

The acetate VIIc, after recrystallization from ether-hexane, possessed m.p. 184–186° undepressed upon admixture with an authentic sample,⁴ $[\alpha]^{25D} +6^\circ$, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.78 and 5.89 μ ; identity was confirmed by infrared comparison.

Anal. Calcd. for $\text{C}_{29}\text{H}_{44}\text{O}_5$: C, 73.69; H, 9.38. Found: C, 73.95; H, 9.55.

Δ^8 -22a,5 α -Spirostan-3,11-dione (IX). (a) By Hydrogenation of Δ^4 ,8-22a-Spirostadiene-3,11-dione (VIII).—The catalytic hydrogenation of 0.18 g. of the diene-dione VIII⁹ was carried out exactly as described above for IV and resulted in the uptake of 1.1 equivalents of hydrogen after 1 hour. The crude crystalline material (0.18 g.) exhibited m.p. 190–195° and was chromatographed on 30 g. of neutral alumina (activity III). Elution with benzene-ether (9:1) and recrystallization from methanol gave needles, m.p. 210–212°, $[\alpha]^{25D} +79^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 253 μ , $\log \epsilon$ 3.97, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.88 and 6.0 μ .

Anal. Calcd. for $\text{C}_{27}\text{H}_{38}\text{O}_4$: C, 76.02; H, 8.98. Found: C, 76.06; H, 8.91.

(b) By Oxidation of Δ^8 -22a,5 α -Spirosten-3 β -ol-11-one.—This unsaturated keto alcohol (0.2 g.)¹⁶ in 20 cc. of pyridine was oxidized with 0.2 g. of chromium trioxide in 20 cc. of pyridine for 14 hours at room temperature. Dilution with water, followed by extraction with ether, washing with dilute acid and water, drying, evaporation and recrystallization from methanol furnished the dione IX with m.p. 209–212°, undepressed when mixed with a sample prepared according to (a); the infrared curves of the two samples were superimposable.

7 ξ ,8 ξ ;9 α ,11 α -Diepoxy-22a,5 β -Spirostan-3-one (XIIa).—The catalytic hydrogenation of 0.5 g. of the unsaturated diepoxide III⁹ in 30 cc. of ethyl acetate was carried out in the standard manner with 10% palladized charcoal catalyst. The crude product (0.5 g., m.p. 224–228°) was chromatographed on 50 g. of neutral alumina (activity III) and the benzene-ether eluates were recrystallized from methanol; needles, m.p. 228–230°, $[\alpha]^{25D} -30^\circ$, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.89 μ .

Anal. Calcd. for $\text{C}_{27}\text{H}_{38}\text{O}_5$: C, 73.27; H, 8.65. Found: C, 73.37; H, 8.70.

7 ξ ,8 ξ ;9 α ,11 α -Diepoxy-22a,5 β -spirostan-3 α -ol (XIIb).—The above diepoxy ketone XIIa (0.2 g.) in 15 cc. of methanol was reduced for 20 minutes at room temperature with 0.03 g. of sodium borohydride dissolved in 4 cc. of methanol and 0.5 cc. of water. The crude product (0.19 g., m.p. 221–225°) was recrystallized from methanol; m.p. 228–231°, $[\alpha]^{25D} -37^\circ$, no carbonyl absorption in the infrared.

Anal. Calcd. for $\text{C}_{27}\text{H}_{40}\text{O}_5$: C, 72.94; H, 9.07. Found: C, 72.71; H, 9.14.

The acetate XIIc was recrystallized from methanol and exhibited m.p. 268–270°, $[\alpha]^{25D} -12^\circ$, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.79 μ .

Anal. Calcd. for $\text{C}_{29}\text{H}_{42}\text{O}_6$: C, 71.57; H, 8.70. Found: C, 71.53; H, 8.79.

7 ξ ,8 ξ ;9 α ,11 α -Diepoxy-22a,5 α -Spirostan-3 β -ol (XIa).—A solution of 1.0 g. of $\Delta^{7,9(11)}$ -22a,5 α -spirostadien-3 β -ol (Xa)²⁰ in 50 cc. of chloroform was treated with an excess of an ethereal solution of monopero-phthalic acid for 24 hours at room temperature. After washing with sodium bicarbonate and water, drying, evaporation and crystallization from chloroform-methanol, there was obtained 0.85 g. of the diepoxide XIa with m.p. 284–288°, $[\alpha]^{25D} -57^\circ$.

Anal. Calcd. for $\text{C}_{27}\text{H}_{40}\text{O}_5$: C, 72.94; H, 9.07. Found: C, 73.07; H, 9.08.

The acetate XIb was recrystallized from methanol-chloroform whereupon it melted at 312–316°; reported^{8b} for a sample prepared by epoxidation of the diene acetate Xb, m.p. 312–316°.

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[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID Co.]

Steroidal Cyclic Ketals. X.¹ 16-Hydroxylated Steroids. I. The Preparation of 16 α -Hydroxyprogesterone

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Reaction of Δ^5 -pregnene-16 α -benzyloxy-3 β -ol-20-one acetate (II) with ethylene glycol (benzene, *p*-toluenesulfonic acid) gave the 20-ethylene ketal IIIb which on treatment with lithium-liquid ammonia-alcohol was converted into the 3 β ,16 α -diol (IV). The 3-hydroxyl group of the latter could be preferentially oxidized to afford Δ^4 -pregnene-16 α -ol-3,20-dione 20-ethylene ketal (VI). Acid hydrolysis gave 16 α -hydroxyprogesterone (VIIa). Proof of the non-rearrangement of the double bond on ketalization of a Δ^{16} -20-ketone also has been presented.

In the past few years a number of 16 α -hydroxylated steroids have been isolated as metabolites from and pregnant mare's human urine.² The interest aroused has stimulated attempts to produce, synthetically, these compounds and also any possible metabolic precursors. The successful synthesis of Δ^4 -pregnene-16 α -ol-3,20-dione acetate (VIIb)³ and Δ^4 -pregnene-16 α ,21-diol-3,20-dione diacetate⁴ and its enzymatic hydrolysis product has been reported. More recently, Cole and Julian⁵ have described a procedure for the introduction of a 16 α -hydroxyl group by an atypical opening of a 16 α ,17 α -oxide by chromous salts. Δ^4 -Pregnene-

16 α -ol-3,20-dione (VIIa) and Δ^4 -pregnene-16 α ,21-diol-3,20-dione, among other compounds, were prepared successfully in this manner. It is interesting to note that both of these compounds have been prepared by microbiological hydroxylation of progesterone⁶ and desoxycorticosterone,⁷ respectively.

The purpose of the work described in this report was to investigate chemical methods which would give in a facile manner 16 α -hydroxylated pregnene derivatives, and which would allow concomitantly complete control of the labile 16 α -hydroxyl group. It seemed possible to utilize our experience with the protective ethylene ketal group⁸ to accomplish this end. In particular, our efforts were directed to a synthesis of Δ^4 -pregnene-16 α -ol-3,20-dione (VIIa) as a desirable example.

(1) Paper IX, R. Antonucci, S. Bernstein and R. Lenhard, *THIS JOURNAL*, **76**, 2956 (1954).

(2) See S. Lieberman, B. Praetz, P. Humphries and K. Dobriner, *J. Biol. Chem.*, **204**, 491 (1953), for discussion and pertinent references.

(3) H. Hirschmann, F. B. Hirschmann and J. W. Corcoran, *Federation Proc.*, **12**, 218 (1953).

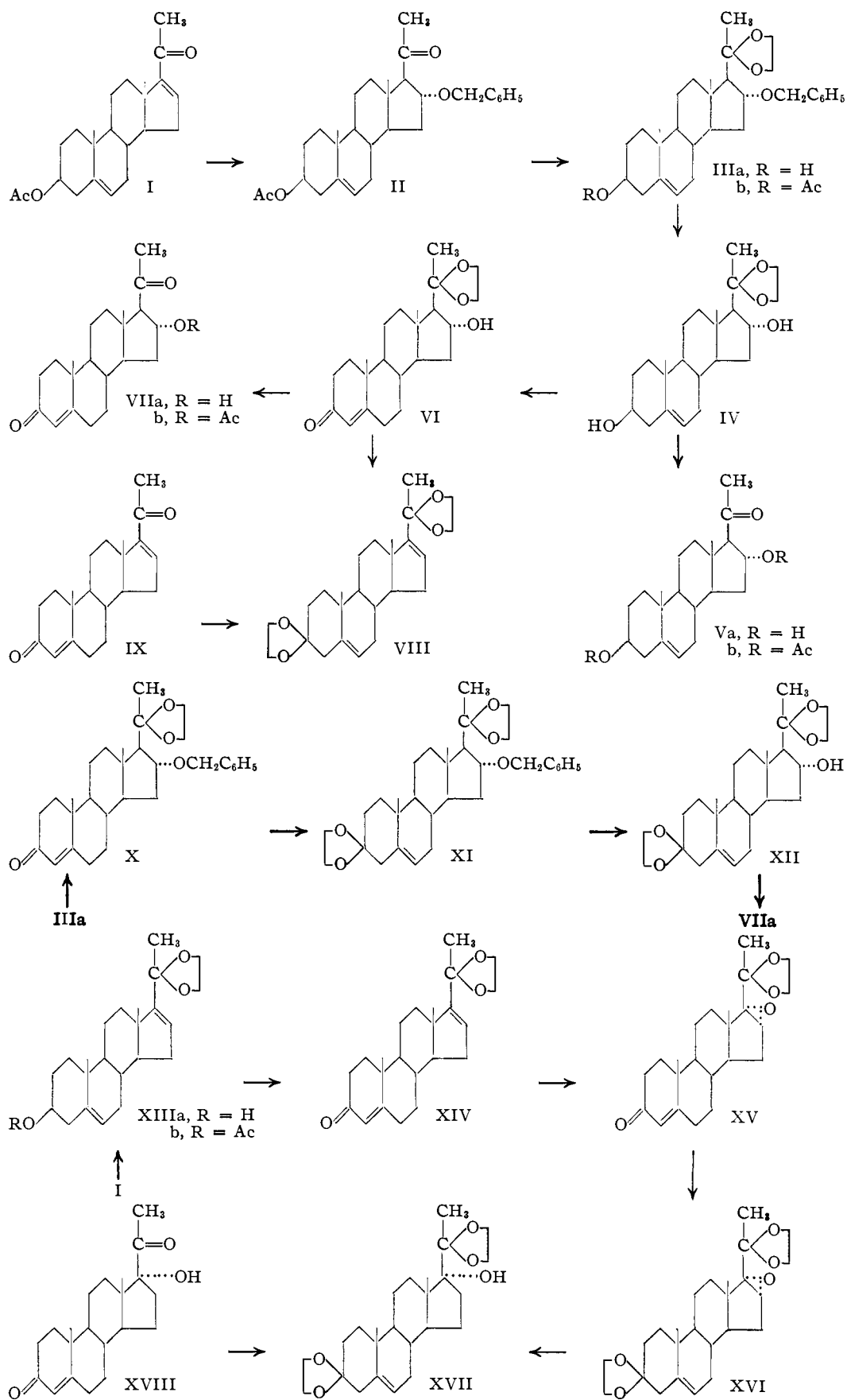
(4) H. Hirschmann, F. B. Hirschmann and G. L. Farrel, *THIS JOURNAL*, **75**, 4862 (1953).

(5) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

(6) D. Perlman, E. Titus and J. Fried, *THIS JOURNAL*, **74**, 2126 (1952).

(7) E. Vischer, J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **37**, 321 (1954).

(8) See ref. 1 and preceding papers.



The conversion of $\Delta^{5,16}$ -pregnadiene-3 β -ol-20-one acetate (I) to Δ^5 -pregnene-16 α -benzyloxy-3 β -ol-20-one acetate (II), which has been described already,⁹ seemed a convenient point of entry for our projected synthesis. The transformation of II to the ethylene ketal derivative IIIb was accomplished in the conventional manner.¹⁰ This compound in liquid ammonia-alcohol solution underwent hydrolysis and hydrogenolysis when treated with lithium to afford Δ^5 -pregnene-3 β ,16 α -diol-20-one ethylene ketal (IV). Ten-minute acid hydrolysis of IV gave the diolone Va in satisfactory yield (52%), the structure of which was confirmed by the preparation of the diacetate Vb. This procedure established the stability of the 16 α -hydroxyl group under *cer-tain* acidic conditions.

Oppenauer oxidation of the diol-ketal IV resulted in the Δ^4 -3-ketone VI which on acid hydrolysis gave Δ^4 -pregnene-16 α -ol-3,20-dione (VIIa), the properties of which were identical in almost all respects to those reported previously.^{5,6} It is interesting to note that a Nujol mull preparation of our compound exhibited an anomalous absorption in the carbonyl region of the infrared absorption spectrum. Three carbonyl bands at 1709, 1696 and 1678 cm^{-1} (this last band is typical of a Δ^4 -3-ketone) were present. The infrared absorption spectrum of a chloroform solution of VIIa, however, showed only the two expected carbonyl bands, *i.e.*, at 1710 and 1675 cm^{-1} . Acetylation of VIIa afforded the acetate VIIb, the properties of which were also identical in almost all respects to those previously reported.⁶ No anomalous carbonyl band was present in its infrared absorption spectrum.

In connection with other work the monoketal VI was treated in the usual way in an attempt to prepare the bisethylene ketal XII. Only a mixture of materials resulted. However, a further treatment on the residues of the first attempt gave the bisethylene ketal VIII, identical with the product obtained from the condensation of $\Delta^{4,16}$ -pregnadiene-3,20-dione (IX) with ethylene glycol. Apparently during the course of the reaction, the ketal VI was in equilibrium with a free 20-carbonyl compound and ethylene glycol. Thus, opportunity for the dehydration of the 16 α -hydroxyl group under these acidic conditions prevailed. It is interesting to compare the stability of the 16 α -benzyloxy group under these same conditions (*vide supra*).

It was possible, however, to prepare the 16 α -ol-bisethylene ketal (XII) by means of a slightly modified pathway which utilized the stability of the benzyloxy group to ketal formation conditions. Saponification of the monoketal IIIb to the free alcohol IIIa followed by Oppenauer oxidation gave the unsaturated ketone X. Formation of the bisethylene ketal XI followed by treatment with lithium in liquid ammonia and alcohol gave the desired product XII. This bisethylene ketal was successfully submitted to acid hydrolysis in the manner described above to afford Δ^4 -pregnene-16 α -ol-3,20-dione (VIIa).

Our attention was next directed to the establish-

(9) H. Hirschmann, F. B. Hirschmann and M. A. Daus, *THIS JOURNAL*, **74**, 539 (1952).

(10) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

ment in an unequivocal manner of the final position of the double bond when a Δ^{16} -20-ketone was converted into a 20-ketal. The solution of this problem was of special interest in view of the coincident rearrangement of the double bond during the formation of an ethylene ketal of a Δ^4 -3-ketosteroid,¹⁰ and was required for the establishment of the structure VIII. Ketalization of $\Delta^{5,16}$ -pregnadiene-3 β -ol-20-one acetate (I) to form XIIIb was followed by saponification to give the alcohol XIIIa. An Oppenauer oxidation on this product gave the $\Delta^{4,16}$ -3-ketone (XIV), which was treated with perbenzoic acid to yield Δ^4 -pregnene-3,20-dione-16 α ,17 α -oxide 20-ethylene ketal (XV). Condensation of XV with ethylene glycol afforded XVI which upon treatment with lithium aluminum hydride was converted into the 17 α -ol-bisethylene ketal (XVII). The structure of this compound was confirmed by its preparation directly from 17 α -hydroxyprogesterone (XVIII). In this manner it was shown that the Δ^{16} -double bond does not rearrange when the 20-carbonyl group was condensed with ethylene glycol, and that the structure of VIII was as pictured.

Infrared absorption data have been reported in the Experimental section. Besides the usual hydroxyl, carbonyl and double bond bands, we have indicated one of the principal "C-O" stretching bands of the ketal function at approximately 1100 cm^{-1} , the most prominent "C-O" stretching band of the 16 α ,17 α -oxide at about 1050 cm^{-1} , and the phenyl band (or doublet) at about 735-750 cm^{-1} .

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Experimental

Melting Points.—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

Optical Rotations.—The sample was dissolved in chloroform (unless otherwise noted) to make a 2-ml. solution, and the rotation was determined in a 1-dm. semimicro tube at wave length 5893 Å. (D).

Absorption Spectra.—The ultraviolet spectra were determined in absolute alcohol with a Beckman spectrophotometer (model DU) or a Cary recording spectrophotometer (model 11S). The infrared spectra (Nujol mull, chloroform solution, or pressed potassium bromide as indicated) were determined with a Perkin-Elmer spectrophotometer (model 21).

Δ^5 -Pregnene-16 α -benzyloxy-3 β -ol-20-one Acetate Ethylene Ketal (IIIb).—A mixture of Δ^5 -pregnene-16 α -benzyloxy-3 β -ol-20-one acetate⁹ (II, 0.57 g.) [m.p. 135.5-136.5°; λ_{max} 247 $\text{m}\mu$ (ϵ 144, shoulder), 252 $\text{m}\mu$ (ϵ 183), 258 $\text{m}\mu$ (ϵ 225), 264 $\text{m}\mu$ (ϵ 186), 267 $\text{m}\mu$ (ϵ 135, shoulder) and 285 $\text{m}\mu$ (ϵ 74)], benzene (35 ml.), ethylene glycol (10 ml.) and *p*-toluenesulfonic acid monohydrate (30 mg.) was treated in the same manner as described in a previous publication¹⁰ (reflux 5 hours). An additional 15 mg. of *p*-toluenesulfonic acid monohydrate was added after one hour. Three crystallizations from acetone-Skellysolve B gave 0.28 g. (44%) of IIIb, m.p. 163.5-164.5°; λ_{max} 247 $\text{m}\mu$ (ϵ 122, shoulder), 252 $\text{m}\mu$ (ϵ 163), 258 $\text{m}\mu$ (ϵ 201), 264 $\text{m}\mu$ (ϵ 155), and 267 $\text{m}\mu$ (ϵ 86, shoulder); infrared: $\lambda_{\text{max}}^{\text{Nujol}}$ 1740, 1250, 1088, 748 and 742 cm^{-1} ; $[\alpha]_{\text{D}}^{25}$ -75° (19.8 mg., α_{D} -0.74°), $[\text{M}]_{\text{D}}^{\text{D}}$ -379.

Anal. Calcd. for $\text{C}_{32}\text{H}_{44}\text{O}_6$ (508.67): C, 75.55; H, 8.72. Found: C, 75.77; H, 8.87.

In another run (reflux 7 hours), 0.505 g. (62%) of IIIb,

m.p. 163–164.5°, was obtained from 0.75 g. of II. Generally, maximum yields could best be obtained by combining mother liquor fractions and recycling.

Δ^5 -Pregnene-16 α -benzyloxy-3 β -ol-20-one Ethylene Ketal (IIIa).—A solution of 2.79 g. of IIIb in 150 ml. of 5% potassium hydroxide in methanol was refluxed for one hour, poured into 500 ml. of water, and filtered to give 2.64 g., m.p. 182–186°. Recrystallization from acetone gave 1.74 g. of IIIa, m.p. 184.5–186°; λ_{\max} 247 m μ (ϵ 112, shoulder), 252 m μ (ϵ 156), 258 m μ (ϵ 196), 204 m μ (ϵ 149) and 267 m μ (ϵ 86, shoulder); infrared: $\lambda_{\max}^{\text{Nujol}}$ 3480, 1120 and 741 cm.⁻¹; $[\alpha]^{25}_{\text{D}} - 103^\circ$ (34.55 mg., $\alpha_{\text{D}} - 1.77^\circ$), $[M]_{\text{D}} - 479$.

Anal. Calcd. for C₃₀H₄₂O₄ (466.64): C, 77.21; H, 9.07. Found: C, 77.23; H, 9.19.

Δ^5 -Pregnene-3 β ,16 α -diol-20-one Ethylene Ketal (IV).—To a solution of 165 mg. of IIIb in 4 ml. of ether and 1 ml. of absolute ethanol was added 60 ml. of liquid ammonia. Lithium (150 mg.) was added with continuous stirring in several small pieces (the blue color was allowed to disappear between additions), and then the excess ammonia was permitted to evaporate spontaneously. Water was added, and the resultant precipitate was filtered and washed with additional water to yield 100 mg., m.p. 190–210°. Two crystallizations from acetone–Skellysolve B gave 65 mg. of IV, m.p. 219–221°; infrared: $\lambda_{\max}^{\text{Nujol}}$ 3500 and 1088 cm.⁻¹; $[\alpha]^{25}_{\text{D}} - 43^\circ$ (11.3 mg., $\alpha_{\text{D}} - 0.24^\circ$), $[M]_{\text{D}} - 160$.

Anal. Calcd. for C₂₈H₃₈O₄ (376.5): C, 73.36; H, 9.64. Found: C, 72.98; H, 9.80.

In another run from 3.11 g. of IIIb there was obtained 2.21 g. of IV, m.p. 214–220° and 0.11 g., m.p. 214–218° (ca. 100%), of suitable purity for the further transformations described.

Δ^5 -Pregnene-3 β ,16 α -diol-20-one (Va).—A solution of 130 mg. of IV, 1 ml. of 8% (v./v.) sulfuric acid and 15 ml. of methanol was refluxed for 10 minutes, added to a large amount of water, chilled and filtered to give 0.105 g., m.p. 220–226°. Three crystallizations from acetone gave 60 mg. (52%) of Va, m.p. 252–255°; infrared: $\lambda_{\max}^{\text{Nujol}}$ 3350, 1705 and 1045 cm.⁻¹; $[\alpha]^{25}_{\text{D}} - 20^\circ$ (6 mg., ethanol, $\alpha_{\text{D}} - 0.06^\circ$) $[M]_{\text{D}} - 67$.

Anal. Calcd. for C₂₁H₃₂O₂ (332.47): C, 75.86; H, 9.70. Found: C, 75.66; H, 9.80.

Δ^5 -Pregnene-3 β ,16 α -diol-20-one Diacetate (Vb).—The diol (Va, 95 mg.) in pyridine (2 ml.) was treated with acetic anhydride (1 ml.) (room temperature, 18 hours). The solvents were removed under reduced pressure, methanol was added and removed under reduced pressure. The latter step was repeated. Recrystallization from dilute acetone gave 90 mg. of Vb, m.p. 173.5–175°; infrared: $\lambda_{\max}^{\text{Nujol}}$ 1739, 1706 and 1240 cm.⁻¹; $[\alpha]^{25}_{\text{D}} - 36^\circ$ (17.45 mg., $\alpha_{\text{D}} - 0.31^\circ$), $[M]_{\text{D}} - 148$.

Anal. Calcd. for C₂₅H₃₆O₆ (416.54): C, 72.08; H, 8.71. Found: C, 72.39; H, 8.91.

Δ^4 -Pregnene-16 α -ol-3,20-dione 20-Ethylene Ketal (VI).—A solution of 2.31 g. of IV in 270 ml. of toluene and 25 ml. of cyclohexanone was distilled to remove traces of water (about 85 ml. of distillate was collected). A solution (10 ml.) of aluminum isopropoxide in toluene (0.25 g./ml.) was added to the hot solution, and the mixture was refluxed for 45 minutes. Water and ether were added to the cooled solution, and the organic layer was washed with 2% sodium hydroxide and then with water until neutral. The resultant solution was steam distilled for removal of cyclohexanone, cooled and extracted with ether. The ether solution was treated with Norit, dried and the solvent removed under reduced pressure. Three crystallizations from acetone–Skellysolve B gave 80 mg. (35%), m.p. 190.5–192°; λ_{\max} 240 m μ (ϵ 15,000); infrared: $\lambda_{\max}^{\text{Nujol}}$ 3620, 1688, 1625 and 1095 cm.⁻¹; $[\alpha]^{25}_{\text{D}} + 89^\circ$ (17.13 mg., $\alpha_{\text{D}} + 0.76^\circ$), $[M]_{\text{D}} + 334$.

Anal. Calcd. for C₂₈H₃₄O₆ (374.5): C, 73.76; H, 9.15. Found: C, 73.47; H, 9.28.

Δ^4 -Pregnene-16 α -ol-3,20-dione (VIIa). A.—A solution of 200 mg. of VI in 15 ml. of methanol and 1.5 ml. of 8% sulfuric acid (v./v.) was refluxed for ten minutes, poured into salt water and extracted with ethyl acetate. After drying over sodium sulfate, the solvent was removed under reduced pressure. Two crystallizations from acetone–Skellysolve B gave 126 mg. (71.5%) of VIIa, m.p. 225–

226°¹¹; λ_{\max} 240 m μ (ϵ 16,200); infrared: $\lambda_{\max}^{\text{Nujol}}$ 3470, 1709, 1696, 1678 and 1630 cm.⁻¹; $\lambda_{\max}^{\text{CHCl}_3}$ 3675, 3500, 1710, 1675 and 1629 cm.⁻¹; $[\alpha]^{25}_{\text{D}} + 157^\circ$ (20.25 mg., $\alpha_{\text{D}} + 1.59^\circ$), $[M]_{\text{D}} + 519$.

Anal. Calcd. for C₂₁H₃₀O₃ (330.45): C, 76.32; H, 9.15. Found: C, 76.60; H, 9.46.

B.—A solution of 60 mg. of XII in 7 ml. of methanol and 0.5 ml. of 8% (v./v.) sulfuric acid was treated as above. Three crystallizations from acetone–Skellysolve B gave 8.4 mg. (16%) of VIIa, m.p. 224–225°, λ_{\max} 240 m μ (ϵ 15,400). Admixture melting point determination with the sample prepared above indicated identity, m.p. 224–225°. The infrared absorption spectra of preparations A and B were identical in all respects.

Δ^4 -Pregnene-16 α -ol-3,20-dione Acetate (VIIb).—To a solution of 0.27 g. of VIIa in 3 ml. of pyridine was added 1.5 ml. of acetic anhydride, and the mixture was allowed to stand at room temperature overnight. The solution was poured into ice-water, salt was added and the mixture was extracted with ether and ethyl acetate. The combined organic extracts were washed with salt water, dried over sodium sulfate and evaporated under reduced pressure to give an oil. Crystallization from ether–Skellysolve B gave 0.215 g., m.p. 132.5–134°. Recrystallization from ether–Skellysolve B gave 0.182 g. of VIIb, m.p. 133–134°¹² λ_{\max} 239 m μ (ϵ 16,900); infrared: $\lambda_{\max}^{\text{Nujol}}$ 1725, 1709, 1688, 1620 and 1245 cm.⁻¹; $[\alpha]^{25}_{\text{D}} + 102^\circ$ (15.43 mg., $\alpha_{\text{D}} + 0.79^\circ$), $[M]_{\text{D}} + 880$.

Anal. Calcd. for C₂₃H₃₂O₄ (372.49): C, 74.16; H, 8.66. Found: C, 74.37; H, 8.91.

Δ^5 ,16-Pregnadiene-3,20-dione Bisethylene Ketal (VIII).—A.—A mixture of 1.845 g. of VI, 150 ml. of benzene, 8 ml. of ethylene glycol and 30 mg. of *p*-toluenesulfonic acid monohydrate reacted in the usual manner (reflux 4 hours). Several crystallizations from methanol did not give a constant melting point, so that the remaining solid and the residue from all mother liquors were combined and recycled with the same amounts of benzene, ethylene glycol and *p*-toluenesulfonic acid monohydrate (reflux 7 hours). Several crystallizations of this product from methanol gave 0.25 g. of VIII, m.p. 182.5–184°; infrared: $\lambda_{\max}^{\text{Nujol}}$ 1629 and 1100 cm.⁻¹; $[\alpha]^{25}_{\text{D}} - 47^\circ$ (36.6 mg., $\alpha_{\text{D}} - 0.86^\circ$), $[M]_{\text{D}} - 187$.

Anal. Calcd. for C₂₈H₃₆O₄ (400.54): C, 74.96; H, 9.06. Found: C, 75.27; H, 9.25.

B.—A mixture of 16-dehydropregesterone (IX, 2.8 g.), benzene (175 ml.), ethylene glycol (28 ml.) and *p*-toluenesulfonic acid monohydrate was heated and stirred in the fashion described (reflux 6 hours). Two crystallizations from acetone afforded 1.44 g., m.p. 180–184°, λ_{\max} none. A portion (200 mg.) of this product was crystallized to constant m.p. 184.5–187°. There was no depression of melting point when mixed with the sample above, and the infrared absorption spectra were identical.

Anal. Calcd. for C₂₅H₃₆O₄ (400.54): C, 74.96; H, 9.06. Found: C, 74.97; H, 9.15.

Δ^4 -Pregnene-16 α -benzyloxy-3,20-dione 20-Ethylene Ketal (X).—A solution of IIIa (1.96 g.), toluene (210 ml.) and cyclohexanone (25 ml.) was distilled for drying purposes until 75 ml. of toluene was removed. Then 9 ml. of aluminum isopropoxide in toluene (0.25 g./ml.) was added, and the solution was refluxed for 45 minutes. The reaction mixture was worked up as in the case of Δ^4 -pregnene-16 α -ol-3,20-dione 20-ethylene ketal (VI), and resulted in an oil. Chromatography on 150 g. of acid-washed alumina (*pH* 5) gave solid in the benzene–ether (14:1) fractions. Solid continued to be eluted, although in diminishing quantities, until the benzene–ether (1:1) fraction was reached. The solid fractions were combined and recrystallized from acetone–Skellysolve B to yield 1.06 g. (54.5%) of X, m.p. 125.5–126.5°, λ_{\max} 240 m μ (ϵ 16,800); infrared: $\lambda_{\max}^{\text{Nujol}}$ 1680, 1627, 1103 and 737 cm.⁻¹; $[\alpha]^{25}_{\text{D}} - 7.1^\circ$ (62.22 mg., $\alpha_{\text{D}} - 0.22^\circ$), $[M]_{\text{D}} - 32$.

Anal. Calcd. for C₃₀H₄₀O₄ (464.62): C, 77.55; H, 8.68. Found: C, 77.72; H, 8.82.

(11) Reference 5: m.p. 226–227°; $\lambda_{\max}^{\text{methanol}}$ 241 m μ (ϵ 16,400); $[\alpha]_{\text{D}} + 160^\circ$ (chloroform); ref. 6: m.p. 225–226°; $\lambda_{\max}^{\text{alc.}}$ 239 m μ (ϵ 17,000); infrared: $\lambda_{\max}^{\text{Nujol}}$ 3.04, 5.90, 6.02 and 6.20 μ ; $[\alpha]^{25}_{\text{D}} + 158^\circ$ (chloroform).

(12) Reference 6, m.p. 134–135°; $[\alpha]^{25}_{\text{D}} + 107^\circ$ (chloroform).

Δ^5 -Pregnene-16 α -benzyloxy-3,20-dione Bisethylene Ketal (XI).—A mixture of 0.95 g. of X, 60 ml. of benzene, 10 ml. of ethylene glycol and 50 mg. of *p*-toluenesulfonic acid monohydrate reacted in the usual manner (reflux for 5 hours), with an additional 30 mg. of *p*-toluenesulfonic acid monohydrate after one hour. Several crystallizations from acetone gave 0.47 g. (45%) of XI, m.p. 185–187°; λ_{\max} 248 $m\mu$ (ϵ 120, shoulder), 252 $m\mu$ (ϵ 163), 258 $m\mu$ (ϵ 198), 264 $m\mu$ (ϵ 152) and 268 $m\mu$ (ϵ 92, shoulder); infrared: $\lambda_{\max}^{\text{Nujol}}$ 1092, 743 and 735 cm^{-1} ; $[\alpha]_D^{25}$ -78.1° (30.77 mg., $\alpha_D -1.20^\circ$), $[M]_D -396$.

Anal. Calcd. for $\text{C}_{32}\text{H}_{44}\text{O}_6$ (508.67): C, 75.55; H, 8.72. Found: C, 75.33; H, 8.84.

Δ^5 -Pregnene-16 α -ol-3,20-dione Bisethylene Ketal (XII).—To a solution of 0.21 g. of XI in 13 ml. of tetrahydrofuran, 1.5 ml. of ethanol and 80 ml. of liquid ammonia was added 0.2 g. of lithium in the manner indicated in the preparation of IV. After the ammonia had evaporated, water was added, and 0.155 g. (90%) of solid, m.p. 191–200.5°, was collected. Two crystallizations from acetone-Skellysolve B gave 0.095 g. of XII, m.p. 206.5–208.5°; infrared: $\lambda_{\max}^{\text{KBr}}$ 3580 and 1099 cm^{-1} ; $[\alpha]_D^{25}$ -32° (16.73 mg., $\alpha_D -0.27^\circ$), $[M]_D -135$.

Anal. Calcd. for $\text{C}_{28}\text{H}_{38}\text{O}_6$ (418.55): C, 71.74; H, 9.15. Found: C, 71.48; H, 9.38.

$\Delta^5,16$ -Pregnadiene-3 β -ol-20-one Acetate Ethylene Ketal (XIIIb).¹³—A mixture of 5 g. of $\Delta^5,16$ -pregnadiene-3 β -ol-20-one acetate (I), 20 ml. of ethylene glycol, 175 ml. of benzene and 150 mg. of *p*-toluenesulfonic acid monohydrate was treated in the usual manner (reflux 4.5 hours). Recrystallization from acetone gave 3.04 g., m.p. 141–155°. Several further crystallizations from acetone-methanol gave 1.19 g. of XIIIb, m.p. 165–166.5°; λ_{\max} none; infrared: $\lambda_{\max}^{\text{Nujol}}$ 1735, 1245 and 1104 cm^{-1} ; $[\alpha]_D^{30}$ -68° (18.9 mg., $\alpha_D -0.64^\circ$), $[M]_D -271$.

Anal. Calcd. for $\text{C}_{28}\text{H}_{36}\text{O}_4$ (400.54): C, 74.96; H, 9.06. Found: C, 74.94; H, 9.26.

In another run 12.53 g. (56.5%), m.p. 163–165°, of XIIIb suitable for further transformations was obtained from 20 g. of I.

$\Delta^5,16$ -Pregnadiene-3 β -ol-20-one Ethylene Ketal (XIIIa).¹⁵—A solution of XIIIb (500 mg.) in 2.5% alcoholic potassium hydroxide (10 ml.) was refluxed for 40 minutes. Water was added, and the mixture was cooled, filtered and washed with water to give 427 mg., m.p. 171.5–174°. Three crystallizations from acetone-Skellysolve B yielded 245 mg. of XIIIa, m.p. 177–179°; infrared: $\lambda_{\max}^{\text{Nujol}}$ 3510, 1630 and 1100 cm^{-1} ; $[\alpha]_D^{25}$ -67° (22.85 mg., $\alpha_D -0.77^\circ$), $[M]_D -240$.

Anal. Calcd. for $\text{C}_{28}\text{H}_{34}\text{O}_3$ (358.5): C, 77.05; H, 9.56. Found: C, 76.74; H, 9.69.

$\Delta^4,16$ -Pregnadiene-3,20-dione 20-Ethylene Ketal (XIV).—A solution of the ketal (9 g., XIIIa) in a mixture of 370 ml. of toluene and 45 ml. of cyclohexanone was distilled for removal of moisture until 50 ml. of distillate was collected. A solution of 50 ml. of aluminum isopropoxide in toluene (0.25 g./ml.) was added dropwise over 15 minutes to the refluxing toluene-cyclohexanone mixture. The final solution was allowed to reflux an additional 30 minutes, then a solution of 35 g. of sodium potassium tartrate in 100 ml. of water was added, and the mixture was steam distilled until all traces of cyclohexanone were removed. The resultant mixture was extracted with ethyl acetate, which was

then washed with sodium chloride solution, and dried over sodium sulfate. Evaporation under reduced pressure yielded an oil which was crystallized from Skellysolve B to give 3.72 g., m.p. 115–118°. Several crystallizations gave pure XIV, m.p. 120.5–123°, λ_{\max} 240 $m\mu$ (ϵ 16,600); infrared: $\lambda_{\max}^{\text{Nujol}}$ 1679, 1622 and 1106 cm^{-1} ; $[\alpha]_D +92^\circ$ (19.54 mg., $\alpha_D +0.90^\circ$), $[M]_D +324$.

Anal. Calcd. for $\text{C}_{28}\text{H}_{32}\text{O}_3$ (356.49): C, 77.49; H, 9.05. Found: C, 77.34; H, 9.15.

In another run, 13.84 g. of XIIIa afforded 6.45 g. (47%) of XIV, m.p. 118–119.5°, suitable for further transformations.

Δ^4 -Pregnene-3,20-dione-16 $\alpha,17\alpha$ -oxide 20-Ethylene Ketal (XV).—To a solution of 0.713 g. of the unsaturated ketone XIV in 20 ml. of ethyl acetate was added 12 ml. of a solution of perbenzoic acid in ethyl acetate (29 mg./ml.). After standing 19 hours at room temperature in the dark, additional ethyl acetate was put in, and the resultant solution was washed with sodium carbonate and then salt water until the washings were neutral. The extract was dried over sodium sulfate and evaporated under reduced pressure to yield 0.50 g. (67%), m.p. 173–177°. Several crystallizations from acetone-Skellysolve B gave 0.215 g. of XV, m.p. 198.5–199°; λ_{\max} 240 $m\mu$ (ϵ 14,600); infrared: $\lambda_{\max}^{\text{Nujol}}$ 1678, 1624, 1107 and 1041 cm^{-1} ; $[\alpha]_D^{24}$ $+99.2^\circ$ (28.25 mg., $\alpha_D +1.40^\circ$), $[M]_D +370$.

Anal. Calcd. for $\text{C}_{28}\text{H}_{32}\text{O}_4$ (372.49): C, 74.16; H, 8.66. Found: C, 74.10; H, 8.81.

Δ^5 -Pregnene-3,20-dione-16 $\alpha,17\alpha$ -oxide Bisethylene Ketal (XVI).—A mixture of XV (1.29 g.), 80 ml. of benzene, 10 ml. of ethylene glycol and 30 mg. of *p*-toluenesulfonic acid monohydrate reacted as described previously. An additional 30 mg. of *p*-toluenesulfonic acid was put in after one hour (total reflux 4 hours). The crude product (0.48 g.) had a m.p. 174.5–179°. Several crystallizations from methanol afforded 0.2 g. of XVI, m.p. 183.5–185°; infrared: $\lambda_{\max}^{\text{Nujol}}$ 1095 and 1048 cm^{-1} ; $[\alpha]_D^{24}$ -24° (23.02 mg., $\alpha_D -0.27^\circ$), $[M]_D -98$.

Anal. Calcd. for $\text{C}_{28}\text{H}_{36}\text{O}_5$ (416.54): C, 72.08; H, 8.71. Found: C, 72.06; H, 8.69.

Δ^5 -Pregnene-17 α -ol-3,20-dione Bisethylene Ketal (XVII). A.—A mixture of 1.0 g. of Δ^4 -pregnene-17 α -ol-3,20-dione (XVIII), 8 ml. of ethylene glycol, 50 ml. of benzene and 30 mg. of *p*-toluenesulfonic acid monohydrate was treated in the usual fashion (4 hours reflux). The crude product (0.485 g.) had a m.p. 206–210°. Several crystallizations from acetone-Skellysolve B yielded XVII, 0.17 g., m.p. 209.5–212°; infrared: $\lambda_{\max}^{\text{KBr}}$ 3610 and 1098 cm^{-1} ; $[\alpha]_D^{24}$ -50° (21.04 mg., $\alpha_D -0.53^\circ$), $[M]_D -210$.

Anal. Calcd. for $\text{C}_{28}\text{H}_{36}\text{O}_3$ (418.55): C, 71.74; H, 9.15. Found: C, 71.46; H, 8.95.

B.—A solution of 0.5 g. of XVI in 150 ml. of dry ether was added dropwise over a period of 30 minutes to a stirred suspension of 1.0 g. of lithium aluminum hydride in 100 ml. of dry ether. The resultant mixture was refluxed and stirred for an additional 1.5 hours, cooled and the excess lithium aluminum hydride was cautiously decomposed with water. The layers were separated and the water layer was extracted with ether and ethyl acetate. The combined organic extracts were washed with sodium chloride solution until neutral. The dried extract was evaporated under reduced pressure to give 0.36 g. (72%), m.p. 201–206°. One crystallization from acetone-Skellysolve B afforded 0.24 g., m.p. 209–212°. Admixture melting point with the sample prepared above showed identity, m.p. 209–212°. The infrared absorption spectra of preparations A and B were identical in all respects.

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(13) This experiment was done by Miss Rose Antonucci.

(14) H. J. Dauben, Jr., B. Lökken and H. J. Ringold, THIS JOURNAL, **76**, 1359 (1954); report m.p. 157–158°, $[\alpha]_D^{24}$ -71.1° (chloroform).

(15) This experiment was done by Robert Lenhard.