235. *Modified Steroid Hormones. Part XXVIII.** 17α-*Acetoxy*-4α-*methyl*-5α-*pregn*-1-*ene*-3,20-*dione*.

By Derek Burn and Vladimir Petrow.

The preparations of 17α-acetoxy-4α-methyl-5α-pregn-1-ene-3,20-dione and some related compounds are described.

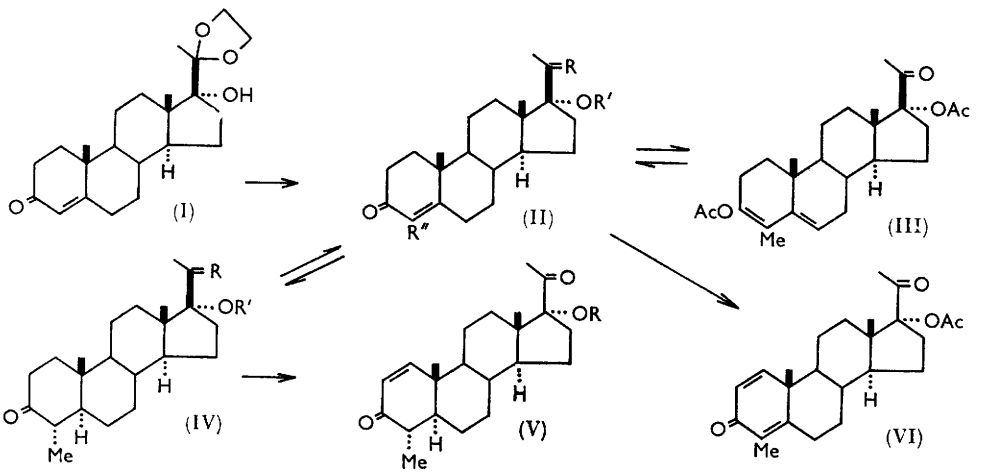
17α-Acetoxy-4α-methyl-5α-pregn-1-ene-3,20-dione (V; R = Ac) has been found [1] to be an orally-active progestational agent in the Clauberg assay. In contrast with other progestational agents such as the isomeric 17α-acetoxy-6α-methylpregn-4-ene-3,20-dione, however, it proved to be inactive as an ovulation inhibitor in the rat. Its preparation is described below.

Reaction of 20,20-ethylenedioxy-17α-hydroxypregn-4-en-3-one (I) [2] with toluene-*p*-thiol and 40% formaldehyde in ethanol in the presence of triethylamine as catalyst,[3]

* Part XXVII, *J.*, 1962, 1091.

[1] Personal communication from Dr. A. David.
[2] Julian, Meyer, and Ryden, *J. Amer. Chem. Soc.*, 1950, **72**, 367.
[3] Kirk and Petrow, *Proc. Chem. Soc.*, 1961, 114.

furnished 20,20-ethylenedioxy-17α-hydroxy-4-*p*-tolylthiomethylpregn-4-en-3-one [II; R = O·CH_2·CH_2·O, R′ = H, R″ = CH_2S·C_6H_4Me-*p*]. Treatment of this product in acetone with deactivated Raney nickel gave 20,20-ethylenedioxy-17α-hydroxy-4-methylpregn-4-ene-3,20-dione (II; R = O·CH_2·CH_2·O, R′ = H, R″ = Me), the structure of which followed from its conversion into the known 17α-acetoxy-4-methylpregn-4-ene-3,20-dione (II; R = O, R′ = Ac, R″ = Me) [4] as follows: deketalisation with aqueous acetic acid, acetylation to 3,17α-diacetoxy-4-methylpregna-3,5-dien-20-one (III), and generation of the 3-oxo-Δ^4-function by partial hydrolysis with methanolic hydrochloric acid.



Reduction of the 20,20-ethylenedioxy-intermediate (II; R = O·CH_2·CH_2·O, R′ = H, R″ = Me) with lithium in liquid ammonia furnished 20,20-ethylenedioxy-17α-hydroxy-4α-methyl-5α-pregnan-3-one (IV; R = O·CH_2·CH_2·O, R′ = H) * which passed into the corresponding 20-ketone (IV; R = O, R′ = H) on treatment with aqueous acetic acid.

Enforced acetylation of the last compound gave 17α-acetoxy-4α-methyl-5α-pregnane-3,20-dione (IV; R = O, R′ = Ac); the failure to form a $C_{(3)}$ enol acetate contrasts with the behaviour of the αβ-unsaturated ketone (II; R = O, R′ = H, R″ = Me) (above). Monobromination of this dione, followed by isolation of the crude 2-bromo-derivative and its immediate dehydrobromination with lithium chloride–carbonate in dimethylformamide furnished the required 17α-acetoxy-4α-methyl-5α-pregn-1-ene-3,20-dione (V; R = Ac). The 17α-octanoyloxy-derivative was also prepared for biological study but proved to be less active than the 17-acetate in the Clauberg assay.[1]

When 17α-acetoxy-4α-methyl-5α-pregnane-3,20-dione (IV; R = O, R′ = H) was monobrominated as above and the crude bromination product set aside at room temperature for several days and then dehydrobrominated as before, the product obtained was identified as 17α-acetoxy-4-methylpregn-4-ene-3,20-dione (II; R = O, R′ = Ac, R″ = Me). It reacted smoothly with 2,3-dichloro-5,6-dicyanobenzoquinone [7] to give 17α-acetoxy-4-methylpregna-1,4-diene-3,20-dione (VI).

Experimental

Optical rotations were determined in a 1 dm. tube for chloroform solutions. Ultraviolet spectra (in ethanol) were kindly determined by Mr. M. T. Davies, B.Sc.

* That lithium and liquid ammonia reduction of a 4-methyl-Δ^4-3-ketone affords the desired 4α-Me,5α-H stereochemistry has been established by Mazur and Sondheimer.[5] The choice of the 20-ketal intermediates was dictated by the instability of α-acetoxy-ketones to this reducing medium.[6]

[4] Camerino, Cattapan, Valcavi, and Patelli, *Gazzetta*, 1959, **89**, 674.
[5] *J. Amer. Chem. Soc.*, 1958, **80**, 5220.
[6] Cf. for example, Chapman, Elks, Phillips, and Wyman, *J.*, 1956, 4344.
[7] Burn, Kirk, and Petrow, *Proc. Chem. Soc.*, 1960, 14.

20,20-*Ethylenedioxy*-17α-*hydroxy*-4-p-*tolylthiomethylpregn*-4-*en*-3-*one*.—A mixture of 20,20-ethylenedioxy-17α-hydroxypregn-4-en-3-one (5 g.), toluene-*p*-thiol (3·5 g.), 40% formaldehyde (5 ml.), triethylamine (6 ml.), and ethanol (10 ml.) was heated at *ca.* 60° for 52 hr. Water was added and the product was extracted with ether. The extract was washed with dilute aqueous sodium hydroxide and water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The 4-p-*tolylthiomethyl compound* (II; R = O·CH_2·CH_2·O, R′ = H, R″ = CH_2·S·C_6H_4·CH_3-*p*) crystallised from dichloromethane–methanol (containing a trace of pyridine) as plates, m. p. 158—159°, $[\alpha]_D^{20}$ +72·7° (*c* 1·2), $\lambda_{max.}$ 227 (ε 11,390) and 254·5 mμ (ε 14,300) (Found: C, 73·15; H, 7·85; S, 6·6. $C_{31}H_{42}O_4S$ requires C, 72·9; H, 8·3; S, 6·3%).

Treatment with aqueous acetic acid at room temperature gave the 20-*ketone* (II; R = O, R′ = H, R″ = CH_2·S·C_6H_4·Me-*p*), laths (from aqueous methanol), m. p. 169—171°, $[\alpha]_D^{17}$ +94·15° (*c* 1·25), $\lambda_{max.}$ 227 (ε 14,510) and 252·5 mμ (ε 17,730) (Found: C, 74·6; H, 8·1; S, 6·9. $C_{29}H_{38}O_3S$ requires C, 74·65; H, 8·2; S, 6·85%).

20,20-*Ethylenedioxy*-17α-*hydroxy*-4-*methylpregn*-4-*en*-3-*one*.—Raney nickel (40 ml. of settled aqueous suspension) was partially deactivated by refluxing it in acetone (200 ml.) for 1·5 hr. The foregoing 4-*p*-tolylthiomethyl ketal (3 g.) was added and refluxing was continued for a further 11 hr. The Raney nickel was removed by filtration and the filter-cake was washed with hot ethanol (1 l.). Concentration of the mother-liquor, followed by dilution with water, afforded a solid product which was crystallised from dichloromethane–methanol (containing a trace of pyridine) to give the 4-*methyl-steroid* (II; R = O·CH_2·CH_2·O, R′ = H, R″ = Me), needles, m. p. 228—230°, $[\alpha]_D^{21}$ +77·2° (*c* 1·55), $\lambda_{max.}$ 250 mμ (ε 14,530) (Found: C, 73·8; H, 9·2. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·35%).

Treatment with aqueous acetic acid at room temperature gave the corresponding 20-*ketone* (II; R = O, R′ = H, R″ = Me), laths (from dichloromethane–methanol), m. p. 239—241°, $[\alpha]_D^{21}$ +98·95 (*c* 0·95), $\lambda_{max.}$ 250 mμ (ε 15,540) (Found: C, 76·1; H, 9·4. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·35%).

17α-*Acetoxy*-4-*methylpregn*-4-*ene*-3,20-*dione*.—(*a*) Treatment of the foregoing 20-ketone with acetic anhydride–acetic acid–toluene-*p*-sulphonic acid at room temperature overnight gave 3,17-*diacetoxy*-4-*methylpregna*-3,5-*dien*-20-*one* (III), needles (from dichloromethane–methanol), m. p. 249—251°, $[\alpha]_D^{15}$ −131·5° (*c* 0·7), $\lambda_{max.}$ 236 mμ (ε 17,470) (Found: C, 72·8; H, 8·5. $C_{26}H_{36}O_5$ requires C, 72·85; H, 8·45%).

(*b*) Treatment of the foregoing enol diacetate with hydrochloric acid in methanol gave 17α-acetoxy-4-methylpregn-4-ene-3,20-dione (II; R = O, R′ = Ac, R″ = Me), flakes (from acetone–hexene), m. p. 174—176°, identical with a sample prepared by 4-methylation of 17α-acetoxyprogesterone.

20,20-*Ethylenedioxy*-17α-*hydroxy*-4α-*methyl*-5α-*pregnan*-3-*one*.—20,20-Ethylenedioxy-17α-hydroxy-4-methylpregn-4-en-3-one (1·8 g.) in dioxan (40 ml.) was added to lithium (0·25 g.) in liquid ammonia (75 ml.), and the mixture stirred for 5 min. Ammonium chloride (10 g.) was added and the ammonia was allowed to evaporate overnight. Dilution of the residue with water gave a solid product which was recrystallised from dichloromethane–methanol (containing a trace of pyridine) to yield the saturated 3-*ketone* (IV; R = O·CH_2·CH_2·O, R′ = H) as felted needles, m. p. 223—225°, $[\alpha]_D^{15}$ −9·55° (*c* 1·0) (Found: C, 73·65; H, 9·8. $C_{24}H_{38}O_4$ requires C, 73·8; H, 9·8%).

Treatment of the last compound with aqueous acetic acid for 8 hr. at room temperature gave 17α-*hydroxy*-4α-*methyl*-5α-*pregnane*-3,20-*dione* (IV; R = O, R′ = H), laths (from dichloromethane–methanol), m. p. 259—267°, $[\alpha]_D^{20}$ −9·9° (*c* 0·9) (Found: C, 76·2; H, 9·85. $C_{22}H_{34}O_3$ requires C, 76·25; H, 9·9%).

Acetylation of the foregoing compound with acetic acid–acetic anhydride in the presence of toluene-*p*-sulphonic acid for 16 hr. at room temperature gave 17α-*acetoxy*-4α-*methyl*-5α-*pregnane*-3,20-*dione* (IV; R = O, R′ = Ac), flakes (from aqueous methanol), m. p. 208—210°, $[\alpha]_D^{19}$ −1·5° (*c* 0·95) (Found: C, 73·65; H, 9·25. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·35%).

17α-*Acetoxy*-4α-*methyl*-5α-*pregn*-1-*ene*-3,20-*dione*.—A solution of bromine (0·45 g., 1·1 mol.) in acetic acid (5 ml.) was added dropwise to a stirred solution of 17α-acetoxy-4α-methyl-5α-pregnane-3,20-dione (1 g.) in acetic acid (30 ml.). After 5 min. water was added and the precipitated bromo-ketone was collected.* It (1·15 g.) was heated at 100° with lithium chloride

* A sample of this crude bromo-ketone which had been kept for *ca.* 1 week was similarly dehydrobrominated. The product obtained after chromatography was largely the Δ^4-3-ketone (II; R = O, R′ = Ac, R″ = Me), m. p. 172—174°, and not the Δ^1-3-ketone (V; R = Ac).

(1·2 g.), lithium carbonate (1·2 g.), and dimethylformamide (12 ml.) for 5 hr., and the mixture poured into water. The precipitate was chromatographed on alumina in benzene solution, and the residue obtained from the benzene eluates was crystallised from aqueous methanol to give the αβ-*unsaturated ketone* (V; R = Ac) as needles, m. p. 177—179°, $[\alpha]_D^{24}$ +18·05° (*c* 1·25), $\lambda_{max.}$ 230 mμ (ε 8350) (Found: C, 74·3; H, 9·0. $C_{24}H_{34}O_4$ requires C, 74·55; H, 8·9%).

4α-*Methyl*-17α-*octanoyloxy*-5α-*pregnane*-3,20-*dione*.—A mixture of 17α-hydroxy-4α-methyl-5α-pregnane-3,20-dione (9·5 g.), octanoic acid (100 ml.), octanoic anhydride (50 ml.), and toluene-*p*-sulphonic acid (1·5 g.) was kept at room temperature for 65 hr., during which time all the steroid dissolved. The solution was poured into pyridine (200 ml.) and steam-distilled. The insoluble residue gave the 17α-*octanoate* [IV; R = O, R′ = CO·$(CH_2)_6$·CH_3] as needles (from hexane), m. p. 131—133°, $[\alpha]_D^{22}$ +4·7° (*c* 0·75) (Found: C, 76·1; H, 10·3. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%).

4α-*Methyl*-17α-*octanoyloxy*-5α-*pregn*-1-*ene*-3,20-*dione*.—A solution of bromine in dioxan (10%, 25 ml.) was added dropwise to a stirred solution of the foregoing octanoate (6·6 g.) in dioxan (65 ml.). The gum obtained by pouring the solution into water was extracted with ether, the extract was washed with dilute aqueous sodium carbonate and water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The gummy residue was then refluxed with collidine (50 ml.) for 2 hr., and collidine hydrobromide was filtered off. The solution was diluted with ether, washed with dilute hydrochloric acid, dilute aqueous sodium carbonate and water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Crystallisation of the residue from hexane and aqueous methanol afforded the αβ-*unsaturated ketone* (V; R = CO·$[CH_2]_6$·CH_3) as needles, m. p. 98—100°, $[\alpha]_D^{21}$ +16° (*c* 0·25), $\lambda_{max.}$ 231 mμ (ε 9200) (Found: C, 76·55; H, 9·65. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%).

17α-*Acetoxy*-4-*methylpregna*-1,4-*diene*-3,20-*dione*.—A mixture of 17α-acetoxy-4-methylpregn-4-ene-3,20-dione (1·2 g.), 2,3-dichloro-5,6-dicyanobenzoquinone (1 g.), and dry dioxan (10 ml.), was heated under reflux for 10 hr. The solution was diluted with ether, washed with dilute aqueous sodium hydroxide and water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Crystallisation of the residue from aqueous methanol gave the *dienedione* (VI) as rods, m. p. 169—171°, $[\alpha]_D^{25}$ +42·25° (*c*, 1·1), $\lambda_{max.}$ 243·5 mμ (ε 11,200) (Found: C, 74·6; H, 8·55. $C_{24}H_{32}O_4$ requires C, 74·95; H, 8·4%).

THE BRITISH DRUG HOUSES LTD.,
GRAHAM STREET, LONDON, N.1.

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