550. *Modified Steroid Hormones. Part XXII.*[1] 6α,16α-*Dimethylprogesterone and* 17α-*Acetoxy*-6α-*methyl*-16-*methyleneprogesterone.*

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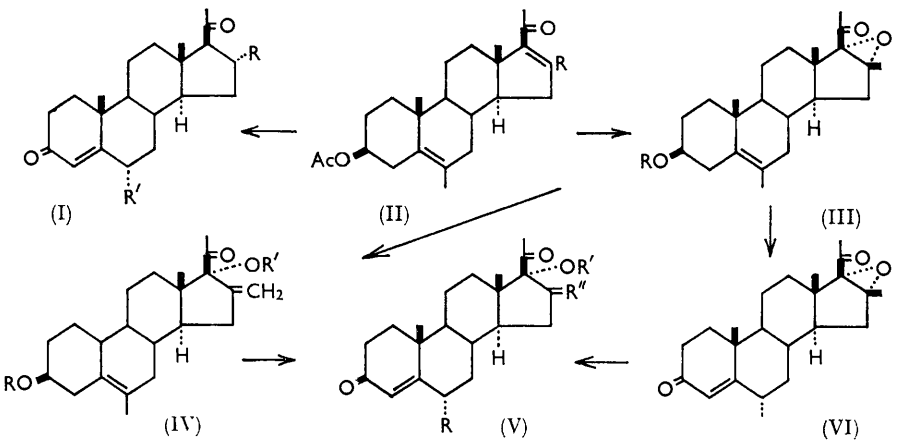
The preparation of the two compounds named in the title, from 3β-acetoxy-6-methylpregna-5,16-dien-20-one (II; R = H), is described.

6-Methylation of progesterone (I; R = R′ = H) and 17α-acetoxyprogesterone (V; R = H, R′ = Ac, R″ = H_2) leads to enhancement of progestational activity. The introduction of a 16-methylene group into the last compound is likewise accompanied by increase in biological potency. The preparation of the 6,16-disubstituted derivatives of progesterone and 17α-acetoxyprogesterone was consequently deemed to be of interest.

6α,16α-Dimethylprogesterone (I; R = R′ = Me) was obtained by using the readily available 3β-acetoxy-6-methylpregna-5,16-dien-20-one (II; R = H) as starting material. Reaction of this acetoxy-ketone with methylmagnesium iodide gave 3β-hydroxy-6,16α-dimethylpregn-5-en-20-one, mixed with 6-methylbisnorchola-5,16-diene-3,20-diol, from which it was separated by means of its ether-insoluble semicarbazone. Oppenauer oxidation then furnished the diketone (I; R = R′ = Me).



3β-Acetoxy-6-methylpregna-5,16-dien-20-one (II; R = H) condensed with diazomethane, to give 3β-acetoxy-6-methylpyrazolino(3′,4′-17α,16α)pregn-5-en-20-one. Pyrolysis of the last compound furnished 3β-acetoxy-6,16-dimethylpregna-5,16-dien-20-one (II; R = Me), which was oxidised by alkaline hydrogen peroxide to 16α,17α-epoxy-3β-hydroxy-6,16β-dimethylpregn-5-en-20-one (III; R = H). Oppenauer oxidation gave 16α,17α-epoxy-6α,16β-dimethylpregn-4-ene-3,20-dione (VI).

[1] Part XXI, *J.*, 1961, 2091.

Earlier work [2] in this laboratory had established the conversion of 16α,17α-epoxy-16β-methylpregnan-20-ones into 17α-hydroxy-16-methylenepregnan-20-ones under the influence of hydrogen ions. In accordance therewith, reaction of our product (VI) with a catalytic quantity of sulphuric acid in dioxan furnished 17α-hydroxy-6α-methyl-16-methylenepregn-4-ene-3,20-dione (V; R = Me, R′ = H, R″ = CH_2). Forced acetylation gave 3,17α-diacetoxy-6-methyl-16-methylenepregna-3,5-dien-20-one, which was converted into the required 17α-acetoxy-6α-methyl-16-methylenepregn-4-en-3-one (V; R = Me, R′ = Ac, R″ = CH_2) by cautious alkaline hydrolysis.

In examining an alternative route to the last compound, the 3-hydroxy-derivative (III; R = H) was acetylated and the product treated with an excess of hydrogen bromide in acetic acid. The product, however, proved to be 3β-acetoxy-6,16-dimethylpregna-5,14,16-trien-20-one in place of the required 3β-acetoxy-17α-hydroxy-6-methyl-16-methylenepregn-5-en-20-one (IV; R = Ac, R′ = H). The latter was obtained, however, by treating the acetylated epoxide (III; R = Ac) with a molar equivalent of a 50% w/v solution of hydrogen bromide in acetic acid–dioxan or with a catalytic quantity of sulphuric acid in tetrahydrofuran. Forced acetylation of the 17α-hydroxy-derivative (IV; R = Ac, R′ = H) with acetic anhydride and toluene-*p*-sulphonic acid in acetic acid gave a *ca.* 1 : 1 mixture of 3β,17α-diacetoxy-6-methyl-16-methylenepregn-5-en-20-one (IV; R = R′ = Ac) and 3β-acetoxy-6,16-dimethylpregna-5,14,16-trien-20-one. By omitting acetic acid from the acetylation mixture, however, the pure diacetate (IV; R = R′ = Ac) could be obtained in excellent yield. Its partial hydrolysis with methanolic hydrochloric acid furnished the 3-hydroxy-derivative (IV; R = H, R′ = Ac), which was converted into the required ketone (V; R = Me, R′ = Ac, R″ = CH_2) by Oppenauer oxidation .

Experimental

Rotations were determined in a 1 dm. tube for $CHCl_3$ solutions unless otherwise stated. Ultraviolet absorption spectra (of EtOH solutions) were kindly determined by Mr. M. T. Davies, B.Sc. Alumina (B.D.H. chromatography grade) was used throughout.

3β-*Acetoxy*-6-*methylpyrazolino*(3′,4′-17α,16α)*pregn*-5-*en*-20-*one*.—3β-Acetoxy-6-methylpregna-5,16-dien-20-one (20 g.) was treated with an ethereal solution of diazomethane prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (30 g.). After 18 hr. at room temperature, the ether and excess of diazomethane were distilled off and the residue crystallised from methanol, to give the *pyrazoline* as plates, m. p. 156—158° (decomp.), $[\alpha]_D^{24}$ +7° (*c* 0·44) (Found: C, 72·6; H, 8·8; N, 6·9. $C_{25}H_{36}N_2O_3$ requires C, 72·7; H, 8·8; N, 6·8%).

3β-*Acetoxy*-6,16-*dimethylpregna*-5,16-*dien*-20-*one* (II; R = Me).—The foregoing pyrazoline (20 g.) was heated in dibutyl ether (200 ml.) under reflux for 3 hr. The butyl ether was removed under reduced pressure and the residue crystallised from methanol, to give 3β-*acetoxy*-6,16-*dimethylpregna*-5,16-*dien*-20-*one*, plates, m. p. 158—160°, $[\alpha]_D^{23}$ −99° (*c* 0·65), $\lambda_{max.}$ 251 mμ (log ε 3·94) (Found: C, 77·8; H, 9·4. $C_{25}H_{36}O_3$ requires C, 78·1; H, 9·4%).

3β-*Hydroxy*-6,16β-*dimethyl*-16α,17α-*epoxypregn*-5-*en*-20-*one* (III; R = H).—To a solution of the foregoing diene (5 g.) in boiling ethanol (50 ml.) containing 40% aqueous sodium hydroxide (2·5 ml.), 30% hydrogen peroxide (10 ml.) was added dropwise. Heating was continued for a further 30 min. The crystalline product was collected and purified from methanol, to give 3β-*hydroxy*-6,16β-*dimethyl*-16α,17α-*epoxypregn*-5-*en*-20-*one* (III; R = H), m. p. 161—162°, $[\alpha]_D^{22}$ −17° (*c* 0·94) (Found: C, 75·4; H, 10·0. $C_{23}H_{34}O_3,\frac{1}{2}H_2O$ requires C, 75·2; H, 9·6%).

3β-*Acetoxy*-16α,17α-*epoxy*-6,16β-*dimethylpregn*-5-*en*-20-*one* (III; R = Ac), needles (from methanol), m. p. 118—120°, $[\alpha]_D$ −49° (*c* 0·35), was prepared by acetylation with acetic anhydride–pyridine at 100° for 1 hr. (Found: C, 75·1; H, 9·0. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·0%).

16α,17α-*Epoxy*-6α,16β-*dimethylpregn*-4-*ene*-3,20-*dione* (VI).—16α,17α-Epoxy-3β-hydroxy-6,16β-dimethylpregn-5-en-20-one (5 g.) was dissolved in cyclohexanone (60 ml.) and the solution distilled until 10 ml. of distillate had been collected. Aluminium t-butoxide (5 g.) in dry toluene (40 ml.) was added and the mixture was heated under reflux for 45 min. Rochelle salt

[2] Kirk, Petrow, Stansfield, and Williamson, *J.*, 1960, 2385.

solution was added and the mixture was steam-distilled for 6 hr. The product was isolated with chloroform and crystallised from methanol. 16α,17α-*Epoxy*-6α,16β-*dimethylpregn*-4-*ene*-3,20-*dione* formed needles, m. p. 182—184°, $[\alpha]_D^{22}$ +130° (*c* 0·43), $\lambda_{max.}$ 239 mμ (log ε 4·22) (Found: C, 77·8; H, 9·0. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·0%).

17α-*Hydroxy*-6α-*methyl*-16-*methylenepregn*-4-*ene*-3,20-*dione* (V; R = Me, R′ = H, R″ = CH_2).—(*a*) 16α,17α-Epoxy-6,16β-dimethylpregn-4-ene-3,20-dione (4 g.), dissolved in glacial acetic at 10°, was treated, with stirring, with 4 ml. of a 50% w/v solution of hydrogen bromide in acetic acid. After 15 min. the mixture was poured into water. The product was extracted with ether and crystallised from methanol, to give 17α-*hydroxy*-6α-*methyl*-16-*methylenepregn*-4-*ene*-3,20-*dione*, needles, m. p. 212—214°, $[\alpha]_D^{21}$ −15° (*c*, 0·6), $\lambda_{max.}$ 239·5 mμ (ε 17,638) (Found: C, 77·2; H, 8·7. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·0%).

(*b*) Concentrated sulphuric acid (1 ml.) was added to a solution of 16α,17α-epoxy-6α,16β-dimethylpregn-4-ene-3,20-dione (10 g.) in dioxan (200 ml.). After being kept overnight at room temperature, the mixture was poured into water, and the precipitated solids were collected, washed with water, and crystallised from methanol, to give the preceding diketone, m. p. and mixed m. p. 210—214°.

3,17α-*Diacetoxy*-6-*methyl*-16-*methylenepregna*-3,5-*dien*-20-*one*.—The foregoing compound (V; R = Me, R′ = H, R″ = CH_2) (500 mg.) was dissolved in acetic acid (5 ml.) and acetic anhydride (2·5 ml.) containing toluene-*p*-sulphonic acid monohydrate (0·05 mg.). The mixture was left at room temperature for 24 hr., and then poured into ice and water. The dark brown precipitate was extracted with ether, and the ether extracts were washed with sodium hydrogen carbonate solution and water. The residue obtained by evaporation of the ether extracts was purified from methanol containing a few drops of pyridine. 3,17α-*Diacetoxy*-6-*methyl*-16-*methylenepregna*-3,5-*dien*-20-*one* crystallised in plates, m. p. 148—149°, $[\alpha]_D^{25}$ −237° (*c* 0·8), $\lambda_{max.}$ 244 mμ (ε 18,400) (Found: C, 73·2; H, 8·27. $C_{27}H_{36}O_5$ requires C, 73·5; H, 8·2%).

17α-*Acetoxy*-6α-*methyl*-16-*methylenepregn*-4-*ene*-3,20-*dione* (V; R = Me, R′ = Ac, R″ = CH_2).—The foregoing diacetate (0·5 g.) was dissolved in methanol (100 ml.), and a solution of potassium hydroxide (0·5 g.) in water (2 ml.) and methanol (5 ml.) was added. After 10 min. acetic acid (1 ml.) was poured into the reaction mixture, which was then evaporated under reduced pressure to small volume and poured into water. The precipitated solids were purified from methanol, to give 17α-*acetoxy*-6α-*methyl*-16-*methylenepregn*-4-*ene*-3,20-*dione*, needles, m. p. 206—208°, $[\alpha]_D$ −98° (*c* 0·21), $\lambda_{max.}$ 240 mμ (ε 15,200) (Found: C, 75·0; H, 8·4. $C_{25}H_{34}O_5$ requires C, 75·2; H, 8·5%). An alternative preparation is described below.

3β-*Acetoxy*-6,16-*dimethylpregna*-5,14,16-*trien*-20-*one*.—3β-Acetoxy-16α,17α-epoxy-6,16β-dimethylpregn-5-en-20-one (10 g.) in glacial acetic acid (500 ml.) was treated at 0° with 15 ml. of a 50% w/v solution of hydrogen bromide in acetic acid with stirring. After 30 min. the mixture was poured into water. The precipitated solids were purified from methanol, to give 3β-*acetoxy*-6,16-*dimethylpregna*-5,14,16-*trien*-20-*one*, needles, m. p. 225—227°, $[\alpha]_D^{21}$ +282° (*c* 0·234), $\lambda_{max.}$ 309 mμ (ε 11,650), $\nu_{max.}$ (in CH_2Cl_2) 1729, 1627, 1534 cm.$^{-1}$ (Found: C, 78·4; H, 8·8. $C_{25}H_{36}O_3$ requires C, 78·2; H, 9·3%).

3β-*Acetoxy*-17α-*hydroxy*-6-*methyl*-16-*methylenepregn*-5-*en*-20-*one* (IV; R = Ac, R′ = H).—(*a*) 3β-Acetoxy-16α,17α-epoxy-6,16β-dimethylpregn-5-en-20-one (III; R = Ac) (20 g.) was dissolved in dioxan (200 ml.) and mixed with 10 ml. of a 50% w/v solution of hydrogen bromide in acetic acid. After 10 min. at room temperature, the mixture was poured into water. The product was extracted with ether. Crystallisation from hexane gave 3β-*acetoxy*-17α-*hydroxy*-6-*methyl*-16-*methylenepregn*-5-*en*-20-*one*, needles, m. p. 126—128° and 147—149°, $[\alpha]_D^{24}$ −161° (*c* 0·31) (Found: C, 74·7; H, 9·2. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·0%).

(*b*) Concentrated sulphuric acid (0·5 ml.) was added to a solution of 3β-acetoxy-16α,17α-epoxy-6,16β-dimethylpregn-5-en-20-one (5 g.) in tetrahydrofuran (100 ml.), and the mixture was left overnight at room temperature, then poured into water. The precipitated solids crystallised from hexane, to give 3β-acetoxy-17α-hydroxy-6-methyl-16-methylenepregn-5-en-20-one, m. p. and mixed m. p. 147—149°.

3β,17α-*Diacetoxy*-6-*methyl*-16-*methylenepregn*-5-*en*-20-*one* (IV; R = R′ = Ac).—(*a*) A solution of the 17α-hydroxy-derivative (IV; R = Ac, R′ = H) (5 g.) and toluene-*p*-sulphonic acid monohydrate (0·75 g.) in acetic anhydride (25 ml.) and acetic acid (50 ml.) was left at room temperature overnight and then poured into ice–water. The product was extracted with ether. It crystallised from hexane in two forms which were separated by hand: (i) clusters of yellow plates, m. p. 218—220°, shown by their infrared spectrum and mixed m. p. to be

3β-acetoxy-6,16-dimethylpregna-5,14,16-trien-20-one, and (ii) 3β,17α-*diacetoxy*-6-*methyl*-16-*methylenepregn*-5-*en*-20-*one*, needles, m. p. 166—168°, $[\alpha]_D^{25}$ −178° (*c* 0·88) (Found: C, 73·2; H, 8·75. $C_{21}H_{38}O_5$ requires C, 73·3; H, 8·6%).

(*b*) 3β-Acetoxy-17α-hydroxy-6-methyl-16-methylenepregn-5-en-20-one (IV; R = Ac, R′ = H) (4 g.) and toluene-*p*-sulphonic acid monohydrate (600 mg.) were dissolved in acetic anhydride (40 ml.) and left at room temperature overnight, yielding, from hexane, 3β,17α-diacetoxy-6-methyl-16-methylenepregn-5-en-20-one, m. p. 166—168°, identical with the specimen described above.

17α-*Acetoxy*-3β-*hydroxy*-6-*methyl*-16-*methylenepregn*-5-*en*-20-*one* (IV; R = H, R′ = Ac).—The foregoing diacetate (IV; R = R′ = Ac) (5 g.) was heated under reflux in methanol (150 ml.) containing concentrated hydrochloric acid (3 ml.) for 90 min. The solution was concentrated under reduced pressure and poured into water, and the precipitated solids were collected. Crystallisation from aqueous methanol gave 17α-*acetoxy*-3β-*hydroxy*-6-*methyl*-16-*methylenepregn*-5-*en*-20-*one*, needles, m. p. 163—165°, $[\alpha]_D^{25}$ −165° (*c* 0·33) (Found: C, 74·8; H, 9·1. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·0%).

17α-*Acetoxy*-6α-*methyl*-16-*methylenepregn*-4-*ene*-3,20-*dione* (V; R = Me, R′ = Ac, R″ = CH_2).—17α-Acetoxy-3β-hydroxy-6-methyl-16-methylenepregn-5-en-20-one (IV; 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 mixture was heated under reflux for 45 min. The product was isolated with methylene chloride and purified from methanol, yielding 17α-acetoxy-6α-methyl-16-methylenepregn-4-ene-3,20-dione, needles, m. p. 208—210°, identical with a specimen prepared as described above.

3β-*Hydroxy*-6,16α-*dimethylpregn*-5-*en*-20-*one*.—3β-Acetoxy-6-methylpregn-5-en-20-one (II; R = H) (10 g.) in dry toluene (200 ml.) was added to a solution of methylmagnesium iodide prepared from magnesium (10 g.) and methyl iodide (40 g.) in dry ether (200 ml.). The mixture was heated and stirred and the ether distilled off until the vapour temperature reached 80°, then the mixture was heated under reflux for 8 hr. The Grignard complex was hydrolysed with ammonium chloride solution, and the product was extracted with ether. The residue of 3β-hydroxy-6,16α-dimethylpregn-5-en-20-one and 3β,20-dihydroxy-6-methylbisnorchola-5,16-diene was heated with semicarbazide hydrochloride (10 g.) and sodium acetate (10 g.) in water (50 ml.) and methanol (150 ml.) for 1 hr. and then poured into water. The precipitate was collected, dried, and heated under reflux in ether (1 l.) for 1 hr. The ether-insoluble material, which was the semicarbazone of the required compound, was heated on the steam-bath with pyruvic acid (5 ml.), acetic acid (35 ml.), sodium acetate (6 g.) and water (12 ml.) for 5 hr.; this mixture was then evaporated to dryness *in vacuo* and the residue extracted with ether; the ether extracts were washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated; the residue crystallised from acetone–hexane, to give 3β-hydroxy-6,16α-dimethylpregn-5-en-20-one, m. p. 170—172°, $[\alpha]_D$ −6° (*c* 0·46) (Found: C, 79·9; H, 10·3. Calc. for $C_{23}H_{36}O_2$: C, 80·2; H, 10·5%) (Schneider and Murray [3] give m. p. 170—172°, $[\alpha]_D$ −5°). Acetylation with acetic anhydride–pyridine at 100° for 1 hr. gave 3β-*acetoxy*-6,16α-*dimethylpregn*-5-*en*-20-*one*, m. p. 135—137°, $[\alpha]_D$ −17° (*c* 0·80) (Found: C, 77·6; H, 10·1. $C_{25}H_{38}O_3$ requires C, 77·7; H, 9·8%).

6α,16α-*Dimethylpregn*-4-*ene*-3,20-*dione* (I; R = Me).—3β-Hydroxy-6,16α-dimethylpregn-5-en-20-one (4 g.) was dissolved in dry cyclohexanone (60 ml.), and the solution was distilled until 10 ml. of distillate had been collected. To this solution was added aluminium t-butoxide (4 g.) in dry toluene (32 ml.), and the mixture was heated under reflux for 45 min. The product was extracted with ether and crystallised from aqueous methanol, to give 6α,16α-dimethylpregn-4-ene-3,20-dione, needles, m. p. 120—122°, $\lambda_{max.}$ 241 mμ (ε 16,230), $[\alpha]_D^{23}$ +144° (*c* 1·12) (Found: C, 80·4; H, 10·0. Calc. for $C_{23}H_{34}O_2$: C, 80·6; H, 9·9%) {Graber and Meyers [4] give m. p. 122—126°, $[\alpha]_D$ +144°, $\lambda_{max.}$ 241 mμ (ε 15,450)}.

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[*Received, February 7th*, 1961.]

[3] Schneider and Murray, *Chem. and Ind.*, 1960, 1163.
[4] Graber and Meyers, *Chem. and Ind.*, 1960, 1478.