product does not show melting up to 310° and was characterized as follows: $\epsilon_{3190}^{CH_3OH}$ 21,000; μ^{KBr} 2.90, 3.12, 5.80, 6.10, 6.25 and 6.47.

Anal. Calcd. for $C_{21}H_{28}O_5$ (360.43): C, 69.97; H, 7.83. Found: C, 69.91; H, 7.54.

CHICAGO 80, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

7-Keto Steroids. II.[1] Steroidal 3β-Hydroxy-Δ⁵-7-ones and Δ³,⁵-7-Ones

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A series of steroidal 3β-hydroxy-Δ⁵-7-ones and Δ³,⁵-7-ones were prepared as potential anti-cortisone agents. Biological evaluation showed 7-ketopregnenolone, 7-keto-21-acetoxypregnenolone 3-acetate and pregna-3,5-diene-7,20-dione to have a mild order of activity. The 3β-hydroxy (or acetoxy)-Δ⁵-7-ones were prepared by oxidation in the allylic (C-7) position with either *t*-butyl chromate or sodium chromate. The Δ³,⁵-diene-7-ones were prepared by boiling the 3β-acyloxy-Δ⁵-7-ones one hour in glacial acetic acid with 0.5% (w./v.) of *p*-toluenesulfonic acid.

In a concurrent publication[1] from this Laboratory, there was described the synthesis of a series of steroidal 3-hydroxy-3,5-diene-7-ones which were biologically evaluated as anti-cortisone agents. That study and the currently reported investigation were instituted upon the finding by our Division of Biological Research early in 1953 that 7-ketocholesterol possesses striking anti-cortisone properties in experimental animals. Accordingly we studied two additional series of 7-keto steroids, namely, the 3β-hydroxy-Δ⁵-7-ones and the Δ³,⁵-7-ones, which are described in this paper.

At the time this study was initiated the only steroidal 3-hydroxy-7-ones or 3β-hydroxy-Δ⁵-7-ones in the chemical literature, other than cholic and chenodesoxycholic acid derivatives, were those with C-17 side chains of the following types: cholesterol[2a,b] stigmasterol,[2c] sapogenin; as well as with these C-17 substituents: 17-keto,[3] 17β-acyloxy[3a,b,4] and 17β-hydroxy.[3a,b,4] There also had been reported 7-ketopregnenolone as the 3β-acetate,[3a,d,5] but not as the 3-ol and more recently 3β,20β-diacetoxypregn-5-ene-7-one.[6]

In planning the synthesis of a series of 3β-hydroxy-Δ⁵-7-one steroids, embracing C-17 side chains of the 20,21-ketol and 17α-21-dihydroxy-20-ketone types, it was essential, prior to the oxidative introduction of the 7-carbonyl, to protect the 3-hydroxy function with a blocker that could be removed under conditions comparable to the mild conditions required for safe cleavage of the protective esters in these alkali- and acid-sensitive side chains at C-17. Pregnenolone acetate was oxidized to the 7-keto derivative (III)[3a,d,5] by the *t*-butyl chromate procedure[4b,7] and also by the sodium chromate method.[8] In a like manner were made the following: 3β,17α-diacetoxypregn-5-ene-7,20-dione (IV), 3β,21-diacetoxypregn-5-ene-7,20-dione (IXa), 3β-ethoxycarbonyloxy-21-acetoxypregn-5-ene-7,20-dione (IXb), 3β-trifluoroacetoxy-21-acetoxypregn-5-ene-7,20-dione (IXc), 3β,17α,21-triacetoxypregn-5-ene-7,20-dione (Xa), 3β-ethoxycarbonyloxy-17α,21-diacetoxypregn-5-ene-7,20-dione (Xb), 3β-acetoxy-17β-trifluoroacetoxy-17-methylandrost-5-en-7-one (XV) and 3β-acetoxy-17β-trifluoroacetoxy-17-ethylandrost-5-en-7-one (XVI).

The esterc leavage of these 3β,17α-, 3β,21- and 3β,17β(17α-alkyl)-diesters and the 3β,17α,21-triesters required carefully controlled conditions. 7-Ketopregnenolone acetate, on standing 24 hr. at 25°, or boiling 30 minutes, in 0.5 *N* alkali or 0.5 *N* mineral acid, undergoes dehydration at C-3 to produce pregna-3,5-diene-7,20-dione.[3a] Accordingly III, IV, XV and XVI were saponified by the action of 0.2 *N* alkali for 2.5 to 3 hr. at room temperatures. Titrations of aliquots from the saponification of III indicated 95% completion in 2.5 hr. Despite these precautions, after crystallization had provided a 75% yield of the 3β-ol (V), the mother liquors furnished a 10% yield of pregna-3,5-diene-7,20-dione. By these means were prepared 7-ketopregnenolone (3β-hydroxypregn-5-ene-7,20-dione) (V), 3β,17α-dihydroxypregn-5-ene-7,20-dione (VI), 7-keto-17α-methylandrostenediol (3β,17-dihydroxy-17α-methylandrost-5-en-7-one) (XVIIb) and 7-keto-17α-ethylandrostenediol (3β,17-dihydroxy-17α-ethylandrost-5-en-7-one) (XVIIIb).

XVIIb and XVIIIb were selectively monoacetylated to form, respectively, 3β-acetoxy-17-hydroxy-17α-methylandrost-5-en-7-one (XVIIa) and 3β-acetoxy-17-hydroxy-17α-ethylandrost-5-en-7-one (XVIIIa).

Employing the fast base-catalyzed exchange conditions of Huang-Minlon,[9] using 1.05 times theory of potassium hydroxide at 0.05 *N* concentration for 5 to 10 minutes at 25°, the following were completely de-esterified: IXb and IXc to give 3β,21-dihydroxypregn-5-ene-7,20-dione (XIb) and Xb to provide 3β,17α-21-trihydroxypregn-5-ene-7,20-dione (XII). XIb was monoacetylated to 21-acetoxy-3β-hydroxypregn-5-ene-7,20-dione (XIa).

(1) Paper I, C. W. Marshall, R. E. Ray, Ivar Laos and Byron Riegel, THIS JOURNAL, **79**, 6303 (1957).

(2) (a) J. Mauthner and W. Suida, *Monatsh.*, **17**, 579 (1896); (b) A. Windaus, H. Lettré and Fr. Schenck, *Ann.*, **520**, 98 (1935); (c) O. Linsert, *Z. physiol. Chem.*, **241**, 125 (1930).

(3) (a) A. Butenandt and W. Logemann, U. S. Patent 2,170,124 (1939); (b) A. Butenandt, E. Hausemann and J. Paland, *Ber.*, **71**, 1316 (1938); (c) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **31**, 629 (1948); (d) W. Logemann and P. Giraldi, *Gazz. chim. ital.*, **81**, 548 (1951).

(4) (a) A. Ogata and I. Kawakami, *J. Pharm. Soc. Japan*, **58**, 94 (1938); (b) K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **35**, 281 (1952).

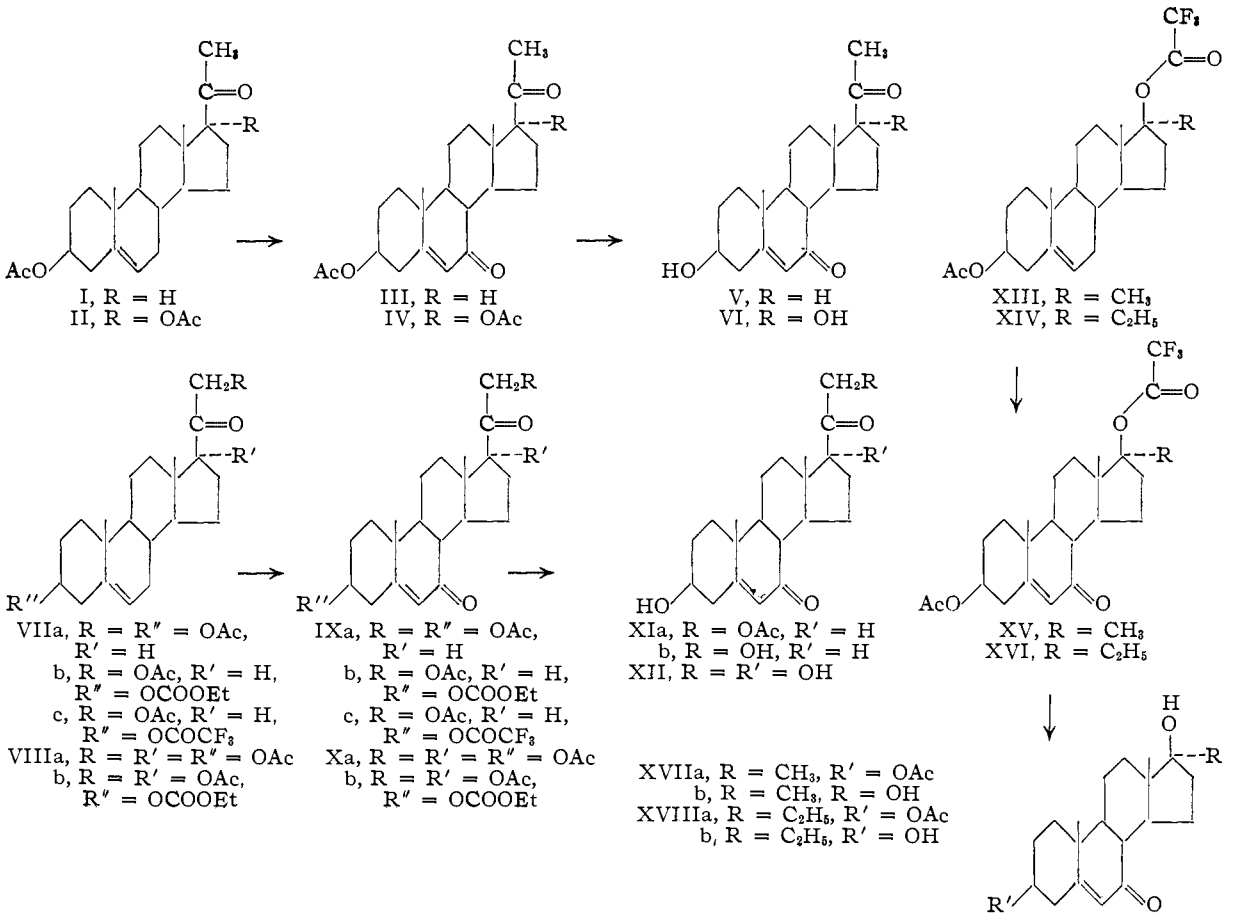
(5) W. Klyne, *J. Chem. Soc.*, 3449 (1951).

(6) J. Romo, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, 1413 (1952).

(7) R. V. Oppenauer and H. Oberrauch, *Anales Asoc. Quim. Argentine*, **37**, 246 (1949).

(8) W. C. Meuly, U. S. Patent 2,505,646 (1950).

(9) Huang-Minlon, U. S. Patent 2,634,277 (1953).



The splitting out of a 3β-acyloxy or 3β-hydroxy group from the corresponding Δ⁵-7-one to extend conjugation had been reported for cholesta-3,5-dien-7-one,[1a,10] androsta-3,5-diene-7,17-dione,[3a,c] 17-acetoxyandrosta-3,5-dien-7-one and its 17-ol.[3a,b,4a] Pregna-3,5-diene-7,20-dione (XIX) has never been described in the literature, but its preparation was implied in the Butenandt and Logemann patent.[3a] We wish to report herein its preparation by the mineral acid catalyzed method and its characterization. However, for the preparation of the steroid 3,5-dien-7-ones, with ketol and dihydroxyacetone side chains at C-17, the classical methods of dilute mineral acid or dilute alkali treatment were too drastic. A procedure was devised that proved successful, namely, boiling 1 hr. in glacial acetic acid in the presence of 0.5% (w./v.) of *p*-toluenesulfonic acid. By such means IV, IXa and Xa were converted to, respectively, 17α-acetoxypregna-3,5-diene-7,20-dione (XX), 21-acetoxypregna-3,5-diene-7,20-dione (XXI) and 17α, 21-diacetoxypregna-3,5-diene-7,20-dione (XXII).

Ester cleavage of XXII proceeded smoothly by the 10-minute base-catalyzed exchange method of Huang-Minlon[9] to furnish 17α,21-dihydroxypregna-3,5-diene-7,20-dione (XXIV). However, such treatment of 17α-acetoxypregna-3,5-diene-7,20-dione (XX) left the 17α-acetate unchanged, even after 30 minutes at 25°. It is therefore evident that the extreme ease of base-catalyzed hydrolysis or ester exchange cleavage of the 17α-acetate in cortisone diacetate[11] is dependent not only on the proximity of the 20-carbonyl but also on the presence of the 21-ester. A mechanism, which accounts for this result, would be the rapid formation of the 20,21-enediol 21-acetate 20-enolate anion and migration of the 17-acyl group to produce the 20,21-enediol diacetate 17α-oxide anion. Successful cleavage of the 17α-acetate of XX was accomplished in aqueous methanol–dioxane with an excess of 0.2 *N* potassium hydroxide for 4 hr. at 25°, yielding 17α-hydroxypregna-3,5-diene-7,20-dione (XXIII).

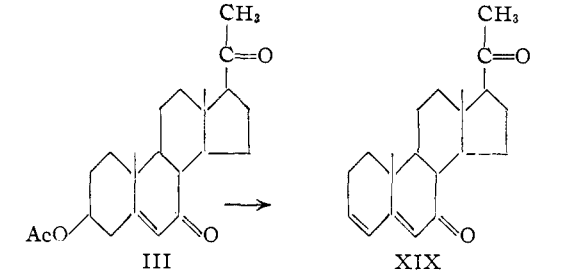
In a number of routine biological tests conducted by our Division of Biological Research,[12] these compounds have shown some blocking effects on undesirable cortisone properties. Weak to moderate inhibition of cortisone-induced fulmination of Coxsackie virus infection in mice was exhibited by IV, V, IXa, XIa, XXI and XXIV. Weak blocking of cortisone-induced spreading of pneu-

(10) (a) H. E. Stavely and W. Bergmann, *J. Org. Chem.*, **1**, 567 (1937); (b) R. E. Marker, O. Kamm, G. H. Fleming, A. H. Popkin and E. L. Wittle, THIS JOURNAL, **59**, 619 (1937); (c) O. Wintersteiner and S. Bergstrom, *J. Biol. Chem.*, **137**, 785 (1941).

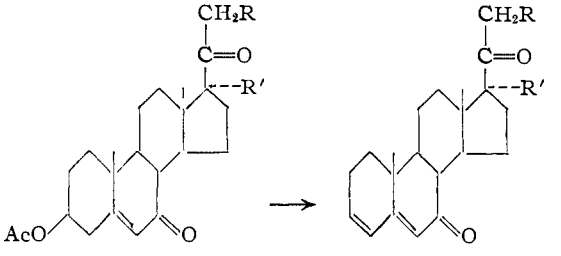
(11) A. H. Soloway and D. K. Fukushima, THIS JOURNAL, **75**, 5442 (1953).

(12) A detailed account of this testing will be published elsewhere. We are indebted to Dr. Gregory Pincus of the Worcester Foundation for Experimental Biology (Worcester, Mass.) for some of the biological testing here reported. For most of the testing we gratefully acknowledge the contributions from our Division of Biological Research, under the direction of Dr. Victor A. Drill, and especially to our biological colleagues, Drs. J. Clampit, R. Craig, L. Hershberger and F. Saunders.

mococcus infection in mice was shown by XIa and XIX. Anti-neoglycogenetic property, when administered simultaneously with cortisone, was exhibited in low degree by one compound, namely, XIb. When given with cortisone, compounds IV, V, IXa and XIX caused moderate blocking of the lymph node atrophying influence of cortisone in the mouse. Compounds XIX and XXIV inhibited the thymus involution effect of cortisone in mice. In anti-inflammatory properties, compounds V, IXa and XXIII showed mild activity only as

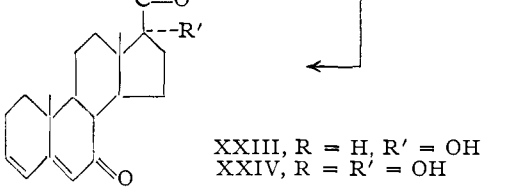


III XIX



IV, R = H, R′ = OAc
IXa, R = OAc, R′ = H
Xa, R = R′ = OAc

XX, R = H, R′ = OAc
XXI, R = OAc, R′ = H
XXII, R = R′ = OAc



XXIII, R = H, R′ = OH
XXIV, R = R′ = OH

tested in rabbit iritis. The 17α-methyl- and 17α-ethyl-7-ketoandrostenediol were evaluated for anabolic, androgenic and anti-androgenic characteristics. Both the 17-methyl and 17-ethyl compounds were inactive as androgens as the diols, XVIIb and XVIIIb and also as their respective 3-monoacetates. Weak anabolic action was exhibited by 3β-acetoxy-17-hydroxy-17α-ethylandrost-5-en-7-one (XVIIIa). Weak anti-androgenic properties were exhibited by 3β,17-dihydroxy-17α-methylandrost-5-en-7-one (XVIIb) and its 3-monoacetate (XVIIa) in both the chick comb growth test and in the rat prostate test.

Experimental[13]

Many of the preparations presented here involved oxidation of Δ⁵-steroids in the allylic C-7 position. Two general methods were employed for this purpose and only one detailed example of each will be given.

General Method A. Oxidation with Sodium Chromate.[8] 3β-Acetoxypregn-5-ene-7,20-dione (III).[14]—To a solution of 40 g. of pregnenolone acetate (I) in 135 ml. of acetic acid and 74 ml. of acetic anhydride, cooled to 35°, there was added portionwise 34 g. of solid anhydrous sodium chromate with intermittent cooling to maintain the mixture in the range of 30–40°. The reaction mixture was stirred for 46 hr. at 30–40° and then poured into 3 liters of cold water. The precipitate, after collection and washing on a suction filter, was resuspended in cold water, recollected on a filter, washed thereon and air-dried. (In some cases, the precipitated steroid was poorly filterable and was extracted into either dichloromethane or ethyl acetate. The extracts were then washed with carbonate until neutral.) The dried crude crystals weighed 34 g., $\epsilon_{2360}^{CH_3OH}$ 10,300 (79% Δ⁵-7-one). Crystallization from 1:1 benzene-petroleum ether provided 15 g. of nearly pure III, m.p. 152–153°. Recrystallization alternately from methanol and benzene–petroleum ether provided pure III, m.p. 153–153.5°,[15] [α]D −68° (0.5% in CH_3OH), $\epsilon_{2360}^{CH_3OH}$ 13,200; μ^{KBr} 5.80, 5.87, 6.01, 6.16 and 8.05.

Anal. Calcd. for $C_{23}H_{32}O_4$ (372.49): C, 74.16; H, 8.66. Found: C, 74.27; H, 8.76.

General Method B. Oxidation with *t*-Butyl Chromate.[4b,7] 3β,21-Diacetoxypregn-5-ene-7,20-dione (IXa).[16]—To a solution of 25 g. of 3β,21-diacetoxypregn-5-en-20-one (VIIa)[17] in 200 ml. of carbon tetrachloride, was added 50 ml. of acetic acid and 13 ml. of acetic anhydride and the mixture warmed to 55°. With stirring and over a 45-minute period at 55–60°, there was added a solution consisting of 50 ml. of acetic acid, 13 ml. of acetic anhydride and 280 ml. of a carbon tetrachloride solution of *t*-butyl chromate (anhydrous, free of *t*-butyl alcohol and equivalent to 34 g. of CrO_3). The mixture was stirred at 60–65° for 20 hr., cooled to 20° and reductively hydrolyzed by the portionwise addition of 920 ml. of aqueous 10% oxalic acid. After stirring an additional 1 hr., the reaction was worked up in the conventional manner using chloroform as additional extraction solvent. After solvent removal the crude solids weighed 24.4 g., $\epsilon_{2350}^{CH_3OH}$ 9,500 (71% Δ⁵-7-one), and were crystallized from methanol to give 14 g., m.p. 185–187°. Two recrystallizations from methanol provided pure IXa, m.p. 189–190°, [α]D −30° (0.5% in CH_3OH), $\epsilon_{2350}^{CH_3OH}$ 13,400; μ^{KBr} 5.74, 5.80, 6.02, 6.17, 7.97 and 8.09.

Anal. Calcd. for $C_{25}H_{34}O_6$ (430.53): C, 69.74; H, 7.96. Found: C, 69.63; H, 7.88.

3β-Hydroxypregn-5-ene-7,20-dione (V).[18]—To a solution of 10 g. of the 7-keto acetate III, in 550 ml. of 10:1 methanol-dioxane under nitrogen, was added 50 ml. of aqueous 2.2 *N* sodium hydroxide and the, at first cloudy, mixture stirred for 3 hr.[19] at room temperatures. After the usual work-up, the water-precipitated, washed, dried solids were crystallized from methanol to give 7.56 g. of nearly pure V (85% yield). Recrystallization alternately from ethyl acetate and methanol afforded flat blades of pure V, m.p. 209–210°, [α]D −72° (0.5% in CH_3OH), $\epsilon_{2380}^{CH_3OH}$ 13,200; μ^{KBr} 2.91, 5.95, 6.02 and 6.16.

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15. Found: C, 76.39; H, 9.13.

Molecular Compound: 2 Moles 3β-Hydroxypregn-5-ene-7,20-dione (V) and 1 Mole Pregna-3,5-diene-7,20-dione (XIX).—From the methanolic mother liquors of the isolation of V, were obtained 600 mg. of fine needles, m.p. 199–203°. Recrystallization from ethyl acetate provided additional V.

(13) All melting points are uncorrected. All ultraviolet spectra were taken in methanol. Silica gel used was Davison Chemical Corporation No. 923 (80–200 mesh). Petroleum ether, unless specified, means Skellysolve-B (boiling range 60–70°). Brine refers to aqueous sodium chloride. All analytical data including spectra were determined by our Analytical Department under Dr. Robert T. Dillon.

(14) Previously prepared by the classical CrO_3–AcOH method, ref. 3a, 5, and by the *t*-butyl chromate method, ref. 3d.

(15) In another preparation, using the *t*-butyl chromate method, a higher melting form, m.p. 162.5–165° and [α]D −67° (CH_3OH), was isolated from either solvent system. Klyne, ref. 5, reported m.p. 151–153°; Logemann and Giraldi, ref. 3d, reported 152–153°.

(16) IXa was also made by the sodium chromate method in comparable yield.

(17) (a) T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939); (b) C. Djerassi and C. T. Lenk, THIS JOURNAL, **75**, 3495 (1953).

(18) Butenandt and Logemann, ref. 3a, referred to this structure—trivial name 7-ketopregnenolone—but gave no experimental example or data.

(19) A rate study on 500 mg. had previously determined that 0.95 equivalent of base is consumed in 2.5 hr.

From these ethyl acetate liquors upon drying and repeated crystallizations of the residue from methanol there was obtained 150 mg. of needles, m.p. 196–198°, which proved to be a molecular compound of 2 moles of V with 1 mole of XIX, $\epsilon_{2390}^{CH_3OH}$ 8400 (64.6% pure Δ⁵-7-one), $\epsilon_{2780}^{CH_3OH}$ 8200 (34.2% pure Δ³,⁵-dien-7-one).

Anal. Calcd. for $C_{21}H_{29.5}O_{2.67}$ (324.52): C, 77.72; H, 9.12. Found: C, 78.29; H, 9.16.

3β,17α-Diacetoxypregn-5-ene-7,20-dione (IV).—17α-acetoxypregnenolone 3-acetate (II)[20] (24.3 g.) was oxidized with sodium chromate by general method A and worked up in a similar fashion. After removal of the ethyl acetate solvent, the residue weighed 19 g., $\epsilon_{2350}^{CH_3OH}$ 10,700 (86% Δ⁵-7-one). Crystallization from methanol gave 13 g. of needles, m.p. 230–234°. Recrystallization furnished pure IV, m.p. 231–234°, [α]D −142° (1.01% in $CHCl_3$), $\epsilon_{2350}^{CH_3OH}$ 12,400; μ^{KBr} 5.76–5.78 (broad), 5.84 (shoulder), 6.03 and 6.12.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.64; H, 7.55.

3β,17α-Dihydroxypregn-5-ene-7,20-dione (VI).—To a solution of 7 g. of the 7-keto diacetate IV in 250 ml. of dioxane at 22° and with stirring, was added 125 ml. of aqueous 0.6 *N* potassium hydroxide. During the addition the mixture turned cloudy but cleared as the water content approached 33%. Aliquots were titrated at intervals and after 2 hr. 93% of 2 equivalents of base had been consumed. After standing a total of 80 minutes at 22°, the mixture was chilled and the steroid precipitated with an excess of cold acidified aqueous 5% brine. The solids were collected on a filter, washed, air-dried and weighed as 4.90 g. Crystallization from methanol gave 3.49 g. of slender blades which were recrystallized alternately from ethyl acetate and methanol to provide pure VI, m.p. 267–270°, [α]D −122° (0.47% in CH_3OH), $\epsilon_{2375}^{CH_3OH}$ 13,100; μ^{KBr} 2.95, 2.98, 5.95 (shoulder), 6.02 and 6.14.

Anal. Calcd. for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.69; H, 8.51.

3-Ethoxycarbonyloxy-21-acetoxypregn-5-en-20-one (VIIb).—To a solution of 35 g. of 21-acetoxypregnenolone[21] in 200 ml. of pyridine, there was added portionwise 44 ml. of ethyl chloroformate with stirring and intermittent cooling to maintain the mixture at about 30°. The mixture was stored at room temperatures overnight, poured into ice-cold water and the precipitate collected. After resuspension in water, filtration and air-drying, 41 g. of crude crystals were obtained of m.p. 156–158°. Recrystallization from methanol provided pure VIIb, m.p. 158–161°; μ^{KBr} 5.75, 5.83, 7.99 and 8.06.

Anal. Calcd. for $C_{26}H_{38}O_6$ (446.56): C, 69.92; H, 8.58. Found: C, 69.88; H, 8.47.

3-Ethoxycarbonyloxy-21-acetoxypregn-5-ene-7,20-dione (IXb).—The 3β,21-diester VIIb (18 g.) was oxidized with sodium chromate by general method A. After removal of solvent from the ethyl acetate extracts, there was obtained a residue of 15.9 g., $\epsilon_{2345}^{CH_3OH}$ 9900 (71% Δ⁵-7-one). Two recrystallizations from methanol furnished pure IXb, m.p. 208.5–210°, [α]D −41° (1.05% in $CHCl_3$), $\epsilon_{2345}^{CH_3OH}$ 14,000.

Anal. Calcd. for $C_{26}H_{36}O_7$ (460.55): C, 67.80; H, 7.88. Found: C, 67.80; H, 8.01.

3β,21-Dihydroxypregn-5-ene-7,20-dione (XIb from IXb).—A solution of 8.9 g. of the 7-keto-3β-ethoxycarbonyloxy-21-acetate in 150 ml. of dioxane at 25° was treated, under nitrogen, with 1.05 liters of methanolic 0.066 *N* potassium hydroxide. The mixture was stirred for 10 minutes, 7 ml. of water added and stirring continued another 5 minutes. After acidification with 80 ml. of aqueous 10% acetic acid, most of the methanol was removed *in vacuo*. The 250-ml. residue was poured into an excess of cold aqueous 10% brine, the precipitate dissolved in dichloromethane and the extracts washed, dried and distilled to a dry residue of 6.3 g. Crystallization from ethyl acetate gave 4.79 g., m.p. 195–197°. Two recrystallizations from the same solvent afforded pure XIb, m.p. 199–202°, [α]D −82° (0.9% in $CHCl_3$), $\epsilon_{2375}^{CH_3OH}$ 13,100; μ^{KBr} 2.88, 2.93 (shoulder), 5.85, 6.06, 6.15 and 9.32–9.36 (broad).

Anal. Calcd. for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.71; H, 8.67.

Alternate Synthesis: 3β,21-Dihydroxypregn-5-ene-7,20-dione (XIb from IXc).—To a solution of 21-acetoxypregnenolone[21] (25 g.) in 175 ml. of dioxane under nitrogen, there was added 50 ml. of trifluoroacetic anhydride and the mixture stored at 25° for 20 hr. Most (45 ml.) of the anhydride was removed by vacuum distillation using a 45°-bath, and the residue was chilled, diluted with 2.2 l. of cold water and extracted with ethyl acetate. The extracts were washed until neutral, dried and concentrated *in vacuo*. The residue was crystallized from ethyl acetate–petroleum ether (b. range 90–100°) to give 28.1 g. of fine needles, m.p. 140–142°. Recrystallization alternately from methanol and ethyl acetate–petroleum ether (90–100°) provided nearly pure VIIc, m.p. 146–151°; μ^{KBr} 2.79 (very weak), 5.62, 5.72, 5.80, 8.15 and 8.58. This material was used for the preparation of the 7-keto derivative.

The crude crystalline (m.p. 146–151°) 3β-trifluoroacetoxy-21-acetoxypregn-5-en-20-one (VIIc) (23.5 g.) was oxidized with *t*-butyl chromate by general method B. After removal of the carbon tetrachloride extraction solvent, the dried residue weighed 18 g., crude IXc. This crude material was taken directly to ester cleavage to form the 7-keto-3β,21-diol XIb.

A solution of 18 g. of crude 3β-trifluoroacetoxy-21-acetoxypregn-5-en-7,20-dione (IXc) in 500 ml. of methanol was stirred under nitrogen, and there was added 185 ml. of methanolic 0.4 *N* potassium hydroxide. The mixture was stirred 4 minutes at 25°, 2 ml. of water added, stirring continued for 4 minutes and the mixture acidified by the addition of 500 ml. of cold aqueous 1% acetic acid. The solution was then vacuum distilled to dryness using a 40–45° bath, the residue triturated with 200 ml. of ice-cold aqueous 5% brine and the solids collected on a filter and washed with water. The solids were crystallized from ethyl acetate to produce 9.2 g. of crude crystalline 7-keto-3β,21-diol XIb, m.p. 180–182°, which proved identical with the pure XIb prepared above.

21-Acetoxy-3β-hydroxypregn-5-ene-7,20-dione (XIa).—A pyridine solution was prepared to contain exactly 2.08 g. (0.02 mole) of acetic anhydride per 70 ml.; 70 ml. of this solution was used to dissolve 7 g. (0.02 mole) of crude (m.p. 180–182°) 3β,21-dihydroxypregn-5-ene-7,20-dione (XIb). The mixture was stored at 25° overnight, poured in excess water and extracted with ethyl acetate. The extracts were washed neutral, dried and the solvent removed *in vacuo*. The residue was crystallized from ethyl acetate to give 5.04 g. of crude product, m.p. 218–230°. Three recrystallizations from the same solvent furnished pure XIa, m.p. 237–241°, [α]D −53° (1.01% in $CHCl_3$), $\epsilon_{2375}^{CH_3OH}$ 14,300; μ^{KBr} 2.79, 5.70, 5.82, 6.00, 6.14 and 8.09.

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.04; H, 8.46.

3β,17α,21-Triacetoxypregn-5-en-20-one (VIIIa).—A solution of 10 g. of 21-acetoxy-3β,17α-dihydroxypregn-5-en-20-one[22] in 400 ml. of acetic acid and 80 ml. of acetic anhydride was treated with 10 g. of *p*-toluenesulfonic acid monohydrate and stored at 25° overnight (method of R. B. Turner[20]). The reaction mixture was poured slowly into an excess of cold water and the precipitate collected. Resuspension of the crystalline solid in water, refiltering and air-drying produced 10.9 g. of crude product, m.p. 210–213°. Three recrystallizations from methanol provided pure VIIIa, m.p. 214–215.5°, [α]D −61° (1.01% in $CHCl_3$); μ^{KBr} 5.72, 5.79, 7.99 and 8.05 (broad).

Anal. Calcd. for $C_{27}H_{38}O_7$ (474.57): C, 68.33; H, 8.07. Found: C, 68.70; H, 7.94.

3β,17α,21-Triacetoxypregn-5-ene-7,20-dione (Xa).—The triacetate VIIIa (10.2 g.) was oxidized with sodium chromate by general method A.[23] Upon concentration of the washed ethyl acetate extraction solvent to a volume of 200 ml., 6.7 g. of crude product was obtained, m.p. 242–245°. Two recrystallizations from the same solvent afforded pure Xa, m.p. 246–248°, [α]D −116° (1.03% in $CHCl_3$), $\epsilon_{2360}^{CH_3OH}$ 13,300; μ^{KBr} 5.67, 5.78, 6.04, 6.12, 7.91 and 8.08–8.17 (broad).

Anal. Calcd. for $C_{27}H_{36}O_8$ (488.56): C, 66.37; H, 7.43. Found: C, 66.64; H, 7.52.

(20) R. B. Turner, THIS JOURNAL, **75**, 3489 (1953).

(21) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).

(22) J. Heer and K. Miescher, *ibid.*, **34**, 360 (1951).

(23) Oxidation of this compound with *t*-butyl chromate gave very poor yields.

3β-Ethoxycarbonyloxy-17α,21-diacetoxypregn-5-en-20-one (VIIIb).—To a solution of 25.7 g. of 21-acetoxy-3β,17α-dihydroxypregn-5-en-20-one[22] in 350 ml. of pyridine, there was added portionwise 31 ml. of ethyl chloroformate with stirring and intermittent cooling to maintain the mixture at about 30°. After storage at 25° overnight, the mixture was poured into ice-cold water and the precipitate collected. After resuspension in water, filtration and air-drying, 28.3 g. of crude crystals was obtained of m.p. 197–201°. Two recrystallizations from methanol provided pure 3-ethoxycarbonyloxy-21-acetoxy-17α-hydroxypregn-5-en-20-one, m.p. 199–202.5°; μ^{KBr} 2.84, 5.74, 5.80, 7.80–7.92 (broad) and 8.10.

Anal. Calcd. for $C_{28}H_{38}O_7$ (462.56): C, 67.51; H, 8.28. Found: C, 67.21; H, 7.86.

The 3β,21-diester (27.8 g.) was acetylated in the tertiary 17α-hydroxy position by the acetic anhydride (400 ml.) reflux method of Huang-Minlon, *et al.*[24] After boiling at reflux for 12 hr., the anhydride was removed *in vacuo* and the oily residue extracted with ethyl acetate. The extracts were washed until neutral, dried and decolorized with Darco G-60 charcoal. After filtering, the solvent was removed *in vacuo* to give a residue of 30.7 g. which was crystallized from methanol to produce 22.4 g. of fine needles, m.p. 189–192°. Recrystallization from methanol furnished pure VIIIb, m.p. 190–192.5°; μ^{KBr} 5.70, 5.74 (faint shoulder), 7.85–7.97 (broad) and 8.10.

Anal. Calcd. for $C_{28}H_{40}O_8$ (504.60): C, 66.64; H, 7.99. Found: C, 66.16; H, 8.01.

3β-Ethoxycarbonyloxy-17α,21-diacetoxypregn-5-ene-7,20-dione (Xb).—The triester VIIIb (18 g.) was oxidized with sodium chromate by general method A. The water precipitated and filtered product was dissolved in ethyl acetate. The solution was washed until neutral and the solvent removed *in vacuo* to give crude solids, 16.4 g., $\epsilon_{2350}^{CH_3OH}$ 10,100 (84% Δ^5-7-one). Crystallization from methanol produced 11.8 g., m.p. 150–155°, clear 195–198°.[25] Two recrystallizations from methanol gave pure Xb, m.p. 196–200° (after drying *in vacuo* at 110°), $\epsilon_{2350}^{CH_3OH}$ 12,000; μ^{KB} 5.70, 5.74 (faint shoulder), 5.95, 6.10, 7.85–7.94 (broad) and 8.07.

Anal. Calcd. for $C_{28}H_{39}O_9$ (518.58): C, 64.85; H, 7.39. Found: C, 64.39; H, 7.43.

3β,17α,21-Trihydroxypregn-5-ene-7,20-dione (XII).—To a solution of 5.18 g. of the triester Xb in 400 ml. of methanol, at 30° with stirring and under nitrogen, was added 144 ml. of a methanolic 0.33 *N* potassium hydroxide. After 9 minutes, 5 ml. of water was added and, after stirring another 6 minutes, the reaction mixture was acidified with dilute acetic acid and poured into an excess of cold 5% brine. The suspension was extracted with dichloromethane and the extract was washed, dried and evaporated *in vacuo* yielding 3.3 g. of a crystalline residue. Crystallization from ethyl acetate gave pure XII, m.p. 224–227°, $[\alpha]_D$ −95° (0.63% in dioxane), $\epsilon_{2375}^{CH_3OH}$ 12,300; μ^{KBr} 2.98 (broad), 5.83–5.88 (double-pointed), 6.02, 6.07 and 6.12.

Anal. Calcd. for $C_{21}H_{30}O_5$ (362.45): C, 69.58; H, 8.34. Found: C, 69.68; H, 8.40.

7-Keto-17α-methylandrostenediol 3β-Acetate (XVIIa).—To a solution of 13.7 g. of 17α-methylandrost-5-ene-3β,17-diol 3-acetate in 100 ml. of pyridine, was added 21 ml. of trifluoroacetic anhydride with stirring and intermittent cooling to maintain a reaction temperature of about 30°. The mixture was stored at 25° for 3 hr. and then poured slowly into 1150 ml. of cold aqueous 15% hydrochloric acid. The gummy precipitate was filtered off, dissolved in ether and the extracts washed free of pyridine and until neutral. The solvent was removed *in vacuo* to give 16.6 g. of crude semi-solid (infrared showed no hydroxyl bands). This crude product resisted crystallization and was used directly for the oxidation with *t*-butyl chromate.

A solution of 16.6 g. of crude 17α-methylandrost-5-ene-3β,17-diol 3-acetate 17-trifluoroacetate (XIII) in 110 ml. of carbon tetrachloride was oxidized with *t*-butyl chromate solution by general method B. Upon removal of the carbon tetrachloride extraction solvent, there was obtained an amorphous residue, 14.6 g., $\epsilon_{2350}^{CH_3OH}$ 10,500 (80% Δ^5-7-one). This crude intermediate (XV) resisted crystallization and was subjected directly to ester cleavage, as shown below.

To a solution of 14.6 g. of crude (*ca.* 80%) 3β-acetoxy-17-trifluoroacetoxy-17α-methylandrost-5-en-7-one (XV) in 900 ml. of 1:2 dioxane–methanol was added 120 ml. of aqueous 2 *N* potassium hydroxide. The mixture was stored at 25° for 90 minutes, acidified with dilute acetic acid and poured into an excess of cold dilute brine. The precipitate was collected, washed with water and air-dried to give the crude diol XVIIb, 8.2 g., $\epsilon_{2350}^{CH_3OH}$ 10,500. Crystallization from ethyl acetate gave 5.23 g., m.p. 199–203°, $\epsilon_{2350}^{CH_3OH}$ 10,700. Since, obviously, crystallization was not purifying the diol, all fractions were combined for monoacetylation.

The crude 7-keto diol XVIIb (8.2 g.) was monoacetylated with pyridine and acetic anhydride for 18 hr. at 25° and the reaction mixture worked up in the customary manner. The crude solids were crystallized from 1:1 benzene–petroleum ether to give 5.33 g., m.p. 209–211°, $\epsilon_{2350}^{CH_3OH}$ 12,800. Recrystallization from the same solvent mixture provided pure XVIIa, m.p. 211.5–212°, $[\alpha]_D$ −146° (0.99% in $CHCl_3$), $\epsilon_{2350}^{CH_3OH}$ 13,000; μ^{KBr} 2.76, 2.86, 5.78, 6.02, 6.15 (shoulder) and 8.0. Note two peaks for one hydroxyl (2.76 and 2.86 μ) which indicates partial H-bonding.

Anal. Calcd. for $C_{22}H_{32}O_4$ (360.48): C, 73.30; H, 8.95. Found: C, 73.39; H, 8.94.

7-Keto-17α-methylandrostenediol (XVIIb).—To a solution of 3.3 g. of the 3-monoacetate XVIIa in 120 ml. of 1:2 dioxane–methanol was added 15.8 ml. of aqueous 2 *N* potassium hydroxide. The mixture was stored for 3 hr. at 25°, acidified with dilute acetic acid and poured into an excess of cold 5% brine. The precipitate was collected, washed and air-dried to give 2.91 g. of crude product. Crystallization from ethyl acetate furnished 1.83 g., m.p. 207–209°; recrystallized, m.p. 207.5–210°; $[\alpha]_D$ −157° (0.83% in $CHCl_3$), $\epsilon_{2375}^{CH_3OH}$ 13,100; μ^{KBr} 2.90, 2.95 (shoulder), 6.03 and 6.14 (shoulder).

Anal. Calcd. for $C_{20}H_{30}O_3$ (318.44): C, 75.43; H, 9.50. Found: C, 75.52; H, 9.62.

7-Keto-17α-ethylandrostenediol 3β-Acetate (XVIIIa).—A solution of 21 g. of 17α-ethylandrost-5-ene-3β,17-diol 3-acetate (m.p. 166–168°)[26] in 140 ml. of pyridine was acylated with 30 ml. of trifluoroacetic anhydride for 3 hr. at 25°. The mixture was worked up exactly as for the preparation of XVIIa above. After removal of the ether extraction solvent, there was obtained 25.2 g. of crude XIV (infrared in KBr disk showed no hydroxyl bands) which resisted crystallization and was subjected directly to oxidation with *t*-butyl chromate.

A solution of 25.2 g. of crude 17α-ethylandrost-5-ene-3β,17-diol 3-acetate 17-trifluoroacetate (XIV) in 145 ml. of carbon tetrachloride was oxidized with *t*-butyl chromate by general method B. Upon removal of the carbon tetrachloride extraction solvent, there was found an amorphous residue, 23 g., $\epsilon_{2350}^{CH_3OH}$ 9600 (71% Δ^5-7-one). This crude intermediate (XVI) was refractory to crystallization and was taken directly to ester cleavage, below.

To a solution of 23 g. of crude (*ca.* 71%) 3β-acetoxy-17-trifluoroacetoxy-17α-ethylandrost-5-en-7-one (XVI) in 960 ml. of 1:2 dioxane–methanol was added 125 ml. of aqueous 2 *N* potassium hydroxide. The mixture was stored at 25° for 90 minutes, acidified with dilute acetic acid and poured into an excess of cold 5% brine. The precipitate was collected, washed and air-dried to give 13.2 g. of the crude 7-keto diol XVIIIb, infrared in KBr showing no ester bands.

The crude 7-keto diol XVIIIb (13.2 g.) was monoacetylated with pyridine and acetic anhydride for 18 hr. at 25° and the reaction mixture worked up in the usual manner. The crude solids were crystallized from 4:5 benzene–petroleum ether to give 6.8 g., m.p. 192–195°. Two recrystallizations from 1:2 benzene–petroleum ether afforded pure XVIIIa, m.p. 200–201°, $[\alpha]_D$ −147° (1.04% in $CHCl_3$), $\epsilon_{2350}^{CH_3OH}$ 13,400; μ^{KBr} 2.83, 2.89, 5.77, 6.03, 6.14 and 8.04. Note two peaks for the one hydroxyl caused by partial H-bonding.

Anal. Calcd. for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15. Found: C, 73.82; H, 8.82.

(24) Huang-Minlon, E. Wilson, N. L. Wendler and M. Tishler, THIS JOURNAL, **74**, 5394 (1952).

(25) All crops from methanol held solvent and gave partial melting in the range 140–155°. Drying *in vacuo* at 110° invariably gave a 195–200° m. range.

(26) A. Butenandt, J. Schmidt-Thomé and H. Paul, *Ber.*, **72B**, 1112 (1939).

7-Keto-17α-ethylandrostenediol (XVIIIb).—To a solution of 4 g. of the 3-monoacetate XVIIIa in 135 ml. of 1:2 dioxane–methanol was added 18.5 ml. of aqueous 2 *N* potassium hydroxide. The mixture was stored for 3 hr. at 25°, acidified with dilute acetic acid and poured into an excess of cold 3% brine. The precipitate was collected, washed and air-dried to give 3.6 g. of crude product. Crystallization from 10:1 ethyl acetate–acetone provided 3.15 g., m.p. 226–228°. Recrystallization from acetone afforded pure XVIIIb, m.p. 227–229°, $[\alpha]D$ −161° (1.04% in $CHCl_3$), $\epsilon_{2375}^{CH_3OH}$ 12,500; μ^{KBr} 2.90 (shoulder), 2.95, 6.04 and 6.15.

Anal. Calcd. for $C_{21}H_{32}O_3$ (332.47): C, 75.86; H, 9.70. Found: C, 75.92; H, 9.91.

Pregna-3,5-diene-7,20-dione (XIX).[27]—A solution of 20 g. of 3β-acetoxypregn-5-ene-7,20-dione (III)[3a,d,5] in 400 ml. of 95% ethanol was treated with 10 ml. of 12 *N* hydrochloric acid and heated under nitrogen and reflux for 2 hr. After precipitation with cold water, filtration and air-drying, there was found 17.5 g. of light yellow powder. Crystallization from methanol gave 9.96 g., m.p. 155–160°. Two recrystallizations provided pure XIX, m.p. 159–161°, $[\alpha]D$ −297° (1.15% in $CHCl_3$), $\epsilon_{2790}^{CH_3OH}$ 21,200; μ^{KBr} 5.90, 6.08, 6.20 and 6.32.

Anal. Calcd. for $C_{21}H_{28}O_2$ (313.41); C, 80.73; H, 9.03. Found: C, 80.71; H, 9.03.

17α-Acetoxypregna-3,5-diene-7,20-dione (XX).—To a solution of 4.15 g. of 3β,17α-diacetoxypregn-5-ene-7,20-dione (IV) in 60 ml. of acetic acid was added 0.30 g. of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed for 50 minutes, chilled and 72 ml. of cold water slowly added with stirring. The crystalline precipitate was filtered, washed and dried to give 3.03 g., m.p. 230–231°. Two recrystallizations from ethyl acetate furnished pure XX, m.p. 234–236°, $\epsilon_{2780}^{CH_3OH}$ 21,700; μ^{KBr} 5.77, 5.82 (shoulder), 6.05, 6.17, 6.28, 7.94 and 8.16.

Anal. Calcd. for $C_{23}H_{30}O_4$ (370.47): C, 74.56; H, 8.18. Found: C, 74.56; H, 8.25.

17α-Hydroxypregna-3,5-diene-7,20-dione (XXIII).—To a solution of 1.5 g. of the 7-keto-diene 17α-acetate XX in 150 ml. of 1:2 dioxane–methanol, was added 20 ml. of aqueous 2 *N* potassium hydroxide. Aliquots of the reaction mixture were titrated at intervals, and, after 4.5 hr., 0.94 equivalent of base had been consumed. After another 15 minutes, the mixture was acidified with cold dilute acetic acid and poured into cold 5% brine. The precipitate was filtered, washed and air-dried to give 1.02 g., m.p. 217–218°. Two recrystallizations from ethyl acetate afforded pure XXIII, m.p. 223–224°, $[\alpha]D$ −387° (0.89% in $CHCl_3$), $\epsilon_{2775}^{CH_3OH}$ 22,600; μ^{KBr} 2.95, 5.86, 6.10, 6.20 and 6.30.

Anal. Calcd. for $C_{21}H_{28}O_3$ (328.43): C, 76.79; H, 8.59. Found: C, 76.87; H, 8.69.

21-Acetoxypregna-3,5-diene-7,20-dione (XXI).—To a solution of 1 g. of 3β,21-diacetoxypregn-5-ene-7,20-dione (IXa) in 20 ml. of acetic acid was added 120 mg. of *p*-toluenesulfonic acid monohydrate. The mixture was heated under reflux for 1 hr., chilled and 30 ml. of cold water slowly added with stirring. The crystalline precipitate was filtered, washed with cold water and dried to 0.79 g., m.p. 170–172°. Two recrystallizations from acetone–methanol provided pure XXI, m.p. 173–174°, $[\alpha]D$ −219° (1.02% in $CHCl_3$), $\epsilon_{2780}^{CH_3OH}$ 22,400; μ^{KBr} 5.70, 5.80, 6.05, 6.16, 6.27 and 8.12.

Anal. Calcd. for $C_{23}H_{30}O_4$ (370.47): C, 74.56; H, 8.16. Found: C, 74.32; H, 8.05.

17α,21-Diacetoxypregna-3,5-diene-7,20-dione (XXII).—To a solution of 8 g. of 3β,17α,21-triacetoxypregn-5-ene-7,20-dione (Xa) in 120 ml. of acetic acid, was added 0.6 g. of *p*-toluenesulfonic acid monohydrate. The mixture was heated under reflux for 1 hr., chilled and 140 ml. of cold water slowly added with stirring. The crystalline precipitate was filtered, washed with cold water and dried to 6.14 g. Recrystallization from methanol gave 5.22 g., m.p. 234–235°. Two recrystallizations provided pure XXII, m.p. 241–242°, $[\alpha]D$ −313° (1% in $CHCl_3$), $\epsilon_{2785}^{CH_3OH}$ 23,600; μ^{KBr} 5.70, 5.76–5.78 (broad), 6.07, 6.18, 6.30, 8.0 (shoulder), 8.09 and 8.17.

Anal. Calcd. for $C_{25}H_{32}O_6$ (428.51): C, 70.07; H, 7.53. Found: C, 69.82; H, 7.40.

17α,21-Dihydroxypregna-3,5-diene-7,20-dione (XXIV).—To a solution of 5 g. of the 7-keto-diene diacetate XXII in 140 ml. of 9:5 dioxane–methanol under nitrogen at 25°, and with stirring, was added 150 ml. of methanolic 0.16 *N* potassium hydroxide. After 4 minutes, 1 ml. of water was added. After another 5 minutes, the mixture was chilled, acidified with dilute acetic acid and poured into cold 5% brine. The precipitate was filtered, washed and air-dried to give 3.80 g. of powder. Crystallization from ethyl acetate and from acetone gave 2.80 g. of crude product in four crops, m. range 202–212°. Two recrystallizations from methanol furnished pure XXIV, m.p. 216–216.5°, $[\alpha]D$ −338° (1.15% in $CHCl_3$), $\epsilon_{2780}^{CH_3OH}$ 23,200; μ^{KBr} 2.90, 2.96, 5.84, 6.11, 6.20 and 6.30.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.43): C, 73.23; H, 8.19. Found: C, 73.20; H, 8.14.

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(27) References 3a and 5. These authors mention this structure but give no experimental data nor characteristics.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. I. Synthesis of 18,19-Dinorprogesterone and 14-Hydroxy-18,19-dinorprogesterone[1]

BY NORMAN A. NELSON AND ROBERT B. GARLAND[2]

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The total synthesis of 14-hydroxy-18,19-dinorprogesterone (14-hydroxy-18,19-dinorpregn-4-ene-3,20-dione) is described. A by-product at one point in the synthesis of this substance was used in the preparation of 18,19-dinorprogesterone (18,19-dinorpregn-4-ene-3,20-dione). Conversion of 1-keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene to the hormone analogs utilized the method of attachment of ring D recently described by Sarett and co-workers in their synthesis of cortisone. The stereochemistry of the two products is discussed and it is felt that in each case the configuration corresponds to that of natural progesterone.

In recent years a number of 3-keto-Δ^4-19-nor-steroidal hormones have been prepared.[3-5] In most instances the 19-nor analogs have similar but

(1) Abstracted from the thesis submitted by Robert B. Garland to the Massachusetts Institute of Technology, 1957, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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