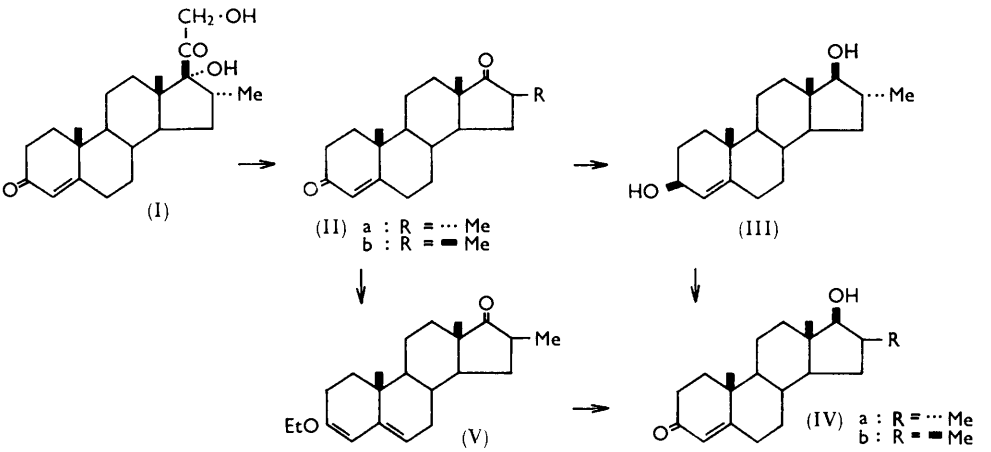
790. *Steroids. Part CLXIX.* The Preparation of 16α-Methyl- and 16β-Methyl-testosterone.*

By A. Bowers, P. G. Holton, E. Necoechea, and F. A. Kincl.

Oxidation of 17α,21-dihydroxy-16α-methylpregn-4-ene-3,20-dione (I) by sodium bismuthate afforded 16α-methylandrost-4-ene-3,17-dione (IIa), which was converted by acid or alkali completely into the 16β-methyl isomer (IIb). Reduction of the isomers (II) with lithium aluminium hydride, followed by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone, gave the respective 16-methyltestosterones (IV). Reduction of the enol ether of the 16β-isomer (IIb) by potassium borohydride, followed by hydrolysis, also gave 16β-methyltestosterone (IVb).

The search for a modified hormone which would display myotrophic activity and yet be free from undesirable features such as pituitary inhibition or androgenic effects has led to the preparation of a number of methylated analogues in both the androstane and the œstrane series.[1] Extension of this work to the preparation of the 16α- and 16β-methyl analogues of testosterone was of interest since 16α-methyl substitution is known to increase anti-inflammatory activity in the cortical hormone series,[2] and moreover the relative stabilities of 16α- and 16β-substituents in 17-keto-steroids is of interest because of their atypical conformational situation.



Oxidation of 17α,21-dihydroxy-16α-methylpregn-4-ene-3,20-dione [3] (I), with chromium trioxide in acetic acid, or, better, with sodium bismuthate gave 16α-methylandrost-4-ene-3,17-dione (IIa), in which the configuration at position 16 had been preserved, since subsequent equilibration with hydrochloric acid in acetic acid or with potassium hydroxide in methanol gave essentially complete conversion into the epimer (IIb). After equilibration of either isomer, we were unable to detect the presence of the 16α-methyl epimer by chromatography, while the specific rotations of equilibrated solutions were that

* Part CLXVIII, Crabbé, Ringold, and Zderic, *Bull. Soc. chim. belges*, in the press.

[1] *Inter alia*, Ringold and his co-workers, *J. Amer. Chem. Soc.*, 1959, **81**, 424, 427; *J. Org. Chem.*, 1956, **21**, 1333; 1957, **22**, 99, 602; Campbell, Babcock, and Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 4717.

[2] Arth *et al.*, *J. Amer. Chem. Soc.*, 1958, **80**, 3160, 3161; Oliveto *et al.*, *ibid.*, pp. 4428, 4431, 6687; Taub, Hoffsomer, Slates, and Wendler, *ibid.*, p. 4435.

[3] Edwards, Zaffaroni, Ringold, and Djerassi, *Proc. Chem. Soc.*, 1959, 87.

of the 16β-methyl-dione.* The relative stabilities of the epimeric 16-methyl-17-ketones are thus in qualitative agreement with those of the 16-bromo-17-ketones, for which, in the androst-5-ene and 5α- and 5β-androstane series, Fajkoš [5] has demonstrated that 16β is the preferred configuration. After equilibration the 16β-bromo-epimer predominates in the ratio 3 : 1. The 16β-bromo-isomer is also the more stable in the œstra-1,3,5(10)-triene series.[6] Compound (IIb) proved to be identical with the known 16-methylandrost-4-ene-3,17-dione [7,8] which had been formed by hydrogenation of a 16-methylene derivative.[7,9]

For the preparation of 16α-methyltestosterone (IVa), the dione (IIa) was reduced with lithium aluminium hydride in tetrahydrofuran (thereby avoiding equilibration at position 16) to give 16α-methylandrost-4-ene-3β,17β-diol (III). The 17β-configuration is assigned since reduction of 17-ketones containing bulky 16α-substituents (*e.g.*, bromine) by lithium aluminium hydride is known to be stereoselective in favour of the 17β-epimer.[6,10,11] Oxidation of the diol (III) with 2,3-dichloro-5,6-dicyanobenzoquinone at room temperature [12] gave 16α-methyltestosterone (IVa) smoothly.

For the preparation of the 16β-methyl isomer (IVb), the enol ether (V) was reduced with potassium borohydride, and the crude product hydrolysed to give a single 17-alcohol to which the β-configuration is assigned. This rests on the identity of the product with that obtained by reduction of the 16β-methyldiketone (IIb), followed by oxidation, as above. These conditions for reduction ensure formation of the 17β-alcohol, since they have been shown to be stereospecific for 16β-substituted 17-ketones.[6] The 16β-methyltestosterone (IVb) obtained was identical with that prepared previously [7,9] without configurational assignments.

In view of the *cis*-arrangement of the 13β- and 16β-methyl groups, one might have expected that the 16α-methyl-17-ketone system would be the more stable. However, molecular models of compounds (IIa and b) show that in the rigidly held cyclopentanone ring the non-bonded interactions between the 16α-methyl and 14α-hydrogen are probably greater than those between the 13β- and 16β-methyl groups. The introduction of either the 16α- or the 16β-methyl group into testosterone did not increase anabolic or androgenic activity.†

Experimental

M. p.s are corrected. Optical rotations were measured for 1% solutions in chloroform at 25°, and ultraviolet absorption for ethanol solutions by using a Beckman D.U. spectrometer. Infrared absorption spectra were determined for KBr pellets on a Perkin–Elmer model 21 spectrometer equipped with sodium chloride optics. Alumina for chromatography was neutralised by heating it under reflux in ethyl acetate for 6 hr. and reactivated by heating it for 62 hr. at 120°.

16α-*Methylandrost-4-ene-3,17-dione* (IIa).—(a) *With chromium trioxide.* Chromium trioxide (0·8 g.) in water (2 ml.) containing a few drops of acetic acid was added slowly to a solution of 17α,21-dihydroxy-16α-methylpregn-4-ene-3,20-dione (I) (1·0 g.) in acetic acid (15 ml.) with stirring at $<30°$. After 48 hr. the mixture was poured into water and extracted with methylene

* Since completion of this work the degradation of 17α,21-dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione to 16α-methylandrost-1,4,9(11)-triene-3,17-dione has been described.[4] The 16α-configuration was demonstrated by the non-identity of the product with that obtained by degradation of the corresponding 16β-methylpregnatriene derivative. The epimeric 3,17-diones were not equilibrated.

† The androgen anabolic assay was carried out in castrated immature male rats. Compounds were administered by injection. We thank Dr. R. I. Dorfman, The Worcester Foundation for Experimental Biology, Shrewsbury, Mass., U.S.A., for these bioassays.

[4] Robinson, Finchener, Tiberi, Eisler, Neri, Watnick, Perlman, Holroyd, Charni, and Oliveto, *J. Amer. Chem. Soc.*, 1960, **82**, 4611.
[5] Fajkoš, *J.*, 1959, 3966.
[6] Fishman and Biggerstaff, *J. Org. Chem.*, 1958, **23**, 1190.
[7] Neumann, Mancera, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1955, **77**, 5676.
[8] Romero, Romo, and Lepe, *Bol. Inst. Quím. Univ. nac. auton. México*, 1952, **4**, 115.
[9] Julian, Meyer, and Printy, *J. Amer. Chem. Soc.*, 1948, **70**, 3872.
[10] Biggerstaff and Gallagher, *J. Org. Chem.*, 1957, **22**, 1220.
[11] Fajkoš and Šorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 766.
[12] Burn, Petrow, and Weston, *Tetrahedron Letters*, 1960, No. 9, 14.

chloride (3 × 20 ml.). The washed and dried extract was evaporated to an oil (800 mg.) and chromatographed over alumina (50 g.). Elution with benzene–hexane (1 : 1) and crystallisation from acetone–hexane gave 16α-*methylandrost-4-ene*-3,17-*dione* (IIa), m. p. 135—136°, $[\alpha]_D$ +166°. The analytical sample had m. p. 136·5—137·5°, $[\alpha]_D$ +168°, $\lambda_{max.}$ 240 mμ (log ε 4·22), $\nu_{max.}$ 1740 (C=O in 5-membered ring), 1680 (unsaturated C=O) and 1620 cm.$^{-1}$ (conjugated C=C) (Found: C, 80·0; H, 9·3; O, 10·7. $C_{20}H_{28}O_2$ requires C, 80·0; H, 9·4; O, 10·7%).

(b) *With sodium bismuthate.* Sodium bismuthate (370 g.) was added in portions to a stirred solution of 17α,21-dihydroxy-16α-methylpregn-4-ene-3,20-dione (I) (28·0 g.) in 5% acetic acid (2·1 l.) at 0°. After the solution had been stirred for a further 35 min. at 0°, 3N-potassium hydroxide (4·4 l.) was added. The product was collected and the filtrate extracted with ethyl acetate (3 × 500 ml.). The washed and dried extract was evaporated and the combined crude product was chromatographed on alumina (1 kg.). Elution with benzene–hexane (1 : 1) and subsequently with benzene alone, followed by crystallisation from acetone–hexane, gave the 3,17-dione (IIa) (15·9 g., 68%), m. p. 136—137°, $[\alpha]_D$ +166°.

16β-*Methylandrost-4-ene*-3,17-*dione* (IIb).—(a) *With acid.* A solution of the dione (IIa) (100 mg.) in acetic acid (5 ml.) containing concentrated hydrochloric acid (0·5 ml.) was left at room temperature for 4 hr., then poured into water, and the product (m. p. 170—173°) was collected, washed with water, dried, chromatographed on alumina (5 g.), eluted with hexane–benzene (3 : 2), and crystallised from acetone–hexane, giving 16β-methylandrost-4-ene-3,17-dione (IIb), m. p. 173—176°, $[\alpha]_D$ +178°, $\lambda_{max.}$ 240 mμ (log ε 4·21).

(b) *With base.* A solution of the dione (IIa) (100 mg.) in methanol (2 ml.) containing 2% of potassium hydroxide was left at room temperature for 4 hr. Isolation and chromatography as above similarly gave the 16β-methyl isomer (IIb), m. p. 174—176°. A solution of the dione (7·0 g.), after equilibration with 2% methanolic potassium hydroxide (50 ml.), gave the same product (5·9 g., 84%), m. p. 174—176°, $[\alpha]_D$ +177°, $\lambda_{max.}$ 240 mμ (log ε 4·22), $\nu_{max.}$ 1740 (C=O in 5-membered ring), 1677 (unsaturated C=O), and 1619 cm.$^{-1}$ (conjugated C=C) (lit.,[7] m. p. 178—179°, $[\alpha]_D$ +175°).

16α-*Methylandrost-4-ene*-3β,17β-*diol* (III).—Lithium aluminium hydride (1·0 g.) was added to a stirred solution of 16α-methylandrost-4-ene-3,17-dione (IIa) (1·0 g.) in tetrahydrofuran (100 ml.), and the mixture was heated under reflux for 4 hr. Dilute sulphuric acid was added, and the product was extracted with ethyl acetate (3 × 100 ml.). The residue obtained on evaporation of the washed and dried extract crystallised from acetone–hexane to give 16α-*methylandrost-4-ene*-3β,17β-*diol* (III) (750 mg.), m. p. 159—161°. The analytical sample had m. p. 163—166°, $[\alpha]_D$ +35°, $\nu_{max.}$ 3330—3430 cm.$^{-1}$ (OH) (Found: C, 78·2; H, 10·5; O, 11·3. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6; O, 10·5%).

17β-*Hydroxy*-16α-*methylandrost-4-en*-3-*one* (IVa).—A solution of the diol (III) (500 mg.) and 2,3-dichloro-5,6-dicyanobenzoquinone (450 mg.) in dioxan (6 ml.) was left at room temperature for 16 hr. The precipitated quinol was collected and washed with methylene chloride (20 ml.). The filtrate and washings were evaporated, and the residue was dissolved in methylene chloride (50 ml.) and washed repeatedly with 10% sodium hydroxide solution, followed by water until neutral. Evaporation of the dried solution and crystallisation of the residue from acetone–hexane gave 17β-*hydroxy*-16α-*methylandrost*-4-*en*-3-*one* (IVa) (330 mg.), m. p. 154—156°, $[\alpha]_D$ +79·5°, $\lambda_{max.}$ 242 mμ (log ε 4·22), $\nu_{max.}$ 3450 (OH), 1674 (unsaturated C=O) and 1625 cm.$^{-1}$ (conjugated C=C) (Found: C, 79·4; H, 10·2; O, 10·5. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0; O, 10·6%).

3β-*Ethoxy*-16β-*methylandrosta*-3,5-*dien*-17-*one* (V).—A mixture of 16β-methylandrost-4-ene-3,17-dione (IIb) (3·0 g.) and toluene-*p*-sulphonic acid monohydrate (120 mg.) in dioxan (22·5 ml.), containing ethyl orthoformate (3·0 ml.), was stirred at room temperature for 2 hr., then diluted slowly with water (50 ml.) containing a little pyridine. The product was collected and crystallised from methanol containing one drop of pyridine, to give the *enol ether* (V) (2·55 g., 78%), m. p. 124—128°, $[\alpha]_D$ −81°. The analytical sample had m. p. 132—133°, $[\alpha]_D$ −79°, $\lambda_{max.}$ 242 mμ (log ε 4·35) (Found: C, 79·8; H, 9·7; O, 10·4. $C_{22}H_{32}O_2$ requires C, 80·4; H, 9·8; O, 9·8%).

17β-*Hydroxy*-16β-*methylandrost*-4-*en*-3-*one* (IVb).— A solution of the enol ether (V) (2·0 g.) and potassium borohydride (1·0 ml.) in tetrahydrofuran (60 ml.) and water (2 ml.) was left at room temperature for 16 hr., then heated under reflux for 2 hr. The solution was concentrated somewhat *in vacuo* and aqueous acetic acid was added. The product was extracted with methylene chloride (3 × 50 ml.) and the extracts were washed with water, dried, and evaporated.

The residual oil was dissolved in acetic acid (10 ml.), and 10% hydrochloric acid (1·2 ml.) was added. After 30 min., the mixture was poured into water and extracted with methylene chloride (3 × 50 ml.). The residue obtained by evaporation of the washed and dried extracts was chromatographed on alumina (100 g.). Elution with hexane–benzene (9 : 1) gave 16β-methylandrost-4-ene-3,17-dione (IIb) (510 mg.). Subsequent elution with ether, followed by crystallisation from acetone–hexane, gave 17β-hydroxy-16β-methylandrost-4-en-3-one (IVb) (640 mg.), m. p. 177—180°, $[\alpha]_D$ +103°, $\lambda_{max.}$ 242 mμ (log ε 4·23), $\nu_{max.}$ 3520 (OH), 1672 (unsaturated C=O), and 1625 $cm.^{-1}$ (conjugated C=C) (Found: C, 79·2; H, 9·9; O, 11·0. Calc. for $C_{20}H_{30}O_2$: C, 79·4; H, 10·0; O, 10·6%) (lit.,[7] m. p. 182—183°, $[\alpha]_D$ +106°; [9] m. p. 182—184°, $[\alpha]_D$ +106°). Alternatively the diol (III) was reduced with lithium aluminium hydride and the crude diol oxidised with 2,3-dichloro-5,6-dicyanobenzoquinone, as described for the 16α-methyl isomer, to give an identical product (m. p. and mixed m. p. 176—179°; infrared absorption spectra superimposable).

SYNTEX S.A., APARTADO POSTAL 2679, MEXICO, D.F. [*Received, April 27th,* 1961].