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Anabolic Agents. Derivatives of 5α-Androst-1-ene

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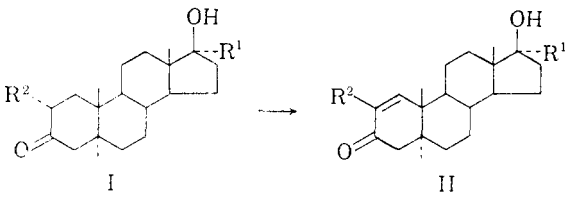
Various derivatives of 5α-androst-1-ene have been prepared in the hope of obtaining compounds with high anabolic and minimal androgenic activity. The initial high order of biological activity in this series prompted the synthesis of other modifications. The preparation of 2α-methyl and 6β-methyl-5α-androst-1-ene derivatives as well as a new method for the synthesis of the intermediate 2α-methyl-3-ketosteroids is described. Anabolic and androgenic activities of a number of these compounds are reported.

As early as 1935 Kochakian and Murlin[1] demonstrated that testosterone had a marked affect on protein biosynthesis. The androgenicity of testosterone, however, has limited its clinical use for protein anabolic effects. As a consequence, there has been a considerable effort to synthesize potent anabolic agents possessing little or no virilizing activity.[2]

In 1940 Butenandt and Dannenberg[3] reported that the Δ^1 isomer of testosterone (IIa) was much less androgenic than testosterone itself. No information, however, has appeared pertaining to the myotrophic activity of this compound. Since this compound possessed all of the structural features generally associated with high anabolic activity, a program was initiated to prepare various substituted 5α-androst-1-enes.[4]

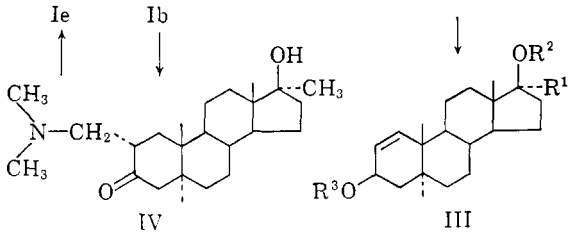
While 17β-hydroxy-5α-androst-1-en-3-one (IIa) could be prepared readily by bromination of 5α-androstan-17β-ol-3-one and subsequent dehydrobromination, preparation of the 17α-alkyl homologs necessitated bromination under buffered conditions in order to keep the acid labile tertiary hydroxyl group intact. Bromination in an acetic acid-sodium acetate buffer or dimethylformamide was found to be suitable for this purpose.

Moreover, the synthesis of the 3-keto-Δ^1-steroids was further complicated by the fact that dehydrohalogenation of the intermediate 2-bromo-compounds gave some Δ^4 isomer as a contaminant. This was not unexpected since Djerassi and Scholz[5] have shown that dehydrohalogenation of 2α-bromo-5α-androstan-17β-ol-3-one hexahydrobenzoate with collidine gave 42% and 18% of the Δ^1 and Δ^4 isomers, respectively. We have also found that dehydrobromination of pure 2α-bromo-17α-methyl-5α-androstan-17β-ol-3-one with lithium chloride and lithium carbonate in dimethylformamide gives both isomers. Thin layer chromatography of the crude dehydrobrominated product demonstrated the presence of approximately 5–10% of methyl testosterone.[6]



I II

a. $R^1 = R^2 = H$
b. $R^1 = CH_3$, $R^2 = H$
c. $R^1 = C_2H_5$, $R^2 = H$
d. $R^1 = H$, $R^2 = CH_3$
e. $R^1 = R^2 = CH_3$
f. $R^1 = C_2H_5$, $R^2 = CH_3$
g. $R^1 = CH_3$, $R^2 = Br$



IV III

a. $R^1 = R^2 = R^3 = H$
b. $R^1 = R^3 = H$, $R^2 = CH_3CO$
c. $R^1 = H$, $R^2 = R^3 = CH_3CO$
d. $R^1 = CH_3$, $R^2 = R^3 = H$
e. $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3CO$
f. $R^1 = C_2H_5$, $R^2 = R^3 = H$
g. $R^1 = C_2H_5$, $R^2 = H$, $R^3 = CH_3CO$

Although the 3-keto-Δ^1-steroids can be purified by chromatography, a more expedient method was sought. A modification of the recently reported[7] use of sodium metabisulfite for purification of isomeric corticoid derivatives was found to be particularly suitable and also obviated initial purification of the 2-bromo compound. In this process, advantage was taken of the differences in the rate of reaction of the various products with bisulfite ion. Brief treatment (two to three minutes) of the crude dehydrohalogenated mixture with excess bisulfite in aqueous methanol at room

(1) C. D. Kochakian and J. R. Murlin, *J. Nutrition*, 10, 437 (1935).

(2) *Cf.* L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, p. 592.

(3) A. Butenandt and H. Dannenberg, *Ber.*, 73, 206 (1940).

(4) The 1957 IUPAC rules on steroid nomenclature as set forth in *J. Am. Chem. Soc.*, 82, 5577 (1960), have been followed.

(5) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, 69, 2404 (1947).

(6) We are indebted to Dr. E. G. Daskalakis and Mrs. J. Beilstein of our chromatography section for this data.

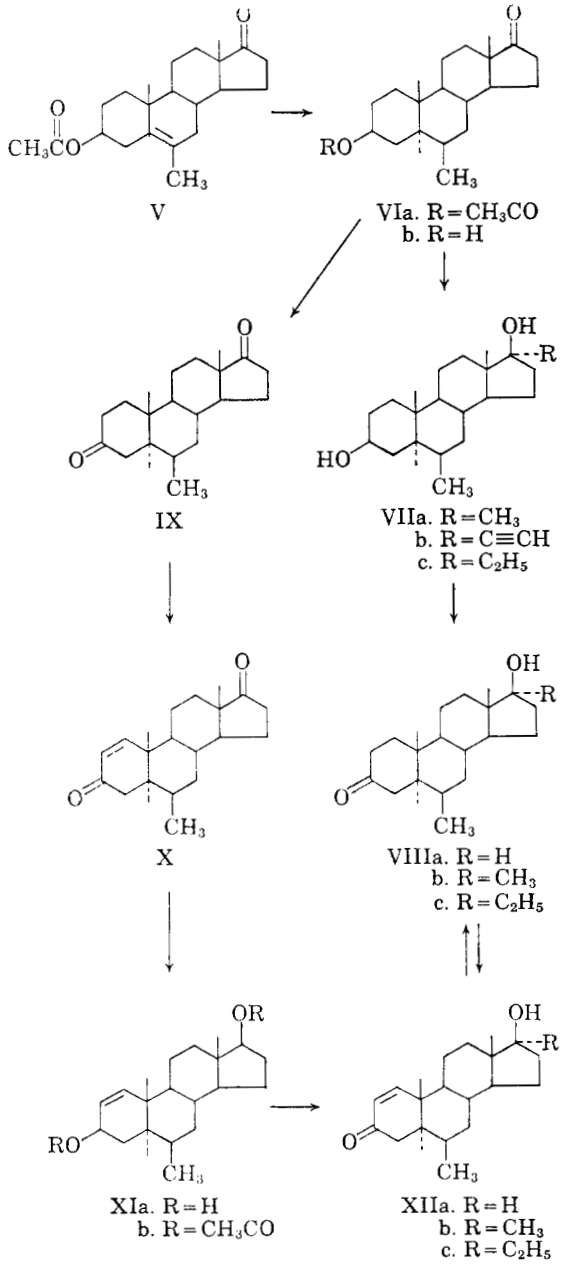
(7) A. G. Long and L. J. Wyman, U. S. Patent 2,908,695 (1959).

temperature furnished the water soluble adduct of any unchanged saturated 3-ketosteroid. The less reactive unsaturated derivatives were removed by extraction and the residue obtained after removal of the solvent was retreated with bisulfite for one and one-half hours at the reflux temperature. This afforded a water-soluble adduct which upon alkaline decomposition gave pure 3-keto-Δ^1 material. Chromatography of the water insoluble residues showed that 2-bromo-3-keto-Δ^1, 3-keto-$\Delta^{1,4}$- and 3-keto-Δ^4-androstene derivatives were resistant to bisulfite-adduct formation under these conditions.

When it was found that the 5α-androst-1-ene derivatives exhibited high anabolic activity, our study was expanded to include modifications of these molecules in the hope of potentiating this effect. The C-3 carbonyl group was reduced to the 3β-ol with either lithium aluminum hydride or lithium tri-*t*-butoxyaluminohydride. The stereospecific course of hydride reduction of 3-keto-Δ^1-steroids to the 3β-alcohols is well established.[8] The corresponding acetates were also prepared for biological evaluation.

Since methyl substituents at C-2[9] and C-6[10] in the androstane series have been reported to increase the anabolic-androgenic ratio, these modifications were made in the 5α-androst-1-ene series. The 2-methyl analogs[11] were prepared from the corresponding 2α-methyl-5α-androstane derivatives. Ringold and coworkers[9] have reported recently on the preparation of these intermediates by two general methods. One method involved condensation of the saturated 3-ketosteroid with excess ethyl oxalate and methylation of the resulting 2-ethoxyoxalate followed by reversal of the oxalate condensation with alkoxide. The other method, which they found to be more convenient, consisted of catalytic hydrogenation of the 2-hydroxymethylene derivatives. We have found that these compounds can also be prepared by hydrogenolysis of the 2α-dimethylaminomethyl derivative readily obtained *via* the Mannich reaction on the 3-ketosteroid progenitor. For example, hydrogenation of 2α-dimethylaminomethyl-17α-methyl-5α-androstan-17β-ol-3-one (IV) in isopropyl alcohol at 130° under pressure over palladium-on-barium sulfate afforded after chromatography 71.5% yield of 2α,17α-dimethyl-5α-androstan-17β-ol-3-one (Ie).

The 6β-methyl analogs were prepared from 6-methyl-3β-acetoxy-androst-5-en-17-one (V).[12] Catalytic hydrogenation of this material in acetic acid over palladium-on-carbon furnished the corresponding 6β-methyl-5α-androstane derivative. Although the initial assignment of the 6β-methyl A/B *trans* configuration was based on the normal steric course of hydrogenation of Δ^5-steroids, conclusive proof was obtained by reduction of 6β-methyl-17β-hydroxy-5α-androst-1-en-3-one (XIIa) to the known 6β-methyl-5α-androstan-17β-ol-3-one (VIIIa).[10] Alkylation of the C-17 carbonyl of VIb with methyl magnesium bromide produced the 17α-methyl homolog while ethynylation followed by reduction furnished the 17α-ethyl derivative. Oxidation, bromination, and dehydrobromination of VIb and the 17α-alkyl homologs gave the cor-



(8) W. Bergmann, M. Kita, and D. J. Giancala, *J. Am. Chem. Soc.*, **76**, 4974 (1954).

(9) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

(10) H. J. Ringold, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(11) Some of the compounds in this series were reported recently by R. Mauli, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5494 (1960).

(12) This compound was first prepared in these laboratories from 6-methyl-16-dehydropregnenolone by Dr. Walter R. Benn, unpublished work.

responding 3-keto-Δ^1-compounds. The 6β-methyl diol (XIa) obtained by lithium tri-*t*-butoxyaluminohydride reduction of X was converted smoothly to 6β - methyl - 17β - hydroxy - 5α - androst - 1-en-3-one (XIIa) by manganese dioxide oxidation.

Biological activity.[13] The assay used to determine androgenic and myotrophic activities was an adaptation[14] of that employed by Eisenberg and Gordan.[15] The compounds were injected intramuscularly into castrate male rats and their effect on the seminal vesicles, ventral prostates and levator ani muscles compared with those produced by testosterone propionate. Table I shows the estimates of the androgenic and myotrophic potencies obtained in this assay. In contrast with earlier studies, the Δ^1 isomer of testosterone (IIa) was found to be much more active than testosterone both androgenically and myotrophically. Alkylation at C-17 resulted in a diminution of activity which appeared to be nullified by reduction of the C-3 carbonyl group (IIId and IIIe). Methylation at C-2 appeared to have little effect on the relative potencies; but a slight decrease in activity was observed for the C-6 methylated analogs. Some of the more potent compounds in this series are being evaluated in other biological assays, the results of which will be reported elsewhere.

TABLE I

ANABOLIC-ANDROGENIC ACTIVITIES OF SOME 5α-ANDROST-1-ENE DERIVATIVES

Compound	Androgenic[a] Potency	Myotrophic[a] Potency
Testosterone propionate	100	100
Testosterone	35	26
IIa	100	200
IIb	25	50
IIc	2	5
IId	50	50
IIe	25	50
IIf	1	4
IIIa	50	40
IIIc	50	40
IIId	100	50
IIIe	100	200
IIIf	5	2
IIIg	2	2
XIIa	10	25
XIIb	10	50
XIIc	<1	<5

[a] Potencies are given in terms of per cent of the activity of testosterone propionate and were determined from the minimal levels at which significant increases in seminal vesicle or levator ani muscle weights were obtained.

(13) We are grateful to Dr. Francis J. Saunders of our Endocrinology Division for furnishing us with this information.

(14) F. J. Saunders and V. A. Drill, *Proc. Soc. Exptl. Biol. Med.*, **94**, 646 (1957).

(15) E. Eisenberg and G. S. Gordan, *J. Pharmacol. and Exp. Therap.*, **99**, 38 (1950).

EXPERIMENTAL[16]

17β-Hydroxy-5α-androst-1-en-3-one (IIa). To a solution of 5α-androstan-17β-ol-3-one (15 g.) in acetic acid (65 ml.) containing 48% hydrobromic acid (0.3 ml.) was added dropwise with stirring a solution of bromine (9.1 g.) and anhydrous sodium acetate (4.6 g.) in acetic acid (65 ml.). The solution was poured slowly into ice water containing sodium acetate (4.6 g.) and the resulting precipitate collected by filtration. After washing with 5% sodium bicarbonate solution and water, the product was dissolved in ether (200 ml.) and the solution dried with anhydrous potassium carbonate. Removal of the solvent *in vacuo* afforded the crude bromo compound as an oil (21 g.). The crude product was dehydrobrominated by refluxing with lithium chloride (7.1 g.) and lithium carbonate (4.1 g.) in dimethylformamide (150 ml.) for 4 hr. under an atmosphere of nitrogen. Ether was added to the cooled reaction mixture and the solution washed successively with water, dilute hydrochloric acid (1:3), 5% sodium bicarbonate solution, and water. The ether extract was dried with anhydrous potassium carbonate and the solvent removed under reduced pressure to give an oil (14.7 g.), λ_{max} 232 mμ, log ϵ 3.95. The crude product was dissolved in methanol (300 ml.) and a solution of sodium metabisulfite (50 g.) in water (250 ml.) added. The solution was stirred at room temperature for 3 min., water (100 ml.) added, and the mixture immediately extracted with methylene chloride (4 × 100 ml.). The extract was washed with water and dried with anhydrous potassium carbonate. Removal of the solvent afforded an oil (13.5 g.) which was dissolved in methanol (250 ml.) and retreated with sodium metabisulfite (40 g.) in water (150 ml.). After refluxing the solution for 1.5 hr., water (500 ml.) was added and the resulting mixture extracted with methylene chloride as described above (fraction A). Removal of the solvent gave a yellow oil (4.8 g.) which was chromatographed over silica gel. Elution with benzene-ethyl acetate (4:1) gave testosterone (1.5 g.), m.p. 153–154° undepressed by admixture with an authentic sample while elution with benzene-ethyl acetate (3:1) afforded 1-dehydrotestosterone (0.7 g.), m.p. 168–170° (reported[17] m.p. 168.5–170°), λ_{max} 244 mμ, log ϵ 4.15. Sodium hydroxide was added to the aqueous phase and the solution refluxed for 20 min. Extraction of the cooled solution with methylene chloride (fraction B) and isolation in the usual manner gave pure IIa (7.9 g.), m.p. 157–159°, $[\alpha]_D^{23}$ +57° (ethanol) (reported[3] m.p. 150°, $[\alpha]_D^{18}$ +53.3° (ethanol), λ_{max} 229 mμ, log ϵ 3.99.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.07; H, 9.67.

2α-Bromo-17α-methyl-5α-androstan-17β-ol-3-one (Ig). Buffered bromination of 17α-methyl-5α-androstan-17β-ol-3-one (1.5 g.) as described above afforded an oil which upon trituration with anhydrous ether furnished crude Ig (0.8 g.), m.p. 192.5–193°. Chromatography over silica gel and recrystallization of the benzene-ethyl acetate (9:1) eluates from methylene chloride-ethyl acetate gave a pure sample, m.p. 203–206° dec., $[\alpha]_D^{26}$ +20° (reported m.p.[18] 196–198° $[\alpha]_D$+19°), λ_{max} 283 mμ, log ϵ 1.49.

Anal. Calcd. for $C_{20}H_{31}BrO_2$: C, 62.65; H, 8.15. Found: C, 62.70; H, 7.99.

17α-Methyl-17β-hydroxy-5α-androst-1-en-3-one (IIb). Pure Ig (0.7 g.) was refluxed with lithium chloride (0.23 g.) and lithium carbonate (0.13 g.) in dimethylformamide (10 ml.)

(16) Optical rotations, spectra and analytical data were furnished by our Analytical Department under the supervision of Dr. R. T. Dillon. Optical rotations and infrared spectra were obtained in chloroform and ultraviolet spectra in methanol.

(17) A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 2125 (1946).

(18) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magana, H. Jimenez, A. Bowers, and H. J. Ringold, *Chem. and Ind.*, 1625 (1960).

for 5 hr. Ether was added to the cooled reaction mixture and the solution washed successively with dilute hydrochloric acid (1:3), 10% sodium bicarbonate solution, and water. After drying the ether extract with anhydrous sodium sulfate, the solvent was removed to give 0.5 g. of brown crystalline material, λ_{max} 230.5 mμ, log ε 4.01.[19] Thin layer chromatography[6] showed the presence of approximately 5–10% methyl testosterone as a contaminant. The product was purified by chromatography on silica gel. Crystallization of the benzene-ethyl acetate (9:1) eluates from ethanol-water gave pure IIb, (0.21 g.) m.p. 155–156°, $[\alpha]_D^{25}$ +25.8°, λ_{max} 230 mμ, log ε 4.03.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.75; H, 10.03.

17α-Ethyl-17β-hydroxy-5α-androst-1-en-3-one (IIc). To a solution of 17α-ethyl-5α-androstan-17β-ol-3-one (19.2 g.) in dimethylformamide (200 ml.) and 48% hydrobromic acid[20] (1.2 ml.) was added dropwise with stirring a solution of bromine (10.2 g.) in dimethylformamide (200 ml.). When addition was completed (6 hr.), the solution was poured slowly into ice water and the resulting precipitate collected by filtration. After washing with water, the residue was dissolved in ether and the solution dried over anhydrous potassium carbonate. Removal of the solvent afforded the crude 2-bromo compound which was dehydrobrominated by treatment with lithium chloride (8.0 g.) and lithium carbonate (9.0 g.) in dimethylformamide (150 ml.) as described above. The crude product (14.0 g.) was purified by the bisulfite method described above. The residue (4.5 g.) obtained from fraction A was chromatographed on silica gel. Elution with benzene-ethyl acetate (19:1) gave 2-bromo-17α-ethyl-17β-hydroxy-5α-androst-1-en-3-one (0.8 g.), m.p. 162–164°, $[\alpha]_D^{26}$ +13°, λ_{max} 255 mμ, log ε 3.90.

Anal. Calcd. for $C_{21}H_{31}BrO_2$: C, 63.79; H, 7.90. Found: C, 63.92; H, 7.82.

Further elution with the same solvent system afforded 17α-ethyltestosterone (0.9 g.), m.p. 140–141.5° (reported[21] m.p. 143°), λ_{max} 241 mμ, log ε 4.20. The residue from fraction B was recrystallized from acetone-hexane to give pure IIc (5.0 g.), m.p. 135–137°, $[\alpha]_D^{26}$ +32.4°, λ_{max} 229 mμ, log ε 4.00.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.82; H, 9.86.

2-Methyl-17β-hydroxy-5α-androst-1-en-3-one (IId). Bromination and dehydrobromination of 2α-methyl-5α-androstan-17β-ol-3-one[9] (6.1 g.) was performed as described under IIa. The crude product (6.0 g.) was dissolved in benzene (50 ml.) and chromatographed on silica gel. Elution with benzene-ethyl acetate (19:1) furnished 2-methyl-17β-hydroxy-5α-androst-1-en-3-one acetate (0.4 g.), m.p. 146–149°, $[\alpha]_D^{26}$ +60° (reported[11] m.p. 145–148°, $[\alpha]_D$ +32°), λ_{max} 240 mμ, log ε 4.06. Further elution with benzene-ethyl acetate (9:1) afforded crude IId (1.8 g.). Recrystallization from acetone-petroleum ether (b.p. 90–100°) gave an analytical sample, m.p. 155–157°, $[\alpha]_D^{26}$ +47° (reported[11] m.p. 155–158°, $[\alpha]_D$ +52°), λ_{max} 240 mμ, log ε 3.99.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.44; H, 10.05.

This was closely followed by the Δ^4 isomer (1.0 g.) which upon crystallization from acetone-petroleum ether (b.p. 90–100°) melted at 151–153°, λ_{max} 240 mμ, log ε 4.16. Infrared analysis showed that the Δ^4 isomer was identical with authentic 2α-methyltestosterone.[22]

2,17α-Dimethyl-17β-hydroxy-5α-androst-1-en-3-one (IIe). 2α,17α - Dimethyl - 5α - androstan - 17β - ol - 3 - one[9] (5.1 g.) was brominated in dimethylformamide as described above. Dehydrobromination in the usual manner gave a crude product (4.6 g.) which was dissolved in benzene (30 ml.) and chromatographed on silica gel. Crystallization of the benzene–ethyl acetate (19:1) eluates from acetone–petroleum ether (b.p. 90–100°) afforded IIe (2.0 g.), m.p. 163–166°, raised by one additional recrystallization to 165.5–167.5°, $[\alpha]_D^{26}$ +27° (reported[11] m.p. 146–151°, $[\alpha]_D$ +29°), λ_{max} 240 mμ, log ε 4.01.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.64; H, 10.02.

2-Methyl-17α-ethyl-17β-hydroxy-5α-androst-1-en-3-one (IIf) was prepared from 2α-methyl-17α-ethyl-5α-androstan-17β-ol-3-one[9] (4.0 g.) as described above. Crystallization of the crude product from acetone-hexane gave an analytical sample of IIf (1.3 g.), m.p. 113–114°, $[\alpha]_D^{28}$ +34°, λ_{max} 240 mμ, log ε 4.02.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.58; H, 10.48.

5α-Androst-1-ene-3β,17β-diol (IIIa). To a solution of 5α-androst-1-ene-3,17-dione (4 g.) in purified tetrahydrofuran (50 ml.) cooled in an ice bath was added all at once lithium tri-*t*-butoxyaluminohydride (9 g.) in purified tetrahydrofuran (70 ml.). Stirring at ice bath temperature was continued for 3 hr., and the mixture poured into ice and 5% acetic acid (700 ml.). The resulting precipitate was removed by filtration and washed successively with water, 5% sodium bicarbonate solution, and water. Recrystallization from methanol-water gave pure diol (3.0 g.), m.p. 161–163°, $[\alpha]_D^{26}$ +38°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.30; H, 10.22.

5α-Androst-1-ene-3β,17β-diol 17-Monoacetate (IIIb). To a chilled solution of 17β-hydroxy-5α-androst-1-en-3-one acetate (2.0 g.) in purified tetrahydrofuran (20 ml.) was added a suspension of lithium tri-*t*-butoxyaluminohydride (4.0 g.) in purified tetrahydrofuran (20 ml.). After 2 hr., the mixture was poured slowly into 5% acetic acid (300 ml.) and the resulting precipitate removed by filtration. Alternate recrystallization from ethanol-water and petroleum ether (b.p. 90–100°) afforded pure diol 17-monoacetate (IIIb), m.p. 111–112°/139–141°, $[\alpha]_D^{25}$ +33.4°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.30; H, 9.87.

5α-Androst-1-ene-3β,17β-diol diacetate (IIIc). A solution of IIIa (1.7 g.) in acetic anhydride (15 ml.) and pyridine (30 ml.) was allowed to stand at room temperature for 15 hr. The solution was poured into ice water and the resulting mixture extracted with ether. The ether extract was washed successively with dilute hydrochloric acid (1:3), 5% sodium carbonate solution, and water and dried over a mixture of anhydrous potassium carbonate and Darco. Removal of the solvent *in vacuo* left an oil which crystallized from methanol-water to give the desired diacetate (1.5 g.), m.p. 92–93°, $[\alpha]_D^{26}$ +41°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.11; H, 9.02.

17α-Methyl-5α-androst-1-ene-3β,17β-diol (IIId). A solution of 11b (0.6 g.) in purified tetrahydrofuran (15 ml.) was added dropwise with stirring to a slurry of lithium aluminum hydride (0.2 g.) in anhydrous ether (20 ml.) in an atmosphere of nitrogen. The reaction mixture was cooled with the aid of an ice bath during the addition period. After allowing the reaction mixture to stir at room temperature for 2.5 hr., the excess reagent was decomposed by the careful addition of ethyl acetate. A saturated solution of sodium sulfate was added until the precipitate began to adhere to the sides of the flask and this followed by the addition of anhydrous sodium sulfate. The salts were removed by filtration and washed with ether. Evaporation of the solvents from the filtrate yielded a crystalline product which upon recrystallization from ethyl acetate-methanol gave pure IIId (0.5 g.), m.p. 213.5–214.5°, $[\alpha]_D^{26}$ +17°.

(19) Dehydrobromination of crude 2-bromo compound gave material with λ_{max} 232 mμ, log ε 3.98.

(20) A catalytic amount of *p*-toluenesulfonic acid monohydrate was found to be as suitable as hydrobromic acid.

(21) L. Ruzicka and H. R. Rosenberg, *Helv. Chim. Acta*, 19, 357 (1936).

(22) We are grateful to Dr. N. W. Atwater for kindly providing us with the infrared curve of 2α-methyltestosterone.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 79.35; H, 10.35.

17α-Methyl-5α-androst-1-ene-3β,17β-diol 3-monoacetate (IIIe). Acetylation of IIId in the usual manner and crystallization from hexane afforded the 3-monoacetate (IIIe), m.p. 131.5–134°, $[\alpha]_D^{26}$ +16.5°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.27; H, 9.97.

17α-Ethyl-5α-androst-1-ene-3β,17β-diol (IIIf). A solution of IIc (2.4 g.) in anhydrous ether (100 ml.) was added dropwise with stirring to a slurry of lithium aluminum hydride (2.4 g.) in anhydrous ether (100 ml.). Isolation in the usual manner and crystallization from acetone-petroleum ether (b.p. 90–100°) gave pure diol (IIIf), m.p. 208.5–211°, $[\alpha]_D^{25}$ +28°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.19; H, 10.56.

17α-Ethyl-5α-androst-1-ene-3β,17β-diol 3-monoacetate (IIIg). Acetylation of IIIf in the usual manner and crystallization from acetone-petroleum ether (b.p. 60–68°) gave the 3-monoacetate (IIIg), m.p. 148–150°, $[\alpha]_D^{25}$ +20°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.67; H, 10.07.

2α-Dimethylaminomethyl-17α-methyl-5α-androstan-17β-ol-3-one (IV). A mixture of 17α-methyl-5α-androstan-17β-ol-3-one (15 g.), formalin (20 ml.), and dimethylamine hydrochloride (25 g.) in ethanol (130 ml.) was heated on the steam bath under reflux for 2 hr. The solution was allowed to stand overnight at room temperature and a mixture of dilute hydrochloric acid (1:9, 200 ml.) and water (500 ml.) added. The turbid solution was washed with ether (2 × 250 ml.) and the cooled aqueous phase made basic with saturated sodium carbonate solution. The resulting precipitate was removed by filtration and washed with water. This afforded the crude Mannich base (12.5 g. which upon recrystallization from ethyl acetate gave an analytical sample, m.p. 161–163°, $[\alpha]_D^{25}$ −33°.

Anal. Calcd. for $C_{23}H_{39}NO_2$: C, 76.40; H, 10.87; N, 3.88. Found: C, 76.46; H, 10.87; N, 3.99.

Hydrogenolysis of Mannich base. A solution of IV (5.4 g.) in isopropyl alcohol (65 ml.) was hydrogenated over 5% palladium-on-barium sulfate (0.5 g.) at 130° and 1100 p.s.i. When hydrogen uptake ceased[23] (4 hr.), the catalyst was removed by filtration and washed well with isopropyl alcohol. The solvent was removed from the filtrate by distillation under reduced pressure to afford a viscous yellow oil. The product was dissolved in benzene (30 ml.) and adsorbed on alumina (300 g.), Gradient elution of the column with benzene containing increasing amounts of ethyl acetate (from 0 to 20%) furnished 3.4 g. (71.5%) of 2α,17α-dimethyl-5α-androstan-17β-ol-3-one, (Ie), m.p. 138–140°. Recrystallization from acetone gave an analytical sample, m.p. 139–140.5°, $[\alpha]_D^{26}$ +9° (reported[9] m.p. 151–154°, $[\alpha]_D$ +8°).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: 78.81; H, 10.68.

6β-Methyl-5α-androstan-3β-ol-17-one acetate (VIa). A solution of 6-methyl-3β-acetoxy-androst-5-en-17-one[24] (V, 1.0, g.) in acetic acid (5 ml.) was hydrogenated at atmospheric pressure and room temperature using 5% palladium-on-carbon (0.2 g.) as catalyst. After hydrogen uptake ceased (12 hr.), the catalyst was removed by filtration. Cold water was slowly added to the filtrate and the resulting crystalline product removed by filtration. This afforded crude VIa (0.88 g.), m.p. 153–156°. Recrystallization from acetone-water gave an analytical sample, m.p. 154–157°, $[\alpha]_D^{26}$ +49°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.09; H, 9.90.

(23) The pressure data is not significant because of the formation of dimethylamine.

(24) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957).

6β-Methyl-5α-androstan-3β-ol-17-one (VIb). Hydrolysis of VIa (1.0 g.) was accomplished by refluxing in methanol (25 ml.) with concentrated hydrochloric acid (1.7 ml.) for 2 hr. The cooled solution was poured slowly into ice water and the resulting product removed by filtration and washed with water. Recrystallization from acetone petroleum ether (b.p. 60–68°) gave pure VIb (0.88 g.), m.p. 157–158°, $[\alpha]_D^{26}$ +74°.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.86; H, 10.52.

6β,17α-Dimethyl-5α-androstan-3β,17β-diol (VIIa). A solution of 6β-methyl-5α-androstan-3β-ol-17-one (15 g.) in anhydrous benzene (400 ml.) was added with stirring to a 3*M* solution of methylmagnesium bromide in ether (200 ml.). The solvent was removed until the boiling point reached 78° and refluxing continued for 5 hr. After allowing the mixture to stand overnight at room temperature, a solution of ammonium chloride (40 g.) in water (300 ml.) was added dropwise with stirring. The layers were separated and the aqueous phase extracted alternately with chloroform and ethyl acetate. The combined extract was washed with dilute hydrochloric acid (1:3), 5% sodium bicarbonate solution, and water. After drying the organic phase with anhydrous sodium sulfate, the solvent was removed by distillation to afford 15.4 g. of crude diol. Recrystallization from ethyl acetate–petroleum ether (b.p. 90–100°) gave an analytical sample, m.p. 173–177°, $[\alpha]_D^{26}$ −28.9°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.27; H, 11.50.

6β-Methyl-17α-ethynyl-5α-androstan-3β,17β-diol (VIIb). To a solution of diethylene glycol dimethyl ether (500 ml.) and diethylene glycol monoethyl ether (27 ml.) heated to 135° were added portion-wise under nitrogen potassium hydroxide flakes (80 g.). The mixture was heated at this temperature for 0.5 hr. with vigorous stirring and allowed to cool slowly to room temperature. The reaction vessel was surrounded with an ice–isopropyl alcohol bath and acetylene gas passed into the rapidly stirred mixture for 2.25 hr. At this point, 6β-methyl-5α-androstan-3β-ol-17-one (20 g.) was added as a slurry in diethylene glycol dimethyl ether (50 ml.). Stirring and acetylene addition were continued for an additional 1.5 hr. Water (250 ml.) was added to the reaction mixture, and the contents poured slowly into a mixture of ice and dilute hydrochloric acid (1:10, 3 l.) The yellow precipitate was removed by filtration and dissolved in ether. The ether solution was washed successively with water, dilute hydrochloric acid (1:3), 5% sodium bicarbonate solution, and water. After drying the solution over a mixture of anhydrous potassium carbonate and Darco, the solvent was removed by distillation under reduced pressure. The resulting oil was crystallized from acetone to give VIIb (16.7 g.), m.p. 185–188°, $[\alpha]_D^{26}$ −35°.

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.07; H, 10.52.

6β-Methyl-17α-ethyl-5α-androstan-3β,17β-diol (VIIc). A solution of VIIb (17.15 g.) in methanol (200 ml.) was hydrogenated in a Parr low pressure apparatus using 5% palladium-on-charcoal (1.5 g.) as catalyst. After hydrogen uptake was complete (10 min.), the catalyst was removed by filtration and washed well with methanol. The solvent was removed from the filtrate by distillation under reduced pressure. The resulting solid residue was recrystallized from acetone-water to give VIIc (16.35 g.), m.p. 188.5–189.5°, $[\alpha]_D^{25}$ −16° (methanol).

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 78.75; H, 11.18.

6β,17α-Dimethyl-5α-androstan-17β-ol-3-one (VIIIb). To a solution of VIIa (5 g.) in acetone (100 ml.) was added standard chromium trioxide reagent[25] dropwise with stirring until a faint color of the reagent persisted. The excess reagent was decomposed with isopropyl alcohol and the result-

(25) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

ing solution decanted from the salts into a mixture of ice and water. The resulting precipitate was removed by filtration and recrystallized from ethanol-water to afford VIIIb (4.0 g.), m.p. 171–173°, $[\alpha]_D^{25}$ −18.8°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19: H, 10.76. Found: C, 79.28; H, 10.66.

6β-Methyl-17α-ethyl-5α-androstan-17β-ol-3-one (VIIIc). Oxidation of VIIc (14.0 g.) as described above and recrystallization of the product from ethanol-water gave VIIIc (10.5 g.), m.p. 154–156°, $[\alpha]_D^{26}$ −8°.

Anal. Calcd. for $C_{22}H_{36}O_2$: C 79.46; H, 10.91. Found: C, 79.07; H, 10.81.

6β-Methyl-5α-androstan-3,17-dione (IX). Oxidation of an acetone solution of VIb (5.7 g.) with chromic acid as described above afforded the desired dione IX (5.2 g.), m.p. 169–172°. Recrystallization from methanol-water gave an analytical sample, m.p. 171–173°, $[\alpha]_D^{26}$ +81°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.79; H, 9.93.

6β-Methyl-5α-androst-1-en-3,17-dione (X). To a solution of IX (1.07 g.) in acetic acid (25 ml.) was added dropwise with stirring 0.608*N* bromine in acetic acid (12 ml.). Water was added to the colorless solution and the resulting precipitate removed by filtration. The product was dried *in vacuo* to give the crude bromo compound (1.15 g.), a portion of which (0.8 g.) was dehydrobrominated by refluxing in collidine (3 ml.) for 30 min. Ether was added to the cooled solution and the mixture washed successively with 2*N* hydrochloric acid, 5% sodium bicarbonate solution, and water. After drying the ether solution with anhydrous potassium carbonate, the solvent was removed by distillation to give an oily residue. Adsorption of the crude product on silica gel and crystallization of the benzene–ethyl acetate (19:1) eluates from methanol-water gave pure X, m.p. 143–145°, $[\alpha]_D^{27}$ +109°, λ_{max} 228 mμ, log ε 4.01.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.61; H, 9.33.

6β-Methyl-5α-androst-1-en-3β,17β-diol (XIa). To a solution of compound X (2.5 g.) in purified tetrahydrofuran (75 ml.) was added all at once a solution of lithium tri-*t*-butoxyaluminohydride (6.0 g.) in purified tetrahydrofuran (75 ml.). The reaction was carried out under nitrogen and external cooling was provided by an ice bath. The solution was stirred for 2 hr. and poured into ice-cold 5% acetic acid (500 ml.). The precipitate was collected and washed with 5% sodium bicarbonate solution and water. Recrystallization from methanol-water gave pure diol (2.3 g.), m.p. 170–173°, $[\alpha]_D^{27}$ +23°.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89, H, 10.59. Found: C, 78.98; H, 10.31.

6β-Methyl-5α-androst-1-en-3β,17β-diol diacetate (XIb). Acetylation of XIa (0.7 g.) with acetic anhydride–pyridine in the usual manner, and recrystallization of the crude product from methanol-water afforded the diacetate (0.45 g.), m.p. 111–112°, $[\alpha]_D^{25}$ +41.5°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.03; H, 9.10.

6β-Methyl-17β-hydroxy-5α-androst-1-en-3-one (XIIa). A mixture of XIa (0.5 g.), isopropyl alcohol[26] (20 ml.), and manganese dioxide[27] (4.5 g.) was stirred at room temperature for 18 hr. The mixture was filtered and water added to the filtrate until the solution became slightly turbid. Refrigeration and collection of the crystalline product afforded pure XIIa (0.35 g.), m.p. 182–182.5°, $[\alpha]_D^{27}$ +19°, λ_{max} 227.5 mμ, log ε 3.99.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.27; H, 9.99.

Catalytic hydrogenation of XIIa. A solution of XIIa (82 mg.) in ethanol (15 ml.) was hydrogenated at 29.5° and atmospheric pressure over 5% palladium-on-carbon (30 mg.). After hydrogen uptake ceased (3 hr.), the catalyst was removed by filtration and washed with ethanol. Removal of the solvent from the filtrate and recrystallization of the resulting solid from acetone-hexane gave 6β-methyl-5α-androstan-17β-ol-3-one (VIIIa), m.p. 201–203.5° (reported[10] m.p. 203–205°), infrared $\lambda_{max}^{CHCl_3}$ 2.75, 3.37, 5.83 μ.

6β,17α-Dimethyl-17β-hydroxy-5α-androst-1-en-3-one (XIIb) was prepared by bromination of VIIIb in dimethylformamide and the crude product dehydrobrominated in the usual manner. Purification of the product by chromatography on silica gel gave pure XIIb, m.p. 175–177°, $[\alpha]_D^{26}$ +1.5°, λ_{max} 228.5 mμ, log ε 4.00.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.71; H, H, 10.23.

6β-Methyl-17α-ethyl-17β-hydroxy-5α-androst-1-en-3-one (XIIc) was prepared by bromination of VIIIc in dimethylformamide and the crude product dehydrobrominated in the usual manner. Purification of the product by the bisulfite method gave pure XIIc, m.p. 165–168° $[\alpha]_D^{27}$ +7° λ_{max} 228.5 mμ, log ε 3.96.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.78; H, 10.56.

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(26) We are grateful to Dr. C. G. Bergstrom for pointing out the utility of isopropyl alcohol in this reaction.

(27) O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).