18-Norandrosta-8,11,13-trienes. Part III.[1] 1-Amino-derivatives

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The syntheses of 1α-amino-17,17-dimethyl-18-nor-5α-androsta-8,11,13-triene (9e) and its *N*-methyl derivatives are described. Bromination–dehydrobromination of 1α-benzoyloxy-17,17-dimethyl-18-nor-5α-androst-13-ene (6b) gave 1α-benzoyloxy-17,17-dimethyl-18-nor-5α-androsta-7,13-diene (7), which on subsequent bromination–dehydrobromination and saponification gave 17,17-dimethyl-18-nor-5α-androsta-8,11,13-trien-1α-ol (9a). This was converted into the 1α-amino-derivatives *via* the ketone (8a). Reduction of 17,17-dimethyl-18-nor-5α-androsta-8,11,13-trien-1-one (8a) with sodium in alcohol gave a mixture of the 1α- and 1β-alcohols (9a) and (10), whereas reduction with lithium aluminium hydride gave the 1α-epimer (9a) stereospecifically. Both methods of reduction when applied to the corresponding 1-oxime (8b) gave entirely the 1α-amine (9e), a result which is explained in terms of steric interaction between positions 1 and 11. The corresponding 1β-amines could not be prepared.

As part of a programme [2] to evaluate the biological activities of ring-C-aromatic steroids, we have investigated the synthesis of derivatives of 1α-amino-17,17-dimethyl-18-nor-5α-androsta-8,11,13-triene (9e), thereby hoping to incorporate into a steroid the phenethylamino-pharmacophore contained in many biologically active substances, such as (−)-noradrenaline, (+)-amphetamine, and (−)-morphine.

This paper describes a useful route to a ring-C-aromatic steroid containing an oxygen function at position 1, from the corresponding Δ^{13}-18-nor-steroid, by a modification of the procedure previously reported.[1] The intermediate 17,17-dimethyl-18-nor-5α-androst-13-en-1α-ol

[1] Part II, C. L. Hewett, I. M. Gilbert, J. Redpath, D. S. Savage, J. Strachan, T. Sleigh, and R. Taylor, *J.C.S. Perkin I*, 1974, 897.

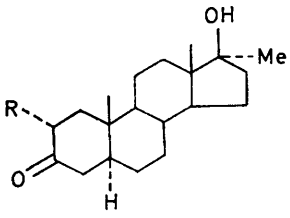
[2] C. L. Hewett, S. G. Gibson, I. M. Gilbert, J. Redpath, and D. S. Savage, *J.C.S. Perkin I*, 1973, 1967.

(6a) was conveniently prepared from the 3-ketone [3] (1a) by an adaptation of the method of Djerassi, Berkoz, and Williams [4] which is shorter and gives better yields than other methods described.[5] Examination of the bromination of 17β-hydroxy-17α-methyl-5α-androstan-3-one (1a) in acetic acid solution, reported [6] to give 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (1b) in poor yield, revealed that the product was 2α-bromo-17,17-dimethyl-18-nor-5α-androst-13-en-3-one (2), formed by an acid-catalysed Wagner–Meerwein shift [7] of the 13β-methyl group to position 17. Optimal yields of the 2α-bromo-3-ketone (2) were obtained by brominating in the presence of 1 equiv. of sodium acetate trihydrate. The 2α-configuration of the bromine atom was confirmed by the n.m.r. spectrum, which shows the 1α-proton signal as a pseudo-triplet at δ 1·82 (J 12 Hz), the 1β-proton signal as a quartet at δ 2·73 (J 6 and 12 Hz), and the 2β-proton signal as a quartet at δ 4·80 (J 6 and 12 Hz). Dehydrobromination was carried out with calcium carbonate in dimethylacetamide [8] to give the Δ^1-ketone (3), which on treatment with alkaline hydrogen peroxide [9] gave 1α,2α-epoxy-17,17-dimethyl-18-nor-5α-androst-13-en-3-one (4). Reduction of the keto-epoxide (4) with hydrazine hydrate [4] gave the 1α-hydroxy-2,13-diene (5), which was hydrogenated selectively to give 17,17-dimethyl-18-nor-5α-androst-13-en-1α-ol (6a).

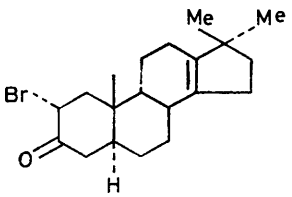
Dehydrogenation of the benzoate (6b) by the bromination technique described in Part II [1] gave the ring-c-aromatic steroid (9b) in high yield; this was converted into the 1α-alcohol (9a) by treatment with lithium aluminium hydride. The aromatic nature of the product was confirmed by the u.v. absorption at 276 nm (ε 900) and by the n.m.r. spectrum which shows a quartet at δ 7·18 and 6·93 (J_{AB} 8 Hz) corresponding to the aromatic 11- and 12-protons, a multiplet centred at δ 2·70 for the four benzylic protons at positions 7 and 15, and a singlet at δ 4·46 ($W_{\frac{1}{2}}$ 6·5 Hz) for the equatorial 1β-proton.

Oxidation of the aromatic 1α-alcohol (9a) with Jones reagent [10] gave the ketone (8a), the oxime (8b) of which on reduction with lithium aluminium hydride or sodium in refluxing propan-2-ol gave exclusively the 1α-amine (9e).

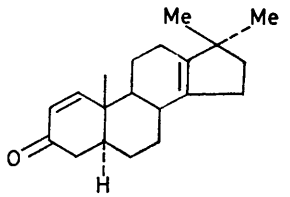
The 1α-configuration of the amino-group was confirmed by the n.m.r. spectrum, which shows the presence of an equatorial 1β-proton [δ 3·46 ($W_{\frac{1}{2}}$ 6 Hz)]. The axial 1α-amine (9e) is thermodynamically favoured because of strong steric interactions between C-1 and C-11 which resist the formation of the 1β-epimer. Martin-Smith and Allaudin [11] have pointed out that similar interactions between C-1 and C-11 favour formation of the axial



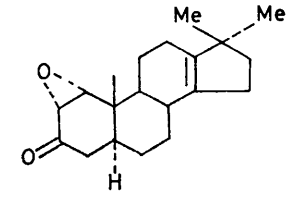
(1) a; R = H
b; R = Br



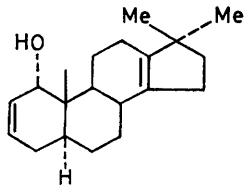
(2)



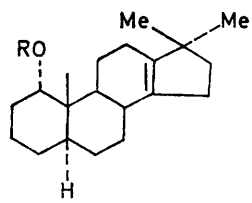
(3)



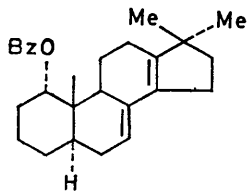
(4)



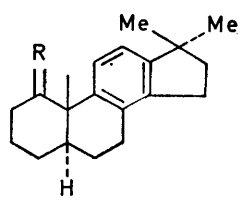
(5)



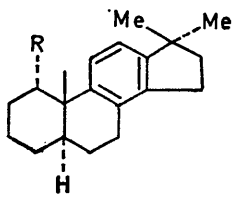
(6) a; R = H
b; R = Bz



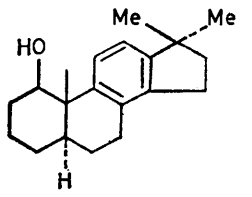
(7)



(8) a; R = O
b; R = NOH



(9) a; R = OH e; R = NH_2
b; R = OBz f; R = NHMe
c; R = OTs g; R = NMe_2
d; R = OMs h; R = NH·CHO



(10)

[3] L. Ruzicka, P. Meister, and V. Prelog, *Helv. Chim. Acta.* 1947, **30**, 867.
[4] C. Djerassi, D. H. Williams, and B. Berkoz, *J. Org. Chem.*, 1962, **27**, 2205.
[5] (*a*) P. Striebel and Ch. Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094; (*b*) P. A. Plattner, A. Furst, and H. Els, *ibid.*, p. 1399; (*c*) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1956, 3289; (*d*) C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *ibid.*, 1961, 1583.
[6] B.P. 750,843/1956.
[7] B. Pelc, *Coll. Czech. Chem. Comm.*, 1964, **29**, 1029 (*Chem. Abs.*, 1964, **60**, 14559a).
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[9] P. S. Wharton, *J. Org. Chem.*, 1961, **26**, 4781.
[10] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.
[11] M. Allaudin and M. Martin-Smith, *J. Org. Chem.*, 1963, **28**, 886.

1α-epimer of 1-aminocholestane [5d] from the corresponding 1-oxime.

The 1α-amino-epimer (9e) was also obtained by hydrolysis of the formylamino-derivative (9h), formed by a Leuckart reaction [12] of the 1-ketone (8a) with formamide–formic acid. Here also steric interaction between the 1β-position and C-11 thermodynamically favours the axial formylamino-compound (9h), which is formed exclusively. Similar reactions with bulky secondary bases such as pyrrolidine, piperidine, and morpholine did not affect the ketone, probably because steric hindrance by the 11-proton precludes the formation of a planar iminium ion intermediate.[13]

Reduction of the 1α-formylamino-compound (9h) with lithium aluminium hydride gave the 1α-methylamino-derivative (9f); the 1α-dimethylamino-derivative (9g) was prepared by the action of formaldehyde and formic acid on the 1α-amine (9e).

Reduction of the 1-ketone (8a) with sodium and propan-2-ol gave a mixture (3 : 1) of the 1α-alcohol (9a) and the 1β-alcohol (10), separated by preparative t.l.c. The 11-proton is unusually deshielded in the 1β-epimer (10), giving an n.m.r. signal at δ 8·10, an effect caused by the strong, non-bonded interaction [14] with the 1β-hydroxy-group. Such an interaction is not shown by the 1α-hydroxy-epimer nor any of the 1α-amino-derivatives, and is taken as further proof of their stereochemistry. The 1α-hydroxy-epimer (9a) was formed exclusively on reduction of the 1-ketone (8a) with lithium aluminium hydride.

Attempts to prepare 1β-amines from the 1α-mesylate (9d) or -tosylate (9c) with secondary bases such as piperidine resulted only in elimination of the mesylate or tosylate group. Similar efforts to replace these groups with an azido-group using sodium azide in *N*-methylpyrrolidone were also unsuccessful.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were determined with a Perkin-Elmer 457 spectrometer. U.v. spectra were determined with a Perkin-Elmer 402 spectrometer for solutions in ethanol. Optical rotations were measured for solutions in chloroform at room temperature unless otherwise stated. G.l.c. was performed with a Pye–Argon chromatograph. Quoted retention times are relative to cholestane (t_R 1·0). N.m.r. spectra for solutions in $CDCl_3$ were determined at 60 Hz with a Perkin-Elmer R12B spectrometer with tetramethylsilane as internal standard. Light petroleum refers to the fraction of b.p. 40—60°.

Unless otherwise stated, products were isolated by diluting the reaction mixture with water, extracting with ether, washing the extract with sodium hydrogen carbonate solution and water, drying (Na_2SO_4), and removing the solvent under vacuum.

17β-*Hydroxy*-17α-*methyl*-5α-*androstan*-3-*one* (1a).—Jones reagent [10] (260 ml) was added carefully to a stirred solution of 17α-methyl-5α-androstane-3β,17β-diol (200 g) in glacial acetic acid (4 l) at 20°, stirring was continued for 10 min, and the solution was diluted with water (60 l). The orange solid was filtered off, dissolved in acetone, and treated with 10N-sulphuric acid. The crude product crystallised from acetone–water to give the hydroxy-ketone (1a) (157 g), m.p. 189—191° (lit.,[3] 190—191°).

2α-*Bromo*-17,17-*dimethyl*-18-*nor*-5α-*androst*-13-*en*-3-*one* (2).—The hydroxy-ketone (1a) (50 g) in acetic acid solution (1 l) containing sodium acetate trihydrate (25 g) and bromine (12·5 ml) was kept in the dark at room temperature for 8 days. The solution darkened and the product crystallised out as long needles. The solution was diluted with aqueous 10% sodium hydrogen sulphite (10 l) and the solid was filtered off, washed several times with water, and air dried. Crystallisation twice from methylene chloride–ether furnished the bromo-ketone (2) (41 g), m.p. 197—200°, $[\alpha]_D$ +4·1° (*c* 0·51) (lit.,[7] m.p. 195—199°, $[\alpha]_D$ +12°), $\nu_{max.}$ (KCl) 1720 cm^{-1} (2α-bromo-3-ketone), $\nu_{max.}$ (CH_2Cl_2) 1730 cm^{-1}, δ 0·93 (6H, s, 17,17-Me_2), 1·06 (3H, s, 10-Me), 1·82 (1H, t, *J* 12 Hz, 1α-H), 2·73 (1H, q, *J* 12 and 6 Hz, 1β-H), and 4·80 (1H, q, *J* 12 and 6 Hz, 2β-H) (Found: C, 65·8; H, 8·0; Br, 21·8. Calc. for $C_{20}H_{29}BrO$: C, 64·8; H, 8·0; Br, 21·9%).

17,17-*Dimethyl*-18-*nor*-5α-*androsta*-1,13-*dien*-3-*one* (3).—The bromo-ketone (2) (11 g) was added to a stirred suspension of calcium carbonate (11 g) in refluxing dimethylacetamide (100 ml) and heating was continued for 5 min. The cooled solution was filtered through Dicalite, the crude product was isolated and dissolved in ether, and the solution was filtered through a small column of alumina (25 g). Crystallisation from methanol–water gave the dienone (3) (7·4 g). Two recrystallisations from methanol–water furnished a sample of m.p. 89—92°, $[\alpha]_D$ +23·6° (*c* 0·5) (lit.,[7] m.p. 90—92°, $[\alpha]_D$ +30°), $\lambda_{max.}$ 230 nm (ε 10,600), $\nu_{max.}$ (KCl) 1682 cm^{-1} (Δ¹-3-ketone), $\nu_{max.}$ (CH_2Cl_2) 1677 cm^{-1}, δ 0·97 (6H, s, 17,17-Me_2), 0·99 (3H, s, 10-Me), 5·88 (1H, d, *J* 10 Hz, 1-H), and 7·20 (1H, d, *J* 10 Hz, 2-H) (Found: C, 84·2; H, 10·2. Calc. for $C_{20}H_{28}O$: C, 84·5; H, 9·9%).

1α,2α-*Epoxy*-17,17-*dimethyl*-18-*nor*-5α-*androst*-13-*en*-3-*one* (4).—Aqueous 4N-sodium hydroxide (15 ml) and aqueous hydrogen peroxide (30%; 18 ml) were added carefully to a solution of the dienone (3) (20 g) in ethanol (200 ml) at 25° over 5 min, and stirring was continued for a further 10 min. The solution was diluted with brine and the product was isolated and crystallised from methanol to give the *epoxy-ketone* (4) (13·4 g), m.p. 87—90°, $[\alpha]_D$ +67·3° (*c* 0·7), $\lambda_{max.}$ 221 nm (ε 1500), $\nu_{max.}$ (KCl) 1700 cm^{-1} (3-ketone), $\nu_{max.}$ (CH_2Cl_2) 1710 cm^{-1}, δ 0·87 (3H, s, 10-Me), 0·96 (6H, s, 17,17-Me_2), 3·27 (1H, d, *J* 4·5 Hz, 1β-H), and 3·62 (1H, d, *J* 4·5 Hz, 2β-H) (Found: C, 80·3; H, 9·4. $C_{20}H_{28}O_2$ requires C, 80·0; H, 9·4%). Chromatography of the crystallisation residue (6 g) on a column of acid-washed alumina [15] (180 g) (elution with 2% benzene–ethyl acetate) yielded a further crop (1·8 g) of epoxide, m.p. 86—89°.

17,17-*Dimethyl*-18-*nor*-5α-*androsta*-2,13-*dien*-1α-*ol* (5).—A suspension of the epoxy-ketone (4) (14 g) in hydrazine hydrate (60 ml) was heated under reflux for 20 min.[4] It was then cooled to room temperature and the hydrazine hydrate was decanted. The residual solid was washed with water and dissolved in ether (200 ml). The solution was washed with brine (2 × 200 ml), dried ($MgSO_4$), and filtered

[12] M. L. Moore, *Org. Reactions*, 1949, **5**, 301.

[13] (*a*) J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1956, 265; (*b*) N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.*, 1957, **79**, 6210.

[14] J. W. ApSimon, R. R. King, and J. J. Rosenfeld, *Canad. J. Chem.*, 1969, **47**, 1991.

[15] K. R. Farrer, J. C. Hamlet, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 1952, 2657.

through a column of acid-washed [15] alumina (100 g) (elution with ether). The solvent was evaporated off and the residue was crystallised from aqueous acetone to give the *dienol* (5) (11·8 g). Recrystallisation from light petroleum furnished a sample of m.p. 126—129°, $[\alpha]_D$ +85·1° (*c* 1·22), $\nu_{max.}$ (KCl) 3325 cm^{-1} $\nu_{max.}$ (CH_2Cl_2) 3610 cm^{-1}, δ 0·69 (3H, s, 10-Me), 0·95 (6H, s, 17,17-Me_2), 3·80 (1H, t, *J* 3 Hz, 1β-H), 5·75 (1H, d, *J* 10 Hz, 3-H), and 5·97 (1H, d, *J* 10 Hz, 2-H) (Found: C, 84·0; H, 10·5. $C_{20}H_{30}O$ requires C, 83·9; H, 10·6%).

17,17-*Dimethyl*-18-*nor*-5α-*androst*-13-*en*-1α-*ol* (6a).—The dienol (5) (2 g) in cyclohexane (20 ml) was shaken with hydrogen over 5% palladium–charcoal (500 mg) at room temperature and atmospheric pressure for 5 h. The solution was filtered through Dicalite, then evaporated, and the residue was crystallised from light petroleum to give the 13-*en*-1α-*ol* (6a) (1·8 g). Recrystallisation from light petroleum furnished a sample of m.p. 109—111°, $[\alpha]_D$ −6·4° (*c* 0·95), $\nu_{max.}$ (KCl) 3390 cm^{-1}, $\nu_{max.}$ (CH_2Cl_2) 3620 cm^{-1}, δ 0·78 (3H, s, 10-Me), 0·95 (6H, s, 17,17-Me_2), and 3·78 (1H, s, 1β-H) (Found: C, 83·6; H, 11·1. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%).

1α-*Benzoyloxy*-17,17-*dimethyl*-18-*nor*-5α-*androst*-13-*ene* (6b).—Benzoyl chloride (1 ml) was added carefully to a stirred solution of the 1α-alcohol (6a) (1 g) in dry pyridine (10 ml) at 0—5° and stirring was continued at room temperature for 10 h. The solution was diluted with water and the solid was filtered off, dried, and crystallised from ether–methanol to give the 1α-*benzoate* (6b) (1·2 g). Recrystallisation from ether–methanol furnished a sample of m.p. 87—90° (Found: C, 82·7; H, 9·0. $C_{27}H_{34}O_2$ requires C, 83·0; H, 8·8%).

17,17-*Dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*trien*-1α-*ol* (9a).—Bromine (1 ml) in methylene chloride (5 ml) was added to a stirred solution of the 1α-benzoate (6b) (5·0 g) in methylene chloride (1 ml) and ether (20 ml) at −70° and stirring at this temperature was continued for 30 min. The temperature was allowed to rise to −20° and a solution of sodium iodide (6·0 g) in acetone (30 ml) was added. The solution was boiled under reflux for 30 min, cooled, diluted with ether (50 ml), and washed with aqueous sodium hydrogen sulphite (2 × 50 ml) and water (2 × 50 ml), and dried (Mg_2SO_4) and concentrated *in vacuo* with minimal heating. Filtration of the residue in light petroleum through a column of alumina (120 g) gave the 7,13-diene (7) as a gum (3·6 g), t_R 2·35 (OV 17; 245°), $\lambda_{max.}$ 235 (ε 24,000), 244 (12,200), and 254 nm (7750).

Bromine (0·7 ml) in methylene chloride (1 ml) was added to a solution of the gum (3·5 g) in ether (25 ml) at −70° and the solution was allowed to come to room temperature. The solution was washed with aqueous sodium hydrogen sulphite (2 × 15 ml) and water (2 × 25 ml), dried ($MgSO_4$), and evaporated. The residue was dissolved in dry benzene (30 ml) and the solution was stirred for 18 h with silica (9 g; Merck 0·05—0·2 mm) filtered, and evaporated under vacuum with minimal heating, to give a gum (3·0 g), t_R 1·97 (OV 17; 245°). The gum (3·0 g) was dissolved in ether (60 ml) and the solution was treated with lithium aluminium hydride (0·75 g) for 30 min. The reaction was stopped by careful addition of wet ether (60 ml) and water (1 ml), and the suspension was filtered and evaporated. The residue (3·0 g) was dissolved in light petroleum–benzene (1 : 1) and chromatographed on a column of alumina (90 g). Elution with light petroleum–benzene (1 : 1) gave a fraction containing a mixture of hydrocarbons which was discarded. Elution with benzene–ethyl acetate (98 : 2) gave a fraction which was crystallised from aqueous ethanol to yield the *trienol* (9a) (1·01 g). Filtration in light petroleum through a column of alumina (5 g) and recrystallisation from aqueous ethanol gave the pure material, m.p. 99—101° $[\alpha]_D$ +103° (*c* 0·58), t_R 0·37 (OV 17; 245°), $\nu_{max.}$ (KCl) 3560 (hydroxy) and 820 (aromatic) cm^{-1}, $\nu_{max.}$ (CH_2Cl_2) 3575 and 822 cm^{-1}, $\lambda_{max.}$ 246 (ε 1600), 255 (1500), 268 (1100), and 276 nm (900), δ 1·08 (3H, s, 10-Me), 1·14 (6H, s, 17,17-Me_2), 2·70 (4H, m, 7- and 15-H_2), 4·36 (1H, s, $W_{\frac{1}{2}}$ 6·5 Hz, 1β-H), 6·93 (1H, d, *J* 8 Hz, 12-H), and 7·18 (1H, d, *J* 8 Hz, 11-H) (Found: C, 84·2; H, 9·8. $C_{20}H_{28}O$ requires C, 84·5; H, 9·9%).

17,17-*Dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*trien*-1-*one* (8a).—Jones reagent [10] (21 ml) was added slowly to a solution of the trienol (9a) (14·5 g) in acetone (150 ml) at 0—15° and stirring was continued at room temperature for 20 min. The solution was poured onto ice, and the product was isolated and crystallised from ethanol–water to give the *trienone* (8a) (11 g). Recrystallisation from ethanol–water gave a sample of m.p. 121—125°, $[\alpha]_D$ +280·9° (*c* 0·54), $\nu_{max.}$ (KCl) 1707 (1-ketone) and 1595 and 822 (aromatic) cm^{-1}, $\nu_{max.}$ (CH_2Cl_2) 1705 and 825 cm^{-1}, δ 1·22 (6H, s, 17,17-Me_2), 1·48 (3H, s, OMe), 2·63 (4H, m, 7- and 15-H_2), 6·94 (1H, d, *J* 8 Hz, 12-H), and 7·18 (1H, d, *J* 8 Hz, 11-H) (Found: C, 84·9; H, 9·4. $C_{20}H_{26}O$ requires C, 85·1; H, 9·3%).

Reduction of 17,17-*Dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*trien*-1-*one* (8a) *with Sodium–Propan*-2-*ol*.—Sodium (600 mg) was added carefully, under nitrogen, to a solution of the trienone (8a) (300 mg) in refluxing propan-2-ol (10 ml) during 1 h, and heating under reflux was continued for a further 1 h. Isolation of the product gave a gum (300 mg) consisting of two components which were separated by preparative t.l.c. (silica gel; heptane–acetone, 19 : 1, with continuous development for 1 h). Crystallisation of the faster-running component from aqueous ethanol gave 17,17-dimethyl-18-nor-5α-androsta-8,11,13-trien-1α-ol (225 mg), m.p. 100—102°, identical with a previously prepared sample. Crystallisation of the slower-running component from aqueous ethanol gave 17,17-*dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*trien*-1β-*ol* (10) (65 mg), m.p. 125—127°, t_R 0·51 (OV 17; 245°), $\nu_{max.}$ (CH_2Cl_2) 3610 (free OH) cm^{-1}, δ 1·15 (3H, s, 10-Me), 1·22 (6H, s, 17,17-Me_2), 2·70 (4H, m, 7- and 15-H), 3·80 (1H, m, $W_{\frac{1}{2}}$ 12 Hz, 1α-H), 6·92 (1H, d, *J* 8 Hz, 12-H), and 8·10 (1H, *J* 8 Hz, 11-H) (Found: C, 84·2; H, 10·0. $C_{20}H_{28}O$ requires C, 84·5; H, 9·9%).

Reduction of 17,17-*Dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*trien*-1-*one* (8a) *with Sodium Borohydride*.—Sodium borohydride (25 mg) was added carefully to a solution of the trien-1-one (8a) (50 mg) in methanol (2 ml). The solution was stirred at room temperature for 20 min and neutralised with acetic acid (50%), and the product was isolated to give 17,17-dimethyl-18-nor-5α-androsta-8,11,13-trien-1α-ol (50 mg), shown by t.l.c. and g.l.c. to be free of the 1β-epimer. Crystallisation from aqueous ethanol gave material, m.p. 96—100°, identical with a previously prepared sample.

Reduction of 17,17-*Dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*trien*-1-*one* (8a) *with Lithium Aluminium Hydride*.—A suspension of lithium aluminium hydride (30 mg) in dry ether (2 ml) containing the trienone (8a) (50 mg) was stirred at room temperature for 20 min. Wet ether (20 ml) was added slowly and the solution was filtered and evaporated to give a solid (50 mg) which was shown by g.l.c. to contain 96% of 17,17-dimethyl-18-nor-5α-androsta-8,11,13-trien-1α-ol and about 4% of the 1β-epimer. Crystallisation from

aqueous ethanol gave a pure sample of the 1α-alcohol, m.p. 98—101°, identical with a previously prepared sample.

1-*Hydroxyimino*-17,17-*dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*triene* (8b).—The trienone (8a) (5 g) was heated under reflux with hydroxylamine hydrochloride (7·5 g) and sodium acetate trihydrate (10 g) in ethanol (180 ml) for 4 h. The cooled solution was concentrated and diluted with water, and the precipitate (5·1 g) was dissolved in ether. The solution was filtered through a small column of acid-washed alumina [15] (40 g) and the solvent was evaporated off to give a gum (5 g). Crystallisation from ethanol–water gave the *oxime* (8b) (4·7 g), m.p. 82—88° (Found: C, 80·5; H, 9·0; N, 4·2. $C_{20}H_{27}NO$ requires C, 80·8; H, 9·2; N, 4·7%).

1α-*Amino*-17,17-*dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*triene Hydrochloride*.—The oxime (8b) (1·5 g) was heated under reflux for 3 h with a stirred suspension of lithium aluminium hydride (600 mg) in tetrahydrofuran (30 ml). Wet ether (200 ml) was added carefully and the solution was filtered through Dicalite and evaporated to give a gum (1·3 g), which was filtered through a small column of acid-washed alumina [15] (15 g) in ether. The solvent was evaporated off, the basic material was dissolved in ether, and the solution was saturated with dry hydrogen chloride to give the 1α-*amine hydrochloride* (1·1 g). Crystallisation from methylene chloride–ether gave a sample of m.p. 240—245° (Found: C, 73·2; H, 9·4; Cl, 11·0; N, 4·1. $C_{20}H_{30}ClN,0·5H_2O$ requires C, 73·0; H, 9·5; Cl, 10·8; N, 4·3%). A regenerated sample of the free base showed δ 1·13 (3H, s, 10-Me), 1·22 (6H, s, 17,17-Me_2) 2·62 (4H, m, 7- and 15-H_2), 3·23 (2H, m, $W_{\frac{1}{2}}$ 6·5 Hz, NH_2), 3·46 (1H, m, $W_{\frac{1}{2}}$ 6 Hz, 1β-H), and 6·91 and 7·06 (each 1H, d, *J* 8 Hz, 11- and 12-H).

Reduction of 1-*Hydroxyimino*-17,17-*dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*triene* (8b) *with Sodium in Refluxing Propan*-2-*ol*.—Sodium (700 mg) was added over 30 min to a heated, refluxing solution of the oxime (500 mg) in propan-2-ol (20 ml) and stirring and heating under reflux were continued for a further 1 h. The solution was diluted with methanol (20 ml); the isolated product (450 mg) was identical with the 1α-amine (g.l.c., t.l.c., and n.m.r.).

1α-*Formylamino*-17,17-*dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*triene* (9h).—A solution of the trienone (8a) (1·5 g) in formamide (20 ml) and formic acid (10 ml) was heated under reflux for 2 h, cooled, and diluted with water (200 ml). The precipitate was filtered off, washed several times with water, and air-dried. Crystallisation from ether–light petroleum gave the 1α-*formylaminotriene* (9h) (1·3 g). Recrystallisation furnished a sample of m.p. 231—233°, $\nu_{max.}$ (CH_2Cl_2) 3440 and 1690 (formylamino) and 1500 and 825 (aromatic) cm^{-1}, δ 1·20 (9H, s, 10-Me and 17,17-Me_2), 2·70 (4H, m, 7- and 15-H_2), 4·60 (1H, d, $W_{\frac{1}{2}}$ 6·5 Hz, 1β-H), 5·43 (1H, $W_{\frac{1}{2}}$ 12·5 Hz, NH), 6·90 (1H, d, *J* 8 Hz, 11-H), 7·08 (1H, d, *J* 8 Hz, 12-H), and 7·94 (1H, s, CHO) (Found: C, 81·1; H, 9·6; N, 4·4. $C_{21}H_{29}NO$ requires C, 81·0; H, 9·4; N, 4·5%).

1α-*Methylamino*-17,17-*dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*triene Hydrochloride*.—A stirred suspension of lithium aluminium hydride (300 mg) in dry tetrahydrofuran (20 ml), containing the 1α-formylaminotriene (9h) (1·5 g), was heated under reflux for 20 h. Wet ether (200 ml) was added carefully and the solution was filtered and evaporated to give a gum (1·5 g), which was chromatographed on a column of alumina (4·5 g). Elution with benzene gave the 1α-methylaminotriene (9f) as a gum (1·01 g). The *hydrochloride* (1·0 g) was crystallised from methylene chloride–ether (Found: C, 75·3; H, 10·0; N, 4·0; Cl, 10·6. $C_{21}H_{32}ClN$ requires C, 75·5; H, 9·7; N, 4·2; Cl, 10·6%).

Hydrolysis of 1α-*Formylamino*-17,17-*dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*triene* (9h).—A solution of the 1α-formylaminotriene (9h) (200 mg) in ethanol (3 ml) containing aqueous 10N-sulphuric acid (0·4 ml) was heated under reflux for 48 h; the product (150 mg), t_R 0·38 (OV 17; 245°) was identical with the 1α-amine (t.l.c., g.l.c., and n.m.r.). The hydrochloride had m.p. 238—245° (from methylene chloride–ether).

1α-*Dimethylamino*-17,17-*dimethyl*-18-*nor*-5α-*androsta*-8,11,13-*triene Hydrochloride*.—A solution of the 1α-amine (9e) (1·5 g) and aqueous formaldehyde (6 ml; 36%) in formic acid (8 ml) was heated on a steam-bath for 12 h, and the product was isolated to give the 1α-dimethylamine (9 g) (1·4 g) as a gum which was crystallised, as the *hydrochloride*, from methylene chloride–ether; m.p. 228—230° (Found: C, 74·7; H, 9·8; Cl, 10·2; N, 4·0. $C_{22}H_{34}ClN,0·25H_2O$ requires C, 75·0; H, 9·9; Cl, 10·1; N, 4·0%).

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