6β-Hydroxygedunin

By **N. S. Ohochuku** and **D. A. H. Taylor,*** Department of Chemistry, University of Ibadan, Ibadan, Nigeria

6β-Hydroxygedunin has been synthesised from gedunin by an unambiguous route. The acetate is different from a 6-acetoxygedunin isolated by Wenkert and Zelnik, which must, therefore, be the 6α-acetoxy-compound.

WENKERT and ZELNIK described the isolation of an acetoxy-derivative of gedunin (Ia) from the seed of *Carapa guianensis* Aubl., and showed that the extra acetate is attached to C-6.[1] The coupling constants of 6-H in this compound were $J_{5,6}$ 12 and $J_{6,7}$ 3 c./sec., which the authors considered would normally represent the coupling expected for a 6β-proton. However, on the basis of the methyl shifts observed in pyridine solution they considered the structure of 6β-acetoxygedunin more likely, and suggested that distortion of the ring skeleton might account for the observed coupling constants. Overton and his co-workers[2] had previously reported the isolation of 6α,11β-diacetoxygedunin from the same species, and the 6-H coupling constants were similar in the two compounds.

We have synthesised 6β-hydroxygedunin from gedunin by an unambiguous route. Deacetylgedunin was dehydrated with phosphorus oxychloride to give the 6,7-anhydro-derivative.[3] The unconjugated double bond in this was oxidised with perphthalic acid to give an oxide. With formic acid, the epoxide ring opened readily to give a glycol monoformate, the n.m.r. spectrum of which showed the X part of an ABX system at δ 5·45 p.p.m. [J^* (= $J_{AX} + J_{BX}$) 4·8 c./sec.], which we ascribe to 6-H, and a multiplet at δ 3·53 p.p.m., which we ascribe to 7-H. It follows that the compound is the 6-formyloxy-7-hydroxy-derivative, since in the isomer the proton resonating at δ 5·45 p.p.m. would be a doublet. The appearance of 15-H as a singlet at δ 3·83 p.p.m. shows that the 7-hydroxy-group is α-oriented, since in 7β-hydroxy-compounds 15-H is strongly shifted downfield.[4] Since the glycol must be *trans* from its method of preparation, it follows that the formate at C-6 is β-oriented, and the compound has the structure (Ib). It

[1] E. Wenkert and R. Zelnik, 5th International Symposium on the Chemistry of Natural Products, I.U.P.A.C., London, 1968, p. 339.

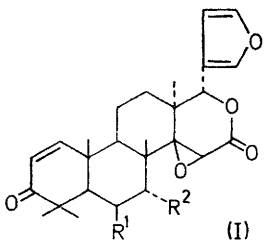
[2] J. D. Connolly, R. McCrindle, K. H. Overton, and J. Feeney, *Tetrahedron*, 1966, **22**, 891.

[3] J. R. Housley, F. E. King, T. J. King, and P. R. Taylor, *J. Chem. Soc.*, 1962, 5095.

[4] D. L. Dreyer, *Tetrahedron*, 1965, **21**, 75.

also follows that the oxide is the α-oxide, as expected from the much greater steric hindrance of the β-face of the molecule.

Acetylation of the formate gave the 7α-acetate (Ic), in which 6-H again appears as the X part of an ABX system (J* 5·6 c./sec.) at δ 5·5 p.p.m., and 7-H gives rise to a doublet (J 3·5 c./sec.) at δ 4·6 p.p.m. Mild hydrolysis of (Ic) readily gave 6β-hydroxygedunin (Id). This was not acetylated by acetic anhydride and pyridine, while with toluenesulphonic acid as catalyst a mixture resulted of the required acetate and two diacetates, produced by *C*-acetylation of the furan ring. We shall describe these compounds elsewhere. The acetate (Ie), m.p. 297—305°, $[\alpha]_D$ +71°, had spectral properties similar to the formate (Ic). In the n.m.r. spectrum, the formyl hydrogen resonance was absent and was replaced by a second acetyl band, the only other difference was that the H-6 resonance was moved slightly upfield from δ 5·5 to 5·35 p.p.m., the coupling constants remaining the same. We have attempted to prepare 6α-hydroxygedunin by *cis*-hydroxylation of the double bond, and by inversion at C-6 in a 6β-compound, but without success. However, since the coupling constants of 6β-acetoxygedunin are quite different from those of the *Carapa* compound reported by Wenkert and Zelnik, the latter must be the 6α-acetate, analogous to the compound isolated by Connolly and his colleagues,[2] and reliance on the pyridine shift method has led to a wrong assignment.



(I)

a; R^1 = H, R^2 = OAc
b; R^1 = O·CHO·, R^2 = OH
c; R^1 = O·CHO, R^2 = OAc
d; R^1 = OH, R^2 = OAc
e; R^1 = R^2 = OAc

The small coupling constants observed for 6α-H are consistent with a normal chair conformation of ring B.

In the formate (Ib) the methyl groups resonate at 73, 73, 73, 73, and 90 c./sec. from tetramethylsilane at 60 Mc./sec., only one being much shifted compared to deacetylgedunin, in which they resonate at 69, 67, 67, 75, and 74 c./sec.[5] From inspection of a model, it appears that the 6β-formyl group is close to the 4α-, 4β-, 8-, and 10-methyl groups, and therefore the resonances of all four might have been expected to shift downfield. The methyl group resonances in the 7α-acetate (Ic) are at 93, 80, 73, 71, and 71 c./sec., while in (Id) the methyl group resonances are at 94, 86, 83, 73, and 70 c./sec., compared to 63, 63, 69, 74, and 75 c./sec. in gedunin. It seems therefore that in the 6β-hydroxy-compound the resonances of three or four methyl groups are shifted downfield, as anticipated, but that on formylation of the hydroxyl-group some of these are shifted back upfield again. We first encountered such a situation in methyl 6-hydroxyangolensate,[6] where the introduction of the 6-hydroxy-group moves the resonances of both the 4β- and 10-methyl groups downfield, while in the 6-acetate, only one of these resonances is shifted downfield, relative to methyl angolensate. This we ascribed to anisotropic shielding by the acetoxy-group; and a similar explanation appears to hold in the present case.

Examination of Courtauld models shows that the oxygen attached to C-6 in the β-position is very close to the 4β-, 8-, and 10-methyl groups and less close to the 4α-methyl group. Therefore, we anticipate that the first three of these methyl groups would be strongly shifted downfield in the hydroxy-compound; the fourth rather less so. The 6β-formate is very crowded and cannot rotate about the alkyl–oxygen bond. The geometry is such that the 10-methyl group is along the axis of the acyl–oxygen bond, with 4β- and 8-methyl groups symmetrically disposed on the sides of this bond, and the 4α-methyl group rather further away. Since only one methyl group suffers a major downfield shift in the formate, it follows from this symmetry, irrespective of the mechanism of shielding, that it must be the 10-methyl group which is strongly shifted. Comparison of the methyl resonances of gedunin and the 6-hydroxy-derivative shows that if the 10-methyl group is one of those shifted downfield, then four, not three, methyl groups must be affected by the hydroxy-group. Based on these considerations, we assign the 4α-, 4β-, 8-, 10-, and 13-methyl groups to the resonances at 70, 83, 86, 94, and 73 c./sec. respectively in 6β-hydroxygedunin (Id); at 71, 71, 80, 93, and 73 c./sec. in 6β-formylgedunin (Ic), and at 73, 73, 73, 90, and 73 c./sec. in 6β-formyldeacetylgedunin (Ib). These assignments give an increment in the various methyl resonances for acetylation at 7α-OH which agrees with that which we have previously found.[5]

EXPERIMENTAL

14β,15β-Epoxy-3-oxomeliac-1,2-6,7-dienolide.— Deacetylgedunin (10 g.) was dissolved in pyridine (100 ml.) and phosphorus oxychloride (20 ml.) was added to the solution. After 3 days the mixture was poured into ice and dilute sulphuric acid, and extracted with chloroform. The chloroform layer was washed with sodium hydrogen carbonate, dried, and evaporated to dryness. After treatment with charcoal, the residue was crystallised from benzene to give the anhydro-compound [3] (4—5 g.), m.p. 260—262°, $[\alpha]_D^{20}$ 72° (Found: C, 73·5; H, 7·0. Calc. for $C_{26}H_{30}O_5$: C, 73·9; H, 7·2%).

6α,7α-14β,15β-Diepoxy-3-oxomeliac-1,2-enolide.—The anhydro-compound (8 g.) in chloroform (400 ml.) was treated with 6M-perphthalic acid (600 ml.) in ether. After 3 days the solution was filtered and the precipitate of phthalic acid was washed with chloroform. The combined organic

[5] N. S. Ohochuku and D. A. H. Taylor, *J. Chem. Soc.* (*C*), 1969, 864.

[6] E. K. Adesogan and D. A. H. Taylor, *J. Chem. Soc.* (*C*), 1968, 1974.

layers were washed with sodium hydrogen carbonate and evaporated to dryness. Crystallisation of the residue from benzene gave the *epoxide* (5·5 g.), m.p. 272—275°, $[\alpha]_D^{20}$ 39° (Found: C, 70·8; H, 7·0. $C_{26}H_{30}O_6$ requires: C, 7·12; H, 6·9%).

14β,15β-*Epoxy*-6β-*formyloxy*-7α-*hydroxy*-3-*oxomeliac*-1,2-*enolide* (Ia).—The oxide (5·5 g.) was dissolved in formic acid (8 ml., 98%), and stored at 25° for 12 hr. The solution was diluted with aqueous sodium hydrogen carbonate and chloroform, and the organic layer was evaporated to dryness. The residue was chromatographed on Kieselgel with ether–light petroleum (b.p. 40—60°) as eluent and then crystallised from benzene to give the *formate* (Ia) (1 g.), m.p. 175—183°, $[\alpha]_D^{20}$ +66° (Found: C, 67·0; H, 6·7. $C_{27}H_{32}O_8$ requires C, 66·9; H, 6·7%). Acetylation of the product with pyridine and acetic anhydride on a steam-bath for 30 min. gave 6β-*formyloxygedunin* (Ib), m.p. 325—330°, $[\alpha]_D^{20}$ +67° (Found: C, 66·45; H, 6·5. $C_{29}H_{34}O_9$ requires C, 66·1; H, 6·5%). Solvolysis of the formate (Ia) with cold sodium methoxide overnight gave the 6β,7α-*glycol*, m.p. 308—311° (from benzene).

6β-*Hydroxygedunin*.—The formyl-acetate (Ib) (350 mg.) was dissolved in methanol (700 ml.), and water was added to the solution until it became cloudy. Sodium hydrogen carbonate (10 g.) was then added to the mixture and the flask was shaken 24 hr. After acidification, the solution was extracted with chloroform. Evaporation and crystallisation from benzene gave 6β-*hydroxygedunin* (Ic) (300 mg.), m.p. 315—320° $[\alpha]_D^{20}$ +41° (Found: C, 65·5; H, 6·9, $C_{28}H_{34}O_8,H_2O$ requires C, 65·1; H, 7·0%). Acetylation with acetic anhydride in acetic acid, with toluene-*p*-sulphonic acid as a catalyst at room temperature gave, after chromatography, 6β-*acetoxygedunin* (Id), m.p. 297—305°, $[\alpha]_D^{20}$ +71°. The same product was obtained by acetylation of the glycol (Found: C, 65·9, 65·8; H, 6·7, 6·4. $C_{30}H_{36}O_9$ requires C, 66·65; H, 6·7%).

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