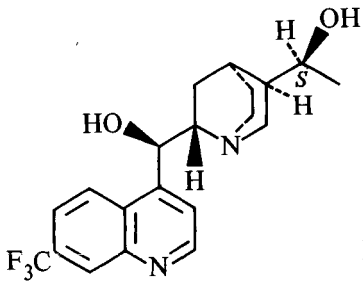
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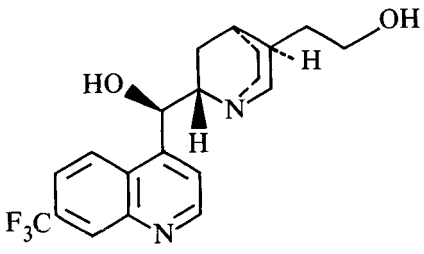
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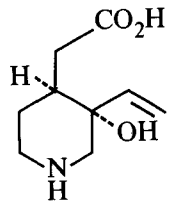
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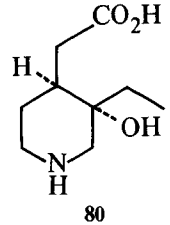
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B. Synthesis of Metabolites

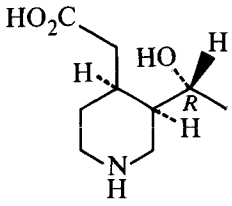
Synthesis of the metabolites hydroxylated in the quinuclidine portion requires the preparation of properly hydroxylated derivatives **79–83** of meroquinene and cincholoipon.



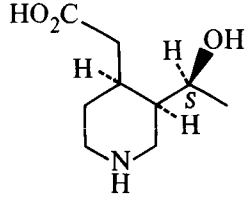
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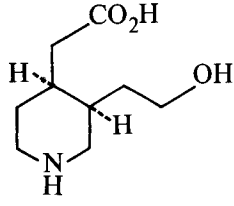
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81



82



83

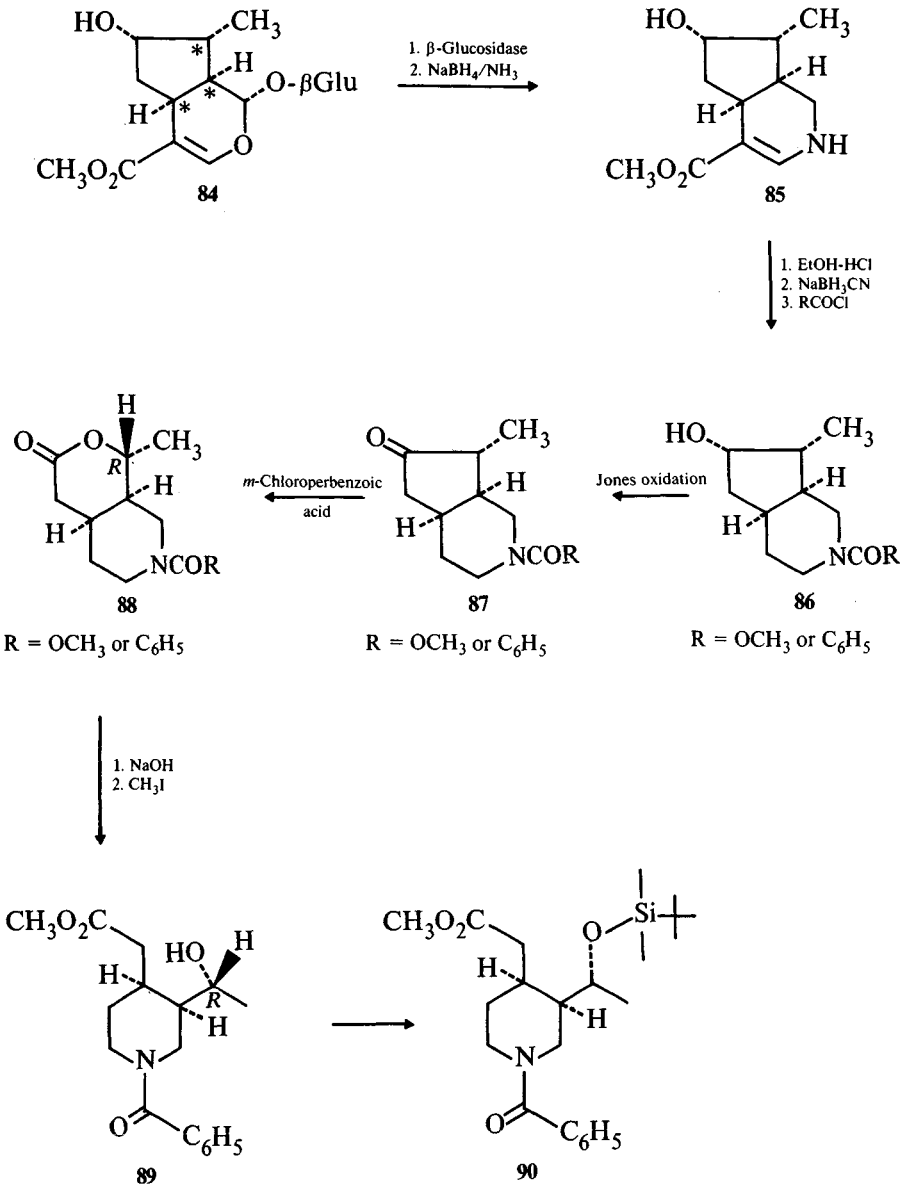
The additional hydroxy group and, in the case of **81** and **82**, the new chiral center require different synthetic methods from those used to prepare the parent compounds. Only derivative **83** can be prepared by previously established routes.

The synthesis of the two diastereomeric cincholoipon derivatives **81** and **82** has been accomplished recently[21] by two different methods. The 3-hydroxy derivatives **79** and **80** have not been prepared as yet.

The preparation of the (10*R*) derivative **89*** started with loganin (**84**), which contains all the carbon atoms of the quinuclidine moiety, the desired absolute configuration at C-3 and C-4, and the correct chirality (*R*) at C-10. Reductive amination of **84** followed by a series of reactions capped by a Baeyer-Villiger oxidation gave the key intermediate lactone **88**[22] (Scheme 10). This compound can also be obtained from 3-acetylpyridine (**91**) (Scheme 11). The incipient center of chirality was introduced by microbiological reduction with *Sporotrichum exile*.[22] Further reduction of the chiral product **92** to the desired tetrahydro analogue **93** followed by a [3.3]sigmatropic rearrangement gave the *Z*-olefin **94**. The corresponding *E* isomer **102** was obtained by the inversion sequence outlined in Scheme 12.

The asymmetric synthesis giving all three chiral centers was completed by oxidative hydroboration of the double bond of **95** and **102** from the less hindered

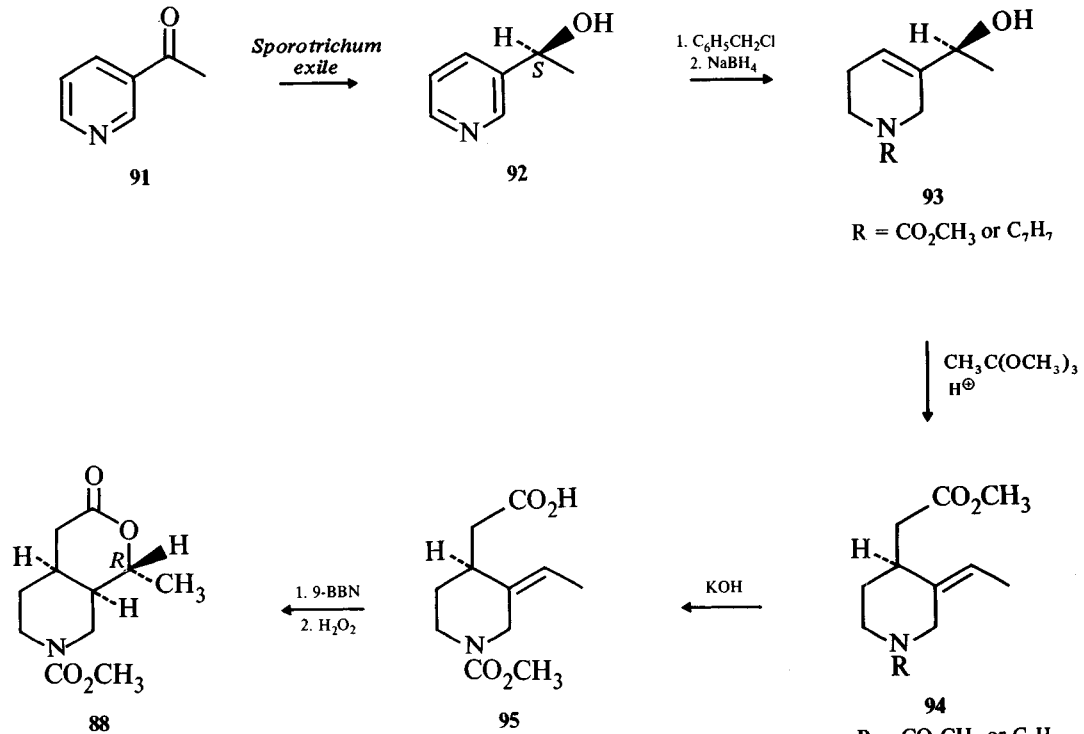
* The numbering in these derivatives is based on that of the alkaloids.



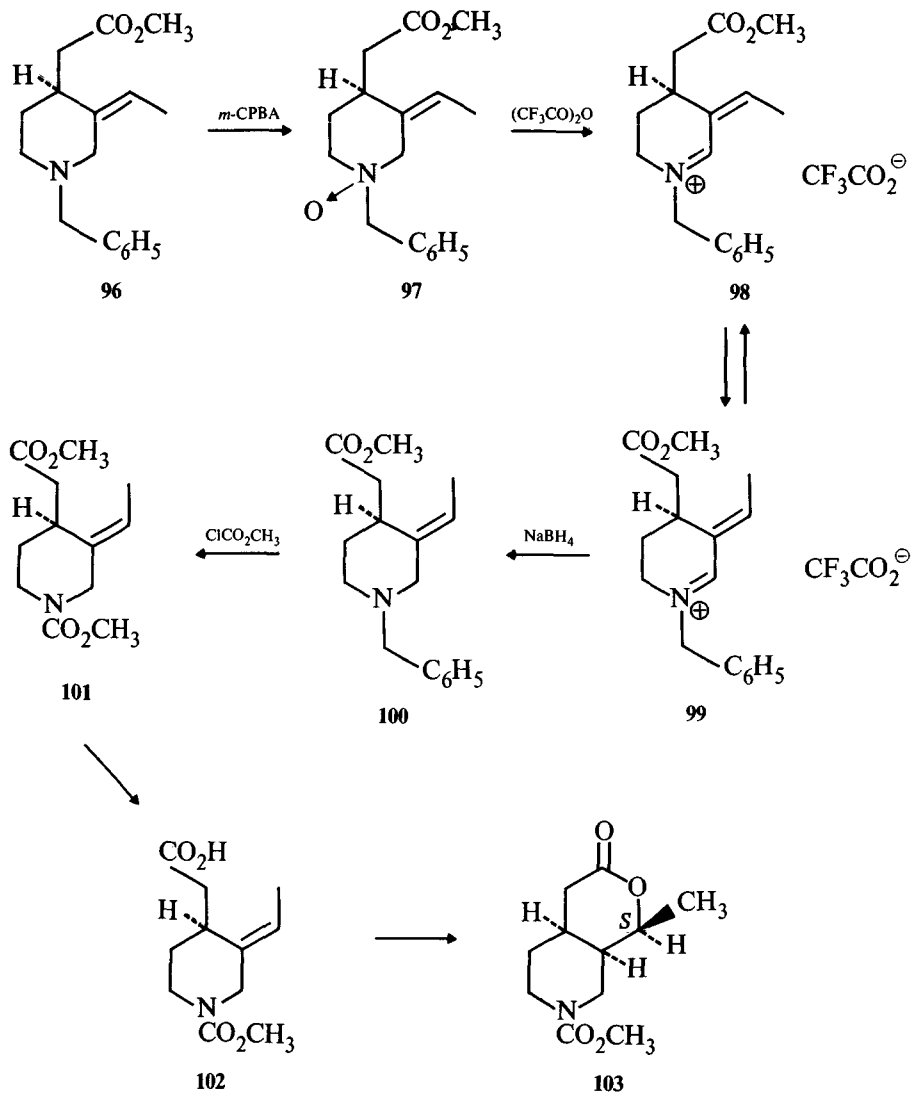
Scheme 10. Synthesis of (10*R*)-hydroxycincholoipon derivatives.

side to give the desired lactones **88** and **103**, respectively. Opening of the δ-lactone ring and subsequent silylation yielded the desired quinuclidine synthons.

The synthesis of the (10*R*)-metabolite **76** was then completed without difficulty following the synthetic scheme used originally for the parent compound[19b] (Scheme 13).



Scheme 11. Synthesis of (10*R*)-hydroxycincholoipon derivatives.



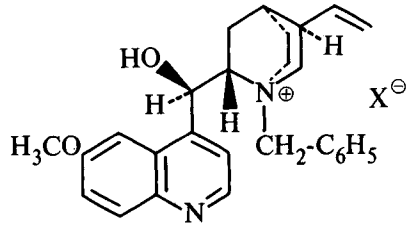
Scheme 12. Synthesis of (10*S*)-hydroxycincholoipon derivatives.

V. *CINCHONA* ALKALOIDS AS CATALYSTS IN ASYMMETRIC SYNTHESIS

The search for efficient asymmetric reactions plays an increasing role in synthetic chemistry. The induction of chirality into achiral molecules is very often achieved by the catalytic effects of alkaloids, including quinine and its derivatives.

In 1969, Pracejus and co-workers reported the use of *Cinchona* alkaloids as catalyst in the addition of alcohols to ketenes to prepare optically active esters.[23] This group then applied the same principle to the preparation of cysteine derivatives by asymmetrically adding benzyl mercaptans and other thiols to the double bond of methyl α-phthalimidoacrylates and to other electrophilic double bonds.[24]

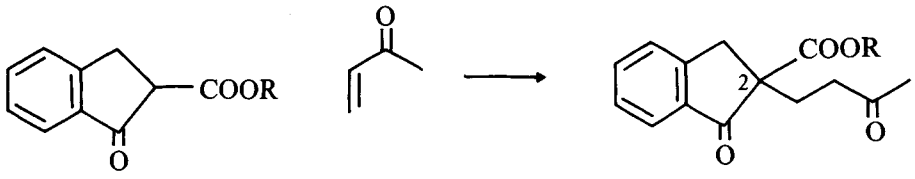
Wynberg and his group published quite extensively on the use of chiral catalysts based on *Cinchona* alkaloids. The preparation of optically active epoxides was one of their first goals, because this class of compounds cannot be resolved by classical methods unless other functional groups are present. The use of quinine as chiral catalyst failed to give any optically active material but when benzylquininium salts **(110)** (QUIBEC) were used under phase-transfer conditions, the epoxides were obtained in reasonable optical yields.[25] The same chiral catalyst was also used in the Darzens condensation, in the ring closure of halohydrins, and in the addition of cyanide to α-haloketones, but the epoxides were obtained in lower optical yields.[25b] Wynberg and his group also showed that QUIBEC **(110)** introduced a considerable degree of asymmetry into products from the Michael reaction involving nitromethanes,[26] and into allyl alcohols obtained by addition of selenophenols to 2-cyclohexen-1-ones.[27]



110

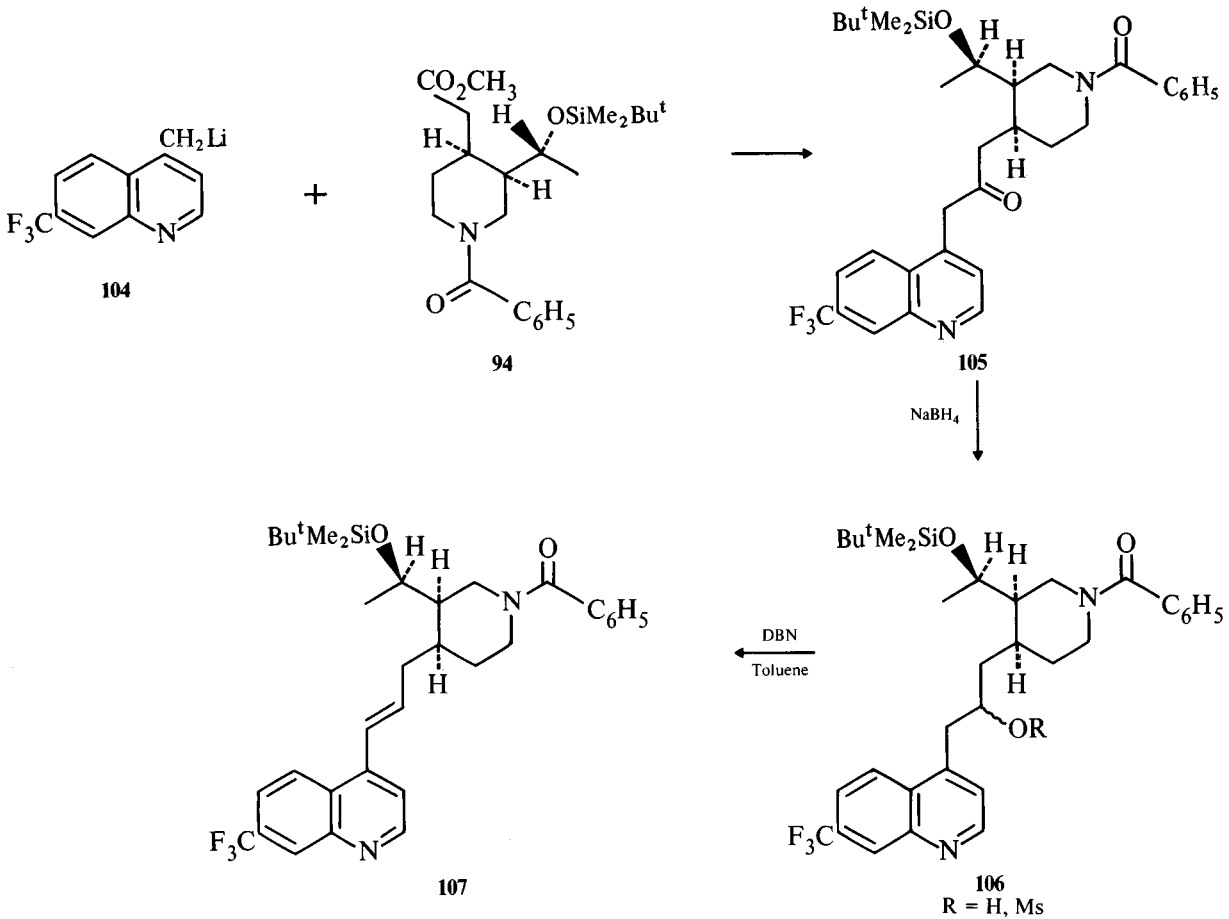
Optically active 2-phthalimidoesters – precursors of amino acids – were prepared by Julia and co-workers[28] with benzylcinchoninium chloride as catalyst.

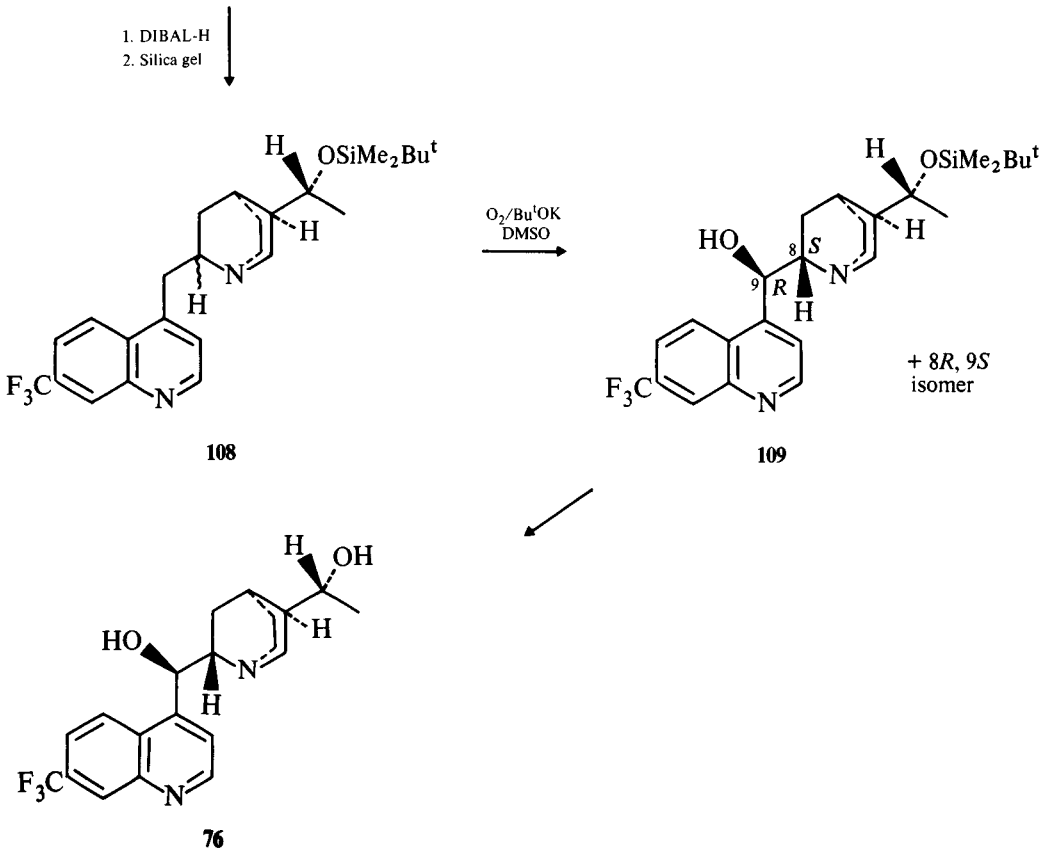
The use of *Cinchona* alkaloids either free[29] or polymer bound[30] as basic catalysts in the Michael reaction of indanones with 3-butene-2-one gave very poor results, but with the stronger base quinine methohydroxide, the desired products were obtained in high chemical and optical yield[29]:



catalyst: quinine methohydroxide (8*S*, 9*R*) ⟶ (2*S*)-enantiomer in excess

quinidine methohydroxide (8*R*, 9*S*) ⟶ (2*R*)-enantiomer in excess


CH2Li
F3C
N
104
+
CO2CH3
H
OSiMe2But
H
H
N
O
C6H5
94
ButMe2SiO
H
H
O
N
C6H5
H
O
F3C
N
105
NaBH4
ButMe2SiO
H
H
N
O
C6H5
H
OR
F3C
N
106
R = H, Ms
DBN
Toluene
ButMe2SiO
H
H
N
O
C6H5
H
F3C
N
107



Scheme 13. Synthesis of 10*R*-hydroxy-7-trifluoromethyldihydrocinchonidine.

This work confirmed previous observations that the spatial arrangement at C-8 and C-9 of the *Cinchona* alkaloids determines the stereochemistry of the products. This so-called C-8,C-9 control was also observed with the acetates of dihydroquinine or dihydroquinidine in the preparation of chiral cis-vicinal diols by osmium tetroxide oxidation.[31] In a recent report[32] on the asymmetric addition of benzylmercaptan to 2-nitrostryrene in the presence of polymeric acrylonitrile-*Cinchona* alkaloid catalysts, it was shown that the chiral center at C-3 also participates in the enantioface differentiating step.

Additional applications for the use of benzylquininium chloride **(110)** as chiral catalyst under phase-transfer conditions are shown in the borohydride reduction of carbonyl compounds[33] and in the alkylation of 3,4-dihydro-β-carbolinones.[34] Complexes of *Cinchona* alkaloids with cobalt in homogeneous hydrogenations[35] and with rhodium in the alcoholysis of organosilanes[36] and the preparation of chiral phosphines[37] are further examples of the use of *Cinchona* alkaloids in asymmetric synthesis.

The latest contribution in this area comes again from the laboratory of Wynberg and has industrial potential. This group reported the quinidine-catalyzed reaction between chloral and ketene to give quantitative yields of *S*-(−)-γ,γ,γ-trichloro-β-butyrolactone in 95% enantiomeric excess. Hydrolysis of the lactone gave the industrially important *S*-(−)-malic acid. Its rare enantiomer was obtained in 76% enantiomeric excess by the catalytic action of quinine.[38]

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CHAPTER XIII

Camptothecin

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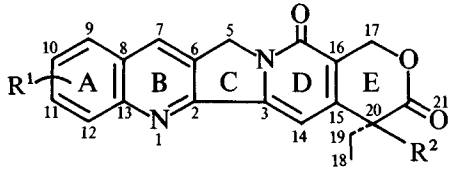
1. INTRODUCTION

Camptotheca acuminata Decne (Nyssaceae) is a tree distributed widely and abundantly in the southern part of China and was originally introduced to the United States in 1911.[1] During a plant antitumor screening program carried out under the auspices of the National Cancer Institute of the U.S. National Institute of Health, it was found that the crude alcoholic extract of *C. acuminata* showed antitumor activity in animal tests.

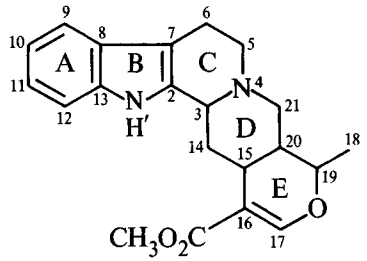
A. Structure and Characterization

Wall et al. isolated the antitumor alkaloid, camptothecin (**1**), from the stem wood of this tree in combination with a bioassay method in 1966.[2] The structure of **1** was deduced from its spectral properties (uv, ir, ^{1}H nmr, mass spectrometry), certain chemical properties (formation of mono-*O*-acetate, reaction with thionyl chloride and pyridine to give chlorocamptothecin, rapid saponification to a sodium salt that gave **1** on acidification, and reduction with sodium borohydride at room temperature to a lactol), and X-ray crystallographic analysis of its iodoacetate derivative.[2-4] The latter technique established that **1** is a pyrrolo[3,4-*b*]quinoline alkaloid, that is, 4(*S*)-4-ethyl-4-hydroxy-1*H*-pyrano-[3′,4′:6,7]indolizino[1,2,-*b*]quinoline-3,14(4*H*,12*H*)-dione. As could be expected, rings ABCD and their substituents (C-17,C-20, and the pyridone oxygen) are coplanar. Atoms C-21 and the lactone ring oxygen deviate from the plane by 0.69 and 0.73 Å. respectively; thus ring E has a boat conformation.[4,6]

Shamma suggested using the Le Men-Taylor numbering system for **1**, based on the probable biogenetic relationship between camptothecin and the indole alkaloids, especially ajmalicine **2**.[5]



	R^1	R^2
1	H	OH
3	10-OH	OH
4	10-OCH_3	OH
5	9-OCH_3	OH
6	11-OH	OH
7	11-OCH_3	OH
8	H	H



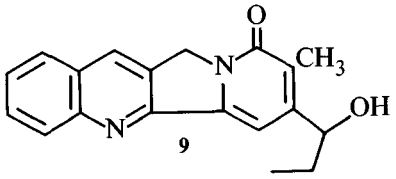
2

Camptothecin has two notable chemical properties. Its lack of significant basicity causes it to behave as a neutral molecule; that is, it does not form stable salts with mineral acids and gives negative tests with Dragendorff and Mayer reagents. Thus it is not an alkaloid in the usual sense of the definition. The presence of the C-20 tertiary alcohol imparts an unusual electrophilicity to the lactone carbonyl group, perhaps via a strong intramolecular hydrogen bond. This structural feature explains the behavior of **1** toward aqueous alkali, amine nucleophiles, and sodium borohydride. It also justifies the difficulty in preparing stable C-21 ester or amide derivatives of **1**; rapid reversion of such derivatives to **1** occurs by intramolecular attack of the C-17 primary alcohol at the electrophilic C-21 carbonyl group.

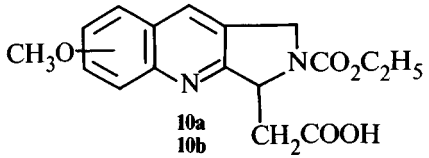
B. Natural Analogues and Sources

Camptothecin and its analogues have also been found in some other plants. Further fractionation of the extract of the stem wood of *C. acuminata* resulted in the isolation of two minor compounds, 10-hydroxycamptothecin (**3**) and 10-methoxycamptothecin (**4**), in 1969 by Wani and Wall.[7] 9-Methoxycamptothecin (**5**), **1**, and another related alkaloid, mappicine (**9**), were isolated by Govindachari et al. from *Nothapodytes foetida* (Wight) Sleumer (Icacinaceae) (formerly *Mappia foetida* Miers).[8,9] Tafur et al. found **1** and **4** in *Ophiorrhiza mungos* L. (Rubiaceae).[10] Gunasekera et al. isolated **1** and **5** from *Ervatamia heyneana* (Wall) T. Cooke (Apocynaceae).[11] Hsu et al. investigated the alkaloidal components of the fruits of *C. acuminata* and found two new minor alkaloids, 11-hydroxycamptothecin (**6**) and 11-methoxycamptothecin (**7**), besides **1**, **3**, and **4**.[12,13] 20-Deoxycamptothecin (**8**) was also found in *C. acuminata*.[12,21]

The exact position of the hydroxy or methoxy group in these alkaloids was established by comparing their nmr spectra with those of the synthetic methoxy pyrrolo[3,4-*b*]quinoline analogues **10**[7,8,12] and was confirmed subsequently by total synthesis.[14,15]



9



10a
10b

Hsu et al. examined the content of camptothecin in different parts of *C. acuminata* and found that it was higher in the fruits than in other parts of the tree[16]:

	%
Twigs	0.004
Stem bark	0.01
Roots	0.01
Root bark	0.02
Fruits	0.03

Buta and Novak isolated camptothecin from dry woody material of *C. acuminata* in 0.05% yield by gel permeation chromatography.[17]

The content of camptothecin in *Nothapodytes foetida* was higher than that in other plants according to the reports of Govindachari and Viswanathan (0.1%)[8a] and Agarwal and Rastogi (0.35%)[8b]:

	%
Stem	0.06
Bark	0.08
Roots	0.1
Leaves	0.01

All the oxygenated analogues were found only as trace constituents: 9-methoxycamptothecin (0.002%,[8a] 0.045%[8b]) in *N. foetida*, 10-methoxycamptothecin (0.005%[10]) in *O. mungos*, and 10-hydroxycamptothecin (0.002%[12]) in *C. acuminata*.

Chu et al. obtained 10-hydroxycamptothecin from camptothecin in 10% yield by biotransformation with fungi T-36.[18]

Sakato et al. obtained camptothecin from the leaves of *C. acuminata* by using a plant cell culture technique.[19,20] A medium containing 2,4-dichlorophenoxyacetic acid, kinetin, and gibberellic acid (GA_3) in the Murashige and Skoog basal medium was used. It was found that addition of tryptophan and phenylalanine markedly promoted the cell growth.

All the oxygenated camptothecin analogues showed antitumor activity in animal tests, and may be produced from **1** as a result of further metabolism in the plant.

Some physical characteristics of camptothecin and its analogues are given in Table I.

TABLE I. PHYSICAL CHARACTERISTICS OF CAMPTOTHECIN AND ITS ANALOGUES

Compound	Mp (°C)	Fluorescence under uv	$[\alpha]_D$	(c, solvent[a])	Ref.
1	264–267 (dec)	Blue	+31.3	(–,[b] A)	2
			+40	(0.475, A)	12
			+42.8	(1, A)	8a, 11
3			–139.5	(1.2, B)	12
	266–267	Red-yellow	–147	(0.674, B)	13
	268–270				7
4	254–255				7
	255–256 (dec)	Blue	–[b]		10
	246–247 (dec)				12
5	258–260 (dec)	Yellow	–76.1	(0.5, B)	8a, 11
6	327–330 (dec)	Dark red	–145.9	(0.19, B)	13
7	264–265 (dec)	Blue	–[b]		12
8	272–274	Blue	+194	(0.58, C)	12
9	251–252	Bright green	–[b]		9

[a] Solvent: A = $CHCl_3$: MeOH, 4 : 1; B = pyridine; C = $CHCl_3$.
[b] Data not available.

II. TOTAL SYNTHESIS

The announcement of camptothecin's structure in 1966 caused considerable excitement in the scientific community for two reasons. First, the molecule represented a new heterocyclic ring system, and second, it exhibited excellent biological activity in the in vivo rodent assay for antitumor activity.

There was an evident need for the development of practical synthetic routes to **1** and its analogues because of the rarity of the natural source. Furthermore, the challenge to devise a general synthesis of the pyrrolo[3,4-*b*]quinoline ring system was not ignored by many research groups.[6,22,23]

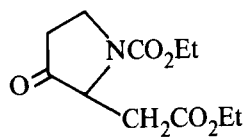
A. Total Synthesis of Camptothecin

1. *Stork and Schultz Synthesis*

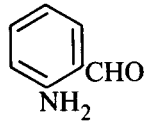
Stork and Schultz achieved the first total synthesis of *dl*-**1** in 1971.[24] A base-catalyzed Friedländer condensation of pyrrolidone **11** with 2-aminobenzaldehyde (**12**) gave the pyrrolo[3,4-*b*]quinoline acid **13** (rings ABC) (Scheme 1). Following hydrolysis and esterification, the resulting amino ester **14** was condensed with carbethoxyacetyl chloride to give the diester amide **15**, which was converted to the tetracyclic β-keto ester **16** by a Dieckmann cyclization. Hydrolysis and decarboxylation of **16**, followed by reduction with sodium borohydride and elimination of water from the resulting β-hydroxylactam **17**, gave the desired dihydropyridine **18** (rings ABCD). The latter reacted efficiently at low temperature with the lithium anion of a protected α-hydroxybutyric acid ester to give the key pentacyclic compound **19** via intermediate **18a**. This transformation represented a new annulation method of an α,β-unsaturated carbonyl compound.[6] Finally, hydrolysis of the ethyl ester of **19** followed by reduction with sodium borohydride gave the hemiacetal-acid **20** which was converted to *dl*-**1** through acetate hydrolysis, hemiacetal reduction, and acidification to form the α-hydroxylactone ring. The overall yield of *dl*-**1** was 1–2%.

2. *Danishefsky et al. Synthesis*

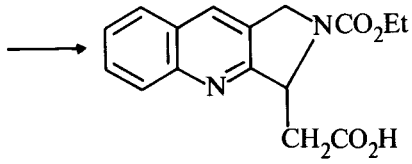
The report of the first synthesis of camptothecin preceded the description of the second total synthesis of *dl*-**1** by only 9 weeks. Volkmann et al.[25] assembled the alkaloid by a Friedländer condensation approach in which the key pyridone **25** (rings ABCD) was prepared by a novel synthetic route to 4,6-disubstituted pyridones (Scheme 2).[26] The latter utilized the Michael addition of enamine **22** to dicarbethoxyallene to yield an *N*,4,5,6-tetrasubstituted pyridone (**23**). Transformation of **23** to **25** through Dieckmann cyclization of an intermediate tetramethyl ester **24** was followed by hydrolysis-decarboxylation in aqueous acid, then a



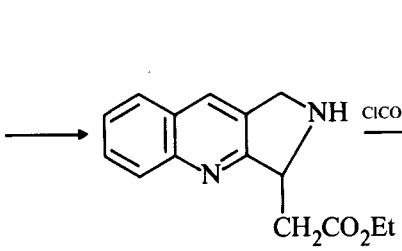
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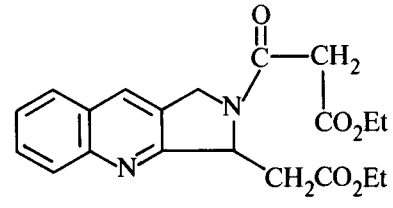
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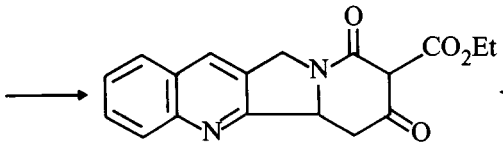
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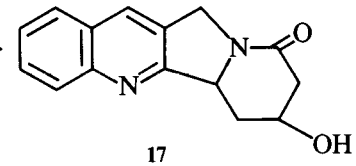
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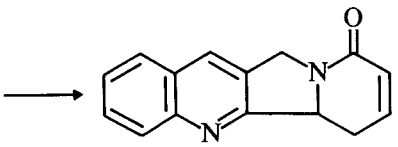
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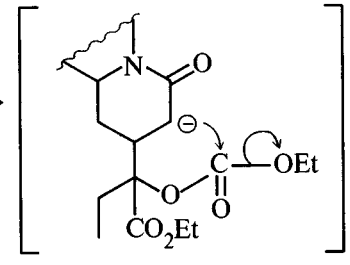
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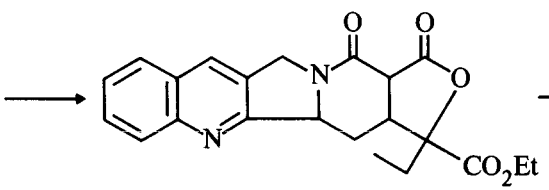
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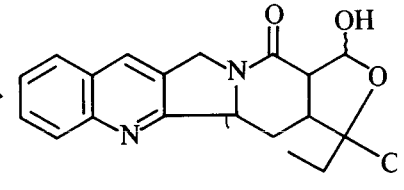
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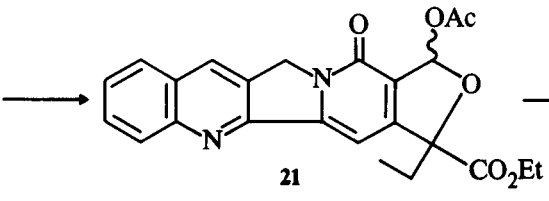
18a



19



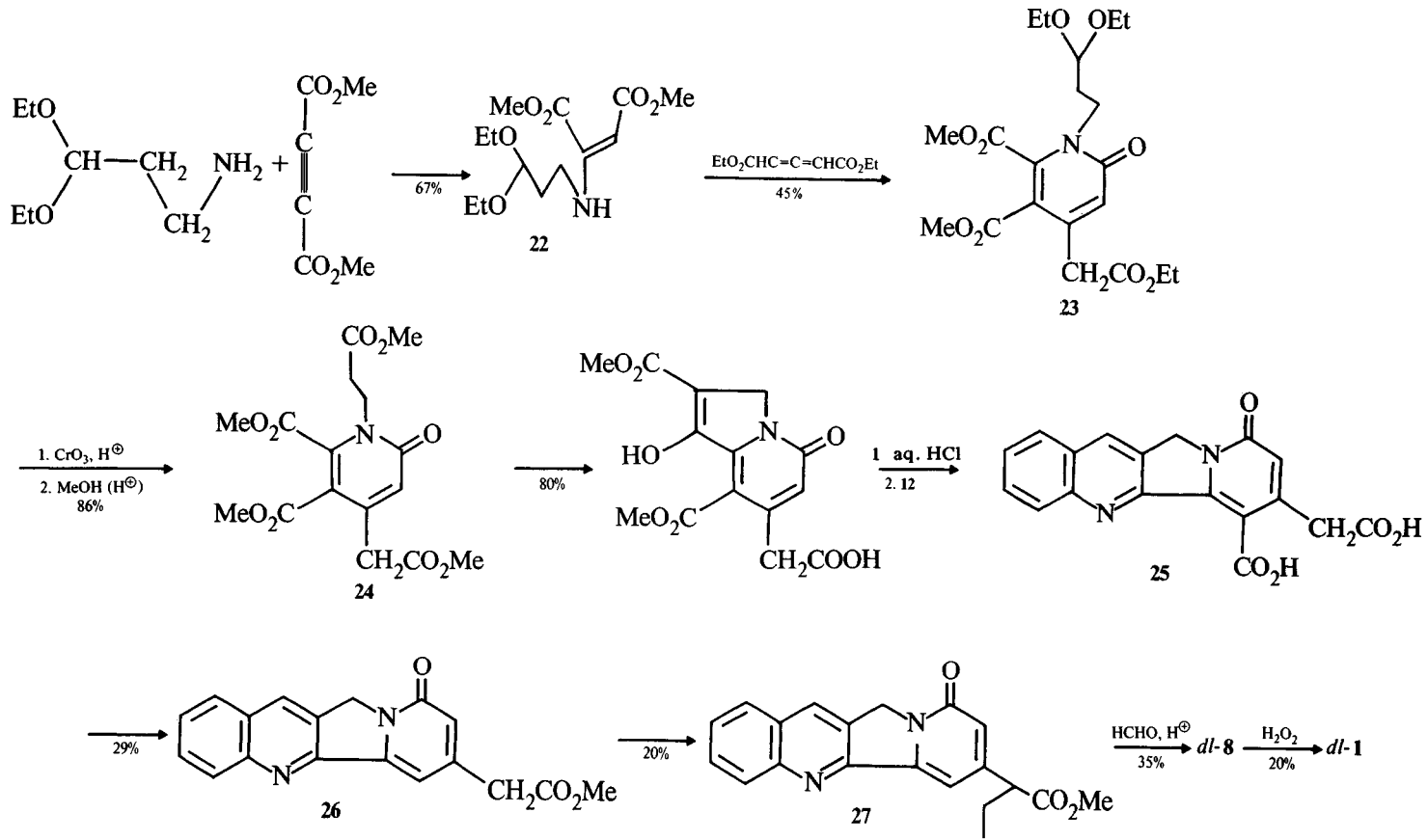
20



21

dl-1

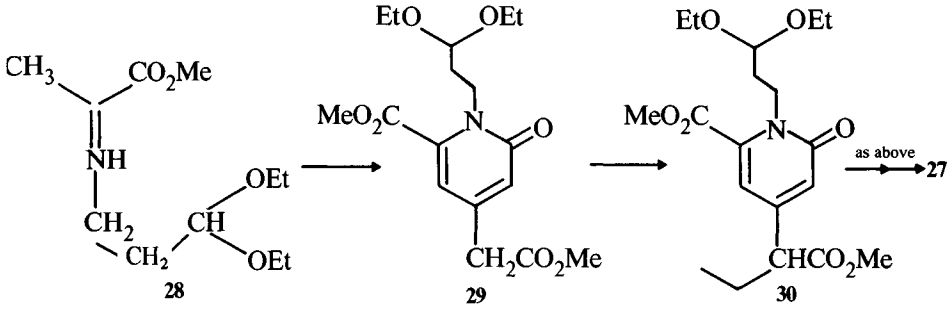
Scheme 1.


EtO
CH—CH2 NH2 +
EtO
CH2
CO2Me
C
C
CO2Me
67%
MeO2C
CO2Me
EtO
EtO
NH
22
EtO2CHC=C=CHCO2Et
45%
EtO OEt
MeO2C
N
O
MeO2C
CH2CO2Et
23
1. CrO3, H⊕
2. MeOH (H⊕)
86%
CO2Me
MeO2C
N
O
MeO2C
CH2CO2Me
24
80%
MeO2C
HO
N
O
MeO2C
CH2COOH
1 aq. HCl
2. 12
O
N
CH2CO2H
CO2H
25
29%
O
N
N
CH2CO2Me
26
20%
O
N
N
CO2Me
27
HCHO, H⊕
35%
dl-8
H2O2
20%
dl-1

Scheme 2.

Friedländer condensation to give the tetracyclic diacid **25**. After selective esterification, the tetracyclic monomethyl ester **26** was obtained in 29% yield by pyrolysis over cuprous oxide. The latter compound was monoethylated to **27** in 20% yield. Treatment of **27** with paraformaldehyde in acidic solution resulted in C-16 hydroxymethylation and lactonization to give *dl*-**20**-deoxycamptothecin (*dl*-**8**) in 35% yield along with a structurally isomeric minor product (isodeoxycamptothecin due to C-14 hydroxymethylation[27]). Synthetic 20-deoxycamptothecin spontaneously oxidized to *dl*-**1** on exposure of its solution to air; on a preparative scale, Danishefsky et al.[27] carried out this oxidation in 20% yield by treating a solution of the C-20 anion of *dl*-**8** with hydrogen peroxide. The ease by which **8** gives **1** may have biogenetic significance.

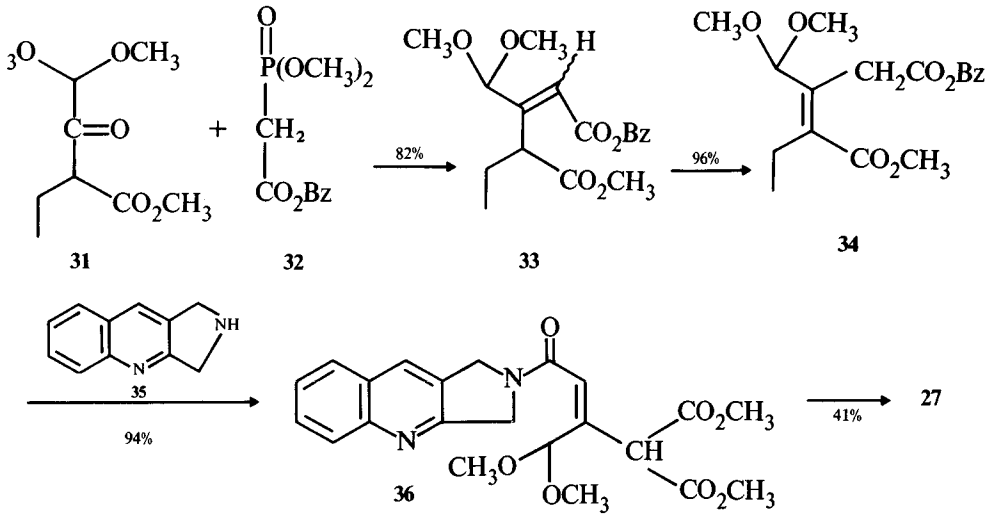
a. QUICK SYNTHESIS OF **27**. Quick, in 1977, modified this synthesis by first using imine **28** as starting material to prepare pyridone **29** (Scheme 3). This pyridone makes it possible to avoid the low-yield decarboxylation of **25** to **26**. Second, the C-20 ethyl group was introduced at an early stage, that is, ethylation of pyridone **29** to afford compound **30**, thus improving the yield of C-20 ethylation from 20 to 65%. According to this report, the overall yield from methyl pyruvate to tetracyclic ester **27** was 9%.[28]



Scheme 3.

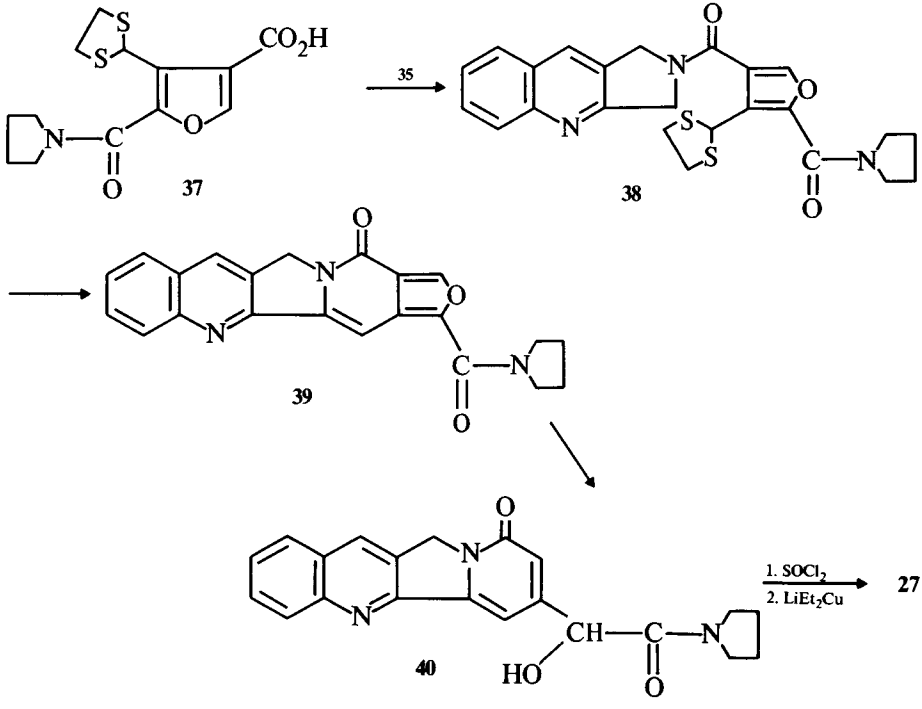
b. BRADLEY AND BÜCHI SYNTHESIS OF **27**. Bradley and Büchi devised a simple route to preparing tetracyclic ester **27** in 1976 (Scheme 4).[29] Starting from ketoester **31**, readily available from methyl dimethoxyacetate and methyl butyrate, **33** was obtained in 82% yield by Wittig condensation. After debenzylation, **33** was converted to a compound similar to **36**, but only in 56% yield. Consequently, **33** was rearranged to **34**, and the latter, after debenzylation, was condensed with tricyclic amine **35** to give **36** in 94% yield. Treatment of **36** with boron trifluoride and trifluoroacetic acid gave tetracyclic ester **27** in 41% yield (the overall yield was 30%).

c. KENDE ET AL. SYNTHESIS OF **27**. Kende et al. reported a novel synthesis of **27** in 1973 (Scheme 5).[30] Trisubstituted furan **37**, prepared from furfural dimethyl acetal via a six-step sequence of reactions in 19% yield, was condensed with **35** to give tricyclic amide **38**, which then was deprotected and cyclized to give pentacyclic amide **39**. The last compound underwent a facile



Scheme 4.

alkaline hydrolysis with loss of one carbon as carbon dioxide to give the hydroxyamide **40** in 74% yield from which tetracyclic ester **27** was obtained through chlorination, ethylation, and methanolysis. The overall yield from furfural to **27** was about 3%.



Scheme 5.

3. *Winterfeldt et al. Biomimetic Synthesis*

Winterfeldt et al. discovered that certain tetrahydro-β-carboline alkaloids could be autoxidized to pyrrolo[3,4-*b*]quinolines in strongly basic dimethylformamide solution.[31] This observation led them to develop an imaginative total synthesis of camptothecin (Scheme 6),[32] whose strategy in part may parallel the alkaloid's biogenesis.

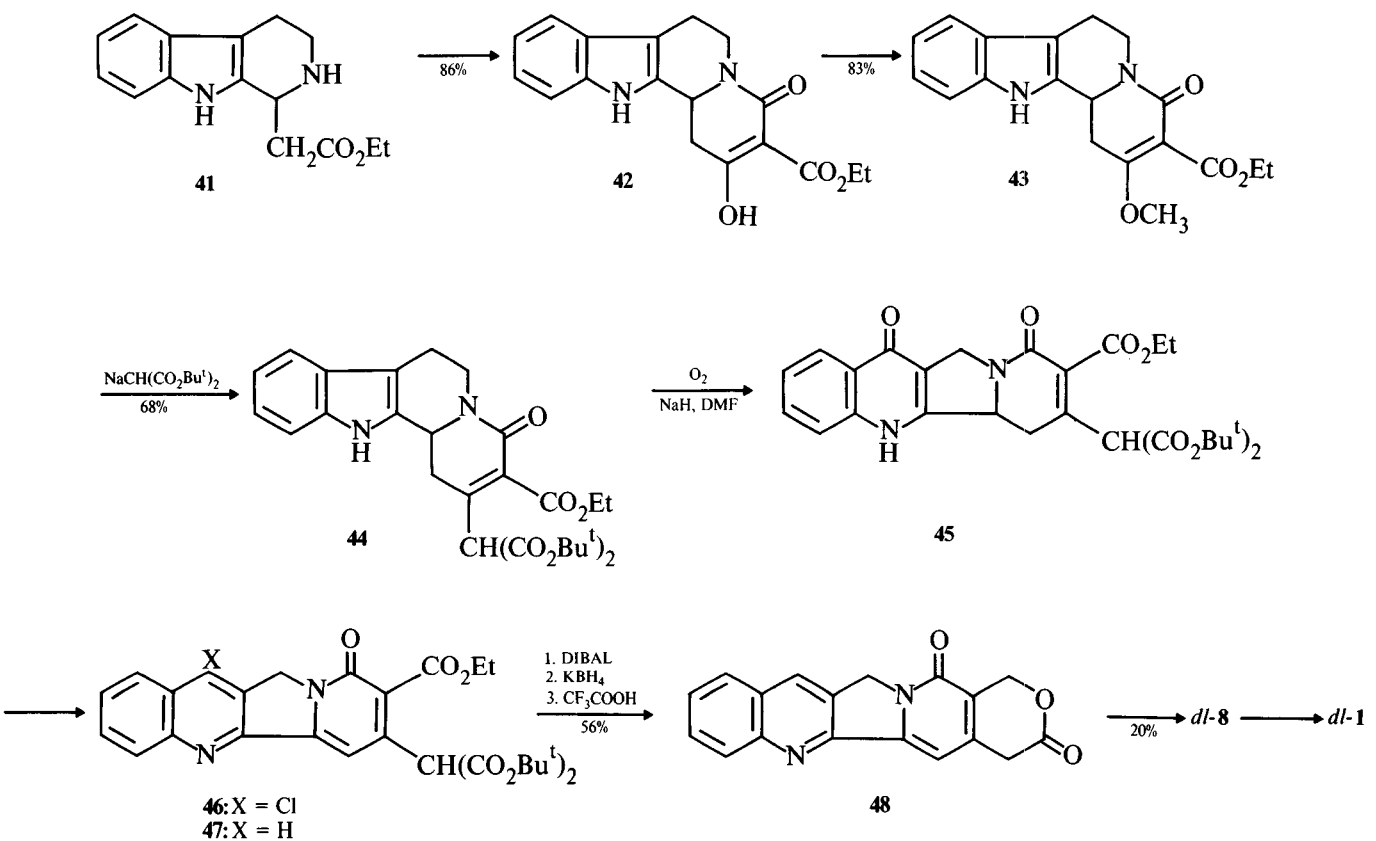
The Winterfeldt et al. synthesis of *dl*-**1** employed the tetracyclic lactam **43** as the keystone for the formation of the pyrrolo[3,4-*b*]quinoline ring system. Lactam **43** was available from **41** via **42**. Thus **41** was condensed with monoethyl malonate and cyclized in potassium *t*-butoxide to obtain **42**, then the latter was reacted with diazomethane which resulted in the formation of the α,β-unsaturated lactam **43**. The 1,4-addition-elimination of sodio di-*t*-butylmalonate to **43** followed by autoxidation of the tetrahydro-β-carboline **44** and treatment of **45** with thionyl chloride in dimethylformamide at room temperature gave the 12-chloro-9-oxo-9,11-dihydro-indolizino[1,2-*b*]quinoline **46** in good overall yield. Introduction of the 10a,6-double bond in **46** was postulated to involve a novel chlorination–dehydrochlorination sequence.[33] After hydrogenolytic removal of the chlorine atom, the carbethoxy group in **47** enabled its chemoselective reduction to a primary alcohol by treatment with, first, diisobutylaluminum hydride at low temperature, then potassium borohydride, from which **48** resulted by treatment of the intermediate δ-hydroxy-di-*tert*-butylmalonate with trifluoroacetic acid. Ethylation at C-20 of **48** proceeded poorly because of concurrent dialkylation at C-5 and C-20, but the resulting deoxycamptothecin was oxidized to *dl*-**1** quantitatively by oxygen in the presence of cupric chloride and aqueous dimethylamine.

Alternatively, **46** could also be converted to 7-chlorocamptothecin and then hydrogenolyzed (to remove the chlorine atom) to give *dl*-**1**.

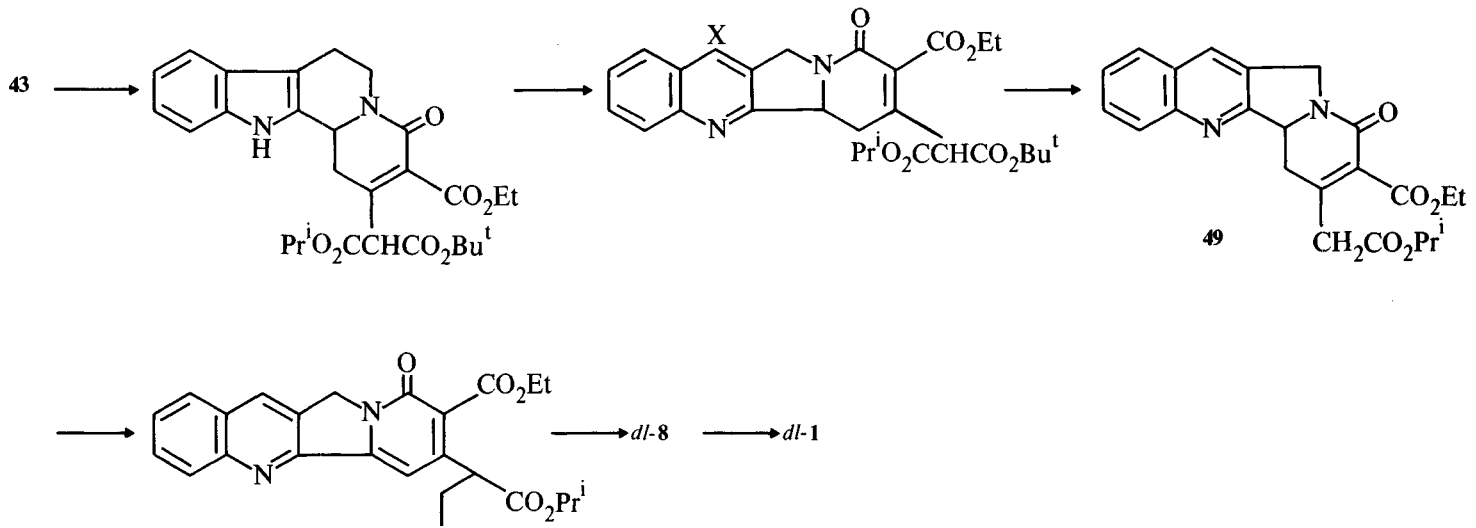
Winterfeldt's group later reported the result of further developments in the synthetic chemistry of camptothecin, which markedly improved the overall yield of their synthesis. The problem of C-5 ethylation was circumvented by ethylation of a monoisopropyl ester analogue **49**, which was obtained by using isopropyl *t*-butyl malonate instead of di-*t*-butyl malonate in preparation of **44** (Scheme 7). This modification made it possible to hydrolyze selectively the *t*-butyl ester for subsequent decarboxylation. From compound **49**, 20-deoxycamptothecin could be obtained as before in 86% yield. The overall yield of *dl*-**1** from **41** was 13–14%.[34]

They also investigated the remarkable ease by which 20-deoxycamptothecin is autoxidized to *dl*-**1**, finding that this reaction has structural limitations.[35] Only **8** and its ring DE analogues (as the N-CH_3 pyridone) could be oxidized at C-20 using their experimental conditions. Three other compounds (dimethyl 2-ethyl malonate, methyl 2-ethyl phenylacetate, and the benzene ring analogue of rings DE of camptothecin) examined as models for this oxidation were completely unreactive. Clearly, the pyridone ring of **8** plays a vital role in the mechanism of C-20 autoxidation.

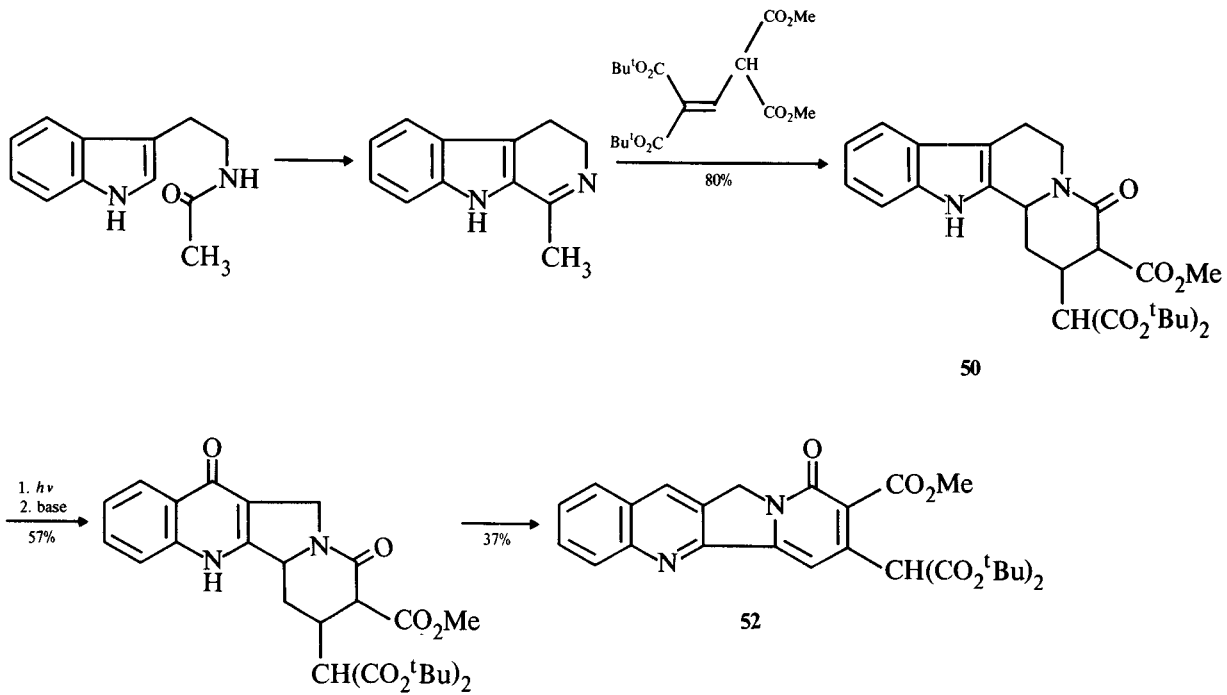
a. KAMETANI ET AL. SYNTHESIS. Kametani et al. prepared methoxycarbonyl derivative **52**, the methyl analogue of **47**, via an enamine annulation as


86%
83%
41
42
43
$NaCH(CO_2Bu^t)_2$
68%
O_2
NaH, DMF
44
45
1. DIBAL
2. KBH_4
3. CF_3COOH
56%
20%
dl-8
dl-1
46: X = Cl
47: X = H
48

Scheme 6.



Scheme 7.


CO2Me
Bu^tO2C
CH
CO2Me
Bu^tO2C
80%
NH
O
N
H
CH3
N
O
CO2Me
CH(CO2tBu)2
50
1. hν
2. base
57%
37%
CO2Me
CH(CO2tBu)2
51
52

Scheme 8.

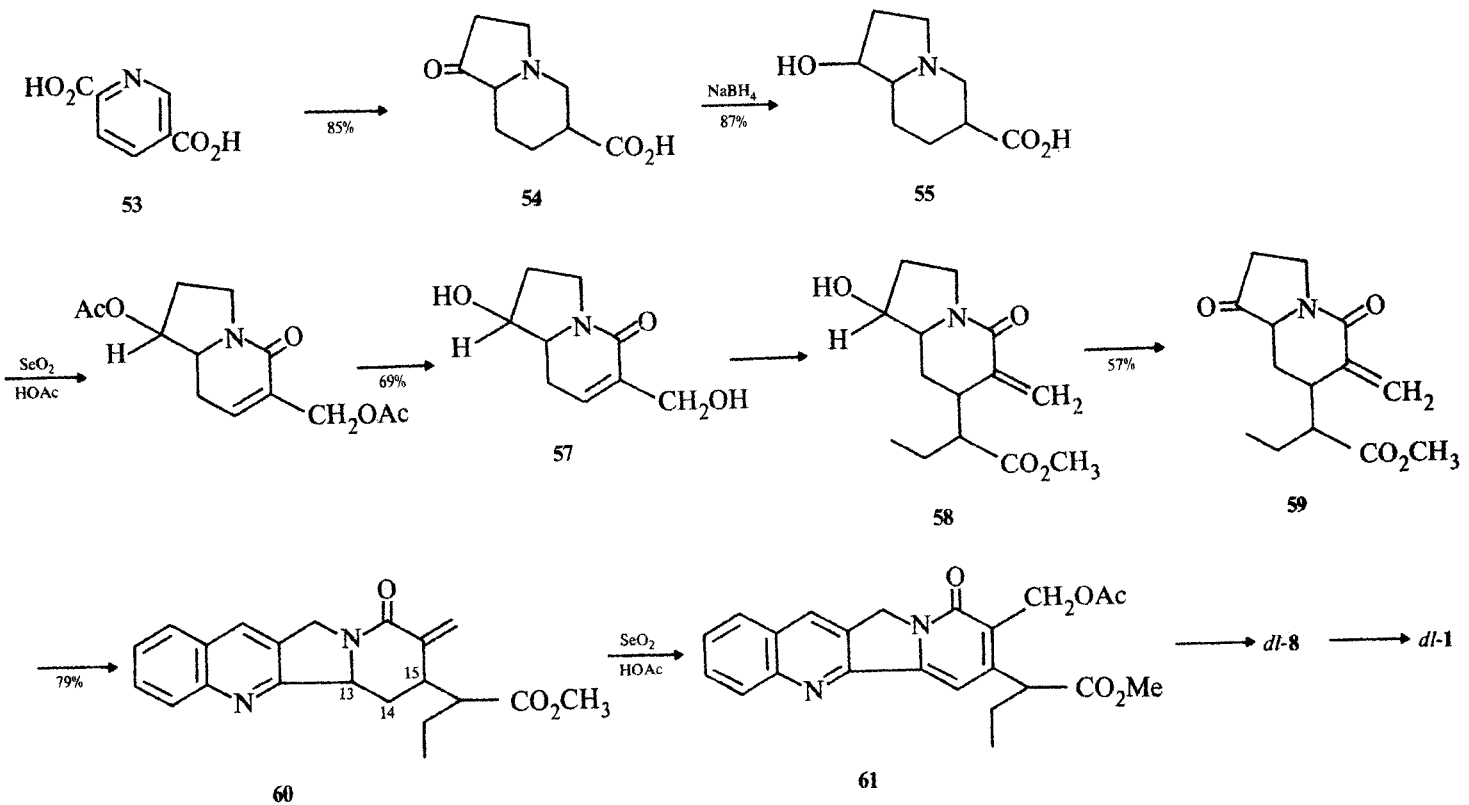
the key step (Scheme 8). Thus 3,4-dihydro-1-methyl-β-carboline, prepared from acetyltryptamine, was condensed with a mixture of unsaturated tetraesters followed by reduction with sodium borohydride to give the indolo[*a*]quinolizin-4-one **50**. The latter after photooxygenation and subsequent base treatment produced the indolizino[1,2-*b*]quinoline **51**, which was converted into the pyridone **52** via chlorination with thionyl chloride, dehalogenation by hydrogenolysis, and dehydrogenation with DDQ.[36]

4. *Rapoport et al. Synthesis*

The total synthesis of *dl*-**1** by Rapoport et al.[37] is notable because of the impressive 15% overall yield from the starting material, pyridine-2,5-dicarboxylic acid (isocinchomeronic acid). In addition, these workers employed a novel rearrangement of a nipecotic acid to an α-methylene lactam in one key synthetic step[38] (Scheme 9). The nipecotic acid derivative (**54**), prepared from **53** via esterification, reduction, alkylation, and Dieckmann cyclization in 85% yield, was reduced with sodium borohydride to the alcoholic β-amino acid **55**. When refluxed with acetic anhydride, **55** underwent the α-methylene lactam rearrangement to afford the piperidone acetate **56** as a diastereoisomeric mixture. Rapoport et al. had planned to carry out this rearrangement at the tetracyclic stage after Friedländer condensation of **54** with 2-aminobenzaldehyde (**12**). Although the rearrangement could be done in 60% yield, the subsequent oxidation with selenium dioxide to the tetracyclic analogue of **57** was not possible (complete aromatization occurred). Consequently, they oxidized **56** with selenium dioxide, hydrolyzed the product to **57**, then employed a Claisen ortho ester rearrangement to obtain a mixture of the free alcohol **58** and its butyrate ester. Hydrolysis of the crude reaction mixture followed by Pfitzner-Moffatt oxidation gave the α-methylene lactam **59**. Friedländer condensation of **59** with **12** gave the expected tetracyclic material **60**, whose oxidation with selenium dioxide simultaneously aromatized the D ring and introduced a C-17 acetoxy substituent. The acetoxy group probably was introduced by [3,3]sigmatropic rearrangement of a 3,14-dehydro-15-acetoxy derivative of **60**, because selenium dioxide oxidation (and also NBS) of a C-17 desacetoxy analogue of **61** failed to occur. Compound **61** was converted to deoxycamptothecin by an acid-catalyzed hydrolysis-lactonization. Finally, the C-20 hydroxy group was introduced by using Winterfeldt's method.

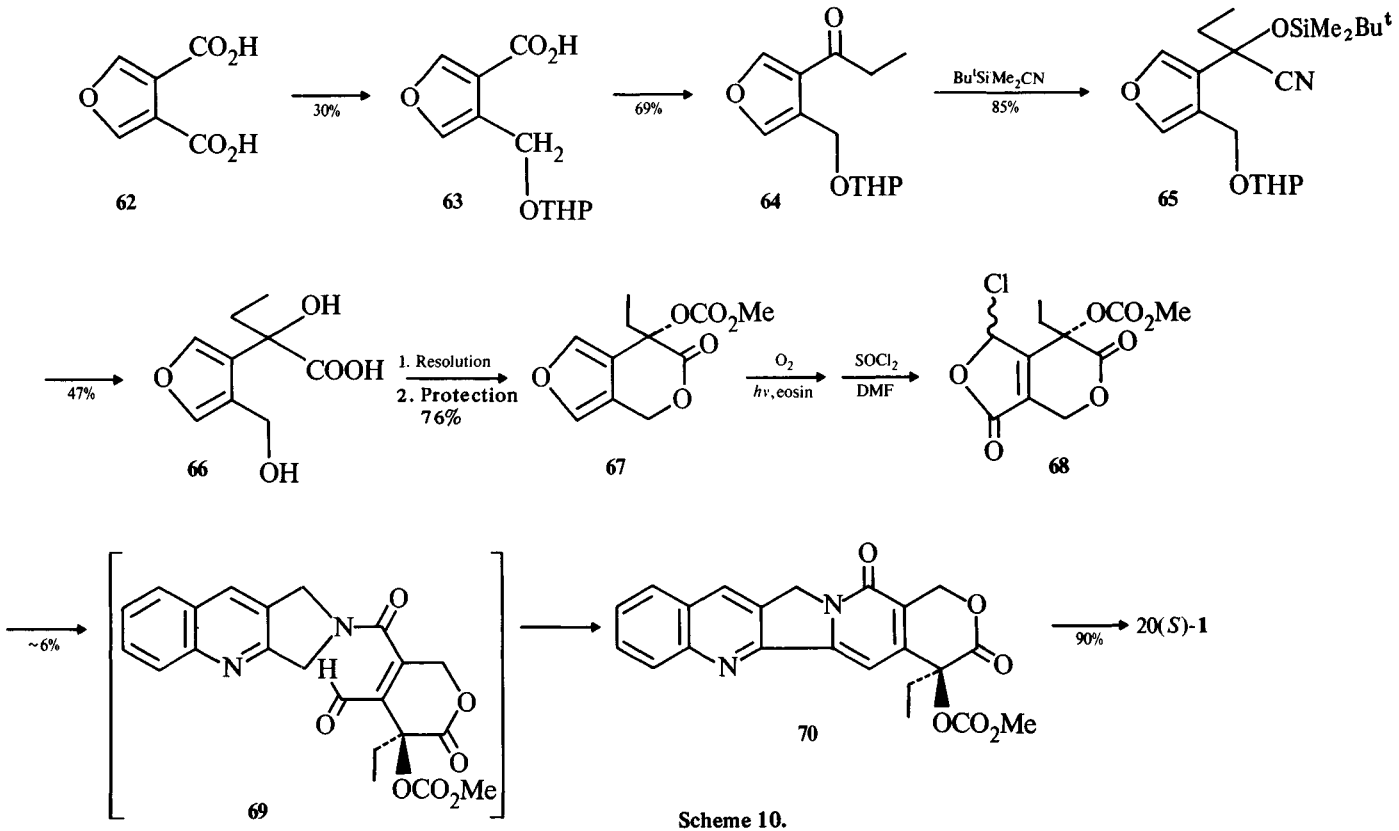
5. *Corey et al. Synthesis of 20(S)-Camptothecin*

The only synthesis of optically active 20(*S*)-camptothecin reported to date is that of Corey et al. (Scheme 10).[39] Although the overall yield of the Harvard group's synthesis was low, their strategy is typically novel. Their convergent synthetic approach brought together a chiral pseudo acid chloride (ring E) with a



53 54 55 57 58 59 60 61

Scheme 9.


CO2H
CO2H
30%
CH2
OTHP
69%
OSiMe2But
CN
Bu'SiMe2CN
85%
62
63
64
65
47%
OH
COOH
OH
1. Resolution
2. Protection
76%
OCO2Me
O2
hν, eosin
SOCl2
DMF
Cl
66
67
68
~6%
H
90%
20(S)-1
69
70

Scheme 10.

tricyclic amine (rings ABC, **35**) through which ring D was formed by cyclization of an intermediate α-aldehydo-*t*-amide (**69**).

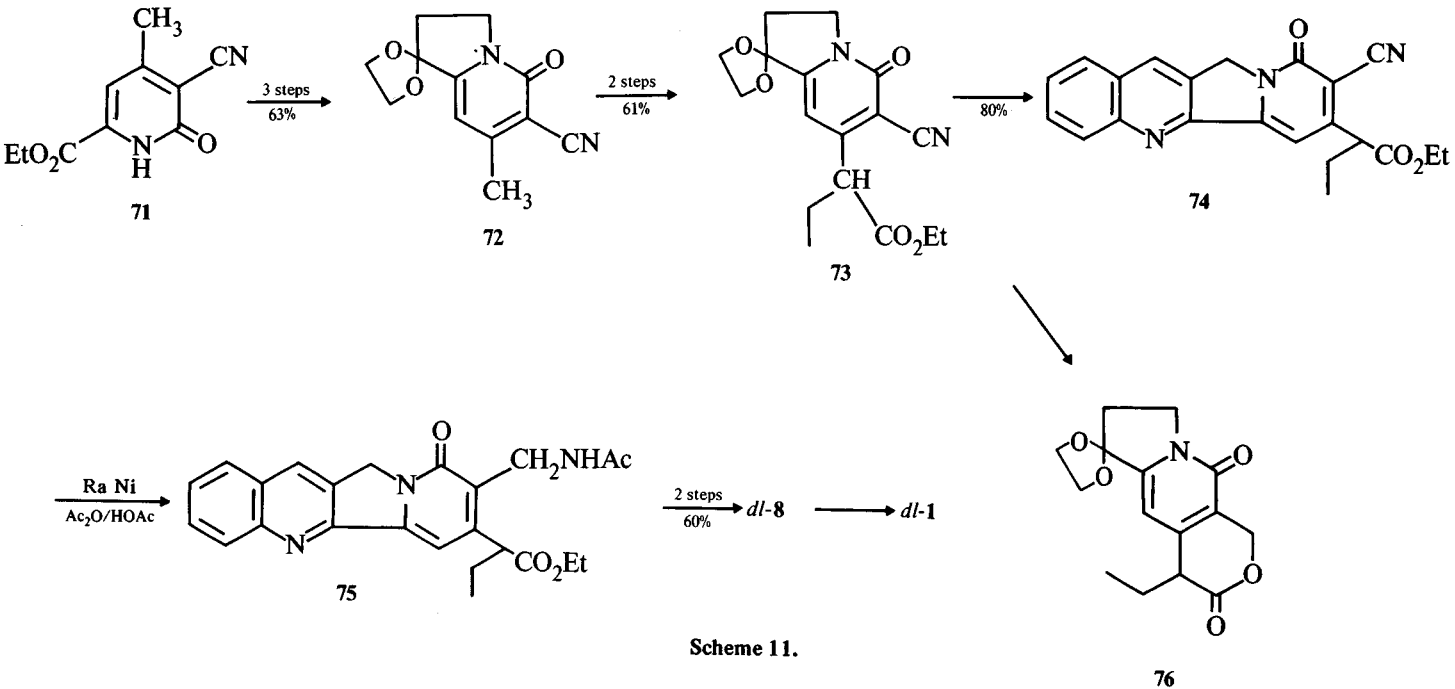
Resolution of the 3,4-disubstituted furan α-hydroxy acid **66** – prepared from 3,4-dicarboxyfuran by standard, but delicate, synthetic transformations in 8% yield – via its diastereomeric quinine salts and protection of the tertiary hydroxy group in the lactonized form of (+)-**66** gave **67** in good yield. Photooxidation of **67** to the hemiacylal followed by its treatment with thionyl chloride in a catalytic amount of dimethylformamide gave a 2.5:1 mixture of pseudo acid chloride **68** and its undesired regioisomer. Condensation of this mixture with **35**, prepared from acridine in three steps (18%), in pyridine-acetonitrile (to **69**) followed by base-catalyzed cyclization gave 20(*S*)-20-methoxycarbonylcamptothecin (**70**) in low yield. Deprotection of **70** by treatment with lithium mercaptide in HMPA gave 20(*S*)-**1** cleanly.

6. *Chinese/Wall et al. Synthesis*

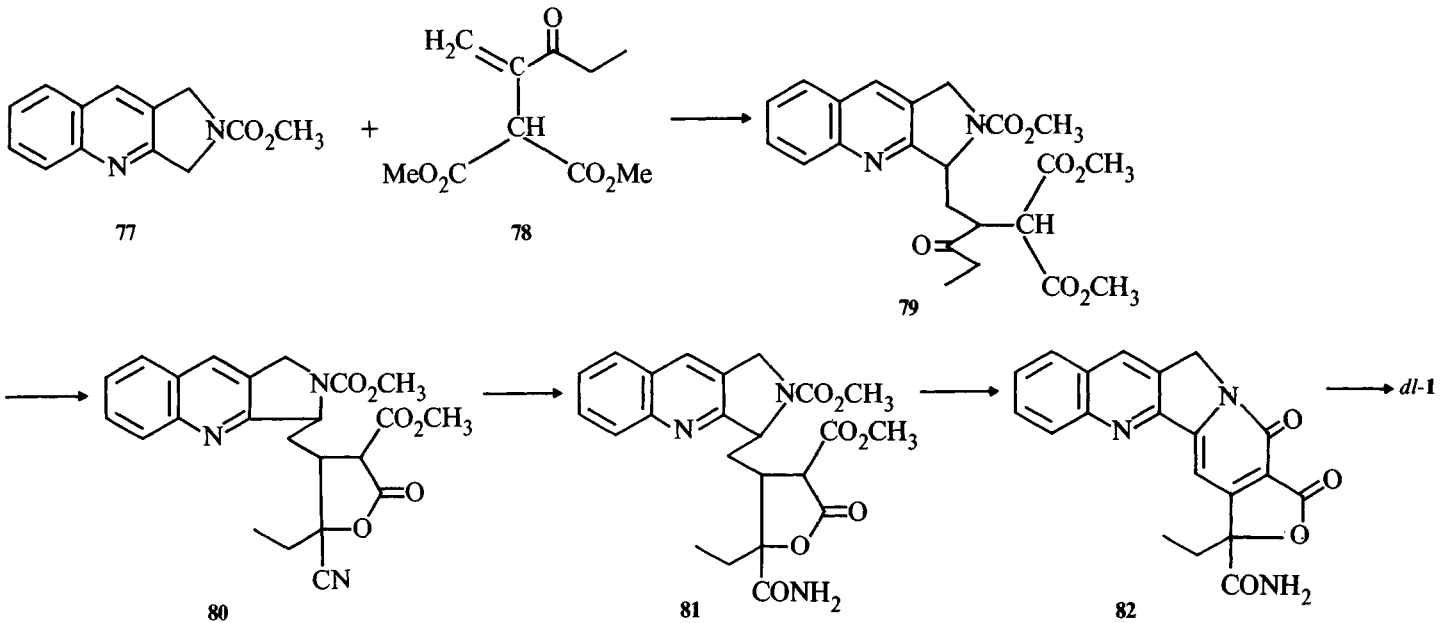
Chemists at the Shanghai Institute of Materia Medica developed an efficient, general, and practical synthesis of *dl*-**1** and its analogues in 1976,[40] but the full details of their work did not appear in the easily available English literature until 1978.[40b] Since Wall et al. used a slightly modified version of the Chinese synthesis for the efficient preparation of *dl*-**1** and several of its analogues in 1980,[41] these two syntheses are discussed together in this chapter. The new chemistry developed in these two laboratories would enable the total synthesis of racemic camptothecin on a large scale, if this becomes advisable in the future.

The Chinese/Wall camptothecin synthesis employed as starting material pyridone **71** (ring D), available from the condensation of cyanoacetamide and the *O*-ethyl ether of ethyl acetopyruvate, to make indolizine **72** by a three-step sequence involving simultaneous Michael addition to methyl acrylate and Dieckmann cyclization, hydrolysis-decarboxylation in aqueous acid, and ketalization (Scheme 11). The C-7 methyl of **72** was sufficiently acidic to permit its carbethoxylation by reaction with sodium hydride and diethyl carbonate. Ethylation of the resulting ester gave **73** in 80% yield. The latter underwent simultaneous deketalization and Friedländer condensation with **12** in acidic media to afford tetracyclic compound **74** (rings ABCD) in 80% yield. The Chinese group found that this Friedländer condensation was more suitably done in acidic media than in alkaline media. Following reductive acetylation of the cyano group of **74**, formation of the *N*-nitrosoacetamide of **75** in situ in the acid filtrate obtained from the hydrogenation reaction resulted in rearrangement to its acetoxy analogue. The researchers then cyclized the latter intermediate to *dl*-**8** in dilute acid from which *dl*-**1** resulted by Winterfeldt's method. The overall yield of this Chinese chemists' ten-step synthesis was an impressive 18%.

Wall's group modified the Chinese group's camptothecin synthesis by first converting **73** to **76**, the complete CDE rings portion of **8**, from which they could prepare *dl*-**1** by Friedländer condensation and subsequent transformations.[41] Their


CH3
CN
EtO2C
N
H
O
71
3 steps
63%
O
O
N
O
CN
CH3
72
2 steps
61%
CN
CH
CO2Et
73
80%
O
CN
N
N
CO2Et
74
Ra Ni
Ac2O/HOAc
CH2NHAc
N
O
CO2Et
75
2 steps
60%
dl-8
dl-1
O
O
N
O
O
O
O
76

Scheme 11.


NCO2CH3
N
77
+
H2C
C
O
CH
MeO2C
CO2Me
78
NCO2CH3
CO2CH3
CH
O
CO2CH3
79
NCO2CH3
CO2CH3
O
O
CN
80
NCO2CH3
CO2CH3
O
CONH2
81
O
O
CONH2
82
dl-1

Scheme 12.

synthetic modification, which the Chinese workers had attempted but could not execute successfully, improved the overall yield of *dl*-**1** significantly.

7. *Miscellaneous Syntheses*

a. WALL ET AL. SYNTHESIS. Wall et al. had published another total synthesis in 1972.[42] In this approach, 1,3-dihydro-2-methoxycarbonyl-2*H*-pyrrolo[3,4-*b*] quinoline (**77**) was used as starting material (Scheme 12). Compound **77** reacted with keto ester **78** to give **79**, which was treated with liquid hydrogen cyanide in the presence of potassium cyanide to yield cyanolactone **80** via the cyanohydrin, from which amide **81** was obtained by treatment with basic hydrogen peroxide. After selective removal of the *N*-carbomethoxy group, treatment with alkali, lactamization, and dehydrogenation with DDQ, pyridone **82** was obtained. Finally, **82** was transformed to *dl*-**1** through reduction with lithium borohydride and acidification.

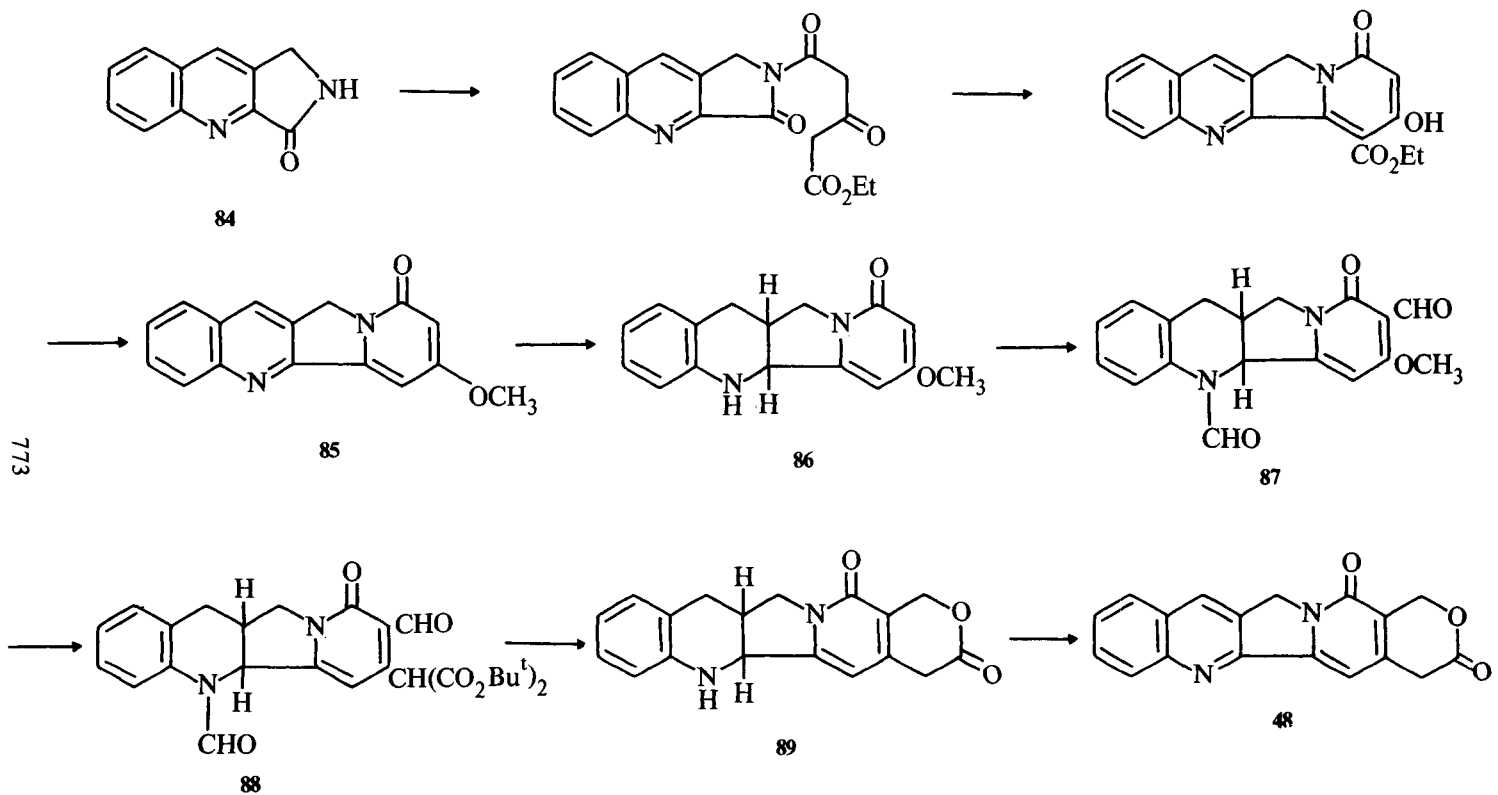
b. SUGASAWA ET AL. SYNTHESIS. Sugasawa et al. utilized tricyclic amide **84** as starting material for the preparation of 7-methoxy-indolizino[1,2-*b*] quinoline derivative **85** through condensation with diethyl acetonedicarboxylate, cyclization, and decarboxylation (Scheme 13). The C-8 formylation of **85** occurred smoothly via Vilsmeier reaction, but the subsequent addition of malonate failed owing to the instability of the reaction intermediate toward base. Consequently, **85** was reduced to tetrahydroquinoline **86**, then formylated to a Michael acceptor **87** which underwent addition with di-*t*-butyl malonate to give **88**. 20-Deoxy-20-desethylcamptothecin (**48**) then was obtained by reduction with borohydride, hydrolysis, and dehydrogenation. Compound **48** was converted to *dl*-**1** by C-20 ethylation and oxidation.[43]

Sugasawa's group later reported a method for introducing the 20-ethyl and 20-hydroxy groups in one step, thus improving the overall yield of camptothecin.[44]

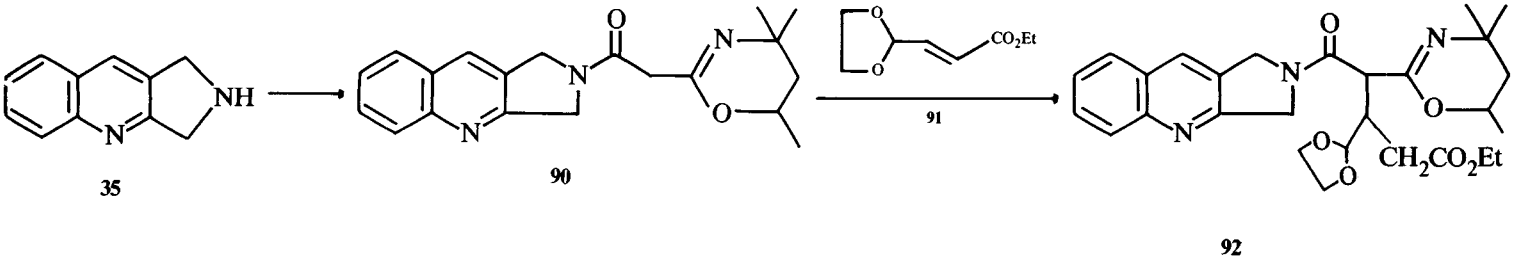
c. MEYERS ET AL. SYNTHESIS. In this synthesis oxazine amide **90**, prepared from tricyclic amine **35** with an oxazine ester, underwent Michael addition with the unsaturated ester **91** to give amide **92** (Scheme 14). Sodium borohydride reduction of **92** followed by cleavage gave aldehyde **93**. The latter, after reduction, was acylated and deketalized to afford **94**. Cyclization of **94** gave the dihydropyridone **95**, which was aromatized with DDQ to the appropriate pyridone. Acid hydrolysis then produced the desired compound **48**.[45]

d. WALRAVEN AND PANDIT SYNTHESIS. Walraven and Pandit prepared lactone **96** from furfural by a six-step reaction sequence (Scheme 15).[46] Compound **96** reacted with tricyclic amide **35** to give amide **97** which, after oxidation, was cyclized to pyridone **98**. Reduction of **98** by lithium borohydride followed by treatment with acid yielded **48**.

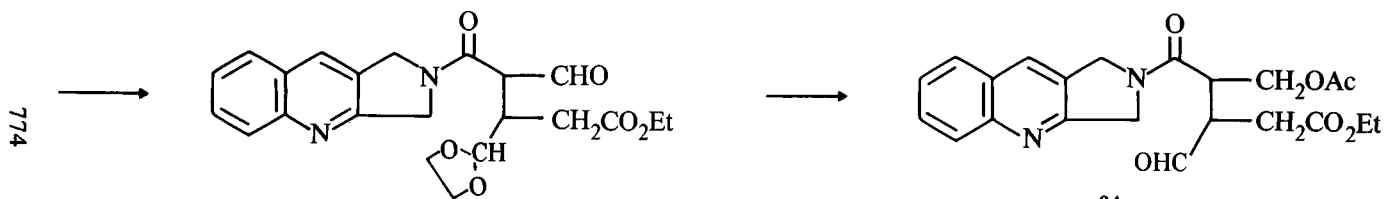
e. SHAMMA ET AL. SYNTHESIS. Pyridone **100**, obtained from urethane **99** through a nine-step sequence of reactions in 16% yield, was condensed with


NH
O
N
84
O
N
O
O
CO2Et
OH
CO2Et
OCH3
85
H
OCH3
86
CHO
OCH3
87
CHO
CH(CO2But)2
88
O
89
48
dl-8
dl-1

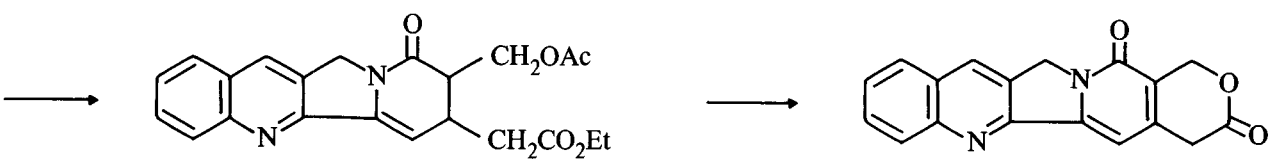
Scheme 13.



35 90 91 92

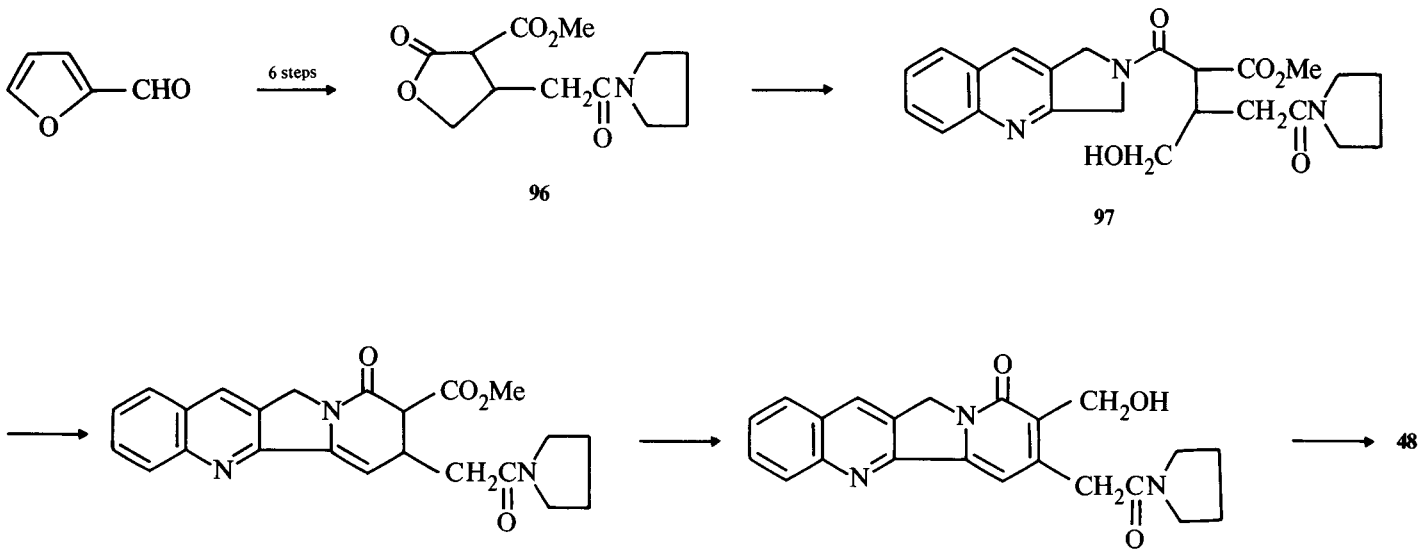


93 94

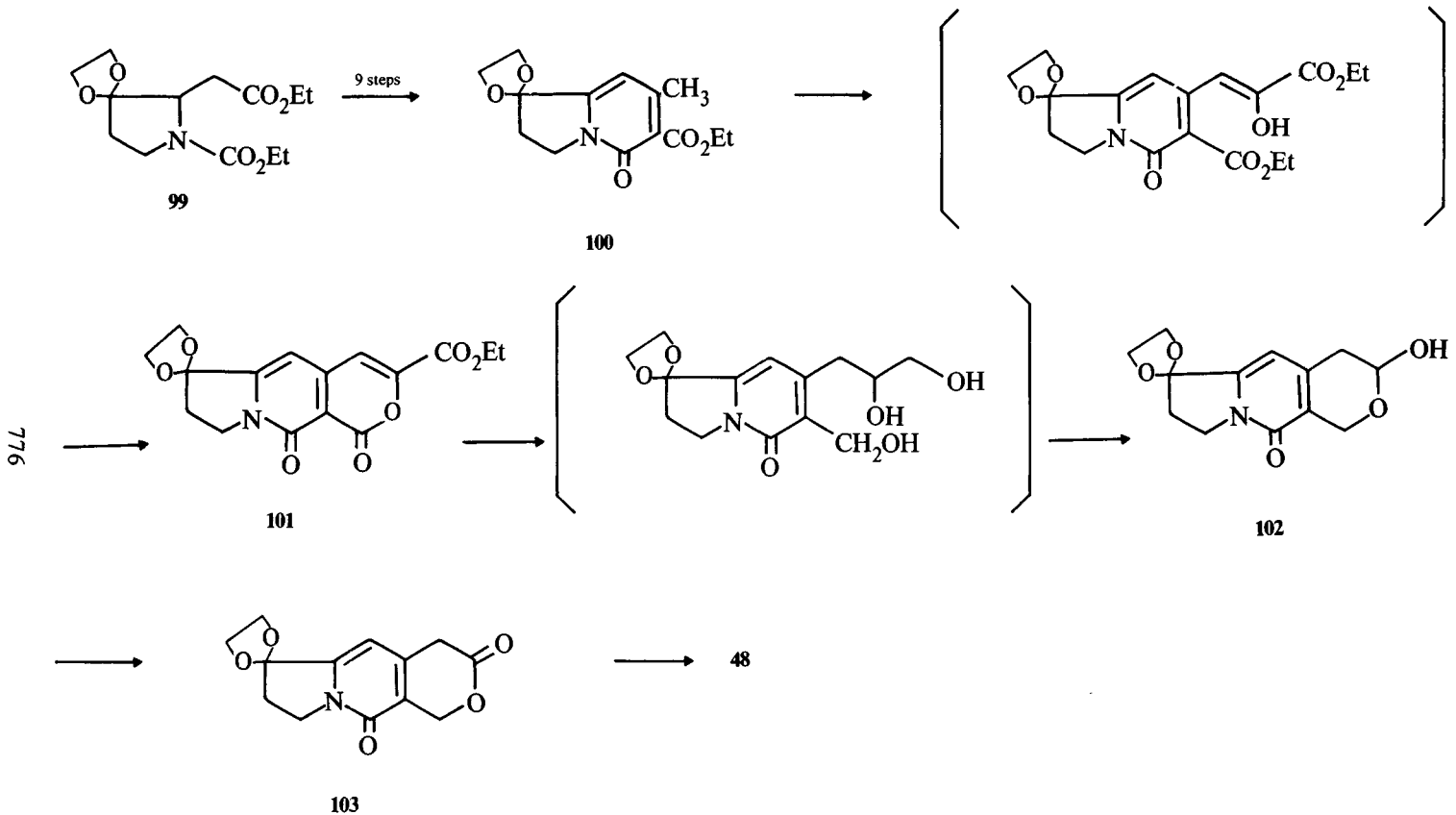


95 48

Scheme 14.


CHO
O
6 steps
O
O
CO2Me
CH2CN
O
96
O
N
N
CO2Me
CH2CN
O
HOH2C
97
O
N
N
CO2Me
CH2CN
O
98
O
N
N
CH2OH
CH2CN
O
48

Scheme 15.



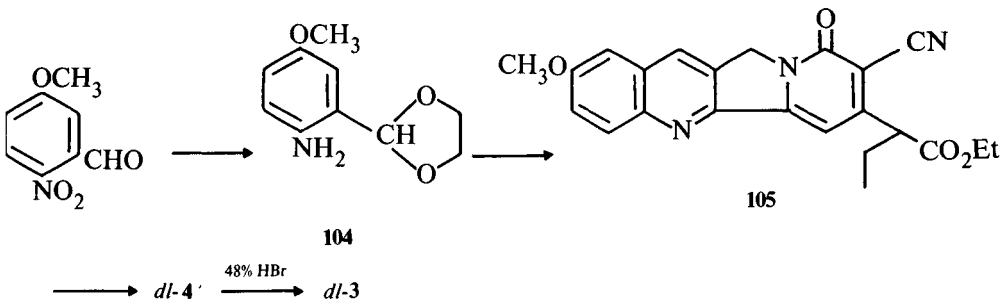
Scheme 16.

diethyl oxalate to give vinyl lactone **101** in 65% yield (Scheme 16). The conversion of the latter to the δ-lactone **103** was carried out with sodium borohydride followed by periodic acid. Catalytic oxidation of the resulting hemiacetal **102** led to the desired δ-lactone **103**. 20-Deoxy-20-desethylcamptothecin (**48**) was then obtained by deketalization and Friedländer condensation.[47]

B. Total Synthesis of Camptothecin Alkaloids

1. *Total Synthesis of Oxygenated Camptothecins*

a. 10-HYDROXYCAMPTOTHECIN (**3**) AND 10-METHOXYCAMPTOTHECIN (**4**). The Chinese scientists announced the first total synthesis of *dl*-**3** and *dl*-**4** in 1977 using their general synthetic method (Section II.A.6). Recently Cai et al. published the details of this work.[14] 2-Nitro-5-methoxybenzaldehyde was protected with ethylene glycol followed by catalytic reduction to give **104** (Scheme 17). This procedure improved the yield of reduction and made **104** suitable for long storage. Compound **104** was condensed with **73** to yield **105**, which was converted to *dl*-**4** by the method described in Section II.A.6. Thence *dl*-**4** was transformed to *dl*-**3** by hydrogen bromide demethylation. The overall yields of *dl*-**3** and *dl*-**4** from **71** were 6.5 and 10%, respectively.



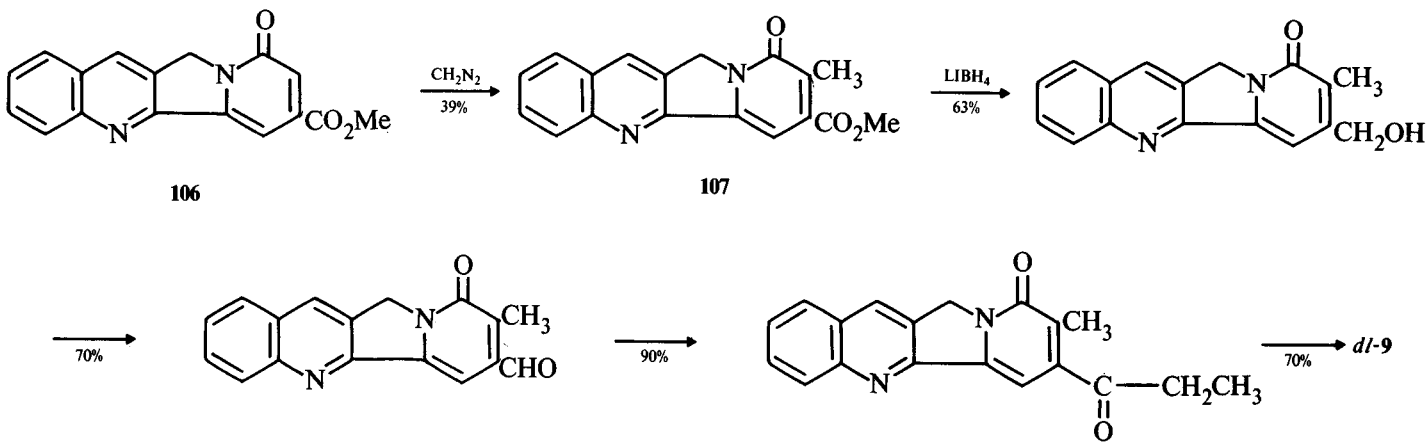
Scheme 17.

Wani et al. reported a yield of 10% and 21% for the synthesis of *dl*-**3** and *dl*-**4**, respectively, by their modification of the Chinese synthesis of *dl*-**1**.[41]

Kametani et al. also synthesized *dl*-**3** and *dl*-**4** by using the methoxy derivative of **49** as starting material in their synthesis (Section II.A.3.a).

b. 11-HYDROXYCAMPTOTHECIN (**6**) AND 11-METHOXYCAMPTOTHECIN (**7**). Cai et al. synthesized these two alkaloids by their general method using 2-nitro-4-methoxybenzaldehyde as the starting material. The overall yield of *dl*-**6** and *dl*-**7** was lower than that of *dl*-**3** and *dl*-**4**.[15]

Up to the present, all the oxygenated camptothecinoid alkaloids isolated from natural sources have been synthesized except for 9-methoxycamptothecin (**5**).

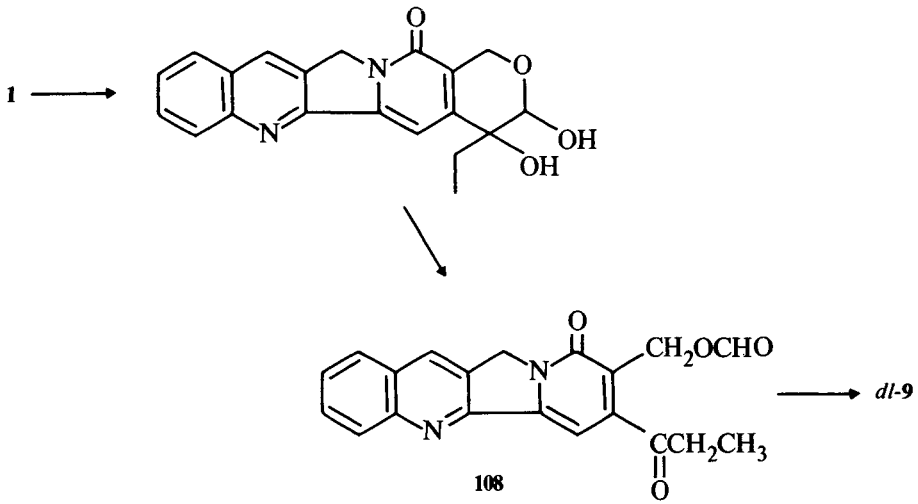

O
N
N
CO2Me
106
CH2N2
39%
CH3
CO2Me
107
LIBH4
63%
CH3
CH2OH
70%
CHO
90%
C
CH2CH3
70%
dl-9

Scheme 18.

2. *Total Synthesis of Mappicine (9)*

Kametani et al. reported the total synthesis of *dl*-mappicine (*dl*-**9**) in 1975 (Scheme 18).[48] Tetracyclic ester **106** was converted to **107** by treatment with diazomethane, from which *dl*-**9** was obtained through a 4-step sequence of reactions. The overall yield of *dl*-**9** from **106** was 11%.

Govindachari et al.[9] synthesized *dl*-**9** from camptothecin for structure elucidation (Scheme 19). Thus reduction of **1** with sodium borohydride yielded the lactol which was cleaved by lead tetraacetate to the keto ester **108**. Reduction of **108** with sodium borohydride under vigorous conditions gave *dl*-**9** in low yield.



Scheme 19.

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CHAPTER XIV

Pharmacology, Biochemistry, and Clinical Applications of the Monoterpenoid Alkaloids

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I. INTRODUCTION

Plant derivatives have been used from the most remote antiquity to treat human disease.[1] Such preparations were described by the Egyptians as early as 1550 BC in the Ebers papyrus, but there can be no doubt that this was merely a codification of practices that extended far back into prehistory. In Western tradition, herbal remedies were described by many authors, from Dioscorides and Galen in the first and second centuries to Culpeper in the seventeenth. Chinese medicine, with its use of complex polypharmaceutical preparations called Fongs, also utilized a wide variety of plants.

During the nineteenth and twentieth centuries, advances in chemical technology permitted the isolation of many of the active principles from medicinal plants, the subsequent elucidation of their chemical structures, and the synthesis of these compounds and new derivatives or analogues. Most of these pharmacologically active substances are alkaloids, but the larger fraction of the known alkaloids have no medicinal use, or their pharmacology is relatively unexplored. Although there are a large number of separate classes of alkaloids, indole derivatives, of which more than 800 are known, are surprisingly well represented among the pharmacologically active compounds.[2-5]

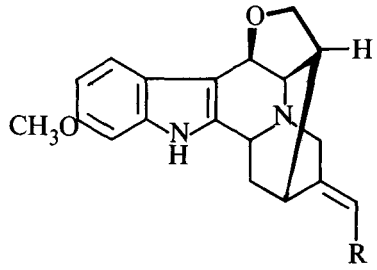
The indole alkaloids run the gamut of biological activity from autonomic and central nervous system actions, through cardiovascular, endocrinologic, diuretic, anti-inflammatory, and anti-infectious to antineoplastic effects. In this chapter we illustrate the types of biological activity associated with the major classes of indole alkaloids, by reference to specific examples. Some of the agents that are well known or that are widely used in medical treatment are considered in greater detail. Attention is also paid to those compounds whose biochemistry and pharmacology have been particularly well studied, irrespective of whether or not they have medical application. We point out their biological actions, mechanisms of action, metabolism and disposition where they are known, and any clinical applications. In the space available it is obviously impossible to be comprehensive, but we try to emphasize the wide range of actions and the usefulness of this interesting group of alkaloids.

II. UNREARRANGED SECOLOGANINS

A. *Gardneria* Alkaloids

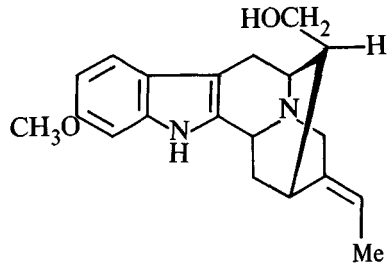
These indole derivatives occur in *Gardneria nutans* Sieb. et Zucc. and *G. multiflora* Makino. The pharmacological properties of these alkaloids have been studied in several species of experimental animals, and it appears that they function as ganglionic blocking agents akin to hexamethonium.[6-8] In a comparison of the effects of six of these alkaloids on rat and rabbit superior cervical ganglion preparations in situ, the most potent agents were gardneramine (**4**), gardnerine (**3**), and Alkaloid I (**6**); gardnutine (**1**) was less effective, and hydroxygardnutine (**2**) and

18-demethylgardneramine (**5**) were almost inactive. These alkaloids were shorter acting than hexamethonium, and gardneramine and gardnerine were one-half (rabbit) to one-quarter (rat) as active as the latter.[9]

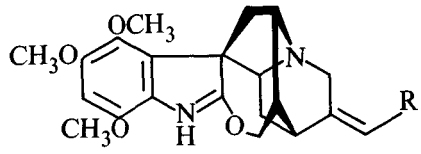


Gardnutine (**1**): R = CH_3

Hydroxygardnutine (**2**): R = CH_2OH

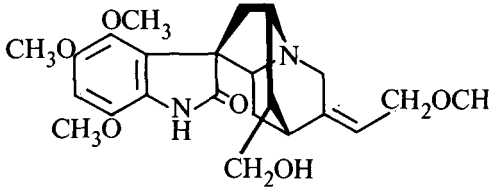


Gardnerine (**3**)

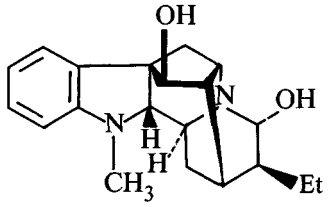


Gardneramine (**4**): R = CH_2OCH_3

Demethylgardneramine (**5**): R = CH_2OH



Alkaloid I (**6**)



Ajmaline (**7**)

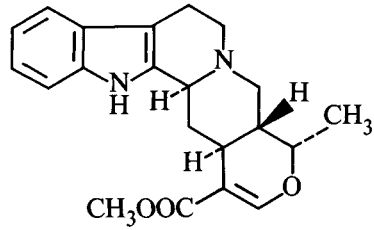
B. Ajmaline

This alkaloid (**7**) is obtained from the roots of *Rauwolfia serpentina* (L.) Benth. (Apocynaceae). Its most prominent action is an antiarrhythmic effect on the heart that is less pronounced than that of propranolol[10] but superior, in terms of the ratio of prolongation of refractory phase over reduced conduction, to that of procaine amide and quinidine.[11] For this reason the drug has been extensively used in Europe to treat arrhythmias. In a study that involved 900 patients with acute or subacute myocardial infarction, ajmaline was found to be useful in the manage-

ment of both ventricular and supraventricular arrhythmias.[12] It should be noted, however, that successful treatment, with return to normal sinus rhythm in 85% or more of the subjects, required two drugs, electrolyte replacement therapy, and the administration of thiamine. Care is needed when the drug is used in those with liver disease. The action of ajmaline involves a dose-dependent reduction in the maximum rate of rise of the muscle action potential, without affecting the resting potential.[13] Like quinidine, and unlike procaine, ajmaline has a slow onset of action and is not readily washed out of the tissue.[11] Ajmaline reduces the hypertension produced by catecholamines and counteracts the fibrillations induced by loading with calcium salts.[14] At the molecular level, the alkaloid reduces the concentrations of ATP and ADP within the myocardial cell, but the relation of this effect to antiarrhythmic action is questionable.[15] In mice ajmaline also exerts a marked diuretic effect,[5] but this has not been exploited clinically. In humans, ajmaline is rapidly distributed into the tissues so that 1 minute after injection only 10% of the drug is in the plasma. The initial distributive half-life is about 2 minutes; only 4% appears in the urine during the first 12 hours.[16]

C. Ajmalicine

Ajmalicine (8), also commonly known as raubasine or δ-yohimbine, is obtained from the bark of *Corynanthe yohimbe* K. Schum. (Rubiaceae) and from the roots of many species of the genus *Rauwolfia*. It is also widely distributed among plants of the genus *Catharanthus* (Apocynaceae). Like vincamine, which is discussed below, ajmalicine is classed as a cerebral blood flow increasing drug. This effect has been demonstrated experimentally in rat and monkey brains in which there is increased tissue perfusion. Concomitant with increase in tissue pO_2 values, a transient initial fall in tissue pO_2 apparently stems from a lowering of the systemic blood pressure.[17] It is likely that the fall in blood pressure is due to depletion of tissue catecholamines.[18] In clinical practice in Europe, ajmalicine has been utilized most frequently in combination with the ergot alkaloid dihydroergocristine as the preparation known as Iskedyl. Apart from cerebral vascular disorders,[19] the combination has been employed to treat hypertension,[20,21] in psychiatry,[22] in neurosurgery,[23] and to help overcome spasm during vascular catheterization.[24] In mice, ajmalicine has been reported to have a slight muscle relaxant action[5] and a significant antidiuretic effect[25]; no clinical use has been made of these observations.

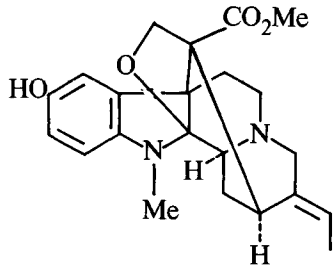


Ajmalicine (8)

In rats, ajmalicine has a plasma half-life of 5–7 hours, is primarily excreted in the bile, and undergoes metabolism to at least seven products.[26] In humans and dogs, plasma levels of ajmalicine are present 1–2 hours after an oral dose. Fecal excretion accounts for more than 50% of the administered dose in dogs over a 3-day period compared with 13 to 22% in the urine, whereas in humans, elimination by the two routes is essentially similar at 24 to 29%.[27]

D. Akuammine

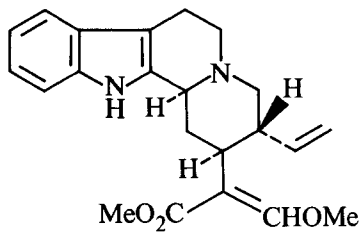
Akuammine (**9**) occurs in *Picralima nitida* (Stapf) Th. & H. Dur. and *Vinca major* L., both of which species belong to the Apocynaceae. This alkaloid has been described as a potentiator of the sympathetic system rather like cocaine.[28] It also inhibits cholinesterase in horse serum, although less effective in this action than physostigmine.[29]



Akuammine (**9**)

E. Corynantheine

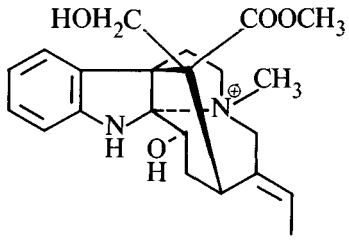
Corynantheine (**10**) is isolated from *Corynanthe yohimbe* K. Schum. and *Pseudocinchona africana* A. Cheval. (Rubiaceae); it also occurs in members of the genus *Catharanthus* (Apocynaceae). The compound exerts a sympatholytic action that leads to hypotension, and in addition produces central excitation, thus resembling to some extent ajmaline and sarpagine.[30,31]



Corynantheine (**10**)

F. Echitamine

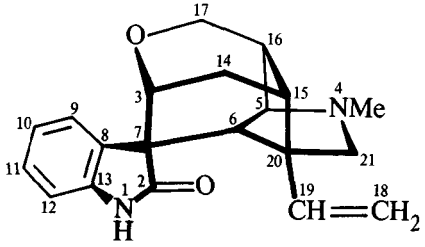
Echitamine (**11**) is found in the bark of *Alstonia scholaris* (L.) R. Br. and *A. congensis* (Apocynaceae). In the century during which it has been known, this alkaloid has been used to treat malaria, but has long been abandoned for more effective drugs. At lower doses, echitamine is a sympathomimetic agent that enhances the hypertension and renal vasoconstriction produced by epinephrine, but at higher doses a sympatholytic action is seen with hypotension, and there is evidence of a curare-like effect on motor nerves.[32]



Echitamine (**11**)

G. Gelsemine

This alkaloid (**12**) is isolated from the roots and rhizomes of the yellow jasmine or jessamine, *Gelsemium sempervirens* (L). Ait. (Loganiaceae). Gelsemine has been used as a CNS stimulant, which use may depend upon its ability to antagonize synaptic inhibition by "glycine-like" amino acids, an action similar to that of strychnine.[33] This alkaloid also acts as an acetylcholine antagonist, converting the hypotensive and bradycardial action of the latter to hypertension and increased heart rate.[34]

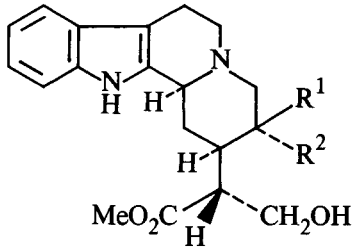


Gelsemine (**12**)

H. Sitsirikine

Sitsirikine (**13**) and isositsirikine (**14**) occur in the leaves and roots of *Catharanthus*

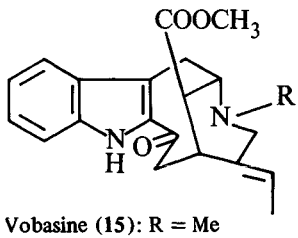
roseus G. Don. In mice sitsirikine acts as a CNS depressant with duration of action of 2–3 hours. Vasodilatation and an antidiuretic action have also been reported[5]; association between these two actions is to be expected.



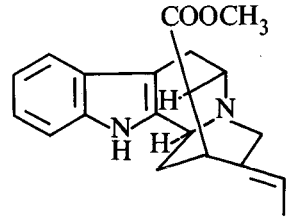
Sitsirikine (**13**): R^1 = H, R^2 = –CH=CH_2
Isositsirikine (**14**): R^1 R^2 = =$CHCH_3$

I. Vobasine Group

Vobasine (**15**), perivine (**16**), periformyline (**17**), and pericyclivine (**18**) are very similar in structure and may be considered together. Vobasine has been isolated from the roots of *Tabernaemontana holstii*,[35] and perivine and pericyclivine are present in *Catharanthus lanceus*, *C. longifolius*, and *C. roseus*; periformyline occurs in *C. lanceus*.[5] Perivine is a CNS depressant in mice as are many other indole alkaloids,[5] perhaps through a reserpine-like depletion of catecholamines, and it has some autonomic action also. All four alkaloids are cytotoxic with ED_{50} levels of 13–20 μg/ml for P388 cells and 70 to more than 100 μg/ml for KB cells; they are thus far less active than the bisindoles.[35,36] Perivine shows antiviral activity against both vaccinia and polio type III, whereas periformyline is effective only against the latter.[37]



Vobasine (**15**): R = Me
Perivine (**16**): R = H
Periformyline (**17**): R = CHO

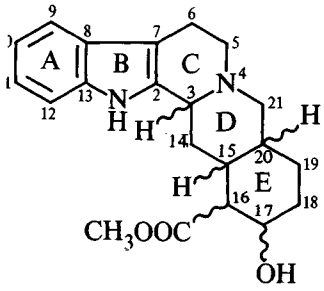


Pericyclivine (**18**)

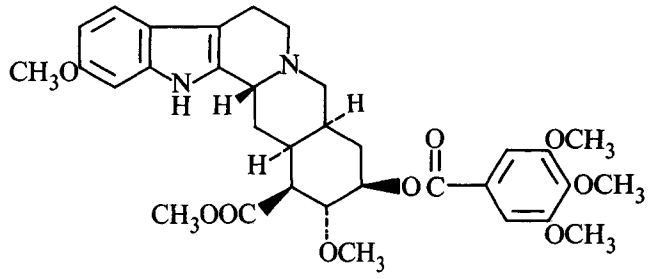
III. YOHIMBINE GROUP

This group of alkaloids includes a number of compounds with profound pharmacological activity. Two distinct classes of agents may be distinguished, the yohimbine congeners proper and the derivatives of reserpine. Although the compounds related

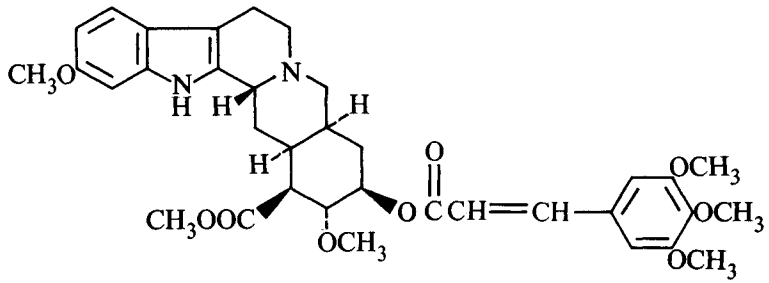
to yohimbine show a marked resemblance to the reserpic acid unit of reserpine in their chemical structure (**19–22**), their biological actions are sufficiently different to warrant a separate treatment.



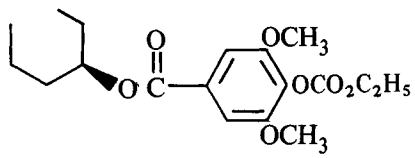
Yohimbine Group (**19**)



Reserpine (**20**)



Rescinnamine (**21**)



3′5′-Dimethoxy-4′-ethoxycarbonyloxybenzoyl group of syrosingopine (**22**)

A. Yohimbine Derivatives

1. *Occurrence and Structure*

The isomers yohimbine (**19a**) and corynanthine (**19b**) occur in the bark of *Corynanthe yohimbe* K. Schum. (Rubiaceae) and in the oriental climbing shrub *Rauwolfia serpentina* (L.) Benth. (Apocynaceae); other isomers of the epi configuration have also been synthesized. Yields of the natural alkaloids from *R.*

serpentina, for example, range from 0.02 to 0.08% by weight.[38] Ten isomers of yohimbine are known (Table I). In the earlier literature there was confusion in the nomenclature of these alkaloids, and even ajmalicine, which has a heterocyclic E ring, was termed δ-yohimbine.

2. *Biological Activity*

Yohimbine (**19a**) exerts a complex pattern of pharmacological actions that include blockade of α-adrenergic and serotonin (5-HT) receptors, central excitation reflected in elevated blood pressures, heart rate, and increased motor activity, sweating, nausea, and antidiuresis due to vasopressin release.[39] Many different mechanisms are involved in these actions.[40]

α-Adrenergic blockade is among the earliest demonstrated actions of these compounds.[41] The degree of blockade does not appear to be affected significantly by esterification at the 16 position with a variety of alkyl functions, nor by diacetylation of the indole NH and alcohol groups. However, ethyl yohimbine and corynanthine may be somewhat less toxic than yohimbine at levels needed for adrenergic blockade.[42] Studies with rabbit pulmonary arterial strips indicated that yohimbine blocks preferentially the presynaptic α-receptors.[43] In the case of α-yohimbine (rauwolscine, **19c**), the presynaptic site is about 1000 times more sensitive than the postsynaptic response; this is a tenfold greater ratio than that seen with yohimbine.[44] Like reserpine, the yohimbines have been reported to cause release of stored norepinephrine.[45]

Serotoninergic actions are now considered to contribute in a major way to the varied biological effects of these alkaloids. In rat fundal strips yohimbine is a potent competitive antagonist of 5-HT, as are α- and β-yohimbine (**19d**); corynanthine and pseudoyohimbine (**19e**) are less potent, noncompetitive antagonists.[40] High levels of yohimbine isomers inhibit the uptake of 5-HT by rat brain synaptosomes.[44] Levels of 5-HT have been reported to rise in mouse brain[46] and in rat brain and intestine[47] after treatment with yohimbine; corynanthine was inactive at the same dosages. Since there was a concomitant fall in the levels of 5-hydroxyindole acetic acid it is likely that inhibition of tryptophan pyrrolase occurs.[47,48]

Cholinergic actions are not particularly prominent, usually requiring high concentration of alkaloid. Those actions that have been reported include inhibition of acetylcholinesterase,[44,49] and antagonism of acetylcholine[50] and carbachol, the latter noncompetitive for all except α-yohimbine.[46]

Central actions are seen at lower doses of drug than those needed to produce peripheral adrenergic blockade.[39] In man, yohimbine produces an unpleasant anxiety state accompanied by elevated blood pressure.[51–53] Although the dog shows similar effects to those of humans, in mice yohimbine has a pronounced sedative action resembling that of reserpine.[46] Like reserpine yohimbine also produces hypothermia in rodents.[46] The mechanisms involved in these central actions are uncertain, but could involve both serotoninergic and adrenergic actions

TABLE I. YOHIMBINE ISOMERS[36]

Isomer	Synonyms	Stereochemistry* (see 19)	pK_a	Partition coefficient octanol/H_2O	Brain/body ratio
Yohimbine (19a)	Quebrachine Aphrodine Corynine Hydroaergotocin	3α, 15α, 16α, 17α, 20β	7.13	131	2.17
Corynanthine (19b)	Rauhimbine	3α, 15α, 16β, 17α, 20β	7.15	246	3.71
β-Yohimbine (19d)	Amsonine	3α, 15α, 16α, 17β, 20β	6.71	166	2.06
ψ-Yohimbine (19e)	Pseudoyohimbine	3β, 15α, 16α, 17α, 20β	7.41	87	1.32
3-Epicorynanthine		3β, 15α, 16β, 17α, 20β			
3-Epiyohimbine		3β, 15α, 16α, 17β, 20β			
Alloyohimbine		3α, 15α, 16β, 17β, 20α	6.88		
α-Yohimbine (19c)	Rauwolscine Isoyohimbine Mesoyohimbine Corynanthidine	3α, 15α, 16β, 17α, 20α	6.34	180	
3-Epialloyohimbine		3β, 15α, 16β, 17β, 20α			
3-Epi-α-yohimbine	Isorauhimbine	3β, 15α, 16β, 17α, 20α			

* The configurations cited refer to H at C-3, 15, and 20; CO_2Me at C-16, and OH at C-17.

in the brain. Certainly yohimbine and its isomers enter the brain of rodents to produce levels of 10^{-7}–10^{-6} *M* after therapeutic doses of 0.1–1.0 mg/kg. The fact that corynanthine lacks the behavioral stimulant and hypertensive properties of yohimbine, and yet enters the brain more readily than the latter,[40] suggests that major differences that exist involve affinities for receptors. That the relative order for efficacy in producing central effects – that is, α-yohimbine > β-yohimbine > yohimbine, with ψ-yohimbine and corynanthine inactive – is the same as for peripheral antagonism of 5-HT receptors may be important.[40] This is not unlikely in view of the fact that a drug such as lysergic acid diethylamide, which antagonizes 5-HT peripherally, stimulates the central 5-HT receptors.[54] However, it should be pointed out that behavioral excitation and cardiovascular effects of yohimbine in dogs are antagonized by hexamethonium, phenoxybenzamine, and reserpine, suggesting that adrenergic mechanisms are involved.[55] Recently, yohimbine has been found to block the Na^+ channels in both squid axons[56] and myocardial cells,[57] but the role of such an effect in the central actions of the alkaloid has not been established. Both yohimbine[51] and 10-acetylyohimbine[58] are hallucinogens.

3. *Clinical Use*

There are no established clinical uses for these alkaloids at present. Once widely used as an aphrodisiac in humans and domestic animals, yohimbine has also been applied in angina pectoris, in arteriosclerosis, and as a mydriatic. Its chief toxicity was renal. Yohimbine still enjoys a vicarious reputation as an aphrodisiac,[59] and although well-controlled experiments in rats failed to show any effect of the drug on sexual function,[60] the predominantly psychological origin of human impotence makes it very improbable that any animal system could be useful as a screen for compounds active in humans.

B. Reserpine Derivatives

1. *Occurrence and Structure*

The main alkaloids in this group are reserpine (**20**), rescinnamine (**21**), and methyl reserpate, which occur in the roots of *Rauwolfia serpentina* (L.) Benth., deserpidine, found in *R. canescens* L., and the semisynthetic derivatives syrosingopine (**22**) and methoserpidine.[38] Reserpine is the most abundant of these compounds in nature, and is found in many members of the genus *Rauwolfia*. The roots of *R. serpentina* contain about 0.14% by weight of this alkaloid. Although in its basic alkaloidal structure, reserpine greatly resembles yohimbine, there is an ester-linked 3,4,5-trimethoxybenzoyl group, and a trisubstituted E ring in the former that confer markedly different biological activity.

2. *Biological Activity*

Extracts from *Rauwolfia* species have been used for centuries in popular medicine to treat a variety of ailments in those subtropical and tropical areas of India, Africa, and Central and South America where the plants grow. The name *Rauwolfia* was intended to honor Leonhard Rauwolf, who traveled through the Middle East in search of drugs in the late sixteenth century, and apparently became acquainted with these plants in India.[61] The first modern description of the value of *Rauwolfia* for treating high blood pressure and insanity was published by Sen and Bose in 1931.[62] In addition to these therapeutic uses, reserpine and its congeners exhibit a wide range of side effects that has greatly reduced the usefulness of these drugs. Although there are interspecies variations in relative potencies for both therapeutic and toxic effects, it appears that the major reserpine alkaloids are very similar in their activities.[38] In all of them central actions seem to predominate, although gastrointestinal, myocardial, and endocrine effects are prominent. These spring from a number of underlying mechanisms.

Central actions of reserpine are in many ways similar to those of the phenothiazines, but there are few or no antihistaminic, direct adrenergic, or cholinergic blocking components.[63] Reserpine exerts sedative and hypnotic effects that show both a latent phase and a prolonged duration. No analgesic action occurs, and although there is a tendency to ignore external stimuli, strong stimuli can arouse the treated subject. There is a reduction in aggressiveness. Respiratory inhibition, miosis, stimulation of peristalsis, and an action on the temperature-regulating center leading to hypothermia have been reported. It does not suppress convulsions.[38]

It is generally considered that reserpine produces its central effects through depletion of catecholamine and 5-HT stores in the brain.[63,64] Slow recovery evidently depends on the synthesis and transport of new storage vesicles along the axons,[65] since reserpine is very tightly bound to the vesicle structure.[66] This may account for the more rapid recovery of young rodents from the inhibition by reserpine of norepinephrine uptake, since in these animals synthesis of new vesicles occurs much more rapidly than in adults.[67] Hypothermia also appears to be related to effects of reserpine on norepinephrine uptake, since compounds that inhibit this uptake modify the reserpine action whereas serotoninergic agents do not.[68] This hypothermic action has been used as a screen for compounds with imipramine-like antidepressant action and monoamine oxidase inhibitors.[69] In the brains of developing rats, reserpine may exert an additional effect on cellular proliferation as reflected in DNA synthesis. This effect was not accompanied by disturbances in adenine nucleotide levels.[70] It is unlikely to play any role in the adult.

Cardiovascular actions include a brief sympathomimetic effect soon after large doses, followed by a characteristic, slowly developing fall in blood pressure, often accompanied by bradycardia. Pressor reflexes are at least partially inhibited, peripheral resistance diminishes, and cardiac output is frequently reduced.[63,71] As with the central effects, catecholamine depletion appears to be the major factor in producing cardiovascular effects. This depletion extends to the sympathetic nervous system, the adrenals, and many other tissues including the myocardium

itself.[63,72] It is possible that some cardiovascular actions are not mediated by catecholamine depletion. Intra-arterial reserpine can produce peripheral vasodilatation even in sympathectomized regions, and direct depression of the myocardium appears to occur.[73]

Among the miscellaneous actions of reserpine, the most interesting is its significant antitumor activity against several experimental rodent tumors; these include adenocarcinoma 755, sarcoma 180, and Walker carcinoma 256.[74] The mechanisms involved are not yet understood.

3. *Clinical Use*

Reserpine is now rarely used for treating psychoses, where daily doses as large as 5 mg orally or 10 mg by the intramuscular route have been employed. The major, but declining, application of these drugs is in the control of hypertension. For mild to moderate degrees of hypertension, diuretic therapy is usually adequate, but in more severe or intractable situations reserpine may be useful. Indeed in a controlled three-arm study, the combination of reserpine with the diuretic hydroflumethiazide was superior to diuretic plus methyldopa or propranolol in patients who did not respond to the thiazide alone.[79] Dosage levels of reserpine are generally around 0.25 mg daily.

Toxicity is relatively common and frequently troublesome.[63] Drowsiness, nightmares, and psychic depression occur frequently[76]; thus the drug is contraindicated in patients with a history of depression. Parkinsonism and other extrapyramidal effects are rare but dose-related. Akathisia, which is the need for constant motion, requires dosage reduction, but may be difficult to distinguish from agitation in psychotic patients for whom increased dosage is indicated. Parasympathetic symptoms may result from diminished sympathetic tone; they include cutaneous vasodilatation, excessive salivation, nausea, bradycardia, diarrhea, nasal congestion, and orthostatic hypotension. Gastric ulceration is not uncommon and appears to be associated with increased gastric acid secretion; in rats zinc sulfate has afforded protection against ulceration related to reserpine.[77] Weight gain with edema, exacerbation of allergic symptoms, depressed fertility, and feminization and impotence in males have been reported. More serious is the indication from retrospective studies that chronic administration of reserpine may give a threefold increase in the incidence of breast carcinoma in women.[78,79] Although careful statistical analysis allowing for duration of hypertensive disease suggested that the correlation did not hold,[80] it is evident that caution in the use of reserpine is indicated until such time as definitive studies have been completed. Since reserpine stimulates prolactin secretion, and prolactin may enhance the growth of mammary tumors,[81] a role for reserpine of a cocarcinogen or promoter is not unlikely. As an alternative therapy to reserpine, ajmaline appears to have less mammotrophic activity.

4. *Biological Fate*

This has been reviewed.[66] Reserpine is absorbed quite readily from the gastrointestinal tract or after subcutaneous or intraperitoneal injection. In the latter case, however, a first-pass effect is seen such that blood levels are low due to metabolism in the liver. Initial and secondary plasma half-lives are about 4 and 48–168 hours, respectively. During the slow phase about 96% of the drug in the plasma is bound, principally to albumin, but with significant association with lipoproteins also.[82] The drug undergoes intracellular binding at many sites containing catecholamine systems, including the locus ceruleus, caudate putamen, nucleus accumbens, dorsolateral septum, and infundibulum of the brain.[83] Metabolism is extensive, such that only about 2% is excreted unchanged in the urine; biliary excretion is prominent.

IV. ULEINE-ELLIPTICINE GROUP

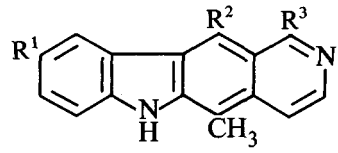
A. Ellipticine Derivatives

1. *Occurrence and Structure*

Ellipticine (**23**) and its 10-methoxy derivative (**25**) are pyridocarbazole alkaloids which were originally isolated from *Ochrosia elliptica* Labill. (Apocynaceae),[84] a small tree native to Australia, Madagascar, and the Pacific islands. Subsequently, these and a number of related alkaloids have been found in other members of the genera *Ochrosia*, *Excavatia*, and *Aspidosperma*.[3] 10-Hydroxyellipticine (**24**) is a normal metabolite of ellipticine that has been described as being more effective than the parent drug. Other closely related alkaloids are olivacine (**27**), which occurs naturally, and 19-demethylolivacine (**28**),[85] thiaellipticine,[86] and the dimethoxyellipticines,[87] which are semisynthetic.

2. *Biological Activity*

These alkaloids exert two major types of biological actions, inhibition of cellular proliferation and cardiovascular interactions. As inhibitors of the growth of L1210 lymphoblastic leukemia in mice, 10-methoxy- and 10-hydroxyellipticine are more active than ellipticine itself, but 10-aminoellipticine is considerably less effective.[88–90] Demethylolivacine, in the same tumor screen, is noticeably more active than olivacine.[85] In cell cultures, mitosis and early G_1 are the cell-cycle phases reported as being most sensitive to ellipticine, and achromatic gaps, chromatid breaks, and interchanges have been noted in DON cells.[91] Initiation of DNA synthe-



	R^1	R^2	R^3
Ellipticine (23)	H	CH_3	H
10-Hydroxyellipticine (24)	OH	CH_3	H
10-Methoxyellipticine (25)	CH_3O	CH_3	H
10-Aminoellipticine (26)	NH_2	CH_3	H
Olivacine (27)	H	H	CH_3
Demethylolivacine (28)	H	H	H

sis and completion of G_2 were also reported as being sensitive in these cells.[92] As part of a general cytotoxic action, hematologic depression is seen.[93]

In dogs and monkeys ellipticine gives rise to hypotension and bradycardia that may be followed by a small hypersensitive action. Antagonism of these actions by propranolol and reserpine indicates that a β-adrenergic mechanism is involved.[94] At low levels there is a cardiotonic action in the dog, but at higher levels, cardiac output and systolic ejection are reduced[95]; this involves the Purkinje cells, as is also the case with the cardiotonic action in the mice.[96] 10-Hydroxyellipticine was not myopathic in these studies.

Other toxic side effects include hemolysis, hypothermia, fatty infiltration of the liver, ataxia, emesis, and paraplegia before death.[96] As is the case with many anticancer agents, ellipticine and several of its congeners are carcinogenic and mutagenic. This latter activity, assayed by the Ames *Salmonella*-microsomes test, appears to be dissociable from cytotoxicity, however, since a derivative such as N_b-methyl-10-hydroxyellipticinium acetate was an effective inhibitor of L1210 leukemia but was not mutagenic when tested.[97]

3. *Mechanism of Cytotoxic Action*

The cytotoxic action of ellipticine derivatives involves marked, essentially irreversible inhibition of the synthesis of nucleic acids and proteins.[98,99] Although there appears to be some specificity of ellipticine for the maturation of 45S nucleolar RNA,[100,101] the major lesion occurs at the template level,[98] where drugs of this class interact strongly with helical DNA[102–104] to form primarily intercalative complexes. It appears that the cationic form of ellipticine is the one that undergoes binding.[104] 10-Hydroxyellipticine has a greater DNA binding constant and a larger DNA unwinding angle than any of the other derivatives.[103] Breakage of

L1210 DNA has been reported,[105] and could be the basis of chromatid aberrations.

Other biochemical interactions of the ellipticines include inhibition of aryl hydrocarbon hydroxylase and binding to reduced liver cytochrome P-450, which may help to explain the ability of these alkaloids to reduce the mutagenic activity of benzo(*a*)pyrene in the Ames test.[106] There are also some membrane-associated effects of these drugs. They include the biphasic initial stabilizing and later lytic effect on erythrocyte membranes that leads to hemolysis at high concentrations,[107,108] and the inhibition of respiration in mitochondria.[109] These drugs are strong inhibitors of microsomal mono-oxygenases, and hence could alter drug metabolism.[110]

4. *Distribution and Metabolism*

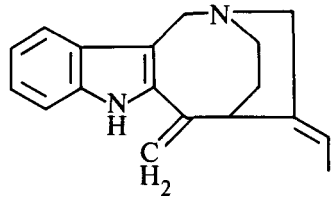
In mice the highest levels of ellipticine are found in the liver, kidney, and spleen; drug also enters the brain, where it may give rise to the neurotoxic effects that have been described. The lactate appears to be a better formulation than the hydrochloride, from the viewpoint of high plasma levels, and 49% of the drug is excreted in the feces in 9 days, after administration to mice.[111] Metabolism of ellipticine is extensive in rats, and the products are largely excreted in the bile.[112] In a comparative study of several species, the plasma half-lives of ellipticine (in minutes) were determined as follows: mice, 22; monkeys, 52; dogs, 160; and rats, 210. Around 80% was excreted in the bile. The major metabolic pathway was conversion to 10-hydroxyellipticine and conjugation to give its glucuronide and *O*-sulfate.[113]

5. *Clinical Trials*

In a study of 10-methoxyellipticine, there were no responses in patients with Hodgkin's disease and acute lymphoblastic leukemia, but among 15 subjects with acute myeloblastic leukemia, there were three complete and six partial remissions.[114] Another derivative, N_b-methyl-10-hydroxyellipticinium, has been introduced into clinical trial recently. It is evident that more studies are needed to evaluate the efficacy of these alkaloids in the treatment of human cancer. Some of the pharmacokinetic and toxicological problems such as hypotension and hemolysis would be obviated if the drug were administered by intravenous infusion.[113] An interesting finding has been that ellipticine may enter cells more readily as a DNA-bound lysosomotropic complex than as free drug, because of the large amount of the latter that becomes associated with the cell membrane.[116] Thus, like the anthracyclines, whose cardiotoxicity may be reduced by this maneuver, there may be clinical advantages to using lysosomotropic forms of the ellipticines.

B. Apparicine

Apparicine or pericalline **(29)** is isolated from *Catharanthus* species, including



Apparicine (29)

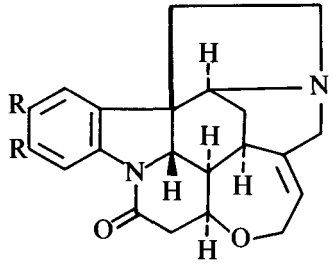
C. roseus and *C. lanceus*, but it also occurs in *Aspidosperma* and *Conopharyngia* species. In its structure it differs markedly from ellipticine (23), although we are considering it in the same group. The alkaloid is notable for its pronounced analeptic properties, being a convulsant of the tonic/clonic variety in mice at doses as low as 2 mg/kg.[117] A second effect of apparicine is its antiviral action on polio type III virus; it was the most active among a series of indole alkaloids that were tested.[37]

V. THE STRYCHNINE GROUP

A. Strychnine Derivatives

1. *Occurrence and Structure*

Strychnine (30) and brucine (31), or dimethoxystrychnine, were among the first alkaloids to be discovered, in 1817 and 1819, respectively. In various forms, strychnine has a long history, since the sixteenth century, of unwarranted medicinal use, as well as a quite justified application as a rat poison. These two compounds are the chief alkaloids in the seeds of *Strychnos nux-vomica* L. and *S. ignatii* Berg. (Loganiaceae), where they reach concentrations of 2 or 3% by weight. *S. nux-vomica* is a tree native to India.[4,118]



Strychnine (30): R = H
Brucine (31): R = OMe

2. *Pharmacological Actions*

Strychnine is a CNS stimulant that is highly toxic; as little as 32 mg has been lethal. It produces excitation of all parts of the CNS, so its effects may be seen in spinal animals. By blocking inhibitory influences, strychnine removes confining influences on nerve impulses, and thus outgoing activity is enhanced, leading to exaggerated reflexes. There is a pattern of tonic convulsions whose natural resultant reflects the pattern of the relative strengths of the musculature. Effects on the cardiovascular system and the gastrointestinal tract have not been demonstrated conclusively, although the extremely bitter taste of strychnine forms the basis of its use as bitters to stimulate the appetite and gastric secretion. In supraconvulsive doses a curariform effect occurs at the neuromuscular junction.[118] Brucine is decidely less potent than strychnine.

3. *Mechanism of Action*

In blocking inhibitory spinal impulses, the locus of action of strychnine is at the postsynaptic level.[119] Both GABA and glycine function as inhibitory neurotransmitters within the CNS, but glycine appears to be the predominant transmitter to motoneurons and interneurons in the spinal cord.[120] The evidence suggests that strychnine, like gelsemine, is a competitive inhibitor of glycine or "glycine-like" amino acids at the postsynaptic inhibitory sites, in a fashion analogous to the interaction between curare and acetylcholine at the neuromuscular junction.[33,121] There may be similar glycine sites in the higher centers where strychnine also acts.[122]

4. *Metabolic Disposition*

Strychnine is readily absorbed from the gastrointestinal tract, and then rapidly taken up by tissues, although there is no evidence for selective uptake into the brain. Metabolism of the alkaloid involves the hepatic microsomal system.[123] About 20% of the administered dose escapes unchanged into the urine.[118]

5. *Therapeutic Use and Toxicology*

There is no rational therapeutic use for strychnine, but the alkaloid is still used as a tonic, because of supposed stimulation of the appetite and an increased tone of skeletal musculature. Poisoning from strychnine has been common because of its use as a rat poison. The normal adult lethal dose is 50–100 mg, but death has resulted from much lower doses and 15 mg may be lethal in children. Initial stiffness of the face and neck muscles, and later on opisthotonic convulsions, are diagnostic. Death results from central hypoxia, because the extensive muscle contracture interferes with normal respiratory movements. The most satisfactory treatment, superior

to the more depressant barbiturates, is intravenous diazepam (10 mg)[124,125]; gastric lavage, especially using 1:5000 potassium permanganate, and activated charcoal may also be helpful.[118]

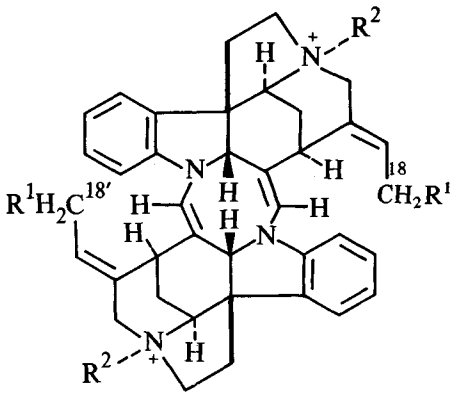
B. Curare Alkaloids

1. *Neuromuscular Blocking Agents*

Neuromuscular blocking agents are found in calabash curare used for preparing poisoned arrowheads. This is derived from many different plants, including *Strychnos toxifera*, *Chondrodendron tomentosum*, and other species of both genera, which belong to the Loganiaceae.[4] Although *d*-tubocurarine is the component that has been studied most intensively and is in widespread clinical use as a neuromuscular blocking agent during surgery, there are at least 40 alkaloids that contribute to the overall toxicity of curare; most of these are indole derivatives.[126] The most active compounds in curare are the toxiferines **32** and **33**,[127] and although these are not presently used, the diallylbis derivative of nortoxiferine known as alcuronium (**34**) is used clinically in Europe. Among other weak muscle-relaxing alkaloids are caracurine V (**35**) and its *N*-oxides from *S. dolichothyrsa* Gilg. ex Onochie et Hepper and *S. angolensis*,[128] *C*-curarine and calebassine from *S. usambarensis*, and the *Erythrina* alkaloids such as β-erythroidine (**36**) and the erysotrine derivatives (e.g., **37**) from species such as *E. variegata* or *E. americana* L.[129,130] All these compounds are in general quaternary ammonium compounds that act as competitive antagonists for acetylcholine at the postjunctional membrane nicotinic cholinergic receptor sites. They thus interfere with initiation of the end plate potential at the neuromuscular junction.[129] The muscle fiber still retains its sensitivity to direct electrical stimulation and to potassium ions, which is why such neuromuscular blocking agents do not block spasms induced by potassium chloride.[130] There is no central action or direct effect of curare on the muscles per se, but high doses block autonomic ganglia.[127] The end plate receptor, a lipoprotein subunit with a molecular weight of 50,000, seems to be associated with, or actually to be, the ionophore for sodium transport.[131] Although several neuromuscular blocking agents are extensively used for muscle relaxation during surgery, thus permitting the use of lighter and safer planes of anesthesia, most of the indole derivatives listed here have only had limited clinical use, for example, toxiferine where long-term paralysis is needed, and alcuronium for short operations.[127] Tubocurarine has a half-life of between 0.25 and 3 hours, undergoes 40 percent binding to plasma proteins, and is excreted to an extent of about 43 percent of administered dose in humans.[131a]

2. *Other Curare Alkaloids*

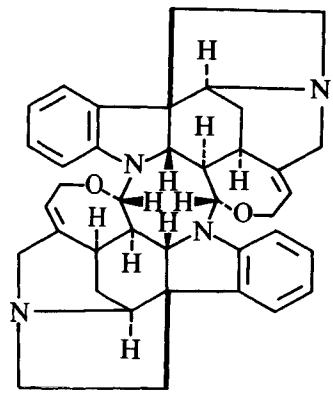
In addition to neuromuscular blockade, other actions have been reported in



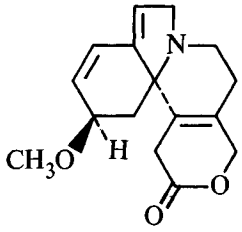
Dihydrotoxiferine I (**32**): R^1 = H, R^2 = Me

Toxiferine (**33**): R^1 = OH, R^2 = Me

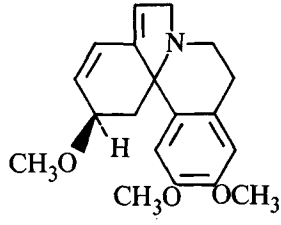
Alcuronium (**34**): R^1 = OH, R^2 = $CH_2CH=CH_2$



Caracurine V (**35**)

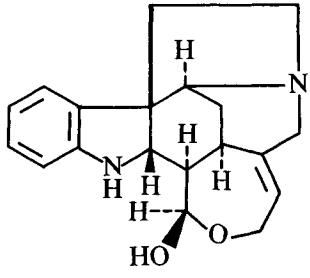


β-Erythroidine (**36**)

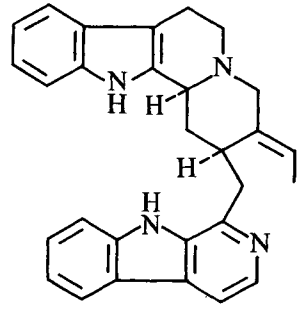


Erysotrine (**37**)

curare extracts. They include antimicrobial (caries) activity associated with tertiary dimeric indole alkaloids in *Strychnos afzelii* Gilg., a plant used as a chewing stick,[132] weak convulsant effects of derivatives of the Wieland-Gumlich aldehyde (**38**) in *S. angolensis*,[133] and an atropine-like spasmolytic action of usambarensine (**39**) from *S. usambarensis*.[134]



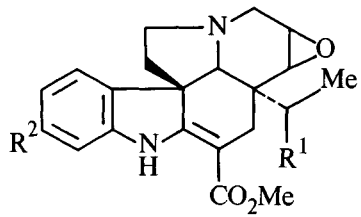
Wieland-Gumlich aldehyde (**38**)



Usambarensine (**39**)

C. Lochnericine Derivatives

These alkaloids have structural features that associate them with the strychnine group. Lochnericine (**40**), lochnerinine (**41**), and hörhammericine (**42**) occur in plants of the genus *Catharanthus*, notably *C. roseus* and *C. lanceus* (Apocynaceae).[5] All three alkaloids show cytotoxicity in vitro against Eagle's 9KB carcinoma cells, a line originally derived from human nasopharyngeal cancer. However, the range of concentrations giving 50% inhibition – 0.1 μg/ml for lochnerinine to 1.1 μg/ml for the other two agents – makes them far less effective than the dimeric alkaloids.[135,136]



Lochnericine (**40**): $R^1 = R^2 = H$

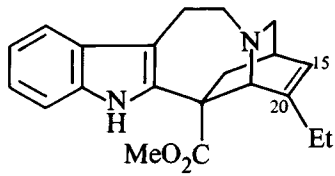
Lochnerinine (**41**): $R^1 = H$, $R^2 = OMe$

Hörhammericine (**42**): $R^1 = OH$, $R^2 = H$

VI. REARRANGED SECOLOGANINS AND VINCAMINE

A. Catharanthine

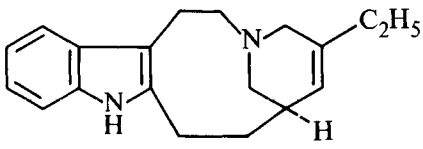
Catharanthine (**43**) is found in many species of *Catharanthus* (Apocynaceae). This alkaloid exhibits a wide range of biological interventions.[5] In rats, catharanthine is a potent diuretic and also exerts a hypoglycemic effect of slow onset but relatively long duration. Although these two properties have been found to be correlated in a number of indole alkaloids, the reason for this is not known. Partial hydrogenation to give dihydrocatharanthine led to the loss of neither activity; indeed hypoglycemic activity increased, but there was a marked increase in toxicity. Like most of the indole alkaloids isolated from *Catharanthus* species, catharanthine is a CNS depressant, the effect being maximal in 10 minutes and persisting for more than 2 hours.[5] A recently discovered action of catharanthine is the ability to stimulate the release of amylase from pancreatic acinar cells and tissue fragments. This action is in no way cholinergic in its mechanism, since it is unaffected by atropine, but it depends on free Ca^{2+}, and the alkaloid causes a release of bound calcium.[137] It is unlikely to involve the microtubule system since catharanthine has only 1/1000 the antimitotic activity of bisindoles.[138]



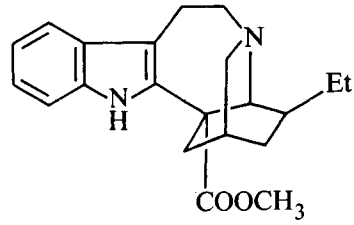
Catharanthine (43)

B. Cleavamine

Cleavamine (44) is obtained by the degradation of the bisindole alkaloid vinleurosine (leurosine).[139] This compound exerts a marked antidiuretic effect in rats.[5]



Cleavamine (44)



Coronaridine (45)

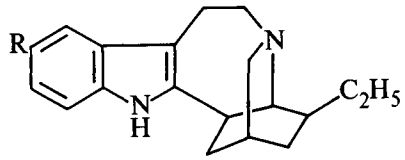
C. Coronaridine

Coronaridine (45) is isolated from *Catharanthus roseus* and *C. ovalis*, but is present in a wide range of plants included in the genera *Conopharyngia*, *Ervatamia*, *Stemmadenia*, *Tabernaemontana*, and *Voacanga*. As with catharanthine, this alkaloid exhibits both a strong diuretic action and a significant delayed hypoglycemia in rats.[5] An interesting action of this compound is its ability to prevent pregnancies in adult female rats when given orally. This contraceptive action appears to relate to its weakly estrogenic nature manifested in its ability to stimulate uterine growth in immature animals.[140]

D. Ibogaine

Ibogaine (46) is an alkaloid obtained from *Tabernanthe iboga* Baill., a plant used by Africans stalking game to help them remain motionless yet alert for long periods and also employed in ceremonials because of its hallucinogenic action. The alkaloid resembles cocaine in its ability to increase the hypertensive response to epinephrine while abolishing that due to occlusion of the carotid artery.[141] However, in the intestine it antagonizes the effect of epinephrine but not acetylcholine;

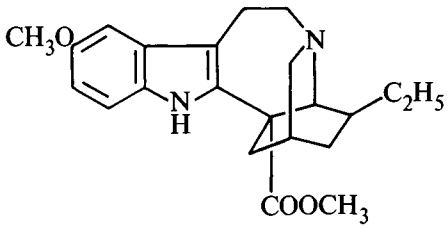
it causes contraction of the uterus.[142] The CNS property of ibogaine is seen in experimental animals as widened pupils, apprehension, and spread limbs. Electroencephalography shows effects on the ascending reticular formation. There is no strychnine-like effect, and surprisingly, both the threshold and latency of electroshock are increased; this may relate to a weak anticonvulsant action.[143] These findings have suggested a clinical use of ibogaine as an antidepressant.



Ibogaine (**46**): R = OMe
Ibogamine (**47**): R = H

E. Ibogamine

This alkaloid (**47**), which has been isolated from a number of plants including *Tabernaemontana johnstonii*, shows marginal cytotoxic action against KB cells at very high concentrations. Thus it resembles the closely related alkaloids voacangine (**48**) and vobasine (**15**).[36,144] In rats, ibogamine shows a diuretic action and a marginal hypoglycemic activity.[5]



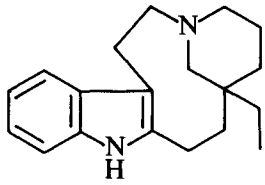
Voacangine (**48**)

F. Quebrachamine

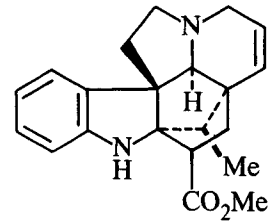
This compound (**49**) is obtained from the bark of *Aspidosperma quebracho blanco* Schlecht (Apocynaceae). It has been described as a sympatholytic agent that antagonizes the hypertensive effects of epinephrine,[144] and has also been shown to inhibit horse serum acetylcholinesterase, as do akuammine and ibogaine.[29]

G. Vindolinine

Vindolinine (**50**) is a very pharmacologically active alkaloid present in most species of the genus *Catharanthus*. It is the most active of the naturally occurring



Quebrachamine (**49**)



Vindolinine (**50**)

Catharanthus alkaloids as a diuretic, and its hypoglycemic action is practically equivalent to that of vinleurosine, the most potent agent in this regard.[5] Although not cytotoxic for mammalian cells, vindolinine is inhibitory for polio type III virus.[37]

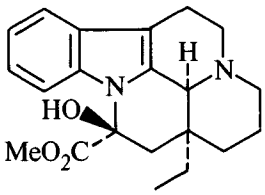
H. Vincamine

Vincamine (**51**) is the major alkaloid of *Vinca minor* L. (Apocynaceae), where it occurs together with lesser amounts of such compounds as vincine, vincaminine, and vincinine.[145,146]

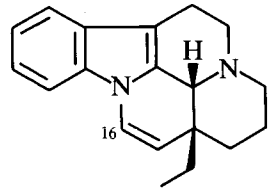
1. *Biological and Clinical Studies*

When injected intravenously into dogs and rats, vincamine produces a steep and rapid initial fall in blood pressure followed by a brief return to more normal levels, and then a second moderate but prolonged depression.[147] However, the effects are influenced by any anesthetic that might be administered, and increased blood pressure and heart rate have also been reported; certainly there are selective local changes such as decreased renal blood flow and increased femoral flow.[148] Vincamine also exerts a sedative action,[149] and it is likely that both this and delayed hypotension result from central and peripheral depletion of catecholamines.[150] A third action that has been identified in studies with animals is a moderate cerebral vasodilatation,[151] and this is the effect that forms the basis for clinical usage of this alkaloid. Other related alkaloids share this property of increasing cerebral blood flow and hence increasing oxygenation of the brain. In a comparative study with curarized rats in whom anoxia had been induced by asphyxia, eburnamonine gave a much longer-lasting protection against hypoxia-induced electroencephalographic disturbances than did vincamine.[152] A number of pharmacologically active derivatives of eburnamenine (**52**), particularly those with substituents at the 16 position, have been synthesized.

Clinical findings with vincamine include a slight reduction in arterial blood pressure, together with increases in the total cerebral blood flow and oxygen consumption.[153,154] There is a significant beneficial hemodynamic effect on ischemic



Vincamine (51)



Eburnamenine (52)

regions of the brain owing to decrease and equalization of the resistance of the cerebral vascular bed.[155] These effects undoubtedly contribute to the general improvement in the intellectual status of patients with cerebral arteriosclerosis on being treated with vincamine.[156]

2. *Disposition Studies*

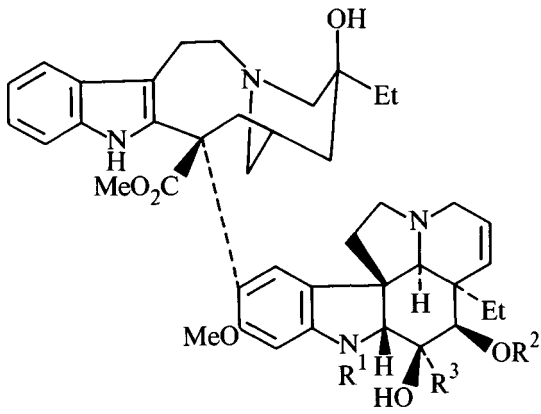
In one study, vincamine had a plasma half-life of 30–60 minutes and there was 90% recovery of administered oral drug in 24 hours, with most of this urinary material in the form of glucuronides.[157] In another study with human subjects, maximum plasma levels were achieved 90 minutes after an oral dose. The plasma clearance curve was biphasic, and only some 7% was excreted unchanged in the urine in 30 hours.[158]

VII. BISINDOLES

A. *Vinca* Alkaloids

1. *Occurrence and Structure*

These bisindole derivatives are isolated in yields of only a few milligrams per kilogram from the leaves of the Madagascan periwinkle plant, *Vinca rosea* L., more correctly referred to as *Catharanthus roseus* G. Don (Apocynaceae), a plant with a long-standing reputation for its medicinal value.[159] Indeed, it was an investigation of the reputed usefulness of the plant for treating diabetes that led to the isolation of the cytotoxic alkaloids.[160,161] Of more than 70 alkaloids that have been identified in this plant, eight are cytotoxic bisindoles composed of a vindoline and a catharanthine moiety. These active alkaloids are vinblastine (vincaleukoblastine; Velban® or Velbe®) (**53**), vincristine (leurocristine, Oncovin®) (**54**), vinleurosine (leurosine) (**57**), vinrosidine (leurosidine) (**58**), leurosivine, 4-desacetylvinblastine, rovidine, and leurocolombine. There are, in addition, several semisynthetic derivatives including 14,15-dihydrovinblastine, vinglycinate (17-*N*,*N*-dimethylaminoacetyl-17-desacetylvinblastine) (**55**), vindesine (17-desacetylvinblastine amide) (**56**), and several 15′,20′-dehydro compounds.[159]

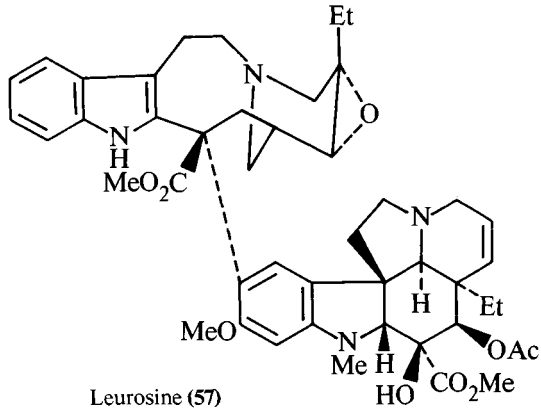


Vinblastine (**53**): R^1 = Me, R^2 = COMe, R^3 = CO_2Me

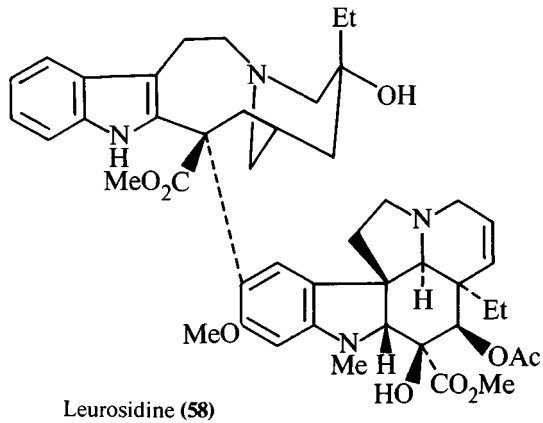
Vincristine (**54**): R^1 = CHO, R^2 = COMe, R^3 = CO_2Me

Vinglycinate (**55**): R^1 = Me, R^2 = $COCH_2NMe_2$, R^3 = CO_2Me

Vindesine (**56**): R^1 = Me, R^2 = H, R^3 = $CONH_2$



Leurosine (**57**)



Leurosidine (**58**)

2. *Structure-Activity Relationships*

The bisindole structure appears essential for full cytotoxic potency, since of the known monomeric alkaloids, lochnericine and lochnerinine are the only ones to have even a very modest activity.[135] Appropriate stereochemical configuration about the catharanthine-vindoline linkage is very critical, and failure to achieve this has been the major obstacle to the synthesis of active bisindoles which has only recently been overcome.[162,163] Among other features that have been identified as being important for cytotoxic potential are the need for a basic nitrogen in the catharanthine nucleus, the requirement for at least one free hydroxyl group, and partial loss of activity after reduction of the 14,15 double bond or dehydration at the 16,17 position. Changes in the 16 and 17 substituents modify the spectrum of activity.

3. *Biological Activity*

The most characteristic effect of these drugs is the arrest of cell division at metaphase, in a manner resembling the effect of colchicine. There is an attack on the spindle itself which then undergoes attrition and finally disappearance. These changes, which may be reversible, have been described in detail for many cell types; chromosomes may adopt unusual metaphase configurations.[164–167]

Cytotoxicity was first recognized in the P1534 leukemia system,[168] but a wide range of experimental animal tumors respond to drugs of this class.[159] The most sensitive tumors are P388 and P1534 leukemia, Ehrlich, Freund, sarcoma 180 and Walker 256 ascites tumors, Ridgeway osteogenic sarcoma, and B82A leukemia; vinblastine and vincristine are generally the most active alkaloids. These drugs block progression of cells through the cell cycle during mitosis, but appear to exert greatest cytotoxicity on cells in the DNA synthetic S phase.[169] Antiviral activity has been demonstrated for vinblastine, vincristine, leurosivine, leurosidine, and desacetylvinblastine, but not for leurosine and lochnerinine. Interestingly, the monomeric alkaloid apparicine, which is not cytotoxic, does have antiviral activity.[37]

Neuromuscular actions are prominent among this group of alkaloids, and in the case of vincristine are the dose-limiting side effects. Vindesine is also markedly neurotoxic. Depression of deep tendon reflexes, paresthesias of the extremities, cranial and sensory nerve involvement,[170] constipation, paralytic ileus, muscle weakness,[171] and reduced nerve conduction velocities[172] have all been reported. Axons may become demyelinated, dorsal root ganglion cells are lysed, Schwann cell proliferation is inhibited,[173] and the rapid transport of neurotransmitter storage granules and enzymes along the axons is greatly reduced.[174] Motor end plates exhibit degenerative changes,[175] and in rat skeletal muscle vincristine causes a fall in calcium uptake and alterations in the phospholipid composition of the microsomes.[176] The uptake of norepinephrine by brain synaptosomes is inhibited by vinblastine,[177] and there is evidence for other autonomic effects that may

alter cardiovascular function.[159] In terms of their effects on the behavior of mice, vincristine, desacetylvinblastine, and leurosidine are CNS depressants, whereas leurosine behaves as an adrenergic blocking agent.[5]

Among other actions of these alkaloids, teratogenesis has been well established in animals, although there is no evidence of mutagenicity in the Ames test or of direct damage to chromosomes.[178] Vincristine may produce inappropriate secretion of antidiuretic hormone,[179] reduced secretion of thyroid hormones,[180] insulin,[181] renin,[182] and plasma lipoproteins.[183] Vinblastine is known to bind to, and cause aggregation of, ribosomes.[184,185] Of these cytotoxic alkaloids, only leurosine causes a delayed-onset depression of blood sugar levels, the activity for which the plant extracts were originally assayed[5]; this alkaloid also produces transient hypotension probably by α-adrenergic blockade.[135]

4. *Biochemical Actions*

The many biological effects produced by these alkaloids suggest the existence of a number of different biochemical interactions. Two of the latter, interaction with microtubule system and inhibition of biosynthetic pathways, are particularly important, and may explain most of the biological effects.

The microtubule system consists of tubular elements of diameter about 250 Å that occur in eukaryote cells, often singly, but usually in groups near cell membranes or intracellular organelles, or as components of structures such as flagella or the mitotic spindle.[186–188] Tubules apparently containing tubulin, the basic component of eukaryote microtubules, have also been found in certain spirochetes which are prokaryotes.[189] It would appear that the microtubule system is primarily involved in maintaining rigidity and in some forms of motion. Microtubules in neurons, termed neurotubules, are associated with the movement of mitochondria and vesicles,[190] whereas in the mitotic spindle a combination of poleward sling and opposite end assembly and disassembly may be responsible for mitotic movements.[191]

Drugs such as the *Vinca* alkaloids resemble colchicine in being able to bind tightly to tubulin, although at different sites, and interfere with the functioning of the microtubule system. For the *Vinca* alkaloids it appears that the configuration at C-14′ and C-16′ as well as the presence of methoxycarbonyl at C-16′ play essential roles in the microtubular interaction.[192] Since the polymerized tubulin in the form of microtubules and formed tubular structures is in equilibrium with the tubulin pool, diminution of the latter by complex formation with drugs soon depletes the whole system at rates dependent on the kinetics of the various equilibria. This interaction, which involves both high affinity and low affinity sites, has been reviewed elsewhere.[138,193] The low affinity sites relate to microtubule crystal formation. More recent findings indicate that the alkaloids actually inhibit the polymerization of tubulin.[194] In addition, the site for binding of vinblastine has cysteine residues in its immediate vicinity.[195] Most striking has been the identification of an endogenous tubulin-binding protein in rat brain that inhibits polymeri-

zation of the protein to microtubules, and competes with colchicine for binding.[196] This may be a natural regulator for the microtubule system much like the endorphan-opiate receptor complex. It is quite logical to ascribe many of the common biological effects of the *Vinca* alkaloids – mitotic arrest, interference with phagocytosis and secretion, and the neurologic toxicity – to interaction with microtubules that are major elements in these processes.

Interference with biosynthetic pathways may be a contributing factor to the cytotoxicity of the *Vinca* alkaloids. Published reports show that DNA, RNA, protein, and synthesis may all be inhibited to various degrees in different systems.[159] In general, much higher levels of drugs are needed than those that block mitosis or lead to significant binding to tubulin when in vitro systems are studied, but these biochemical effects have been observed in animals treated with therapeutic doses. The underlying mechanisms are not always clear, but reduced amino acid transport,[197] inhibition of respiration,[198] and inhibition of RNA polymerase[199,200] would seem to be among the processes that could be involved.

Miscellaneous biochemical effects of the *Vinca* alkaloids include a fall in liver coenzyme A levels,[201] inhibition of histamine release from mast cells,[202] and an increase in cyclic AMP concentrations in lymphoma cells.[203]

5. *Metabolism and Distribution*

Some of the plasma pharmacokinetic data for the *Vinca* alkaloids are summarized in Table II. Of the three major alkaloids, vincristine has the largest plasma half-life especially in the tertiary phase of the triphasic clearance curve. It should be stressed that about 75% of the alkaloid content of the plasma is bound to protein, especially α- and β-globulin.[204] In addition to this bound component, very high levels of these alkaloids enter the platelets which may carry more total drug than is present in the plasma, thereby acting as a reservoir.[205] It appears that the platelets retain vincristine more tenaciously than vinblastine, although the latter drug enters these structures faster than vincristine.[206] There is also some concentration of drug by leukocytes, and the evidence obtained with cells in vitro, as well as the extremely rapid initial distributive phase in the plasma, suggest that the *Vinca* alkaloids are avidly sequestered by many tissues.

TABLE II. PLASMA PHARMACOKINETICS OF THE *VINCA* ALKALOIDS[a]

Species	Half-life (hr)								
	Vinblastine			Vincristine			Vindesine		
	α	β	γ	α	β	γ	α	β	γ
Dog	0.05	4		0.25	1				
Rat				0.25	1				
Human	0.07	1.7	28.8	0.11	3.2	144	0.04	0.08	24.3

[a] Data derived from R. L. Nelson, R. W. Dyke, and M. A. Root, unpublished, and Refs. 159 and 207.

The major route for excretion of these drugs is biliary, with urinary excretion in any species examined reaching no more than 23%. Most of the urinary excretion products consist of unchanged alkaloids, and this is true of the bile also, but degradation by intestinal flora is virtually complete so that little or none appears in the feces. Vincristine appears to undergo less metabolism than vinblastine.[207] Undoubtedly the combination of more prolonged retention by platelets, slower elimination, and less breakdown underlies the greater potency of vincristine.

6. *Clinical Antitumor Activity*

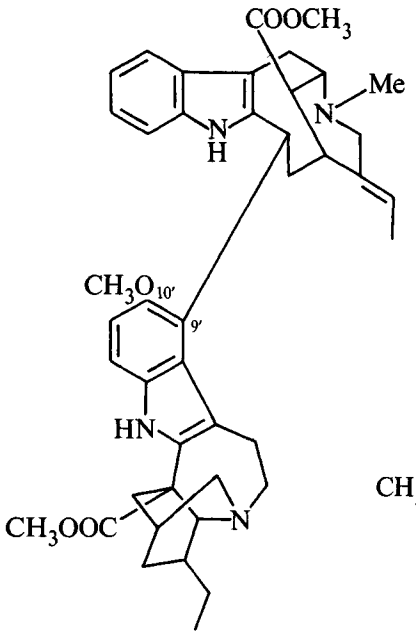
The clinical findings with vinblastine and vincristine as single agents has been reviewed.[5,168] More recently the alkaloids have been employed successfully as important components of complex regimens of combination chemotherapy, rather than alone. Vincristine is most effective in the therapy of acute lymphoblastic leukemia, Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, and Burkitt's lymphoma and is valuable in the treatment of Wilm's tumor, rhabdomyosarcoma, testicular tumors, carcinomas of the breast and bronchus, Ewing's sarcoma, and the nonmalignant Letterer Siwe disease. Vinblastine is of somewhat more limited use, particularly because it is not effective against acute lymphoblastic leukemia. Its major clinical applications have been for Hodgkin's disease, other lymphomas, choriocarcinoma, testicular cancers, and carcinoma of the ovary. The fact that its limiting toxicity is marrow depression, the most frequently encountered toxicity among cancer chemotherapy agents, rather than the unusual neurological toxicity of vincristine, makes it a less versatile component of combination regimens. Leurosine resembles vinblastine in its spectrum of activity and toxicity, but may produce in addition a shocklike syndrome when injected rapidly; this may result from the transient hypotensive and marked hypoglycemic activities of this alkaloid. Vindesine resembles vincristine in its antitumor activity, but exhibits the toxicities of both vinblastine and vincristine. Although, as we have said, platelets accumulate high levels of the *Vinca* alkaloids, thrombocytopenia has not been a prominent side effect of these agents; in fact, thrombocytosis elevation of platelet levels has been more commonly observed.[208,209] However, in the treatment of idiopathic thrombocytopenia purpura, where platelet levels are high, *Vinca* alkaloids may be useful in those patients refractory to the usual therapy such as prednisone and azathioprine.[210] Finally, vinblastine has been found to relieve the pain of acute gouty episodes in the same manner as does colchicine,[211] probably through reduction of metabolic activity and phagocytosis in the leukocytes in the joints, but no further clinical use has been made of this observation.

B. Voacamine Derivatives

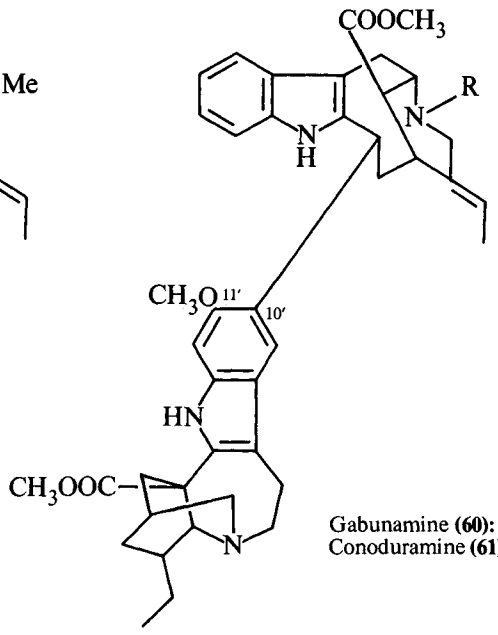
1. *Occurrence and Structure*

These alkaloids have been isolated from several plants of the genus *Tabernae-*

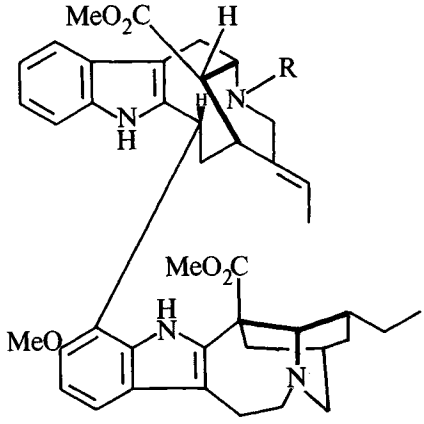
montana as well as from *Voacanga africana* Stapf; both these genera belong to the Apocynaceae.[212,213] These alkaloids have a dimeric structure derived from a vobasane and an iboga moiety (**59–68**).



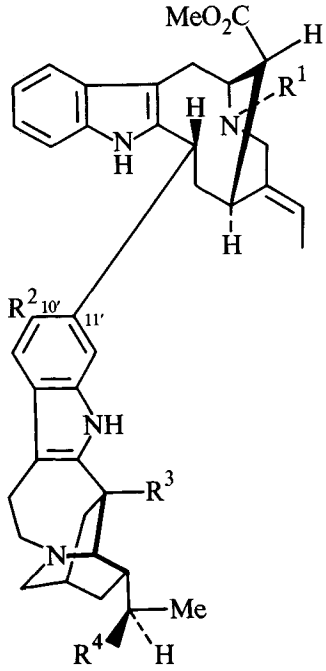
Voacamidine (**59**)



Gabunamine (**60**): R = H
Conoduramine (**61**): R = Me



Gabunine (**62**): R = H
Conodurine (**63**): R = Me



		R^1	R^2	R^3	R^4
11'-Perivoacangine	**(64)**	H	OMe	CO_2Me	H
11'-Peribogamine	**(65)**	H	H	H	H
Voacamine	**(66)**	Me	OMe	CO_2Me	H
Epivoacorine	**(67)**	Me	OMe	CO_2Me	OH
Tabernamine	**(68)**	Me	H	H	H

2. *Biological Activity*

Cytotoxicity has been established for this group of alkaloids against both KB cells and P388 cells in culture. As with the bisindole alkaloids discussed in Section VII.A, these dimeric compounds are much more active than the component simple indoles from which they are derived. Such alkaloids as ibogamine, vobasine, and perivine require concentrations close to or greater than 100 μg/ml for the ED_{50} in KB cells, for example, much greater than the levels of bisindoles that are effective (Table III). Several other points are raised by these data. *N*-Methylation of the vobasane unit produces marked loss in cytotoxic efficacy, whereas modification of the iboga unit by various substitutions has little effect. Furthermore the most active compounds are those in which the vobasane unit is linked to the 11 position of the iboga moiety. Voacamine **(66)** is active in vivo against both Walker 256 carcinosarcoma and sarcoma 180; voacorine is active against Walker 256.[213] Nothing is known of this mechanism of action or the metabolic fate of these alkaloids.

TABLE III. CYTOTOXICITY OF VOACAMINE-TYPE BISINDOLES[35,144]

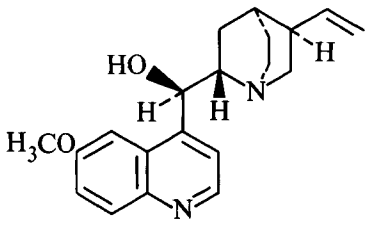
Alkaloid	Cytoxicity as the ED_{50} (μg/ml)	
	P388 cells	KB cells
Voacamidine (59)	14	–
Gabunamine (60)	1.3	5.8
Conoduramine (61)	20	19
Perivoacangine (64)[a]	0.39	0.35
Peribogamine (65)[a]	0.44	2.1
Voacamine (66)	2.6	–
Epivoacorine (67)	1.7	–
Tabernamine (68)	2.1	–
Gabunine (62)	3.2	–
Conodurine (63)	26	31
19-(2-Oxopropyl)conodurine	2.4	–

[a] These bases have not so far been found in Nature, but were synthesized from perivinol and voacangine (→ 64) or ibogamine (→ 65) for pharmacological evaluation.[144]

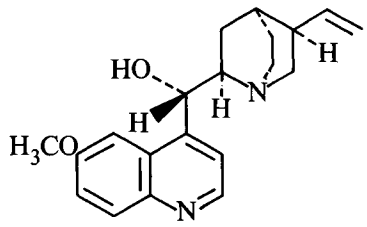
VIII. *CINCHONA* ALKALOIDS

A. History, Occurrence, and Structure

The *Cinchona* alkaloids are obtained from the bark of the cinchona tree, *Cinchona officinalis* L. (Rubiaceae), as well as from other trees of this genus (*C. ledgeriana* and *C. succirubra*) and the genus *Remijia*. The tree is native to South America, and it is believed that the Spanish conquistadors learned of the drug from natives of Peru in the early 1600s.[1,4,214] The genus was given the name *Cinchona* in honor of Countess Anna dell Chinchon, the wife of the viceroy to Peru who was successfully treated for malaria. Subsequently, the bark, used as an infusion in wine, became widely popularized, and remained for almost two centuries the only effective remedy for malaria. The pure alkaloids were isolated in 1820 and soon became the preferred dosage form. Although there are about 30 alkaloids in the bark, four of these, the two pairs of isomers quinine (**69**) and quinidine (**70**), and



Quinine (**69**)



Quinidine (**70**)

cinchonine and cinchonidine, account for the bulk of the pharmacological activity. Trees with quinine levels of about 17% in the bark have been selected, but in general the range is 1 to 8% by weight; quinine represents about 70% of the total alkaloids. Many of the synthetic antimalarial compounds, especially the aminoquinolines, are closely related to the naturally occurring *Cinchona* alkaloids.

B. Pharmacological Actions

The *Cinchona* alkaloids exert a variety of therapeutic and toxic effects, but the compounds vary among themselves with respect to their individual potencies. Thus quinine is the more potent antimalarial and the less toxic alkaloid, whereas quinidine, its diastereoisomer, is less effective as an antimalarial, but more toxic and more potent in treating cardiac arrhythmias.

1. *Antimalarial Action*

Here quinine is most effective, but after the 1920s the use of this compound declined with the advent of more potent synthetics such as amodiaquine, chloroquine, and primaquine. Recently, however, quinine has again become of value in this disease for treating *Plasmodium falciparum* resistant to other drugs; it appears that resistance to quinine is not readily acquired.[215] Quinine is not a true prophylactic drug, but like chloroquine is effective as a suppressive agent and in control of overt disease. This is because it acts primarily on the schizonts and not on the injected sporozoites or the forms present in liver cells. There is also some action on the gametocytes of *P. vivax* and *P. malariae*.[214] The mechanism of action is thought to involve binding of quinine to DNA by an intercalative reaction that leads to inhibition of nucleic acid and ultimately protein synthesis.[215,217]

2. *Cardiovascular Actions*

Quinidine is more effective in its actions on the heart than is quinine, but the two drugs have similar qualitative effects. The primary effect is on the heart in the form of depression of the excitability, contractility, and conduction velocities, but there is in addition an anticholinergic action.[218] These actions are somewhat conflicting. For example, the prolongation of the refractory period that occurs as a result of decreased excitability[219] abolishes fibrillation, whereas reduced conduction velocity may favor an irregular heart action.[11] Again, although an increased refractory period and depression of pacemaker activity[219] would be expected to slow the heart, the anticholinergic action blocks vagal impulses and leads to an increased heart rate, and indeed in unanesthetized animals and humans cardioacceleration occurs. It would appear that quinidine exerts a greater suppressive action on ectopic pacemakers than it does on the sinoauricular node.[220] At the electrophysiological level quinidine decreases the slope of the rising phase of the

action potential,[220] and this occurs even where there is no drug effect on resting membrane potential or intracellular Na^+ and K^+ concentrations.[221] Nevertheless, the actual onset of action of quinidine on the rising phase, as with ajmaline, is a function of the action potential of contraction; that is, electrical activity is needed for interference to occur.[222] The curve that relates the maximal rate of depolarization to the membrane potential, which is membrane responsiveness, is shifted to the right by quinidine. This means that complete repolarization must occur before a propagated action potential can take place.[223] Premature responses during a relatively refractory period thus are not propagated. Quinidine-reduced changes in the electrocardiogram are characterized by a prolonged Q-T interval with greater duration of electrical systole and increased duration of the QRS complex. Like ajmaline, treatment with quinidine leads to a drop in the level of ATP in the myocardium, but since other antiarrhythmics do not cause this to happen, the relationship to cardiac effects is unsure.

Clinically, quinidine is most useful for the treatment of ectopic beats, for paroxysmal supraventricular tachycardia, atrial flutter, and atrial fibrillation. According to mathematical models for the system,[224] quinidine acts by its ability to reduce the number of wavelets possible in a mass of tissue rather than on elimination of one particular circus movement. Since it is a toxic drug, many precautions must be observed. Idiosyncratic reactions are rather common, and signs such as vertigo, visual disturbances, headache, skin rash, cramps, and diarrhea may alert physicians to this possibility. The more severe forms of cinchonism that are found with quinine are seldom encountered with quinidine. Thrombocytopenia, paradoxical tachycardia, ventricular fibrillation, and hypotension due to peripheral vasodilatation are among other hazards. Care is needed in patients being treated with digitalis because unpredictable rhythms may develop, but in atrial fibrillation digitalization is necessary. The existence of partial or complete heart block, congestive heart failure, digitalis intoxication, and a history of thrombocytopenia purpura associated with quinidine are causes for withholding drug.[218]

3. *Miscellaneous Actions*

Among these are a local anesthetic action that may be of long duration, a weak analgesic and antipyretic effect, an oxytocic action on the gravid uterus, a curare-like effect on skeletal muscle with antagonism of physostigmine, and irritation of the gastrointestinal tract.[218]

C. Cinchonism

High doses of or prolonged treatment with *Cinchona* alkaloids may give rise to a complex of toxic symptoms grouped together under the term cinchonism. Some of the symptoms resemble salicylate poisoning, such as ringing in the ears and nausea. In more severe toxicity, blurred vision, diplopia, mydriasis, retinal

edema, hearing disturbance, nausea, vomiting, cramps and diarrhea, fever, confusion, delirium, renal damage, ventricular tachycardia, hemolytic anemia, and asthma have all been reported.[218]

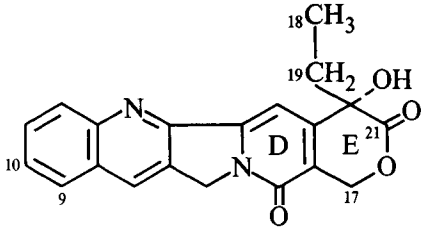
D. Disposition

Both quinine and quinidine are readily absorbed after oral administration with maximal blood levels within 1–3 hours. During chronic therapy, effective quinine levels in the plasma are about 7 μg/ml. Plasma concentrations of 2–5 μg/ml are considered effective for quinidine. The plasma half-lives are 4–6 hours for quinine and 4–7 hours for quinidine. Plasma protein binding reaches about 70% for each drug. Hydroxylated derivatives account for more than half of the urinary excretion products. The primary route of excretion is renal.[225]

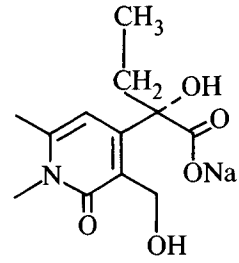
IX. CAMPTOTHECIN AND DERIVATIVES

A. Occurrence and Structure

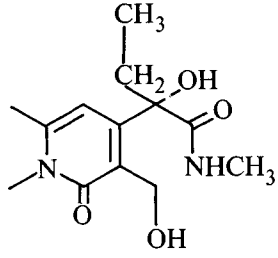
Camptothecin (**71**) was originally isolated from the trunk of the Chinese tree *Camptotheca acuminata* Decne. (Nyssaceae).[226] Both the 10-hydroxy and 10-methoxy derivative occur in the same tree; 9-methoxycamptothecin, as well as the parent compound, are found in *Mappia foetida* (Wight) Miers (Icacinaceae).[213] The techniques used for isolation and structural elucidation of this group have been reviewed.[227] It should be noted that in the sodium salt (**72**) and the methylamide (**73**), the E ring is opened. This is true also of the 17-acyl derivatives of camptothecin 21-isopropylamide that have been synthesized.[228]



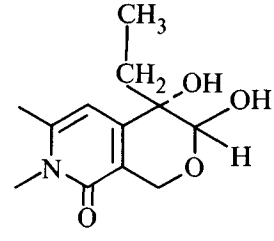
Camptothecin (**71**)



Sodium salt of camptothecin (**72**)



Methylamide of camptothecin (**73**)



Lactol of camptothecin (**74**)

B. Biological Activity

The primary action of the camptothecin group is cytotoxicity that is manifested as inhibition of tumor growth. A very wide range of experimental tumors is sensitive to this alkaloid, which caused considerable eagerness for clinical trials. Among the experimental tumors that respond are L1210 mouse leukemia, Walker 256 carcinosarcoma, L5178Y lymphoma, P388; plasma cell tumor YPC-1, mast cell tumor P815, and A-RCS reticulum cell sarcoma.[226,229] In cell culture there is a block at the S-G_2 transition of the cell cycle and another block, 1000 times more sensitive (evident at 0.01 μg/ml) at the G_2-mitosis interphase; cytotoxicity is greatest during S phase.[230–232]

Related to the cytotoxic effects on mammalian cells is the inhibition of viral replication ascribed to this drug. This has been reported for fowl plague virus replicating on BHK21/13 cells[233] and SV40 in BSC-1 cells.[234]

1. *Structure-Activity Relationships*

The structure-activity relationships of camptothecin derivatives have been studied. There is little difference in activity between camptothecin and its 9- or 10-methoxy derivatives, 10-hydroxycamptothecin, the methylamide, and deoxycamptothecin, but the lactol (**74**) is less active.[235] The lactone and 20-hydroxyl group on the E ring are necessary for activity, but possession of only the D and E rings is not enough to produce active compounds. Oxidation of quinoline to the *N*-oxide reduces activity.[236] The 17-acyl derivatives are also less active than camptothecin, only the hexanoyl compound being comparable.[228]

2. *Biochemical Effects*

The biochemical effects of camptothecin have been reviewed.[235] Biosynthesis of DNA and RNA are inhibited in HeLa, L5178Y, L1210, and human acute myelocytic leukemic leukocytes.[231,237,239] Viral DNA synthesis is also inhibited in cells infected with vaccinia or SV40 viruses,[234,240] but mitochondrial and bacterial nucleic acid synthesis is not sensitive to alkaloid.[237] Protein synthesis is not particularly sensitive, with the exception of viral proteins.[241] Formation of ribosomes is blocked,[242] apparently through effects on ribosomal precursor RNA synthesis[243]; this is supported by the marked reductions in chain length of nuclear RNA that have been reported.[244,245] Another interesting finding that may be relevant to the changes in RNA chain length is the fragmentation of DNA that has been seen when the latter is extracted from treated cells.[246,247] However, the drug may actually produce some destabilization that later leads to breaks during more rigorous alkaline treatment, rather than forming broken fragments directly.[248] The sort of changes that have been identified are the appearance of regions that react with antibody to single-stranded DNA,[249] and in SV40 viral DNA, the formation of relaxed circles containing single-strand breaks.[250]

C. Distribution and Metabolism

Camptothecin has been estimated in biological fluids by extraction with ethyl acetate and fluorometric assay (activation at 370 nm and emission at 433 nm). Determined in this way the plasma half-life of the alkaloid is less than 15 minutes in dogs.[251] In mice the half-life is about 30 minutes, and in humans it is around 65 minutes. In both man and mouse the drug is extensively protein bound (98 and 70%, respectively), is excreted primarily in the bile, with only a mean of 17% in the urine, and undergoes little metabolism.[252-254]

D. Clinical Usefulness

Camptothecin originally appeared very promising when introduced into clinical trial.[252] In that study there were five objective tumor regressions and six other responses out of 18 subjects; alopecia, gastrointestinal distress, and occasional hemorrhagic cystitis were the major toxicities. Later studies have reported lower incidence of response: 2 out of 10,[255] 3 brief responses of 15 with melanoma,[256] and 2 objective responses in 61 patients with bowel cancers.[257] Toxicity in these later studies was severe, with frequent nausea, vomiting, diarrhea, myelosuppression, and hemorrhagic cystitis. In contrast, a recent Chinese report described the results in papillary cancer of the bladder, where instillation of camptothecin into the bladder led to complete regression in 17 of 33 patients and direct injection into the tumor mass caused disappearance of tumor in all of nine treated subjects. There was minimal toxicity.[258] Thus, with this latter exception, which suggests a possible use in rather special circumstances, camptothecin has not fulfilled in the clinic the promise held out by its activity against experimental tumor systems.

X. CONCLUSIONS

This survey has emphasized the range of usefulness of the monoterpenoid indole alkaloids and the types of structure that are biologically active. Many alkaloids have been omitted because of their similarity to others that have been included, or because they are of relatively minor importance. A number do not fall within the purview of the type of structures considered in this volume. Among the latter would be tryptamine derivatives such as the hallucinogenic compound psilocin, and the ergot alkaloids.[4,259] The latter are of considerable clinical value in the treatment of such conditions as postpartum bleeding and migraine headaches; the hallucinogen lysergic acid diethylamide is related to this group of alkaloids.[260] It is hoped that this presentation will serve not only as a review for those interested in the biology of the indole alkaloids, but also to draw attention to possible alternative therapies that for various reasons are unused or little-used in the United States, although employed successfully elsewhere. Ajmaline, which appears to be superior to quinine, ajmalicine, and vincamine comes to mind to this regard, but there are other examples.

Investigation of the indole alkaloids continues actively, and I am sure that in 10 years the list of useful compounds will be much more extensive than it is today.

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