
INDOLES

Part Four

The Monoterpenoid Indole Alkaloids

Edited by

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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

RICHARD B. HERBERT

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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.

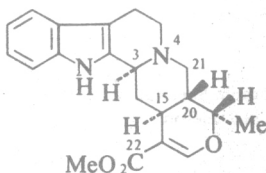
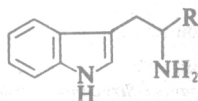
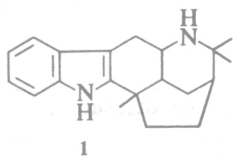
The subject has been reviewed extensively and the reader is referred to some of these reviews for alternative treatment.³

* The *Aristolelia* 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

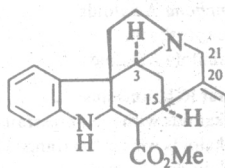
II. BIOSYNTHESIS

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

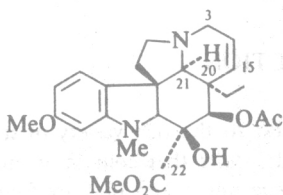
Common to all the terpenoid indole bases is a tryptamine unit (as **2b**, cf. 3-6), which in a convincing variety of alkaloids has been found to have its genesis in tryptophan (**2a**)⁴⁻⁷ via tryptamine (**2b**).^{7,8} Modifications to the tryptamine fragment are generally slight. Those observed involve 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).



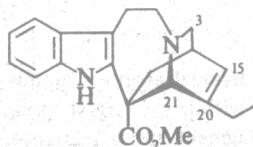
Ajmalicine (3)



Akuammicine (4)



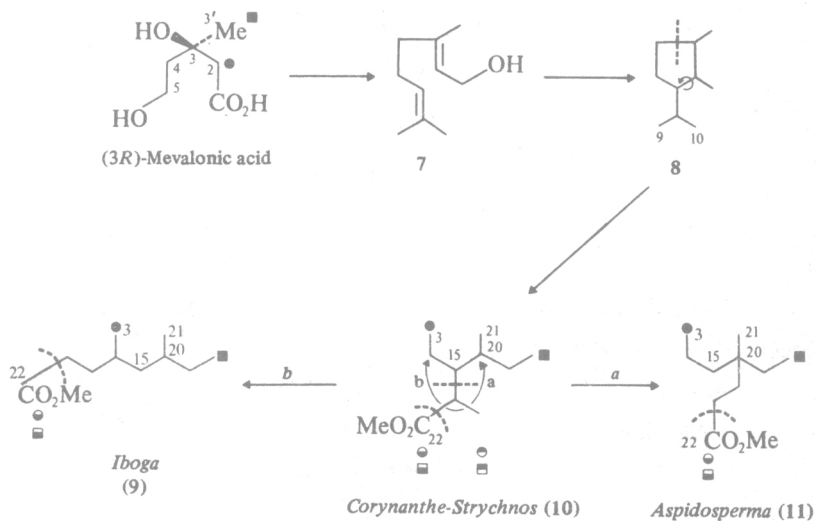
Vindoline (5)



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 C₉/C₁₀ units are formed from a fragmented cyclic monoterpene. Indeed, other sources for these units were examined and were excluded experimentally.¹⁰

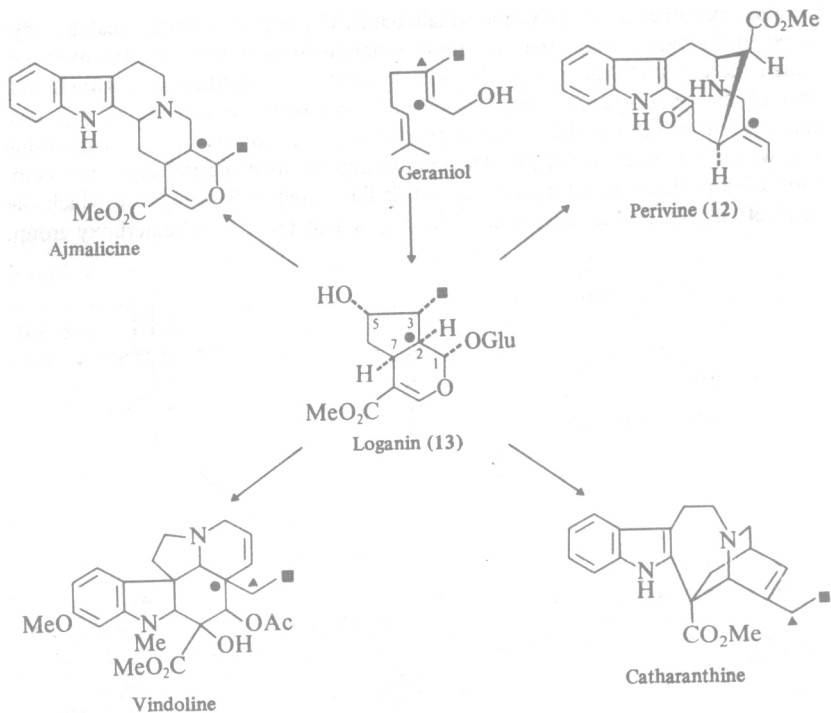
Close examination of the various alkaloidal C_9/C_{10} terpenoid units reveals broadly three major types: first, that of the *Corynanthe-Strychnos* group, for example, ajmalicine (3) and akuammicine (4) where the unit is simplified as in 10; second, that of the *Aspidosperma* group, for example, vindoline (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.

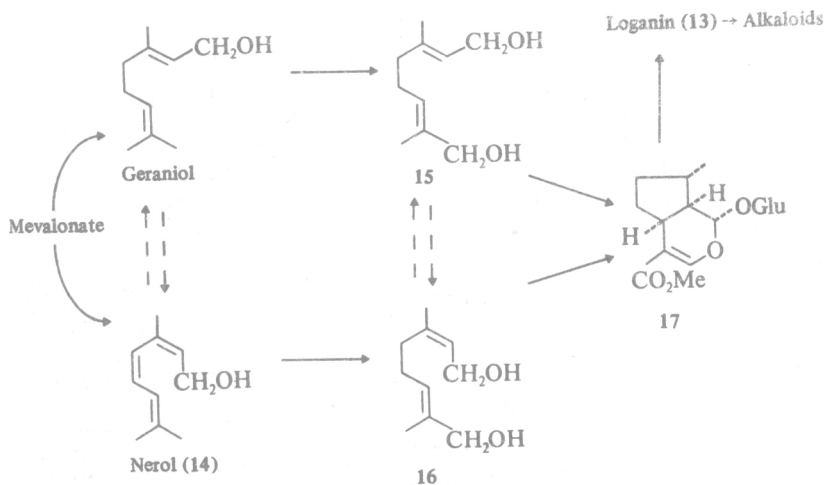
As observed in other systems, the biosynthesis of the alkaloidal monoterpene unit is from (3*R*)-mevalonic acid, not the (3*S*) isomer.¹⁴ The transformation of C-2 or C-3' of mevalonate through C-9 and C-10 of the intermediate 8 into alkaloids



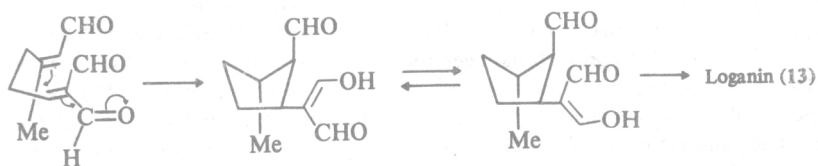
was observed to occur with loss of identity between these termini, as observed in the biosynthesis of cyclopentanoid monoterpenes.¹⁷

Further experimental results established¹⁸ that deoxyloganin (17) is to be sited as an intermediate in biosynthesis before logenin (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 logenin and the alkaloids.^{17a,20}

Alkaloid derivation from logenin (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 secologenin (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 logenin (13) in this plant, and is a precursor for representative terpenoid indole alkaloids.²¹ From secologenin the pathway leads logically to the *Rhazya stricta* Decaisne base, strictosidine (19),

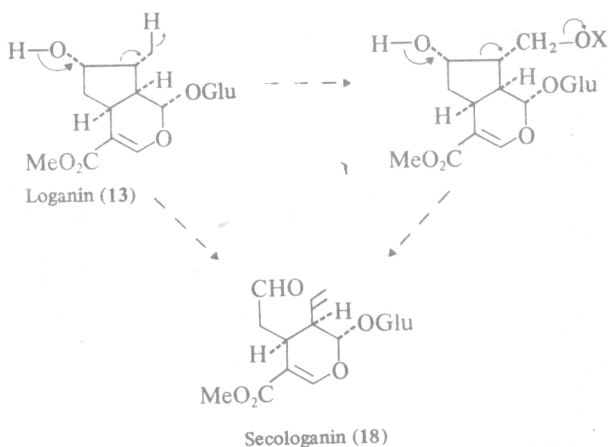


Scheme 3



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 3 α (e.g., 3, 25, and 26) and 3 β 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 3 β 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 3 α configuration.³¹ (The ipecac alkaloids include a C₉/C₁₀ 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}.)

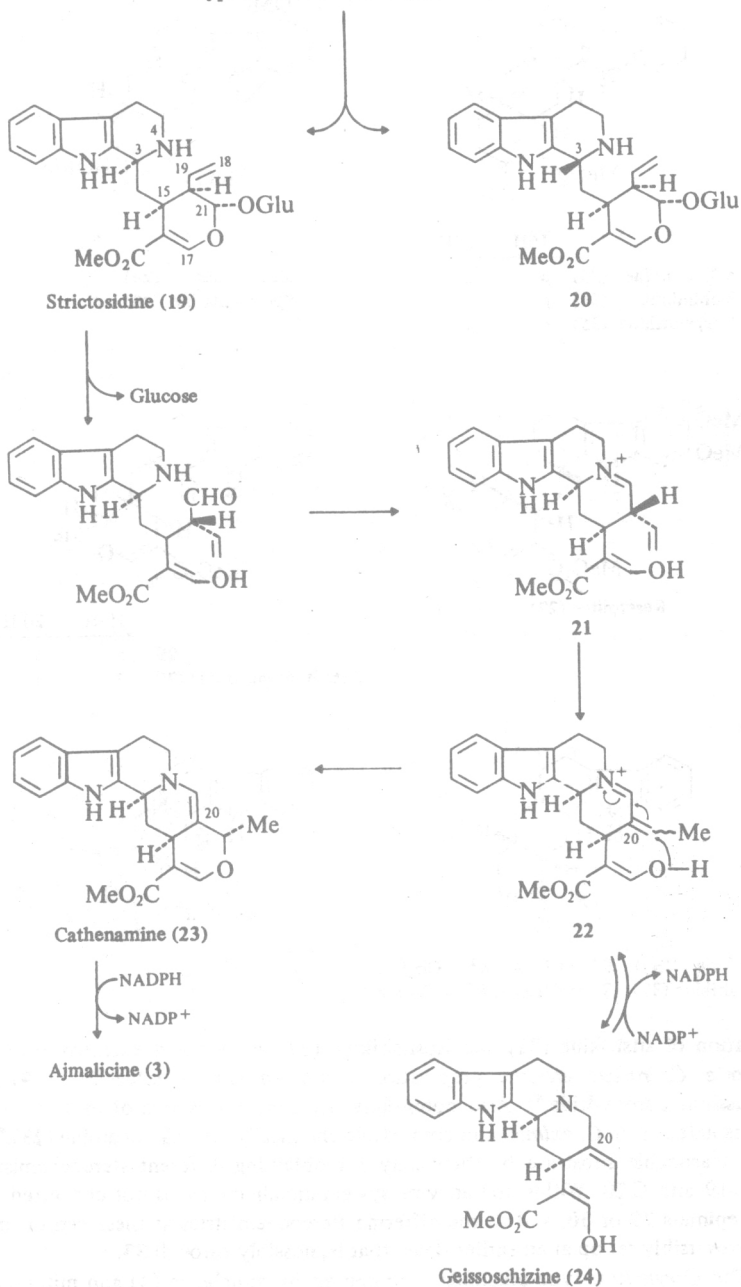


Scheme 5

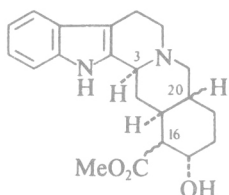
Recent work with enzyme preparations from plant tissue cultures (notably *C. roseus*) has provided exciting results which precisely define the early steps up to and beyond strictosidine. It has been found that tryptamine (2b) and secologanin (18) condense together under enzyme catalysis to give strictosidine (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 [1-¹⁴C]-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

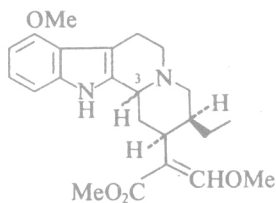
Tryptamine (2b) + secologanin (18)



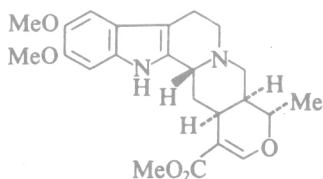
Scheme 6



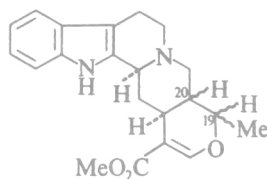
	16H	20H
α-Yohimbine (25)	α	α
Yohimbine (34)	β	β
Corynanthine (35)	α	β



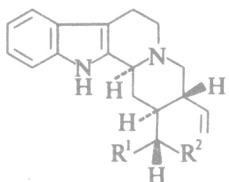
	3H
Mitragynine (26)	α
Speciociliatine (28)	β



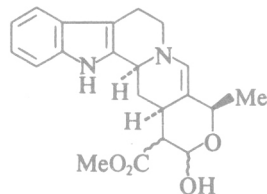
Reserpiline (27)



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



Sitsirikine (31): R¹ = CO₂Me, R² = CH₂OH
 Isositsirikine (32): R¹ = CH₂OH, R² = CO₂Me



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