Steroids. Part LII. Synthesis of Steroidal Hormone Analogues Hydroxylated at $C_{(6)}$.*

By (Miss) C. Amendolla, G. Rosenkranz, and Franz Sondheimer.

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Oxidation of 3β : 6β-dihydroxy-Δ^4-steroids (generally obtainable from the 3β-hydroxy-Δ^5-steroids by a simple and efficient four-step sequence) by manganese dioxide in chloroform at room temperature is shown to provide a general synthesis of 6β-hydroxy-3-keto-Δ^4-steroids. The reaction is employed for the synthesis of 6β-hydroxycholest-4-en-3-one (VI*a*), 6β-hydroxyprogesterone (VI*b*), 6β-hydroxydeoxycorticosterone 21-acetate (VI*c*), 6β-hydroxyandrost-4-ene-3 : 17-dione (VI*d*), 6β-hydroxytestosterone (VI*e*), and 6β : 17α-dihydroxyprogesterone (VI*f*). At the boiling point the 3 : 6-diketo-Δ^4-compounds are formed.

In view of the physiological action of the 11β-hydroxylated hormone, 11β : 17α : 21-trihydroxypregn-4-ene-3 : 20-dione (Kendall's compound F), it is of interest to investigate the activity of steroidal hormone analogues with hydroxyl groups in positions other than at $C_{(11)}$, and for this reason we undertook the preparation of Δ^4-3-ketones hydroxylated at $C_{(6)}$. Moreover such compounds are produced from the Δ^4-3-ketones by microbiological

* Part LI, Sondheimer, Amendolla, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 5932. A preliminary announcement has been made of part of the present work (Sondheimer and Rosenkranz, *Experientia*, 1953, **9**, 62).

methods (Peterson, Murray, *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 5933; 1953, **75**, 408, 412, 416; Abs. Papers, 123rd Meeting Amer. Chem. Soc., 1953, p. 5c), and by incubation with adrenal breis (Haines, " Recent Progress in Hormone Research," Academic Press, New York, 1952, **7**, 282) or with *corpus luteum* homogenates (Berliner, Mont, and Zaffaroni, *J. Amer. Chem. Soc.*, in the press). The latter observations especially are of interest, since they indicate that the 6-hydroxy-Δ^4-3-ketones may well play a significant role in human physiology.

The only chemical method of general applicability hitherto described for preparing 6-hydroxy-Δ^4-3-ketones involves the conversion of a 3β-hydroxy-Δ^5-steroid into the 6β-acetoxy-3β : 5α-dihydroxy-compound by any of several methods, followed by oxidation at $C_{(3)}$ and dehydration at positions 4 : 5 (*inter al.*, Ellis and Petrow, *J.*, 1939, 1078; Ehrenstein *et al.*, *J. Org. Chem.*, 1940, **5**, 318; 1941, **6**, 626, 908; 1951, **16**, 1050; 1952, **17**, 1587; cf. Dane, Wang, and Schulte, *Z. physiol. Chem.*, 1936, **245**, 80). Moreover Professor L. F. Fieser has informed us that 6β-hydroxycholest-4-en-3-one is obtained directly in 16·5% yield from cholesterol by oxidation with sodium dichromate (*J. Amer. Chem. Soc.*, 1953, **75**, 4377).

We now report a new general synthesis of 6β-hydroxy-3-keto-Δ^4-steroids, by partial oxidation of the 3β : 6β-dihydroxy-compounds by manganese dioxide at room temperature (V ⟶ VI). We have applied this method in six cases (*a*—*f*; see reaction scheme).

Use of this oxidant in boiling chloroform gives the Δ^4-3 : 6-diones (examples investigated were VII*a*, *b*, *c*, *d*, and *e*). It is noteworthy that both the 6- and the 3-hydroxyl group are oxidised even at room temperature when the former hydroxyl group is equatorial as in cholest-4-ene-3β : 6α-diol.

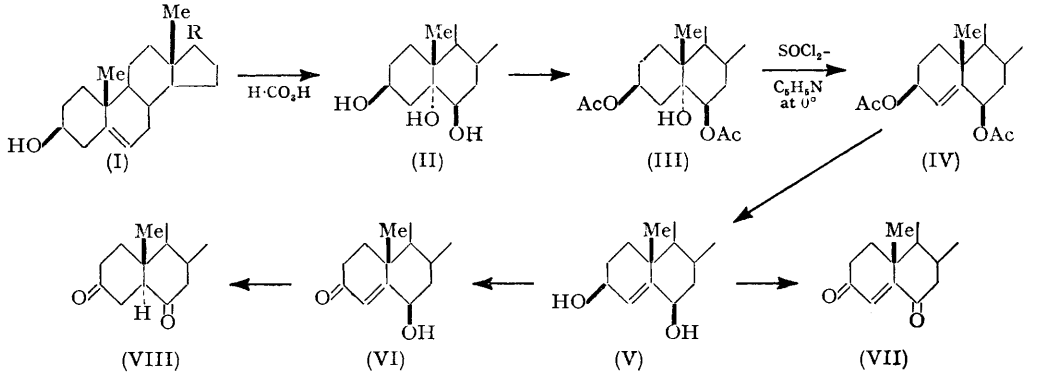
Further applications of the method follow from isomerisation of the acetates of (VI) to the 6α-isomers by hydrogen chloride in chloroform containing alcohol (Ehrenstein *et al.*, *locc. cit.*, 1951, 1952), and from alkaline isomerisation of (VI) to (VIII) (examples reported are *b*, *d*, and *e*; these reactions served as confirmation of structure). It is of interest that lithium in liquid ammonia removes the 6β-hydroxyl group from (VI) to give the 3-keto-Δ^4-steroids (6β-hydroxytestosterone ⟶ testosterone), and the same products are obtained by treating the 6β-acetoxy-compounds with zinc and acetic acid (6β-acetoxyprogesterone ⟶ progesterone). Professor L. F. Fieser (*loc. cit.*)has in dependently reported the latter type of reaction.

The nature of the product (VI) was first proved for 6β-hydroxycholest-4-en-3-one (VI*a*). This and its acetate were identical with known materials (Ellis and Petrow, *loc. cit.*; Romo, Rosenkranz, Djerassi, and Sondheimer, *J. Org. Chem.*, in the press) and different from those of the other possible keto-alcohol (3β-hydroxycholest-4-en-6-one) and its acetate (Heilbron, Jones, and Spring, *J.*, 1937, 801). The products (VI*b*—*f*) were identified by their similarity or that of their acetates or of the derived diketones (VII or VIII) (see above) to recorded compounds (see Experimental section for details). The 6-acetoxyprogesterone (cf. VI*b*) prepared by Ehrenstein *et al.* (*loc. cit.*, 1940) is shown to be the 6β-compound, and this is in line with later work of that school (*loc. cit.*, 1952). On the other hand it is concluded that the 6-acetoxyandrost-4-ene-3 : 17-dione of Ehrenstein (*J. Org. Chem.*, 1941, **6**, 626) must have the 6α-configuration, since it differs from the 6β-acetoxy-compound (VI*d*) prepared by the manganese dioxide route, and this again is in agreement with the recent publication of Ehrenstein *et al.* (*loc. cit.*, 1952).

The 3β : 6β-dihydroxy-Δ^4-steroids (V) used in these syntheses are readily obtained from the accessible 3β-hydroxy-Δ^5-compounds by the reaction sequence (I) ⟶ (II) ⟶ (III) ⟶ (IV) ⟶ (V). In the cholesterol series (*a*) all these reactions are so smooth (cf. Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1949, **71**, 3938; Petrow, Rosenheim, and Starling, *J.*, 1938, 677) that the overall yield of the final product (VI*a*) from cholesterol (I*a*) is *ca.* 60%. Of the materials used in this work, (V*a*), (V*b*), and (IV*c*) were known, and the conversion of the last-named substance into (V*c*) by hydrolysis and partial acetylation at $C_{(21)}$ offered no difficulty. In the androstan-17-one series (*d*), Davies and Petrow (*J.*, 1949, 2536) reported that the dehydration step, (III*d*) ⟶ (IV*d*), occurred only under reflux, and then slowly and in only *ca.* 50% yield. However in our hands an 80% yield was readily obtained under the usual conditions (0°), and hydrolysis then led smoothly to the required (V*d*). Androst-4-

ene-3β : 6β : 17β-triol (V*e*) was simply prepared by reduction of the 17-keto-3β : 6β-diacetate (IV*d*) with lithium aluminum hydride. 6β : 17α-Dihydroxyprogesterone (VI*f*) has been obtained microbiologically from 17α-hydroxyprogesterone (Peterson, Murray, *et al.*, *loc. cit.*, p. 416) but its chemical preparation required variation of our standard procedure : performic oxidations of 3β : 17α-dihydroxy- (I*f*) and 3β-acetoxy-17α-hydroxy-pregn-5-en-20-one did not proceed well owing to unfavourable solubilities, but the more soluble 3β : 17α-diacetate reacted normally ; hydrolysis with potassium carbonate then gave the 3β : 5α : 6β-trihydroxy-17α-acetate (II*g*) which was converted normally into (III*g*) and (IV*g*), whence hydrolysis removed the last acetyl group, to give the required (V*f*).

Recent papers by Ehrenstein and by Peterson, Murray, and their collaborators (*locc. cit.*), as well as the present work, show that introduction of a 6β-hydroxy- or a 6β-acetoxy-group into 3-keto-Δ^4-steroids lowers the position of maximum ultra-violet absorption by *ca.*



a, R = $-C_8H_{17}$. *b*, R = –COMe. *c*, R = –CO·CH_2·OAc. *d*, R = :O.
e, R = –OH. *f*, R =  *g*, R = 

40 Å (to *ca.* 2360 Å) and the intensity (ε) by about 2000 (to 12,500—14,000). On the other hand the 3β-hydroxy-Δ^4-6-ketone in the cholestane series exhibits a maximum with a markedly more reduced intensity ($\lambda_{max.}$ 2390 Å; ε 6300) (Heilbron, Jones, and Spring, *loc. cit.*), doubtless owing to the *s-cis* configuration of the αβ-unsaturated ketone system in this case (Turner and Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 1403). A compound prepared by Davis and Petrow (*loc. cit.*) from 3β : 6β-dihydroxyandrost-4-en-17-one (V*d*) by chromic acid oxidation has an absorption maximum of such high intensity (ε 13,000 at 2370 Å) that it is clearly the 6β-hydroxy-3-ketone (VI*d*). This contradicts the earlier assignment to it of the 3β-hydroxy-6-ketone structure, which followed from a confusion about the stereochemistry at $C_{(6)}$ of 6-acetoxyandrost-4-ene-3 : 17-dione, but is confirmed by agreement of the properties recorded by Davis and Petrow for their compound and its acetate with those of (VI*d*) and its acetate prepared by us.

A number of compounds described in this paper are being tested for their biological properties, and the results will be published subsequently.

Experimental

Rotations were measured in $CHCl_3$ and ultra-violet absorption spectra in 95% EtOH solution unless specified otherwise. Infra-red spectra were obtained, with $CHCl_3$ solutions (unless otherwise stated) and a Perkin-Elmer 12C single-beam spectrophotometer with a sodium chloride prism. We are indebted to Miss Paquita Revaque for these measurments and to Miss Amparo Barba for the microanalyses. The manganese dioxide was prepared from potassium permanganate and manganese sulphate, as described by Mancera, Rosenkranz, and Sondheimer (*J.*, 1953, 2189).

6β-*Hydroxycholest-4-en-3-one* (VI*a*).—A suspension of the 4-ene-3β : 6β-diol (V*a*) (10 g.; finely ground) (Petrow, Rosenheim, and Starling, *J.*, 1938, 677) in chloroform (1 l.) was shaken

with manganese dioxide (100 g.) at room temperature for 24 hr. The dioxide was removed by filtration and washed well with hot chloroform. Crystallization of the product from chloroform–acetone furnished the unsaturated hydroxy-ketone (VI*a*) (6·9 g.), m. p. 188—192°, $\lambda_{max.}$ 2360 Å (ε 13,300). One further crystallization gave material with constant m. p. 194—195°, $[\alpha]_D^{20}$ +38° in dioxan, $\nu_{max.}$ 1670 cm.$^{-1}$ (unsaturated ketone) and a free-hydroxyl band (Ellis and Petrow, *loc. cit.*, give m. p. 192°). Chromatographic purification on alumina of the mother-liquors after removal of the 6·9 g. of (VI*a*) furnished another 0·4 g. of this product, m. p. 190—193° (total yield, 73%), and the 3 : 6-dione (VII*a*) (0·3 g.), m. p. 118—121°. Similar results were obtained when the reaction was performed in benzene suspension.

The 6-acetate was prepared with acetic anhydride and pyridine (steam-bath, 1 hr.) and crystallized from methanol as needles, m. p. 103—104°, $[\alpha]_D^{20}$ + 40° in dioxan, $\lambda_{max.}$ 2360 Å (ε 12,800), $\nu_{max.}$ 1736 (acetate) and 1672 cm.$^{-1}$ (unsaturated ketone) (Ellis and Petrow, *loc. cit.*, give m. p. 101·5°, $[\alpha]_D^{19}$ +36°).

Cholest-4-ene-3 : 6-dione (VII*a*).—(*a*) A stirred solution of cholest-4-ene-3β : 6β-diol (V*a*) (1 g.) in chloroform (600 c.c.) was heated under reflux with manganese dioxide (20 g.) for 6 hr. The total crude product ($\lambda_{max.}$ 2500 Å; ε 9200) was chromatographed on alumina (50 g.). Combination of the fractions eluted with hexane–benzene (1 : 2) and crystallization from methanol furnished the diketone (0·46 g.), m. p. 122—124°, $[\alpha]_D^{20}$ −36°, $\lambda_{max.}$ 2500 Å (ε 11,200), $\nu_{max.}$ 1688 cm.$^{-1}$ (Δ^4-3 : 6-dione; cf. Jones, Humphries, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 956) (*inter al.*, Ross, *J.*, 1946, 737, gives m. p. 124—125°, $[\alpha]_D^{20}$ −38°).

(*b*) [With J. Herrán.] A solution of cholest-4-ene-3β : 6α-diol (1 g.; Prelog and Tagmann, *Helv. Chim. Acta*, 1944, **27**, 1867) in benzene (100 c.c.) was shaken with manganese dioxide (10 g.) for 20 hr. at room temperature. Crystallization of the product from methanol yielded the 3 : 6-dione (0·68 g.), m. p. 123—125°, $\lambda_{max.}$ 2500 Å (ε 10,900), identified with the sample obtained above by a mixed m. p. determination and comparison of the infra-red spectra. The mother-liquors exhibited $\lambda_{max.}$ 2480 Å (ε 10,200) and therefore contained essentially the diketone.

3β : 6β-Dihydroxypregn-4-en-20-one (V*b*).—A solution of 3β : 6β-diacetoxypregn-4-en-20-one (IV*b*) (21 g.; Mancera, Rosenkranz, and Djerassi, *J. Org. Chem.*, 1951, **16**, 192) in methanol (1050 c.c.) was heated under reflux with sodium hydroxide (16 g.) in water (105 c.c.) for 1 hr. The solution was concentrated, then poured into water, and the product collected. Crystallization from methanol yielded the diol (V*b*) (12·5 g.), m. p. 193—196°. Further crystallization led to a specimen with m. p. 201—203°, $[\alpha]_D^{20}$ +95°, $\nu_{max.}$ 1700 cm.$^{-1}$ (saturated ketone) and a free-hydroxyl band (Found : C, 75·95; H, 9·45. Calc. for $C_{21}H_{32}O_3$: C, 75·85; H, 9·7%) (Davis and Petrow, *J.*, 1950, 1185, give m. p. 198—200°).

6β-Hydroxyprogesterone (VI*b*).—A suspension of 3β : 6β-dihydroxypregn-4-en-20-one (10 g.; finely ground) in chloroform (1 l.) was shaken with manganese dioxide (100 g.) at room temperature for 24 hr. The dioxide was removed by filtration and washed very thoroughly with hot chloroform. Crystallization of the product from acetone–ether yielded 6β-hydroxyprogesterone (6·3 g.), m. p. 173—175°. A purified sample exhibited m. p. 179—180°, $[\alpha]_D^{20}$ +105°, $\lambda_{max.}$ 2360 Å (ε 13,600), $\nu_{max.}$ 1700 (saturated ketone) and 1672 cm.$^{-1}$ (unsaturated ketone) and a free-hydroxyl band (Found : C, 76·0; H, 9·3. Calc. for $C_{21}H_{30}O_3$: C, 76·3; H, 9·15%) (Balant and Ehrenstein, *J. Org. Chem.*, 1952, **17**, 1587, give m. p. 178—179°, $[\alpha]_D^{28}$ +107°).

The 6-acetate, prepared as above, crystallized from ether–hexane. It exhibited m. p. 144—145°, $[\alpha]_D^{19}$ +92° in EtOH, $\lambda_{max.}$ 2360 Å (ε 13,200), $\nu_{max.}$ 1736 (acetate), 1700 (saturated ketone), and 1674 cm.$^{-1}$ (unsaturated ketone) (Ehrenstein and Stevens, *ibid.*, 1940, **5**, 318, give m. p. 145—146°, $[\alpha]_D^{18}$ +90° in EtOH; Balant and Ehrenstein, *loc. cit.*, give m. p. 147—148°, $[\alpha]_D^{32}$ +101°).

Reduction of 6β-Acetoxyprogesterone to Progesterone [*with* H. Martinez].—A mixture of zinc dust (1 g.) and 6β-acetoxyprogesterone (0·50 g.) in acetic acid (10 c.c.) and water (3 c.c.) was stirred at room temperature for 2 hr. The filtered solution was evaporated almost to dryness, diluted with water, and extracted with chloroform. The zinc residue was extracted with hot chloroform, and the combined chloroform solutions were washed with aqueous sodium hydrogen carbonate, dried, and evaporated. Crystallization of the residue from acetone–hexane furnished progesterone (0·22 g.), m. p. 127—130°, identified with an authentic specimen (m. p. 128—130°) by mixed m. p. determination and comparison of infra-red spectra.

allo*Pregnane-3 : 6 : 20-trione* (VIII*b*).—A solution of 6β-hydroxyprogesterone (0·2 g.) in methanol (10 c.c.) was heated under reflux under nitrogen with potassium hydroxide (0·2 g.) in water (1 c.c.) for 30 min. Crystallization of the product from acetone–ether yielded the triketone, m. p. 231—233°, $[\alpha]_D^{90}$ +65° in dioxan, no high-intensity absorption in the ultra-violet, $\nu_{max.}$ 1700 cm.$^{-1}$ (saturated ketone), no free-hydroxyl band (Moffett, Stafford, Linsk, and Hoehn,

J. Amer. Chem. Soc., 1946, **68**, 1857, give m. p. 227—230·5°, $[\alpha]_D^{23}$ +53° in dioxan; Balant and Ehrenstein, *loc. cit.*, give m. p. 232·5—233°, $[\alpha]_D^{28}$ +61°).

6-*Oxoprogesterone* (VII*b*).—3β : 6β-Dihydroxypregn-4-en-20-one (V*b*) (0·70 g.), manganese dioxide (7 g.), and chloroform (70 c.c.) were heated under reflux with stirring for 6 hr. The residue ($\lambda_{max.}$ 2500 Å, ε 8200) was chromatographed on alumina (35 g.), and the fractions eluted with hexane–benzene (2 : 1) were pooled. Crystallization from chloroform–ether furnished 6-oxoprogesterone (0·36 g.), m. p. 193—194°, $[\alpha]_D^{20}$ +30°, $\lambda_{max.}$ 2500 Å (ε 10,600), $\nu_{max.}$ 1700 (saturated ketone) and 1686 cm.$^{-1}$ (Δ^4-3 : 6-dione) (Found : C, 76·8; H, 8·85. Calc. for $C_{21}H_{28}O_3$: C, 76·8; H, 8·6%) (Ehrenstein, *J. Org. Chem.*, 1939, **4**, 506, gives m. p. 185—188°; Moffett, Stafford, Linsk, and Hoehn, *loc. cit.*, give m. p. 185—187°).

3β : 6β : 21-*Trihydroxypregn-4-en-20-one*.—An ice-cooled solution of sodium hydroxide (13 g.) in water (60 c.c.) was added to a solution of 3β : 6β : 21-triacetoxypregn-4-en-20-one (IV*c*) (13 g.) (Mancera, Rosenkranz, and Djerassi, *loc. cit.*) in ice-cold methanol (300 c.c.) in an atmosphere of nitrogen. After being allowed to reach room temperature, the solution was set aside under nitrogen overnight. The base was neutralized by excess acetic acid, and the solution was concentrated to small volume and then diluted with water. Extraction with chloroform and crystallization from methanol–ether furnished the *triol* (8·1 g., 85%), m. p. 200—203°. The analytical sample exhibited m. p. 204—206°, $[\alpha]_D^{20}$ +82°, $\nu_{max.}$ (mull) 1700 cm.$^{-1}$ (saturated ketone) and a free-hydroxyl band (Found : C, 72·1; H, 9·4. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%).

21-*Acetoxy*-3β : 6β-*dihydroxypregn-4-en*-20-*one* (V*c*).—A solution of the above triol (5·0 g.) in anhydrous pyridine (13 c.c.) was cooled to −10°, and acetic anhydride (1·76 g., 1·2 mols.) was added. After being kept overnight at −10°, the solution was diluted with water, and the product isolated in the usual way. Chromatographic purification and crystallization from acetone yielded the 21-*monoacetate* (2·6 g. of m. p. 190—192°), m. p. 195—196°, $\nu_{max.}$ 1744 and 1718 cm.$^{-1}$ (21-acetoxy-20-ketone; cf. Jones, Dobriner, *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 2024; 1950, **72**, 956) and a free-hydroxyl band (Found : C, 70·4; H, 8·5. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%). In later experiments a polymorphic form, m. p. 217—219°, was obtained.

6β-*Hydroxydeoxycorticosterone* 21-*Acetate* (VI*c*).—A solution of the triol monoacetate (V*c*) (4·5 g.) in chloroform (450 c.c.) was shaken with manganese dioxide (45 g.) at room temperature for 24 hr. Isolation in the usual manner and crystallization from acetone–hexane yielded 6β-hydroxydeoxycorticosterone 21-acetate (2·81 g. of m. p. 192—195°), m. p. 198—199°, $[\alpha]_D^{20}$ +105°, $\lambda_{max.}$ 2360 Å (ε 12,900), $\nu_{max.}$ 1744 and 1718 (21-acetoxy-20-ketone) and 1670 cm.$^{-1}$ (unsaturated ketone), and a free-hydroxyl band (Found : C, 71·4; H, 8·3. Calc. for $C_{23}H_{32}O_5$: C, 71·1; H, 8·3%) (Eppstein *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 408, give m. p. 196—198°, $[\alpha]_D^{23}$ +113°, for the product obtained by monoacetylation of the free diol, prepared by a microbiological method).

The 6 : 21-diacetate, prepared as above and crystallized from ether–pentane, had m. p. 130—131°, $[\alpha]_D^{20}$ +102°, $\lambda_{max.}$ 2360 Å (ε 13,100), $\nu_{max.}$ 1742 and 1718 (21-acetoxy-20-ketone and acetate), 1672 cm.$^{-1}$ (unsaturated ketone), and no free-hydroxyl band (Found : C, 69·45; H, 8·1. Calc. for $C_{25}H_{34}O_6$: C, 69·75; H, 7·95%) (Eppstein *et al.*, *loc. cit.*, give m. p. 127—129°, $[\alpha]_D^{23}$ +103°, for a microbiological product, and Herzig and Ehrenstein, *J. Org. Chem.*, 1951, **16**, 1050, give m. p. 125—127°, $[\alpha]_D^{16}$ +110°).

6-*Oxodeoxycorticosterone* 21-*Acetate* (VII*c*).—A solution of 3β : 6β-dihydroxy-21-acetoxypregn-4-en-20-one (V*c*) (1·0 g.) in chloroform (100 c.c.) was heated under reflux with manganese dioxide (10 g.) for 8 hr., with stirring. The product ($\lambda_{max.}$ 2480 Å, ε 8700) was chromatographed on alumina (50 g.), and the fractions eluted with benzene were pooled and crystallized from acetone–ether. The resulting 6-*oxodeoxycorticosterone acetate* (0·42 g.) showed m. p. 138—139°, $[\alpha]_D^{20}$ +36°, $\lambda_{max.}$ 2500 Å (ε 10,800), $\nu_{max.}$ 1744 and 1718 (21-acetoxy-20-ketone), 1688 cm.$^{-1}$ (Δ^4-3 : 6-dione), and no free-hydroxyl band (Found : C, 71·45; H, 7·95. $C_{22}H_{30}O_5$ requires C, 71·5; H, 7·8%).

3β : 6β-*Diacetoxy*-5α-*hydroxyandrostan*-17-*one* (III*d*).—3β-Hydroxyandrost-5-en-17-one (I*d*) (140 g.) was heated on the steam-bath with formic acid (840 c.c.; 90%) for 5 min., cooled to room temperature, and then treated with hydrogen peroxide (140 c.c.; 30%) in small portions, the temperature being kept below 40°. After 6 hr. at room temperature, water was added, and the precipitate was collected. This was then heated under reflux for 15 min. with potassium hydroxide (40 g.) in methanol (1·4 l.) and water (140 c.c.). Evaporation under reduced pressure, addition of water, and filtration yielded 3β : 5α : 6β-trihydroxyandrostan-17-one (II*d*) (73 g.), m. p. 297—300° (Zelinskii and Ushakov, *Bull. Acad. Sci., Russia*, 1936, 879, give m. p. 301—302°; Miescher and Fischer, *Helv. Chim. Acta*, 1938, **21**, 336, give m. p. 299—302°).

Acetylation of the above triol (35 g.) as usual and crystallization from ether–hexane afforded

the 3 : 6-diacetate (III*d*) (39·2 g. of m. p. 178—182°), m. p. 184—185°, $[\alpha]_D^{20}$ −3°, $\nu_{max.}$ 1732 cm.$^{-1}$ (acetate and 17-ketone) and a free-hydroxyl band (Found: C, 67·75; H, 8·25. Calc. for $C_{23}H_{34}O_6$: C, 67·95; H, 8·45%) (Zelinskii and Ushakov, *loc. cit.*, give m. p. 171—172°; Ehrenstein and Decker, *J. Org. Chem.*, 1940, **5**, 544; 1941, **6**, 626, give m. p. 216·5—217°).

The discrepancy in m. p. with that given by Ehrenstein and Decker was due to polymorphism. When recrystallized in the presence of a trace of material (m. p. 215—216°) kindly supplied by Dr. Ehrenstein, the m. p. rose directly to 216—218°, and there was no m. p. depression on admixture with Dr. Ehrenstein's sample.

3β : 6β-*Diacetoxyandros*-4-*en*-17-*one* (IV*d*) (cf. Davis and Petrow, *J.*, 1949, 2536).—Thionyl chloride (10·5 c.c.) was added to an ice-cooled solution of 5α-hydroxy-3β : 6β-diacetoxyandrostan-17-one (35 g.) in pyridine (160 c.c.). After 5 min. at 0°, the product was precipitated with water and crystallized from acetone–hexane. In this way the unsaturated diacetate (26·5 g., 80%), m. p. 156—160°, was obtained. Further crystallization yielded material with m. p. 163—164°, $\nu_{max.}$ 1736 cm.$^{-1}$ (acetate and 17-ketone) and no free-hydroxyl band (Found: C, 71·0; H, 8·4. Calc. for $C_{23}H_{32}O_5$: C, 71·1; H, 8·3%) (Davis and Petrow, *loc. cit.*, give m. p. 163—164°).

3β : 6β-*Dihydroxyandrost*-4-*en*-17-*one* (V*d*).—This substance was obtained in *ca.* 75% yield by heating the preceding diacetate with sodium hydroxide in methanol for 1 hr. Crystallized from acetone–methanol, it had m. p. 274—276°, $\nu_{max.}$ (mull) 1736 cm.$^{-1}$ (17-ketone) and a free-hydroxyl band (Davis and Petrow, *loc. cit.*, give m. p. 269—270°).

6β-*Hydroxyandrost*-4-*ene*-3 : 17-*dione* (VI*d*).—A suspension of 3β : 6β-dihydroxyandrost-4-en-17-one (V*d*) (2·5 g.; finely ground) in chloroform (250 c.c.) was shaken at room temperature with manganese dioxide (25 g.) for 24 hr. Crystallization from methanol–ether afforded 6β-hydroxyandrost-4-ene-3 : 17-dione (1·67 g. of m. p. 186—190°), m. p. 192—193°, $[\alpha]_D^{20}$ +114°, $\lambda_{max.}$ 2360 Å (ε 13,200), $\nu_{max.}$ 1736 (17-ketone), 1672 cm.$^{-1}$ (unsaturated ketone), and a free-hydroxyl band (Found: C, 75·2; H, 8·35. Calc. for $C_{19}H_{26}O_3$: C, 75·45; H, 8·65%). Davis and Petrow, *loc. cit.*, give m. p. 192—193° for this substance, then believed to be the 3-hydroxy-Δ^4-6-ketone; Balant and Ehrenstein, *loc. cit.*, give m. p. 193·5—194·5°, $[\alpha]_D^{28}$ + 109°.

The 6-acetate, prepared in the usual manner and crystallized from methanol, had m. p. 199—201°, $[\alpha]_D^{20}$ +106° in $COMe_2$, $\lambda_{max.}$ 2360 Å (ε 13,600), $\nu_{max.}$ 1736 (acetate and 17-ketone), 1674 cm.$^{-1}$ (unsaturated ketone), and no free hydroxyl band (Found: C, 73·25; H, 8·25. Calc. for $C_{21}H_{28}O_4$: C, 73·25; H, 8·2%) (Davis and Petrow, *loc. cit.*, give m. p. 200° for this substance, then believed to be the 3-acetoxy-Δ^4-6-ketone; Balant and Ehrenstein, *loc. cit.*, give m. p. 201—201·5, $[\alpha]_D^{27}$ +111°; Ehrenstein, *J. Org. Chem.*, 1941, **6**, 626, gives m. p. 174—176°, $[\alpha]_D^{27}$ +153·5° in $COMe_2$, for a product now known to be the 6α-isomer).

Androstane-3 : 6 : 17-*trione* (VIII*d*).—This was prepared by heating under reflux 6β-hydroxyandrost-4-ene-3 : 17-dione (0·3 g.) and potassium hydroxide (0·3 g.) in methanol (14 c.c.) and water (1·5 c.c.) for 30 min. After crystallization from methanol–ether, it had m. p. 192—193°, $[\alpha]_D^{20}$ +72°, no high-intensity absorption in the ultra-violet, $\nu_{max.}$ 1736 (17-ketone), 1706 cm.$^{-1}$ (saturated ketone), but no free-hydroxyl band (Ushakov and Lyutenberg, *J. Gen. Chem. Russia*, 1939, **9**, 69, and Davis and Petrow, *loc. cit.*, give m. p. 191—192°).

Androst-4-*ene*-3 : 6 : 17-*trione* (VII*d*).—A suspension of 3β : 6β-dihydroxyandrost-4-en-17-one (V*d*) (1 g.; finely ground) in chloroform (100 c.c.) was heated under reflux with manganese dioxide (10 g.) for 8 hr. with stirring. The product ($\lambda_{max.}$ 2480 Å, ε 9200) was chromatographed on alumina (50 g.), and the fractions eluted with benzene were combined. Crystallization of this material from acetone–ether furnished the triketone (0·43 g.), m. p. 223—225°, $[\alpha]_D^{20}$ +43° in $COMe_2$, $\lambda_{max.}$ 2500 Å (ε 10,600), $\nu_{max.}$ 1736 (17-ketone), 1684 cm.$^{-1}$ (Δ^4-3 : 6-dione), but no free-hydroxyl band (Found: C, 76·15; H, 8·15. Calc. for $C_{19}H_{24}O_3$: C, 75·95; H, 8·05%) (Butenandt and Riegel, *Ber.*, 1936, **69**, 1163, give m. p. 216—217°, $[\alpha]_D^{22}$ +42° in $COMe_2$; Ushakov and Lyvtenberg, *J. Gen. Chem. Russia*, 1937, **7**, 1821, give m. p. 221—222°).

Androst-4-*ene*-3β : 6β : 17β-*triol* (V*e*).—3β : 6β-Diacetoxyandrost-4-en-17-one (IV*d*) (7·8 g.) in tetrahydrofuran (200 c.c.) was gradually added to a solution of lithium aluminium hydride (3·9 g.) in ether (200 c.c.). The mixture was heated under reflux for 30 min., the excess of reagent was decomposed by means of ethyl acetate, and the product was isolated by the sodium sulphate procedure (cf. Mancera, Rosenkranz, and Sondheimer, *loc. cit.*). Crystallization from acetone furnished the unsaturated *triol* (4·8 g., 78%), m. p. 213—216°. Further crystallization gave material with m. p. 220—222°, $[\alpha]_D^{20}$ +13° in dioxan, $\nu_{max.}$ (mull) free-hydroxyl band only (Found: C, 74·2; H, 9·8. $C_{19}H_{30}O_3$ requires C, 74·45; H, 9·85%).

6β-*Hydroxytestosterone* (VI*e*).—A suspension of the foregoing triol (V*e*) (1 g.; finely ground) in chloroform (100 c.c.) was shaken at room temperature for 24 hr. with manganese dioxide (10 g.). Crystallization of the product from methanol–ether furnished 6β-*hydroxytestosterone*

(0·48 g.), m. p. 217—218°, $[\alpha]_D^{20}$ +34°, $\lambda_{max.}$ 2360 Å (ε 13,800), $\nu_{max.}$ 1670 cm.$^{-1}$ (unsaturated ketone) and free-hydroxyl band (Found: C, 74·7; H, 9·15. $C_{19}H_{28}O_3$ requires C, 74·95; H, 9·25%).

The 6 : 17-*diacetate*, prepared in the usual manner and crystallized from ether–pentane, had m. p. 134—135°, $[\alpha]_D^{20}$ +26°, $\lambda_{max.}$ 2360 Å (ε 13,100), $\nu_{max.}$ 1736 (acetate) and 1674 cm.$^{-1}$ (unsaturated ketone) (Found: C, 71·2; H, 8·3. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

Lithium–Ammonia Reduction of 6β-*Hydroxytestosterone* (VI*e*) *to Testosterone* [with Miss M. Velasco].—6β-Hydroxytestosterone (1 g.) dissolved in dry tetrahydrofuran (30 c.c.) was added dropwise to a solution of lithium metal (0·5 g.) in liquid ammonia (200 c.c.), with stirring. After another 15 minutes' stirring, *tert.*-butanol was slowly added until the blue colour of the mixture was discharged. The ammonia was allowed to evaporate, water was added, and the product was isolated with chloroform. Crystallization from acetone–hexane then furnished testosterone (0·47 g.), m. p. 152—153°, identified with an authentic sample by mixed m. p. determination and comparison of infra-red spectra. Under similar reduction conditions testosterone was reduced to 17β-hydroxyandrostan-3-one.

17β-*Hydroxyandrostane*-3 : 6-*dione* (VIII*e*).—A solution of 6β-hydroxytestosterone (0·30 g.) and potassium hydroxide (0·30 g.) in methanol (14 c.c.) and water (1·5 c.c.) was heated under reflux for 30 min. Crystallization from ether–pentane yielded 17β-hydroxyandrostane-3 : 6-dione (0·21 g.), m. p. 233—235°, no appreciable absorption in the ultra-violet, $\nu_{max.}$ 1700 cm.$^{-1}$ and a free-hydroxyl band. The substance proved to be identical (mixture m. p., infra-red spectra) with a sample (m. p. 235—236°) prepared by an independent method (Sondheimer, Kaufmann, Romo, Martinez, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 4712).

6-*Oxotestosterone* (VII*e*).—Androst-4-ene-3β : 6β : 17β-triol (V*e*) (1 g.) and manganese dioxide (10 g.) in chloroform (100 c.c.) were heated under reflux with stirring for 8 hr. The product ($\lambda_{max.}$ 2480 Å, ε 9200) was chromatographed on alumina (50 g.), and the fractions eluted with benzene–ether (4 : 1) were combined. Crystallization from acetone–ether furnished 6-oxotestosterone (0·45 g.), m. p. 212—213°, $[\alpha]_D^{20}$ − 53° in $COMe_2$, $\lambda_{max.}$ 2500 Å (ε 11,200), $\nu_{max.}$ 1684 cm.$^{-1}$ (Δ^4-3 : 6-dione) and a free-hydroxyl band (Found: C, 75·4; H, 8·65. Calc. for $C_{19}H_{26}O_3$: C, 75·45; H, 8·65%) (Butenandt and Riegel, *loc. cit.*, give m. p. 203—205°, $[\alpha]_D$ −58° in $COMe_2$). A mixture m. p. determination with androst-4-ene-3 : 6 : 17-trione resulted in a *ca.* 20° depression, thus showing that the saturated 17β-hydroxyl group had not been oxidized. In the above chromatogram a small amount of 6β-hydroxytestosterone could be isolated from the later fractions.

17α-*Acetoxy*-3β : 5α : 6β-*trihydroxypregnan*-20-*one* (II*g*).—The performic acid hydroxylation was carried out as described above for 3β-hydroxyandrost-5-en-17-one (I*d*), with 3β : 17α-diacetoxypregn-5-en-20-one (20 g.; Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3489), formic acid (120 c.c.; 90%), and hydrogen peroxide (20 c.c.; 30%). The precipitate after addition of water was heated under reflux with potassium carbonate (13 g.) in methanol (300 c.c.) and water (60 c.c.) for 30 min. under nitrogen. Most of the solvent was removed under reduced pressure, water was added, and the precipitated *tetrol monoacetate* (14·6 g.), m. p. 285—288°, was collected. The analytical sample, obtained by crystallization from methanol–ether, had m. p. 296—298°, $[\alpha]_D^{20}$ −23°, $\nu_{max.}$ (mull) 1736 (acetate), 1704 cm.$^{-1}$ (saturated ketone), and a free-hydroxyl band (Found: C, 67·35; H, 8·65. $C_{23}H_{36}O_6$ requires C, 67·6; H, 8·9%).

3β : 6β : 17α-*Triacetoxy*-5α-*hydroxypregnan*-20-*one* (III*g*).—The crude precipitated monoacetate (II*g*) (14·0 g.), acetylated as usual and crystallised from methanol, furnished the *triacetate* (14·1 g.), m. p. 163—165°, $[\alpha]_D^{20}$ −50°, $\nu_{max.}$ 1732 (acetate), 1700 cm.$^{-1}$ (saturated ketone), and a free-hydroxyl band (Found: C, 65·55; H, 8·45. $C_{27}H_{40}O_8$ requires C, 65·85; H, 8·2%).

3β : 6β : 17α-*Triacetoxypregn*-4-*en*-20-*one* (IV*g*).—To the above triacetate (14·0 g.), dissolved in pyridine (46 c.c.) and cooled in ice, thionyl chloride (4·6 c.c.) was added. After another 5 min. at 0°, water was added, and the solid product was collected and crystallized from acetone–hexane. The unsaturated *triacetate* (10·2 g.), m. p. 180—184°, thus obtained, was suitable for the subsequent step. A purified sample showed m. p. 195—196°, $[\alpha]_D^{20}$ −19° (Found: C, 67·9; H, 7·8. $C_{27}H_{38}O_7$ requires C, 68·35; H, 8·05%).

3β : 6β : 17α-*Trihydroxypregn*-4-*en*-20-*one* (V*f*).—The unsaturated triacetate (9·0 g.) was heated under reflux with potassium hydroxide (5·0 g.) in methanol (450 c.c.) and water (50 c.c.) for 1 hr. in nitrogen. Isolation in the usual manner and crystallization from methanol–ether yielded the unsaturated *triol* (4·7 g.), m. p. 266—268°, $[\alpha]_D$ +27° in dioxan, $\nu_{max.}$ (mull) 1700 cm.$^{-1}$ (saturated ketone) and a free hydroxyl band (Found: C, 72·1; H, 8·9. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%).

6β : 17α-*Dihydroxyprogesterone* (VI*f*).—A suspension of the unsaturated triol (1 g.; finely

ground) in chloroform (100 c.c.) was shaken with manganese dioxide (10 g.) at room temperature for 24 hr. Crystallization of the product from methanol–ether furnished 6β : 17α-dihydroxyprogesterone, m. p. 254—256°, $[\alpha]_D^{20}$ +10°, $\lambda_{max.}$ 2360 Å (ε 12,800), $\nu_{max.}$ (mull) 1700 (saturated ketone), 1670 $cm.^{-1}$ (unsaturated ketone), and a free-hydroxyl band (Found : C, 73·05; H, 9·0. Calc. for $C_{21}H_{30}O_4$: C, 72·8; H, 8·75%) (Meister *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 416, give m. p. 250—252°, $[\alpha]_D^{23}$ +4°, +6°).

RESEARCH LABORATORIES, SYNTEX, S.A.,
LAGUNA MAYRAN 413, MEXICO, D.F.

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