from a large amount of methanol; 70 mg of IIIa was obtained, m.p. 297–298° dec. The infrared spectrum indicates a hydroxyl group (3450 cm.$^{-1}$), an α,β-unsaturated ketone (1667 and 1605 cm.$^{-1}$) and shows characteristic bands for the isopropyl group, for the trisubstituted double bond (839 cm.$^{-1}$) and a strong band at 787 cm.$^{-1}$; ϵ_{302} 2040.

Anal. Calcd. for $C_{44}H_{66}O_4Se_2$: C, 64.69; H, 8.14. Found: C, 64.35; H, 8.19.

After the diselenide IIIa was separated, the mother liquors were neutralized with 2 *N* hydrochloric acid, evaporated, and the residue extracted with ether. The extract was washed with water, dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed and the fractions with 5% ethyl acetate in benzene gave after recrystallization from ether–petrol. ether, 30 mg. of II, m.p. 178–180° (transformation at 167–170°). The infrared analysis indicates a hydroxyl group (3550 cm.$^{-1}$) and an α,β-unsaturated ketone (1670 and 1637 cm.$^{-1}$); ϵ_{233} 6134.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.90; H, 10.27.

When the oxidation was carried out for 48 hours the diselenide IIIa could be separated off. Chromatography of the mother liquor gave the conjugated ketone II and led also to the isolation of Ia in the 25% ethyl acetate–benzene fractions; m.p. 192–194°, λ_{max} 238 mμ. The infrared analysis shows the absorption band for a hydroxyl group (3550 cm.$^{-1}$) for a keto group (1667 cm.$^{-1}$) for an enol acetate (1752 and 1155 cm.$^{-1}$).

The diosphenol acetate Ib was hydrolyzed by refluxing in 1% methanolic sodium hydroxide for 1.5 hr. After cooling, the reaction mixture was poured into a large excess of ether, the extract washed with water, dried and evaporated. The oily residue gave a strong color reaction with ferric chloride and potassium ferricyanide, and showed a strong maximum at 271 mμ, indicating the presence of Ia; ν_{max} 3600 (hydroxyl), 1680 cm.$^{-1}$ (conj. ketone).

16-Bis-(3β-acetoxy-17a,17a-dimethyl-D-homoandrost-15-en-17-one) Diselenide (IIIb) from IIIa.—The suspension of 50 mg. of IIIa in 5 ml. of glacial acetic acid was refluxed under nitrogen for 24 hours. After 20 hours all substance was in solution. Upon cooling, the reaction mixture was poured into a large excess of water, then extracted with ether, the extract washed with 2 *N* sodium carbonate solution and ester, dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed and the fractions with 1 and 2% ethyl acetate in benzene gave, after recrystallization from methanol, IIIb, m.p. 263–264°, ϵ_{302} 5183; ν_{max} at 1670, 1605 (conj. ketone), 1737, 1238 (acetate) and a strong band at 786 cm.$^{-1}$.

Anal. Calcd. for $C_{48}H_{70}O_6Se_2$: C, 63.98; H, 7.83. Found: C, 64.23; H, 7.92.

3β-Acetoxy-17a,17a-dimethyl-D-homoandrostane-17-one (VIb) from IIIb.—To the solution of 25 mg. of IIIb in 5 ml. of glacial acetic acid was added 100 mg. of zinc powder, and the reaction mixture was refluxed under nitrogen for 2 hours. The zinc was filtered off and washed with a large amount of ethyl acetate. The filtrate was washed with 2 *N* sodium carbonate solution, dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed and the fractions with 2% ethyl acetate in benzene gave, after recrystallization from methanol, VIb, m.p. 172–175°, identical in all respects with the compound obtained before.

3β,16-Dihydroxy-17a,17a-dimethyl D-homoandrosta-5,15-dien-17-one 3β-Acetate (XVII) from XIIIb.—The suspension of 150 mg. of XIIIb and 50 mg. of selenium dioxide in 10 ml. of anhydrous *t*-butyl alcohol and 0.1 ml. of glacial acetic acid was refluxed under nitrogen for 24 hours. After that time another 50 mg. of selenium dioxide was added and refluxed for an additional 24 hours. The mixture then was worked up as usual. The crude product was chromatographed and the fractions obtained from the 10% ethyl acetate in benzene eluates were distilled at 160° (0.01 mm.), furnishing XVII as a pale yellow oil which resisted crystallization, λ_{max} 272 mμ; ν_{max} at 3600 (hydroxyl), 1680 (conj. ketone), 1737, 1245 (acetate) and 815 cm.$^{-1}$ (trisubstituted double bond). The product gave a strong color reaction with ferric chloride and with potassium ferricyanide.

3β,16-Diacetoxy-17a,17a-dimethyl-D-homoandrost-5,15-dien-17-one (XVI) from XVII.—The diosphenol XVII was acetylated with acetic anhydride in pyridine and the resulting crude diacetate chromatographed. The fractions, obtained with 5% ethyl acetate in benzene, were recrystallized from ether to give XVI, m.p. 245–252°, λ_{max} at 234 mμ; ν_{max} at 1745, 1245, 1225 (acetates), 1675 (conj. ketone), 826, 818 cm.$^{-1}$ (trisubstituted double bonds). Unfortunately there was not sufficient amount of material to submit for elemental analysis.

WORCESTER, MASS.

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

Steroids. CXXIII.[1] 19-Nor-6-methylandrostane Derivatives

BY R. VILLOTTI, CARL DJERASSI AND H. J. RINGOLD

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6α- and 6β-methyl-19-nortestosterone and Δ^4-androstene-3,17-dione have been synthesized from 19-nor-Δ^5-androstene-3,17-diol (III). Peracid epoxidation of III gave the 5α,6α-oxide which was cleaved with methylmagnesium bromide to the 6β-methyl-5α-ol (V), key intermediate for the preparation of VII, IX, X and XII. The rotatory dispersion curves of 6-methyl steroids with either a 10-hydrogen atom or 10-methyl group are discussed in terms of steric interaction between C-6 and C-10 substituents.

While C-2[2] and C-4[2,3a,b] alkyl substituted 19-nor steroids have been reported, the synthesis of 19-nor-6-methyltestosterone derivatives has not yet been recorded. Such compounds are of interest for biological evaluation since 6-methyl substitution in the 10-methyl steroids has in many cases favorably influenced biological activity.[4] Further, the pair of 19-nor-6-methyltestosterone derivatives would help to resolve a rather fundamental point in the role played by steric factors in the rotatory dispersion of 6-methyl steroids.[5] While the curve of the equatorially substituted 6α-methyltestosterone is identical with that of the parent substance, that of the axial 6β-methyl isomer differs greatly. If this difference is attributable to a diaxial interference of the 6β,10β-methyl groups,[5] then substitution of the 10-methyl group by hydrogen would remove the source of

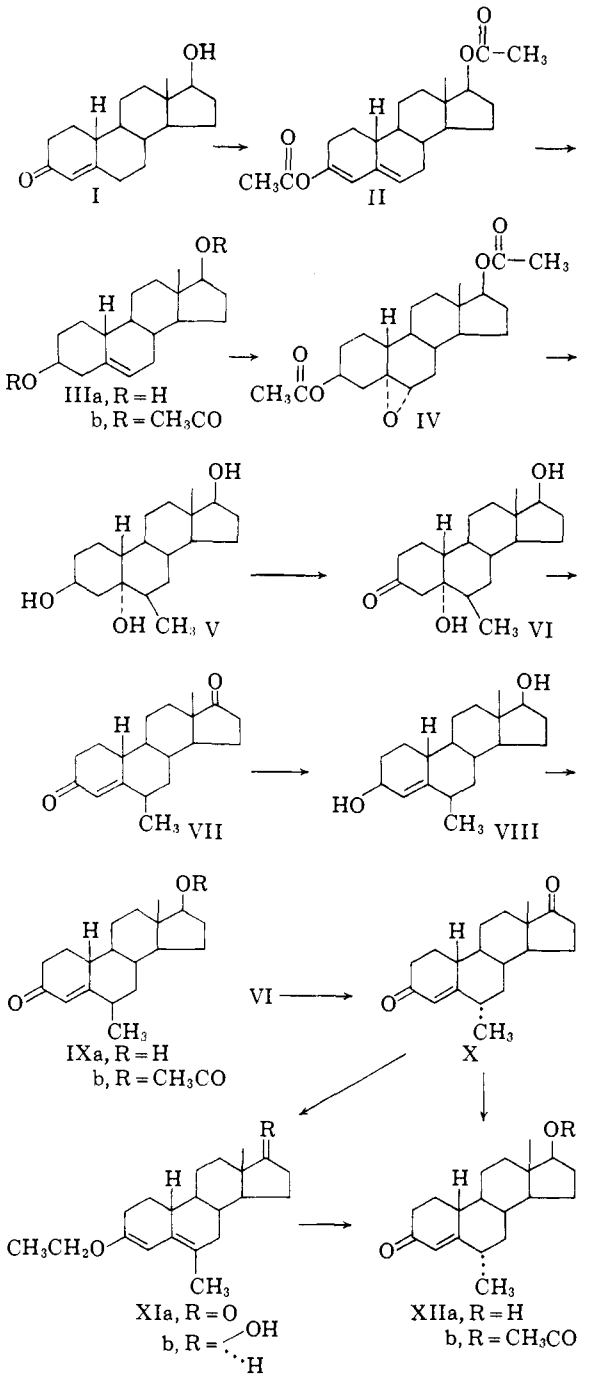
(1) Paper CXXII, J. A. Edwards, H. J. Ringold and C. Djerassi, THIS JOURNAL, **81**, 3156 (1959).

(2) A. Bowers and H. J. Ringold, *ibid.*, **81**, 424 (1959).

(3) (a) J. A. Hartman, A. J. Tomasewski and A. S. Dreiding, *ibid.*, **78**, 5662 (1956); (b) N. W. Atwater, *ibid.*, **79**, 5315 (1957).

(4) (a) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956); (b) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); (c) A. David, F. Hartley, D. R. Millson and V. Petrow, *J. Pharm. and Pharmacol.*, **9**, 929 (1957); (d) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stuck, L. E. Barnes and W. E. Dulin, THIS JOURNAL, **80**, 2904 (1958); (e) H. J. Ringold, J. Perez Ruelas, E. Batres and C. Djerassi, *ibid.*, **81**, 3712 (1959).

(5) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *ibid.*, **80**, 4001 (1958).



steric distortion and the rotatory dispersion curves of 6α- and 6β-methyl-19-nortestosterone should be essentially identical. We have synthesized this requisite isomer pair and find indeed that their curves (of the 17-acetates) are very similar (see Fig. 1).[6]

Our synthesis proceeded from 19-nor-Δ⁵-androstene-3β,17β-diol diacetate (IIIb) which was prepared in high yield by a minor experimental modification of the method of Hartman.[7] 19-Nortestosterone[8a,8] (I) was converted to the 3-enol acetate 17-acetate (II)[8a] by treatment with acetic anhydride–acetyl chloride and then reduced with sodium borohydride[9] in ethanol–tetrahydrofuran solution to give 19-nor-Δ⁵-androstene-3β,17β-diol (IIIa).[7] From this point the reaction sequence essentially paralleled our synthesis[4b] of the 6-methyl-10-methyl compounds utilizing as the key step the methyl Grignard cleavage of a 5α,6α-oxide yielding the 6β-methyl-5α-hydroxy compound.[10] Thus epoxidation of IIIb with monoperphthalic acid led in 90% yield to the 5α,6α-epoxide IV, which was heated with excess methylmagnesium bromide in tetrahydrofuran to give about 70% of 19-nor-6β-methylandrostane-3β,5α,-17β-triol (V). Oxidation with chromium trioxide in acetone–sulfuric acid[11] provided the 6β-methyl-3,17-diketone (VI), which was dehydrated with thionyl chloride–pyridine at −10° to afford a good yield of 19-nor-6β-methyl-Δ⁴-androstene-3,17-dione

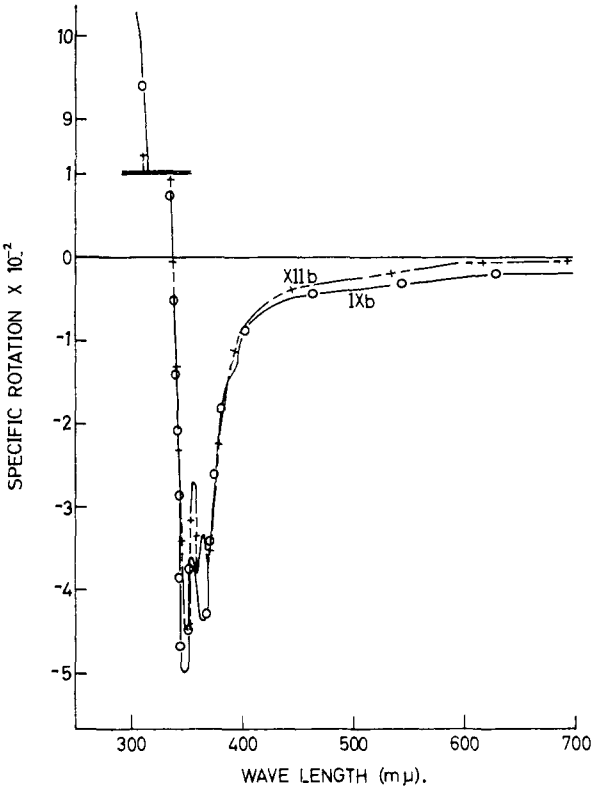


Fig. 1.

(6) On the other hand, unpublished work by Dr. J. A. Zderic in our laboratory has shown that the rotatory dispersion curve of a 6β-chloro-19-nor-Δ⁴-3-ketone (*e.g.*, 6β-chloro-17α-methyl (or 17α-ethynyl)-19-nortestosterone) is quite different from that of the corresponding 10-methyl steroid (see C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, THIS JOURNAL, **80**, 1216 (1958)), indicating that in 6-halogenated-Δ⁴-3-ketones electronic factors in addition to steric ones must be taken into consideration.

(7) J. A. Hartman, *ibid.*, **77**, 5151 (1955).

(8) A. J. Birch, *J. Chem. Soc.*, 367 (1950); A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5366 (1953).

(9) E. Schwenk, M. Gut and J. Belisle, *Arch. Biochem. Biophys.*, **31**, 456 (1951); B. Belleau and T. F. Gallagher, THIS JOURNAL, **73**, 4458 (1951); W. G. Dauben and J. F. Eastham, *ibid.*, **73**, 4463 (1951).

(10) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 436 (1939); *C. A.*, **33**, 9309 (1939); O. S. Madaeva, M. I. Ushakov and N. F. Kosheleva, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 213 (1940); *C. A.*, **34**, 7292 (1940); L. F. Fieser and J. Rigaudy, THIS JOURNAL, **73**, 4660 (1951); R. B. Turner, *ibid.*, **74**, 5362 (1952).

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); see also C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(VII). Alternately, room temperature dehydration of VI with dilute sodium hydroxide in methanol for 24 hours was accompanied by inversion of the axial 6β-methyl group yielding 19-nor-6α-methyl-Δ^4-androstene-3,17-dione (X).

19-Nor-6β-methyltestosterone (IXa) was synthesized from VII by a two-step sequence developed by Sondheimer, Amendolla and Rosenkranz[12] for the preparation of testosterone from Δ^4-androstene-3,17-dione. The dione VII in tetrahydrofuran solution was reduced with lithium aluminum hydride to give in over 50% yield a homogeneous alcohol to which we assign the 6β-methyl-Δ^4-3β,17β-diol (VIII) structure. The equatorial 3β-orientation, while not proved, is assumed from the known[13] direction of hydride reduction of a 19-nor-Δ^4-3-ketone which gives a preponderance of the 3β-alcohol. Treatment of the diol with manganese dioxide in chloroform effected re-oxidation of the allylic 3-alcohol thus yielding crystalline 19-nor-6β-methyltestosterone (IXa) further characterized as the 17-acetate IXb. Greater difficulty was experienced in preparing 19-nor-6α-methyltestosterone (XIIa) which was obtained as an oil in the free form but crystalline as the 17-acetate XIIb. However, we have prepared the compound by several separate routes, the simplest being the direct acid inversion of 19-nor-6β-methyltestosterone acetate with anhydrous hydrogen chloride in chloroform, reacetylation of the crude product yielding crystalline XIIb. Similarly, acid inversion of free 19-nor-6β-methyltestosterone (IXa) gave XIIa as an oil. Alternately, 19-nor-6α-methyl-Δ^4-androstene-3,17-dione (X) was converted to the 3-enol ether (XIa) by *p*-toluenesulfonic acid-catalyzed reaction with ethyl orthoformate. The crude reaction product, a gum, was reduced with sodium borohydride to yield the crystalline ethyl enol ether of 19-nor-6-methyltestosterone (XIb), λ_{max} 247 mμ, log ε 4.25. Hydrolysis with dilute hydrochloric acid in methanol then gave an oil (XIIa) whose properties were identical with those of the product obtained above and which yielded crystalline XIIb after acetylation at room temperature. Finally, XIIa was synthesized by selective sodium borohydride reduction of the 17-keto function of 19-nor-6α-methylandrostene-3,17-dione (X) according to the general conditions of Norymberski and Woods[14] or by complete reduction of X to the 3,17-diol followed by re-oxidation with N-bromoacetamide.[15]

In Fig. 1 and the Experimental section are collected rotatory dispersion data for two pairs of epimeric 6-methyl-19-nor-Δ^4-3-ketones (VII *vs.* X; IXb *vs.* XIIb). The similarity in shape and amplitude of these curves when contrasted with the situation obtaining[5] in analogous 10-methyl steroids, leaves little doubt that diaxial methyl–methyl interference between the substituents at C-6 and C-10 is responsible for the earlier observed[5] differences in the rotatory dispersion curves of 6α- and 6β-methyltestosterone.

(12) F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5930 (1953).

(13) The reduction of 19-nortesosterone is reported (ref. 3a) to yield 55% of the 3β- and 25% of the 3α-alcohol.

(14) S. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

(15) *Cf.* K. Morita, *Bull. Chem. Soc. (Japan)*, **31**, 450 (1958).

Experimental[16]

19-Nor-$\Delta^{3,5}$-androstadiene-3,17β-diol Diacetate (II).—A solution of 19-nortestosterone[3] (10 g.) in acetic anhydride (40 ml.) and acetyl chloride (45 ml.) was boiled for 4 hours in a nitrogen atmosphere. The reaction mixture then was distilled almost to dryness, cooled and ice water added. The crude enol acetate was filtered, washed with water, then bicarbonate and finally water. Crystallization of the dried residue first from acetone and then from ethyl alcohol, gave long plates of II (8.2 g.), m.p. 169–172°, $[\alpha]_D$ −149°, λ_{max} 235 mμ, log ε 4.32; λ_{max}^{KBr} 1755, 1724, 1653(m), 1625(m) cm.$^{-1}$ (reported[3a] m.p. 170–174°, $[\alpha]_D$ −151°).

Concentration of the mother liquors afforded an additional 1.1 g. of material melting at 165–168°.

19-Nor-Δ^5-androstene-3β,17β-diol (IIIa) and Diacetate (IIIb).—A solution of 8 g. of enol diacetate II in a mixture of 95% ethanol (700 ml.) and tetrahydrofuran (300 ml.) was cooled to 10° and added dropwise, with occasional stirring, over a one hour period, to a cold (0°) solution of sodium borohydride (18 g.) in 80% ethanol (400 ml.), the reaction temperature not being allowed to exceed 5°. After completion of addition, the solution was held at 0–5° for an additional 2 hours, then 10% sodium hydroxide (200 ml.) was added and the solution boiled for 15 minutes. Most of the solvent was removed *in vacuo*, the residue acidified with 20% hydrochloric acid and the crystalline precipitate collected and washed to yield 6.2 g. of IIIa, m.p. 158–160°. Ethyl acetate extraction of the mother liquors gave an additional 1.3 g. of material melting at 149–153°. Recrystallization of the combined fractions from acetone furnished 6.0 g. of material, m.p. 162–164°, $[\alpha]_D$ +9° (reported[7] m.p. 165.0–165.8°, $[\alpha]_D$ + 11.7°).

Pyridine–acetic anhydride treatment of the above diol IIIa gave the corresponding 19-nor-Δ^5-androstene-3β,17β-diol diacetate (IIIb). A sample crystallized from methanol melted at 135–137°, $[\alpha]_D$ −16°; reported[7] m.p. 135–137°, $[\alpha]_D$ −16°.

19-Nor-5α,6α-oxidoandrostane-3β,17β-diol Diacetate (IV).—A cold solution of monoperphthalic acid (2.52 g., 1.55 equiv.) in ether (35 ml.) was added to a solution of diacetate IIIb in dry ether (20 ml.) and the mixture allowed to stand for 24 hours at −5°. Ice-water was added and the ether solution washed successively with sodium bicarbonate solution, water, 5% ferrous sulfate solution and water. The dried solution (sodium sulfate) was evaporated and the residue crystallized from a small volume of methanol to yield 2.7 g. of α-epoxide IV, m.p. 146–148°, $[\alpha]_D$ −28°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; O, 21.35. Found: C, 69.96; H, 8.68; O, 21.25.

19-Nor-6β-methylandrostane-3β,5α,17β-triol (V).—A solution of 4 *N* methylmagnesium bromide in ether (20 ml.) was added, with stirring, to a solution of IV (1.35 g.) in dry tetrahydrofuran (30 ml.) and the stirred mixture heated under reflux for 30 minutes. The condenser was then replaced by a calcium chloride tube, the ether allowed to boil off and when the internal temperature reached 54°, the condenser was replaced and the mixture boiled for an additional 4 hours. A saturated solution of ammonium chloride (200 ml.) was added slowly to the cooled mixture which was then stirred for 15 minutes before transfer to a separatory funnel. The tetrahydrofuran layer was separated, dried and evaporated, whereupon crystallization of the residue from aqueous methanol gave 950 mg. of 6-methyl-triol V, m.p. 191–193°, $[\alpha]_D$ −40° (pyridine).

Anal. Calcd. for $C_{19}H_{32}O_3 \cdot {}^1/_2CH_4O$: C, 72.22; H, 10.49; O, 17.30. Found: C, 72.35; H, 10.17; O, 17.35.

19-Nor-6β-methylandrostan-5α-ol-3,17-dione (VI).—Over 20-minute period, and at room temperature, a solution of 0.84 ml. (1.15 equiv.) of 8 *N* chromic acid in sulfuric acid[11]

(16) Melting points were determined with a Fisher apparatus and are uncorrected. Rotations were measured in chloroform, unless specified otherwise, and ultraviolet absorption spectra in 95% ethanol solution. The infrared spectra were obtained with a Perkin-Elmer model 21 spectrophotometer with a sodium chloride prism. We are grateful to Dr. L. Throop for rotations and spectral data. The elemental analyses were carried out by Dr. A. Bernhardt, Mülheim/Ruhr, Germany.

was added to a solution of 490 mg. of triol V in acetone (50 ml.). The solution was stirred for an additional 5 minutes then water was added and the product extracted with ethyl acetate which was washed to neutrality. Evaporation of the dried extract and recrystallization of the solid residue from aqueous acetone or from acetonitrile afforded 350 mg. of 3,17-dione VI as prismatic needles, m.p. 209–211°, $[\alpha]_D$ +100°; λ_{max}^{KBr} 3480, 1725(shoulder), 1715 cm.$^{-1}$, no maximal absorption in the ultraviolet.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27; O, 15.77. Found: C, 74.56; H, 9.23; O, 16.02.

19-Nor-6β-methyl-Δ^4-androstene-3,17-dione (VII).—A solution of diketone VI (150 mg.) in dry pyridine (1 ml.) was cooled to −10°, treated with thionyl chloride (0.1 ml.) and the mixture allowed to stand for 4 minutes at this temperature. Ice-water was added and the crystalline precipitate was filtered, washed and dried, yielding 45 mg. of VII, m.p. 160–165°. Extraction of the aqueous solution with ethyl acetate, evaporation of solvent and crystallization of the residue from methanol, after charcoal decolorization in the same solvent, yielded an additional 65 mg. of material melting at 155–160°. Recrystallization of the combined crops from acetone gave 70 mg. of pure VII, m.p. 173–175°, $[\alpha]_D$ + 86°, λ_{max} 240 mμ, log ε 4.16; λ_{max}^{KBr} 1735, 1668 cm.$^{-1}$; R.D. in dioxane (c 0.065): $[\alpha]_{700}$ +28°, $[\alpha]_{589}$ + 65°, $[\alpha]_{397.5}$ + 389°, $[\alpha]_{390}$ +366°, $[\alpha]_{385}$ + 392°, $[\alpha]_{367.5}$ + 251°, $[\alpha]_{362.5}$ + 295°, $[\alpha]_{360}$ + 259°, $[\alpha]_{317.5}$ +3215° $[\alpha]_{300}$ +1560°.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; O, 11.17. Found: C, 79.65; H, 9.21; O, 11.55.

19-Nor-6β-methyl-Δ^4-androstene-3β,17β-diol (VIII).—A solution of dione VII (950 mg.) in tetrahydrofuran (50 ml.) was added over a 30-minute period to a stirred suspension of lithium aluminum hydride (3 g.) in boiling anhydrous tetrahydrofuran (50 ml.). The mixture was boiled for an additional 2 hours then cooled and cautiously treated with ethyl acetate (5 ml.) and water (3 ml.). Solid sodium sulfate was added and the inorganic material filtered and thoroughly washed with hot ethyl acetate. The combined solutions on evaporation yielded 920 mg. of colorless oil which was thrice crystallized from acetone–hexane providing 500 mg. of VIII, m.p. 187–189°, $[\alpha]_D$ +54°, no maximal absorption in the ultraviolet nor carbonyl absorption in the infrared.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41; O, 11.02. Found: C, 78.64; H, 10.52; O, 11.52.

19-Nor-6β-methyltestosterone (IXa).—The diol VIII (300 mg.) in chloroform (30 ml., distilled from calcium chloride) was oxidized by stirring for 18 hours at room temperature with 3 g. of freshly precipitated manganese dioxide.[12] The inorganic material was filtered, washed with hot chloroform and the solution evaporated to yield 290 mg. of a colorless oily residue which crystallized on trituration with hexane. Recrystallization from acetone–hexane gave IXa (190 mg.) as prisms melting at 136–138°, $[\alpha]_D$ +130°, λ_{max} 240 mμ, log ε 4.22; $\lambda_{max}^{CHCl_3}$ 3420, 1660 cm.$^{-1}$. R.D. in dioxane (c 0.051): $[\alpha]_{700}$ +13°, $[\alpha]_{589}$ + 30°, $[\alpha]_{360}$ −612°, $[\alpha]_{357.5}$ −515°, $[\alpha]_{350}$ −809°, $[\alpha]_{305}$ +2292°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79; O, 11.10. Found: C, 79.03; H, 9.65; O, 11.45.

19-Nor-6β-methyltestosterone Acetate (IXb).—Acetylation of IXa with acetic anhydride–pyridine in the usual manner and crystallization from acetone–hexane furnished the acetate IXb, needles, m.p. 136–137°, λ_{max} 240 mμ, log ε 4.26; λ_{max}^{KBr} 1730, 1655, 1235 cm.$^{-1}$; $\lambda_{max}^{CHCl_3}$ 1718, 1665, 1245 cm.$^{-1}$; R.D. (Fig. 1) in dioxane (c 0.056): $[\alpha]_{700}$ −14°, $[\alpha]_{589}$ −16°, $[\alpha]_{362.5}$ −434°, $[\alpha]_{357.5}$ −365°, $[\alpha]_{347.5}$ −501°, $[\alpha]_{305}$ +1026°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.94; H, 9.26.

19-Nor-6α-methyl-Δ^4-androstene-3,17-dione (X).—A solution of 19-nor-6β-methylandrostan-5α-ol-3,17-dione (VI) (500 mg.) in methanol (56 ml.) and 1 *N* aqueous sodium hydroxide (28 ml.) was allowed to stand at room temperature under a nitrogen atmosphere for 24 hours. The solution then was concentrated without heating to half its volume, water and ice were added and the crystalline precipitate filtered, washed and dried yielding 440 mg. of crude IXb, m.p. 153–156°. Two recrystallizations from aqueous acetone gave the analytical specimen, m.p. 163–165°, $[\alpha]_D$ +95°, λ_{max}240 mμ, log ε 4.17; λ_{max}^{KBr} 1732, 1662 cm.$^{-1}$. A mixture m.p. with the 6β-methyl epimer VII showed 155–163°; R.D. in dioxane (c 0.064): $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +58°, $[\alpha]_{390}$ +381°, $[\alpha]_{367.5}$ +321°, $[\alpha]_{335}$ +391°, $[\alpha]_{365}$ +176.5°, $[\alpha]_{355}$ +339°, $[\alpha]_{350}$ +267°, $[\alpha]_{317.5}$ +3675°, $[\alpha]_{300}$ +1417°.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; O, 11.17. Found: C, 79.37; H, 9.46; O, 11.21.

19-Nor-6-methyl-3-ethoxy-Δ^{3,5}-androstadien-17β-ol (XIb).—A suspension of X (300 mg.) in anhydrous peroxide-free dioxane (1.6 ml.) and freshly distilled ethyl orthoformate (0.4 ml.) was treated with 0.27 ml. of a solution of 0.244 g. of *p*-toluenesulfonic acid·H_2O, 2.7 ml. of anhydrous dioxane and 0.55 ml. of absolute ethanol. The suspension, at room temperature, was occasionally swirled and at the end of 1 hour solution was complete.[17] Pyridine (1.1 ml.) was added and the solvent removed under reduced pressure. The resultant gum (XIa) was dissolved in methanol (15 ml.) and then treated with a solution of sodium borohydride (350 mg.) in water (1 ml.). Crystallization of white needles began immediately after addition of the hydride, and after the reaction mixture had stood for 25 minutes the precipitate XIb (150 mg.), m.p. 72–76°, was collected. The filtrate was boiled for 30 minutes, cooled and diluted with water to give an additional 100 mg. of product with m.p. 65–72°. The analytical sample, from methanol–water, exhibited m.p. 79–83°, $[\alpha]_D$ −143°, λ_{max} 247 mμ, log ε 4.25; λ_{max}^{KBr} 3365, 1650, 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{32}O_2 \cdot CH_4O$: C, 75.81; H, 10.41; O, 13.78. Found: C, 76.02; H, 9.98; O, 13.96.

19-Nor-6α-methyltestosterone (XIIa) and its Acetate XIIb. (a) By Hydrolysis of Enol Ether XIb.—The enol ether XIb (100 mg.) was dissolved in methanol (5.6 ml.) and treated with 0.24 *N* hydrochloric acid (0.8 ml.). The solution was allowed to stand for 42 hours under nitrogen, then a small amount of solid sodium carbonate was added and most of the methanol evaporated *in vacuo*. Water was added and the product, an oil (85 mg.), isolated by ethyl acetate extraction. Chromatography of this material over neutral alumina gave, in the benzene–ether (9:1 and 4:1) extracts, 55 mg. of 19-nor-6α-methyltestosterone (XIIa) as a colorless oil, $[\alpha]_D$ +160°, λ_{max} 241 mμ, log ε 4.13; $\lambda_{max}^{CHCl_3}$ 3430, 1660 cm.$^{-1}$. Acetylation of XIIa with excess acetic anhydride–pyridine for 24 hours at room temperature followed by neutral alumina chromatography of the crude product gave, in the benzene eluate, crystalline 19-nor-6α-methyltestosterone acetate (XIIb). Recrystallization from methanol–water gave pure XIIb, m.p. 119–121°, λ_{max} 241 mμ, log ε 4.27; λ_{max}^{KBr} 1715, 1668, 1242 cm.$^{-1}$; $\lambda_{max}^{CHCl_3}$ 1725, 1660, 1245 cm.$^{-1}$. Gross differences were noted in the comparison of the infrared spectra of XIIb with the 6β-methyl epimer IXb; R.D. (Fig. 1) in dioxane (c 0.071): $[\alpha]_{700}$ −7°, $[\alpha]_{589}$ −11°, $[\alpha]_{370}$ −363°, $[\alpha]_{365}$ −324°, $[\alpha]_{362.5}$ −345°, $[\alpha]_{357.5}$ −262°, $[\alpha]_{352.5}$ −450°, $[\alpha]_{310}$ +859°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; O, 14.53. Found: C, 76.24; H, 9.45; O, 14.67.

(b) By Selective Hydride Reduction of X.—A solution of 19-nor-6α-methyl-Δ^4-androstene-3,17-dione (X) (300 mg.) in methanol (50 ml.) containing sodium borohydride (46.5 mg.) was kept at 0° for one hour. A few drops of 50% acetic acid was added and the solvent evaporated. Water was added, the residue extracted with ethyl acetate, the extract washed with water, dried and evaporated leaving 290 mg. of oil, λ_{max} 240 mμ, log ε 3.92. Chromatographic purification of the oil on neutral alumina afforded in the benzene–ether (9:1 and 4:1) fractions, 115 mg. of XIIa as an oil, λ_{max} 241 mμ, log ε 4.12, infrared spectrum ($CHCl_3$) identical with that of the product obtained above in (a).

(c) By Selective Allylic Oxidation of 19-Nor-6α-methyl-Δ^4-androstene-3,17β-diol.—A solution of 3,17-diketone X (105 mg.) in methanol (5 ml.) was treated with 150 mg. of sodium borohydride dissolved in 1 ml. of water and boiled for one hour. The cooled solution was poured into dilute hydrochloric acid and the crude 19-nor-6α-methyl-Δ^4-androstene-3,17β-diol(s), an oil, isolated by ethyl acetate extraction. This oil, in dry benzene (1.5 ml.) and dry pyridine (0.5 ml.), was treated with N-bromoacetamide (55 mg.) and allowed to stand, in the dark, at room temperature, for 22 hours. The solution, after decantation from a brown oil which had separated, and dilution with 10 ml. of

(17) This procedure is one utilized in another series by C. W. Marshall, J. W. Ralls, F. J. Saunders and B. Riegel, *J. Biol. Chem.*, **228**, 339 (1957).

benzene and 30 ml. of ether, was washed successively with 10% sodium bicarbonate, 10% sodium hydroxide, water, 5% sulfuric acid and water. Evaporation of solvent yielded 95 mg. of yellow oil which, on chromatography as described above for (a), gave 45 mg. of XIIa, λ_{max} 241 mμ, log ε 4.11, infrared spectrum identical with the product obtained above.

(d) **By Inversion** of 19-Nor-6β-methyltestosterone Acetate.—A slow stream of dry hydrogen chloride was passed for 45 minutes through a solution of 40 mg. of IXb in 20 ml. of dry chloroform held at 0 to −5°. The acid then was removed by a stream of nitrogen and the chloroform solution washed to neutrality with water and finally evaporated. The oily residue was reacetylated and the product crystallized from aqueous methanol to yield XIIb, m.p. 118–120°, identical with the product obtained in (a).

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

Steroids. CXXV.[1] The Synthesis of 6-Phenyl Hormone Analogs

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When 5α,6α-oxidoprogesterone-3,20-biscycloethylene ketal is treated with phenylmagnesium bromide the corresponding 6β,5α-phenylhydrin is produced in high yield. Ketal hydrolysis of this fission product followed by dehydration of the 5α-hydroxyl group then leads to 6β-phenylprogesterone which may be epimerized to 6α-phenylprogesterone. The synthesis of 6α-phenyl-17α-hydroxyprogesterone by a similar reaction sequence is also described. While 5α,6α-oxidocortisone biscycloethylene ketal also provides its phenylhydrin in high yield, no satisfactory method for its conversion to 6α-phenylcortisone was found.

The literature contains numerous examples[2] of epoxide openings with arylmagnesium bromides. This knowledge combined with the fact that the steroid 5α,6α-epoxide is so labile toward methylmagnesium bromide[3] made the use of phenylmagnesium bromide appear attractive as a method for introducing the phenyl group in the C-6 position.[4]

Thus when 5α,6α-oxidoprogesterone biscycloethylene ketal (Ia) was treated for five hours with a large excess of phenylmagnesium bromide in boiling tetrahydrofuran the epoxide was smoothly opened to afford in 80% yield the corresponding 6β-phenyl-5α-hydroxy compound (IIa). Support for the structure of IIa in addition to its elemental analysis was found in the low intensity maxima which it exhibited at 254 and 260 mμ in the ultraviolet and also by bands at 2.83 (hydroxyl), 6.26, 13.26 and 14.34 μ in the infrared.[5]

When II was allowed to stand for one hour at room temperature in acetic acid containing a few drops of hydrochloric acid, hydrolysis of the ethylene ketal groups was effected thus providing the phenylhydrin-3,20-dione (IIIa) in 65% yield after chromatography. This yield was raised to 80% when the tetrahydrofuran–perchloric acid method[6] was employed. Thionyl chloride dehydration of III in pyridine then led to 6β-phenylprogesterone (IV) whose structure followed from its ultraviolet spectrum, λ_{max}^{EtOH} 242 mμ, log ε 4.14, and conversion to the more stable equatorial 6α-phenylprogesterone (Va) under alkaline epimerizing conditions. Alternatively the 6α-phenyl epimer Va could be obtained directly from the phenylhydrin-3,20-dione (IIIa) by the action of dilute methanolic potassium hydroxide at room temperature overnight.

Comparison of the optical rotatory dispersion curves for the two C-6 epimers does not disclose any striking differences between them as would be expected on the basis of all C-6 epimeric pairs previously examined. In the case of the α-phenyl isomer as compared to progesterone one observes an intense lowering of the peak in the 310 mμ region which may be due to an electronic effect and/or the relatively large bulk of the phenyl group.[7]

Employing a similar set of reactions 6α-phenyl-17α-hydroxyprogesterone (Vb) also was prepared and the relevant details can be found in the Experimental section.

In the case of 5α,6α-oxidocortisone biscycloethylene ketal acetate (VI)[8] the epoxide opening was equally efficacious in producing the corresponding phenylhydrin VII. Upon treatment of VII with perchloric acid in tetrahydrofuran[6] selective hydrolysis of the 3-cycloethylene ketal group resulted to yield the phenylhydrin-3-one (VIII) which after standing overnight with dilute alkali was converted to 6α-phenylcortisone-20-cycloethylene ketal (IX). When IX was treated under conditions known to effect hydrolysis of 20-cycloethylene ketals[9] the resulting non-crystalline product, λ_{max}^{EtOH} 236–238 mμ, log

(1) Paper CXXIV, A. Bowers, E. Denot, M. B. Sánchez, M. Sánchez Hidalgo and H. J. Ringold, THIS JOURNAL, **81**, in press (1959).

(2) See N. G. Gaylord and E. I. Becker, *J. Org. Chem.*, **15**, 305 (1950) and references therein.

(3) (a) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem. (U.S.S.R.)*, **9**, 436 (1939); (b) L. F. Fieser and J. Rigaudy, THIS JOURNAL, **73**, 4660 (1951); (c) R. B. Turner, *ibid.*, **74**, 5362 (1952); (d) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956); (e) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); (f) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957), and preceding papers; (g) A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 3091 (1958).

(4) Since the completion of this work a report has appeared describing the preparation of 6-phenylcholesterol by the action of phenylmagnesium bromide on 6-ketocholestanol; see R. A. Sneen, *ibid.*, **80**, 3971 (1958).

(5) The latter three bands are characteristic for monosubstituted benzenes: see L. J. Bellamy "The Infra-red Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 71, 76–77.

(6) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(7) In all cases previously observed 6α-substituted steroids have shown maxima of almost equal intensity with the parent steroid; see for example C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958), and C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *ibid.*, **80**, 4001 (1958).

(8) This substance was originally prepared in these laboratories by Dr. John Edwards and its preparation will be described in a later publication. The physical constants for 5α,6α-oxidocortisone biscycloethylene ketal acetate are m.p. 217–219°, $[\alpha]_D$ −5.4°.

(9) W. S. Allen, S. Bernstein and R. Littell, THIS JOURNAL, **76**, 6116 (1954).