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1α,2β-DIHYDROXYCHOLESTEROL

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Abstract—1α,2β-Dihydroxycholesterol has been prepared from 1α,2α-epoxy-5α-cholestan-3β,6β-diol-3-acetate on reaction with methansulphonyl chloride and hydrochloric acid. The structure was confirmed by independent synthesis from 1α,2α-epoxycholest-5-en-3β-yl acetate.

Some time ago preparation of '1α-hydroxycholesterol' has been described[1] but structure of the product came in doubt when several syntheses of 1α-hydroxycholesterol gave product with different physical properties.[2-6] The reaction of 1α,2α - epoxy - 5α - cholestan - 3β,6β - diol - 3 - acetate (1) with methansulphonyl chloride in pyridine gave an unstable mesylate (2). Its reaction with hydrochloric acid in ether-methanol under reflux gave a product to which a structure of epoxide (6) was wrongly ascribed.[1]

The reaction of mesylate 2 with hydrochloric acid has now been found to give triol 3 as the main product. Acetylation of the reaction mixture afforded triacetate 4; NMR spectrum showed three singlets at δ 1.97, 2.07 and 2.11, corresponding to three acetoxy groups and a multiplet centered at 5.10. Gradual addition of the paramagnetic shift reagent tris-dipivalomethanatoeuropium (III)[7] resolved multiplet into a doublet (at δ 5.66) corresponding to proton at C_1 and an unresolved multiplet (at δ 6.25) corresponding to protons at C_2 and C_3. Mass spectrum gave M^+544 and fragments, corresponding to elimination of three molecules of acetic acid (485, 425, 367, 364). Alkaline hydrolysis of the triacetate 4 gave triol 3 with the expected mass spectrum M^+ 418 and fragments 400, 382 and 364). Structure of the triol was further confirmed by synthesis from the epoxy-derivative (5) on reaction with 3 N-perchloric acid.[8]

EXPERIMENTAL

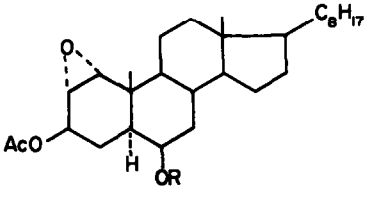
M.ps were determined with a Kofler hot-stage apparatus. NMR spectra were obtained with a Varian HA-100 instrument in $CDCl_3$ solns, using TMS as internal standard. Mass spectra were taken with a GEC-AEI MS 902 instrument.

1α,2α - Epoxy - 6β - methansulphonyloxy - 5α - cholestan - 3β - yl acetate (2)

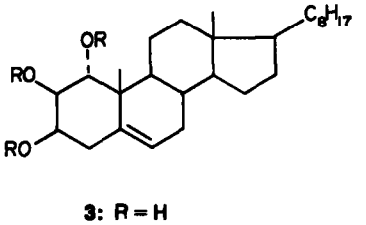
A soln of 1 (450 mg) in pyridine (3 ml) was cooled in an ice bath, methansulphonyl chloride (0.4 ml) added and the reaction mixture was left aside for 48 hr. Ice and ether were added and the ether extract was washed with dil HCl, water, $NaHCO_3$ aq soln and water. Crystallization from petroleum ether and n-hexane–ether gave 2, m.p. 109–111°, IR (film): 1745, 1245, 1030 (OAc), 1170, 1360 cm^{-1} (OSO_2CH_3), Ms: *m/e* 538, 478, 400, 383, 382, 367, 251. Before further analyses could have been performed, the sample deteriorated.

Cholest-5-en-1α,2β,3β-triyl triacetate (4)

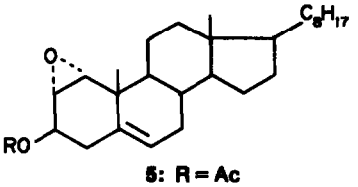
Epoxide 1 (2 g) was converted into 2 as described. The amorphous unpurified product was dissolved in ether (5 ml); MeOH (30 ml) and conc HCl (5 ml) was added and the mixture was heated under reflux for 90 min. Water was added, the product extracted in ether and washed with dil NaOH aq and water. The residue after evaporation of ether was acetylated with Ac_2O (10 ml) under reflux for 1 hr. After the usual work-up 4 was obtained after three crystallizations from 85% EtOH, m.p. 69–72°, IR: 1750, 1250, 1050 cm^{-1}; Ms: *m/e* 544, 485, 425, 367, 364, NMR: δ ($CDCl_3$) 0.90 (18-H_3, s), 1.20 (19-H_3, s), 1.97 (s), 2.07 (s)



1: R = H
2: R = SO_2CH_3



3: R = H
4: R = Ac



5: R = Ac
6: R = H

and 2.11 (s) (three OAc), 5.10 (1,2,3-H_3, m) 5.56 (6-H, d). (Found: C, 72.4; H, 9.5. $C_{33}H_{52}O_6$ requires: C, 72.8; H, 9.6%).

1α,2β-Dihydroxycholesterol (3)

(a) Triacetate 4 (200 mg) in 90% MeOH (5 ml), containing NaOH (250 mg) was left overnight at room temp. Water was added, the product filtered off, washed with water and crystallized twice from 90% MeOH and acetone to give 3, m.p. 166–169°. Ms: *m/e* 418, 400, 382, 364. (Found: C, 77.6; H, 11.3. $C_{27}H_{46}O_3$ requires: C, 77.5; H, 11.1%).

(b) Epoxide 5 (400 mg) in THF (10 ml) was treated with 3N-perchloric acid (3 ml) at room temp. for 5 hr. Product was extracted into ether and crystallized from acetone to give 3, m.p. 164–168°.

Note added in proof. Triacetate 3 was converted to the 7-dehydroderivative by a known bromination-dehydrobromination procedure (for details see for instance Ref. 2). Irradiation of the triacetate and of the corresponding triol with a medium pressure Hanovia lamp failed to give the expected previtamin D and tachysterol derivatives.

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