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THE STRUCTURE OF ASPERULOSIDE

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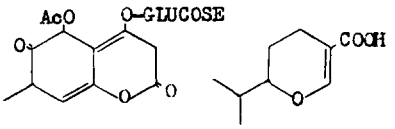
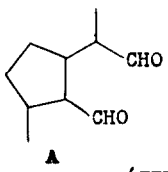
IN an earlier paper[1] structure (I) was proposed for asperuloside. This was based partly on the premise that the ultraviolet absorption band at 234.5 mμ (log ε = 3.83), was due to an abnormal diene chromophore affected

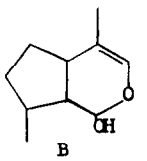


(I)

(II)



A



B

(III)

by substituents linked through oxygen. This absorption band is now ascribed to the chromophore R-O-C=C-COO-R' [cf. 6-isopropyl-3-carboxy-5,6-dihydro-4H-pyran (II)][2] now known to exist in a series of naturally occurring compounds derived from the enol-hemiacetal form (IIIB) of iridodial (IIIA),[3]

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[1] L.H. Briggs and B.F. Cain, J. Chem. Soc. 4182 (1954).

[2] F. Korte, K.-H. Büchel and L. Schiffer, Chem. Ber. 91, 759 (1958).

[3] G.W.K. Cavill, Rev. Pure Appl. Chem. (Australia) 10, 169 (1960).

e.g. plumieride and related compounds,[4] aucubin,[5] agnoside,[6] verbenalin,[7] genipin,[8] loganin,[9] and catalposide,[10] most of which are characterised by the formation of a black polymer on oxidative acid hydrolysis. The name "pseudoindican" has been ascribed to this class of compound, but in reflection of a common skeleton we propose the name "iridoid", derived from the parent compound, iridodial. The aglycone of asperuloside contains ten carbon atoms but the structure previously suggested did not fit the isoprene pattern or the acetate theory of biogenesis. Reinterpretation of the existing evidence, coupled with further data (see below), indicate that asperuloside, like the other iridoids, is a derivative of (IIIB), and, specifically, may be formulated as (IV; R = H).[11] Grimshaw has suggested the same formula [12,13] and has provided further confirmatory evidence.

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4 G. Albers-Schönberg and H. Schmid, Helv. Chim. Acta 44, 1447 (1961) and earlier papers.

5 A.J. Birch, J. Grimshaw and H.R. Juneja, J. Chem. Soc. 5194 (1961) and references therein.

6 E. Winde and R. Hansel, Arch. Pharm. 65, 556 (1960).

7 G. Büchi and R.E. Manning, Tetrahedron Letters No. 26, 5 (1960).

8 C. Djerassi, T. Nakano, A.N. James, L.H. Zalkow, E.J. Eisenbraun and J.N. Shoolery, J. Org. Chem. 26, 1192 (1961).

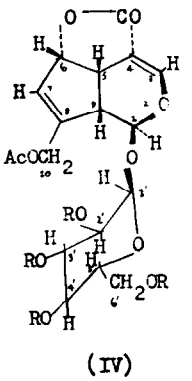
9 K. Sheth, E. Ramstad and J. Wolinsky, Tetrahedron Letters No. 12, 394 (1961).

10 J.M. Bobbitt, D.W. Spiggle, S. Mahboob, W. von Philipsborn and H. Schmid, Tetrahedron Letters No. 8, 321 (1962), and references therein.

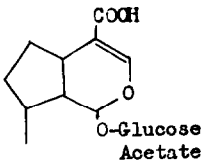
11 L.H. Briggs, Venkataraman Commemoration Volume, in the press.

12 J. Grimshaw, Chem. and Ind. 403 (1961).

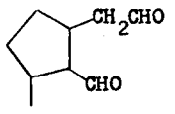
13 In personal correspondence Professors A.J. Birch and H. Schmid have informed us of the same independent conclusion.



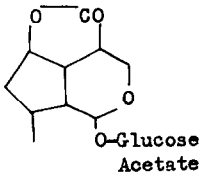
(IV)



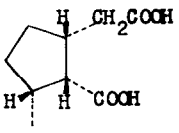
(V)



(VI)



(VII)



(VIII)

A redetermination of the C-Me value, in confirmation of Grimshaw's result,[12] indicated no group additional to that of the acetyl group known to be present. The alleged decarboxylated product[1] of "compound A" has now been shown, by redetermination of the infrared spectra, to be a different crystalline form of "compound A". Further examination of the polymers from asperuloside and toluquinone has shown that they are not identical (cf. also ref.[6]).

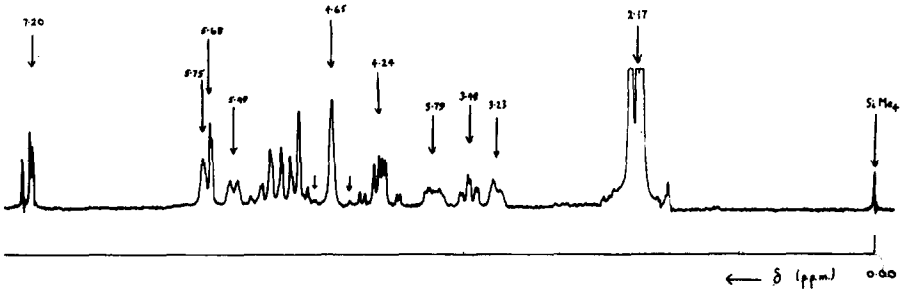
On the new formulation of asperuloside the tetraacetate has the structure (IV; R = Ac) and the acid from hydrogenation of the tetraacetate formula (V), while the alleged 5-acetyl-2-methylcyclohexanone is the dialdehyde (VI). In addition to (V) we have isolated a neutral lactone, $C_{24}H_{32}O_{13}$, m.p. 196.5-197° (Found: C, 54.8; H, 6.4; Ac, 30.6. $C_{24}H_{32}O_{13}$ requires C, 54.5; H, 6.1; 4Ac, 32.6%), from hydrogenation of asperuloside tetraacetate, which appears to have the structure (VII), arising from hydrogenation of both double bonds and hydrogenolysis of the allylic acetoxyl group.

The infrared spectrum reveals the presence of a saturated γ-lactone group (ν_{KBr} 1773 cm.$^{-1}$), an acetyl group (1742 cm.$^{-1}$), but the absence of double bonds and an enol-ether function.

The formation of a dialdehyde (VI) rather than the previously alleged diketone follows from its oxidation to the dicarboxylic acid (VIII), identical (including sign of rotation) with that from genipin[8] of proved absolute configuration, and thus accounts for nine of the ten carbon atoms in the aglycone of asperuloside. The introduction of a glucosyl group to the hydroxyl group on C_1 of the enol-hemiacetal form of the dialdehyde (VI) and a carboxyl group in β-position to the enol-aldehyde group to account for the ready loss of carbon dioxide leads to (V) for the acid formed by hydrogenation of asperuloside acetate. With the inclusion of a γ-lactone and an acetoxy group, with both the potential hydroxyl groups in an allyl position to a further double bond, asperuloside must consequently be represented by (IV; R = H). The absolute configuration at all asymmetric points, with the exception of that at C_1 follows from the identification of the dicarboxylic acid (VIII). Models indicate that the sugar moiety, in taking up the more favourable quasi-equatorial position, is better accommodated in the β-position as in (IV; R = H).

Grimshaw has shown[12] that supplementary infrared data of asperuloside and its derivatives support the structures (IV; R = H), (IV; R = Ac) and (V) for asperuloside, its tetraacetate and the acid from the hydrogenation of the acetate, respectively.

The n.m.r. spectra, measured at 60 mc, are also in full accord with these structures as well as with (VII) for the lactone. The spectrum of asperuloside tetraacetate (see Figure) measured in $CDCl_3$ at 100 mc with a field of 23,500 gauss is particularly enlightening as it allows assignments to be made for all the protons and completely supports the stereochemistry illustrated in (IV). Only this spectrum will be discussed in detail.



The olefinic proton on C_3, β to carbonyl and adjacent to oxygen falls at 7.20δ* [at 7.48 and 7.45δ for (IV; R = H)** and (V)*** respectively], cf. genipin (7.52),[8] loganin (7.83),[9] and plumericin (7.43δ),[4] and disappears in (VII)*** on hydrogenation. In (VII) it is replaced by peaks centred at 3.89δ assigned to the protons on C_3, spin coupled with the proton on C_4, cf. the protons on C_2 of tetrahydropyran with a peak at 3.56δ.[14]

The olefinic proton on C_7 falls at 5.75δ [at 5.67δ in (IV; R = H)], cf. genipin (5.86δ),[8] aucubin (5.80δ),[5] and plumericin,[4] and is broadened by weak long-range couplings to the protons on C_{10} and possibly those on C_6 and C_9. The peak disappears on hydrogenation e.g. in (V) and (VII).

The doublet peak at 5.68δ is assigned to the proton on C_1. It exhibits weak spin coupling to the proton on C_9, consistent with a dihedral angle of ca. 120° as in (IV). The proton on C_6 at 5.49δ is split into a doublet with the same spacing (6 cps.) as the large coupling in the triplet at 3.48δ of C_5.

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* Reference tetramethylsilane is taken as 0.00 on the δ scale.

** Measured in D_2O with tetramethylsilane as external reference.

*** Measured in $CDCl_3$.

14 L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, London, 1959, p.55.

A group of signals between 5.49δ and 4.65δ is assigned to the four axial protons on the sugar ring, attached to C_1' through C_4'.

The methylene protons on C_{10} are slightly non-equivalent resulting in the strong signal at 4.65δ and the weak satellites shown by small arrows. A more pronounced non-equivalence of the same kind is observed for the methylene protons on C_6' (multiplet centre 4.24δ) resulting in the typical eight line AB part of an ABX pattern. In (V) and (VII) the peak at 4.65δ is replaced by a doublet centred at 1.01 and 0.96δ respectively, typical of a secondary methyl group spin coupled to a single proton, cf. Figs. 2 and 3 in the genipin series.[8]

The proton on C_5' is found at 3.79 δ and shows a flat-topped characteristic due to being coupled with an axial-axial coupling to the proton on C_4', with each component of this doublet being split into four lines due to the unequal coupling with the two protons on C_6'.

The proton on C_5 exhibits the triplet of double lines at 3.48δ. The triplet arises from equal coupling of this proton to those on C_6 and C_9 and the doubling to the coupling with the proton on C_3.

The 3.23δ peak is assigned to the proton on C_9, split into a doublet through coupling with the proton on C_5 and broadened by unresolved couplings to other protons.

A single peak at 2.17δ in the spectrum of asperuloside and multiple peaks in the same region of the spectra of the remaining compounds correspond to the acetyl groups.

The authors are indebted to Professor Djerassi for data on and the ester of the acid (VIII) and to Professor W. Klyne for the measurement of the optical rotatory dispersion of (VIII). We also gratefully acknowledge assistance from the Chemical Society, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science and the Research Grants Committee of the University of New Zealand.