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UNEDOSIDE, A NOVEL IRIDOID COMPOUND

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Unedoside was first isolated from Arbutus unedo L. (Ericaceae) by Bridel and Bourdouil (1), who showed that it was a glycoside, hydrolyzable by emulsin to an unstable aglycon, unedol. Sosa (2) prepared an acetate, showed that the sugar was glucose, and proposed the formula $C_{18}H_{26}O_{12}$. No information leading to a structural proposal was provided in these early studies.

Our studies of unedoside lead to its formulation as I. It is a member of the group of iridoid (3) compounds whose structures have become established by the work of numerous investigators since 1960; but it is unique in that it lacks the extracyclic carbon atom characteristically present in the 5-membered ring, and thus is a representative of a third class of these compounds. The first two types are typified by verbenalin (II), a C_{10}-compound, and aucubin (III), a C_9-compound. Unedoside, m.p. 232-4°, has the composition $C_{14}H_{20}O_9$ (4). It yields a penta-acetate, a penta-benzoate (V) and a penta-methoxyacetate (VI) which gave satisfactory elemental and functional group analyses and molecular weight of the acetate (by mass spectrometry). Neither unedoside nor its acetate show ultraviolet absorption. Infrared analysis shows that a carbon-carbon double bond is present; this was confirmed by the hydrogenation of unedoside and its acetate to the corresponding dihydro compounds (VII, VIII). The NMR

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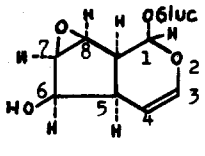
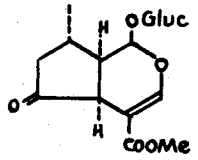


I



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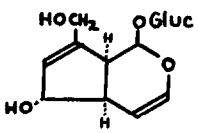

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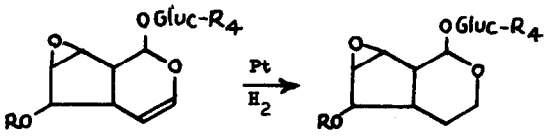
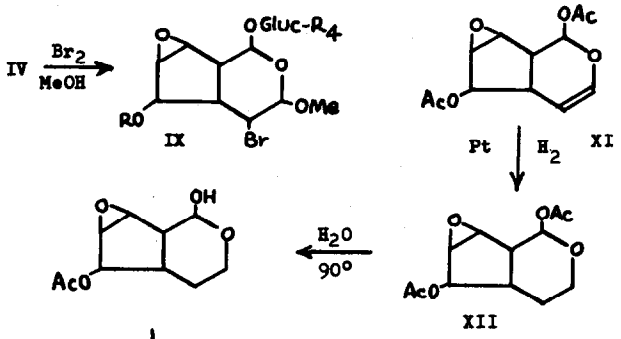


IV R=CH_3CO
V R=C_6H_5CO
VI R=$MeOCH_2CO$
X R=Me_3Si

VII Dihydro-I
VIII Dihydro-IV



IX

XI

XII

XIII

XIV

spectra of these derivatives integrate to the required number of protons, and give additional information to be described.

The presence of the dihydropyran ring was first revealed by the NMR spectra, and confirmed by the preparation of the methoxybromo derivative (IX), the NMR spectrum of which shows the loss of the vinylic protons (at C-3,C-4) and the appearance of the corresponding protons of the -CHBr and -CHOMe groupings. In the NMR spectra of IV and V the two acetal-linked protons (C-1 and in the sugar residue) are obscured by the numerous methine protons of the acyloxy groups. This difficulty was surmounted by the preparation of the crystalline penta-O-trimethylsilyl derivative (X) of unedoside, the NMR spectrum of which showed the C-3 proton as a low-field doublet, three protons at ca. 5τ(one vinyl proton at C-4, two acetal protons), and two highfield protons (C-5, C-9), The acetal protons showed coupling constants of 7 and 9 cps, indicating that unedoside is a β-glucoside and C-1 and C-9 bear a trans relationship.

Enzymatic hydrolysis of unedoside yielded an unstable aglucon which was immediately acetylated to a crystalline diacetate (XI), which was found to have the composition $C_{12}H_{14}O_6$ by elemental analysis and mass spectrometric molecular weight. The NMR spectrum of XI revealed clearly the structural features described above. The C-4 proton at low field was split into a pair of doublets (J=6 and 1.5 cps), indicating its coupling to C-3 and to the allylic proton at C-5. A sharp doublet at 4.4τ(J=9.5 cps) could be assigned to the proton at C-1. The remainder of the spectrum shows the vinylic proton at C-3 (5.0τ), a secondary acetate methine proton at 5.1τ(1 H, quartet), two acetyl methyl singlets (3 H, 3 H, 7.85τ), two high-field protons at 8.5τ, and two ether-linked protons (2 H, mult.) centered at 6.4τ(J =2.8 cps), characteristic of the protons of an epoxide on a 5-membered ring (5): one is coupled with the proton at C-6 (J=1.5 cps), the other with the bridgehead proton at C-9 (J=1 cps).

Hydrogenation of unedol diacetate gave the crystalline dihydro compound XII, the ready hydrolysis of which by hot water to a monoacetate provided the opportunity for controlled oxidation of XII to a lactone, XIII. This compound was an α,β-unsaturated lactone (λ_{max} 218 mμ, log ε 4.0) which contained a hydroxyl and an acetoxyl group but no oxide ring. The NMR spectrum of XIII showed the vinylic proton at C-8 (3.0 τ), the two protons at C-3 (displaced to lower fields than in XII), and the expected protons for the acetyl methyl group and those at C-4 and C-5. Acetylation of XIII gave XIV, whose NMR spectrum showed the new acetyl group (methine hydrogen) at higher field than that of the acetyl group present in XIII, unchanged in XIV. This showed that the new acetyl group was at C-6 and that the acetyl group present in XIII is at C-7, and thus allylically situated. These observations require the conclusion that after oxidative formation of the lactone, the labilization of the proton at C-9 results in the opening of the oxide ring and concomitant migration of the acetyl group from C-6 to C-7. The formation of the unsaturated lactone with retention of the acetyl group shows that the acetoxyl group is not at C-8, and thus that the oxide ring is at C-7/C-8 and the acetoxyl group at C-6 in XII.

The above observations are in accord with the formulations given in the chart. The indicated stereochemistry of unedoside is supported by the NMR data. The 9.5 cps coupling between C-1 and C-9 indicates the trans relationship between these positions, and the 7.5 cps coupling of C-5/C-6 is in agreement with a cis disposition and a small dihedral angle. The cis ring junction is in accord with the stereochemistry established for several other iridoid compounds. The protons on the epoxide ring are known in comparable systems (5) to couple weakly with adjacent cis protons and not at all with trans protons. The observed

couplings of the proton on C-7 with the adjacent methine proton at C-6, and that of the C-8/C-9 protons are about 1-1.5 cps, which is in agreement with the β-orientation of the epoxide ring and thus of the acetoxyl (hydroxyl in unedoside) group at C-6. An α-orientation of the oxide ring would require C-8/C-9 and C-5/C-6 couplings that are not observed.

References

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3. L. H. Briggs, B. F. Cain, P. W. LeQuesne, J. N. Shoolery, Tetrahedron Letters, 1963, 69.

4. All of the compounds described gave satisfactory elemental analyses and, where appropriate, functional group analyses.

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