21-*Hydroxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione*.

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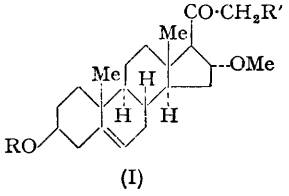
21-Hydroxy-16α-methoxypregn-4-ene-3 : 20-dione (III; R = OH), required for study as a mineralocorticoid antagonist, has been prepared by bromination of 3β-hydroxy-16α-methoxypregn-5-en-20-one (I; R = R′ = H) at $C_{(21)}$, followed by acetolysis, Oppenauer oxidation at $C_{(3)}$ and hydrolysis of the resulting 21-acetoxy-16α-methoxypregn-4-ene-3 : 20-dione (III; R = Ac). 3β : 20-Diacetoxypregna-5 : 15 : 17-triene is prepared from 3β-acetoxypregna-5 : 16-dien-20-one.

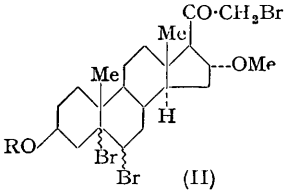
DIRECT conversion of a pregnan-20-one into the 21-bromo-derivative is not generally possible owing to the superior mobility of the tertiary hydrogen atom at $C_{(17)}$. It seemed likely, however, that such bromination might occur in the 16α-methoxypregnan-20-one series in which the (+*I*) methoxyl group introduces a measure of deactivation at $C_{(17)}$. We therefore treated 3β-acetoxy-16α-methoxypregn-5-en-20-one (I; R = Ac; R′ = H) (Fukushima and Gallagher, *J. Amer. Chem. Soc.*, 1951, **73**, 196) in acetic acid first with one and then with a second equivalent of bromine, obtaining thereby a product from which crystalline material consisting essentially of a tribromide was isolated. The constitution of 3β-acetoxy-5 : 6 : 21-tribromo-16α-methoxypregnan-20-one (II; R = Ac) is assigned to this compound since on reaction at room temperature with sodium iodide in benzene–ethanol, followed by acetolysis of the intermediate 3β-acetoxy-21-iodo-16α-methoxypregn-5-en-20-one (I; R = Ac, R′ = I) with potassium acetate in boiling acetone, it was converted into 3β : 21-diacetoxy-16α-methoxypregn-5-en-20-one (I; R = R′ = Ac), also obtained in very low yield by the oxidation of (I; R = Ac, R′ = H) with lead tetra-acetate (cf. Ehrhart, Ruschig, and Anmüller, *Ber.*, 1939, **72**, 2035).

Extension of this reaction to 16α-methoxypregnenolone (I; R = R′ = H) (Gould, Gruen, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 2510) readily gave (III; R = OH) in excellent overall yield. Bromination of (I; R = R′ = H) in *ethereal* solution gave 5 : 6 : 21-tribromo-3β-hydroxy-16α-methoxypregnan-20-one (II; R = H), converted by sodium iodide into the 21-iodide (I; R = H, R′ = I) and thence into the 21-acetate (I; R = H, R′ = OAc) by acetolysis. Oppenauer oxidation of the last compound furnished 21-acetoxy-16α-methoxypregn-4-ene-3 : 20-dione (III; R = OAc), smoothly converted into 21-hydroxy-16α-methoxypregn-4-ene-3 : 20-dione (III; R = OH) by hydrolysis with aqueous methanolic potassium hydrogen carbonate.

Attempted acetolysis of (III; R = OAc) to 16α : 21-diacetoxypregn-4-ene-3 : 20-dione employing acetic anhydride–toluene-*p*-sulphonic acid under the conditions of Huffman and Lott (*J. Biol. Chem.*, 1948, **172**, 789) gave a product which gave correct analyses for the required compound but proved to be the enol acetate of the starting material, as it passed into (III; R = Ac) on mild hydrolysis followed by acetylation. Its formulation as 20 : 21-diacetoxy-16α-methoxypregna-4 : 17(or 4 : 20)-dien-3-one was rendered unlikely by the observation that both (I; R = R′ = Ac) and (I; R = Ac, R′ = H) were recovered unchanged after heating with acetic anhydride–toluene-*p*-sulphonic acid for 30 minutes at 100°. We therefore assign it the alternative constitution 3 : 21-diacetoxy-16α-methoxypregna-3 : 5-dien-20-one (IV; R = Ac) and in support thereof find that cholest-4-en-3-one and 16α-methoxyprogesterone (III; R = H) pass smoothly into the corresponding 3-enol acetates under the same experimental conditions. *Inter alia* we find that prolonged acetolysis of (I; R = Ac, R′ = H) leads to loss of the elements of methanol with formation of a diacetoxypregnatriene, also obtained, together with an isomeric enol acetate, directly from 3β-acetoxypregna-5 : 16-dien-20-one. Conversion of the last compound into 3β : 20-diacetoxypregna-5 : 16 : 20-triene by *iso*propenyl acetate has been described by Moffett and Weisblat (*J. Amer. Chem. Soc.*, 1952, **74**, 2183). This material differs from either of our two products which are therefore regarded as *cis*- and *trans*-isomers (about positions 17 and 20) of 3β : 20-diacetoxypregna-5 : 15 : 17-triene (V), in analogy with the production of isomeric 3β : 20-diacetoxy*allo*pregn-17-enes (Marshall, Kritchevsky, Liebermann, and Gallagher, *ibid.*, 1948, **70**, 1837) and 3β : 20-diacetoxypregna-5 : 17-dienes (Fieser and Huang-Minlon, *ibid.*, 1949, **71**, 1840) from 3β-hydroxy-*allo*pregnan-20-one and -pregn-5-en-3-one, respectively.



(I)



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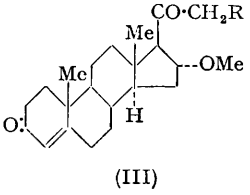

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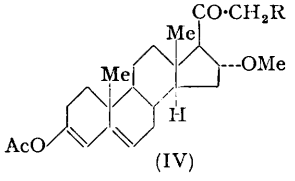

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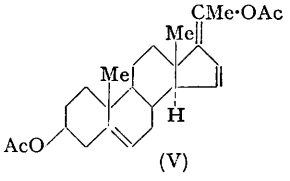

(V)

Experimental

Ultra-violet absorption spectra were determined for *iso*propyl alcoholic solutions by Dr. R. E. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses Ltd. Optical rotation were determined in chloroform solutions in a 2-dm. tube.

3β-Acetoxy-5 : 6 : 21-tribromo-16α-methoxypregnan-20-one (II; R = Ac).—3β-Hydroxy-16α-methoxypregn-5-en-3-one acetate (11 g.) in acetic acid (150 ml.) was treated at room temperature with bromine (4·75 g.) in acetic acid (15 ml.), decolorisation being complete within 1 min. Thereafter, more bromine (4·75 g.) in acetic acid (15 ml.) was added, and when absorption was complete (1·5 hr.) the mixture was poured into water. The solids obtained were

washed, air-dried, and crystallised from chloroform–methanol, giving a product (11·2 g.), m. p. 148—152°. Thrice crystallised from the same solvent mixture, the *tribromo*-compound formed needles, m. p. 159—160° (decomp.), $[\alpha]_D^{20}$ −18·2° (*c*, 2·15) (Found: C, 44·1; H, 5·3. $C_{24}H_{35}O_4Br_3$ requires C, 45·95; H, 5·6%). Although the m. p. of the material remained unchanged on further recrystallisation, the low analytical figure for carbon suggests contamination with a more highly brominated substance.

3β : 21-*Diacetoxy*-16α-*methoxypregn*-5-*en*-20-*one* (I; R = R′ = Ac).—(*a*) The foregoing tribromide (8 g.) in benzene (80 ml.) was treated for 24 hr. at room temperature with sodium iodide (16 g.) in absolute ethanol (100 ml.). After dilution with water, the mixture was extracted with ether, and the extract washed with 3% aqueous sodium thiosulphate, then with water, and dried. The crystalline residue obtained on removal of the solvents *in vacuo* at ≯30° was heated for 12 hr. under reflux in acetone (100 ml.) containing freshly fused potassium acetate (15 g.). Precipitation with water gave a colourless solid (5·2 g.), m. p. 128—130°. Purified from acetone and then from aqueous methanol, 3β : 21-*diacetoxy*-16α-*methoxypregn*-5-*en*-20-*one* formed flat needles, m. p. 140—142°, $[\alpha]_D^{21}$ −20·6° (*c*, 2·25) (Found: C, 69·7; H, 8·7. $C_{26}H_{38}O_6$ requires C, 69·9; H, 8·4%).

In one experiment, the intermediate 3β-*acetoxy*-21-*iodo*-16α-*methoxypregn*-5-*en*-20-*one* was isolated as plates (from ethanol), m. p. 126°, $[\alpha]_D^{24}$ +40·6° (*c*, 0·48) (Found: C, 56·0; H, 6·45; I, 25·1. $C_{24}H_{35}O_4I$ requires C, 56·0; H, 6·85; I, 25·0%).

(*b*) (By Mrs. W. J. Adams.) 3β-Hydroxy-16α-methoxypregn-5-en-20-one acetate (900 mg.) in a saturated solution of lead tetra-acetate in acetic acid (41 ml.) containing a little acetic anhydride was kept for 17 hr. at 75—80°. The product, isolated with ether, was chromatographed on B.D.H. alumina (20 g.), elution with benzene giving unchanged acetate (350 mg.). Further elution with ether and ether–acetone (1 : 1) gave 3β : 21-diacetoxy-16α-methoxypregn-5-en-20-one (50 mg.), needles (from methanol), m. p. 139—140°, not depressed in admixture with a specimen prepared by method (*a*).

5 : 6 : 21-*Tribromo*-3β-*hydroxy*-16α-*methoxypregnan*-20-*one* (II; R = H).—Bromine (9·5 g.) in acetic acid (20 ml.) was added dropwise during 15 min. to a stirred suspension of 3β-hydroxy-16α-methoxypregn-5-en-3-one (10 g.) in ether (500 ml.), absorption being complete after a further 5 min. The solution was washed with water, aqueous sodium hydrogen carbonate, and water, and cooled to 0°. The crystalline product [6·7 g.; m. p. 140° (decomp.)] was removed and the mother-liquor concentrated to give a further quantity [5·5 g.; m. p. 135° (decomp.)] of less pure material. Recrystallised from ethyl acetate–light petroleum the *tribromide* formed prisms, m. p. 140—143° (decomp.), $[\alpha]_D^{22}$ +2·5° (*c*, 0·53) (Found: C, 45·7; H, 5·2. $C_{22}H_{33}O_3Br_3$ requires C, 45·2; H, 5·7%).

21-*Acetoxy*-3β-*hydroxy*-16α-*methoxypregn*-5-*en*-20-*one* (I; R = H, R′ = Ac).—The foregoing tribromide (30 g.), suspended in benzene (300 ml.), was treated for 24 hr. at room temperature with sodium iodide (60 g.) in absolute ethanol (350 ml.). The mixture was diluted with water and extracted with ether, and the extract washed with 3% aqueous sodium thiosulphate and then water. After being dried, the solvents were removed *in vacuo* at ≯30°. The crystalline residue was heated for 18 hr. under reflux in acetone (450 ml.) containing freshly fused potassium acetate (60 g.), and the product (17·2 g., m. p. 160—162°) obtained on the addition of water was purified from aqueous methanol. 21-*Acetoxy*-3β-*hydroxy*-16α-*methoxypregn*-5-*en*-20-*one* separated in flat needles, m. p. 164—166°, $[\alpha]_D^{24}$ −6·2° (*c*, 0·42) (Found: C, 71·0; H, 8·95. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%). Acetylation in pyridine gave 3β : 21-diacetoxy-16α-methoxypregn-5-en-20-one, m. p. and mixed m. p. 140—142°.

21-*Acetoxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione* (III; R = Ac).—A solution of 21-acetoxy-3β-hydroxy-16α-methoxypregn-5-en-20-one (16·7 g.) in toluene (700 ml.) and *cyclo*hexanone (160 ml.) was distilled until 150 ml. of distillate had collected. After the addition of aluminium *iso*propoxide (8 g.) in toluene (35 ml.), the mixture was refluxed for 30 min., cooled somewhat, and treated with acetic acid (4 ml.) in toluene (25 ml.). The solvents were removed by steam-distillation and the solids obtained were collected and air-dried. These were extracted with hot ethyl acetate, and the extract was concentrated and treated with light petroleum to give a crystalline solid (10·2 g.; m. p. 155—156°). Recrystallised from acetone–hexane, 21-*acetoxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione* formed prisms, m. p. 162—163°, $[\alpha]_D^{23}$ +116° (*c*, 0·47) (Found: C, 71·5; H, 8·5. $C_{24}H_{34}O_5$ requires C, 71·6; H, 8·5%). Light absorption: $\lambda_{max.}$ 240 mμ (ε 16,800).

21-*Hydroxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione* (III; R = OH).—The foregoing compound (1 g.) in methanol (100 ml.) was treated for 18 hr. at room temperature with potassium hydrogen carbonate (1 g.) in water (20 ml.). The product, isolated with ether after dilution of the reaction

mixture with brine, crystallised from acetone–hexane, to give 21-*hydroxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione*, needles, m. p. 137—138°, $[\alpha]_D^{20}$ +105° (*c*, 1·2) (Found: C, 73·1; H, 8·6. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·9%). Acetylation in pyridine gave the 21-acetoxy-compound, m. p. and mixed m. p. 162—163°.

3 : 21-*Diacetoxy*-16α-*methoxypregna*-3 : 5-*dien*-20-*one* (IV; R = Ac).—21-Acetoxy-16α-methoxypregn-4-ene-3 : 20-dione (1 g.) and toluene-*p*-sulphonic acid (500 mg.) were heated with acetic anhydride (50 ml.) for 30 min. at 100°. Crystallisation from aqueous methanol gave the *enol acetate* (60%), flat needles, m. p. 132—134·5°, $[\alpha]_D^{20}$ −64·5° (*c*, 1·62) (Found: C, 69·7, 70·4; H, 8·3, 8·0. $C_{26}H_{36}O_6$ requires C, 70·2; H, 8·2%). Light absorption: $\lambda_{max.}$ 235 mμ (ε 19,700).

The enol acetate (450 mg.) was hydrolysed at room temperature with potassium hydrogen carbonate (500 mg.) in aqueous methanol (60 ml. of 80%). After 48 hr., the product was isolated with ether and acetylated in pyridine, to give 21-acetoxy-16α-methoxypregn-4-ene-3 : 20-dione (50 mg.), prisms, m. p. and mixed m. p. 158—162° (from ethyl acetate–light petroleum).

16α-*Methoxyprogesterone*.—3β-Hydroxy-16α-methoxypregn-5-en-3-one (5 g.) and aluminium *iso*propoxide (8 g.) in toluene (120 ml.) and *cyclo*hexanone (40 ml.) were heated under reflux for 40 min. The mixture was washed with dilute sulphuric acid, then with water, and the solvents were removed by steam-distillation. The product on crystallisation from ethyl acetate–light petroleum gave 16α-methoxyprogesterone (70%) in needles, m. p. 131—132°, $[\alpha]_D^{20}$ +102° (Fukushima and Gallagher, *loc. cit.*, give m. p. 134—135·5°, $[\alpha]_D^{22}$ +106°).

3-*Acetoxy*-16α-*methoxypregna*-3 : 5-*dien*-20-*one* (50%), prepared by heating 16α-methoxyprogesterone (800 mg.) and toluene-*p*-sulphonic acid (400 mg.) in acetic anhydride (40 ml.) for 30 min. at 100°, formed plates (from aqueous methanol), m. p. 129—130°, $[\alpha]_D^{22}$ −84° (*c*, 1·1) (Found: C, 74·2; H, 8·8. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

3-Acetoxycholesta-3 : 5-diene (60%), prepared from cholest-4-en-3-one under conditions identical with those cited above, formed needles (from methanol), m. p. 79—80°, $[\alpha]_D^{20}$ −96° (Westphal, *Ber.*, 1937, **70**, 2128, gives m. p. 81°, $[\alpha]_D$ −100·4°).

*Prolonged Action of Acetic Anhydride and Toluene-*p*-sulphonic Acid on* 3β-*Acetoxy*-16α-*methoxypregn*-5-*en*-3-*one*.—A solution of the steroid (4·5 g.) and toluene-*p*-sulphonic acid (2·5 g.) in acetic anhydride (500 ml.) was gently boiled, the solvent being permitted to distil during 7 hr. The residual dark mixture (50 ml.) was treated with water, and the product isolated with ether. Light petroleum (50 ml.; b. p. 40—60°) was added to its solution in ether (50 ml.), a small precipitate of dark amorphous material was removed by filtration, and the filtrate was passed through a column (11 × 3·3 cm.) of acid-washed alumina. Elution with ether–light petroleum (1 : 1) gave a gummy solid (2·1 g.), which, purified from aqueous methanol, gave 3β : 20-*diacetoxypregna*-5 : 15 : 17-*triene* (*isomer A*), flat blades, m. p. 113—114°, $[\alpha]_D^{20}$ −155° (*c*, 1·02) (Found: C, 75·6; H, 8·6. $C_{25}H_{34}O_4$ requires C, 75·35; H, 8·6%). Light absorption: $\lambda_{max.}$ 242 mμ (ε 13,700). Hydrolysis with hot aqueous-methanolic potassium hydrogen carbonate converted it into 3β-hydroxypregna-5 : 16-dien-20-one, m. p. and mixed m. p. 212—214°, also obtained (as acetate) on one occasion when the enol acetate (isomer A) in methanol was warmed briefly with charcoal. The compound appeared to be unstable in the solid state, the m. p. falling to *ca.* 100° after six weeks.

Enol Acetylation of 3β-*Acetoxypregna*-5 : 16-*dien*-20-*one*.—A solution of 3β-acetoxypregna-5 : 16-dien-20-one (6 g.) and toluene-*p*-sulphonic acid (3 g.) in acetic anhydride (600 ml.) was gently boiled, the solvent being permitted to distil during 7 hr. The dark product, isolated with ether, was dissolved in ether–light petroleum (150 ml. of 1 : 1), and the solution filtered through a column (10 × 2·5 cm.) of acid-washed alumina. The yellowish solid (4·3 g.) obtained was fractionated from warm aqueous acetic acid, giving *isomer B* of 3β : 20-*diacetoxypregna*-5 : 15 : 17-*triene* (0·8 g.), long needles (from methanol), m. p. 167—168°, $[\alpha]_D^{22}$ −245° (*c*, 1·31) (Found: C, 75·1; H, 8·6. $C_{25}H_{34}O_4$ requires C, 75·35; H, 8·6%). Light absorption: $\lambda_{max.}$ 246 mμ (ε 17,100). 3β-Hydroxypregna-5 : 16-dien-20-one was obtained on hydrolysis of the enol acetate (isomer B) with hot aqueous-methanolic potassium hydrogen carbonate.

Careful dilution of the aqueous acetic acid mother-liquor gave isomer A (1 g.), blades (from aqueous methanol), m. p. 113—114°, not depressed in admixture with a specimen prepared as in the preceding experiment.

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