Structure, Stereochemistry, and Biosynthesis of Loganin

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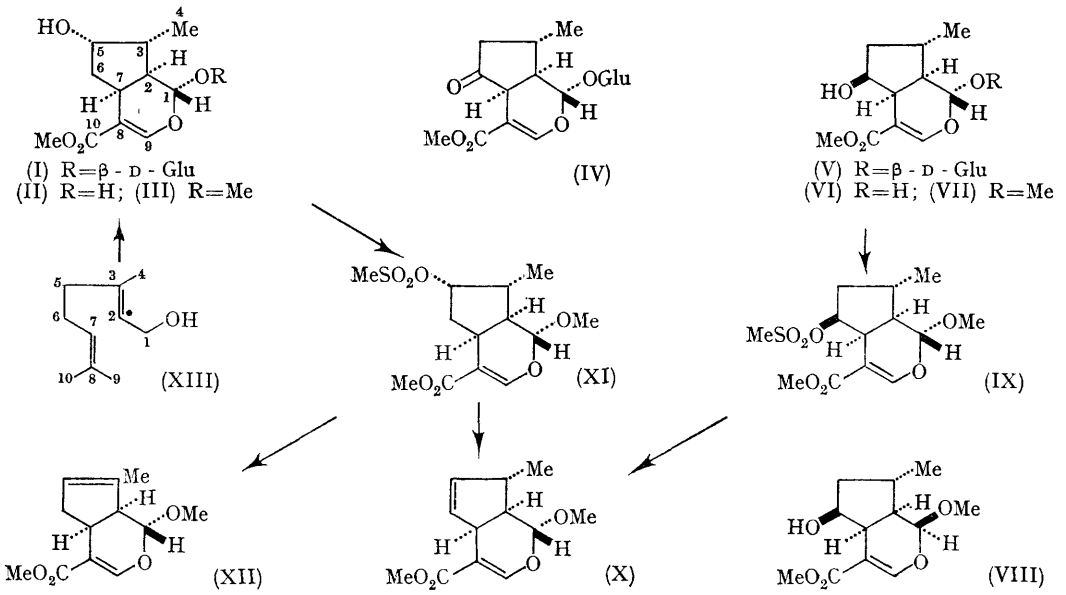
THE structure of loganin[1,2] is currently written as (I), without stereochemical assignment, and though various parts of this representation are well supported,[1,2] (I) as a whole rests heavily on biogenetic considerations. The structure had not been established nor was the stereochemistry known. With the discovery[3,4] that loganin plays a central role in the biosynthesis of the *Corynanthe*, *Iboga*, and *Aspidosperma* groups of indole alkaloids, it became essential to define the constitution precisely. This was achieved[5] in part by correlation with verbenalin.

The structure and absolute stereochemistry (IV) for verbenalin are rigorously established by chemical correlation through to primary standards.[2] Dihydroverbenalin[2] (V), prepared by reduction of verbenalin with borohydride, was hydrolysed with emulsin to afford dihydroverbenalol (VI; M^+ 228), m.p. 123—124°. This reacted with methanol and boron trifluoride etherate to yield two isomeric methyl ethers (M^+ 242) differing in configuration at C-1. The best fit of the observed chemical shifts and J-values for the C-1 protons in these isomers with published data,[6] with molecular models and the Karplus relationship, is obtained by assigning structure (VII) to that isomer in which the C-1 proton appeared as a doublet at τ 5·42 (J 4·5 c./sec.); the corresponding signal for the isomer (VIII) was at τ 5·12 (J 3·0 c./sec.). The *O*-methanesulphonyl derivative (IX) prepared from (VII) had m.p. 65—67° (M^+ 320) and was converted by hot, 2,6-dimethylpyridine into the olefin (X; M^+ 224) which showed the following important n.m.r. signals: *C*-methyl as doublet, τ 8·95 (3H, J 7 c./sec.), olefinic protons as multiplets τ 4·49 and 4·21 (1H each). Olefin (X) gave $[\alpha]_D$ + 20·9° ± 1° ($CHCl_3$).

When loganin aglucone (II) reacted with methanol and boron trifluoride etherate, it afforded almost entirely one ether (III; M^+ 242) showing an n.m.r. signal at τ 5·40 (J 4 c./sec.) which corresponds to the C-1 proton. The aglucone was converted into its *O*-methanesulphonyl derivative (XI; M^+ 320), m.p. 65—68°, which was heated with 2,6-dimethylpyridine as for the verbenalin series; two separable olefins resulted. Olefin (A) (M^+ 224) showed a broad singlet corresponding to the *C*-methyl group at τ 8·19 (allylic coupling) and a multiplet at τ 4·5 (1 olefinic proton); this evidence, taken with all other spectroscopic



and chemical data, proves olefin (A) to be (XII). The signal from the *C*-methyl group of olefin (B) (M^+ 224) was a doublet at τ 8·96 (J 7 c./sec.) and olefinic protons appeared as multiplets at τ 4·50 and τ 4·22 (1H each). This and other evidence establish structure (X) for olefin (B) which was identical with the olefin (X) prepared above from verbenalin (by n.m.r., u.v., i.r., and mass spectrometry). The loganin olefin (B) (X) showed $[\alpha]_D$ + 22·0 ± 1° ($CHCl_3$) and therefore has the same absolute stereochemistry as (X) prepared from verbenalin. Further, the two specimens of (X) gave identical o.r.d. curves (kindly determined by Prof. W. Klyne and Dr. P. M. Scopes). Structure (I) is established for loganin and the stereochemistry at C-2, -3, and -7 is also defined. Importantly, the absolute stereochemistry at C-7 of loganin is the same as that found for the corresponding position in indole alkaloids of the *Corynanthe* type[7] (including *Strychnos*) with only very rare exceptions.[8] The correct absolute stereochemistry of *Aspidosperma* and *Iboga* alkaloids can also be derived in principle by chemically plausible steps which make use of asymmetry at C-7 of loganin to dictate that of the new chiral centres formed. Detailed discussion will follow further experiments.

Two methods were used to study the stereochemistry at C-5. When the ether (III) reacted with α-phenylbutyric anhydride, the corresponding ester was formed virtually quantitatively together with (−)-α-phenylbutyric acid. Such a "partial resolution" indicates[9] that the hydroxy-group at C-5 is α-oriented. Brewster's method[10] led to the same result in that *O*-benzoylation of (III) caused a strong positive shift in rotation (Δ $[M]_D$ + 92·8°). The illustrated C-5 stereochemistry is therefore strongly supported. In keeping with this, reduction of dehydrologanin[1] by Dr. P. G. Parsons using borohydride yields as the main product an isomer of loganin characterised as its penta-acetate, m.p. 147—148° (reduction from least hindered α-face). The configuration shown at C-1 for loganin (I) corresponds to that determined for other cyclopentane monoterpenes[11] and is based at present on the similar J-value observed for the doublet from the C-1 proton in loganin trimethylsilyl ether (4·5 c./sec.) and that recorded above for the corresponding proton in (III).

The biosynthesis of loganin was examined by feeding [1-^{3}H]geraniol to *Menyanthes trifoliata* plants; the labelled material was prepared by reduction of geraniol with sodium borotritiide. Radioactive loganin was isolated (0·2% incorp.) together with other highly active glycosides which are under examination. Parallel experiments with [2-^{14}C]geraniol (XIII) gave ^{14}C-labelled loganin (0·25% incorp.) which was shown to be specifically labelled by transformation into indole alkaloids *in vivo* followed by unambiguous degradation.[4] Biological derivation of the C_{10}-cyclopentane system of loganin (I) from geraniol is thus established.

Related work bearing on the biosynthesis of

loganin and leading to part of the stereochemistry of loganin is outlined in accompanying communications from Arigoni and co-workers and from Coscia and Guarnaccia.

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