3-Methoxy-19-norpregna-1,3,5(10)-trien-20α-ol (VIb).—Forty milliliters of 1 *M* BH_3–THF complex in THF was added rapidly to a stirred solution of 4.5 g. of 3-methoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene (Vb) in 200 ml. of dry THF under nitrogen. After stirring at room temperature for 72 hr. (2 hr. is probably sufficient), 120 ml. of 10% NaOH solution was added cautiously, and, after cooling to 0°, 40 ml. of 30% H_2O_2 was added over 15 min. After an additional 1.5 hr. at 0°, the reaction mixture was partitioned between ethyl acetate and water and the original layer was washed with 10% $NaHSO_3$ and water, dried, and evaporated. The crude product was chromatographed on a column of 150 g. of alumina (grade I). The material, eluted with benzene–ether (7:3), was recrystallized from ether–petroleum ether to yield 1.78 g. of product, m.p. 104–105°, $[\alpha]^{25}D$ +76.4° (*c* 2.00%).

Anal. Calcd. for $C_{21}H_{30}O$: C, 80.21; H, 9.02. Found: C, 79.92; H, 9.75.

19-Norpregna-1,3,5(10)-triene-3,20α-diol (VIa).—A solution of 3.0 g. of *cis*-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol (Va) in 90 ml. of dry THF was treated at room temperature with 22 ml. of BH_3–THF complex for 2 hr., and then processed as above (40 ml. of 10% NaOH, 15 ml. of 30% H_2O_2). After the reaction was complete, 2 *N* HCl was added until the mixture was slightly acidic and the mixture was partitioned between CH_2Cl_2 and water and processed as above. The crude product, 2.7 g., was recrystallized from CH_2Cl_2–ether to give 1.375 g., m.p. 178–179°, $[\alpha]^{25}D$ +77.2° (*c* 1.00%). A second crop of 238 mg., m.p. 173–175°, was obtained (total 1.61 g., 50%).

Anal. Calcd. for $C_{20}H_{28}O$: C, 79.95; H, 9.39. Found: C, 80.20; H, 9.25.

19-Nor-4-pregnen-3-on-20α-ol.—To a solution of 250 mg. of 3-methoxy-19-norpregna-1,3,5(10)-trien-20α-ol (VIb) in 25 ml. of dry THF was added, by distillation, about 25 ml. of ammonia. While stirring, 250 mg. of lithium wire was added rapidly as small pieces. After 15 min., 4 ml. of absolute ethanol was added rapidly. The blue color disappeared after 15 min. and the ammonia was evaporated, water and ether were added, and the organic extract was washed with water, dried, and evaporated. The crude product (240 mg.) was dissolved in 8 ml. of methanol, treated with 5 ml. of 4 *N* HCl, and heated at reflux for 1 hr. After pouring into saturated salt solution, extraction with ether, and washing the organic layer with 5% $NaHCO_3$ solution, it was dried and evaporated to afford 202 mg. of product. This material was chromatographed on a column of 6 g. of alumina (grade I). The benzene and benzene–ether (9:1) eluates (180 mg.) were combined and recrystallized from ether–petroleum ether, m.p. 124–127°. This material, without further characterization, was oxidized to 19-norprogesterone, as described below.

19-Norprogesterone (VII).—To a solution of 50 mg. of 19-nor-4-pregnen-3-on-20α-ol in 4 ml. of dry DMF was added 50 mg. of CrO_3 followed by 0.7 ml. of DMF containing 0.02 ml. of concentrated H_2SO_4. After 1 hr. at room temperature, the reaction mixture was partitioned between ether and water. The ether extracts were washed with water, dried, and evaporated to afford 46 mg. of crystalline product, m.p. 139–141°, which, after crystallization from ether, melted at 141.5–142.5° and was identical with an authentic sample[14] (lit.[2] m.p. 141–144°).

Acknowledgment.—We are indebted to Dr. A. Steyermark for the microanalyses, Dr. F. Vane for the n.m.r. spectra, and Mr. H. Lucas for technical assistance.

(14) Kindly supplied by Dr. A. Bowers, Syntex Corp.

16-Alkylated Corticoids. IV.[1] Synthesis of 16β-Methyl Analogs of Cortisone, Prednisone, and 9α-Fluoroprednisolone[2]

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The synthesis of 16β-methyl analogs of cortisone, prednisone, 9α-fluoroprednisolone, and related compounds is described, starting with intermediates readily prepared from bile acids.

It is well known that the introduction of a chlorine or fluorine atom at the C-9 position of the natural adrenal substances cortisone and hydrocortisone (and their 1-dehydro analogs) markedly enhances the anti-inflammatory activity of these agents and is accompanied by a striking increase in both salt and water retention.[4] These undesirable side effects, manifested generally by 9-halo steroids, preclude their use systemically in the management of disorders normally responsive to adrenocortical steroid therapy.

Introduction of a 16α-hydroxyl or 16α-methyl group into the 9α-fluorocorticoid molecule has suppressed these severe electrolyte disturbances,[4a,c] but other side effects have been reported.[4a,5]

The first reports of the synthesis of 16β-methyl cortical steroids and their efficacy as antiinflammatory agents came from these laboratories in 1958.[2a,b]

We now wish to report the detailed synthesis of several 16β-methyl steroids, one of which (9α-fluoro-16β-methylprednisolone[6]) is the most potent anti-inflammatory steroid marketed and is also devoid of electrolyte imbalance and water retention at clinically effective dose levels.[7]

The readily available 3α-acetoxy-16-methyl-16-pregnene-11,20-dione[8] (I) was catalytically reduced using palladium on charcoal in acetic acid to give 3α-acetoxy-16β-methylpregnane-11,20-dione (II) (Scheme I). Reaction of II with *p*-toluenesulfonic acid in hot acetic anhydride produced the 17(20)-enol acetate III. Epoxidation with peracetic acid in benzene[9] gave the

(1) Paper III: E. P. Oliveto, *et al.*, *J. Am. Chem. Soc.*, **80**, 6687 (1958).

(2) A portion of this work was communicated earlier: (a) E. P. Oliveto, *et al.*, *ibid.*, **80**, 4428 (1958); (b) paper III, ref. 1. See also (c) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *ibid.*, **80**, 4435 (1958); (d) D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *ibid.*, **82**, 4012 (1960); (e) T. R. Carrington, *et al.*, *J. Chem. Soc.*, 4560 (1961); (f) G. G. Nathansohn, G. Winters, and E. Testa, *Experientia*, **17**, 448 (1961); D. Kluepfel and C. Coronelli, *ibid.*, **18**, 441 (1962).

(3) Hoffman-LaRoche, Inc., Nutley, N. J.

(4) (a) For a discussion of the effects of antiinflammatory steroids on electrolyte metabolism, see G. W. Liddle, *Ann. N. Y. Acad. Sci.*, **82**, 854 (1959); (b) L. H. Sarett, *ibid.*, **82**, 802 (1959); (c) J. Fried, *Vitamin Hormones*, **16**, 304 (1958); (d) L. H. Sarett, A. A. Patchett, and S. A. Steelman, *Progr. Drug Res.*, **5**, 11 (1963).

(5) (a) R. H. Freyberg, C. A. Berntsen, Jr., and L. Hellman, *Arthritis Rheumat.*, **1**, 215 (1958); (b) J. J. Bunim, R. L. Black, L. Lutwak, R. E. Peterson, and G. D. Whedon, *ibid.*, **1**, 313 (1958); (c) M. Pechet, E. L. Carroll, M. Mitchell, and M. J. Wegner, *J. Clin. Invest.*, **37**, 921 (1958).

(6) Celestone is the registered trademark for the Schering Corp. brand of 9α-fluoro-16β-methylprednisolone (Betamethasone).

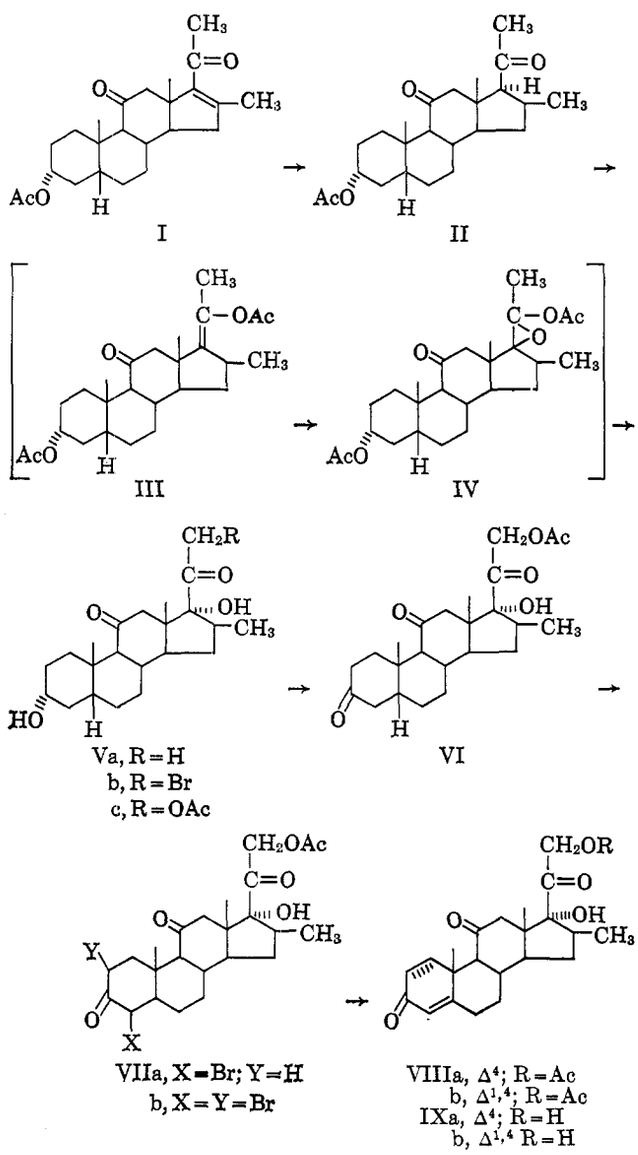
(7) (a) M. M. Pechet, personal communications; (b) reports to the Clinical Division, Schering Corp.; (c) Swiss Conference on Celestone, Zurich, 1961; (d) *Praxis* (Bern), **51**, 238 (1962).

(8) *Cf.* (a) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944); (b) H. L. Slates and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 5472 (1959).

(9) E. P. Oliveto and E. B. Hershberg, *ibid.*, **76**, 5167 (1954).

17(20)-epoxide IV, which was hydrolyzed with base to give 3α,17α-dihydroxy-16β-methylpregnane-11,20-dione (Va) in 29% yield from II. When the 11,20-dione II was subjected to enol acetylation using the method of Barton, *et al.*,[10] followed by epoxidation and hydrolysis as previously described, yields of over 80% of the 16β-methyldioldione Va were easily obtained.

SCHEME I



The Merck group[2d] also obtained Va from II by the latter sequence but in low yield. They attribute this to steric hindrance of the side-chain carbonyl group by the 16β-methyl group. Although inspection of molecular models indicates some hindrance about the C-20 carbonyl group, we find that the introduction of a 17α-hydroxyl group into 16β-methyl steroids proceeds nearly as easily as it does in the 16-desmethyl series. In addition (*vide infra*), the bulky cyclic ethylene ketal can be formed at C-20 in the presence of a 16β-methyl group in nearly quantitative yield and then removed, regenerating the C-20 ketone without causing D-ring rearrangement. A more serious problem discussed by Taub, *et al.*,[2d] is the case of D-homoannulation of 16β-methyl-17α-hydroxy-20-keto steroids, which we have experienced in the preparation of Va from IV and which required adjustment of the hydrolysis conditions for IV to minimize this side reaction.

Bromination of Va in chloroform gave the 21-bromide Vb, which was further allowed to react with sodium acetate in dimethylformamide[11] or with potassium acetate in acetone to give 16β-methyl-3α,17α,21-trihydroxypregnane-11,20-dione 21-acetate (Vc). Oxidation with N-bromoacetamide in a *t*-butyl alcohol–acetic acid mixture gave the 3-ketone VI. Bromination in *t*-butyl alcohol produced the 4-bromide VIIa which was dehydrobrominated with semicarbazide base in *t*-butyl alcohol. The resulting 3-semicarbazone that formed was reversed using pyruvic acid to give 16β-methylcortisone 21-acetate (VIIIa). Hydrolysis of VIIIa with base gave 16β-methylcortisone (IXa). The 1-dehydro analog of VIIIa was prepared by dibromination of the 3-ketone VI, affording the 2,4-dibromide VIIb, which was dehydrobrominated with lithium bromide–lithium carbonate in hot dimethylformamide[12] yielding 16β-methylprednisone 21-acetate (VIIIb). Hydrolysis of VIIIb with base gave 16β-methylprednisone (IXb).

Our early work on approaches leading to 9α-fluoro-16β-methylprednisolone *via* reduction of the bissemicarbazone derivative of 16β-methylcortisone 21-acetate (VIIIa)[13] to 16β-methylhydrocortisone proceeded in very low yield, confirming the experience of the Merck group.[2d] An alternate pathway (see Scheme II) was devised utilizing the readily available intermediate 3α,17α-dihydroxy-16β-methylpregnane-11,20-dione Va, which reacted with ethylene glycol in refluxing benzene, catalyzed with *p*-toluenesulfonic acid,[14] to give the cyclic ethylene ketal X in modest yield. Treatment of X with warm aqueous acetic acid regenerated the starting dioldione Va in high yield, providing proof that rearrangement had not occurred over these two steps. When pyridine hydrochloride was substituted for *p*-toluenesulfonic acid as the catalyst in the ketal step, X was formed in 95% yield.

Reduction of 3α,17α-dihydroxy-16β-methylpregnane-11,20-dione-20-ethylene ketal (X) with sodium in refluxing *n*-propyl alcohol[15] gave the 3α,11α,17α triol-20-dioxolane (XI), which was hydrolyzed with aqueous acetic acid to the triol-20-one XIIa, further characterized as its 3,11-diacetate XIIb by acetylation with acetic anhydride in pyridine.

Bromination at C-21 of the triol-20-one XIIa, in chloroform (which had proceeded satisfactorily on the dioldione Va to give the corresponding 21-bromide Vb), proved to be difficult, producing a multicomponent mixture from which was isolated 3α,11α-dihydroxy-16-methyl-16-pregnen-20-one. Examination of the sta-

(10) D. H. R. Barton, R. M. Evans, J. C. Hamlett, P. G. Jones, and T. W. Walker, *J. Chem. Soc.*, 747 (1954).

(11) R. Joly, J. Warnant, and G. Nomine, *Bull. soc. chim. France*, 330 (1957).

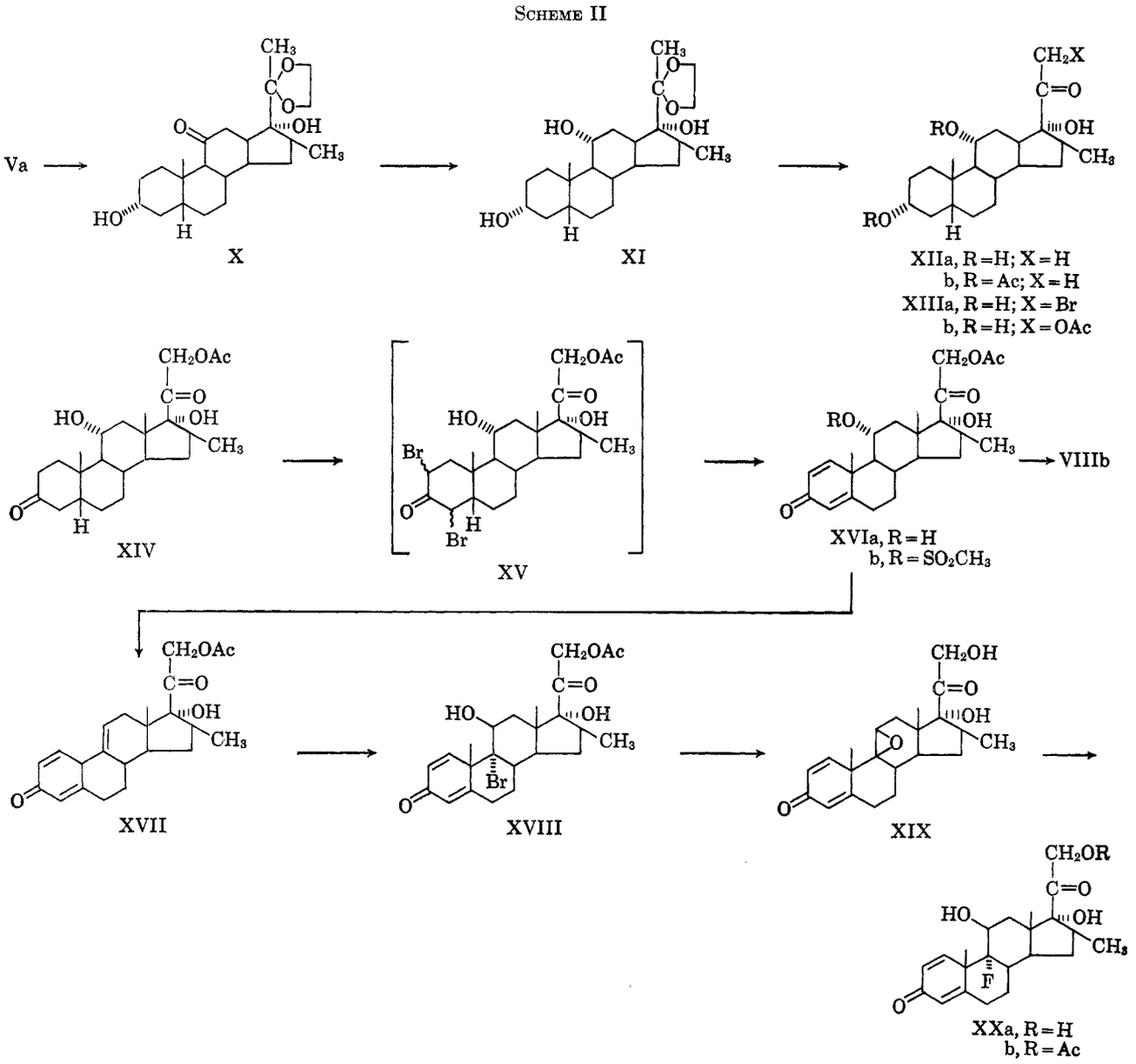
(12) R. Joly and J. Warnant, *ibid.*, 367 (1958).

(13) *Cf.* E. P. Oliveto, R. Rausser, L. Weber, E. Shapiro, D. Gould, and E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 1736 (1956).

(14) E. P. Oliveto, T. Clayton, and E. B. Hershberg, *ibid.*, **75**, 486 (1953).

(15) (a) H. L. Herzog, E. P. Oliveto, M. A. Jevnik, and E. B. Hershberg, *ibid.*, **74**, 4470 (1952); (b) E. P. Oliveto, H. L. Herzog, and E. B. Hershberg, *ibid.*, **75**, 1505 (1953).

SCHEME II



bility of 16β-methyl-3α,11α,17α-trihydroxypregnan-20-one in chloroform saturated with hydrogen bromide gas revealed that after 10–15 min. at 20–30° no starting material remained, and paper chromatograms displayed several spots absorbing in the ultraviolet. When the level of hydrogen bromide used to initiate 21-bromination of 16β-methyl-3α,11α,17α-trihydroxypregnane (XIIa) was limited to 1.05–1.2 equiv./equiv. of steroid, the 21-bromide XIIIa was obtained in crystalline form in 70–75% yield.

Reaction of XIIIa with sodium acetate in dimethylformamide[11] proceeded in almost theoretical yield to give 16β-methyl-3α,11α,17α,21-tetrahydroxypregnan-20-one 21-acetate (XIIIb). Selective oxidation at C-3 with N-bromoacetamide in aqueous acetone produced the ketone XIV.

Dibromination of XIV in dioxane gave the 2,4-dibromo compound XV which was dehydrobrominated in hot dimethylformamide with the aid of lithium bromide and lithium carbonate,[12] finally yielding 16β-methyl-11α,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (XVIa). Oxidation of XVIa with chromic acid in acetone[16] gave 16β-methylprednisone 21-acetate (VIIIb), identical in every respect with VIIIb prepared from the 2,4-dibromide VIIb, thereby excluding the possibility that structural rearrangement had occurred in the transformation of Va to XVIa.

Conversion of 16β-methyl-11α,17,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (XVIa) to the 11α-mesylate XVIb by reaction with methanesulfonyl chloride in pyridine, followed by dehydromesylation using sodium acetate in acetic acid, produced the 1,4,9-(11)-triene XVII. Reaction of XVII with hypobromous acid generated from N-bromoacetamide and perchloric acid in tetrahydrofuran gave the bromohydrin XVIII, which was simultaneously closed with base and hydrolyzed at C-21 to give the 9(11)-oxido-17α,21-diol XIX. Finally, reaction with aqueous 70% hydrofluoric acid[17] yielded 9α-fluoro-16β-methylprednisolone (XXa). Acetylation with an acetic anhydride–pyridine mixture gave the 21-acetate XXb.

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

(17) H. A. Gerber, U. S. Patent 3,086,032 (1963).

Experimental Section[18]

3α-Acetoxy-16β-methylpregnane-11,20-dione (II).—A solution of 12.0 g. of 3α-acetoxy-Δ^{16}-16-methylpregnene-11,20-dione (I) in 250 ml. of acetic acid was hydrogenated at 25–30° at atmospheric pressure with the aid of 3 g. of 10% palladium-on-charcoal catalyst, until hydrogen uptake ceased (overnight). The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to about 100 ml. and then precipitated into ice–water. The precipitate was collected by filtration, washed neutral with water, then dried to yield 11.4 g. of II. The analytical sample prepared by crystallization from acetone–hexane had m.p. 160–163°, $[\alpha]_D$ +93.6°, and no ultraviolet absorption.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.37; H, 9.06.

3α,17α-Dihydroxy-16β-methylpregnane-11,20-dione (Va). Method A.—A solution of 7.77 g. of 3α-acetoxy-16β-methylpregnane-11,20-dione (II) in 156 ml. of acetic anhydride containing 3.89 g. of *p*-toluenesulfonic acid was heated at 95–100° for 6 hr., removing every 30 min. *ca.* 12 ml. of distillate under reduced pressure. The reaction mixture was then cooled, diluted with 80 ml. of benzene, and washed neutral with water. The water washes were back extracted with benzene, and the extracts were combined, washed with a solution of 1.55 g. of sodium acetate in 20 ml. of water, dried with magnesium sulfate, filtered, then epoxidized by stirring for 19 hr. at room temperature with a solution of 12 ml. of 40% peracetic acid containing 0.52 g. of sodium acetate. The reaction mixture was cooled in an ice bath and the excess peracetic acid was decomposed by slowly adding a solution of 15.5 g. of sodium sulfite in 52 ml. of water with rapid stirring, maintaining the temperature between 10 and 20°. An additional 1.57 g. of solid sodium sulfite was added to the reaction mixture and stirring at room temperature was continued for 18 hr. The benzene layer was separated, washed three times with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to an oil which was dissolved in a small amount of methanol and again evaporated to dryness. The residue was redissolved in 345 ml. of methanol and refluxed 15 min. with a solution of 3.62 g. of sodium hydroxide in 39.5 ml. of water. The reaction mixture was neutralized with 4 ml. of acetic acid and concentrated under reduced pressure to an oil. Precipitation in ice–water gave a solid which was recovered by filtration, yielding 6.69 g. of crude Va. The filtrate was extracted with methylene chloride giving an additional 0.32 g. of semisolid product. The total combined crude Va (7.01 g.) was chromatographed on 70 g. of hexane-washed Florisil. The column was developed with hexane containing increasing amounts of ether. The eluates obtained from 2:1 and 1:1 hexane–ether mixture were combined and crystallized from ether, affording 2.82 g. of Va. Recrystallization from acetone–hexane gave 2.09 g. of Va, m.p. 181.5–185°, $[\alpha]_D$ +83.6°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.82; H, 9.25.

Method B.—A stirred solution of 11.64 g. of 3α-acetoxy-16β-methylpregnane-11,20-dione (II) in 150 ml. of carbon tetrachloride was treated with 11.6 ml. of acetic anhydride and 0.3 ml. of 70% perchloric acid at 0–5°. Stirring was continued for 18 hr. at 0–5°, and then the mixture was diluted with 30 ml. of water. The organic layer was separated and washed three times with dilute sodium bicarbonate solution and twice with water. The extract was dried over sodium sulfate, filtered, and concentrated *in vacuo* to an oil which was redissolved in 150 ml. of benzene and epoxidized by stirring at room temperature with a solution of 34.9 ml. of 40% peracetic acid containing 1.62 g. of sodium acetate. The excess peracid was decomposed after 24 hr. by the addition of excess sodium sulfite solution at 10–20°. The benzene layer was separated, washed several times with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure to an oil. The oily residue was dissolved in 525 ml. of methanol and stirred together with 50.1 ml. of 2 *N* sodium hydroxide for 10 min., brought rapidly to reflux for 2 min., and then acidified slightly with acetic acid. The reaction mixture was concentrated under reduced pressure to a small volume, then precipitated in ice–water. The product was recovered by filtration, washed neutral with water, and dried. Crystallization from acetone–hexane gave 8.8 g. (81.0%) of Va whose infrared spectrum and other physical constants were in agreement with the properties of Va prepared by procedure A. On occasion a polymorphic form of Va has been isolated which exhibits m.p. 195–197°. Comparison of solution infrared spectra of these two materials shows them to be identical. Acetylation of 50 mg. of Va in pyridine with acetic anhydride at room temperature for 18 hr. followed by addition of water gave a crystalline product which was isolated by filtration and dried, affording 50 mg. of 3α,17α-dihydroxy-16β-methylpregnane-11,20-dione 3-acetate, m.p. 169–172°. The analytical sample was obtained by crystallization from acetone–hexane, m.p. 170–172°, $[\alpha]_D$ +101.1°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.29; H, 8.92.

16β-Methyl-3α,17α,21-trihydroxypregnane-11,20-dione 21-Acetate (Vc). Method A.—A stirred solution of 3.36 g. of 3α,-17α-dihydroxy-16β-methylpregnane-11,20-dione in 182 ml. of chloroform was cooled to −20° and treated with a solution of 36 ml. of chloroform containing 0.66 g. of hydrogen bromide. A solution of 1.65 g. of bromine in 36 ml. of chloroform was added dropwise over a 2.5-hr. period. The temperature was controlled at −15° throughout the addition period. The reaction mixture was stirred an additional 30 min., and the solvent was removed under reduced pressure. The residue was dissolved in 72 ml. of dimethylformamide, 7.2 g. of sodium acetate was added, and the mixture was stirred at 65° for 6 hr. The reaction mixture was poured into ice and water with rapid stirring and the resulting precipitate was collected by filtration, washed neutral with water, and dried, giving 2.62 g. of crude Vc. Additional Vc (1.23 g.) was recovered by extraction of the filtrate with methylene chloride to give a total yield of 3.85 g., which was chromatographed on 40 g. of hexane-washed Florisil. The column was developed with hexane containing increasing amounts of ether. Crystalline material obtained from the 100% ether eluates was recrystallized from acetone–ether, giving 1.53 g. of Vc, m.p. 210–215° (solvated). The analytical sample obtained by two crystallizations from acetone–hexane had m.p. 225–230°, $[\alpha]_D$ +119.4°.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.56; H, 8.63. Found: C, 68.79; H, 8.39.

Method B.—A stirred solution of 36.2 g. of Va in 905 ml. of chloroform containing a catalytic amount of hydrogen bromide was treated at 27–30° with a solution of 16.5 g. of bromine in 400 ml. of chloroform, added dropwise over 1 hr. Excess sodium bicarbonate was added to the reaction mixture, stirring was continued for several minutes, then the insolubles were removed by filtration. The chloroform was removed *in vacuo* and the 21-bromide was crystallized from ether–hexane giving 35.5 g. of Vb, m.p. 168–173° dec. This was refluxed with 59.5 g. of anhydrous potassium acetate in 59.5 ml. of water and 770 ml. of acetone for 26 hr. The mixture was distilled to a low volume, diluted with 1 l. of water, and chilled overnight. The crude 21-acetate Vc was recovered by filtration and dried. Crystallization from acetone–hexane gave 23.8 g. of substantially pure Vc, m.p. 220–225°, suitable for use in the next reaction.

17α,21-Dihydroxy-16β-methylpregnane-3,11,20-trione 21-Acetate (VI).—A stirred solution of 22.6 g. of Vc in 227 ml. of acetic acid and 550 ml. of *t*-butyl alcohol was cooled to 10° and treated with 22.6 g. of N-bromoacetamide and 1.97 ml. of hydrochloric acid. Stirring was continued in the dark at 5–10° for 5 hr., and then the reaction was placed in the refrigerator for 15 hr. The mixture was treated with a solution of 18.8 g. of sodium sulfite in 200 ml. of water, then distilled under reduced pressure to a crystalline slurry which was diluted with 5 l. of ice–water. The product was collected by filtration, washed with water, and dried, giving 21.4 g. of impure VI, m.p. 199–201°. Crystallization from acetone–hexane yielded 18.9 g. of VI, m.p. 200–204°. The analytical sample was prepared by crystallization from acetone–hexane, m.p. 206–208°, $[\alpha]_D$ +128°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.04; H, 8.10.

4-Bromo-17,21-dihydroxy-16β-methylpregnane-11,20-dione 21-Acetate (VIIa).—A stirred solution of 15.45 g. of VI in 135 ml. of methylene chloride and 69.5 ml. of *t*-butyl alcohol was treated with a solution of 7.0 g. of bromine in 20 ml. of methylene chloride, added dropwise over 3 hr. controlling the temperature between 25 and 30°. The mixture was concentrated *in vacuo* to *ca.*

(18) Melting points were taken in capillaries and are corrected. Rotations were measured in dioxane at 25 ± 2° and at a concentration of *ca.* 1%. Ultraviolet spectra were obtained in methanol. Rotational and spectral data were obtained by the Physical Chemistry Department, Schering Corp. Microanalyses were performed by Mr. E. Conner, Microanalytical Laboratories, Schering Corp., and by Galbraith Laboratories, Knoxville, Tenn.

50 ml., then 20 ml. of ice–water was added slowly with stirring, and the solution was allowed to crystallize overnight in the cold. The product was removed by filtration, washed with water, and air dried. The resulting crude 4-bromide was stirred with ether, filtered, washed with cold ether, and air dried, yielding 13.75 g. of VIIa, m.p. 154–156° dec.

Anal. Calcd. for $C_{24}H_{33}BrO_6$: C, 57.94; H, 6.68; Br, 16.06. Found: C, 57.64; H, 6.59; Br, 16.30.

16β-Methylcortisone 21-Acetate (VIIIa).—A stirred slurry of 13.70 g. of the 4-bromide VIIa in 137.5 ml. of chloroform and 234 ml. of *t*-butyl alcohol, blanketed by a CO_2 atmosphere, was stirred with 4.14 g. of semicarbazide base at 25–30°. After 2 hr. a solution of 3.03 g. of sodium acetate in 9 ml. of water was added to the reaction mixture, the solvents were removed under reduced pressure, and the residue was diluted with about 1 l. of water. The semicarbazone was collected by filtration, washed with water, air dried briefly, and then added to a solution of 13.4 ml. of 65% pyruvic acid, 8.3 ml. of water, and 137 ml. of acetic acid. The reaction was blanketed with a CO_2 atmosphere and stirred at 25–30° for 17 hr. A solution of 14 g. of sodium acetate in 100 ml. of water was added and the reaction mixture was concentrated under reduced pressure to about 50 ml. and then diluted with water. The crude 16β-methylcortisone 21-acetate was isolated by filtration, washed with water, and dried to yield 10.65 g., m.p. 204–207°. Crystallization from acetone–hexane gave 7.0 g. of VIIIa, m.p. 223–229°. The analytical sample, crystallized from acetone–hexane, had m.p. 228–230°, $[\alpha]_D$ +227.8 (chloroform), λ_{max}^{MeOH} 238 mμ (ε 14,800).

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75. Found: C, 69.36; H, 7.62.

16β-Methylcortisone (IXa).—A stirred solution of 416 mg. of 16β-methylcortisone 21-acetate (VIIIa) in 3.7 ml. of chloroform and 11.8 ml. of methanol under nitrogen was cooled to *ca.* 2° and treated with 1.0 ml. of 1 *N* sodium hydroxide solution added dropwise over a 15-min. period. The reaction mixture was stirred an additional 15 min., acidified slightly with acetic acid, and treated with decolorizing charcoal. The charcoal was removed by filtration and the filtrate was concentrated under reduced pressure to a crystalline slurry which was diluted with water and chilled in an ice bath. The product was recovered by filtration, washed with water, and dried, yielding 326 mg. of IXa. The analytical sample obtained from acetone–hexane had m.p. 218–225° dec., $[\alpha]_D$ +208.0°, and λ_{max}^{MeOH} 238 mμ (ε 15,100).

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.09. Found: C, 70.29; H, 8.17.

16β-Methylprednisone 21-Acetate (VIIIb).—A solution of 41.8 g. of 17α,21-dihydroxy-16β-methylpregnane-3,11,20-trione 21-acetate (VI) in 936 ml. of dioxane was treated over a 10-min. period at 20–25° with a solution of 32.6 g. of bromine in 326 ml. of dioxane. The mixture was poured into 10 l. of ice–water and the resulting precipitate was removed by filtration, washed with water, and air dried. The crude 2,4-dibromide VIIb (59.3 g.) was heated at 100° in 865 ml. of dimethylformamide together with 28.8 g. of lithium bromide and 28.8 g. of lithium carbonate with vigorous stirring. Approximately 75 ml. of solvent was distilled from the reaction mixture under reduced pressure. The reaction mixture was stirred at 95–100° for an additional 20 hr. and concentrated under reduced pressure to *ca.* 300 ml. The solution was poured into 4 l. of ice–water containing 90 ml. of concentrated hydrochloric acid, and the resulting precipitate was removed by filtration, washed neutral with water, and dried. The crude product was dissolved in 207 ml. of pyridine and treated with 41 ml. of acetic anhydride at room temperature for 2 hr. The product was reprecipitated in 2 l. of ice–water containing 225 ml. of hydrochloric acid and collected by filtration, yielding 38.05 g. after drying. Crystallization from acetone gave 19.63 g. of VIIIb, m.p. 229–234°. The analytical sample was obtained from acetone–hexane and had m.p. 232–235°, $[\alpha]_D$ +214.0°, and λ_{max}^{MeOH} 238 mμ (ε 15,200).

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.55; H, 7.30. Found: C, 69.24; H, 7.21.

16β-Methylprednisone (IXb).—A solution of 828 mg. of VIIIb in 10 ml. of chloroform and 25 ml. of methanol was stirred under argon atmosphere with 2 ml. of 1 *N* sodium hydroxide solution at 0° for 25 min. A few drops of acetic acid were added. The solvents were removed under reduced pressure. The residue was stirred with water and extracted with methylene chloride. The extracts were washed with water, dried with magnesium sulfate, filtered, and crystallized by adding hexane: yield 630 mg., m.p. 199–204°. Recrystallization from acetone–hexane gave 400 mg. of IXb, m.p. 201–204°, $[\alpha]_D$ +190.2°, λ_{max}^{MeOH} 238 mμ (ε 14,700).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.19; H, 7.37.

3α,17α-Dihydroxy-16β-methylpregnane-11,20-dione-20-ethylene Ketal (X).—A mixture of 139.8 g. of 3α,17α-dihydroxy-16β-methylpregnane-11,20-dione (Va), 13.9 l. of benzene, 1.4 l. of ethylene glycol, and 21.0 g. of pyridine hydrochloride was refluxed together with stirring for 24 hr., collecting the condensate in a Dean–Stark trap packed with about 20 g. of anhydrous sodium sulfate to remove water formed in the reaction. The mixture was concentrated to 3 l., 14 ml. of 50% sodium hydroxide solution was added, and the mixture was further concentrated until crystals appeared and then poured into 10 l. of ice and water. The resulting precipitate was removed by filtration, washed neutral with water, and dried: yield 160 g. (95%), m.p. 191–206°, suitable for use in the next reaction. The analytical sample was obtained by crystallization of a small portion from benzene–hexane containing 1 drop of pyridine, m.p. 202–208°, $[\alpha]_D$ +55.40.

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.41. Found: C, 70.90; H, 9.32.

16β-Methyl-3α,11α,17α-Trihydroxypregnan-20-one-20-ethylene Ketal (XI).—A refluxing solution of 159.8 g. of 3α,17α-dihydroxy-16β-methylpregnane-11,20-dione-20-ethylene ketal (X) in 10 ml. of propyl alcohol was reduced with 480 g. of sodium added in several portions as rapidly as possible. After 50 min, 2 l. of methanol was added cautiously, and the mixture was refluxed until the sodium completely reacted, whereupon 1 l. of water was added. The mixture was concentrated to about 5 l., and poured into 25 l. of ice–water; the resulting precipitate was recovered by filtration, washed neutral with water, and dried to give 126 g. of XI. Crystallization from acetone–ether gave 104 g. of XI. The analytical sample prepared from acetone–hexane had m.p. 206–209°, $[\alpha]_D$ +16.2°.

Anal. Calcd. for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.58; H, 10.05.

16β-Methyl-3α,11α,17α-trihydroxypregnan-20-one (XIIa).—To a solution of 103 g. of 16β-methyl-3α,11α,17α-trihydroxypregnan-20-one-20-ethylene ketal (XI) in 520 ml. of acetic acid warmed to *ca.* 95° was added 832 ml. of hot water. The temperature was maintained at 90–95° for 20 min., and the mixture was set aside to cool slowly to room temperature, then finally chilled in an ice bath. The crystalline XIIa was removed by filtration, washed with water, and dried: yield 82.0 g., suitable for use in the next reaction. Crystallization of a portion from aqueous methanol gave the analytical sample, m.p. 180–183°, $[\alpha]_D$ +40.7°.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.28; H, 9.72.

16β-Methyl-3α,11α,17α-trihydroxypregnan-20-one 3,11-Diacetate (XIIb).—A solution of 300 mg. of XIIa in 5 ml. of pyridine was treated with 1 ml. of acetic anhydride overnight at room temperature. Addition of 10 ml. of water gave crystals which were isolated by filtration, washed with water, and dried, affording 340 mg. of 3,11-diacetate. Crystallization from acetone–hexane mixture gave pure XIIc, m.p. 185–186.5°, $[\alpha]_D$ +37.2°.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.53; H, 9.03.

21-Bromo-16β-methyl-3α,11α,17α-trihydroxypregnan-20-one (XIIIa).—A rapidly stirred slurry of 10.95 g. of 16β-methyl-3α,-11α,17α-trihydroxypregnan-20-one in 546 ml. of chloroform was treated with a solution of 108 ml. of chloroform saturated with hydrogen bromide gas followed by dropwise addition over 5 hr. of a solution of 4.95 g. of bromine in 108 ml. of chloroform, controlling the reaction temperature between 8 and 10°. Stirring was continued for 30 min. longer, and the mixture was washed twice with water, then with dilute sodium bicarbonate solution. The washes were back extracted with chloroform, and the chloroform extracts were combined and concentrated under reduced pressure to a thick crystalline slurry which was chilled in an ice bath, filtered, washed with cold chloroform–ether, and dried: yield 7.45 g. of XIIIa, m.p. 185–187° dec. Two additional crops of 21-bromide were obtained from the mother liquor amounting to 0.39 g., m.p. 180–182° dec., $[\alpha]_D$ +72.3°, and bringing the total yield of 21-bromide to 7.84 g. (72%).

16β-Methyl-3α,11α,17α,21-tetrahydroxypregnan-20-one 21-Acetate (XIIIb).—A solution of 7.0 g. of 21-bromo-16β-methyl-

3α,11α,17α-trihydroxypregnan-20-one (XIIIa) was stirred together with 21.0 g. of sodium acetate in 140 ml. of dimethylformamide at 70° for 16 hr. The mixture was cooled to room temperature, diluted with an equal volume of water, and poured into 1.4 l. of brine containing 140 ml. of hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, and dried: yield 6.45 g. of XIIIb. The analytical sample obtained from ether–hexane had m.p. 188–190°, $[\alpha]_D$ +70.1°.

Anal. Calcd. for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 68.37; H, 9.01.

16β-Methyl-11α,17α,21-trihydroxypregnane-3,20-dione 21-Acetate (XIV).—A solution of 6.35 g. of 16β-methyl-3α,11α,17α-21-trihydroxypregnan-20-one 21-acetate in 128 ml. of *t*-butyl alcohol and 32 ml. of water was cooled to 10° and treated with 6.4 g. of N-bromoacetamide and 6 drops of hydrochloric acid. The mixture was stirred in the dark at 10° for 4 hr. and a solution of 6.4 g. of sodium sulfite in 60 ml. of water was added. The solution was concentrated under reduced pressure to a crystalline slurry; the crystals were collected by filtration, washed with water, and dried, giving 6.15 g. of XIV as white needles. Crystallization from aqueous isopropyl alcohol furnished in two crops 5.77 g. of XIV, m.p. 178–181°. The analytical sample obtained from acetone–hexane as needles had m.p. 187.5–190.5°, $[\alpha]_D$ +77.9°.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.43; H, 8.61.

16β-Methyl-11α,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate. (XVIa *via* the 2,4-Dibromide XV).—A solution of 45 g. of 16β-methyl-11,17α,21-trihydroxypregnane-3,20-dione 21-acetate (XIV) in 297 ml. of dioxane was cooled to 15° and treated over a 5-min. period with a solution of 34.2 g. of bromine in 594 ml. of dioxane, precooled to 18°. After 2 min. a solution of 60 g. of sodium acetate in 600 ml. of water was added to the reaction and the mixture was poured into 8 l. of ice–water. The precipitated dibromide XV was recovered by filtration, washed neutral with water, and dried to give 55.7 g., m.p. 125–126°. dec., $[\alpha]_D$ +58.0°. A mixture of 55.5 g. of XV was refluxed together with 27.8 g. of lithium bromide and 27.8 g. of lithium carbonate in 1.110 l. of dimethylformamide, employing rapid stirring for 6 hr. The mixture was concentrated *in vacuo* to about 250 ml., poured into 8 l. of ice–water containing 250 ml. of hydrochloric acid, and extracted with methylene chloride. The extracts were washed neutral with water and evaporated to dryness. The residue was dissolved in acetone, evaporated under reduced pressure to dryness, redissolved in acetone, and crystallized by addition of hexane: yield 24.4 g. of XVIa, m.p. 236–239°. Recrystallization from acetone–hexane gave the analytical sample, m.p. 239–241°, $[\alpha]_D$ +95.2°, λ_{max}^{MeOH} 247 mμ (ε 17,380).

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.35; H, 7.79.

16β-Methylprednisone 21-Acetate (VIIIb) by Oxidation of XVIa.—A solution of 417 mg. of 16β-methyl-11α,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate in 42 ml. of acetone was oxidized with 0.39 ml. (0.001 mole) of Jones reagent[16] at 25–30° for 30 min. then diluted with 400 ml. of water and extracted with methylene chloride. The extracts were neutralized with solid sodium bicarbonate, dried with magnesium sulfate, and concentrated to about 5 ml. under reduced pressure until crystals appeared. The crystallization was chilled in an ice bath, and the product was collected by filtration, washed with ether, and dried, giving 350 mg. of VIIIb, m.p. 230–235°, $\lambda_{max.}^{MeOH}$ 238 mμ (ε 15,250). The infrared spectrum was identical with that of VIIIb prepared from VIIa.

16β-Methyl-11α,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 11-Mesylate 21-Acetate (XVIb).—A stirred solution of 24.0 g. of XVIa in 96 ml. of pyridine was cooled to 5° and 9.6 ml. of methanesulfonyl chloride was added dropwise over a 5-min. period. The mixture was stirred 5 min. longer at 5° and then for 2 hr. at room temperature. The 11α-mesylate was isolated by precipitation in water followed by filtration, washing with water, and drying at 60°, furnishing 27.9 g. of XVIb, m.p. 134–146° dec. The analytical sample, crystallized from acetone, had m.p. 145–151° dec., $[\alpha]_D$ +120.3°, λ_{max}^{MeOH} 243 mμ (ε 16,400).

Anal. Calcd. for $C_{25}H_{34}O_8S$: C, 60.71; H, 6.93; S, 6.48. Found: C, 60.74; H, 6.62; S, 6.60.

17α,21-Dihydroxy-16β-methyl-1,4,9(11)-pregnatriene-3,20-dione 21-Acetate (XVII).—A solution of 14.5 g. of 16β-methyl-11α,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 11α-mesylate 21-acetate (XVIb) and 43.5 g. of sodium acetate in 290 ml. of acetic acid was refluxed for 50 min., cooled, and poured into 360 ml. of ice–water. The resulting precipitate was recovered by filtration, washed neutral with water, and dried, yielding 9.45 g. of triene XVII. Crystallization from methanol gave 6.39 g. of XVII, m.p. 215–221°. The analytical sample obtained from ethyl acetate had m.p. 220–223°, $[\alpha]_D$ +74.8°, λ_{max}^{MeOH} 239 mμ (ε 15,400).

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.09; H, 7.63.

9α-Bromo-16β-methyl-11α,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (XVIII).—A solution of 9.0 g. of triene XVII in 90 ml. of tetrahydrofuran was cooled to 15° and treated with 48 ml. of 0.46 *N* aqueous perchloric acid followed by 4.1 g. of N-bromoacetamide. After stirring 4 hr. in the dark at 25–30°, enough saturated aqueous sodium sulfite solution was added to the reaction mixture to discharge the excess hypobromous acid. The mixture was poured into ice and water, and the resulting precipitate was collected by filtration, washed neutral with water, and dried: yield 10.9 g. of XVII, m.p. 145–156° dec. The analytical sample crystallized from ethyl acetate had m.p. 170–175° dec., $[\alpha]_D$ +132.8°, λ_{max}^{MeOH} 242 mμ (ε 13,800).

17α,21-Dihydroxy-16β-methyl-9,11β-oxido-1,4-pregnadiene-3,20-dione (XIX).—A stirred solution of 13.5 g. of 9α-bromo-16β-methyl-11β,17α,21-trihydroxypregnane-3,20-dione 21-acetate in 675 ml. of a methanol–chloroform mixture (3:2) was treated in a nitrogen atmosphere at 0–5° with 54 ml. of 1 *N* sodium hydroxide solution added dropwise over 50 min. Stirring was continued for 2 hr. and the mixture was neutralized by the addition of acetic acid. The solution was concentrated under reduced pressure to a thick crystalline slurry which was poured into 675 ml. of ice and water. The resulting precipitate was isolated by filtration, washed neutral with water, and dried to give 9.6 g. of crude XIX. Crystallization from methanol gave 8.5 g. of XIX, m.p. 232–240°, $[\alpha]_D$ +71.3°, λ_{max}^{MeOH} 249 mμ (ε 15,200).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.79; H, 7.69.

9α-Fluoro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (XXa).—To 160 ml. of 70% aqueous hydrogen fluoride contained in a polyethylene flask chilled to −30° was added, with stirring, a total of 64 g. of 17α,21-dihydroxy-16β-methyl-9,11β-oxido-1,4-pregnadiene-3,20-dione in small amounts while maintaining the temperature below −20°. The reaction mixture was stirred 4 hr. and poured into a solution of 560 g. of potassium carbonate in 640 ml. of water. The resulting precipitate was isolated by filtration, washed to neutrality with water, and dried. Crystallization from ethyl acetate gave 55.0 g. of XXa, m.p. 240–243°. The analytical sample crystallized from acetone had m.p. 242–243°, $[\alpha]_D$ +115.5°, $\lambda_{max.}^{MeOH}$ 239 mμ (ε 15,500).

Anal. Calcd. for $C_{22}H_{29}FO_5$: C, 67.33; H, 7.45; F, 4.84. Found: C, 67.18; H, 7.25; F, 4.64.

9α-Fluoro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (XXb).—A solution of 75 g. of XXa in 300 ml. of pyridine was treated at room temperature with 75 ml. of acetic anhydride for 1.5 hr. The solution was poured into a stirred mixture of 2 l. of ice and water containing 306 ml. of concentrated hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, and dried, giving 79.1 g. of XXb, m.p. 210–218°, $[\alpha]_D$ +124°, λ_{max}^{MeOH} 238 mμ (ε 15,900). Recrystallization of a portion from acetone did not raise the melting point.

Anal. Calcd. for $C_{24}H_{31}FO_6$: C, 66.35; H, 7.19; F, 4.37. Found: C, 66.27; H, 7.31; F, 4.17.