Hydroxylation of Pregn-16-en-20-ones. Part III. Formation of 3β-Acetoxy-16α : 17α-dihydroxypregna-5 : 14-dien-20-one and 16α-Hydroxy-derivatives of "Compound S" and of Cortisone.*

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Oxidation of 3β-acetoxypregna-5 : 16-dien-20-one (I) with potassium permanganate in acetone containing acetic acid can give rise not only to 3β-acetoxy-16α : 17α-dihydroxypregn-5-en-20-one (II) (see Parts I and II*), but also to its 14 : 15-dehydro-derivative (III). The latter product closely resembles the former in its behaviour on D-homo-annulation with basic alumina; the diolone (IV; R = H) is obtained, and undergoes alkaline dehydration to (VII). Oxidation of the dibromide of the dehydro-compound yields the Köster–Logemann ketone (VI).

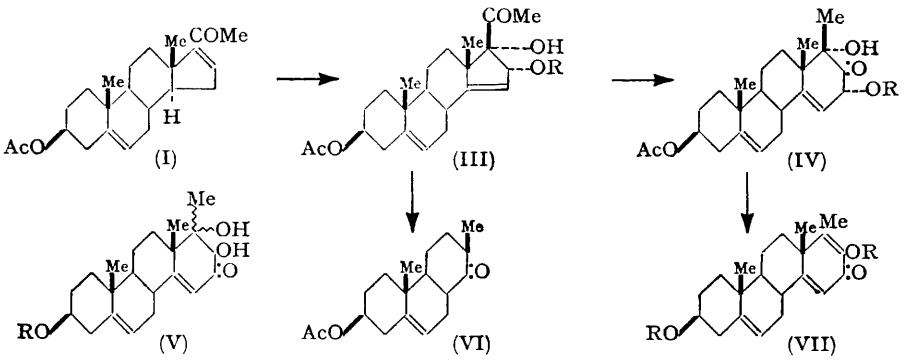
The method of hydroxylation developed in Part I has been extended to the preparation of 16α-hydroxy-"Compound S" (acetate) (XII; R = H_2, R′ = H) and of 16α-hydroxycortisone (acetate) (XII; R = O, R′ = H) from 21-acetoxypregna-4 : 16-diene-3 : 20-dione (XI; R = H_2) and 21-acetoxypregna-4 : 16-diene-3 : 11 : 20-trione (XI; R = O), respectively.

(i) In Part I * oxidation of 3β-acetoxypregna-5 : 16-dien-20-one (I) with potassium permanganate in acetone containing a limited quantity of acetic acid was shown to give a crystalline mixture from which 3β-acetoxy-16α : 17α-dihydroxypregn-5-en-20-one (II) was readily obtained; several crystallisations were required to free it from a contaminant (compound X). The amount of acetic acid critically affected the relative proportions of these products; in its absence the oxidation gave only the ketone (II), but in very low yield. When 1·2 mols. of acetic acid, relative to potassium permanganate, were used, the yield of this ketone rose to 20%, but compound X could be identified, though with difficulty. Larger

* Parts I and II, preceding papers.

amounts of acetic acid decreased the yield of the ketone (II) and increased that of compound X, which was the sole product (30%) when 15 mols. of acid were used.

Compound X had not the ultraviolet absorption spectrum of an αβ-unsaturated ketone (cf. I). Its analysis approached that required by (II), from which, however, it differed in optical rotation. The presence, in its molecule, of *cis*-hydroxy-groups (one secondary and one tertiary) followed from the ready formation of an *iso*propylidene derivative and a



diacetate. Treatment with one equivalent of bromine, followed by chromic acid and debromination, furnished the Köster–Logemann ketone, 7β-acetoxy-$\Delta^{9:14}$-dodecahydro-2 : 13-dimethyl-1-oxophenanthrene (VI) (Köster and Logemann, *Ber.*, 1940, **73**, 298), which established the presence of a 5 : 6-ethylenic linkage and of a 14 : 15-unsaturated linkage (not evident from the analytical data). That two double bonds are present was confirmed by perbenzoic acid titration.

The ready formation of this new oxidation product from the ketone (I) under mildly acidic conditions which are not favourable to the D-homo-annulation of 17-hydroxypregnan-20-ones, together with results recorded above and in Parts I and II, led us to assign the constitution of 3β-acetoxy-16α : 17α-dihydroxypregna-5 : 14-dien-20-one (III; R = H) to compound X. Its formation is regarded as taking place by allylic oxidation at $C_{(15)}$, dehydration to a 5 : 14 : 16-trien-20-one, and hydroxylation (cf. the formation of ergosta-7 : 14 : 22-triene-3β : 5α : 6α-triol from ergosterol by oxidation with potassium permanganate; Fieser, Quilico, Nickon, Rosen, Tarlton, and Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4066).

D-Homo-annulation of the diene (III; R = H) was closely similar to that of the monoene (II) (cf. preceding communication): chromatography on basic alumina led to an isomer, 3β-acetoxy-16α : 17*a*α-dihydroxy-17*a*β-methyl-D-homoandrosta-5 : 14-dien-17-one (IV; R = H), which formed a diacetate (IV; R = Ac) on acetylation in pyridine and an *iso*propylidene derivative on treatment with acetone and hydrochloric acid. The alternative formulation of the D-homo-steroid as (V; R = Ac) is excluded in this instance by the transparency of the compound to ultraviolet light in the region 220—300 mμ, which establishes the absence of an αβ-unsaturated ketonic system. As ethylene linkages tend towards conjugation, the formation of the diene (IV; R = H) and not the isomer (V; R = Ac) from the dehydro-compound (III; R = H) provides further evidence in support of the formulation previously assigned in Part II to the alumina-catalysed D-homo-annulation product of the monoene (II).

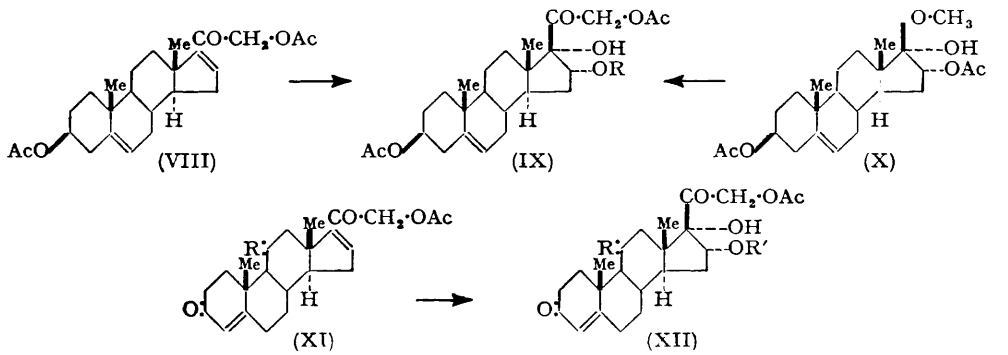
Hot methanolic potassium hydroxide converted the D-homo-compound (IV; R = H), presumably by dehydration of an initially formed (not isolated) product (V; R = H) of α-ketol rearrangement, into a diosphenol, $C_{21}H_{28}O_3$, which gave a purple colour with ethanolic ferric chloride, a quinoxaline derivative, and a diacetate. This ester is regarded as 3β : 17-diacetoxy-17*a*-methyl-D-homoandrosta-5 : 14 : 17-trien-16-one (VII; R = Ac), and its ultraviolet absorption (max. at 246·5 mμ; ε 17,600) is consistent with this. The spectrum of the parent diosphenol, however, shows 2 bands [max. at 252 (ε 11,740) and 300 mμ (ε 3960)], the first of which is not inconsistent with the condition of cross-conjugation shown in (VII; R = H); the second band is much too intense to be due to a carbonyl

group and may indicate that in solution the enol (VII; R = H) is in equilibrium with a second form (see Dorfman, *Chem. Rev.*, 1953, **53**, 79—83).

Alkaline hydrolysis of the *iso*propylidine derivative of the diol (III; R = H) gave the corresponding 3-alcohol, which passed into 16α : 17α-*iso*propylidenedioxypregna-4 : 14-diene-3 : 20-dione on Oppenauer oxidation. The last compound was recovered unchanged after prolonged treatment with hot aqueous acetic acid.

(ii) Oxidation of 3β : 21-diacetoxypregna-5 : 16-dien-20-one (VIII) (Djerassi and Lenk, *J. Amer. Chem. Soc.*, 1954, **76**, 1722) with potassium permanganate in acetone containing a limited quantity of acetic acid led to a dihydroxy-derivative of (VIII) which (*a*) did not show the ultraviolet absorption spectrum of an αβ-unsaturated ketone, (*b*) readily formed an *iso*propylidene derivative (*cis*-glycol group), and (*c*) passed into a triacetate on acetylation in pyridine, thus establishing that only one of the two new hydroxyl groups is secondary. We therefore assign it the constitution of 3β : 21-diacetoxy-16α : 17α-dihydroxypregn-5-en-20-one (IX; R = H) and in support find that its triacetate (IX; R = Ac) may be prepared by an alternative route involving the reaction sequence: (*a*) tribromination of 3β : 16α-diacetoxy-17α-hydroxypregn-5-en-20-one (X) (Part I), (*b*) conversion of the 5 : 6 : 21-tribromide into the corresponding Δ^5-21-iodo-compound by reaction with sodium iodide, and (*c*) treatment with potassium acetate in boiling acetone to give the triacetate (IX; R = Ac). Its formulation as the 14 : 15-dehydro-derivative of (IX; R = H) [cf. preceding section] is thereby excluded. The triacetate (IX; R = Ac), it may be added, differs from 3β : 16β : 21-triacetoxy-17α-hydroxypregn-5-en-20-one (Heusler and Wettstein, *Chem. Ber.*, 1954, **87**, 1301), with which it is epimeric at $C_{(16)}$.

Oxidation of 21-acetoxypregna-4 : 16-diene-3 : 20-dione (XI; R = H_2) (Cole and Julian, *J. Org. Chem.*, 1954, **19**, 131) with potassium permanganate under similar experimental conditions led to a dihydroxy-derivative, regarded as 21-acetoxy-16α : 17α-dihydroxypregn-4-ene-3 : 20-dione (XII; R = H_2, R′ = H) on the basis of (*a*) its method of preparation, (*b*) its ultraviolet absorption spectrum (max. at 240 mμ; ε 16,900), (*c*) its conversion into



an *iso*propylidene derivative, and (*d*) its acetylation to a diacetate. The constitution of 16α : 21-diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione assigned to the last compound is supported by its molecular rotation (see Table), which falls unequivocally within the expected range.

Molecular-rotation differences of epimeric 16-*acetoxypregnan*-20-*ones.*

	16α-Acetoxy	16β-Acetoxy	$[M]_D^{\beta} - [M]_D^{\alpha}$
3β : 16-Diacetoxy-17α-hydroxypregn-5-en-20-one	−320° [a]	−104° [d]	+216°
16-Acetoxy-17α-hydroxypregn-4-ene-3 : 20-dione	+190 [a]	+392 [c]	+202
3β : 16 : 21-Triacetoxy-17α-hydroxypregn-5-en-20-one...	−333 [b]	−118 [c]	+215
16 : 21-Diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione	+232 [b]	+442 [c]	+210

[a] Part I (*loc. cit.*). [b] Present paper. [c] Heusler and Wettstein (*loc. cit.*). [d] Heusler and Wettstein give $[M]_D$ − 164°. The value shown was obtained in the present work.

21-Acetoxypregn-4 : 16-diene-3 : 11 : 20-trione (XI; R = O) (Allen and Bernstein, *J. Amer. Chem. Soc.*, 1955, **77**, 1028; McGuckin and Mason, *ibid.*, p. 1822) with potassium

permanganate gave 21-acetoxy-16α : 17α-dihydroxypregn-4-ene-3 : 11 : 20-trione (XII; R = O, R′ = H), which formed a diacetate (XII; R = O, R′ = Ac). The infrared absorption (kindly determined by Dr. A. E. Kellie, Courtauld Institute of Biochemistry) of the latter compound is entirely consistent with the proposed structure.

Experimental

3β-*Acetoxy*-16α : 17α-*dihydroxypregna*-5 : 14-*dien*-20-*one* (III; R = H).—A solution of potassium permanganate (18 g.) in aqueous acetone (1·05 l. of 85%) was added during 30 min. to a stirred ice-cooled solution of 3β-acetoxypregna-5 : 16-dien-20-one (40 g.) in a mixture of acetone (1·2 l.) and acetic acid (100 ml.). After treatment with sulphur dioxide, the solution was decanted from inorganic salts, and most of the solvents were removed by distillation *in vacuo*. The product was extracted into ether (*ca.* 2 l.), and the extract washed with water, aqueous sodium hydrogen carbonate, and water, and then dried. Concentration to crystallisation, followed by cooling to 0°, gave a product (21 g.; m. p. 185—203°) from which, after two crystallisations from methanol, 3β-*acetoxy*-16α : 17α-*dihydroxypregna*-5 : 14-*dien*-20-*one* (12 g.) was obtained as needles, m. p. 220—222°, $[\alpha]_D^{20}$ −107° (*c*, 1·25) (Found: C, 70·8; H, 8·4. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). On treatment with perbenzoic acid in benzene–chloroform for 3 days at 0°, 373 mg. were oxidised by 254 mg. of perbenzoic acid, equiv. to 1·99 atoms of oxygen. In admixture with 3β-acetoxy-16α : 17α-dihydroxypregn-5-en-20-one, m. p. 210—212° (Part I, *loc. cit.*), an m. p. of 213—215° was obtained.

Acetylation in pyridine for 1 hr. at 100° gave the 3β : 16α-*diacetate* (III; R = Ac), flat needles (from aqueous ethanol), m. p. 178°, $[\alpha]_D^{21}$ −136° (*c*, 0·91) (Found: C, 69·2; H, 8·1. $C_{25}H_{34}O_6$ requires C, 69·7; H, 8·0%) after drying for several hours at 120°.

3β-*Acetoxy*-16α : 17α-iso*propylidenedioxypregna*-5 : 14-*dien*-20-*one*.—The diene (III; R = H) (4 g.) in boiling acetone (150 ml.) was treated with 3 drops of concentrated hydrochloric acid and the mixture kept overnight. The solids obtained on dilution with water were purified from methanol. The iso*propylidene derivative* (3·6 g.) formed fine needles, m. p. 184°, $[\alpha]_D^{22}$ −40° (*c*, 1·29) (Found: C, 73·0; H, 8·6. $C_{26}H_{36}O_5$ requires C, 72·9; H, 8·5%).

Oxidative Degradation of the Diene (III; R = H).—Bromine (1·7 g.) in chloroform (30 ml.) was added dropwise during 45 min. to a stirred solution of the dihydroxy-ketone (3·9 g.) in chloroform cooled to −60°. On reaching room temperature, the solvent was removed *in vacuo* below 40°, and the gummy residue triturated with methanol (20 ml.). The white crystalline product (4·6 g.; m. p. 155°) was suspended in acetic acid (70 ml.) and treated with chromium trioxide (3·5 g.) in 85% acetic acid (25 ml.). Next morning zinc dust (15 g.) was introduced, and the mixture stirred for 10 min. and then heated at 100° for a further 10 min. After dilution with water, the product was extracted with ether, and the neutral fraction chromatographed on a column (12 × 2 cm.) of B.D.H. alumina made up in benzene. The early fractions obtained on elution with benzene were combined and purified from aqueous methanol, to give 7β-acetoxy-$\Delta^{9:14}$-dodecahydro-2 : 13-dimethyl-1-oxophenanthrene (400 mg.), blades, m. p. 129°, $[\alpha]_D^{20}$ −90° (*c*, 0·5) (Found: C, 74·6; H, 9·0. Calc. for $C_{18}H_{26}O_3$: C, 74·4; H, 9·0%), identical with a specimen kindly supplied by Sir Robert Robinson, F.R.S.

3β-*Acetoxy*-16α : 17*aα*-*dihydroxy*-17*aβ*-*methyl*-D-*homoandrosta*-5 : 14-*dien*-17-*one* (IV; R = H).—A solution of the dihydroxy-ketone (III; R = H) (2 g.) in methylene dichloride–ethanol (40 ml.; 9 : 1) was passed slowly through a column (10 × 2 cm.) of alkaline alumina. Elution with the same solvent mixture gave a product (1·9 g.; m. p. 167—169°), readily purified from aqueous acetone. The D-*homo-steroid* separated in hexagonal plates, m. p. 175—176°, $[\alpha]_D^{22}$ −7° (*c*, 0·96) (Found: C, 71·0; H, 8·5. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). Acetylation in pyridine gave the 3β : 16α-*diacetoxy-derivative*, needles (from aqueous methanol), m. p. 169°, $[\alpha]_D^{20}$ −157° (*c*, 0·99) (Found: C, 69·5; H, 8·1. $C_{25}H_{34}O_6$ requires C, 69·7; H, 8·0%). The iso*propylidene derivative* formed plates (from aqueous acetone), m. p. 166—168°, $[\alpha]_D^{20}$ +20° (*c*, 1·0) (Found: C, 72·7; H, 8·2. $C_{26}H_{36}O_5$ requires C, 72·9; H, 8·5%).

Action of Hot Methanolic Potassium Hydroxide on the D-*Homo-compound* (IV; R = H).—The D-homo-steroid (1 g.) in methanolic 12% potassium hydroxide (25 ml.) was refluxed for 4 hr., a yellow crystalline potassium salt separating after the first 1½ hr. A suspension of the salt in ether (100 ml.)–water (75 ml.) was treated with concentrated hydrochloric acid (1 ml.), the mixture vigorously shaken, and the ethereal layer washed, dried, and evaporated. The residue was purified from aqueous ethanol to give the *diosphenol* (60%), needles, m. p. 185—186°, $[\alpha]_D^{23}$ +161° (*c*, 1·1) (Found: C, 76·6; H, 8·75. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%). Light

absorption: max. at 252 (ε 11,740) and 300 mμ (ε 3960). Acetylation in pyridine for 15 min. at 100° gave 3β : 17-*diacetoxy*-17α-*methyl*-D-*homoandrosta*-5 : 14 : 17-*trien*-16-*one* (VII; R = Ac), needles (from aqueous ethanol), m. p. 225—226°, $[\alpha]_D^{19}$ +71° (*c*, 0·8) (Found: C, 73·0; H, 8·0. $C_{25}H_{32}O_5$ requires C, 72·8; H, 7·8%). Light absorption: max. at 246·5 mμ (ε 17,600). The *quinoxaline derivative*, prepared by heating the diosphenol (250 mg.) with *o*-phenylenediamine (150 mg.) for 30 min. at 150°, crystallised from ethanol in pale yellow needles, m. p. 258—260° (Found: C, 80·6; H, 8·1; N, 7·05. $C_{37}H_{32}ON_2$ requires C, 81·0; H, 8·05; N, 7·0%).

16α : 17α-iso*Propylidenedioxypregna*-4 : 14-*diene*-3 : 20-*dione*.—3β-Acetoxy-16α : 17α-*iso*-propylidenedioxypregna-5 : 14-dien-20-one (3·1 g.) in methanolic 1% potassium hydroxide (100 ml.) was refluxed for 45 min. Addition of water gave needles (2·55 g.), m. p. 225° (Found: C, 74·4; H, 9·1. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%). A solution of this *product* (2·5 g.) in toluene (80 ml.) and *cyclo*hexanone (20 ml.) was distilled until 25 ml. of distillate had collected. Aluminium *iso*propoxide in toluene (18 ml. of 25% solution) was added, and the mixture refluxed for 30 min., cooled, and extracted with concentrated aqueous Rochelle salt. Removal of solvents by steam-distillation, followed by purification of the residue from aqueous ethanol, gave 16α : 17α-iso*propylidenedioxypregna*-4 : 14-*diene*-3 : 20-*dione*, needles, m. p. 200—202°, $[\alpha]_D^{21}$ +73·5 (*c*, 0·95) (Found: C, 74·6; H, 8·3. $C_{24}H_{32}O_4$ requires C, 75·0; H, 8·4%). In admixture with 16α : 17α-*iso*propylidenedioxypregn-4-en-3 : 20-dione, m. p. 210° (Part I), m. p. 204—205° was obtained.

The compound was recovered substantially unchanged after being heated in aqueous acetic acid (70%) for 2 hr. at 100°.

3β : 21-*Diacetoxy*-16α : 17α-*dihydroxypregn*-5-*en*-20-*one* (IX; R = H).—A solution of potassium permanganate (3·2 g.) in aqueous acetone (175 ml. of 85%) was added dropwise during 30 min. to a stirred ice-cooled solution of 3β : 21-diacetoxypregna-5 : 16-dien-20-one (7 g.) in acetone (200 ml.) and acetic acid (3 ml.). After treatment with sulphur dioxide, the solution was decanted from inorganic salts, and most of the solvents removed *in vacuo*. The product was extracted into ether, and the extract washed with water, aqueous sodium hydrogen carbonate, water, and then dried. The crude material (3·95 g.; m. p. 180—215°) obtained on partial removal of the solvent was purified from methylene dichloride–methanol, to give 3β : 21-*diacetoxy*-16α : 17α-*dihydroxypregn*-5-*en*-20-*one*, flat needles, m. p. 235—237°, $[\alpha]_D^{21}$ −53° (*c*, 1·0) (Found: C, 66·8; H, 7·7. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·1%). The iso*propylidene derivative* formed needles (from aqueous acetone), m. p. 194—195°, $[\alpha]_D^{20}$ −16° (*c*, 0·68) (Found: C, 69·0; H, 8·1. $C_{28}H_{40}O_7$ requires C, 68·8; H, 8·25%).

3β : 16α : 21-*Triacetoxy*-17α-*hydroxypregn*-5-*en*-20-*one* (IX; R = Ac).—(*a*) Acetylation of the foregoing dihydroxy-ketone (IX; R = H) in pyridine for 18 hr. at room temperature gave the *triacetate*, needles (from methanol), m. p. 214—215°, $[\alpha]_D^{22}$ −68° (*c*, 0·97) (Found: C, 66·1; H, 7·7. $C_{27}H_{38}O_8$ requires C, 66·1; H, 7·8%).

(*b*) Bromine (2·25 g.) in carbon tetrachloride (10 ml.) was added dropwise during 30 min. to 3β : 16α-diacetoxy-17α-hydroxypregn-5-en-20-one (3 g.) in 1 : 1 carbon tetrachloride–acetic acid (60 ml.). The product obtained by dilution with water and isolation with carbon tetrachloride was dissolved in benzene (60 ml.) and treated for 24 hr. with sodium iodide (12 g.) in ethanol (70 ml.). The mixture was poured into water and extracted with ether, and the extract washed with 3% aqueous sodium thiosulphate and water, and dried. The brown gum obtained on removal of the solvent was triturated with ethanol–*n*-hexane to give a cream-coloured solid [0·8 g.; m. p. 190° (decomp.)]. This material, in acetone (40 ml.) containing freshly fused potassium acetate (4 g.), was heated under reflux for 18 hr., and the solids obtained on the addition of water were purified from methanol. 3β : 16α : 21-Triacetoxy-17α-hydroxypregn-5-en-20-one separated in needles, m. p. 214—215°, not depressed in admixture with a specimen prepared by method (*a*).

21-*Acetoxy*-16α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione* (XII; R = H_2, R′ = H).—Potassium permanganate (800 mg.) in aqueous acetone (40 ml. of 85%) was added dropwise during 40 min. to a stirred ice-cooled solution of 21-acetoxypregna-4 : 16-diene-3 : 20-dione (1·75 g.) in acetone (50 ml.) containing acetic acid (0·5 ml.). After treatment with sulphur dioxide, the mixture was diluted with water, and the product isolated with ether. Crystallisation from acetone–*n*-hexane gave material (420 mg.; 194—198°), followed by a second crop (370 mg.; m. p. 180—185°). The combined crops, purified from ethyl acetate–*n*-hexane, gave 21-*acetoxy*-16α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione*, needles, m. p. 200—202°, $[\alpha]_D^{20}$ +121° (*c*, 0·63) (Found: C, 68·0; H, 8·0. $C_{23}H_{32}O_6$ requires C, 68·3; H, 8·0%). Light absorption: max. at 240 mμ (ε 16,900). The iso*propylidene derivative* separated from aqueous ethanol in needles, m. p. 249—250°, $[\alpha]_D^{22}$ +133° (*c*, 0·53) (Found: C, 69·8; H, 8·1. $C_{26}H_{36}O_6$ requires C, 70·2;

H, 8·2%). Acetylation in pyridine gave 16α : 21-*diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione*, flat needles (from aqueous methanol), m. p. 199—200°, $[\alpha]_D^{20}$ +52° (*c*, 0·78) (Found : C, 66·2; H, 7·7. $C_{25}H_{34}O_7$ requires C, 67·2; H, 7·7%) after drying for 5 hr. at 100°. The dried material was hygroscopic. The compound separated from aqueous solvents in a hydrated form, m. p. 115—120° (effervescence).

21-*Acetoxy*-16α : 17α-*dihydroxypregn*-4-*ene*-3 : 1 : 20-*trione* (XII; R = O, R′ = H).—21-Acetoxypregna-4 : 16-diene-3 : 11 : 20-trione (1·7 g.) was oxidised with potassium permanganate (800 mg.) as in the preceding preparation. The crude product was triturated with warm methanol (10 ml.), and the insoluble fraction (510 mg.; m. p. 245°) purified from aqueous dioxan. 21-*Acetoxy*-16α : 17α-*dihydroxypregn*-4-*ene*-3 : 11 : 20-*trione* separated in needles, m. p. 245—247°, $[\alpha]_D^{22}$ +166·5° (*c*, 0·97 in dioxan) (Found : C, 66·2; H, 7·1. $C_{23}H_{30}O_7$ requires C, 66·0; H, 7·2%). Light absorption : max. at 238 mμ (ε 15,900). Acetylation in pyridine gave the 16α : 21-*diacetate*, needles (from 95% ethanol), double m. p. 185° and 225—226° (after drying for 2 hr. at 100°), $[\alpha]_D^{20}$ +118° (*c*, 0·43) (Found : C, 64·0; H, 7·1. $C_{25}H_{32}O_8,\frac{1}{2}H_2O$ requires C, 63·95; H, 7·1%).

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