A-norallopregnane-2,20-dione and A-norpregnane-3,20-dione, as evidenced by the infrared spectrum, λ_{max} 1742 and 1714 cm.$^{-1}$.

When this material was chromatographed on 3 g. of alumina, 3 fractions were eluted with 1:1 benzene–petroleum ether, as follows: (1) 50 ml. eluted 0.0215 g. which gave 0.011 g., m.p. 152–159°, after crystallization from ethanol–water; (2) 200 ml. eluted 0.0148 g. which could not be obtained crystalline; and (3) 200 ml. eluted 0.0189 g. which gave 0.0060 g., m.p. 161–167°, after recrystallization from ethanol–water (reported for the 2,20-diketone,[9a] m.p. 180°, and for the 3,20-diketone,[9b] m.p. 144–146°).

PROVIDENCE 12, R. I.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY, AND THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

D-Homosteroids. I. 3β-Hydroxy-17a,17a-dimethyl-D-homoandrostane-17-one and Related Compounds[1]

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Treatment of 3β,17α-dihydroxypregn-5-en-20-one 3β-acetate with methylmagnesium iodide gave bisnorchol-5-ene-3β,17α,20-triol, the structure of which was ascertained by its oxidation with sodium bismuthate to dehydroepiandrosterone. Bisnorcholane-17α,20-diols rearrange under acidic conditions and give 17a,17a-dimethyl-D-homoandrostane-17-one derivatives; arguments in support of that structure are presented.

Many publications[2–7] dealing with the synthesis and the biological activities of 17a-monomethyl-D-homosteroids have appeared in previous years; we now wish to report our work on the synthesis of some 17a,17a-dimethyl-D-homoandrostanes, obtained by the rearrangement of bisnorcholane-17α,20-diol derivatives with acid.

These bisnorcholane-17α,20-diols were obtained by the Grignard reaction on the corresponding 17α-hydroxy-20-keto-pregnanes. Thus, 3β,17α-dihydroxypregn-5-en-20-one 3β-acetate (VIII) was treated with methylmagnesium bromide and the resulting bisnorchol-5-en-3β,17α-20-triol (IXa) was obtained in 75% yield. The structure of IXa was ascertained by its elemental analysis, by the absence of a ketonic band in its infrared spectrum, and finally by obtaining dehydroepiandrosterone (X) as the only reaction product from its oxidation with sodium bismuthate. The acetylation of the triol IXa with acetic anhydride and pyridine gave bisnorchol-5-ene-3β,17α,20-triol 3β-acetate (IXb) which was reduced catalytically to bisnorallocholane-3β,17α,20-triol 3β-acetate (Vb) in quantitative yield; Vb also was obtained from 3β,17α-dihydroxyallopregnane-20-one 3β-acetate (IV) by treating it first with methylmagnesium iodide followed by reactylation of the thus produced triol Va. The 17α,20-dihydroxybisnorchol-4-en-3-one (XI) was obtained from 17α-hydroxyprogesterone (XVIII). Partial etherification of XVIII was accomplished with one mole of triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid. The usual procedure, using hydrochloric acid as catalyst, failed in this case for unknown reasons. The quantitatively produced 17α-hydroxyprogesterone 3-ethyl enol ether (XIX) showed the characteristic infrared absorption bands at 1650 and 1625 cm.$^{-1}$ for a conjugated diene and showed ether bands at 1230 and 1178 cm.$^{-1}$. The enol ether XIX was treated with a 10 molar excess of methylmagnesium iodide and the resulting mixture was separated chromatographically into 17α,20-dihydroxybisnorchola-3,5-diene 3-ethyl ether (XV) and XI. These products were characterized by elemental analysis, infrared absorption spectra and by a positive periodic acid test.

The Oppenauer oxidation of bisnorchol-5-ene-3β-17α,20-triol (IXa) did not give the expected XI. Although the product appeared to be pure judging from its sharp melting point and from its single ultraviolet maximum at 242 mμ, it was definitely different from XI as could be seen in the infrared absorption spectrum. Its periodic acid test was positive, but it did not undergo the rearrangement as did XI which will be discussed below. It seems probable that we deal here with a rearrangement of the glycolic side chain under Oppenauer conditions and attempts to elucidate the structure of this product are being continued.

The rearrangement of the glycols was studied under the following conditions: (1) either in refluxing glacial acetic acid containing catalytic amounts of elemental iodine or *p*-toluenesulfonic acid or (2) in 98% formic acid at 100°.

The main product was in every case the 17a,17a-dimethyl-17-keto-D-homosteroid, though the yields varied from 30% (elemental iodine) to 86% (formic acid). The rearrangement[8] proceeds very likely by the dissociation of the 20-hydroxyl group,[9]

(1) Taken in part from a dissertation by Milan Uskoković in partial fulfillment of the requirements for the Ph.D. degree in Organic Chemistry, Clark University, June, 1960. Presented, in part, before the Division of Organic Chemistry, 134th National A.C.S. Meeting, Chicago, Ill., Sept., 1958. This investigation was supported, in part, by grants PHS-CY-2193 and PHS-C-321.

(2) W. A. Yarnall and E. S. Wallis, THIS JOURNAL, **59**, 951 (1937).

(3) K. Miescher and H. Kägi, *Chem. Ind.*, **57**, 276 (1938).

(4) K. Miescher and H. Kägi, *Helv. Chim. Acta*, **22**, 184 (1939).

(5) L. Ruzicka and H. F. Meldahl, *ibid.*, **23**, 364 (1940).

(6) F. Ramirez and S. Stafiej, THIS JOURNAL, **77**, 134 (1955).

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

(8) Compare A. Serini, W. Logemann and W. Hildebrand, *Ber.*, **72B**, 391 (1939); H. L. Herzog, C. C. Joyner, M. J. Gentles, M. T. Hughes, E. P. Oliveto, E. B. Hershberg and D. H. R. Barton, *J. Org. Chem.*, **22**, 1413 (1957); D. K. Fukushima and T. F. Gallagher, *J. Biol. Chem.*, **226**, 725 (1957).

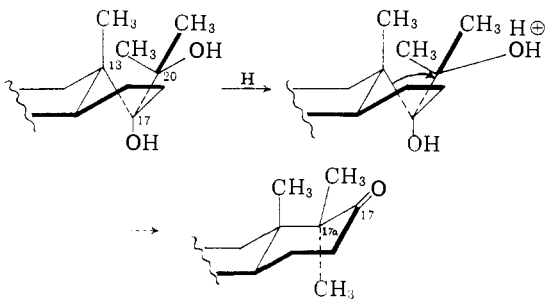
(9) Compare these results with the rearrangement of pregn-5-ene-3β,17α,20β-triol, pregn-5-ene-3β,17α,20β-triol 3β-acetate and 17α,20β-dihydroxypregn-4-en-3-one with acetic acid and a catalytic amount of elemental iodine (unpublished results), whereby in all three cases the 17β-acetyl product was obtained.[10] These results indicate that 17α,20β-dihydroxypregnane derivatives rearrange through initial formation of a 17-carbonium ion, while the 17α,20β-dihydroxybisnorcholane derivatives favor a 20-carbonium ion, due to its stabilization by the inductive effects of an additional methyl group.

(10) Compare D. K. Fukushima and T. F. Gallagher, *J. Biol. Chem.*, **226**, 725 (1957).

TABLE I

	Keto group absorption C=O, cm.$^{-1}$ [12]	Isopropyl group: *sym*-C–H vibration of CH_3 group, cm.$^{-1}$	Charact. band, cm.$^{-1}$	CH_3–C rocking, cm.$^{-1}$	C–C vibration, cm.$^{-1}$	Hydroxyl absorption, cm.$^{-1}$	Acetate absorption, cm.$^{-1}$
3β-Hydroxy-17a,17a-dimethyl-D-homo-androst-5-en-17-one (XIIIa)	1705	1393 1382 1373	1330	1165	960	3540	..
3β-Acetoxy-17a,17a-dimethyl-D-homo-androst-5-en-17-one (XIIIb)	1705	1398 1382 1370	1335	1170	962	..	1730 1255
3β-Hydroxy-17a,17a-dimethyl-D-homo-androstane-17-one (VIa)	1705	1395 1385 1365	1343	1175	955	3550	..
3β-Acetoxy-17a,17a-dimethyl-D-homo-androstane-17-one (VIb)	1705	1395 1385 1370	1330	1170	953	..	1730 1250
17a,17a-Dimethyl-D-homoandrost-4-ene-3,17-dione (XIV)	1705 1675	1397 1385 1370	1335	1170	953	..	..
17a,17a-Dimethyl-D-homoandrostane-3,17-dione (VII)	1712	1395 1385 1375	1320	1165	950	..	..

with subsequent migration of the C-13,17 bond



The assignment of structure of the D-homosteroids is deduced from these various observations: 3β-Hydroxy-17a,17a-dimethyl-D-homoandrost-5-en-17-one (XIIIa) and its acetate XIIIb as well as VIa and its acetate VIb, gave a positive Zimmermann test, due to an α-methylene group of a ketone. The ultraviolet spectrum of XIIIa, and of VIa ($\epsilon_{288\ m\mu}$ 35.4) and $\epsilon_{290\ m\mu}$ 30.2) showed absorption peaks characteristic of saturated hexacyclic ketones. This consideration was confirmed by the infrared spectrum. The latter showed a ketonic absorption peak at 1705 cm.$^{-1}$. Further characteristic absorption maxima for most of the compounds described in the Experimental part are given in Table I. A measure of the expected strong steric hindrance of the 17-ketone was obtained by measuring the amount of hemiketal formation in methanolic 0.05 *M* hydrochloric acid solution[11]; practically no hemiketal was formed.

The crude rearrangement product of bisnorchol-5-ene-3β,17α-20-triol (IXa) (acetic acid–elemental iodine) was separated into a highly unsaturated product XII, the elemental analysis of which showed the product to be formed by the elimination of two molecules of water. Its infrared analysis and ultraviolet spectrum (262 mμ, ε 8400) showed a cross-conjugated triene. The structure of XII (yellow prisms) was not established. The main product was eluted from the column later and identified as 3β-hydroxy-17a,17a-dimethyl-D-homoandrost-5-en-17-one (XIIIa). The rearrangement was repeated under similar conditions with IXb, whereby 3β-acetoxy-17a,17a-dimethyl-D-homoandrost-5-en-17-one (XIIIb) was obtained as the only reaction product with 60% yield. The rearrangement of IXa in acetic acid with a catalytic amount of *p*-toluenesulfonic acid gave besides 60% XIIIa also a very small amount of XIIIb. The rearrangement of IXa with formic acid, followed by hydrolysis, gave 85% XIIIa.

Similar yields were obtained with saturated compounds. Bisnorallocholane-3β,17α-20-triol (Va) and its monoacetate Vb gave 3β-hydroxy-17a,17a-dimethyl-D-homoandrostane-17-one (VIa) and its acetate VIb. The chromic acid oxidation of (VIa) yielded quantitatively 17a,17a-dimethyl-D-homoandrostane-3,17-dione (VII).

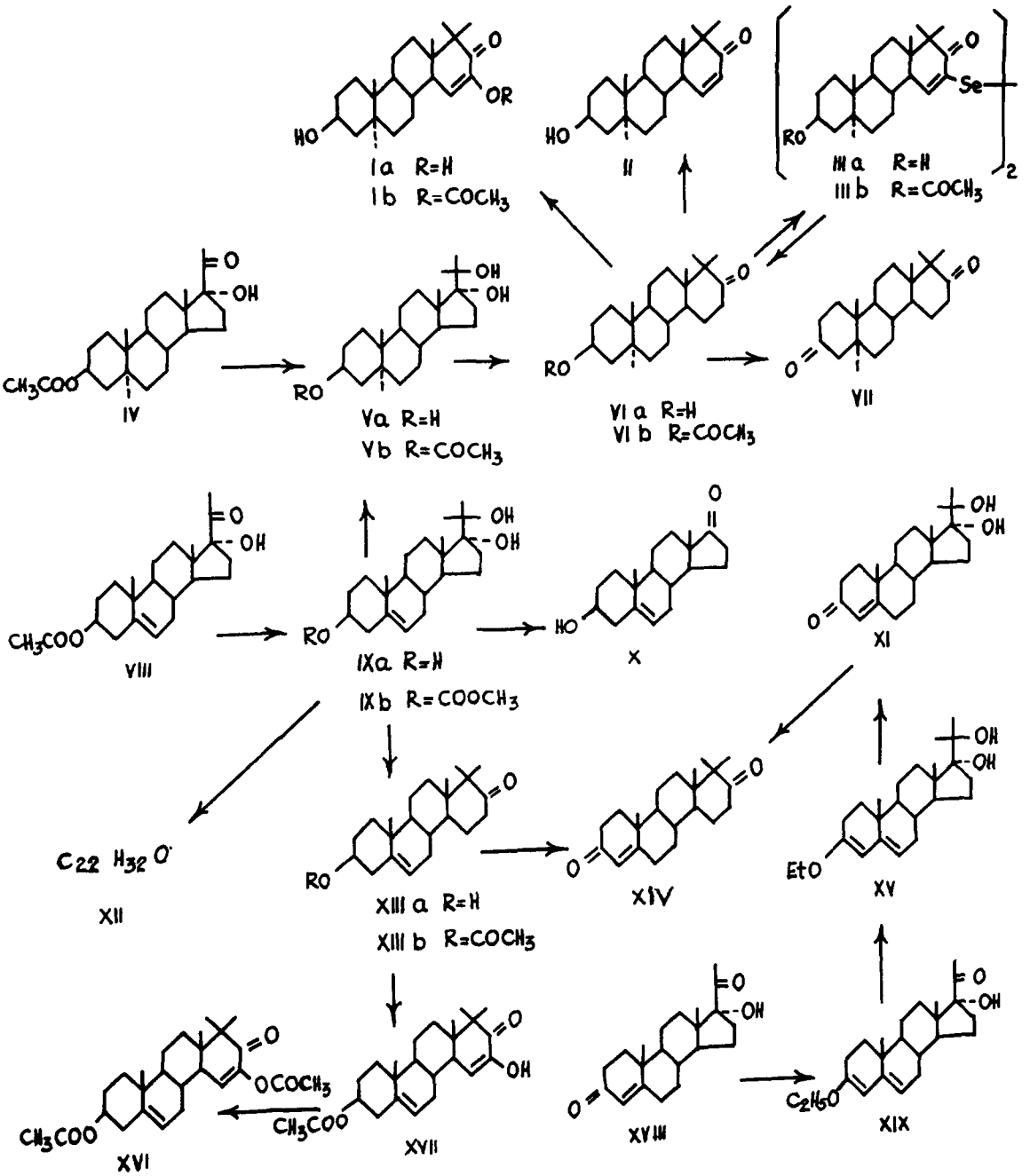
The rearrangement of 17α,20-dihydroxy-bisnorchol-4-en-3-one (XI) in acetic acid with elemental iodine gave 17a,17a-dimethyl-D-homoandrost-4-ene-3,17-dione (XIV). The latter also was obtained by the Oppenauer oxidation of 3β-hydroxy-17a,17a-dimethyl-D-homoandrost-5-en-17-one (XIIIa).

The 3β-acetoxy-17a,17a-dimethyl-D-homoandrostane-17-one (VIb) was oxidized with selenium dioxide.[13] When the oxidation was carried out for 24 hours the reaction product remained sirupy after chromatography. It therefore was hydrolyzed with excess methanolic sodium hydroxide solution at room temperature. The precipitation of crystalline 16-bis-(3β-hydroxy-17a,17a-dimethyl-D-homoandrost-15-en-17-one) diselenide (IIIa), the structure of which was deduced from its elemental analysis, infrared and ultraviolet spectra, began 1 hour after the addition of base; IIIa is a high melting substance and practically insoluble in most

(11) O. H. Wheeler and J. L. Mateos, *Anal. Chem.*, **29**, 538 (1957).

(12) Compare E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957); Y. Mazur and F. Sondheimer, THIS JOURNAL, **80**, 5220 (1958).

(13) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).



ordinary solvents. The infrared spectrum showed absorption peaks at 3450 (hydroxyl), 1667 and 1605 (conj. ketone), 839 (trisubstituted double bond) and a strong band at 787 cm.$^{-1}$. The ultraviolet absorption ϵ_{302} 2040 is in full agreement with values given for similar compounds by Baran.[14] The diselenide was acetylated with boiling glacial acetic acid and the diacetate IIIb gave the starting ketone VIb upon reduction with zinc and acetic acid.[15]

(14) J. S. Baran, THIS JOURNAL, **80**, 1687 (1958).

(15) K. Florey and A. R. Restivo, *J. Org. Chem.*, **22**, 406 (1957), have reported that the diselenide analog of cholesta-1,4-dien-3-one, upon treatment with Raney nickel, gave cholesta-1,4-diene-3-one as main product and small amounts of cholest-4-en-3-one and cholestanone. The diselenide analog of 1-dehydrotestosterone acetate was resistant to reduction by hydrogen and palladium or platinum catalyst.

The mother liquors of IIIa gave, after chromatography, crystalline 3β-hydroxy-17a,17a-dimethyl-D-homoandrost-15-en-17-one (II). The unsaturated ketone absorbs in the ultraviolet at 233 mμ (ε 6134).[16]

When the oxidation of VIb was carried out for 48 hours, crystalline IIIa was obtained. From its mother liquor little II and another crystalline product were isolated. The assignment of the diosphenol structure Ib to the latter product is suggested by its infrared absorption peaks at 3550 (hydroxyl), 1667 (conj. ketone), 1752 and 1155 cm.$^{-1}$ (enol ester), and an ultraviolet maximum at 238 mμ. 3β,16-Dihydroxy-17a,17a-dimethyl-D-homoandrost-15-en-17-one 16-acetate (Ib) upon

(16) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

hydrolysis with methanolic sodium hydroxide solution at elevated temperature gave an oily yellow product. This product gave an intensive color reaction with ferric chloride and potassium ferricyanide and a single ultraviolet absorption maximum at 271 mμ. Both these data are in agreement with the diosphenol structure Ia.

When 3β-acetoxy-17a,17a-dimethyl-D-homoandrost-5-en-17-one (XIIIb) was oxidized with selenium dioxide for 48 hours, the oily product isolated was 3β,16-dihydroxy-17a,17a-dimethyl-D-homoandrosta-5,15-dien-17-one 3β-acetate (XVII). The ultraviolet spectrum had an absorption maximum at 272 mμ. Upon acetylation of the diosphenol XVII with acetic anhydride and pyridine the crystalline diacetate XVI was obtained, having an ultraviolet maximum at 234 mμ.

Experimental[17]

Bisnorchol-5-ene-3β,17α,20-triol (IXa) and Bisnorchol-5-ene-3β,17α,20-triol 3β-Acetate (IXb).—To the Grignard reagent, prepared from 9.74 g. of magnesium and 45.7 g. of methyl bromide in anhydrous ether, was added the benzene solution of 3.6 g. of 3β,17α-dihydroxypregn-5-en-20-one 3β-acetate (VIII) and the reaction mixture stirred for 12 hours at room temperature. After hydrolysis with an ice-cold aqueous ammonium chloride solution, the precipitate was filtered off, washed with water, dried and concentrated. The crude product was crystallized from methanol and gave crystals melting from 167–185°. Upon chromatography, the fractions with 25 and 50% ethyl acetate in benzene gave after recrystallization from methanol 2.7 g. of IXa, m.p. 182–185°, $[\alpha]^{21}D$ −82° (*c* 1.04). The infrared analysis showed no absorption in the ketonic region.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.56; H, 10.20.

Compound IXa was dissolved in 15 ml. of pyridine, 3 ml. of acetic anhydride was added and the mixture kept overnight at room temperature. The excess of acetic anhydride was hydrolyzed by a small amount of water, and then the reaction mixture was poured into a large excess of water. The crystalline precipitate was filtered off, washed with water and dried. Recrystallization from methanol gave in quantitative yield the acetate IXb, m.p. 181–182°, $[\alpha]^{21}D$ −84.5° (*c* 1.364).

Dehydroepiandrosterone (X) from IXa.—To the solution of 100 mg. of IXa in 100 ml. of 50% aqueous acetic acid was added 5 g. of sodium bismuthate and the resulting suspension was shaken overnight at room temperature. The excess reagent then was reduced with 20 ml. of a 10% aqueous potassium pyrosulfite solution, and after addition of 150 ml. 2 *N* sodium hydroxide solution the mixture was taken up in ether, the ether solution washed with water, dried over anhydrous sodium sulfate and finally evaporated. The crystalline residue was recrystallized from ethanol and gave pure dehydroepiandrosterone, m.p. 139–141°, identical in every respect with an authentic sample.

Bisnorallocholane-3β,17α,20-triol 3β-Acetate (Vb) from IXb.—To the solution of 1 g. of IXb in 25 ml. of glacial acetic acid was added 0.25 g. of 5% palladium-on-charcoal and the suspension was shaken overnight under a hydrogen pressure of 40 p.s.i. The catalyst was filtered off, the solution added to a large excess of water, the crystalline precipitate filtered off and dried. Crystallization from acetone–hexane gave Vb, m.p. 207–208°, $[\alpha]^{20}D$ −27° (*c* 0.74). The infrared spectrum failed to show a maximum at 818 cm.$^{-1}$, due to the disappearance of the trisubstituted double bond.

Anal. Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.36; H, 10.67.

Bisnorallocholane-3β,17α-triol (Va) and its 3β-Acetate (Vb) from IV.—To the Grignard reagent prepared from 14.59 g. of magnesium and 38 ml. of methyl iodide in ether, was added the ether solution of 7.6 g. of IV, and the reaction mixture stirred for 12 hours at room temperature. After hydrolysis with an ice-cold aqueous solution of ammonium chloride, the insoluble product was filtered off, washed with water and dried. Crystallization from methanol yielded 5.5 g. of Va, m.p. 185–195°, $[\alpha]^{20}D$ −7.5° (*c* 0.672). The infrared analysis did not show any absorption in the ketonic region.

The residual mother liquors were acetylated with pyridine–acetic anhydride and the resulting product was chromatographed. The fractions with 5% ether in benzene gave after recrystallization from acetone–pentane the acetate Vb, m.p. 205–207°, identical in all respect with the compound obtained from IXb.

17α-Hydroxy-3-ethoxy-pregna-3,5-dien-20-one (XIX) from XVIII.—Water was removed azeotropically from the solution of 3.3 g. of 17α-hydroxyprogesterone in 100 ml. of benzene and the distillation was continued until all substance was in solution. Then 1.48 g. of ethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid were added, the reaction mixture refluxed for 20 hours, cooled, and taken up in a large amount of methylene chloride. The extract was washed, first with an aqueous solution of 1% sodium hydroxide and 5% sodium sulfate, and then with a 5% sodium sulfate solution, until the solution was neutral. It was dried over anhydrous sodium sulfate and finally evaporated. The residue was crystallized from ligroin, giving XIX, m.p. 136–138°. The product showed the characteristic infrared absorption maxima for 1,3-unsaturated enol ethers at 1650, 1625, 1230, 1178 cm.$^{-1}$ and lacked the maxima of a conjugated ketone.

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 77.05; H, 9.56. Found: C, 76.96; H, 9.68.

17α,20-Dihydroxybisnorchola-3,5-diene 3-Ethyl Ether (XV) and 17α,20-Dihydroxybisnorchol-4-en-3-one (XI) from XIX.—To the Grignard reagent prepared from 382 mg. of magnesium and 2.23 g. of methyl iodide, was added 564 mg. of XIX in 20 ml. of ether. The reaction mixture was stirred for 12 hours at room temperature and then hydrolyzed with an ice-cold saturated solution of ammonium chloride. The ether layer, containing some suspended substance, was separated off, evaporated and the residue chromatographed. The fractions with 5 and 10% ethyl acetate in benzene gave crystalline XV, which was recrystallized from ether, m.p. 158–165°. Infrared analysis shows the characteristic bands for hydroxyl groups and 1,3-unsaturated enol ethers and the absence of ketonic absorption.

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 77.21; H, 10.06.

The fractions with 25% ethyl acetate in benzene, after recrystallization from ether, yielded XI, m.p. 186–187°, $[\alpha]^{20}D$ +39° (*c* 0.906). The infrared analysis showed the maxima of a conjugated ketone (1660 and 1615 cm.$^{-1}$) and indicated the absence of a saturated ketone. Furthermore, the product consumed periodic acid rapidly, characteristic for a glycol.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.10; H, 9.90.

Oppenauer Oxidation of Bisnorchol-5-ene-3β,17α,20-triol (IXa).—The solution of 200 mg. of IXa in 100 ml. of toluene and 10 ml. of cyclohexanone was azeotropically distilled until all water was removed, then 100 mg. of aluminum isopropoxide was added. After the solution turned intense yellow, the slow distillation was continued for another half-hour. Acetic acid then was added for the hydrolysis of the aluminum complex. The reaction mixture was steam distilled until all the solvents were distilled off. After cooling, a sodium chloride solution containing 2 g. of Celite was added and the mixture filtered. The filter cake was dried, then extracted quantitatively with ethyl acetate, the solvent evaporated and the residue chromatographed. The fractions with 10% ethyl acetate in benzene, gave, after recrystallization from ether, colorless prisms, m.p. 182–185°, $[\alpha]^{20}D$ −9° (*c* 1.112), λ_{max} 242 mμ; infrared absorption maxima ν_{max} 3600, 3500 (–OH), 1650 and 1605 cm.$^{-1}$ (conj. >C=O).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.50; H, 10.12.

(17) All melting points were taken on a Kofler block. Rotations were taken in a 1-dm. tube in chloroform. Ultraviolet absorption spectra were determined in methanol by means of a Cary model 11 MS spectrophotometer. The infrared spectra were obtained from a pressed potassium bromide pellet taken on a Perkin–Elmer model 12C spectrometer. All chromatographic separations were made on Davison silica gel mesh 60–200, unless otherwise indicated. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

3β-Hydroxy-17a,17a-dimethyl-D-homoandrost-5-en-17-one (XIIIa) and its Acetate XIIIb from IXa. (a) Rearrangement with Acetic Acid and Elemental Iodine.—The solution of 300 mg. of IXa and 6 mg. of iodine in 100 ml. of glacial acetic acid was refluxed under nitrogen for half an hour, allowed to cool, and the iodine reduced with several drops of saturated sodium sulfite solution. The cold reaction mixture was poured into 500 ml. of ice-cold 2 *N* sodium hydroxide solution. After quantitative extraction with ether the extract was washed with water, dried over anhydrous sodium sulfate and evaporated. The non-crystalline residue was chromatographed and the fractions with 2% ethyl acetate in benzene, after recrystallization from methanol, gave yellow prisms (XII), m.p. 155–160°, $[\alpha]^{20}D$ + 113° (*c* 0.620), ϵ_{262} 8400; the infrared analysis indicated a conj. polyene, and a hydroxyl group.

Anal. Calcd. for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.08; H, 10.39.

The fractions with 5% ethyl acetate in benzene gave, after recrystallization from methanol, 115 mg. of XIIIa, m.p. 199–200°, $[\alpha]^{20}D$ −91° (*c* 1.450). Data from the infrared and ultraviolet spectra are given in Table I. The Zimmermann test was positive.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.73; H, 10.56.

(b) **Rearrangement with Acetic Acid and *p*-Toluenesulfonic Acid.**—The solution of 348.5 mg. of IXa and 9.5 mg. of *p*-toluenesulfonic acid in 100 ml. of glacial acetic acid was refluxed under nitrogen for two hours, and after the reaction mixture was cooled to room temperature, it was poured into 500 ml. of ice-cold 2 *N* sodium hydroxide solution. After quantitative extraction with ether, the extract was washed with water, dried over anhydrous sodium sulfate and evaporated. The sirupy residue was chromatographed and the fractions with 1% ethyl acetate in benzene, after sublimation in high vacuum and recrystallization from methanol, gave 40 mg. of XIIIb (elongated colorless prisms), m.p. 180–181°, $[\alpha]^{20}D$ −83° (*c* 0.946). The infrared data are given in Table I. The Zimmermann test was positive.

The fractions with 5% ethyl acetate in benzene gave 220 mg. of XIIIa, which was proved to be identical with the material obtained with acetic acid and iodine.

(c) **Rearrangement in Formic Acid.**—Compound IXa (500 mg.) was treated with 2 ml. of 98% formic acid for 7 minutes at 100°, the reaction mixture cooled and poured into a large excess of water. After quantitative extraction with ether, the extract was washed with water and a saturated sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate and evaporated. The residue was hydrolyzed by refluxing for one hour with 200 mg. of potassium carbonate in 10 ml. of methanol. The solvent was evaporated off *in vacuo* and the residue taken up in ether. The ether was washed with water, dried and evaporated. The residue was chromatographed and the 5% ethyl acetate in benzene fraction furnished 425 mg. of XIIIa.

3β-Acetoxy-17a,17a-dimethyl-D-homoandrost-5-en-17-one (XIIIb) from IXb. (a) With Acetic Acid and Iodine.—The rearrangement was carried out exactly as described before. The reaction product was chromatographed and the fractions with 2% ether in benzene gave, after recrystallization from methanol, XIIIb, m.p. 180–181°, in 60% yield.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.53; H, 9.79.

(b) **With Formic Acid.**—Compound IXb (1 g.) was heated with 4 ml. of 98% formic acid for 7 minutes at 100° and after the reaction mixture was cooled, it was poured in a large excess of water. After quantitative extraction in ether, the extract was washed with water and a saturated sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate and evaporated. The crystalline residue was chromatographed and the fractions with 2% ethyl acetate in benzene gave 760 mg. of XIIIb, m.p. 178–181°, identical with the material described above.

17a,17a-Dimethyl-D-homoandrost-4-ene-3,17-dione (XIV) from XIIIa.—The solution of 200 mg. of XIIIa in 100 ml. of toluene and 10 ml. of cyclohexanone was azeotropically distilled until all water was removed, then 100 mg. of aluminum isopropoxide was added. The reaction mixture was refluxed 1 hour, then 1 ml. of acetic acid was added for the hydrolysis of the aluminum complex. The hydrolyzed mixture then was steam distilled until all the solvents were distilled off. After cooling, a sodium chloride solution containing 2 g. of Celite was added and the mixture filtered. The filter cake was dried, then extracted quantitatively with ethyl acetate, the solvent evaporated and the residue chromatographed on aluminum oxide. The fractions with 5% ether in benzene, after recrystallization from ether, gave 80 mg. of XIV, m.p. 180–182°, $[\alpha]^{20}D$ +66.5° (*c* 0.752), λ_{max} 242 mμ. The infrared absorption maxima account for a conjugated ketone (1665 and 1612 cm.$^{-1}$).

17a,17a-Dimethyl-D-homoandrost-4-ene-3,17-dione (XIV) from XI.—The rearrangement was carried out in acetic acid with elemental iodine, exactly as it was described before. The crude product was chromatographed and the fractions with 5% ether in benzene, after recrystallization from ether, gave XIV, m.p. 178–182°. The product was identical in all respects with the compound obtained by Oppenauer oxidation from XIIIa.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.23; H, 9.92.

3β-Hydroxy-17a,17a-dimethyl-D-homoandrostane-17-one (VIa) and 3β-Acetate VIb from Va.—The rearrangements were carried out exactly as described for their unsaturated analogs; VIa was obtained after chromatography from fractions with 10% ether in benzene and recrystallization from acetone; m.p. 204–205°, $[\alpha]^{20}D$ + 3° (*c* 0.790). The infrared and ultraviolet absorption data have been given before. The yield was 30% with acetic acid and iodine, and 70% with formic acid.

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92. Found: C, 79.12; H, 10.81.

Compound VIa (200 mg.) was dissolved in 2 ml. of pyridine, 1 ml. of acetic anhydride added and the mixture left overnight at room temperature. 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 water, dried and evaporated. The crystalline residue, after recrystallization from acetone, gave 180 mg. of VIb, m.p. 174–176°, $[\alpha]^{21}D$ −3.5° (*c* 0.90). The Zimmermann test was positive.

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 77.09; H, 10.75.

3β-Acetoxy-17a,17a-dimethyl-D-homoandrostane-17-one (VIb) from Vb.—The rearrangement was carried out in acetic acid with elemental iodine, and in formic acid, in 60 and 72% yields, respectively. The obtained VIb, m.p. 175–176°, was identical with the compound obtained by acetylation of VIa. The alkaline hydrolysis of VIb gave quantitatively VIa.

17a,17a-Dimethyl-D-homoandrostane-3,17-dione (VII) from VIa.—To the solution of 200 mg. of VIa in 50 ml. of methylene chloride was added 3 ml. of a 2% chromic trioxide solution in 80% acetic acid. The reaction mixture was shaken for 24 hours at room temperature after which the solution turned green. After several drops of a saturated sodium hydrogen sulfite solution was added, the methylene chloride layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The crystalline residue was chromatographed and the fractions with 2% ethyl acetate in benzene gave after recrystallization VII, m.p. 202–205°, $[\alpha]^{20}D$ +11.5° (*c* 0.436) with a yield of over 90%. The infrared absorption data are given in Table I.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.97; H, 10.44.

16-Bis-(3β-hydroxy-17a,17a-dimethyl-D-homoandrost-15-en-17-one) Diselenide (IIIa), 3β-Hydroxy-17a,17a-dimethyl-D-homoandrost-15-ene-17-one (II), 3β,16-Dihydroxy-17a,-17a-dimethyl-D-homoandrost-15-en-17-one 16-Acetate (Ib) from VIb.—To the solution of 150 mg. of VIb in 10 ml. of anhydrous *t*-butyl alcohol and 0.1 ml. of glacial acetic acid, 100 mg. of selenium dioxide was added, and the reaction mixture refluxed under nitrogen for 24 hours. After cooling, the mixture was taken up in a large amount of ethyl acetate, the solution washed successively with a cold diluted potassium hydrogen carbonate solution, with fresh ice-cold ammonium sulfide solution, ice-cold dilute ammonia solution, water, 2 *N* hydrochloric acid and water, and then dried over anhydrous sodium sulfate and evaporated. The yellow oily residue was dissolved in 15 ml. of methanol and 1 ml. of 1 *N* sodium hydroxide solution was added. The mixture turned intensely yellow in color and after one hour the crystalline product precipitated. After 24 hours at room temperature, the crystals were filtered off and the product recrystallized

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

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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

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