481. *Modified Steroid Hormones. Part XIV.** 17α-*Acetoxy*-16-*methylenepregn*-4-*ene*-3,20-*dione*.

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Reaction of the 16α,17α-epoxy-16β-methylpregnan-20-one system (cf. I) with hydrobromic acid followed by Raney nickel, or with sulphuric acid in aqueous dioxan, leads to a 17α-hydroxy-16-methylenepregnan-20-one (cf. II). By utilising these reactions, 3β-acetoxy-16α,17α-epoxy-16β-methylpregn-5-en-20-one (I; R = Ac) has been converted by alternative routes into the compound named in the title.

Although 16α-methylation of progesterone leads to a decrease in progestational activity,[1] it nevertheless seemed worth while to examine the effect of this structural alteration upon the biological activity of the orally active progestational agent 17α-acetoxyprogesterone. Methods for the preparation of 17α-hydroxy-16-methylpregnan-20-ones were not available at the time this work was initiated. Attention was therefore directed to an extension of the standard Julian procedure to appropriate 16-methylpregn-16-en-20-ones.

Reaction of 3β-acetoxy-16-methylpregna-5,16-dien-20-one with alkaline hydrogen peroxide led to 16α,17α-epoxy-3β-hydroxy-16β-methylpregn-5-en-20-one (I; R = H) in excellent yield. The last compound was acetylated and the acetate treated with 50% hydrogen bromide in acetic acid. In accordance with the normal practice the total product so obtained was treated without purification with Raney nickel to give a crystalline material, conveniently referred to at this stage as product X.

Initially the constitution of a 3β-acetoxy-17α-hydroxy-16ξ-methylpregn-5-en-20-one was assigned to product X on the basis of its mode of formation and its infrared absorption spectrum, which clearly revealed the presence of a 17-hydroxypregnan-20-one moiety. It was reasoned, however, that a definite orientation could not be assigned to the 16-methyl group believed to be present in this product, as information was not available at the time on the behaviour of the 16β-bromo-16α-methyl system on reduction by Raney nickel. Attempts were made to define the stereochemistry about $C_{(16)}$ by degradation of product X to a 3β-hydroxy-16-methylandrost-5-en-17-one employing reduction of the 20-oxo-group with lithium aluminium hydride or sodium borohydride,† followed by periodate oxidation. These numerous experiments unexpectedly proved abortive. Product X passed normally into a 17α-acetoxy-3-oxo-Δ^4-derivative which showed marked progestational activity on oral administration.

After the above experiments attention was directed to the preparation of 3β-acetoxy-16,17α-dihydroxy-16-methylpregn-5-en-20-ones by (i) osmic acid oxidation of the appropriate 16-methylpregn-16-en-20-one, and (ii) hydrolysis of 3β-acetoxy-16α,17α-epoxy-16-methylpregn-5-en-20-one with sulphuric acid in aqueous dioxan. Method (i) proved discouraging. Method (ii), in contrast, furnished material which surprisingly proved to be identical with product X.

The formation of product X by the above two routes is clearly incompatible with its original formulation as a 3β-acetoxy-17α-hydroxy-16ξ-methylpregn-5-en-20-one. Its constitution as 3β-acetoxy-17α-hydroxy-16-methylenepregn-5-en-20-one (II; R = Ac, R′ = H) is established by (i) its conversion into the known 3β-acetoxy-16-methyleneandrost-5-en-17-one (IV) (reduction with lithium borohydride in anhydrous tetrahydrofuran to the corresponding 17,20-diol, followed by cleavage of the glycol group with periodic acid), and (ii) by formation of formaldehyde (isolated as its dimedone derivative) when product X was treated with peracetic acid and the resulting epoxy-derivative oxidised with periodic acid. In addition, the infrared spectrum of 3β,17α-dihydroxy-16-methylenepregn-5-en-20-one (II; R = R′ = H; derived from product X by alkaline

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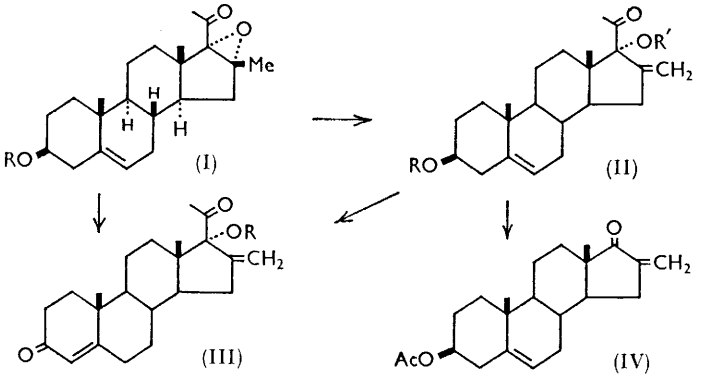
† Lithium borohydride (see below) was not available at the time.

[1] Unpublished work.

hydrolysis) showed strong bands at 1659 and 892 cm.$^{-1}$, characteristic of an exocyclic methylene group.[2] The infrared spectrum of product X in the region of 890—905 cm.$^{-1}$ was ambiguous, and did not permit certain identification of the methylene band, probably owing to interference from the 3β-acetoxy-Δ^5-system which absorbs in the region 902—905 cm.$^{-1}$.[3]



The residues from the purification of product X afforded a small quantity of an isomeric compound which we tentatively formulate as the Δ^{15}-16-methyl isomer. Its infrared spectrum did not show an absorption maximum near 1660 cm.$^{-1}$, and differed appreciably from that of product X in the " fingerprint " region. Treatment with 100% formic acid at room temperature transformed it into the 16-methylene isomer (II; R = Ac, R′ = H), identified by its infrared spectrum. Examination of molecular models indicates that ring D is greatly strained by the presence of two trigonal carbon atoms in the Δ^{15}-isomer, but relatively unstrained in the 16-methylene isomer where only one trigonal carbon atom is present in the ring.

Forced acetylation of 3β-acetoxy-17α-hydroxy-16-methylenepregn-5-en-20-one (II; R = Ac, R′ = H) gave the 3,17-diacetate (II; R = R′ = Ac). The constitution of this compound was established by its alkaline hydrolysis to 3β,17α-dihydroxy-16-methylenepregn-5-en-20-one (II; R = R′ = H), which gave the original 3-acetate on mild acetylation. This reveals the stability of the 17α-hydroxy-16-methylenepregnan-20-one system to enforced acylation. Acid hydrolysis of the 3,17-diacetate (II; R = R′ = Ac) gave 17α-acetoxy-3β-hydroxy-16-methylenepregn-5-en-20-one (II; R = H, R′ = Ac), converted by the Oppenauer method into 17α-acetoxy-16-methylenepregn-4-ene-3,20-dione (III; R = Ac). The last compound was additionally obtained by Oppenauer oxidation of the epoxide (I; R = H) to 16α,17α-epoxy-16-methylpregn-4-ene-3,20-dione, reaction with hydrobromic acid and Raney nickel to 17α-hydroxy-16-methylenepregn-4-ene-3,20-dione (III; R = H), and finally enforced acetylation.

Experimental

Rotations were determined in a 1 dm. tube. Ultraviolet and infrared absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc.

16,17α-Epoxy-3β-hydroxy-16β-methylpregn-5-en-20-one (I; R = H).—To 3β-acetoxy-16-methylpregna-5,16-dien-20-one (60 g.) in ethanol (600 ml.) heated under reflux, aqueous 40% sodium hydroxide (30 ml.) was added, followed dropwise by hydrogen peroxide (100-vol.; 120 ml.). The mixture was heated under reflux for 20 min., then allowed to cool, and the resultant solids were collected and purified from acetone–hexane, to give *16,17α-epoxy-3β-hydroxy-16β-methylpregn-5-en-20-one* as prisms, m. p. 189—191°, $[\alpha]_D^{23}$ −16° (*c* 0·64 in $CHCl_3$) (Found: C, 76·5; H, 9·6. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%).

3β-Acetoxy-16,17α-epoxy-16β-methylpregn-5-en-20-one (I; R = Ac) separated from methanol

[2] Sondheimer and Mechoulam, *J. Amer. Chem. Soc.*, 1957, **79**, 5029.
[3] Jones and Herling, *J. Amer. Chem. Soc.*, 1956, **78**, 1152.

in blades, m. p. 179—181°, $[\alpha]_D^{23}$ −17° (*c* 0·78 in $CHCl_3$) (Found: C, 74·2; H, 8·8. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

3β-*Acetoxy*-17α-*hydroxy*-16-*methylenepregn*-5-*en*-20-*one* (II; R = Ac, R′ = H).—(*a*) The epoxide (I; R = Ac) (63 g.), dissolved in glacial acetic acid (1 l.) and benzene (1 l.), was treated at 0° with 50% hydrogen bromide in acetic acid (100 ml.), with stirring for 30 min. An equal volume of water was added and the benzene layer was separated, washed until neutral, dried, and evaporated under reduced pressure. The crude product (67 g.) in acetone (2 l.) was stirred with Raney nickel (300 ml. of acetone suspension) to remove bromine at room temperature for 4 hr. Crystallisation from methanol gave 3β-*acetoxy*-17α-*hydroxy*-16-*methylenepregn*-5-*en*-20-*one* as blades, m. p. 204—206°, $[\alpha]_D^{24}$ −143° (*c* 0·70 in $CHCl_3$) (Found: C, 74·5; H, 9·1. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

The residues from the preparation of the 16-methylene compound were repeatedly crystallised from methanol, and afforded a small quantity of a compound believed to be 3β-*acetoxy*-17α-*hydroxy*-16-*methylpregna*-5,15-*dien*-20-*one*, which formed flakes, m. p. 180—182°, $[\alpha]_D^{24}$ −126° (*c* 0·36 in $CHCl_3$) (Found: C, 74·5; H, 9·1. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

A sample of the foregoing compound was dissolved in pure formic acid and kept at room temperature for 3 hr. After precipitation in water and drying *in vacuo* at 50°, the product gave an infrared spectrum identical with that of the 16-methylene isomer (II; R = Ac, R′ = H).

(*b*) 3β-Acetoxy-16,17α-epoxy-16β-methylpregn-5-en-20-one (I; R = Ac) (5 g.) was dissolved in dioxan (50 ml.) containing concentrated sulphuric acid (0·5 ml.). After 24 hr. at room temperature the mixture was poured into water, and the solid was collected. Crystallisation from methanol gave 3β-acetoxy-17α-hydroxy-16-methylpregn-5-en-20-one, m. p. 204—206° not depressed on admixture with a sample prepared as described in (*a*).

3β-*Acetoxy*-16-*methyleneandrost*-5-*en*-17-*one* (IV).—3β-Acetoxy-17α-hydroxy-16-methylenepregn-5-en-20-one (II; R = Ac, R′ = H) (2 g.) and lithium borohydride (0·25 g.) suspended at 0° in anhydrous tetrahydrofuran (50 ml.) were stirred for 2 hr. The mixture was poured into water, and the precipitated 17,20-diol (no C=O band in the infrared spectrum) was dried. It was dissolved in ethanol (50 ml.) and treated with 50% periodic acid (5 ml.) in water (20 ml.) at room temperature overnight. An aqueous solution of sodium metabisulphite was added until the iodine colour was discharged and the product was precipitated. The solids were collected and crystallised from methanol, to give 3β-acetoxy-16-methyleneandrost-5-en-17-one, needles, m. p. 163—165°, $[\alpha]_D^{27}$ −60° (*c* 0·48 in $CHCl_3$), $\lambda_{max.}$ (in EtOH) 228 mμ (log ε 3·92) {lit.,[4] m. p. 160—165°, $[\alpha]_D^{27}$ −57·5° (in $CHCl_3$), $\lambda_{max.}$ (in EtOH) 228 mμ (log ε 3·9)}.

Degradation of 3β-*Acetoxy*-17α-*hydroxy*-16-*methylenepregn*-5-*en*-20-*one to give Formaldehyde.*—Peracetic acid (10 ml.; 40% solution in acetic acid) was added dropwise to the 16-methylene-compound (II; R = Ac, R′ = H) (4 g.) and potassium acetate (0·5 g.) in chloroform (100 ml.), with stirring in 15 min. Stirring was continued for 3 hr. and the mixture was left at room temperature for 60 hr. The residue left after washing and evaporation crystallised from methanol, to give the epoxy-derivative (m. p. 178—180°) which (1 g.), without purification, was dissolved in ethanol (100 ml.) and treated with periodic acid (2 ml. of 50% solution) in water (8 ml.) at room temperature for 3 hr. Sulphuric acid (0·5 ml.) was added to the mixture which was then steam-distilled. The distillate was mixed with aqueous dimedone, and the ethanol was evaporated. The dimedone derivative of formaldehyde crystallised in needles, m. p. and mixed m. p. 187—189°.

3β-*Acetoxy*-20,20-*ethylenedioxy*-16-*methylenepregn*-5-*en*-17α-*ol*.—A solution of the 20-ketone (II; R = Ac, R′ = H) (5 g.) in benzene (200 ml.) and ethylene glycol (10 ml.) was distilled until traces of moisture had been removed. Toluene-*p*-sulphonic acid monohydrate (0·5 g.) was then added and the mixture stirred under reflux for 5 hr., the water formed being continuously removed in a Dean–Stark separator. The mixture was cooled, aqueous sodium carbonate added, and the product isolated with ether. Evaporation of the ethereal extract and crystallisation from methanol (containing a trace of pyridine) gave 3β-*acetoxy*-20,20-*ethylenedioxy*-16-*methylenepregn*-5-*en*-17α-*ol* as needles, m. p. 183—184°, $[\alpha]_D$ −101° (*c* 0·33 in $CHCl_3$ containing 1 drop of pyridine) (Found: C, 72·1; H, 9·1. $C_{26}H_{38}O_6$ requires C, 72·5; H, 8·9%).

16,17α-*Epoxy*-16β-*methylpregn*-4-*ene*-3,20-*dione*.—Aluminium isopropoxide (0·75 g.) and 16,17α-epoxy-3β-hydroxy-16β-methylpregn-5-en-20-one (I; R = H) (1·5 g.) in dry toluene (75 ml.) and dry ethyl methyl ketone (10 ml.) were heated under reflux for 2½ hr. Recrystallisation of the product from hexane gave 16,17α-*epoxy*-16β-*methylpregn*-4-*ene*-3,20-*dione*,

[4] Julian, Meyer, and Printy, *J. Amer. Chem. Soc.*, 1948, **70**, 3872.

needles, m. p. 161—162°, $[\alpha]_D^{24}$ +150° (*c* 0·76 in $CHCl_3$), $\lambda_{max.}$ 239 mμ (log ε 4·21) (Found: C, 77·6; H, 8·7. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·8%).

17α-*Hydroxy*-16-*methylenepregn*-4-*ene*-3,20-*dione* (III; R = H).—16,17α-Epoxy-16β-methylpregn-5-ene-3,20-dione (4 g.) in acetic acid (250 ml.) and benzene (100 ml.) was cooled to 0°, and 50% hydrogen bromide in acetic acid (6 ml.) added with stirring which was continued for a further 30 min. The crude product (4·5 g.) in acetone (200 ml.) was stirred with Raney nickel (10 ml. of aqueous suspension) at room temperature for 4 hr. to remove bromine. Crystallisation of the product from methanol gave 17α-*hydroxy*-16-*methylenepregn*-4-*ene*-3,20-*dione*, needles, m. p. 208—210°, $[\alpha]_D^{22}$ −9° (*c* 0·73 in $CHCl_3$), $\lambda_{max.}$ (in EtOH) 239·5 mμ (log ε 4·24), $\nu_{max.}$ (in Nujol) 3596, 3488, 1707, 1684, 1660, 1605 cm.$^{-1}$ (Found: C, 77·3; H, 8·6. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·8%).

17α-*Acetoxy*-16-*methylenepregn*-4-*ene*-3,20-*dione* (III; R = Ac).—(*a*) The foregoing 17-hydroxy-compound (III; R = H) (1 g.) was dissolved in acetic anhydride (25 ml.) and acetic acid (50 ml.), toluene-*p*-sulphonic acid monohydrate (0·5 g.) was added, and the mixture was set aside overnight at room temperature. Water was added and the product isolated with ether. It was dissolved in methanol (50 ml.) containing concentrated hydrochloric acid (1 ml.). After 3 hr. at room temperature water was added and the product isolated with ether. 17α-*Acetoxy*-16-*methylenepregn*-4-*ene*-3,20-*dione* formed needles, m. p. 222—224°, $[\alpha]_D^{23}$ −68° (*c* 0·19 in $CHCl_3$), $\lambda_{max.}$ (in EtOH) 239 mμ (log ε 4·25), $\nu_{max.}$ (in Nujol) 1738, 1715, 1666, 1615 cm.$^{-1}$ (Found: C, 74·5; H, 8·9. $C_{24}H_{32}O_4$ requires C, 74·9; H, 8·4%), after crystallisation from acetone–hexane.

(*b*) 17α-Acetoxy-3β-hydroxy-16-methylenepregn-5-en-20-one (II; R = H, R′ = Ac) (5 g.) in dry cyclohexanone (60 ml.) was added to aluminium t-butoxide (5 g.) in dry toluene (40 ml.) and the whole heated under reflux for 45 min. Crystallisation of the product from acetone–hexane gave 17α-acetoxy-16-methylenepregn-4-ene-3,20-dione, needles, m. p. 222—224°, not depressed on admixture with a sample prepared as in (*a*).

3β,17α-*Diacetoxy*-16-*methylenepregn*-5-*en*-20-*one* (II; R = R′ = Ac).—3β-Acetoxy-17α-hydroxy-16-methylenepregn-5-en-20-one (II; R = Ac, R′ = H) (10 g.) and toluene-*p*-sulphonic acid monohydrate (1·5 g.) were suspended in acetic anhydride (200 ml.) and stirred for 24 hr. at room temperature. Water (500 ml.) was added dropwise to the stirred and cooled mixture, and the product which crystallised was collected, washed with water, and crystallised from methanol, to give 3β,17α-*diacetoxy*-16-*methylenepregn*-5-*en*-20-*one* (II; R = R′ = Ac), needles, m. p. 144—146°, $[\alpha]_D^{25}$ −157° (*c* 0·29 in $CHCl_3$) (Found: C, 72·9; H, 8·6. $C_{26}H_{36}O_5$ requires C, 72·8; H, 8·4%).

17α-*Acetoxy*-3β-*hydroxy*-16-*methylenepregn*-5-*en*-20-*one* (II; R = H, R′ = Ac).—The above diacetate (II; R = R′ = Ac) (5 g.) was heated under reflux for 1 hr. with methanol (100 ml.) containing concentrated hydrochloric acid (0·5 ml.). The mixture was poured into water (300 ml.), and the precipitated solid collected and crystallised from methanol, to yield 17α-*acetoxy*-3β-*hydroxy*-16-*methylenepregn*-5-*en*-20-*one* (II; R = H, R′ = Ac), needles, m. p. 168—170°, $[\alpha]_D^{27}$ −167° (*c* 0·43 in $CHCl_3$) (Found: C, 74·8; H, 8·7. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·8%).

3β,17α-*Dihydroxy*-16-*methylenepregn*-5-*en*-20-*one* (II; R = R′ = H).—(*a*) 3β,17α-Diacetoxy-16-methylenepregn-5-en-20-one (1·65 g.) in methanol (50 ml.) was heated in nitrogen under reflux while potassium hydroxide (0·58 g.) in water (1 ml.), and methanol (7 ml.) was added dropwise during 20 min. Heating was continued for a further 90 min. The mixture was cooled to room temperature, made acid with acetic acid, and poured into water (200 ml.). The precipitated solids were collected, dried, and crystallised from methanol–chloroform, to give 3β,17α-*dihydroxy*-16-*methylenepregn*-5-*en*-20-*one*, needles, m. p. 252—254°, $[\alpha]_D^{22}$ −155° (*c* 0·375 in $CHCl_3$), $\nu_{max.}$ (in Nujol) 3320, 1691, 1659, and 892 cm.$^{-1}$ (Found: C, 76·7; H, 9·5. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%).

(*b*) 3β-Hydroxy-16,17α-epoxy-16β-methylpregn-5-en-20-one (I; R = H) was treated with hydrogen bromide, followed by Raney nickel (see above), and crystallisation of the product from acetone gave 3β-17α-dihydroxy-16-methylenepregn-5-en-20-one, m. p. 251—253°, alone or in admixture with a sample prepared as described under (*a*).

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