446. *Studies in the Sterol Group. Part LIV.* The Preparation of Some 7α-Methoxy-steroids.*

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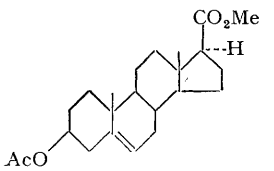
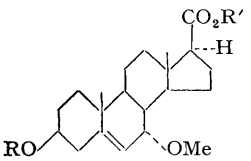
7α-Bromo-steroids, prepared from methyl 3β-acetoxychol-5-enate and methyl 3β-acetoxyeti-5-enate with *N*-bromosuccinimide, have been converted into 7α-methoxy-compounds by means of silver nitrate in methanol. Replacement of the methoxyl group by acetoxyl occurs very readily in warm acetic acid, and thus an attempted preparation of 7α-methoxydesoxycorticosterone terminated at the stage, 7α : 21-diacetoxypregnenolone (VIII).

As a continuation of the work described in the preceding paper towards the preparation of 7-oxygenated analogues of cortisone, a preliminary study has been made of possible ways of obtaining 7-methoxy-derivatives of deoxycorticosterone and related compounds. Previous studies by Henbest and Jones (*J.*, 1948, 1798) had shown that 7α-methoxycholesterol could be prepared from 7α-bromocholesteryl acetate, and that it could be oxidized by the Oppenauer method to 7α-methoxycholest-4-en-3-one, containing the physiologically important 3-keto-Δ^4-grouping.

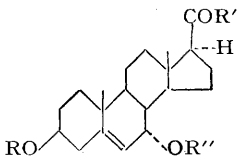
Methyl 3β-acetoxyeti-5-enate (I) and *N*-bromosuccinimide reacted readily in carbon tetrachloride, to give a 7-bromo-compound (not isolated) which with silver nitrate in



(I)



(II; R = Ac, R′ = Me)
(III; R = H, R′ = Me)
(IV; R = R′ = H)
(V; R = Ac, R′ = H)



(VI; R = Ac, R′ = CHN_2, R″ = Me)
(VII; R = H, R′ = CHN_2, R″ = Me)
(VIII; R = H, R′ = CH_2·OAc, R″ = Ac)
(IX; R = R″ = Ac, R′ = CH_2·OAc)

methanol afforded the 7α-methoxy-compound (II) in 25% overall yield. Attempted hydrolysis of this compound [to yield the hydroxy-acid (IV)] by the method employed by von Euw and Reichstein (*Helv. Chim. Acta*, 1946, **29**, 1913) for a methyl 11-ketoeti-5-

* Part LIII, preceding paper.

enate (warm 10% methanolic potassium hydroxide) gave an acid of low and variable melting point in moderate yield. Decreasing the alkali concentration to 5% resulted in only partial hydrolysis, the hydroxy-ester (III) being isolated in good yield. Addition of water to the hydrolysis medium, however, enabled complete hydrolysis to be achieved at room temperature.

Acetylation of the resultant hydroxy-acid (IV) with acetic anhydride and pyridine gave a product containing some neutral material, probably a mixed anhydride with acetic acid, which was separated from the required acetoxy-acid (V) by conversion of the latter into its sodium salt. A sample of this salt on acidification yielded the acid (V), which on treatment with diazomethane gave the original acetoxy-ester (II).

The remainder of the synthesis involving the elaboration of the ketol side-chain was carried out as described by Wilds and Shunk (*J. Amer. Chem. Soc.*, 1948, **70**, 2427). The above sodium salt was treated with oxalyl chloride to give the acid chloride, which with diazomethane afforded the crystalline diazo-ketone (VI). Alkaline hydrolysis gave the corresponding 3β-hydroxy-steroid, which was treated with hot acetic acid in order to convert the diazo-ketone into the ketol-acetate side-chain. The major product of this last reaction (obtained crystalline in nearly 30% yield from the sodium salt) was found to contain no methoxyl group, and could not therefore be the expected 21-acetoxy-3β-hydroxy-20-keto-7α-methoxypregn-5-ene. Its large lævorotation suggested the presence of a 7α-substituent. Analytical data agreed with those for a 7α : 21-diacetoxypregnenolone (VIII), and further acetylation gave a compound which analysed correctly for the triacetoxy-steroid (IX).

Replacement of a 7α-methoxyl by an acetoxyl group had previously been carried out by means of acetic acid containing sulphuric acid (Henbest and Jones, *loc. cit.*). When 7α-methoxycholesterol was subjected to the hot acetic acid treatment used above for formation of (VIII), a product was obtained which on alkaline hydrolysis gave the known 7α-hydroxycholesterol in 50% yield. This experiment thus provided confirmation of the replacement of the methoxyl by an acetoxyl group under these relatively mild conditions.

It had been hoped to convert the expected 7α-methoxypregnenolone into 7α-methoxydeoxycorticosterone acetate by mild Oppenauer oxidation. It was not feasible to attempt a similar oxidation with (VIII) in order to obtain the corresponding 7α-acetoxy-compound, because it had been found previously that 7α-acetoxycholesterol gave cholesta-4 : 6-dien-3-one as the only detectable product (cf. preceding paper).

The preparation of the 7α-methoxy-derivative of methyl 3β-acetoxychol-5-enate is described in the Experimental section.

Experimental

Methyl 3β-Acetoxy-7α-methoxychol-5-enate.—Finely powdered *N*-bromosuccinimide (1·6 g.) was added to methyl 3β-acetoxychol-5-enate (3·21 g.; m.p. 156—157°, $[\alpha]_D$ −43°) dissolved in carbon tetrachloride (25 c.c.), the suspension being heated under reflux with vigorous mechanical stirring. An exothermic reaction began after 5 minutes, and after a further 2 minutes' heating the yellow reaction mixture was cooled and the succinimide (0·9 g.) removed by filtration. Evaporation of the filtrate under reduced pressure gave the bromo-compound as a gum, which was dissolved in methanol (50 c.c.) and ether (15 c.c.) and then treated with silver nitrate (1·5 g.) in water (10 c.c.) at 20°. Silver bromide was precipitated immediately, and after 15 minutes the steroid was isolated with ether. Crystallization from methanol first yielded some unchanged starting material (0·45 g.; m. p. 140—151°), followed by the methoxy-compound (1·25 g.), m. p. 105—114°. Further recrystallization of the latter from methanol afforded the pure *methoxy*-steroid as needles, m. p. 129—130°, $[\alpha]_D$ −127° (*c*, 0·86) (Found : C, 72·7; H, 9·8; OMe, 13·9. $C_{28}H_{44}O_5$ requires C, 73·0; H, 9·65; OMe, 13·5%).

3-Hydroxy-7α-methoxychol-5-enic Acid.—The above ester (100 mg.) in methanol (5 c.c.) was added to a solution of potassium hydroxide (3·0 g.) in methanol (15 c.c.), the mixture being then kept at 20° for 48 hours. Addition of water followed by extraction with ether gave only a trace of neutral material. Acidification and ether-extraction gave a product which after 2 recrystallizations from methanol gave the *hydroxy-methoxy-acid* (47 mg.) as needles, m. p. 176—178°, $[\alpha]_D$ −120° (*c*, 0·59) (Found : C, 74·35; H, 10·15; OMe, 7·7. $C_{25}H_{40}O_4$ requires C, 74·2; H, 9·95; OMe, 7·7%).

Methyl 3β-*Acetoxy*-7-*ketochol*-5-*enate*.—A solution of the above acetoxy-methoxy-ester (300 mg.) in acetic acid (10 c.c.), containing chromic acid (300 mg.), was kept at 20° for 24 hours. The steroid was isolated with ether, and the product recrystallized from ethanol and then from methanol, to give the ketone (110 mg.) as needles, m. p. 177·5—179° (Haslewood, *J.*, 1938, 224, gives m. p. 177—178°).

Methyl 3β-*Acetoxy*-7α-*methoxyeti*-5-*enate* (3β-*Acetoxy*-7α-*methoxyandrost*-5-*ene*-17β-*carboxylate*) (II).—Finely powdered *N*-bromosuccinimide (1·42 g.) was added to a solution of methyl 3β-acetoxyeti-5-enate {2·5 g.; m. p. 155—156°, $[\alpha]_D$ −5° (*c*, 1·03)} in carbon tetrachloride (25 c.c.), and the suspension heated under reflux with stirring. An exothermic reaction which began after 2 minutes rapidly subsided. The cooled reaction mixture was then filtered (0·79 g. succinimide) and evaporated under reduced pressure, to give the bromo-compound as a gum. Silver nitrate (1·13 g.) in water (8 c.c.) was added to a solution of the bromo-compound in methanol (50 c.c.) and ether (25 c.c.). After 20 minutes the steroid was isolated with ether. Recrystallization from methanol gave needles (0·92 g.), m. p. 172—177°; further recrystallization from methanol gave the *methoxy*-steroid, m. p. 179—180°, $[\alpha]_D$ −116° (*c*, 0·70) (Found: C, 71·1; H, 8·75; OMe, 15·6. $C_{24}H_{36}O_5$ requires C, 71·25; H, 8·95; OMe, 15·35%).

Methyl 3β-*Hydroxy*-7α-*methoxyeti*-5-*enate* (3β-*Hydroxy*-7α-*methoxyandrost*-5-*ene*-17β-*carboxylate*) (III).—Potassium hydroxide (1·0 g.) and the foregoing ester (200 mg.) in methanol (20 c.c.) were heated under reflux for 1½ hours. The cooled reaction mixture was diluted with water, and the steroid isolated with ether. The product (150 mg.), m. p. 169—170·5°, was recrystallized from methanol, to give the pure *hydroxy*-ester as needles, m. p. 172—173°, $[\alpha]_D$ −12° (*c*, 0·64) (Found: C, 73·05; H, 9·5; OMe, 17·1. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·45; OMe, 17·1%).

3β-*Acetoxy*-7α-*methoxyeti*-5-*enic Acid* (3β-*Acetoxy*-7α-*methoxyandrost*-5-*ene*-17β-*carboxylate*) (V).—A solution of potassium hydroxide (15 g.) in water (25 c.c.) was added to a solution of methyl 3β-acetoxy-7α-methoxyeti-5-enate (500 mg.) in methanol (75 c.c.), the solution then being kept at 20° for 48 hours. The acidic fractions (450 mg.) on recrystallization from aqueous acetone afforded the hydroxy-methoxy-acid (IV) (320 mg.) as needles, m.p. 193—205°, $[\alpha]_D$ −16° (*c*, 1·1).

This crude hydroxy-acid (0·95 g.) was acetylated with acetic anhydride (8 c.c.) in pyridine (13 c.c.) at 20° for 26 hours. The steroid was isolated with ether, and recrystallized from aqueous *iso*propyl alcohol, giving somewhat impure acetate (0·95 g.), m. p. 193—196°. For purification, it was treated in ethanol (125 c.c.) with N/20-sodium hydroxide until neutral to phenolphthalein. Evaporation under reduced pressure gave the sodium salt, which was washed with ether and dried. The ethereal washings on evaporation yielded a solid (0·2 g.), m. p. 110—115°—possibly a mixed anhydride with acetic acid—which could be hydrolysed to the original hydroxy-methoxy-acid. A sample of the above sodium salt in ethanol was treated with aqueous hydrochloric acid. The *acetoxy-methoxy-acid* obtained had m. p. 202—207° and $[\alpha]_D$ −126° (*c*, 0·46) (Found: C, 70·75; H, 9·05; OMe, 7·7. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8; OMe, 7·95%). Treatment with ethereal diazomethane gave the acetoxy-methoxy-ester, m. p. 179—180°, in good yield.

7α : 21-*Diacetoxy*-3β-*hydroxypregn*-5-*en*-20-*one* (VIII).—A suspension of the foregoing sodium salt (0·45 g.; dried at 100°/10^{-5} mm.) in dry benzene (10 c.c.) containing pyridine (3 drops) was cooled to 0° and then treated with oxalyl chloride (4 c.c.). When the evolution of gas had ceased, the mixture was kept at 15° for 5 minutes. Evaporation under reduced pressure gave a solid, which was treated with benzene (3 × 3 c.c.), each portion being successively removed under reduced pressure. The residue was treated with benzene (5 c.c.), and the suspension filtered through a dry sintered-glass funnel into a cooled (0°) receiver. This solution was added during 10 minutes to a stirred ethereal solution of excess of diazomethane at −15° (dry nitrogen atmosphere). The mixture was stirred for 1 hour at −15° and then for 30 minutes at 0°. Evaporation of the solvent under reduced pressure gave the diazo-ketone (VI) as a gum which crystallized on contact with methanol as needles (0·40 g.), m. p. 150—152° (decomp.). For hydrolysis of the 3-acetoxy-group, the diazo-ketone (0·40 g.), dissolved in methanol (40 c.c.) and ether (3 c.c.), was treated with methanol (6 c.c.) containing potassium hydroxide (0·6 g.) and the mixture kept at 20° for 5 hours. Isolation with ether gave the hydroxy-methoxy-diazoketone as a gum (0·38 g.), which was dissolved in dry ether (3 c.c.) and added dropwise during 2 minutes to boiling AnalaR acetic acid (25 c.c.). After 3 minutes' boiling the mixture was evaporated under reduced pressure (below 50°) to give a pale yellow gum, which was dissolved in benzene and chromatographed on alumina (40 g.; neutralized and deactivated with 2 c.c. of 10% acetic acid in water). Development with benzene–ether (5 : 1) yielded a gum (310 mg.) which crystallized on contact with ether. Recrystallization from ether–light petroleum (b. p. 40—60°) gave

the *diacetoxy-ketone* (130 mg., 28% from the sodium salt), m. p. 173—176°. Two recrystallizations gave the pure compound, m. p. 182·5—183°, $[\alpha]_D$ −133° (*c*, 0·44) (Found : C, 69·65, 69·0; H, 8·75, 8·55; OMe, nil. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). Acetylation of this compound with acetic anhydride and pyridine at 20° gave 3β : 7α : 21-*triacetoxypregn*-5-*en*-20-*one* (IX), crystallizing from methanol as needles, m. p. 197·5—198°, $[\alpha]_D$ −139° (*c*, 0·42) (Found : C, 68·5; H, 8·25. $C_{27}H_{38}O_7$ requires C, 68·3; H, 8·05%).

7α-*Hydroxycholesterol from* 7α-*Methoxycholesterol.*—A solution of 7α-methoxycholesterol (150 mg.) in dry ether (3 c.c.) was added rapidly to boiling AnalaR acetic acid (15 c.c.), the solution then being boiled for a further 2 minutes. Evaporation of the solution under reduced pressure gave a gum which was dissolved in light petroleum (b. p. 40—60°) and introduced on to a column of alumina (15 g.). Development of the chromatogram with benzene–ether (9 : 1) gave several fractions as gums (total, 125 mg.). The combined fractions were hydrolysed with methanolic potassium hydroxide, the cooled solution giving needles, m. p. 172—178°. Recrystallization from methanol gave pure 7α-hydroxycholesterol (70 mg., 50%), m. p. and mixed m. p. 184—185°.

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