810. *Modified Steroid Hormones. Part V.* 6-Methylandrostane Derivatives.*

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The method developed in Part IV for converting 3β-hydroxy-Δ^5-steroids into 6-methyl-3-oxo-Δ^4-steroids *via* the 5α : 6α-epoxides has been employed to prepare the 6-methyl derivatives of androstenedione, testosterone, and 17α-methyl- and 17α-ethynyl-testosterone.

In Part IV methods were recorded for the conversion of 3β-hydroxy-Δ^5-steroids into 6-methyl-3-oxo-Δ^5-steroids *via* (i) the 3β-hydroxy-5α : 6α-epoxides, (ii) the 6β-hydroxy-3 : 5-*cyclo*steroids, and (iii) the 3β-hydroxy-5α : 6β-bromohydrins. In addition, 6α- and 6β-methylprogesterone were prepared. An extension of this work to the partial synthesis of some 6-methyl homologues of androstane, using 5α : 6α-epoxides as starting materials, is now reported.†

Androst-5-ene-3β : 17β-diol was converted into 3β : 17β-diacetoxy-5α : 6α-epoxyandrostane,[1] which gave 3β : 17β-diacetoxy-6β-methylandrostan-5α-ol (I; R = R′ = ---H, $^-$OAc) on reaction with methylmagnesium iodide followed by acetylation. Dehydration by Darzens's method yielded 3β : 17β-diacetoxy-6β-methylandrost-4-ene (II; R = R′ = ---H, $^-$OAc, R″ = ---H, $^-$Me), which was hydrolysed by alcoholic potassium hydroxide to the corresponding diol. The concomitant formation of the isomeric Δ^5-compound (III; R = R′ = ---H, $^-$OAc) by dehydration of the diacetate (I; R = R′ = ---H, $^-$OAc) could not be established (cf. the results of Fieser and Rigaudy [2] on the Darzens dehydration of 3β-acetoxy-5α-hydroxy-6β-methylcholestane). Oxidation of the last compound with manganese dioxide [3] gave the required 6β-methyltestosterone (II; R = :O, R′ = ---H, $^-$OH, R″ = ---H, $^-$Me), smoothly converted by hot methanolic potassium hydroxide [4,5] into the thermodynamically more stable 6α-methyltestosterone (II; R = :O, R′ = ---H, $^-$OH, R″ = ---Me, $^-$H).

Oxidation of 6β-methyltestosterone with the chromic acid–pyridine complex furnished 6β-methylandrost-4-ene-3 : 17-dione (II; R = R′ = :O, R″ = ---H, $^-$Me), which was epimerised by alkali to 6α-methylandrost-4-ene-3 : 17-dione (II; R = R′ = :O, R″ = ---Me, $^-$H), also obtained by oxidation of 6α-methyltestosterone.

A 6ξ-methylandrost-4-ene-3 : 17-dione was described by Madaeva *et al.*[1] in 1940. The Russian workers oxidised 6β-methylandrostane-3β : 5α : 17β-triol (I; R = R′ = ---H, $^-$OH) with chromium trioxide in acetic acid to the impure diketone (I; R = R′ = :O), which was dehydrated with hydrogen chloride in chloroform solution to the 6ξ-methylandrostenedione. We have repeated these experiments and find that the product so formed is identical with our 6α-methyl isomer (II; R = R′ = :O, R″ = ---Me, $^-$H), dehydration to the enedione evidently being accompanied by inversion at $C_{(6)}$. The α-isomer was likewise obtained when dehydration was effected with aluminium *tert.*-butoxide in toluene. Thionyl chloride in pyridine, in contrast, furnished the β-epimer (II; R = R′ = :O, R″ = ---H, $^-$Me). Oppenauer oxidation of the triol (I; R = R′ = ---H, $^-$OH), followed by treatment of the product with chromium trioxide—pyridine, surprisingly afforded 6β-methylandrost-4-ene-3 : 17-dione, although in low yield.

* Part IV, preceding paper.

† A preliminary communication by Ringold, Batres, and Rosenkranz (*J. Org. Chem.*, 1957, **22**, 99) appeared when the present work was in typescript and covers some common ground.

[1] Madaeva, Uschakov, and Koscheleva, *J. Gen. Chem.* (*U.S.S.R.*), 1940, **10**, 213; *Chem. Abs.*, 1940, **34**, 7292.

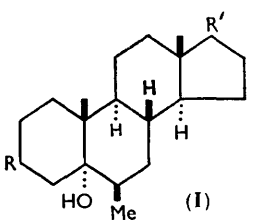
[2] Fieser and Rigaudy, *J. Amer. Chem. Soc.*, 1951, **73**, 4660.

[3] Sondheimer, Amendolla, and Rosenkranz, *ibid.*, 1953, **75**, 5930.

[4] Cf. Turner, *ibid.*, 1952, **74**, 5362.

[5] Burn, Ellis, Petrow, Stuart-Webb, and Williamson, *J.*, 4092.

17β-Methylandrost-5-ene-3β : 17β-diol (IV; R = Me, R′ = H) was converted into 3β-acetoxy-5α : 6α-epoxy-17α-methylandrostan-17β-ol,[6] which proved to be a more soluble and convenient intermediate than the corresponding alcohol (V; R = Me, R′ = H). Reaction with methylmagnesium iodide gave 6β : 17α-dimethylandrostane-3β : 5α : 17β-triol (VI; R = Me, R′ = ···H, ···OH), which was oxidised to 5α : 17β-dihydroxy-6β : 17α-dimethylandrostan-3-one (VI; R = Me, R′ = :O). Reaction of the last compound with hot ethanol containing a trace of hydrochloric acid, or with aluminium *tert.*-butoxide in toluene, or warming its semicarbazone with acetic acid and subsequently regenerating the oxo-group, led to the formation of an αβ-unsaturated ketone assigned the constitution of 17β-hydroxy-6α : 17α-dimethylandrost-4-en-3-one (VII; R = Me, R″ = ···Me, ···H). The same compound was also obtained by Oppenauer oxidation of 6β : 17α-dimethylandrostane-3β : 5α : 17β-triol (VI; R = Me, R′ = ···H, ···OH). Its formulation as the 6α-methyl derivative followed from its stability to potassium *tert.*-butoxide and its alternative formation from the corresponding 3β-hydroxy-6-methyl-Δ^5-derivative (see Part VI).



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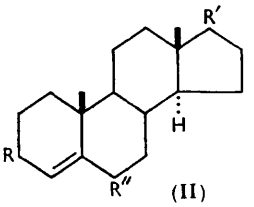

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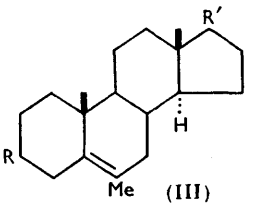

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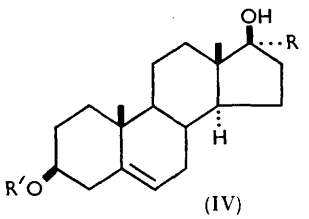

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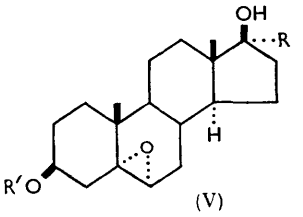

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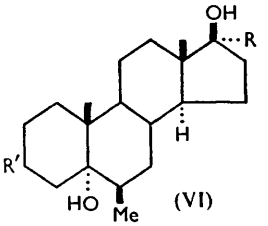

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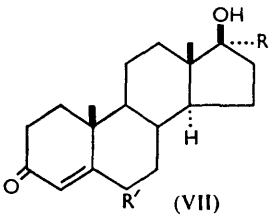

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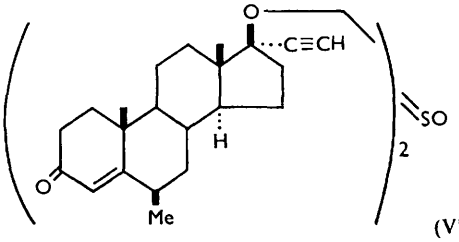

(VIII)

Oxidation of 3β-acetoxy-17α-ethynylandrost-5-en-17β-ol[7] (IV; R = C:CH, R′ = Ac) with monoperphthalic acid gave the 5α : 6α-epoxide (V; R = C:CH, R′ = Ac) with a small quantity of the 5β : 6β-epoxide. The 5α : 6α-epoxide was converted into 17α-ethynyl-6β-methylandrostane-3β : 5α : 17β-triol (VI; R = C:CH, R′ = ···H, ···OH) and thence into the 3-one (VI; R = C:CH, R′ = :O). Oppenauer oxidation of the triol (VI; R = C:CH, R′ = ···H, ···OH) was accompanied by dehydration with formation of 6β-methylethisterone (VII; R = C:CH, R′ = ···H, ···Me), isomerised by ethanolic potash or hydrochloric acid into the 6α-methyl epimer (VII; R = C:CH, R′ = ···Me, ···H). The last compound was also obtained by heating the ketone (VI; R = C:CH, R′ = :O) with ethanolic hydrochloric acid. Attempted dehydration of the ketone (VI; R = C:CH, R′ = :O) by Darzens's method led to the formation of the sulphite (VIII), also formed from 6β-methylethisterone under similar conditions.

[6] Julia and Heusser, *Helv. Chim. Acta*, 1952, **35**, 2080.
[7] Ruzicka and Hofmann, *ibid.*, 1937, **20**, 1280.

Experimental

Rotations were measured for $CHCl_3$ solution in a 1 dm. tube unless otherwise stated. Ultraviolet absorption spectra in propan-2-ol were kindly determined by Mr. M. T. Davies, B.Sc. B.D.H. alumina (chromatography grade) was used throughout.

3β : 17β-Diacetoxy-5α : 6α-epoxyandrostane was obtained essentially as described by Madaeva *et al.*,[1] except that the crude mixed acetates (from 2·9 g.) were purified by chromatography on 90 g. of alumina; elution with benzene to ether then gave the required compound, m. p. 165°, plates (from methanol).

3β : 17β-*Diacetoxy*-6β-*methylandrostan*-5α-*ol* (I; R = R′ = ---H, ⁻OAc).—The foregoing diacetate (4 g.) in benzene (750 ml.) was added to a Grignard mixture prepared from magnesium (9·4 g.) and methyl iodide (30 ml.) in ether (150 ml.). The solvent was removed until the boiling point reached 78°. Heating was then continued for a further 3 hr. Ice and dilute sulphuric acid were added and the product was isolated with ethyl acetate. The residual oil, after evaporation of the solvent, was re-acetylated for 1 hr. on the steam-bath with acetic anhydride–pyridine (20 ml. of each). After isolation the product was purified by passage in benzene through a short column of alumina. It formed needles, m. p. 176°, from acetone–hexane (lit.,[1] m. p. 176—178°).

3β : 17β-*Diacetoxy*-6β-*methylandrost*-4-*ene* (II; R = R′ = ---H, ⁻OAc, R″ = ⁻Me, ---H).—3β : 17β-Diacetoxy-6β-methylandrostan-5α-ol (1·55 g.) in dry pyridine (9 ml.) was treated at 0° with thionyl chloride (0·45 ml.). After 5 min. at 0°, water was added and the product isolated with ether. Purification from aqueous methanol gave 3β : 17β-*diacetoxy*-6β-*methylandrost*-4-*ene*, needles, m. p. 123—124°, $[\alpha]_D^{24}$ −43° (*c* 0·318) (Found: C, 74·0; H, 9·5. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%). The compound gave a positive Rosenheim test for a Δ^4-steroid.

6β-*Methylandrost*-4-*ene*-3β : 17β-*diol* (II; R = R′ = ---H, ⁻OH, R″ = ---H, ⁻Me).—The foregoing diacetate (900 mg.) was refluxed for 30 min. with N-potassium hydroxide (135 ml. in 95% ethanol). Purification from aqueous methanol gave 6β-*methylandrost*-4-*ene*-3β : 17β-*diol hemihydrate*, needles, m. p. 195—200° (variable), $[\alpha]_D^{20}$ +28° (*c* 0·302) (Found: C, 76·9; H, 10·3. $C_{20}H_{32}O_2,\frac{1}{2}H_2O$ requires C, 76·7; H, 10·5%). The *dipropionate*, needles or plates from aqueous methanol, had m. p. 95°, $[\alpha]_D^{23}$ −41° (*c* 0·406) (Found: C, 75·0; H, 9·6. $C_{26}H_{40}O_4$ requires C, 75·0; H, 9·6%).

17β-*Hydroxy*-6β-*methylandrost*-4-*en*-3-*one* (II; R = :O, R′ = ---H, ⁻OH, R″ = ---H, ⁻Me).—The foregoing diol (600 mg.) in dry benzene (120 ml.) was shaken for 72 hr. at room temperature with freshly prepared manganese dioxide (4 g.). The manganese dioxide was filtered off through " Hyflo," which was washed with much hot benzene. The benzene filtrate and washings were washed with dilute hydrochloric acid, dilute sodium carbonate solution, and water, dried, and evaporated. The residue, crystallised from acetone–hexane, gave 17β-hydroxy-6β-methylandrost-4-en-3-one,[8] needles, m. p. 212—214°, $[\alpha]_D^{26}$ +57° (*c* 0·837), $\lambda_{max.}$ 241—242 mμ (log ε 4·19) (Found: C, 79·8; H, 9·9. Calc. for $C_{20}H_{30}O_2$: C, 79·5; H, 9·9%). The *acetate* formed needles, m. p. 155—156°, $[\alpha]_D^{26}$ +46° (*c* 0·312) (Found: C, 76·7; H, 9·2. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·3%), from acetone–hexane.

17β-*Hydroxy*-6α-*methylandrost*-4-*en*-3-*one* (II; R = :O, R′ = ---H, ⁻OH, R″ = ---H, ⁻Me).—17β-Hydroxy-6β-methylandrost-4-en-3-one (100 mg.) was heated under reflux for 20 hr. in an atmosphere of nitrogen, with potassium hydroxide (400 mg.) in water (4 ml.) and methanol (36 ml.). After dilution with water and acidification with acetic acid the product was isolated with ether. Crystallisation from acetone–hexane gave 17β-hydroxy-6α-methylandrost-4-en-3-one,[8] needles, m. p. 154°, $[\alpha]_D^{26}$ +90° (*c* 0·340), $\lambda_{max.}$ 241 mμ (log ε 4·2) (Found: C, 79·3; H, 10·0. Calc. for $C_{20}H_{30}O_2$: C, 79·5; H, 9·9%). The *acetate* formed needles, m. p. 140°, $[\alpha]_D^{26}$ +84° (*c* 0·28) (Found: C, 76·1; H, 9·3. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·3%), from acetone–hexane.

6α-*Methylandrost*-4-*ene*-3 : 17-*dione* (II; R = R′ = :O, R″ = ---Me, ⁻H).—17β-Hydroxy-6α-methylandrost-4-en-3-one (100 mg.) was dissolved in pyridine (2 ml.) and left overnight at room temperature with the pyridine–chromic acid complex prepared from pyridine (2 ml.) and chromium trioxide (100 mg.). Hot benzene was added and the mixture filtered through " Hyflo." The benzene filtrate was washed with dilute hydrochloric acid, dilute sodium carbonate solution, and water, dried, and evaporated. The residue, crystallised from acetone–hexane, gave 6α-methylandrost-4-ene-3 : 17-dione,[8] needles or prisms, m. p. 167—168°, $[\alpha]_D^{22}$ +172° (*c* 0·344) (Found: C, 79·7; H, 9·4. Calc. for $C_{20}H_{28}O_2$: C, 80·0; H, 9·3%). Madaeva

[8] Ringold, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 99.

et al.[1] give m. p. 167°, but no rotation, for a 6-methyl compound with configuration at $C_{(6)}$ unspecified.

6β-*Methylandrost-4-ene*-3 : 17-*dione* (II; R = R′ = :O, R″ = ···H, ⁻Me).—17β-Hydroxy-6β-methylandrost-4-en-3-one (200 mg.) was oxidised by the chromic acid–pyridine complex. Crystallisation from acetone–hexane gave 6β-methylandrost-4-ene-3 : 17-dione,[8] needles or prisms, m. p. 212—213°, $[\alpha]_D^{22}$ +141° (*c* 0·356), $\lambda_{max.}$ 240 mμ (log ε 4·2) (Found: C, 79·6; H, 9·7. Calc. for $C_{20}H_{28}O_2$: C, 80·0; H, 9·3%).

6α-*Methylandrost-4-ene*-3 : 17-*dione* (II; R = R′ = :O, R″ = ···Me, ⁻H).—The foregoing 6β-methyl compound (25 mg.) was isomerised by heating it under reflux for 19 hr. under nitrogen with methanol (9 ml.), potassium hydroxide (100 mg.), and water (1 ml.). Isolation with ether followed by crystallisation from acetone–hexane gave 6α-methylandrost-4-ene-3 : 17-dione, m. p. 167—168°, not depressed on admixture with the compound prepared by the alternative route (above).

6β-*Methylandrostane*-3β : 5α : 17β-*triol* (I; R = R′ = ···H, ⁻OH).—The diacetate (I; R = R′ = ···H, ⁻OAc) (6·03 g.) in methanol (300 ml.) was hydrolysed with potassium hydroxide (1·8 g.) in water (33 ml.) at 50—55° for 4 hr. Water was added and the precipitated solids were collected. Crystallisation from aqueous methanol gave 6β-methylandrostane-3β : 5α : 17β-triol, m. p. 112—115°. Madaeva *et al.*[1] give m. p. 117—120°.

5α-*Hydroxy*-6β-*methylandrostane*-3 : 17-*dione* (I; R = R′ = :O).—The foregoing triol (2·57 g. crude), dissolved in acetic acid (100 ml.), was cooled to <10°. Chromium trioxide (2·5 g.) in acetic acid (40 ml.) and water (10 ml.) was added during 20 min., the temperature being kept between 10° and 15°. The mixture was stirred at room temperature for a further 2½ hr. Methanol was added, and most of the acetic acid was removed under reduced pressure. Isolation with ethyl acetate gave 5α-hydroxy-6β-methylandrostane-3 : 17-dione, needles, m. p. 226—227°, $[\alpha]_D^{24}$ +68° (*c* 0·324), after crystallisation from acetone–hexane. Madaeva *et al.*[1] give m. p. 187—188°. Both of the secondary hydroxyl groups had been oxidised in our product because the compound was recovered unchanged after being heated on the steam-bath for 1 hr. with acetic anhydride–pyridine.

6α-*Methylandrost-4-ene*-3 : 17-*dione* (II; R = R′ = :O, R″ = ···Me, ⁻H).—(*a*) 5α-Hydroxy-6β-methylandrostane-3 : 17-dione (400 mg.) in dry toluene (40 ml.) was slowly distilled until a few ml. of solvent had been removed. A solution of aluminium *tert.*-butoxide (800 mg.) in toluene (10 ml.) was added and the distillation continued for a further 25 min. Rochelle salt solution was added and the product isolated with ether. The residue, after evaporation of the ether, was passed in benzene through a short column of alumina. Crystallisation from acetone–hexane then gave 6α-methylandrost-4-ene-3 : 17-dione, m. p. 167—168°, not depressed when mixed with a sample prepared as above.

(*b*) 5α-Hydroxy-6β-methylandrostane-3 : 17-dione (60 mg.) in chloroform (5 ml.) was treated with dry hydrogen chloride for 1 hr. at 0°. The product was isolated with chloroform. Crystallisation from acetone–hexane gave a compound identical (m. p. and mixed m. p.) with that prepared as under (*a*) above.

6β-*Methylandrost-4-ene*-3 : 17-*dione* (II; R = R′ = :O, R″ = ···H, ⁻Me).—(*a*) 5α-Hydroxy-6β-methylandrostane-3 : 17-dione (200 mg.) in dry pyridine (3 ml.) at 0° was treated with thionyl chloride (0·12 ml.) for 5 min. Crystallisation of the product from acetone–hexane gave 6β-methylandrost-4-ene-3 : 17-dione identical (m. p. and mixed m. p.) with the sample prepared as above.

(*b*) 6β-Methylandrostane-3β : 5α : 17β-triol (820 mg.) in *cyclo*hexanone (10 ml.) and toluene (8 ml.) was heated under reflux for 2 hr. with aluminium *tert.*-butoxide (1 g.). Isolation of the product with benzene gave an oil which was added in pyridine (8 ml.) at 5° to the pyridine–chromic acid complex prepared from pyridine (8 ml.) and chromium trioxide (800 mg.). The mixture was left overnight at room temperature, and worked up with hot benzene (as above), to give an oil. This was chromatographed in benzene on alumina (25 g.). From the benzene eluates was obtained 6β-methylandrost-4-ene-3 : 17-dione, m. p. 206—208°, identical with the compound prepared as in (*a*) above.

3β-*Acetoxy*-5α : 6α-*epoxy*-17α-*methylandrostan*-17β-*ol* (V; R = Me, R′ = Ac) (cf. Julia and Heusser [6]).—A solution of 17α-methylandrost-5-ene-3β : 17β-diol (10 g.) in ether (500 ml.) and chloroform (300 ml.) was treated at −10° with a solution of monoperphthalic acid in ether (300 ml. containing 0·03913 g./ml.). The mixture was left at 0° for 30 hr. and at room temperature for 64 hr. The precipitated solids were collected, washed with dilute sodium carbonate

solution, dried, and acetylated with acetic anhydride–pyridine overnight at room temperature. The product obtained (7·4 g.) was chromatographed on alumina (200 g.). From the benzene–ether (4 : 1) to ether eluates, 3β-acetoxy-5α : 6α-epoxy-17α-methylandrostan-17β-ol was obtained, m. p. 167—169°, after purification from acetone–hexane. Julia and Heusser [6] give m. p. 167—168°. The same compound was obtained by a similar reaction on 3β-acetoxy-17α-methylandrost-5-en-17β-ol.

6β : 17α-*Dimethylandrostane*-3β : 5α : 17β-*triol* (VI; R = Me, R′ = ···H, ⁻OH).—The foregoing compound (3 g.) in benzene (200 ml.) was added to a Grignard solution prepared from magnesium (7·05 g.) and methyl iodide (25 ml.) in ether (120 ml.). Solvent was removed by distillation until the temperature of the distillate reached 78°. Refluxing was continued for 3 hr., then ammonium chloride solution was added at 0°. The precipitated solids were collected, dried, and crystallised from ethyl acetate. 6β : 17α-Dimethylandrostane-3β : 5α : 17β-triol [8] formed plates, m. p. 212—215° or 229°, $[\alpha]_D^{23}$ −37° (*c* 0·313 in EtOH) (Found: C, 74·7; H, 10·4. Calc. for $C_{21}H_{36}O_3$: C, 75·0; H, 10·7%). Alternatively the crude solid product was acetylated overnight at room temperature with acetic anhydride–pyridine, and purified by chromatography. From the ether to ether–acetone eluates was obtained the 3-acetate (crude m. p. 150°), which was hydrolysed for 1 hr. under reflux with potassium carbonate in aqueous methanol. The triol obtained was identical with the compound isolated by the former method. The 3-*monoacetate*, had m. p. 156—157°, $[\alpha]_D^{25}$ −51° (*c* 0·500) (Found: C, 73·3; H, 10·2. $C_{23}H_{38}O_4$ requires C, 73·0; H, 10·1%), after purification from acetone–hexane. When this acetate was crystallised from aqueous methanol a *hemihydrate* was obtained, m. p. 99—110° (Found: C, 71·1; H, 10·0. $C_{23}H_{38}O_4,\frac{1}{2}H_2O$ requires C, 71·3; H, 10·1%).

5α : 17β-*Dihydroxy*-6β : 17α-*dimethylandrostan*-3-*one* (VI; R = Me, R′ = :O).—6β : 17α-Dimethylandrostane-3β : 5α : 17β-triol (500 mg.) was dissolved in acetic acid (100 ml.) and left at room temperature for 17 hr. with potassium chromate (1·6 g.) in water (6 ml.). Methanol was added, and most of the solvents removed under reduced pressure. Water was added and the product isolated with chloroform. Crystallisation from acetone–hexane gave 5α : 17β-dihydroxy-6β : 17α-dimethylandrostan-3-one,[8] m. p. 255°, $[\alpha]_D^{22}$ −29° (*c* 0·291) (Found: C, 74·7; H, 10·0. Calc. for $C_{21}H_{34}O_3$: C, 75·4; H, 10·2%).

17β-*Hydroxy*-6α : 17α-*dimethylandrost*-4-*en*-3-*one* (VII; R = Me, R′ = ···Me, ⁻H).—(*a*) The foregoing compound (35 mg.) in ethanol (20 ml.) was heated under reflux for 35 min. with concentrated hydrochloric acid (3 drops). Water was added and the product isolated with ether. It was purified by passage in benzene through a short column of alumina. Crystallisation of the product from ether–hexane gave 17β-hydroxy-6α : 17α-dimethylandrost-4-en-3-one,[8] m. p. 134—135°, $[\alpha]_D^{22}$ +49° (*c* 0·421 in EtOH), $\lambda_{max.}$ 241 mμ (log ε 4·18) (Found: C, 79·3; H, 10·1. Calc. for $C_{21}H_{32}O_2$: C, 79·7; H, 10·1%).

(*b*) 5α : 17β-Dihydroxy-6β : 17α-dimethylandrostan-3-one (700 mg.) in toluene (110 ml.) was heated under reflux for 1 hr. with aluminium *tert.*-butoxide (1·4 g.). The product was passed in benzene through a short column of alumina. Crystallisation gave a compound identical in all respects with that prepared as under (*a*).

(*c*) 5α : 17β-Dihydroxy-6β : 17α-dimethylandrostan-3-one (1·1 g.) in methanol (55 ml.) was heated under reflux for 1·5 hr. with semicarbazide hydrochloride (0·83 g.) and anhydrous sodium acetate (0·66 g.). The solution was evaporated to half its volume, and then poured into water. The semicarbazone separated as a white solid (0·91 g.), m. p. 185—195°, $\lambda_{max.}$ 228—229 mμ (log ε 4·12), 271—272 mμ (log ε 3·5). The latter absorption was presumably due to a small amount of the semicarbazone of the 3-oxo-Δ^4-compound. The semicarbazone (0·91 g.) in ethanol (45 ml.) was heated under reflux with acetic acid (5 ml.) for 2½ hr. Water was added and the precipitated solids (0·75 g.) [$\lambda_{max.}$ 271 mμ (log ε 4·36) in EtOH] were collected, dissolved in acetic acid (28 ml.), and left at room temperature for 24 hr. in an atmosphere of carbon dioxide with *p*-hydroxybenzaldehyde (3·2 g.) in water (12 ml.). Water (200 ml.) was added and the product isolated with ether. The ethereal extracts were washed with 2% aqueous sodium carbonate solution until just alkaline, and then with N-hydrochloric acid, sodium hydrogen carbonate solution, and water. The residue left after evaporation of the ether was purified by passage in benzene through a short column of alumina. Crystallisation from ether–hexane gave the product, m. p. 128—131°, identical with that prepared as in (*a*) above.

(*d*) The triol (VI; R = Me, R′ = ···H, ⁻OH) (1·2 g.) in *cyclo*hexanone (8·2 ml.) was heated under reflux for 45 min. with aluminium *tert.*-butoxide (1·1 g.) in toluene (5 ml.). The product was isolated with ether and chromatographed in benzene solution on alumina (35 g.). From

the benzene–ether (2 : 1) through to ether–acetone (9 : 1) eluates was obtained 17β-hydroxy-6α : 17α-dimethylandrost-4-en-3-one, identical with the compound prepared previously.

5α : 6α- and 5β : 6β-Epoxides derived from 3β-Acetoxy-17α-ethynyl-17β-hydroxyandrost-5-ene.—3β-Acetoxy-17α-ethynyl-17β-hydroxyandrost-5-ene (25 g.) in chloroform (250 ml.) was treated for 18 hr. at 0° with monoperphthalic acid (17·5 g.) in ether (340 ml.). The mixture was washed with dilute aqueous alkali and water, then dried and the solvents were removed. The residue was fractionated from methanol, and the less soluble fraction purified from the same solvent, to give 3β-*acetoxy*-5α : 6α-*epoxy*-17α-*ethynyl*-17β-*hydroxyandrostane*, dense needles, m. p. 235—237°, $[\alpha]_D^{20}$ −108° (*c* 1·37) (Found: C, 74·0; H, 8·6. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%).

The more soluble fraction (3·2 g., m. p. 180—190°) was purified from aqueous ethanol, to give the 5β : 6β-*epoxide*, flat needles, m. p. 190°, $[\alpha]_D^{20}$ −61° (*c* 1·2) (Found: 74·1; H, 8·9%).

17α-Ethynyl-6β-methyl-3β : 5α : 17β-trihydroxyandrostane (VI; R = C:CH, R′ = ---H, –OH).—The Grignard reagent prepared from magnesium (4·8 g.) and methyl iodide (29 g.) in ether (150 ml.) was treated with a solution of the foregoing 5α : 6α-epoxide (6·9 g.) in benzene (440 ml.). Solvents were partially removed by distillation until a vapour-temperature of 70° was reached, then the mixture was heated under reflux for 5 hr. After cooling and treatment with aqueous ammonium chloride, the product was collected by filtration and crystallised from aqueous ethanol. The *triol* separated in needles, m. p. 145—150° (effervescence), raised to 193—195° after several hours' heating at 100°, $[\alpha]_D^{21}$ −47° (*c* 0·7 in pyridine) (Found: C, 72·4; H, 10·2. $C_{22}H_{34}O_3,H_2O$ requires C, 72·5; H, 10·0%). The 3β-*acetate* crystallised from benzene–hexane in plates, m. p. 130°, $[\alpha]_D^{21}$ −59° (*c* 1·13) (Found: C, 75·0; H, 9·4. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

5α : 17β-Dihydroxy-17α-ethynyl-6β-methylandrostan-3-one (VI; R = C:CH, R′ = :O).—The foregoing triol (1 g.) in pyridine (10 ml.) was added to chromium trioxide (1 g.) in pyridine (10 ml.), and the mixture set aside overnight. The product, isolated with ether, crystallised from aqueous ethanol to give the *ketone*, flat needles, m. p. 243—244°, $[\alpha]_D^{19}$ −42° (*c* 1·14) (Found: C, 73·2; H, 9·7. $C_{22}H_{32}O_3,H_2O$ requires C, 72·9; H, 9·4%).

6β-Methylethisterone (VII; R = C:CH, R′ = ---H, –Me).—A solution of 17α-ethynyl-6β-methylandrostane-3β : 5α : 17β-triol (4·5 g.) in toluene (180 ml.) and *cyclo*hexanone (40 ml.) was distilled until 40 ml. of distillate had collected. After the addition of aluminium *iso*propoxide (2·5 g.) in toluene (10 ml.), the mixture was refluxed for 1½ hr., cooled, and washed with dilute hydrochloric acid and then with water. The solvents were removed by steam-distillation, and the solids obtained were taken into ether. Concentration of the dried extract to small volume gave a crystalline solid (2 g.; m. p. 215—217°) which was purified from aqueous ethanol. 6β-*Methylethisterone* formed dense plates or fine needles, m. p. 223—225°, $[\alpha]_D^{20}$ −22° (*c* 0·8), $\lambda_{max.}$ 241·5 mμ (log ε 4·25) (Found: C, 80·5; H, 9·3. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

6α-Methylethisterone (VII; R = C:CH, R′ = ---Me, –H).—(*a*) 6β-Methylethisterone (1·5 g.) and potassium hydroxide (1·5 g.) in 95% ethanol (60 ml.) were heated under reflux for 5 hr. The product was extracted with ether, and the washed and dried extract concentrated to low bulk; a solid (m. p. 185°) separated. Purified from aqueous methanol, 6α-*methylethisterone* formed dense crystals, m. p. 195—197°, $[\alpha]_D^{22}$ +35° (*c* 0·87), $\lambda_{max.}$ 241 mμ (log ε 4·19) (Found: C, 80·7; H, 9·5. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

(*b*) 6β-Methylethisterone (8·5 g.) in ethanol (250 ml.) was treated with 6 drops of concentrated hydrochloric acid and the mixture refluxed for 30 min. The product was taken into ether (1·5 l.), and the solution washed, dried, and concentrated to low bulk. 6α-Methylethisterone separated in dense crystals, m. p. 195—197°, not depressed on admixture with a specimen prepared by method (*a*) above.

(*c*) Two drops of concentrated hydrochloric acid were added to 5α : 17β-dihydroxy-17α-ethynyl-6β-methylandrostan-3-one (0·75 g.) in methanol (20 ml.), and the mixture was refluxed for 20 min. 6α-Methylethisterone with m. p. 192—195° was obtained.

The Sulphite (VIII).—(*a*) 5α : 17β-Dihydroxy-17α-ethynyl-6β-methylandrostan-3-one (1 g.) in pyridine, cooled in ice–salt, was treated with thionyl chloride (0·8 ml.), added dropwise at such a rate that the temperature did not rise above 0°. After a further 10 min. at 0° the mixture was poured into ice-water and the product isolated with ether. Trituration with a little methanol gave material (450 mg.) which was purified from chloroform–methanol. The *sulphite* formed small rhombs, m. p. 200—202° (effervescence), $[\alpha]_D^{22}$ −48° (*c* 0·82), $\lambda_{max.}$ 241 mμ (log ε 4·2) (Found: C, 75·2; H, 8·3; S, 4·7. $C_{44}H_{58}O_5S$ requires C, 75·6; H, 8·4; S, 4·6%).

(*b*) 6β-Methylethisterone (250 mg.) in pyridine (2·5 ml.) was treated with thionyl chloride

(0·2 ml.) as described above. The product (80 mg.) had m. p. 200—202°, alone or in admixture with a specimen prepared by method (*a*).

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