A sample was recrystallized from methanol–ethyl acetate; m.p. 249–252° (lit.[17] 252–255°); ν_{max}^{KBr} 3525, 3450, 1695, 1040, 1030, 1010 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{34}O$: C, 71.96; H, 9.78. Found: C, 72.00; H, 9.67.

(17) O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **16**, 192 (1951).

3β,6β-Diacetoxy-5α-hydroxypregnan-20-one (VIb).—The acetate was prepared by treatment of VIa with acetic anhydride and pyridine. The recovered VIb was recrystallized from ethyl acetate; m.p. 207–209° (lit.[17] 212–215°); ν_{max}^{KBr} 3480, 1730, 1720, 1705, 1235 cm.$^{-1}$; τ (in $CDCl_3$) 5.32 (1H), 7.90, 7.93, 7.98, 8.85, 9.37.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.24; H, 8.76.

Studies in Syntheses of Steroid Metabolites. II

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Hydrogenation of hydrocortisone acetate and of cortisone acetate in ethyl acetate in the presence of palladium on charcoal leads to the formation of appreciable amounts of 5β isomers. Raney nickel hydrogenation of IIb gives VIIa and a low yield of Reichstein's compound C acetate. Similarly hydrogenation of VIb leads to Xa and a small amount of Reichstein's 11-dehydro compound C acetate. Independent syntheses of Reichstein's compound C and 11-dehydro C diacetate are reported. Raney nickel hydrogenation of 3-keto-5β compounds furnishes a mixture of 3α and 3β epimeric derivatives and is the basis of a synthesis of tetrahydro compound F.

It was previously observed[1] that, when a solution of hydrocortisone in ethyl acetate was hydrogenated in the presence of palladium on charcoal, the two epimers 5α- and 5β-pregnane-11β,17α,21-triol-3,20-dione (IIa) and (IIIa) could be isolated by crystallization in 46 and 35% yield, respectively. Since the literature indicates that the saturation of the 4,5 double bond in hydrocortisone acetate and cortisone acetate leads to the predominant formation of the 5α isomers, it was decided to examine the problem in a little more detail. In this connection it is of interest that Caspi[2] obtained relatively large amounts of 5β compounds by hydrogenation of hydrocortisone in acetic acid in the presence of rhodium on alumina or platinum (Scheme I).

While Pataki, *et al.*,[3] found that hydrogenation of hydrocortisone acetate with palladium on barium sulfate in ethyl acetate afforded an 84% yield of the 5α-dihydro derivative IIb, it was now observed that with palladium on charcoal in ethyl acetate there was obtained an 80% yield of a solid which proved to be a mixture of the two epimeric acetates IIb and IIIb which, unlike the free alcohols IIa and IIIa, were inseparable by crystallization. This mixture of IIb and IIIb, on sodium borohydride–sodium periodate degradation, gave 5α-androstane-3β,11β-diol-17-one and 5β-androstane-3α,11β-diol-17-one (IX) in the ratio of 3:1. While the 5α isomer IIb could be purified by hydrolysis followed by crystallization, the 5β isomer IIIb was not easily isolated from the hydrolysis mixture.

Similarly, palladium-on-barium sulfate hydrogenation of cortisone acetate in ethyl acetate is reported[4] to lead to a 72% yield of the 5α-dihydro compound VIb, while palladium-on-charcoal hydrogenation in ethyl acetate gave[5] the same compound in 70% yield. Other workers report[6] that hydrogenation in the presence of potassium hydroxide gave VIb in 43% yield and also some 5β isomer Vb. In our hands the hydrogenation of cortisone acetate in ethyl acetate in the presence of palladium on charcoal afforded a 44–52% yield of VIb and a 26–30% yield of Vb, separable by fractional crystallization. Hydrogenation of cortisone under similar conditions gave a hard to separate mixture which appeared to contain the two dihydro compounds VIa and Va in the ratio of 4:1.

Next the Raney nickel hydrogenation of several 3-keto corticoids was studied. The Syntex group reported[3] that 5α-pregnane-11β,17α,21-triol-3,20-dione-21-acetate (IIb) was reduced in dioxane with this catalyst to Reichstein's compound V monoacetate (VIIa), isolated as the diacetate VIIb in 25% yield. A similar hydrogenation of the 11-keto analog VIb furnished[7c] Reichstein's compound D monoacetate (Xa) in 70% yield. In repeating the former, we have been able to isolate VIIa in 65–69% yield, and by chromatography of the acetylated filtrate a 2.7–3.2% yield of Reichstein's compound C diacetate (VIIIa), and also a small amount of VIIb. Reichstein's compound C was previously obtained by Caspi[2] together with several other compounds by hydrogenation of hydrocortisone with rhodium on alumina. Fukushima and Daum[8a] obtained it in 17% over-all yield from hydrocortisone by lithium–ammonia reduction of its bismethylenedioxy (BMD) derivative, formation of the tosylate at position 3, epimerization, and splitting off the BMD moiety. Confirmation of the identity of our sample of VIIIa was achieved by a synthesis which, like Fukushima and Daum's approach, involved epimerization at position 3. However we did not employ a BMD derivative for the protection of the corticoid side chain, having obtained Reichstein's compound V monoacetate (VIIa) from the hydrogenation experi-

(1) M. Harnik, *Isreal J. Chem.*, in press.

(2) E. Caspi, *J. Org. Chem.*, **24**, 669 (1959).

(3) J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952); see also O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **77**, 5669 (1955).

(4) C. Djerassi, G. Rosenkranz, J. Pataki, and S. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952).

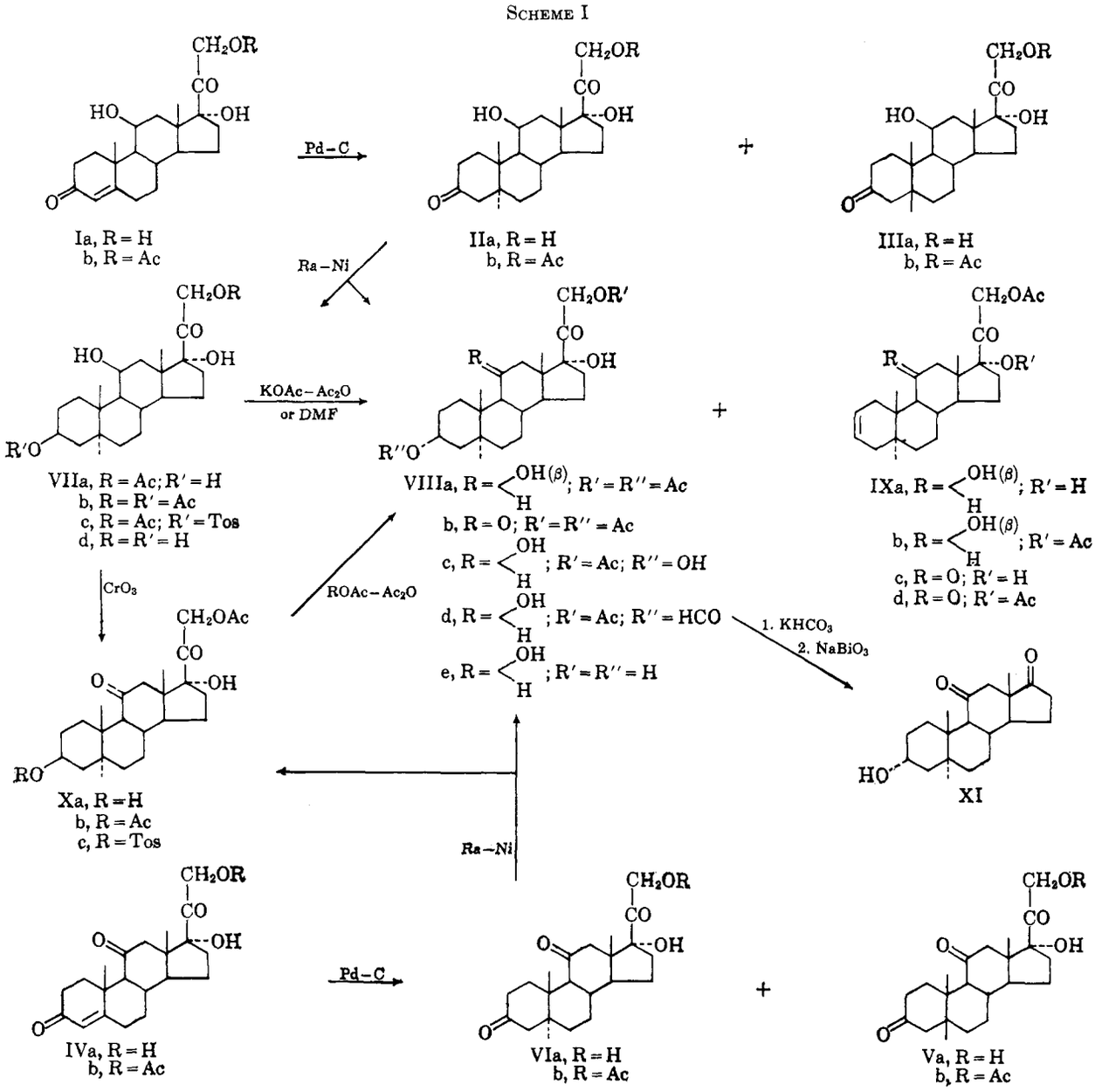
(5) E. P. Oliveto, C. Gerold, and E. B. Hershberg, *J. Am. Chem. Soc.*, **74**, 2248 (1952).

(6) E. Wilson and M. Tishler, *ibid.*, **74**, 1609 (1952).

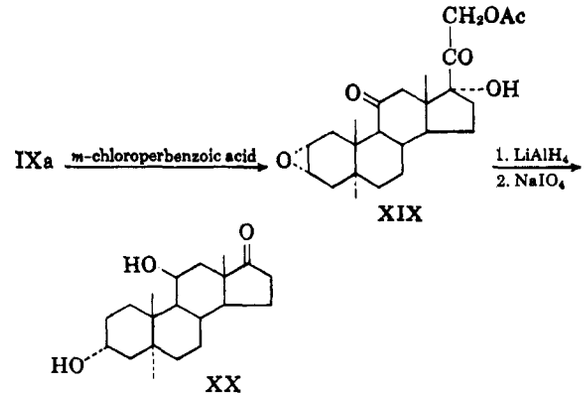
(7) (a) J. Pataki, G. Rosenkranz, and C. Djerassi, *ibid.*, **74**, 5615 (1952); (b) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker, and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956); (c) British Patent 718,640 [*Chem. Abstr.*, **49**, 14043 (1955)]; (d) E. M. Chamberlin and J. M. Chemerda, *J. Am. Chem. Soc.*, **77**, 1221 (1955); (e) A. Crawshaw, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 731 (1954).

(8) (a) F. K. Fukushima and S. Daum, *J. Org. Chem.*, **26**, 520 (1961); (b) F. C. Chang and R. T. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).

SCHEME I



ments described previously. Potassium acetate–acetic acid–acetic anhydride solvolysis of its tosylate VIIc afforded a mixture of three compounds which were separated by chromatography: 5α-pregn-2-ene-11β,-17α,21-triol-20-one-21-acetate (IXa, 18–21%), the corresponding 17-acetate IXb (11–13%), and VIIIa (20–25%). The last compound showed no melting point depression when admixed with an authentic sample.[9] From the preparative point of view it is of interest that when the dimethylformamide epimerization procedure[8b] was applied to VIIc, in addition to a 9–11% yield of IXa, there was obtained the formate VIIId in 70–73% yield and the 3α-ol VIIIc in 9–12% yield. Mild hydrolysis[10] of VIIIc and of VIIId afforded Reichstein's compound C (VIIIe), the over-all yield from hydrocortisone being 28–31%. As described for the related case of 5α-androst-2-ene-11β-ol-17-one-17-ethylene ketal,[1] epoxidation of IXa followed by lithium aluminum hydride reduction of the resultant epoxide XIX introduced a 3α-hydroxy group. Sodium periodate oxidation of the crude mixture of pentols afforded 11β-hydroxyandrosterone (XX).



Parallel experiments were carried out in the 5α-11-keto series. In repeating the Raney nickel hydrogenation[7c] of 5α-dihydrocortisone acetate (VIb), in addi-

(9) We are indebted to Professor T. Reichstein, University of Basel, for performing the melting point determinations.

(10) J. v. Euw, C. Meystre, R. Neher, T. Reichstein, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1516 (1958).

tion to a 67% yield of Xa it was possible to isolate from the acetylated filtrate by chromatography a 3.7% yield of 5α-pregnane-3α,17α,21-triol-11,20-dione-3,21-diacetate (VIIIb), also known as Reichstein's 11-dehydro compound C diacetate. 11-Dehydro compound C has been isolated[10] from mother liquors of aldosterone and other fractions obtained from beef adrenal extracts. As before, confirmation of the identity of the compound now obtained was desirable and was achieved as previously by potassium acetate–acetic acid–acetic anhydride treatment of the tosylate of Reichstein's compound D 21-acetate (Xc). This reaction was previously reported[11] to afford the elimination product 5α-pregn-2-ene-17α,21-diol-11,20-dione 21-acetate (IXc). In analogy with the 11-hydroxy series, there were now obtained three compounds: IXc (8–12%), the diacetate IXd (9–13%), and Reichstein's 11-dehydro compound C diacetate (VIIIb, 12–18% yield). The last compound did not depress the melting point of an authentic sample[9] and could be degraded to 11-ketoandrosterone XI by treatment with bicarbonate followed by sodium bismuthate oxidation and hydrolysis. The relationship between the four unsaturated compounds was confirmed by chromic acid oxidation in pyridine of IXa and IXb to IXc and IXd, respectively, and by mild hydrolysis of IXd, followed by acetylation, to the monoacetate IXc.[12]

Next the Raney nickel hydrogenation was studied in the 5β series and, as expected, found to be less stereospecific than in the 5α series. The dioltrione Vb gave a 30–35% yield of 5β-pregnane-3β,17α,21-triol-11,20-dione 21-acetate (XIIa). The oily filtrate must have contained XIVb for on degradation with lithium aluminum hydride and sodium periodate there was obtained a 24–30% yield of the 3α isomer XV and a 15–18% yield of the 3β epimer XVIIa identical with an authentic sample.[14] On this basis the hydrogenation of Vb lead to a 7:4 ratio of the 3β- to the 3α-alcohol, which is subject to some uncertainty due to the incomplete material balance. This synthesis of XIVb is of small preparative value because the compound is more conveniently obtained by other methods.

The 11-hydroxy compound IIIb was hydrogenated under similar conditions to afford a 20–23% yield of 5β-pregnane-3β,11β,17α,21-tetrol-20-one 21-acetate (XVIa) and a 53–58% yield of the 3α epimeric XIIIc.[15] Hydrolysis of the latter with potassium bicarbonate furnished the free tetrolone XIIIa[16] (Scheme II). This compound was previously isolated by Caspi[2] from the rhodium-on-alumina hydrogenation mixture (*vide supra*). The fact that the compound presently obtained in a facile manner was indeed the biologically important[17] THF could be confirmed by an independent synthesis. 5β-Pregnane-3α,17α,21-triol-11,20-dione (XIVa), obtained by a mild hydrolysis of its 21-acetate, was converted into the 20-ketal derivative XVIII. Sodium borohydride reduction in tetrahydrofuran followed by acid cleavage of the blocking group afforded a compound identical with THF obtained previously.

In summary, the results of palladium hydrogenations of cortisone and hydrocortisone acetates indicate that the 5β isomers are obtained in considerably larger amounts than was thought previously. Similar results were obtained in the 17-desoxy series and will be the subject of a forthcoming communication. Raney nickel hydrogenations of 5α-dihydrocortisone and 5α-dihydrocortisol acetates afforded the equatorial 3β-hydroxy derivatives as the major, and the 3α-hydroxy derivatives as the minor, products. In the 5β series corresponding Raney nickel hydrogenations furnished mixtures of the two epimers, the amounts of the axial hydroxy compounds being appreciably higher than in the 5α series.

Experimental

Ultraviolet spectra were measured in 95% ethanol. Infrared spectra were taken in potassium bromide disks. Melting points are uncorrected. Optical rotations were measured in chloroform, except where stated otherwise. Sodium metaperiodate and not periodic acid has been used throughout this investigation to prevent or minimize oxidation of the 11β-hydroxy group to the ketone.[18] Raney nickel (No. 28) was purchased from the Raney Catalyst Co., Inc., Chattanooga, Tenn., and was washed with water before use.

Hydrogenation of Hydrocortisone Acetate.—A solution of 40 g. of hydrocortisone acetate in 4 l. of ethyl acetate was hydrogenated for 6 hr. at atmospheric pressure in the presence of 10 g. of 10% palladium on charcoal. Concentration of the filtered solution afforded, in two crops, 32 g. of material, m.p. 208–210°. Recrystallization from ethyl acetate raised the m.p. to 213–215°, but was not helpful in removing the impurity XIb identified by inflections in the spectrum of IIb in the 7.0-, 7.9-, 9.0-, 9.6-, 9.9-, and 11.7-μ regions. Purification was effected by hydrolysis as described subsequently. The presence of the 5β epimer was proved by degradation of the recrystallized hydrogenation product (22 g.) with sodium borohydride and sodium metaperiodate, as previously described.[1] After filtration of 5α-androstane-3β,11β-diol-17-one (9.8 g.) the aqueous filtrate was exhaustively extracted with chloroform. Evaporation of the extract afforded a crude solid which by a combination of chromatography and crystallization afforded additional 1.2 g. of the same diolone, m.p. 232–235°,[1] and 2.8 g. of 5β-androstane-3α,11β-diol-17-one (XV), m.p. 235–237°.[1]

5α-Pregnane-11β,17α,21-triol-3,20-dione (IIa).—IIa was prepared by hydrolysis for 1 hr. at 0° of a 3% solution in methanol of the crude acetate (12.5 g.), m.p. 208–210°, with 36% aqueous potassium hydroxide (17.5 ml.). Acetic acid (9 ml.) was added, the solution taken *in vacuo* to dryness, and water added. The product was collected and combined with more material obtained by extraction of the filtrate with chloroform. Recrystallization from methanol furnished 6.5 g. of a product, m.p. 230–233°, identical with IIa obtained[1] by hydrogenation of hydrocortisone; both gave the same product (IIb) on acetylation,[1] m.p. 220–224°.

Hydrogenation of Cortisone Acetate.—A solution of 50 g. of cortisone acetate in 3 l. of ethyl acetate was stirred under hydrogen for 16 hr. in the presence of 5 g. of 10% palladium on charcoal. The mixture was filtered and the precipitated **5α-pregnane-17α,-21-diol-3,11,20-trione 21-acetate (VIb)** separated from the catalyst by chloroform extraction and evaporation. Careful concentration of the main filtrate to 500 ml. and crystallization gave an additional amount of VIb, bringing the total to 22–26 g., m.p. 227–223°. Recrystallization from acetone afforded a sample, m.p. 229–230°, $[\alpha]^{23}D$ +91° (lit.[7a] 234–236°, $[\alpha]^{20}D$ +89°, +78° in acetone; lit.[5] 229–231°, $[\alpha]^{23}D$ +93°; lit.[7b] 231–236°, $[\alpha]^{25}D$

(11) J. A. Edwards and A. Bowers, *Chem. Ind.* (London), 1962 (1961).

(12) VIIIa was previously oxidized to VIIIb, ref. 13.

(13) J. v. Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 988 (1942).

(14) Comparison of the infrared spectra was kindly carried out by Dr. E. Caspi, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

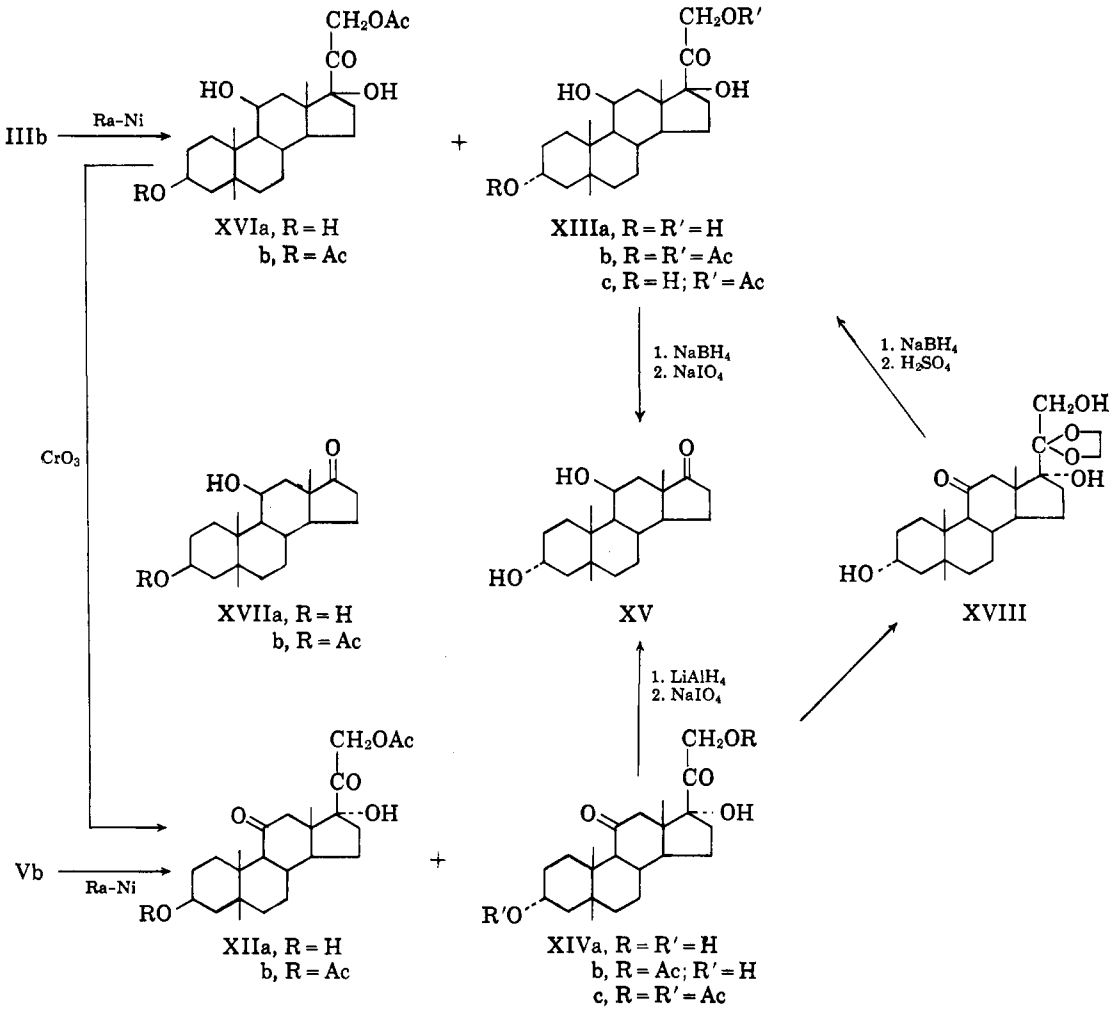
(15) A. H. Soloway, A. S. Deutsch, and T. F. Gallagher, *J. Am. Chem. Soc.*, **75**, 2356 (1953), selectively reduced IIIb with sodium borohydride and acetylated the product to afford XIIIb in 30% yield.

(16) Trivial names: tetrahydro compound F; THF.

(17) For instance, (a) S. Lieberman, E. R. Katzenellenbogen, R. Schneider, P. E. Studer, and K. Dobriner, *J. Biol. Chem.*, **205**, 87 (1953); (b) E. M. Nadel, S. Burstein, and R. I. Dorfman, *Arch. Biochem. Biophys.*, **61**, 144 (1956); (c) E. Caspi and M. E. Pechet, *J. Biol. Chem.*, **230**, 843 (1958).

(18) R. A. Harkness and K. Fotherby, *Experientia*, **17**, 253 (1961).

SCHEME II



+103°, +89° in acetone); λ_{max}^{KBr} 6.88 (m), 6.96 (m), 7.11 (m), 7.21 (m), 7.32 (m), 7.90 (m), 8.10 (s), 9.05 (m), 9.52 (m), 9.62 (m), 10.79 (m), 11.10 (m), and 10.29 μ (w).

Further concentration to 200 and to 100 ml. afforded 15 g. of **5β-pregnane-17α,21-diol-3,11,20-trione 21-acetate (Vb)**, in the form of prismatic needles, m.p. 224–226°. Recrystallization from ethyl acetate raised the m.p. to 226–228°, $[\alpha]^{24}D$ +80° (lit.[19] 228–230°, $[\alpha]^{25}D$ +82°; lit.[6] 225–230°); λ_{max}^{KBr} 7.15 (m), 7.36 (m), 7.90 (s), 8.16 (m), 8.41 (m), 9.48 (m), 9.62 (s), 11.05 (m), and 11.72 μ (m).

5α-Pregnane-3α,11β,17α,21-tetrol-20-one (Reichstein's Compound C) (VIIIe) and Derivatives. A. By Hydrogenation of IIb.—A solution of 6.8 g. of pure IIb in 400 ml. of dioxane was hydrogenated[3] for 5 hr. with three teaspoonfuls of well washed Raney nickel. The filtered solution was evaporated *in vacuo* to dryness and the solid residue recrystallized from ethyl acetate. In three crops there was obtained 4.5 g. of 5α-pregnane-3β,11β,-17α,21-tetrol-20-one (Reichstein's compound V) 21-acetate (VIIa), m.p. 225–232°. The pure sample melted at 227–229° (acetone), $[\alpha]^{23}D$ +80° in methanol.

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.45; H, 8.82.

The residue could either be stirred with benzene and the crude Reichstein's compound C 21-acetate (VIIIc) filtered, or, more conveniently, could be acetylated with acetic anhydride–pyridine and chromatographed on 100 g. of Florisil. With benzene–ether (3:1) there was obtained the 3α isomer VIIIa, which after recrystallization from acetone–ether, weighed 199 mg. and melted at 203–205°. It was identical in all respects with a sample described subsequently. Further elution with the same solvent mixture and with benzene–ether (2:1) furnished the diacetate VIIb, which after recrystallization from acetone–ether afforded 440 mg., m.p. 215–21[illegible]°. Recrystallization from methanol raised the m.p. to 225–227° (lit.[13] 225–227°, lit.[3] 229–231°), identical with the product obtained by acetylation of VIIa. Hydrolysis of VIIa in the usual manner with potassium bicarbonate in aqueous methanol afforded VIId, m.p. 218–222° (lit.[13] 220–225°, lit.[8] 211–215°).

B. By Epimerization.—A solution of 3.4 g. of VIIa in 20 ml. of pyridine was treated with 4 g. of *p*-toluenesulfonyl chloride. After 4 hr. at 0° ice and water were added and the gum scratched until crystallization occurred (addition of some methanol accelerated the process). The **tosylate VIIc** was collected, washed with water, and recrystallized from ethyl acetate–heptane; 4.6 g., m.p. 147°, $[\alpha]^{22}D$ +45°.

Anal. Calcd. for $C_{30}H_{42}O_8S$: C, 64.04; H, 7.52; S, 5.70. Found: C, 63.86; H, 7.42; S, 5.94.

To a warm solution of 22 g. of potassium acetate in 208 ml. of acetic acid and 17 ml. of acetic anhydride was added 4.45 g. of VIIc. After refluxing for 2 hr. the solvents were removed *in vacuo* on the steam bath and water was added. The solid was filtered and combined with a chloroform extract of the filtrate. Evaporation (3.5 g.) and chromatography on 100 g. of Florisil eluted the following. With 5% ether in benzene 649 mg. of the elimination product **5α-pregn-2-ene-11β,17α,21-triol-20-one 21-acetate (IXa)**, m.p. 190–193°, was obtained which after several recrystallizations from ether–petroleum ether melted at 195–197°, 210 mg., $[\alpha]^{24}D$ +94°; λ_{max}^{KBr} 5.76 and 5.85 μ.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.00; H, 8.66.

With 10% ether in benzene 384 mg. of a solid was obtained, m.p. 200–209°, to which the formula **5α-pregn-2-ene-11β,17α,21-triol-20-one 17,21-diacetate (IXb)** is ascribed. Recrystallization from ether afforded a sample, m.p. 202–204°, $[\alpha]^{25}D$ +29°; λ_{max}^{KBr} 5.70, 5.78, and 5.84 μ.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.51; H, 8.50.

By elution with 20% ether in benzene there was obtained 860 mg. of VIIIa, m.p. 198–202°. Recrystallization from acetone–

(19) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1454 (1948).

ether gave a sample melting at 203–205°, $[\alpha]^{23}D$ +65° (lit.[13] 204–205°, $[\alpha]D$ +74° in dioxane; lit.[20] 191–194°; lit.[2] 188–190°, $[\alpha]^{19}D$ +65° in methanol; lit.[8] 197–200°, $[\alpha]^{26}D$ +62°). Mixture melting point with an authentic sample, m.p. 204–206°, showed no depression.[9]

The tosylate VIIc (38.4 g.) was also epimerized by heating its solution in dimethylformamide (1.5 l.) at 80° for 72 hr. The solvent was distilled *in vacuo*, water was added, and the solid filtered. Recrystallization from 500 ml. of methanol afforded a total of 21.5 g. of **Reichstein's compound C-3-formate 21-acetate (VIIId)**, m.p. 228–229°. Further recrystallizations did not raise the melting point; λ_{max}^{KBr} 5.78 μ (broad).

Anal. Calcd. for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 65.77; H, 8.59.

The filtrate was evaporated to a gum and diluted with ether. The solution deposited a solid which was recrystallized from methanol to furnish 1.03 g. of **Reichstein's compound C 21-acetate (VIIIc)**. Dilution of the filtrate with benzene yielded an additional 1.12 g. of the same material, m.p. 217–222°. The analytical sample melted at 221–223° (methanol); λ_{max}^{KBr} 5.72 μ (broad).

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.41; H, 9.03.

The ether filtrate was evaporated and the oily residue chromatographed on 220 g. of Florisil. Fractions eluted with 5% ether in benzene deposited the crude unsaturated acetate IXa which after recrystallization from ether–petroleum ether weighed 3.02 g., m.p. 190–194°. Further elution with 20% and 50% ether in benzene gave, after recrystallization, 0.15 g. and 0.46 g., respectively, of VIIId and VIIIc.

Reichstein's Compound C (VIIIe).—VIIIe was prepared by potassium bicarbonate–methanol–water hydrolysis of VIIIc or VIIId in the usual manner[10] at room temperature for 40 hr. The product was isolated with ethyl acetate and recrystallized from ethanol, 75–85%, m.p. 248–256°, $[\alpha]^{26}D$ +70° in ethanol (lit.[13] 276°; lit.[2] 244–245°, $[\alpha]^{21}D$ +59.7° in methanol; lit.[8a] 242–246°, $[\alpha]^{27}D$ +72.2° in ethanol). Acetylation afforded VIIIa.

2α,3α-Epoxy-5α-pregnane-17α,21-diol-11,20-dione 21-Acetate (XIX).—A solution of 200 mg. of IXa and 400 mg. of *m*-chloroperbenzoic acid (Food Machinery Corporation) in 20 ml. of chloroform was allowed to stand overnight at room temperature. After washing with bicarbonate the organic phase was evaporated and the solid washed with ether. It weighed 94 mg. and melted at 227–231°. The analytical sample (acetone–ether–petroleum ether) melted at 227–228°; λ_{max}^{KBr} 5.68, 5.74, and 5.82 μ.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.31; H, 8.27.

Degradation of XIX to 11β-Hydroxyandrosterone (XX).—A solution of 50 mg. of the epoxide XIX in 7 ml. of benzene was added dropwise to a stirred suspension of 350 mg. of lithium aluminum hydride in 40 ml. of ether. The mixture was refluxed for 2 hr., then cooled and treated with water and hydrochloric acid. The aqueous phase was thoroughly extracted with ethyl acetate and the combined organic solutions washed with bicarbonate. Evaporation afforded a semisolid which was directly dissolved in 5 ml. of methanol and treated with a solution of 50 mg. of sodium periodate in 2 ml. of water. After standing overnight the product was isolated with chloroform. Dilution of the oil with ether caused precipitation of 21 mg. of a solid, m.p. 185–192°; the infrared spectrum of which showed it to be XX.[1]

5α-Pregnane-3α,17α,21-triol-11,20-dione (Reichstein's 11-Dehydro Compound C) 3,21-Diacetate (VIIIb). A. By Hydrogenation of VIb.[7c]—A mixture of 10.8 g. of VIb, 10 teaspoonfuls of Raney nickel, and 1 l. of dioxane was agitated under hydrogen for 5 hr. Filtration and removal of solvent followed by recrystallization of the residual solid from methanol afforded in two crops 7.2 g. of 5α-pregnane-3β,17α,21-triol-11,20-dione (Reichstein's compound D) 21-acetate (Xa), m.p. 230–237°. Further crystallizations from methanol furnished a sample, m.p. 232–234°, $[\alpha]^{23}D$ +65° in acetone (lit.[7a] 235–237°, $[\alpha]^{20}D$ +66° in acetone; lit.[7d] 229.5–230°, $[\alpha]^{24}D$ + 68° in acetone; lit.[7c] 224–227°; lit.[7b] 237–238°, $[\alpha]^{20}D$ +89°, +66° in acetone). The filtrate was evaporated, acetylated, and the product chromatographed on 96 g. of Florisil. With 5% and 10% ether in benzene there was eluted 450 mg. of the 3α isomer VIIIb, m.p. 200–220°. Recrystallization from acetone–ether gave 320 mg., m.p. 220–224°, identical with a sample described subsequently. Further elution with 10% and 20% ether in benzene afforded 120 mg. of the diacetate Xb, which after recrystallization from methanol melted at 221–222°, $[\alpha]^{23}D$ +70° in dioxane (lit.[13] 223–224°, $[\alpha]^{15}D$ +72° in dioxane; lit.[7c] 223–224°, $[\alpha]$ +72° in dioxane; lit.[7d] 219–222°, $[\alpha]D$ +72° in dioxane).

B. By Epimerization.—A cold solution of 6.7 g. of Xa in 40 ml. of pyridine was treated with 8 g. of *p*-toluenesulfonyl chloride and stored at 0° for 4.5 hr. The product, which crystallized upon addition of ice and water, was recrystallized from methanol to furnish 9.05 g. of the 3-tosylate Xc, m.p. 158–160° dec.; lit.[11] 143–144°. The same product also was obtained by oxidation of the tosylate VIIc in acetic acid (5% solution) at 0° for 1 hr. with an equal volume of 5% chromic acid in acetic acid. Addition of water, filtration, and recrystallization from methanol gave Xc, m.p. 162–164°.

Treatment of Xc (7.7 g.) with boiling acetic acid (350 ml.), acetic anhydride (28 ml.) and potassium acetate (37 g.) for 3 hr. was followed by distillation *in vacuo* on the steam bath, addition of water, and extraction with chloroform. The oily product was chromatographed over 180 g. of Florisil. With 5% ether in benzene there was eluted 550 mg. of the diacetylated elimination product IXd, m.p. 179–182°. Recrystallization from acetone–petroleum ether gave a sample melting at 180–181°; $[\alpha]^{21}D$ +57°; λ_{max}^{KBr} 5.69, 5.75, and 5.86 μ.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.91; H, 7.88.

The same product could also be obtained when IXb (20 mg.) was stirred for 2 hr. at 0° with a mixture of 50 mg. of chromic acid and 2 ml. of pyridine. The usual work-up with chloroform and recrystallization from acetone–petroleum ether afforded 8 mg. of IXd, m.p. 180–182°. The infrared spectra were identical.

With 10% ether in benzene there was obtained 620 mg. of IXc, m.p. 212–222°. Two recrystallizations from acetone–petroleum ether raised the m.p. to 226–228°; $\alpha^{22}D$ +139°; λ_{max}^{KBr} 5.75–5.89 μ.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 71.10; H, 8.30. Found: C, 71.39; H, 8.18.

The same product could also be obtained when IXa was oxidized with chromic acid in pyridine as described previously.

With 20% and 50% ether in benzene there was obtained 930 mg. of VIIIb, m.p. 218–224°. After recrystallization from acetone–ether it melted at 222–226°, lit.[13] 221–223°; mixture melting point with an authentic sample of Reichstein's 11-dehydro compound C diacetate, m.p. 223–225°, showed no depression.[9]

Preparation of IXc from IXd.—A solution of 240 mg. of potassium bicarbonate[21] in 4 ml. of water was added to a solution of 243 mg. of IXd in 20 ml. of methanol. After stirring overnight the solution was evaporated *in vacuo* to a small volume and exhaustively extracted with ether. Concentration of the extract afforded a crude solid (152 mg.) which on acetylation gave 140 mg. of IXc, m.p. 218–220°, identical with the sample obtained previously.

Degradation of Reichstein's 11-Dehydro Compound C 3,21-Diacetate (VIIIb) to 5α-Androstan-3α-ol-11,17-dione (XI).—A solution of 213 mg. of VIIIb in 17 ml. of methanol was kept overnight with a solution of 190 mg. of potassium bicarbonate in 3.6 ml. of water. After removal of methanol *in vacuo* at room temperature the crude product was filtered to yield 190 mg. A solution of 70 mg. of the crude product in 20 ml. of 50% acetic acid was stirred with 2 g. of sodium bismuthate for 18 hr. The filtered solution was exhaustively extracted with chloroform, the extract washed with dilute potassium hydroxide, evaporated, and the residue refluxed for 30 min. with 3 ml. of 5% methanolic potassium hydroxide. The gummy product was isolated with chloroform. Crystallization from acetone–heptane at first deposited some impure material and then 22 mg. of XI as needles; m.p. 153–155° (lit.[22] 153–155°; lit.[1] 156.5–158.5°); identical with an authentic specimen.

Hydrogenation of 5β-Pregnane-11β,17α,21-triol-3,20-dione 21-Acetate (IIIb).—A solution of 10.30 g. of IIIb in 1 l. of dioxane was hydrogenated for 5 hr. with 10 teaspoonfuls of Raney nickel. The solid product was triturated with acetone and the fine solid filtered (filtrate A) to afford 2.4 g. of **5β-pregnane-3β,11β,17α,21-tetrol-20-one 21-acetate (XVIa)**, m.p. 230–235°. After three recrystallizations from acetone the m.p. was 240–242°, $[\alpha]^{22}D$ +55° in methanol.

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(21) H. J. Ringold, S. H. Burstein, and M. Gut, *J. Org. Chem.*, **28**, 575 (1963).

(22) S. Lieberman, D. K. Fukushima, and K. Dobriner, *J. Biol. Chem.*, **182**, 299 (1950).

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.42; H, 8.99.

The diacetate XVIb crystallized from ether–petroleum ether (b.p. 60–80°), melted at 188–189°, $[\alpha]^{21}D$ +65°, lit.[2] 203–206°. The diacetate (80 mg.) was oxidized with chromic acid (4 ml. of a 5% solution in acetic acid) for 1 hr. at 0°. Precipitation with water afforded 55 mg. of XIIb, m.p. 164–167°, identical with a sample prepared subsequently.

The filtrate A was evaporated and treated with ether. In three crops there was obtained 4.14 g. of **5β-pregnane-3α,11β,17α,21-tetrol-20-one 21-acetate (XIIIc)**, m.p. 185–195°. Two recrystallizations from acetone–ether gave a sample, m.p. 192–193°, $[\alpha]^{23}D$ +93°.

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.41; H, 9.17.

The ether filtrate was evaporated and chromatographed on 120 g. of Florisil. With ether–benzene (1:1) there was obtained additional 50 mg. of XVIa followed by 1.85 g. of XIIIc, m.p. 186–192°.

Degradation of XIIIc with sodium borohydride–sodium metaperiodate in the usual manner[1] afforded **5β-androstane-3α,11β-diol-17-one (XV)**, m.p. 235–237°. Acetylation of XIIIc gave the **diacetate XIIIb**, m.p. 208–210°, $[\alpha]^{24}D$ +88° (lit.[17a] 209–211°, $[\alpha]^{28}D$ +90°; lit.[15] 212–222°, $[\alpha]^{24}D$ +91°, +85° in acetone; lit.[17b] 204–209°; lit.[17c] 212–215°).

When XIIIc (200 mg.) in 16 ml. of methanol was allowed to stand overnight with a solution of potassium bicarbonate (200 mg.) in water (3 ml.), the solution was concentrated *in vacuo* at room temperature to the point of incipient turbidity followed by concentration of its ether extract. The yield was 135 mg. of **5β-pregnane-3α,11β,17α,21-tetrol-20-one (XIIIa)**, m.p. 195–203°, as a finely divided solid. Recrystallization from acetone–ether raised the melting point to 202–204°. The product was identical with a sample of THF obtained subsequently.

Hydrogenation of 5β-Pregnane-17α,21-diol-3,11,20-trione 21-Acetate (Vb).—A solution of 12.5 g. of Vb was hydrogenated for 5 hr. in 1 l. of dioxane containing 10 teaspoonfuls of Raney nickel as described previously. The resulting solid was recrystallized from methanol to afford in two crops a total of 4.2 g. of **5β-pregnane-3β,17α,21-triol-11,20-dione 21-acetate (XIIa)**, m.p. 234–242°. The pure sample (from methanol) melted at 250–254°.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.98; H, 8.29.

The diacetate XIIb melted at 167–168° (methanol), $[\alpha]^{22}D$ +82°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.69; H, 7.87.

One-half of the original methanolic filtrate was evaporated and degraded with lithium aluminum hydride and sodium metaperiodate as described subsequently. The crude solid was filtered and heated with 15 ml. of methanol. The insoluble XVIIa was filtered, 420 mg., m.p. 245–252°. The filtrate was evaporated and chromatographed on alumina to afford additional 320 mg. of the same compound and 1.31 g. of XV.

Degradation of 5β-Pregnane-3β,17α,21-triol-11,20-dione 21-Acetate (XIIa) to 5β-Androstane-3β,11β-diol-17-one (XVIIa).—A solution of 1.00 g. of XIIa in 200 ml. of tetrahydrofuran was reduced with a suspension of 2 g. of lithium aluminum hydride in 300 ml. of tetrahydrofuran. After refluxing for 2 hr. and cooling, the reaction mixture was treated with 20 ml. of water, the inorganic material filtered off, washed with ethyl acetate and chloroform, and the washings combined with the residue obtained by evaporation of the tetrahydrofuran solution. The oily product which was dissolved in 10 ml. of methanol was treated with a solution of 1.5 g. of sodium metaperiodate in 30 ml. of water. The precipitated XVIIa (0.49 g.) was recrystallized from ethyl acetate to give 0.36 g. of needles, m.p. 250–252° (lit.[2] 259–261°); the 3-acetate XVIIb melted at 209–210° (methanol) (lit.[2] 212–215°). The infrared spectra of the samples XVIIa and XVIIb were identical with those of authentic compounds.[14]

5β-Pregnane-3α,17α,21-triol-11,20-dione-20-ethylene Ketal (XVIII) and XIIIa.[23]—A mixture of 9.5 g. of 5β-pregnane-3α,17α,21-triol-11,20-dione (XIVa), 1 g. of *p*-toluenesulfonic acid monohydrate, and 750 ml. of ethylene glycol was slowly distilled at 70–75° *in vacuo* during 6 hr. until 50 ml. remained. Dilute bicarbonate solution was added to the residual clear liquid and the resultant mixture exhaustively extracted with chloroform. The product was recrystallized from ethyl acetate containing a drop of pyridine, giving 2.99 g. of XVIII, m.p. 216–222°. Several recrystallizations raised the m.p. to 226–228°, $[\alpha]^{22}D$ +41°, λ_{max}^{KBr} 5.92 μ.

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.69; H, 8.72.

The ketal (XVIII) in 120 ml. of tetrahydrofuran was mixed with a solution of 1.5 g. of sodium borohydride in 21 ml. of 2.5% aqueous sodium hydroxide and refluxed with stirring for 6 hr. An additional 1 g. of sodium borohydride was added and reflux was continued overnight. The organic layer was distilled *in vacuo*, water added, and the solid filtered (2.8 g.). A solution of 2.3 g. of the reduced ketal in 115 ml. of methanol and 11 ml. of 8% (v./v.) sulfuric acid was refluxed for 50 min. Concentration *in vacuo* at room temperature and addition of water was followed by extraction with ether and a bicarbonate wash. Concentration of the ether afforded 0.56 g. of XIIIa, m.p. 196–204°. Further recrystallization from acetone–ether gave a product, m.p. 204–205°, $[\alpha]^{24}D$ +76° (methanol) (lit.[17c] 231–233°, lit.[2] 207–209°). Further confirmation of its structure was obtained when its diacetate XIIIb was oxidized with chromic acid in acetic acid to 5β-pregnane-3α,17α-21-triol-11,20-dione 3,21-diacetate (XVIc), m.p. 232–234° (lit.[19] 233–236°), identical with an authentic specimen.

(23) This series of experiments was carried out only once. The yields undoubtedly could be improved by further experimentation.