812. *Modified Steroid Hormones. Part VII.* The Conversion of 3-Oxo-Δ⁴-steroids into their 6-Methyl Homologues.*

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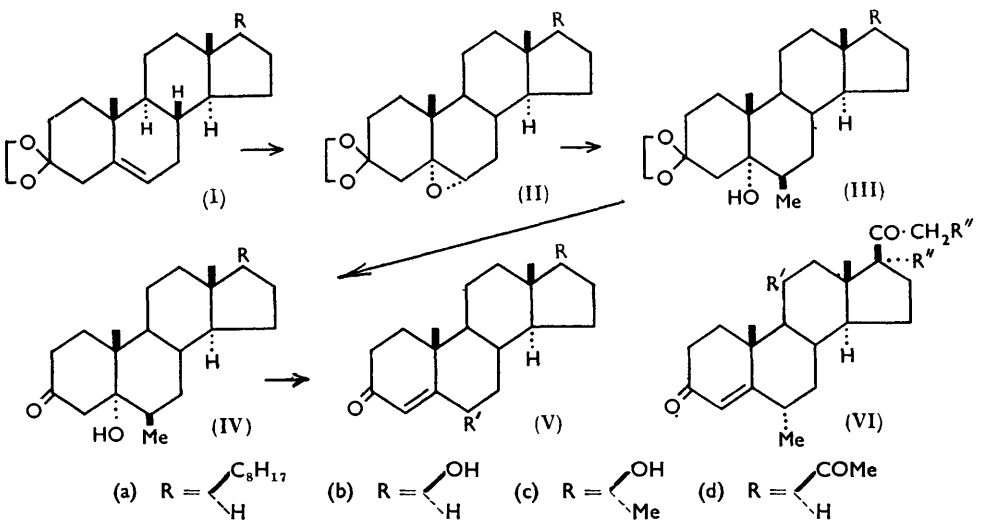
A method is described for converting 3-oxo-Δ⁴-steroids into their 6-methyl homologues: the keto-steroid is transformed into the 3 : 3-ethylenedioxy-Δ⁵-steroid (I) which is oxidised to the 5α : 6α-epoxide (II): this with methylmagnesium iodide gives the 3 : 3-ethylenedioxy-5α-hydroxy-6β-methyl steroid (III) from which 6-methyl-3-oxo-Δ⁴-steroids (V) may be obtained by deketalisation followed by dehydration.

The method is applied to the preparation of the 6-methyl derivatives of cholest-4-en-3-one, testosterone, 17α-methyltestosterone, progesterone, 11α-hydroxyprogesterone, and hydrocortisone.

Parts IV—VI dealt with the conversion of 3β-hydroxy-Δ⁵-steroids into 6-methyl-3-oxo-Δ⁴-steroids. The present communication reports a new route to the latter employing 3-oxo-Δ⁴-steroids as starting materials.

Cholest-4-en-3-one, employed as a model, was converted into 3 : 3-ethylenedioxycholest-5-ene [1] (Ia) and thence by reaction with monoperphthalic acid into a mixture of 5 : 6-epoxides. The more lævorotatory of these was assigned the constitution 5α : 6α-epoxy-3 : 3-ethylenedioxycholestane (IIa). In contrast to 5α : 6α-epoxy-3β-hydroxy-steroids, which require elevated temperatures for fission of the epoxide ring by Grignard



reagents,[2] the ketal epoxide (Ia) reacted smoothly with methylmagnesium iodide at room temperature, to give 3 : 3-ethylenedioxy-5α-hydroxy-6β-methylcholestane (IIIa). Regeneration of the 3-oxo-function by solution of the ketal (IIIa) in hot methanol led to 5α-hydroxy-6β-methylcholestan-3-one [3] (IVa) from which 6α- and 6β-methylcholest-4-en-3-one may be obtained.[3]

Oxidation of 3 : 3-ethylenedioxy-17β-hydroxyandrost-5-ene [4] (Ib) with monoperphthalic

* Part VI, preceding paper.

[1] U.S.P. 2,378,918.
[2] See Ushakov and Madaeva, *J. Gen. Chem.* (*U.S.S.R.*), 1939, **9**, 436; *Chem. Abs.*, 1939, **33**, 9309.
[3] Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 5362.
[4] See Antonucci, Bernstein, Littell, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1341.

acid gave a mixture of 5β : 6β- and 5α : 6α-epoxides. Reaction of the latter epoxide with methylmagnesium iodide followed the pattern established in the preceding series, 3 : 3-ethylenedioxy-5α : 17β-dihydroxy-6β-methylandrostane (IIIb) being readily formed. Its treatment with hot acetic acid, followed by acetylation of the product, furnished 17β-acetoxy-5α-hydroxy-6β-methylandrostan-3-one (IVb acetate) which passed on Darzens's dehydration into the previously described [5] 6β-methyltestosterone acetate (Vb acetate; R′ = ---H, -Me).

Attempts to prepare the 3-ketal derivative of 17α-methyltestosterone by conventional methods failed as concomitant dehydration at $C_{(17)}$ invariably occurred. 17β-Acetoxy-17α-methylandrost-4-en-3-one [6] was therefore employed, and successfully transformed into 17β-acetoxy-3 : 3-ethylenedioxy-17α-methylandrost-5-ene (Ic acetate) from which the corresponding 5α : 6α-epoxide (IIc acetate) was obtained on oxidation. Reaction with methylmagnesium iodide followed by removal of the ketal grouping gave 5α : 17β-dihydroxy-6β : 17α-dimethylandrostan-3-one (IVc), the immediate precursor of 6α : 17α-dimethyl testosterone (Vc; R = ---Me, -H) into which it was transformed as previously described.[5]

The 3 : 20-bisethylenedioxy-derivative of progesterone was similarly converted into the 5α : 6α-epoxide and thence, by epoxide ring fission with the Grignard reagent and subsequent removal of the protective groupings at $C_{(3)}$ and $C_{(20)}$, into 5α-hydroxy-6β-methylpregnane-3 : 20-dione (IVd). Methods for transforming the last compound into 6α- (Vd; R = ---Me, -H) and 6β-methylprogesterone (Vd; R = ---H, -Me) are reported in Part IV.[7]

11α-Hydroxyprogesterone was likewise converted into the 3 : 20-bisethylenedioxy-derivative and thence *via* the 5α : 6α-epoxide into 5α : 11α-dihydroxy-6β-methylpregnane-3 : 20-dione [8] and finally into 11α-hydroxy-6α-methylprogesterone (VI; R′ = ---OH, -H, R″ = H).

5α : 6α-Epoxy-3 : 3-20 : 20-bisethylenedioxypregnane-11β : 17α-21-triol [9] reacted with the Grignard reagent, to give 3 : 3-20 : 20-bisethylenedioxy-6β-methylpregnane-5α : 11β : 17α : 21-tetraol which on deketalisation and dehydration passed into 6α-methylhydrocortisone [8] (VI; R′ = ---H, -OH, R″ = OH).

Experimental

Optical rotations were measured for $CHCl_3$ solution in a 1 dm. tube unless otherwise stated. Alumina (B.D.H.) of chromatography grade was used.

5α : 6α- and 5β : 6β-Epoxy-3 : 3-ethylenedioxycholestane.—3 : 3-Ethylenedioxycholest-5-ene [1] (15 g.) in chloroform (140 ml.) was treated for 4 days at 0° with monoperphthalic acid (10 g.) in ether (140 ml.). The product crystallised from warm methanol as fluffy needles (6 g.; m. p. 100—105°), the mother-liquor depositing silky blades (3·9 g.; m. p. 116—119°) on long storage. Purification of the latter fraction from methanol gave 5α : 6α-epoxy-3 : 3-ethylenedioxycholestane,[10] blades, m. p. 118—120°, $[\alpha]_D^{25}$ −33° (*c* 0·87) (Found: C, 78·4; H, 10·7. Calc. for $C_{29}H_{48}O_3$: C, 78·3; H, 10·9%). Recrystallisation of the less soluble fraction gave the 5β : 6β-*epoxide*, needles (from methanol), m. p. 126—127°, $[\alpha]_D^{27}$ +9° (*c* 0·9) (Found: C, 77·1; H, 11·0. $C_{29}H_{48}O_3,\frac{1}{2}H_2O$ requires C, 76·8; H, 10·9%).

3 : 3-*Ethylenedioxy-5α-hydroxy-6β-methylcholestane* (IIIa).—The 5α : 6α-epoxide (1 g.) in ether (45 ml.) was added to a Grignard reagent prepared from magnesium (0·6 g.) and methyl iodide (1·55 ml.) in ether (50 ml.). The mixture was stirred for 5 hr. at room temperature and then set aside overnight. After addition of ammonium chloride (5 g.) in water (20 ml.) to the

[5] Ackroyd, Adams, Ellis, Petrow, and Stuart-Webb, *J.*, 1957, 4099.
[6] Mischer and Klarer, *Helv. Chim. Acta*, 1939, **22**, 962.
[7] Burn, Ellis, Petrow, Stuart-Webb and Williamson, *J.*, 1957, 4092.
[8] Cf. the preliminary communication by Spero, Thompson, Magerlein, Hanze, Murray, Sebek, and Hogg, *J. Amer. Chem. Soc.*, 1956, **78**, 6213, which appeared after the present work had been completed.
[9] Littell and Bernstein, *J. Amer. Chem. Soc.*, 1956, **78**, 984.
[10] See Fernholz and Stavely, Abs. 102nd Meeting Amer. Chem. Soc., Sept. 8–12th, 1941, p. M39.

stirred, well-cooled mixture, the product was isolated in the usual manner and obtained as a yellow-brown gum. Chromatography on alumina (20 g.), employing light petroleum and light petroleum–benzene (4 : 1) as eluants, gave material (0·42 g.; m. p. 85—88°) crystallising in needles from cold methanol. 3 : 3-*Ethylenedioxy*-5α-*hydroxy*-6β-*methylcholestane* had m. p. 86—87°, $[\alpha]_D^{24}$ −5° (*c* 0·83 in dioxan) (Found: C, 77·8; H, 11·3. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·4%).

5α-*Hydroxy*-6β-*methylcholestan*-3-*one* (IVa), obtained by heating briefly a solution of the foregoing compound (150 mg.) in methanol (5 ml.), crystallised in plates (from methanol), m. p. 228—229° (decomp.), $[\alpha]_D^{24}$ +19° (*c* 0·51 in dioxan) (Found: C, 80·6; H, 11·6. Calc. for $C_{28}H_{48}O_2$: C, 80·7; H, 11·6%) {Turner [3] gives m. p. 227—228° (decomp.), $[\alpha]_D$ +20·5° in dioxan}.

5α : 6α- *and* 5β : 6β-*Epoxides derived from Testosterone* 3-(*Ethylene Ketal*).—Testosterone 3-(ethylene ketal) [4] (4·8 g.) in chloroform (60 ml.) was treated for 18 hr. at 0° with monoperphthalic acid (4 g.) in ether (46 ml.). Fractionation of the product from acetone containing a trace of pyridine gave 5α : 6α-*epoxy*-3 : 3-*ethylenedioxyandrostan*-17β-*ol*, flat needles, m. p. 201—203°, $[\alpha]_D^{21}$ −68·5° (*c* 0·54) (Found: C, 72·2; H, 9·5. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%), and the 5β : 6β-*epoxide*, large prisms, m. p. 206—209°, $[\alpha]_D^{20}$ −14° (*c* 0·65 in pyridine) (Found: C, 72·2; H, 9·2%).

3 : 3-*Ethylenedioxy*-6β-*methylandrostane*-5α : 17β-*diol* (IIIb).—The foregoing 5α : 6α-epoxide (3 g.) in benzene (200 ml.) and ether (135 ml.) was added to a Grignard reagent prepared from magnesium (1·8 g.) and methyl iodide (4·65 ml.) in ether (100 ml.). The mixture was stirred for 5 hr. at room temperature and then set aside overnight. The product was isolated in the usual way and crystallised from methanol–pyridine (50 : 1). The *diol* separated in plates, m. p. 103°, $[\alpha]_D^{26}$ −28° (*c* 0·72) (Found: C, 69·9; H, 9·9. $C_{22}H_{36}O_4,CH_3{\cdot}OH$ requires C, 69·6; H, 10·2%). The 17β-*acetate* crystallised in needles (from aqueous ethanol containing a trace of pyridine), m. p. 169—170°, $[\alpha]_D^{22}$ −30° (*c* 0·99) (Found: C, 70·4; H, 9·2. $C_{24}H_{38}O_5$ requires C, 70·9; H, 9·4%).

17β-*Acetoxy*-5α-*hydroxy*-6β-*methylandrostan*-3-*one* (IVb *acetate*).—3 : 3-Ethylenedioxy-6β-methyladrostane-5α : 17β-diol (1 g.) in acetic acid (15 ml. of 98%) was heated at 100° for 40 min. The solid obtained on the addition of water was acetylated in pyridine, and the product purified from ethanol. The *ketone* formed prisms, m. p. 216—217°, $[\alpha]_D^{28}$ −11° (*c* 0·37) (Found: C, 72·1; H, 9·3. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·45%).

6β-*Methyltestosterone Acetate* (Vb *acetate*; R′ = ···H, ⁻Me).—Thionyl chloride (0·12 ml.) was added dropwise to a solution of the foregoing compound (200 mg.) in pyridine (2·5 ml.) cooled in ice–salt. After a further 10 min., the mixture was poured into water and the solid product crystallised from aqueous ethanol. 6β-Methyltestosterone acetate formed needles, m. p. 157—158°, $[\alpha]_D^{27}$ +49° (*c* 0·65). No depression in m. p. was obtained in admixture with an authentic specimen.[5]

17β-*Acetoxy*-3 : 3-*ethylenedioxy*-17α-*methylandrost*-5-*ene* (Ic *acetate*).—17α-Methyltestosterone acetate [6] (13 g.) in dry benzene (300 ml.) and freshly redistilled ethylene glycol (20 ml.) containing toluene-*p*-sulphonic acid (300 mg.) were heated under reflux for 4½ hr., in an apparatus fitted with a take-off head for the removal of water. The mixture was washed with aqueous sodium hydrogen carbonate, then water, and dried, and the solvents were removed *in vacuo*. The solid residue crystallised from methanol–pyridine (50 : 1), to give the *ketal* as needles, m. p. 179—180°, $[\alpha]_D^{23}$ −35° (*c* 0·77) (Found: C, 74·5; H, 9·2. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

5α : 6α- *and* 5β : 6β-*Epoxides derived from the Foregoing Ketal*.—The ketal (19·3 g.) in chloroform (200 ml.) was treated for 24 hr. at 0° with monoperphthalic acid (13·6 g.) in ether (340 ml.). Fractionation of the product from acetone–pyridine (100 : 1) gave 17β-*acetoxy*-5α : 6α-*epoxy*-3 : 3-*ethylenedioxy*-17α-*methylandrostane*, plates, m. p. 202—203°, $[\alpha]_D^{23}$ −67° (*c* 1·03) (Found: C, 70·8; H, 8·4. $C_{24}H_{36}O_5$ requires C, 71·2; H, 9·0%), and the 5β : 6β-*epoxide*, needles, m. p. 175—176°, $[\alpha]_D^{23}$ −11° (*c* 0·73) (Found: C, 71·8; H, 8·9%).

5α : 17β-*Dihydroxy*-6β : 17α-*dimethylandrostan*-3-*one* (IVc).—The foregoing 5α : 6α-epoxide (8·7 g.) in benzene (300 ml.) and ether (100 ml.) was added to a Grignard reagent prepared from magnesium (5·4 g.) and methyl iodide (15 ml.) in ether (200 ml.). The mixture was stirred for 5 hr. and then set aside for 2 days. The product was a gum. The major part (7·4 g.) was treated with acetic acid (120 ml.) and water (7·5 ml.) for 24 hr. at room temperature, and the crystalline solid obtained (4·2 g.) purified from acetone–hexane. 5α : 17β-Dihydroxy-6β : 17α-dimethylandrostan-3-one separated in plates, m. p. 253°, $[\alpha]_D^{25}$ −28° (*c* 0·4) (Found: C, 74·9;

H, 10·5. Calc. for $C_{21}H_{34}O_3$: C, 75·4; H, 10·25%), identical with a specimen prepared as described in Part V.[5]

5α : 6α-*Epoxy*-3 : 3-20 : 20-*bisethylenedioxypregnane*.—Progesteron 3 : 20-di(ethylene ketal) [11] (4 g.) in chloroform (60 ml.) was treated for 18 hr. at 0° with monoperphthalic acid (2·9 g.) in ether (40 ml.). Crystallisation of the product from acetone–hexane gave the 5α : 6α-*epoxide*, blades, m. p. 186—187°, $[\alpha]_D^{20}$ −51° (*c* 0·73) (Found: C, 71·5; H, 9·0. $C_{25}H_{38}O_5$ requires C, 70·7; H, 9·15%).

3 : 3-20 : 20-*Bisethylenedioxy*-6β-*methylpregnan*-5α-*ol* (1·3 g.), prepared from the foregoing epoxide (3 g.) and the Grignard reagent from magnesium (1·8 g.) and methyl iodide (4·65 ml.), crystallised from methanol–pyridine (50 : 1) in prisms, m. p. 134°, $[\alpha]_D^{28}$ −23·5° (*c* 0·48) (Found: C, 71·9; H, 9·9. $C_{26}H_{42}O_5$ requires C, 71·8; H, 9·7%).

5α-*Hydroxy*-6β-*methylpregnane*-3 : 20-*dione* (IVd), prepared by treating the foregoing compound (200 mg.) with acetic acid (2·5 ml.) and a drop of water for 50 min. at 100°, formed needles (from ethanol), m. p. 247—250° (decomp.), $[\alpha]_D^{30}$ +73° (*c* 0·49) (Found: C, 75·8; H, 9·7. Calc. for $C_{22}H_{34}O_3$: C, 76·3; H, 9·7%), identical with a specimen prepared as described in Part V.[5]

3 : 3-20 : 20-*Bisethylenedioxypregn*-5-*en*-11α-*ol*.—11α-Hydroxyprogesterone (30 g.) in dry benzene (1 l.) and ethylene glycol (400 ml.) containing toluene-*p*-sulphonic acid (500 mg.) were heated under reflux for 16 hr., under a Dean–Stark separator. The product was isolated in the usual way and purified from methylene chloride–acetone. The *bisketal* had m. p. 214—217°, $[\alpha]_D^{23}$ −39° (*c* 0·26) (Found: C, 70·6; H, 9·1. $C_{25}H_{38}O_5$ required C, 71·7; H, 9·1%).

5α : 6α- *and* 5β : 6β-*Epoxides derived from the Foregoing Bisketal*.—The ketal (7·1 g.) in chloroform (110 ml.) containing 1 drop of pyridine was treated for 24 hr. at 0° with monoperphthalic acid (4·7 g.) in ether (54 ml.). Fractionation of the product from acetone–hexane (1 : 2) gave 5α : 6α-*epoxy*-3 : 3-20 : 20-*bisethylenedioxypregnan*-11α-*ol*, flakes, m. p. 199—201°, $[\alpha]_D^{21}$ −65° (*c* 0·31) (Found: C, 69·7; H, 8·7. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%), and the 5β : 6β-*epoxide*, flakes, m. p. 195—197°, $[\alpha]_D^{23}$ −1° (*c* 0·25) (Found: C, 68·9; H, 8·9%).

5α : 11α-*Dihydroxy*-6β-*methylpregnane*-3 : 20-*dione*.—The foregoing 5α : 6α-epoxide (3 g.) in dry ether (100 ml.) and benzene (60 ml.) was added to a Grignard reagent prepared from magnesium (1·5 g.) and methyl iodide (3·9 ml.) in ether (20 ml.). The mixture was stirred for 6 hr. at room temperature and set aside overnight. The product was isolated in the usual way and heated under reflux for 30 min. with a solution of oxalic acid (1 g.) in aqueous methanol (60 ml. of 90%). Concentration gave 5α : 11α-dihydroxy-6β-methylpregnane-3 : 20-dione,[8] needles (from ethyl acetate), m. p. 226—228°, $[\alpha]_D^{24}$ +19° (*c* 0·25) (Found: C, 72·0; H, 8·9. Calc. for $C_{22}H_{34}O_2$: C, 72·9; H, 8·8%).

11α-*Hydroxy*-6α-*methylprogesterone* (VI; R′ = ···OH, ···H, R″ = H).—The foregoing compound (300 mg.) in methanol (25 ml.) containing concentrated hydrochloric acid (0·2 ml.) was heated under reflux for 1 hr. The product was isolated with methylene chloride and purified from acetone–hexane. 11α-*Hydroxy*-6α-*methylprogesterone* separated in flakes, m. p. 151—153°, $[\alpha]_D^{23}$ +122° (*c* 0·29), $\lambda_{max.}$ 241 mμ (log ε 4·17) (Found: C, 75·9; H, 9·3. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·3%).

3 : 3-20 : 20-*Bisethylenedioxy*-6β-*methylpregnane*-5α : 11β : 17α : 21-*tetraol*.—5α : 6α-Epoxy-3 : 3-20 : 20-bisethylenedioxypregnane-11β : 17α : 21-triol [9] (1·6 g.) in dry tetrahydrofuran (70 ml.) and ether (40 ml.) was added to a solution of methylmagnesium iodide prepared from magnesium (1·8 g.), methyl iodide (7 ml.), and ether (70 ml.). The mixture was heated under reflux for 6 hr., then treated with excess of aqueous ammonium chloride, and the product isolated with chloroform. Purified from acetone–hexane containing a trace of pyridine, the *tetraol* formed prismatic needles, m. p. 229—232°, $[\alpha]_D^{23}$ −29° (*c* 0·83 in pyridine) (Found: C, 64·5; H, 8·9. $C_{26}H_{42}O_8$ requires C, 64·7; H, 8·8%).

5α : 11β : 17α : 21-*Tetrahydroxy*-6β-*methylpregnane*-3 : 20-*dione*.—The foregoing compound (1·3 g.) in methanol (72 ml.) and dilute sulphuric acid (7·2 ml. of 8·5% v/v) was heated under reflux for 10 min. The product was isolated with chloroform and crystallised from acetone. The *dione* had m. p. 224—226° (decomp.), $[\alpha]_D^{22}$ +35° (*c* 0·40 in pyridine) (Found: C, 65·5; H, 8·5. $C_{22}H_{34}O_6, \frac{1}{2}H_2O$ requires C, 65·5; H, 8·7%).

6α-*Methylhydrocortisone* (VI; R′ = ···H, ···OH, R″ = OH).—The foregoing compound (200 mg.) in methanol (20 ml.) was treated for 21 hr. at room temperature with 0·1N-aqueous sodium hydroxide (1 ml.). After neutralisation with dilute hydrochloric acid, the mixture was diluted

[11] Antonucci, Bernstein, Lenhard, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1369.

with water, and the product isolated with chloroform. Purification from acetone gave 6α-methylhydrocortisone,[8] m. p. 199—203°, $[\alpha]_D^{22}$ +81° (*c* 0·21 in acetone) (Found: C, 68·6; H, 8·7. Calc. for $C_{22}H_{32}O_5,\frac{1}{2}H_2O$: C, 68·5; H, 8·6%).

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