[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Chemical Studies with 11-Oxygenated Steroids. III. 17α-Hydroxycorticosterone[1a,b]

BY R. H. LEVIN, B. J. MAGERLEIN, A. V. MCINTOSH, JR., A. R. HANZE, G. S. FONKEN, J. L. THOMPSON, A. M. SEARCY, M. A. SCHERI AND E. S. GUTSELL

RECEIVED SEPTEMBER 10, 1953

The synthesis of 17α-hydroxycorticosterone (Kendall's Compound F) from 4-chloro-17α-hydroxypregnane-3,11,20-trione is described. The preparation of other 4-pregnen-3-ones, such as cortisone acetate, 17α-hydroxy-4-pregnene-3,11,20-trione (21-desoxy Compound E) and 11β,17α-dihydroxy-4-pregnene-3,20-dione (21-desoxy Compound F) from this intermediate is described.

The discovery in these laboratories of the bioöxygenation of progesterone[2] coupled with the report of the therapeutic activity of 17α-hydroxycorticosterone[3,4] suggested that a practical synthesis of this hormone from 11α-hydroxyprogesterone be devised.

Various biosyntheses of 17α-hydroxycorticosterone from 17α,21-dihydroxy-4-pregnene-3,20-dione (Reichstein's Substance S) have been reported.[5] The chemical synthesis of 17α-hydroxycorticosterone from cortisone,[6a,b] 11α,17α,21-trihydroxy-4-pregnene-3,20-dione (epi Compound F),[7] and 20-cyano-21-hydroxy-17-pregnene-3,11-dione[8] also have been reported. This paper describes the synthesis of 17α-hydroxycorticosterone from intermediates readily available from 11α-hydroxyprogesterone.

4-Chloro-17α-hydroxypregnane-3,11,20-trione (III), the key intermediate in this synthesis, was prepared by three methods. The simultaneous oxidation and chlorination[9] of 3α,17α-dihydroxypregnane-11,20-dione (IV)[10] with *t*-butyl hypochlorite gave a 72% yield of 4-chloro-17α-hydroxypregnane-3,11,20-trione (III). Dechlorination of the mother liquors gave 16% recovery of 17α-hydroxypregnane-3,11,20-trione (V).[10] Likewise, 3α,11α,-17α-trihydroxypregnan-20-one (I)[11] was simultaneously oxidized and chlorinated with *t*-butyl hypochlorite[9] to give 4-chloro-11α,17α-dihydroxypregnane-3,20-dione (II), which was further oxidized to 4-chloro-17α-hydroxypregnane-3,11,20-trione (III). 4-Chloro-17α-hydroxypregnane-3,11,20-trione (III) was also prepared in high yield by the chlorination of 17α-hydroxypregnane-3,11,20-trione (V) with *t*-butyl hypochlorite.[9]

Dehydrochlorination of 4-chloro-17α-hydroxypregnane-3,11,20-trione (III) with semicarbazide and removal of the semicarbazone grouping[12] gave the previously reported 17α-hydroxy-4-pregnene-3,11,20-trione (21-desoxy Compound E) (XV).[10,13]

Treatment of 4-chloro-17α-hydroxypregnane-3,-11,20-trione (III) with ethylene glycol in benzene solution in the presence of *p*-toluenesulfonic acid gave 71% yield of the 3,20-bis-(ethylene ketal) (VIa). Lithium aluminum hydride reduction of the diketal VIa gave 90% yield of 4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3,20-bis-(ethylene ketal) (VIIIa). Contrary to early reports that the lithium aluminum hydride reduction of 11-ketopregnanes gives almost exclusively the 11β-isomer,[14] varying amounts of the 11α-isomer are usually formed in the reduction of 11-ketopregnanes. This is in accord with the observation of Antonucci, *et al.*,[6b] who reported that the reduction of the 3,20-diketal of cortisone gave approximately 58% of the β-isomer and 8% of the α-isomer. The approximate isomer ratio formed in the lithium aluminum hydride reduction of various 11-ketopregnanes is given in Table I. Fortunately there is no evidence of formation of significant amounts of the 11α-isomer in the reduction of 4-chloro-17α-hydroxypregnane-3,11,20-trione 3,20-bis-(ethylene ketal) (VIa).

Acidic hydrolysis of the chloroketals VIa and VIIIa in acetone solution at room temperature selectively removes the 20-ketal group in 87–94% yield to give the 3-monoketals VII and Xa, respectively. For removal of the 3-ketal adjacent to the 4-chloro group it was necessary to heat under reflux for prolonged periods. In this manner the chloroketones III and IX were prepared from 4-chloro-17α-hydroxypregnane-3,11,20-trione 3,20-bis-(ethylene ketal) (VIa) and 4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3,20-bis-(ethylene ketal) (VIIIa), respectively.

Bromination of 4-chloro-11β,17α-dihydroxypreg-

(1) (a) A preliminary announcement of this work was reported in a Communication to the Editor, THIS JOURNAL, **75**, 502 (1953); (b) preceding paper in this series, B. J. Magerlein and R. H. Levin, *ibid.*, **75**, 3654 (1953).

(2) D. H. Peterson and H. C. Murray, *ibid.*, **74**, 1871 (1952); D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister and H. M. Leigh, *ibid.*, **74**, 5933 (1952); U. S. Patent 2,602,769 (July 8, 1952).

(3) P. S. Hench, E. C. Kendall, C. H. Slocumb and H. F. Polley, *Arch. Int. Med.*, **85**, 545 (1950).

(4) 17α-Hydroxycorticosterone is also known as Reichstein's "Substance M" (T. Reichstein, *Helv. Chim. Acta*, **20**, 953 (1937)), Kendall's "Compound F" (H. L. Mason, W. M. Hoehn and E. C. Kendall, *J. Biol. Chem.*, **124**, 459 (1938)) and "Hydrocortisone" (E. C. Kendall in a paper presented before the American Academy of Orthopedic Surgeons at Chicago, Illinois, January, 1951).

(5) O. Hechter, R. P. Jacobsen, R. Jeanloz, H. Levy, C. W. Marshall, G. Pincus and V. Schenker, *Arch. Biochem.*, **25**, 457 (1950); D. A. McGinty, G. N. Smith, M. L. Wilson and C. S. Worrel, *Science*, **112**, 506 (1950); R. W. Kahnt and A. Wettstein, *Helv. Chim. Acta*, **34**, 1790 (1951); M. L. Sweat, THIS JOURNAL, **73**, 4056 (1951); D. R. Colingsworth, M. P. Brunner and W. J. Haines, *ibid.*, **74**, 2381 (1952).

(6) (a) N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951); (b) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. R. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(7) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

(8) N. L. Wendler, R. P. Graber, R. E. Jones and M. Tishler, *ibid.*, **74**, 3630 (1952).

(9) A. R. Hanze, G. S. Fonken, A. V. McIntosh, Jr., A. M. Searcy and R. H. Levin, unpublished data.

(10) L. H. Sarett, THIS JOURNAL, **70**, 1454 (1948).

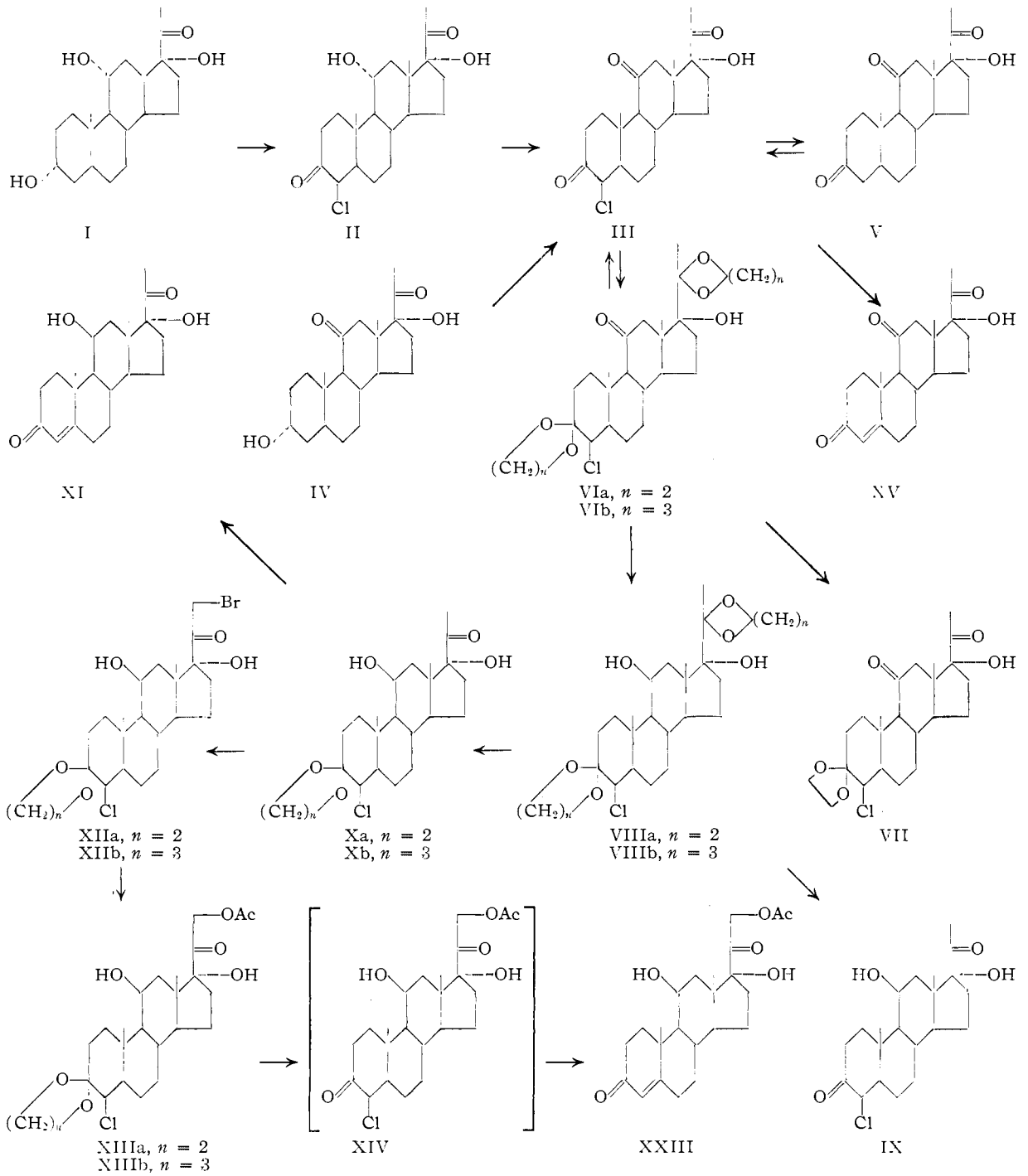
(11) H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, *ibid.*, **74**, 4471 (1952).

(12) B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *ibid.*, **71**, 3262 (1949). See also V. R. Mattox and E. C. Kendall, *ibid.*, **70**, 882 (1948), and E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(13) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, THIS JOURNAL, **74**, 483 (1952).

(14) L. H. Sarett, M. Feurer and K. Folkers, *ibid.*, **73**, 1777 (1951).

CHART I



nane-3,20-dione 3-ethylene ketal (Xa) with bromine in chloroform solution gave an 81% yield of the bromide XIIa. Reaction of the bromide XIIa with potassium acetate in acetone gave a 97% yield of 21-acetoxy-4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3-ethylene ketal (XIIIa). Dehydrohalogenation of the chloroketone XIV, which was formed *in situ* by the hydrolysis of the chloroketal XIIIa and was not isolated, gave about 60% yield of 17α-hydroxycorticosterone acetate (XXIII), identical with a known sample of the steroid.

An alternate synthesis of 21-acetoxy-4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3-ethylene ketal (XIIIa) was also investigated (Chart II). The simultaneous oxidation–chlorination of 21-acetoxy-3α,17α-dihydroxypregnane-11,20-dione (XVI) gave 21-acetoxy-4-chloro-17α-hydroxypregnane-3,11,20-trione (XVII). This chloroketone shows markedly greater stability than 21-acetoxy-4-bromo-17α-hydroxypregnane-3,11,20-trione,[15] be-

(15) V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

TABLE I

LITHIUM ALUMINUM HYDRIDE REDUCTION OF 11-KETOPREGNANES

Compound reduced	Compound isolated	11α-OH, %	11β-OH, %
4-Chloro-17α-hydroxypregnane-3,11,20-trione 3,20-bis-(ethylene ketal) (VIa)	4-Chloro-11,17α-dihydroxypregnane-3,11,20-trione 3,20-bis-(ethylene ketal)	Trace[b]	90
3α,17α-Dihydroxypregnane-11,20-dione 20-ethylene ketal	3α,11,17α-trihydroxypregnan-20-one	11	60[16]
Cortisone 3,20-bis-(ethylene ketal)	11,17α,21-Trihydroxy-4-pregnene-3,20-dione	8	58[6b,a]
4-Pregnene-3,11,20-trione 3,20-bis-(ethylene ketal)	11-Hydroxy-4-pregnene-3,20-dione	5	87[17]

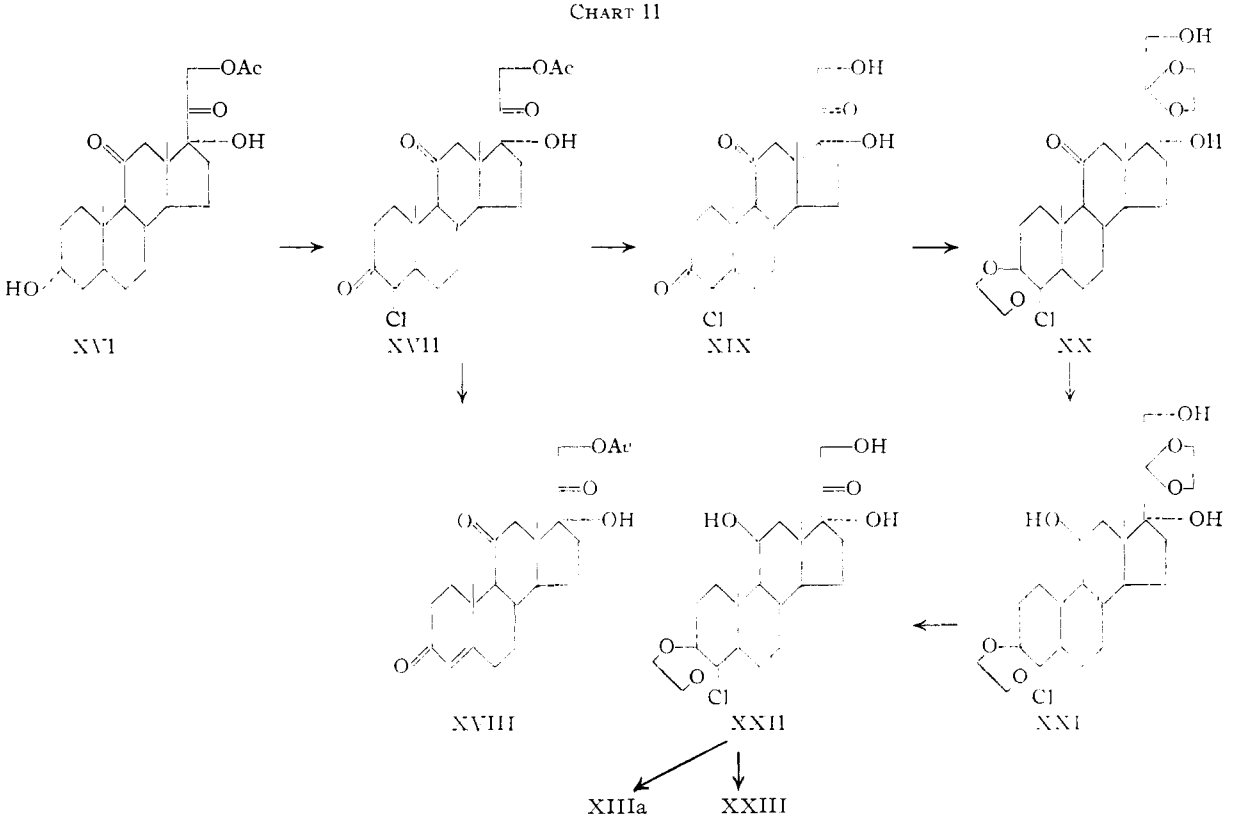
[a] Similar results were obtained in this laboratory. [b] Determined by papergram analysis.

ing easily purified by recrystallization. Its dehydrohalogenation by the semicarbazide–pyruvic acid procedure[12] proceeded smoothly to give a high yield of cortisone acetate (XVIII). Hydrolysis of the 21-acetate (XVII) gave the alcohol XIX. When treated with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid 4-chloro-17α,21-dihydroxypregnane-3,11,20-trione (XIX) gave, in moderate yield, the non-crystalline diketal XX. The ketals of compounds containing the dihydroxyacetone side chain are formed in reduced yield, the chief by-product invariably being an oily material whose infrared absorption spectrum is characterized by lack of OH absorption.[18] Reduction of 4-chloro-17α,21-dihydroxypregnane-3,11,20-trione, 3,20-bis-(ethylene ketal) with lithium aluminum hydride gave the hydroxy-diketal XXI. Selective acidic hydrolysis of the diketal of XXI gave the monoketal XXII. These ketals were not purified. Treatment of XXII through the semicarbazide procedure gave hydrocortisone in low yield while acylation gave XIIIa.

Hydrolysis and dehydrohalogenation of 4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3-ethylene ketal (Xa) as described for the chloroketal XIIIa gave a high yield of 11β,17α-dihydroxy-4-pregnene-3,20-dione (XI) (21-desoxy Compound F).[19] This compound also was prepared by bromination of 11β,17α-dihydroxypregnane-3,20-dione[16] followed by dehydrohalogenation in similar fashion.

The conversion of 4-chloro-17α-hydroxypregnane-3,11,20-trione (III) to 17α-hydroxycorticosterone acetate (XXIII) using 1,3-propylene glycol as the ketalizing agent was accomplished in a manner similar to that described above for the ethylene ketal.

CHART II



(16) *Cf.* E. P. Oliveto, T. Clayton and E. B. Hershberg, *ibid.*, **75**, 486 (1953), who report a 95% yield of the 11β-isomer using sodium borohydride.

(17) B. J. Magerlein and R. H. Levin, *ibid.*, **75**, 3654 (1953).

(18) *Cf.* the low yields of cortisone 3,20-bis-(ethylene ketal) ref. 6b. Similar results were obtained in this laboratory with cortisone and 17α,21-dihydroxypregnane-3,11,20-trione. Also note V. R. Mattox. THIS JOURNAL, **74**, 4340 (1952).

(19) The biological testing of 11β,17α-dihydroxy-4-pregnene-3,20-dione will be reported elsewhere by K. J. Olson, R. O. Stafford, W. W. Byrnes, *et al.*, of our Department of Endocrinology.

Acknowledgment.—The authors are indebted to V. R. Shellman, A. Koning and G. Beyer for technical assistance; to L. M. Reineke and associates for papergram analyses: to Dr. J. L. Johnson, J. E. Stafford and Mrs. G. S. Fonken for infrared and ultraviolet absorption studies; and to W. A. Struck and associates for microanalyses and optical rotations.

Experimental[20]

4-Chloro-11α,17α-dihydroxypregnane-3,20-dione (II).—A solution of 3.49 g. of 3α,11α,17α-trihydroxypregnane-20-one monohydrate (I)[11] in 165 ml. of *t*-butyl alcohol and 5 ml. of water was cooled to 10°, then 2.87 ml. of *t*-butyl hypochlorite[21] and 1.32 ml. of concentrated hydrochloric acid were added. The reaction mixture was allowed to warm to 25° over a period of 4 hours. After this time nearly all of the hypochlorite was consumed as shown by titration of an aliquot with sodium thiosulfate.[9] The mixture was poured into 800 ml. of water containing 0.5 g. of sodium bisulfite and refrigerated for 16 hours. The precipitate was discarded and the aqueous solution extracted with methylene chloride. After concentration to dryness the residue was chromatographed over Florisil[22] and twice recrystallized from acetone–Skellysolve B[23] to give 4-chloro-11α,17α-dihydroxypregnane-3,20-dione,[11] m.p. 183–185° after melting at 160–165° and then resolidifying, $[\alpha]^{23}D$ +48° (acetone). This compound was highly solvated and was difficult to dry for analysis. Its structure was determined by infrared data and its oxidation to 4-chloro-17α-hydroxypregnane-3,11,20-trione (III).

4-Chloro-17α-hydroxypregnane-3,11,20-trione (III). (a) From IV.—Two hundred grams of 3α,17α-dihydroxypregnane-11,20-dione (IV)[10] was dissolved in 3 l. of *t*-butyl alcohol by warming. After cooling to 26°, 96 ml. of water and 40 ml. of concentrated hydrochloric acid were added. The solution was cooled to 7–10° and 144 ml. of *t*-butyl hypochlorite added. The reaction mixture was kept in the dark. The temperature slowly rose to 25–30° where it was maintained for 6 hours. At the end of this time titration showed only a trace of active halogen. The reaction mixture was diluted with 20 l. of water which precipitated crystalline chloroketone III. After filtering, washing with water and drying at 50°, the crude product weighed 210 g. (96.1% yield), m.p. 210–230° dec., $[\alpha]^{25}D$ +92° (acetone). The crude product was dissolved in 3.8 l. of warm acetone and 3 l. of water added. The purified product recovered by filtration weighed 157 g. (72% yield), m.p. 230–236° dec., $[\alpha]^{23}D$ +101° (acetone). An additional crystallization from dilute acetone gave an analytical sample, m.p. 239.5–242° dec., $[\alpha]^{23}D$ +103° (acetone).

Anal. Calcd. for $C_{21}H_{29}ClO_4$: C, 66.16; H, 7.67; Cl, 9.31. Found: C, 66.10; H, 7.83; Cl, 9.30.

The acetone–water mother liquor was partially concentrated under vacuum and diluted with water to precipitate 44.5 g. of crystals, m.p. 180–195° dec., $[\alpha]^{23}D$ +64° (acetone). A solution of this material in 600 ml. of acetic acid was stirred with 40 g. of zinc dust for 4 hours, filtered and diluted with water to give 32.2 g. (16% recovery) of 17α-hydroxypregnane-3,11,20-trione (V), m.p. 185–195°. Recrystallization from dilute acetic acid gave material melting at 201–203°.[10]

(b) From II.—A solution of 104 mg. of 4-chloro-11α,17α-dihydroxypregnane-3,20-dione (II) in 8 ml. of pyridine was added to a solution of 104 mg. of chromic acid in 5 ml. of pyridine.[24] After standing at 26° for 16 hours dilute hydrochloric acid and benzene were added and the mixture filtered. The filtrate was extracted with benzene. The extract was washed, dried and concentrated under vacuum. The residue was triturated with dilute acetone to give a small amount of crystals. Recrystallization from dilute acetone gave 4-chloro-17α-hydroxypregnane-3,11,20-trione (III), m.p. 235–239°.

(c) From V.—To a suspension of 28.07 g. of 17α-hydroxypregnane-3,11,20-trione (V) in 510 ml. of *t*-butyl alcohol were added successively 16.8 ml. of water, 11.0 ml. (1.2 mole equivalents) of *t*-butyl hypochlorite and 10.0 ml. (1.5 mole equivalents) of concentrated hydrochloric acid. The mixture was stirred in the dark at about 12° for 21 hours, after which time titration of an aliquot with sodium thiosulfate showed that all of the active halogen was consumed. The reaction mixture was diluted to 2 l. with water, cooled in an ice-bath, and the product recovered by filtration. It weighed 27.5 g. (90% yield corrected for the aliquots which were withdrawn for titration), and melted at 220–229°. Recrystallization from aqueous acetone afforded 20.6 g. of material, m.p. 234–238°, $[\alpha]^{23}D$ +96° (acetone).

4-Chloro-17α-hydroxypregnane-3,11,20-trione 3,20-Bis-(ethylene Ketal) (VIa).—A mixture of 10.0 g. of 4-chloro-17α-hydroxypregnane-3,11,20-trione (III), 0.60 g. of *p*-toluenesulfonic acid, 50 ml. of ethylene glycol and 1 l. of benzene was stirred vigorously while heating under reflux. The water formed in the reaction was codistilled with the benzene and removed by a water trap. After 6 hours of heating, the reaction mixture was cooled and washed twice with dilute sodium bicarbonate, once with water, and dried over sodium sulfate. Filtration and evaporation of the solvent under reduced pressure gave crystalline VIa which was recrystallized from ethyl acetate to give 8.31 g. (67.5% yield), m.p. 235–242° and 1.68 g. (13.5% yield), m.p. 225–232°. After several recrystallizations the ketal melted 239–242°, $[\alpha]^{23}D$ +55° (acetone).

Anal. Calcd. for $C_{25}H_{37}ClO_6$: C, 64.02; H, 7.95; Cl, 7.56. Found: C, 64.57; H, 7.86; Cl, 7.55.

4-Chloro-17α-hydroxypregnane-3,11,20-trione 3,20-Bis-(1,3-propylene Ketal) (VIb).—In a manner similar to the preparation of the ethylene ketal described above, VIb, the propylene ketal was prepared in 44% yield, m.p. 198–202°, $[\alpha]^{22}D$ +60° (benzene).

Anal. Calcd. for $C_{27}H_{41}ClO_6$: C, 65.24; H, 8.31. Found: C, 65.60; H, 8.35.

Hydrolysis of 4-Chloro-17α-hydroxypregnane-3,11,20-trione 3,20-Bis-(ethylene ketal). (a) 4-Chloro-17α-hydroxy-3,11,20-trione 3-Ethylene Ketal (VII).—To a solution of 100 mg. of 4-chloro-17α-hydroxypregnane-3,11,20-trione 3,20-bis-(ethylene ketal) (VIa) in 16 ml. of acetone and 4 ml. of water was added one drop of sulfuric acid. The solution was allowed to stand for 24 hours and then diluted with water. The crystals were separated by filtration (yield 79%, m.p. 194–204°). The needle-like crystals, recrystallized from methylene chloride–hexane, melted 194–203°, $[\alpha]^{25}D$ +83° (acetone). Infrared data confirmed the given structure.

Anal. Calcd. for $C_{23}H_{33}ClO_5$: C, 65.00; H, 7.82; Cl, 8.34. Found: C, 65.16; H, 7.90; Cl, 8.37.

(b) 4-Chloro-17α-hydroxypregnane-3,11,20-trione (III).—A solution of 0.28 g. of diketal VIa in a mixture of 10 ml. of acetone and 2.8 ml. of 3 *N* hydrochloric acid was heated under reflux for 2 hours. Dilution with 50 ml. of water gave a precipitate which was crystallized from a mixture of ethyl acetate and hexane and then recrystallized from aqueous acetone to give 42 mg. of crystals, m.p. 233–237°. This material was identical with 4-chloro-17α-hydroxypregnane-3,11,20-trione by infrared analysis.

4-Chloro-11β,17α-dihydroxypregnane-3,20-dione 3,20-Bis-(ethylene Ketal) (VIIIa).—A solution of 25.0 g. of diketal VIa in 375 ml. of benzene was added to a slurry of 3.6 g. of lithium aluminum hydride in 2 l. of anhydrous ether at such a rate as to cause gentle refluxing. The reaction mixture was heated under reflux for one hour and hydrolyzed with 200 ml. of water. The ether solution was decanted, washed with water, and dried over sodium sulfate. The ether was distilled under vacuum and the residue recrystallized from ethyl acetate to give 17.3 g. (69.2% yield), m.p. 221–224°, and a second crop of 5.2 g. (20.8% yield), m.p. 216–221°. Recrystallization of the first crop crystals gave an analytical sample, m.p. 222–224°, $[\alpha]^{23}D$ +41° (acetone).

Anal. Calcd. for $C_{25}H_{39}ClO_6$: C, 63.74; H, 8.35; Cl, 7.53. Found: C, 63.80; H, 8.30; Cl, 7.35.

Papergram analysis of the total reduction mixture showed but a trace of material believed to be the 11α-isomer.

(20) Melting points are uncorrected and taken on a Fisher–Johns block.

(21) H. M. Teeter, R. C. Buchmann, E. W. Bell and J. C. Cowan, *Ind. Eng. Chem.*, **41**, 849 (1949).

(22) A synthetic magnesia–silica gel made by the Florindin Co., Warren, Pa.

(23) A saturated hydrocarbon fraction, b.p. 60–71°.

(24) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

4-Chloro-11β,17α-dihydroxypregnane-3,20-dione 3,20-Bis-(1,3-propylene Ketal) (VIIIb).—Reduction of the bis-(propylene ketal) VIb in the manner described for the reduction of the bis-(ethylene ketal) VIa gave 73% yield of VIIIb, m.p. 197–203°, $[\alpha]^{23}D$ +38° (benzene).

Anal. Calcd. for $C_{27}H_{43}ClO_6$: C, 64.97; H, 8.68; Cl, 7.11. Found: C, 65.41; H, 8.54; Cl, 6.92.

4-Chloro-11β,17α-dihydroxypregnane-3,20-dione (IX).—A solution of 500 mg. of 4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3,20-bis-(ethylene ketal) (VIIIa) in 20 ml. of acetone and 5 ml. of 3 *N* hydrochloric acid was heated under reflux for 4 hours. The solution was diluted with 120 ml. of water. The crystals which precipitated were filtered, washed and dried. They weighed 251 mg., m.p. 173–212°. Recrystallization from dilute acetone and then from ethyl acetate–hexane gave 94 mg. of 4-chloro-11β,17α-dihydroxypregnane-3,20-dione (IX), m.p. 219–232°. Infrared data confirmed the given structure.

Anal. Calcd. for $C_{21}H_{31}ClO_4$: C, 65.86; H, 8.16; Cl, 9.26. Found: C, 65.79; H, 8.16; Cl, 9.05.

4-Chloro-11β,17α-dihydroxypregnane-3,20-dione 3-Ethylene Ketal (Xa).—A solution of 35.6 g. of diketal VIIIa in 1.3 l. of acetone and 400 ml. of water containing 5.7 ml. of concentrated sulfuric acid was permitted to stand at 26° for 4.5 hours. The *p*H was adjusted to 7 with sodium bicarbonate and the acetone distilled under reduced pressure. The residue was diluted with 1.5 l. of water and extracted several times with methylene dichloride. The combined methylene dichloride extracts were washed with water, dried and concentrated. The residue was dissolved in 200 ml. of ethyl acetate, 200 ml. of Skellysolve **B** was added and the solution concentrated to 250 ml. There was thus obtained 27.3 g. of crystals (70.1% yield), m.p. 184–188°. Concentration of the mother liquor gave an additional 5.37 g. (16.9% yield), m.p. 178–183°. After several recrystallizations an analytical sample was obtained, m.p. 194–196° dec., $[\alpha]^{23}D$ +82° (acetone).

Anal. Calcd. for $C_{23}H_{35}ClO_5$: C, 64.70; H, 8.26. Found: C, 64.57; H, 8.13.

4-Chloro-11β,17α-dihydroxypregnane-3,20-dione 3-(1,3-Propylene Ketal) (Xb).—The selective hydrolysis of 4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3,20-bis-(1,3-propylene ketal) (VIIIb) in the manner described for the bis-(ethylene ketal) VIIIa gave 59% yield of monoketal Xb, m.p. 185–190°, $[\alpha]^{22}D$ +44° (benzene).

Anal. Calcd. for $C_{24}H_{37}ClO_5$: C, 65.36; H, 8.46; Cl, 8.04. Found: C, 65.57; H, 8.54; Cl, 8.21.

4-Chloro-21-bromo-11β,17α-dihydroxypregnane-3,20-dione 3-Ethylene Ketal (XIIa).—To 25 g. of 4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3-ethylene ketal (Xa) in 1550 ml. of chloroform was added dropwise with vigorous stirring 9.78 g. (1.05 molar equivalents) of bromine in 500 ml. of chloroform over a period of 2 hours. The bromine solution was added at such a rate that the solution did not become colored due to excess bromine. At the end of the addition the solution was cooled with ice and washed with 300 ml. of cold 1% sodium hydroxide and twice with 300-ml. portions of cold water. The chloroform layer was dried with anhydrous sodium sulfate, filtered and concentrated to dryness. The residue was dissolved in 500 ml. of methylene dichloride and concentrated until crystallization took place. There was thus obtained 18.46 g. (62.3% yield) of bromide XIIa, m.p. 221–223° dec. Concentration of the mother liquor gave an additional 5.64 g. (19.1% yield), m.p. 212–214° dec.

One recrystallization from acetone–Skellysolve B gave material melting at 211–223° dec., $[\alpha]^{23}D$ +91° (acetone).

Anal. Calcd. for $C_{23}H_{34}BrClO_5$: C, 54.60; H, 6.77; Br, 15.79. Found: C, 54.42; H, 7.01; Br, 15.3.

4-Chloro-21-acetoxy-11β,17α-dihydroxypregnane-3,20-dione 3-Ethylene Ketal (XIIIa).—To 10.6 g. of 21-bromo-4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3-ethylene ketal (XIIa) in 630 ml. of acetone was added 143 mg. of potassium iodide, 40.28 g. of potassium acetate and 6.3 ml. of glacial acetic acid. The mixture was heated under reflux with stirring for 16 hours, filtered and the solids washed well with acetone. The filtrate was concentrated under reduced pressure to a small volume and water added until crystallization took place. The crystals weighed 9.8 g. (96.6% yield), m.p. 235–238° dec. Recrystallization from dilute acetone raised the melting point to 247–249°, $[\alpha]^{22}D$ +96° (acetone).

Anal. Calcd. for $C_{25}H_{37}ClO_7$: C, 61.91; H, 7.69; Cl, 7.31. Found: C, 62.17; H, 7.73; Cl, 7.16.

4-Chloro-21-acetoxy-17α-hydroxypregnane-3,11,20-trione (XVII).—Oxidation–chlorination of 21-acetoxy-3α,17α-dihydroxypregnane-11,20-dione (XVI) with *t*-butyl hypochlorite in the manner described for the preparation of 4-chloro-17α-dihydroxypregnane-3,11,20-trione (III) gave, after recrystallization from dilute acetone, 72.5% yield of XVII, m.p. 238–244°, $[\alpha]^{24}D$ +100° (acetone). A second crop of crystals was obtained by concentration of the mother liquor, m.p. 173–185°, $[\alpha]^{24}D$ +82° (acetone), 22% yield. Recrystallization of first crop crystals from dilute acetone gave pure material, m.p. 244–249°, $[\alpha]^{25}D$ +112° (acetone).

Anal. Calcd. for $C_{23}H_{31}ClO_6$: C, 62.93; H, 7.09; Cl, 8.08. Found: C, 63.10; H, 6.84; Cl, 8.14.

Cortisone Acetate (XVIII).—A solution of 0.826 g. of 4-chlorodihydrocortisone acetate (XVII) and 0.282 g. of semicarbazide in 20 ml. of *t*-butyl alcohol in 10 ml. of methylene dichloride was stirred at 26° for 2 hours under nitrogen. During this time the characteristic color change from colorless to orange to colorless was noted. The solvent was evaporated under vacuum; 600 mg. of sodium acetate, 20 ml. of acetic acid, 8 ml. of water and 0.8 ml. of pyruvic acid were added. The solution was heated at 70° for one hour and concentrated under vacuum. The residue was dissolved in methylene dichloride and worked up in the usual manner. Evaporation of the solvent gave 743 mg. (98.5% yield) of crude cortisone acetate; λ_{max}^{EtOH} 238 mμ, *E* 13,197. This material, on recrystallization from acetone, gave 57.2% yield of first crop crystals, m.p. 239–243°, λ_{max}^{EtOH} 239 mμ, *E* 15,270 and 12.6% yield of second crop crystals, m.p. 227–230°, λ_{max}^{EtOH} 239 mμ, *E* 14,734.

4-Chloro-17α,21-dihydroxypregnane-3,11,20-trione (XIX).—To 10 g. of 21-acetoxy 4-chloro-17α-hydroxypregnane-3,-11,20-trione (XVII) dissolved in 350 ml. of methanol and 110 ml. of methylene dichloride was added with cooling in an ice-bath 22 ml. of concentrated hydrochloric acid in 35 ml. of water. The mixture was stirred at room temperature for two days and then 500 ml. of water added. The methylene dichloride and methanol were removed under reduced pressure until crystallization began. More water (300 ml.) was added and the mixture refrigerated for one hour, filtered and the solid washed well with water, yield 8.02 g. (88.7%), m.p. 210–214°. An analytical sample was obtained on one recrystallization from acetone–Skellysolve B and one from ethyl acetate–Skellysolve B, m.p. 214–218°.

Anal. Calcd. for $C_{21}H_{30}ClO_5$: C, 63.38; H, 7.60; Cl, 8.91. Found: C, 63.55; H, 7.51; Cl, 9.04.

4-Chloro-17α,21-dihydroxypregnane-3,11,20-trione 3,20-Bis-(ethylene Ketal) (XX).—A mixture of 4.5 g. of 4-chloro-17α,21-dihydroxypregnane-3,11,20-trione (XIX), 675 ml. of benzene, 9 ml. of ethylene glycol and 90 mg. of *p*-toluenesulfonic acid was heated under reflux for 5 hours. The mixture was then washed with water, saturated sodium bicarbonate and water. The benzene solution was dried over anhydrous sodium sulfate, filtered, concentrated to dryness and chromatographed on Florisil. Fractions 21–26 (ethylene chloride–acetone 5:1) weighing 2.23 g. (33% of chromatogram) were recrystallized from ethyl acetate (20 ml.) and Skellysolve B (30 ml.); yield 825 mg. (14.9%), m.p. 242–246°. Recrystallization from acetone–water gave an analytical sample, m.p. 242–246°.

Anal. Calcd. for $C_{25}H_{38}ClO_7$: C, 61.78; H, 7.88; Cl, 7.30. Found: C, 62.33; H, 7.72; Cl, 7.34.

17α-Hydroxycorticosterone Acetate (XXIII). (a) Semicarbazide Procedure.—A mixture of 3.0 g. of 4-chloro-21-acetoxy-11β,17α-dihydroxypregnane-3,20-dione 3-ethylene ketal (XIIIa), 0.15 ml. of sulfuric acid, 30 ml. of acetic acid and 9 ml. of water was heated at 70° for 1.5 hours. The steroid gradually dissolved during this time. The solution was cooled to 25° and 475 mg. of anhydrous sodium acetate added. The reaction mixture was covered with nitrogen at this point. A solution of 1.01 g. of sodium acetate and 1.36 g. of semicarbazide hydrochloride in 3 ml. of water was added. After stirring at 25° for 30 minutes, during which time the characteristic color change of this reaction was noted, 3 ml. of distilled pyruvic acid was added. The reaction mixture was heated at 50° for 30 minutes,

cooled to 25°, and 3 g. of sodium acetate added. The solvent was removed under reduced pressure. The residue was triturated with three 75-ml. portions of methylene dichloride. The combined methylene dichloride solution was treated with 15 ml. of acetic anhydride and 30 ml. of pyridine for one hour at 25°. The solution was then washed with water, dilute acid, cold 1% sodium hydroxide and water. The solvent was distilled under vacuum after drying over sodium sulfate. The partially crystalline residue was triturated with ethyl acetate to give 1.77 g. (70.9% yield) of crude 17α-hydroxycorticosterone acetate, m.p. 207–214°, λ_{max}^{EtOH} 242 mμ, E 14,625. Evaporation of the solvent gave approximately 25% of steroidal material which contained some XXIII by papergram. Recrystallization from ethyl acetate gave 1.31 g. (52.6% yield), m.p. 217–220°, λ_{max}^{EtOH} 242 mμ, E 15,950. A second crop of 175 mg. (7.1%), m.p. 213–216°, λ_{max}^{EtOH} 242 mμ, E 15,275, was also obtained.

(b) **2,4-Dinitrophenylhydrazine Procedure.**—A solution of 440 mg. of 2,4-dinitrophenylhydrazine in 3 ml. of acetic acid and 3 ml. of water containing 0.2 ml. of sulfuric acid was prepared by warming to 70–80°. This solution was added to a suspension of 4-chloro-21-acetoxy-11β,17α-dihydroxypregnane-3,20-dione 3-ethylene ketal (XIIIa) in 5 ml. of acetic acid. The entire reaction was carried out in an atmosphere of nitrogen. The mixture was heated at 70° for 0.5 hour, during which time the solution became dark red in color. The solution was permitted to stand at room temperature for 2 hours. Red needles of the unsaturated hydrazone crystallized on standing. These crystals were redissolved by the addition of 10 ml. of acetic acid and 10 ml. of chloroform. One ml. of pyruvic acid was added and the reaction mixture heated at 50° for 2 hours. Two grams of sodium acetate was added and the solution stirred for 5 minutes. The solvent was distilled under vacuum. The residue was triturated three times with chloroform and filtered to remove the insoluble sodium salt of the 2,4-dinitrophenylhydrazone of pyruvic acid. The chloroform solution was washed with water, sodium bicarbonate, water, dried over sodium sulfate and concentrated. The residue weighed 1.10 g.

The crude product was reacylated with 2 ml. of acetic anhydride and 2 ml. of pyridine for one hour at 26°. The excess anhydride was destroyed with water, the product extracted with methylene dichloride and worked up in the usual fashion. The residue was crystallized from acetone to give 470 mg. (56.6%) of first crop crystals, λ_{max}^{EtOH} 242 mμ, E 14,875. The second crop, obtained by concentration of the solution, weighed 120 mg. (14.6%), λ_{max}^{EtOH} 242 mμ, E12,425. The total yield of crude orange crystals was 71.1%. Five hundred and sixty mg. of this material was recrystallized from about 50 ml. of methanol. The methanol solution was treated with two 120-mg. portions of Darco G-60. The first crop crystals weighed 330 mg., m.p. 208–211° and the second crop 80 mg., m.p. 205–211° (sinter 195°). Papergram analysis showed only Compound F acetate to be present.

(c) **From XX.**—A solution of 1.23 g. of 4-chloro-17α,21-dihydroxypregnane-3,11,20-trione 3,20-bis-(ethylene ketal) (XX) in 15 ml. of tetrahydrofuran was added to 1.2 g. of lithium aluminum hydride in 150 ml. of anhydrous ether. The mixture was stirred at 25° for 90 minutes and heated under reflux for one hour. The excess hydride was destroyed with acetone and dilute hydrochloric acid added. Evaporation of the ether gave 1.28 g. of oily diketal XXI. A 100-mg. portion of this oil was treated with 2,4-dinitrophenylhydrazine as described in (b) above to give a semicrystalline material which contained 20% of 17α-hydroxycorticosterone by papergram analysis. A second portion of diketal XXI (300 mg.) was dissolved in a solution of 24 ml. of acetone, 6 ml. of water and 1.2 ml. of perchloric acid. After 24 hours at 25° the solution was neutralized with solid sodium bicarbonate. Concentration of the solution gave 175 mg. of crystals, m.p. 126–134°, which when treated with 2,4-dinitrophenylhydrazine as described in (b) above followed by acylation gave 10 mg. of 17α-hydroxycorticosterone acetate.

(d) **From Xb.**—Bromination of 4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3-(1,3-propylene ketal) (Xb) as described for the bromination of the ethylene ketal (Xa) gave 15% yield of crude crystals, m.p. 214–216°. This product was not purified but converted directly to the acetate XIIIb as described for the preparation of the acetate XIIIa. The crude acetate was treated with semicarbazide hydrochloride, followed by pyruvic acid to give a low yield of 17α-hydroxycorticosterone acetate, identified by papergram analysis.

17α-Hydroxy-4-pregnene-3,11,20-trione (XV).—Dehydrohalogenation of 25 g. of 4-chloro-17α-hydroxypregnane-3,11,20-trione in the manner previously described gave 8 g. of 21-desoxy Compound E (XV), m.p. 233–237°, $[\alpha]^{23}D$ +184°, λ_{max}^{EtOH} 239 mμ, E 15,625 and 3.9 g., m.p. 219–226°, λ_{max}^{EtOH} 239 mμ, E 14,050.

4-Bromo-11β,17α-dihydroxypregnane-3,20-dione.—To a solution of 3.0 g. of 11β,17α-dihydroxypregnane-3,20-dione in 50 ml. of acetic acid there was added 29.2 ml. of a solution of bromine in acetic acid (0.310 millimole of bromine/ml.) which contained 702 mg. of sodium acetate. The reaction was initiated with a drop of hydrobromic acid in acetic acid. The addition was at such a rate as to permit decolorization after each drop of bromine solution. After all of the bromine was added the solution was poured into 900 ml. of sodium chloride solution, cooled in ice-water for one hour, and filtered. There was obtained 3.18 g. (86.7%) of crude bromide, $[\alpha]^{23}D$ +62° (acetone). The crude bromide was crystallized from 15 ml. of acetone to give 0.78 g. (21.2%) of white crystals, m.p. 195–197° dec., $[\alpha]^{24}D$ +88° (acetone). There was also obtained 0.56 g. (15.3%) of second crop crystals, m.p. 187–189° dec., $[\alpha]^{24}D$ +83° (acetone) and 1.27 g. (34.6%) of third crop crystals, m.p. 180–183° dec., $[\alpha]^{24}D$ + 47° (acetone). Recrystallization of first crop bromide from acetone gave an analytical sample, m.p. 196–198° dec., $[\alpha]^{24}D$ +92° (acetone).

Anal. Calcd. for $C_{21}H_{31}BrO_4$: C, 59.01; H, 7.31; Br, 18.70. Found: C, 59.13, 59.05; H, 7.33, 7.49; Br, 18.20, 18.45.

The crystals rotating +47° were dissolved in 15 ml. of acetic acid and stirred at 26° for 2.5 hours with 1 g. of powdered zinc. The zinc was removed by filtration. Dilution of the acetic acid solution with water gave 690 mg. of material which when crystallized from ethyl acetate gave 370 mg. of 11β,17α-dihydroxypregnane-3,20-dione, m.p. 205–214°.

11β,17α-Dihydroxy-4-pregnene-3,20-dione (XI). Method A.—Treatment of 50 g. of 4-chloro-11β,17α-dihydroxypregnane-3,20-dione 3-ethylene ketal (Xa) with sulfuric acid followed by dehydrohalogenation with semicarbazide, as described for the preparation of 17-hydroxycorticosterone, gave on crystallization from acetone, 16.1 g. (39.6% yield), m.p. 200–206°, λ_{max}^{EtOH} 241 mμ, E 15,125; 4.2 g. (10.5% yield), m.p. 200–208°, λ_{max}^{EtOH} 241 mμ, E 14,650, and 1.0 g. (2.5% yield), m.p. 195–205°, λ_{max}^{EtOH}241 mμ, E 14,650. Several recrystallizations from acetone gave a sample melting 225–228°, $[\alpha]^{24}D$ +136° (acetone), λ_{max}^{EtOH} 241 mμ, E 15,725.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.72; H, 8.70.

Method B.—A solution of 720 mg. of 4-bromo-11β,17α-dihydroxypregnane-3,20-dione $[\alpha]^{23}D$ +87° (acetone), and 250 mg. of semicarbazide in 12 ml. of 80% dioxane–water was stirred at room temperature for 2 hours. During this time a characteristic color change was noted. The resulting semicarbazone was not isolated, but was treated with 0.3 ml. of pyruvic acid in 3 ml. of water at 60° for 2 hours. The reaction mixture was poured into water and extracted with methylene dichloride. The methylene dichloride solution was washed with water, cold 1% sodium hydroxide, water, and dried. Concentration gave 581 mg. (99.4%) of white crystals of XI, m.p. 195–210°. Recrystallization from acetone gave 260 mg., m.p. 225–228°, λ_{max}^{EtOH} 241 mμ, E 15,325, $[\alpha]^{23}D$ +136° (acetone).

3α,11β,17α-Trihydroxypregnan-20-one and 3α,11α,17α-Trihydroxypregnan-20-one.—To 10.8 g. of lithium aluminum hydride in 500 ml. of dry ether was added 10.8 g. of 3α,17α-dihydroxypregnane-11,20-dione 20-ethylene ketal[16] in 70 ml. of dry benzene. The mixture was stirred at room temperature for one hour and at reflux for 1.5 hours. Water was added cautiously and the aqueous solution was acidified with hydrochloric acid. The mixture was stirred vigorously overnight. The layers were separated and the aqueous layer extracted twice with ether. The combined ether fractions were washed twice with water, dried, filtered and concentrated to give a crystalline mass. The residue was extracted with 500 ml. of hot ethylene dichloride. Cooling of the extract and filtration yielded 2.95 g. (30.6%) of 3α,-11β,17α-trihydroxypregnan-20-one, m.p. 207–210°. The

filtrate was chromatographed over 1300 g. of Florisil. Fractions 20–27 (ethylene chloride:acetone 5:1) were recrystallized from ethyl acetate–Skellysolve B to give an additional 2.92 g. (30.2%), m.p. 206–210° of 3α,11β,17α-trihydroxypregnan-20-one.

Fractions 32–34 (acetone) were recrystallized from ethyl acetate–Skellysolve B to give 1.05 g. (10.9%) of 3α,11α,17α-trihydroxypregnan-20-one, melting at 157–158°.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Steroid Homologs Containing Pyridazinone and Related Nuclei[1]

BY FRANK L. WEISENBORN, DAVID C. REMY AND THOMAS L. JACOBS

RECEIVED AUGUST 14, 1953

Heterocyclic analogs of cholesterol and testosterone in which the A ring of these compounds is replaced by a pyridazinone ring have been prepared. The synthesis involved degradation of the A ring of these steroids by removal of carbon atoms 3 and 4 to form γ-keto acids which were then allowed to react with hydrazine. In cholesterol the A ring was also replaced by the tetrahydropyridazone nucleus.

Steroids in which one or more of the rings of the cyclopentanoperhydrophenanthrene system have been replaced by heterocyclic nuclei may be expected to have interesting physiological properties. Compounds of this kind, especially where the heterocyclic ring contains nitrogen,[2-4] are rare and none containing pyridazine, pyridazinone or related systems are known. This paper describes the preparation of cholesterol and testosterone derivatives in which the A ring has been replaced by the pyridazinone or tetrahydropyridazone nucleus. The accompanying chart details the steps in the syntheses of these compounds and the yields realized in the cholesterol series [R = $CH_3CHCH_2CH_2$-$CH_2CH(CH_3)_2$].

Route I → IX → VI was superior to the alternative Barbier–Wieland degradation (II → III → IV → V → VI) in the cholesterol series and the latter was therefore not carried out with testosterone (I, R = OH). However, II (R = OH) was obtained in 75% yield without difficulty by ozonization of testosterone. Lower yields of II (R = OH) were reported from ozonization of testosterone acetate.[2]

Keto acid II (R = C_8H_{17}) which is well known[5] gave ketal ester III as a glass, presumably a mixture of the mono- and di-esters of ethylene glycol. III was used directly to prepare crystalline IV. Hydrolysis of ketal IV and simultaneous dehydration gave a crude product which was converted without difficulty to VI. Keto acid VI showed no characteristic carbonyl absorption in the ultraviolet and gave a single carbonyl band at 5.67 μ in the infrared. Such a band is characteristic of a five-membered lactone and indicates that VI exists in the lactol form.

No crystalline product could be isolated from the hydrolysis mixture, which presumably contained mainly V (R = C_8H_{17}), but a crystalline 2,4-dinitrophenylhydrazone of the correct composition was obtained in high yield. V was regenerated almost quantitatively from this derivative as an oil which had the expected ultraviolet absorption.

Ozonization of V (R = C_8H_{17}) and reductive decomposition of the ozonide gave an oil from which a bis-2,4-dinitrophenylhydrazone corresponding in composition to a derivative of a ketoaldehyde was obtained. Treatment of the oil with hydrazine hydrate produced a complex reaction mixture from which was isolated by chromatography very low yields of several crystalline compounds. None of these proved to be the desired dihydropyridazine and structures were not determined. This reaction and alternative methods for preparing the dihydropyridazine are being examined and will be reported at a later time.

Although hydroxymethylenecholestenone[6] and hydroxymethylenetestosterone[7,8] are known, the latter has never been described carefully, and no report of the ozonization of either has appeared. In the cholestenone series lactol VI (R = C_8H_{17}) was isolated without difficulty when three molecular equivalents of ozone were allowed to react with hydroxymethylenecholestenone and the reaction mixture treated with hydrogen peroxide. No attempt was made to obtain diacid X (R = C_8H_{17}). The same procedure was applied to hydroxymethylenetestosterone, but water-soluble material made up most of the product and only a very low yield of pyridazinone VII (R = OH) was isolated from the hydrazine hydrate reaction on the portion insoluble in water. Diacid X (R = OH) was the only easily isolable product when less ozone was used, but reaction of the residue with hydrazine hydrate gave somewhat better yields of the pyridazinone. Lactol VI (R = OH) was isolated in crystalline form by chromatographing the mixture of crude acids from the ozonization.

An attempt was made to synthesize lactol VI (R = C_8H_{17}) by ozonization of the condensation product of cholestenone and ethyl oxalate[7-9]; crystalline material was not readily obtained from the product, and the infrared spectrum of the crude

(1) Taken in part from a thesis submitted by David C. Remy in partial fulfillment of the requirements for the M.S. degree, University of California, Los Angeles, August, 1952. Presented before the Organic Division of the American Chemical Society, Chicago, Illinois, September, 1953.

(2) C. C. Bolt, *Rec. trav. chim.*, **57**, 905 (1938).

(3) W. E. Bachmann and F. Ramirez, THIS JOURNAL, **72**, 2527 (1950).

(4) St. Kaufman, *ibid.*, **73**, 1779 (1951).

(5) R. B. Turner, *ibid.*, **72**, 579 (1950).

(6) J. G. Burr, W. F. Holton and G. N. Webb, *ibid.*, **72**, 4903 (1950).

(7) Soc. pour Ind. chim. à Bâle, Swiss Patent 207,498 (Feb. 16, 1940); *C. A.*, **35**, 3038 (1941).

(8) L. Ruzicka, U. S. Patent 2,281,622 (May 5, 1942); *C. A.*, **36**, 5958 (1942).

(9) L. Ruzicka and P. A. Plattner, *Helv. Chim. Acta*, **21**, 1717 (1938).