A PREPARATION OF 3α-METHYL-5α-CHOLESTANE-2β,3β-DIOL (1)

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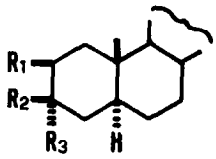
ABSTRACT

A simple preparation of 3α-methyl-5α-cholestane-2β, 3β-diol (1a) by a four-step synthesis from 2α,3α-epoxy-5α-cholestane is described.

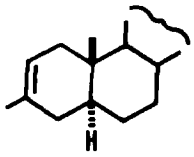
In connection with another work (2), we required large amounts of 3α-methyl-5α-cholestane-2β,3β-diol (1a). Although the Woodward cis-hydroxylation is the method of choice to obtain vicinal 5α-cholestane-2β,3β-diols, it failed (3) to give the diol 1a from 3-methyl-5α-cholest-2-ene (2). We have now found that the diol 1a may be conveniently prepared by a four-step synthesis from 2α,3α-epoxy-5α-cholestane (3) (4) (overall yield 65%).

Treatment of the epoxide 3 with benzyl alcohol and perchloric acid gave the trans-diaxial monobenzyl ether 1c which was quantitatively transformed into the benzyloxy ketone 1d by Jones oxidation. Reaction of the ketone 1d with methyllithium led to the alcohol 1e through exclusive attack from the less hindered α-side. Hydrogenolysis ($Pd(C)/H_2$) of the alcohol 1e afforded 3α-methyl-5α-cholestane-2β,3β-diol (1a), m.p. 151-3°.

Rather surprisingly, the physical and spectroscopic properties of the diol 1a were different from those reported (5) for the diol which is obtained together with the more abundant 2α,3α-diol 4 by oxidation of the olefin 2 with osmium tetroxide and to which the same structure 1a was assigned. Repetition of this last reaction under the reported



1a $R_1=R_2=OH$, $R_3=CH_3$
1b $R_1=OAc$, $R_2=OH$, $R_3=CH_3$
1c $R_1=OCH_2C_6H_5$, $R_2=H$, $R_3=OH$
1d $R_1=OCH_2C_6H_5$, $R_2,R_3=O$
1e $R_1=OCH_2C_6H_5$, $R_2=OH$, $R_3=CH_3$



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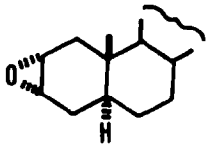

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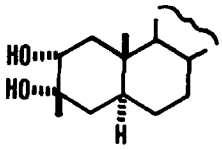

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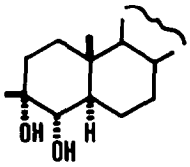

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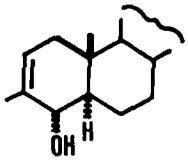

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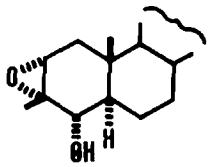

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(5) conditions has now shown that together with the 2α,3α-diol 4 (87% yield) two other diols are obtained, namely a diol (4% yield), m.p. 151-3°, identical (NMR, IR, TLC) with the diol 1a prepared as above, and a diol (5% yield), m.p. 177-9°, identical (NMR, IR, TLC) with that described in the earlier report (5). However, when the reaction was performed on the olefin 2 crystallized several times from acetone only the diols 4 (92% yield) and 1a (4% yield), m.p. 151-3°, were obtained.

The NMR (90 MHz) spectrum of the diol m.p. 177-9° displayed a doublet at δ 3.18 (J 9 Hz) due to a proton on a hydroxyl bearing carbon. The compound was tentatively assigned structure 5, with the assumption that it were formed by cis-hydroxylation of some 3-methyl-5α-cholest-3-ene which

might contaminate the Δ^2-isomer because of its method of preparation (4). The product was indeed found to be identical with authentic diol 5 prepared from the allylic alcohol 6 (6) by peracid epoxidation, followed by lithium aluminum hydride reduction.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. IR spectra were taken on a Perkin-Elmer 137 spectrometer. NMR spectra were determined on Perkin-Elmer R12A (60 MHz) or R32 (90 MHz) spectrometers with TMS as internal standard. Rotations were measured in $CHCl_3$ soln. at r.t. with a Perkin-Elmer 141 polarimeter. Mass spectra were taken on a AEI 92 spectrometer. TLC was performed on silica gel F_{254} (Merck). Silica gel 0.05-0.20 (Merck) or aluminum oxide (Woelm) were used for column chromatography. PLC was performed with silica gel F_{254} (Merck) (thickness 2 mm). GLC was carried out on a Perkin-Elmer F30 gas chromatograph.

2β-Benzyloxy-5α-cholestan-3α-ol (1c). A quantity of 1.76 g of 2α,3α-epoxy- 5α-cholestane (3) (4) in benzyl alcohol (15 ml) was treated with 70% $HClO_4$ (0.2 ml) and allowed to stand at room temperature for 1 h. Ether was added and the solution was washed with sat $NaHCO_3$ and water and evaporated in vacuo. The residue(2.7 g) was chromatographed on silica gel (80 g). Elution with 4:1 hexane-ether gave the monobenzyl ether 1c (1.9 g), m.p. 115-6° (from ethanol) (found: C 82.50; H 11.00; $C_{34}H_{54}O_2$ requires: C 82.53; H 11.00%), $[\alpha]_D$ +25° (c=1.2), NMR (CCl_4): δ 3.42 (m, 3β-H), 3.86 (m, 2α-H), 4.46 (d, $-OCH_2-$).

2β-Benzyloxy-5α-cholestan-3-one (1d). The alcohol 1c (1.55 g) was dissolved in acetone (50 ml) and oxidized with the Jones reagent at 0-5°. Usual work-up gave an oil (1.55 g) which was filtered through silica gel (10 g) (solvent: 9:1 hexane-ether) yielding the ketone 1d (1.53 g) as an oil, NMR (CCl_4): δ 3.60 (m, 2α-H), 4.35 (AB q,$-OCH_2$); IR (CCl_4): 1715 cm^{-1}.

2β-Benzyloxy-3α-methyl-5α-cholestan-3β-ol (1e). To a solution of the ketone (1d) (1.5 g) in dry THF (20 ml) CH_3Li (15 ml of a 2M solution in ether) was added in a nitrogen atmosphere and at 0°. The mixture was stirred at 0° for 1 h, water (1.5 ml) was added slowly, the solvent was evaporated and the residue was treated with water and extracted with ether. The organic layers were washed with water and evaporated to give a solid (1.6 g) which was chromatographed on silica gel (45 g). Elution with 9:1 hexane-ether gave the hydroxy ether 1e (1.2 g), m.p.126-8° (from acetone) (found: C 82.54; H 11.03; $C_{35}H_{56}O_2$ requires: C 82.62; H 11.09%), $[\alpha]_D$ +34° (c=1), NMR (CCl_4): δ 3.30 (m, 2α-H), 4.49 (AB q, $-OCH_2-$).

3α-Methyl-5α-cholestane-2β,3β-diol (1a). A)from 2β-benzyloxy-3α-methyl-5α-cholestan-3β-ol (1e). The hydroxy ether (1e) (1.1 g) was dissolved in AcOEt (70 ml) and hydrogenolized on 10% Pd/C (300 mg) (3 atm., room temperature). Usual work-up gave a solid (1.1 g) which was chromatographed on aluminum oxide (20 g, activity III). Elution with 4:1 benzene-ether gave the diol 1a (890 mg), m.p.151-3° (from methanol) (found: C 80.26; H 11.99; $C_{28}H_{50}O_2$ requires: C 80.32; H 12.04%), $[\alpha]_D$ +40° (c=0.7), NMR ($CDCl_3$): δ 1.26 (s, CH_3-C-OH), 3.64 (m, 2α-H).

The diol 1a (100 mg) was treated with Ac_2O (1 ml) in dry pyridine (2 ml) at room temperature for 24 h. Usual work-up gave a solid (112 mg). Crystallization from acetone afforded the monoacetate 1b (104 mg), m.p. 140-2° (found: C 78.12; H 11.35; $C_{30}H_{52}O_3$ requires: C 78.20; H 11.38%), $[\alpha]_D$ +47° (c=1), NMR (CCl_4): δ 1.99 (s, CH_3COO-), 4.63 (m, 2α-H).

B) from 3-methyl-5α-cholest-2-ene (2). The olefin 2 (400 mg), prepared as reported in ref. 4, crystallized once from acetone, m.p. 83-4°, one peak at GLC (2.5% SE-30 on 80-100 mesh Chromosorb W AW-DMCS, column temperature 200°, flow rate (N_2): 30 ml/min, column dimensions: 6 ftx1/8 in o.d.), was treated with OsO_4 as described (5). PLC on silica gel/H_3BO_3 (97:3 benzene-methanol, 4 runs) of crude diols (416 mg) gave the diol 4 (5) (379 mg) (87% yield), the diol 5 (22 mg, 5% yield) and the diol 1a (17 mg, 4% yield). This latter was identical (mixed m.p., IR, NMR, TLC) with the diol 1a obtained by hydrogenolysis of the hydroxy ether 1e.

The diol 5 had m.p. 177-9° (from methanol) (found: C 80.28; H 11.98: $C_{28}H_{50}O_2$ requires: C 80.32; H 12.04%),

$[\alpha]_D$ +8° (c=0.6), MS: M^+ 418, NMR ($CDCl_3$): δ 1.27 (s, CH_3-C-OH), 3.18 (d, J 9 Hz, 4β-H).

When the olefin 2 was crystallized six times from acetone (m.p. 84-84.5°), the above oxidation with OsO_4 gave only diols 4 (400 mg) and 1a (18 mg).

3β-Methyl-5α-cholestane-3α,4α-diol (5) from 3-methyl-5α-cholest-2-en-4α-ol (6). The allylic alcohol 6 (6) (150 mg) was dissolved in ether (10 ml) and p-nitroperbenzoic acid (100 mg) was added at 0°. The mixture was allowed to stand at 0° overnight. Usual work-up gave pure 2α,3α-epoxy-3β-methyl-5α-cholestan-4α-ol (7) (150 mg), m.p. 197-200° (from ethanol) (found: C 80.65; H 11.57; $C_{28}H_{48}O_2$ requires: C 80.71; H 11.61%), $[\alpha]_D$ +1° (c=1), NMR (CCl_4): δ 1.36 (s, 3β-CH_3), 3.00 (d, J 5 Hz, 4β-H), 3.25 (m, 2β-H).

The epoxy alcohol 7 (100 mg) was treated in ether (10 ml) with $LiAlH_4$ (50 mg) (reflux, 3 h). Usual work-up gave the pure diol 5 (97 mg). It was identical (mixed m.p., IR, NMR, TLC) with the diol 5, m.p. 177-9°, obtained as above.

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1. This work has been supported by the Consiglio Nazionale delle Ricerche.
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