Unsaturated Steroids. Part 8.[1] Synthesis of Ergosta-5,7-diene-1α,3β-diol, the 4,4-Dimethyl Analogue, and 4,4-Dimethylergosta-5,7-dien-3β-ol

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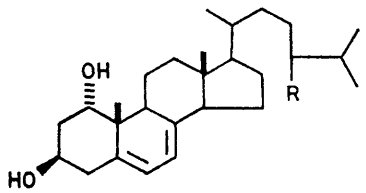
From 5α-ergost-7-en-3-one, by employing the method used [2] for the preparation of the cholestane analogue, ergosta-5,7-diene-1α,3β-diol (1; R = Me) has been synthesised. Methylation of ergosta-1,4,7-trien-3-one (2) gave 4,4-dimethylergosta-1,5,7-trien-3-one. The corresponding 1α,2α-epoxide (3), furnished 4,4-dimethylergosta-5,7-diene-1α,3α-diol (4; R = α-OH) and the corresponding 1α,3β-diol (4; R = β-OH). 4,4-Dimethylergosta-5,7-dien-3β-ol has been obtained from 22,23-dihydroergosterol by standard methods.

In connection with our interest in hydroxylated steroidal 5,7-dienes [2,3] and their potential vitamin D-like activity we have recently [2] synthesised cholesta-5,7-diene-1α,3β-diol (1; R = H) from 5α-cholest-7-en-3-one. By a similar approach [2] from 5α-ergost-7-en-3-one we have now synthesised ergosta-5,7-diene-1α,3β-diol (1; R = Me) and certain derivatives for biological evaluation.

Methylation of ergosta-1,4,7-trien-3-one (2), derived from the synthesis of (1; R = Me), gave 4,4-dimethylergosta-1,5,7-trien-3-one, which readily furnished the 1α,2α-epoxide (3), without prior protection of the 5,7-diene system (*cf.* ref. 3). Reduction of (3) with aluminium amalgam formed 1α-hydroxy-4,4-dimethylergosta-5,7-dien-3-one, which on further reduction with



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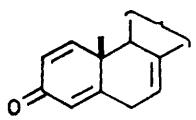

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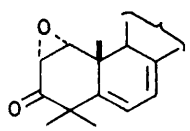

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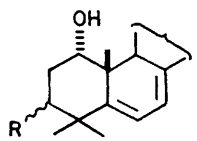

(4)

sodium borohydride gave 4,4-dimethylergosta-5,7-diene-1α,3α-diol (4; R = α-OH) and the epimeric 1α,3β-diol (4; R = β-OH). The structural assignments of these diols are based upon arguments previously advanced.[3]

In an alternative approach to (4; R = β-OH) neither 3β-acetoxy-4,4-dimethylergosta-5,7,22-triene nor the corresponding 3β-ol [4] could be selectively hydrogenated at the 22,23-position under a variety of conditions: the 22,23- and 5,6-double bonds were reduced simultaneously to yield, finally, 3β-acetoxy-4,4-dimethylergost-7-ene.

The biological results will be reported elsewhere.

EXPERIMENTAL

Optical rotations were observed for solutions in chloroform; i.r. spectra were determined for Nujol mulls; n.m.r. spectra were recorded for solutions in deuteriochloroform at 60 MHz and u.v. spectra for solutions in ethanol.

5α-Ergost-7-en-3-one.—Prepared as for the cholestane analogue [2] from ergost-7-en-3β-ol (7 g) during 10 min, *5α-ergost-7-en-3-one* formed needles (5.6 g), m.p. 161—163° (from methanol–acetone); $[\alpha]_D^{22}$ +21° (*c* 2.35); $\nu_{max.}$ 1 705 cm^{-1} (C=O) (Found: C, 84.7; H, 11.8. $C_{28}H_{46}O$ requires C, 84.4; H, 11.6%).

Ergosta-1,4,7-trien-3-one.—Prepared from a solution of 5α-ergost-7-en-3-one (10 g) in tetrahydrofuran (200 ml) containing phenyltrimethylammonium perbromide (18 g) as for the cholestane analogue,[2] 2ξ,4ξ-dibromo-5α-ergost-7-en-3-one (9.1 g) was normally used directly for the next reaction. Purification from ether–methanol gave the *dibromide* in needles, m.p. 187—188°; $[\alpha]_D^{22}$ −17.2° (*c* 0.99); $\nu_{max.}$ 1 740 cm^{-1} (C=O); τ 4.75 (1 H, d, *J* 5.2 Hz, H-7) and 4.91—5.12br (2 H, m, H-2 and -4) (Found: C, 60.4; H, 8.0; Br, 28.8. $C_{28}H_{44}Br_2O$ requires C, 60.5; H, 8.0; Br, 28.7%).

Prepared from the unpurified dibromide (9 g), as for the cholestane analogue,[2] *ergosta-1,4,7-trien-3-one* (3.5 g) formed needles, m.p. 141° (from ether–methanol); $[\alpha]_D^{22}$ −17.1° (*c* 2.35); $\nu_{max.}$ 1 660 cm^{-1} (C=O); τ 2.90 (1 H, d, $J_{1,2}$ 10 Hz, H-1), 3.15 (1 H, d, $J_{1,2}$ 10 Hz, H-2), and 4.75br (1 H, s, H-7); $\lambda_{max.}$ 242 nm (log ε 4.18) (Found: C, 85.0; H, 10.8. $C_{28}H_{42}O$ requires C, 85.2; H, 10.7%).

Ergosta-1,5,7-trien-3β-ol.—Prepared from a solution of ergosta-1,4,7-trien-3-one (5 g) in benzene (200 ml), containing toluene-*p*-sulphonic acid (2.5 g) and isopropenyl acetate (50 ml) at the b.p. during 2 h, *ergosta-1,3,5,7-tetraen-3-yl acetate* (3.8 g) formed pale yellow needles, m.p. 137—139° (from ether–methanol containing a trace of pyridine); $[\alpha]_D^{23}$ −430° (*c* 1.12); $\nu_{max.}$ 1 760, 1 640, and 1 580 cm^{-1}; $\lambda_{max.}$ 251 (log ε 4.97) and 360 nm (4.86); τ 4.03br (4 H, s) and 7.81 (3 H, s, CH_3COO) (Found: C, 82.4; H, 10.2. $C_{30}H_{44}O_2$ requires C, 82.5; H, 10.2%).

A solution of this acetate (1 g) in ether (100 ml) was reduced at 4 °C during 20 min with a solution of calcium borohydride [prepared from calcium chloride (6 g) and sodium borohydride (5 g) dissolved in methanol (140 ml) and ethanol (160 ml) at 0 °C]. The resultant *ergosta-1,5,7-*

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[2] A. Emke, D. Hands, J. M. Midgley, W. B. Whalley, and (in part) R. Ahmad, *J.C.S. Perkin I*, 1977, 820.

[3] J. Brynjolffissen, J. M. Midgley, and W. B. Whalley, *J.C.S. Perkin I*, 1977, 812.

[4] G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 1955, 2998.

trien-3β-*ol* (0.6 g) separated from ether–methanol in needles, m.p. 142°; $[\alpha]_D^{22}$ −134° (*c* 0.62); $\nu_{max.}$ 3 400—3 250 cm^{-1}; $\lambda_{max.}$ 262 (log ε 3.86), 270 (3.98), 280 (4.01), and 290 nm (3.73) (Found: C, 84.6; H, 11.3. $C_{28}H_{44}O$ requires C, 84.8; H, 11.2%).

The *adduct* of this alcohol (0.5 g) with 4-phenyl-1,2,4-triazoline-3,5-dione formed needles (0.5 g), m.p. 148° (from ether–methanol); $[\alpha]_D^{23}$ −9.8° (*c* 1.38) (Found: C, 75.7; H, 8.8; N, 7.0. $C_{36}H_{49}N_3O_3$ requires C, 75.6; H, 8.6; N, 7.4%).

Ergosta-5,7-*diene*-1α,3β-*diol*.—Prepared from the previous adduct (1 g) as for the cholestane analogue,[2] the *t-butyldimethylsilyl ether* (1 g) formed needles, m.p. 184—185° (from ether–methanol); $[\alpha]_D^{25}$ +5.4° (*c* 1.04) (Found: C, 73.5; H, 9.3; N, 6.1. $C_{42}H_{63}N_3O_3Si$ requires C, 73.6; H, 9.4; N, 6.1%). This silyl ether (1 g) furnished the corresponding 1α,2α-*epoxide* (0.8 g) (*cf.* ref. 2) in needles, m.p. 172—174° (from ether–methanol); $[\alpha]_D^{22}$ −35.0° (*c* 1.21); τ 2.58 (5 H, s, ArH), 3.65 (2 H, dd, $J_{6,7}$ 8 Hz, H-6 and -7), 5.05 (1 H, m, H-3α), 6.81br (4 H, s, H-1, -2, and -4), 9.11 (9 H, s, Bu^t), and 9.98 (6 H, s, $SiMe_2$) (Found: C, 71.8; H, 9.1; N, 5.7. $C_{42}H_{63}N_3O_4Si$ requires C, 71.9; H, 9.0; N, 6.0%).

Removal of the silyl ether residue from this epoxide (1 g) as for the cholestane analogue [2] gave the *adduct* of 1α,2α-epoxyergosta-5,7-dien-3β-ol in needles (0.5 g), m.p. 202° (from ether–methanol); $[\alpha]_D^{23}$ −90° (*c* 1.69); $\nu_{max.}$ 3 420 cm^{-1}; τ 2.62 (5 H, s, ArH), 3.73 (2 H, dd, $J_{6,7}$ 8 Hz, H-6 and -7), 5.05 (1 H, m, H-3α), and 6.81br (2 H, s, H-1 and -2) (Found: C, 73.4; H, 8.4; N, 7.1. $C_{36}H_{49}N_3O_4$ requires C, 73.6; H, 8.4; N, 7.2%).

Reduction of this epoxide adduct (0.5 g) with lithium aluminium hydride (0.5 g) (*cf.* ref. 2) gave *ergosta*-5,7-*diene*-1α,3β-*diol* (0.25 g) in needles, m.p. 168—170° (from ether–methanol); $[\alpha]_D^{22}$ −35° (*c* 1.0); $\nu_{max.}$ 3 400—3 300 cm^{-1}; $\lambda_{max.}$ 263 (log ε 3.90), 2.71 (4.04), 282 (4.07), and 293 nm (3.84); τ 4.22 (1 H, d, $J_{6,7}$ 5.2 Hz, H-6) and 4.60 (1 H, d, $J_{6,7}$ 5.2 Hz, H-7) (Found: C, 80.8; H, 11.2%; M^+, 414.3478. $C_{28}H_{46}O_2$ requires C, 81.1; H, 11.2%; *M*, 414.3498).

4,4-*Dimethylergosta*-5,7-*diene*-1α,3β-*diol*.—Methyl iodide (4 ml) was added to a solution of ergosta-1,4,7-trien-3-one (2 g) in t-butyl alcohol (40 ml) containing dissolved potassium (1 g) at 0 °C under nitrogen. Next day the product was isolated in the usual manner and purified from ether–methanol to yield 4,4-*dimethylergosta*-1,5,7-*trien*-3-*one* (1.5 g) in needles, m.p. 102°; $[\alpha]_D^{26}$ +54.9° (*c* 1.46); $\lambda_{max.}$ 274 (ε 10 611) and 215 nm (11 966); τ 3.24 (1 H, d, $J_{1,2}$ 10 Hz, H-1), 4.19 (1 H, d, $J_{1,2}$ 10 Hz, H-2), 4.27 (2 H, q, $J_{6,7}$ 26.4 Hz, H-6 and -7), 8.71 (6 H, s, 4-Me_2), 8.80 (3 H, s, 10-Me), and 9.39 (3 H, s, 13-Me); $\nu_{max.}$ 1 675 cm^{-1} (C=O) (Found: C, 85.3; H, 11.2%; M^+, 422. $C_{30}H_{46}O$ requires C, 85.2; H, 11.0%; *M*, 422).

4N-Sodium hydroxide (1 ml) and hydrogen peroxide (100 vol; 2 ml) were added to a stirred solution (at 0 °C) of this triene (2 g) in ether (100 ml) and methanol (200 ml). Next day, the product was isolated, with ether, to yield 1α,2α-*epoxy*-4,4-*dimethylergosta*-5,7-*dien*-3-*one* (1.8 g), which formed needles, m.p. 148—150° (from ether–methanol); $[\alpha]_D^{26}$ +27.3° (*c* 2.49); $\nu_{max.}$ 1 710 cm^{-1} (C=O); τ 4.30 (2 H, q, *J* 28 Hz, H-6 and -7), 6.46 (2 H, s, H-1 and -2), and 8.64 (6 H, s, 4-Me_2); $\lambda_{max.}$ 271 (ε 9 537) and 282 nm (9 442) (Found: C, 82.3; H, 10.7%; M^+, 438. $C_{30}H_{46}O_2$ requires C, 82.1; H, 10.6%; *M*, 438).

Aqueous sodium hydrogen carbonate (10%; 1 ml) and freshly prepared aluminium amalgam [from aluminium turnings (10 g)] were added to a solution of this epoxide (1 g) in ether (100 ml) and ethanol (30 ml). The mixture was stirred overnight, chloroform (60 ml) was added, and the mixture was filtered through Celite and evaporated. The residue was purified from acetone to give 1α-*hydroxy*-4,4-*dimethylergosta*-5,7-*dien*-3-*one* (0.85 g) in plates, m.p. 188—190°; $[\alpha]_D^{26}$ −86° (*c* 1.87); $\nu_{max.}$ 1 705 cm^{-1} (C=O); $\lambda_{max.}$ 273 (ε 12 222) and 282 nm (11 707); τ 4.23 (2 H, q, $J_{6,7}$ 28 Hz, H-6 and -7), 8.64 (9 H, s, 4-Me_2 and 10-Me), and 9.35 (3 H, s, 13-Me) (Found: C, 81.9; H, 11.3%; M^+, 440. $C_{30}H_{48}O_2$ requires C, 81.8; H, 11.0%; *M*, 440).

A solution of the preceding ketone (0.4 g) in methanol (100 ml) was reduced by addition of sodium borohydride (1 g), during 15 min, to yield a mixture which was purified by chromatography on silica [benzene–ether (85 : 15)] to yield (i) 4,4-*dimethylergosta*-5,7-*diene*-1α,3α-*diol* (0.1 g) in needles, m.p. 195—198° (from methanol); $[\alpha]_D^{26}$ −142° (*c* 0.81); $\nu_{max.}$ 3 100—3 540 cm^{-1}; $\lambda_{max.}$ 273 (ε 10 241) and 282 nm (10 241); τ 4.29 (2 H, q, $J_{6,7}$ 34 Hz, H-6 and -7), 6.38 (2 H, m, H-1 and -3), and 8.77 (6 H, s, 4-Me_2) (Found: C, 80.8; H, 11.5%; M^+, 442. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.4%; *M*, 442), (ii) [eluted with benzene–ether (3 : 1)] 4,4-*dimethylergosta*-5,7-*diene*-1α,3β-*diol* (0.2 g), which formed needles, m.p. 180° [from light petroleum (b.p. 60—80 °C)]; $[\alpha]_D^{26}$ −132° (*c* 0.83); $\nu_{max.}$ 3 200—3 610 cm^{-1}; $\lambda_{max.}$ 273 (ε 10 332) and 282 nm (10 332); τ 4.22 (2 H, q, $J_{6,7}$ 35 Hz, H-6 and -7), 6.22 (2 H, m, H-1 and -3), and 8.76 (6 H, s, 4-Me_2) (Found: C, 81.0; H, 11.5%; M^+, 442. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.4%; *M*, 442).

4,4-*Dimethylergost*-7-*en*-3β-*yl Acetate*.—Oppenauer oxidation of 22,23-dihydroergosterol [1] (2 g) gave a mixture of the 4-en- and 5-en-3-ones, which was methylated directly by potassium t-butoxide–methyl iodide process to yield 4,4-*dimethylergosta*-5,7-*dien*-3-*one*; this was purified by chromatography on silica from light petroleum (b.p. 60—80 °C)–ether (98 : 2) to yield needles (0.8 g), m.p. 142° (from acetone); $[\alpha]_D^{25}$ −46° (*c* 1.0); $\nu_{max.}$ 1 710 cm^{-1} (C=O) (Found: C, 84.6; H, 11.5. $C_{30}H_{48}O$ requires C, 84.8; H, 11.4%).

Reduction of this ketone (0.13 g) with lithium aluminium hydride gave 4,4-*dimethylergosta*-5,7-*dien*-3β-*ol* (0.1 g) in plates, m.p. 174° (from methanol); $[\alpha]_D^{25}$ −143° (*c* 1.0); $\nu_{max.}$ 3 400 and 3 050 cm^{-1} (OH); $\lambda_{max.}$ 273 nm (log ε 4.07) (Found: C, 84.4; H, 11.8. $C_{30}H_{50}O$ requires C, 84.4; H, 11.8%).

The *acetate* formed plates, m.p. 164° (from methanol); $[\alpha]_D^{25}$ −113° (*c* 0.81) (Found: C, 81.6; H, 11.2. $C_{32}H_{52}O_2$ requires C, 82.0; H, 11.2%).

Hydrogenation of 3β-acetoxy-4,4-dimethylergosta-5,7,22-triene [4] (1 g) dissolved in ethyl acetate (200 ml) containing W2 Raney nickel (5 g) occurred during 12 h, to yield 4,4-*dimethylergost*-7-*en*-3β-*yl acetate* (0.7 g), which formed needles, m.p. 148° (from methanol–ether); $[\alpha]_D^{20}$ 4.8° (*c* 1.3); τ 4.80 (1 H, m, H-7), 5.45 (1 H, m, H-3), and 7.96 (3 H, s, $OCOCH_3$) (Found: C, 82.2; H, 11.8. $C_{32}H_{54}O_2$ requires C, 81.6; H, 11.6%).

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