BIOORGANIC CHEMISTRY 1, 194–206 (1971)

REVIEW

Studies on Indole Alkaloid Biosynthesis

JAMES P. KUTNEY, JOHN F. BECK, CHARLES EHRET, GERALD POULTON, RATTAN S. SOOD, AND NEIL D. WESTCOTT

Department of Chemistry, University of British Columbia, Vancouver 8, Canada

Received March 1, 1971

A series of experiments concerned with the later stages of indole alkaloid biosynthesis is described. Incorporation studies with tritium- and carbon-14-labeled 16,17-dihydrosecodin-17-ol (XXIV) and secodine (XXV) employing young plants of *Vinca rosea* L., *Vinca minor* L., and *Aspidosperma pyricollum* are presented. The overall implications of these results with respect to currently popular biosynthetic postulates are discussed.

The indole alkaloids constitute a very large family of natural products. The fantastic array of structures inherent in this group has stimulated ingenious speculation about the mode of synthesis in the plants from which they are derived. Discussion and comment on their biogenesis date back to the 1930's when Barger (*1*) and Hahn (*2*, *3*) first considered a biosynthetic pathway to the alkaloid, yohimbine. Their hypothesis was followed by the elegant speculations of Robinson as summarized in the first Weizmann Memorial Lectures (*4*). Robinson's views stimulated Woodward (*5*, *6*), Wenkert (*7–9*) and Thomas (*10*) to modify, expand, and propose new postulates.

Attempts to evaluate these postulates are revealed in many elegant experiments published from different laboratories. Numerous publications are available from the laboratories of Arigoni, Battersby, Leete, and Scott, but other groups have also entered the field. A recent review by Scott (*11*) summarizes the various results which have been obtained in this area and, therefore, mention of only those experiments which are directly relevant to the present discussion will be made. We wish presently to outline some of our investigations on certain phases of indole alkaloid biosynthesis with particular emphasis on selected *Aspidosperma* and *Iboga* bases. In order to provide some background and a rationale for our most recent experiments discussed in the latter portion of this publication, it becomes essential to present first a brief review of our earlier investigations.

Our own interests in this area took a rather different approach from that of our colleagues. Our investigations, which were initiated some 4 years ago, were concentrated entirely on the later stages of the pathway, i.e., in the reactions involved after the indole and C_9–C_{10} units had undergone initial condensations to form the appropriate higher molecular weight "complex(es)" for eventual elaboration to the different alkaloid families. Such questions as (a) the structure of this "complex(es)" and (b) the eventual biochemical elaboration of it to the various indole and dihydroindole alkaloid families became primary targets for our investigations. It was obviously of considerable interest to establish whether the living system, which is capable of elaborating a very substantial structural variation in this class of natural product, was utilizing a common

precursor in the later stages of the pathway. In other words, could one obtain a precursor which is rather equivalent to squalene in isoprenoid biosynthesis?

In actual fact our initial investigations were stimulated largely by our results on the laboratory syntheses of the indole alkaloids. During these studies (*12–18*) we had demonstrated that the transannular cyclization of appropriate nine-membered ring

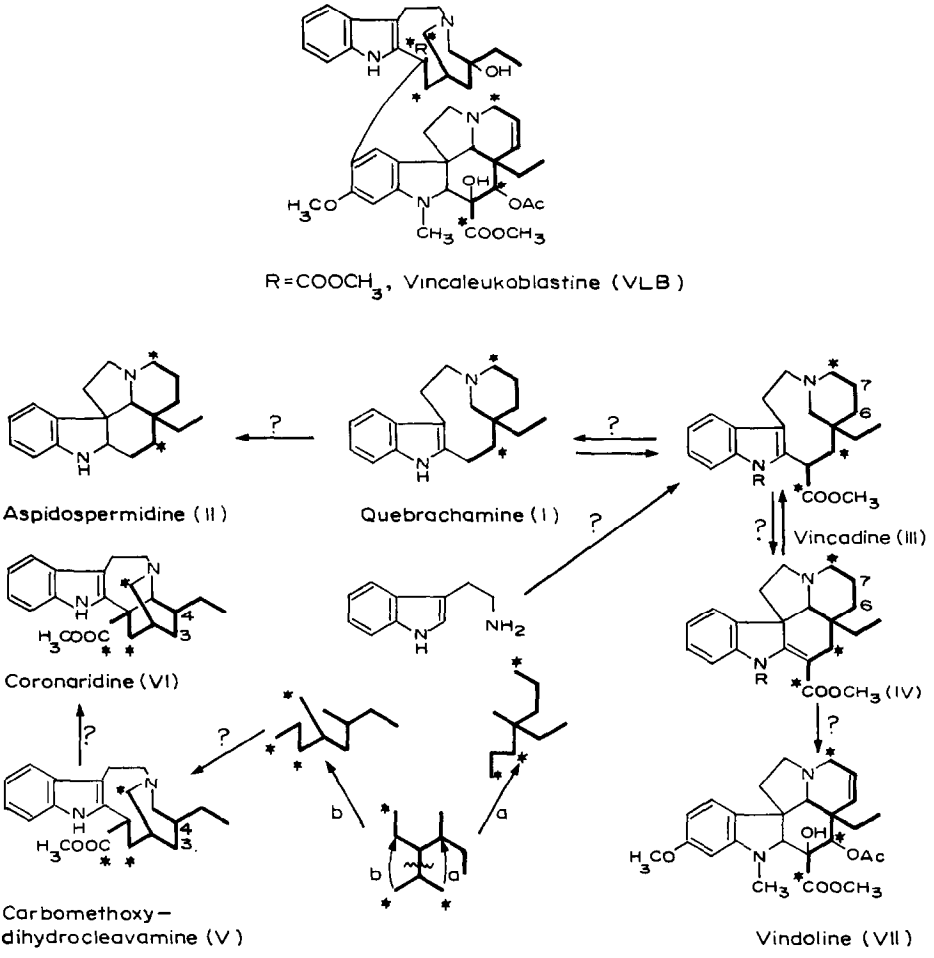


FIG. 1. Schematic outline of our objectives as they pertain to later stages of *Aspidosperma* and *Iboga* alkaloid biosynthesis.

systems in the *Aspidosperma* and *Iboga* series could serve as a remarkably general synthetic approach to a wide variety of these alkaloid members. For example, the conversions, quebrachamine (I) → aspidospermidine (II), vincadine (III, R = H) → vincadifformine (IV, R = H), and carbomethoxydihydrocleavamine (V) → coronaridine (VI), represent some of the significant *in vitro* cyclizations. With respect to our biosynthetic interests Fig. 1 portrays, in schematic fashion, the following initial objectives: (1) In the later stages of *Aspidosperma* and *Iboga* alkaloid biosynthesis, was the transannular cyclization reaction of any significance? and (2) If not, what was

the relationship, if any, between the nine-membered ring compounds (quebrachamine, cleavamine, etc.) and the rigid cyclic systems (aspidospermidine, vindoline, coronaridine, etc.)?

This approach was also directly concerned with an attempt to evaluate one of the published hypotheses on the biosynthesis of indole alkaloids. Wenkert (*9*) had already commented on the possible intermediacy of such nine-membered ring systems as precursors for the *Aspidosperma* and *Iboga* bases. Figure 2 reveals his elegant speculations as they relate to the later stages of the biosynthetic pathway.

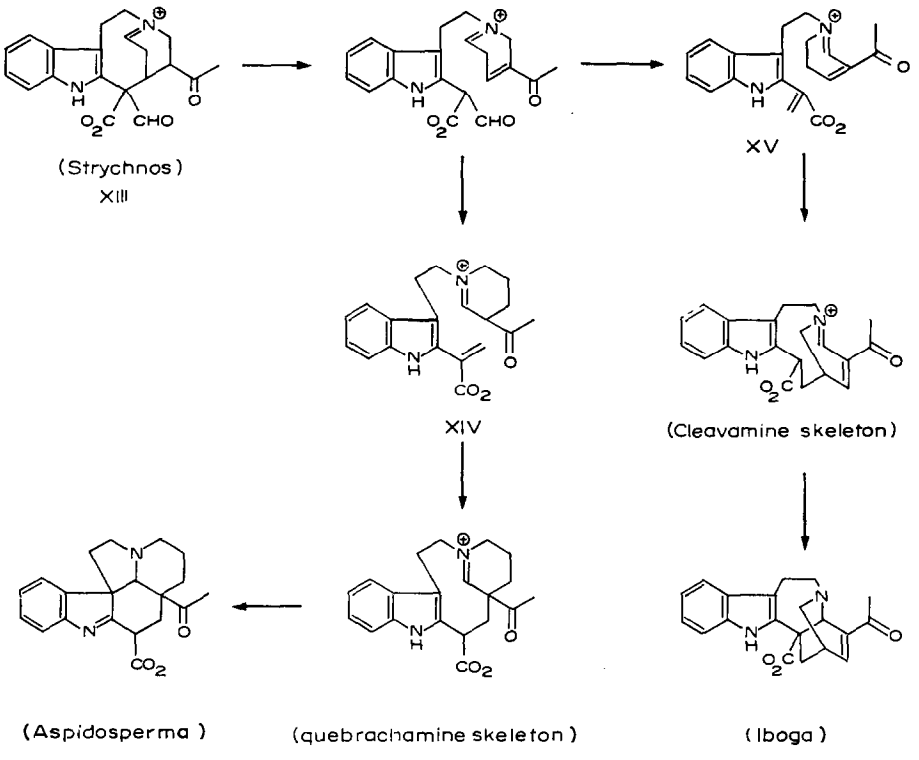


FIG. 2. Wenkert's postulates as they relate to later stages of *Aspidosperma* and *Iboga* alkaloid biosynthesis.

Preliminary publications of our attempts to evaluate the *in vivo* transannular cyclization process have already appeared (*19*, *20*) but some additional discussion is essential here in order to clarify the sequence of events which led to our eventual consideration of the secodine intermediates as presented later. Two totally different approaches were employed to study the possible significance of the cyclization reaction. The first of these (*19*) made repeated attempts to incorporate tritium-labeled cleavamine (V, 3,4-double bond) and quebrachamine (III, R = H, 6,7-double bond) derivatives into catharanthine (VI, 3,4-double bond) and vindoline (VII), respectively, in *Vinca rosea* L. plants while vincaminoreine (III, R = CH_3) was evaluated as a potential precursor for aspidospermidine (II) and minovine (IV, R = CH_3) in *Vinca minor* L. plants. In more than 20 experiments utilizing various feeding techniques in both plant systems, no significant incorporation could be detected. This rather frustrating and somewhat

disappointing result was difficult to interpret. The lack of any positive utilization of these substances could simply involve difficulties with permeability and/or transport of these high molecular-weight substances to the site of biosynthesis or it could imply that the cyclization process was of little biosynthetic significance.

In the hope of providing some positive information with respect to the possible utilization of more complex substances in the biosynthetic pathway, we decided to evaluate the alkaloid, tabersonine (IV, R = H, 6,7-double bond) labeled with tritium in the aromatic ring, as a possible precursor for vindoline (VII) in *V. rosea* L. plants. This alkaloid with its preformed cyclic *Aspidosperma* system and several of the essential functional groups intact could perhaps serve in this capacity. Indeed, the observed positive incorporation (0.03%) of tabersonine into vindoline revealed that the plant system was capable of utilizing this intermediate rather efficiently and performing a significant functionalization process in the biosynthesis of the highly oxygenated vindoline molecule.

A much more surprising result concerned the positive incorporation (0.05%) of tabersonine into the *Iboga* alkaloid, catharanthine (VI, 3,4-double bond), a process which involves a very substantial rearrangement of the alkaloid skeleton. Scott, in his sequential studies in *V. rosea* L. seedlings, reported a similar experiment (*21*, *22*) and more recently has also confirmed our plant feedings (*23*).

The above results left little doubt that our experimental method did allow incorporation of high molecular weight substances into the biosynthetic pathway and therefore tended to strengthen the suggestion that negative incorporation of the nine-membered ring intermediates was an indication that the *in vivo* transannular cyclization was an unnecessary step in the biosynthesis of cyclic *Aspidosperma* and *Iboga* bases. In an attempt to provide further strength to this argument we have studied a rather different approach to this problem (*20*). During our synthetic investigations already noted above, we had established an *in vitro* relationship between the vincadine, vincaminoreine (III, R = H or CH_3) and the vincadifformine, minovine (IV, R = H or CH_3) series. Thus facile cyclization of the former to the latter alkaloids or the reverse process could be readily achieved under laboratory conditions. It was clearly of interest to determine whether this relationship existed in the plant system. For this purpose DL-tryptophan-3^{14}C was administered to *V. minor* L. plants over varying time intervals (4 hr–2 weeks). Careful isolation of the appropriate alkaloids and determination of their radioactivity in each experiment revealed a remarkably constant ratio between these two families. The lack of any tendency for the ratio to progressively decrease or increase with time provided a strong suggestion against any direct biosynthetic relationship between these two groups of alkaloids, i.e., the nine-membered ring family would not appear to be the direct precursor of the pentacyclic *Aspidosperma* bases or vice versa. The possibility of equilibration in the plant which could also account for a constant ratio was excluded by showing that neither vincaminoreine (III, R = CH_3) nor minovine (IV, R = CH_3) transfers any activity to each other when they are incorporated in the plant over a 1-week period. All of these results strongly suggest that the latter stages of Wenkert's postulate (Fig. 2) are open to question and that the appropriate relationships between I, II; III, IV; and V, VI as outlined in Fig. 1 may be unimportant in the overall biosynthetic pathway in the plant.

At the outset the above results seemed somewhat puzzling. In fact the observed conversion, tabersonine (*Aspidosperma*) → catharanthine (*Iboga*) in *V. rosea* plants, in conjunction with the other experiments mentioned demanded that we consider an alternative postulate which need not invoke the transannular cyclization process as an integral step of the biosynthetic pathway. The formal bond-breaking bond-making

processes which must prevail in the plant conversion of the *Aspidosperma* to the *Iboga* system are outlined in Fig. 3. It is clear that in the initial bond fission (dashed lines in Fig. 3) an intermediate VIII (no functionality implied at this point) is obtained. The structural features of this intermediate imply an overall transfer of three carbon atoms of the initial C_{10} monoterpene unit to the α position of the indole ring with the remaining seven carbon atoms involved in the piperidine ring system. The manner of elaboration of intermediate VIII could then determine the overall course of the biosynthetic pathway. Thus, if the bond formation were enzymatically controlled at this level, the various natural systems are readily discernible. Bond formation involving d → c provides the cleavamine skeleton (IX), presently known to occur only in the dimeric *Vinca* alkaloids (see vincaleukoblastine in Fig. 1), while the conversions, e → a and

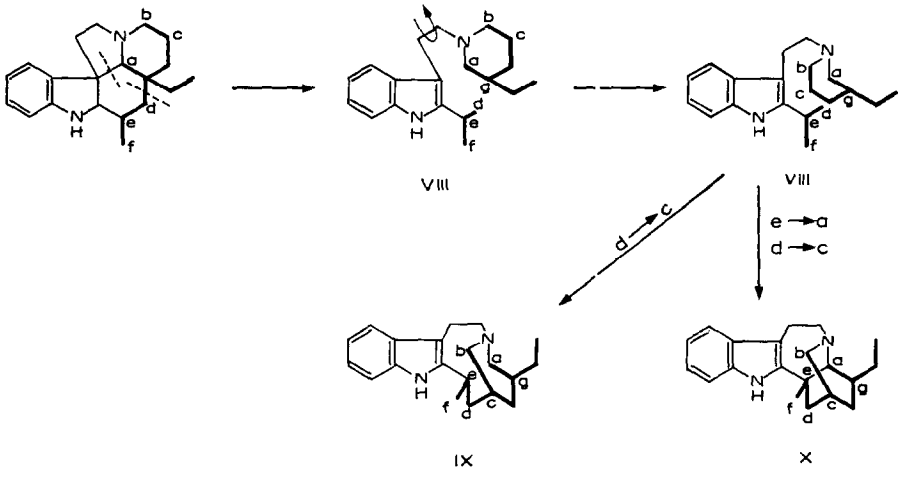


FIG. 3. Outline of formal bond-breaking and bond-making process in the skeletal rearrangement of *Aspidosperma* to *Iboga* systems.

d → c (no definite order implied here), allow the biosynthesis of the rigid, cyclic *Iboga* bases (X).

Figure 4 outlines the formal processes which can allow construction of the relevant quebrachamine (XI) and aspidospermidine-like (XII) systems of the *Aspidosperma* family. These postulates imply a central role for an intermediate having the general skeletal features illustrated in VIII but obviate the necessity of invoking the transannular cyclization of quebrachamine and/or cleavamine derivatives for the eventual biosynthesis of the more elaborate *Aspidosperma* and *Iboga* alkaloids. These speculations would be in accord with our experimental findings and would, in effect, depart from Wenkert's views (Fig. 2) (*9*) only in the very last stages of the pathway.

Clearly, the requirement of establishing more precisely the structure of an intermediate possessing the skeletal arrangement portrayed in VIII attains particular importance. It was attractive to consider again some of the postulated steps in Wenkert's hypothesis, particularly those prior to the stages involving the transannular cyclization process. Indeed, his speculations concerning the possible involvement of the Strychnos skeleton (Fig. 2, structure XIII) were confirmed in Scott's elegant experiments on germinated *V. rosea* seedlings (*21*, *22*) in which stemmadenine (XVI), merely a reduced form of XIII, was incorporated into vindoline (VII) and catharanthine (VI, 3,4-double

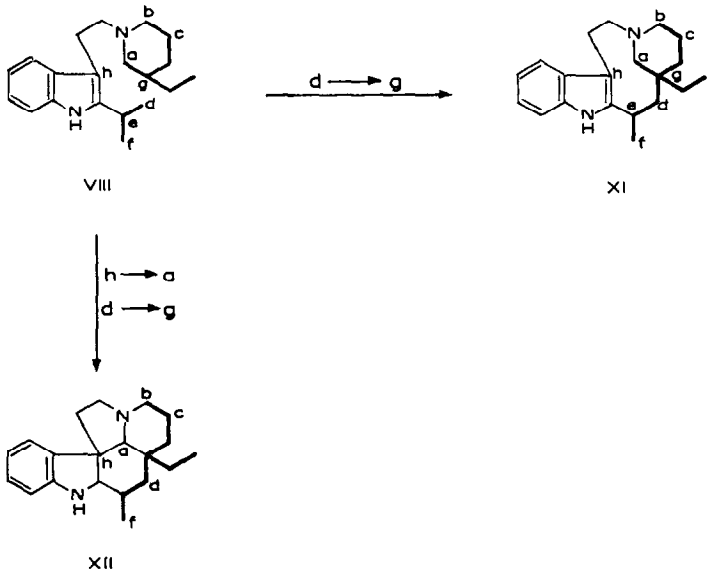


FIG. 4. Outline of formal bond-making process in the biosynthesis of *Aspidosperma* alkaloids from intermediate VIII.

bond). When these and other experiments (*21*) were coupled with our results discussed above, a plausible sequence could be postulated by our respective groups (*20*, *21*) (Fig. 5). It is particularly relevant to the present discussion to realize that the acrylic ester intermediate, XVII, reveals some of the possible functionality which the formal

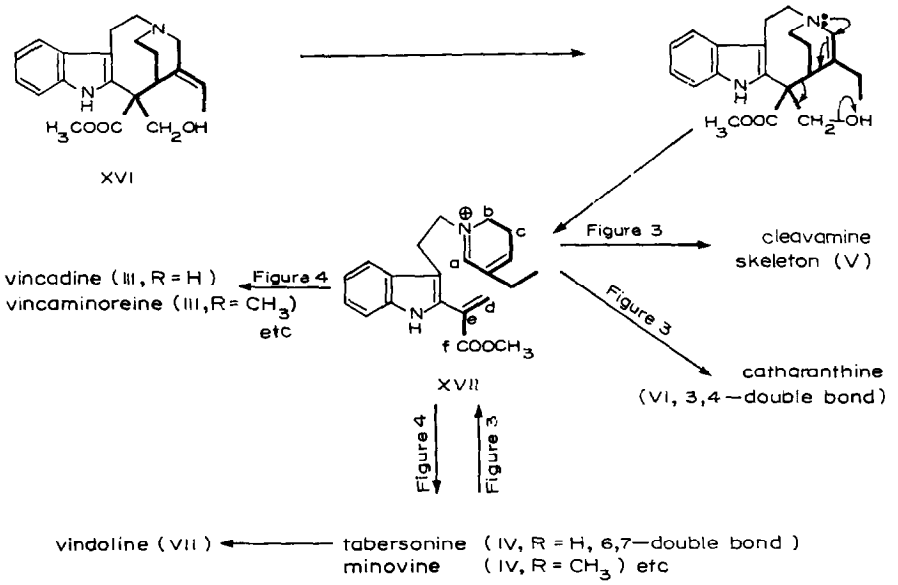


FIG. 5. Postulated scheme for conversion of acrylic ester intermediate XVII to various *Aspidosperma* and *Iboga* alkaloids.

intermediate VIII may possess in its biochemical conversion to the various alkaloids under discussion. It is also relevant to note that XVII bears a striking similarity to some of the intermediates (see Fig. 2, XIV and XV) which Wenkert postulated some 6 years prior to any experimental findings.

The obvious importance for providing experimental support for intermediates bearing the features portrayed in VIII and XVII directed our attention to studies in this area. The first requirement for this purpose involved laboratory syntheses of the appropriate compounds. A direct synthesis of the intermediate XVII is by no means trivial since the established instability of dihydropyridine systems and the high reactivity of acrylic esters would suggest that the eventual isolation of such a compound would provide considerable difficulty. It was reasonable to assume that the more stable

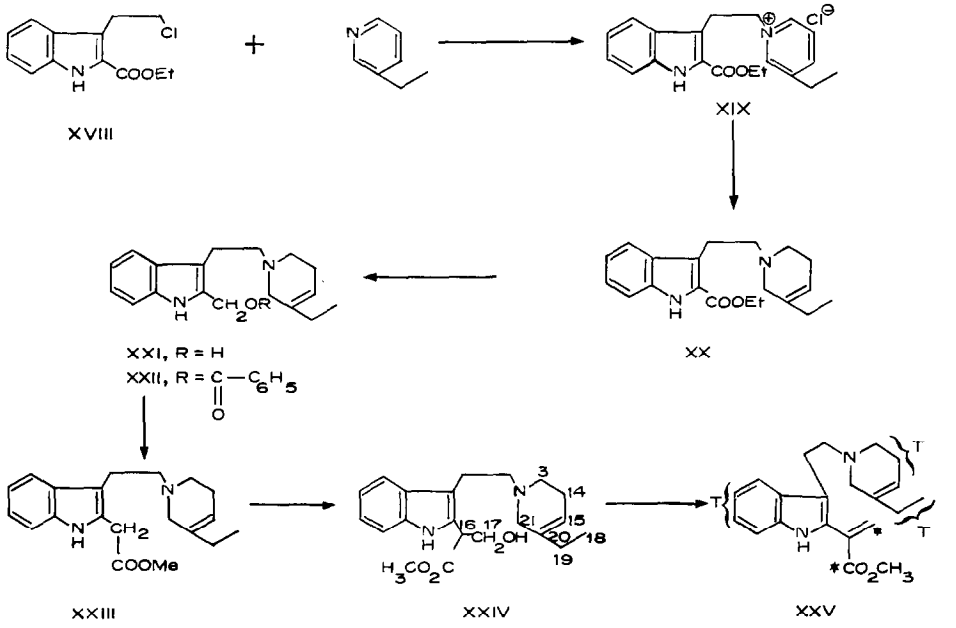


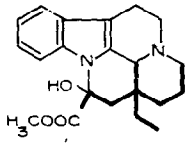
FIG. 6. Synthesis of 16,17-dihydrosecodin-17-ol (XXIV) and secodine (XXV).

analogues XXIV and XXV (Fig. 6) could be converted *in vivo* by the plant to intermediates such as XVII, and they, therefore, became targets for our synthetic efforts. At the outset we desired a sequence which via simple modifications could allow introduction of tritium and/or carbon-14 at either or both halves of the molecule. Figure 6 outlines a sequence which accomplishes this goal.

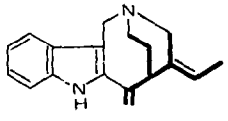
The 2,3-disubstituted indole derivative (XVIII) reacted with 3-ethyl pyridine to provide the crystalline pyridinium salt (XIX), mp 87–89°C. Borohydride reduction of the latter yielded the piperideine XX which on further reduction with lithium aluminum hydride provided the crystalline hydroxymethylene derivative XXI, mp 108–110°C. Normal conversion of XXI to the benzoate (XXII), mp 110–112°C proceeded without difficulty. In fact, the above operations could be performed without isolation of the intermediate products and in this instance an overall 70% yield of benzoate could be obtained from the starting indole XVIII. Displacement of the benzoate by cyanide ion and acidic methanolysis of the resulting nitrile afforded the

crystalline ester (XXIII), mp 85–87°C, in 70% yield. Formylation with methyl formate and sodium hydride as base provided the expected enol which on reduction afforded crystalline 16,17-dihydrosecodin-17-ol (XXIV), in overall yield of 40% from ester XXIII (*24*). Careful dehydration finally completed the synthesis of secodine (XXV) (*25*, *26*). Appropriate manipulations of the above synthetic steps allow introduction of tritium and carbon-14 (asterisked carbons) as indicated in XXV. More specific experimental details will be presented elsewhere. Essentially all of these radioactive intermediates are now in hand and appropriate experiments in various plant species are now under way. Some of our recent results in *V. minor* L. plants have been reported (*27*) while the most recent experiments are the subject for the remaining portion of the present discussion.

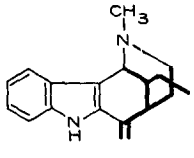
Incorporation studies with labeled XXIV and XXV were initiated in three different plant systems (*V. rosea* L., *V. minor* L., and *A. pyricollum*). Each of these investigations had somewhat complementary but yet different goals. The experiments with *V. rosea* L. would provide information on *Aspidosperma* (vindoline, VII) and *Iboga* (catharanthine, VI, 3,4-double bond) alkaloid biosynthesis while those on *V. minor* L. would allow evaluation of the eburnamine–vincamine (vincamine, XXVI) group for which no experimental data were available (*27*). Finally, the alkaloids of *A. pyricollum* (apparicine, XXVII and uleine, XXVIII) are distinctly interesting since they lack the normal tryptophan side chain and various published postulates for these compounds required evaluation.



XXVI



XXVII



XXVIII

The present discussion will concentrate mainly on the investigations in *V. rosea* L. but some mention is made of results in the other plants for purposes of comparison.

Since 16,17-dihydrosecodin-17-ol (XXIV) was much more stable and thereby more readily accessible, its role as a possible intermediate was first evaluated. Tables 1 and 2 summarize the various experiments which were carried out with tritium-labeled XXIV.

The above results left little doubt that 16,17-dihydrosecodin-17-ol was not being incorporated into any of the plant species studied. In fact this intermediate appeared to be toxic since many of the plants deteriorated badly in a short period after administration of labeled XXIV.

Our attention now turned to secodine, XXV, the acrylic ester intermediate which differed from the previously proposed unit, XVII, only in terms of oxidation level in the piperidine ring. Its expected instability provided initially some experimental

TABLE 1

RESULTS OF INCORPORATION OF [ar^{3}H]-16,17-DIHYDROSECODIN-17-OL INTO DIFFERENT PLANT SYSTEMS[a]

Expt.	Plant fed	Feeding time (hr)	Activity fed (dpm)	% Incorporation into alkaloid isolated		
				Catharanthine	Vindoline	Ajmalicine
1	*V. rosea*	215	1.9×10^7	<0.001	<0.001	<0.001
				Vincamine	Minovine	
2	*V. minor*	24	1.9×10^7	<0.001	<0.001	
3	*V. minor*	96	2.4×10^7	<0.001	<0.001	
4	*V. minor*	96	3.45×10^7	<0.001	<0.001	
				Apparicine	Uleine	
5	*A. pyricollum*	120	9.20×10^7	<0.001	<0.001	

[a] See Table 2 for other experimental details.

TABLE 2

SPECIFIC ACTIVITIES ASSOCIATED WITH EXPERIMENTS IN TABLE 1

Expt.	Feeding method	Specific activity fed (dpm/mmole)	Specific activity isolated (dpm/mmole)		
			Catharanthine	Vindoline	Ajmalicine
1	Wick[a]	8.46×10^8	913	0	627
			Vincamine	Minovine	
2	Hydroponic	7.33×10^8	2.12×10^4	0	
3	Hydroponic	8.90×10^8	4.34×10^3	4.18×10^3	
4	Hydroponic	8.90×10^8	4.69×10^3	3.55×10^3	
			Apparicine	Uleine	
5	Hydroponic	1.82×10^{10}	1.43×10^4	4.98×10^4	

[a] In all the experiments, XXIV was fed as the acetate salt. Full experimental details will be published later.

difficulties but under very carefully controlled conditions we could evaluate its role as a possible precursor. We wish to emphasize here that the elegant experiments of the Manchester group on the presecamines (*29*) published just at this time were of great help in unraveling some of our problems. The established facility in the conversion, secodine → presecamines (*29*), required initially a careful study of appropriate blank experiments to determine the extent of this transformation under conditions essential for the plant incorporation experiments. For this purpose [$^{14}COOCH_3$]-secodine was employed and its conversion to the presecamines was evaluated by isolation and characterization of these dimeric compounds. In the maximum time required (2 hr) for the plants to absorb the radioactive solution, we could show that the mixture contained 61% secodine, 32% dimeric compounds, and 7% "baseline" material. These results established that secodine could be administered, under controlled conditions, to the plants while it was still in the "monomeric" state. Tables 3 and 4 summarize our results with tritium-labeled secodine.

The results outlined in Tables 3 and 4 were much more encouraging than those concerning 16,17-dihydrosecodin-17-ol. Indeed, it appeared that secodine showed a low but definite incorporation into a number of the alkaloids isolated, and in two plant systems, *V. rosea* L. (vindoline, 0.01–0.02%) and *A. pyricollum* (apparicine, 0.01%),

TABLE 3

RESULTS OF INCORPORATION OF [ar^{3}H]-SECODINE INTO DIFFERENT PLANT SYSTEMS[a]

Expt.	Plant fed	Feeding time (hr)	Activity fed (dpm)	% Incorporation into alkaloid isolated		
				Catharanthine	Vindoline	Ajmalicine
1	*V. rosea*	216	3.3×10^8	<0.001	0.01	<0.001
2	*V. rosea*	216	1.2×10^8	<0.001	0.02	<0.001
				Vincamine	Minovine	
3	*V. minor*	24	3.4×10^8	<0.001	<0.001	
4	*V. minor*	96	2.6×10^8	0.001	0.001	
5	*V. minor*	96	2.5×10^8	<0.001	<0.001	
6	*V. minor*	95	2.1×10^8	0.001	0.001	
				Apparicine	Uleine	
7	*A. pyricollum*	120	2.6×10^8	0.01	0.003	

[a] See Table 4 for other experimental details.

TABLE 4

SPECIFIC ACTIVITIES ASSOCIATED WITH EXPERIMENTS IN TABLE 3

Expt.	Feeding method	Specific activity fed (dpm/mmole)	Specific activity isolated (dpm/mmole)		
			Catharanthine	Vindoline	Ajmalicine
1	Wick[a]	2.83×10^{10}	1.28×10^5	1.10×10^6	4.25×10^4
2	Wick	2.83×10^{10}	2.55×10^4	7.54×10^5	9.61×10^3
			Vincamine	Minovine	
3	Hydroponic	2.83×10^{10}	4.67×10^4	2.76×10^5	
4	Hydroponic	2.83×10^{10}	9.49×10^4	2.03×10^5	
5	Hydroponic[b]	2.83×10^{10}	5.31×10^4	2.00×10^5	
6	Hydroponic	2.83×10^{10}	9.98×10^4	1.84×10^5	
			Apparicine	Uleine	
7	Hydroponic	1.82×10^{10}	7.68×10^5	1.10×10^6	

[a] In all experiments except 5, XXV was fed as the acetate salt. Full experimental details will be published later.

[b] Compound fed as Tween 20 suspension.

containing rather different alkaloid families reasonable incorporations were observed. For this reason further experiments were carried out using doubly labeled secodine. These experiments are summarized in Tables 5 and 6.

Table 5 reveals that in the three plant systems studied there is essentially no change in the ratio of ^{3}H to ^{14}C activity in the various alkaloids isolated. First of all these data indicate that significant exchange or loss of tritium in the indole ring does not occur

TABLE 5

RESULTS OF INCORPORATION OF [ar-^{3}H, $^{14}COOCH_3$]-SECODINE INTO DIFFERENT PLANT SYSTEMS[a]

Expt.	Plant fed	Ratio of activity fed (^{3}H/^{14}C)	Ratio of activity isolated (^{3}H/^{14}C)
1	*V. rosea*	8.8	Vindoline 8.3
2	*V. minor*	8.4	Vincamine 8.6 Minovine 10.1
3	*A. pyricollum*	8.7	Apparicine 8.4

[a] In all experiments the acetate salt was fed. Full experimental details will be published later.

TABLE 6

INCORPORATION OF [$^{14}COOCH_3$, 3,14,15,21-^{3}H]-SECODINE INTO DIFFERENT PLANT SYSTEMS

Expt.	Plant fed	Ratio of activity fed (^{3}H/^{14}C)	Ratio of activity isolated (^{3}H/^{14}C)
1	*V. rosea*	3.5	Vindoline 1.4[a]
2	*A. pyricollum*	4.2	Apparicine 2.2[b]

[a] This value corresponds to 60% loss of tritium.
[b] This value corresponds to 48% loss of tritium.

during biosynthesis, confirming a previous result observed with tryptophan (*28*), and establishing the validity of the experiments in Tables 3 and 4. Second, it is also clear that the indole portion of the secodine unit is not altered to a significant extent during its incorporation into the plant alkaloids. Additional information which establishes the correctness of this prediction at least for vindoline comes forth from the degradation of this radioactive alkaloid as obtained in Expt. 1, Fig. 6. Figure 7 outlines the degradation scheme which we employed. The expected and obtained retention of activity in the isolated formaldehyde unit indicates that the ester function in secodine also becomes this functionality in vindoline. The virtual identity in the ratios shown in Table 5 is then explicable only if little or no alteration occurs in this portion of the molecule during its utilization in the biosynthesis.

The biosynthetic elaboration of secodine to the various alkaloids requires the appropriate bond-making processes formally outlined in Figs. 4 and 5. Regardless of the exact nature of these operations, the piperidine ring in secodine must be involved in some manner and the unit XVII (Fig. 5) is only one possible alternative. Table 6 presents the results of two experiments which provide some preliminary information in this direction. Experiment 1 illustrates that approximately 60% loss of tritium occurs in the piperidine ring during the conversion of secodine to vindoline while only 48% loss is noted in the biosynthesis of apparacine. Obviously this difference is related to

the overall alterations which must prevail in the later stages of the biosynthetic pathway leading to these alkaloids. More definite comments concerning these aspects must await further experiments with other doubly labeled secodine intermediates, some of which are already under way in our laboratory.

Finally, we wish to mention that the experiments in *A. pyricollum* concerning apparicine (XXVII) and uleine (XXVIII) have interesting implications which are rather

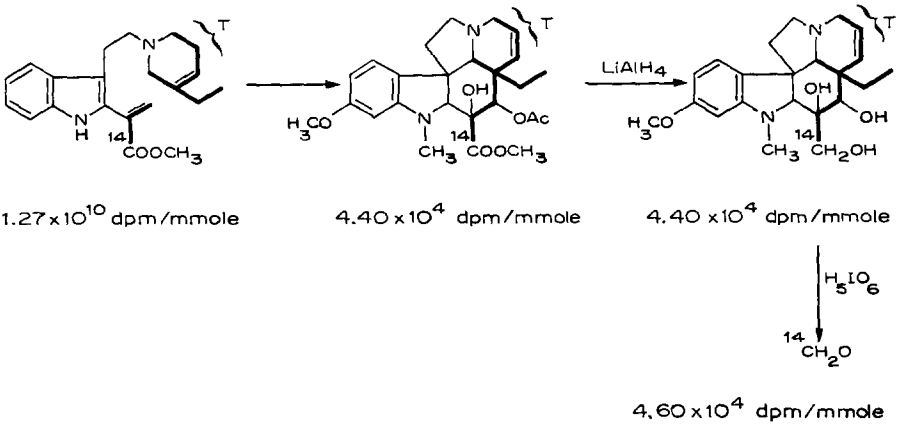


FIG. 7. Degradation of vindoline from incorporation of [$^{14}COOCH_3$, 3,14,15,21-^{3}H]-secodine.

different from those discussed for the normal *Aspidosperma* and *Iboga* bases. One of the unique features of these natural products is the apparent absence of the two carbon side chain normally associated with the tryptophan-derived alkaloids. It has been necessary in some of our previous work (*28*) to question some of the published postulates and the additional results now presented would appear to cast doubt on yet another hypothesis which has been recently proposed (*30*). This latter suggestion requires a loss of the ester group in secodine during its eventual elaboration to apparicine, a situation which is not compatible with the results obtained in our present investigations. However, we wish to perform some additional experiments before making any more definitive comments in this regard.

ACKNOWLEDGMENTS

Financial aid from the National Research Council of Canada is gratefully acknowledged. We express our thanks to Professor Carl Djerassi, Stanford University, and Dr. Benjamin Gilbert, Rio de Janeiro, for samples of the alkaloids apparicine and uleine. Dr. Gilbert was also very helpful in collecting the seeds of *A. pyricollum* and we thank him for his cooperation.

REFERENCES

1. G. BARGER AND C. SCHOLZ, *Helv. Chim. Acta* **16**, 1343 (1933).
2. G. HAHN, E. KAPPES, AND H. LUDWIG, *Chem. Ber.* **67**, 686 (1934).
3. G. HAHN AND H. WERNER, *Justus Liebigs Ann. Chem.* **520**, 123 (1935).
4. R. ROBINSON, "The Structural Relations of Natural Products." Oxford Univ. Press, London, 1955.
5. R. B. WOODWARD, *Nature, London* **162**, 155 (1948).
6. R. B. WOODWARD, *Angew. Chem.* **68**, 13 (1956).

7. E. WENKERT AND N. V. BRINGI, *Experientia* **15**, 165 (1959).
8. E. WENKERT AND N. V. BRINGI, *J. Amer. Chem. Soc.* **81**, 1474 (1959).
9. E. WENKERT, *J. Amer. Chem. Soc.* **84**, 98 (1962).
10. R. THOMAS, *Tetrahedron Lett.*, 544 (1961).
11. For a recent review and collection of references, see A. I. SCOTT, *Accounts Chem. Res.* **3**, 151 (1970).
12. J. P. KUTNEY AND E. PIERS, *J. Amer. Chem. Soc.* **86**, 953 (1964).
13. J. P. KUTNEY, R. T. BROWN, AND E. PIERS, *J. Amer. Chem. Soc.* **86**, 2286 (1964).
14. J. P. KUTNEY, R. T. BROWN, AND E. PIERS, *J. Amer. Chem. Soc.* **86**, 2287 (1964).
15. A. CAMERMAN, N. CAMERMAN, J. P. KUTNEY, E. PIERS, AND J. TROTTER, *Tetrahedron Lett.*, 637 (1965).
16. J. P. KUTNEY, K. K. CHAN, A. FAILLI, J. M. FROMSON, C. GLETSOS, AND V. R. NELSON, *J. Amer. Chem. Soc.* **90**, 3891 (1968).
17. J. P. KUTNEY, E. PIERS, AND R. T. BROWN, *J. Amer. Chem. Soc.* **92**, 1700 (1970).
18. J. P. KUTNEY, R. T. BROWN, E. PIERS, AND J. R. HADFIELD, *J. Amer. Chem. Soc.* **92**, 1708 (1970).
19. J. P. KUTNEY, W. J. CRETNEY, J. R. HADFIELD, E. S. HALL, V. R. NELSON, AND D. C. WIGFIELD, *J. Amer. Chem. Soc.* **90**, 3566 (1968).
20. J. P. KUTNEY, C. EHRET, V. R. NELSON, AND D. C. WIGFIELD, *J. Amer. Chem. Soc.* **90**, 5929 (1968).
21. A. I. SCOTT, 2nd Natural Product Symposium, Jamaica, Jan. 1968; A. A. QURESHI AND A. I. SCOTT, *Chem. Commun.*, 948 (1968).
22. A. I. SCOTT, P. C. CHERRY, AND A. A. QURESHI, *J. Amer. Chem. Soc.* **91**, 4932 (1969).
23. In a recent private communication (Nov. 1970), Professor Scott has kindly informed us that they have confirmed the conversion, tabersonine → vindoline and catharanthine in *V. rosea* plants (ca. 0.05% incorporation).
24. While our synthetic work in the inactive series was essentially complete, another synthetic route to this compound was reported, A. R. BATTERSBY AND A. K. BHATNAGAR, *Chem. Commun.*, 193 (1970). These workers also showed that this substance is a natural product in *Rhazya orientalis*.
25. Monomeric secodine-type alkaloids have also been reported from *Rhazya stricta* and *R. orientalis*, G. A. CORDELL, G. F. SMITH, AND G. N. SMITH, *Chem. Commun.*, 189 (1970). The numbering system and nomenclature for XXIV and XXV is that given in this paper.
26. Tetrahydrosecodine has been synthesized and shown to be present in *Rhazya orientalis*, R. T. BROWN, G. F. SMITH, K. S. J. STAPLEFORD, AND D. A. TAYLOR, *Chem. Commun.*, 190 (1970).
27. J. P. KUTNEY, J. F. BECK, V. R. NELSON, AND R. S. SOOD, *J. Amer. Chem. Soc.* **93**, 255 (1971).
28. J. P. KUTNEY, V. R. NELSON, AND D. C. WIGFIELD, *J. Amer. Chem. Soc.* **91**, 4278, 4279 (1969).
29. G. A. CORDELL, G. F. SMITH, AND G. N. SMITH, *Chem. Commun.*, 191 (1970).
30. A. AHOND, A. CAVE, C. KAN-FAN, Y. LANGLOIS, AND P. POTIER, *Chem. Commun.*, 517 (1970).