571. *Modified Steroid Hormones. Part XVII.*[1] *Some 6-Methyl-4,6-dien-3-ones.*

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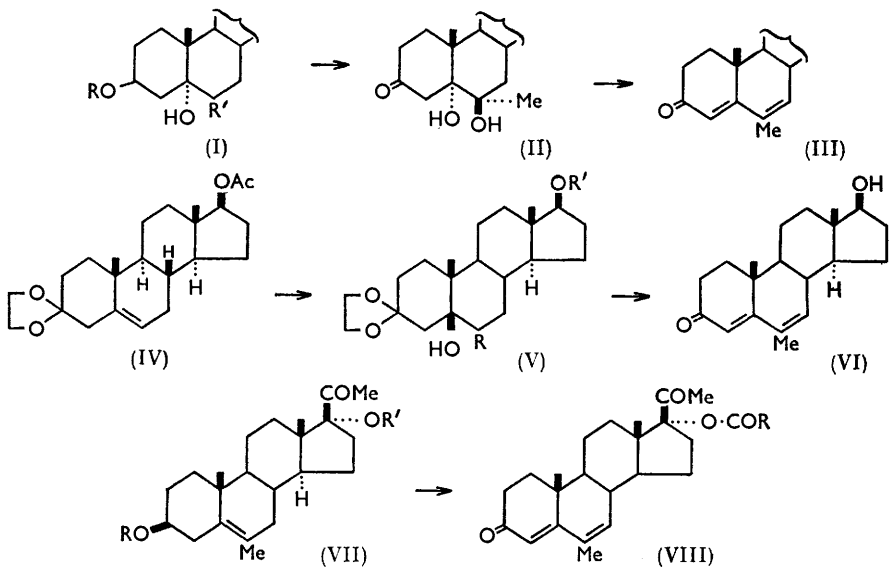
Methods are described for the conversion of 3β-acetoxy-5α-hydroxy-6-oxo-, 3,3-ethylenedioxy-Δ⁵-, 3β-hydroxy-6-methyl-Δ⁵-, and 6α-methyl-3-oxo-Δ⁴-steroids into the corresponding 6-methyl-4,6-diene-3-ones.

The biological activity of steroidal hormones of the 3-oxo-Δ⁴-type is generally decreased by the introduction of a 6β-methyl group or of a 6,7-unsaturated linkage. A 6α-methyl group, in contrast, often enhances certain types of biological activity such as progestational, anti-inflammatory, and glucocorticoid activity. Steroidal hormones containing a combination of these structural features, *i.e.*, 6-methyl-Δ⁶-derivatives (III), had not been reported when this work was initiated in 1957. In such structures (III), the 6-methyl group has been oriented to some extent away from the biologically favourable α-, and towards the biologically unfavourable β-position. This change has been superimposed upon a second structural feature (6,7-double bond) of at least doubtful utility in so far as biological potency in the series without the 6-methyl group is concerned. Against the background of these considerations our discovery that some of the products described below are many times more potent biologically than the 6α-methyl-3-oxo-Δ⁴-structures from which they are formally derived was completely unexpected.



The first method developed for the preparation of certain 6-methyl-4,6-dien-3-ones employed the corresponding 3β-acetoxy-5α-hydroxy-6-ketone (I; R = Ac, R′ = :O) as starting material. Reaction of an intermediate of this type with excess of methylmagnesium iodide furnished the 6α-methyl-3β,5α,6β-triol * (I; R = H; R′ = ····Me, —OH) which passed on oxidation into the 5α,6β-dihydroxy-6α-methyl-3-ketone (II). Dehydration of the latter compound to the required 6-methyl-4,6-dien-3-one (III) was

* The configurations of the groups at $C_{(6)}$ are assigned by analogy.[1]

[1] Part XVI, Ellis, Petrow, and Waterhouse, *J.*, 1960, 2596.

effected by hot methanolic hydrochloric acid. In this way, 3β-acetoxy-5α-hydroxycholestan-6-one,[2] 3β-acetoxy-5α,17β-dihydroxy-17α-methylandrostan-6-one,[1] and 3β,17β-diacetoxy-5α-hydroxyandrostan-6-one [3] were converted into the corresponding 6-methyl derivatives of cholesta-4,6-dien-3-one, 17β-hydroxy-17α-methylandrosta-4,6-dien-3-one and androsta-4,6-diene-3,17-dione. The 6-methyl derivatives of 17α-ethynyl-17β-hydroxyandrosta-4,6-dien-3-one, 25D-spirosta-4,6-dien-3-one, and pregna-4,6-diene-3,20-dione were likewise prepared from the hitherto undescribed intermediates 3β-acetoxy-17α-ethynyl-5α,17β-dihydroxyandrostan-6-one, 3β-acetoxy-5α-hydroxy-25D-spirostan-6-one, and 3β,20β-diacetoxy-5α-hydroxypregnan-6-one, respectively, which were obtained from the corresponding 3β-acetoxy-5α,6α-epoxides by conversion with periodic acid [4] in aqueous acetone into the 3β-acetoxy-5α,6β-diols followed by oxidation at $C_{(6)}$.

In a modification of the foregoing procedure, 17β-acetoxy-3,3-ethylenedioxy-5β-hydroxyandrostan-6-one (V; R = :O; R′ = Ac) was treated with methylmagnesium iodide, to give a 3,3-ethylenedioxy-6ξ-methylandrostane-5β,6ξ,17β-triol (V; R = ~~OH, ~~Me; R′ = H) (not isolated) which in warm methanolic hydrochloric acid passed into 17β-hydroxy-6-methylandrosta-4,6-dien-3-one (VI) by dehydration and concomitant hydrolysis of the ketal group. The ketone (V; R = :O; R′ = Ac) had perforce to be prepared from the 5β,6β-diol (V; R = --H, -OH; R′ = Ac) which was obtained from the ketal (IV) only by the use of osmium tetroxide [5] with which it formed an osmate ester. The necessity for employing this relatively expensive reagent limits the potential utility of this route. Other attempts to convert the ketal (IV) into the corresponding 5,6-diol *via* the 5,6-epoxides, or by direct hydroxylation with potassium permanganate, or with hydrogen peroxide catalysed by osmic acid, were unsuccessful. An attempt to prepare 6,7-dehydro-6-methylcortisone did not succeed as cortisone di(ethylene ketal) failed to form an osmate ester.

The foregoing methods were unsuitable for the preparation of the 6,7-dehydro-6-methyl-derivatives of 17α-acyloxyprogesterone. The first member of this series of compounds, *i.e.*, 17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione (VIII; R = Me), was conveniently obtained by oxidation of 17α-acetoxy-3β-hydroxy-6-methylpregn-5-en-20-one [6] (VII; R = H, R′ = Ac) with the Oppenauer reagent, employing benzoquinone as hydrogen-acceptor.[7] The higher homologues (VIII; R = Et, Pr^n, and n-C_5H_{11} respectively) were likewise prepared from the diol (VII; R = R′ = H) [6] by the reaction sequence: acetylation at $C_{(3)}$, enforced acylation at $C_{(17)}$, hydrolysis of the resulting 3β,17α-diester by mineral acid to the 17α-acyloxy-3β-hydroxy-6-methylpregn-5-en-20-one (VII; R = H, R′ = acyl), and oxidation to the 6-methyl-4,6-dien-3-one (VIII; R = alkyl).

An additional route to 6-methyl-4,6-dien-3-ones involved the dehydrogenation of 6-methyl-3-oxo-Δ^4-steroids with chloranil. The method proved of general applicability (see p. 2833) and has since been independently described by three separate groups.[8,9]

Experimental

Optical rotations were measured in a 1 dm. tube for $CHCl_3$ solutions unless otherwise stated. Ultraviolet absorption spectra were kindly determined (for EtOH solutions) by Mr. M. T. Davies, B.Sc. B.D.H. chromatographic alumina was used.

6α-Methyl-5α-cholestane-3β,5α,6β-triol.—3β-Acetoxy-5α-hydroxycholestan-6-one [2] (10 g.) in benzene (100 ml.) and ether (300 ml.) was added to a Grignard reagent prepared from magnesium (4·8 g.), methyl iodide (12·4 ml.), and ether (300 ml.). The mixture was kept at room temperature for 24 hr., then treated with an excess of dilute sulphuric acid, and the organic layer was washed, dried, and evaporated. A solution of the residue in 3% ethanolic potassium

[2] Pickard and Yates, *J.*, 1908, **93**, 1678.
[3] Heusler and Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284.
[4] Cf. Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1949, **71**, 3938.
[5] Cf. Bernstein, Allen, Linden, and Clemente, *J. Amer. Chem. Soc.*, 1955, **77**, 6612.
[6] Barton, Ellis, and Petrow, *J.*, 1959, 478.
[7] Wettstein, *Helv. Chim. Acta*, 1940, **23**, 388.
[8] Ringold, Ruelas, Batres, and Djerassi, *J. Amer. Chem. Soc.*, 1959, **81**, 3712.
[9] U.S.P. 2,891,079; Ruggieri, Ferrani, and Gandolfi, *Ann. Chim.* (*Italy*), 1959, **49**, 1371.

hydroxide was refluxed for 30 min. The product obtained by the addition of water was dried and purified from ether to give the *triol* as needles, m. p. 223—225°, $[\alpha]_D^{22}$ 0° (*c* 0·85) (Found: C, 77·0; H, 11·6. $C_{28}H_{50}O_3$ requires C, 77·4; H, 11·6%).

5α,6β-*Dihydroxy*-6α-*methyl*-5α-*cholestan*-3-*one*.—The foregoing triol (5·8 g.) in acetic acid (120 ml.) was treated at 35° with chromium trioxide (2·5 g.) in 80% acetic acid (20 ml.). The mixture was poured into water after 3 hr., and the product isolated with ether. Purification of the neutral fraction from aqueous ethanol gave the *ketone*, needles, m. p. 225—226°, $[\alpha]_D^{20}$ +22° (*c* 1·04) (Found: C, 77·4; H, 11·4. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%).

6-*Methylcholesta*-4,6-*dien*-3-*one*.—A solution of the foregoing ketone (2 g.) in ethanol (50 ml.) to which 2 drops of concentrated hydrochloric acid had been added was heated under reflux for 30 min. The product, isolated with ether, crystallised from methanol, giving 6-*methylcholesta*-4,6-*dien*-3-*one*, needles, m. p. 91—92°, $[\alpha]_D^{21}$ +37° (*c* 1·07), $\lambda_{max.}$ 290 mμ (log ε 4·37) (Found: C, 84·6; H, 11·2. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%).

6α,17α-*Dimethyl*-5α-*androstane*-3β,5α,17β-*tetrol*.—3β-Acetoxy-5α,17β-dihydroxy-17α-methyl-5α-androstan-6-one [1] (6·5 g.) in ether (300 ml.) was added to a Grignard reagent from magnesium (6·5 g.) and methyl iodide (42 g.) in ether (300 ml.) and benzene (200 ml.). The mixture was refluxed for 3½ hr., cooled, and treated with aqueous ammonium chloride. The product, isolated in the usual way, was saponified with hot aqueous methanolic potassium carbonate, and purified from acetone–hexane. The *tetrol* crystallised in needles, m. p. 233—234°, $[\alpha]_D^{23}$ −24° (*c* 0·55 in ethanol) (Found: C, 71·1; H, 10·0. $C_{21}H_{36}O_4$ requires C, 71·55; H, 10·3%). The 3β-*acetate* formed needles (from acetone–hexane), m. p. 225—227° (Found: C, 69·6; H, 9·6. $C_{23}H_{38}O_5$ requires C, 70·0; H, 9·7%).

6α,17α-*Dimethyl*-5α,6β,17β-*trihydroxyandrostan*-3-*one*.—The foregoing tetrol (1·8 g.) in pyridine (18 ml.) was added to chromium trioxide (1·8 g.) in pyridine (18 ml.), and the mixture set aside for 18 hr. The product, isolated with benzene, crystallised from acetone–hexane, giving the *ketone*, needles, m. p. 223—224°, $[\alpha]_D^{23}$ −25° (*c* 0·53) (Found: C, 71·8; H, 9·8. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·8%).

17β-*Hydroxy*-6,17α-*dimethylandrosta*-4,6-*dien*-3-*one*.—A solution of the foregoing ketone (1·85 g.) in methanol (20 ml.) containing concentrated hydrochloric acid (0·3 ml.) was refluxed for 1 hr. The product was isolated with ether and purified from acetone–hexane to give the *dienone*, needles, m. p. 157—158°, $[\alpha]_D^{23}$ +38° (*c* 0·52), $\lambda_{max.}$ 290 mμ (log ε 4·37) (Found: C, 79·9; H, 9·6. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

3β,17β-*Diacetoxy*-6α-*methylandrostane*-5α,6β-*diol*, prepared from 3β,17β-diacetoxy-5α-hydroxyandrostane-6-one [3] and methylmagnesium iodide followed by acetylation of the product, crystallised from acetone–hexane in plates, m. p. 192—193°, $[\alpha]_D^{23}$ −41° (*c* 0·48) (Found: C, 68·0; H, 8·9. $C_{24}H_{38}O_6$ requires C, 68·2; H, 9·0%).

5α,6β-*Dihydroxy*-6α-*methylandrostane*-3,17-*dione*.—A solution of the foregoing compound (4·7 g.) and potassium carbonate (2·4 g.) in methanol (45 ml.) and water (5 ml.) was heated under reflux for 1 hr. The product obtained on the addition of water crystallised from acetone as needles, m. p. 242—245°. This material (3·3 g.) in pyridine (35 ml.) was added to chromium trioxide (6·6 g.) in pyridine (65 ml.), and the mixture set aside overnight. The product was isolated with benzene and purified from aqueous acetone to give the *dione*, needles, m. p. 242—244°, $[\alpha]_D^{21}$ +65° (*c* 0·57) (Found: C, 71·6; H, 9·1. $C_{20}H_{30}O_4$ requires C, 71·9; H, 9·0%).

6β-*Hydroxy*-6α-*methylandrost*-4-*ene*-3,17-*dione* (with Mr. G. O. Weston, B.Sc.).—The foregoing compound (1 g.) in methanol (50 ml.) containing potassium hydroxide (0·25 g.) was heated under reflux for 1 hr. The solid obtained on the addition of water was purified from aqueous ethanol to give the *enedione*, flat needles, m. p. 237—239°, $[\alpha]_D^{20}$ +105° (*c* 0·8), $\lambda_{max.}$ 237 mμ (log ε 4·14) (Found: C, 75·65; H, 8·8. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%).

6-*Methylandrosta*-4,6-*diene*-3,17-*dione*, prepared from the foregoing compound, or from 5α,6β-dihydroxy-6α-methylandrostane-3,17-dione by treatment with hot methanolic hydrochloric acid, crystallised from acetone–hexane in needles, m. p. 164°, $[\alpha]_D^{21}$ +139° (*c* 0·51), $\lambda_{max.}$ 287 mμ (log ε 4·37) (Found: C, 80·5; H, 8·5. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·7%).

3β-*Acetoxy*-17α-*ethynylandrostane*-5α,6β,17β-*triol*.—3β-Acetoxy-5α,6α-epoxy-17α-ethynylandrostan-17β-ol [10] (6 g.) in acetone (100 ml.) was treated with periodic acid (1·8 g.) in water (20 ml.), and the mixture refluxed for 15 min. Addition of water gave crystals which were purified from aqueous acetone. The *triol* formed needles, m. p. 255—256°, $[\alpha]_D^{21}$ −69·5° (*c* 1·0 in dioxan) (Found: C, 71·1; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·8%).

[10] Ackroyd, Adams, Ellis, Petrow, and Stuart-Webb, *J.*, 1957, 4099.

3β-*Acetoxy*-5α,17β-*dihydroxy*-17α-*ethynylandrostan*-6-*one*, prepared by oxidation of the foregoing compound with chromium trioxide–pyridine, crystallised from acetone–hexane in fine needles or dense prisms, m. p. 245—247°, $[\alpha]_D^{21}$ −103° (*c* 1·03) (Found: C, 70·8; H, 8·5. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

17α-*Ethynyl*-6α-*methylandrostane*-3β,5α,6β,17β-*tetrol*.—The foregoing ketone (10·5 g.) in dry tetrahydrofuran (100 ml.) and ether (100 ml.) was added to a Grignard reagent from magnesium (5·4 g.), methyl iodide (15 ml.) and ether (360 ml.). The mixture was set aside for 18 hr., then the product was isolated, saponified, and crystallised from aqueous methanol. The *tetrol* formed needles, m. p. 254—255°, $[\alpha]_D^{20}$ −51° (*c* 1·07) (Found: C, 72·7; H, 9·3. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·45%).

17α-*Ethynyl*-5α,6β,17β-*trihydroxy*-6α-*methylandrostan*-3-*one*, prepared by oxidation of the foregoing compound with chromium trioxide–pyridine, separated from aqueous ethanol in needles, having m. p. 246—248° and $[\alpha]_D^{22}$ −36° (*c* 1·02) (Found: C, 70·2, 69·9; H, 9·1, 9·0. $C_{22}H_{32}O_4,H_2O$ requires C, 69·8; H, 9·05%) after prolonged drying at 100°.

17α-*Ethynyl*-17β-*hydroxy*-6-*methylandrosta*-4,6-*dien*-3-*one* crystallised from aqueous methanol in needles, m. p. 200—201°, $[\alpha]_D^{20}$ −58° (*c* 1·03), $\lambda_{max.}$ 290 mμ (log ε 4·36) (Found: C, 81·2; H, 8·4. $C_{22}H_{28}O_2$ requires C, 81·4; H, 8·7%).

3β-*Acetoxy*-25D-*spirostane*-5α,6β-*diol*, prepared by treating 3β-acetoxy-5α,6α-epoxy-25D-spirostane [11] with periodic acid in aqueous acetone, crystallised from chloroform–methanol in needles, m. p. 286—288°, $[\alpha]_D^{23}$ −98° (*c* 0·44) (Found: C, 71·3; H, 9·4. $C_{29}H_{46}O_6$ requires C, 71·0; H, 9·4%).

3β-*Acetoxy*-5α-*hydroxy*-25D-*spirostan*-6-*one* crystallised from chloroform–methanol in plates, m. p. 273—275°, $[\alpha]_D^{23}$ −127° (*c* 0·89) (Found: C, 71·5; H, 9·2. $C_{29}H_{44}O_6$ requires C, 71·3; H, 9·0%).

6α-Methyl-25D-spirostane-3β,5α,6β-triol crystallised from methanol in needles, m. p. 266—270°, $[\alpha]_D^{23}$ −84° (*c* 0·32) (Found: C, 70·4; H, 10·3. Calc. for $C_{28}H_{46}O_5$: C, 72·7; H, 10·0%). Despite intensive drying of this compound, satisfactory analyses could not be obtained.

5α,6β-*Dihydroxy*-6α-*methyl*-25D-*spirostan*-3-*one* separated from acetone–hexane in needles, m. p. 245—247°, $[\alpha]_D^{22}$ −75° (*c* 0·29) (Found: C, 72·7; H, 9·7. $C_{28}H_{44}O_5$ requires C, 73·0; H, 9·6%).

6β-*Hydroxy*-6α-*methyl*-25D-*spirost*-4-*en*-3-*one* formed needles (from acetone–hexane), m. p. 233—235°, $[\alpha]_D^{24}$ −52° (*c* 0·73), $\lambda_{max.}$ 239 mμ (log ε 4·12) (Found: C, 76·2; H, 9·3. $C_{28}H_{42}O_4$ requires C, 76·0; H, 9·5%).

6-*Methyl*-25D-*spirosta*-4,6-*dien*-3-*one* crystallised from acetone–hexane in prisms, m. p. 215—217°, $[\alpha]_D^{20}$ −67° (*c* 0·39), $\lambda_{max.}$ 289·5 mμ (log ε 4·38) (Found: C, 79·2; H, 9·5. $C_{28}H_{40}O_3$ requires C, 79·2; H, 9·4%).

3β,20β-*Diacetoxypregnane*-5α,6β-*diol*, prepared from 3β,20β-diacetoxy-5α,6α-epoxypregnane [12] and periodic acid in aqueous acetone, crystallised from aqueous methanol in plates, m. p. 230—231°, $[\alpha]_D^{23}$ −6° (*c* 0·49) (Found: C, 68·4; H, 9·2. $C_{25}H_{40}O_6$ requires C, 68·8; H, 9·2%).

3β,20β-*Diacetoxy*-5α-*hydroxypregnan*-6-*one* formed plates (from acetone–hexane), m. p. 224—225°, $[\alpha]_D^{20}$ −48° (*c* 0·81) (Found: C, 68·8; H, 9·0. $C_{25}H_{38}O_6$ requires C, 69·0; H, 8·7%).

6α-*Methylpregnane*-3β,5α,6β,20β-*tetrol* crystallised from acetone–hexane in needles, m. p. 220—224°, $[\alpha]_D^{22}$ −17° (*c* 0·24) (Found: C, 71·7; H, 10·3. $C_{22}H_{38}O_4$ requires C, 72·1; H, 10·4%).

5α,6β-*Dihydroxy*-6α-*methylpregnane*-3,20-*dione* crystallised from acetone–hexane in needles, m. p. 247—249°, $[\alpha]_D^{22}$ +69° (*c* 0·39) (Found: C, 73·2; H, 9·1. $C_{22}H_{34}O_4$ requires C, 72·8; H, 9·4%).

6-Methylpregna-4,6-diene-3,20-dione [9] crystallised from hexane in plates, m. p. 152—154°, $[\alpha]_D^{22}$ +176° (*c* 0·56), $\lambda_{max.}$ 288·5 mμ (log ε 4·37) (Found: C, 80·5; H, 9·0. Calc. for $C_{22}H_{30}O_2$: C, 80·9; H, 9·2%).

17β-*Acetoxy*-3,3-*ethylenedioxyandrostane*-5β,6β-*diol* (V; R = ---H, -OH; R′ = Ac).—A mixture of 17β-acetoxy-3,3-ethylenedioxyandrost-5-ene [13] (3 g.) and osmium tetroxide (2·2 g.) in benzene (200 ml.) and pyridine (3 ml.) was set aside for 2 days. Sodium sulphite (13 g.), potassium hydrogen carbonate (13 g.), water (120 ml.), and methanol (40 ml.) were added, the mixture was stirred for 4 hr., then filtered, and the precipitate was washed with hot chloroform (1 l.). Removal of the solvents from the combined filtrate and washings gave an oil which

[11] Tsukamoto, Ueno, and Ota, *J. Pharm. Soc. Japan*, 1937, **57**, 985.
[12] Ringold, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 99.
[13] Antonucci, Bernstein, Littell, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1341.

was chromatographed on alumina (90 g.). Elution with benzene and benzene–ether gave small quantities of unchanged 17β-acetoxy-3,3-ethylenedioxyandrost-5-ene. Further elution with ether and ether–acetone gave material which was purified from acetone–hexane. 17β-*Acetoxy*-3,3-*ethylenedioxyandrostane*-5β,6β-*diol* separated in needles, m. p. 178—179°, $[\alpha]_D^{21}$ +12·5° (*c* 0·32) (Found: C, 67·5; H, 8·9. $C_{23}H_{36}O_6$ requires C, 67·6; H, 8·8%).

17β-*Acetoxy*-3,3-*ethylenedioxy*-5β-*hydroxyandrostan*-6-*one* (V; R = O, R′ = Ac).—The foregoing compound (1·6 g.) in pyridine (16 ml.) was added to chromium trioxide (1·6 g.) in pyridine (16 ml.), and the mixture set aside for 24 hr. The product, isolated with benzene, was purified by passage of its benzene solution through a short column of alumina and crystallisation from acetone–hexane containing a trace of pyridine. The *ketone* separated in needles, m. p. 161—162°, $[\alpha]_D^{25}$ −46° (*c* 0·17) (Found: C, 68·0; H, 8·6. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

17β-*Hydroxy*-6-*methylandrosta*-4,6-*dien*-3-*one* (VI).—The foregoing ketone (0·7 g.) in benzene (30 ml.) was added dropwise to a Grignard reagent from magnesium (0·9 g.), methyl iodide (6 ml.), and ether (10 ml.). The mixture was heated under reflux for 2 hr., cooled, and treated with aqueous ammonium chloride, and the product (a gum) was isolated with chloroform. Its solution in methanol (25 ml.) containing concentrated hydrochloric acid (3 drops) was refluxed for 2 hr. The product was isolated with chloroform and crystallised from aqueous methanol to give 17β-*hydroxy*-6-*methylandrosta*-4,6-*dien*-3-*one*, needles, m. p. 161—163°, $[\alpha]_D^{22}$ +67° (*c* 1·02), $\lambda_{max.}$ 289·5 mμ (log ε 4·37) (Found: C, 77·4, 77·3, 77·4; H, 9·5, 9·4, 9·35. $C_{20}H_{28}O_2,\frac{1}{2}H_2O$ requires C, 77·6; H, 9·5%) after prolonged drying at 140°/0·1 mm. The 17β-*acetate* (prepared with Mr. G. O. Weston, B.Sc.) formed plates (from acetone–hexane), m. p. 173—174°, $[\alpha]_D^{30}$ +34° (*c* 0·73) (Found: C, 77·1; H, 8·6. $C_{22}H_{30}O_3$ requires C, 77·15; H, 8·8%).

17α-*Acetoxy*-6-*methylpregna*-4,6-*diene*-3,20-*dione* (VIII; R = Me).—17β-Acetoxy-3β-hydroxy-6-methylpregn-5-en-20-one [6] (1·5 g.), *p*-benzoquinone (2·5 g.), and aluminium t-butoxide (1·5 g.) were suspended in dry benzene (150 ml.). The mixture was stirred for 60 hr., and washed with dilute aqueous sodium hydroxide, then with water, and the solvent was removed *in vacuo*. Crystallisation of the residue from aqueous methanol gave the dienedione [8,9] in needles, m. p. 214—216°, $[\alpha]_D^{24}$ +5° (*c* 0·43), $\lambda_{max.}$ 287·5 mμ (log ε 4·4) (Found: C, 74·5; H, 8·2. Calc. for $C_{24}H_{32}O_4$: C, 74·85; H, 8·3%).

3β-*Acetoxy*-17α-*hydroxy*-6-*methylpregn*-5-*en*-20-*one* (VII; R = Ac, R′ = H), prepared by treating 3β,17α-dihydroxy-6-methylpregn-5-en-20-one [6] with acetic anhydride–pyridine for 30 min. at 100°, crystallised from aqueous methanol in needles, m. p. 112—114°, or from acetone–hexane in needles, m. p. 133—134°, $[\alpha]_D^{24}$ −88° (*c* 0·3) (Found: C, 74·3; H, 9·4. $C_{24}H_{36}O_4$ requires C, 74·2, 9·3%).

3β-*Acetoxy*-6-*methyl*-17α-*propionyloxypregn*-5-*en*-20-*one* (VII; R = Ac, R′ = COEt).—A solution of the foregoing compound (1 g.) and toluene-*p*-sulphonic acid (0·2 g.) in benzene (25 ml.) was distilled until 5 ml. of distillate had collected. Propionic anhydride (1 ml.) was added, and the mixture refluxed for 1 hr. After being kept overnight, the mixture was shaken with water for 4 hr., and the product isolated with ether. Purification from aqueous ethanol gave the *diester*, needles, m. p. 181—183°, $[\alpha]_D^{23}$ −73° (*c* 0·74) (Found: C, 72·8; H, 9·0. $C_{27}H_{40}O_5$ requires C, 72·9; H, 9·1%).

3β-*Hydroxy*-6-*methyl*-17α-*propionyloxypregn*-5-*en*-20-*one* (VII; R = H, R′ = COEt).—The foregoing compound (2 g.) in methanol (100 ml.) was treated with concentrated hydrochloric acid (1 ml.), and the mixture heated under reflux for 1½ hr. Addition of water gave crystals which were purified from aqueous methanol. The *monoester* separated in needles, m. p. 170—172°, $[\alpha]_D^{22}$ −70° (*c* 0·94) (Found: C, 74·5; H, 9·3. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%).

6-*Methyl*-17α-*propionyloxypregna*-4,6-*diene*-3,20-*dione* (VIII; R = Et), prepared from the foregoing compound, crystallised from methanol in needles, m. p. 134—135°, $[\alpha]_D^{21}$ +9° (*c* 0·35) $\lambda_{max.}$ 288 mμ (log ε 4·37) (Found: C, 74·9; H, 8·6. $C_{25}H_{34}O_4$ requires C, 75·3; H, 8·5%).

17α-*Butyryloxy*-3β-*hydroxy*-6-*methylpregn*-5-*en*-20-*one* (VII; R = H, R′ = $COPr^n$).—A solution of 3β-acetoxy-17α-hydroxy-6-methylpregn-5-en-20-one (5 g.) and toluene-*p*-sulphonic acid (0·75 g.) in butyric acid (50 ml.) and butyric anhydride (25 ml.) was kept at room temperature for 48 hr. After the addition of pyridine, the mixture was steam-distilled, and the product isolated with ether and crystallised from aqueous methanol. The crude diester (m. p. 170—171°) was hydrolysed with hot methanolic hydrochloric acid to give 17α-*butyryloxy*-3β-*hydroxy*-6-*methylpregn*-5-*en*-20-*one*, needles (from acetone–hexane), m. p. 156—158°, $[\alpha]_D^{25}$ −66·5° (*c* 0·95) (Found: C, 74·8; H, 9·7. $C_{26}H_{40}O_4$ requires C, 75·0; H, 9·7%).

17α-*Butyryloxy*-6-*methylpregna*-4,6-*diene*-3,20-*dione* (VIII; R = Pr^n), prepared from the

foregoing compound, crystallised from hexane in needles, m. p. 102—104°, $[\alpha]_D^{21}$ −27° (*c* 0·95), $\lambda_{max.}$ 288 mμ (log ε 4·37) (Found: C, 75·9; H, 8·7. $C_{26}H_{36}O_4$ requires C, 75·7; H, 8·8%).

3β-*Acetoxy*-17α-*hexanoyloxy*-6-*methylpregn*-5-*en*-20-*one* (VII; R = Ac, R′ = $CO{\cdot}C_5H_{11}$) formed needles (from methanol), m. p. 111—113°, $[\alpha]_D^{25}$ −63° (*c* 0·28) (Found: C, 74·3; H, 9·3. $C_{30}H_{46}O_5$ requires C, 74·1; H, 9·5%).

17α-*Hexanoyloxy*-3β-*hydroxy*-6-*methylpregn*-5-*en*-20-*one* (VII; R = H, R′ = $CO{\cdot}C_5H_{11}$) separated from aqueous methanol in needles, m. p. 152—154°, $[\alpha]_D^{25}$ −56° (*c* 0·24) (Found: C, 75·7; H, 10·2. $C_{28}H_{44}O_4$ requires C, 75·6; H, 9·9%).

17α-*Hexanoyloxy*-6-*methylpregna*-4,6-*diene*-3,20-*dione* (VIII; R = C_5H_{11}) crystallised from aqueous methanol in needles, m. p. 128—130°, $[\alpha]_D^{24}$ −12° (*c* 0·72), $\lambda_{max.}$ 286·5 mμ (log ε 4·38) (Found: C, 75·95; H, 8·8. $C_{28}H_{40}O_4$ requires C, 76·3; H, 9·1%).

17α-*Acetoxy*-6-*methylpregna*-4,6-*diene*-3,20-*dione* (VIII; R = Ac).—17α-Acetoxy-6α-methylprogesterone [6] (0·5 g.) and chloranil (0·4 g.) in isobutyl alcohol (15 ml.) were heated under reflux for 10 hr. The cooled mixture was poured into dilute aqueous potassium hydroxide, and the product isolated with ether. Crystallisation from aqueous methanol gave the diene-dione in needles, m. p. 214—216°, not depressed in admixture with a specimen prepared as described above.

Other Dehydrogenations accomplished with Chloranil.—Treatment of 6α-methylprogesterone,[14] 6β-methylandrost-4-ene-3,17-dione,[10] 6α-methylethisterone,[10] and 6α-methylcholest-4-en-3-one [15] with chloranil, as described above, furnished the corresponding 6-methyl-4,6-dien-3-ones, identified by comparison with specimens prepared by the previously described routes.

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