# The Chemistry and Biosynthesis of Loganin

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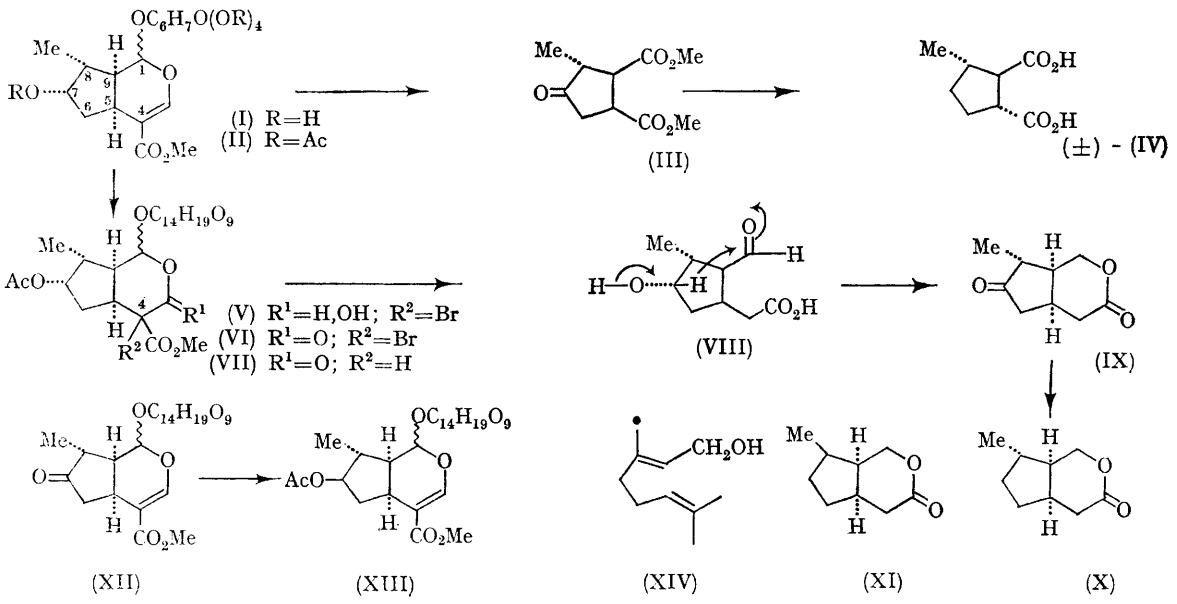
LOGANIN, a monoterpene glucoside first isolated from *Strychnos nux vomica*,[1] has been assigned the tentative formula (I) (without stereochemical details) on the basis of preliminary chemical characterization and biogenetic assumptions.[2,3] Attention has been focussed on the structure of loganin because of an early postulate[4] that a compound with similar features plays an important role in the biosynthesis of seco-iridoids; more recently, evidence has been found for a possible implication of loganin in the biosynthesis of indole alkaloids.[5] We now present new results which strongly support the correctness of the original suggestion and define part of the stereochemistry of loganin.

Ozonolysis of penta-acetyl-loganin (II), followed by treatment with silver oxide in alkaline solution, esterification with diazomethane and oxidation with chromic acid, gave, after g.l.c. purification, the oily keto-diester (III; $M^+$ 214, $[\alpha]_D$ +21°). This compound did not behave like a $\beta$-keto-ester and gave upon Clemmensen reduction, in keeping with the assigned constitution, the known[6] racemate of *trans, trans*-nepetic acid (IV), m.p. 110—112°, $pK^*_{MCS}$[7] 6·04 and *ca.* 9·64. The presence in loganin of a five-membered ring and its substitution pattern, but not its stereochemistry, are thus established.

Reaction of (II) with bromine in tetrahydrofuran–water yielded a bromohydrin (V), m.p. 149—151°, $[\alpha]_D$ −38°, smoothly oxidized with chromic acid to the bromo-lactone (VI), m.p. 173°, $[\alpha]_D$ −31°. Brief treatment of (VI) with zinc in cold acetic acid produced a mixture of two compounds epimeric at C-4 (VII), A: m.p. 175°, $[\alpha]_D$ −38°; B: m.p. 149—152°, $[\alpha]_D$ +9°. Hydrolysis of both epimers with potassium hydroxide in refluxing dioxan–water took an unexpected course and led, after acidification, to a moderate yield (*ca.* 30%) of a keto-lactone $C_9H_{12}O_3$ (IX), m.p. 122—124°, $M^+$ 168, $[\alpha]_D$ +83°, the formation of which is best interpreted as a result of an internal oxidation–reduction in one of the expected hydrolysis products (*cf.* VIII, arrows). Removal of the keto-group of (IX) through Raney nickel desulphurization of the corresponding thioketal generated the deoxo-lactone (X), m.p. 55–56°, $[\alpha]_D$ +97°, which differed from the known boschnialactone (XI), m.p. *ca.* 25°, $[\alpha]_D$ −18°[8] but displayed an essentially similar mass spectrum. Both in (IX) and (X) the n.m.r. signals of the $CH_2O$ group show up as the AB part of an ABX spectrum and the observed values ($J_{AX}$ 5 c./sec., $J_{BX}$ 4 c./sec.) are consistent only with a *cis*-fusion of the ring system, which is also supported by the ease of lactonization of the corresponding hydroxy-acids. This, together with the non-identity of (X) and (XI), establishes the complete relative configuration of the former. The formation of (IX) can then be taken as a proof for the *trans*-relationship of the hydrogens at C-5 and C-7 in (I), irrelevant of any epimerization at C-8 and C-9 which might be involved in this process. Next, the tetra-acetate (XII), m.p. 104—106°, $[\alpha]_D$ −139° of dehydrologanin[3] was treated with sodium borohydride in methanol solution; reduction occurred from the convex side of the molecule to afford, after acetylation, penta-acetyl-7-epi-loganin (XIII), m.p. 145—146°, $[\alpha]_D$ −116° as the only detectable product. In the light of familiar rules,[9] the large negative shift ($\Delta M_D$ −288°) observed in going from (II) to (XIII) requires for C-7, and hence for C-5, the absolute stereochemistry indicated in the formulae. The same conclusion has been reached in a different approach by Battersby and his co-workers (see accompanying communication), who, in addition, have provided clear-cut evidence for the configuration at C-8 and C-9 as in (I).

The biosynthesis of loganin was studied with whole and sliced rhizomes of *Menyanthes trifoliata*. Surprisingly, administration of sodium (±)-[2-$^{14}$C]mevalonate failed to produce radioactive loganin, although good and specific incorporation was observed for the triterpene and sterol fractions. Evidence for the biosynthetic ability of the plant material was first obtained in feeding experiments with L-[*methyl*-$^{14}$C]methionine; the radioactive loganin was carefully purified through the penta-acetate (1% incorp.) and, upon hydrolysis with barium hydroxide, gave methanol, isolated as the 3,5-dinitrobenzoate and shown to contain all (101%) of the original activity.[10] Eventually, exposure of the rhizomes to [$^{14}$C]geraniol, specifically labelled in the C-3 methyl group as in (XIV), led to a 0·1% recovery of radioactivity in the isolated penta-acetyl-loganin. Degradation of the deacetylated material by Kuhn–Roth and Schmidt reactions indicated that at least 85% of the label was located specifically in the C-8 methyl group of (I), thus settling the origin of the iridoid




carbon skeleton of loganin. Independent evidence bearing on this point has been obtained also by Battersby and his co-workers, and by Coscia and Guarnaccia, and is outlined in the accompanying communications.

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