Preparation of Secologanin: its Conversion into Ipecoside and its Role in Indole Alkaloid Biosynthesis

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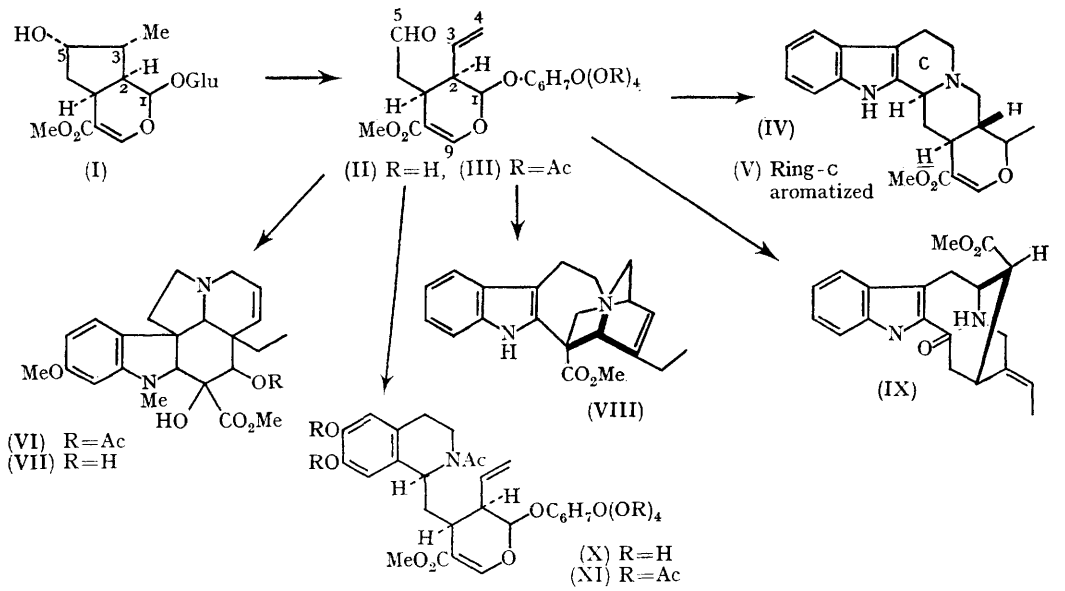
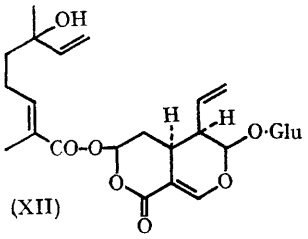
BIOGENETIC REASONING suggests that secologanin (II) is an intermediate[1] between loganin (I), an established biological precursor,[2] and the non-tryptamine portion of the indole alkaloids, *e.g.* (IV), (VI), and (VIII). The presence of residue (XIII) in the structures of foliamenthin, dihydrofoliamenthin, and menthiafolin[3,4] was therefore of considerable interest in that (XIII) represents the masked lactol form of (II). The conversion of menthiafolin (XII) into (II) is now outlined.

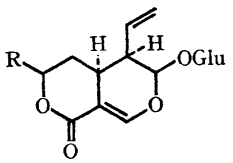
Mild alkaline hydrolysis of (XII),† under rigorous control, gave a water-soluble product which, though not fully characterised, has properties expected for the salt (XV). Release of the corresponding acid followed by methylation with diazomethane then afforded (II), $[\alpha]_D$ — 96°



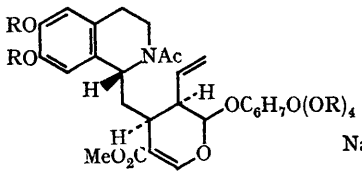
† Mixtures of menthiafolin, foliamenthin, and dihydrofoliamenthin can also be used successfully for the preparation of secologanin.



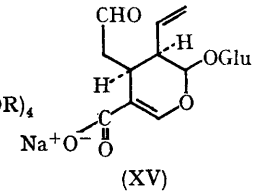
(XII)



(XIII) R=Acyl—O
(XIV) R=H



(XVI) R=Ac
(XVII) R=H



(XV)

(MeOH), ν_{max} 1700 and 1630 cm.$^{-1}$; λ_{max} 235 mμ (log ϵ 3·96). This was converted by mild acetylation into its tetra-*O*-acetate (III), $[\alpha]_D$ — 100° ($CHCl_3$), M^+ 556. The n.m.r. spectra of the glucoside (II) and its tetra-acetate (III) supported the assigned structures. That of the latter showed the following signals (τ values) with assignments: 0·35, (t, CHO), 2·62, (d, 9-H), 4·54, (dd, 3-H), 5·76 (dd) and 5·90 (dd) (CH_2OAc of glucose), 6·34, (s, CO_2Me) and four singlets 7·9—8·2 (4OAc). The glycoside (II) was readily hydrolysed by β-glucosidase in agreement with a β-glucosidic link.

The constitution (X) has recently been established[5] for ipecoside and in order to confirm both the ipecoside structure and that of secologanin (II) was condensed with 3,4-dihydroxyphenethylamine; two products were isolated after acetylation. The major product formed in 64% yield, $[\alpha]_D$ — 144° ($CHCl_3$), was identical with hexa-*O*-acetylipecoside (XI), $[\alpha]_D$ — 143° ($CHCl_3$), by full spectroscopic and chromatographic comparison. In confirmation, Zemplen *O*-deacylation yielded ipecoside (X), identical with the natural material.[6] This partial synthesis also provides a second independent proof for the structure of the seco-cyclopentane portion of menthiafolin (XII).

The minor product from the condensation reaction also yielded a hexa-*O*-acetate, $[\alpha]_D$ — 128° ($CHCl_3$), M^+ 817, which is assigned structure (XVI) on the basis of its spectroscopic properties and mode of formation. *O*-Deacetylation afforded isoipecoside (XVII), m.p. 173—174°, $[\alpha]_D$ — 164° (H_2O).

When (I) is incorporated into the indole alkaloids,[2] the *O*-methyl group is carried through to the final alkaloids[2,7] (IV), (VI), and (VIII). Labelling at the *O*-methyl group can therefore be safely used for secologanin and this was achieved by repetition of the above work with [^{3}H]diazomethane. [*O-methyl*-^{3}H]Secologanin so obtained was taken up by *Vinca rosea* shoots to yield radioactive alkaloids as follows: serpentine [(V) 0·65% incorporation], ajmalicine [(IV) 0·55% incorporation], vindoline [(VI) 0·12% incorporation], catharanthine [(VIII) 0·16% incorporation] and perivine [(IX) 0·013% incorporation]. Zeisel demethylation of ajmalicine and catharanthine proved all the radioactivity (94% and 96%, respectively) to be located at the ester methyl group. Vindoline (VI) by hydrolysis yielded desacetylvindoline [(VII); 98% of original activity] and this by reduction[8] gave the triol (VII; CH_2OH in place of CO_2Me). Less than 1% of the original activity remained in the triol, proving the label to be located at the ester methyl group of vindoline (VI). In addition, it is proved that no significant general methyl transfer occurs (since aryl *O*-methyl and *N*-methyl groups are radio-inactive) and the evidence in sum establishes the specific incorporation of secologanin (II) into the *Corynanthe*, *Aspidosperma* and *Iboga* families of alkaloids.

The incorporation of sweroside (XIV) into vindoline (VI) has recently been demonstrated[9] in *Vinca rosea* and it is probable that sweroside enters the direct pathway by biological conversion first into secologanin (II).

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[1] For a review, see A. R. Battersby, *Pure Appl. Chem.*, 1967, **14**, 117.
[2] 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 Mrs. L. Mo, *ibid.*, 1968, 133; P. Loew and D. Arigoni, *ibid.*, 1968, 137.
[3] P. Loew, Ch. v. Szczepanski, C. J. Coscia, and D. Arigoni, *Chem. Comm.*, 1968, 1276.
[4] A. R. Battersby, A. R. Burnett, and P. G. Parsons, following Communication.
[5] A. R. Battersby, B. Gregory, H. Spencer, J. C. Turner, M.-M. Janot, P. Potier, P. Francois, and J. Levisalles, *Chem. Comm.*, 1967, 219.
[6] P. Bellet, *Ann. pharm. franç.*, 1952, **10**, 81.
[7] A. R. Battersby and E. S. Hall, unpublished work.
[8] M. Gorman, N. Neuss, G. H. Svoboda, A. J. Barnes, jun., and N. J. Cone, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1959, **58**, 256.
[9] H. Inouye, S. Ueda, and Y. Takeda, *Tetrahedron Letters*, 1968, 3453.