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REVIEW

Biogenetic-type Synthesis of the Indole Alkaloids[1]

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A review of the rationale and methodology for the laboratory construction of the major classes of indole alkaloid based on their known or presumed biosynthesis is presented. The experimental results obtained provide analogies for the principal condensation and rearrangement reactions uncovered in biochemical investigations in this field and suggest new incorporation experiments. The prediction and discovery of new classes of alkaloid based on the observed transformations have been made and, in turn, new theories have been developed to explain some of the hitherto unsolved problems of biotransformation and structure in this series.

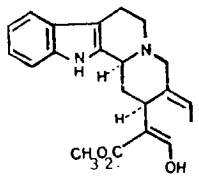
Finally, the suggestion is made that many of the complex structures encountered in the various families may arise through rather unspecific processes, some indeed of a nonenzymic nature.

The family of alkaloids derived from tryptophan now boasts over 1000 members (*1*) thus accounting for almost 10% of known natural product structures (*2*). Therefore, it seemed particularly appropriate to apply the principles of biogenetic analysis and biogenetic-type synthesis (*3*) to this group, many of whose members and indeed whole subclasses are endowed with interesting biological and chemotherapeutic properties. To this end several laboratories have, over the years, devoted considerable effort towards the laboratory construction of tryptophan-derived alkaloids based on authenticated or presumptive biochemistry. Much of the early work in this field has been reviewed in depth (*1*b, *4*) and a seminal essay on the progress and philosophy of biogenetic-type synthesis (*5*) sets the background for the present description of more recent work, largely but by no means exclusively selected from the author's own published and unpublished experiments which have been directed toward solutions to the many and diverse problems in the intermediary metabolism of tryptophan in higher plants. Several detailed accounts of the nontryptophan-derived segment of the major classes of indole alkaloid have appeared (*6–9*) and we shall, therefore, only refer briefly to the major incorporation results in this area which have set the stage for so many of the interconversion and condensation reactions described in the sequel.

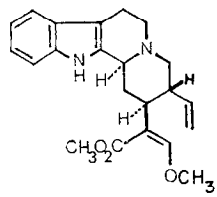
The Tryptophan → Corynanthé Sequence

The observation (*7, 10*) that the *Coryanthé* alkaloids geissoschizine (**1**), corynantheine (**2**), and ajmalicine (**3**) are laid down as the earliest recognizable members of the indole

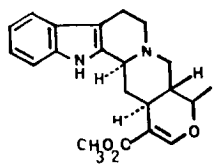
[1] This review is based on a discussion of Biogenetic-type Synthesis presented to the Industrial Affiliates Symposium "Synthesis. A Science for all Seasons," Stanford University, November 30, 1973.



Gelsoschizine (1)

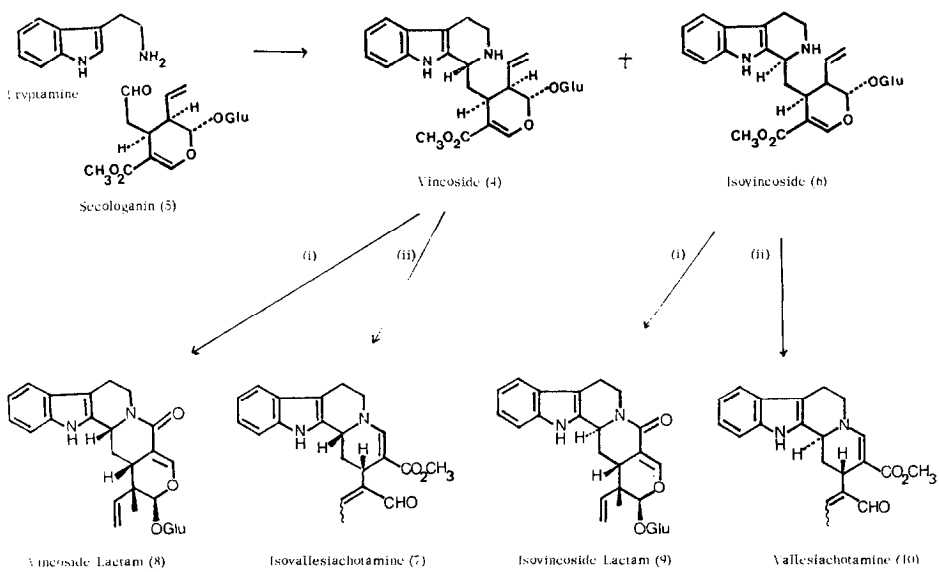


Corynantheine (2)



Ajmalicine (3)

family in *Catharanthus roseus* could be easily reconciled with the recognition of vincoside (**4**) as the "primordial" alkaloid of the series. Thus the structure and stereochemistry enjoyed by (**4**) represents the first encounter of tryptophan (or tryptamine) with the "C_{10}" unit contained in the proven monoterpenoid precursor secologanin (**5**). In order

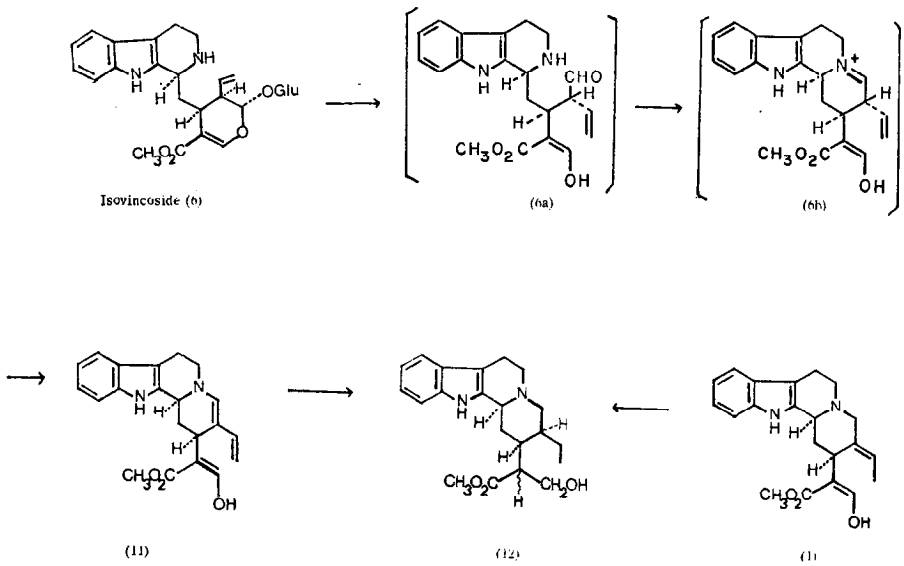


SCHEME 1

to maintain a logical rather than a historical account of this field, a most important reaction viz. the condensation of tryptamine and secologanin to a separable mixture of vincoside (**4**) and the C_3 epimer isovincoside (**6**) described by Battersby, can be regarded as the first biogenetic-type transformation. Both (**4**) and (**6**) occur as natural products

(e.g., in *C. roseus*) but only the 3βH diastereisomer, vincoside, serves as an efficient precursor of the *Corynanthé*, *Aspidosperma*, and *Iboga* alkaloids *in vivo* (*8*, *11*, *12*). Although until recently of extreme scarcity, secologanin has now become available in considerable abundance, thus paving the way for further experiments designed to transform vincoside (**4**) and/or its isomer (**6**) into the *Corynanthé* and other alkaloids. Earlier work in this field had been performed with vincoside to give the C_3 epimer (*7*) of vallesiochotamine (**7**) and vincoside lactam (**8**) by appropriate condensations as shown (*12*b, c) in Scheme 1. Similarly the isolactam (**9**) and vallesiochotamine (**10**) could be prepared from (**6**).

The effect of removing the glucoside function with β-glucosidase at pH 5.2 has been reexamined. In the case of vincoside (3β-H) (**4**) the resultant product was again (see Scheme 1) mainly C_3 epimer (*7*) of vallesiachotamine (**10**). However, as portrayed in Scheme 2, when the same reaction was carried out using isovincoside (3α-H) (**6**) as

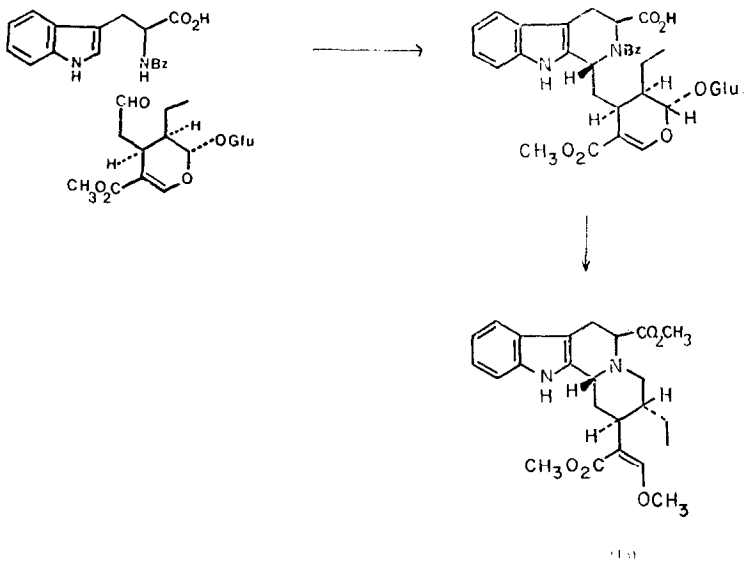


SCHEME 2

substrate there was isolated in addition to vallesiochotamine (**10**) a small but reproducible yield (2–3%) of an alkaloid $C_{21}H_{22}O_3N_2$ which has been assigned (*13*) the structure of the dieneamine (**11**) corresponding to a "dehydro geissoschizine." The gross structure of (**11**) was readily demonstrated (Scheme 2) by catalytic hydrogenation to the tetrahydro compound (**12**) identical with the reduction product (**12**) of geissoschizine (**1**). The structure (**11**) is of more than passing interest since this formula was proposed (*14*) for a very active biosynthetic intermediate uncovered in previous work with short-term incubations of *C. roseus*. Comparison of the autoradiographs of (**11**) from these latter studies and the tlc behavior of the new dehydro *Corynanthé* alkaloid (**11**) showed complete identity (*13*). Thus, the *Corynanthé* series has been reached in this simple experiment which, however, does not simulate the unusual switch of the stereochemistry at C_3 implicit in the biochemical conversion vincoside (3β-H) to geissoschizine (3α-H).

In a recent, related investigation, Brown (*15*) has prepared the alkaloid (**13**) by an ingenious variant on this theme in which tryptophan is condensed with dihydrosecologanin and the subsequent condensation is controlled *via* *N*-benzylation (Scheme 3). Obviously, the next refinement in this series requires the exercise of control in the generation of the reactive species such as (**6a**) and (**6b**) (Scheme 2) and these experiments are in hand.

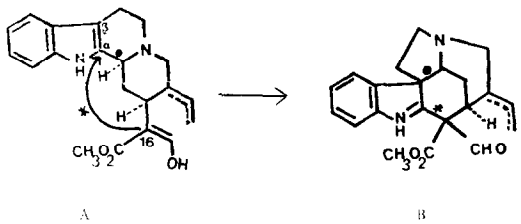
With the successful conversion of secologanin and tryptophan to the *Corynanthé* and vallesiachotamine series the stage now appears to be set for the logical progression to the more complex alkaloids e.g., *Strychnos*, *Aspidosperma*, and *Iboga*.



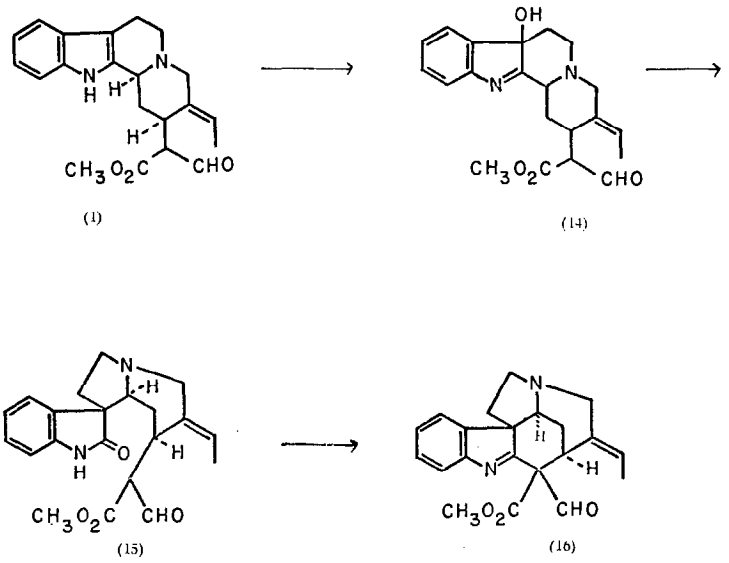
SCHEME 3

From Corynanthé to Strychnos—The Missing Link

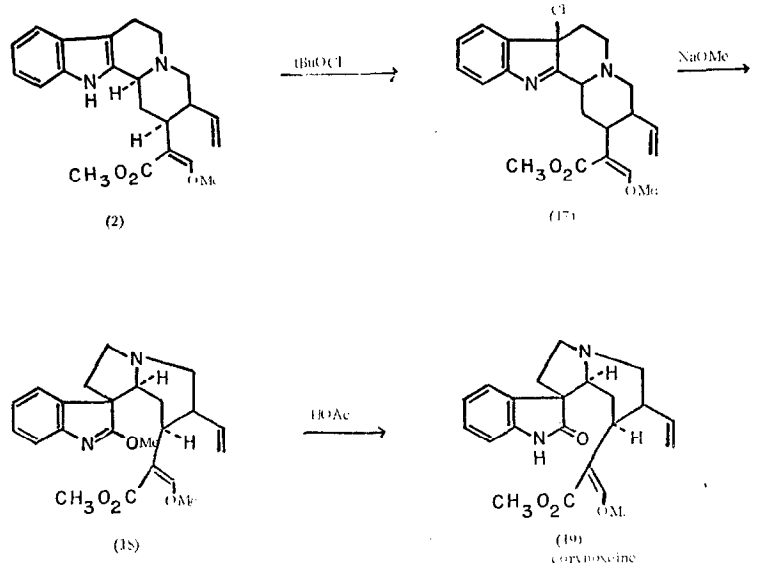
In spite of many interesting theories and even more ingenious experiments, it has not yet proved possible to emulate Nature in passing between structural classes (A) and (B). The pattern of the "C_{10}" unit is not disturbed in this process, the net result being the migration of bond marked "O" from the α- to the β-position of the indole nucleus, followed by formation of the new bond (*) from the activated C_{16} position to the α-indole position. The sole working process for this theme is the special but very



instructive case of Harley-Mason and Waterfield (*16*). An earlier experiment with geissoschizine (refluxing acetic acid) in which conversion to type (B) was observed (*17*) suffers from extensive side reactions and variability in yield and obviously requires further definition. Other analogies involving β-oxidation (**1**) → (**14**) and oxindole chemistry (**15**) → (**16**) have been proposed (*7*), there being preliminary feeding evidence to support the latter pathway *in vivo* (Scheme 4). However, no satisfactory chemical operation on a *Corynanthé* alkaloid has yet been discovered to bridge this major gap.



SCHEME 4

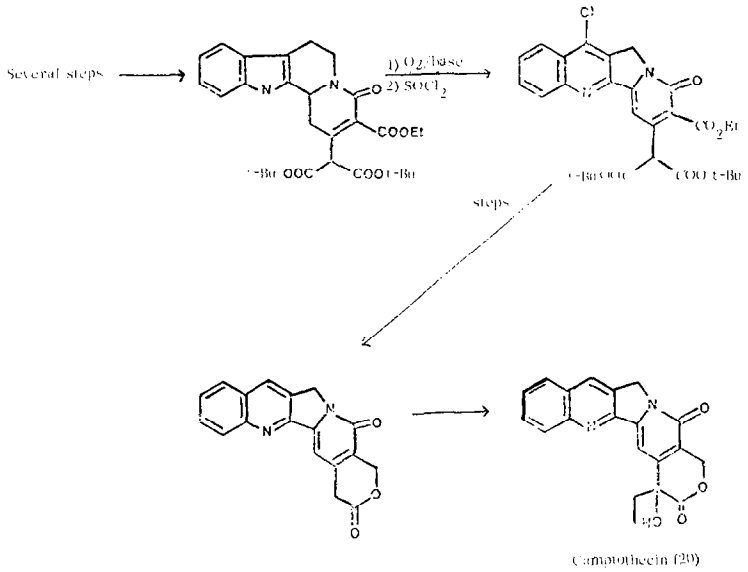


SCHEME 5

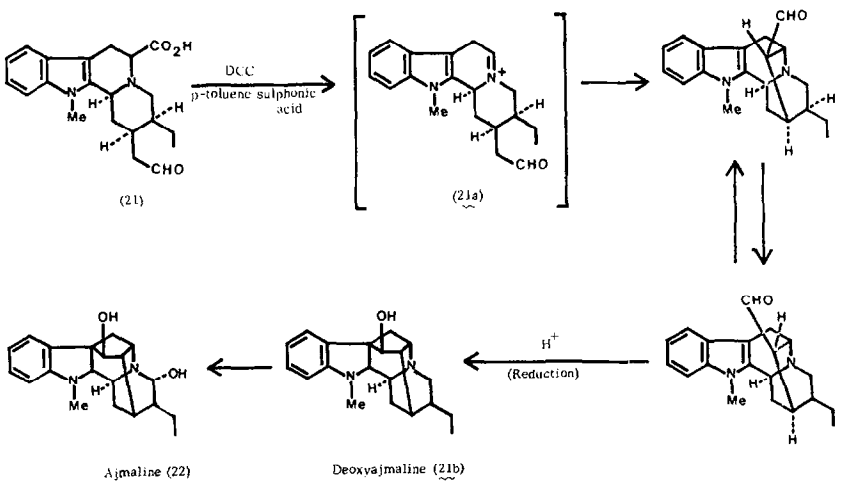
At this juncture we should, however, note that several *Corynanthé* alkaloids have been used as substrates for some interesting interconversions to related families and some of these branch-lines are now explored.

Oxindoles. The use of *t*-butyl hypochlorite has provided entry into the β-chloroindolenine series (**17**) which in turn serves as a useful substrate for the oxindole corynoxeine (**19**) and imino ether formation (**18**) (Scheme 5). The problems of the stereochemical control of these reactions and the equilibration at C_3 and C_7 has been reviewed in full detail (*18*).

Camptothecin (**20**). An ingenious partial synthesis (based on biogenetic analogy) of the camptothecin system has been described by Winterfeldt (*19*) and his colleagues as summarized in Scheme 6.



SCHEME 6

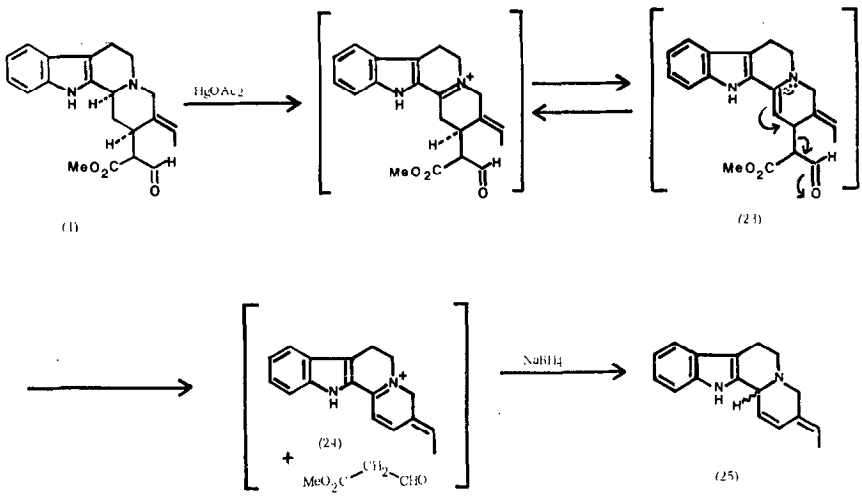


SCHEME 7

Ajmaline (**22**). A most plausible and interesting model for the formation of ajmaline from the aldehydocarboxylic acid (**21**) (Scheme 7) has been presented (*20*), in which generation of the immonium species (**21a**) leads to the desired bond formation ($C_{16} \rightarrow C_8$) and thence to the relay substance (**21b**). This is a particularly important model for the timing of the biochemical decarboxylation of the tryptophan moiety of the *Corynanthé* series.

Flavoperierine and Related Alkaloids

A simple model for the generation of the flavoperierine system (**24, 25**) has been found (*21*) in the reverse Mannich chemistry of the enamine (**23**) (Scheme 8) which



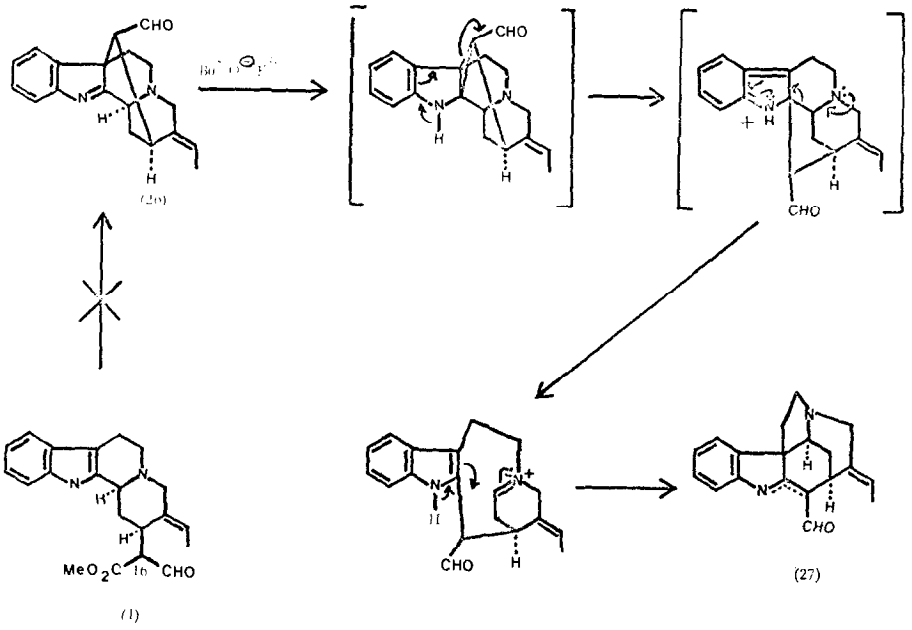
SCHEME 8

can be formed by mercuric acetate oxidation of geissoschizine (**1**). Although the appropriate biochemical correlation has not been made, the above experiment suggests that loss of the "C_3" segment may well arise by such a process which occurs with facility *in vitro*.

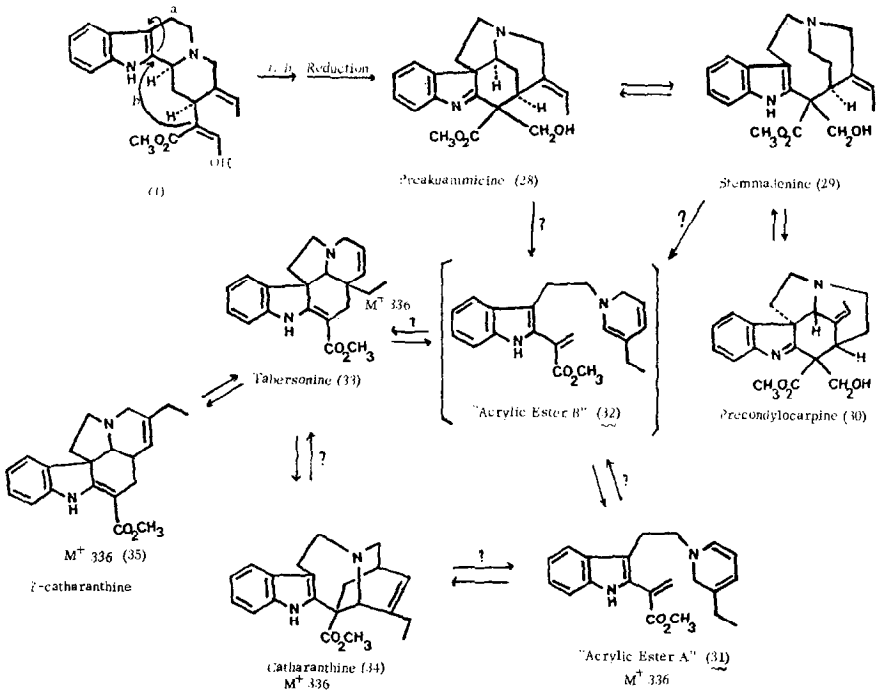
Related reactions of the Picralima alkaloids. A close analogy for *Strychnos* alkaloid biosynthesis from a *Corynanthé* precursor concerns the manipulation (*22*) of the indolenine system of (**26**) (Scheme 9) in the presence of potassium *t*-butoxide in a remarkable rearrangement to nor-fluorocurarine (**27**). Successful conversion of a *Corynanthé* alkaloid, e.g. (**1**) to (**26**), would complete this intriguing system but with the exception of some work by Dolby on models for echitamine synthesis a satisfactory method for the vital bond-making process from C_{16} has yet to be described. In fact, all attempts to utilize the anionic or radical-forming propensity of C_{16} in the array

$$\underset{16}{\text{CHO}}\text{—}\underset{16}{\text{CH}}\text{—}\text{CO}_2\text{CH}_3$$

have been uniformly unsuccessful, indicating the necessity for finding a new approach to the chemistry of this apparently reactive center.



SCHEME 9

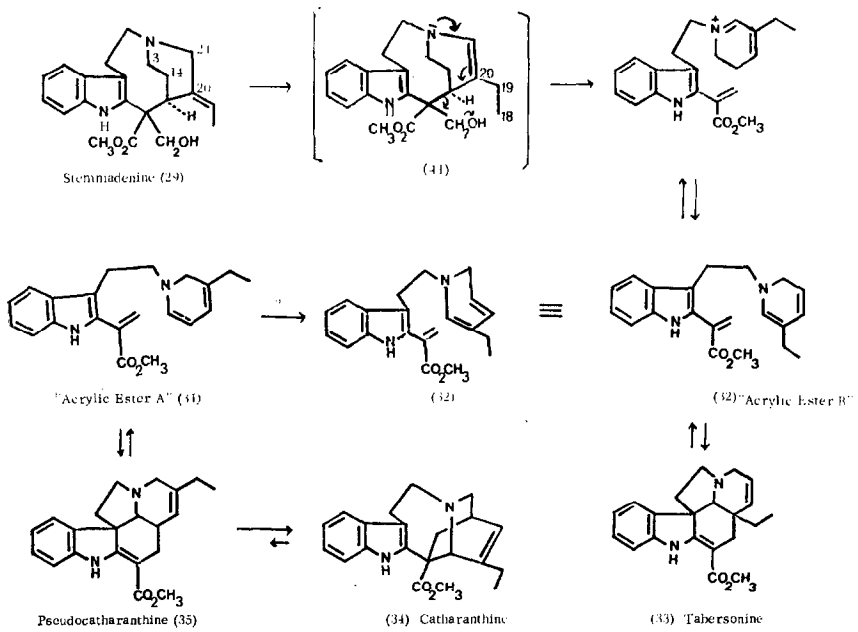


SCHEME 10

With the key link (*Corynanthé → Strychnos*) still missing from the chain of events in the biogenetic synthesis of the major classes, we now consider some of the successful conversions wrought upon the *Strychnos* and related systems in the quest for further analogies in the biochemical pathway. The overall scheme is shown again for the sake of clarity in Scheme 10 which emphasizes the importance of the acrylic ester or secodine intermediates (**31** and **32**). The latter have proved valuable touchstones in considering the deep-seated rearrangements which must convert *Corynanthé/Strychnos* alkaloids to the typical members of *Aspidosperma* and *Iboga* series.

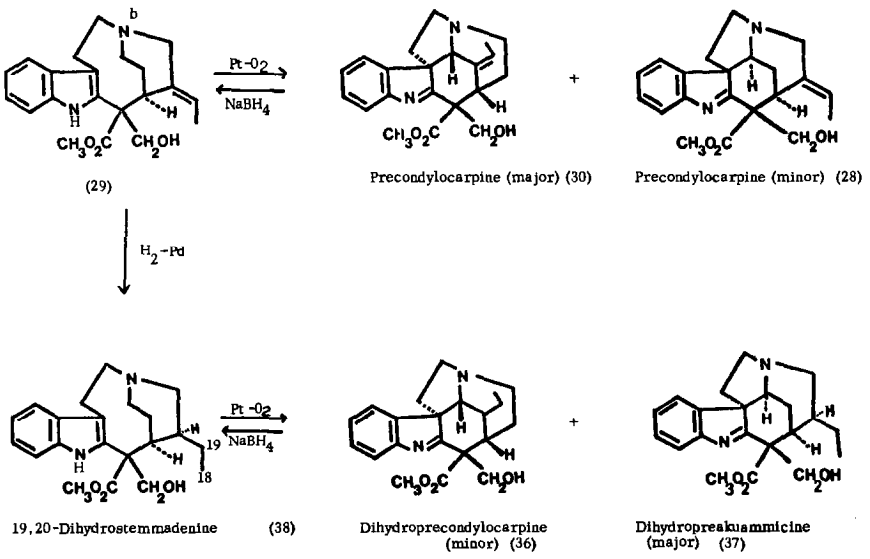
From Stemmadenine to Aspidosperma and Iboga Alkaloids—The "336" Concept

As soon as the discovery of the intermediacy of stemmadenine (**29**) and tabersonine (**33**) in the main pathway of indole alkaloid biosynthesis was made it was suggested (*7*, *10*) that the formal dehydration of stemmadenine (mol wt 354) to the species mol wt 336 introduced an intriguing consequence viz. the cycloaddition or extended Mannich chemistry of the hypothetical achiral reactive intermediate (**32**). Thus, it was predicted that the dihydropyridine acrylic ester (**32**) or its isomer (**31**) could account for the skeletal rearrangements in going from the *Corynanthé* pattern (**1**) or stemmadenine (**29**) and preakuammicine (**28**) to either the *Aspidosperma* or *Iboga* families. An especially attractive facet of this theory which represents a modification and simplification of the earlier ideas of Wenkert (*23*) is its ability to explain the occurrence of pentacyclic *Aspidosperma* alkaloids in racemic and antipodal versions. Yet another interesting consequence of this speculation (which was originally conceived as a result of the mass spectral behavior of tabersonine!) involves the various recombination characteristics of the hypothetical intermediate (**32**) which not only serves as



SCHEME 11

a highly plausible model for the observed biochemical conversions of stemmadenine (**29**) to tabersonine (**33**) but also forges a mechanistic link between tabersonine (**33**) (*Aspidosperma* series) and the isomeric catharanthine (**34**) (*Iboga* series) as shown in Scheme 11. In its simplest form this isomerization process operates at the oxidation level of mol wt 336. In fact, our first experiments (*24*) with the rare alkaloid stemmadenine provided a welcome model for these concepts which, as the subsequent biochemical experiments and the structures of new isolates of *Apocyanacae* were to show, constituted not only a working laboratory analogy for the labyrinth of interconnecting pathways between families, but allowed the prediction of hitherto undiscovered structural types. The logical evolution of this area of bioorganic chemistry was, however, not to prove facile and a trenchant criticism (*25*, *26*) of the first communication (*24*) on this topic required some reinvestigation in order to define extremely critical reaction conditions. Due to the scarcity of stemmadenine a series of expeditions to the state of Vera Cruz (Mexico) was made to identify and collect the fruits of *Stemmadenia Donelli-Smithii* in early November 1971 (*27*). Harvesting and extraction of this plant at other times of the year appear to be particularly unpropitious, the yield of (**29**) falling from 0.5% to less than 0.001%. With a fresh supply of the vital *Corynanthé-Strychnos* alkaloid in hand, the early experiments were examined with a most satisfactory outcome viz. the achievement of both regiospecific and stereospecific control in the transformation of stemmadenine to both *Aspidosperma* and *Iboga* alkaloids as described below (the "later" experiments). In addition to the *in vivo* conversion indicated, it could be shown that platinum-catalyzed oxidation of (**29**) gave the pentacyclic system corresponding to oxygenation or dehydrogenation of the carbon adjacent to N (b) in stemmadenine. These reactions could be reversed by treatment of (**28**) and (**30**) with sodium borohydride (Scheme 12). Thus, the facile redox equilibria depicted in Scheme 12 may indicate the branch point at which the stemmadenine molecule is drawn enzymatically into either the *Aspidosperma* or *Iboga* series. In this first set of



SCHEME 12

preliminary experiments stemmadenine was heated under vigorous reflux conditions in acetic acid over silica boiling stones at high (~200°C) external bath temperatures. Great variability in composition and yield of the products was encountered from such reactions which were frequently maintained for 1–2 days with concomitant loss of solvent. However, it was shown by analytical and preparative tlc techniques that stemmadenine was converted first to the *O*-acetate, a reaction that can be effected very simply by reflux at 150°C (bath temperature). The latter undergoes a deep-seated rearrangement to give products of the mol wt 336 set viz. tabersonine (**33**) and the structural isomer of catharanthine, pseudocatharanthine (**35**). A small amount of catharanthine could also be detected. Thus, although the reactions are extremely sensitive to concentration, surface and/or thermal conditions, the discovery of the formal dehydration products of stemmadenine in racemic form—as would be required by any mechanism involving (**32**)—lends credence to a most rewarding concept. As originally described in a communication (*24*) this biogenetic-type interconversion, however, turned out to have severe limitations as a practical and reproducible route to the more complex alkaloids of the indole family. A complete account of this phase of the study is out with the scope of our review and the interested reader is referred to several full papers (*24, 26*) for a discussion of the problem and its eventual solution.

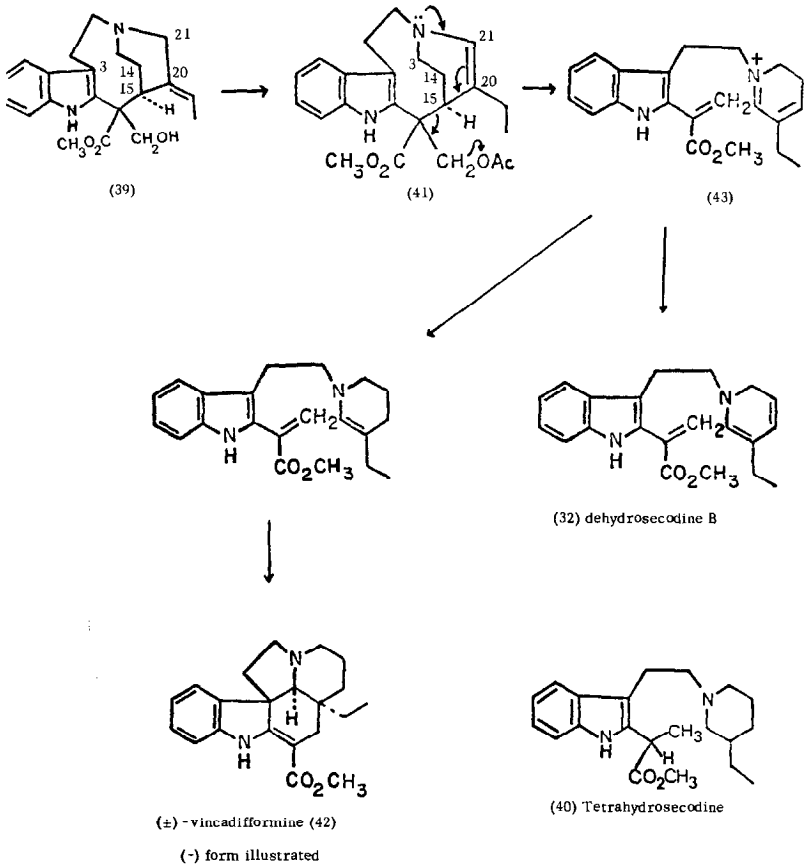
The "Later" Experiments—Evolution of a Regio and Stereospecific Model

In order to rationalize the promising but erratic results of the early (acetic acid) experiment the new source of stemmadenine was used to explore and define the conditions necessary, not only for the generation of the seco ester (**32**), but also its recombination to the known isomers of the "336" series in a more rigorous manner.

The Corynanthé–Aspidosperma Relationship

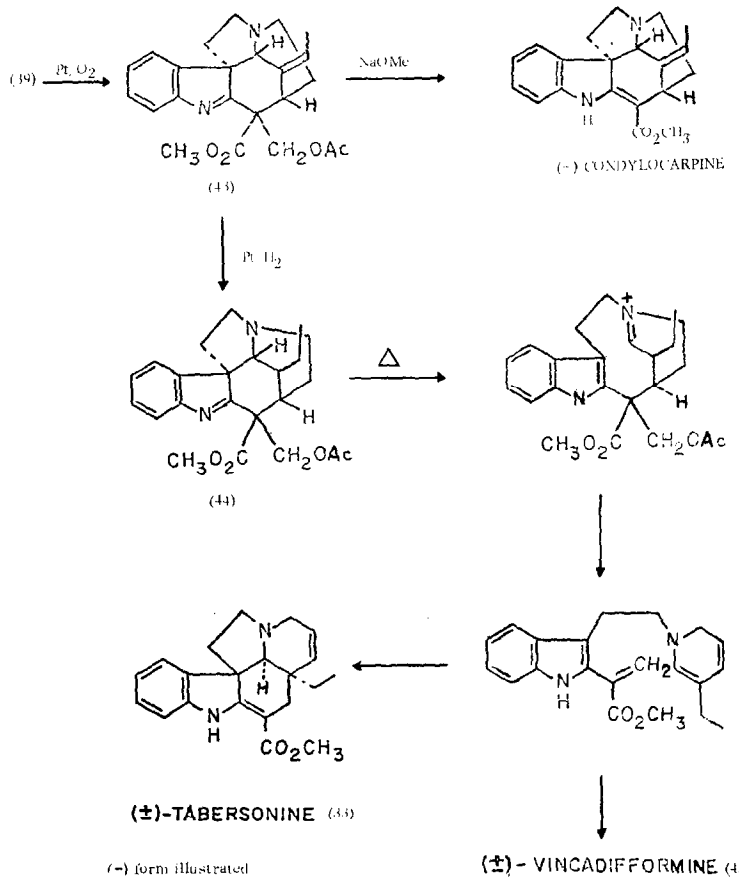
The reverse Mannich chemistry discussed above (Schemes 10, 11) for *Aspidosperma* biosynthesis via dehydrosecodine B (**32**) differs in regiospecificity from the *Iboga* model described below in that formation of the secodine system B can take place via $C_{20,21}$ rather than $C_{3,14}$. The introduction of unsaturation at C_{21} could, in principle be realized by two methods. First it was hoped that the simple isomerization process (Scheme 11) previously adduced for reaction of stemmadenine (acetate) in hot acetic acid solution, might be capable of more rigorous control and thus lead only to *Aspidosperma* framework by formation and recombination of dehydrosecodine B (**32**). A further spur toward a search for isomerization conditions was the discovery that, whereas stemmadenine (**29**) is hydrogenated unexceptionally to the 19,20-dihydro derivative (**38**) in presence of platinum catalyst (Scheme 12), the behavior of stemmadenine acetate (**39**) is quite different toward reduction. Thus, at atmospheric pressure, hydrogenation of (**39**) over platinum in ethanol solution leads to (±)-tetrahydrosecodine (**40**) (Scheme 13) in 75% yield. The facile cleavage of the 15, 16 sigma bond in (**39**), but not in (**29**) is suggestive that the primary acetoxyl at C_{17} aids the irreversible loss of acetate from the Δ20, 21 isomer (**41**) which is in equilibrium with the Δ18, 19 exocyclic olefinic group of the starting material. This high-yielding partial synthesis (*29*) of the naturally occurring member of the secodine family could be regarded as a model for the biosynthesis of these alkaloids from stemmadenine.

Experiments designed to capture the fugitive dihydropyridine (**32**) in the cyclized



SCHEME 13

form corresponding to the *Aspidosperma* alkaloids were carried out as follows. Firstly, in a reaction designed to separate the *Aspidosperma* pathway of the "early" experiments, conversion of (**39**) to (±) vincadifformine (**42**) was achieved in low yield (0.15–0.20%) by thermolysis at 150°C on a silica gel surface for 25 min. The analytical and preparative procedures used for this and the succeeding experiments left no doubt that tabersonine was not a product of the reaction. A plausible reaction pathway via (**41**) is shown in Scheme 13 which suggests that the intermediate immonium species (**43**) suffers reduction by disproportionative release of hydride to dehydrosecodine B (**32**) which then cyclizes to (±) vincadifformine and that this sequence is favored over the more direct rearrangement (without reduction) to (±) tabersonine. An alternative method was then studied, which takes into account the ready aerial oxidation (which must have occurred under the vigorous conditions of the "early" experiment) in acetic acid solution of (**39**) to the acetate (**43**) of the naturally occurring pentacyclic alkaloid, precondylocarpine (**30**) (*30*) a step which can be achieved more efficiently using platinum-catalyzed oxidation (*31*) (Scheme 14). Catalytic reduction of the ethylidene group of (**43**) affords the dihydroacetate (**44**) which is now formally capable of regiospecific collapse to dehydrosecodine B as shown in Scheme 14. When the acetate was subjected to thermolysis (150°C, silica gel, 25 min) a separable mixture of (±) tabersonine (**33**) (0.2%) and



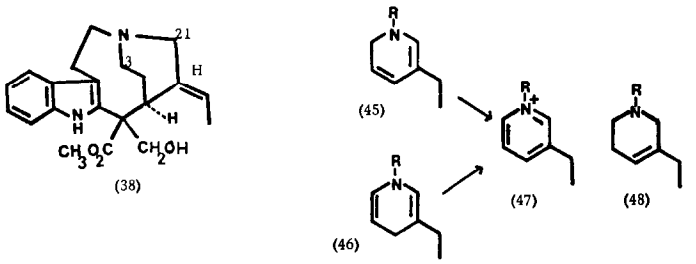
SCHEME 14

(±)-vincadifformine (**42**) (0.2%) was produced, while no trace of pseudocatharanthine (**35**) could be detected. It was concluded from these results that the generation of the acrylic ester B takes place without rearrangement to the A isomer according to Scheme 11. Although the yields in these models for "*Aspidosperma* synthetase" are extremely low, the reactions provide a working hypothesis for the complex series of rearrangements which accompany the biochemical conversion of the *Corynanthé* to the *Aspidosperma* and *Secodine* families. At the same time, it is believed that the multistep reaction sequence which was concealed in the earlier model experiments can now be understood in terms of the operation of indiscriminate oxidative and reductive attack on stemmadenine acetate, the first-formed product of the reaction between acetic acid and the original substrate, stemmadenine. Depending on the timing of the oxidative and reductive steps, the acetate is converted to both the preakuammicine and precondylocarpine skeletons which at the appropriate oxidation level collapse to *Iboga* and *Aspidosperma* alkaloids, respectively.

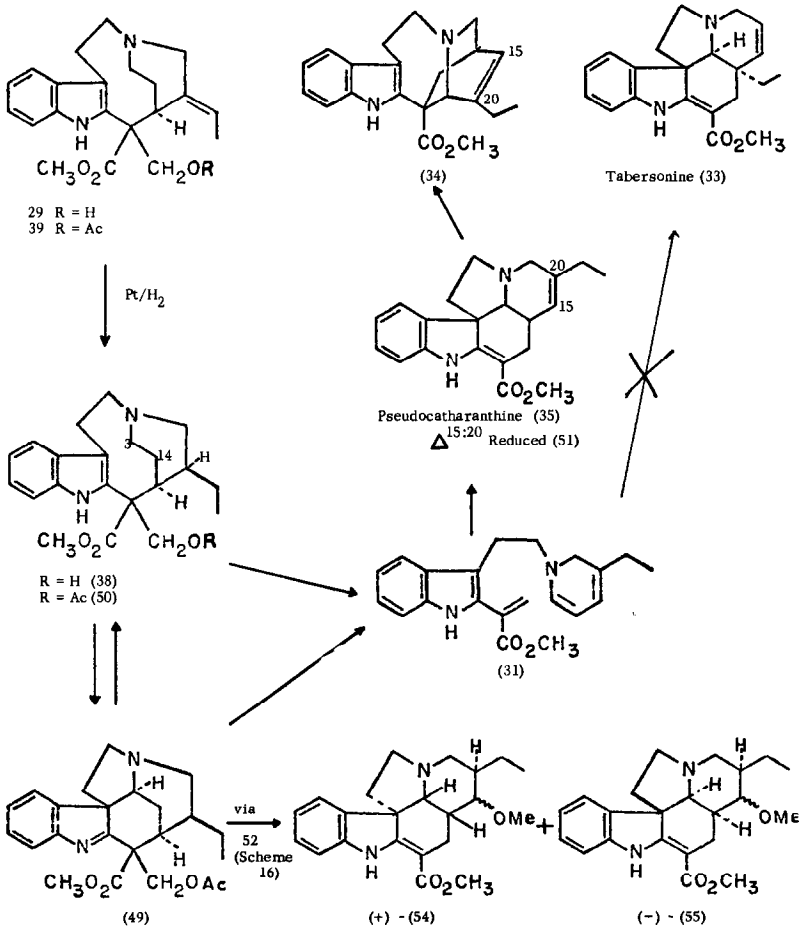
The Corynanthé-Iboga Relationship (32)

The thermolysis of 19,20-dihydrostemmadenine was next examined. This work took the reductive factor of the "early" experiment into account, for it is well known that

systems such as (**45**, **46**) readily disproportionate to the pyridinium salt (**47**) and the tetrahydropyridine (**48**). Allowance was also made for the regiospecific (aerial) oxidation of (**38**) at C_3 to dihydropreakuammicine (**37**). In order to complete the analogy with the

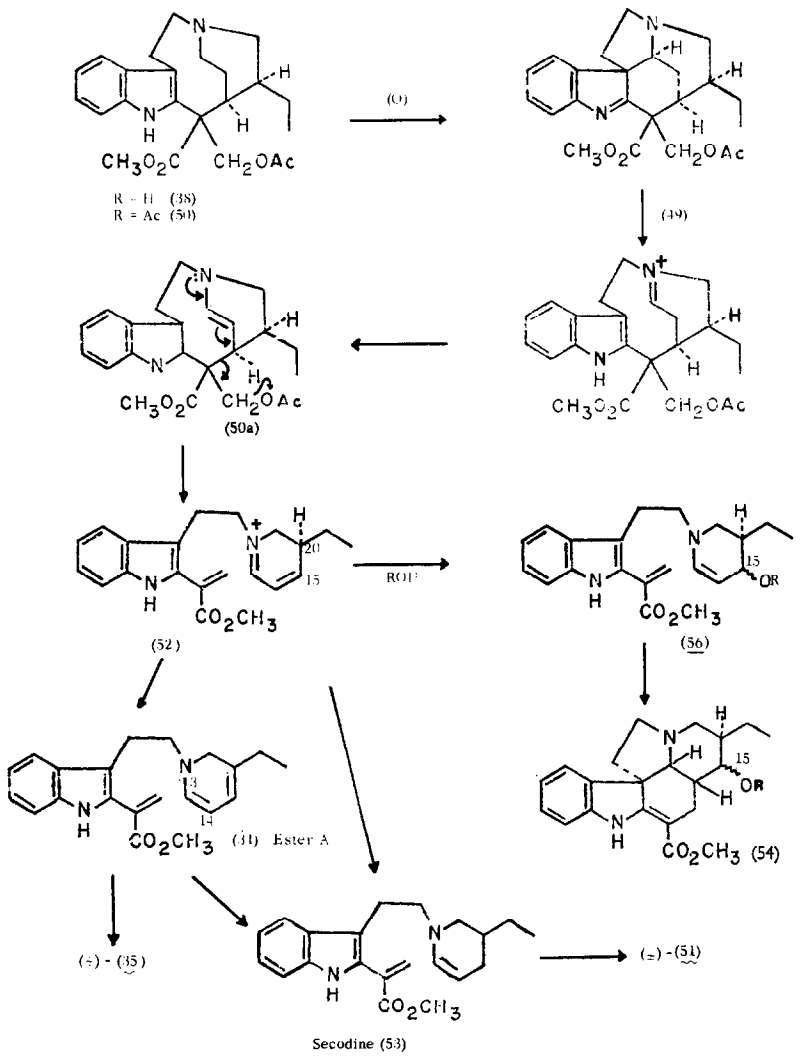


earlier work using acetic acid (which has been shown to form the primary acetate), dihydrostemmadenine was converted to the acetate (**50**). When the latter compound was heated on a silica gel tlc plate at 150°C for 45 min the resultant mixture afforded



SCHEME 15

(±) pseudocatharanthine (**35**) (1%)—and its dihydro derivative (**51**) (0.5%) (Scheme 15). No trace of tabersonine (**33**) was detectable in this experiment. In order to rationalize this result, it is necessary to generate a double bond at C_{3-14} (**50a**) so that the extended reverse Mannich chemistry shown in Scheme 16 can operate. The further reaction of the iminium salt (**52**) is seen as a rearrangement to 3,14-dehydrosecodine (**31**), which we have designated dehydrosecodine A. (See Scheme 16).



SCHEME 16

Recombination of the achiral ester (**31**) affords (±)-pseudocatharanthine (**35**) (*33*) whereas conjugate reduction of (**52**) leads to the secodine (**53**) whose cyclization to (±) dihydropseudocatharanthine (**51**) is unexceptional. A more efficient way of demonstrating this regio- and stereospecific rearrangement was found by preparing

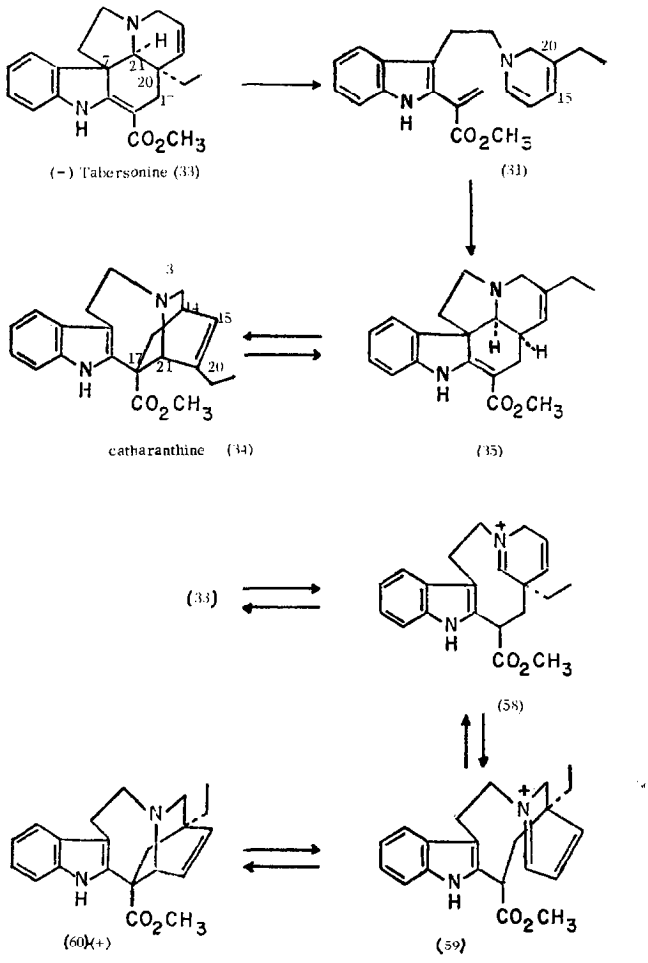
19,20-dihydropreakuammicine acetate (**49**), a known autoxidation product of (**50**), by Pt-02 oxidation of (**50**). Thermolysis of (**49**) at 150°C for 20 min afforded (±) (**35**) in yields which, although by no means optimized, average 5%. The known equilibrium between (**35**) and catharanthine (**34**) completes the partial synthesis of the latter member of the *Iboga* family in racemic form.

Further insight into the mechanism of this remarkable reaction was gained by methanolysis of the acetate (**49**) at room temperature for 4 hr, or at 80°C for 15 min. The products of this reaction were now optically active and were separated to afford a dextrorotatory 15-methoxydihydropseudocatharanthine (**54**) and the levorotatory diastereomer (**55**) in the ratio 9:1. The combined overall yield of this reaction from dihydrostemmadenine (**38**) was 3.5%. This result is in full accord with the postulate that the immonium species (**52**) is an intermediate in the rearrangement process and that conjugate addition of methanol affords the diastereomeric mixture (**54, 55**) via (**56**). The stereospecific preference for the absolute configuration (**54**) over (**55**) may well be dictated by the configuration of the methoxyl group at C_{15} which controls the observed stereochemistry of the cyclization process. This particular model is also illustrative of the remarkable variation (*34*) in absolute configuration of the pentacyclic *Aspidosperma* alkaloids even within the same plant, which could be mediated by conjugate addition of the appropriate prosthetic group of the synthesizing enzyme to such an immonium species. Another pertinent example is the co-occurrence of (–) coronaridine (**57**) (see scheme 19 for formula) and (+) catharanthine (**34**) within the same species (*Catharanthus roseus*) (*35*). This duality of absolute stereochemistry for such complex alkaloids again can be viewed as the result of the timing of the reduction step of the immonium ion (**52**) which can either be reduced and cyclized to give (–) coronaridine or pass through the achiral intermediate (**31**) with protropic loss of C_{20} stereochemistry and thence by enzymic control to the antipodal series represented by catharanthine (**34**). In this connection it is of interest to note that the *in vitro* conversion described above in which (**52**) is suggested as the first formed chano intermediate, the thermal reaction serves to epimerize this center so that the products of the reactions are (±) pseudocatharanthine and the corresponding racemic dihydro compound (**51**). The milder conditions used in the methanolysis experiment, however, give products which on the basis of molecular rotation differences with other members of this series indicate an optical purity of ca. 70–80%. The configuration of the methoxyl group at C_{15} in these diastereoisomers is at present unknown. A similar reaction was observed when dihydropreakuammicine acetate was heated in ethanol at 80°C for 15 min to yield a separable mixture of the dextrorotatory and levorotatory diastereomers of 15-ethoxy-15,20-dihydropseudo-catharanthine in the ratio 10:1, in 10% (combined) yield.

The above experiments indicate that an "*Iboga* synthetase" model in the form of dehydrosecodine A has been demonstrated to operate and that not only the regiospecific generation and recombination of (**31**) mediated by the collapse of reduced preakuammicine (**49**) but the stereospecificity of the recyclization process leads to the *Iboga* isomer, (±) pseudocatharanthine which in turn is convertible to (±) catharanthine. Although the yields in this reaction are not yet of preparative value, it is our view that the synthesis and reactivity of the dehydrosecodine system is worthy of more detailed study as a new method of preparing quite complex pentacyclic alkaloids from simple starting materials, with full stereospecific control.

Further Isomerizations of the "336" series. The Aspidosperma–Iboga–Secodine Relationship

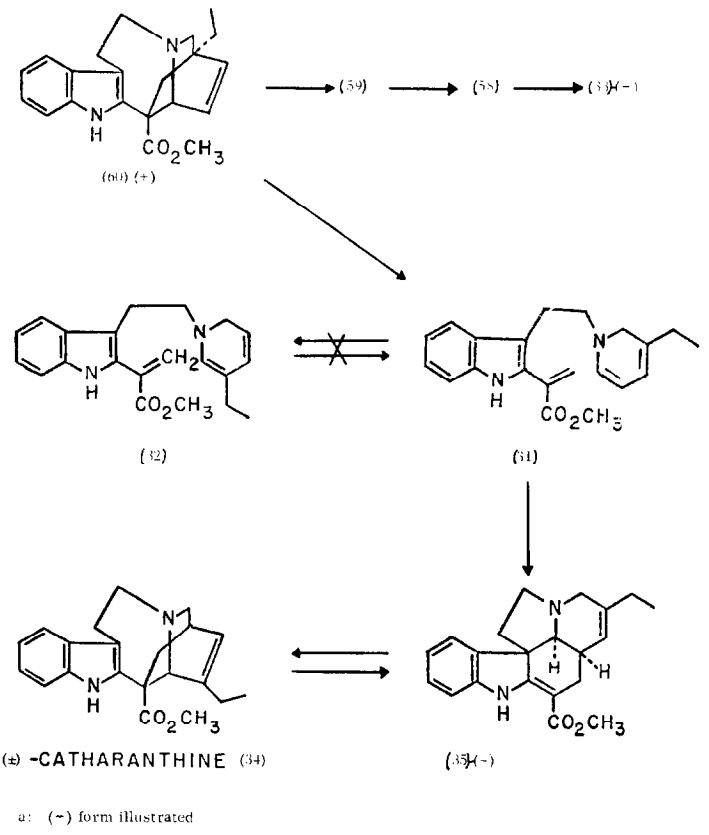
In 1968, a report (*24*) on the *in vivo* and *in vitro* transformations of the *Aspidosperma* alkaloid tabersonine (**33**) to the *Iboga* alkaloid catharanthine included the proposal for an intermediate (**31**) in this reaction which has since been found in a variety of stabilized versions. In 1969, Smith et al. (*25*) concluded that this reaction, which involves rupture of both the 7-21 and 17-20 bonds of (**33**) proceeds only as far as



SCHEME 17

cleavage of the 7-21 bond (Scheme 17). The resultant immonium species (**58**) then rearranges (**59**) and cyclizes to allocatharanthine (**60**) an optically active isomer of catharanthine (**34**) and pseudocatharanthine (**35**), the latter two *Iboga* structures being interconvertible (Scheme 17). It has been stated, (*37*) however, that both ionic and thermal requirements must be met in carrying out the full transformation which by passing through (**60**) affords the racemic products described earlier. In a reconfirmation

and simplification of the 1968 report, the separation of the ionic and thermal components has been described in a recent publication (*36*).

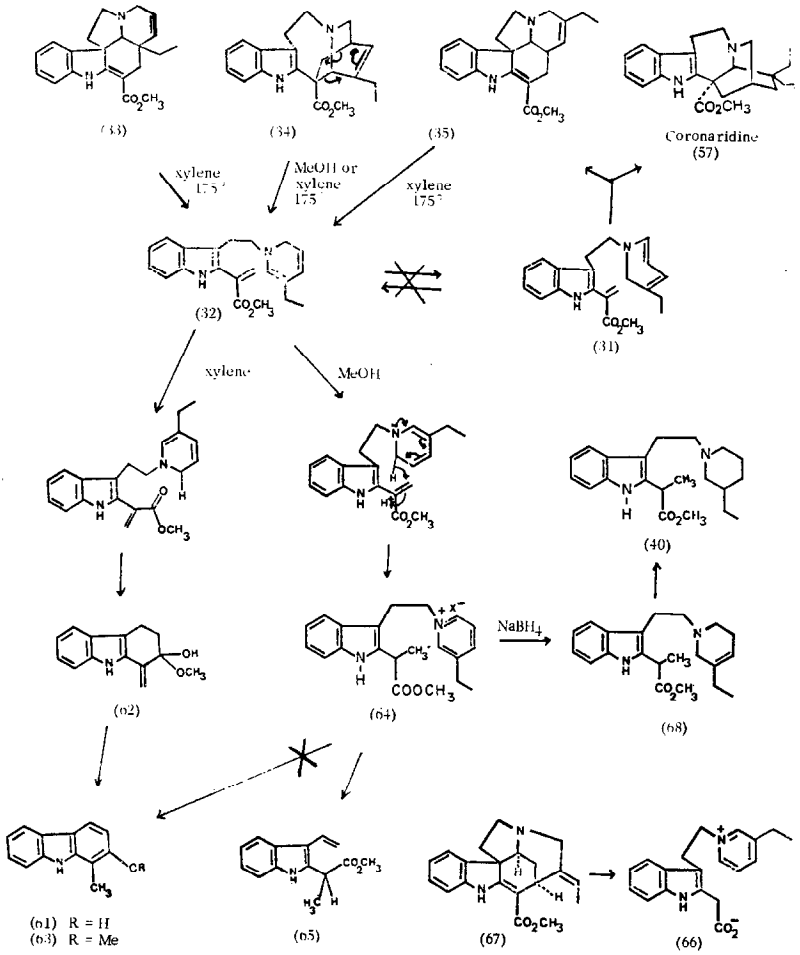


SCHEME 18

(–)-Tabersonine (**33**) was heated in acetic acid for 15 hr (external bath temperature 140°C). The resultant mixture was separated and (+) allocatharanthine (**60**) (11%) isolated. A solution of (**60**) was applied to a silica gel tlc plate, the solvent removed, and the plate heated at 150°C for 30 min. Elution and chromatography on $AgNO_3$-impregnated silica gel plates afforded two major products. These were (±) pseudocatharanthine (**35**) (4%) identical with authentic material and optically pure (–)-tabersonine (**33**) (4%). The absence of any racemization of tabersonine indicates reversal of the formation of allocatharanthine without cleavage at $C_{17,20}$, i.e., by the pathway (**60**) → (**59**) → (**58**) → (**33**) (Scheme 18). Thus, not only is the *Aspidosperma* framework stable toward retro-Diels-Alder reaction but in confirmation of the complete specificity noted in the previous section for the reaction of dehydro secodines A and B, only the racemic product (**35**) of cyclization of dehydrosecodine A (**31**) is observed, there being no evidence for equilibration with the B isomer (**32**) which would have yielded (±) tabersonine.

In order to gain further evidence regarding the intermediacy of the secodine esters (**31** and **32**) a study was made of the thermal reactions of the key members of this series.

When xylene solutions of the isomeric alkaloids (–)-tabersonine (**33**), (+)-catharanthine (**34**), and (±)-pseudocatharanthine (**35**) were maintained in sealed tubes for 1.5 hr at the temperatures indicated (Scheme 19) in each case (but with a different energy requirement) the same products were isolated and characterized as 3-ethylpyridine and 1-methyl-2-hydroxycarbazole (**61**) (*37*).



SCHEME 19

We suggest that the formation of these products takes place by way of a retro-Diels-Alder reaction to afford the fugitive ester (*32*) followed by an intramolecular rearrangement and hydrogen transfer from the dihydropyridine to the acrylic ester function yielding the hemiketal (**62**) with loss of 3-ethylpyridine as indicated. Elimination of methanol and further rearrangements then give the carbazole (**61**). In support of the latter process 1-methyl-2-methoxycarbazole (**63**) could be detected and characterized as a minor product of the reaction.

More direct evidence for the formation of 32 was obtained by the capture in 50%

yield of the racemic salt 64 when catharanthine was heated in methanol at 140°C for 2 hr (*37*).

In contrast to the intramolecular formation of the carbazole from the dihydropyridineacrylic ester in the aprotic solvent xylene, the availability of solvent protons in the latter case appears to divert the collapse of this intermediate in methanol via an ionic mechanism to the pyridinium salt. When the reaction is carried out in CH_3OD solution, the nmr spectrum of the salt no longer shows a signal at τ6.12 ($CD(CH_3)CO_2$—CH_3) and the doublet at τ8.62 ($CH(CH_3)CO_2CH_3$) is replaced by a singlet (3 H) in accord with the mechanism **32** → **64** as shown in Scheme 19. This salt is stable in methanol at 175°C but on pyrolysis at this temperature affords the carbazole (**61**) presumably via elimination of ethylpyridine and cyclization of the resulting vinyl ester (**65**). The generation (*32*) in methanol solution could also be rationalized by an ionic mechanism which recalls the formation of the betaine (**66**) from akuammicine (**67**) (*38*). Since the species **32** and **64** could be reached *in vivo* from stemmadenine, tabersonine, and catharanthine, it will be of interest to test these three alkaloids as biochemical precursors for secodines and secamines and also to consider the system **32**–**64** as a labile but isolable biosynthetic entity in the *Aspidosperma* and *Iboga* metabolic grid (*37*).

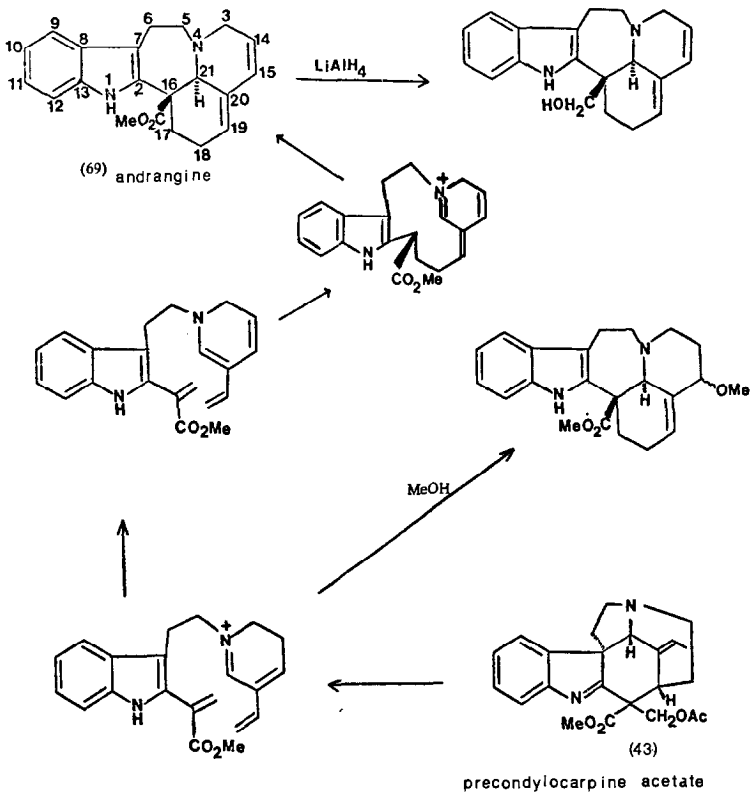
Laboratory analogy for secodine formation from the salt (**64**) was obtained by reduction of (**64**) with sodium borohydride which gave (±) dihydrosecodine (**68**) as a crystalline racemic base (35% yield) identical in all spectroscopic properties with the amorphous natural alkaloid obtained from *Rhazya stricta* (*39*). Further (catalytic) reduction of (**68**) afforded tetrahydrosecodine (**40**) which co-occurs in *R. stricta*. This mode of formation of dihydrosecodine may be contrasted as a biosynthetic model with the extremely facile formation of (±)-tetrahydrosecodine (**40**) from stemmadenine acetate in 75% yield where it was suggested that rupture of the C_{15-17} bond was facilitated by platinum-catalyzed isomerization of the 19,20-double bond to the endo position thereby allowing collapse to the secodine system, as discussed earlier.

Finally, we note that the earlier difficulties in rationalizing the lack of biochemical conversion of (+) catharanthine (**34**) to its 15,20-dihydro derivative coronaridine (**57**) can now be understood, since in *Catharanthus roseus* it has been found that these *Iboga* alkaloids bear antipodal absolute stereochemistry at C_{14}, C_{17}, and C_{21} (*40*). The co-occurrence of such antipodal species in the same plant may once again signify the onset of different synthetases acting on the same intermediate. Thus (–)-coronaridine is detectable at very early stages of germination of *C. roseus* whereas (+)-catharanthine is found only after prolonged germination and seedling growth (*10*). The achiral ester dehydrosecodine A (**31**) (or its isomer B (**32**)) could serve as an intermediate which can undergo cyclization (Scheme 19) to either coronaridine (**57**) or (+)-catharanthine (**34**) and predictably the pseudo series represented by (**35**) which still awaits discovery from a natural plant source (*41*).

Andranginine, Pseudocatharanthine, and Vindolinine

During the *in vitro* conversion of precondylocarpine (**30**) and related pentacyclic alkaloids it was observed that thermolysis of (**43**) in ethyl acetate solution afforded (in 28% yield) a new racemic pentacyclic compound (**69**) mol wt 334, i.e., corresponding

to dehydrogenation of the 336 series. The reaction was interpreted as shown in Scheme 20 where the stability of the vinyl dihydropyridine species is believed to have mediated in a relatively high-yielding reaction to produce the new system (**69**) corresponding to the ionic addition depicted. In the course of structural investigation of a Madagascar



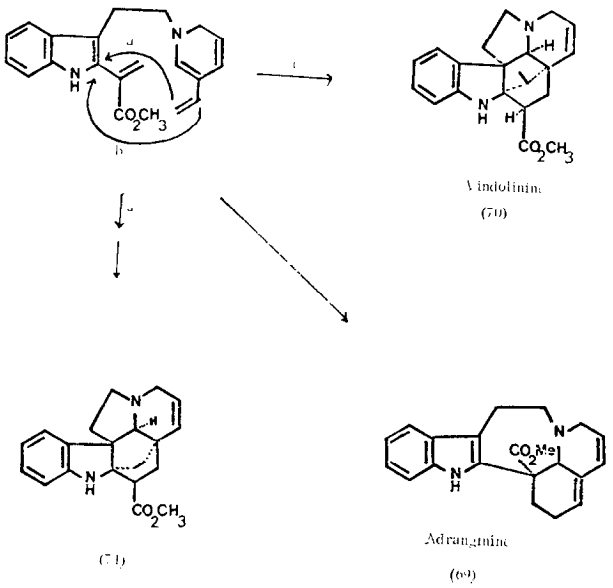
SCHEME 20

species undertaken some months after this experiment was completed it was discovered that the compound andranginine (mol wt 334 $[\alpha]_{300-600}$ 0°) was, in fact, identical in every respect with this novel, partially synthetic alkaloid (*42*). The full power of biogenetic type synthesis was thus revealed in two independent studies which converged in a most satisfying manner. The implications of this and related discoveries of racemic alkaloids is discussed in the final section of this review.

Pseudocatharanthine. Although this compound (**35**) has never been described as a natural product, its synthesis from catharanthine, tabersonine, and preakuammicine are suggestive that the *Aspidosperma*-like structure of yet another mode of cyclization of the acrylic ester will appear as a natural series (*41*). This postulate may have important consequences for the biosynthesis of the "double" alkaloids discussed below.

Vindolinine and its relatives. In surveying the modes of cyclization of secodine system, there exists a rather puzzling feature of the structure of a class of hexacyclic alkaloids exemplified by vindolinine (**70**) inasmuch as the stereochemistry required by the ethano-bridge ($C_{19} \rightarrow C_5$) confers a *trans-syn* configuration on the fusion of rings D

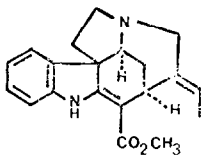
and E, a feature which is absent from all known *Aspidosperma* alkaloids. In an earlier article (*43*) we commented on this fact which has now been satisfactorily explained by the correction of the structure of vindolinine to the bridged system (**70**) (*44*). A possible derivation based on biogenetic condensations is shown in Scheme 21 which incidentally allows prediction of the relative stereochemistry of the asymmetric centers of vindolinine and also traces the connection with the hexacyclic series (**71**).



SCHEME 21

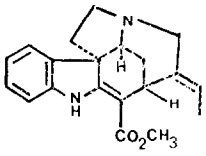
Stereochemical and Structural Relationships Within Alkaloid Families

A. *Strychnos series.* A perennial problem encountered in the theory of *Strychnos* biosynthesis has been the occurrence of enantiomeric and diastereoisomeric pairs of alkaloids exemplified by (+) and (−) akuammicine (**67**) and (−) lochneridine and (+)-20 *epi*lochneridine. The crux of the stereochemical enigma in this series concerns the apparent inversion at C_{15} which in the absence of any satisfactory rationale for the racemization or epimerization of this center, has led to the logical suggestion that C_{15} retains its absolute stereochemical identity ($C_{15}\alpha$-H or $C_{15}\beta$-H) from an earlier precursor of the *Corynanthé* series or indeed that the inverted $C_{15}\beta$-H configuration comes all the way from a secoiridoid of "unnatural" configuration at this site. However, a recent series of experiments (*45*) portrayed in Scheme 22 has shown that epimerization of C_3, C_7, and C_{15} is accomplished by a simple equilibration experiment in methanol solution at 95°C (50 hr): this result now rationalizes the appearance of the so-called antipodal *Strychnos* family. The implications of these findings are discussed in the concluding section of this review. At this point we note that the intermediate "seco" system (**72**) may serve as a useful and easily accessible relay for total synthesis in this field. These experiments conducted with 19,20α-dihydroakuammicine (R = H) also constitute a model for the lochneridine series (R = OH).



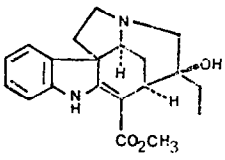
(-)-AKUAMMICINE

(-)-(67)

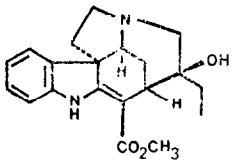


(+)-AKUAMMICINE

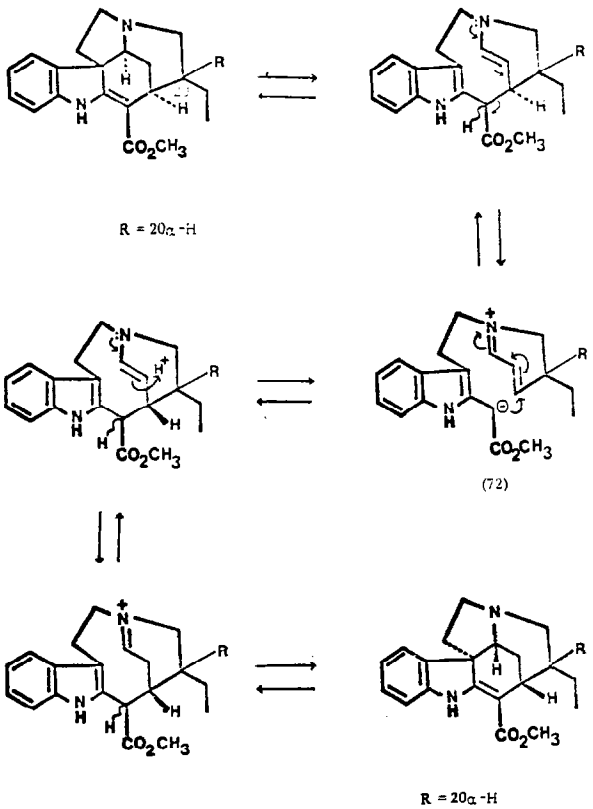
(+)-(67)



(-)-LOCHNERIDINE



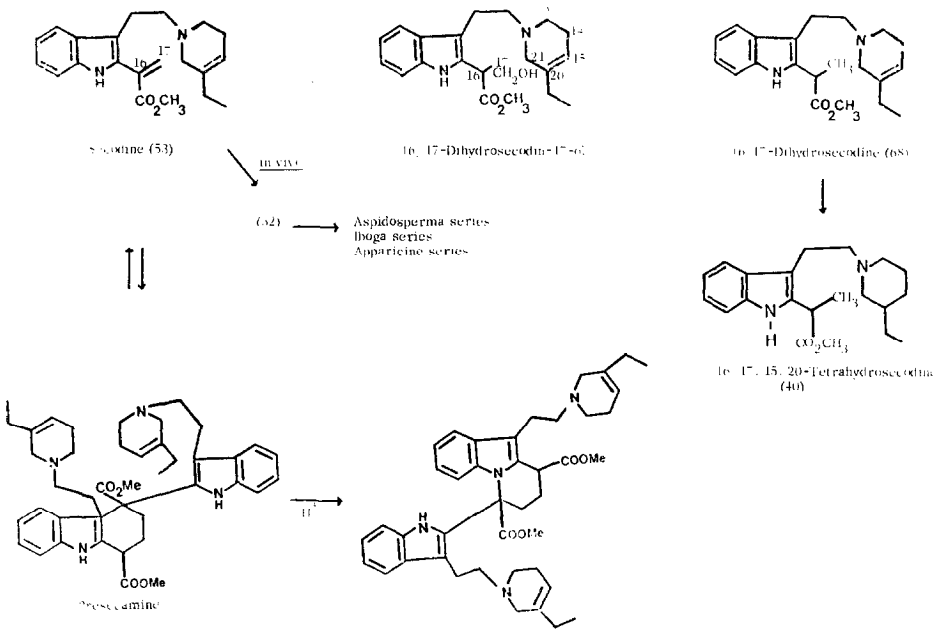
(+)-LOCHNERIDINE 20-epi



(72)

SCHEME 22

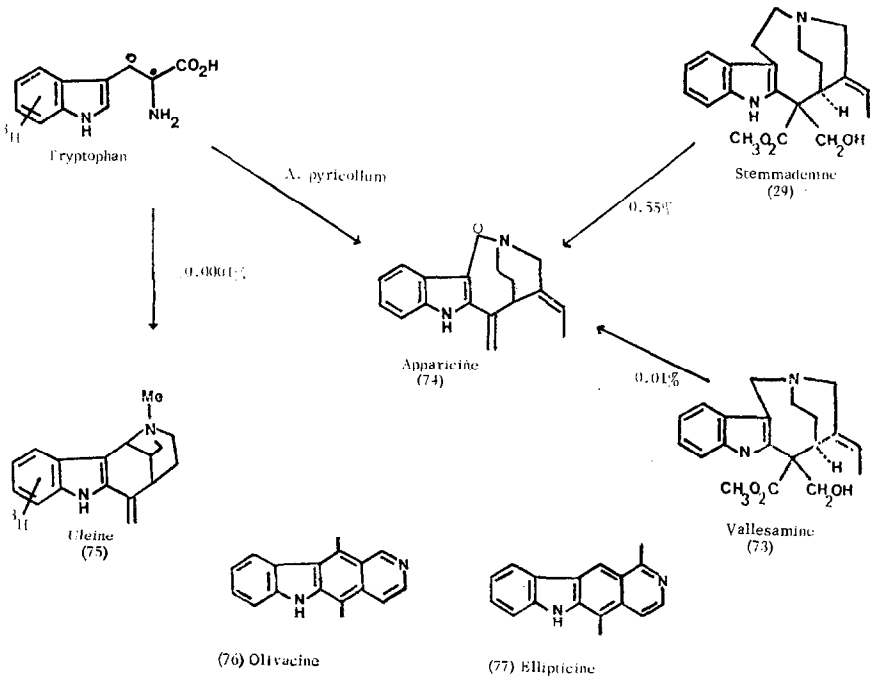
B. *Secodines and related compounds.* The discovery beginning in 1968 (*46*a) of a whole new range of "chano" alkaloids based on the secodine array was indeed welcome testimony to the "336 concept" engendered by our preliminary experiments carried out the previous year. A selection of these structures and their chemical interrelationship is shown in Scheme 23. Secodine (**53**) is involved in several important biochemical transformations leading to the various classes (*Aspidosperma, Iboga,* and Apparicine series) (*46*b). The chemical manipulation of the fully activated dihydropyridine system in Scheme 23 has so far been studied indirectly (*29, 32*) but a recent stabilization



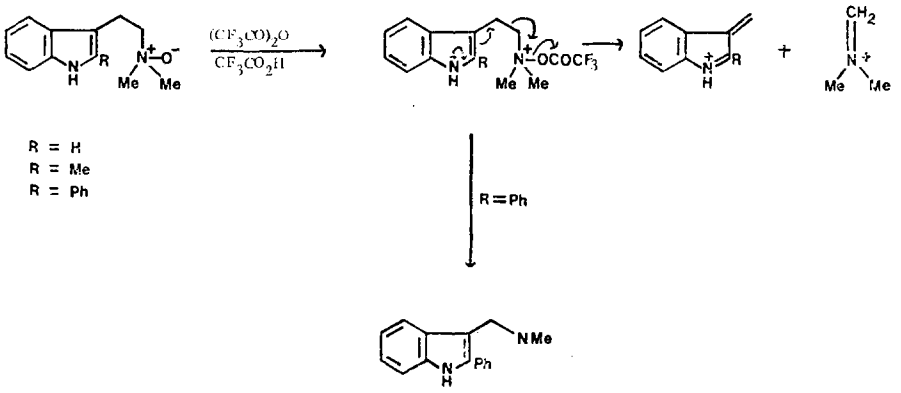
SCHEME 23

experiment (*47*) on some simpler models augurs well for more intensive and successful studies on the capture of (**32**) and its relatives. An extremely efficient method of arriving at the tetrahydro secodine alkaloids (as **40**) was portrayed in Scheme 19 where the *in vitro* chemistry of tabersonine, and especially catharanthine can be marshalled to afford first the pyridinium salt (**64**) and then by further reduction to the naturally occurring compound (**40**) which is found in *Rhazya stricta.*

C. *N-oxides as substrates for "Nor"-alkaloids.* An intriguing reaction discovered recently by Potier (*48*) and his colleagues provides a striking model for yet another puzzling feature of a set of alkaloids in which the ethanamino bridge of the original tryptophan moiety has been shortened by one methylene group. Such alkaloids as vallesamine (**73**), apparicine (**74**), uleine (**75**), olivacine (**76**), ellipticine (**77**) fall into this class. The work of Kutney (*49*) has shown that apparicine (**74**) is indeed derived from tryptophan in *A. pyricollum* by loss of C_2 and retention of C_3 (Scheme 24). A most satisfactory rationale for this process has been provided by Potier (*50*) as summarized in Scheme 25 where a modified Polonovsky reaction serves as a model for the



SCHEME 24

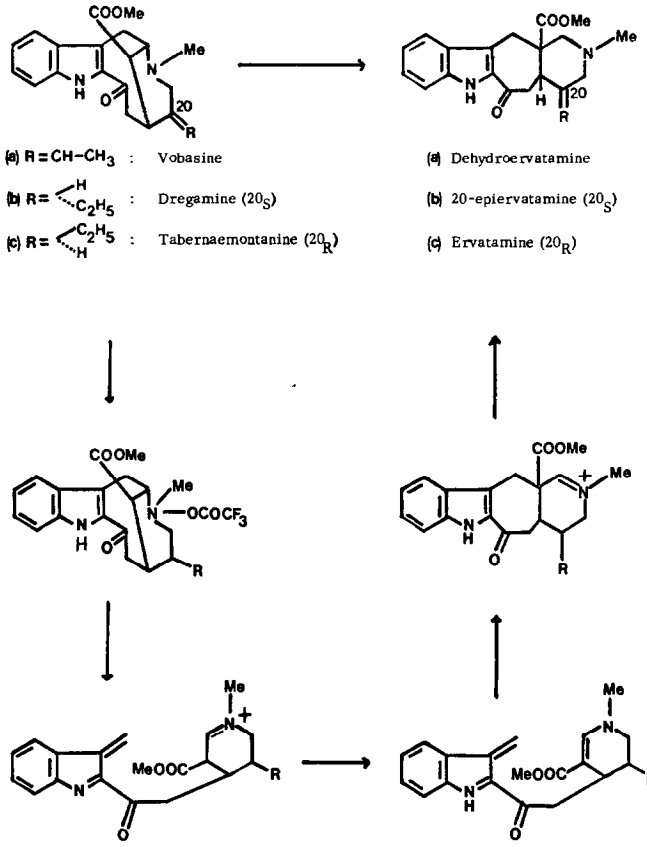


SCHEME 25

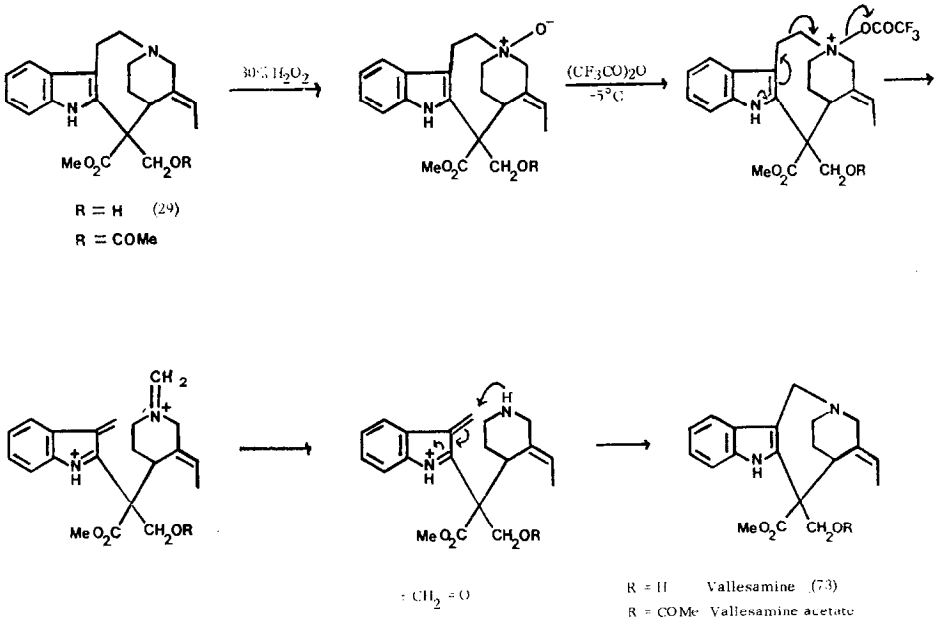
possible biogenetic relationships portrayed. An elegant experiment (*51*) has forged the link between the vobasine alkaloids and the rearranged compound of the ervatamine series (R = $CHCH_3$) (Scheme 26).

In another recent series of experiments (*52*) the transformation of stemmadenine (**29**) to vallesamine (**73**) in ca. 20% yield has been achieved (Scheme 27). Whether *N*-oxides turn out to be viable biochemical intermediates remains to be proved, however.

D. *Reactions of Aspidosperma alkaloids.* A series of rearrangement products (*53*) derived from the structure of the *Aspidosperma* alkaloid tabersonine (**33**) can only be

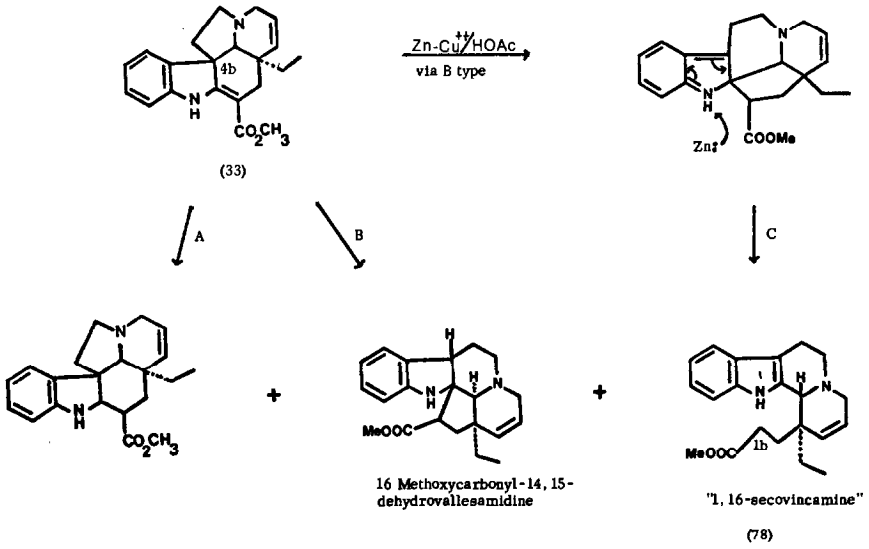


SCHEME 26



SCHEME 27

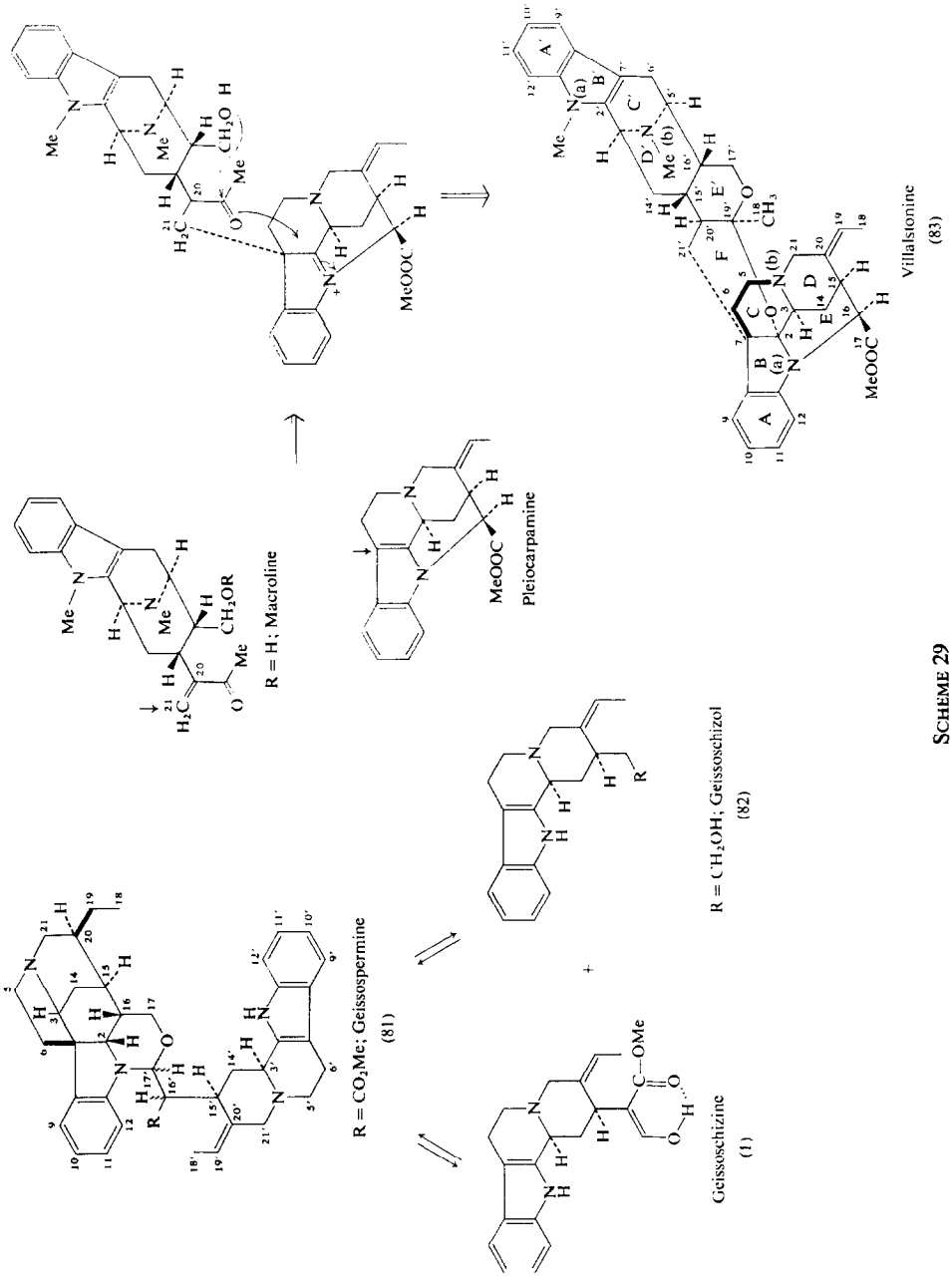
described as spectacular. Several of these are reproduced in Scheme 28 together with the suggested mechanism (LeMen et al. [*53*]). Of particular interest is the biogenetic-like connection made with the vincamine (**78**) series using zinc and copper ions in acetic acid.



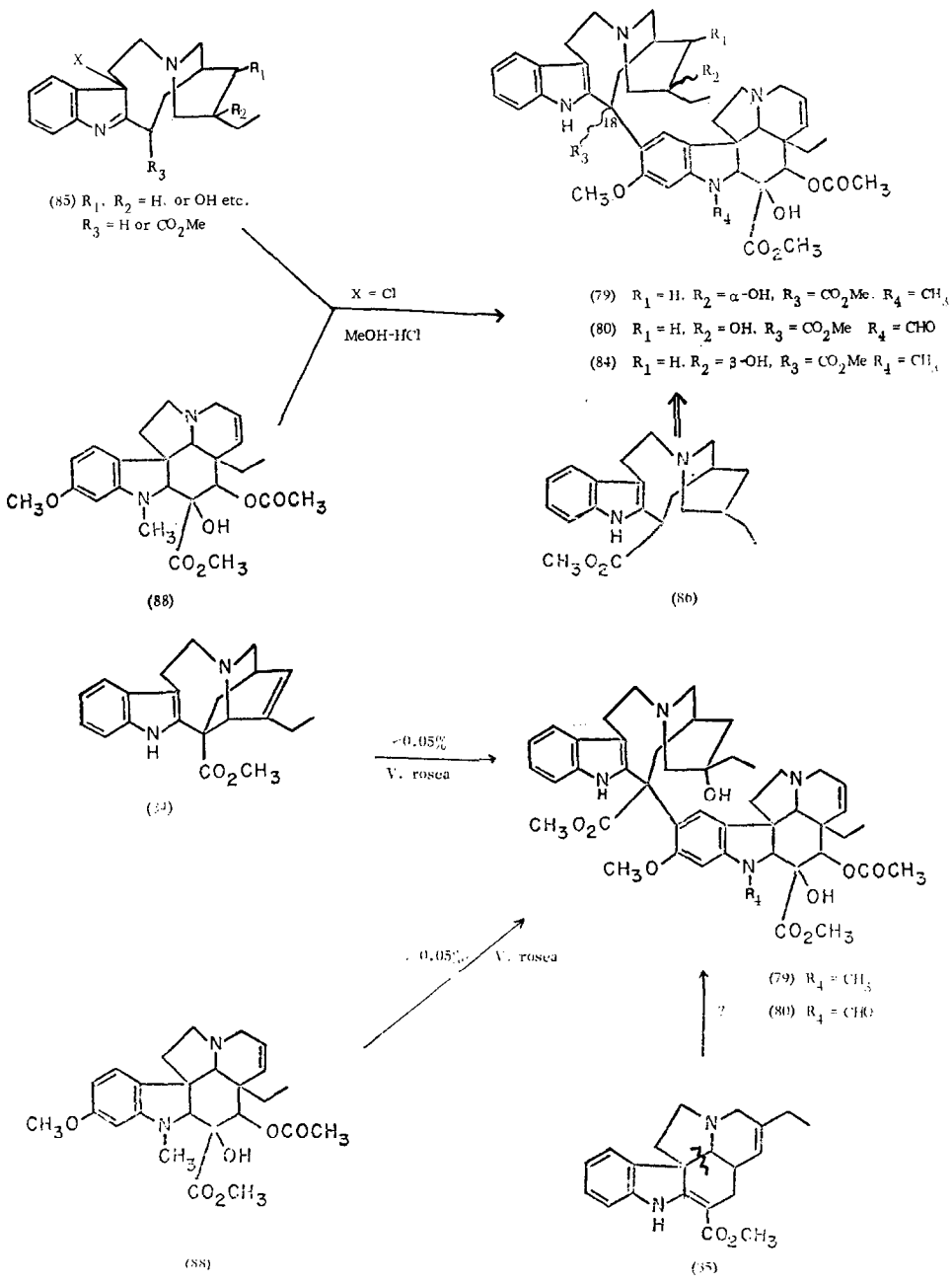
SCHEME 28

E. "*Double*" *or dimeric indolic alkaloids.* The chemistry of these complex substances which have gained prominence due to the antitumor properties of several members of the *Aspidosperma–Iboga* double alkaloids, e.g., vinblastine, VLB (**79**), and vincristine, VLC (**80**) has been treated in an excellent recent review (*54*). From the standpoint of biogenetic-type synthesis it appears certain that many (but by no means all) of these structures could be readily formed as artifacts. Examples of successful coupling reactions include the preparation of geissospermine (**81**) which is formed from geissoschizine (**1**) and geissoschizol (**82**) under extremely mild conditions (*54*), the classical work on the Calebash-curare dimers (*54*) and a more recent biogenetic-type synthesis (*55*) of villalstonine (**83**) as illustrated in Scheme 29.

It seems unlikely that the antitumor series exemplified by VLB (**79**), VLC (**80**), and leurosidine (**84**) occur without enzymic intervention in *C. roseus* since a successful coupling reaction which leads to the desired stereochemistry at C_{18} in the dimer remains to be described (*54*). Considerable progress has been made, however, in refining the coupling reactions pioneered by Büchi (*56*), Neuss (*57*), Harley-Mason (*58*), and Kutney (*59*) of substituted, modified structures such as (**85**) and (**86**) with vindoline (**88**) to give dimeric products whose stereochemistry is under investigation (Scheme 30, *in vitro*). Preliminary feeding experiments (Scheme 30, *in vivo*) have not settled the problem in *C. roseus*; the specific incorporation of vindolinine (**88**) and catharanthine (**34**) into VLB being ca. 0.05% and 0.005%, respectively. An intriguing possibility is that the pseudo series (**35**) may be involved (*60*).


R = H; Macroline
Pleiocarpamine
Villalstonine
(83)
R = CO_2Me; Geissospermine
(81)
R = CH_2OH; Geissoschizol
(82)
Geissoschizine
(1)

SCHEME 29



SCHEME 30

SUMMARY, CONCLUSIONS, AND PROGNOSIS

Within the last decade, and particularly since 1968, the apparent diversity and complexity of the approximately 1000 members of the mevalonate-derived indole alkaloids has been rationalized in terms of a main pathway beginning with vincoside and passing

through geissoschizine, stemmadenine ⇄ preakuammicine, tabersonine, and their more highly oxygenated, rearranged, and degraded derivatives. The important fact that all of the observed skeletal rearrangements take place on a preformed alkaloidal template such as geissoschizine and stemmadenine can now be used not only to clear up several remaining mysteries e.g., the *Corynanthé* → *Strychnos* mechanism but also to predict within each category new classes of alkaloid based, for example, on the "336" concept, which represent highly reactive species upon which the rearrangement mechanisms may operate.

We feel that many short- and eventually high-yielding synthesis of little-studied and rare alkaloidal structures await the development of methodology based on the pathway followed by nature in arriving at these rather complex and challenging structures. Now that the innate beauty of the biochemical pathway has been revealed (at least in broad detail) there seems no doubt that many improvements can and will be made on existing and still quite primitive methods of interfamilial connection. However, the facility of several of the biogenetic-type syntheses reviewed even in this rather selective survey lead to a highly speculative—even bizarre—suggestion that the occurrence of many racemic, enantiomeric, and diastereomeric sets within the *Apocyanaceae* may reflect either a lack of substrate specificity on the part of a rearranging enzyme or indeed the complete absence of any such enzyme. In other words the latter alternative implies that especially in the tropical regions, where so many of the most rearranged structures occur in species subjected to long periods of warmth, a number of transformations including rearrangement, dimerization, and racemization may have taken place without the agency of enzyme control on a highly reactive substrate.

This final suggestion and many others implicit in our survey remain to be tested by rigorous experiment. Such experiments would, we believe, have profound implications for chemotaxonomy and perhaps reduce the apparent multitude of enzymes in plant alkaloid biochemistry ot a reasonable number. At the same time the "artificial" nature of many complex alkaloids may have to be recognized, the examples of vallesiachotamine (**10**), geissospermine (**81**), and even andranginine (**69**) falling into this category.

In spite of the many frustrations and experimental difficulties encountered by the investigators of biogenetic type synthesis in the field of indole alkaloids, there is emerging the most satisfying viewpoint that many of Nature's processes can be simulated in a significant way. Most importantly, work from various laboratories has made available substrates which can be tested in biochemical experiments and which may be used to test model reactions for enzymic and nonenzymic transformations.

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