drops of saturated aqueous sodium sulfite solution, the methylene chloride layer was washed with aqueous sodium hydroxide solution and water to neutrality, then dried over sodium sulfate and evaporated to dryness. The crystalline residue was recrystallized from methanol to give XIX, m.p. 106–108°, in quantitative yield.

Ozonization of 17,17a-Dimethyl-D-homoandrost-17(17a)-en-3β-ol Acetate (VI) to XX.—The solution of 0.5 g. of VI in 100 ml. of ethyl acetate was cooled to −70° and an ozone–oxygen mixture was introduced for 45 minutes, or until the solution turned blue. The ethyl acetate was evaporated *in vacuo* at room temperature, the residue dissolved in 30 ml. of glacial acetic acid, followed by the addition of 1 ml. of 30% hydrogen peroxide. The reaction mixture was left overnight and then evaporated *in vacuo* at room temperature. The residue was taken up in benzene, the benzene solution washed with 2 *N* aqueous sodium carbonate and water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The amorphous residue was chromatographed whereby the eluates with 5 and 10% ether in benzene gave, after several recrystallizations from methanol, XX, m.p. 183–184.5°, $[\alpha]^{20}D$ + 24° (*c* 1.02); infrared absorption maxima ν_{max} 3550 and 1440 (hydroxyl), 1737 and 1245 (acetoxy), 1698 (ketone) and 1123 cm.$^{-1}$ (ether). The result of the molecular weight determination (406) showed the product to be a monomer. The product oxidizes potassium iodide to iodine in boiling acetic acid solution.

Anal. Calcd. (for expected diketone XXI) $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Calcd. (for hydroperoxide) $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.19; H, 9.48.

To the solution of 100 mg. of XX in 50 ml. of methanol and 50 ml. of methylene chloride was added 2.5 ml. of 1 *N* aqueous sodium hydroxide solution and the reaction mixture allowed to stand for 24 hours. The excess base was neutralized quantitatively with 1 *N* aqueous hydrochloric acid solution, revealing that only one equivalent of sodium hydroxide had been used for the hydrolysis. The solution was evaporated, the residue extracted with methylene chloride, the extract washed with water, dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The amorphous residue was chromatographed whereby the eluates with 50% ethyl acetate in benzene gave, after recrystallization from methanol, XXIV, m.p. 187–188°, $[\alpha]^{20}D$ −89° (*c* 0.534); infrared absorption maxima ν_{max} 3475 and 1042 (hydroxyl), 1140 (ether) and 1695 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.02; H, 10.09.

The molecular weight indicated for substance XXV a value of 390. The acetylation of XXIV in pyridine solution with acetic anhydride at room temperature gave quantitatively XX, and left untouched the other hydroxyl group present in the molecule. The same hydrolysis product was also obtained when XX was refluxed with alkali and, here again, reacetylation furnished starting material.

3β-Acetoxy-16-acetyl-17-methyl-16,17-*seco*-androstan-17-one (XXI) from XX.—A molecular still, containing 300 mg. of XX was gradually heated to 180° at 0.01 mm., when suddenly a decomposition occurred, which transformed the product into a sirupy substance. It was first crystallized from methanol, then from ether–petroleum ether, giving XXI, m.p. 154–157°, $[\alpha]^{20}D$ + 18.6° (*c* 1.61); infrared absorption maxima ν_{max} 1733 and 1240 (acetoxy). 1698 (methyl ketone) and 1420 cm.$^{-1}$ (methylene group alpha to carbonyl).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.44; H, 9.88.

Ten mg. of XXI was chromatographed on an aluminum oxide column, whereby the eluates with 5% ethyl acetate-in-benzene gave crystalline XXIII, recrystallized from ether, m.p. 202–203°; infrared absorption maxima ν_{max} 3550 and 1200 (tertiary hydroxyl), 1720 and 1260 (acetoxy) and 1700 cm.$^{-1}$ (methyl ketone).

16-Acetyl-17-methylandrost-16-en-3β-ol Acetate (XXII) from XX and XXI.—The solution of 50 mg. of XX or XXI and 5 mg. of *p*-toluenesulfonic acid in 25 ml. of glacial acetic acid was refluxed for 4 hours. After cooling, the reaction mixture was poured into a large excess of ethyl acetate, then washed with 1 *N* aqueous sodium hydroxide solution and water, dried over sodium sulfate and evaporated. The sirupy residue was chromatographed, whereby the eluates with 5% ethyl acetate-in-benzene gave XXII as a glassy colorless substance, λ_{max} 249 mμ[16]; infrared absorption maxima ν_{max} 1737 and 1245 (acetoxy), 1667 and 1625 cm.$^{-1}$ (conj. ketone).

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

WORCESTER, MASS.

[CONTRIBUTION FROM THE MEDICAL RESEARCH LABORATORY, DEPARTMENT OF MEDICINE, VETERANS ADMINISTRATION HOSPITAL, INDIANAPOLIS, IND.]

The Synthesis of 20-Methyl-5-pregnen-3β-ol

BY ROBERT T. BLICKENSTAFF

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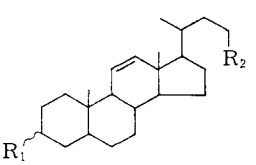
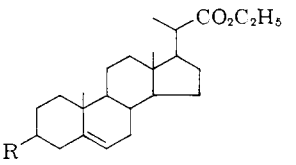
Ethyl 3β-hydroxy-5-bisnorcholenate was converted to 20-methyl-5-pregnen-3β-ol by two routes each involving stepwise reduction of carbethoxy to methyl. In one sequence the 3β-hydroxyl was converted to 3β-chloro, which was stable to the lithium aluminum hydride reductions. Alternatively the 3-hydroxyl function could be protected in the form of the trityl ether. 20-Methyl-5-pregnen-3β-ol was also synthesized from pregnenolone.

Ethyl 3β-chloro-11-cholenate (Ia) is one of a group of derivatives of bile acid esters that exhibit interesting seroflocculating properties.[1] Activity is retained when the ω-carbethoxy group is converted to methyl, as in 3β-chloro-11-cholene (Ib).[2] Other side-chain variations such as acetoxymethyl and chloromethyl (compare Ic with Id and Ie) also produced active compounds.[2] Of the derivatives of 3β-hydroxy-5-bisnorcholenic acid that have been screened as seroflocculants, ethyl 3β-chloro-5-bisnorcholenate (IIe) is highly active.[1] This paper reports the preparation of 20-methyl-5-pregnen-3β-ol (IVb) and 3β-chloro-20-methyl-5-pregnene (IIId), the reduced side chain analogs of 3β-hydroxy-5-bisnorcholenic acid and IIe, respectively, and of the 22-acetoxy (IIIb) and 22-chloro (IIIe) derivatives of IIId.

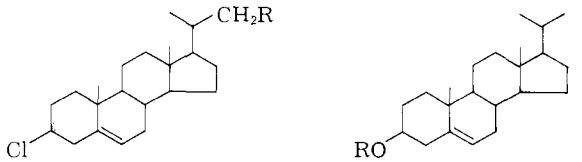




Ia, R_1 = β-Cl, R_2 = $CO_2C_2H_5$
b, R_1 = β-Cl, R_2 = CH_3
c, R_1 = α-AcO, R_2 = $CO_2C_2H_5$
d, R_1 = α-AcO, R_2 = CH_2OAc
e, R_1 = α-AcO, R_2 = CH_2Cl

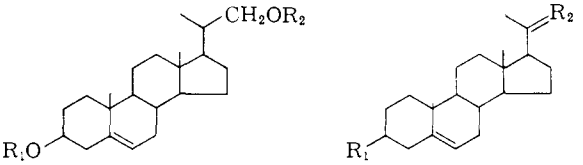
IIa, R = HO
b, R = BzO
c, R = *p*-$C_7H_7SO_3$
d, R = $(C_6H_5)_3CO$
e, R = Cl

(1) F. C. Chang, *et al.*, THIS JOURNAL, **79**, 2161 (1957).
(2) R. T. Blickenstaff and F. C. Chang, *ibid.*, **81**, 2835 (1959).



IIIa, R = HO
b. R = AcO
c. R = p-$C_7H_7SO_3$
d. R = H
e. R = Cl

IVa, R = Ac
b. R = H
c. R = Bz
d. R = $(C_6H_5)_3C$



Va. R_1 = $(C_6H_5)_3C$. R_2 = H
b, R_1 = $(C_6H_5)_3C$. R_2 = p-$C_7H_7SO_2$
c. R_1 = R_2 = H
d. R_1 = R_2 = Ac

VIa. R_1 = AcO, R_2 = CH_3, OH
b. R_1 = AcO, R_2 = CH_2
c, R_1 = HO, R_2 = CH_2
d. R_1 = Cl, R_2 = CH_2

In the C_{24}-series the side chain analogs were prepared by reducing the appropriate ester to a C-24 alcohol, with subsequent selective tosylation of the primary hydroxyl group and reduction of the tosylate.[2,3] 5-Bisnorcholen-3β,22-diol (Vc), however, did not tosylate selectively; at reduced temperature no reaction occurred, while at room temperature an intractable mixture resulted.

Ethyl 3β-chloro-5-bisnorcholenate (IIe) served as the starting point for an alternative synthesis of IVb. The ester group was reduced preferentially with lithium aluminum hydride[4]; the resulting 3β-chloro-5-bisnorcholen-22-ol (IIIa) was readily tosylated, but the product was contaminated with 3β,22-dichloro-5-bisnorcholene (IIIe).[5] Although the two can be separated by chromatography and fractional crystallization, it was more convenient to reduce the mixture with lithium aluminum hydride and separate 3β-chloro-20-methyl-5-pregnene (IIId) and IIIe chromatographically. Acetolysis of IIId under conditions used by Shoppee to convert cholesteryl chloride to the acetate[6] gave 20-methyl-5-pregnen-3β-yl acetate (IVa), from which 20-methyl-5-pregnen-3β-ol (IVb) was obtained by hydrolysis.[7] The over-all yield from IIa was 25%.

The intermediate tosylate, 3β-chloro-5-bisnorcholen-22-yl tosylate (IIIc), is stable to refluxing 2,6-lutidine, but in 2,4,6-collidine it is dehydrotosylated to 3β-chloro-20-methyl-5,20-pregnadiene (VId).

In a second synthesis of 20-methyl-5-pregnen-3β-ol, protection of the hydroxyl group of ethyl 3β-hydroxy-5-bisnorcholenate was afforded by formation of the trityl ether. Reduction of ethyl 3β-trityloxy-5-bisnorcholenate (IId) with lithium aluminum hydride provided 3β-trityloxy-5-bisnorcholen-22-ol (Va). Its tosylate (Vb) did not crystallize, but was reduced in crude state to 20-methyl-3β-trityloxy-5-pregnene (IVd). Treatment of the ether with acetic acid[8] gave triphenylmethanol and 20-methyl-5-pregnen-3β-ol (IVb), which were separated easily by chromatography on alumina. By this route the yield of IVb from ethyl 3β-hydroxy-5-bisnorcholenate was 32%.[9]

A more direct route to 20-methyl-5-pregnen-3β-ol (IVb) is that employed by Bergmann, *et al.*, for the preparation of other cholesterol homologs.[10] The action of methylmagnesium iodide on pregnenolone acetate, and then reacetylation, gave 3β-acetoxy-20-methyl-5-pregnen-20-ol (VIa). Dehydration with phosphorus oxychloride gave a mixture from which 20-methyl-5,20-pregnadien-3β-yl acetate (VIb) was separated by chromatography and fractional crystallization. Its structure is shown by its hydrolysis to the known 20 - methyl - 5,20 - pregnadien - 3β - ol (VIc), previously prepared by the Wittig reaction on pregnenolone,[11] and by its infrared absorption at 6.07 and 11.22 μ, typical of the methylene structure. The remainder (about 75%) of the dehydration product,[12] probably a mixture of VIb and the $\Delta^{17(20)}$-isomer, on catalytic hydrogenation at a pressure of 12 cm.,[13] gave the acetate IVa. which was hydrolyzed to 20-methyl-5-pregnen-3β-ol (IVb).

Screening Results.—Of the fifteen compounds screened in the seroflocculation reaction, only ethyl 6β-methoxy-3,5-cyclobisnorcholanate (VII, ref. 9) was sufficiently soluble to be tested by the usual method; it is inactive. At low concentration the others either: (1) flocculate cancer and normal sera indiscriminately (IIc, IIIc, IVa and VId), (2) form no floccules with the test sera

(3) R. T. Blickenstaff and F. C. Chang, THIS JOURNAL, **80**, 2726 (1958).

(4) Bis-(3β-chloro-5-androsten-17β-yl) sulfite is converted to 3β-chloro-5-androsten-17β-ol with lithium aluminum hydride: M. Gut and M. Uskokovic, *J. Org. Chem.*, **24**, 673 (1959).

(5) The simultaneous formation of the chloro derivative in a tosylation reaction has been noted previously (ref. 3). Compound IIIe also was obtained by the reaction of IIIc and pyridinium chloride in dimethylformamide.

(6) C. W. Shoppee, *J. Chem. Soc.*, 1147 (1946).

(7) Compound IVb, m.p. 139°, $[\alpha]D$ −69.1°, has the same structure as that assigned by Fränkel and Dombacher [*Ber.*, **60**, 1484 (1927)] to "hypocholesterol," m.p. 83°, $[\alpha]$ +68, +69°. Their structure has been discredited previously (see Elsevier's "Encyclopaedia of Organic Chemistry," Series III, Vol. 14 Suppl., Elsevier Publishing Co., New York, N. Y., 1954, p. 1600s). NOTE ADDED IN PROOF.—Methyl-5-pregnen-3β-ol and several other compounds in this series have been reported recently by J. P. Dusza and W. Bergmann, *J. Org. Chem.*, **25**, 79 (1960).

(8) H. R. Rosenberg and S. G. Turnbull, U. S. Patent 2,386,636, Oct. 9, 1945.

(9) The conversion of ethyl 3β-hydroxy-5-cholenate to IVb by way of the 3,5-cyclo series was investigated briefly. The tosylate IIc was converted in good yield to ethyl 6β-methoxy-3,5-cyclobisnorcholanate (VII), but reduction of this ester and tosylation of the reduction product gave materials which, though positive in rotation, were extremely difficult to crystallize and were not purified satisfactorily.

(10) E. D. Bergmann, M. Rabinovitz and Z. H. Levinson, THIS JOURNAL, **81**, 1239 (1959).

(11) F. Sondheimer and R. Mechoulam, *ibid.*, **79**, 5029 (1957).

(12) These fractions had broad melting ranges, and on hydrolysis gave a product m. 60–135°, presumably a mixture of VIc and 20-methyl-5,17(20)-pregnadien-3β-ol. Dehydration of VIa with acetic acid gave an acetate mixture with similar properties, although its infrared spectrum closely resembled that of VIb. 20-Methyl-5,17(20)-pregnadien-3β-ol, m.p. 72°, has been isolated from the products of dehydration of 20-methyl-5-pregnen-3β,20-diol with acetic acid [R. E. Marker, *et al.*, THIS JOURNAL, **64**, 1276 (1942)].

(13) Bergmann, *et al.*,[10] hydrogenated homologs of VIb selectively in the side chain by conducting the reaction in the presence of acetic acid and platinum oxide at room temperature and atmospheric pressure for 7.5 hr. In our hands, the dienes under these conditions were recovered unchanged. When the pressure was raised to 5–6 p.s.i., they were hydrogenated to 20-methyl-5α-pregnan-3β-yl acetate.

(IIb, IIIb, IVc, Vd and VIb) or (3) are insoluble (IId, IIId, IIIe, IVd and VIa).

Acknowledgments.—We wish to thank Mr. George Hayes for technical assistance, Dr. F. C. Chang for a sample of ethyl 3β-chloro-11-cholenate, and Mr. Paul Landis and Dr. Eugene Farkas of Eli Lilly and Co. for the infrared spectra.

Experimental[14]

Ethyl 3β-hydroxy-5-bisnorcholenate (IIa) was prepared by refluxing for 48 hr. a 2.2% solution of 3β-acetoxy-5-bisnorcholenic acid in ethanol containing a little concentrated sulfuric acid; 74% yield, needles out of benzene–ligroin[15] (1:4), m.p. 161–163.0° (lig.[16] m.p. 162–164°).

Anal. Calcd. for $C_{24}H_{38}O_3$ (374.54): C, 76.96; H, 10.23. Found: C, 77.33; H, 10.44.

The benzoate IIb crystallized from acetone in the form of prisms, m.p. 194.0–197.5°, $[\alpha]D$ −28.1°.

Anal. Calcd. for $C_{31}H_{42}O_4$ (478.65): C, 77.78; H, 8.85. Found: C, 77.82; H, 8.81.

The tosylate IIc crystallized from isopropyl ether as fine needles, m.p. 148–150.5°, $[\alpha]D$ −52.4°.

Anal. Calcd. for $C_{31}H_{44}O_5S$ (528.72): C, 70.42; H, 8.39; S, 6.06. Found: C, 70.06; H, 8.03; S, 5.86.

The trityl ether IId was prepared from IIa and trityl chloride in refluxing pyridine (2 hr.). The solution was diluted with ice and water, acidified and extracted with ether. The ether solution was washed with aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on alumina (ligroin–benzene 1:1) and crystallized from acetone–methanol (2:3) to give plates, m.p. 126–135° (66% yield). Further recrystallizations from isopropyl ether and from ethanol did not narrow the melting range. The analytical sample crystallized from ethanol; plates, m.p. 125.4–134.0°, $[\alpha]D$ −45.3° (1%).

Anal. Calcd. for $C_{43}H_{52}O_3$ (616.85): C, 83.72; H, 8.50. Found: C, 83.81; H, 8.45.

Ethyl 3β-chloro-5-bisnorcholenate (IIe) was prepared in 87% yield from IIa and thionyl chloride, as laths out of 90% ethanol, m.p. 119.0–121.1°, $[\alpha]D$ −44.7° (lit.[18] m.p. 120–123°, $[\alpha]D$ −47.3°).

3β-Chloro-5-bisnorcholen-22-ol (IIIa).—A solution of 6.66 g. (16.8 mmoles) of ethyl 3β-chloro-5-bisnorcholenate (IIe) in 215 ml. of ether was added in 10 min. to a stirred suspension of 648 mg. (17.1 mmoles) of lithium aluminum hydride in 53 ml. of ether. After refluxing for 2 hr. the mixture was treated with ethyl acetate and dil. hydrochloric acid and extracted with ether. The ethereal solution was washed with aq. $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated, giving 5.83 g. of crude product, m.p. 157–164°. Recrystallization in acetone, then in methanol–water (49:1) gave 4.83 g. (81% yield) of platelets, m.p. 161.0–164.5°; another 0.27 g. recovered from the mother liquor raised the yield to 86%. The analytical sample was chromatographed in benzene on alumina; m.p. 171.0–173.8°, $[\alpha]D$ −45.6° (1%).

Anal. Calcd. for $C_{22}H_{35}OCl$ (350.96): C, 75.28; H, 10.05; Cl, 10.10. Found: C, 75.33; H, 10.08; Cl, 10.01.

The acetate IIIb crystallized from methanol as needles, m.p. 126.8–129.0°, $[\alpha]D$ −36.8° (1%).

Anal. Calcd. for $C_{24}H_{37}O_2Cl$ (393.00): C, 73.34; H, 9.49; Cl, 9.02. Found: C, 73.10; H, 9.41; Cl, 8.85.

The tosylate IIIc was isolated in crude form, m.p. 132–135°. Recrystallization in acetone gave laths, m.p. 135.2–140.0° (74% yield), sufficiently pure for subsequent reactions, though contaminated with 3β,22-dichloro-5-bisnorcholene. The analytical sample was recrystallized from acetone–methanol (1:5), chromatographed in benzene on alumina and recrystallized from isopropyl ether; m.p. 135–137.8°, $[\alpha]D$ −34.3°.

Anal. Calcd. for $C_{29}H_{41}O_3SCl$ (505.14): C, 68.95; H, 8.18; Cl, 7.02; S, 6.35. Found: C, 68.80; H, 8.37; Cl, 7.04; S, 6.13.

3β-Chloro-20-methyl-5-pregnene (IIId).—A cloudy solution of 3.14 g. (6.22 mmoles) of 3β-chloro-5-bisnorcholen-22-yl tosylate (IIIc) in 80 ml. of ether and 25 ml. of benzene was added in 30 min. to a stirred suspension of 350 mg. of lithium aluminum hydride in 16 ml. of ether. After refluxing for 5 hr. the mixture was worked up in the usual fashion. The crude product, 1.98 g., was slightly yellow; its acetone solution was decolorized with charcoal and chilled to give 1.38 g. of needles, m.p. 144.8–150.0°. A second crop amounting to 0.045 g. melted at 147–167°. A portion (1.56 g.) of both crops was chromatographed on alumina; the first fraction, eluted by ligroin, 1.20 g. (58% yield), represents the 3β-chloro-20-methyl-5-pregnene. Recrystallization in dimethylformamide gave the analytical sample as needles, m.p. 148.0–149.0°, $[\alpha]D$ −46.2°.

Anal. Calcd. for $C_{22}H_{35}Cl$ (334.96): C, 78.88; H, 10.53; Cl, 10.59. Found: C, 79.06; H, 10.32; Cl, 10.72.

The second fraction, also eluted by ligroin, 0.27 g., crystallized from acetone to give **3β,22-dichloro-5-bisnorcholene** (IIIe) as needles, m.p. 205.0–209.0°, $[\alpha]D$ −31.4°.

Anal. Calcd. for $C_{22}H_{34}Cl_2$ (369.41): C, 71.52; H, 9.28; Cl, 19.20. Found: C, 71.35; H, 9.59; Cl, 18.91.

3β,22-Dichloro-5-bisnorcholene (IIIe).—A mixture of 505 mg. (1.00 mmole) of 3β-chloro-5-bisnorcholene-22-yl tosylate (IIIc) and 0.50 g. of pyridinium chloride (Eastman Kodak Co., practical grade) in 5 ml. of dimethylformamide was kept at room temp. 40 hr. Complete solution was not achieved, so the mixture was agitated gently from time to time. On dilution of the mixture with water the crude product precipitated quantitatively. It crystallized from ligroin in the form of needles, m.p. 193–203°, 347 mg. (94%). This crystallized from acetone in the form of very fine needles, m.p. 201–208.0°, m.p. undepressed when mixed with the sample separated from IIId.

20-Methyl-5-pregnen-3β-yl Acetate (IVa).—**(A) By Acetolysis of 3β-Chloro-20-methyl-5-pregnene.**—A solution of 1.09 g. (3.26 mmoles) of IIId and 1.75 g. of freshly fused potassium acetate in 44 ml. of redistilled glacial acetic acid was refluxed for 6.5 hr. The solution was evaporated with the aspirator to a volume of about 10 ml., diluted with water to 180 ml. and filtered. The precipitate was washed thoroughly with water, dried and recrystallized from methanol to give 0.97 g. (83% yield) of laths, m.p. 125.5–127.0°, $[\alpha]D$ −70.6°.

Anal. Calcd. for $C_{24}H_{38}O_2$ (358.54): C, 80.39; H, 10.68. Found: C, 80.24; H, 10.53.

(B) By Hydrogenation.—A solution of 500 mg. of VIb[17] and 0.5 ml. of glacial acetic acid in 25 ml. of dioxane was hydrogenated in the presence of 125 mg. of Adams catalyst at a pressure of 12 cm. for 30 min. The crude product crystallized out of methanol in the form of broad laths, m.p. 124–126.5°, m.p. unreduced when mixed with IVa prepared by acetolysis of IIId, but m.p. 120–125° when mixed with 20-methyl-5α-pregnan-3β-yl acetate. The latter was obtained when the hydrogenation was carried out at 5–6 p.s.i. for 7 hr.; laths out of methanol, m.p. 123.0–124.0° (lit.[18] m.p. 124–125°), $[\alpha]D$ −22.5° (1%).

20-Methyl-5-pregnen-3β-ol (IVb).—**(A) From the Acetate.**—Hydrolysis of 20-methyl-5-pregnen-3β-yl acetate (IVa) in refluxing 4% methanolic KOH (30 min.) gave a 98% yield of IVb, m.p. 136.5–139.0°. The analytical sample formed feathery needles out of acetone; m.p. 138.9–139.8°, $[\alpha]D$ −69.1°.

Anal. Calcd. for $C_{22}H_{36}O$ (316.51): C, 83.48; H, 11.47. Found: C, 83.69; H, 11.47.

(B) From the Trityl Ether.—A solution of 200 mg. of 20-methyl-3β-trityloxy-5-pregnene (IVd) in 20 ml. of glacial acetic acid was warmed at 56° for 7.5 hr. The solution was poured on ice, and the crude product was filtered, washed with aq. $NaHCO_3$ and water, and dried *in vacuo* over P_2O_5. Chromatography of the crude product on

(14) Microanalyses by Galbraith Laboratories, Knoxville, Tenn. Melting points were taken on an electrical hot-stage and are uncorrected. Optical rotations were determined in 2% chloroform solutions, except where noted, at about 25°, using a Keston polarimeter attachment (Standard Polarimeter Co., 6 Banta Place, Hackensack, N. J.) to a Beckman DU spectrophotometer.

(15) The ligroin used in these experiments was Skellysolve B (Skelly Oil Co.), b.p. 63–70°, purified by sulfuric acid treatment and distillation.

(16) F. C. Chang, *et al.*, THIS JOURNAL, **79**, 2164 (1957).

(17) This sample, m. 105–123°, presumably is a mixture of the $\Delta^{17(20)}$- and Δ^{20}-isomers.

(18) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

alumina gave two distinct fractions. The first, 89 mg., eluted by benzene, thick laths out of methanol, m.p. 163.0–164.0°, is triphenylmethanol (lit.[19] m.p. 164–165°). The second fraction, 108 mg. (96% yield), eluted by ether–benzene (1:1), crystallized from acetone in the form of needles and from methanol in the form of laths, m.p. 139.2–140.0°, m.p. unreduced when mixed with IVb from the acetate.

The benzoate IVc crystallized from benzene–acetone (1:4) in the form of laths, m.p. 171.8–173.5°, $[\alpha]_D$ −31.1°.

Anal. Calcd. for $C_{29}H_{40}O_2$ (420.61): C, 82.81; H, 9.59, Found: C, 82.92; H, 9.46.

20-Methyl-3β-trityloxy-5-pregnene (IVd).—Reduction of the crude tosylate Vb with lithium aluminum hydride in refluxing ether (4.5 hr.) and chromatography of the product on alumina (ligroin) gave a 77% yield (based on Va) of IVd, m.p. 191–195°. The analytical sample crystallized from acetone as needles, m.p. 195.0–198.0°, $[\alpha]_D$ −45.5°.

Anal. Calcd. for $C_{41}H_{50}O$ (558.81): C, 88.12; H, 9.02. Found: C, 87.85; H, 8.76.

3β-Trityloxy-5-bisnorcholen-22-ol (Va).—Ethyl 3β-trityloxy-5-bisnorcholenate (IId) was reduced with lithium aluminum hydride in a manner similar to the reduction of ethyl 3β-chloro-5-bisnorcholenate (IIe). Crystallization of the crude product from methanol, chromatography on alumina (ether–toluene, 1:4) and crystallization from methanol again gave an 84% yield of product, m.p. 131–138°. Recrystallization of this in ethylene dichloride–ligroin (3:10) raised the m.p. to 175–182°, 67% yield based on IId. The analytical sample crystallized out of ethylene dichloride–ligroin (1:4) as hemispherical clusters of white crystals, m.p. 178.0–183.0°, $[\alpha]_D$ −39.4°.

Anal. Calcd. for $C_{41}H_{50}O_2$ (574.81): C, 85.66; H, 8.77. Found: C, 85.72; H, 8.78.

The tosylate Vb was obtained as an amorphous product which resisted crystallization. It was used in this form for the preparation of IVd.

5-Bisnorcholen-3β,22-diol (Vc).—Reduction of methyl 3β-hydroxy-5-bisnorcholenate with $LiAlH_4$ gave the diol, laths out of acetone, m.p. 194.5–198.0° (lit. m.p. 202–206°,[20] 275–280°,[21] 196–205°[22]).

Anal. Calcd. for $C_{22}H_{36}O_2$ (332.51): C, 79.46; H, 10.92. Found: C, 79.65; H, 11.12.

The diacetate Vd crystallized from acetone–water (10:1) in the form of fine needles, m.p. 129.6–130.5°, $[\alpha]_D$ −49.8° (lit. m.p. 220–225°,[21] 127–129°,[22] $[\alpha]_D$ −51.0°[22]).

Anal. Calcd. for $C_{26}H_{40}O_4$ (416.54): C, 74.96; H, 9.68. Found: C, 74.98; H, 10.09.

3β-Acetoxy-29-methyl-5-pregnen-20-ol (VIa).—Following the method of Bergmann, *et al.*,[10] pregnenolone acetate was treated with a 4:1 mole ratio of methylmagnesium iodide. The crude product was reacetylated and chromatographed on alumina. After a small fraction eluted by ether–ligroin (1:1), the main fraction VIa, m.p. 151–153° (66% yield), was eluted by ether–ligroin (4:1). The analytical sample crystallized out of acetone–water (20:1) as tiny laths, m.p. 153–154°, $[\alpha]_D$ −67.2°.

Anal. Calcd. for $C_{24}H_{38}O_3$ (374.54): C, 76.96; H, 10.23. Found: C, 76.88; H, 10.20.

20-Methyl-5,20-pregnadien-3β-yl Acetate (VIb).—Dehydration of 1.19 g. of 3β-acetoxy-20-methyl-5-pregnen-20-ol (VIa) with phosphorus oxychloride and pyridine gave 1.07 g. (91%) of crude product, m. 103–118°. Chromatography on alumina (ligroin) and crystallization once from methanol and twice from acetone gave 207 mg. of VIb, plates, m.p. 134.8–135.1°, $[\alpha]_D$ −68.4°; $\lambda_{max}^{HCCl_3}$ 6.07, 11.22 μ. The remaining fractions from the recrystallizations melted variously at 105–123°, 111–125° and 112–141°, and are presumed to be mixtures of VIb and 20-methyl-5,17(20)-pregnadien-3β-yl acetate (m.p. 139–141°, Marker, ref. 12). Dehydration of VIa with acetic acid gave a similar product, m. 104–123°.

Anal. Calcd. for $C_{24}H_{36}O_2$ (356.53): C, 80.84; H, 10.18. Found: C, 80.87; H, 10.10.

20-Methyl-5,20-pregnadien-3β-ol (VIc) was obtaind by hydrolysis of VIb (m.p. 134.8–135.1°) with methanolic KOH; minute laths out of methanol, m.p. 134.0–135.0°, mixed m.p. with VIb 107–135°, $[\alpha]_D$ −64.3° (1%) (lit.[11] m.p. 133–134°, $[\alpha]_D$ −59°).

3β-Chloro-20-methyl-5,20-pregnadiene (VId).—A solution of 800 mg. of 3β-chloro-5-bisnorcholen-22-yl tosylate (IIIc) in 6 ml. of 2,4,6-collidine was refluxed 2.75 hr., cooled to room temperature and poured into ice and HCl. The mixture was extracted with ether, and the ether solution was washed with aq. $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated. Chromatography of the residue on alumina gave two fractions: A (ligroin), 273 mg., and B (ether), 157 mg.; the latter, crystallized from acetone–methanol, m.p. 134.5–137.8°, represents recovered IIIc. Recrystallization of fraction A in acetone gave 201 mg. of crude VId, m.p. 109–114° (48% yield based on IIIc consumed), and a small amount of impure 3β,22-dichloro-5-bisnorcholene (IIIe), m.p. 162–198° (presumably present as a contaminant in the starting material). The analytical sample of VId was obtained as miniature laths out of benzene–methanol (1:9); m.p. 109–111.0°, $[\alpha]_D$ −53.3°; $\lambda_{max}^{HCCl_3}$ 6.07, 11.22 μ.

Anal. Calcd. for $C_{22}H_{33}Cl$ (332.94): C, 79.36; H, 9.99; Cl, 10.65. Found: C, 79.53; H, 9.97; Cl, 10.78.

Ethyl 6β-Methoxy-3,5-cyclobisnorcholanate (VII).—Ethyl 3β-tosyloxy-5-bisnorcholenate (IIc), 1.13 g., was gradually dissolved in a hot solution of 1.13 g. of potassium acetate in 100 ml. of methanol, according to the method of Riegel, *et al.*[23] After refluxing 3.25 hr. the methanol was removed by distillation, and the residue was dissolved in ether and water. The ether layer was washed with aq. NaOH and water, dried over Na_2SO_4 and evaporated. Chromatography of the residue on alumina (ligroin–ether, 20:1) gave 0.64 g. (77%) of VII, m.p. 83–84°. The analytical sample crystallized out of methanol–water (10:3) in the form of laths, m.p. 83.0–84.4°, $[\alpha]_D$ +29.6° (0.7%).

Anal. Calcd. for $C_{25}H_{40}O_3$ (388.57): C, 77.27; H, 10.38. Found: C, 77.35; H, 10.13.

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