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REGIO- AND STEREOSPECIFIC MODELS FOR THE BIOSYNTHESIS OF THE INDOLE ALKALOIDS—I

DEVELOPMENT OF STRATEGIC APPROACHES AND PRELIMINARY EXPERIMENTS

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Abstract—Potential models for both proven and presumed rearrangement processes of indole alkaloid biosynthesis are presented which impute a key role to the reactive dihydropyridine-acrylic ester, dehydrosecodine (**19**). Plausible mechanisms are considered for the generation of **19** from the *Corynanthé-Strychnos* alkaloids which lead to several important consequences for both regio- and stereochemical control of the cyclisation of **19** and its close relatives, including the prediction of some hitherto undiscovered classes of indole alkaloid. Preliminary experimental observations are described which indicate the feasibility of generating and utilising dehydrosecodines (as **19**) as models for several rearrangement processes of the biosynthetic pathway. A recent criticism of these experiments is analyzed.

It has been established that three major classes of indole alkaloid, *viz Corynanthe-Strychnos*, *Aspidosperma* and *Iboga*, arise in nature by combination of the iridoid glucoside secologanin with tryptophan, in conformity with the early demonstration of the role of mevalonate and geraniol in the genesis of the "C_9–C_{10}" unit of these complex metabolites of higher plants.[1] Concurrent with our biochemical experiments designed to define the nature of the intermediates in these processes, we have sought *in vitro* analogies for many of the condensation and rearrangement steps involved. In this series of papers we shall examine the various types of problems encountered in a complete solution to this goal *i.e.* the *in vitro* transformation of tryptophan and secologanin to representatives of all three alkaloid families with retention of as many aspects of the "natural" regio- and stereospecific controls as possible.

As portrayed in Scheme 1 the primary event in the biosynthesis of the indole alkaloids is the combination of secologanin and tryptophan (or tryptamine) to form vincoside (**1**) and isovincoside (**2**) although the timing of the biochemical decarboxylation step has not yet been determined. It has been recently established[2,3] that, of these two epimers, only vincoside (**1**) with 3β-H stereochemistry is biotransformed to the *Corynanthé* and complex alkaloids in *Catharanthus roseus* and further that the epimerisation at C_3 necessary to furnish the observed 3α-H stereochemistry of the major *Corynanthé* alkaloids is not accompanied by loss of the C_3-proton. An excellent *in vitro* model was provided for the important first step *viz* the biosynthesis of vincoside, when it was shown that vincoside (**1**) and isovincoside (**2**) are formed under mild conditions from tryptamine and secologanin.[2] The ready availability of secologanin from *Lonicera tartarica*[4] suggests that, in conjunction with the strategies developed in the sequel, a complete practical solution to the biogenetic-type synthesis of the *Corynanthe*, *Strychnos*, *Aspidosperma* and *Iboga* series of alkaloids from secologanin and tryptamine is now feasible.

The various *in vitro* sequences of the overall pathway which set the stage for our model experiments are as follows:

A. The conversion of vincoside (or isovincoside) to geissoschizine (**3**), the prototype of the *Corynanthé* series.

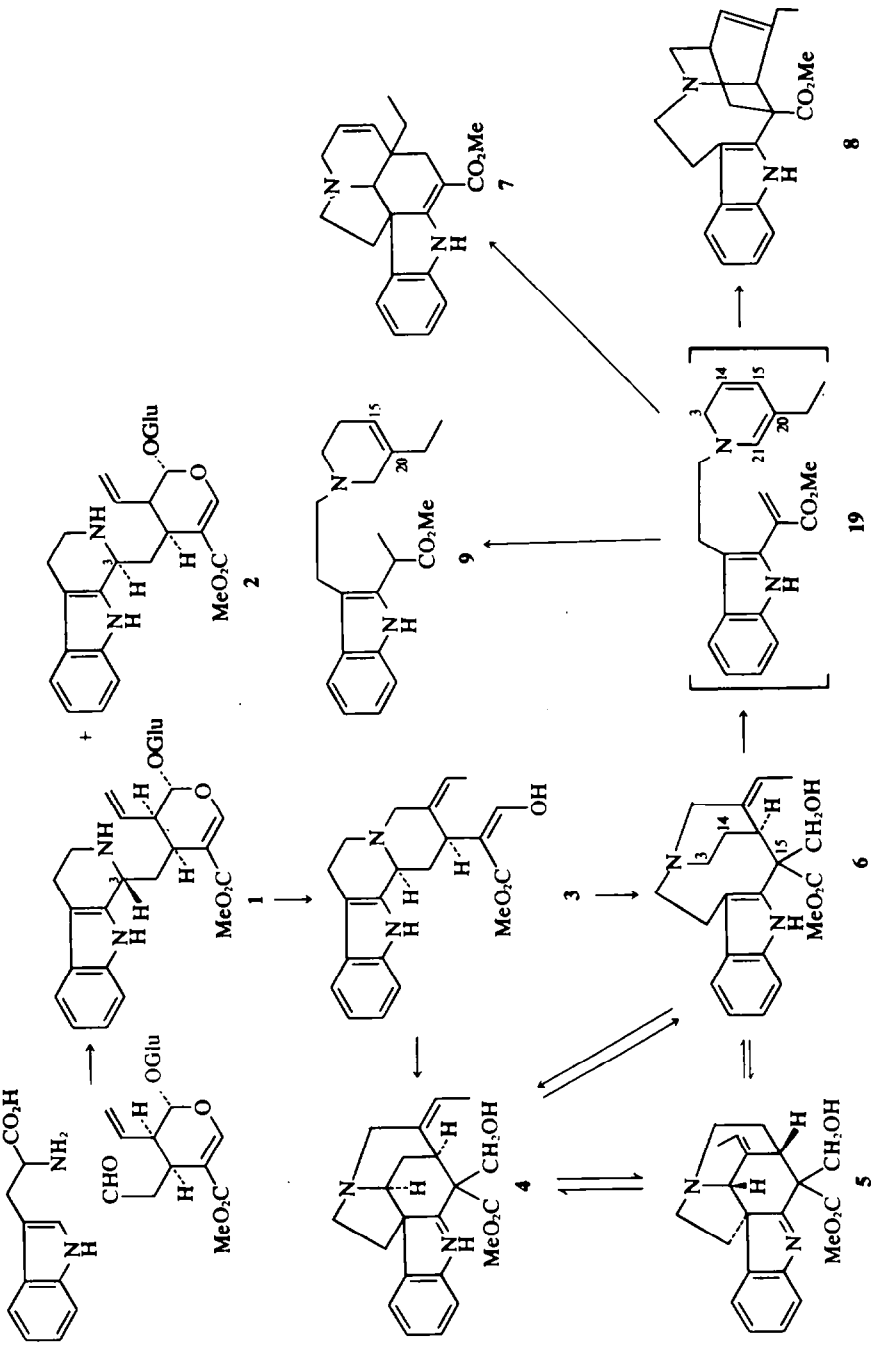
B. The rearrangement of geissoschizine to preakuammicine (**4**) and/or precondylcarpine (**5**).[1a]

C. The equilibrium between the pentacyclic alkaloids (**4**) and (**5**) and stemmadenine (**6**).[1a,5]

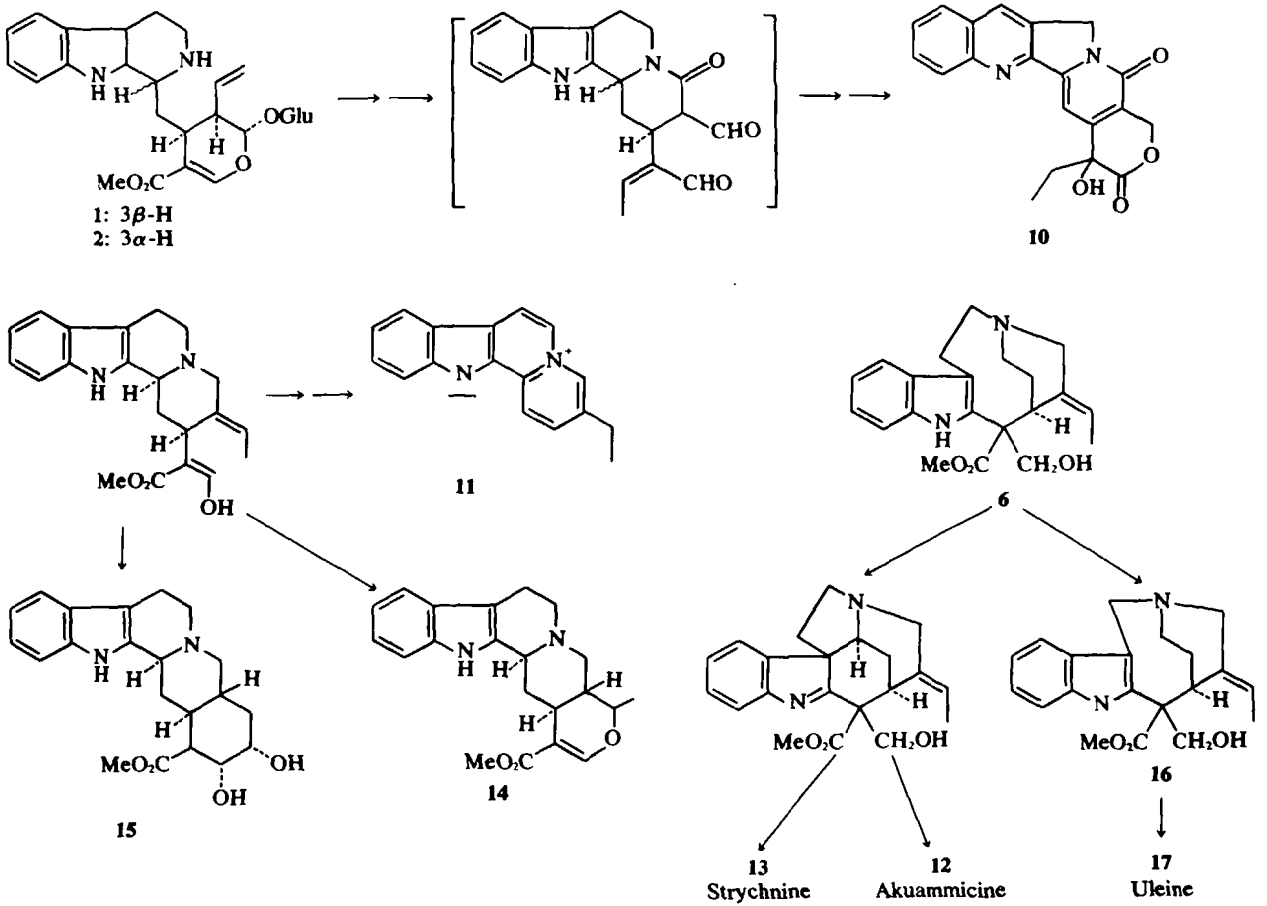
D. The rearrangement of **4**, **5** and **6**[6] to *Aspidosperma* (as **7**) and *Iboga* alkaloids (as **8**) and to the secodine family (as **9**).

E. The conversion of the *Aspidosperma* prototype tabersonine (**7**) to the *Iboga* prototype, catharanthine (**8**).[6]

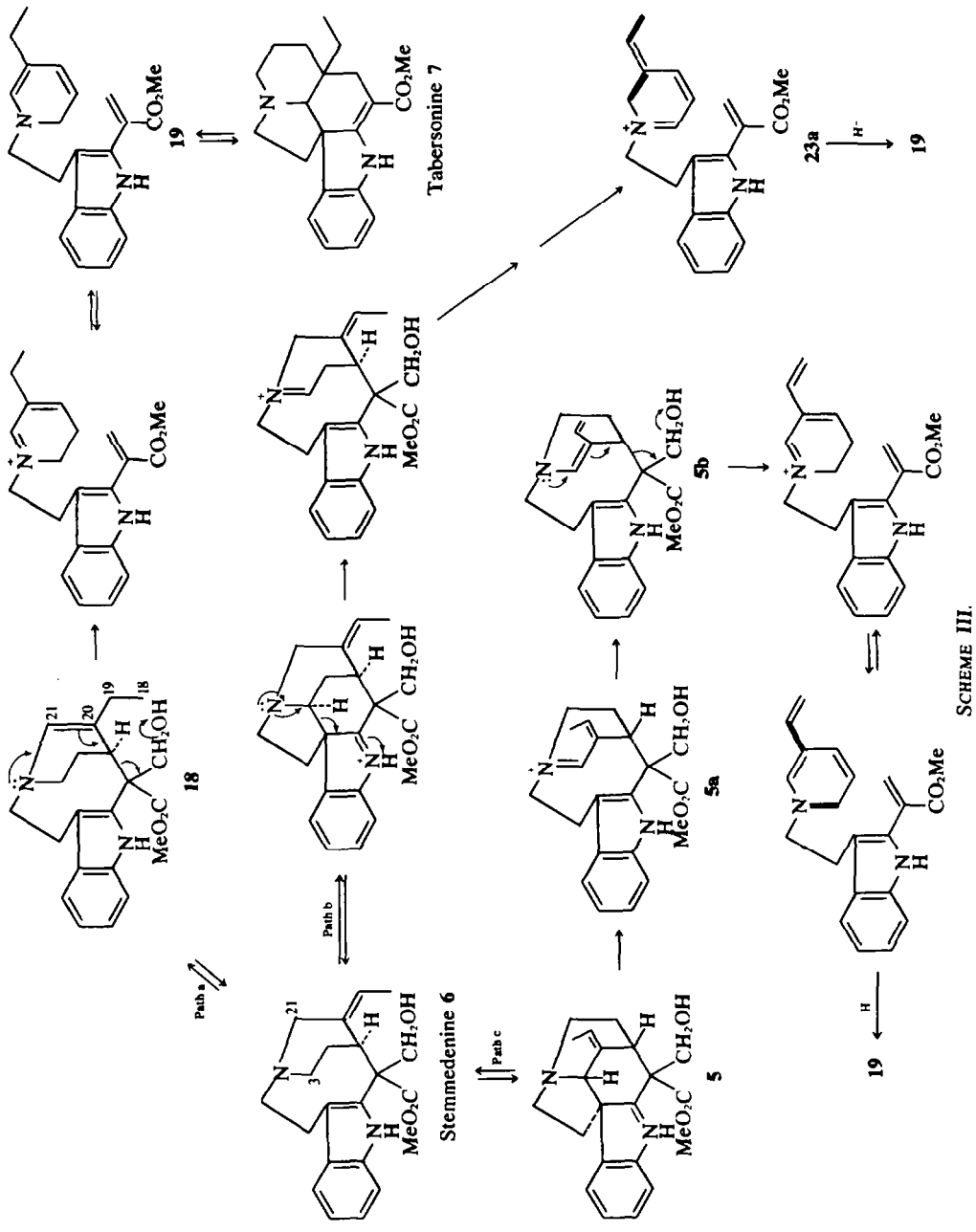
In addition, several subclasses of alkaloid could



SCHEME I.


1: 3β-H
2: 3α-H
10
11
6
15
14
13
Strychnine
12
Akuammicine
16
17
Uleine

SCHEME II.


Path a
Path b
Path c
18
19
Tabersonine 7
Stemmedenine 6
5
5a
5b
23a
19
SCHEME III.

in principle be reached from the major intermediates described above *e.g.* vincoside (**2**)→ camptothecin (**10**)[7]; geissoschizine (**3**)→ flavoperierine (**11**);[8] preakuammicine (**4**)→ akuammicine (**11**)[9] and strychnine (**13**);[10] vincoside (**1**)→ajmalicine (**14**) and the *Yohimbé* alkaloids (**15**);[1,11] and stemmadenine (**6**) to vallesamine (**16**) and uleine (**17**),[12] as summarized in Scheme II. Plausible mechanisms can be invoked for all of these secondary transformations* and progress in the laboratory realization of several of these processes will be described in detail in the subsequent papers of this series.

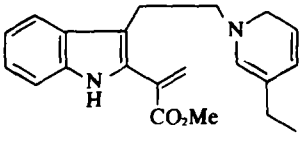
Our preliminary experiments centered on the intriguing problems (sequences D and E) of the *Corynanthé → Aspidosperma → Iboga* conversion which had been demonstrated *in vivo.*[1a] Thus the isolation of the rare alkaloid stemmadenine[13]† (**6**) from short-term germination experiments was suggestive that a key role must be attributed to this compound, which may be viewed as a hybrid of the *Corynanthé* and *Strychnos* families. Indeed, the reactivity inherent in stemmadenine on the one hand for conversion to preakuammicine (**4**) and precondylocarpine[1a] (Scheme I) or more directly by isomerisation of the 18, 19 double bond to the 14, 18 (**5**) position[6,14] *via* **18** (Scheme III) would formally place this substance† as an ideal source of the rearranged alkaloids tabersonine (**7**) (*Aspidosperma*) (**7**) and/or catharanthine (**8**) (*Iboga*) *via* the reactive seco acrylic ester **19** (Scheme I). Recombination of this ester provides a rationale for the production of these major classes as portrayed in Scheme I. Similar processes were considered possible[1a,6,14] in the conversion of tabersonine (**7**) to catharanthine (**8**) (Scheme I) which had been demonstrated in two independent studies (albeit in minor radiochemical yield) in *Catharanthus roseus.*[15,16]

Although unknown at the outset of this investigation several versions of the *seco* acrylic ester (as **19**) have since been discovered in a series of natural alkaloids in which the reactive conjugated ester function is diversely masked *e.g.* in dimeric form as the presecamines (**20**),[17] reduced as in the secodines (**21a** and **b**)[17,18] or hydrated in the secodinols (**22a** and **b**).[18,19]

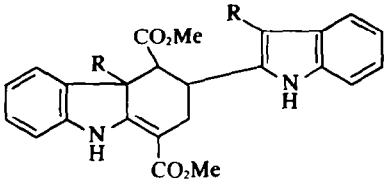
Mechanisms for the dehydrative rearrangement of stemmadenine (**6**) to tabersonine (**8**) were now considered as a guide for the development of experimental conditions for this key transformation. In Scheme III, Path a, the result of direct isomerisa-

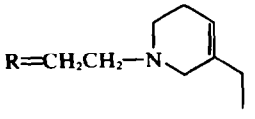
*A discussion of the putative mechanistic pathways for each of these subsets will be given in the appropriate full paper.

†The authors of Ref 13 first noted the formal connection between the structure of this *Corynanthé-Strychnos* "hybrid" and the rearranged *Aspidosperma* and *Iboga* skeletons in terms of Wenkert's[11] 1,5-dicarbonyl cleavage mechanism (see also Ref 1*a* for a fuller discussion of this point).

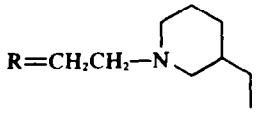


19 Dehydrosecodine

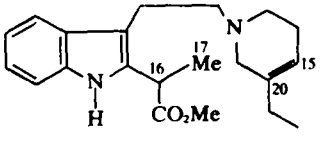




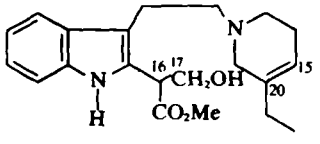
and



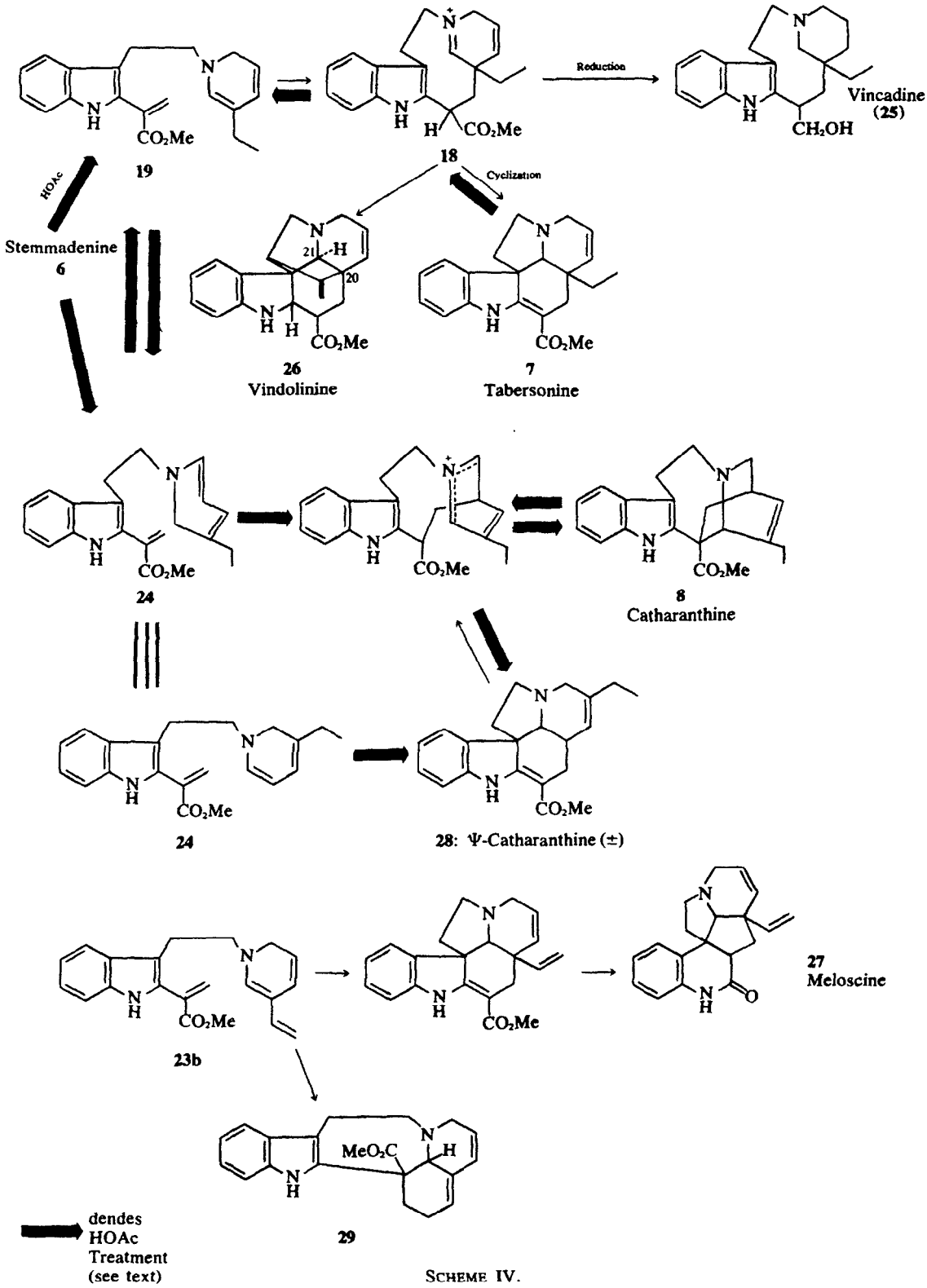
20 The Presecamines



21a: 16,17-Dihydrosecodine
21b: 16,17,15,20-Tetrahydrosecodine (Δ15,20 reduced)



22a: 16,17-Dihydrosecodin-17-ol
22b: Δ15,20 reduced


Reduction
Vincadine
(25)
19
18
HOAc
Cyclization
Stemmadenine
6
26
Vindolinine
7
Tabersonine
24
8
Catharanthine
24
28: Ψ-Catharanthine (±)
23b
27
Meloscine
29
dendes
HOAc
Treatment
(see text)

SCHEME IV.

tion of the 19, 20 *exo*cyclic double bond to the 20, 21-*endo* position allows the collapse of the enamine system of **18** and dehydration to generate the dihydropyridinium salt which by prototropic rearrangement affords the dehydrosecodine (**19**). Operation of the following mechanism (or its Diels-Alder counterpart) on **19** then leads to tabersonine (**7**). On the other hand the oxidation of stemmadenine to preakuammicine (**4**) could lead *via* Path **b**, Scheme III by a more complex route to the immonium salt (**23a**) whose reduction and rearrangement also rationalises the genesis of dehydrosecodine (**19**). Finally a third route involving oxidative cyclization of **6** at the reactive allylic position (C_{21}) may be readily envisioned (Path c, Scheme III) whereby precondylocarpine becomes the pivot in the formation of *chano* series. An interesting requirement however in Path c is the generation of the vinyl group (**5b**) from the ethylidene function in **5a** in order to allow the migration of electrons through the system in the fragmentation reaction (**5b**)→(**23b**). Once again by adjustment of the oxidation level *via* reduction of the ethylidene double bonds of stemmadenine (**6**), precondylocarpine (**5**) or preakuammicine (**4**) similar mechanisms emerge which will be considered in full detail in the accompanying papers. The seco-acrylic ester (**19**) and the isomeric dihydropyridine (**24**) are desirable models as they are formally endowed with the propensity towards cyclisation not only to the more complex *Aspidosperma* and *Iboga* constituents of *C. roseus* but, as illustrated in Scheme IV could lead to the vincadine (**25**), vindolinine (**26**) and meloscine (**27**) types. Most significantly, if our model is indeed chosen to correspond closely to the substrates actually used by the synthetases of higher plants then several natural classes formally derivable from **19** and its relatives can be predicted in advance of their authentication by isolation and structural studies. In the latter category we have selected for illustration in Scheme IV the synthetic compound, pseudocatharanthine (**28**) formally derived in Nature *via* **24** and the new pentacyclic system (**29**) which represent possible future isolates from natural sources and is the result of an alternative Mannich reaction on **23b**.

Of the known alkaloids portrayed in Scheme IV perhaps the most surprising structure is that displayed by vindolinine (**26**) for dissection of its presumed biosynthesis from the dehydrosecodine (**19**) has apparently disrupted the relative stereochemistry at C_{21}. The latter centre in every naturally occurring alkaloid of the *Aspidosperma* family is known to be *cis* to the ethyl (or modified ethyl) side chain at C_{20}. If the biogenetic rules developed in the succeeding paper of this series are of potential utility for prediction of structure and stereochemistry then a minor revision of the structures of the vindolinine series would be required in order to conform with the "*cis* rule".

Initial *in vitro* work was designed to test the possibility that the acrylic ester (**19**) could be generated from (+)-stemmadenine and (−)-tabersonine and was sufficiently promising to warrant further investigation. Since the authenticity as well as the reproducibility of these early results has been challenged,* it is the purpose of the present paper to describe to the best of our ability, sets of reaction conditions which proved to be successful in our hands as well as reporting on those which failed to furnish the desired products. In the succeeding papers of this series appropriate modifications of these thermal reactions are detailed which allow rigorous analysis of the several steps of these processes which proceeded without conscious control in the first set of experiments[6] described in full below, and portrayed in Scheme IV.

Action of acetic acid on stemmadenine (**6**). In the first group of many runs employing refluxing acetic acid it was noted that facile formation of stemmadenine O-acetate occurred. However during an examination of the effect of increasing external oil bath temperatures (180–210°), analysis by TLC of

*Following the publication of these preliminary experiments a critical and in part valid response in the scientific literature appeared[20] in which an Anglo-French group pointed out that the apparent facility of the reactions as delineated in our first communication was misleading and that they were unable to reproduce the results cited. We wish to accept full responsibility for leaving such an erroneus impression, for in fact the experiments are critically sensitive to the thermal and concentration factors as described below. The importance of the experiments in our opinion lay not so much in the yields obtained (which were low and variable) but rather in the practical illustration of a concept which in the light of our own and subsequent work has provided the impetus for many interesting biochemical and synthetic experiments based on the reactivity of the ester (**19**). Thus with the excpetions noted in the text we accept the published criticism of our work on the grounds that the preliminary note in question did not specify certain difficulties associated with the reaction conditions. However we must comment on the important distinction between such valid criticism and the unfortunate impression which has been conveyed and perpetuated in review literature, *albeit* unintentionally, that the early results obtained by us were of doubtful authenticity. It is quite clear from comparing the experiments described herein with those of the Manchester group, that, for example, the apparently simple treatment of optically active catharanthine leads to rather different ratios of product which in our hands always contains an isolable amount of *racemic* catharanthine. Since 100 mg quantities of this racemate have been supplied to other investigators for spectroscopic studies it is quite apparent that, for reasons which may require much further experimentation to evaluate, the (±)-pseudocatharanthine ⇄ (±)-catharanthine equilibrium does not lie so far to the left as stated by Brown *et al*,[21] for this would have required us to have in hand an inordinate amount of a precious natural starting material for this conversion (or alternatively to have carried out a very large number of equilibrations).

the alkaloidal mixture revealed the appearance of several ceric ammonium sulphate—"blue positive" materials (Experimental) which indicated generation of the β-anilino acrylate chromophore. Preparative TLC of these mixtures with two solvent systems left no doubt that transformation of stemmadenine acetate to both tabersonine (7) and pseudo-catharanthine (28) had taken place. Unfortunately this result is not consistently reproducible but in our view depends on maintenance of extremely vigorous reflux, which has the effect of increasing the local concentration of stemmadenine acetate (in the 5 or 10 ml pear shaped flasks used) almost to saturation. In effect the successful experiments involved almost complete evaporation of solvent and therefore superheating of the substrate on a silica or glass surface provided by the silica boiling stones ("alundum" grain) or the flask surface used in the experiment. Since these conditions are obviously difficult to obtain in a consistent way and were not appreciated fully at the outset, new and reproducible techniques have been developed for effecting the same results and these are described in the accompanying papers. However there could be no doubt that the conversions actually occurred since the products of the reaction not only correspond in R_f, IR, UV and mass spectral characteristics with tabersonine (7) catharanthine (8) and pseudo catharanthine* (28) but most importantly revealed complete racemization of these products as judged by ORD data and CD spectra which were devoid of optical activity between 300 and 600 nm. Furthermore (±)-catharanthine and (±)-tabersonine were unknown substances at the time of the experiments and could not have been present as an impurity in the starting material as judged by careful TLC analysis of stemmadenine before each experiment. A further point of controversy concerns the equilibrium between catharanthine and its pseudo-isomer (28), the latter compound serving as a criterion for entry into the *Iboga* series. Two points are worthy of note in this connection. First, the action of hot acetic acid on (+)-catharanthine hydrochloride in our hands and those of the Lilly group[22] affords a separable mixture of catharanthine and the crystalline Ψ-isomer (28) m.p. 119° $[\alpha]^{25°}_{300\ 600\,nm}$ = 0°. The English group has reported that only 90% racemisation of Ψ-catharanthine occurs in this experiment and the product is amorphous. However we find that if the reaction proceeds for 12 h not only is Ψ-catharanthine isolable as a beautifully crystalline substance in *ca* 40% yield but most importantly *the "recovered" catharanthine* (5–10%) *is in fact also racemic*, which confirms that the catharanthine/Ψ-catharanthine equilibrium, although in favor of the latter, does allow the isolation of (±)-catharanthine. In their study of this aspect Smith *et al.*[20a,b] did not report on the chiroptical properties of a minute quantity of catharanthine recovered from the reaction mixture but assumed that it was completely unchanged. Thus their comment[20a] that their work "hardly supports the claim that the change (pseudocatharanthine → catharanthine) is a synthetically useful process" would seem to rest on an incomplete analysis of the equilibrium or possibly the use of rather different conditions. Obviously the catharanthine–pseudocatharanthine equilibrium merits more detailed study, but even allowing for the fact that the pseudo-isomer is favored *ca* 5:1 in our hands, the stereospecific interconversion of complex pentacyclic alkaloids in yields of even a few percent compares very favorably with multi (15–20)-step total synthesis involving 70–80% yields at each stage. A further recent comment on the catharanthine ⇄ Ψ-catharanthine change states that "catharanthine survives to the extent of less than 1% after 12 h in refluxing acetic acid". Reference to the experimental section below shows that in our hands after 12 h a 5·5% isolated yield of *pure racemic* catharanthine can be isolated. (A TLC/spectroscopic yield of at least 8–10% is indicated). We should note that our experiments with catharanthine were carried out on the hydrochloride rather than the free base.

We must however state that several of the reported yields of the products from stemmadenine must be revised downwards in the light of subsequent experimentation as follows (average of several runs): (±) catharanthine (8) from 9% to 3% (range 2–4%), tabersonine (7) from 12% to 5% (range 3–7%), Ψ-catharanthine (28) from 16% to the range 12–16%.

The effect of acetic acid on tabersonine (7). In seeking a biogenetic model for the conversion of tabersonine (7) to catharanthine (8) in *C. roseus* (Scheme IV), we examined the affect of prolonged (16–72 h) reflux under the vigorous conditions described above for stemmadenine. In these experiments careful analytical and preparative TLC experiments were carried out on the products. Followed identification of the new materials produced (TLC, mass spectrum, UV, IR) the samples were subjected to ORD analysis. In those cases where conversion of tabersonine to a mixture of Ψ-catharanthine (28) and catharanthine (8) took place,† the latter alkaloids were separated from starting material using silver nitrate impregnated silica gel plates according to the solvent systems delineated in Table 1, a set of conditions which were also found to be effective for both analytical and preparative studies by Smith[20b] *et al.*

In summary the preliminary experiments reported herein and summarized earlier[6] are indica-

*Hereafter referred to as Ψ-catharanthine.

†In our preliminary communication the yields of these two alkaloids were reported as 28% and 12% respectively. These values should be 15–20% and 3–5% respectively (Experimental).

Table 1. R_f Values of reference alkaloids

Compound	R_f values		
	System A	System B	System C
(+) Catharanthine	0·55	0·15	
(±) Pseudocatharanthine	0·65	0·52	0·65
(+)-Stemmadenine	0·15		
Tabersonine	0·65	0·52	0·52

1. A. Silica gel F_{254}, benzene, EtOAc, MeOH (2:2:1).
2. B. Silica gel F_{254}, $CHCl_3$/EtOAc (9:1).
3. C. Silica gel G, $AgNO_3$[a] petroleum ether/ether (2:1) 40–60°.

[a]Prepared from silica gel G (50 g) and 2 or 3% $AgNO_3$ solution (100 ml). The plates were air dried for at least 16 h. Caution: considerable variation from batch to batch has been noted for this adsorbent system by ourselves and others.[20]

tive of the potential use of the acrylic ester model (**19**) both for indole alkaloid biosynthesis and as a synthetic strategy. We have suggested previously that in spite of the rather variable yields obtained in these earlier experiments modification of the reaction conditions bears considerable potential for the preparation of extremely complex pentacyclic structures with regio- and stereospecific control. At the same time we agree with and welcome the published criticism of the shortcomings of these exploratory experiments with respect to their consistent reproducibility and wish to thank Dr. G. F. Smith and Professors J. Poisson and J. LeMen for a fruitful exchange of experimental results.

EXPERIMENTAL

M.ps were determined on the Köfler block and are uncorrected. Thin layer chromatography was carried out on silica gel F using ceric sulfate spray as indicator. The reference alkaloids used (see Table 1 for details of TLC R_f values) were (+) catharanthine, (±) pseudocatharanthine (−) tabersonine, and (+) stemmadenine. We thank Drs. N. Neuss, D. Stauffacher and Professor J. LeMen for generous gifts of these materials. The glacial acetic acid used was AR or reagent grade quality and was not redistilled.

Reactions of stemmadenine

(a) *In acetic acid at* 140–150°. Stemmadenine (5 mg) was heated in glacial AcOH (5 ml) using alundum grain boiling stones with external oil bath temp maintained at 140–150°. After 16–24 h TLC analysis indicated that no observable conversion to Ψ-catharanthine (blue color with CAS spray) had occurred. Preparative TLC afforded unchanged stemmadenine 0·5–1·0 mg and O-acetyl stemmadenine (1–2 mg) as average yields over 10 runs.

(b) *In acetic acid at* 200–210°. Stemmadenine (30 mg) was dissolved in AcOH (8 ml) in a pear shaped 25 ml flask containing 5–10 boiling stones (alundum grain) in a N_2 atmosphere. The flask was immersed in an oil bath maintained at 200–210° to a depth which ensured vigorous reflux. After 3 h the soln had become yellow and the reflux rate and N_2 entrainment had reduced the soln volume to *ca* 1–2 ml. In two of the runs where successful conversion was demonstrated the soln had formed a thin film on the flask wall and in one case (run overnight) the solvent had evaporated after 10 h. In the latter experiment a further 5 ml of AcOH was added and reflux contained for 10 h.

Analytical TLC of these experiments revealed the presence of a CAS- "blue-positive" spot with R_f identical with that of Ψ-catharanthine in solvent systems A and B (Table 1). Preparative TLC of a typical run afforded (±)-Ψ-catharanthine (4 mg; 15%) as an amorphous solid, identical with authentic (±)-Ψ-catharanthine.[22]* Further preparative TLC of the reaction mixture afforded (±) tabersonine identical, except for optical activity [R_f in solvent systems A–C; IR, UV, MS] with (−)-tabersonine 1·5 mg (5%) and (±)-catharanthine, 0·8 mg (3%; erroneously given as 9% in our original communication) identical (mass spectrum, TLC, UV, IR, ORD) with a sample prepared by treatment of (+)-catharanthine with refluxing acetic acid (*vide infra*).

Action of acetic acid on (−) *tabersonine*

(a) *At* 140–150° *bath temperature.* (−) Tabersonine (50 mg) was heated for 24 h in AcOH (5 ml) under N_2. Preparative TLC of the resultant mixture afforded allocatharanthine (5 mg; 10%) and unchanged (−) tabersonine (25 mg; 50%) together with several unidentified alkaloids.[20c]

(b) *At* 205–210° *bath temperature.* A soln of (−) tabersonine (50 mg) in AcOH (3 ml) containing 10–12 alundum grain boiling chips was maintained at vigorous reflux in an oil bath at 210° for 16 h. Addition of 0·5–1·0 ml portions of AcOH every few h was necessary to prevent complete evaporation in the apparatus used (N_2 flow). In all successful runs the soln had developed a deep yellow color. Preparative TLC of the products gave the following (averaged) composition.

(±) catharanthine	3–5%
(±)-Ψ-catharanthine	15–20%
(−) tabersonine	30–50%.

*In many runs employing a greater dilution of acetic acid stemmadenine (*ca* 20%) and its O-acetate (*ca* 50%) were recovered after 16 h reflux. No ψ-catharanthine was detected in these experiments [42 runs under "normal" reflux conditions *i.e.* without appreciable solvent loss, bath temperature 140–180°].

In each case the isolated alkaloid was compared with authentic material (TLC [Table 1], UV, IR, mass spectrum and ORD) and shown to be identical in every respect.

Action of acetic acid on (+)-*catharanthine* (with Dr. C. C. Wei)

(+) Catharanthine hydrochloride (1·04 g) was refluxed in AcOH (45 ml) under nitrogen for 12 h (bath temp 145–155°) and the soln then kept at room temp for 12 h. The solvent was completely removed *in vacuo*, the residue dissolved in EtOAc and extracted with 1 N HCl. Basification and reextraction with chloroform afforded a mixture of bases (540 mg) which were separated by silica gel chromotography to afford pseudocatharanthine (360 mg) m.p. 118–119° $[\alpha]_{300-600\,nm} = 0°$ identical (mixed m.p., IR, UV spectrum) with a sample provided by Dr. N. Neuss (Eli Lilly). Further purification of later fractions eluted with ($CHCl_3$: MeOH, 5:1) afforded (±) catharanthine (55 mg) further purified by crystallisation from MeOH, m.p. 67–68°. This material had identical TLC, and mass, UV, and IR spectral data with natural (+)-catharanthine but showed $[\alpha]_{300-600\,nm} = 0°$. Identity of this substance (mass spectrum, TLC, m.p., mixed m.p. 67–68°) was confirmed by comparison with a sample of totally synthetic (±)-catharanthine[24] m.p. 66–68° kindly supplied by Professor G. Büchi.

Acknowledgement—We thank S.R.C., The Nuffield Foundation and N.I.H. for support of this work.

REFERENCES

[1]For a recent review see [a]A. I. Scott, *Accounts Chem. Res.* **3**, 151 (1970); [b]E. Leete in *Biosynthesis* I. Chem. Soc. Spec. Periodical Report Ch. 6 (1971); [c]J. A. Joule *The Alkaloids* I. Chem. Soc. Spec. Periodical Report, Ch. 5 (1971); J. Staunton, *Ibid.* II Ch. 1 (1972)
[2]A. R. Battersby, A. R. Burnett and P. G. Parsons, *J. Chem. Soc.* (C), 1187 (1969); *Ibid.* (C) 1193 (1969)
[3]A. R. Battersby and K. H. Gibson, *Chem. Commun.* 902 (1971)
[4]I. Souzu and H. Mitsuhashi, *Tetrahedron Letters* 191 (1970)
[5]*Cf.* A. Walser and C. Djerassi, *Helv. Chim. Acta* **48**, 391 (1965)
[6]A. A. Qureshi and A. I. Scott, *Chem. Commun.* 947 (1968)
[7]*Cf.* E. Winterfeldt and H. Radunz, *Ibid.* 374 (1971)
[8]O. Bejair, R. Goutarel, M. M. Janot and A. LeHir, *C.R. Aead Sci, Paris* **244**, 2066 (1957)
[9]A. I. Scott and A. A. Qureshi, *J. Am. Chem. Soc.* **91**, 5874 (1969)
[10]A. I. Scott and S. I. Heimberger, *Chem. Comm.* 217 (1973)
[11]*Cf.* E. Wenkert, *J. Am. Chem. Soc.* **84**, 98 (1962)
[12]P. Potier and M-M. Janot, *C.R. Acad. Sci. Paris*, **270**, 1727 (1973)
[13]A. Sandoval, F. Walls, J. N. Shoolery, J. M. Wilson, H. Budzikiewicz and C. Djerassi, *Tetrahedron Letters* 609 (1962)
[14]A. I. Scott, *Chimia, Switzerland* **12**, 310 (1968)
[15]A. A. Qureshi and A. I. Scott, *Chem. Commun.* 948 (1968)
[16]J. P. Kutney, C. Ehret, V. R. Nelson and D. C. Wigfield, *J. Am. Chem. Soc.* **90**, 5929 (1968)
[17]G. A. Cordell, G. F. Smith and G. N. Smith, *Chem. Commun.* **189**, 191 (1970)
[18]R. T. Brown, G. F. Smith, K. S. J. Stapleford and D. A. Taylor, *Ibid.* 190 (1970)
[19]A. R. Battersby and A. K. Bhatnagar, *Ibid.* 193 (1970)
[20][a]R. T. Brown, J. S. Hill, G. F. Smith, K. S. T. Stapleford, J. Poisson, M. Muquet and N. Kunesch, *Ibid.* 1475 (1969); [b]R. T. Brown, J. S. Hill, G. F. Smith and K. S. J. Stapleford, *Tetrahedron* **27**, 5217 (1971); [c]M. Muquet, N. Kunesch and J. Poisson, *Ibid.* **28**, 1363 (1972)
[21]R. T. Brown, G. F. Smith, J. Poisson and N. Kunesch, *J. Am. Chem. Soc.* **95**, 5778 (1973)
[22]M. Gorman, N. Neuss and N. J. Cone, *Ibid.* **87**, 93 (1965)
[23]*Annu. Rep. Chem. Soc.* (London) 66B, 483 (1969); J. A. Joule, *Chem. Soc. Specialist Periodical Rep. The Alkaloids* **1** Chap 3. (1971)
[24]G. Büchi, P. Kulsa, K. Ogasawara and R. L. Rosali, *J. Am. Chem. Soc.* **92**, 999 (1970)