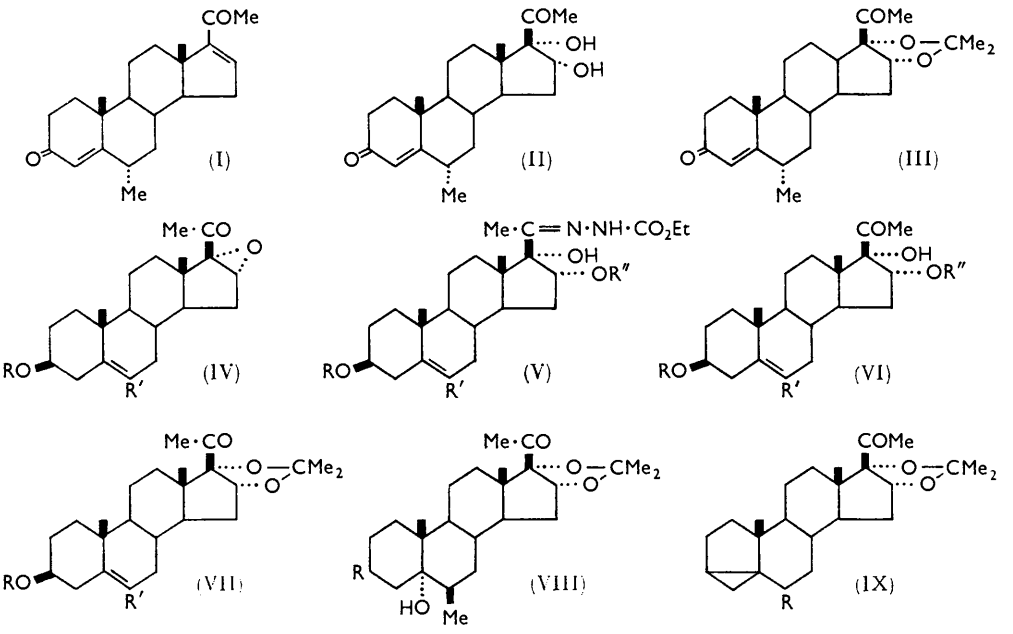
803. *Modified Steroid Hormones. Part XXIV.** 16α,17α-*Isopropylidenedioxy*-6α-*methylpregn*-4-*ene*-3,20-*dione*.

By B. Ellis, (Mrs.) S. P. Hall, V. Petrow, and (Mrs.) S. Waddington-Feather.

Three methods for the preparation of the compound named in the title are described.

Elsewhere [1] we have reported the sequence of reactions: 6α-methylpregna-4,16-diene-3,20-dione [2] (I) ⟶ 16α,17α-dihydroxy-6α-methylpregn-4-ene-3,20-dione (II) ⟶ 16α,17α-isopropylidenedioxy-6α-methylpregn-4-ene-3,20-dione (III). Oxidation of the last compound with 2,3-dichloro-5,6-dicyanobenzoquinone [3] furnished its 1-dehydro-derivative. Both this compound and (III) were found to be potent anti-inflammatory agents in the turpentine–agar pellet assay.[1] In consequence thereof we sought a more convenient route to the diketone (III).

Initially we examined the preparation of 16α,17α-dihydroxypregnan-20-ones from 16α,17α-epoxypregnan-20-ones by reactions involving condensation with phenylhydrazine.[4] Though satisfactory for samples of a few grams, in our hands these processes broke down on a large scale. We ultimately found that reaction of 16α,17α-epoxy-3β-hydroxypregn-



5-ene-20-one (IV; R = R′ = H) with ethyl hydrazinecarboxylate [5] in acetic acid afforded an excellent yield of 16α-acetoxy-3β,17α-dihydroxypregn-5-en-20-one ethoxycarbonylhydrazone (V; R = R′ = H, R″ = Ac). The structure of the last compound followed from (i) its hydrolysis with pyruvic acid to 16α-acetoxy-3β,17α-dihydroxypregn-5-en-20-one

* Part XXIII, preceding paper.

[1] Bianchi, David, Ellis, Petrow, Waddington-Feather, and Woodward, *J. Pharm. Pharmacol.*, 1961, **13**, 355.

[2] Burn, Ellis, Petrow, Stuart-Webb, and Williamson, *J.*, 1957, 4092.

[3] Burn, Kirk, and Petrow, *Proc. Chem. Soc.*, 1960, 14.

[4] U.S.P. 2,727,909, 2,803,399.

[5] Cf. Joly and Nominé, *Bull. Soc. chim. France*, 1956, 1381.

(VI; R = R′ = H, R″ = Ac), which afforded the known 3β,16α-diacetate [6] (VI; R = R″ = Ac, R′ = H), and (ii) its alternative formation from the 16α-acetate (VI; R = R′ = H, R″ = Ac) and ethyl hydrazinecarboxylate.

Alkaline saponification of 16α-acetoxy-hydrazone (V; R = R′ = H, R″ = Ac) to the corresponding triol (V; R = R′ = R″ = H), followed by hydrolysis with aqueous pyruvic acid, gave 3β,16α,17α-trihydroxypregn-5-en-20-one [4] (VI; R = R′ = R″ = H), which was readily converted into the isopropylidene derivative (VII; R = R′ = H).[6] 3β-Acetoxy-16α,17α-epoxypregn-5-en-20-one (IV; R = Ac, R′ = H) similarly yielded 3β,16α-diacetoxy-17α-hydroxypregn-5-en-20-one ethoxycarbonylhydrazone (V; R = R″ = Ac, R′ = H) and thence the triol intermediate (V; R = R′ = R″ = H). Preparation of the isopropylidene derivative (VII; R = R′ = H) was further simplified in that it was obtained directly from the 16α-acetate (VI; R = R′ = H, R″ = Ac) by treatment with acetone, methanol, and perchloric acid, thereby permitting the preparation of this compound from the readily available 16α,17α-epoxypregnenolone by a simple 3-stage process which has proved satisfactory on the kilogram scale.

3β-Hydroxy-16α,17α-isopropylidenepregn-5-en-20-one with peracetic acid furnished a mixture of the 5,6-epoxides in which the 5α,6α-isomer predominated. When the 3β-acetate of the last compound was treated with an excess of methylmagnesium iodide reaction with the epoxide residue took place without concomitant attack upon the unprotected 20-oxo-group, yielding 3β,5α-dihydroxy-16α,17α-isopropylidenedioxy-6β-methyl-5α-pregnan-20-one (VIII; R = $^{-}$OH, $\cdots$H). Oxidation of this diol with chromic acid in acetone furnished the 3-ketone (VIII; R = O), which passed smoothly into 16α,17α-isopropylidenedioxy-6β-methylpregn-4-ene-3,20-dione on brief treatment with hot dilute ethanolic potassium hydroxide. More drastic experimental conditions led to the formation of the 6α-methyl isomer (III), which was also obtained by alkali-promoted epimerisation of its 6β-methyl precursor.

A second route to compound (III) involved conversion of the isopropylidene derivative (VII; R = R′ = H) into its 3β-toluene-*p*-sulphonate, followed by rearrangement into the 6β-hydroxy-3,5-cyclosteroid (IX; R = $^{-}$OH, $\cdots$H). Oxidation furnished the 6-ketone (IX; R = O) which with methylmagnesium iodide gave a mixture from which 6ξ-hydroxy-16α,17α-isopropylidenedioxy-6ξ-methyl-3,5-cyclopregnan-20-one (IX; R = ~Me, ~OH) was isolated by chromatography. Reaction of the last compound with acetic acid and sulphuric acid gave the corresponding 3β-acetoxy-6-methylpregn-5-ene (VII; R = Ac, R′ = Me), which was converted into compound (III) by saponification followed by Oppenauer oxidation.

A third route to compound (III) employed the readily available 6-methylpregnadienolone [2] as starting material. Its 16α,17α-epoxide (IV; R = H, R′ = Me) reacted smoothly with ethyl hydrazinecarboxylate in acetic acid, to give 16α-acetoxy-3β,17α-dihydroxy-6-methylpregn-5-en-20-one ethoxycarbonylhydrazone (V; R = H. R′ = Me, R″ = Ac) which, by the transformations described above for its 6-demethyl analogue, led to compound (VII; R = H, R′ = Me).

6α-Ethyl-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione, required for comparative anti-inflammatory study, was prepared from 3β-acetoxy-5α,6α-epoxy-16α,17α-isopropylidenedioxy-5α-pregnan-20-one by the reaction sequence: epoxide cleavage with ethylmagnesium iodide; oxidation of the resulting (not isolated) 6β-ethyl-3β,5α-diol to the 3-ketone; and dehydration and concomitant epimerisation (with alcoholic hydrochloric acid) to the 6α-ethyl homologue of the compound (III).

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.

[6] Cooley, Ellis, Hartley, and Petrow, *J.*, 1955, 4373.

16α-*Acetoxy*-3β,17α-*dihydroxypregn*-5-*en*-20-*one Ethoxycarbonylhydrazone* (V; R = R′ = H, R″ = Ac).—Redistilled ethyl hydrazinecarboxylate (50 g.) in acetic acid (50 ml.) was added to 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one (50 g.) in acetic acid (350 ml.). The mixture was stirred for 8 hr., set aside overnight, then poured into ice-water (3 l.). The washed and dried product crystallised from benzene–methanol and then from aqueous methanol to give the named *hydrazone*, needles, m. p. 242—249° (decomp., depending upon the rate of heating), $[\alpha]_D^{20}$ −110° (*c* 0·75) (Found: C, 65·65; H, 8·45; N, 5·8. $C_{26}H_{40}N_2O_6$ requires C, 65·5; H, 8·5; N, 5·9%).

16α-*Acetoxy*-3β,17α-*dihydroxypregn*-5-*en*-20-*one* (VI; R = R′ = H, R″ = Ac). The foregoing compound (50 g.) in acetic acid (250 ml.) was treated at 100° with 50% aqueous pyruvic acid (25 ml.). After 5 min. at this temperature, the mixture was transferred to a hot-plate, and water (150 ml.) gradually added. The precipitated solid was redissolved by further heating, and the solution allowed to cool to room temperature. The crystalline product was purified from aqueous ethanol, to give the 16α-*acetate* as needles, m. p. 220—221°, $[\alpha]_D^{22}$ −67° (*c* 1·01) (Found: C, 70·1; H, 9·0. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%).

Acetylation in pyridine for 1 hr. at 100° gave 3β,16α-diacetoxy-17α-hydroxypregn-5-en-20-one,[6] silky needles (from methanol), m. p. and mixed m. p. 214—215°.

The 20-ethoxycarbonylhydrazone, prepared by treating the ketone (1 g.) in ethanol (15 ml.) with ethyl hydrazinecarboxylate (1 g.) and 2 drops of concentrated hydrochloric acid for 18 hr. at room temperature, separated from aqueous methanol in needles, m. p. 242—243° (decomp.), not depressed in admixture with a specimen prepared as described above.

3β,16α,17α-*Trihydroxypregn*-5-*en*-20-*one Ethoxycarbonylhydrazone* (V; R = R′ = R″ = H).—Potassium hydroxide (1 g.) in methanol (15 ml.) was added to 16α-acetoxy-3β,17α-dihydroxypregn-5-en-20-one ethoxycarbonylhydrazone (7 g.) in hot methanol (25 ml.). The mixture was heated under reflux for 1½ min., then treated with acetic acid (2·4 ml.), and water was added until crystallisation began. Purification of the product from aqueous methanol gave the *triol derivative*, needles, m. p. 190—192°, $[\alpha]_D^{22}$ −140° (*c* 0·85) (Found: C, 66·6; H, 8·75; N, 6·2. $C_{24}H_{38}N_2O_5$ requires C, 66·3; H, 8·8; N, 6·45%). A second form, m. p. 160—162°, was obtained by crystallisation from acetone–hexane.

3β,16α,17α-*Trihydroxypregn*-5-*en*-20-*one* [4] (VI; R = R′ = R″ = H).—The foregoing ethoxycarbonylhydrazone (14 g.) in acetic acid (50 ml.) and 50% aqueous pyruvic acid (10 ml.) was heated at 100° for 5 min. Water (5 ml.) was added, causing the product to separate. The mixture was heated for a further 15 min., during which more water (55 ml.) was added in portions. The product was collected, washed with aqueous methanol, and crystallised from acetone, giving 3β,16α,17α-trihydroxypregn-5-en-20-one, needles, m. p. 242—249° after softening at 225°, $[\alpha]_D^{20}$ −86° (*c* 0·93 in pyridine) (Found: C, 72·2; H, 9·3. Calc. for $C_{21}H_{32}O_4$: C, 72·4; H, 9·3%). Acetylation in pyridine gave 3β,16α-diacetoxy-17α-hydroxypregn-5-en-20-one, identified by m. p. and mixed m. p. with an authentic specimen.

3β-*Hydroxy*-16α,17α-*isopropylidenedioxypregn*-5-*en*-20-*one* (VII; R = R′ = H).—A suspension of the foregoing triol (2 g.) in acetone (60 ml.) was treated with 4 drops of 72% perchloric acid, and the mixture stirred for 2 hr. The solid isopropylidene derivative obtained by the addition of water crystallised from aqueous ethanol as needles, m. p. 217—218°, $[\alpha]_D^{22}$ −7·5° (*c* 1·2). No depression in m. p. was obtained in admixture with an authentic specimen.[6]

3β,16α-*Diacetoxy*-17α-*hydroxypregn*-5-*en*-20-*one Ethoxycarbonylhydrazone* (V; R = R″ = Ac, R′ = H).—(*a*) 3β-Acetoxy-16α,17α-epoxypregn-5-en-20-one (5 g.) and ethyl hydrazinecarboxylate (5 g.) in acetic acid (20 ml.) was set aside overnight. The *product* obtained by addition of water was washed, dried, and crystallised from acetone–hexane as needles, m. p. 226—230° (decomp.), $[\alpha]_D^{19}$ −114° (*c* 0·75) (Found: C, 64·75; H, 8·1; N, 5·0. $C_{28}H_{42}N_2O_7$ requires C, 64·8; H, 8·2; N, 5·4%). (*b*) 3β,16α-Diacetoxy-17α-hydroxypregn-5-en-20-one (0·7 g.) and ethyl hydrazinecarboxylate (0·7 g.) in acetic acid (10 ml.) was set aside for 18 hr. The product was purified from acetone–hexane, giving needles, m. p. 226—228°, not depressed in admixture with a specimen prepared by method (*a*).

Saponification with methanolic potassium hydroxide gave 3β,16α,17α-trihydroxypregn-5-en-20-one ethoxycarbonylhydrazone, identical with a specimen prepared as described above.

Conversion of the 16α-*Acetate* (VI; R = R′ = H, R″ = Ac) *into the Isopropylidene Derivative* (VII; R = R′ = H).—A solution of 16α-acetoxy-3β,17α-dihydroxypregn-5-en-20-one (9·6 g.) in acetone (800 ml.) and methanol (200 ml.), to which 60% aqueous perchloric acid (40 ml.) had been added, was heated under reflux for 1 hr. Addition of water gave crystals,

m. p. 194—198°. Purification from aqueous methanol gave 3β-hydroxy-16α,17α-isopropylidenedioxypregn-5-en-20-one, identified by m. p. and mixed m. p. determination.

Oxidation of 3β-*Hydroxy*-16α,17α-*isopropylidenedioxypregn*-5-*en*-20-*one* (VII; R = R′ = H).—A stirred solution of the isopropylidene derivative (7 g.) in chloroform (164 ml.) to which anhydrous sodium acetate (0·88 g.) had been added was treated at 0° with 40% peracetic acid (8·75 ml.). After being stirred for 1 hr., the mixture was kept for 18 hr. at 0°, then washed with dilute aqueous alkali and water and dried, and the chloroform was removed. Fractionation of the residue from acetone gave the 5α,6α-*epoxide*, needles (from aqueous methanol), m. p. 206·5°, $[\alpha]_D^{22}$ −17° (*c* 0·93) (Found: C, 68·15; H, 9·0. $C_{24}H_{36}O_5,H_2O$ requires C, 68·2; H, 9·1%), and the 5β,6β-*epoxide*, prisms (from aqueous acetone), m. p. 215°, $[\alpha]_D^{22}$ +36° (*c* 0·81) (Found: C, 71·6; H, 8·9. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%). The configurations assigned to these epoxides follow from the observation made, *inter alia*, by Bowers, Cuéllar Ibáñez, and Ringold [7] that 5β,6β-epoxides are more dextrorotatory than their 5α,6α-isomers.

3β-*Acetoxy*-5α,6α-*epoxy*-16α,17α-*isopropylidenedioxy*-5α-*pregnan*-20-*one*, prepared by acetylation of the foregoing 3β-hydroxy-5α,6α-epoxide, separated from methanol in plates, m. p. 216—217°, $[\alpha]_D^{21}$ −11·5° (*c* 0·85) (Found: C, 69·8; H, 8·6. $C_{26}H_{38}O_6$ requires C, 69·9; H, 8·6%).

3β,5α-*Dihydroxy*-16α,17α-*isopropylidenedioxy*-6β-*methyl*-5α-*pregnan*-20-*one* (VIII; R = ⁻OH, • • • H).—The foregoing acetate-epoxide (25 g.) in benzene (1 l.) was added to a Grignard reagent prepared from magnesium (25 g.), methyl iodide (72 ml.) and ether (425 ml.). The mixture was distilled until the vapour-temperature reached 76°, then refluxing was continued for 3 hr. After decomposition of the complex with aqueous ammonium chloride, the organic layer was washed and dried, and the solvent removed. The residue crystallised from aqueous methanol to give the *diol* as needles, m. p. 208°, $[\alpha]_D^{20}$ +26° (*c* 1·04), $\nu_{max.}$ (in Nujol) 1700 cm.$^{-1}$ (20 C=O) (Found: C, 71·25; H, 9·8. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·6%).

5α-*Hydroxy*-16α,17α-*isopropylidenedioxy*-6β-*methyl*-5α-*pregnane*-3,20-*dione* (VIII; R = :O).—4N-Chromium trioxide solution [8] (19 ml.) was added dropwise during 10 min. to a stirred solution of the foregoing compound (30 g.) in acetone (180 ml.), the product separating after the first 4—5 min. After dilution with water, the crystals were collected, washed, dried, and purified from methylene dichloride–methanol. The *diketone* separated in blades, m. p. 259—261°, $[\alpha]_D^{25}$ +43° (*c* 0·74) (Found: C, 71·9; H, 9·2. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·15%).

16α,17α-*Isopropylidenedioxy*-6β-*methylpregn*-4-*ene*-3,20-*dione*.—A refluxing suspension of the foregoing diketone (1 g.) in ethanol (15 ml.) was treated with 5% aqueous potassium hydroxide (2 ml.). The mixture was heated for 1½ min., then acidified, and water was added until crystals appeared. Purified from aqueous methanol, the *isopropylidene*-6β-*methyl derivative* formed needles, m. p. 203—204°, $[\alpha]_D^{20}$ +85° (*c* 0·87), $\nu_{max.}$ (in Nujol) 1675 and 1600 cm.$^{-1}$ (Δ^4-3-ketone) (Found: C, 75·2; H, 9·1. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·1%).

16α,17α-*Isopropylidenedioxy*-6α-*methylpregn*-4-*ene*-3,20-*dione* (III).—A refluxing suspension of the ketone (VIII; R = :O) (15 g.) in ethanol (150 ml.) was treated with potassium hydroxide (135 mg.) in ethanol (15 ml.). The mixture was refluxed for 2 hr., then acidified, and the product isolated with ether. Crystallisation from ether–light petroleum gave the 6α-methyl derivative, needles, m. p. 166—167°, not depressed in admixture with a specimen prepared by the method described previously.[1]

The same compound was obtained from the 6β-methyl derivative (above) by similar treatment with ethanolic potassium hydroxide.

16α,17α-*Isopropylidenedioxy*-3β-*toluene*-p-*sulphonylpregn*-5-*en*-20-*one*.—This *ester* was prepared by treating the 3β-hydroxy-compound (VII; R = R′ = H) (2 g.) in pyridine (15 ml.) with toluene-*p*-sulphonyl chloride (4 g.) for 3 days at room temperature; it crystallised from methylene dichloride–ethanol in needles, m. p. 183° (decomp.), $[\alpha]_D^{21}$ +1° (*c* 1·2) (Found: C, 68·75; H, 7·8. $C_{31}H_{42}O_6S$ requires C, 68·6; H, 7·8%).

6β-*Hydroxy*-16α,17α-*isopropylidenedioxy*-3,5-*cyclopregnan*-20-*one* (IX; R = ⁻OH, • • • H).—The foregoing sulphonate (4·7 g.) was heated under reflux for 22 hr. with potassium acetate (5·2 g.) in 50% aqueous acetone (132 ml.). The product was isolated with ether and purified from ether–light petroleum, to give the *alcohol*, needles, m. p. 178—180°, $[\alpha]_D^{21}$ +76° (*c* 0·95) (Found: C, 74·05; H, 9·35. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

16α,17α-*Isopropylidenedioxy*-3,5-*cyclopregnane*-6,20-*dione* (IX; R = :O).—The foregoing compound (5·6 g.) in acetone (112 ml.) was treated with 4N-chromium trioxide,[8] dropwise,

[7] Bowers, Cuéllar, Ibáñez, and Ringold, *Tetrahedron*, 1959, **7**, 141.
[8] See Djerassi, Engle, and Bowes, *J. Org. Chem.*, 1956, **21**, 1547.

until the supernatant liquid was slightly orange. The mixture was filtered, the filtrate poured into water, and the precipitated solid crystallised from aqueous methanol. The *ketone* separated in needles, m. p. 200—202°, $[\alpha]_D^{23}$ +64° (*c* 1·15) (Found: C, 74·1; H, 8·7. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

6ξ-*Hydroxy*-16α,17α-*isopropylidenedioxy*-6ξ-*methyl*-3,5-*cyclopregnan*-20-*ones* (IX; R = ~OH, ~Me).—The foregoing ketone (2·9 g.) in benzene (100 ml.) was added to a Grignard reagent prepared from magnesium (1·8 g.), methyl iodide (6 ml.), and ether (50 ml.). The mixture was distilled until the vapour-temperature reached 75°, then refluxing was continued for 2 hr. The product was isolated in the usual way and chromatographed on alumina (80 g.). Elution with benzene–ether (4 : 1) gave 6ξ-*hydroxy*-16α,17α-*isopropylidenedioxy*-6ξ-*methyl*-3,5-*cyclopregnan*-20-*one*, blades (from aqueous methanol), m. p. 192—193°, $[\alpha]_D^{21}$ +71° (*c* 0·82) (Found: C, 74·5; H, 9·4. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%). Further elution with the same solvent mixture gave a substance, needles (from acetone–hexane), m. p. 209—210° (Found: C, 72·6, 72·8; H, 10·0, 10·1%).

3β-*Acetoxy*-16α,17α-*isopropylidenedioxy*-6-*methylpregn*-5-*en*-20-*one* (VII; R = Ac, R′ = Me).—(*a*) A solution of the foregoing compound (m. p. 192—193°) (0·5 g.) in acetic acid (10 ml.) and concentrated sulphuric acid (0·2 ml.) was set aside overnight. The solid obtained on addition of water crystallised from aqueous methanol, giving the 3β-*acetate*, leaflets, m. p. 166—168°, $[\alpha]_D^{22}$ −25° (*c* 0·86) (Found: C, 72·8; H, 9·0. $C_{27}H_{40}O_5$ requires C, 72·9; H, 9·1%).

(*b*) A suspension of 3β,5α-dihydroxy-16α,17α-isopropylidenedioxy-6β-methyl-5α-pregnan-20-one (2 g.) in acetic acid (25 ml.) and acetic anhydride (4 ml.) was treated with 72% perchloric acid (2 drops). After 30 min., the mixture was diluted with water, and the product isolated with ether and crystallised from aqueous methanol. 3β-Acetoxy-16α,17α-isopropylidenedioxy-6-methylpregn-5-en-20-one separated in needles, m. p. 164—166°, not depressed in admixture with a specimen prepared by method (*a*).

3β-*Hydroxy*-16α,17α-*isopropylidenedioxy*-6-*methylpregn*-5-*en*-20-*one* (VII; R = H, R′ = Me), prepared by saponification of the foregoing compound with methanolic potassium hydroxide, formed needles (from chloroform–methanol), m. p. 232—234°, $[\alpha]_D^{22}$ −18° (*c* 0·48) (Found: C, 74·25; H, 9·4. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%).

16α,17α-*Isopropylidenedioxy*-6α-*methylpregn*-4-*en*-3,20-*dione* (III).—A solution of the foregoing compound (20·6 g.) in toluene (300 ml.) and cyclohexanone (500 ml.) was distilled until 150 ml. of distillate had collected. After the addition of aluminium t-butoxide (30 g.), the mixture was refluxed for 30 min., cooled, and washed with aqueous Rochelle salt, and the solvents were removed by steam-distillation. The gummy product was isolated with ether and purified from ether–hexane to give the 6α-methyl diketone, identical with samples prepared by the method described previously.

16α-*Acetoxy*-3β,17α-*dihydroxy*-6-*methylpregn*-5-*en*-20-*one Ethoxycarbonylhydrazone* (V; R = H, R′ = Me, R″ = Ac).—Ethyl hydrazinecarboxylate (12·5 g.) in acetic acid (12·5 ml.) was added to 16α,17α-epoxy-3β-hydroxy-6-methylpregn-5-en-20-one [9] (12·5 g.) in acetic acid (75 ml.). The mixture was stirred for 7 hr., then set aside overnight. The resulting jelly was treated with water (250 ml.), stirred, heated to 60°, and kept at this temperature for 30 min., during which the mixture thickened and the solid present appeared to become crystalline. The product was filtered off while hot, washed, and purified from aqueous ethanol. 16α-*Acetoxy*-3β,17α-*dikydroxy*-6-*methylpregn*-5-*en*-20-*one ethoxycarbonylhydrazone* formed needles, m. p. 262—265° (decomp.), $[\alpha]_D^{21}$ −134° (*c* 1·15) (Found: C, 66·5; H, 8·6; N, 5·8. $C_{27}H_{42}N_2O_6$ requires C, 66·1; H, 8·6; N, 5·7%).

16α-*Acetoxy*-3β,17α-*dihydroxy*-6-*methylpregn*-5-*en*-20-*one* (VI; R = H, R′ = Me, R″ = Ac).—The foregoing compound (27·5 g.) in acetic acid (138 ml.) was heated with 50% aqueous pyruvic acid (22 ml.) at 100° for 15 min. After addition of water (138 ml.) and acetic acid (10 ml.), the whole was heated to the b. p. and the clear solution set aside to cool. The crystalline product was purified from aqueous ethanol to give the 16α-*acetate*, needles, m. p. 226—227°, $[\alpha]_D^{25}$ −74° (*c* 1·01) (Found: C, 71·5; H, 9·1. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%).

3β,16α-*Diacetoxy*-17α-*hydroxy*-6-*methylpregn*-5-*en*-20-*one* (VI; R = R″ = Ac, R′ = Me), prepared by treating the foregoing compound (0·5 g.) in pyridine (2 ml.) with acetic anhydride (2 ml.) for 2 hr. at 100°, crystallised from aqueous acetone in prisms, m. p. 170°, $[\alpha]_D^{20}$ −82° (*c* 1·05) (Found: C, 69·75; H, 8·9. $C_{26}H_{38}O_6$ requires C, 69·9; H, 8·6%).

[9] Barton, Ellis, and Petrow, *J.*, 1959, 478.

6-*Methyl*-3β,16α,17α-*trihydroxypregn*-5-*en*-20-*one Ethoxycarbonylhydrazone* (V; R = R″ = H, R′ = Me).—A solution of potassium hydroxide (2 g.) and 16α-acetoxy-3β,17α-dihydroxy-6-methylpregn-5-en-20-one ethoxycarbonylhydrazone (13·6 g.) in methanol (100 ml.) was refluxed for 20 min., acidified with acetic acid (2·5 ml.), concentrated to half bulk, and treated with water (150 ml.). Purification of the crystalline product from aqueous methanol gave the triol derivative in needles, m. p. 219—220° (decomp.), $[\alpha]_D^{19}$ −147° (*c* 1·1) (Found: C, 64·6; H, 8·7; N, 6·7. Calc. for $C_{25}H_{40}N_2O_5$: C, 66·9; H, 9·0; N, 6·25%). Despite intensive drying of this compound, satisfactory analyses could not be obtained.

6-*Methyl*-3β,16α,17α-*trihydroxypregn*-5-*en*-20-*one* (VI; R = R″ = H, R′ = Me). The foregoing hydrazone (4·8 g.) in acetic acid (20 ml.) and 50% aqueous pyruvic acid (8 ml.) was heated at 100° for 15 min. After addition of water (50 ml.), the product was collected and crystallised from aqueous ethanol. The *triol* separated in needles, m. p. 213—215°, $[\alpha]_D^{25}$ −65° (*c* 1·0) (Found: C, 73·1; H, 9·4. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·45%).

Acetylation in pyridine gave the 3β,16α-diacetate, m. p. and mixed m. p. 170°.

3β-*Hydroxy*-16α,17α-*isopropylidenedioxy*-6-*methylpregn*-5-*en*-20-*one* (VII; R = H, R′ = Me).—(*a*) A solution of 16α-acetoxy-3β,17α-dihydroxy-6-methylpregn-5-en-20-one (2·5 g.) in acetone (40 ml.) and methanol (10 ml.) was treated with 60% aqueous perchloric acid (2 ml.), and the mixture kept for 18 hr. The crystals which had separated had m. p. 216—217°, raised to 232° by purification from chloroform–methanol. No depression of m. p. was obtained in admixture with a specimen of the isopropylidene derivative prepared as described above.

(*b*) A solution of 3β,16α,17α-trihydroxy-6-methylpregn-5-en-20-one (3·4 g.) in boiling acetone (70 ml.) was treated with 72% perchloric acid (3 drops). The crystals which separated were purified from chloroform–methanol to give needles, m. p. 232—233°, not depressed in admixture with specimens prepared by other methods (above).

6β-*Ethyl*-5α-*hydroxy*-16α,17α-*isopropylidenedioxy*-5α-*pregnane*-3,20-*dione*. — 3β-Acetoxy-5α,6α-epoxy-16α,17α-isopropylidenedioxy-5α-pregnan-20-one (43 g.) in benzene (1·7 l.) was added to a Grignard reagent prepared from magnesium (36 g.), ethyl iodide (136 ml.), and ether (600 ml.). The mixture was distilled until the vapour-temperature reached 70°, then refluxing was continued for 5 hr. The product, isolated in the usual way, was obtained as a gum. It (24 g.) in benzene (300 ml.) was shaken for 3 hr. with chromium trioxide (9 g.) in acetic acid (240 ml.) and water (60 ml.). The organic phase was washed with dilute alkali and then water, and dried and the solvent was removed. Trituration of the residue with ether–hexane gave a *ketone* which crystallised from aqueous ethanol in plates, m. p. 268—270° (decomp.), $[\alpha]_D^{23}$ +29° (*c* 1·1) (Found: C, 72·3; H, 9·4. $C_{26}H_{40}O_5$ requires C, 72·2; H, 9·3%).

6α-*Ethyl*-16α,17α-*isopropylidenedioxypregn*-4-*ene*-3,20-*dione*.—The foregoing compound (1 g.) was heated under reflux for 3 hr. with potassium hydroxide (9 mg.) in ethanol (70 ml.). The crystals obtained by the addition of water were purified from aqueous ethanol to give the 6α-*ethyl compound*, needles, m. p. 158°, $\nu_{max.}$ (in Nujol) 1680 and 1610 cm.$^{-1}$ (Δ^4-3-ketone) (Found: C, 75·15; H, 9·6. $C_{26}H_{38}O_4$ requires C, 75·3; H, 9·2%).

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