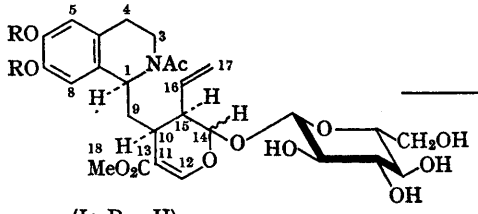
Constitution of Ipecoside: A Monoterpenoid Isoquinoline

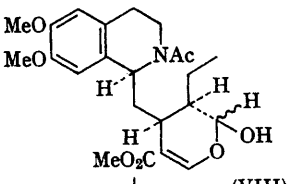
By A. R. BATTERSBY, B. GREGORY, H. SPENCER, and J. C. TURNER
(*The Robert Robinson Laboratories, University of Liverpool*)
and M.-M. JANOT and P. POTIER
(*Institut de Chimie des Substances Naturelles du C.N.R.S., Gif-sur-Yvette*)
and P. FRANCOIS and J. LEVISALLES
(*Faculté des Sciences, Université de Nancy*)

Ipecacuanha plants are rich in alkaloids, the pharmacologically important emetine being one, and they also contain[1] a neutral glucoside, ipecoside, which was characterised and assigned[1] the molecular formula $C_{27}H_{35}NO_{12}$. Evidence is now presented which establishes the novel structure (I) for ipecoside.[2] Only the essential data are outlined here and further chemical, spectroscopic, and mass spectrometric results, all supporting structure (I), will be reported in our full Paper.

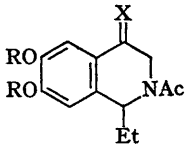
Ipecoside is a catechol derivative as shown by its u.v. spectrum (λ_{max} 285 mμ) which was ununchanged in acid but was displaced to 306 mμ in alkali and this forms part of an *N*-acetyltetrahydroisoquinoline system (see later). When the spectrum of (V) was subtracted from that of ipecoside, the remaining absorption (238 mμ; ϵ 9100) corresponded to the chromophore[3] $MeO_2C{-}C{=}C{-}O{-}$. Infrared absorption at 1690 cm.$^{-1}$ was in agreement with this system and a band at 1630 cm^{-1} indicated that ipecoside is an amide. Its molecular formula, $C_{27}H_{35}NO_{12}$, is supported by mass spectrometry of many substances in this series but no parent ion could be detected for ipecoside itself (involatility). However, important fragments at *m/e* 220, 206, 178, 164, and 43 are



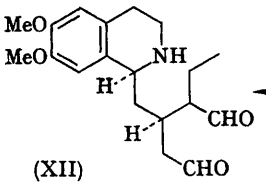
(I; R = H)
(II; R = H, C-16, 17 reduced)
(III; R = Me)
(IV; R = Me, C-16, 17 reduced)



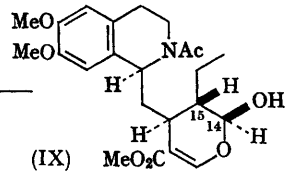
(VIII)



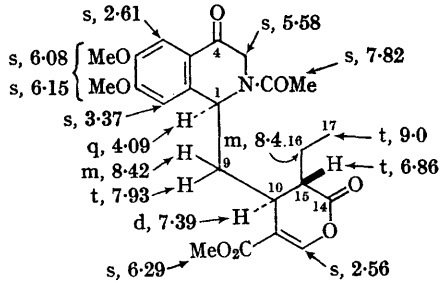
(V; R = H, X = H_2)
(VI; R = Me, X = H_2)
(VII; R = Me, X = O)



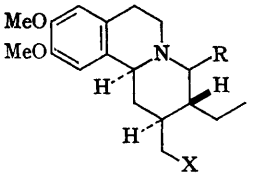
(XII)



(IX)



(X)
(XI; H_2 for O at C-4)



(XIII; R = OH, X = CHO)
(XIV; R = H, X = CH_2OH)

characteristic of *N*-acetyl-1-alkyl-1,2,3,4-tetrahydroisoquinolines and this breakdown pattern was matched in the mass spectrum of (V). The main initial fragmentation occurs between C-1 and C-9 and between C-9 and C-10 (see I).

D-Glucose was isolated (*cf.* ref. 1) from mild acidic hydrolysis of ipecoside, and acetic acid resulted under vigorous conditions. Hydrogenation gave dihydroipecoside (II), $C_{27}H_{37}NO_{12}$, m.p. 160–161°, which showed unchanged u.v. and i.r. spectra (carbonyl region). Thus, the $\alpha\beta$-unsaturated ester is unaffected by hydrogenation and the original olefin cannot be in conjugation with the catechol or carbonyl residues. *OO*-Dimethyldihydroipecoside (IV) was prepared similarly from *OO*-dimethylipecoside[1] (III).

The foregoing functional groups in a molecule $C_{27}H_{35}NO_{12}$ require ipecoside to be tetracyclic, *i.e.*, one ring in addition to the isoquinoline and glucose residues.

The n.m.r. spectrum of ipecoside, determined as the trimethylsilyl ether, showed the following important signals* (τ values): s, 2·52 (H-12); s, 3·42 (H-8); s, 3·47 (H-5); m, 4·2–4·8 (3H at 16, 17); s, 6·31 (H-18); s, 7·83 (NAc). No signals appeared above τ 8·0. The spectra of dihydroipecoside (II) and its derivatives showed replacement of the vinylic signals by those from a *C*-ethyl group at τ 8·95 (t, 3H at 17) and τ 8·4 (u, 2H at 16) and this residue was confirmed by Kuhn–Roth oxidation. Dihydroipecoside gave propionic and acetic acids (total 1·65 mol.) whereas ipecoside yielded only acetic acid (1·0 mol.).

Ipecoside is hydrolysed by β-glucosidase and on

* The integrals for all spectra agreed with the recorded assignments (s = singlet, d = doublet, t = triplet, m = multiplet, u = unresolved).

this basis a β-glucosidic link is assigned. The enzyme also hydrolyses dimethyldihydroipecoside (IV), though slowly, to yield aglucone-A (VIII), $C_{23}H_{31}NO_7$ (M^+, *m/e* 433). Treatment of this product with acid or acid hydrolysis of (IV) affords aglucone-B (IX), $C_{23}H_{31}NO_7$ (M^+, *m/e* 433). The latter is unaffected by extended treatment with acid and must be the most stable form. Partial reversal to aglucone-A occurred when aglucone-B was treated with alkali and then neutralised. Examination of the two aglucones chemically and by mass spectrometry, u.v., i.r., and n.m.r. showed that the only gross structural change from (IV) was fission of glucose. It is probable that the stereochemical change in the conversion of aglucone-A into -B involves C-15 since by n.m.r. the proton at C-14 appears as a singlet in B (τ 4·6) whereas coupling of the corresponding proton is evident in the spectra of aglucone-A and of (II). This and other data are best interpreted by the illustrated configuration at C-15 in (I) and (VIII) but this point requires confirmation.

Oxidation of aglucone-B afforded the keto-lactone (X), $C_{23}H_{27}NO_8$ (*m/e* 445) and the lactone (XI), $C_{23}H_{29}NO_7$ (*m/e* 431). The lactone ring in each is six-membered (ν_{max} 1773 cm.$^{-1}$) and all the spectroscopic data, including full comparison with (VII), support the illustrated structures. Further, the 100 Mc./sec. n.m.r. spectrum of the keto-lactone completely assigned (see X) and the coupling of each proton to its neighbour over the sequence C-1, C-9, C-10, C-16, C-17 was demonstrated by double-resonance. The observed couplings require the relative stereochemistry shown at (X) for C-10 and C-15.

To determine the absolute stereochemistry of ipecoside, [^{3}H-O-*methyl*]-*OO*-dimethyldihydroipecoside (IV) was hydrolysed vigorously with acid to (XII) which is in equilibrium with (XIII) and several isomeric benzoquinolizidines (40% yield of mixture). From this, after reduction, was isolated [^{3}H-O-*methyl*]dihydroprotoemetine (XIV), identical with authentic material,[4] and shown to be the (−)-form by dilution analysis with radio-inactive (−)- and (+)-dihydroprotoemetine. This proves the absolute stereochemistry at C-1 and C-10 of ipecoside to be as shown and the same as the corresponding centres in the *Ipecacuanha* alkaloids.[5] The latter are structurally related to the indole alkaloids whose monoterpenoid origin has recently been established.[6] Ipecoside is thus of particular biosynthetic interest and further experiments will determine whether or not it is an alkaloidal intermediate blocked by acetylation.

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[1] P. Bellet, *Ann. pharm. franc.*, 1952, **10**, 81.

[2] Outlined in part at the I.U.P.A.C. 4th International Symposium on The Chemistry of Natural Products, Stockholm, June, 1966.

[3] *Inter alia* M.-M. Janot and R. Goutarel, *Bull. Soc. chim. France*, 1951, 588; F. E. Bader, *Helv. Chim. Acta*, 1953, **37**, 216.

[4] A. R. Battersby and B. J. T. Harper, *J. Chem. Soc.*, 1959, 1748.

[5] A. R. Battersby and S. Garratt, *J. Chem. Soc.*, 1959, 3512, and refs. therein; E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, *J. Amer. Chem. Soc.*, 1959, **81**, 6214, and refs. therein; A. Brossi, A. Cohen, J. M. Osbond, P. Plattner, O. Schnider, and J. C. Wickens, *J. Chem. Soc.*, 1959, 3630; Y. Ban, M. Terashima, and O. Yonemitsu, *Chem. and Ind.*, 1959, 568.

[6] A. R. Battersby, R. T. Brown, J. A. Knight, J. A. Martin, and A. O. Plunkett, *Chem. Comm.*, 1966, 346; P. Loew, H. Goeggel, and D. Arigoni, *Chem. Comm.*, 1966, 347; E. S. Hall, F. McCapra, T. Money, K. Fukumoto, J. R. Hanson, B. S. Mootoo, G. T. Phillips, and A. I. Scott, *Chem. Comm.*, 1966, 348: *cf.*, E. Leete and S. Ueda, *Tetrahedron Letters*, 1966, 4915; A. R. Battersby, R. T. Brown, R. S. Kapil, J. A. Knight, J. A. Martin, and A. O. Plunkett, *Chem. Comm.*, 1966, 888.