[CONTRIBUTION FROM THE DIVISION OF STEROID METABOLISM AND BIOCHEMISTRY, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Chemistry of D-Homosteroids[1]

DAVID K. FUKUSHIMA, SHIRLEY DOBRINER, AND R. S. ROSENFELD

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3β,17β-Dihydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIb) has been synthesized and found to be the 17a-D-homo ketone obtained from the base-catalyzed D-homoannulation of 3β-acetoxy-17α-hydroxyallopregnane-20-one. The axial 17β-substituent of the 3-monoacetate and 3,17-diacetate of VIIIb was readily cleaved with zinc and acetic acid to 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X). Its epimer, 3β-acetoxy-17β-methyl-D-homoandrostane-17a-one (Ia), was synthesized. IXa was readily isomerized to X with base or acid. Ring D in IX was found to exist in the boat form by rotatory dispersion study.

In the study of reductive dehydroxylation of the epimeric pair of 17a-hydroxy-17a-methyl-D-homo-17-ketosteroids with zinc and acetic acid, it was found that the axial 17aα-hydroxyl group in 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (Ia) was readily removed whereas the equatorial 17aβ-hydroxyl group in the epimer (IIa) was stable under the same condition.[2] Of the epimeric pair of 17-hydroxy-17-methyl-D-homo-17a-ketones only 3β,17α-diacetoxy-17β-methyl-D-homoandrostane-17a-one (IIIa) was available which has the acetoxyl group in the equatorial conformation when ring D is in the chair form. The 17α-acetoxyl group was readily deacetoxylated with zinc and acetic acid to yield 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X), suggesting that the reduction of IIIa proceeded with ring D in the boat form in which the 17α-acetoxyl group is in the axial conformation.[2] In order to extend the study of the reductive elimination of the hydroxyl or acetoxyl group in the D-homosteroids with zinc and acetic acid, the synthesis of 3β,17β-dihydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIb) and its 3-monoacetate VIIIa and 3,17-diacetate VIIIc as well as 3β-acetoxy-17β-methyl-D-homoandrostane-17a-one (IXa) has been accomplished. The results of the dehydroxylation studies of the epimeric ketols VIIIa and IIIb are fully in accord with the concept of axial conformation of the outgoing hydroxyl group.[2]

The preparation of 3β-acetoxy-17β-hydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIa) followed the procedure described for 3α-acetoxy-17β-hydroxy-17α-methyl-D-homoetiocholane-11,17-dione.[3] 3β-Acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one (IIIb), obtained by the acid-catalyzed D-homoannulation of 3β-acetoxy-17α-hydroxyallopregnane-20-one,[4] was treated with methanesulfonyl chloride in pyridine and the resulting mesylate IIIc was converted to 3β-acetoxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVa) with potassium acetate in acetic acid. The presence of the α,β-unsaturated ketone was established by the absorption at 235 mμ (ε = 8,200) which corresponds to that in the 11-keto-Δ^{16}-D-homoetiocholene derivative.[3] The unsaturated ketone IVa was treated with *N*-bromosuccinimide and perchloric acid to give the bromohydrin V which was converted to 3β-acetoxy-16β,-17β-oxido-17α-methyl-D-homoandrostane-17a-one (VI) with alkali. The preparation of 3β-acetoxy-17β-hydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIa) was achieved by the opening of the oxide ring of VI with hydrogen bromide to VII and the reductive debromination of the 16α-halogen. Saponification of the monoacetate VIIIa afforded the dihydroxy ketone VIIIb and acetylation of VIIIa with acetic anhydride, acetic acid and toluene-sulfonic acid yielded the diacetate VIIIc. The synthesis of 3β-acetoxy-17β-hydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIa), m.p. 158–158.5°, completes the series of four epimeric D-homoandrostane-17,17a-ketols.

In the base-catalyzed D-homoannulation of 3β-acetoxy-17α-hydroxyallopregnane-20-one,[4] 3β,17aβ-dihydroxy-17aα-methyl-D-homoandrostane-17-one (IIb) and its 17aα-hydroxy-17aβ-methyl epimer (Ib) were the principal products. In addition a small amount of an unknown 17a-ketone was obtained. Its monoacetate, m.p. 156.5–158.5°, had an infrared spectrum in carbon disulfide solution identical with that of the newly synthesized 3β-acetoxy-17β-hydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIa). Therefore the unknown compound can now be assigned the structure of the 17β-hydroxy-17α-ketone VIIIa.

When 3β-acetoxy-17β-hydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIa) was refluxed for twenty-four hours with zinc dust in glacial acetic acid, 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X) was obtained in 83% yield. The di-

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) R. S. Rosenfeld, *J. Am. Chem. Soc.*, **79**, 5540 (1957).

(3) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Am. Chem. Soc.*, **78**, 5027 (1956).

(4) D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling, and G. Roberts, *J. Am. Chem. Soc.*, **77**, 6585 (1955).

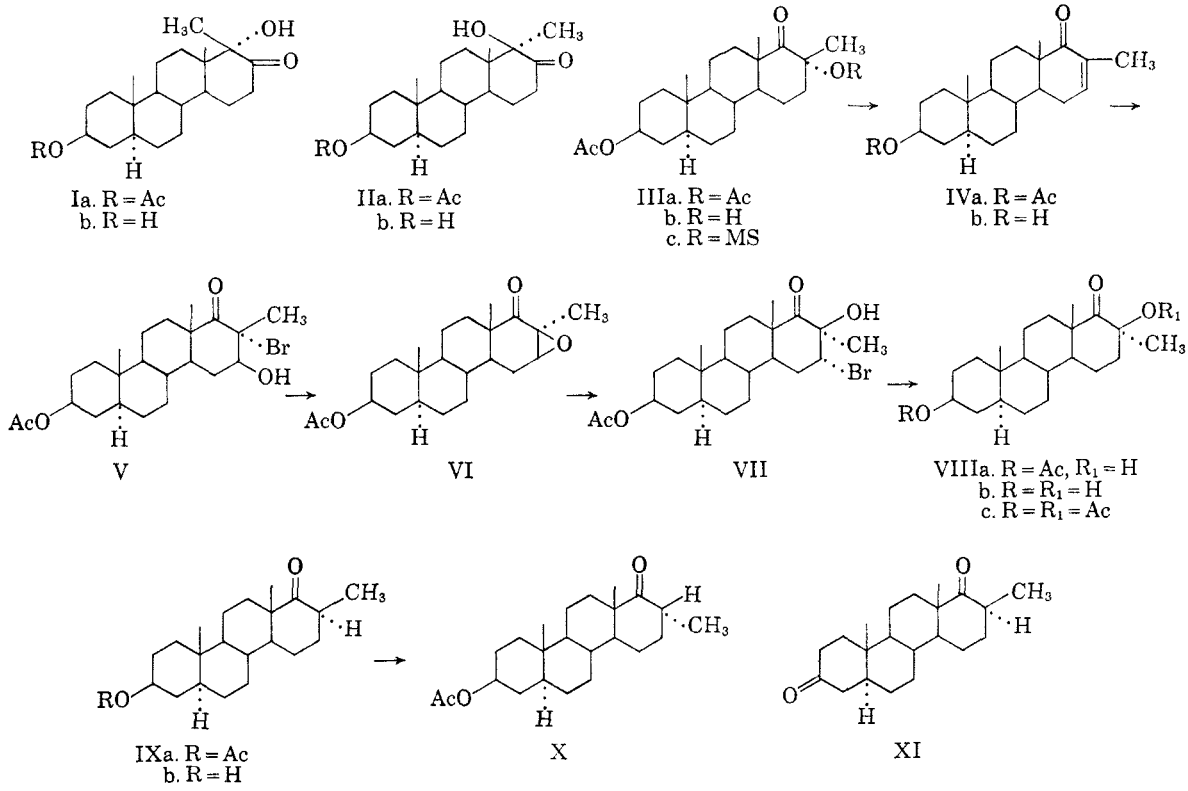

Figure 1

acetate VIIIc was reduced quantitatively to X. The 17β-substituents in these compounds were readily cleaved since they are in the axial conformation in the chair form of ring D. The lower conversion with the 17β-hydroxy derivative VIIIa is in accord with the earlier findings with 17α-hydroxy-and 17α-acetoxy-20-ketosteroids[2] in which the ketol acetates were more readily reduced due to the greater anionic stability of the acetate ion *vs.* the hydroxide ion. Under identical conditions 3β-acetoxy - 17α - hydroxy - 17β - methyl - D - homoandrostane - 17a - one (IIIb) afforded 22% of X and 58% of the starting material, and the fully acetylated derivative IIIa yielded X quantitatively. The formation of the reductive dehydroxylation product X in a low yield from the 17α-hydroxy-17a-ketone IIIb is probably the result of ring D existing primarily in the chair conformation despite the 1,3 interaction of the methyl groups at C-13 and C-17.[5] However under the conditions of reductive dehydroxylation, ring D may assume the boat conformation (B in Fig. 2) with the 17α-hydroxyl group axial. The slow reduction of hydroxy ketones accounts for the small amount of X in the reaction IIIb → X. However, the fully acetylated derivative IIIa, the rapid reductive cleavage of B to X shifts the equilibrium A⇆B

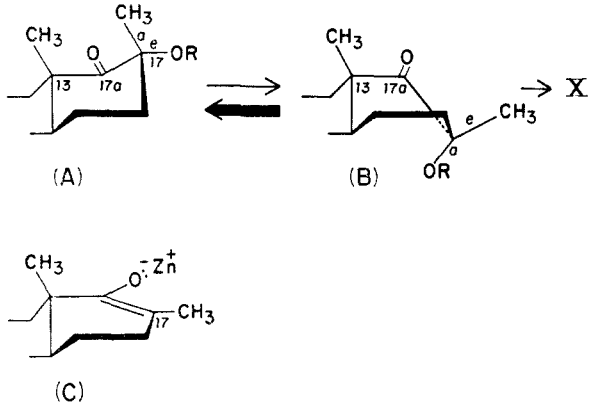

Figure 2

to the right and the reduction is essentially quantitative.

The dehydroxylation of IIIb and VIIIa as well as the deacetoxylation of IIIa resulted in the isolation of 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X), the more stable isomer. The enol-zinc transition complex C probably has a structure intermediate between the chair and boat forms. Proton addition at C-17 then afforded the more stable product X in which ring D has the chair conformation and the 17-methyl group is α (no 1,3 interaction) and equatorial.

Catalytic hydrogenation of 3β-acetoxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVa) introduced the hydrogen from the α face[6] to yield 3β-acetoxy - 17β - methyl - D - homoandrostane - 17a-

(5) The optical rotatory dispersion curve of IIIb showed a + 79, a value consistent with that expected for IIIb with ring D in the chair conformation (A in Fig. 2). (The authors thank Dr. W. Klyne for this information.)

one (IXa). Its physical constants differed from the known uranolone acetate, 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X).[7] With ring D in the chair form the 17β-methyl group in IXa is in the axial conformation and there is an 1,3 interaction with the angular methyl group at C-13. Optical rotatory dispersion studies[8] of 3β-acetoxy-17β - methyl - D - homoandrostane - 17a - one (IXa) showed a very strong positive curve (amp + 160) compatible with a twist form[9] of ring D in which the 17β-methyl group is in the equatorial conformation. The 17-methyl group in IXa was readily isomerized to the equatorial 17α-methyl with methanolic potassium hydroxide or by refluxing in glacial acetic acid to give 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X). The rotatory dispersion curve of X is similar to that of the unsubstituted D-homo-17a-ketone[10] and is abnormal in not exhibiting a Cotton effect.[8] Because of the instability of the 17β-methyl-17a-ketone IXa to alkali, the hydroxy ketone IXb was prepared by catalytic reduction of 3β-hydroxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVb), the hydrogen atoms entering from the rear face at C-16 and C-17. Oxidation of the hydroxy ketone IXb with chromic acid yielded 17β-methyl-D-homoandrostane - 3,17a - dione (XI) which differed from the known uranedione, 17α-methyl-D-homoandrostane-3,17a-dione.[7] The molecular rotation difference (ΔM_D 17α-17β) between the diketones, +301, was similar to that between the acetoxy ketones IX and X, +282.

EXPERIMENTAL[11]

3β-Acetoxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVa). Freshly distilled methanesulfonyl chloride (9 ml.) was added to a cold solution of 7.10 g. of 3β-acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one (IIIb)[4] in 170 ml. of pyridine. The mixture was stored at 5° for 16 hr. and then at 30° for 2 hr., poured onto ice and water and the reaction product extracted with ether. The ether solution was washed with dilute acid, dilute base and water, dried over sodium sulfate and the ether evaporated to give 7.75 g. of crude mesylate IIIc.[12] Without further purification the crude mesylate was refluxed for 3 hr. with 16 g. of freshly fused potassium acetate in 2 l. of acetic acid and 12 ml. of acetic anhydride. The solution was concentrated to one-half the volume *in vacuo* and poured into 10% sodium chloride solution. The precipitate was extracted with ethyl acetate, washed with sodium carbonate and water. The ethyl acetate solution was dried and the solvent evaporated to give 3.68 g. of crystalline product. Chromatography on acid-washed alumina and elution with benzene afforded 3.06 g. of 3β-acetoxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVa). Recrystallizations from acetone yielded 2.75 g. of needles, m.p. 206.5–210°; $[\alpha]_D^{29}$ −71.2; $\lambda_{max}^{ethanol}$ 235 mμ (8,200); $\nu_{max}^{CS_2,CCl_4}$ 1736, 1676, 1429 and 1243 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.04; H, 9.56. Found: C, 77.37; H, 9.67.

Saponification of 205 mg. of 3β-acetoxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVa) in 2.5% methanolic potassium hydroxide at room temperature afforded 163 mg. of 3β-hydroxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVb). Recrystallizations from acetone yielded rods, m.p. 196–196.5°; $[\alpha]_D^{27}$ −67.9° (ethanol); $\lambda_{max}^{ethanol}$ 237 mμ (8,800); $\nu_{max}^{CS_2,CCl_4}$ 3610, 1677 and 1430 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.70; H, 10.01.

3β-Acetoxy-16β,17β-oxido-17α-methyl-D-homoandrostane-17a-one (VI). A solution of 42.5 ml. of 1*N* perchloric acid was slowly added with stirring to a cold solution of 1.70 g. of 3β-acetoxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVa) and 9.0 g. of *N*-bromosuccinimide in 96 ml. of dioxane and 11 ml. of water. The reaction mixture was then stirred for 3 hr. at room temperature. The excess *N*-bromosuccinimide was destroyed with sodium bisulfite solution and the product extracted with ether. The ether solution was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 2.91 g. of oily product. Without further purification, the crude bromohydrin was dissolved in 57 ml. of methanol and treated with 1.7 g. of potassium hydroxide in 3 ml. of water and 11 ml. of methanol. After 30 min. at room temperature the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate and processed in the usual manner to give 1.25 g. of oil. Acetylation with acetic anhydride and pyridine afforded 1.55 g. of 3β-acetoxy-16β,17β-oxido-17α-methyl-D-homoandrostane-17a-one (VI). Chromatography on silica gel and elution with ethyl acetate–petroleum ether (b.p. 30–60°) yielded 927 mg. of the β-oxido VI, m.p. 160.5–164°. Recrystallization from methanol gave the analytical sample of 3β-acetoxy-16β,17β-oxido-17α-methyl-D-homoandrostane-17a-one (VI), m.p. 164–166°; $[\alpha]_D^{27}$ −43.3°; $\nu_{max}^{CS_2,CCl_4}$ 1737, 1705, and 1243 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.45; H, 8.81.

3β-Acetoxy-17β-hydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIa). A cold solution of 542 mg. of 3β-acetoxy-16β-17β-oxido-17α-methyl-D-homoandrostane-17a-one (VI) in 36 ml. of acetic acid was treated with 4 ml. of 30% hydrogen bromide in acetic acid. The mixture was allowed to stand at 15° for 45 min. and the solvent evaporated *in vacuo*. The residue was crystallized by solution in acetone-ether and removal of the solvent *in vacuo*. 3β-Acetoxy-17β-hydroxy-17α-methyl-16α-bromo-D-homoandrostane-17a-one (VII) thus obtained melted at 166.5–168.5°. Without purification the bromohydrin was hydrogenated in 15 ml. of ethyl acetate, 50 ml. of methanol and 6.5 ml. of water in the presence of 25% palladium on calcium carbonate. Recrystallization of the reduction product yielded 289 mg. of 3β-acetoxy-17β-hydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIa), m.p. 153.5–156.5°. Chromatography of the mother liquor afforded an additional 180 mg. of VIIIa, m.p. 152–153.5°. The analytical sample from acetone-cyclohexane melted at 158–158.5°; $[\alpha]_D^{28}$ +13.6°; $\nu_{max}^{CS_2,CCl_4}$ 3600, 3530, 1737, 1707 and 1243 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.61; H, 9.84.

A solution of 204 mg. of 3β-acetoxy-17β-hydroxy-17α-

(6) N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 953 (1958).

(7) W. Klyne, *Nature*, 166, 559 (1950). The authors are grateful to Dr. W. Klyne for an authentic sample.

(8) The authors thank Dr. W. Klyne for these results.

(9) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

(10) C. Djerassi, W. Closson, and A. E. Lippman, *J. Am. Chem. Soc.*, **78**, 3163 (1956).

(11) The melting points were taken on a micro-hot stage and are corrected. The optical rotations were determined in chloroform unless otherwise specified. The infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer; calcium fluoride prism 4000–2750 cm.$^{-1}$, 1800–1600 cm.$^{-1}$, 1500–1280 cm.$^{-1}$; sodium chloride prism 1300–650 cm.$^{-1}$; sh = shoulder.

(12) N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 1828 (1958), isolated an isomeric side product in 25–30% yield from an analogous mesylation reaction.

methyl-D-homoandrostane-17a-one (VIIIa) in 20 ml. of 5% methanolic potassium hydroxide was refluxed for 1 hr. The saponification mixture was worked up in the usual manner to yield 185 mg. of 3β,17β-dihydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIb). Recrystallization from acetone afforded 104 mg. of the dihydroxy ketone, m.p. 175–178°. The analytical sample of VIIIb melted at 180–182°, and 184–186.5°; $[\alpha]_D^{26}$ +23.4°; $\nu_{max}^{CHCl_3}$ 3600 and 1702 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.23; H, 10.09.

Acetylation with pyridine and acetic anhydride at room temperature afforded the 3-monoacetate VIIIa.

3β,17β-Diacetoxy-17α-methyl-D-homoandrostane-17a-one (VIIIc). To 80 mg. of the monoacetate VIIIa and 0.8 ml. of acetic anhydride dissolved in 4.0 ml. of glacial acetic acid was added 100 mg. of toluenesulfonic acid monohydrate. After 4 hr. at room temperature, the solution was mixed with crushed ice and the mixture was extracted with ether. The ether solution was washed with water, 5% sodium hydroxide, and again with water until neutral. After drying with sodium sulfate and concentrating the ether solution, 79 mg. of 3β,17β-diacetoxy-17α-methyl-D-homoandrostane-17a-one (VIIIc) was obtained. Recrystallization from methanol yielded 43 mg., m.p. 192–196°, and 24 mg. of a second crop m.p. 187–193°. The analytical sample of VIIIc melted at 196–199°; $[\alpha]_D^{27}$ −16.9°; $\nu_{max}^{CS_2,CCl_4}$ 1749 (sh), 1737, 1721, and 1245 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 72.09; H, 9.11.

Deacetoxylation of 23 mg. of VIIIc according to the conditions described below afforded 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X) in quantitative yield.

3β-Acetoxy-17β-methyl-D-homoandrostane-17a-one (IXa). A solution of 500 mg. of 3β-acetoxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVa) in ethyl acetate was hydrogenated in the presence of 10% palladium-charcoal. Recrystallization from cyclohexane afforded 307 mg. of 3β-acetoxy-17β-methyl-D-homoandrostane-17a-one (IXa), m.p. 150–154°. The analytical sample melted at 150.5–153°; $[\alpha]_D^{26}$ +48.2° (acetone); $\nu_{max}^{CS_2}$ 1737, 1709, and 1243 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.66; H, 10.03.

A solution of 125 mg. of 3β-hydroxy-17-methyl-Δ^{16}-D-homoandrostene-17a-one (IVb) in 20 ml. of ethyl acetate was hydrogenated in the presence of 65 mg. of 10% palladium-charcoal. Recrystallizations from acetone yielded 3β-hydroxy-17β-methyl-D-homoandrostane-17a-one (IXb), m.p. 152–155.5°; $[\alpha]_D^{29}$ +93.6°; $\nu_{max}^{CS_2,CCl_4}$ 3605 and 1708 cm.$^{-1}$ The melting point of the mixture with its 3-acetate (IXa), 150.5–153°, was depressed to 134–138°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.32; H, 10.83.

3β-Acetoxy-17α-methyl-D-homoandrostane-17a-one (X). A solution of 20 mg. of 3α-acetoxy-17β-methyl-D-homoandrostane-17a-one (IXa), m.p. 150–154°, in 20 ml. of glacial acetic acid was refluxed for 24 hr. After cooling, the solution was evaporated and gave needles melting 158–161°. One recrystallization from methanol afforded 16 mg. of epimeric 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X), m.p. 166–168°; the infrared spectrum was identical with an authentic sample of X.[7]

3β-Acetoxy-17β-methyl-D-homoandrostane-17a-one (IXa, 26 mg.) was refluxed with 2.5% methanolic potassium hydroxide for 2 hr. The mixture was extracted with ether, washed with water, dried, and the ether evaporated to give 31 mg. of product. Acetylation and recrystallization from methanol yielded 16 mg. of 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X), m.p. 170.5–172°; the melting point was not depressed upon mixing with an authentic sample. The infrared spectrum in carbon disulfide solution was identical with that of the authentic sample.

1 β-Methyl-D-homoandrostane-3,17a-dione (XI). A solution of 32 mg. of 3β-hydroxy-17β-methyl-D-homoandrostane-17a-one (IXb) and 15 mg. of chromic oxide in 2.7 ml. of acetic acid was allowed to stand at room temperature for 2 hr. The oxidation product was chromatographed on alumina and elution with benzene-petroleum ether (3:1) yielded 19 mg. of 17β-methyl-D-homoandrostane-3,17a-dione (XI), m.p. 130, 144.5–146.5°. Recrystallizations from acetone–petroleum ether afforded plates, m.p. 151–152.5°; $[\alpha]_D^{26}$ +74.4°; $\nu_{max}^{CS_2,CCl_4}$ 1717 (sh), 1710, 1427 (sh), and 1417 cm.$^{-1}$ The infrared spectrum differed from that of an authentic sample of 17α-methyl-D-homoandrostane-3,17a-dione (uranedione), m.p. 170–172°, reported[7] m.p. 171–174°; $[\alpha]_D^{25}$ −21°.

Dehydroxylation of 3β-acetoxy-17β-hydroxy-17α-methyl-D-homoandrostane-17a-one (VIIIa) *with zinc in acetic acid.* A solution of 94 mg. of VIIIa in 70 ml. of glacial acetic acid was refluxed for 24 hr. with 10 g. of zinc dust. The mixture was cooled, filtered through Celite, and the filtrate was concentrated on a steam bath *in vacuo*. This material was dissolved in ether and the solution was washed with water, 5% sodium hydroxide, and water until the washings were neutral. The ether solution was dried over sodium sulfate and concentrated to afford 82 mg. of crystalline material, m.p. 142–168°; after one recrystallization from methanol, m.p. 163–165°. The infrared spectrum in carbon disulfide was identical with a sample of 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X).

Dehydroxylation of 3β-acetoxy-17α-hydroxy-17β-methyl-D-homandrostane-17a-one (IIIb) *with zinc in acetic acid.* Two hundred sev. n milligrams of IIIb in 125 ml. of glacial acetic acid was refluxed for 24 hr. with 20 g. of zinc dust. Following the procedure described in the previous paragraph, an oil was obtained which was chromatographed on 40 g. of silica gel. Two principal fractions were recovered from the ether–petroleum ether eluates. The first (petroleum ether–ether, 9:1) weighed 44 mg., m.p. 153–160°; with an infrared spectrum identical in carbon disulfide with 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (X). The second fraction, 119 mg. eluted by petroleum ether–ether (4:1) melted at 102–106° and had an infrared spectrum in carbon disulfide identical with the starting material (IIIb).

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