4. *Modified Steroid Hormones. Part XXV.*[1] 16α-*Acetoxy-*, 16α-*Methyl, and* 16β-*Methyl Derivatives of* 17α-*Acetoxy*-6-*methylpregna*-4,6-*diene*-3,20-*dione.*

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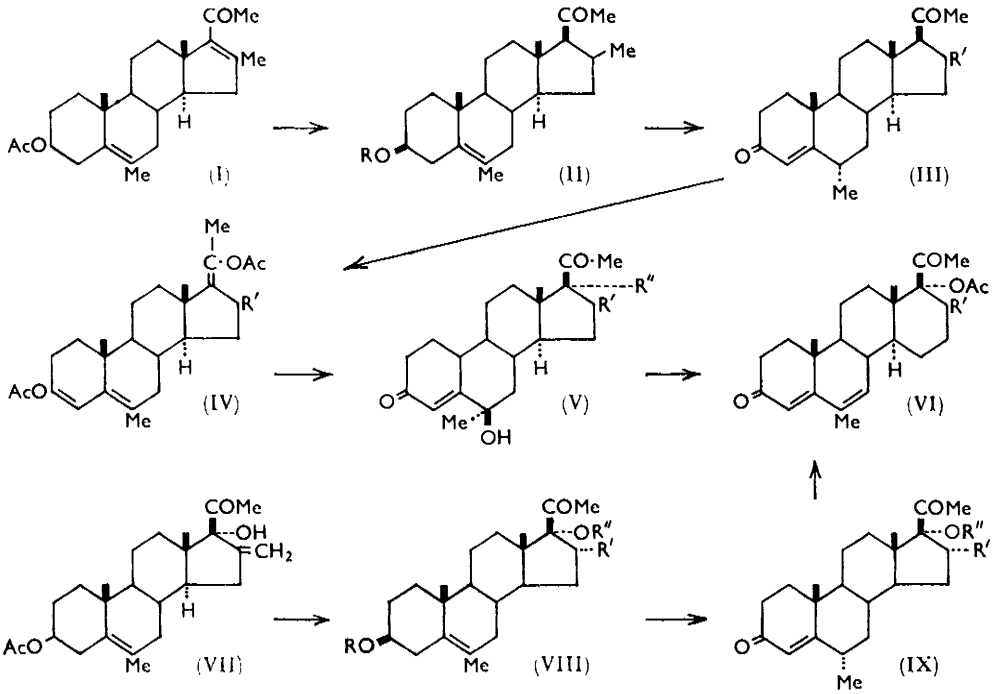
Preparation of the compounds named in the title is reported.

Elsewhere [2] we have described the partial synthesis of 16α,17α-dihydroxy-6α-methylpregn-4-ene-3,20-dione (IX; R′ = OH, R″ = H). Its conversion into 16α,17α-diacetoxy-6-methylpregna-4,6-diene-3,20-dione (VI; R′ = ···OAc) involved (i) acetylation of the α-glycol group and (ii) dehydrogenation at positions 6 and 7. Discouraging results were initially obtained at the acetylation stage, although conditions were ultimately developed which afforded the required diacetyl derivative (IX; R′ = OAc, R″ = ···Ac) in low yield (see p. 25). A more convenient route to the last compound utilised 16α-acetoxy-3β,17α-dihydroxy-6-methylpregn-5-en-20-one [1] (VIII; R = R″ = H, R′ = OAc). This

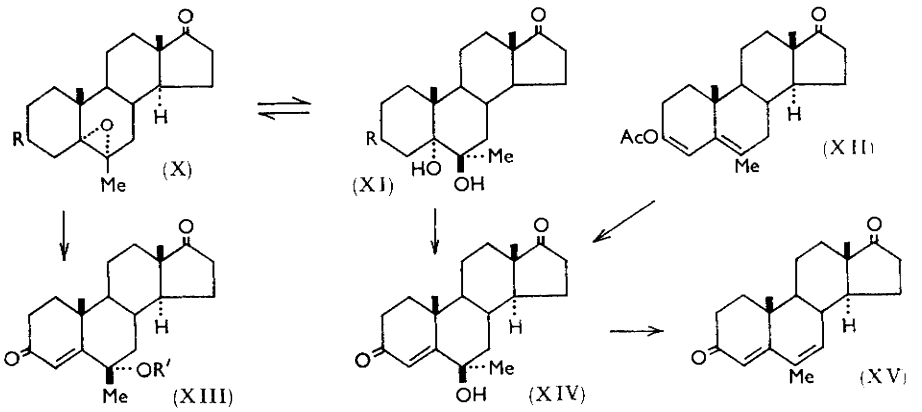


starting material was converted into its 3-formate (VIII; R = CHO, R′ = OAc, R″ = H), which was treated with acetic anhydride and toluene-*p*-sulphonic acid at room temperature. The resulting product failed to crystallise, but passed smoothly into 16α,17α-diacetoxy-6α-methylpregn-4-ene-3,20-dione (IX; R′ = OAc, R″ = Ac) on Oppenauer oxidation. As the acyl group in 17α-acetoxypregnan-20-ones is resistant to acid hydrolysis,[3] we attempted to prepare, *inter alia*, 17α-acetoxy-16α-hydroxy-6α-methylpregn-4-ene-3,20-dione (IX; R′ = OH, R″ = Ac) by treating the last compound with hot methanolic hydrochloric acid. The product proved to be the corresponding α-glycol

[1] Part XXIV, Ellis, Hall, Petrow, and Waddington-Feather, *J.*, 1961, 4111.
[2] Bianchi, David, Ellis, Petrow, Waddington-Feather, and Woodward, *J. Pharm. Pharmacol.*, 1961, **13**, 355.
[3] See, *e.g.*, Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3489.

(IX; R′ = OH, R″ = H), formed possibly through an orthoacetate as intermediate. Brief treatment of 16α,17α-diacetoxy-6α-methylpregn-4-ene-3,20-dione with acetic anhydride and toluene-*p*-sulphonic acid at 100° gave 3,16α,17α-triacetoxy-6-methylpregna-3,5-dien-20-one, which on reaction with one equivalent of bromine, followed by dehydrobromination of the product with collidine, afforded the required 16α,17α-diacetoxy-6-methylpregna-4,6-diene-3,20-dione (VI; R′ = ···OAc).

The first method developed for the preparation of 17α-acetoxy-6,16α-dimethylpregna-4,6-diene-3,20-dione (VI; R′ = ···Me) arose from some work in the androstane series. Epoxidation of 3β-acetoxy-6-methylandrost-5-en-17-one with monoperphthalic acid has been shown by Cooley *et al.*[4] to give an epoxide which can be converted into a 5α-hydroxy-6α-methylandrostan-3-one derivative. This establishes its constitution as 3β-acetoxy-5α,6α-epoxy-6β-methyl-5α-androstan-17-one (X; R = ⁻OAc). We now find that fission of the epoxide ring present in the last compound with aqueous periodic acid in acetone leads to an α-glycol which, on the basis of the " diaxial opening of epoxides " rule, can be formulated as 3β-acetoxy-5α,6β-dihydroxy-6α-methyl-5α-androstan-17-one (XI; R = ⁻OAc). The constitution assigned to the last compound is supported by its conversion into its 5α,6α-epoxy-precursor (X; R = ⁻OAc) by reaction with thionyl chloride.



Hydrolysis of the acetoxy-glycol led to 3β,5α,6β-trihydroxy-6α-methyl-5α-androstan-17-one (XI; R = ⁻OH), which underwent smooth oxidation to 5α,6β-dihydroxy-6α-methyl-5α-androstane-3,17-dione (XI; R = O). The last compound was previously obtained [5] from 3β,17β-diacetoxy-5α-hydroxy-5α-androstan-6-one by reaction with methylmagnesium bromide, followed by oxidation of the product, a process which incidentally establishes unequivocally the α-configuration of the 5-hydroxyl group present in both (XI; R = ⁻OAc) and (XI; R = O). Treatment of the 3,17-dione with alkali has been shown [5] to lead to selective dehydration with formation of 6β-hydroxy-6α-methylandrost-4-ene-3,17-dione (XIV), $\lambda_{max.}$ 237 mμ. We now find that the last compound is further dehydrated by acetic acid–acetic anhydride–perchloric acid to 6-methylandrosta-4,6-diene-3,17-dione [5] (XV). The same 6β-hydroxy-6α-methyl derivative (XIV) was obtained by treating 3-acetoxy-6-methylandrosta-3,5-dien-17-one (XII) with an excess of monoperphthalic acid.[6]

When 3β-acetoxy-5α,6α-epoxy-6β-methyl-5α-androstan-17-one (X; R = ⁻OAc) was hydrolysed by alkali and the resulting secondary alcohol (X; R = ⁻OH) oxidised [7] with chromium trioxide in pyridine, 5α,6α-epoxy-6β-methyl-5α-androstane-3,17-dione (X; R = O) was obtained in reasonable overall yield. Its treatment with ethanolic potassium

[4] Cooley, Ellis, and Petrow, *J.*, 1960, 3676.
[5] Ellis, Kirk, Petrow, Waterhouse, and Williamson, *J.*, 1960, 2828.
[6] Cf. Romo, Rosenkranz, Djerassi, and Sondheimer, *J. Org. Chem.*, 1954, **19**, 1509.
[7] Cf. Ellis and Petrow, *J.*, 1956, 4417.

hydroxide afforded a new αβ-unsaturated ketone of $\lambda_{max.}$ 241·5 mμ, isomeric with authentic 6β-hydroxy-6α-methylandrost-4-ene-3,17-dione (XIV) and consequently assigned the constitution 6α-hydroxy-6β-methylandrost-4-ene-3,17-dione (XIII; R′ = H). This compound, in striking contrast to its 6β(axial)-hydroxy-isomer (XIV), passed into 6α-acetoxy-6β-methylandrost-4-ene-3,17-dione (XIII; R′ = Ac) on treatment with acetic acid–acetic anhydride–perchloric acid. We concluded from these observations (i) that 6α-hydroxy-6β-methyl-3-oxo-Δ^4-steroids (cf. XIII) can be distinguished from their 6β-hydroxy(axial)-epimers (cf. XIV) by their absorption in which respect they resemble their 6-demethyl [8] but differ from their 6-ethynyl analogues,[9] (ii) that the 6β-hydroxy-6α-methyl isomers (XIV) alone form suitable intermediates for the preparation of 6-methyl-3-oxo-4,6-diene steroids by the method described above, and (iii) that such 6β-hydroxy-6α-methyl isomers may be formed from the enol acetates of 6-methyl-3-oxo-Δ^4-steroids by oxidation with monoperphthalic acid.

Returning to the main theme of our investigation, we planned to prepare 17α-acetoxy-6,16α-dimethylpregna-4,6-diene-3,20-dione (VI; R′ = ···Me) from the readily available 6α,16α-dimethylpregn-4-ene-3,20-dione [10,11,12] (III; R = ···Me) by conversion into a dienol diacetate (IV; R′ = ···Me), which we hoped would undergo in one operation 6-hydroxylation and 17,20-epoxidation so that alkaline hydrolysis would furnish a 6β,17α-dihydroxy-derivative readily convertible into the dienedione (VI; R′ = ···Me).

Enol acetylation of 6α,16α-dimethylpregn-4-ene-3,20-dione afforded a mixture of non-crystalline enol acetates from which, after epoxidation followed by mild alkaline hydrolysis, 6β,17α-dihydroxy-6α,16α-dimethylpregn-4-ene-3,20-dione ($\lambda_{max.}$ 238 mμ) (V; R′ = ···Me, R″ = OH) was obtained in only modest yield, admixed with approximately half its weight of 6β-hydroxy-6α,16α-dimethylpregn-4-ene-3,20-dione ($\lambda_{max.}$ 237 mμ) (V; R′ = ···Me, R″ = H) from which it was readily separated by virtue of its very different solubility. As the progesterone derivative (V; R′ = ···Me, R″ = H) could only have arisen from 3-acetoxy-6,16α-dimethylpregna-3,5-dien-20-one, the products of enol acetylation (above) must have contained a significant proportion of the 3-monoenol acetate. A similar difficulty in preparing the 17α-hydroxy-16α-methylpregnan-20-one system by the enol-acetylation procedure has since been reported by other workers.[13]

Reaction of the alcohols (V; R′ = ···Me, R″ = H or OH) with acetic anhydride–perchloric acid afforded 6,16α-dimethylpregna-4,6-diene-3,20-dione (which has since been described by Graber and Meyers [10]) and the required 17β-acetoxy-6,16α-dimethylpregna-4,6-diene-3,20-dione (VI; R′ = ···Me), respectively.

A more convenient route to the last compound was subsequently developed when 3β-acetoxy-17α-hydroxy-6-methyl-16-methylenepregn-5-en-20-one [12] (VII) had become available. On catalytic hydrogenation this passed into the 16α-methyl derivative (VIII; R = Ac, R′ = Me, R″ = H), which was converted by vigorous acetylation into 3β,17α-diacetoxy-6,16α-dimethylpregn-5-en-20-one (VIII; R = R″ = Ac, R′ = Me). Selective hydrolysis with methanolic hydrochloric acid afforded 17α-acetoxy-6,16α-dimethyl-3β-hydroxypregn-5-en-20-one (VIII; R = H, R′ = Me, R″ = Ac), which passed into the required 17α-acetoxydienedione (VI; R′ = ···Me) on Oppenauer oxidation with benzoquinone as hydrogen acceptor. The corresponding Δ^4-derivative (IX; R′ = Me, R″ = Ac) was obtained by the usual Oppenauer technique.

17α-Acetoxy-6,16β-methylpregna-4,6-diene-3,20-dione (VI; R′ = –Me) was prepared as follows. 3β-Acetoxy-6,16-dimethylpregna-5,16-dien-20-one [12] (I) was converted into 3β-acetoxy-6,16β-dimethylpregn-5-en-20-one (II; R = Ac) by selective hydrogenation

[8] Bird, Cookson, and Dandegaonker, *J.*, 1956, 3675.
[9] Ellis, Petrow, and Waterhouse, *J.*, 1960, 2596.
[10] Graber and Meyers, *Chem. and Ind.*, 1960, 1478.
[11] Bernstein, Cantrall, and Dusza, *J. Org. Chem.*, 1961, **26**, 269.
[12] Kirk, Petrow, and Williamson, *J.*, 1961, 2821.
[13] *E.g.*, Edwards, Ringold, and Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 2318; Batres, Cardenas, Edwards, Monroy, Mancera, Djerassi, and Ringold, *J. Org. Chem.*, 1961, **26**, 871.

with Raney nickel as catalyst. Mild alkaline saponification [14] gave the 3β-hydroxy-derivative (II; R = H). Its Oppenauer oxidation on one occasion furnished 6α,16β-dimethylpregn-4-ene-3,20-dione (III; R′ = –Me), which could be converted into the more stable and more lævorotatory 6α,16β-dimethyl-17α-pregn-4-ene-3,20-dione by treatment with mineral acid.[15] In general, however, the product from Oppenauer oxidation consisted of a crystalline mixture of the two epimers (about $C_{(17)}$) from which the 17α-pregna-3,20-dione could be isolated by chromatography on alumina. Enol acetylation of the mixture of isomers by the technique of Barton *et al.*,[16] followed by oxidation of the crude (not isolated) dienol diacetate (IV; R′ = –Me) with monoperphthalic acid and subsequent alkaline hydrolysis, gave 6β,17α-dihydroxy-6α,16β-dimethylpregn-4-ene-3,20-dione ($\lambda_{max.}$ 238 mμ) (V; R′ = –Me, R″ = •••OH). Treatment of the last compound with acetic anhydride and perchloric acid furnished the required 17α-acetoxy-6,16β-dimethylpregna-4,6-diene-3,20-dione (VI; R′ = –Me).

Experimental

Optical rotations were measured for chloroform solutions in a 1 dm. tube, unless otherwise stated. Ultraviolet absorption spectra (in EtOH) were kindly determined by Mr. M. T. Davies, B.Sc. Infrared observations were made with a Perkin-Elmer Infracord spectrophotometer; no calibration corrections were applied.

16α-*Acetoxy*-3β-*formyloxy*-17α-*hydroxy*-6-*methylpregn*-5-*en*-20-*one* (VIII; R = CHO, R′ = OAc, R″ = H), prepared by treating 16α-acetoxy-3β,17α-dihydroxy-6-methylpregn-5-en-20-one [1] (24·5 g.) with 90% formic acid (80 ml.) for 15 min. at 100° and precipitating the product with water, crystallised from aqueous methanol in plates, m. p. 178—179°, $[\alpha]_D^{24}$ −100° (*c* 1·14) (Found: C, 69·4; H, 8·8. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%).

16α,17α-*Diacetoxy*-6α-*methylpregn*-4-*ene*-3,20-*dione* (IX; R′ = OAc, R″ = Ac).—(*a*) A suspension of 16α,17α-dihydroxy-6α-methylpregn-4-ene-3,20-dione [2] (3 g.) in acetic anhydride (75 ml.) to which toluene-*p*-sulphonic acid (1·8 g.) had been added, was stirred for 30 min., and the clear solution set aside overnight. It was poured into water (75 ml.), then left for 1 hr., and the product was isolated by dilution with water and extraction with ether. Purification from aqueous methanol gave the *diacetate*, blades, m. p. 215—216°, $[\alpha]_D^{24}$ +4° (*c* 1·14), $\lambda_{max.}$ 240 mμ (log ε 4·17) (Found: C, 70·1; H, 8·1. $C_{26}H_{36}O_6$ requires C, 70·2; H, 8·2%).

(*b*) The diester (VIII; R = CHO, R′ = OAc, R″ = H) (13·2 g.) was added to toluene-*p*-sulphonic acid (1·2 g.) in acetic anhydride (60 ml.), and the mixture slightly warmed to effect dissolution. After 2 days at room temperature, the whole was poured into water and the product isolated with ether. The brown gum obtained was dissolved in toluene (200 ml.) and cyclohexanone (200 ml.), and the solution distilled until 100 ml. of distillate had collected. After addition of aluminium t-butoxide (20 g.), the mixture was refluxed for 30 min., cooled, and washed with dilute mineral acid, then with water, and the solvents were removed by steam-distillation. The product was isolated with ether and purified from acetone–hexane to give 16α,17α-diacetoxy-6α-methylpregn-4-ene-3,20-dione, prisms, m. p. 215°, not depressed on admixture with a specimen prepared by method (*a*).

Acid Hydrolysis of the Diacetate (IX; R′ = OAc, R″ = Ac).—A solution of the foregoing compound (1 g.) in methanol (20 ml.) was treated with concentrated hydrochloric acid (0·3 ml.). The mixture was refluxed for 1½ hr., then diluted with water, and the product extracted with methylene dichloride. Removal of the solvent from the washed and dried extract gave a residue which was triturated with ether (10 ml.). Crystallisation of the insoluble fraction (250 mg.; m. p. 215°) from aqueous acetic acid gave 16α,17α-dihydroxy-6α-methylpregn-4-ene-3,20-dione,[2] blades, m. p. 232°, identified by mixed m. p. determination and by its infrared spectrum.

3,16α,17α-*Triacetoxy*-6-*methylpregna*-3,5-*dien*-20-*one*, prepared by heating the diacetate (IX; R′ = OAc, R″ = Ac) (1 g.), toluene-*p*-sulphonic acid (0·33 g.), and acetic anhydride (10 ml.) for 10 min. at 100°, crystallised from aqueous methanol in flakes, m. p. 192° (after

[14] Cf. Wettstein, *Helv. Chim. Acta*, 1944, **27**, 1803.
[15] Cf. Romo, Lepe, and Romero, *Bol. Inst. Quím. Univ. nac. auton. México*, 1952, **4**, 125.
[16] Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747.

softening at 184°), $[\alpha]_D^{24}$ +93° (*c* 0·4), $\lambda_{max.}$ 243 mμ (log ε 4·29) (Found: C, 69·0; H, 8·0. $C_{28}H_{38}O_7$ requires C, 69·1; H, 7·9%).

16α,17α-*Diacetoxy*-6-*methylpregna*-4,6-*diene*-3,20-*dione* (VI; R′ = ···OAc).—Bromine (0·35 ml.) in acetic acid (10 ml.) was added to the foregoing enol acetate (2·86 g.) in acetic acid (25 ml.) containing anhydrous sodium acetate (1 g.). After 15 min. the mixture was poured into water and the precipitate collected, washed, and air-dried. A solution of this crude bromo-compound [2 g.; m. p. 145—147° (decomp.)] in collidine (25 ml.) was refluxed for 30 min. The product was isolated with ether, and its solution in benzene passed through a column of alumina (10 g.). Further purification from aqueous methanol gave 16α,17α-*diacetoxy*-6-*methylpregna*-4,6-*diene*-3,20-*dione*, needles, m. p. 213—215°, $[\alpha]_D^{24}$ −22° (*c* 0·42), $\lambda_{max.}$ 286 mμ (log ε 4·38) (Found: C, 70·55; H, 7·5. $C_{26}H_{34}O_6$ requires C, 70·6; H, 7·7%).

3β-*Acetoxy*-5α,6β-*dihydroxy*-6α-*methyl*-5α-*androstan*-17-*one* (XI; R = –OAc).—A solution of 3β-acetoxy-5α,6α-epoxy-6β-methyl-5α-androstan-17-one [4] (4 g.) in hot acetone (70 ml.) was treated with periodic acid (1·2 g.) in water (15 ml.) and set aside overnight. The crystalline product which had separated was purified from aqueous acetic acid, giving the *acetoxy-glycol*, needles, m. p. 270—271°, $[\alpha]_D^{26}$ +30° (*c* 0·57 in dioxan), $\nu_{max.}$ (in Nujol) 3500, 3450 cm.$^{-1}$ (OH) (Found: C, 69·4; H, 9·2. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·05%).

When this compound (1 g.) in pyridine (10 ml.) at 0° was treated with thionyl chloride (0·5 ml.), the mixture poured into water, and the precipitate crystallised from aqueous ethanol, there was obtained in high yield 3β-acetoxy-5α,6α-epoxy-6β-methylandrostan-17-one, m. p. and mixed m. p. 189°.

3β,5α,6β-*Trihydroxy*-6α-*methyl*-5α-*androstan*-17-*one* (XI; R = –OH), obtained by alkaline saponification of the acetate (XI; R = –OAc), crystallised from aqueous ethanol in needles, m. p. 229°, $[\alpha]_D^{26}$ +53° (*c* 0·72) (Found: C, 71·55; H, 9·8. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6%).

5α,6β-*Dihydroxy*-6α-*methyl*-5α-*androstane*-3,17-*dione* (XI; R = O).—A 4N-chromium trioxide–sulphuric acid solution [17] was added dropwise to a stirred solution of the foregoing compound (1·35 g.) in acetone (40 ml.) until the mixture became permanently orange. After addition of water, the product was isolated with ether and crystallised from aqueous ethanol. The dione-diol formed small prisms, m. p. 244—245°, not depressed in admixture with a specimen prepared by another method.[5]

3-*Acetoxy*-6-*methylandrosta*-3,5-*dien*-17-*one* (XII).—A solution of 6α-methylandrost-4-ene-3,17-dione [18] (10 g.) and toluene-*p*-sulphonic acid (5 g.) in acetic anhydride (500 ml.) was heated for 30 min. at 100°, cooled, and poured into water. The product crystallised from aqueous methanol to give the *enol acetate*, needles, m. p. 170—171°, $[\alpha]_D^{20}$ −110° (*c* 0·94), $\lambda_{max.}$ 244 mμ (log ε 4·25) (Found: C, 77·5; H, 9·0. $C_{22}H_{30}O_3$ requires C, 77·15; H, 8·8%).

6β-*Hydroxy*-6α-*methylandrost*-4-*ene*-3,17-*dione* (XIV).—The foregoing acetate (XII) (10·3 g.) in methylene dichloride (80 ml.) was treated with monoperphthalic acid (9·3 g.) in ether (180 ml.). After 3 days at 0°, the mixture was washed with aqueous sodium carbonate and water, then dried, and the solvent was removed. Trituration of the gummy residue with a small volume of ether gave a solid (4 g.), m. p. 180—210°, which was purified from acetone–hexane. 6β-Hydroxy-6α-methylandrost-4-ene-3,17-dione separated in needles, m. p. 236—238°, $[\alpha]_D^{21}$ +97° (*c* 0·8), $\lambda_{max.}$ 237 mμ (log ε 4·13). There was no depression of m. p. in admixture with an authentic specimen prepared by another route.[5]

6-*Methylandrosta*-4,6-*diene*-3,17-*dione* (XV).—The foregoing compound (500 mg.) in acetic acid (10 ml.) and acetic anhydride (2·5 ml.) was treated with 1 drop of 72% perchloric acid. After 30 min., the mixture was poured into water and the product isolated with ether. Crystallisation from acetone–hexane gave the diene-dione in needles, m. p. 174°, alone or in admixture with an authentic specimen.[5]

5α,6α-*Epoxy*-3β-*hydroxy*-6β-*methylandrostan*-17-*one* (X; R = –OAc), obtained by alkaline saponification of the 3β-acetate,[4] crystallised from aqueous methanol in needles, which had double m. p. 175° and 189—190°, $[\alpha]_D^{20}$ +13° (*c* 0·7) (Found: C, 75·2; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%), after drying for several hours at 100°.

5α,6α-*Epoxy*-6β-*methylandrostane*-3,17-*dione* (X; R = O).—The foregoing compound (10 g.) in pyridine (100 ml.) was added to chromium trioxide (10 g.) in pyridine (100 ml.), and the mixture set aside overnight. The product was isolated with ether and purified from aqueous

[17] Cf. Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.
[18] See Ackroyd, Adams, Ellis, Petrow, and Stuart-Webb, *J.*, 1957, 4099.

methanol. The *dione* separated in plates, m. p. 189—190°, $[\alpha]_D^{21}$ +19° (*c* 1·0) (Found: C, 75·4; H, 8·8. $C_{20}H_{28}O_3$ rquires C, 75·9; H, 8·9%).

6α-*Hydroxy*-6β-*methylandrost*-4-*ene*-3,17-*dione* (XIII; R′ = H), formed by heating the foregoing compound (3 g.) with potassium hydroxide (1 g.) in ethanol (25 ml.) and water (5 ml.) for 5 min. at 100°, separated from aqueous ethanol in irregular blades, m. p. 220—222°, $[\alpha]_D^{28}$ +141° (*c* 0·75), $\lambda_{max.}$ 241·5 mμ (log ε 4·15), $\nu_{max.}$ (in Nujol) 3450 cm.$^{-1}$ (OH) (Found: C, 75·5; H, 8·8. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%).

The compound was recovered largely unchanged after a solution of it (250 mg.) in methanol (5 ml.) containing 2 drops of concentrated hydrochloric acid had been refluxed for 30 min.

6α-*Acetoxy*-6β-*methylandrost*-4-*ene*-3,17-*dione* (XIII; R′ = Ac).—The foregoing alcohol (1 g.) in acetic acid (20 ml.) and acetic anhydride (5 ml.) was treated with 2 drops of 72% perchloric acid. After 20 min. the mixture was poured into water, and the precipitated solid collected, washed, and purified from aqueous ethanol. The *acetate* formed prisms, m. p. 235—236°, $[\alpha]_D^{19}$ +121° (*c* 1·02), $\lambda_{max.}$ 242·5 mμ (log ε 4·07), $\nu_{max.}$ (in Nujol) 1745 and 1220 cm.$^{-1}$ (OAc) (Found: C, 73·3; H, 8·3. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%).

6β,17α-*Dihydroxy*- (V; R′ = •••Me, R″ = OH) and 6β-*Hydroxy*-6α,16α-*dimethylpregn*-4-*ene*-3,20-*dione* (V; R′ = •••Me, R″ = H).—A solution of 6α,16α-dimethylpregn-4-ene-3,20-dione (15·75 g.) in acetic anhydride (1600 ml.) to which toluene-*p*-sulphonic acid (6 g.) had been added was slowly distilled during 7 hr. The cooled residue (150 ml.) was poured into water, and the product extracted with ether. The extract was washed with dilute aqueous sodium hydrogen carbonate and water, dried, and evaporated, leaving a black syrup. Its solution in 2 : 1 light petroleum (b. p. 40—60°)–ether (300 ml.) was percolated through alumina (200 g.) which had previously been washed with ethyl acetate and then with the same light petroleum–ether mixture. Removal of the solvents gave a pale yellow gum (18 g.), which was treated overnight with monoperphthalic acid (23 g.) in ether (450 ml.). The neutral fraction, an almost colourless gum (13·5 g.), was heated for 10 min. under reflux with potassium hydroxide (3 g.) in methanol (80 ml.) and water (20 ml.), a fine crystalline deposit being formed within the first few minutes. After neutralisation with acetic acid and cooling, the product was filtered, giving colourless plates, m. p. 270—274°. Purified from methylene dichloride–ethanol, 6β,17α-*dihydroxy*-6α,16α-*dimethylpregn*-4-*ene*-3,20-*dione* formed plates, m. p. 288—290°, $[\alpha]_D^{20}$ +17° (*c* 0·83 in pyridine), $\lambda_{max.}$ 238 mμ (log ε 4·08) (Found: C, 73·7; H, 8·9. $C_{23}H_{34}O_4$ requires C, 73·7; H, 9·15%). The mother liquor from the saponification deposited a solid on storage for some hours. Crystallisation from aqueous methanol gave 6β-*hydroxy*-6α,16α-*dimethylpregn*-4-*ene*-3,20-*dione*, flat needles, m. p. 272—273°, $[\alpha]_D^{20}$ +82° (*c* 0·6), $\lambda_{max.}$ 237 mμ (log ε 4·11) (Found: C, 76·8; H, 9·2. $C_{23}H_{34}O_3$ requires C, 77·05; H, 9·5%).

6,16α-*Dimethylpregna*-4,6-*diene*-3,20-*dione*.—A suspension of the foregoing monohydroxy-compound (1·5 g.) in acetic anhydride (25 ml.) was treated with 72% perchloric acid (3 drops). After 10 min. the mixture was poured into water, and the product isolated with ether and chromatographed on alumina (45 g.). Elution with light petroleum (b. p. 40—60°)–benzene (3 : 2) gave a solid which was purified from acetone–hexane. The diene-dione separated in blades, m. p. 163—164°, $[\alpha]_D^{20}$ +135° (*c* 1·11), $\lambda_{max.}$ 288 mμ (log ε 4·43) (Found: C, 80·9; H, 9·3. Calc. for $C_{23}H_{32}O_2$: C, 81·1; H, 9·5%). {Graber and Meyers [10] give m. p. 158—162°, $[\alpha]_D$ +179°, $\lambda_{max.}$ 290 mμ (log ε 4·39)}.

17α-*Acetoxy*-6,16α-*dimethylpregna*-4,6-*diene*-3,20-*dione* (VI; R′ = •••Me).—A suspension of 6β,17α-dihydroxy-6α,16α-dimethylpregn-4-ene-3,20-dione (1·3 g.) in acetic anhydride (15 ml.) was treated with 72% perchloric acid (2 drops). The mixture was stirred for 10 min., then poured into water, and the product isolated with ether. Chromatography on alumina (30 g.), with light petroleum–benzene (1 : 1) as eluent, gave 17α-*acetoxy*-6,16α-*dimethylpregna*-4,6-*diene*-3,20-*dione*, prisms (from aqueous methanol), m. p. 202—204°, $[\alpha]_D^{22}$ +21° (*c* 0·99), $\lambda_{max.}$ 286 mμ (log ε 4·35) $\nu_{max.}$ (in Nujol) 1745 (OAc), 1710 (20-C:O), 1655, 1625, and 1590 cm.$^{-1}$ ($\Delta^{4,6}$-3-C:O system) (Found: C, 75·5; H, 8·8. $C_{25}H_{34}O_4$ requires C, 75·3; H, 8·6%).

3β-*Acetoxy*-17α-*hydroxy*-6,16α-*dimethylpregn*-5-*en*-20-*one* (VIII; R = Ac, R′ = Me, R″ = H).—3β-Acetoxy-17α-hydroxy-6-methyl-16-methylenepregn-5-en-20-one [12] (1·8 g.) in absolute ethanol (250 ml.) was hydrogenated over 5% palladium–charcoal (0·5 g.). The hydrogenation was stopped when one mol. of hydrogen had been absorbed. The residue obtained after removal of the catalyst and solvent crystallised from acetone–hexane to give 3β-*acetoxy*-17α-*hydroxy*-6,16α-*dimethylpregn*-5-*en*-20-*one*, needles, m. p. 126—128°, $[\alpha]_D^{26}$ −88° (*c* 1·11) (Found: C, 74·4; H, 9·35. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%).

3β,17α-*Diacetoxy*-6,16α-*dimethylpregn*-5-*en*-20-*one* (VIII; R = R″ = Ac, R′ = Me).—The foregoing compound (0·5 g.) with toluene-*p*-sulphonic acid monohydrate (0·05 g.) was heated in acetic anhydride (10 ml.) for 30 min. at 90°. The mixture was cooled and poured on crushed ice, and the product crystallised from methanol to give 3β,17α-*diacetoxy*-6,16α-*dimethylpregn*-5-*en*-20-*one*, needles, m. p. 186—187°, $[\alpha]_D^{26}$ −55° (*c* 1·17) (Found: C, 72·8; H, 8·9. $C_{27}H_{40}O_5$ requires C, 72·9; H, 9·1%).

17α-*Acetoxy*-3β-*hydroxy*-6,16α-*dimethylpregn*-5-*en*-20-*one* (VIII; R = H, R′ = Me, R″ = Ac).—The foregoing diacetate (1·0 g.) in methanol (50 ml.) containing concentrated hydrochloric acid (1 ml.) was heated under reflux for 1 hr. 17α-*Acetoxy*-3β-*hydroxy*-6,16α-*dimethylpregn*-5-*en*-20-*one* crystallised from aqueous methanol as needles, m. p. 177—178°, $[\alpha]_D^{26}$ −48° (*c* 0·97) (Found: C, 74·4; H, 9·3. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%).

17α-*Acetoxy*-6α,16α-*dimethylpregn*-4-*ene*-3,20-*dione* (IX; R′ = Me, R″ = Ac).—A solution of the foregoing compound (2 g.) and aluminium t-butoxide (2 g.) in dry cyclohexanone (24 ml.) and dry toluene (16 ml.) was heated under reflux for ½ hr. After the addition of Rochelle salt solution, the reaction mixture was steam-distilled for 4 hr. and the product isolated with methylene dichloride. Crystallisation from methanol gave 17α-*acetoxy*-6α,16α-*dimethylpregn*-4-*ene*-3,20-*dione*, needles, m. p. 164—165°, $[\alpha]_D^{26}$ +74° (*c* 1·13), $\lambda_{max.}$ 240 mμ (ε 15,540) (Found: C, 74·9; H, 8·95. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·1%).

17α-*Acetoxy*-6,16α-*dimethylpregna*-4,6-*diene*-3,20-*dione* (VI; R′ = ···Me).—17α-Acetoxy-6,16α-dimethyl-3β-hydroxypregn-5-en-20-one (2·5 g.), aluminium t-butoxide (2·5 g.), and *p*-benzoquinone (4·0 g.) were suspended in dry benzene (100 ml.) and the mixture was stirred at room temperature for 72 hr., diluted with ether, and washed with dilute sodium hydroxide solution and water. The residue from the organic layer crystallised from acetone–hexane to give 17α-acetoxy-6,16α-dimethylpregna-4,6-diene-3,20-dione, needles, m. p. 202—204°, $[\alpha]_D^{24}$ +21° (*c* 0·64). A depression of m. p. was not obtained in admixture with a specimen prepared as described above.

3β-*Acetoxy*-6,16β-*dimethylpregn*-5-*en*-20-*one* (II; R = Ac).—Raney nickel sludge (150 ml.) was washed with water until the washings were neutral, then with ethanol, and a suspension in ethanol (300 ml.) agitated in an atmosphere of hydrogen until uptake of gas had ceased. 3β-Acetoxy-6,16-dimethylpregna-5,16-dien-20-one [12] (37 g.) in ethyl acetate (300 ml.) was added to the suspension, and the mixture hydrogenated until uptake of hydrogen had ceased. The product obtained after removal of the catalyst and solvents was purified from aqueous ethanol, to give 3β-*acetoxy*-6,16β-*dimethylpregn*-5-*en*-20-*one*, needles, m. p. 153—154°, $[\alpha]_D^{20}$ −42° (*c* 0·94) (Found: C, 77·6; H, 9·8. $C_{25}H_{38}O_3$ requires C, 77·7; H, 9·9%).

3β-*Hydroxy*-6,16β-*dimethylpregn*-5-*en*-20-*one* (II; R = H), obtained by saponification of the foregoing compound with hot aqueous-methanolic potassium hydrogen carbonate, crystallised from aqueous ethanol in needles, m. p. 134—135° (after drying for several hours at 40°), $[\alpha]_D^{23}$ −32° (*c* 0·9) (Found: C, 76·3; H, 10·7. $C_{23}H_{36}O_2,H_2O$ requires C, 76·2; H, 10·6%).

Oppenauer Oxidation of 3β-*Hydroxy*-6,16β-*dimethylpregn*-5-*en*-20-*one*.—A solution of the foregoing compound (9·5 g.) in dry toluene (250 ml.) and cyclohexanone (130 ml.) was distilled until 70 ml. of distillate had collected. Aluminium t-butoxide (15 g.) in toluene (150 ml.) was then added, and the mixture heated under reflux for 2 hr. After addition of Rochelle salt, the solvents were removed in steam, and the product was isolated with chloroform. One crystallisation from aqueous methanol gave a product, m. p. 125—130°, $[\alpha]_D^{27}$ +41°. Chromatography on alumina (60 g.) utilised light petroleum–benzene mixtures as eluants, and finally benzene alone. Early fractions consisted of unresolved material with m. p. *ca.* 135°, $[\alpha]_D^{23}$ +41°. Later fractions gave higher-melting material which was purified from aqueous ethanol, giving 6α,16β-*dimethyl*-17α-*pregn*-4-*ene*-3,20-*dione* as flakes, m. p. 153—154°, $[\alpha]_D^{27}$ +16° (*c* 1·08), $\lambda_{max.}$ 240 mμ (log ε 4·15) (Found: C, 80·8; H, 10·2. $C_{23}H_{34}O_2$ requires C, 80·65; H, 10·0%).

In another experiment on a 2-g. scale, the product had m. p. 182—188° after the first crystallisation from aqueous methanol. Further purification from the same solvent gave 6α,16β-*dimethylpregn*-4-*ene*-3,20-*dione*, needles, m. p. 189—192°, $[\alpha]_D^{23}$ +114° (*c* 1·36), $\lambda_{max.}$ 240 mμ (log ε 4·16) (Found: C, 80·4; H, 10·05%).

Isomerisation of 6α,16β-*Dimethylpregn*-4-*ene*-3,20-*dione*.—A solution of the last compound (17β) (140 mg.) in ethanol (15 ml.) was heated with concentrated hydrochloric acid (1·5 ml.) under reflux for 40 min. The product, isolated with ether, crystallised from aqueous ethanol to give 6α,16β-dimethyl-17α-pregn-4-ene-3,20-dione (70 mg.), m. p. 153°, not depressed in admixture with a specimen obtained as described above.

Similar isomerisation of the mixed isomers (500 mg.), m. p. 125—130°, $[\alpha]_D$ +41°, referred to above, likewise gave the 17α-compound (350 mg.), m. p. 153°.

6β,17α-*Dihydroxy*-6α,16β-*dimethylpregn*-4-*ene*-3,20-*dione* (V; R′ = -Me, R″ = OH).—A mixture of 6α,16β-dimethylpregn-4-ene-3,20-dione and its 17α-epimer (11·7 g.; m. p. 125—130°) in carbon tetrachloride (117 ml.) was treated for 3 hr. at room temperature with acetic anhydride (17 ml.) to which 50% aqueous perchloric acid (0·3 ml.) had been added. The mixture was diluted with chloroform, washed with ice-cold 5% aqueous sodium hydroxide, and water, and dried (Na_2SO_4). Removal of the solvents under reduced pressure gave a dark gum which, in chloroform (50 ml.), was treated with monoperphthalic acid (29·5 g.) in ether (360 ml.). The mixture was set aside overnight and the neutral product isolated in the usual way. Its solution in methanolic 0·8N-potassium hydroxide (80 ml.) was heated under reflux for 15 min., and the product isolated with ether. Crystallisation from acetone–hexane gave 6β,17α-*dihydroxy*-6α,16β-*dimethylpregn*-4-*ene*-3,20-*dione*, needles, m. p. 240—248°, $[\alpha]_D^{25}$ +31° (*c* 0·49), $\lambda_{max.}$ 238 mμ (log ε 4·10) (Found: C, 73·6; H, 9·1. $C_{23}H_{34}O_4$ requires C, 73·7; H, 9·15%).

17α-*Acetoxy*-6,16β-*dimethylpregna*-4,6-*diene*-3,20-*dione* (VI; R′ = -Me).—A suspension of the foregoing compound (310 mg.) in acetic anhydride (5 ml.) was treated with 72% perchloric acid (2 drops). After 15 min., water was added and the product isolated with ether. It was purified by chromatography on alumina (10 g.), with light petroleum–benzene (3 : 2) as eluant, and crystallisation from acetone–hexane. The *diene-dione* separated in blades, m. p. 204—209°, $\lambda_{max.}$ 287·5 mμ (log ε 4·33), $\nu_{max.}$ (in Nujol) 1735 (OAc), 1705 (20-C:O), 1655, 1625, and 1580 $cm.^{-1}$ ($\Delta^{4,6}$-3-:CO system) (Found: C, 74·9; H, 8·9. $C_{25}H_{34}O_4$ requires C, 75·3; H, 8·6%). A significant depression in m. p. was obtained in admixture with 17α-acetoxy-6,16α-dimethylpregna-4,6-diene-3,20-dione.

CHEMICAL RESEARCH LABORATORIES.
THE BRITISH DRUG HOUSES LTD., LONDON, N.1.

[*Received, July 28th*, 1961.]