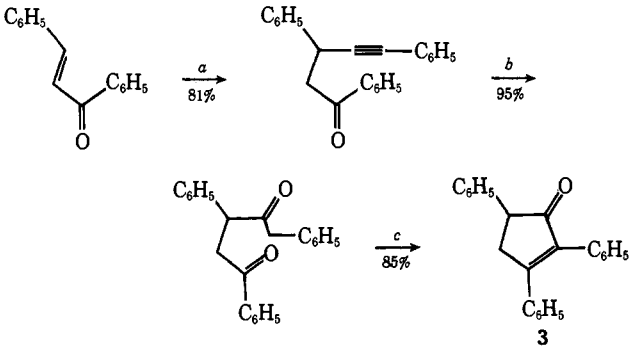
taining the temperature below *ca.* 15°. After stirring the suspension for 15 min at 20°, 15 ml of dry ether was added. Then a solution of 80 mmol of diethylaluminum chloride (Alfa Inorganics, Inc.) in 20 ml of ligroin was added to the cooled (*ca.* 15°) suspension, followed by an additional 60 ml of ligroin. After stirring for 30 min at *ca.* 25°, the precipitate of LiCl was allowed to settle. To the decanted supernatant[14] was added a solution of 8.32 g (40 mmol) of benzalacetophenone in 15 ml of ether–ligroin (3:1) at 25°, and the mixture was stirred for 4 hr. After slowly pouring into a mixture of ice–concentrated HCl, the organic layer was cooled, and afforded, after crystallization, 10 g (81%) of 1,3,5-triphenylpent-4-yn-1-one, mp 93.5–94.5°. *Anal.* Calcd for $C_{23}H_{18}O$: C, 89.00; H, 5.85. Found: C, 88.78; H, 6.06.

Using benzalacetophenone as an example, the synthesis of cyclopentenone **3** by chain extension, specific hydration,[1] and cyclization (Scheme I), in 65% yield (with

Scheme I



[a] $Et_2AlC{\equiv}CC_6H_5$, N_2, 4 hr, 25°. [b] $HgSO_4$ (3 mol %), 4 drops of concentrated H_2SO_4, 10:1 EtOH–H_2O, 14-hr reflux. [c] NaOH (4%) in MeOH, N_2, 1-hr reflux.

isolation of each intermediate[15] and no attempt at optimization), demonstrates the usefulness of this method.[16] In concert with the Stork–Borch hydration method,[1] a variety of other useful structures (*e.g.*, furans, pyrroles) also become easily accessible from acetylene precursors.

Acknowledgment. We thank the National Research Council of Canada and the University of Alberta for financial support.

(14) The enone may be introduced directly into the heterogeneous reaction mixture without significantly diminishing the yield of conjugate addition product.

(15) See footnote *b*, Table I.

(16) For syntheses of *cis*-jasmone from γ-ketoacetylenes, see G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 936 (1964); J. E. McMurry and T. E. Glass, *Tetrahedron Lett.*, 2578 (1971).

(17) Holder of a 1967 (Centennial) Science Scholarship.

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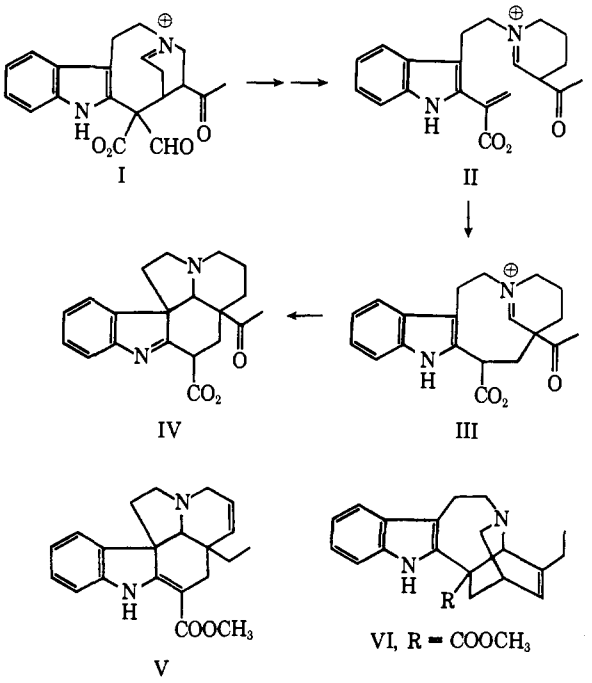
Studies on Indole Alkaloid Biosynthesis. VII.[1] The Later Stages of Aspidosperma Alkaloid Biosynthesis

Sir:

Although numerous investigations on the earlier stages of Aspidosperma alkaloid biosynthesis are now available,[2] experimental data on many aspects of the later stages are as yet lacking. Wenkert[3] proposed that the Strychnos skeleton (I) was a precursor of the Aspidosperma series and invoked the intermediacy of appropriate acrylic acid (II) and nine-membered ring (III) intermediates in the overall conversion, Strychnos (I) → Aspidosperma (IV). Our previous investigations in *Vinca rosea* L.[4] and *Vinca minor* L.[5] plants suggested that the transannular cyclization III → IV did not appear to be a required *in vivo* pathway. On the other hand, in an elegant series of experiments in *V. rosea* seedlings,



Scott[6,7] provided support for Wenkert's implication of the Strychnos skeleton by demonstrating that stemmadenine, a reduced form of I, is incorporated into the Aspidosperma alkaloids. In our respective studies,[4,6] designed to attain rather different objectives, we were able to demonstrate the *in vivo* conversion, tabersonine (V, Aspidosperma) → catharanthine (VI, Iboga),[8] a process which required a substantial rearrangement of the tabersonine molecule. Attempts to rationalize these and other results[5–7] implicated the acrylic ester derivative VII as a possible intermediate in these biosynthetic conversions. It is clear that VII is a close relative of the intermediate II previously proposed by Wenkert and it also relates directly to the more recently isolated secodine family (for example, IX).[9–11] Bat-

(1) Part VI: J. P. Kutney, J. F. Beck, V. R. Nelson, and R. S. Sood, *J. Amer. Chem. Soc.*, **93**, 255 (1971).

(2) For a recent review, see A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).

(3) E. Wenkert, *J. Amer. Chem. Soc.*, **84**, 98 (1962).

(4) J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, V. R. Nelson, and D. C. Wigfield, *ibid.*, **90**, 3566 (1968).

(5) J. P. Kutney, C. Ehret, V. R. Nelson, and D. C. Wigfield, *ibid.*, **90**, 5929 (1968).

(6) A. I. Scott, 2nd Natural Product Symposium, Jamaica, Jan 1968; A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 948 (1968).

(7) A. I. Scott, P. C. Cherry, and A. A. Qureshi, *J. Amer. Chem. Soc.*, **91**, 4932 (1969).

(8) In a private communication, Professor Scott has informed us that they have confirmed our results concerning the conversion, tabersonine → vindoline and catharanthine in *V. rosea* plants (both *ca.* 0.05% incorporation).

(9) G. A. Cordell, G. F. Smith, and G. N. Smith, *Chem. Commun.*, 189, 191 (1970).

(10) R. T. Brown, G. F. Smith, K. S. J. Stapleford, and D. A. Taylor, *ibid.*, 190 (1970).

(11) A. R. Battersby and A. K. Bhatnagar, *ibid.*, 193 (1970).

Table I. Results of Incorporation of 16,17-Dihydrosecodin-17-ol and Secodine into Vindoline[a]

Expt no.	Compound fed	% incorporation	Ratio of activity fed ($^3H/^{14}C$)	Ratio of activity isolated ($^3H/^{14}C$)
1	[ar-^{3}H]-16,17-Dihydrosecodin-17-ol (IX)	<0.001		
2	[ar-^{3}H]Secodine (VIII)	0.01		
3	[ar-^{3}H]Secodine	0.02		
4	[ar-^{3}H,^{14}COOCH$_3$]-Secodine	0.04 (^{14}C), 0.04 (^{3}H)	8.8	8.3
5	[3,14,15,21-^{3}H,-^{14}COOCH$_3$]Secodine	0.03 (^{14}C), 0.01 (^{3}H)	3.5	1.4
6	[19-^{3}H,^{14}COOCH$_3$]-Secodine	0.07 (^{14}C), 0.06 (^{3}H)	1.54	1.35

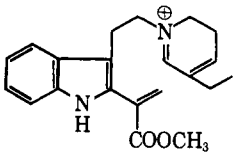
[a] See Table II for other experimental details.

to vindoline. From experiment 4 it is clear that there was essentially no change in the ratio of activity in the isolated alkaloid from that originally administered *via* the doubly labeled secodine molecule. This result suggested that significant exchange or loss of tritium in the indole ring does *not* occur during biosynthesis. Verification of this prediction came forth from the degradation of the radioactive alkaloid as obtained from the incorporation of the various doubly labeled secodine molecules. The retention of all carbon-14 activity in the isolated formaldehyde unit indicates that the ester function in secodine also becomes this functionality in vindoline. Furthermore this result, when coupled with the $^3H/^{14}C$ ratio thus obtained for this alkaloid (expt 4), establishes that the indole

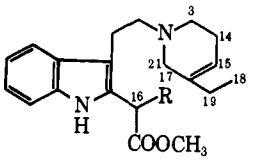
Table II. Specific Activities Associated with the Experiments in Table I

Expt no.	Activity fed		Specific activity fed		Specific activity isolated	
	^3H	^{14}C	^3H, dpm/mmol	^{14}C, dpm/mmol	^3H, dpm/mmol	^{14}C, dpm/mmol
1	1.89×10^7		8.46×10^8			
2	3.31×10^8		2.83×10^{10}			
3	1.23×10^8		2.83×10^{10}			
4	8.47×10^7	9.58×10^6	1.10×10^{10}	1.28×10^9	1.77×10^6	2.13×10^5
5	3.50×10^7	1.01×10^7	9.82×10^9	1.27×10^9	5.96×10^4	4.40×10^4
6	4.30×10^7	2.78×10^7	7.61×10^9	4.94×10^9	3.67×10^5	2.79×10^5

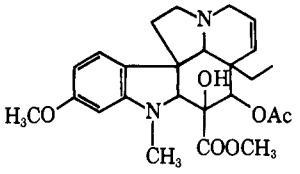
tersby also reports[11] a laboratory synthesis of IX. We



VII



VIII, R = CH_2
IX, R = CH_2OH



X

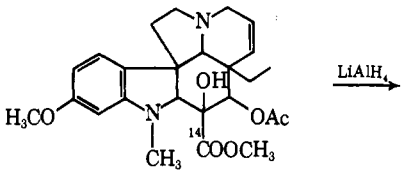
wish to present some of our recent findings concerning the relevance of such intermediates in the later stages of Aspidosperma alkaloid biosynthesis.

Radioactively labeled forms of 16,17-dihydrosecodin-17-ol (IX) and secodine (VIII) available from synthetic studies in our laboratory[12] were administered *via* the cotton wick technique to *V. rosea* plants. All experiments were conducted over a 9-day period and the acetate salts of the labeled compounds were employed. In each instance the alkaloid vindoline (X) was isolated. The results of the various experiments are presented in Table I.

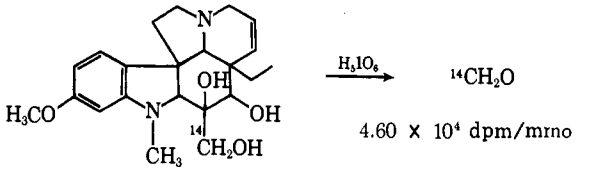
As Table I reveals, 16,17-dihydrosecodin-17-ol is not incorporated into vindoline, a result similar to that observed with vincamine and minovine in *V. minor*,[1] while secodine is utilized effectively by the plant. Experiments 4–6 provide an informative set of results in terms of the biosynthetic conversion of secodine

(12) J. P. Kutney, J. F. Beck, C. Ehret, G. A. Poulton, R. S. Sood, and N. D. Wescott, *Bioorg. Chem.*, 1, 194 (1971).

portion of the secodine molecule is incorporated into vindoline with little or no alteration.



4.40 × 10^4 dpm/mmol



4.60 × 10^4 dpm/mmo

4.40 × 10^4 dpm/mmol

Experiment 6 provides the important result that the *entire* secodine molecule is incorporated intact during its conversion to vindoline. The retention of the $^3H/^{14}C$ ratio in the isolated alkaloid is compatible only with this situation.

The biosynthetic elaboration of VIII to vindoline requires a series of bondmaking processes. Even though the exact nature of these operations is presently unknown, the piperideine unit in VIII must be involved in some manner. Experiment 5 provides some preliminary information in this direction. The reduction in the ratio from 3.5 to 1.4 corresponds to a 60% loss of tritium from the piperideine portion of the secodine molecule.

In conclusion, the above results demonstrate that secodine is specifically and completely incorporated into the Aspidosperma alkaloid, vindoline. These re-

sults, when considered in conjunction with our other published[1,12] and unpublished observations in several different plant species and involving completely different indole alkaloid families, suggest that there probably exists a biointermediate with structural features resembling secodine which plays a central role in the later stages of many indole alkaloid biosynthetic pathways. Obviously some of the results already suggest that a secodine derivative possessing a higher oxidation level in the piperideine unit, for example VII or its isomers, may be a better representation of the biointermediate. However, the high instability associated with dihydropyridine derivatives will provide considerable difficulty in isolation and utilization of such systems for biosynthetic studies. Additional support for the above postulates will be published shortly.

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Scheme I

$$Ar_2C{=}O \xrightarrow[\text{reflux 5 days}]{(CF_3CO)_2O,\ T_2O} Ar_2C{=}O \text{ (ring tritiated)}$$

$$Ar_2C{=}O \xrightarrow[n\text{-PrOH, reflux 2 hr}]{\text{excess } LiBH_4\ 90\%\ \text{yield}} Ar_2CHOH$$

(mp 67–68°, from MeOH)

$$Ar_2CHOH \xrightarrow[\text{reflux 0.5 hr, 83\% yield}]{CH_3COCl,\ \text{benzene}} Ar_2CHCl$$

(mp 80–81°, from hexane)

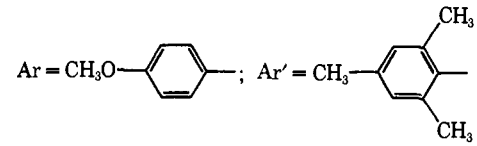
$$Ar'COOH \xrightarrow[AgNO_3]{NH_4OH} Ar'COOAg$$

$$Ar_2CHCl + Ar'CO_2Ag \xrightarrow[20\ \text{hr, 85\% yield}]{\text{benzene, reflux}} Ar_2CHO_2CAr'$$

(mp 76–77°, from petroleum ether)

$$Ar_2CHCl \xrightarrow[\text{aq acetone}]{NaN_3} Ar_2CHN_3 \text{ (mp 46–47°, from MeOH)}$$

$$Ar_2CHCl \xrightarrow{MeOH} Ar_2CHOMe \text{ (mp 33.5–34°, from petroleum ether)}$$



Cation–Anion Combination Reactions. VI. Trapping of Solvolysis Reaction Intermediates with Azide Ion

Sir:

In the previous papers of this series[1] and in further work under way, we have found that the selectivities of a wide range of cations toward nucleophiles are independent of the nature of the cation (*i.e.*, aryldiazonium, triarylmethyl, and tropylium ions show the same selectivities toward a series of nucleophiles). This finding appeared to be in conflict with the results of many studies involving the trapping of intermediates in solvolysis reactions,[2] in which the selectivities toward nucleophiles vary considerably among various reactants. For example, Swain[3] found that the intermediate in the solvolysis of trityl compounds shows greater reactivity with azide than with hydroxide ions, while the reverse is true for benzhydryl compounds. More recently, both Sneen[4] and Schleyer[5] have shown that there exists a reactivity–selectivity relationship in the trapping of solvolysis intermediates by azide ion and solvent.

I wish to report the results of a preliminary study of the solvolysis and azide trapping in the methanolysis of *p,p'*-dimethoxybenzhydryl mesitoate which resolves the conflict of the earlier studies and provides a simple and rational explanation of the selectivity–reactivity relationships explored by Sneen and Schleyer.

The syntheses of ester, tritium-labeled ester, and other compounds used are summarized in Scheme I.

The solvolysis reaction in methanol could be followed by observing the change in absorbance in the ultraviolet spectrum of the methanol solution of the ester. Using this direct method, high precision (*i.e.*, precision was about ±5% in rate constant) of rate measurement was not possible because the changes in absorbance were not great. Much better precision was obtained using added *p*-nitrophenoxide ion as an indicator. Since the p*K*'s of mesitoic acid (p*K* = 8.69) and *p*-nitrophenol (p*K* = 11.15) in methanol are quite different, the use of a slight excess of *p*-nitrophenoxide ensures virtually complete reaction of the mesitoic acid to form *p*-nitrophenol. The results of the kinetic studies are summarized in Table I.

The kinetic studies show that: (1) the addition of *p*-nitrophenoxide indicator does not change the rate of methanolysis; (2) the addition of sodium azide does not change the rate of methanolysis; (3) the reaction, as expected, shows a small positive salt effect; and (4) there is a small mass law effect on the rate of reaction.

Under the conditions used to establish that added azide did not influence the rate of reaction, the observed loss of *p*-nitrophenoxide absorption showed that approximately 90% of the product was the benzhydryl azide. The fact that no further changes in absorption occurred over a period of 24 hr shows that the products are stable under reaction conditions.

The product distributions resulting from methanolyses of the ester in the presence of azide ion were determined by isotope dilution techniques. A carefully measured volume of a solution of the tritiated ester in heptane was added to a buffered methanolic solution of sodium azide. The reaction was allowed to proceed at ambient temperature for ten half-lives of the methanolysis reaction. A carefully weighed quantity of *p,p'*-dimethoxybenzhydryl azide or methyl ether was then dissolved in the reaction solution and reisolated by dilution with water and extraction into pentane. The isolated

(1) C. D. Ritchie and P. O. I. Virtanen, *J. Amer. Chem. Soc.*, in press.
(2) L. C. Bateman, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 974, 979 (1940).
(3) C. G. Swain, C. B. Scott, and K. H. Lohmann, *J. Amer. Chem. Soc.*, 75, 136 (1953).
(4) R. A. Sneen, J. V. Carter, and P. S. Kay, *ibid.*, **88**, 2594 (1966).
(5) D. J. Raber, J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *ibid.*, **93**, 4821, 4829 (1971). I thank Professor Schleyer for allowing me to read this work prior to publication.