[CONTRIBUTION FROM THE COLLIP MEDICAL RESEARCH LABORATORY, UNIVERSITY OF WESTERN ONTARIO]

Steroids and Related Products. V.[1] The Synthesis of 11-Dehydro-17α-methylcorticosterone[2]

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The synthesis of 11-dehydro-17α-methylcorticosterone, a new analog of cortisone, is described.

Recently, the syntheses of 17α-methyldesoxycorticosterone[4,5] and of its biologically inactive epimer, 17β-methyl-17-isodesoxycorticosterone[6] have been described. The preparation of 17-methyl analogs of cortical adrenal hormones appeared desirable because of the great biological activity of 17-methylated sex hormones.[7] The study of 17α-methyl adducts of 11-oxygenated cortical adrenal hormones seemed to merit special attention; indeed, cortisone and cortisol, which also possess a substituent in the 17α-position, in the form of a hydroxy group, are not only the most potent natural glucocorticoids but the only natural cortical adrenal factors with marked antiarthritic activity. (In the series of 9α-halo- and of 1-dehydro-steroids the representatives with the most potent antiinflammatory action have likewise a 17α-hydroxy substituent.[8,9]) It is noteworthy that corticosterone and 11-dehydrocorticosterone, which lack the 17α-hydroxy substituent, also exhibit appreciable glucocorticoid activity but appear to have no therapeutic value in the treatment of rheumatoid arthritis. It therefore seemed desirable to study the biological effects of the replacement of the biologically important 17α-hydroxy group by a 17α-methyl group, especially as the introduction of the latter had given rise to pharmacologically interesting compounds in other steroid series.

The present paper deals with the synthesis of 11-dehydro-17α-methylcorticosterone (XII), the 17-methyl analog of cortisone and homolog of 11-dehydrocorticosterone. The preparation of the corresponding 11β-hydroxy adduct, the analog of cortisol, will be reported in a subsequent article of this series.

An intermediate in various syntheses of cortisone, 3α-acetoxy-11,20-dioxopregnane (I), served as starting material for the described synthesis.[10] Bromination of this diketone with one mole of bromine gave a crystalline reaction product from which a monobromide and a dibromide could be isolated by fractional crystallization. By chromatography on aluminum oxide unreacted starting material was separated from the bromide fractions. Since it has been established that the 20-ketone function undergoes α-bromination with greater ease than the 11-ketone function[11a-c] and that the monobromination of a 20-ketone proceeds preferentially in position 17,[12a,b,c,d] the structure of a 17-bromide II has to be attributed to the monobromide fraction, representing the major reaction product. This assignment is in accordance with the work of Julian, who reported the bromination of I without giving experimental details.[13] The physical constants of the monobromide II are in good agreement with those published by Anderson, *et al.*, who reported recently the preparation of 17-bromo-3α-acetoxy-11,20-dioxopregnane by the action of hypobromous acid on the 17-enol acetate of I.[14a] After completion of the work here described Shock and Karpel disclosed in a patent[14b] the preferential bromination of I in position 17, in good yield, by the use of N-bromosuccinimide. The dibromide has to be considered the 17,21-dibromide IIa because of the previously mentioned more facile α-bromination of a 20-ketone compared with that of an 11-ketone.[11a-c] Furthermore, it has been shown that a 17,21-dibromo-20-ketone of type IIa underwent, under the influence of alkali in aqueous methanol, a Faworsky rearrangement,[15] yielding a Δ^{17}-unsaturated acid of type III.[16a-g] When

(1) Paper IV of this series: Ch. R. Engel and R. L. Noble, *J. Endocrin.*, **14**, in press (1956).

(2) Part of the results reported in this paper were published in a preliminary form [Ch. R. Engel, THIS JOURNAL, **77**, 1064 (1955)], others were included in a communication presented before the 3rd International Congress of Biochemistry in Brussels, August, 1955.

(3) Holder of a Medical Fellowship of the Canadian Life Insurance Officers Association.

(4) Ch. R. Engel and G. Just, THIS JOURNAL, **76**, 4909 (1954).

(5) H. Heusser, E. Beriger and Ch. R. Engel, *Helv. Chim. Acta*, **37**, 2166 (1954).

(6) Ch. R. Engel and G. Just, *Can. J. Chem.*, **33**, 1515 (1955).

(7) Compare for instance references 2, 3, 4, 5, 6 and 7 of the article cited under footnote 2 of this paper.

(8) (a) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953), **76**, 1455 (1954); (b) A. Borman, F. M. Singer and P. Numerof, *Proc. Soc. Exp. Biol. Med.*, **86**, 570 (1954); (c) F. M. Singer and A. Borman, *Federation Proc.*, **14**, 281 (1955); (d) W. E. Dulin, *Proc. Soc. Exp. Biol. Med.*, **90**, 114 (1955).

(9) (a) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg and P. L. Perlman, *Science*, **121**, 176 (1955); (b) J. J. Bunim, M. M. Pechet and A. J. Bollet, *J. Am. Med. Assoc.*, **157**, 311 (1955).

(10) Sincere thanks are extended to the Ciba Ltd., Basle, for providing this starting material.

(11) Compare for instance: (a) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, THIS JOURNAL, **74**, 483 (1952); (b) J. M. Chemerda, E. M. Chamberlain, E. H. Wilson and M. Tishler, *ibid.*, **73**, 4052 (1951); (c) G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, **73**, 4055 (1951).

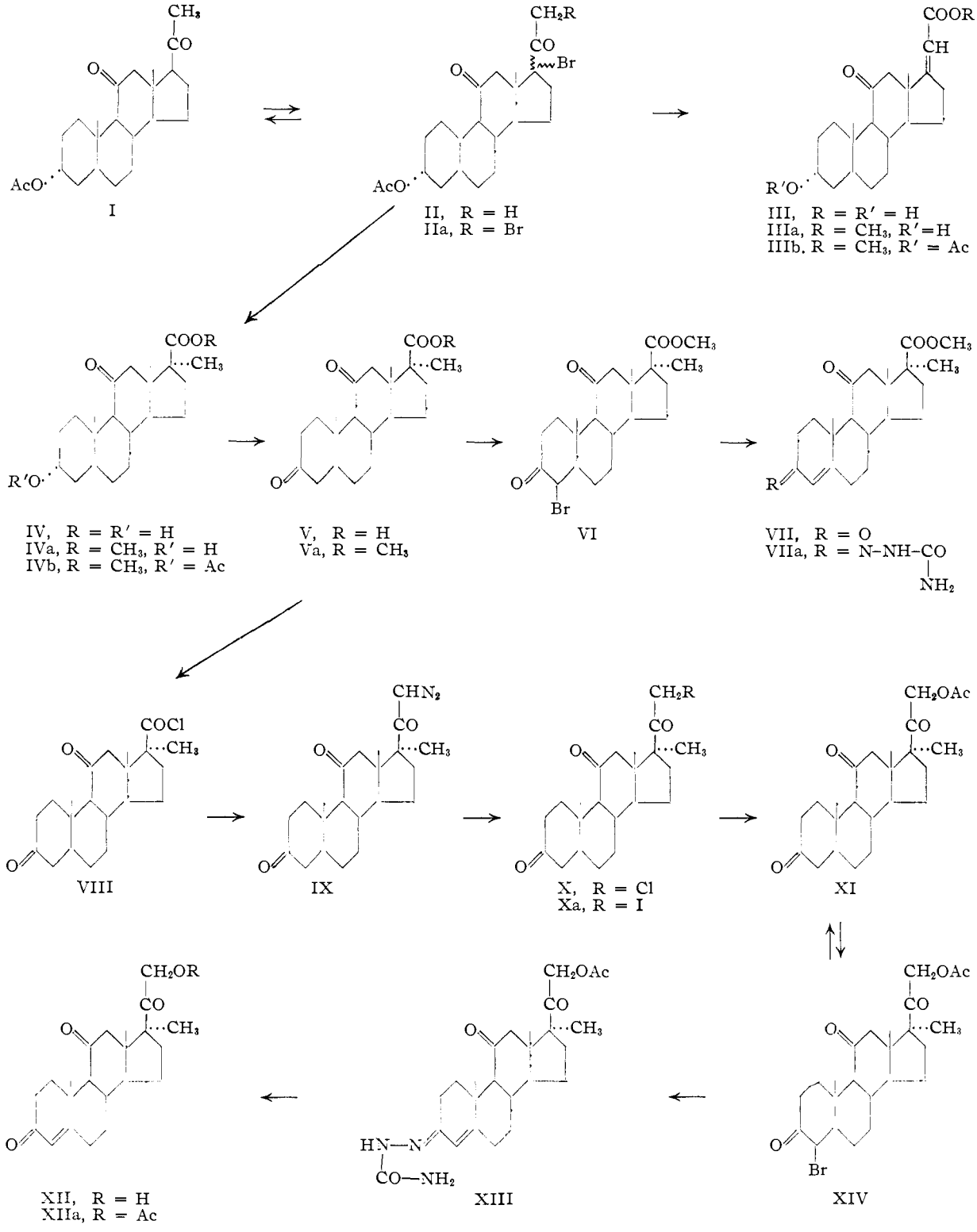
(12) Compare for example: (a) R. E. Marker, H. M. Crooks, Jr., and R. B. Wagner, *ibid.*, **64**, 210 (1942); (b) R. E. Marker, H. M. Crooks, Jr., R. B. Wagner and E. L. Wittbecker, *ibid.*, **64**, 2089 (1942); (c) H. Heusser, Ch. R. Engel, P. Th. Herzig and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 2229 (1950); (d) H. L. Herzog, C. C. Payne, M. E. Tully and E. B. Hershberg, THIS JOURNAL, **75**, 5751 (1953).

(13) P. L. Julian, *Recent Progr. in Hormone Research*, **6**, 195 (1951).

(14) (a) H. V. Anderson, E. R. Garrett, F. H. Lincoln, Jr., A. H. Nathan and J. A. Hogg, THIS JOURNAL, **76**, 743 (1954); (b) R. U. Shock and W. J. Karpel, U. S. Patent 2,684,963 (1954).

(15) (a) Al. Faworsky, *J. prakt. Chem.*, [2] **88**, 658 (1913); (b) H Ssemenow, *J. Russ. Phys.-chem. Soc.*, **43**, 693 (1911).

(16) (a) R. E. Marker, H. M. Crooks, Jr., and R. B. Wagner, THIS JOURNAL, **64**, 817 (1942); (b) R. E. Marker, H. M. Crooks, Jr., R. B. Wagner, A. C. Shabica, E. M. Jones and E. L. Wittbecker, *ibid.*, **64**, 822 (1942); (c) R. E. Marker, H. M. Crooks, Jr., E. M. Jones and A. C. Shabica, *ibid.*, **64**, 1276 (1942); (d) H. H. Inhoffen, U. S. Patent 2,409,943 (1946); (e) P. L. Julian and W. J. Karpel, THIS JOURNAL, **72**, 362 (1950); (f) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944); (g) compare also: Pl. A. Plattner, H. Heusser and S. F. Boyce, *ibid.*, **31**, 603 (1948).



the crude bromination product of I was subjected to the action of potassium bicarbonate in aqueous methanol, the α,β-unsaturated acid III was separated from the acid fraction; it showed the typical ultraviolet absorption spectrum (λ_{max}^{EtOH} 220 mμ, log ϵ 4.2) and was further characterized by its methyl ester IIIa and the 3α-acetate IIIb of the latter. Acid III could have been formed, under the experimental conditions employed, only from the 17,21-dibromide IIa; a 16,17-dibromo-20-ketone would also have given acid III under the rearrangement conditions,[17] but a 16,17-dibromide could not have

(17) Compare R. E. Marker, R. B. Wagner and E. L. Wittbecker, THIS JOURNAL, **64**, 2093 (1942).

been the product of bromination of a saturated 20-ketone of type I.

The monobromide fraction underwent an Aston–Greenburg or Faworsky rearrangement[15a,18] under the influence of potassium bicarbonate in methanol–water, affording after debromination and acetylation of the neutral reaction product the desired methyl 3α-acetoxy-11-oxo-17α-methyletianate (IVb) in 60–75% yield.[19] Acid IV was isolated in 5–10% yield from the acid fraction of the rearrangement product. Since the fractionation of the bromination product of I was costly, the crude product was also subjected to a Faworsky rearrangement under the same conditions, and methyl ester IVb and acid IV were isolated in approximate yields of 40 and 5%, respectively; the tertiary ester IVb was accompanied by an isomer, the constitution of which will be discussed elsewhere; as already mentioned, the α,β-unsaturated acid III was also isolated from the acid fraction in approximately 5% yield (calculated on I).

Boiling methanolic potassium hydroxide saponified the acetate grouping of IVb, yielding the corresponding hydroxy ester IVa, which could be reacetylated easily to ester IVb. Total saponification of the latter was accomplished in high yield by heating it for 48–50 hours with a 7% methanolic potassium hydroxide solution at 170° in a sealed tube. The resulting free acid IV proved to be identical with the main acid fraction from the rearrangement reaction; it was remethylated readily to the hydroxy ester IVa with diazomethane and oxidized in over 85% yield to the 3,11-dioxo acid V by the action of chromic acid. The diketo acid V was characterized by its methyl ester Va, also obtained by chromic acid oxidation of the hydroxy ester IVa. The keto ester Va was further characterized by its Δ^4-analog, the preparation of which was also desirable for synthetic experiments of another series. The unsaturated ester VII was obtained *via* the 4β-bromo derivative VI and the semicarbazone VIIa, according to Kendall's method.[20] The structures of the rearrangement products and their derivatives were also confirmed by infrared analyses of the ester IVb and of the unsaturated diketo ester VII.[21]

The diketo acid V was transformed to its chloride VIII with oxalyl chloride, in the absence of pyridine, according to Reichstein's modification[22a–c] of Wilds' method.[23a–c] By the action of diazomethane on the crude chloride VIII, at low temperature, the diazoketone IX was formed; it was decomposed without further purification with hydrogen chloride, giving the chlorotriketone X. The latter was separated by chromatography from relatively small amounts of diketo ester Va (5–10%) and of acid V (7–12%). Considering the recovery of these products in the pure state the yield of the chloro triketone X from acid V was 70–75%. In order to replace the inert chlorine atom of the chloro triketone by an acetoxy grouping, the chloride X was converted to the iodide Xa by the action of sodium iodide in acetone in a nitrogen atmosphere. The iodide Xa was refluxed with a solution of silver acetate in pyridine, in presence of small amounts of acetic anhydride and in a nitrogen atmosphere, using a modification of a previously described method.[4–6] The ketol acetate XI, thus obtained in a yield of 69%, was brominated in position 4β, the resulting crude bromide XIV was purified by crystallization from methylene chloride–methanol and the mother liquors were debrominated with zinc and acetic acid to the ketol acetate XI; considering this recovery, the yield of pure bromide XIV was 90–95%. Using Kendall's method,[20] the purified bromide was converted *via* the semicarbazone XIII to the crystalline 11-dehydro-17α-methylcorticosterone acetate (XIIa) in a yield of approximately 90%; the yield of the completely purified product amounted to 77%. By the prolonged action of potassium bicarbonate in methanol–water, at room temperature and in a nitrogen atmosphere, the acetate was hydrolyzed to the free alcohol, 11-dehydro-17α-methylcorticosterone (XII), in quantitative yield. The alcohol could be reacetylated in high yield to the ketol acetate XIIa, with acetic anhydride in pyridine under nitrogen. The ketol XII and its acetate XIIa showed the expected ultraviolet absorption spectra of Δ^4-3,11-dioxosteroids (λ_{max}^{EtOH} 237–238 mμ, log ε 4.2–4.4). The structures of the two products were further confirmed by their infrared spectra.[24]

Dr. E. H. Venning and Prof. R. Meier and Dr. P. Desaulles kindly tested 11-dehydro-17α-methylcorticosterone acetate for its glucocorticoid activity, using Venning's liver glycogen deposition test[25] and a modification of this assay, and found it to possess one-fourth to one-fifth of the activity of 11-dehydrocorticosterone acetate and of cortisone acetate. Prof. Meier and Dr. Desaulles established that its antiinflammatory activity, assayed in Meier's local granuloma test,[26] amounted also to one-fourth to one-fifth of the activity of cortisone acetate and equalled approximately that of 11-dehydrocorticosterone acetate. The same authors found that 11-dehydro-17α-methylcorticosterone acetate showed no effect on electrolyte metabolism and water retention at dose levels at which cortisone acetate exhibited marked activity. According to preliminary observations by Prof. J. A. F. Stevenson, the product seems to differ also qualitatively from cortisone acetate with respect to its mineralo-corticoid activity. The free alcohol, 11-dehydro-17α-methylcorticosterone, was tested by Dr. Venning in her

(18) J. G. Aston and R. B. Greenburg, THIS JOURNAL, **62**, 2590 (1940).

(19) Comparable rearrangements have been described by (a) R. E. Marker and R. B. Wagner *ibid.*, **64**, 216, 1273 (1942); (b) in the articles cited under footnotes 12c and 16c.

(20) W. F. McGuckin and E. C. Kendall, *ibid.*, **74**, 5811 (1952).

(21) The author is indebted to Prof. Hs. H. Günthard, Swiss Federal Institute of Technology, Zurich, and to Dr. G. Papineau-Couture, Ayerst, McKenna and Harrison, Ltd., Montreal, for these infrared analyses.

(22) (a) F. Reber, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **37**, 45 (1954); (b) A. Lardon and T. Reichstein, *ibid.*, **37**, 388, 443 (1954); (c) compare also the article cited under footnote 6.

(23) (a) A. L. Wilds, U. S. Patent 2,538,611 (1948); (b) A. L. Wilds and C. H. Shunk, THIS JOURNAL, **70**, 2427 (1948); (c) see also R. Adams and L. H. Ulich, *ibid.*, **42**, 599 (1920).

(24) The infrared spectral analyses of these compounds were kindly performed by Dr. R. N. Jones, National Research Council, Ottawa, and Mr. R. W. White, Science Service Laboratory, London, Ontario.

(25) E. H. Venning, V. E. Kazmin and J. C. Bell, *Endocrinology*, **38**, 79 (1946).

(26) R. Meier, W. Schuler and P. Desaulles, *Experientia*, **6**, 469 (1950).

glycogen deposition test and was found to possess only approximately one-twelfth of the activity of cortisone and one-sixth of the activity of 11-dehydrocorticosterone.

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Experimental[27-29]

Bromination of 3α-Acetoxy-11,20-dioxopregnane (I). (a).—To a solution of 486 mg. of 3α-acetoxy-11,20-dioxopregnane (I) in 8 cc. of acetic acid were added at room temperature two drops of 25% hydrogen bromide solution in acetic acid and subsequently, dropwise and with stirring, 207 mg. of bromine in 1.37 cc. of acetic acid. The bromine addition was completed within 25 minutes and the mixture was stirred for another 35 minutes. The practically colorless solution was poured into 200 cc. of water, the precipitate was extracted with ether, the ethereal layer was washed with cold sodium bicarbonate solution, iced dilute sodium carbonate solution and water and was dried. The solution was reduced *in vacuo* to 1 cc., hot methanol (6 cc.) was added and after cooling the crystalline precipitate (420 mg.) was filtered off and subjected to a fractional crystallization from methanol. The dibromide IIa was isolated as the less soluble component in the pure state, after 7 recrystallizations; colorless needles, m.p. 177° dec., $[\alpha]^{25}D$ 22.3° (*c* 1.121, in $CHCl_3$).

Anal. Calcd. for $C_{23}H_{32}O_4Br_2$: C, 51.89; H, 6.06; Br, 30.03. Found: C, 51.85; H. 6.24; Br, 29.82.

The monobromide, 17-bromo-3α-acetoxy-11,20-dioxopregnane (II) was isolated as the more soluble component of the mixture (by 2 recrystallizations of the second mother liquors); colorless needles, m.p. 168–170°, $[\alpha]^{25}D$ 0.8° (*c* 0.864 in $CHCl_3$).

Anal. Calcd. for $C_{23}H_{33}O_4Br$: C, 60.92; H, 7.34; Br, 17.63. Found: C, 60.86, 61.14; H, 7.47, 7.43; Br, 17.51, 17.45.

(b).—A solution of 2.5 g. of 3α-acetoxy-11,20-dioxopregnane (I) in 35 cc. of acetic acid was treated with 1.068 g. of bromine in 6.68 cc. of acetic acid and worked up as described under (a). The dried ethereal solution of the reaction product was taken to dryness *in vacuo* and the crystalline residue (3.18 g.) was chromatographed rapidly on 96 g. of slightly acid activated aluminum oxide. The petroleum ether–benzene (4:1 and 1:1) mixtures eluted bromide fractions (2.254 g.); the petroleum ether–benzene (1:4) fractions gave 440 mg. of starting material, the acetoxy diketone I, m.p. 118–126°. Admixture with authentic material did not depress the melting point. Two crystallizations of a petroleum ether–benzene fraction (4:1), melting between 156 and 158°, gave pure monobromide II, m.p. 169.5–170.5°, $[\alpha]^{23}D$ −2° (*c* 1.532, in $CHCl_3$).

Anal. Calcd. for $C_{23}H_{33}O_4Br$: Br, 17.63. Found: Br, 17.59.

Debromination.—A fraction of the bromination product (170 mg., m.p. 153–155°) containing a mixture of mono- and dibromides, the monobromide II prevailing, was dissolved in 4 cc. of acetic acid and 0.4 cc. of water. To this solution 400 mg. of zinc dust was added portionwise over a period of 20 minutes at 70°, with repeated shaking. The mixture was heated on a boiling water-bath for 30 minutes. After cooling ether and water were added, the mixture was filtered and the ethereal layer was washed with iced hydrochloric acid, cold sodium bicarbonate solution and water and was dried and the solvent was removed. The residue (150 mg.) crystallized after seeding with starting material; m.p. 126–129°, not depressed upon admixture with I.

(c).—To a solution of 10 g. of 3α-acetoxy-11,20-dioxopregnane in 157 cc. of acetic acid were added, at room temperature, dropwise and with stirring, 0.1 cc. of a 25% solution of hydrogen bromide in acetic acid and subsequently 4.268 g. of bromine in 27.36 cc. of acetic acid. The addition took one hour and 50 minutes. The only slightly yellow mixture was stirred for another 20 minutes, poured into 3.5 l. of water, the precipitate was extracted with ether and the ethereal solution was worked up as described under (b). Thus 12.35 g. of crude crystalline bromination product was obtained; it was used without further purification in the following rearrangement reaction.

Methyl 3α-Acetoxy-11-oxo-17α-methyletianate (IVb), 3α-Hydroxy-11-oxo-17α-methyletianic Acid (IV) and Δ^{17}-3α-Hydroxy-11-oxopregnene-21-acid (III). (a) Rearrangement of the Crude Bromination Product of Diketone I.—A solution of 12.35 g. of crude crystalline bromination product, obtained from 10 g. of ketone I (see above), in 540 cc. of methanol was refluxed for 4.5 hours with 27 g. of potassium bicarbonate in 120 cc. of water. The mixture was poured into 7 l. of water and the precipitate was extracted with ether. The ethereal solution was washed with water and was dried; after removal of the solvent there was obtained 7.45 g. of neutral amorphous material, referred to as "Neutral Fraction A."

The alkaline aqueous solution was acidified and extracted with chloroform. The organic solution was washed with water and dried, and the chloroform was taken off. The resulting acid fraction (1.458 g.) crystallized after having been moistened with acetone. Recrystallization afforded 375 mg. of 3α-hydroxy-11-oxo-17α-methyletianic acid (IV), m.p. 275–276° (4.7% yield, considering the recovery of starting material contained in the neutral fraction). Three further recrystallizations gave colorless needles, m.p. 285–286°, $[\alpha]^{25}D$ 29.5° (*c* 1.099, in dioxane).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.34; H, 9.04.

The mother liquors of the crystallizations of acid IV were at first treated with charcoal in ether and were then methylated overnight in absolute methanol with an ethereal diazomethane solution. The usual working up afforded 887 mg. of an amorphous product which was acetylated in the usual manner with 5 cc. of acetic anhydride in 8 cc. of pyridine. The resulting amorphous product (930 mg.), referred to as "Neutral Fraction B," was worked up together with "Neutral Fraction C," as described below.

The neutral rearrangement product "Neutral Fraction A" (7.45 g.), which still gave a positive Beilstein test, was dissolved in 67 cc. of acetic acid and 6.7 cc. of water and was debrominated with 6.7 g. of zinc dust at 90–100°. The usual working up yielded 7.8 g. of an amorphous product which was dissolved in 16 cc. of pyridine and acetylated overnight with 12 cc. of acetic anhydride. The crude reaction product (8.7 g.) crystallized to the greatest extent after being moistened with methanol. Crystallization from methanol afforded 3.012 g. of methyl 3α-acetoxy-11-oxo-17α-methyletianate (IVb), m.p. 170–179°. A sample was recrystallized three times from methanol for analysis; coarse cubes, m.p. 184°, $[\alpha]^{25}D$ 63.7° (*c* 0.982, in $CHCl_3$), γ_{max}^{nujol} 1727, 1242, 1040 cm.$^{-1}$ (3α-acetate), 1704 cm.$^{-1}$ (11-ketone), 1137 cm.$^{-1}$ (17-carbomethoxy).

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.99. Found: C, 71.21; H, 8.80.

The mother liquors of the crystallizations of ester IVb

(27) All melting points were taken in evacuated capillaries and the temperatures were corrected.

(28) The microanalyses were carried out by Mr. J. F. Alicino, Metuchen, N. J., to whom high appreciation is expressed. The analysis on the isomer of ester IVa was kindly performed by Mr. W. Manser of the Swiss Federal Institute of Technology.

(29) The aluminum oxide used for chromatography was treated as described under footnote 31 of reference 4. Sincere thanks are rendered to Messrs. Merck and Co., Montreal, for kindly providing this reagent.

("Neutral Fraction C") were combined with "Neutral Fraction B" from the methylated and acetylated acid fraction (see above), and chromatographed on 200 g. of aluminum oxide. The petroleum ether–benzene (4:1) fractions eluted an acetoxy ester, isomeric with ester IVb. A sample was recrystallized four times from methanol for analysis; colorless needles, m.p. 155.5°, depressed upon admixture with ester IVb, $[\alpha]^{25}D$ 41.9° (*c* 0.702, in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.99. Found: C, 71.40; H, 8.81.

The constitution of this product will be discussed elsewhere.

The following petroleum ether–benzene fractions and the first benzene–ether fractions eluted mixtures of ester IVb and its isomer. Further benzene–ether fractions afforded 1.5 g. of starting material which, after one recrystallization, melted at 124–128°. The fractions representing mixtures were rechromatographed and recrystallized. *In toto* 3.942 g. (42.4%) of ester IVb and 950 mg. (8%) of its isomer were obtained.

In a series of analogous experiments in which 15 g. of diketone I had been employed, 2.688 g. of an acid fraction, m.p. 174–223°, was obtained by rearrangement of the crude bromination product. Fractional crystallization from acetone afforded 520 mg. of acid IV as the less soluble component and 980 mg. of an acid fraction melting at 230–234°. The melting point of this fraction containing mostly the unsaturated **acid III** was depressed upon admixture with acid IV and the substance showed in the ultraviolet an absorption maximum at 219–220 mμ (log ε 3.8), typical of an α,β-unsaturated acid. The product was recrystallized four times for analysis and retained one mole of acetone even after thorough drying in high vacuum; colorless needles, m.p. 246.5–247.5°, $[\alpha]^{21}D$ 28.5° (*c* 1.098, in $CHCl_3$), λ_{max}^{EtOH} 220 mμ (log ε 4.2).

Anal. Calcd. for $C_{21}H_{30}O_4 \cdot CH_3COCH_3$: C, 71.25; H, 8.97. Found: C, 71.55; H, 8.60.

The acetone of crystallization was removed at 150° in high vacuum.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.74; H, 8.63.

Methyl Ester IIIa.—The mother liquors of the above described acid III (846 mg.) were dissolved in 7 cc. of absolute methanol and 20 cc. of absolute ether and methylated in the usual manner overnight with diazomethane. There was obtained 865 mg. of a crystalline material, m.p. 173.5–176°, λ_{max}^{EtOH} 221 mμ (log ε 3.9). Four further crystallizations raised the m.p. to 184°, $[\alpha]^{23}D$ 29.2° (*c* 0.922, in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.08; H, 8.97.

Acetoxy Methyl Ester IIIb.—The mother liquors of the above described crystallizations of ester IIIa (830 mg.) were dissolved in 8 cc. of pyridine and acetylated in the usual manner with 5 cc. of acetic anhydride. There was obtained 880 mg. of a product crystallizing from methanol. One recrystallization afforded 340 mg. of methyl ester IVb, crystallizing in coarse cubes, m.p. 176.5–178°; the melting point was not depressed upon admixture with authentic ester IVb, and the product showed no absorption maximum in the ultraviolet between 215 and 260 mμ. The mother liquors (450 mg.) were chromatographed on 13 g. of aluminum oxide. Petroleum ether–benzene (19:1 and 4:1) eluted 221 mg. of fine needles, m.p. 113–114°, λ_{max}^{EtOH} 223 mμ (log ε 3.8). The product, representing IIIb, was recrystallized three times from methanol, for analysis; m.p. 127–128°, $[\alpha]^{23}D$ 49° (*c* 0.43, in $CHCl_3$), λ_{max}^{EtOH} 222 mμ (log ε 4.1).

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.71; H, 8.51. Found: C, 71.86; H, 8.26.

(b) **Rearrangement of the Monobromide Fraction (II).**—A solution of 113 mg. of a monobromide fraction, m.p. 162–167°, obtained by fractional recrystallization of the crude product, in 4.1 cc. of methanol was refluxed with 245 mg. of potassium bicarbonate in 0.95 cc. of water, during 4 hours. The usual working up afforded 30 mg. of an acid product from which 4 mg. (4.6%) of acid IV, m.p. 272–274°, was obtained. The neutral fraction (105 mg.) was debrominated, methylated and acetylated, and the resulting product was chromatographed in the usual way. Petroleum ether–benzene, benzene and benzene–ether (4:1) eluted 64 mg. (63.5%) of ester IVb, m.p. 150–172°. One recrystallization raised the m.p. to 179.5–181°. From the mother liquors of the first petroleum ether–benzene fractions 26 mg. of the isomeric ester was obtained. The methylated and acetylated mother liquors of the acid crystallization afforded a further 17 mg. (16.9%) of impure, crystalline ester IVb.

In another series of experiments 365 mg. of purified monobromide gave 20 mg. (7.1%) of acid IV, m.p. 268–272°, 120 mg. of ester IVb, melting between 172.5 and 179.5°, and 95 mg. of the same product of lesser purity (total yield of crude ester IVb 70%) and 50 mg. (20%) of the crude isomeric ester.

3α-Hydroxy-11-oxo-17α-methyletianic Acid (IV) from **Methyl 3α-Acetoxy-11-oxo-17α-methyletianate (IVb).**—In a sealed tube, 2.769 g. of methyl 3α-acetoxy-11-oxo-17α-methyletianate (IVb), m.p. 175–182°, was heated with 100 cc. of a 6.9% methanolic potassium hydroxide solution for 49 hours at 170°. After dilution with water and extraction of the neutral fraction with ether the alkaline solution was acidified with 2 *N* sulfuric acid and the crystalline acid IV (2.17 g.) was filtered off. The colorless needles melted at 269–277°. The melting point was not depressed upon admixture with acid IV obtained from the acid fraction of the rearrangement. The filtrate was extracted with chloroform, the organic layer was washed with water and dried. Removal of the solvent afforded 90 mg. of crystalline acid; upon recrystallization from acetone it gave 51 mg. of acid IV, m.p. 280–282°; total yield 95%.

Methyl 3α-Hydroxy-11-oxo-17α-methyletianate (IVa). (a) **From Methyl 3α-Acetoxy-11-oxo-17α-methyletianate (IVb).**—A solution of 440 mg. of acetoxy ester IVb, m.p. 178.5–181.5°, in 44 cc. of 6% methanolic hydroxide was refluxed for 2.5 hours. The usual working up yielded 20 mg. of amorphous acid material and 385 mg. of crystalline neutral material, m.p. 159–164°, giving a depression of melting point upon admixture with the starting material IVb (yield 95%). A sample was recrystallized three times from ether–hexane for analysis; colorless needles, m.p. 165–166°, $[\alpha]^{22}D$ 41.5° (*c* 1.077, in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.78; H, 9.3.

(b) **From 3α-Hydroxy-11-oxo-17α-methyletianic Acid (IV).**—To a solution of 121 mg. of dried acid IV in 13 cc. of absolute methanol was added, with repeated shaking, 6 cc. of a 2% ethereal diazomethane solution at 0°. The yellow mixture was left at 0° for 2.5 hours, then at room temperature for 2 further hours. After addition of a further 1.5 cc. of diazomethane solution the mixture was left for 30 minutes at room temperature, the excess diazomethane was destroyed with 2 drops of acetic acid, and the solvent was removed *in vacuo*. There was obtained 125 mg. of a partly crystalline material, crystallizing totally upon moistening with ether–hexane. Two recrystallizations from ether–hexane afforded colorless needles, m.p. 163–165°, giving no depression of melting point with ester IVa, obtained by partial saponification of IVb.

Acetylation.—The hydroxy ester IVa (119 mg.) was acetylated in the usual manner with 3 cc. of acetic anhydride in 3 cc. of pyridine. There was obtained 121 mg. of crystalline acetoxy ester IVb, which melted after one recrystallization at 181°. The melting point was not depressed upon admixture with authentic ester IVb.

3,11-Dioxo-17α-methyletianic Acid (V).—To a solution of 2.768 g. of 3α-hydroxy-11-oxo-17α-methyletianic acid (IV) in 153 cc. of glacial acetic acid was added at 17°, 885 mg. of chromic acid in 8.7 cc. of 90% acetic acid. The mixture was allowed to stand at room temperature for 13 hours and subsequently 20 cc. of methanol was added. The solution was poured into 2.5 l. of water and the crystalline precipitate was filtered off and washed repeatedly with water. The product was dissolved in chloroform and the solution was filtered through sodium sulfate. Removal of the solvent afforded 2.34 g. of acid V, m.p. 284–285°, giving a depression of melting point with the starting material. The filtrate of the original precipitate was extracted with chloroform; the usual working up gave another 54 mg. of acid V, m.p. 282–285° (total yield of V, 87%). A sample was recrystallized three times from acetone for analysis; colorless needles, m.p. 288.5°, $[\alpha]^{22}D$ 45.1° (*c* 0.941, in dioxane).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.8; H, 8.73. Found: C, 72.68; H, 8.75.

In another series of experiments 9.48 g. of acid V was obtained from 9.6 g. of acid IV.

Methyl 3,11-Dioxo-17α-methyletianate (Va). (a) **From Methyl 3α-Hydroxy-11-oxo-17α-methyletianate (IVa).**—To a solution of 213 mg. of hydroxy ester IVa in 12.3 cc. of glacial acetic acid was added, at room temperature, 79 mg. of chromic acid in 7 cc. of 90% acetic acid. After 15 hours, 15 cc. of methanol was added and the mixture was poured into 255 cc. of water and extracted with ether. The organic solution was washed with water, cold sodium bicarbonate solution and water. After drying and removal of the solvent, 235 mg. of a crude product, m.p. 166–178°, was obtained. Recrystallization from ether–hexane gave 68 mg. of prisms, m.p. 182.5–183.5°. The mother liquors were chromatographed on 7 g. of aluminum oxide. Petroleum ether–benzene (1:4) and benzene eluted 140 mg. of ester Va, m.p. 178–182°. Admixture with the starting material gave a depression of melting point; total yield 208 mg. A sample was recrystallized three times for analysis, m.p. 185–185.5°, $[\alpha]^{23}D$ 49.8° (*c* 1.002, in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.27; H, 8.95. Found: C, 73.49; H, 8.81.

(b) **From 3,11-Dioxo-17α-methyletianic Acid (V).**—Mother liquors from a crystallization of impure keto acid V (112 mg.) were dissolved in 10 cc. of absolute methanol and 10 cc. of absolute ether and methylated in the usual manner overnight with a 3.8% ethereal diazomethane solution. The chromatogram of the reaction product yielded 58 mg. of colorless prisms, m.p. 173–177°, giving no depression of melting point with authentic material prepared by oxidation of IVa. One recrystallization raised the melting point to 181–181.5°.

Methyl Δ⁴-3,11-Dioxo-17α-methyletianate (VII).—To a solution of 153 mg. of diketo ester Va, m.p. 174–179°, in 2 cc. of acetic acid were added 1 drop of a 25% HBr solution in acetic acid and subsequently, with stirring, 63 mg. of bromine in 0.8 cc. of acetic acid, in the course of 10 minutes. The mixture was stirred for another 7 minutes, diluted with 180 cc. of water and extracted with methylene chloride. The usual working up afforded a solid product which gave upon moistening with ether 215 mg. of crystalline bromide VI, m.p. 154–157° dec., giving a positive halogen test.

The bromide was dissolved in 7.5 cc. of absolute, alcohol-free chloroform and 12.5 cc. of dry *t*-butyl alcohol and there was added 75 mg. of dry semicarbazide base to the solution. The mixture was flushed with carbon dioxide, sealed and shaken repeatedly. The usual color changes occurred.[20] After 120 minutes, unreacted semicarbazide was removed by filtration, the solvent was taken off *in vacuo* and 8 cc. of ethanol was added to the residue. The semicarbazone was precipitated with water. Filtration and drying afforded 204 mg. of **semicarbazone VIIa**, m.p. 210°. The product was dissolved in 6 cc. of acetic acid and 1.5 cc. of water and there was added 0.5 cc. of a 1.66 *N* aqueous pyruvic acid solution. The air was displaced by carbon dioxide, the flask was sealed and stored at room temperature for 17 hours. The product was poured into 200 cc. of cold water and extracted with chloroform. The usual working up afforded 223 mg. of an amorphous product which crystallized partly from acetone–petroleum ether; it was chromatographed on 7 g. of aluminum oxide. Petroleum ether–benzene (4:1 and 1:1) eluted 90 mg. of crystalline **ester VII**, m.p. 177–183°. The product was recrystallized twice from ether–hexane for analysis; coarse prisms, m.p. 183.5–184.5°, λ_{max}^{EtOH} 238 mμ (log ε 4.4), $\gamma_{max}^{CS_2}$ 1733 cm.$^{-1}$ (carbomethoxy), 1712 cm.$^{-1}$ (11-ketone), 1674 cm.$^{-1}$ (Δ⁴-3-ketone).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.62; H, 8.41.

3,11-Dioxo-17α-methyletianic Acid Chloride (VIII).—To a suspension of 850 mg. of dried diketo acid V in 45 cc. of absolute benzene was added, at 5°, 6 cc. of oxalyl chloride in 22 cc. of absolute benzene. The mixture was shaken repeatedly with exclusion of moisture. After 30 minutes the greater part of the acid was dissolved; a solution of a further 4 cc. of oxalyl chloride in 15 cc. of absolute benzene was added and the mixture kept at 28° for 45 minutes, with repeated shaking. Filtration from the unreacted diketo acid V (15 mg., m.p. 285°, giving no depression of melting point upon admixture with authentic acid V) and evaporation of the solvent *in vacuo*, with the exclusion of moisture, gave a colorless crystalline residue which was redissolved in absolute benzene. Removal of the solvent *in vacuo* gave 870 mg. of crude crystalline acid chloride V which was used without further purification in the following reaction.

Another crop of acid V (1.52 g.) gave under similar conditions 1.515 g. of crude acid chloride VIII.

21-Chloro-3,11,20-trioxo-17α-methylpregnane (X).—A solution of 870 mg. of crude acid chloride VIII in 30 cc. of absolute benzene was added, within 3 minutes and with stirring, to 20 cc. of a 2.9% ethereal diazomethane solution at −10°. The mixture was allowed to warm to 0° within 30 minutes and was kept at that temperature for 18 hours and at 25° for 15 minutes. The solvents were removed *in vacuo* at 22°; the resulting crude amorphous **diazoketone IX** was dissolved in 30 cc. of absolute benzene and a solution of 480 mg. of hydrogen chloride in 6 cc. of absolute ether was added dropwise, with vigorous stirring within 4 minutes. A marked evolution of gas was observed. The mixture was stirred for 40 minutes at 22–26°, poured into ice-water and extracted with ether; the ethereal layer was washed repeatedly with water, dried over sodium sulfate and the solvent was reduced at atmospheric pressure to 500 cc. and then taken off *in vacuo*. The foamy, almost colorless product (1.055 g.) was dissolved in 5 cc. of benzene and chromatographed on 35 g. of aluminum oxide. Petroleum ether–benzene (1:1) eluted 122 mg. methyl 3,11-dioxo-17α-methyletianate (Va) and a mixture of that substance with chloride X, petroleum ether–benzene (1:4), benzene and benzene–ether (4:1) 535 mg. of 21-chloro-3,11,20-trioxo-17α-methylpregnane (X), m.p. 145–149.5°, methanol containing 1% acetic acid 65 mg. of acid V, m.p. 276–286°, and 100 mg. of a less pure crop of this acid (m.p. 235–250°). The m.p. of the acid was not depressed upon admixture with authentic acid V. The fractions containing ester V were rechromatographed repeatedly and gave a further 80 mg. of chloride X, m.p. 146–150°, and 31 mg. of methyl 3,11-dioxo-17α-methyletianate (Va), m.p. 168–175°, giving no depression of melting point upon admixture with authentic Va. The yield of chloroketone X, m.p. 145–150°, was 71.6%, considering the recovery of pure acid (65 mg.). The melting point of the chloride was raised by one recrystallization from ether–hexane to 149.5–150.5°. A sample was recrystallized three times for analysis; colorless needles, m.p. 151–151.5°, $[\alpha]^{25}D$ 48.1° (*c* 0.89, in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{31}O_4Cl$: C, 69.73; H, 8.25; Cl, 9.36. Found: C, 69.93; H, 8.38; Cl, 9.32.

In an analogous series of experiments 8 g. of acid V was transformed to 5.2 g. of chloride X, and 850 mg. of crude ester Va and 810 mg. of crude acid V were recuperated.

3,11,20-Trioxo-21-acetoxy-17α-methylpregnane (XI).—A solution of 631 mg. of 21-chloro-3,11,20-trioxo-17α-methylpregnane (X), m.p. 148–150.5°, in 15 cc. of absolute acetone was refluxed under nitrogen with 490 mg. of sodium iodide in 9 cc. of absolute acetone for 45 minutes. Ether was added to the slightly yellow mixture, containing a precipitate of sodium chloride, and the ethereal solution was washed with water, 2 cc. of ice-cold 0.8% sodium hydroxide solution and water and was dried; the solvent was removed *in vacuo*. The resulting crude, solid **21-iodo-3,11,20-trioxo-17α-methylpregnane (Xa)** (744 mg.), m.p. 116–120° dec., was dissolved in 12 cc. of absolute pyridine, nitrogen was passed through the orange colored solution and there was added 2.3 g. of recrystallized and dried silver acetate in 12 cc. of absolute pyridine. The mixture was refluxed for 40 minutes under nitrogen, with exclusion of moisture, and 10 cc. of pyridine containing 0.2 cc. of acetic anhydride was added, compensating for the solvent displaced by the nitrogen current. The mixture was refluxed under nitrogen for a further 65 minutes, cooled, diluted with ether and filtered through sodium sulfate. The ethereal solution was washed repeatedly with iced 2 *N* sulfuric acid, water, cold 1% sodium hydroxide solution, cold bicarbonate solution and water. After drying and removal of the solvent, 622 mg. of neutral, solid, partly yellowish, partly brownish material was obtained. The alkaline washings were acidified and extracted with chloroform, the organic layer was washed until neutral and after removal of the solvent 42 mg. of solid acid material was obtained. The neutral fraction was chromatographed on 21 g. of aluminum oxide. Petroleum ether–benzene (1:1, 1:4), benzene and benzene–ether (4:1) gave 460 mg. (68.7%) of crystalline acetate XI, m.p. 177–191°, from which 345 mg. of crystals, m.p. 181–191.5°, and 50 mg. of crystals melting between 180 and 188° were obtained

by crystallization from ether–hexane. Admixture with chloride X depressed the melting point. Methanol and methanol containing 1% acetic acid eluted 89 mg. of impure acid V, m.p. 206–221°. A sample of acetate XI was recrystallized three times from ether–hexane for analysis; colorless needles, m.p. 191.5–192.5°, $[\alpha]^{24}D$ 45.9° (*c* 1.051, in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.67; H, 8.44.

In another series of experiments 3.1 g. of acetate XI was obtained from 4.8 g. of chloride X.

4β-Bromo-3,11,20-trioxo-21-acetoxy-17α-methylpregnane (XIV).—To a solution of 2.5 g. of the triketo acetate XI, m.p. 186–191°, in 50 cc. of acetic acid were added, at room temperature, two drops of a 25% hydrogen bromide solution in acetic acid and subsequently, dropwise and with stirring, within 25 minutes, 993 mg. of bromine in 12.6 cc. of acetic acid. Part of the reaction product crystallized during the end of the bromine addition. The rest of the product was precipitated with water. The bromide was filtered off, washed repeatedly with water and dried. The almost colorless crystals (2.569 g.) melted with decomposition between 173 and 179°. Extraction of the mother liquors afforded another crop of 180 mg. By crystallizations from methylene chloride–methanol, 1.95 g. of bromide XIV, m.p. 179–186° dec., was obtained. A sample was recrystallized for analysis, m.p. 184° dec., $[\alpha]^{26}D$ 46.2° (*c* 1.043, in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{33}O_5Br$: Br, 16.6. Found: Br, 16.15.

Debromination.—The crystalline mother liquors of the above described crystallizations of bromide XIV (836 mg.) were dissolved in 15 cc. of acetic acid and 1.5 cc. of water and debrominated in the usual manner with 1.5 g. of zinc dust at 80–90°. There was obtained 770 mg. of crystalline, partly yellowish acetoxy triketone XI, m.p. 168–177°, giving no depression of melting point upon admixture with authentic XI. Considering this recovery of starting material, the yield of purified bromide XII was 94.2%.

11-Dehydro-17α-methylcorticosterone Acetate (XIIa).—The purified bromide XIV (1.95 g., m.p. 179–186°) was dissolved in 61 cc. of absolute, alcohol-free chloroform and 102 cc. of dry *t*-butyl alcohol and the air was displaced with carbon dioxide. To the mixture was added 620 mg. of recrystallized semicarbazide base and the flask was again flushed with carbon dioxide, sealed and shaken repeatedly. The usual typical color changes were observed.[20] After 130 minutes, unreacted semicarbazide was filtered off and the filtrate was taken to dryness *in vacuo*. To the powdery residue 85 cc. of ethanol and 5 cc. of water were added and the solution was reduced *in vacuo*, at 50°, to 45 cc. After dilution with a further 400 cc. of water the mixture was cooled to −10°. The crystalline precipitate was filtered, washed repeatedly with water and dried *in vacuo*. Thus, 1.735 g. of **semicarbazone XIII**, m.p. 223–225°, λ_{max}^{EtOH} 270 mμ (log ε 4.5), was obtained. Extraction of the mother liquors afforded another 25 mg. of less pure material.

The semicarbazone (1.735 g.) was dissolved in 53 cc. of acetic acid and 19 cc. of water and the air was displaced with carbon dioxide. To the mixture was added 4.6 cc. of an aqueous 1.66 *N* pyruvic acid solution and the flask was flushed with carbon dioxide and sealed. After 17.5 hours the mixture was poured into water and extracted with ether. The organic solution was washed with iced sodium bicarbonate and sodium carbonate solutions, cold dilute hydrochloric acid, iced bicarbonate solution and water and was dried. Removal of the solvent afforded 1.504 g. (92.8%) of crude acetoxy triketone XIIa, which crystallized after trituration with ether–hexane (m.p. 141.5–144.5°). One crystallization gave 837 mg. of crystals, melting at 153.5–154.5°. Chromatography and recrystallizations of the mother liquors afforded 405 mg. of a slightly less pure crop of the same material (total yield of purified acetate XIIa, 76.7%). A sample was recrystallized twice for analysis; colorless, hygroscopic needles, m.p. 157–158°, $[\alpha]^{24}D$ 170° (*c* 0.79, in $CHCl_3$); λ_{max}^{EtOH} 237 mμ (log ε 4.4); $\gamma_{max}^{CHCl_3}$ 1750 and 1720 cm.$^{-1}$ (21-acetoxy-20-ketone doublet); 1710 cm.$^{-1}$ (11-ketone); 1670 and 1620 cm.$^{-1}$ (Δ^4-3-ketone doublet); γ_{max}^{KBr} 1740 and 1708 cm.$^{-1}$ (21-acetoxy-20-ketone doublet), 1698 cm.$^{-1}$ (11-ketone), 1671 and 1621 cm.$^{-1}$ (Δ^4-3-ketone doublet), 1230 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.23; H, 7.96.

11-Dehydro-17α-methylcorticosterone (XII).—A solution of 440 mg. of the acetate XIIa, m.p. 152–155°, in 44 cc. of methanol was flushed with nitrogen and subsequently there was added 455 mg. of potassium bicarbonate in 7.8 cc. of water at room temperature. The air was displaced with nitrogen and the flask was sealed. Crystals formed but disappeared again after 12 hours. The solution was kept in a nitrogen atmosphere for 90 hours and was subsequently diluted with 450 cc. of ice-water. No precipitate formed. The solution was extracted with 12 l. of ether and the ethereal solution was washed to neutral and worked up in the usual manner. There was obtained 397 mg. of almost colorless ketol XII, m.p. 154.5–155°, giving a marked depression of m.p. with acetate XIIa and a positive blue tetrazolium test. The product could best be recrystallized from acetone–water or from ether. A sample was recrystallized twice from ether for analysis; cubes, m.p. 154–155.5°; $[\alpha]^{22}D$ 174.2° (*c* 0.97, in $CHCl_3$); λ_{max}^{EtOH} 238 mμ (log ε 4.2); γ_{max}^{KBr} 3425 cm.$^{-1}$ (assoc. hydroxyl) 1700 and 1695 cm.$^{-1}$ (11,20-diketone), 1666 and 1616 cm.$^{-1}$ (Δ^4-3-ketone doublet).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.90; H, 8.28.

Acetylation.—A solution of 60 mg. of ketol XII, m.p. 155°, in 1.5 cc. of pyridine was flushed with nitrogen and mixed with 0.8 cc. of acetic anhydride. The solution was again flushed with nitrogen, the flask was sealed and kept at room temperature for 17 hours. Subsequently 40 cc. of ice-water was added and after 40 minutes the reaction product was worked up in the usual fashion. There was obtained 74 mg. of crystalline acetate XIIa, m.p. 154–156.5°, not depressed upon admixture with authentic acetate XIIa. The product was recrystallized from ether–hexane for analysis; m.p. 156–156.5°.

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.12; H, 8.26.

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5-Cholestene-3β,26-diol

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The preparation of 5-cholestene-3β,26-diol (II) from kryptogenin (I) is described.

5-Cholestene-3β,26-diol (II) is of interest since it may be an intermediate in the catabolism of cholesterol to bile acids and therefore it appeared desirable to prepare this compound for reference purposes. This paper describes the preparation of II from kryptogenin (I).

Clemmensen reduction of I yielded a crystalline mixture of II and 5-cholestene-3β,26-diol-16-one (III) in approximately a 1:1 ratio. After chromatography on alumina, the residue from the mother liquor yielded crystalline III. The initial mixture of II and III was quite inseparable even after ex-