Partial Synthesis and Isolation of Vincoside and Isovincoside: Biosynthesis of the Three Major Classes of Indole Alkaloids from the β-Carboline System

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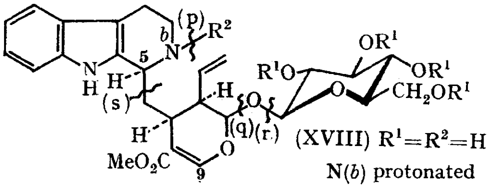
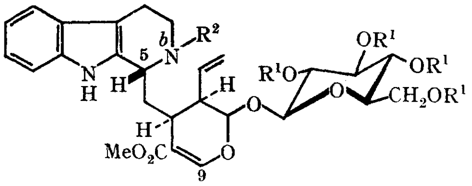
THE main features are now known of the pathway from mevalonate through geraniol and loganin (I)† to secologanin (II) which then serves as precursor of the non-tryptamine units present in the three large classes of indole alkaloids.[1,2] Attention is now focussed on the processes whereby the tryptamine unit is introduced for assembly of the *Corynanthe* [*e.g.* (IV)], *Aspidosperma* [*e.g.* (VI)] and *Iboga* [*e.g.* (VIII)] families by reactions taking place with or without rearrangement.

Tryptophan is incorporated specifically into indole alkaloids[3] and it seemed probable, by analogy with dihydroxyphenylalanine,[4] that decarboxylation occurs first to yield tryptamine which is then utilised. It was essential to gain support for this sequence before plans for the synthetic work described below were on a secure basis. When generally ^{3}H-labelled tryptamine hydrochloride was fed to *Vinca rosea*, the incorporations recorded in the Table were obtained. Accordingly, tryptamine was used with confidence in the following experiment.



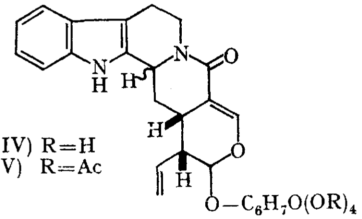
(XVIII) $R^1=R^2=H$
N(*b*) protonated

(XIX) $R^1=R^2=Ac$ (XX) $R^1=H$, $R^2=Ac$

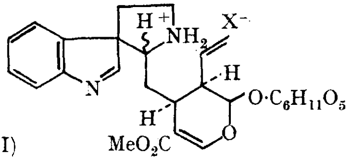


(XXI) $R^1=R^2=H$, N(*b*) protonated
(XXII) $R^1=R^2=Ac$ (XXIII) $R^1=H$,$R^2=Ac$

Secologanin[2] (II) reacted with tryptamine to generate the β-carbolines (XVIII) and (XXI) which yielded crystalline hydrochlorides. Acetylation gave the corresponding penta-acetyl derivatives (XIX) and (XXII) which showed virtually



(XXIV) R=H
(XXV) R=Ac



(XXVI)

identical spectroscopic properties apart from optical rotation, $[\alpha]_D$ − 126° and −75° ($CHCl_3$) respectively. The u.v. spectra of (XIX) and (XXII) corresponded to the sum of indolic and $O–C=C–CO_2Me$ chromophores, the i.r. spectra showed the indolic NH, acetate ester, αβ-unsaturated ester and amide residues (ν_{max} 3450, 1750, 1695, and 1635 $cm.^{-1}$), and the n.m.r. spectra supported all the main features, particularly the CO_2Me (τ 6·30), 4 aromatic protons and 5 acetyl groups. Removal of the *O*-acetyl groups from (XIX) and (XXII) by Zemplen's method generated the *N*-acetyl derivatives (XX) and (XXIII), m.p. 179° and 171°. Confirmation of the structures (XIX) and (XXII) came from the mass spectra which displayed the parent ion (*m/e* 740) and ions at *m/e* 697, 393, 392, 331, 213 and 171 corresponding to the fragmentations (p), (q), (r), (s), and (p + s), see (XIX). Similarly, the mass spectra of (XX) and (XXIII) showed the parent ion (*m/e* 572) and fragment ions at *m/e* 529, 392, 213, and 171.

Further support for the structures of the β-carbolines was obtained by basification of a

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† One set of formulae is used for this and the preceding Communication.

mixture of (XVIII) and (XXI), when one lactam (XXIV) was formed, M^+ 666. The corresponding tetra-acetate (XXV) showed $[\alpha]_D + 38°$ ($CHCl_3$), its u.v. spectrum was very similar to that of the β-carbolines (XIX) and (XXII), and the i.r. spectrum showed the expected changes in carbonyl absorption (ν_{max} 1740, 1655 cm.$^{-1}$). No *O*-methyl signal was present in the n.m.r. spectrum which otherwise was broadly similar to those of (XIX) and (XXII).

The products from a short reaction of secologanin (II) with tryptamine contained, in addition to (XVIII) and (XXI), an unstable substance which lacked appreciable indolic absorption (λ_{max} 214, 254, and weak at 299 mμ); this material generated the β-carbolines (XVIII) and (XXI) by being kept in solution or more rapidly on treatment with acid. These properties are those expected of the indolenine (XXVI); isolation is in progress.

The β-carbolines (XVIII) and (XXI) were prepared in labelled form by repetition of the foregoing work with [*O-methyl*-^{3}H]secologanin[2] (II) and they were fed in admixture to *Vinca rosea* shoots; it was proved that no secologanin was present with the β-carbolines. Incorporations into alkaloids representing all three classes of indole alkaloids were obtained (Table).

Incorporations into alkaloids of Vinca rosea

Experiment	Precursor	Ajmalicine (IV)	Serpentine (VI)	Vindoline (VI)	Catharanthine (VIII)	Perivine (IX)
1	[^{3}H]Tryptamine	0·26	2·79	0·39	0·61	0·053
2	[*O-methyl*-^{3}H]Vincoside and isovincoside, (XVIII) and (XXI)	0·47	3·91	0·57	0·84	0·056
3	Doubly labelled vincoside and isovincoside; ratio of labels[a] 1·44 : 1	0·65	1·28	0·31	0·41	0·037
	Ratio found in alkaloids from expt. 3	1·41 : 1	1·43 : 1	1·48 : 1	1·45 : 1	1·46 : 1

[a] Ratio reported is *O*-methyl label : tryptamine label.

Refinement of the tracer experiment was made by preparing doubly-labelled β-carbolines from [*O-methyl*-^{3}H]secologanin and generally labelled [^{3}H]tryptamine. Again, good incorporations into the alkaloids were achieved (Table) and suitable degradation showed that the biosynthesis had occurred without appreciable change in the ratio of the labels present in the indolic and secologanin parts of the β-carboline system (Table). Accordingly, the name vincoside will be used for the β-carboline (XVIII) and isovincoside for (XXI)

Secologanin (II), vincoside (XVIII) and isovincoside (XXI) were sought by dilution analysis in *Vinca rosea* plants which had previously taken up [5-^{3}H]loganin[5] (I); radio-inactive specimens of the three materials were added as carriers. The isolated secologanin fraction was condensed with 3,4-dihydroxyphenethylamine and the activity of the resultant ipecoside[2] (X) corresponded to >6% incorporation from loganin into secologanin (II). Acetylation of the β-carboline fraction gave the penta-acetates of vincoside and isovincoside which were converted separately into the corresponding crystalline *N*-acetyl derivatives (XX) and (XXIII), incorporation both 1·5%.

The foregoing work demonstrates (*a*) that secologanin (II), vincoside (XVIII), and isovincoside (XXI) are present in *Vinca rosea* plants in accord with the earlier proposal[1,‡] (*b*) that all three are efficiently labelled from loganin as precursor, and (*c*) that specific incorporation occurs of one or both β-carbolines (XVIII) and (XXI) into the three types of alkaloids. The relatively high incorporation of a β-carboline system into unrearranged (IV) and rearranged [(VI) and (VIII)] skeletons is of considerable interest. Conversion of vincoside (XVIII) into the *Corynanthe* group [*e.g.* (IV)] requires straightforward steps. However, an early stage in the rearrangement processes leading to the *Aspidosperma* (VI) and *Iboga* (VIII) systems could be the formation of the pentacyclic *Strychnos* system.[6,8] If so, conversion of (XVIII)

[‡] The possibility that these skeletons are entirely present in the plants as the *N*-acetyl derivative was eliminated by a separate extraction of *Vinca rosea* with chromatographic control using (XVIII) (XX), (XXI), and (XXIII). G. N. Smith (Manchester) reported at the I.U.P.A.C. Meeting, London, July, 1968, that a glycoside, shown to have structure (XVIII) without stereochemical implications, has been isolated from *Rhazia stricta* and in work with R. T. Brown and J. K. S. Stapleford, [^{3}H]loganin has been shown to be incorporated into it. *Added in proof:* Penta-acetylvincoside, identified by comparison with the material described above, has also been isolated from an acetylated extract of *V. rosea* seedlings [personal communication from Professor A. I. Scott (Sussex).]

into (XXVI) probably occurs and there are chemical analogies for this change.[7] These aspects are under investigation together with the use of (XVIII) and (XXI) for syntheses of indole alkaloids.

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[1] For review see A. R. Battersby, *Pure Appl. Chem.*, 1967, **14**, 117.

[2] A. R. Battersby, A. R. Burnett, and P. G. Parsons, preceding Communication, and references therein.

[3] *E.g.* E. Leete, *Tetrahedron*, 1961, **14**, 35.

[4] *E.g.* A. R. Battersby, and R. J. Francis, *J. Chem. Soc.*, 1964, 4078.

[5] A. R. Battersby and E. S. Hall, unpublished work.

[6] A. R. Battersby, J. C. Byrne, R. S. Kapil, P. Loew, J. A. Martin, T. G. Payne and D. Arigoni, *Chem. Comm.*, 1968, 951, and references therein.

[7] *E.g.* J. Harley-Mason and W. R. Waterfield, *Tetrahedron*, 1963, **19**, 65.

[8] A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 945, 947, 948.