Preparation and Isolation of Deoxyloganin: Its Role as Precursor of Loganin and the Indole Alkaloids

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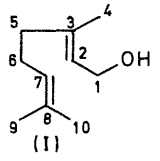
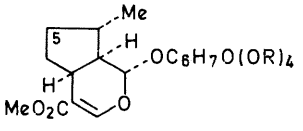
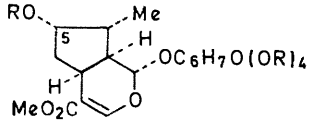
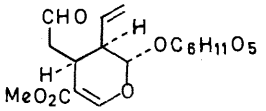
Summary Deoxyloganin is isolated from natural sources and is proved to be a biological precursor of loganin and the indole alkaloids.

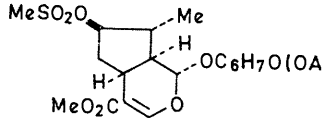
LOGANIN (IV) is established[1,2] as a key precursor of secologanin[3] (VI) and this aldehyde is converted *in vivo* into all

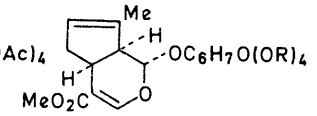

(I)

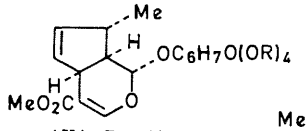

(II) R = H
(III) R = Ac

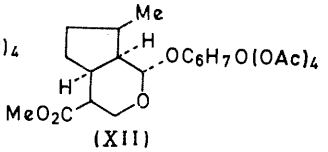

(IV) R = H
(V) R = Ac

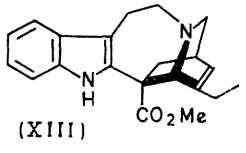

(VI)

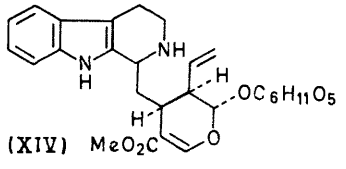

(VII)

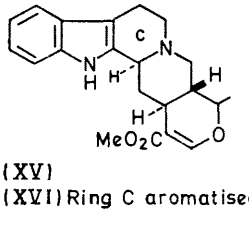

(VIII) R = H
(IX) R = Ac

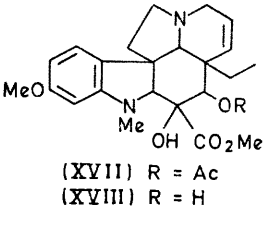

(X) R = H
(XI) R = Ac


(XII)


(XIII)


(XIV)


(XV)
(XVI) Ring C aromatised


(XVII) R = Ac
(XVIII) R = H

three major types of indole alkaloids by way of vincoside[4] (XIV). Studies of the biosynthesis of loganin have (*a*) proved that its C_{10}-skeleton is derived specifically from geraniol[1,2,5] and (*b*) determined the fate of the hydrogen atoms at positions 1,2, and 7 of geraniol during its transformation into loganin.[6] Experiments aimed to fill the gap between (I) and (IV) are outlined here and in the following communication.

It was argued from structural relations that biological insertion of the C-5 hydroxy-group of loganin is probably the last step; deoxyloganin (II) was therefore required. Inouye and his co-workers[7] had obtained this substance (bisdeoxydihydromonotropeine methyl ester) by transformation of monotropeine, but a route from readily available loganin was desirable. When *O*-mesyl-5-epiloganin tetra-acetate[5] (VII) was treated with 2,6-lutidine, the separable olefins (IX) and (XI) were obtained in 22 and 40% yield, respectively. Hydrogenation of the latter gave deoxyloganin tetra-acetate (III), m.p. 115—116°, having all constants in exact agreement with ref. 7. Olefin (IX) underwent slow hydrogenation also to yield largely (III) but of m.p. 105—110°, probably due to traces of the tetrahydro-derivative (XII) being present. The acid corresponding to (II) obtained by hydrolysis of (III), was methylated with ^{3}H-diazomethane to afford [O-*methyl*-^{3}H]deoxyloganin (II). This was administered to *Vinca rosea* shoots and gave the incorporations recorded in the Table. Proof of radiochemical purity of the alkaloids was as in earlier work and that of loganin by controlled hydrolysis of the isolated penta-acetate (constant activity) to yield loganin. After recrystallisation, this carried a constant 98% of the original activity and the activity was unchanged by reconversion of loganin into its penta-acetate. Zeisel demethylation (Table) demonstrated specific labelling of loganin and of the alkaloids. Vindoline (XVII) yielded deacetylvindoline (XVIII; 97% of the original activity) and vindolinol (XVIII; CH_2OH in place of CO_2Me) which retained only 1% of the original activity. Significant labelling is thus confined to the ester *O*-methyl group of (XVII).

In contrast, neither component of a [O-*methyl*-^{3}H]-labelled mixture of the olefins (VIII) and (X) was incorporated (Table). The labelled material was prepared from the olefins (IX) and (XI) as above for deoxyloganin. Further, no significant incorporation occurred (Table) when [O-*methyl*-^{3}H]deoxyloganin aglucone, prepared from the glucoside by cleavage with emulsin, was fed to *Vinca rosea* shoots, though further work is necessary in this case to eliminate possible penetration problems.

Deoxyloganin was shown by dilution analysis to be present in *Menyanthes trifoliata* and in *Vinca rosea* plants which had absorbed [1-^{3}H]geraniol. Large-scale extractions of the latter plant and also of fruit from *Strychnos nux vomica* both yielded deoxyloganin, identified as its crystalline tetra-acetate by full comparison with the foregoing partially synthetic material.

Deoxyloganin (II) is thus a natural product, it is derived from geraniol, and it acts as an efficient precursor of loganin (IV) and of the indole alkaloids. These results interlock

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Incorporations (%) *into loganin and alkaloids of* Vinca rosea

Expt.	Precursor	Loganin (IV)	Serpentine (XVI)	Ajmalicine (XV)	Catharanthine (XIII)	Vindoline (XVII)	Perivine
1.	[O-*methyl*-^{3}H]Deoxyloganin (II)	6·4	0·51	0·10	0·29	0·24	0·015
	% of total activity at *O*-methyl in Expt. 1 by Zeisel	99	97	98	97		
2.	[O-*methyl*-^{3}H]Olefins (VIII) and (X) ..	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001
3.	[O-*methyl*-^{3}H]Deoxyloganin aglucone ..	<0·08	<0·001	<0·001	<0·001	<0·001	<0·001

precisely with the recent findings of Inouye and his co-workers[8] who showed that deoxyloganic acid (II; CO_2H in place of CO_2Me) acts as precursor of loganin and other cyclopentane glucosides. Probably deoxyloganin is the biochemical parent of most of the cyclopentane monoterpene glucosides and this aspect and the stereochemistry of the hydroxylation step (II) → (IV) are under investigation.

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[1] A. R. Battersby, R. T. Brown, R. S. Kapil, J. A. Martin, and A. O. Plunkett, *Chem. Comm.*, 1966, 890; A. R. Battersby, R. S. Kapil, J. A. Martin, and L. Mo, *ibid.*, 1968, 133.
[2] P. Loew and D. Arigoni, *Chem. Comm.*, 1968, 137.
[3] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc.* (*C*), 1969, 1187.
[4] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc.* (*C*), 1969, 1193.
[5] A. R. Battersby, E. S. Hall, and R. Southgate, *J. Chem. Soc.* (*C*), 1969, 721.
[6] A. R. Battersby, J. C. Byrne, R. S. Kapil, J. A. Martin, T. G. Payne, D. Arigoni, and P. Loew, *Chem. Comm.*, 1968, 951; R. Guarnaccia, L. Botta, C. J. Coscia, *J. Amer. Chem. Soc.*, 1969, **91**, 204.
[7] H. Inouye, T. Arai, and Y. Miyoshi, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 888; H. Inouye and K. Fuji, *ibid.*, 901.
[8] H. Inouye, S. Ueda, Y. Aoki, and Y. Takeda, *Tetrahedron Letters*, 1969, 2351.