X-Ray Determination of the Structure of *OO*-Dimethylipecoside

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Summary The structure and stereochemistry of *OO*-dimethylipecoside has been shown to be (**2**), Figure, by direct *X*-ray analysis of the sesquihydrate.

IPECOSIDE was the first substance shown to be a nitrogenous secocyclopentane monoterpene glucoside and its structure (**1**)[1] led[2] to an understanding of the late biosynthetic stages in the Ipecac series[3] (*e.g.* for emetine) and for the indole alkaloids.[2,4] The latter are derived[5] from vincoside (**3**), the indolic analogue of desacetylipecoside. Chemical and optical correlations[1] had related ipecoside [proposed[1] (**1A**)] and its C-5 epimer isoipecoside[5]† with (−)-dihydroprotoemetine (**4**). These correlations were further extended[5] to vincoside and its C-5 epimer isovincoside (≡ strictosidine[6] by direct comparison) and strictosidine was correlated chemically[7] with antirhine. The conflicting results indicated[8] that inversion at C-5 [see (**1**) and (**3**)] had occurred at some stage in the chemical operations and therefore *X*-ray studies were undertaken to provide an unambiguous answer.

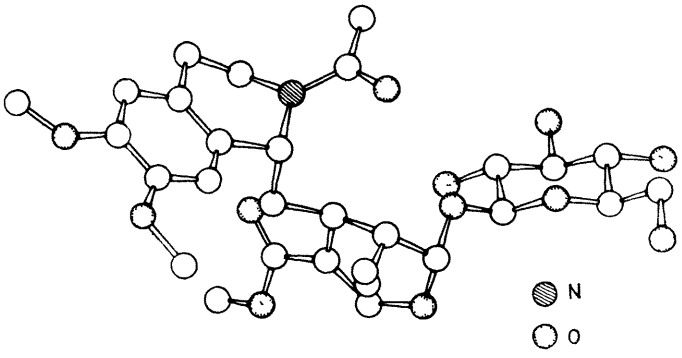


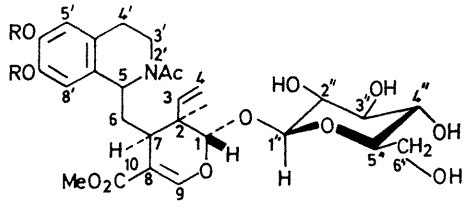
FIGURE. *The structure of* OO-*dimethylipecoside*

Suitable crystals of ipecoside could not be grown but the crystalline *OO*-dimethyl ether[9] (diazomethane; 20°) yielded an excellent diffraction pattern. The cell dimensions, and intensity data for 2163 independent reflexions with $\sin\theta \leqslant 0{\cdot}896$, were measured with a Picker 4-circle automatic diffractometer by use of monochromatised Cu-radiation.

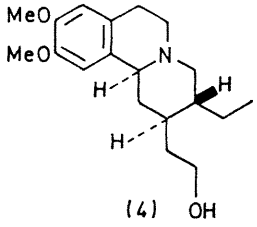
Crystal data: dimethylipecoside sesquihydrate, $C_{29}H_{39}NO_{12}$-$(1{\cdot}5H_2O)$; orthorhombic, $a = 29{\cdot}57(3)$, $b = 8{\cdot}25(1)$, $c = 29{\cdot}52(3)$ Å; $U = 7201(6)$ Å^3; $D_X = 1{\cdot}14$ g cm^{-3}, $Z = 8$. Absent spectra: (hkl) when $h + k = 2n + 1$, $(00l)$ when $l = 2n + 1$, uniquely determine the space group as $C222_1$ (D_2^5, No. 20).

† Numbering of the monoterpene unit is based upon that of loganin and secologanin.[5]

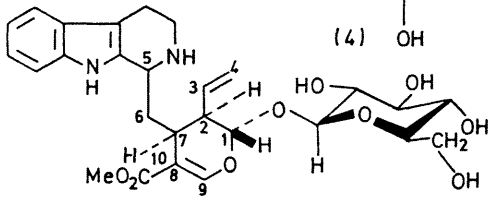
The structure was solved by direct methods using 220 reflexions with $|E| > 1{\cdot}655$. Numerous attempts were made to solve the structure using the tangent formula



(1A) R = H, 5α-H
(1B) R = H, 5β-H
(2) R = Me, 5β-H



(4)



(3A) 5α-H
(3B) 5β-H

approach,[10,11] as modified in this laboratory.[12] In these, some starting sets were selected by hand methods and others by specially developed programs. The choice of starting set was critical, since the likelihood of new phases being generated with large errors by any interaction between three reflexions increases in proportion to the total number of atoms in the unit cell. In the present structure, the cell contained 348 non-hydrogen and 336 hydrogen atoms.

A successful starting set was eventually obtained by symbolic addition computed manually. Three reflexions were used to fix the origin and enantiomorph, and three others allotted symbolic phases; early in the manual procedure the phase of 008 was strongly indicated to be π. Using these seven reflexions, with different numerical combinations for the symbolic phases, 32 phase sets were generated. One of these gave an R_{Karle} value of 23·2%, and was used to prepare a Karle map based on 211 E-values. The gross structure could be recognised directly, and positions assigned to 38 atoms. After one cycle of least-squares refinement, a difference Fourier map confirmed the positions of the remaining atoms including the water molecules, one of them being in a special position (on 2a). A further least-squares cycle reduced the conventional R to 18%, and gave reasonable molecular geometry; the three dimensional structure so obtained is in the Figure.

The isoquinoline ring has the expected geometry. The aromatic ring, C-4′, and C-5 are coplanar (r.m.s. deviation 0·04 Å from the mean plane), with C-3′ and N-2′ displaced by 0·37 Å either side of the plane. The dihydropyranyl ring is a 'half-chair', with C-1 and C-2 displaced above and below the plane formed by the remaining atoms. The glucose residue is in the 'chair' form with a mean torsion angle of 62 ± 3°.

Hydrolysis of ipecoside affords D-glucose[1] and this internal stereochemical standard allowed the correct absolute configuration [Figure, (**2**)] to be selected for *OO*-dimethylipecoside knowing the complete relative stereochemistry from the *X*-ray results. This structure confirms in detail that derived chemically[1,5] save that the hydrogen atom at C-5 has the β-configuration. With this point established for ipecoside (**1B**), it follows from the previous correlations[5] that the C-5 configuration for vincoside is as (**3B**) and for isovincoside (≡ strictosidine) is as (**3A**). Parallel work in the indolic series is reported in an accompanying Communication.[7] The biosynthetic implications of these findings are considered elsewhere.[3,13]

Further refinement of the analysis is in progress and full details of the molecular dimensions and angles will be published elsewhere.

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