61. 16-*Oxo-* and 16α-*Hydroxy-testosterone.*

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An improved route to 16-oxotestosterone (IX; R = H) is described. Androst-5-ene-3β : 16α : 17β-triol (V; R = R′ = H), hitherto obtained only with difficulty, has been prepared by reduction of 3β : 16α-diacetoxyandrost-5-en-17-one. It has been converted into 16α-hydroxytestosterone (VI; R = H) by microbiological oxidation.

The compounds named in the title were required for biological study.

Preparation of 17β-acetoxyandrost-4-ene-3 : 16-dione (IX; R = Ac) by the methods of Stodola and Kendall [1a] and Butenandt, Schmidt-Thomé, Weiss, Dresler, and Meinerts [1b] proved unsatisfactory owing to low overall yield. We therefore developed an improved procedure from methyl 3β-acetoxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (I; R = Ac, R′ = Me).

3β-Hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-dioic acid (I; R = R′ = H) was originally prepared by oxidation of cholesteryl acetate dibromide with chromic acid.[2] Its acetate (I; R = Ac, R′ = H) was later obtained by hypoiodite oxidation of 3β-acetoxyandrost-5-en-17-one.[3] An improved route to the hydroxy-ester (I; R = H, R′ = Me), for which we are indebted to Dr. B. Ellis of these Laboratories, lies in the chromic acid oxidation of 3β-acetoxy-5ξ : 6ξ-dibromopregn-16-en-20-one, followed by debromination of the product to give the acetate (I; R = Ac, R′ = H), which is then converted into the 16-monomethyl ester of the acid (I; R = H) with methanolic hydrogen chloride and thence into the required hydroxy-diester with diazomethane.

Methyl 3β-hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (I; R = H, (R′ = Me) was oxidised to methyl 3-oxo-16 : 17-*seco*androst-5-ene-16 : 17-dioate (IV; R = CO_2Me) by aluminium *tert.*-butoxide–*cyclo*hexanone. The crude product (>90% yield) was converted into methyl 3 : 3-ethylenedioxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (VII; R = CO_2Me) by treating its solution in ethylene glycol with boron trofluoride–ether complex. Intramolecular acyloin condensation of this ester with sodium in liquid ammonia [4] led to the formation of 3 : 3-ethylenedioxy-17β-hydroxyandrost-5-en-16-one (VIII; R = H). Removal of the ethylenedioxy-residue and reacetylation furnished the required 17β-acetoxyandrost-4-ene-3 : 16-dione (IX; R = Ac). Its cautious hydrolysis with methanolic potassium hydrogen carbonate gave 16-oxotestosterone (IX; R = H), since described by Meyer and Lindberg.[5]

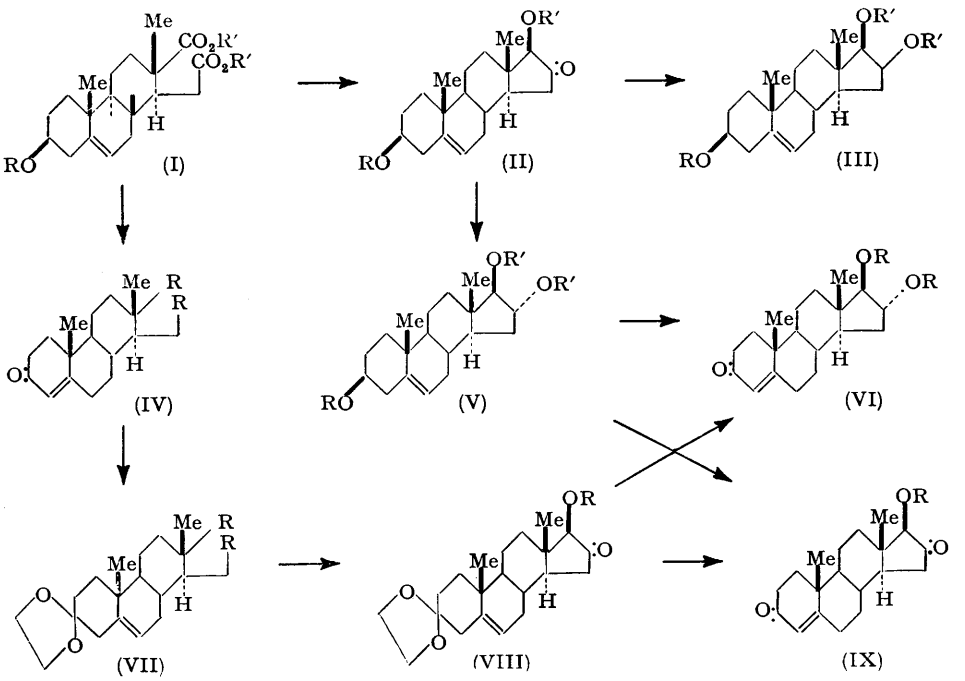
Partial synthesis of 16α-hydroxytestosterone (VI; R = H) offered considerable difficulty, but was finally achieved from 17β-acetoxy-3β-methoxyandrost-5-en-16-one (II; R = Me, R′ = Ac), which was converted into androst-5-ene-3β : 16α : 17β-triol (V; R = R′ = H) and thence into the dihydroxy-ketone (VI; R = H).

The ether (II; R = Me, R′ = H) was prepared by Huffman and Lott [6] by Stodola reduction [7] of 16-hydroxyimino-3β-methoxyandrost-5-en-17-one. An alternative route lies in the acyloin condensation of methyl 3β-methoxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate with sodium in liquid ammonia [4] followed by acetylation of the product. The diacetate (II; R = R′ = Ac) may similarly be prepared from the ester acetate (I; R = Ac, R′ = Me).

Reduction of the ketone (II; R = Me, R′ = Ac) to the alcohol (V; R = Me, R′ = H) represents the least satisfactory stage of the process. Stereospecific reduction of the

[1] (*a*) Stodola and Kendall, *J. Org. Chem.*, 1941, **6**, 837; 1942, **7**, 326; (*b*) Butenandt, Schmidt-Thomé, Weiss, Dresler, and Meinerts, *Ber.*, 1939, **72**, 417.
[2] Kuwada, *J. Pharm. Soc. Japan*, 1936, **56**, 75.
[3] Wettstein, Fritzsche, Hunziker, and Miescher, *Helv. Chim. Acta*, 1941, **24**, 332; von Seeman and Grant, *J. Amer Chem. Soc.*, 1950, **72**, 4073.
[4] Sheehan, Coderre, and Cruikshank, *ibid.*, 1953, **75**, 6231.
[5] Meyer and Lindberg, *ibid.*, 1954, **76**, 3033.
[6] Huffman and Lott, *J. Biol. Chem.*, 1948, **172**, 789.
[7] Stodola, Kendall, and McKenzie, *J. Org. Chem.*, 1941, **6**, 841.

ketone (II; R = Ac, R′ = H) to the alcohol (III; R = Ac, R′ = H) with Raney nickel had been reported by Butenandt *et al.*[1b] Stereospecific reduction of the methoxy-ketone (II; R = Me, R′ = Ac) to its alcohol (V; R = Me), in contrast, could not be realised. Huffman and Lott [8] obtained a mixture of alcohols (III; R = Me) and (V; R = Me) by reducing the ketone (II; R = Me) with sodium amalgam, and this probably represents the best route to the required intermediate. Thus we find that Ponndorf reduction of the ketone (II; R = Me, R′ = Ac or H) gives the 16β-isomer almost exclusively, whilst lithium aluminium hydride, sodium borohydride, or sodium in liquid ammonia–ethanol gives the 16β-isomer (III; R = Me) with smaller quantities of the 16α-form (V; R = Me). Epimerisation of the former to the latter through the 16α-toluene-*p*-sulphonate also failed to provide an alternative route, since the ditoluene-*p*-sulphonate was obtained in place of the expected 16-mono-ester.[9] Separation of the 16α-isomer (V; R = Me, R′ = H) from the reduction products of the 16-ketone with sodium amalgam required tedious fractionation, which was more difficult if the ether group was replaced by acetoxyl.[10] Conversion of the ether (V; R = Me, R′ = H)in to the triol (V; R = R′ = H) followed the procedure of Huffman and Lott.[6]



Careful Oppenauer oxidation of the triol (V; R = R′ = H) followed by acetylation furnished the acetoxy-dione (IX; R = Ac) in place of the monoketone (VI; R = Ac). An attempt to prepare the acetate dibenzoate (V; R = Ac, R′ = Bz) for partial hydrolysis at $C_{(3)}$ and then oxidation to the ketone (VI; R = Bz) failed, acetolysis of the ether dibenzoate (V; R = Me, R′ = Bz) with acetic anhydride–toluene *p*-sulphonic acid [6,8] giving a diacetate benzoate. The desired conversion into the dihydroxy-ketone (VI; R = H) was ultimately achieved by microbiological oxidation of the triol (V; R = R′ = H) by *Corynebacterium mediolanum*. Acetylation gave the diacetate (VI; R = Ac), also obtained in very low yield from the ketal (VIII; R = H) by reduction with sodium amalgam, hydrolysis, and acetylation.

Additional transformations carried out included (i) reduction of the ketal-diester

[8] Huffman and Lott, *J. Amer. Chem. Soc.*, (*a*) 1947, **69**, 1835; (*b*) 1949, **71**, 719.
[9] Cf. Elks and Shoppee, *J.*, 1953, 241.
[10] Cf. Huffman, U.S.P. 2,584,271/1952; also refs. 6 and 8.

(VII; R = CO_2Me) with lithium aluminium hydride to the ketal dialcohol (VII; R = CH_2·OH), which was hydrolysed to the keto-dialcohol (IV; R = CH_2·OH), (ii) hydrolysis of 16-hydroxyimino-3β-methoxyandrost-5-en-17-one [6] with sodium sulphite in acetic acid to 3β-methoxyandrost-5-ene-16 : 17-dione, (iii) attempted conversion of 3β-hydroxyandrost-5-en-17-one into androsta-5 : 16-dien-3β-ol by reaction of its toluene-*p*-sulphonylhydrazone with sodium in ethylene glycol,[11] 3β : 17β-diacetoxyandrost-5-ene being isolated after acetylation, (iv) conversion of 3β-acetoxyandrost-5-en-17-one into into 3β : 17-diacetoxyandrosta-5 : 16-diene,[12] followed by treatment of the latter with 1 mol. of perbenzoic acid; alkaline hydrolysis of the total product, followed by acetylation and chromatography, furnished a low yield of 3α : 17β-diacetoxyandrost-5-en-16-one (II; R = R′ = Ac) (cf. Leeds, Fukushima, and Gallagher [13] whose paper appeared subsequently to our experiments).

After completion of the above work, 3β : 16α-diacetoxyandrost-5-en-17-one became available.[14] Its reduction with lithium aluminium hydride proceeded stereospecifically [13] to the triol (V; R = R′ = H), to which this is the most convenient route.

Experimental

Optical rotations refer to $CHCl_3$ solutions in a 1-dm. tube. Ultraviolet absorption spectra in propan-2-ol were kindly determined by Mr. M. T. Davies, B.Sc. Alumina (B.D.H.) of chromatography grade was used.

Methyl 3β-*Hydroxy*-16 : 17-seco*androst*-5-*ene*-16 : 17-*dioate* (I; R = H, R′ = Me) (with Dr. B. Ellis).—(i) Bromine (45 g.) in chloroform (500 ml.) was added during 30 min. to a stirred solution of 3β-acetoxypregna-5 : 16-dien-20-one (100 g.) in chloroform (1 l.) at −60°. The mixture was allowed to warm to room temperature, then the solvent was removed completely under reduced pressure and with the minimum of warming. The viscous residue in acetic acid (2 l.) was treated, with stirring and cooling, with chromium trioxide (85 g.) in 80% acetic acid (600 ml.) dropwise during 1 hr. After 18 hr. at room temperature, zinc dust (300 g.) was added, and the mixture stirred for 45 min., then heated at 100° for 15 min., cooled, and decanted into a large volume of water. The product was isolated with ether, and the ethereal extract washed with water until nearly neutral. Extraction of the ethereal solution with 10% aqueous potassium carbonate, followed by acidification of the alkaline extract, gave the crude ester (I; R = Ac, R′ = H) (36·5—42·5 g.; m. p. 238—245°). Purified from aqueous ethanol, it formed plates, m. p. 262—264°, $[\alpha]_D^{23}$ −97° (*c*, 1·33) (Found: C, 66·7; H, 8·1%; equiv., 190. Calc. for $C_{21}H_{30}O_6$: C, 66·6; H, 8·0%; equiv., 189) (Butenandt *et al.* [1b] give m. p. 251°).

(ii) The foregoing ester (I; R = Ac, R′ = H) (30 g.; crude; m. p. 238—245°) in methanol (300 ml.), to which acetyl chloride (5 ml.) had previously been added, was heated under reflux for 1 hr. The mixture was concentrated to half its bulk under reduced pressure, then poured into water, and the product extracted with ether. The dried ethereal extract was treated at 0° with an excess of ethereal diazomethane, the solution acidified with acetic acid and concentrated, and *n*-hexane added to faint turbidity. The dimethyl ester (I; R = H, R′ = Me) (18 g.) separated in needles, m. p. 112° (Kuwada [2] gives m. p. 112°).

In one experiment the product was separated into the 16-methyl ester of 3β-hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-diacid, needles, m. p. 173—177° (from aqueous acetone) (Kuwada [2] gives m. p. 176—177°), and a small proportion of the dimethyl ester, m. p. 112°.

Methyl 3-*Oxo*-16 : 17-seco*androst*-4-*ene*-16 : 17-*dioate* (IV; R = CO_2Me).—A solution of methyl 3β-hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (10 g.) in *cyclo*hexanone (66 ml.) was added to a solution of aluminium *tert.*-butoxide (10 g.) in toluene (40 ml.), heated under reflux for *ca.* 45 min., then cooled, and water was added. After steam-distillation (*ca.* 10 hr.) the residue was cooled and the solids were collected and used directly for conversion into the 3 : 3-ethylenedioxy-derivative. A portion, on purification from ether–hexane, furnished *methyl* 3-*oxo*-16 : 17-seco*androst*-4-*ene*-16 : 17-*dioate*, m. p. 99—101°, $[\alpha]_D^{24}$ +28° (*c*, 0·524), $\lambda_{max.}$ 239 mμ (log ε 4·24) (Found: C, 68·8; H, 8·2. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%).

Methyl 3 : 3-*Ethylenedioxy*-16 : 17-seco*androst*-5-*ene*-16 : 17-*dioate* (VII; R = CO_2Me).—Crude methyl 3-oxo-16 : 17-*seco*androst-5-ene-16 : 17-dioate (9—10 g., from 10 g. of the

[11] Bamford and Stevens, *J.*, 1952, 4735; cf. Elks, Phillips, Taylor, and Wyman, *J.*, 1954, 1739.
[12] Moffett and Weisblat, *J. Amer. Chem. Soc.*, 1952, **74**, 2183.
[13] Leeds, Fukushima, and Gallagher, *ibid.*, 1954, **76**, 2943.
[14] Cooley, Ellis, Hartley, and Petrow, *J.*, 1955, 4373.

hydroxy-ester) in ethylene glycol (100 ml.) was treated with boron trifluoride–ether complex (10 ml.) for 12 hr. at room temperature. The mixture was decomposed with water, and the precipitated solids were collected, washed with dilute sodium hydrogen carbonate solution and water, and purified from aqueous methanol. *Methyl* 3 : 3-*ethylenedioxy*-16 : 17-seco*androst*-5-*ene*-16 : 17-*dioate* had m. p. 187—189°, $[\alpha]_D^{24}$ −63° (*c*, 0·326) (Found : C, 68·0; H, 8·4. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

3 : 3-*Ethylenedioxy*-17β-*hydroxyandrost*-5-*en*-16-*one* (VIII; R = H).—Sodium (800 mg.) was added to a stirred mixture of ether (200 ml.) and liquid ammonia (300 ml.) in a 1-l. three-necked flask fitted with dropping funnel, solid carbon dioxide condenser, and nitrogen inlet. After 30 minutes' stirring methyl 3-ethylenedioxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (2 g.) was added as a suspension in ether during 1½ hr. The solution was allowed to warm to room temperature, methanol (2 ml.) in ether (100 ml.) added, and the mixture acidified with 5% (w/v) hydrochloric acid (*ca.* 60 ml.). The ethereal layer was removed, washed with water, dried, and evaporated. The aqueous fraction was made alkaline and freed from ether by warming and the separated solids were collected and combined with the solids from the ethereal extract. Crystallisation from ethanol gave 3 : 3-*ethylenedioxy*-17β-*hydroxyandrost*-5-*en*-16-*one*, plates, m. p. 238—241° (sinters at 235°), $[\alpha]_D^{22}$ −125° (*c*, 0·2986) (Found : C, 72·8; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

17β-*Acetoxy*-3 : 3-*ethylenedioxyandrost*-5-*en*-16-*one* (VIII; R = Ac), prepared by acetylation of the foregoing compound (300 mg.) with acetic anhydride–pyridine (10 ml. of each) for 1 hr. on the steam-bath, had m. p. 217—221°, $[\alpha]_D^{24}$ −165° (*c*, 0·504) (Found : C, 70·7; H, 8·3. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·2%).

17β-*Acetoxyandrost*-4-*ene*-3 : 16-*dione* (IX; R = Ac).—(i) 3 : 3-Ethylenedioxy-17β-hydroxyandrost-5-en-16-one (600 mg.; crude) in 90% acetic acid (50 ml.) was heated on the steam-bath for 45 min. The acid was removed under reduced pressure and the residue isolated with chloroform, acetylated, and percolated in benzene through alumina (2 × 0·75 cm.), which was washed with 20 ml. of benzene. The benzene solution was taken to dryness and the residue crystallised from acetone–hexane, to give the diketone (IX; R = Ac), m. p. 196—198°, $[\alpha]_D^{24}$ −48° (*c*, 0·414) (Found : C, 72·9; H, 8·4. Calc. for $C_{21}H_{28}O_4$: C, 73·3; H, 8·1%).

(ii) The ketal (VIII; R = H) (2·4 g.) was heated with methanol (75 ml.) containing water (15 ml.) and concentrated sulphuric acid (3·5 ml.) for 45 min. under reflux. After precipitation with water, isolation with chloroform, and treatment as in (i), the diketone (IX; R = Ac) was obtained, having m. p. 199—200°, not depressed on admixture with the product obtained as in (i) or with a specimen prepared by Stodola and Kendall's [1a] method.

Hydrolysis of the foregoing compound (300 mg.) in methanol (30 ml.) with potassium hydrogen carbonate (300 mg.) in water (20 ml.) for 18 hr. at room temperature furnished 16-oxotestosterone, m. p. 160°, $[\alpha]_D^{24}$ −65° (*c*, 0·472) (Found : C, 75·7; H, 8·7. Calc. for $C_{19}H_{26}O_3$: C, 75·5; H, 8·6%) (Meyer and Lindberg [5] give m. p. 152—158°, $[\alpha]_D^{22}$ −52°).

Methyl 3β-*Methoxy*-16 : 17-seco*androst*-5-*ene*-16 : 17-*dioate* (I; R = R′ = Me).—Methyl 3β-hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (3 g.) was treated with toluene-*p*-sulphonyl chloride (3 g.) in pyridine (20 ml.) overnight at room temperature. The crude toluene-*p*-sulphonate (2 g.) was heated with anhydrous methanol (200 ml.) under reflux for 3 hr.; the mixture was evaporated to small bulk and water added until crystallisation occurred, giving *methyl* 3β-*methoxy*-16 : 17-seco*androst*-5-*ene*-16 : 17-*dioate*, plates, m. p. 87°, $[\alpha]_D^{23}$ −58° (*c*, 0·548) (Found : C, 69·7; H, 8·8. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·0%), after purification from aqueous methanol.

Treatment of the foregoing compound with sodium–liquid ammonia–ether furnished 17β-hydroxy-3β-methoxyandrost-5-en-16-one, m. p. 188—191°, not depressed on admixture with an authentic specimen.[8b]

3β : 17β-*Dihydroxyandrost*-5-*en*-16-*one* (II; R = R′ = H).—Methyl 3β-acetoxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (5·46 g.) in ether (540 ml.) was added during 1½ hr. to a solution from sodium (2·4 g.) in liquid ammonia (900 ml.) and ether (600 ml.). Excess of sodium was destroyed with methanol (6 ml.) in ether (300 ml.), and the mixture acidified with 5% (w/v) hydrochloric acid and worked up as before. Crystallisation from aqueous methanol gave 3β : 17β-*dihydroxyandrost*-5-*en*-16-*one*, m. p. 202—205°, $[\alpha]_D^{20}$ −195° (*c*, 0·476) (Found : C, 70·8; H, 8·8. $C_{19}H_{28}O_3,H_2O$ requires C, 70·8; H, 9·3%), probably identical with the product, m. p. 197° (no analysis given), of Butenandt *et al.*[1b] (cf. ref. 7).

Acetylation of the foregoing compound gave 3β : 17β-diacetoxyandrost-5-en-16-one,[1b] m. p. 123—124°, $[\alpha]_D^{23}$ −183° (*c*, 0·676) (Found : C, 71·0; H, 8·3. Calc. for $C_{23}H_{32}O_5$: C, 71·1; H, 8·2%).

3β-*Methoxy*-16β : 17β-*ditoluene*-p-*sulphonyloxyandrost*-5-*ene* (III; R = Me, R′ = *p*-$C_6H_4Me{\cdot}SO_2$).—The diol (III; R = Me, R′ = H) (200 mg.) in pyridine (2 ml.) was treated at room temperature for 16 hr. with toluene-*p*-sulphonyl chloride (500 mg.), and the product isolated with chloroform. The *diester* formed had m. p. 180—181° (Found: C, 65·2; H, 6·4; S, 11·6. $C_{34}H_{44}O_7S_2$ requires C, 65·0; H, 7·0; S, 10·2%) after crystallisation from acetone–hexane.

Starting material was recovered when the diol (III; R = Me; R′ = H) was treated with 1·1 mol. of toluene-*p*-sulphonyl chloride in pyridine for 5 days at room temperature.

Oxidation of the Triol (V; R = R′ = H) (cf. Ushakov *et al.*[15]).—The triol (500 mg.) in dry benzene (85 ml.) was heated under reflux for 40 min. with aluminium *tert.*-butoxide (1·33 g.) in benzene (12 ml.). Acetone (12 ml.) was added and the mixture heated for a further 18 hr. The product was isolated with ether–chloroform, acetylated, and chromatographed in benzene solution on to alumina (12 g.). The ether to ether–acetone (1 : 1) eluates yielded the diketone (IX; R = Ac), m. p. and mixed m. p. 196° (from acetone–hexane).

16α : 17β-*Dibenzoyloxy*-3β-*methoxyandrost*-5-*ene* (V; R = Me, R′ = Bz), needles, m. p. 200°, $[\alpha]_D^{24}$ −162° (*c*, 0·26) (Found: C, 77·2; H, 7·7. $C_{34}H_{40}O_5$ requires C, 77·3; H, 7·6%), after crystallisation from acetone–hexane, was prepared by treating the ether (V; R = Me, R′ = H) (70 mg.) in pyridine (2 ml.) with benzoyl chloride (1 ml.) for 16 hr. at room temperature.

Treatment of the foregoing compound (230 mg.) in acetic anhydride (9·5 ml.) with toluene-*p*-sulphonic acid (10 mg.) for 1 hr. on the steam-bath gave 3β : 16α(?17β)-*diacetoxy*-17β(?16α)-*benzoyloxyandrost*-5-*ene*, m. p. 148° (from acetone–hexane (Found: C, 72·3; 72·4, H, 6·9, 6·8. $C_{30}H_{38}O_6$ requires C, 72·9; H, 7·7. 3β-Acetoxy-16α : 17β-dibenzoyloxyandrost-5-ene, $C_{35}H_{40}O_6$, requires C, 75·5; H, 7·2%).

16α-*Hydroxytestosterone* (VI; R = H), prepared by microbiological oxidation of (V; R = R′ = H) as described in "Newer Methods of Preparative Organic Chemistry"[16] and crystallised from acetone–hexane, had m. p. 191—192,° $[\alpha]_D^{20}$ +80° (*c*, 0·2596), $\lambda_{max.}$ 240·5 mμ (log ε 4·2) (Found: C, 73·3; H, 9·1. $C_{19}H_{28}O_3,\frac{1}{2}H_2O$ requires C, 72·8; H, 9·3%). The *diacetate* formed needles, m. p. 139—140°, $[\alpha]_D^{23}$ +12° (*c*, 0·259) (Found: C, 71·2; H, 8·4. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%), from acetone–hexane.

Reduction of 3 : 3-*Ethylenedioxy*-17β-*hydroxyandrost*-5-*en*-16-*one* (VIII; R = H).—(i) The ketal (VIII; R = H) (700 mg.) was stirred in ethanol (100 ml.) and acetic acid (9·1 ml.) at 40°, and 5% sodium amalgam (70 g.) added at such rate that the temperature did not exceed 40°. After *ca.* 20 min. 50% acetic acid (7 ml.) was added. When addition of amalgam was complete stirring at room temperature was continued until no more reaction occurred. The product, isolated with ether, was heated with 90% acetic acid (50 ml.) for 45 min. on the steam-bath to remove the ethylenedioxy-residue and after acetylation chromatographed in benzene on alumina (15 g.). Early benzene–ether eluates yielded 16α : 17β-diacetoxyandrost-4-en-3-one, m. p. and mixed m. p. 139—140°.

(ii) The ketal (VIII; R = H) (370 mg.) in ethanol (75 ml.) and acetic acid (4·8 ml.) was stirred at 40° for 2 hr. while 5% sodium amalgam (37 g.) was added. 50% Acetic acid (4 ml.) was added after ½ hr.. After 2 hr. a further 10 g. of sodium amalgam were added as rapidly as possible without raising the temperature and stirring continued at 40° for a further hour and at room temperature for an hour. After working up as in (i) and chromatography on alumina, the 20%—50% acetone–ether eluates yielded 16β : 17β-diacetoxyandrost-4-en-3-one, m. p. 198—199° alone or on admixture with an authentic specimen.[1b]

3 : 3-*Ethylenedioxy*-16 : 17-seco*androst*-5-*ene*-16 : 17-*diol* (VII; R = $CH_2{\cdot}OH$).—A suspension of the ester (VII; R = CO_2Me) (1·8 g.) in ether (300 ml.) was added dropwise to a boiling suspension of lithium aluminium hydride (2 g.) in ether (200 ml.), after which refluxing was continued for a further hour. The product, isolated in the usual way, crystallised from aqueous methanol, to yield the *diol*, m. p. 182—184°, $[\alpha]_D^{24}$ −47° (*c*, 0·386) (Found: C, 69·9; H, 9·8. $C_{21}H_{34}O_4,\frac{1}{2}H_2O$ requires C, 70·2; H, 9·8%). The *diacetate* had m. p. 105—107°, $[\alpha]_D^{24}$ −30° (*c*, 0·412) (Found: C, 68·6; H, 8·6. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

16 : 17-*Dihydroxy*-16 : 17-seco*androst*-4-*en*-3-*one* (IV; R = $CH_2{\cdot}OH$), m. p. 151—152° (from acetone–hexane), $[\alpha]_D^{25}$ +111° (*c*, 0·398) (Found: C, 74·3; H, 9·8. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·8%), was prepared by hydrolysing the ketal (VII; R = $CH_2{\cdot}OH$) (1 g.) in methanol (30 ml.) and water (6 ml.) with concentrated sulphuric acid (1·5 ml.) for 45 min. under reflux, diluting the mixture with water, and extracting the product with chloroform.

[15] Ushakov and Chinaeva, *J. Gen. Chem.* (*U.S.S.R.*), 1954, **15**, 661.

[16] Fischer, "Newer Methods of Preparative Organic Chemistry," Interscience Publ. Inc., New York, 1948, p. 191.

3β-*Methoxyandrost-5-ene*-16 : 17-*dione*.—Crude 3β-methoxy-16-hydroxyiminoandrost-5-en-17-one [6] (2 g.; m. p. 197—199°) was heated with anhydrous sodium sulphite (20 g.) in acetic acid (80 ml.) for 20 min. on the steam-bath. Water (20 ml.) was then added and heating continued for a further 45 min. The mixture was transferred to a separatory funnel with 3% sodium sulphite solution (800 ml.) and extracted twice with alcohol-free, peroxide-free ether. The ethereal layer was removed and extracted with sodium sulphite solution. The combined sulphite fractions were treated with concentrated hydrochloric acid (*ca.* 200 ml.), and the mixture was heated on the steam-bath for *ca.* 30 min. After being kept at 0° overnight the precipitated solids were collected and purified from acetone–hexane. 3β-*Methoxyandrost-5-ene*-16 : 17-*dione* formed mustard-yellow crystals, m. p. 204—206°, $[\alpha]_D^{28}$ −206° (*c*, 0·294) (Found : C, 75·5; H, 8·9. $C_{20}H_{28}O_3$ requires C, 76·0; H, 8·9%). The compound gave a purple-red colour with concentrated sulphuric acid, but no colour with ferric chloride. Its infrared absorption, kindly determined by Dr. L. J. Bellamy, revealed its existence as >99% as the diketone in the solid state. The *dioxime* had m. p. 230—232° (darkening at 220°) (Found : C, 69·0; H, 9·0; N, 8·5. $C_{20}H_{30}O_3N_2$ requires C, 69·4; H, 8·7; N, 8·1%).

3β-*Hydroxyandrost-5-ene*-17-*one toluene*-p-*sulphonylhydrazone*, m. p. 170—172° (Found : C, 69·5; H, 8·7; N, 5·8; S, 4·5. $C_{26}H_{36}O_3N_2S$ requires C, 68·4; H, 7·9; N, 6·1; S, 7·0%) (1·15 g.), was heated with sodium (5·75 g.) in ethylene glycol (250 ml.) under reflux for 7 hr. Acetylation of the product and purification by chromatography furnished 3β : 17β-diacetoxyandrost-5-ene, m. p. and mixed m. p. 159°.

3β : 17β-*Diacetoxydrost-5-en*-16-*one* (II; R = R′ = Ac).—3β : 17-Diacetoxyandrosta-5 : 16-diene [12] (6·56 g.) was treated with 1 mol. of perbenzoic acid in benzene. After 72 hr. at 0° the product was isolated with ether and hydrolysed by methanol (150 ml.), water (10 ml.), and potassium hydroxide (10 g.) for 1 hr. under reflux, and the material isolated with ether–chloroform. After acetylation at room temperature, the product was chromatographed in benzene on alumina (120 g.). The benzene–ether (1 : 1) to pure ether eluates yielded 3β : 17β-diacetoxyandrost-5-en-16-one, m. p. and mixed m. p. 123°. The ether to ether–acetone (1 : 1) eluates gave a small amount of 3β-acetoxy-5α : 6α-epoxyandrostan-17-one, m. p. and mixed m. p. 215°.

3β : 16α : 17β-*Tripropionyloxyandrost-5-ene* (V; R = R′ = Et·CO).—3β : 16α-Diacetoxyandrost-5-en-17-one [14] (2·72 g.) in ether (250 ml.) was added dropwise during 15 min. to a stirred solution of lithium aluminium hydride (2·1 g.) in ether (250 ml.), and the mixture heated under reflux for 1 hr., after which it was decomposed with ice-water and acidified, the ethereal layer was removed, and the solids were collected and dried. These were extracted (Soxhlet) for 8 hr. with ethyl acetate, and the extract was combined with the ethereal extract and taken to dryness. Part of the residue was acetylated to give 3β : 16α : 17β-triacetoxyandrost-5-ene, m. p. 183—184° (from acetone–hexane) not depressed on admixture with an authentic specimen. The remainder was heated with propionic anhydride–pyridine for 1 hr. on the water-bath, to give 3β : 16α : 17β-*tripropionyloxyandrost-5-ene*, plates, m. p. 149°, $[\alpha]_D^{23}$ −103° (*c*, 0·301) (Found : C, 71·4; H, 9·0. $C_{28}H_{42}O_6$ requires C, 70·9; H, 8·9%).

The authors thank the Directors of the British Drug Houses Ltd. for permission to publish this work.

Chemical Research Laboratories,
The British Drug Houses Ltd., London, N.1. [*Received, August 25th*, 1955.]