15 minutes with stirring and cooling (alcohol–Dry Ice). The cooled mixture was stirred 4 hours more and 50 g. of ammonium chloride was then added carefully in portions. The ammonia was allowed to evaporate, ether and water were added to the residue and the organic layer was washed with hydrochloric acid, sodium bicarbonate solution and water. The dried extract was evaporated and the residue (9.3 g., $\lambda_{max.}$ 244 mμ, $E^{1\%}_{1\,cm.}$ 288 and 328 mμ, $E^{1\%}_{1\,cm.}$ 118[21]) was chromatographed on 400 g. of alumina. The fractions eluted with benzene–ether on crystallization from acetone–ether produced 1.35 g. (12%) of 1-dehydroethinyltestosterone with m.p. 227–229°, $[\alpha]_D$ $-15°$, $\lambda_{max.}$ 244 mμ, log ϵ 4.20, ν^{mull}_{max} 1660, 1620 and 1600 cm.$^{-1}$ and free hydroxyl band. A heavy precipitate was formed when an alcoholic solution of the substance was added to aqueous ammoniacal silver nitrate.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 80.87; H, 8.67.

When the reaction was carried out with lithium acetylide (5 g. of lithium for 10 g. of $\Delta^{1,4}$-androstadiene-3,17-dione, no ferric nitrate catalyst, other conditions identical) the yield of II was 11%. When $\Delta^{1,4}$-androstadiene-3,17-dione was allowed to react with acetylene in toluene solution in the presence of potassium *t*-amylate[20] an intractable product with m.p. *ca.* 320–325°, λ_{max} 244 mμ, $E^{1\%}_{1\,cm.}$ 62 and 328 mμ, $E^{1\%}_{1\,cm.}$ 91, was obtained and none of the required II could be isolated.

4-Methyl-17α-ethinyl-$\Delta^{1,3,5(10)}$estratriene-1,17-diol Diacetate (XII).—A solution of 300 mg. of 1-dehydroethinyltestosterone and 90 mg. of *p*-toluenesulfonic acid in 12 cc. of acetic anhydride was heated at 90° for 4 hours. The cooled solution was poured into water, the anhydride was allowed to hydrolyze and the precipitate was collected, washed with water and dried. Crystallization from acetone–hexane yielded 260 mg. (68%) of the phenol diacetate XII with m.p. 191–192°, $[\alpha]_D$ $+75°$, $\lambda_{max.}$ 266 mμ, log ϵ 2.55.

Anal. Calcd. for $C_{25}H_{30}O_4$: C, 76.11; H, 7.67. Found: C, 76.38; H, 7.97.

MEXICO D. F., MEXICO

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. LXXII.[1] 16-Methylenetestosterone

BY F. NEUMANN, O. MANCERA, G. ROSENKRANZ AND FRANZ SONDHEIMER

RECEIVED MAY 2, 1955

16-Methylene-Δ^4-androsten-17β-ol-3-one (16-methylenetestosterone) (Ia) has been synthesized from 16ξ-dimethylaminomethyl-Δ^5-androsten-3β-ol-17-one (III) through successive steam distillation to IVa, Oppenauer oxidation to V, sodium borohydride reduction to VIa and VIb and finally differential manganese dioxide oxidation at C-3. In addition the known 16ξ-methyl-Δ^4-androsten-17ξ-ol-3-one (16ξ-methyltestosterone) (II) has been prepared from IVa by a variant of the methods described previously.

In this paper we describe the synthesis of 16-methylene-Δ^4-androsten-17β-ol-3-one (16-methylenetestosterone (Ia), an analog of testosterone prepared in these laboratories in connection with a program aimed at making available new anabolic agents. As part of the same program the 16ξ-methyltestosterone (II) of Julian, *et al.*,[2] has been synthesized by a variant of the routes used previously.[2]

For the preparation of Ia, 16ξ-dimethylaminomethyl-Δ^5-androsten-3β-ol-17-one (III) was employed as starting material, a substance readily obtainable in *ca.* 75% yield by the Mannich condensation of Δ^5-androsten-3β-ol-17-one with paraformaldehyde and dimethylamine.[2a] The cleavage of III by means of acetic acid and acetic anhydride to 16-methylene-Δ^5-androsten-3β-ol-17-one acetate (IVb) has been described,[2a] but the next step in our projected synthesis of Ia, the saponification of IVb to IVa, was unsuccessful. Treatment of the acetate IVb under mild basic or acidic conditions led mainly to polymeric, intractable materials, doubtless due to the unstable nature of the 16-methylene-17-keto function. The required free 16-methylene-Δ^5-androsten-3β-ol-17-one (IVa) was finally obtained in over 90% yield by carrying out the cleavage of the dimethylaminomethylene compound III by distillation with steam.[3]

The next step involved the Oppenauer oxidation of IVa, which when carried out with aluminum isopropoxide and cyclohexanone in toluene under carefully defined conditions, furnished about 20% of 16-methylene-Δ^4-androstene-3,17-dione (V) in addition to polymeric material. The structure of V follows from its ultraviolet maximum at 236 mμ, ϵ 23,400 (due to the superposition of the maxima at 228 mμ, ϵ 8000[2a] and at 241 mμ, ϵ 16,600[4] to be expected for the 16-methylene-17-ketone and Δ^4-3-ketone systems, respectively) and from the infrared band at 890 cm.$^{-1}$ (which however was rather weak), indicative of a methylene grouping.[5] Reduction of V with sodium borohydride yielded what we believe to be a mixture consisting of 16-methylene-Δ^4-androstene-3β,17β-diol (VIa) and the 3α,17β-diol VIb,[6] without appreciable absorption in the ultraviolet. The mixture, without purification, was subjected to oxidation with manganese dioxide[7] at room temperature. Although the diols VIa and VIb each contain two allylic alcohol functions, the 17β-hydroxy groups appear to be situated in a suf-

---

[1] Paper LXXI, F. Sondheimer, M. Velasco and G. Rosenkranz, THIS JOURNAL, **77**, 5673 (1955).

[2] (a) P. L. Julian, E. W. Meyer and H. C. Printy, *ibid.*, **70**, 3872 (1948); (b) M. Romero, J. Romo and J. Lepe, *Bol. inst. quim. univ. nacl. auton. Mex.*, **4**, 115 (1952).

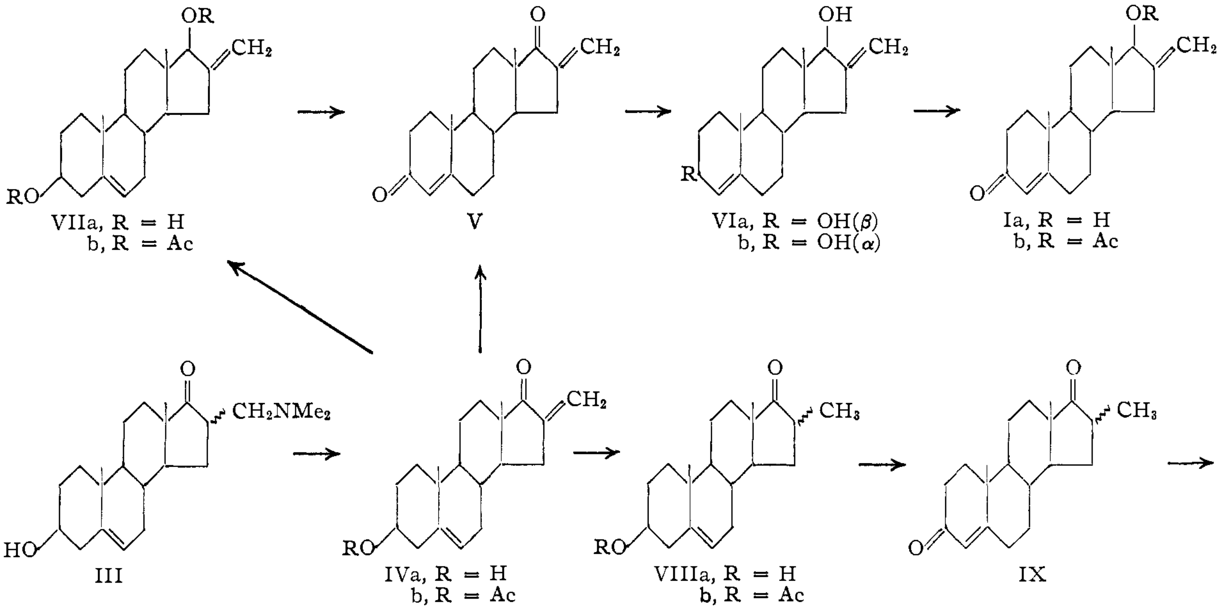
[3] *Cf.* F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 318.

[4] L. Dorfman, *Chem. Revs.*, **53**, 47 (1953), Table 7.

[5] N. Sheppard and D. M. Simpson, *Quart. Revs.*, **6**, 26 (1952).

[6] For the stereochemical course of the reduction of Δ^4-3-ketones with sodium borohydride, see W. G. Dauben, R. A. Micheli and J. F. Eastham, THIS JOURNAL, **74**, 3852 (1952). The reduction of ring D unsubstituted 17-keto-androstanes with the metal hydride gives almost exclusively the 17β-ol; inspection of a model of a 16-methylene-17-ketone such as V shows that the methylene group does not hinder the α-side of the molecule and the 17β-ol should therefore be formed in this case as well. However, the 17α-ol configuration for VIa, VIb, VIIa and Ia, although unlikely, cannot definitely be excluded at present. Unfortunately, no conclusions can be reached from rotational data, since 17α-ols and 17β-ols show almost identical rotations.

[7] *Cf.* (a) F. Sondheimer, C. Amendolla and G. Rosenkranz, *ibid.*, **75**, 5930 (1953); (b) F. Sondheimer, O. Mancera, M. Urquiza and G. Rosenkranz, *ibid.*, **77**, 4145 (1955), footnote 17.



VIIa, R = H
b, R = Ac

V

VIa, R = OH(β)
b, R = OH(α)

Ia, R = H
b, R = Ac

III

IVa, R = H
b, R = Ac

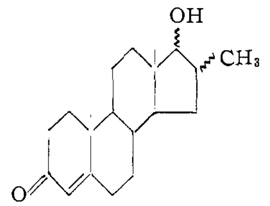
VIIIa, R = H
b, R = Ac

IX

ficiently crowded environment that their oxidation was prevented under the conditions employed. The product, obtained in about 40% yield, was assigned the 16-methylenetestosterone structure Ia since it showed an ultraviolet maximum at 240 mμ, log ϵ 4.22, typical of a Δ^4-3-ketone,[4] and since it formed a monoacetate (Ib). Indications that no reduction of the 16-methylene double bond had occurred during the sodium borohydride reaction[8] were provided by the elementary analysis of Ia and from its non-identity with the 16-methyltestosterone II of Julian, *et al.*,[2] and confirmation for the presence of the methylene function in Ia was obtained from the presence of a strong infrared band at 894 mμ[5] (as well as bands due to the unsaturated ketone and hydroxyl groups) in this compound.

An alternative route to 16-methylenetestosterone (Ia) from 16-methylene-Δ^5-androsten-3β-ol-17-one (IVa) which was investigated involved first the sodium borohydride reduction of the latter to 16-methylene-Δ^5-androstene-3β,17β-diol (VIIa),[6] further characterized as the diacetate VIIb. It was hoped that preferential Oppenauer oxidation of VIIa at C-3 would lead to Ia directly. In this case, however, this type of differential oxidation could not be realized and only the dione V was isolated.

For the synthesis of the 16-methyltestosterone II of Julian, *et al.*,[2] 16-methylene-Δ^5-androsten-3β-ol-17-one (IVa) was hydrogenated over a 5% palladium–charcoal catalyst to give 71% of 16ξ-methyl-Δ^5-androsten-3β-ol-17-one (VIIIa).[2b] Alternatively the acetate IVb[2a] was hydrogenated to VIIIb over the above-mentioned catalyst (this procedure results in a considerably higher yield than the reported hydrogenation over Raney nickel[2a]) and VIIIb was then saponified. Conventional Oppenauer oxidation of 16ξ-methyl-Δ^5-androsten-3β-ol-17-one (VIIIa) produced 82% of 16ξ-methyl-Δ^4-androstene-3,17-dione (IX).[2b] The latter was then reduced with sodium borohydride and the resulting diol mixture was oxidized with manganese dioxide at room temperature, as described previously in the 16-unsubstituted series.[7a] The 16ξ-methyl-Δ^4-androsten-17ξ-ol-3-one (16-methyltestosterone) (II) thus produced in 66% yield showed physical properties in good agreement with those reported by Julian, *et al.*[2a]



II

Experimental[9]

16-Methylene-Δ^5-androsten-3β-ol-17-one (IVa).—A suspension of 25 g. of 16ξ-dimethylaminomethyl-Δ^5-androsten-3β-ol-17-one (III) (m.p. 172–175°)[2a] in 1 l. of water was distilled in steam until the distillate no longer gave an alkaline reaction. The suspension was then cooled in ice and the crystalline precipitate was collected. This procedure yielded directly 20.2 g. (93%) of 16-methylene-Δ^5-androsten-3β-ol-17-one with m.p. 174–178° (large depression on admixture with starting material) which was used for the next step. Crystallization from acetone produced the analytical sample as fine needles with m.p. 183–184°, $[\alpha]_D$ $-56°$, $\lambda_{max.}$ 228 mμ, log ϵ 3.91, $\nu_{max.}$ 1722 and 890 (weak) cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.68; H, 9.37.

16-Methylene-Δ^4-androstene-3,17-dione (V).—About 100 cc. was distilled from a solution containing 42.4 g. of 16-methylene-Δ^5-androsten-3β-ol-17-one in 1500 cc. of toluene and 150 cc. of cyclohexanone, in order to remove moisture. Aluminum isopropoxide (40 g.) dissolved in 200 cc. of toluene was then added to the refluxing solution during 10 minutes and refluxing was continued for a further 30 minutes with exclusion of moisture. After the volatile components

---

(8) *Cf.* F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz, *Chemistry & Industry*, 1482 (1954).

(9) Melting points are uncorrected. Rotations were determined at 20° in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are indebted to Miss T. Cardenas and Mrs. P. Lopez for these measurements as well as for the infrared spectra which were determined in chloroform solution on a Perkin-Elmer model 12C single beam spectrophotometer with sodium chloride prism. We would like to thank also Mrs. A. Gonzalez for the microanalyses.

had been removed by steam distillation, the residue was extracted well with ethyl acetate and the organic extract was washed with water, dried and evaporated. The amorphous residue ($\lambda_{max.}$ 238 mμ, log ϵ 4.29) was chromatographed on 2 kg. of neutral alumina. Crystallization of the fractions eluted with benzene from acetone–ether furnished 7.78 g. (18.5%) of the dione V as heavy rods with m.p. 159–161°, $[\alpha]_D$ +110°, $\lambda_{max.}$ 236 mμ, log ϵ 4.37, $\nu_{max.}$ 1722, 1660 and 890 (weak) cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.81; H, 8.78.

If the reaction time of the Oppenauer oxidation was prolonged, the amount of high-melting, insoluble polymeric material which is obtained in the reaction was considerably increased.

16-Methylene-Δ^4-androsten-17β-ol-3-one (16-Methylenetestosterone) (Ia).—A solution of 5 g. of sodium borohydride in 15 cc. of water was added to an ice-cooled solution of 5.14 g. of 16-methylene-Δ^4-androstene-3,17-dione in 600 cc. of methanol and the mixture was allowed to stand for 16 hours at room temperature. The excess reagent was decomposed by addition of acetic acid, the solution was concentrated to small volume *in vacuo* and diluted with water. The product was extracted with ethyl acetate and the extract was washed with water, dried and evaporated. The solid residue (5.12 g.) consisting of the diols VIa and VIb (probably together with some of the corresponding 17α-isomers) showed no appreciable absorption in the ultraviolet and was shaken at 20° for 8 hours in 500 cc. of chloroform with 50 g. of manganese dioxide.[7] The dioxide was removed, washed well with hot chloroform and the solvent was evaporated. The residue was chromatographed on 250 g. of neutral alumina and the fractions eluted with benzene–ether on crystallization from acetone then yielded 2.02 g. (39%) of 16-methylenetestosterone as regular laths with m.p. 187–188°, $[\alpha]_D$ −15°, $\lambda_{max.}$ 240 mμ, log ϵ 4.22, $\nu_{max.}$ 1660 and 894 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.02; H, 9.37.

The acetate Ib was prepared by heating Ia with acetic anhydride and pyridine for 1 hour at 90° and after crystallization from acetone–hexane gave needles with m.p. 148–150°, $[\alpha]_D$ −4°, $\lambda_{max.}$ 240 mμ, log ϵ 4.24, $\nu_{max.}$ 1736, 1660 and 894 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.23; H, 9.00.

16-Methylene-Δ^5-androstene-3β,17β-diol (VIIa).—A solution of 2 g. of 16-methylene-Δ^5-androsten-3β-ol-17-one (IVa) in 300 cc. of methanol was reduced with 2 g. of sodium borohydride in 6 cc. of water, as described above for V. The solid was collected from the concentrated and water-diluted reaction mixture and after being dried and crystallized from acetone gave 1.44 g. (71.5%) of the diol VIIa with m.p. 195–196°, $[\alpha]_D$ −136°, no appreciable absorption in the ultraviolet.

Anal. Calcd. for $C_{20}H_{30}O_2 \cdot H_2O$: C, 74.95; H, 10.07. Found: C, 74.71; H, 10.01.

The diacetate VIIb on recrystallization from acetone showed m.p. 189–191°, no appreciable absorption in the ultraviolet, $\nu_{max.}$ 1736 and 892 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.76; H, 8.96.

On Oppenauer oxidation of VIIa and careful chromatography of the product only a small amount of 16-methylene-Δ^4-androstene-3,17-dione and none of the 16-methylenetestosterone could be isolated.

16ξ-Methyl-Δ^5-androsten-3β-ol-17-one (VIIIa).—A solution of 10 g. of 16-methylene-Δ^5-androsten-3β-ol-17-one (IVa) in 500 cc. of ethanol was shaken in hydrogen over 2 g. of a 5% palladium–charcoal catalyst at 23° and 586 mm. The hydrogenation was stopped when about 1 equivalent of gas had been absorbed and uptake had become very slow. Removal of catalyst and solvent followed by crystallization of the residue from ether–hexane furnished 7.1 g. of the 16-methyl compound VIIIa as fine needles with m.p. 174–175°, $[\alpha]_D$ +2°; reported[2b] m.p. 176–178°, $[\alpha]_D$ 0°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.68; H, 10.13.

Alternatively VIIIa (m.p. 170–172°, undepressed on admixture with the above sample) could be prepared in 75% yield by saponification of its acetate VIIIb[2a] by boiling for 2 hours with potassium carbonate in 90% aqueous methanol. 16ξ-Methyl-Δ^5-androsten-3β-ol-17-one acetate (VIIIb) with m.p. 143–145° was obtained in 88% yield by hydrogenation of the corresponding 16-methylene derivative IVb[2a] in ethanol solution over a 5% palladium–charcoal catalyst, as described above for the free 3β-ol IVa (Julian, *et al.*,[2a] obtained a 53% yield of VIIIb by carrying out this hydrogenation over Raney nickel).

16ξ-Methyl-Δ^4-androstene-3,17-dione (IX).—An Oppenauer oxidation was carried out with 7 g. of 16ξ-methyl-Δ^5-androsten-3β-ol-17-one (VIIIa) through refluxing it for 90 minutes with 6 g. of aluminum isopropoxide in 600 cc. of toluene and 50 cc. of cyclohexanone. The product was isolated as described for the corresponding 16-methylene derivative V and on crystallization from acetone–hexane gave 5.7 g. (82%) of the dione IX with m.p. 178–179°, $[\alpha]_D$ +175°, $\lambda_{max.}$ 240 mμ, log ϵ 4.23; reported[2b] m.p. 182–183°, $[\alpha]_D$ +184°.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.11; H, 9.66.

16ξ-Methyl-Δ^4-androsten-17ξ-ol-3-one (16ξ-Methyltestosterone) (II).—16ξ-Methyl-Δ^4-androstene-3,17-dione (5.7 g.) was reduced with 4 g. of sodium borohydride in 300 cc. of methanol and 20 cc. of water as described above for the 16-methylene derivative V. The crude diol mixture precipitated by water (no appreciable absorption in the ultraviolet) was dissolved in 400 cc. of chloroform and shaken with 50 g. of manganese dioxide for 16 hours at room temperature. The solid was removed and washed well with hot chloroform. Evaporation of solvent followed by crystallization of the residue from acetone produced 3.80 g. (66%) of 16-methyltestosterone with m.p. 182–183°, $[\alpha]_D$ +106°, $\lambda_{max.}$ 240 mμ, log ϵ 4.23, $\nu_{max.}$ 1660 cm.$^{-1}$ and free hydroxyl band; reported[2a] m.p. 182–184°, $[\alpha]_D$ +106°.

MEXICO D. F., MEXICO