6β-(2′-HYDROXYETHOXY)-5α-CHOLESTAN-3β-OL 2′,3-DIACETATE*

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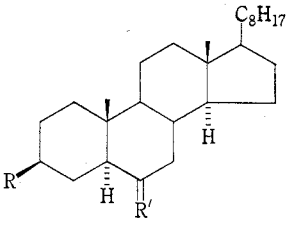
In a previous communication from this Laboratory, it was shown that the alkaline decomposition of the 6-tosylhydrazone (I) of 5α-cholestan-3β-ol-6-one 3-acetate (VI) in ethylene glycol gave, after acetylation, 6α-(2′-hydroxyethoxy)-5α-cholestan-3β-ol 2′,3-diacetate (II) as one of the products.[1] The identity of the ether (II) was established through spectral data and chemical studies. In an attempt to synthesize (II), 6,6-ethylenedioxy-5α-cholestan-3β-ol 3-acetate (III) was reduced with $LiAlH_4/AlCl_3$ in ether (cf.[2]). The reduced product, i.e. the diol (IV), on acetylation furnished 6β-(2′-hydroxyethoxy)-5α-cholestan-3β-ol 2′,3-diacetate (V) as the sole product. Treatment of the ethylene ketal (III) with acetic acid quantititively regenerated 5α-cholestan-3β-ol-6-one 3-acetate (VI).



	R	R′
(I)	OAc	=NNHTs
(II)	OAc	α-OCH_2CH_2OAc, β-H
(III)	OAc	—O—CH_2 / —O—CH_2
(IV)	OH	α-H, β-OCH_2CH_2OH

	R	R′
(V)	OAc	α-H, β-OCH_2CH_2OAc
(VI)	OAc	O
(VII)	H	α-OCH_3, β-H
(VIII)	H	α-H, β-OCH_3

The structure of the ether (V) is compatible with spectral data (n.m.r. and i.r.) and its behaviour towards BF_3–acetic anhydride.[3,4] The ether (V) analysed correctly for $C_{33}H_{56}O_5$ and its i.r. spectrum showed peaks at 1738 (CH_3COO–), 1240 (acetate), 1117, 1050, 1026 cm^{-1} (ether linkage). Its n.m.r. spectrum exhibited signals at δ 4·7 br (AcO–C3–**H**); 3·3 m (AcOCH_2CH_2O–C6–**H**); 3·58 q (OCH_2CH_2OAc); 4·12 q (OCH_2CH_2OAc);[1] 2·05 s (CH_3COO); 2·0 s (CH_3COO); 0·96, 0·90, 0·80, 0·68 (five methyl groups).

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The configurations of substituents at C3 and C6 in (V) were ascertained by measuring half-band widths of C3 and C6 protons. The H3 signal at δ 4·7 exhibited a half-band width of 14 c/s (axial)[5,6] and the H6 signal at δ 3·3 a half-band width of 7 c/s (equatorial), thereby implying that 3-acetate is equatorial and the 6-ether moiety is axial. Further, a 6α-equatorial proton always resonates at a lower field than the β-proton of the epimer.[6] A comparison of the n.m.r. data for ethers (II) and (V) has been made in Table 1.

TABLE 1

N.M.R. DATA (p.p.m.) FOR (II) AND (V)

Compound	H3	H6	6-O–CH_2–	6-O–CH_2–CH_2OAc	6- and 3-OAc
(II)	4·7 (13)*†	2·98 (14)*†	3·60	4·12	2·01, 2·07
(V)	4·7 (14)*†	3·3 (7)*‡	3·58	4·12	2·05, 2·0

* Figures in parentheses give width at half-height in c/s. † Axial. ‡ Equatorial.

It is interesting to note that whereas the ethers (II), (VII), and (VIII) were readily cleaved by boron trifluoride etherate in acetic anhydride,[1] the ether (V) remained indifferent towards this reagent and gave only a very small amount of cholesteryl acetate (product of elimination);[4] most of the unchanged ether (V) was recovered even after extended reaction time. It is quite probable that the initial step of ether cleavage, that is the complexing of BF_3 with ether oxygen, becomes difficult due to increased 1,3-diaxial interaction between the C6-axial ether moiety and the C10-methyl group. In the case of ether (VIII), the C6-axial OCH_3 group being smaller than the OCH_2CH_2OAc group as in the case of (V), the 1,3-diaxial interaction is not realized to the same degree and hence (VIII) undergoes cleavage under similar reaction conditions.

Experimental

All melting points are uncorrected. I.r. spectra were determined in KBr with a Perkin–Elmer 137 Infracord. N.m.r. spectra were run in $CDCl_3$ on a Varian A60 with TMS as the internal standard. Rotations were determined in chloroform.

6,6-Ethylenedioxy-5α-cholestan-3β-ol 3-Acetate (III)

A mixture of 5α-cholestan-3β-ol-6-one 3-acetate (VI) (1·0 g; m.p. 128°),[7] ethylene glycol (5 ml, azeotropically dried), sodium-dried benzene (50 ml), and *p*-toluenesulphonic acid monohydrate (100 mg) were heated for 8 hr in a Dean and Stark apparatus. After allowing the reaction mixture to attain room temperature, it was treated with $NaHCO_3$ solution (5%) and extracted with ether. The ether layer was washed with water and dried (Na_2SO_4). Removal of the solvents under reduced pressure gave (III) as an oil which crystallized from methanol–ether as cubes (0·8 g), m.p. 117–118°, $[\alpha]_D^{17}$ −75°; ν_{max} 1733s, 1238s (acetate), 1133m, 1111m, 1093m, 1081m, 1047s, 1026s cm^{-1} (ketal group) (Found: C, 75·9; H, 10·6. Calc. for $C_{31}H_{52}O_4$: C, 76·2, H, 10·7%).

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Regeneration of 5α-Cholestan-3β-ol-6-one 3-Acetate (VI) from (III)

The ketal (III) (240 mg) was dissolved in acetic acid (20 ml) and water (1 ml) and the resultant solution allowed to stand at room temperature for 24 hr. On gradual addition of water a white precipitate was obtained, which was filtered and crystallized (methyl alcohol) to give (VI) (215 mg), m.p. and mixed m.p. 128–129°.

6β-(2′-Hydroxyethoxy)-5α-cholestan-3β-ol (IV)

To a slurry of anhydrous $AlCl_3$ (2·0 g) and $LiAlH_4$ (1·0 g) in sodium-dried ether (200 ml) was added a solution of the ketal (III) (1·0 g) in ether (25 ml) over a period of 15 min. The reaction mixture was refluxed with continuous stirring for 4 hr. After this period, the excess of reagent was destroyed by the addition of a mixture of ethyl acetate–ether followed by dilute and cold H_2SO_4. The ether layer was washed with water and dried (Na_2SO_4). Removal of the solvent provided a gum which was chromatographed over neutral alumina (20 g; NCL, Poona). Elution with light petroleum (60–80°)–ether (1 : 1) gave (IV) as a solid, which was recrystallized from light petroleum (40–60°) (0·63 g), m.p. 108–110°; $[\alpha]_D^{17}$ −66·4°; ν_{max} 3345m (br) (OH), 1150m, 1095m, 1050 cm^{-1} (C–O–) (Found: C, 77·3; H, 11·5. Calc. for $C_{29}H_{52}O_3$: C, 77·6; H, 11·7%). The diol (IV) was also obtained from (V) on alkaline hydrolysis.

6β-(2′-Hydroxyethoxy)-5α-cholestan-3β-ol 2′,3-Diacetate (V)

The diol (IV) (500 mg) was dissolved in freshly distilled pyridine (1 ml) and acetic anhydride (1 ml) and the mixture allowed to stand at room temperature for 48 hr. After usual work-up, an oil was obtained which crystallized from methanol–ether mixture to give (V) as needles (330 mg), m.p. 76–77°; $[\alpha]_D^{17}$ −40·5°; ν_{max} 1738, 1240, 117, 1050, 1026 cm^{-1}; n.m.r. ($CDCl_3$) δ 4·7 (C 3–H α); 3·3 ($AcOCH_2CH_2O$–C 6–**H**); 3·58 (OCH_2CH_2OAc); 4·12 (O–CH_2CH_2OAc); 2·05 (CH_3COO); 2·0 (CH_3COO) (Found: C, 74·1; H, 10·7. Calc. for $C_{35}H_{56}O_5$: C, 74·4; H, 10·6%).

Reaction of the Ether (V) with BF_3 Etherate–Ac_2O

The ether (V) (500 mg) was dissolved in sodium-dried ether (5 ml) and to this was added freshly distilled acetic anhydride (12 ml) and the solution cooled in an ice-bath. To the cold solution, freshly distilled BF_3–etherate (3 ml) was added and the reaction mixture was kept at 0–5° for 60 hr. Usual work-up[4] of the reaction mixture provided an oil which was chromatographed over neutral alumina (12 g). Elution with light petroleum (60–80°) gave a small amount of a semi-solid material which was crystallized from acetone–ether (*c.* 10 mg), m.p. and mixed m.p. with cholesteryl acetate,[8] 112–114°. Further elution with light petroleum–ether (10 : 1) gave the unchanged ether (V) (320 mg), recrystallized from methanol–ether, m.p. and mixed m.p. 76–77°. (The reaction of (V) with BF_3 was also carried out for 120 hr, and also at room temperature, but in each case most of the ether (V) was recovered.)

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