811. *Modified Steroid Hormones. Part VI.*[1] *Further 6-Methylandrostane Derivatives.*

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The preparation of 6α-methyl-3-oxo-Δ⁴-steroids from 6β-hydroxy-3 : 5-*cyclo*steroids and from 3β-hydroxy-5α : 6β-bromohydrins developed in Part IV [2] has been extended to the partial synthesis of 6α-methylandrostenedione. The " bromohydrin route " proved unsuitable for the preparation of the 6α-methyl derivative of methyltestosterone, which was successfully prepared from a *cyclo*steroid intermediate. 6α-Methylethisterone was prepared by the 3 : 5-*cyclo*steroid route.

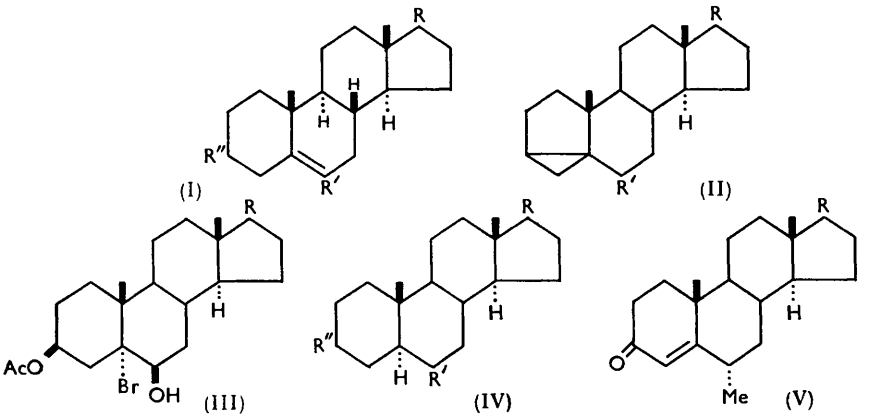
The preparation of 6-methylandrostane derivatives by using 5α : 6α-epoxy-3β-hydroxysteroids as intermediates was described in Part V.[1] Their partial synthesis from a 6β-hydroxy-3 : 5-*cyclo*steroid and a 3β-hydroxy-5α : 6β-bromohydrin (cf. Part IV) [2] forms the subject of the present communication.

3β-Toluene-*p*-sulphonyloxyandrost-5-en-17-one (I; R = :O, R′ = H, R″ = ---H, -*p*-Me·C_6H_4·SO_2·O) was converted into 6β-acetoxy-3 : 5-*cyclo*androstan-17-one [3,4] (II; R = :O, R′ = ---H, -OAc) and thence by reduction with sodium borohydride and acetylation into 6β : 17β-diacetoxy-3 : 5-*cyclo*androstane [3] (II; R = R′ = ---H, -OAc). Oxidation of the last compound with chromic acid [5] led to 17β-acetoxy-3 : 5-*cyclo*androstan-6-one [4] (II; R = ---H, -OAc, R′ = :O), which was not obtained, however, by employing *N*-bromoacetamide or the chromic acid–pyridine complex [6] as oxidant. Reaction with methylmagnesium iodide, followed by acetylation, gave 17β-acetoxy-6ξ-methyl-3 : 5-*cyclo*androstan-6ξ-ol (II; R = ---H, -OAc, R′ = OH, Me), which was converted by acetic–sulphuric acid into 3β : 17β-diacetoxy-6-methylandrost-5-ene (I; R = R″ = ---H, -OAc, R′ = Me). Hydrolysis of the last compound with methanolic sodium hydroxide furnished 6-methylandrost-5-ene-3β : 17β-diol (I; R = R″ = ---H, -OH, R′ = Me), which was oxidised by the Oppenauer method to 6α-methylandrost-4-ene-3 : 17-dione (V; R = :O). Identity of this product with the material described in Part V [1] (see also ref. 7) provides further evidence for the α-configuration assigned to the 6-methyl substituent.

Riegel, Dunker, and Thomas [8] reported the conversion of 3 : 5-*cyclo*-6β-methoxy-structures into 3-iodo-Δ⁵-steroids by heating them with methylmagnesium iodide and a trace of iodine in xylene solution. We find that 6β : 17β-diacetoxy-3 : 5-*cyclo*androstane (II; R = R′ = ---H, -OAc), on reaction with methylmagnesium iodide followed by acetylation, gives a product formulated as 17β-acetoxy-3ξ-iodoandrost-5-ene (I; R = ---H,

[1] Part V, preceding paper.
[2] Burn, Ellis, Petrow, Stuart-Webb and Williamson, *J.*, 1957, 4092.
[3] Wagner, Wolff, and Wallis, *J. Org. Chem.*, 1952, **17**, 529; cf. Shoppee and Summers, *J.*, 1952, 3361, for configuration at $C_{(6)}$ in 3 : 5-*cyclo*-6-hydroxy-steroids.
[4] Butenandt and Surányi, *Ber.*, 1942, **75**, 591.
[5] Cf. Heilbron, Hodges, and Spring, *J.*, 1938, 759.
[6] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[7] Madaeva, Uschakov, and Koscheleva, *J. Gen. Chem.* (*U.S.S.R.*), 1940, **10**, 213; *Chem. Abs.*, 1940, **34**, 7292.
[8] Riegel, Dunker, and Thomas, *J. Amer. Chem. Soc.*, 1942, **64**, 2115.

–OAc, R′ = H, R″ = H, I). The constitution assigned to this compound is supported by its conversion on acetolysis with potassium and silver acetates in acetic acid into 3β : 17β-diacetoxyandrost-5-ene (I; R = R″ = ---H, –OAc, R′ = H). Reduction of the acetate iodide with zinc dust in acetic acid gave an iodine-free product formulated as 17β-acetoxyandrost-5-ene [9] (I; R = ---H, –OAc, R′ = H, R″ = H_2).



3β : 17β-Diacetoxyandrost-5-ene reacted with hypobromous acid, to give 3β : 17β-diacetoxy-5α-bromoandrostan-6β-ol (III; R = ---H, –OAc), which was oxidised with the chromic acid–pyridine complex and then debrominated, giving 3β : 17β-diacetoxyandrostan-6-one [10] (IV; R = R″ = ---H, –OAc, R′ = :O). Reaction of the last compound with methylmagnesium iodide gave 6α-methylandrostane-3β : 6β : 17β-triol (IV; R = R″ = ---H, –OH, R′ = ---Me, –OH) (cf. Fieser and Rigaudy [11] for configuration at $C_{(6)}$ in Grignard products of this type), also obtained from 3β-acetoxy-17β-benzoyloxyandrost-5-ene (I; R = ---H, –OBz, R′ = H, R″ = ---H, –OAc) by the same sequence of reactions. Oxidation of the triol with the chromic acid–pyridine complex furnished 6β-hydroxy-6α-methylandrostane-3 : 17-dione (IV; R = R″ = :O, R′ = ---Me, –OH), which was dehydrated by formic acid to 6α-methylandrost-4-ene-3 : 17-dione (V; R = :O) (see above).

Extension of the method to the preparation of 6α : 17α-dimethyltestosterone (V; R = ---Me, –OH) from 3β-acetoxyandrost-5-en-17-one proved less successful. The last compound was converted into the 5α : 6β-bromohydrin and thence into 3β-acetoxyandrostane-6 : 17-dione [12] (IV; R = R′ = :O, R″ = ---H, –OAc). Reaction with methylmagnesium iodide furnished 6α : 17α-dimethylandrostane-3β : 6β : 17β-triol (IV; R = R′ = ---Me, –OH, R″ = ---H, –OH), which was oxidised by chromic acid–pyridine to 6β : 17β-dihydroxy-6α : 17α-dimethylandrostan-3-one (IV; R = R′ = ---Me, –OH, R″ = :O). Selective dehydration of this compound at $C_{(6)}$, however, could not be realised.

The required product (V; R = ---Me, –OH) was ultimately obtained *via* a 6β-hydroxy-3 : 5-*cyclo*androstane intermediate. 17β-Acetoxy-3 : 5-*cyclo*-6ξ-methylandrostan-6ξ-ol (II; R = ---H, –OAc, R′ = Me, OH) (see above) was hydrolysed to the diol which was oxidised by chromic acid–pyridine to 6ξ-hydroxy-6ξ-methyl-3 : 5-*cyclo*androstan-17-one (II; R = :O, R′ = Me, OH). Treatment of the last compound with sulphuric–acetic acid at room temperature led to 3β-acetoxy-6-methylandrost-5-en-17-one (I; R = :O, R′ = Me, R″ = ---H, –OAc), which was converted into 6 : 17α-dimethylandrost-5-ene-3β : 17β-diol (I; R = ---Me, –OH, R′ = Me, R″ = ---H, –OH) by methylmagnesium iodide.

[9] Marker, Wittle, and Tullar, *J. Amer. Chem. Soc.*, 1940, **62**, 223.
[10] MacPhillamy and Scholz, *ibid.*, 1951, **73**, 5512.
[11] Fieser and Rigaudy, *ibid.*, 1951, **73**, 4660.
[12] Patel, Petrow, and Stuart-Webb, *J.*, 1957, 665.

Oppenauer oxidation of the diol gave 17β-hydroxy-6α : 17β-dimethylandrost-4-en-3-one (V; R = ---Me, -OH) (see ref. 1).

Additionally 3β-hydroxyandrost-5-en-17-one was converted into 6β-hydroxy-3 : 5-*cyclo*androstan-17-one [4] (II; R = :O, R′ = ---H, -OH), which was oxidised by chromic acid to 3 : 5-*cyclo*androstane-6 : 17-dione [3,4] (II; R = R′ = :O), also obtained by oxidation of 6β-acetoxy- and 6β-methoxy-3 : 5-*cyclo*androstan-17-one (cf. ref. 5). Reaction of the diketone with methylmagnesium iodide, however, gave a mixture which failed to yield a homogeneous product either directly or after treatment with sulphuric–acetic acid.

The 3 : 5-*cyclo*-steroid route was also applied to the preparation of 17α-ethynyl-17β-hydroxy-6α-methylandrost-4-en-3-one (V; R = -OH, ---C≡CH). 17α-Ethynyl-3 : 5-*cyclo*androstane-6β : 17β-diol [13] (II; R = -OH, ---C≡CH, R′ = ---H, -OH) was oxidised by pyridine–chromic acid to 17α-ethynyl-17β-hydroxy-3 : 5-*cyclo*androstan-6-one which with methylmagnesium iodide gave 17α-ethynyl-6ξ-methyl-3 : 5-*cyclo*androstane-6ξ : 17β-diol. Acid rearrangement of the latter furnished 3β-acetoxy-17α-ethynyl-6-methylandrost-5-en-17β-ol (I; R = -OH, ---C≡CH, R′ = Me, R″ = ---H, -OAc), which on alkaline hydrolysis followed by Oppenauer oxidation gave the required 17α-ethynyl-17β-hydroxy-6α-methylandrost-4-en-3-one (V; R = -OH, ---C≡CH).

Inter alia, 17β-benzoyloxyandrost-5-en-3β-ol (I; R = ---H, -OBz, R′ = H, R″ = ---H, -OH) was converted into the toluene-*p*-sulphonyl derivative but this failed to undergo the 3 : 5-*cyclo*steroid rearrangement. 6β-Acetoxy-17β-benzoyloxy-3 : 5-*cyclo*androstane (II; R = ---H, -OBz, R′ = ---H, -OAc) was obtained, however, by reduction of 6β-acetoxy-3 : 5-*cyclo*androstan-17-one (II; R = :O, R′ = ---H, -OAc) (above) with sodium borohydride, followed by benzoylation, but the overall yield was too low to justify this approach to the 6-methyl structure.

Experimental

Rotations were determined for $CHCl_3$ solutions in a 1 dm. tube unless otherwise stated. Alumina (B.D.H., chromatography grade) was used.

6β : 17β-*Diacetoxy*-3 : 5-cyclo*androstane* (II; R = R′ = ---H, -OAc).—6β-Acetoxy-3 : 5-*cyclo*androstan-17-one [4] (3·4 g.) in methanol (100 ml.) was left at 0° for 2 hr. with sodium borohydride (500 mg.). Water was added and the product isolated with ether–chloroform as a sticky solid which was acetylated overnight at room temperature with acetic anhydride–pyridine. 6β : 17β-Diacetoxy-3 : 5-*cyclo*androstane crystallised from methanol in prisms, m. p. 127—129°, $[\alpha]_D^{22}$ +36° (*c* 1·03) (Found: C, 73·7; H, 9·1. Calc. for $C_{23}H_{34}O_4$: C, 73·8; H, 9·1%) (Wagner *et al.*[3] give m. p. 128°, $[\alpha]_D^{25}$ +42°).

17β-*Acetoxy*-3 : 5-cyclo*androstan*-6-*one* (II; R = ---H, -OAc, R′ = :O).—The foregoing diacetate (1 g.) in acetic acid (25 ml.) was left at room temperature for 20 hr. with chromium trioxide (300 mg.) in aqueous acetic acid (10 ml. of 90%). Methanol was added and the product isolated with ether. Crystallisation from aqueous methanol or pentane gave 17β-acetoxy-3 : 5-*cyclo*androstan-6-one, prisms, m. p. 114—116° (Found: C, 75·7; H, 8·9. Calc. for $C_{21}H_{30}O_3$: C, 76·4; H, 9·1%). Butenandt and Surányi [4] gave m. p. 109—110°. The compound formed a yellow 2 : 4-dinitrophenylhydrazone.

17β-*Acetoxy*-6ξ-*methyl*-3 : 5-cyclo*androstan*-6ξ-*ol* (II; R = ---H, -OAc, R′ = OH, Me).—17β-Acetoxy-3 : 5-*cyclo*androstan-6-one (3·1 g.) in ether (30 ml.) was added to a Grignard solution prepared from magnesium (2 g.) and methyl iodide (11 ml.) in ether (50 ml.). The mixture was heated under reflux for 1 hr., then decomposed with ammonium chloride solution. The product was isolated with ether, and the crude residue acetylated in the usual way. The resulting compound was purified by trickling through a short column of alumina in benzene–hexane (1 : 1), 17β-*acetoxy*-6ξ-*methyl*-3 : 5-cyclo*androstan*-6ξ-*ol* being obtained in needles, m. p. 114—116°, $[\alpha]_D^{23}$ +25° (*c* 0·94) (Found: C, 76·5; H, 9·9. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·8%), after crystallisation from pentane. The compound did not form a 2 : 4-dinitrophenylhydrazone and did not give a yellow colour with tetranitromethane.

3β : 17β-*Diacetoxy*-6-*methylandrost*-5-*ene* (I; R = R″ = ---H, -OAc, R′ = Me).—The foregoing product (2·8 g.) in acetic acid (50 ml.) was left at room temperature for 18 hr. with

[13] Ruzicka and Muhr, *Helv. Chim. Acta*, 1944, **27**, 503.

sulphuric acid (1 ml.). Water was added and the product was isolated with ether. It was passed through a short column of alumina in benzene–hexane (1 : 4), and crystallised from methanol to give 3β : 17β-*diacetoxy*-6-*methylandrost*-5-*ene*, leaflets, m. p. 125—127°, $[\alpha]_D^{23}$ −82° (*c* 1·02) (Found: C, 74·1; H, 9·3. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%). The compound gave a positive tetranitromethane test.

6-*Methylandrost*-5-*ene*-3β : 17β-*diol* (I; R = R″ = ···H, ⁻OH, R′ = Me).—The above diacetate (2·8 g.) in methanol (125 ml.) was heated on a steam-bath for 15 min. with sodium hydroxide (3 g.) in water (125 ml.). The product was isolated with ether–methylene chloride and purified from methanol, giving 6-*methylandrost*-5-*ene*-3β : 17β-*diol hemihydrate*, needles, m. p. 204—206°, $[\alpha]_D^{27}$ −65° (*c* 1·03) (Found: C, 76·4; H, 10·6. $C_{20}H_{32}O_2,\frac{1}{2}H_2O$ requires C, 76·7; H, 10·5%).

6α-*Methylandrost*-4-*ene*-3 : 17-*dione* (V; R = :O).—The foregoing diol (600 mg.) in *cyclo*hexanone (12 ml.) and toluene (20 ml.) was heated until 10 ml. of distillate had collected. Aluminium *tert.*-butoxide (3 g.) in toluene (10 ml.) was added and the mixture refluxed for 2½ hr. Rochelle salt solution was added, and the mixture was steam-distilled for 8 hr. The product was isolated with ether, and the resulting oil was chromatographed in hexane–benzene (4 : 1) on alumina (15 g.). From the hexane–benzene (4 : 1) to hexane–benzene (1 : 1) eluates was obtained 6α-methylandrost-4-ene-3 : 17-dione, m. p. 163—167°, $[\alpha]_D^{24}$ +175° (*c* 0·866), identical with the compound described previously.[1,7]

Attempts to oxidise the foregoing diol by the reaction sequence bromination, chromic acid oxidation, debromination, and rearrangement to a Δ^4-ketone gave only an oil.

17β-*Acetoxy*-3ξ-*iodoandrost*-5-*ene* (I; R = ···H, ⁻OAc, R′ = H, R″ = I, H).—6β : 17β-Diacetoxy-3 : 5-*cyclo*androstane (1 g.) in ether (50 ml.) was added to a Grignard solution prepared from magnesium (1 g.) and methyl iodide (5·5 ml.) in ether (50 ml.). The mixture was heated under reflux for 1 hr., then aqueous ammonium chloride solution was added and the product isolated with ether. The crude residue was reacetylated and then crystallised from methanol, to give 17β-*acetoxy*-3ξ-*iodoandrost*-5-*ene*, needles, m. p. 148—150°, $[\alpha]_D^{21}$ −30° (*c* 0·964) (Found: C, 56·9; H, 7·2; I, 30·4. $C_{21}H_{31}O_2I$ requires C, 56·9; H, 7·0; I, 28·7%). The compound gave a positive tetranitromethane test.

17β-*Acetoxyandrost*-5-*ene* (I; R = ···H, ⁻OAc, R′ = H, R″ = H_2).—The foregoing iodo-compound (1·2 g.) in acetic acid (20 ml.) was heated on a steam-bath for 1 hr. with zinc dust (2·5 g.). The zinc was filtered off, water was added to the filtrate and the product was isolated with ether. It was chromatographed in light petroleum (b. p. 40—60°) on alumina (20 g.). Elution with this solvent gave 17β-acetoxyandrost-5-ene, leaflets, m. p. 132—135°, $[\alpha]_D^{26}$ −89° (*c* 0·896) (Found: C, 79·3; H, 9·8. Calc. for $C_{21}H_{32}O_2$: C, 79·8; H, 10·1%), after crystallisation from methanol. Marker *et al.*[9] give m. p. 133—135°. The compound gave a yellow colour with tetranitromethane.

3β : 17β-*Diacetoxyandrost*-5-*ene* (I; R = R″ = ···H, ⁻OAc, R′ = H).—The iodo-compound (500 mg.) in acetic acid (20 ml.) was heated under reflux for 1 hr. under nitrogen with silver acetate (400 mg.) and potassium acetate (4 g., freshly prepared). Water and chloroform were added and the mixture filtered through kieselguhr. The chloroform was separated, washed neutral, dried, and evaporated, to give 3β : 17β-diacetoxyandrost-5-ene, m. p. and mixed m. p. 152—154°.

3β : 17β-*Diacetoxy*-5α-*bromoandrostan*-6β-*ol* (III; R = ···H, ⁻OAc).—3β : 17β-Diacetoxyandrost-5-ene (18·75 g.) in dioxan (250 ml.) was stirred for 30 min. at room temperature with *N*-bromoacetamide (10 g.) in water (15 ml.) and perchloric acid (3·5 ml. of a 70% solution) in water (15 ml.). After isolation with ether, and crystallisation from acetone–hexane–chloroform, 3β : 17β-*diacetoxy*-5α-*bromoandrostan*-6β-*ol* (22·1 g.) formed needles, m. p. 159°, $[\alpha]_D^{22}$ −58° (*c* 0·442) (Found: C, 59·1; H, 7·7; Br, 16·7. $C_{23}H_{35}O_5Br$ requires C, 58·6; H, 7·4; Br, 17·1%).

3β : 17β-*Diacetoxyandrostan*-6-*one* (IV; R = R″ = ···H, ⁻OAc, R′ = :O).—The foregoing compound (10 g.) in pyridine (100 ml.) was left overnight at room temperature with the chromic acid–pyridine complex prepared from chromic acid (10 g.) and pyridine (100 ml.). Hot benzene was added and the mixture filtered through Hyflo which was washed well with hot benzene. The benzene extracts were washed with water, dried, and evaporated. The residue crystallised from acetone–hexane in needles, m. p. 190—191° (7·2 g.). It was immediately debrominated by stirring it with zinc dust (7·5 g.) in acetic acid (150 ml.) for 1 hr. on the steam-bath. The zinc was removed by filtration and the product isolated with ether. Crystallisation from acetone–hexane gave 3β : 17β-diacetoxyandrostan-6-one, prisms, m. p. 177—179°, $[\alpha]_D^{25}$ −42° (*c* 0·584)

(Found: C, 70·5; H, 8·7. Calc. for $C_{23}H_{34}O_5$: C, 70·7; H, 8·7%). MacPhillamy and Scholz [10] give m. p. 177—178°, $[\alpha]_D^{23}$ −37°.

6α-*Methylandrostane*-3β : 6β : 17β-*triol* (IV; R = R″ = ---H, ⁻OH, R′ = ---Me, ⁻OH).—3β : 17β-Diacetoxyandrostan-6-one (6 g.) in benzene (200 ml.) was added to a solution of methylmagnesium iodide prepared from magnesium (4 g.) and methyl iodide (22 g.) in ether (100 ml.). The mixture was heated under reflux for 5 hr., cooled, and decomposed with ammonium chloride solution. Isolation with benzene–ether gave a crude product which was dissolved in 95% aqueous methanol (200 ml.) and heated under reflux for 1 hr. with potassium hydroxide (6 g.). Part of the methanol was removed under reduced pressure, water was added, and the product isolated with ether. Crystallisation from acetone–hexane gave 6α-*methylandrostane*-3β : 6β : 17β-*triol*, needles, m. p. 242—246°, $[\alpha]_D^{23}$ −73° (*c* 0·396) (Found: C, 74·3; H, 10·2. $C_{20}H_{34}O_3$ requires C, 74·3; H, 10·6%).

The same triol was prepared from 3β-acetoxy-17β-benzoyloxyandrost-5-ene *via* the following intermediates (crystallised from acetone–hexane):

3β-*Acetoxy*-17β-*benzoyloxy*-5α-*bromoandrostan*-6β-*ol* (III; R = ---H, ⁻OBz), needles, m. p. 166—167°, $[\alpha]_D^{22}$ −3° (*c* 0·362) (Found: C, 62·1; H, 7·2; Br, 15·1. $C_{28}H_{37}O_5Br$ requires C, 63·0; H, 7·0; Br, 15·0%).

3β-*Acetoxy*-17β-*benzoyloxy*-5α-*bromoandrostan*-6-*one*, m. p. 159—160°, $[\alpha]_D^{22}$ −9° (*c* 0·310) (Found: C, 63·3; H, 6·7; Br, 14·8. $C_{28}H_{35}O_5Br$ requires C, 63·3; H, 6·6; Br, 15·1%).

3β-*Acetoxy*-17β-*benzoyloxyandrostan*-6-*one*, needles, m. p. 187—188°, $[\alpha]_D^{22}$ +10° (*c*, 0·414) (Found: C, 73·7; H, 7·9. $C_{28}H_{36}O_5$ requires C, 74·3; H, 7·9%).

A Grignard reaction on the last compound gave, after hydrolysis, the triol identical with the compound prepared as above.

6β-*Hydroxy*-6α-*methylandrostane*-3 : 17-*dione* (IV; R = R″ = :O, R′ = ---Me, ⁻OH).—The foregoing triol (1 g.) in dry pyridine (10 ml.) was left at room temperature overnight with the chromic acid–pyridine complex prepared from chromium trioxide (2 g.) and pyridine (20 ml.). The product was isolated with hot benzene and crystallised from acetone–hexane. The *dione* formed prisms, m. p. 189—191°, $[\alpha]_D^{27}$ +84° (*c* 0·498) (Found: C, 75·2; H, 9·4. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%).

6α-*Methylandrost*-4-*ene*-3 : 17-*dione* (V; R = :O).—6β-Hydroxy-6α-methylandrostane-3 : 17-dione (300 mg.) in 100% formic acid (5 ml.) was kept at 55—60° for 1¼ hr. The solution was poured into water and the product isolated with ether. Crystallisation from acetone–hexane gave 6α-methylandrost-4-ene-3 : 17-dione, m. p. and mixed m. p. 164—165°.

3β-*Acetoxy*-5α-*bromo*-6β-*hydroxyandrostan*-17-*one* (III; R = :O) [with (Mrs.) W. J. Adams, Ph.D.].—3β-Acetoxyandrost-5-en-17-one (6·6 g.) in dioxan (50 ml.) and water (10 ml.) was left overnight at room temperature with *N*-bromoacetamide (2·8 g.) in water (5 ml.) and perchloric acid (1 ml. of 72%). Water was added, and the precipitated solids were collected and dissolved in chloroform. The chloroform extract was washed with aqueous solutions of sodium iodide, sodium thiosulphate, sodium carbonate, and then with water. Evaporation of the solvent gave 3β-*acetoxy*-5α-*bromo*-6β-*hydroxyandrostan*-17-*one*, needles, m. p. 173—175° (decomp.) (variable), $[\alpha]_D^{20}$ 0° (*c* 0·764), after crystallisation from acetone–hexane.

3β-*Acetoxy*-5α-*bromoandrostane*-6 : 17-*dione*.—The foregoing compound (1 g.) in pyridine (10 ml.) was left at room temperature overnight with the chromic acid–pyridine complex prepared from chromium trioxide (1 g.) and pyridine (10 ml.). The product was isolated with hot benzene and crystallised from ethanol. 3β-*Acetoxy*-5α-*bromoandrostane*-6 : 17-*dione* formed plates, m. p. 178—180°, $[\alpha]_D^{21}$ −116° (*c*, 1·02) (Found: C, 59·4; H, 6·6. $C_{21}H_{29}O_4Br$ requires C, 59·4; H, 6·6%).

3β-*Acetoxyandrostane*-6 : 17-*dione* (IV; R = R′ = :O, R″ = ---H, ⁻OAc).—The foregoing compound (3·3 g.) was debrominated on a steam-bath for 20 min. with zinc dust (3·3 g.) in acetic acid (33 ml.). The zinc was removed and water was added to the filtrate. After isolation with ether the product was crystallised from ethanol, giving 3β-acetoxyandrostane-6 : 17-dione, needles, m. p. 214—218°, $[\alpha]_D^{22}$ +59° (*c* 0·256) (Found: C, 72·9; H, 8·4. Calc. for $C_{21}H_{30}O_4$: C, 73·2; H, 8·1%). Ruzicka and Muhr [12] give m. p. 203—205°, $[\alpha]_D^{15}$ +39°; MacPhillamy and Scholz [10] give m. p. 208—209°, $[\alpha]_D^{23}$ +33°.

6α : 17α-*Dimethylandrostane*-3β : 6β : 17β-*triol* (IV; R = R′ = ---Me, ⁻OH, R″ = ---H, ⁻OH).—3β-Acetoxyandrostane-6 : 17-dione (3·6 g.) in benzene (100 ml.) was added to a Grignard solution prepared from magnesium (8·5 g.) and methyl iodide (22 ml.) in ether (150 ml.). The mixture was heated under reflux for 3 hr., and left at room temperature overnight. Ammonium

chloride solution was added, and the product isolated with chloroform. Crystallisation from acetone–hexane gave 6α : 17α-*dimethylandrostane*-3β : 6β : 17β-*triol hemihydrate*, cubes, m. p. 220—223°, $[\alpha]_D^{21}$ −14° (*c* 0·212) (Found: C, 72·9; H, 10·6. $C_{21}H_{36}O_3,\frac{1}{2}H_2O$ requires C, 72·9; H, 10·7%).

6β : 17β-*Dihydroxy*-6α : 17α-*dimethylandrostan*-3-*one* (IV; R = R′ = ---Me, ⁻OH, R″ = :O).—The foregoing triol (0·95 g.) in pyridine (10 ml.) was left for 2 days at room temperature with the chromic acid–pyridine complex prepared from chromium trioxide (0·95 g.) and pyridine (10 ml.). Hot benzene was added and the product isolated in the usual way. 6β : 17β-*Dihydroxy*-6α : 17α-*dimethylandrostan*-3-*one* formed needles, m. p. 226—228°, $[\alpha]_D^{21}$ −20° (*c* 0·236) (Found: C, 74·9; H, 10·2. $C_{21}H_{34}O_3$ requires C, 75·5; H, 10·2%), after crystallisation from chloroform–hexane.

Attempts to dehydrate this compound failed. Starting material was recovered unchanged after (i) refluxing with concentrated hydrochloric acid in ethanol, (ii) refluxing with 100% formic acid, and (iii) formation of semicarbazone, attempted dehydration, and regeneration of the ketone.

Non-crystalline products were obtained: (i) by heating it under reflux for 1 hr. with ethanol saturated with hydrogen chloride, and (ii) by treatment with thionyl chloride–pyridine at 0°. Neither of the last two products showed absorption in the 240 mμ range expected from a 3-oxo-Δ^4-system.

6ξ-*Methyl*-3 : 5-cyclo*androstane*-6ξ : 17β-*diol* (II; R = ---H, ⁻OH, R′ = OH, Me).—17β-Acetoxy-6ξ-methyl-3 : 5-*cyclo*androstan-6ξ-ol (1·8 g.) was heated in methanol (90 ml.) for 1 hr. on a steam-bath with potassium hydroxide (500 mg.) in water (10 ml.). Water was added and the product was isolated with ether. 6ξ-*Methyl*-3 : 5-cyclo*androstane*-6ξ- : 17β-*diol* formed needles, m. p. 94° and 133—134°, $[\alpha]_D^{21}$ +24° (*c* 0·468) (Found: C, 78·2; H, 10·5. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·5%), after crystallisation from acetone–hexane.

6ξ-*Hydroxy*-6ξ-*methyl*-3 : 5-cyclo*androstan*-17-*one* (II; R = :O, R′ = OH, Me).—The foregoing diol (1·25 g.) in pyridine (12 ml.) was shaken at room temperature for 18 hr. with the chromic acid–pyridine complex prepared from chromium trioxide (1·25 g.) and pyridine (12·5 ml.). The product was isolated as before, and was then passed in benzene solution through a short column of alumina. Crystallisation from pentane gave 6ξ-hydroxy-6ξ-methyl-3 : 5-*cyclo*androstan-17-one, needles, m. p. 110—112°, $[\alpha]_D^{22}$ +107° (*c* 0·452).

3β-*Acetoxy*-6-*methylandrost*-5-*en*-17-*one* (I; R = :O, R′ = Me, R″ = ---H, ⁻OAc).—The foregoing compound (950 mg.) in acetic acid (15 ml.) was left at room temperature for 18 hr. with concentrated sulphuric acid (1 ml.). Water was added and the product isolated with ether and purified from methanol. 3β-*Acetoxy*-6-*methylandrost*-5-*en*-17-*one* formed prismatic needles, m. p. 149—151°, $[\alpha]_D^{24}$ −20° (*c* 0·55) (Found: C, 76·8; H, 9·3. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·3%).

6 : 17α-*Dimethylandrost*-5-*ene*-3β : 17β-*diol* (I; R = ---Me, ⁻OH, R′ = Me, R″ = ---H, ⁻OH).—3β-Acetoxy-6-methylandrost-5-en-17-one (2 g.) in ether (25 ml.) was added to a Grignard solution prepared from magnesium (2 g.) and methyl iodide (11 ml.) in ether (50 ml.). The mixture was refluxed for 1 hr., then ice-cold ammonium chloride solution was added. The product was isolated with, and crystallised from, ether to give 6 : 17α-*dimethylandrost*-5-*ene*-3β : 17β-*diol*, needles, m. p. 196—198°, $[\alpha]_D^{25}$ −96° (*c* 0·472) (Found: C, 78·3, 78·0; H, 10·4, 10·8. $C_{21}H_{34}O_2$ requires C, 79·3; H, 10·8%). The 3-*monoacetate* formed needles, m. p. 159—161°, $[\alpha]_D^{27}$ −95° (*c* 0·472) (Found: C, 75·8; H, 10·3. $C_{23}H_{36}O_3$ requires C, 76·7; H, 10·0%), after crystallisation from aqueous methanol.

6α : 17α-*Dimethyltestosterone* (V; R = ---Me, ⁻OH).—6 : 17α-Dimethylandrost-5-ene-3β : 17β-diol (1 g.) in toluene (15 ml.) and *cyclo*hexanone (10 ml.) was heated until 5 ml. of distillate had collected. Aluminium *tert.*-butoxide (2 g.) in toluene (10 ml.) was added and the mixture was heated under reflux for 2 hr. After isolation of the product with ether an oil was obtained which was chromatographed on alumina (30 g.) in benzene. Elution with benzene gave 6α : 17α-dimethyltestosterone, m. p. 134—136°, not depressed in admixture with a sample prepared previously.[1]

3 : 5-cyclo*Androstane*-6 : 17-*dione* (II; R = R′ = :O).—This was prepared by the chromic acid oxidation of 6β-acetoxy-3 : 5-*cyclo*androstan-17-one, 6β-hydroxy-3 : 5-*cyclo*androstan-17-one, or 6β-methoxy-3 : 5-*cyclo*androstan-17-one.[3,4,5] Treatment of this compound with methylmagnesium iodide gave a product which could not be purified and did not rearrange to the required 3β-acetoxy-6 : 17α-dimethylandrost-5-en-17β-ol.

17α-*Ethynyl*-17β-*hydroxy*-3 : 5-cyclo*androstan*-6-*one* (II; R = ---C≡CH, ⁻OH, R′ = :O).—17α-Ethynyl-3 : 5-*cyclo*androstane-6β : 17β-diol [13] (20 g.) in pyridine (200 ml.) was added to the chromic acid–pyridine complex prepared from chromium trioxide (20 g.) and pyridine (200 ml.). The product was isolated as before and purified by passage through a short column of alumina in benzene solution. Crystallisation from acetone–hexane gave 17α-*ethynyl*-17β-*hydroxy*-3 : 5-cyclo*androstan*-6-*one*, m. p. 215—216°, prisms, $[\alpha]_D^{22}$ −12° (*c* 0·771) (Found: C, 80·7; H, 8·7. $C_{21}H_{28}O_2$ requires C, 80·75; H, 9·0%). The compound formed an orange 2 : 4-dinitrophenylhydrazone.

17α-*Ethynyl*-6ξ-*methyl*-3 : 5-cyclo*androstane*-6ξ : 17β-*diol* (II; R = ---C≡CH, ⁻OH, R′ = Me, OH).—The forgoing compound (7·5 g.) in benzene (250 ml.) was added to a Grignard solution prepared from magnesium (2·3 g.) and methyl iodide (12 ml.) in ether (50 ml.). Part of the ether was distilled off until the temperature of the distillate reached 65°. The mixture was refluxed for 1 hr., then cooled, and ammonium chloride solution added. The product was isolated with benzene and a small sample of the resulting oil (1 g.) was chromatographed in benzene on alumina (30 g.). From the ether ⟶ ether–acetone eluates was obtained 17α-*ethynyl*-6ξ-*methyl*-3 : 5-cyclo*androstane*-6ξ : 17β-*diol*, needles, m. p. 85—89°, $[\alpha]_D^{20}$ 0° (*c* 0·370), after crystallisation from acetone–hexane (Found: C, 80·4; H, 10·5. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8%).

3β-*Acetoxy*-17α-*ethynyl*-6-*methylandrost*-5-*en*-17β-*ol* (I; R = ---C≡CH, ⁻OH, R′ = Me, R″ = ---H, ⁻OAc).—The foregoing crude oil (6·5 g.) in acetic acid (50 ml.) was left at room temperature overnight with concentrated sulphuric acid (2 ml.) in acetic acid (50 ml.). The mixture was poured into water and the product isolated with chloroform. The residue was chromatographed on alumina (130 g.) in benzene. From the benzene–ether ⟶ pure ether eluates was obtained 3β-*acetoxy*-17α-*ethynyl*-6-*methylandrost*-5-*en*-17β-*ol*, prisms, m. p. 169—170°, $[\alpha]_D^{22}$ −112° (*c* 0·67), after crystallisation from acetone–hexane (Found: C, 77·5; H, 9·2. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·2%).

17α-*Ethynyl*-6-*methylandrost*-5-*ene*-3β : 17β-*diol* (I; R = ---C≡CH, ⁻OH, R′ = Me, R″ = ---H, ⁻OH).—The foregoing acetate (2 g.) in methanol (50 ml.) was refluxed for 1 hr. with potassium carbonate (1 g.) in water (7 ml.). Water was added and the precipitated solids were collected. Crystallisation from aqueous methanol gave 17α-*ethynyl*-6-*methylandrost*-5-*ene*-3β : 17β-*diol*, needles, m. p. 213—215°, $[\alpha]_D^{20}$ −116° (*c* 0·482) (Found: C, 81·1; H, 9·8. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8%).

17α-*Ethynyl*-17β-*hydroxy*-6α-*methylandrost*-4-*en*-3-*one* (V; R = ---C≡CH, ⁻OH).—The foregoing compound (1·35 g.) in *cyclo*hexanone (13·2 ml.) was refluxed for 1¼ hr. with aluminium *tert.*-butoxide (1·4 g.) in toluene (8 ml.). Water was added and the mixture steam-distilled for 1 hr. The solid residue was filtered off and dissolved in ether–chloroform, which was washed with Rochelle salt solution and water. Crystallisation of the product from acetone–hexane gave 17α-ethynyl-17β-hydroxy-6α-methylandrost-4-en-3-one, m. p. and mixed m. p. with an autentic sample [1] 195—197°.

17β-*Benzoyloxy*-3β-*toluene*-p-*sulphonyloxyandrost*-5-*ene*.—17β-Benzoyloxyandrost-5-en-3β-ol (18 g.) in pyridine (100 ml.) was left at room temperature overnight with toluene-*p*-sulphonyl chloride (18 g.). The mixture was poured into water, and the precipitated solids were collected, washed with water, and dried. Crystallisation from ether gave the *ester*, needles, m. p. 155—156° (Found: C, 72·1; H, 7·4; S, 7·0. $C_{33}H_{40}O_5S$ requires C, 72·3; H, 7·3; S, 5·9%). Treatment of this compound with potassium acetate in aqueous acetone under the usual conditions for formation of a 3 : 5-*cyclo*steroid only gave unchanged starting material.

6β-*Acetoxy*-17β-*benzoyloxy*-3 : 5-cyclo*androstane* (II; R = ---H, ⁻OBz, R′ = ---H, ⁻OAc).—The crude product obtained from the reduction of 6β-acetoxy-3 : 5-*cyclo*androstan-17-one (II; R = :O, R′ = ---H, ⁻OAc) (see first experiment above) was benzoylated, to give 6β-*acetoxy*-17β-*benzoyloxy*-3 : 5-cyclo*androstane*, needles, m. p. 98—100° (Found: C, 76·7; H, 8·5. $C_{28}H_{36}O_4$ requires C, 77·0; H, 8·3%), after crystallisation from methanol.

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