The Synthesis of Δ^{11}-17α-Acetoxyprogesterone and Related Compounds

JOHN P. DUSZA, J. P. JOSEPH, MILTON HELLER, AND SEYMOUR BERNSTEIN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York

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17α-Hydroxypregn-11-ene-3,20-dione (VII) has been synthesized from both 16α,17α-epoxy-3α,12α-dihydroxypregnane-3,20-dione (I) and pregn-11-ene-3,20-dione (XVI). This key intermediate has been converted into 17α-acetoxypregna-4,11-diene-3,20-dione (XX), 17α-acetoxypregna-1,4,11-triene-3,20-dione (XXI), 17α-acetoxypregna-4,6,11-triene-3,20-dione (XXII), and 17α-acetoxypregna-1,4,6,11-tetraene-3,20-dione (XXIV). The biological activities (Clauberg assay) of these compounds are tabulated.

Whereas the biological influence of a 11,12-double bond in parenterally administered progestational agents is inconsistent,[1-4] its effect on oral activity has not been reported. It seemed therefore desirable to synthesize a modification of a known orally active progestin incorporating the 11,12-double bond. For this purpose a series of Δ^{11}-unsaturated compounds related to 17α-acetoxyprogesterone was prepared for biological evaluation.

A convenient starting material for the synthesis of 11-dehydro-17α-oxygenated compounds was 16α,17α-epoxy-3α,12α-dihydroxypregnan-20-one (I), described by Julian and co-workers.[5] Selective esterification employing ethyl chloroformate[6] provided the 3α-carboethoxy derivative II, which on treatment with *p*-toluenesulfonyl chloride in pyridine[7] was converted into 3α-carboethoxy-16α,17α-epoxy-12α-tosyloxypregnan-20-one (III). Two distinct synthetic routes were pursued from this intermediate. In one series of reactions, the elimination of the 12α-tosyl group was achieved, albeit in poor yield, by treatment of III in refluxing collidine and thus afforded the 11-dehydro compound IV. Hydrolysis of the carboethoxy group with sodium methoxide in methanol at reflux temperature provided 16α,17α-epoxy-3α-hydroxypregn-11-en-20-one (V). The latter was oxidized with chromium trioxide in pyridine to yield the corresponding 3-carbonyl derivative (VI). By application of the established Julian procedure,[5] the 16α,17α-epoxide was transformed into the bromohydrin and in turn reduced with Raney nickel[8] to yield 17α-hydroxypregn-11-ene-3,20-dione (VII). Further transformations of VII have been carried out and will be discussed in a later part of this paper.

A second series of reactions based on the mixed ester III was investigated as an alternative pathway to a suitable Δ^{11}-17α-hydroxylated intermediate. An excellent yield of 16α,17α-epoxy-3α-hydroxy-12α-tosyloxypregnan-20-one (VIII) was encountered in the sodium methoxide hydrolysis of III. Chromium trioxide in pyridine oxidation, also in excellent yield, afforded the 3-keto derivative (IX). When the low temperature (−60°) bromination[9] of IX was performed, 4β-bromo-16α,17α-epoxy-12α-tosyloxypregnane-3,20-dione (X) was isolated. On being refluxed with collidine on a small scale (100 mg.), X underwent elimination at two sites to give 16α,17α-epoxypregna-4,11-diene-3,20-dione (XI) in poor yield (approximately 10%). Applying the reaction on a larger scale led unexpectedly to the isolation of 16α,17α-epoxy-12α-tosyloxypregn-4-ene-3,20-dione (XII).[10] Subsequent

(1) C. Meystre, E. Tschopp, and A. Wettstein, *Helv. Chim. Acta*, **31**, 1463 (1948).

(2) C. Meystre and A. Wettstein, *ibid.*, **32**, 1978 (1949).

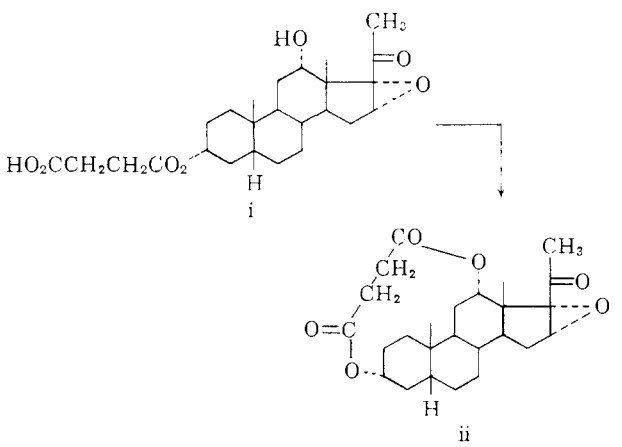
(3) C. Engel, K. Jennings, and G. Just, *J. Am. Chem. Soc.*, **78**, 6153 (1956).

(4) C. Engel, G. Just, and R. Buttery, *Can. J. Chem.*, **39**, 1805 (1961).

(5) P. Julian, C. Cochrane, A. Magnani, and W. Kirpel, *J. Am. Chem. Soc.*, **78**, 3153 (1956).

(6) L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero, and T. T'Ong, *Science*, **74**, 3309 (1952).

(7) It is interesting to note the following transformation. If the esterification at C-12 is performed on 12α-hydroxy-16α,17α-epoxy-3α-hemisuccinoyloxypregnan-20-one[5] (i) there is isolated 16α,17α-epoxy-3α,12α-succinoyldioxypregnan-20-one (ii), m.p. 215–220°; $[\alpha]_D$ +87° (c, 2.145); ν_{max} 2930, 1735, 1450, 1385, 1360, 1275, 1220, 1190, and 1160 mμ; n.m.r.: 2.72 p.p.m. (4 protons), no C(OH protons. *Anal.* Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.38; H, 8.19.

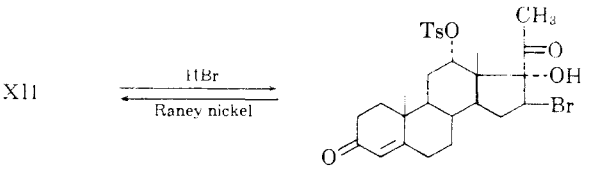


The sodium methoxide hydrolysis of *ii* afforded I and therefore confirmed the macrocyclic dilactone structure.

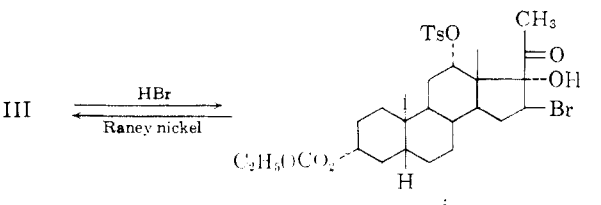
(8) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. Ryden, *J. Am. Chem. Soc.*, **71**, 3574 (1949); **72**, 5145 (1956).

(9) J. Day, U. S. Patent 2,907,776 (Oct. 6, 1959).

(10) The 16α,17α-epoxide XII can be converted into its bromohydrin (iii). Reaction with neutralized Raney nickel, of an activity suitable for the transformation VI → VII and XI → XIV, did not remove the 16β-bromine atom, however did re-establish the epoxide XII.



A similar event was observed when the bromohydrin (iv) prepared from III was treated with Raney nickel.



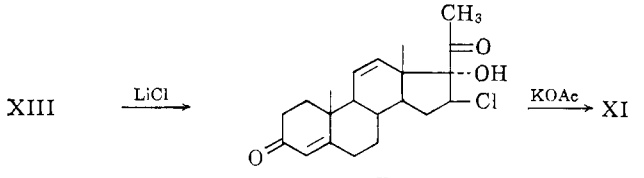
attempts to effect the elimination of the tosylate group from this material were unsuccessful and thus the projected pathway was not investigated further. However, XI could be quite readily prepared from its 4,5-dihydro derivative VI through low temperature bromination followed by collidine–dimethylformamide treatment of the intermediate XIII. By application of the bromohydrin sequence, XI was easily converted to 17α-hydroxypregna-4,11-diene-3,20-dione (XIV). The latter was also obtained from VII through the 4β-bromo intermediate XV.[11]

Investigation of the direct introduction of a hydroxyl group at C-17 through the procedure outlined by Barton and co-workers[12,13] was also pursued. In this series of reactions, pregn-11-ene-3,20-dione (XVI) was first converted to its dimethyl ketal XVII through the selenium dioxide–methanol technique[14] or more conveniently through the use of *p*-toluenesulfonic acid–methanol.[15] When the oxygenation of XVII in the presence of potassium *t*-butoxide was conducted at room temperature employing an excess of oxygen, with subsequent reduction of the intermediate hydroperoxide, only trace amounts of hydroxylated materials were encountered and these results were quite variable. However, employing the reaction conditions more recently described by Amiard and co-workers,[16] which emphasized lower reaction temperature (*ca.* $-$ 7°), the desired 17α-hydroxypregn-11-ene-3,20-dione (VII) could be obtained consistently in a fair yield (58%).[17] Thus direct hydroxylation provided the most convenient route for the preparation of a 17α-hydroxylated substrate. Our attention was now directed toward the synthesis of the title compounds from the advanced intermediate VII.

The acetylation of VII employing acetic anhydride–acetic acid–*p*-toluenesulfonic acid afforded a crude enol diacetate XVIIIa which although isolated, was characterized only by spectral analysis. Careful basic methanolysis afforded the desired 17α-acetoxypregn-11-ene-3,20-dione (XVIII), but other hydrolytic conditions, although very mild, usually converted the enol diacetate into the starting material VII.[18]

(11) Lithium chloride[19] dehydrohalogenation of XIII gave 16β-chloro-17α-hydroxypregna-4,11-diene-3,20-dione (v) m.p. 209–210°; $[\alpha]_D$ +67° (chloroform); λ_{max} 238 mμ (ϵ 14,800); ν_{max} 3300, 3050, 2950, 1735, 1665, 1625, 1355, 1285, 1248, 751, and 718 cm.$^{-1}$. *Anal.* Calcd. for $C_{21}H_{27}ClO_3$: C, 69.50; H, 7.50; Cl, 9.77. Found: C, 69.40; H, 7.73; Cl, 9.98.

The epoxide XI could be obtained from the chlorohydrin (v) on refluxing with potassium acetate in acetone.



v

(12) E. Bailey, J. Elks, and D. Barton, *Proc. Chem. Soc.*, 214 (1960).

(13) E. Bailey, D. Barton, J. Elks, and J. Templeton, *J. Chem. Soc.*, 1578 (1962).

(14) E. Oliveto, C. Gerold, and E. Hershberg, *J. Am. Chem. Soc.*, **76**, 6113 (1954).

(15) M. Janot, X. Lusinchi, and R. Goutarel, *Bull. soc. chim. France*, 2109 (1961).

(16) G. Amiard, M. Legrand, J. Mathieu, R. Heymer, and T. van Thuong, *ibid.*, 2417 (1961).

(17) In the reduction of the intermediate 17α-hydroperoxide employing zinc–acetic acid, the dimethyl ketal protective group was consequently removed.

(18) The relative ease of hydrolysis observed for the 17α-acetate grouping may possibly be ascribed to the absence of a 12α-axial hydrogen in the Δ^{11}-series.

The introduction of the α,β-unsaturated ketone function in ring A presented no difficulty. The low temperature bromination of either XVIII or its enol diacetate XVIIIa afforded an excellent yield of 17α-acetoxy-4β-bromopregn-11-ene-3,20-dione (XIX). Elimination of the elements of hydrogen bromide using lithium chloride in dimethylformamide[19] afforded 17α-acetoxypregna-4,11-diene-3,20-dione (XX). Dehydrogenation of the latter with 2,3-dichloro-5,6-dicyanobenzoquinone[20] in refluxing dioxane gave the corresponding 1,4-dien-3-one (XXI). This material could also be obtained by direct dehydrogenation of the saturated ring A ketone XVIII under similar reaction conditions. Conversion of XX to 17α-acetoxypregna-4,6,11-triene-3,20-dione (XXII) was readily accomplished utilizing the recent procedure of Ringold and Turner[21] wherein XX in the presence of anhydrous hydrogen chloride could be dehydrogenated with the quinone reagent to yield the 4,6-dien-3-one XXII directly. By the same procedure XIV gave 17α-hydroxy pregna-4,6,11-triene-3,20-dione (XXIII). By a two stage sequence, first introduction of the C-6,7-double bond and then the C-1,2-double bond, XX was dehydrogenated to 17α-acetoxypregna-1,4,6,11-tetraene-3,20-dione (XXIV).

The biological assay results for the various Δ^{11}-compounds have been collected in Table I, along with those for 17α-acetoxypregn-4-ene-3,20-dione and 17α-acetoxypregna-1,4,6-triene-3,20-dione.[22] These results indicate that the biological influence of a Δ^{11}-double bond on oral progestational activity is variable.

TABLE I

PROGESTATIONAL RESPONSE–ORAL CLAUBERG ASSAY[23]

Compound	Total dose/rabbit mg.	Average graded endometrial response
17α-Acetoxypregn-4-ene-3,20-dione	2.5	0.75
	5.0	1.5
	10.0	2.3
	20.0	3.0
17α-Acetoxypregna-4,11-diene-3,20-dione (XX)	0.4	0
	1.2	0
	3.6	.75
	7.2	2.2
17α-Acetoxypregna-1,4,11-triene-3,20-dione (XXI)	0.5	0.5
	2.5	3.2
17α-Acetoxypregna-4,6,11-triene-3,20-dione (XXII)	0.25	0
	.75	2
	2.25	2.8
17α-Acetoxypregna-1,4,6,11-tetraene-3,20-dione (XXIV)	0.25	0.3
	.50	.4
	.75	2.4
	1.0	2.2
	2.25	3.0
17α-Acetoxypregna-1,4,6-triene-3,20-dione	0.31	1.5
	.62	3.0

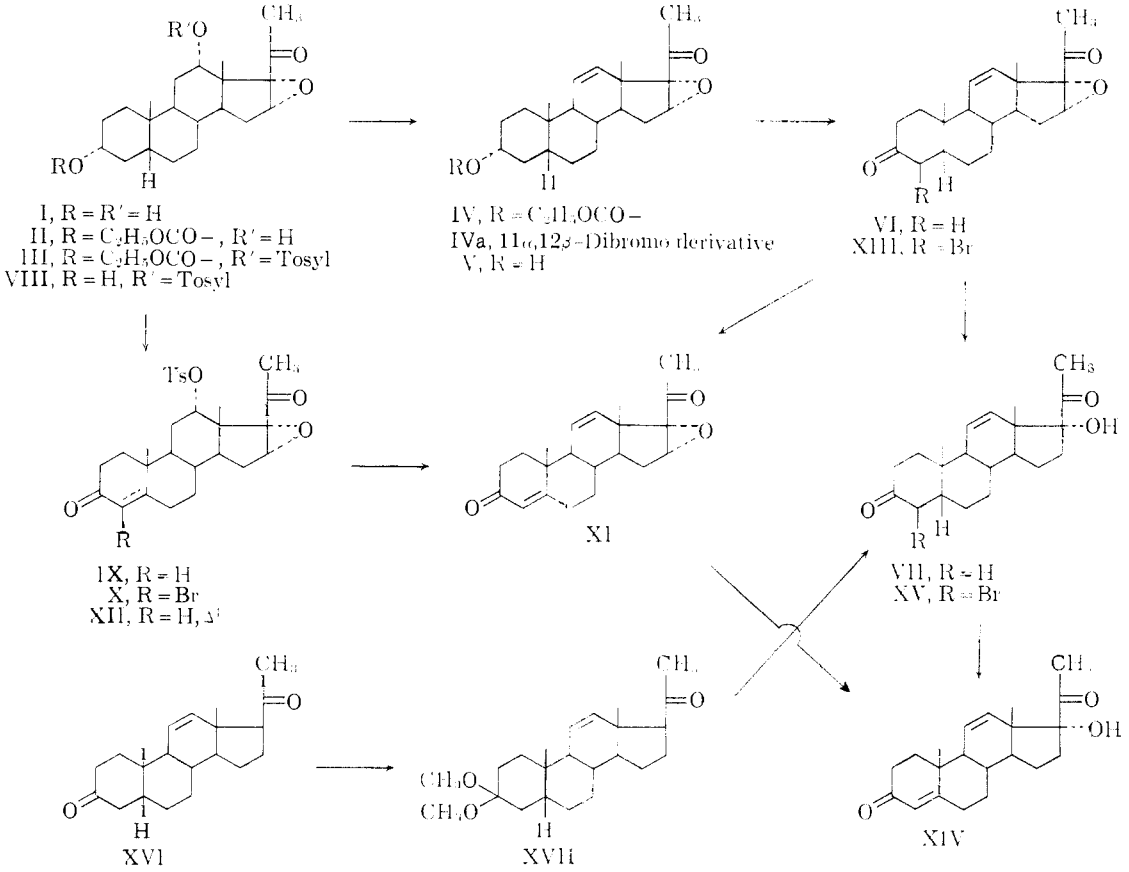
(19) R. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

(20) D. Burn, D. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(21) H. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962); *cf.*, R. Brown and L. Jackman, *J. Chem. Soc.*, 3144 (1960).

(22) J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Org. Chem.*, **28**, 92 (1963).

(23) Assays were performed by Endocrine Laboratories, Madison, Wisconsin.



Flowsheet 1

Experimental[24-28]

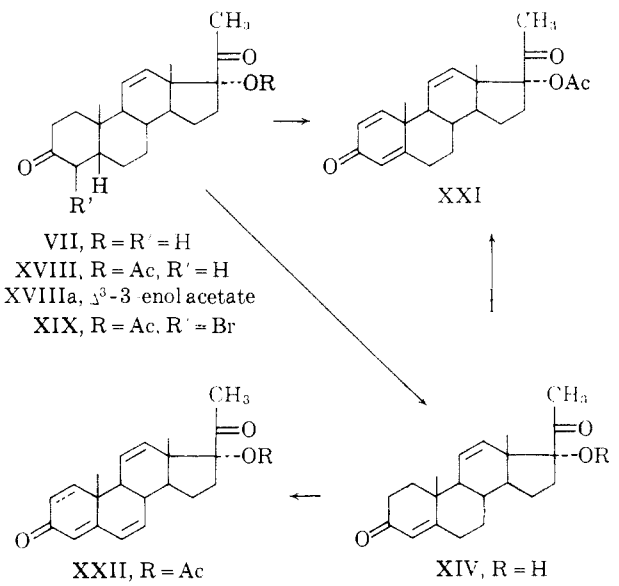
3α-Carbethoxy-16α,17α-epoxy-12α-hydroxypregnan-20-one (II).—A solution of 16α,17α-epoxy-3α,12α-dihydroxypregnan-20-one (I, 0.5 g.) in pyridine (3 ml.) was cooled to 5° and to this was added ethyl chloroformate (0.42 ml.). The reaction mixture was allowed to remain at room temperature for 4 hr., and then poured into 30 ml. of ice water and extracted with ether. The washed and dried extract on evaporation gave a glass which crystallized on the addition of ether, m.p. 189–191°. Recrystallization from acetone-petroleum ether gave 350 mg. of II, m.p. 193–198°; repeated crystallization raised the m.p. to 198–200°; ν_{max}^{KBr} 3500, 2930, 1720, 1705, 1460, 1380, 1275, 1082, 1020 cm.$^{-1}$; $[\alpha]D$ +88° (c 1.0425).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 68.59; H, 8.63. Found: C, 68.60; H, 8.81.

3α-Carbethoxy-16α,17α-epoxy-12α-tosyloxypregnan-20-one (III).—A solution of 3α-carbethoxy-16α,17α-epoxy-12α-hydroxypregnan-20-one (II, 1.4 g.) and *p*-toluenesulfonyl chloride (2.0 g.) in pyridine (10 ml.) was allowed to remain at 37° for 4 days, sealed from atmospheric moisture. The clear yellow solution was poured into water and the resultant tacky white gum which solidified on standing, was collected by filtration. The solid was dissolved in methylene chloride and the solution was washed with excess aqueous saturated sodium bicarbonate and then with water until neutral. Evaporation of the dried solution gave III as solid upon the addition of ether (1.99 g., m.p. 170–172°). In another experiment, purification raised the m.p. to 176–177°; ν_{max}^{KBr} 2950, 1745, 1705, 1450, 1355, 1265, 1255, 1180 cm.$^{-1}$; $[\alpha]D$ +87° (c 1.200).

Anal. Calcd. for $C_{32}H_{42}O_8S$: C, 64.78; H, 7.37; S, 5.58. Found: C, 64.87; H, 7.73; S, 5.53.

3α-Carbethoxy-16α,17α-epoxypregn-11-en-20-one (IV).—A solution of crude 3-carbethoxy-16α,17α-epoxy-12α-tosyloxypregnan-20-one (III, 27.0 g.) in collidine (66 ml.) was refluxed for 24



Flowsheet 2

(24) Melting points were determined with recalibrated National Bureau of Standards Anschütz thermometers in a Hershberg apparatus.

(25) The ultraviolet absorption spectra were determined in methanol, the infrared absorption spectra are for potassium bromide disks, the optical rotations are for chloroform solutions at 25°, and the n.m.r. spectra were recorded on a Varian A-60 spectrometer using solutions of the compounds in deuteriochloroform.

(26) The authors are indebted to William Fulmor and associates for the infrared and ultraviolet absorption, the optical rotation and nuclear magnetic resonance data; to Mr. Charles Pidacks and associates for the partition chromatographic separations; and to Mr. Louis M. Brancone and associates for the elemental analyses.

(27) The thin layer chromatograms were carried out at room temperature on glass plates coated with approximately 0.25 mm. of Silica Gel G. (Merck, Darmstadt) prepared according to E. Stahl, *Chem. Ztg.*, **82**, 323 (1958), and dried for 2 hr. at 70°. Detection of steroids was accomplished with a phosphomolybdic acid (10% in methanol) spray.

(28) Petroleum ether refers to the fraction, b.p. 60–71°.

hr., then cooled and added to 2 *N* hydrochloric acid (7 l.). The mixture was extracted with chloroform and the extract was washed with water until neutral, dried, and evaporated leaving a dark gum. The latter was dissolved in ether (500 ml.) and washed with *N* hydrochloric acid (100 ml.) and then water. Evaporation of the dried solution gave a crude gum which was dissolved in benzene (100 ml.) and added to a column of silica gel (500 g.). Elution with benzene–ether (98:2) gave 12.6 g. of crude IV, which on trituration with methanol afforded 11.3 g., m.p. 147–149.5°. Recrystallization from acetone–petroleum ether gave IV, m.p. 148.5–149.5°; ν_{max} 2930, 1745, 1710, 1455, 1370, 1320, 1360, 1080, 1010 cm.$^{-1}$; $[\alpha]_D$ +87° (*c* 1.130).

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.54; H, 8.56.

Further elution of the column with benzene–ether (9:1) gave 4.6 g. of starting material (III), m.p. 172–175°.

The **11β,12α-dibromo derivative (IVa)**, prepared by bromination at 0° in a methylene chloride solution, had m.p. 178–181°; $[\alpha]_D$ +114° (*c* 0.352); ν_{max} 2960, 1745, 1710, 1470, 1370, 1265, and 995 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}Br_2O_5$: C, 51.27; H, 6.09; Br, 28.42. Found: C, 51.02; H, 6.41; Br, 28.33.

16α,17α-Epoxy-3α-hydroxypregn-11-en-20-one (V).—A solution of 3α-carbethoxy-16α,17α-epoxypregn-11-en-20-one (IV, 1.0 g.) in 0.1 *N* sodium methoxide in methanol (60 ml.) was refluxed for 1 hr. It was then evaporated, and the residue was extracted with methylene chloride. The washed and dried extract was evaporated leaving a semicrystalline solid which was crystallized from acetone-petroleum ether to give V (711 mg.), m.p. 169–170°; ν_{max} 3540, 2940, 1710, 1690, 1370, 1080, 1045 cm.$^{-1}$; $[\alpha]_D$ +86° (*c* 1.824).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.19; H, 9.34.

16α,17α-Epoxypregn-11-ene-3,20-dione (VI).—To an ice-cold solution of 16α,17α-epoxy-3α-hydroxypregn-11-en-20-one (V, 1.7 g.) in pyridine (36 ml.) was added a solution of chromium trioxide (1.62 g.) in cold pyridine (18.7 ml.). The resulting dark brown mixture was stirred for 20 hr. at room temperature, then methanol (about 50 ml.) was added. The solvents were then evaporated to give a gum. Benzene was added and subsequently evaporated to remove the last traces of pyridine. The residue after the addition of water was extracted with methylene chloride and the extract was washed successively with dilute sodium bicarbonate, and water. The dried methylene chloride solution was passed through a column of Magnesol[29] and gave on evaporation the dione VI (1.52 g.), m.p. 143–146°. Crystallization of a sample of this material raised the m.p. to 147–149°; ν_{max} 2930, 1715, 1460, 1375, 1215, 1200 cm.$^{-1}$; $[\alpha]_D$ +94° (*c* 1.002).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.60; H, 8.73.

16α,17α-Epoxy-3α-hydroxy-12α-tosyloxypregnan-20-one (VIII).—A solution of 3α-carbethoxy-16α,17α-epoxy-12α-tosyloxypregnan-20-one (III, 1.0 g.) in 0.1 *N* methanolic sodium methoxide (42 ml.) was refluxed for 0.5 hr. Evaporation *in vacuo* (bath temp. 25°) gave a solid residue which was partitioned between water and methylene chloride. The organic layer was washed with water until neutral, dried and evaporated *in vacuo*. The addition of ether to the residue gave VIII (0.88 g.), m.p. 174–176°. Recrystallization from acetone–petroleum ether did not alter the melting point; $[\alpha]_D$ +75° (*c* 1.051); ν_{max} 3470, 2940, 1695, 1605, 1365, 1355, 1175, 918 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{38}O_6S$: C, 66.91; H, 7.62; S, 6.38. Found, C, 66.57; H, 7.69; S, 6.60.

16α,17α-Epoxy-12α-tosyloxypregnane-3,20-dione (IX).—To a cooled (0–5°) solution of chromium trioxide (1.28 g.) in pyridine (15 ml.) there was added a cold solution of 16α,17α-epoxy-3α-hydroxy-12α-tosyloxypregnan-20-one (VIII, 2.0 g.). The mixture was allowed to stand for 15 min. at 0° and then 3 hr. at room temperature when methanol (10 ml.) was cautiously added, and the mixture was evaporated *in vacuo*. Benzene was added and the evaporation was repeated several times until the residual pyridine was removed. The residue was dissolved in methylene chloride and washed with water. The dried extract was passed through a column of Magnesol[29] to remove the dark color and evaporated to afford crystalline IX (1.8 g.). A sample was recrystallized from acetone–petroleum ether and the m.p. remained unchanged at 206–207°; $[\alpha]_D$ +75° (*c* 0.907); ν_{max} 2950, 1710, 1605, 1335, 1175, 918 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{36}O_6S$: C, 67.18; H, 7.25; S, 6.39. Found: C, 67.35; H, 7.45; S, 6.59.

4β-Bromo-16α,17α-epoxy-12α-tosyloxypregnane-3,20-dione (X).—To a cold (−60°) solution of 16α,17α-epoxy-12α-tosyloxypregnane-3,20-dione (IX, 0.4 g.) in chloroform (8.0 ml.) and acetic acid (0.9 ml.) there was added with stirring over a period of 45 min. bromine (0.041 ml.) in 32% hydrogen bromide–acetic acid (0.196 ml.), and acetic acid (0.6 ml.). The solution was then kept at −60° for 1 hr. when a solution of sodium acetate (131 mg.) in water (1.1 ml.) was added. The mixture was stirred at room temperature for 0.5 hr. when chloroform was removed *in vacuo*, and water was added. The residual mixture was cooled in an ice bath for 1 hr., and the white solid which formed was collected and dried. Recrystallization from acetone–petroleum ether gave X (409 mg.), m.p. 189–191° dec.; ν_{max} 2946, 1738, 1708, 1608, 1355, 1178 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{35}BrO_6S$: C, 58.03; H, 6.08; Br, 13.79; S, 5.53. Found: C, 57.28, 57.35; H, 6.15, 6.15; Br, 13.61; S, 5.76.

16α,17α-Epoxy-12α-tosyloxypregn-4-ene-3,20-dione (XII).—A solution of X (1.25 g.) in collidine (30 ml.) was refluxed for 6 hr., cooled, and the excess collidine was removed *in vacuo* (bath temp. 45–50°). The residue was dissolved in methylene chloride (50 ml.) and washed with *N* hydrochloric acid (50 ml.) and then twice with water. After being dried the solvent was removed *in vacuo;* an infrared analysis of the crude residue indicated the tosyl group was still present but that dehydrohalogenation had taken place as shown by the conjugated ketone absorption. A solution of this crude residue in methylene chloride was filtered through a pad of Magnesol[29] to remove color. Evaporation of the methylene chloride *in vacuo* gave a light yellow crystalline solid (XII) (0.86 g.), m.p. 195–200°. A portion of this material, was crystallized from acetone–petroleum ether, m.p. 203–204°; $[\alpha]_D$ +112° (*c* 0.790); λ_{max} 227 mμ (ϵ 23,400), 238 mμ (ϵ 15,500); ν_{max} 2960, 1710, 1665, 1620, 1605, 1350, 1185, 1175, 912 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{34}O_6S$: C, 67.45; H, 6.87; S, 6.42. Found: C, 67.35, 67.58; H, 6.99, 7.35; S, 6.58.

16α,17α-Epoxypregna-4,11-diene-3,20-dione (XI). A.—A solution of 4β-bromo-16α,17α-epoxy-12α-tosyloxypregnane-3,20-dione (X, 0.1 g.) in collidine (1 ml.) was refluxed for 6 hr., and evaporated *in vacuo*. The residue was dissolved in methylene chloride and passed through a small column of Magnesol.[29] The crude residue after evaporation was triturated with cold ether to give XI (15 mg.), m.p. 185-190°. This material was identical with that obtained in procedure B.

B.—To a cold (−60°) solution of 16α,17α-epoxypregn-11-ene-3,20-dione (VI, 0.38 g.) in methylene chloride (5.5 ml.), chloroform (5.5 ml.), and acetic acid (1.35 ml.) there was added over a period of 20 min., with stirring, bromine (0.038 ml.) in 30% hydrogen bromide–acetic acid (0.29 ml.) and acetic acid (0.91 ml.). After 1 hr. at −60° a solution of sodium acetate (0.19 g.) in water (20 ml.) was added and the mixture was stirred at room temperature for 1 hr. The mixture was evaporated *in vacuo* (bath temp., 30°), and the residue was treated with water to give a gum which partially crystallized. Identification of this material as 4β-bromo-16α,17α-epoxypregn-11-ene-3,20-dione (XIII) was based on an infrared analysis of the carbonyl region which exhibited peaks at 1690 and 1720 cm.$^{-1}$. This crude product (430 mg.) was dissolved in dimethylformamide (2.5 ml.) and collidine (1.0 ml.) and the solution was refluxed for 2.5 hr. After dilution with methylene chloride, the solution was washed with water, *N* hydrochloric acid, and then water and sodium bicarbonate. The dried methylene chloride solution was passed through Magnesol[29] to give XI (0.30 g.), m.p. 195–197°. A recrystallization from ether gave white crystals, m.p. 203–205°; λ_{max} 238 mμ (ϵ 15,000); ν_{max} 3040, 2950, 1712, 1678, 1625, 1380, 752, 722 cm.$^{-1}$; $[\alpha]_D$ +181° (*c* 0.939).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 76.83; H, 7.84.

3,3-Dimethoxypregn-11-en-20-one (XVII). A.—A solution of pregn-11-ene-3,20-dione[30] (XVI, 18.0 g.) and selenium dioxide (18.0 g.) in methanol (500 ml.) was allowed to stand at room temperature. After 0.5 hr. crystals began to separate. These were collected by filtration after 24 hr. and were washed with methanol

(29) Magnesol® (Food Machinery Chemical Corp.), a hydrous magnesium silicate.

(30) "Elseviers Encyclopedia of Organic Chemistry," Vol. 14 Supplement, Springer-Verlag, Berlin, 1959, pp. 2793s–2794s.

to give the ketal XVII (10.7 g.), m.p. 135–137°. The filtrate was concentrated *in vacuo* (bath temp. 30°), and a solution of potassium hydroxide (18 g.) in methanol (360 ml.) was added. The solution was poured into water and the white solid was collected. Crystallization of this material from methanol with a few drops of pyridine added gave additional XVII (5.7 g.), m.p. 136–138°.

B.—A mixture of XVI (10.0 g.) and *p*-toluenesulfonic acid (0.5 g.) in methanol (200 ml.) was refluxed for 0.5 hr. The reaction was terminated by the dropwise addition of *N* methanolic sodium methoxide until the mixture became basic (approx. pH 9–10), and the solution was then concentrated *in vacuo* to about ½ of its original volume. After cooling overnight at 5°, the crystals which had separated were collected and washed with a small amount of cold methanol; 10.2 g., m.p. 131–132°; repeated recrystallization from ether gave m.p. 134–136°; $[\alpha]D$ +92° (*c* 0.975); ν_{max} 3040, 2930, 1710, 1458, 1365, 1100, 1055, 723 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.00, 76.35; H, 10.03, 10.04.

17α-Hydroxypregn-11-ene-3,20-dione (VII). A.—To a cooled (18°) solution of 16α,17α-epoxypregn-11-ene-3,20-dione (VI, 1.2 g.) and acetic acid (1.5 ml.) in methylene chloride (15 ml.) there was added dropwise with stirring over a period of 20 min. 32% hydrogen bromide–acetic acid (2.4 ml.). After an additional 30 min. at 15–20° the reaction mixture was poured into ice water and was extracted with methylene chloride. The extract was washed with water, dried, and evaporated (bath temp. 20–25°). To a solution of the crude residue in methanol (40 ml.) containing water (1.6 ml.), Raney nickel (8 g.) was added, and the mixture was refluxed with stirring for 4 hr. The nickel was removed by filtration from the hot mixture and the filtrate was evaporated. The addition of ether to the gummy residue gave crystalline VII (0.71 g.), m.p. 196–200°. An analytical sample of VII was obtained from methylene chloride–petroleum ether, m.p. 204–206°; $[\alpha]D$ +167° (*c* 1.019); ν_{max} 3010, 2925, 1715, 1345, 718 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.34; H, 9.35.

B.—To a solution of 3,3-dimethoxypregn-11-en-20-one (XVII, 2.0 g.) there was added a solution of ~*N* potassium *t*-butoxide in *t*-butyl alcohol (28 ml.) and the reaction mixture was cooled to approximately −7° in an ice–salt bath. The reaction flask was attached to a gas measuring burette and the system evacuated and filled with oxygen. With magnetic stirring of the reaction mixture the oxygen uptake was measured and when a 10% excess (146 ml. total) of oxygen was consumed the solution was acidified with acetic acid (28 ml.). Zinc dust (4.0 g.) was added with brisk agitation and the mixture was stirred for 2 hr. at room temperature. The zinc was removed by filtration and washed with *t*-butyl alcohol. The combined filtrates were evaporated (bath temp. 40°) leaving a thick oil. The addition of water caused precipitation of a solid which was collected and dried (1.6 g.). Crystallization from acetone–petroleum ether gave VII (1.1 g.), m.p. 190–200°. An infrared analysis showed this material to be identical with the material obtained by procedure A.

4β-Bromo-17α-hydroxypregn-11-ene-3,20-dione (XV).—To a mixture of methylene chloride (7 ml.), chloroform (7 ml.) and acetic acid (1.75 ml.) was added VII (0.5 g.) and the solution was cooled to −50 to −60° while stirring. To this was added dropwise over 1 hr. a solution of bromine (0.079 ml.) in 32% hydrogen bromide–acetic acid (0.38 ml.). The mixture was then stirred for 1 hr. at this temperature, when a solution of sodium acetate (0.25 g.) in water (2.0 ml.) was added, and the stirring was continued for an additional hour at room temperature. After the more volatile organic solvents were removed *in vacuo* (bath temp. 30–35°), water was added to the residue to yield a white gum which solidified on standing. The solid was recrystallized from acetone–petroleum ether to give XV (0.31 g.), m.p. 170–172° dec. For analysis, a methylene chloride solution of this material was passed through a filter pad of Magnesol[29] and the resultant solid obtained on evaporation of the solvent was recrystallized from the above solvent pair to give m.p. 175–176° dec.; $[\alpha]D$ +37° (*c* 1.450); ν_{max} 3490, 2950, 1725, 1710, 1450, 1355, 1185, 712 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}BrO_4$ (409.36): C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.30; H, 7.03; Br, 19.00, 18.72.

17α-Hydroxypregna-4,11-diene-3,20-dione (XIV). A.—In an atmosphere of nitrogen a solution of crude 4β-bromo-17α-hydroxypregn-11-ene-3,20-dione (XV, 2.4 g.) and lithium chloride (4.5 g.) in dry dimethylformamide (80 ml.) was heated at 105–110° for 3 hr. The solvent was removed *in vacuo* and the residue was treated with methylene chloride. The extract was washed with excess sodium bicarbonate solution and then water. Evaporation *in vacuo* gave a crude solid (2.4 g.) which on recrystallization from benzene provided XIV (1.3 g.), m.p. 202–206°. A portion (300 mg.) of this material was chromatographed on Florisil.[30] The fraction eluted with 8% acetone–petroleum ether was crystallized to constant m.p. 213–215°; $[\alpha]D$ +113° (*c* 1.173); λ_{max}^{EtOH} 238 mμ (ε 16,800); ν_{max} 3480, 3020, 2940, 1700, 1665, 1615, 1345, 1233, 1190, 716 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.78; H, 8.55.

B.—A solution of 16α,17α-epoxypregna-4,11-diene-3,20-dione (XI, 266 mg.) in methylene chloride (5 ml.) and acetic acid (0.5 ml.) was treated with 30% hydrogen bromide–acetic acid (0.4 ml.), and the mixture was allowed to stand at room temperature for 0.5 hr. The product was extracted with methylene chloride, which on evaporation yielded the crude bromohydrin. To a suspension of the latter in methanol (10 ml.) and water (0.4 ml.) was added Raney nickel (2.0 g.) and the mixture was refluxed for 4 hr. Evaporation of the filtered reaction mixture yielded XIV. After several crystallizations from acetone–petroleum ether, there was obtained 113 mg., m.p. 211–213°, which was identical with the product obtained by procedure A.

17α-Acetoxypregn-11-ene-3,20-dione (XVIII).—To a solution of acetic acid (30 ml.) and acetic anhydride (10 ml.) there was added 17α-hydroxypregn-11-ene-3,20-dione (VII, 1.0 g.), nitrogen was bubbled through this solution, and *p*-toluenesulfonic acid (1.0 g.) was added. After 18 hr. sealed under a nitrogen atmosphere, the reaction mixture was poured into ice water and extracted with methylene chloride. Evaporation of the washed and dried extract gave a gum which was dissolved in methanol (10 ml.), and *N* sodium methoxide in methanol was added until the pH was about 9. The solution was refluxed for 0.5 hr. and cooled. A thin layer chromatograph showed predominantly one compound less polar than starting material. Neutralization with acetic acid and evaporation gave a residue which crystallized from acetone–petroleum ether to give XVIII (564 mg.), m.p. 180–183°. Crystallization of a sample from ether gave m.p. 185–187°; $[\alpha]D$ +50° (*c* 1.026); ν_{max} 3050, 2970, 1735, 1385, 1265, 1245, 716 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.29; H, 8.93.

In another run the material which separated upon the addition of ice water to the reaction mixture was collected and dried. Its infrared spectrum showed this material to be most likely 3,17α-diacetoxypregna-3,11-dien-20-one (XVIIIa); ν_{max} 1740, and 1210 cm.$^{-1}$.

17α-Acetoxy-4β-bromopregn-11-ene-3,20-dione (XIX). A. A solution (cooled to −50°) of 17α-acetoxypregn-11-ene-3,20-dione (XVIII, 372 mg.) in methylene chloride (4.5 ml.), chloroform (4.5 ml.), and acetic acid (1.1 ml.) was treated (dropwise addition with stirring) with a solution of bromine (160 mg.) in 30% hydrogen bromide–acetic acid (0.25 ml.) and acetic acid (0.75 ml.). The reaction mixture was stirred for a total of 2 hr. at −50° when a solution of sodium acetate (164 mg.) and water (1.4 ml.) was added. The mixture was stirred at room temperature for 0.5 hr., and the volatile solvents were removed *in vacuo* (bath temp. 40°). Water (20 ml.) was added and a gummy precipitate formed which solidified on standing overnight at 5°. The solid was collected, dissolved in methylene chloride, and filtered through a pad of Magnesol.[29] Evaporation of the filtrate gave white crystals of XIX (367 mg.), m.p. 174–175°. Its infrared spectrum was identical with that of an analytical sample obtained in procedure B below.

B.—To a cold (−50°) solution of crude 3,17α-diacetoxypregna-3,11-diene-20-one (XVIIIa, 414 mg.) in methylene chloride (10 ml.) and chloroform (10 ml.) there was added dropwise with stirring over 5 min. a solution of bromine (160 mg.) in chloroform (5 ml.). A solution of sodium acetate (164 mg.) in water (3.0 ml.) was added to the reaction mixture which was now allowed to come to room temperature. After 0.5 hr. at room temperature, the mixture was evaporated *in vacuo* (bath temp. 25°), and water was added to the residue. The resulting gum was dissolved in methylene chloride and filtered through Magnesol.[29] The filtrate was evaporated leaving a gum which crystallized on trituration

(31) Florisil® (Floridin Corporation), a synthetic magnesium silicate adsorbent.

with ether. In this manner there was obtained XIX (81 mg.), m.p. 173–174° dec. Crystallization from ether raised the m.p. to 178–179° dec.; $[\alpha]_D$ +58° (*c* 0.950); ν_{max} 2940, 1735, 1370, 1265, 1250, 725 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}BrO_4$: C, 61.19; H, 6.93; Br, 17.72. Found: C, 60.92; H, 7.08; Br, 17.89.

17α-Acetoxypregna-4,11-diene-3,20-dione (XX). A.—Under an atmosphere of nitrogen, crude 4β-bromo-17α-acetoxypregn-11-ene-3,20-dione (XIX, 1.5 g.) and lithium chloride (2.8 g.) were heated in dry dimethylformamide (50 ml.) for 3 hr. at 100–110°. The solvent was removed *in vacuo* and methylene chloride was added. The extract was washed with a saturated sodium bicarbonate solution and water, dried, and evaporated to give a yellow solid which was dissolved in benzene and added to a column of Florisil[31] (50 g.). Elution with 6% acetone–petroleum ether gave 3 major fractions which were grouped according to the results obtained by thin layer chromatographic analysis. Fraction A contained product contaminated with a less polar material which gave on crystallization from acetone–petroleum ether XX (107 mg.), m.p. 210–211°. Fraction B was essentially pure XX, m.p. 216–219°. Fraction C contained XX with a more polar substance and had a low m.p. Crystallization of a sample of fraction B from ether gave crystals, m.p. 220–222°; $[\alpha]_D$ +123° (*c* 1.160); λ_{max} 238 mμ (ϵ 17,200); ν_{max} 3010, 2930, 1730, 1660, 1620, 1445, 1360, 1265, 1250, 1072, 718 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.50; H, 8.30.

B.—17α-Hydroxypregna-4,11-diene-3,20-dione (XIV, 0.83 g.) was dissolved in a mixture of acetic acid (25 ml.) and acetic anhydride (8 ml.). Nitrogen was bubbled into this solution for a few min. and then *p*-toluenesulfonic acid (0.83 g.) was added and the reaction mixture was sealed for 18 hr. A yellow solid separated when the reaction solution was poured into ice water and the precipitate was collected. A methylene chloride solution of the latter was washed with water, dried, and evaporated. The resulting gum was dissolved in methanol (10 ml.) and a *N* sodium methoxide in methanol solution was added dropwise until the pH was 9–10. The solution was then refluxed for 15 min., neutralized with acetic acid, and evaporated to provide XX (552 mg.), m.p. 208–210°, whose infrared analysis was in agreement with material obtained from procedure A above.

17α-Acetoxypregna-1,4,11-triene-3,20-dione (XXI). A.—A solution of crude 17α-acetoxypregn-11-ene-3,20-dione (XVIII, 585 mg.) and 2,3-dichloro-5,6-dicyanobenzoquinone (600 mg.) in dioxane (5 ml.) was refluxed for 18 hr. The solvent was removed *in vacuo* and the residue was suspended in benzene and filtered to remove the hydroquinone. The filtrate was added to a column of Florisil[31] (30 g.) suspended in petroleum ether and by a linear gradient elution pattern (0–8% dioxane–petroleum ether) with 10-ml. fractions on an automatic collector there was obtained 28 mg. of starting material. A second linear gradient elution pattern (8–20% dioxane–petroleum ether) gave, by ultraviolet absorption analysis of the fractions, in the following order (increasing polarity) 17α-acetoxypregna-4,11-diene-3,20-dione (XX) 17α-acetoxypregna-4,6,11-triene-3,20-dione (XXII), 17α-acetoxypregna-1,4,11-triene-3,20-dione (XXI), and 17α-acetoxypregna-1,4,6,11-tetraene-3,20-dione (XXIV). However, only XXI could be separated and was further purified by partition chromatography on Celite[32] (heptane–methanol). Crystallization of the material thus obtained from acetone–petroleum ether gave 28 mg., m.p. 204–206°; $[\alpha]_D$ +60° (*c* 1.157); λ_{max} 246 mμ (ϵ 15,100); ν_{max} 3050, 2970, 1745, 1670, 1630, 1610, 1265, 1250, 890, 719 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.77; H, 7.70.

B.—A solution of 17α-acetoxypregna-4,11-diene-3,20-dione (XX, 101 mg.) and 2,3-dichloro-5,6-dicyanobenzoquinone (72 mg.) in dioxane (5.0 ml.) was refluxed for 18 hr. The hydroquinone which separated on cooling was removed by filtration, and the filtrate was evaporated. Chromatography of the residue on Florisil[31] (10 g.) with 7% acetone–petroleum ether gave the $\Delta^{1,4}$-3-one (XXI, 36 mg.). Repeated crystallization raised the m.p. to 201–202°. The product was identified with material obtained in procedure A.

17α-Acetoxypregna-4,6,11-triene-3,20-dione (XXII).—A stream of dry hydrogen chloride was passed into a solution of 17α-acetoxypregna-4,11-diene-3,20-dione (XX, 150 mg.) and 2,3-dichloro-5,6-dicyanobenzoquinone (101 mg.) in dioxane (7.5 ml.) for 1 min. After 0.5 hr. at room temperature, crystals of hydroquinone separated and these were removed by filtration. The filtrate was diluted with methylene chloride, and the extract was washed with excess sodium bicarbonate solution, dried, and evaporated to give a yellow residue of XXII (105 mg.), m.p. 190–192°. Since it was impossible to remove the color by repeated crystallization, purification of the sample was accomplished by chromatography on Florisil.[31] Elution with 5% acetone–petroleum ether gave a material which on crystallization from ether gave colorless needles, m.p. 205–207°; $[\alpha]_D$ +17° (*c* 0.500); λ_{max} 285 mμ (ϵ 23,500); ν_{max} 3050, 2960, 1742, 1715, 1665, 1615, 1585, 1258, 1242, 1230, 718 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.83; H, 7.88.

17α-Acetoxypregna-1,4,6,11-tetraene-3,20-dione (XXIV).—Into a solution of 17α-acetoxypregn-4,11-diene-3,20-dione (XX, 300 mg.) and 2,3-dichloro-5,6-dicyanobenzoquinone (202 mg.) in dioxane (10 ml.) was passed a stream of dry hydrogen chloride for about 1 min. After 75 min. at room temperature the mixture was evaporated *in vacuo* (bath temperature 30°), and benzene was added and evaporated *in vacuo* 3 times to remove residual hydrogen chloride. Methylene chloride was added, and hydroquinone was removed by filtration. The filtrate was evaporated, the residue was again dissolved in dioxane (7.0 ml.), and 2,3-dichloro-5,6-dicyanobenzoquinone (202 mg.) was added. The solution was refluxed for 18 hr. and the hydroquinone was removed by filtration and the filtrate was evaporated to yield a gum. This was dissolved in benzene and added to a column of Florisil[31] (15 g.). Elution with 6% acetone–petroleum ether gave ultraviolet absorbing material. Cuts (50 ml.) were taken and analyzed by thin layer chromatography, which revealed essentially one spot. They were therefore combined and evaporated to give a glass (177 mg.). Crystallization from acetone–petroleum ether gave XXIV (130 mg.), m.p. 175–177°; crystallization from ether did not alter the melting point; $[\alpha]_D$ +26° (*c* 0.704); λ_{max} 225 mμ (ϵ 15,900), 252 mμ (ϵ 14,900), 300 mμ (ϵ 13,600); ν_{max} 3000, 2940, 1730, 1660, 1630, 1605, 1585, 1375, 1355, 1260, 1245, 718 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.20; H, 7.52.

17α-Hydroxypregna-4,6,11-triene-3,20-dione (XXIII).—Dry hydrogen chloride was bubbled for approximately 1 min. into a solution of 17α-hydroxypregna-4,11-diene-3,20-dione (XIV, 133 mg.) and 2,3-dichloro-5,6-dicyanobenzoquinone (101 mg.) in dioxane (7.5 ml.). The flask was stoppered and after 30 min. the solid which had separated was removed by filtration. The filtrate was diluted with methylene chloride and the extract was washed with a sodium bicarbonate solution and water, dried, and evaporated to give XXIII (120 mg.), m.p. 200–205°. An analytical sample (59 mg.), m.p. 212–218° dec., was obtained from a Florisil[31] column by elution with 8% acetone-petroleum ether. Crystallization from ether raised the melting point to 222–224° dec., $[\alpha]_D$ +55° (*c* 0.491); λ_{max} 285 mμ (ϵ 20,900); ν_{max} 3410, 3050, 2960, 1708, 1645, 1610, 1580, 1350, 1225, 1185, 720 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 76.64, 77.27; H, 8.22, 8.39.

(32) Celite® (Johns-Manville Company), a diatomaceous silica product.