tion mixture was extracted with three 50-ml. portions of ether and the combined ether extracts were dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the product distilled through a 6-in. Vigreux column. A small forerun was collected, followed by the main fraction, 30.2 g. (87%), b.p. 119° (0.5 mm.), $n^{25}D$ 1.4622.

Anal. Calcd. for $C_{11}H_{20}Cl_2O_2$: C, 51.77; H, 7.90; Cl, 27.79. Found: C, 51.49; H, 8.07; Cl, 28.14.

7,9-Di-(benzylthio)-nonanoic Acid (VII).—Ethyl 7,9-dichlorononanoate (29.6 g., 0.12 mole) was heated under reflux for 14 hours with an ethanol solution (175 ml.) of sodium benzylmercaptide prepared from 5.9 g. (0.26 mole) of sodium and 31.8 g. (0.26 mole) of benzyl mercaptan, and the product isolated in a manner described previously.[3] The crude product was crystallized from 600 ml. of benzene–Skellysolve B[9] (1:5); yield 29.7 g. (64%), m.p. 42.5–43.5°. A sample was recrystallized for analysis, m.p. 43–43.5°.

Anal. Calcd. for $C_{23}H_{30}O_2S_2$: C, 68.61; H, 7.51; S, 15.93. Found: C, 68.73; H, 7.31; S, 15.59.

DL-1,2-Dithiolane-3-caproic Acid (VIII).—7,9-Di-(benzylthio)-nonanoic acid (15.0 g., 0.037 mole) was reduced with sodium in liquid ammonia in a manner described previously.[3] The crude dimercapto acid was oxidized[3] with oxygen in the presence of ferric ion and the product was crystallized[10] from Skellysolve B, to yield 4.08 g. (50%) of low melting (*ca.* 27°) yellow crystals. A sample was recrystallized from Skellysolve B for analysis; m.p. 31–33°; $\lambda_{max}^{95\%\ ethanol}$ 332 mμ (ε 152), λ_{min} 280 mμ.

Anal. Calcd. for $C_9H_{16}O_2S_2$: C, 49.05; H, 7.32; S, 29.10. Found: C, 49.16; H, 7.55; S, 29.36.

Ethyl 5,7-Dichloroheptanoate (X).—A solution of 44.2 g. (0.195 mole) of ethyl 6,8-dichlorooctanoate in 100 ml. of anhydrous ether was added dropwise with stirring (30 minutes) to an ether solution (200 ml.) of phenylmagnesium bromide prepared from 72 g. (0.46 mole) of bromobenzene and 10.3 g. (0.44 mole) of magnesium. The mixture was heated under reflux for 3 hours and then decomposed with a solution of 25 g. of ammonium chloride in 75 ml. of water. The ether layer was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was dehydrated by heating under reflux for 4 hours with 300 ml. of acetic acid and 140 ml. of acetic anhydride. The solvents were removed *in vacuo* to yield 53.7 g. of an oily residue which did not distil at a bath temperature of 220° (0.2 mm.). It was dissolved in 110 ml. of isooctane and 450 ml. of acetic acid. This solution was maintained at 65° while a solution of 62.5 g. of chromic oxide in 45 ml. of water and 330 ml. of acetic acid was added during a period of 1.5 hours. The reaction mixture was poured into 2 l. of water and extracted with ether. The ether extract was washed with water, evaporated *in vacuo* and the residue extracted with 1 *N* sodium hydroxide. The insoluble material was removed by extraction with ether and the aqueous layer was acidified and the product extracted into ether. The ether extract was dried over anhydrous sodium sulfate and evaporated *in vacuo* to give 22.3 g. of crude 5,7-dichloroheptanoic acid. This material was esterified by heating under reflux with 30 ml. of absolute ethanol, 80 ml. of benzene and 3 ml. of sulfuric acid in an apparatus equipped with a Dean–Stark trap. The ester, yield 16.12 g. (39%), boiled at 102° (0.5 mm.), $n^{25}D$ 1.4618. A sample was redistilled for analysis, b.p. 92° (0.2 mm.), $n^{25}D$ 1.4612.

Anal. Calcd. for $C_9H_{16}Cl_2O_2$: C, 47.60; H, 7.10; Cl, 31.23. Found: C, 47.85; H, 7.08; Cl, 30.68.

5,7-Di-(benzylthio)-heptanoic Acid (XI).—Ethyl 5,7-dichloroheptanoate (14.3 g., 0.063 mole) was treated with sodium benzylmercaptide and the product isolated as described previously.[3] It was obtained as a light tan oil, 19.7 g. (84%).

Anal. Calcd. for $C_{21}H_{26}O_2S_2$: C, 67.32; H, 6.99; S, 17.12. Found: C, 67.72; H, 7.22; S, 17.73.

DL-1,2-Dithiolane-3-butyric Acid (XII).—5,7-Di-(benzylthio)-heptanoic acid (19.1 g., 0.051 mole) was reduced with sodium in liquid ammonia as described previously.[3] The crude dimercapto acid was oxidized[3] with oxygen in the presence of ferric ion and the product was crystallized[10] from Skellysolve B to yield 5.22 g. (56%) of yellow crystals, m.p. 38–39°. A sample was recrystallized from Skellysolve B for analysis: m.p. 40–41°; $\lambda_{max}^{95\%\ ethanol}$ 332 mμ (ε 148), λ_{min} 280 mμ.

Anal. Calcd. for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29; S, 33.35. Found: C, 43.77; H, 6.55; S, 33.41.

Acknowledgments.—We are indebted to Dr. C. G. Skinner and staff of the Biochemical Institute and to the Clark Microanalytical Laboratory, Urbana, Illinois, for the elemental analyses.

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(9) A *n*-hexane fraction, b.p. 60–68°, obtained from the Skelly Oil Co., Kansas City, Missouri.

(10) The cyclic disulfides VIII and XII polymerized to a significant extent when extracted with hot Skellysolve B. The sticky polymeric materials were insoluble in Skellysolve B and benzene, and could be converted in high yield to the cyclic disulfides by treatment with dilute alkali (R. C. Thomas and L. J. Reed, THIS JOURNAL, **78**, 6150 (1956).

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

Steroids and Related Products. VI.[1] The Synthesis of 11-Dehydro-17α-methylprogesterone, a Highly Active Gestogen[2]

BY CH. R. ENGEL, K. F. JENNINGS[3] AND G. JUST[4,5]

RECEIVED JULY 13, 1956

The synthesis of a new progesterone analog of high biological activity, 11-dehydro-17α-methylprogesterone, from 3α,12α-diacetoxy-20-oxopregnane is described. The 17α-methyl group was introduced by subjecting the 17-bromide of the starting material to a Faworsky rearrangement and the Δ^{11}-double bond by dehydrotosylation of 12α-tosylates, most effectively performed by the action of slightly alkaline activated aluminum oxide. In the course of this work, ultraviolet spectra of steroid tosylates were studied.

Both 11-dehydroprogesterone (I)[6a–c] and 17α-methylprogesterone (II)[7a–c] exceed the natural

(1) Paper V of this series: Ch. R. Engel, THIS JOURNAL, **78**, 4727 (1956).

(2) The main results of this communication were described in a paper presented before the Division of Medicinal Chemistry at the 126th National Meeting of the American Chemical Society in Dallas, Texas, April, 1956.

(3) In part from the M.Sc. thesis of K. F. Jennings, presented to the Faculty of Graduate Studies of the University of Western Ontario, September, 1953.

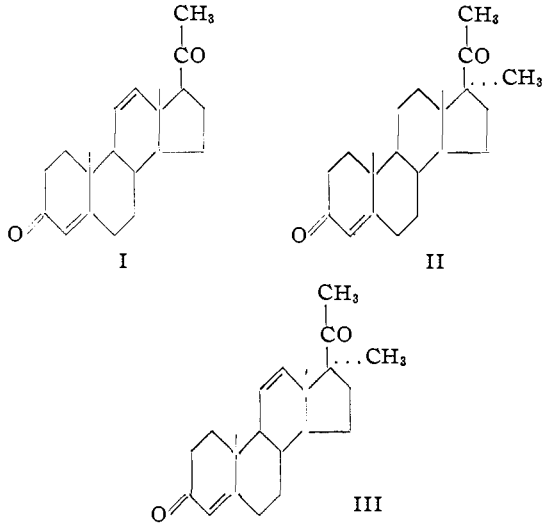
(4) In part from the Ph.D. thesis submitted by G. Just to the Faculty of Graduate Studies of the University of Western Ontario, May, 1956.

(5) Holder of an Ontario Research Council Special Fellowship 1953–1954 and of a Canadian National Research Council Studentship 1954–1955.

(6) (a) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **26**, 715 (1943); (b) J. von Euw and T. Reichstein, *ibid.*, **29**, 654 (1946); (c) Ch. Meystre, E. Tschopp and A. Wettstein, *ibid.*, **31**, 1463 (1948).

(7) (a) Pl. A. Plattner, H. Heusser and P. Th. Herzig, *ibid.*, **32**, 270 (1949); (b) H. Heusser, Ch. R. Engel, P. Th. Herzig and Pl. A. Plattner, *ibid.*, **33**, 2229 (1950); (c) Hs. H. Günthard, E. Beriger, Ch. R. Engel and H. Heusser, *ibid.*, **35**, 2437 (1952).

hormone of the corpus luteum in progestational activity; the former by a factor of three,[6c] the latter by a factor of two to three.[7b] In the case of desoxycorticosterone the addition of a 17α-methyl group enhances the luteoid activity even to a greater extent.[8] It therefore seemed desirable to synthesize 11-dehydro-17α-methylprogesterone (III), containing two chemical features which independently increase the progestational activity and to investigate its biological effects. The interest in new progesterone analogs is the greater because progesterone and some of its derivatives exhibit other important biological activities, such as anti-estrogenic,[9a-i] ovulation inhibiting,[10a-c] anti-androgenic,[9j,11a,b] growth inhibiting and anti-tumorigenic properties.[9-cj,12a-c]



The readily available bile acid derivative 3α,12α-diacetoxy-20-oxopregnane (IV) was chosen as starting material. Apart from having a 3-hydroxy function easily convertible to a Δ^4-3-ketone grouping, its methyl ketone side chain could be expected to yield, through a Faworsky rearrangement of its 17-bromide, a 17α-methyletianic acid derivative[1,7b,13a-h]; furthermore its 12-oxygen function could be considered a precursor of the desired 11,12-double bond since the classical method for the introduction of this unsaturation consists in the elimination of the elements of water from a 12α-hydroxy steroid, preferably *via* a corresponding ester derivative.[14a-c,15]

The diacetoxy ketone was brominated with one mole of bromine in acetic acid and the resulting amorphous product (mostly V) was subjected to a Faworsky rearrangement[16a,b] by the action of potassium bicarbonate in methanol–water in the usual manner.[1,7b,13] From the resulting acid fraction the monoacetoxy acid VIIIa was isolated in approximately 4% yield, together with small amounts of a $\Delta^{17(20)}$-unsaturated acid (compare VI), characterized by its ultraviolet absorption spectrum and by its diacetoxy methyl ester VIa. Previously, Koechlin and Reichstein[13e] had obtained the same unsaturated acid in an impure state by subjecting the product of bromination of ketone IV with three moles of bromine to a Faworsky rearrangement; the Swiss authors ascertained the structure of their product by ozonolysis of the crude methylated and acetylated adduct VIa. The formation of this unsaturated acid is proof that the bromination product of IV contained some 17,21-dibromide Va.[1] The major part of the rearrangement product was neutral; it was debrominated with zinc and acetic acid and reacetylated; by various operations (which are described in the Experimental part and which included chromatography, crystallizations, separations of ketonic and non-ketonic fractions with Girard T reagent[17] and separations of easily saponifiable esters from hindered, tertiary esters) starting material IV and methyl 3α,12α-diacetoxy-17α-methyletianate (VIIb) were isolated in the pure state, together with minor unidentified side products. Considering the recovery of starting material, the tertiary ester VIIb was obtained in 30–35% yield from IV. The same tertiary ester has also been isolated in very small yield by Koechlin and Reichstein[13e] from the neutral fraction of their rearrangement product, but the Swiss authors did not characterize the ester by further derivatives or reactions.

Potassium carbonate in boiling aqueous methanol hydrolyzed only the 3α-acetoxy group of VIIb,

(8) Ch. R. Engel and R. L. Noble, *J. Endocrin.*, **14**, 16 (1956).

(9) Compare, for instance (a) R. Courier and G. Gros, *Compt. rend. soc. biol.*, **125**, 746 (1937); (b) J. Gillman and H. B. Stein, *Endocrinology*, **28**, 274 (1941); (c) R. Hertz, C. D. Larsen and W. Tullner, *J. Natl. Cancer Inst.*, **8**, 123 (1947); (d) A. Lipschütz, R. Murillo and L. Vargas, Jr., *Lancet*, **2**, 420 (1939); (e) A. Lipschütz and L. Vargas, *Endocrinology*, **28**, 669 (1941); (f) A. Lipschütz, O. Vera and S. Gonzalez, *Cancer Research*, **2**, 204 (1942); (g) A. Lipschütz and M. Maas, *ibid.*, **4**, 18 (1944); (h) A. Lipschütz, "Steroid Hormones and Tumors," Williams and Wilkins, Baltimore, Md., 1950, pp. 133–135; (i) E. Mardones, R. Iglesias and A. Lipschütz, *Experientia*, **9**, 303 (1953); *Proc. Soc. Exp. Biol. Med.*, **86**, 451 (1954); (j) C. Huggins and E. V. Jensen, *J. Exp. Med.*, **102**, 347 (1955).

(10) Compare (a) A. A. Makepeace, G. L. Weinstein and M. H. Friedman, *Amer. J. Physiol.*, **119**, 512 (1937); (b) G. Pincus and M. C. Chang, *Acta Physiol. Latinoamer.*, **3**, 177 (1953); (c) R. F. Slechta, M. C. Chang and G. Pincus, *Fertility and Sterility*, **5**, 282 (1954).

(11) (a) W. W. Byrnes, R. O. Stafford and K. J. Olson, *Proc. Soc. Exp. Biol. Med.*, **82**, 243 (1953); (b) R. I. Dorfman, private communication.

(12) Compare also (a) A. L. Goodman, *J. Clin. Endocrinology*, **6**, 402 (1946); (b) D. Gordon, B. N. Horwitt, A. Segaloff, P. J. Murison and J. V. Schlosser, *Cancer*, **5**, 275 (1952); (c) A. C. Barnes and I. Rothchild, *Obstetrics and Gynaecology*, **1**, 147 (1953).

(13) (a) R. E. Marker and R. B. Wagner, THIS JOURNAL, **64**, 216 (1942); (b) R. E. Marker, H. M. Crooks, Jr., and R. B. Wagner, *ibid.*, **64**, 817 (1942); (c) R. E. Marker, H. M. Crooks, Jr., R. B. Wagner, A. C. Shabica, E. M. Jones and E. L. Wittbecker, *ibid.*, **64**, 822 (1942); (d) R. E. Marker, H. M. Crooks, Jr., E. M. Jones and A. C. Shabica, *ibid.*, **64**, 1276 (1942); (e) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944); (f) H. H. Inhoffen, U. S. Patent 2,409,943 (1946); (g) Pl. A. Plattner, H. Heusser and S. F. Boyce, *Helv. Chim. Acta*, **31**, 603 (1948); (h) P. L. Julian and W. J. Karpel, THIS JOURNAL, **72**, 362 (1950).

(14) (a) Compare the review of methods given in reference 6b and see reference 6c; (b) Ch. Meystre and A. Wettstein, *Helv. Chim. Acta*, **31**, 1890 (1948); (c) J. von Euw and T. Reichstein, *ibid.*, **31**, 2076 (1948).

(15) Studies concerning the application to 17-methylated steroids of a recent method for the introduction of the 11,12-double bond, consisting in the reduction of 11,12-bromohydrins with zinc and acetic acid [compare for instance J. Elks, G. H. Phillipps, D. A. H. Taylor and L. J. Wyman, *J. Chem. Soc.*, 1739 (1954)] will be dealt with in a separate communication. (It should, however, be mentioned that a 12α-hydroxy steroid also represents a suitable starting material for the preparation of such bromohydrins.)

(16) (a) Al. Faworsky, *J. prakt. Chem.*, [2] **51**, 533 (1895); [2] **88**, 658 (1913); (b) compare also J. G. Aston and R. B. Greenburg, THIS JOURNAL, **62**, 2590 (1940).

(17) A. Girard and F. Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

giving the monoacetoxy ester VIIa which was also obtained by methylation of the rearrangement acid VIIIa and which was easily reacetylated to VIIb. It is interesting to note that in the 17-non-methylated series also the 12α-acetoxy group is saponified under the conditions employed, even when potassium bicarbonate is used.[18] In the 17-methylated series here described both acetoxy groups are saponified by fairly prolonged treatment with hot methanolic potassium hydroxide. The resulting dihydroxy ester VII could be reacetylated to the diacetoxy ester VIIb by being refluxed with acetic anhydride in pyridine; at room temperature the acetylation was not complete. Total hydrolysis of VIIb to the dihydroxy acid VIII was performed in high yield by prolonged treatment with methanolic potassium hydroxide at 170°, in a sealed tube. Acetylation of acid VIII with acetic anhydride in hot pyridine and subsequent hydrolysis of the resultant anhydride IX of the diacetoxy acid VIIIb with potassium carbonate afforded the monoacetoxy rearrangement acid VIIIa. Selective esterification in position 3α of the dihydroxy ester VII was achieved by succinylation; the hemisuccinate VIIc was further characterized by its methyl ester VIId.

In a preliminary series of experiments it was attempted to develop the Δ^4-3-keto moiety, proceeding from ester VIIa, to introduce subsequently the Δ^{11}-double bond by dehydrotosylation of a 12α-tosylate and to elaborate finally the methyl ketone side chain by methods used in previous experiments.[7e,19] Hence, the hydroxy ester VIIa was oxidized with chromic acid, giving in high yield the keto ester Xa, the acetate group of the latter was saponified with methanolic potassium hydroxide, and the resulting hydroxy keto ester X was transformed in excellent yield to the corresponding tosylate Xb by the action of tosyl chloride in pyridine. Treatment with one mole of bromine gave an amorphous product (compare XIV) from which no crystalline material could be obtained. Consequently, the crude bromide XIV was converted to the Δ^4-3-keto ester XVIII *via* the corresponding 3-semicarbazone XVIIIa, according to Kendall's method.[20] The over-all yield of the introduction of the Δ^4-double bond amounted to over 60%.

In the case of steroids with a methyl ketone side chain or of etio-acid derivatives, the introduction of the Δ^{11}-double bond is most effectively carried out by dehydrotosylation of a 12α-tosylate with an organic base.[6b,15] However, the application of this method to the present series gave disappointing results. When the tosylate XVIII was treated with collidine in xylene, according to the experimental conditions which had given optimum results in the series devoid of the 17-methyl group,[6c,14b] or with collidine in a nitrogen atmosphere, no crystalline reaction product could be obtained. Only after long and tedious purifications was an amorphous fraction isolated, the elementary composition of which corresponded to the desired $\Delta^{4,11}$-unsaturated ester XXII and which showed clearly a positive tetranitromethane reaction and the expected ultraviolet absorption for a Δ^4-3-ketone. In a parallel run the $\Delta^{4,11}$-unsaturated ester was isolated in low yield as its pure, crystalline, 2,4-dinitrophenylhydrazone XXIIa, but hydrolysis of the latter, according to the method developed by Demaecker and Martin,[21] gave again only an amorphous keto ester XXII. In spite of the fact that this route did not seem to present interest from the practical point of view, it was considered worthwhile to attempt the transformation of the small quantities of ester XXII available, to the final product, 11-dehydro-17α-methylprogesterone (III). A small and reasonably pure sample of XXII was converted to its enol ether XXIII which was again only obtained in the amorphous state but which showed the typical levorotatory shift and the expected ultraviolet absorption spectrum. The crude product was subjected to the vigorous action of methanolic potassium hydroxide described before and subsequently to acid hydrolysis.[19] The resulting crude acid (compare XXIV), obtained in a powdery form and showing the expected ultraviolet absorption spectrum, was treated with oxalyl chloride[22] and the reaction product was subjected to the action of dimethylcadmium. No pure, crystalline diketone III could be isolated, but since the product showed the expected ultraviolet absorption and was found to be a highly potent luteoid,[23] it seems permissible to surmise that the crude product contained at least some of the desired progesterone analog III.

In connection with the above described sequence of reactions, a study of the ultraviolet spectra of steroid tosylates was made. In confirmation of the work of Bernoulli[24] who investigated the ultraviolet absorption spectra of *p*-toluenesulfonic acid and of tosylated sugars, it was found that the tosyl group shows a well defined maximum of absorption between 224 and 226 mμ (log ε approximately 4), due to a bathochromic shift of the main benzene band. It is known that *p*-toluenesulfonamides absorb similarly in the ultraviolet.[25] As evidenced by Fig. 1, we found that the ultraviolet absorption of an α,β-unsaturated ketone is easily detectable in the presence of a tosyl group; the observed absorption spectrum, quite distinct from the absorption of either of the single chromophores, corresponds well to the theoretical absorption calculated by adding the values of each chromophore. These findings proved very useful in the course of subsequent experiments, since they made possible not only the detection of a tosyl group by a simple absorption measurement but also the estimation of the purity of the compound in question; the latter was in some cases the more important because some tosylates were unstable or difficult to crystallize, making purification operations not only tedious but also costly.

(18) Ch. Meystre and A. Wettstein, *Helv. Chim. Acta*, **31**, 1890 (1948).

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

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

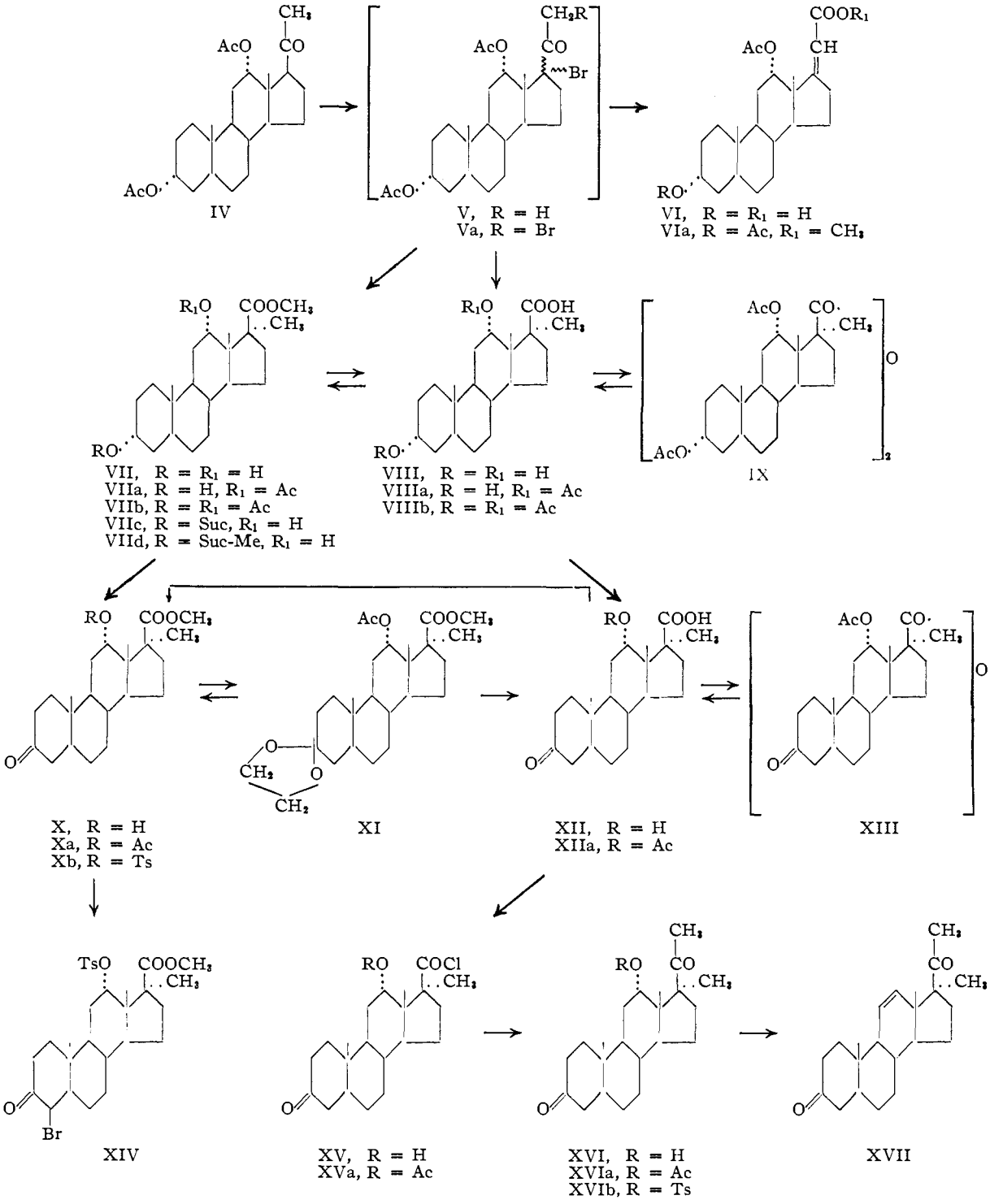
(21) J. Demaecker and R. H. Martin, *Nature*, **173**, 266 (1954).

(22) (a) R. Adams and L. H. Ulich, THIS JOURNAL, **42**, 599 (1920); (b) A. L. Wilds and C. H. Shunk, *ibid.*, **70**, 2427 (1948); (c) F. Reber, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **37**, 45 (1954); (d) Ch. R. Engel and G. Just, *Can. J. Chem.*, **33**, 1515 (1955).

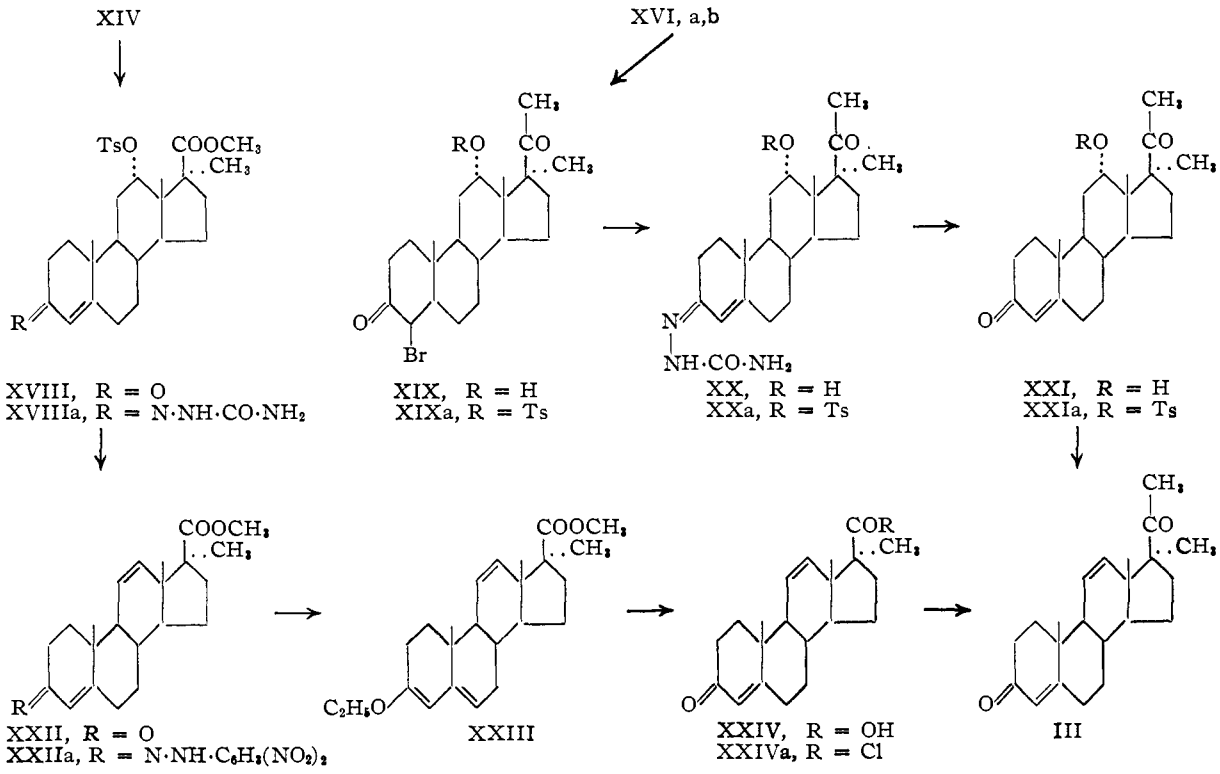
(23) Preliminary biological assays on this product were kindly carried out by Prof. R. L. Noble of the Collip Medical Research Laboratory of this University.

(24) A. L. Bernoulli and H. Stauffer, *Helv. Chim. Acta*, **23**, 615 (1940).

(25) L. Doub and J. M. Vandenbelt, THIS JOURNAL, **69**, 2714 (1947).



The first series of experiments having proved unsatisfactory from the practical point of view, a variation of the synthetic route was investigated. The 3-ketone function of ester Xa was protected by the formation of an ethylene ketal XI, easily hydrolyzed with sulfuric acid; the ethylenedioxy derivative XI was subjected to vigorous alkaline treatment and subsequently to acid hydrolysis. Thus, the 3-keto acid XII was obtained in high yield; the product was easily reconverted to the keto ester Xa by methylation with diazomethane and acetylation with acetic anhydride in boiling pyridine. It is interesting to note that the 3-keto group does not resist the vigorous alkaline treatment necessary for the saponification of the 17-methylated 20-ester grouping, whereas an 11-keto function is not affected under the same reaction conditions.[1] The hydroxy keto acid XII was readily converted to its acetate XIIa by treatment with acetic anhydride in hot pyridine and by sub-



sequent hydrolysis of the resultant anhydride XIII with potassium carbonate in methanol–water. The acetoxy acid XIIa was also obtained by chromic acid oxidation of the rearrangement acid VIIIa and was easily remethylated to ester Xa. The acetoxy keto acid XIIa was converted to its chloride XVa by the direct action of oxalyl chloride in absolute benzene[22c,d]; treatment of the acid chloride with dimethylcadmium afforded in approximately 60% yield the acetoxy diketone XVIa which was readily hydrolyzed to the corresponding hydroxy diketone XVI by the action of methanolic potassium hydroxide. The relative mildness of oxalyl chloride is evidenced by the fact that the free hydroxy keto acid XII can be converted by a similar sequence of reactions to the hydroxy diketone XVI, without protection of the alcohol function; better results are obtained, however, when the alcohol function is acetylated.

Treatment of the hydroxy diketone XVI with *p*-toluenesulfonyl chloride under the usual reaction conditions gave an amorphous product with an ultraviolet absorption spectrum typical of a tosylate; only 44% of the product (XVIb) crystallized from methanol. The tosylate XVIb is an extremely unstable substance which decomposes even when stored *in vacuo*. For preparative purposes, purifications of the crude product should not be attempted.

It was now found that the 12α-tosylate XVIb could be converted in excellent yield (70–88%) to the Δ^{11}-unsaturated diketone XVII by the action of slightly alkaline activated aluminum oxide. It was sufficient to perform three consecutive chromatograms with large amounts of aluminum oxide or a single chromatogram using an even greater excess of aluminum oxide. This method for the introduction of the Δ^{11}-double bond presents a marked improvement over the dehydrotosylation with an or-

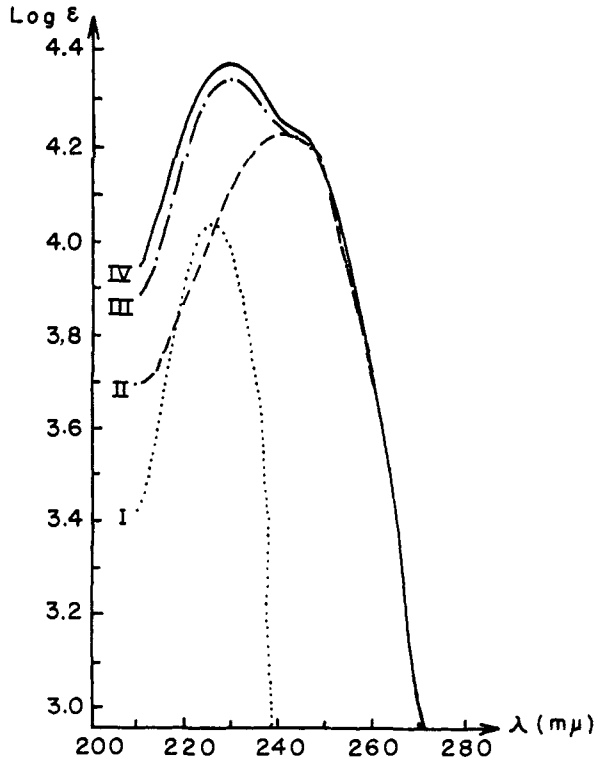


Fig. 1.—Ultraviolet spectra of steroid tosylates: curve I, tosylate; curve II, α,β-unsaturated ketone; curve III, tosylate + α,β-unsaturated ketone, calculated; curve IV, tosylate + α,β-unsaturated ketone, experimental.

ganic base. Ruff and Reichstein[26a] have recently made a similar observation; they found that partial dehydrotosylation took place when 3,20-dioxo-12α-tosyloxypregnane was left on a column of activated aluminum oxide for four days. Cremlyn and Shoppee[26b] observed the formation in 30% yield of a Δ^7-double bond during the chromatography of a 7β-tosylate. The Δ^{11}-unsaturated diketone XVII gave a positive tetranitromethane test and exhibited in the ultraviolet no absorption typical of a tosyl group. The location of the double bond in position 11,12 was substantiated by the infrared spectrum of the substance, which indicated a CH=CH double bond.[27]

It was now planned to complete the synthesis of the desired hormone analog by first introducing the Δ^4-double bond into the saturated diketo tosylate XVIb and by forming subsequently the Δ^{11}-double bond by the action of aluminum oxide. It was disappointing to find that the introduction of the Δ^4-double bond, *via* a solid but not crystalline bromide XIXa and the semicarbazone XXa, proceeded only in poor yield. These results can be attributed in part to the instability of the tosylate XVIb and to the fact that partial dehydrotosylation occurs during the purification of the unsaturated tosylate XXIa; however, the introduction of the Δ^4-double bond into the hydroxy diketone XVI, *via* the intermediates XIX and XX, proceeded likewise not very satisfactorily.

The unsaturated tosyloxy diketone XXIa was converted, again in good yield, to the desired hormone analog, 11-dehydro-17α-methylprogesterone (III), by chromatography on aluminum oxide. The structure of the crystalline product was confirmed by ultraviolet and infrared spectra, by a positive tetranitromethane test and by combustion analysis; the optical rotation of the adduct is in accord with the expected value. An attempt to transform the diketo tosylate XXIa to the progesterone analog III by the classical treatment with collidine afforded only unidentifiable amorphous products.

Preliminary biological tests, carried out in collaboration with Professor R. L. Noble of our Department of Medical Research, indicate that the new hormone analog III is a potent luteoid, exceeding the natural hormone in activity. Detailed biological results and their quantitative comparisons with the activities of other potent gestogens will be published elsewhere.

Acknowledgments.—The authors wish to express sincere thanks to the Ontario Division of the Canadian Cancer Society for supporting this work financially and to Ciba, Ltd., Basle, and the Ciba Pharmaceutical Products, Inc., Summit, N. J., for providing part of the starting material. They are indebted to Prof. R. L. Noble, London, Ontario, for biological assays and to Dr. R. N. Jones, National Research Council, Ottawa, and Mr. R. W. White, Science Service Laboratory, London, Ontario, for their valuable help in determining and interpreting infrared spectra. Dean J. B. Collip's unfailing encouragement and Prof. J. A. Gunton's interest in the work were highly appreciated. C. R. E. wishes to thank sincerely the Canadian Life Insurance Officers' Association for financial assistance.

(26) (a) A. Ruff and T. Reichstein, *Helv. Chim. Acta*, **34**, 70 (1951); (b) R. J. W. Cremlyn and C. W. Shoppee, *J. Chem. Soc.*, 3515 (1954).

(27) The structure of compound XVII was further confirmed by an independent synthesis which we shall describe at a later date.

Experimental[28-30]

Bromination of 3α,12α-Diacetoxy-20-oxopregnane (IV).—To a solution of 80 g. of 3α,12α-diacetoxy-20-oxopregnane (IV) in 1.37 l. of acetic acid were added with stirring a few drops of hydrogen bromide in acetic acid and 202 cc. of a 0.945 *M* bromine solution in acetic acid. The reaction mixture was poured into water and the oily precipitate was extracted with ether. The organic solution was washed with iced sodium carbonate solution and water and was dried, and the solvent was removed. The resulting oil (110 g.), which resisted crystallization and which gave a positive halogen test, was employed without further purification for the following rearrangement reaction.

3α-Hydroxy-12α-acetoxy-17α-methyletianic Acid (VIIIa), $\Delta^{17(20)}$-3α,12α-Diacetoxypregnene-21-acid Methyl Ester (VIa)[13e] and Methyl 3α,12α-Diacetoxy-17α-methyletianate (VIIb).[13e]—The above-described crude bromination product (110 g.) was dissolved in 3.72 l. of methanol and refluxed for 4 hr. with 200.8 g. of potassium bicarbonate in 716 cc. of water. The solvents were removed to a large extent *in vacuo* at 40–50°, and the reaction mixture was diluted with water and extracted with ether. The ethereal layer was washed with water, dried, the solvent was removed, and 65 g. of an amorphous neutral product, referred to as "neutral fraction A," was obtained. The alkaline extract was acidified and the precipitate formed taken up in chloroform; the organic solution was washed with water, dried and the solvent was removed. The foamy acidic residue (9.3 g.) afforded upon three crystallizations from acetone 2.835 g. of **3α-hydroxy-12α-acetoxy-17α-methyletianic acid (VIIIa)**, m.p. 291–294°. Three recrystallizations of a sample gave short needles, m.p. 302–303°, $[\alpha]^{23}D$ 92.1° (*c* 0.357 in methyl Cellosolve).

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.43, 70.33; H, 9.38, 9.36.

The mother liquors of the crystallization were methylated with diazomethane. In order to separate the easily saponifiable esters from the esters of type VII, the crude methylated product was refluxed for 4 hours with 100 cc. of 6.7% methanolic potassium hydroxide. The reaction product was separated in the usual manner into an acidic and a neutral fraction. The neutral fraction (1.56 g.), containing impure ester VII and referred to as "neutral fraction B," was worked up together with another fraction, "neutral fraction C," as described below.

The acid fraction (4.29 g.) was methylated and acetylated and afforded upon repeated chromatography and crystallizations three substances in small yields: (a) **$\Delta^{17(20)}$-3α,12α-diacetoxypregnene-21-acid methyl ester (VIa)**, crystallizing from hexane in fine needles, m.p. 177.5–178.5°, $[\alpha]^{22}D$ 98.5° (*c* 0.78 in $CHCl_3$), λ_{max}^{EtOH} 222 mμ (log ϵ 4.23).

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.92; H, 8.58. Found: C, 70.06, 69.83; H, 8.62, 8.41.

(b) An unidentified compound, crystallizing from methanol, m.p. 168–171°; $[\alpha]^{22}D$ 73° (*c* 0.97 in $CHCl_3$). Found: C, 66.71; H, 8.26.

(c) A second unidentified compound, crystallizing from methanol, m.p. 177.5–178.5°, $[\alpha]^{22}D$ 116° (*c* 0.95 in $CHCl_3$). Found: C, 66.39; H, 7.76.

The neutral product from the rearrangement reaction ("neutral fraction A," described above), weighing 65 g., gave a positive test for halogen. It was dissolved in 960 cc. of acetic acid and 96 cc. of water and treated for 1 hr. at 100° with 96 g. of zinc powder. The usual working up afforded 62.16 g. of a colorless oil which was acetylated overnight with 120 cc. of acetic anhydride in 240 cc. of pyridine. The usual extraction with ether gave 68 g. of an amorphous product which was chromatographed on 1.3 kg. of aluminum oxide. The petroleum ether–benzene (4.1)

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

(29) The microanalyses were performed by Mr. J. Alicino, Metuchen, N. J., to whom sincere appreciation is expressed.

(30) The aluminum oxide used for chromatography was treated as described under footnote 31 of reference 19. Sincere thanks are due to Merck and Co., Montreal, for providing activated aluminum oxide.

elutions afforded after crystallization from methanol 16.115 g. of **methyl 3α,12α-diacetoxy-17α-methyletianate (VIIb)**, m.p. 155–159°. A sample was recrystallized three times for analysis; fine, long needles, m.p. 161–161.5°, $[\alpha]^{25}D$ 117.4° (*c* 0.78 in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.55; H, 8.83.

The residual substance (41.3 g.) was eluted with methanol from the chromatogram column and was refluxed for 45 minutes with 50 g. of Girard T reagent in 400 cc. of absolute ethanol and 40 cc. of glacial acetic acid. The reaction mixture was poured into 4 l. of 0.15 *N* sodium hydroxide solution. Ether extraction afforded the non-ketonic fraction (20.1 g.). The alkaline solution was acidified. Extraction with ether gave the ketonic fraction (22.4 g.), which yielded upon reacetylation and subsequent chromatography 20.46 g. of the starting material IV, m.p. 133–136°. The non-ketonic fraction, together with the mother liquors of the crystallization of ester VIIb (6.67 g.), was hydrolyzed by refluxing for 4 hr. with 200 cc. of 6.7% methanolic potassium hydroxide solution. Thus, 5.31 g. of an acidic and 17.1 g. of a neutral fraction were obtained; the latter is referred to as "neutral fraction C," and contained impure methyl ester VII.

The acid extract was methylated and acetylated. Chromatography and recrystallization from acetone–hexane of the crystalline eluates afforded 1.513 g. of an unidentified compound, m.p. 140–144°. Two further recrystallizations gave needles, m.p. 148–150°, $[\alpha]^{22}D$ 38.5° (*c* 0.908 in $CHCl_3$). Found: C, 72.05; H, 8.43.

The neutral fractions B and C were combined and acetylated by refluxing for 1.5 hr. with 30 cc. of acetic anhydride in 60 cc. of pyridine. The usual working up gave 21.5 g. of an amorphous product which was chromatographed. Crystallization of the petroleum ether–benzene (4:1,1:1) fractions afforded 3.455 g. of methyl ester VIIb, m.p. 158.5–160°.

Considering the recovery of starting material, the total yields of ester VIIb and of acid VIIIa were 30.5 and 4%, respectively.

In another series of experiments there were obtained 10.277 g. of VIIb and 7.436 g. of starting material from 36.49 g. of IV (total yield of ester VIIb 33%).

Methyl 3α-Hydroxy-12α-acetoxy-17α-methyletianate (VIIa). (a) **From Diacetoxy Ester VIIb.**—To a solution of 9.82 g. of VIIb in 300 cc. of methanol was added at room temperature 4.4 g. of potassium carbonate in 52 cc. of water and 130 cc. of methanol. After 22 hr. the reaction mixture was poured into water, extracted with ether and the ethereal layers were washed with water and dried. Removal of the solvent yielded 8.9 g. (quantitative yield) of a colorless crystalline substance melting at 165–167°. The product was recrystallized twice from ether–hexane for analysis; m.p. 167–168°, $[\alpha]^{24}D$ 122.3° (*c* 0.95 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.92; H, 9.23.

In another run 5 g. of diacetoxy ester VIIb in 125 cc. of methanol was refluxed with 5 g. of potassium carbonate in 30 cc. of water. The usual working up afforded 3.5 g. of ester VIIa, m.p. 167–169°, and 1.08 g. of the same product of slightly lesser purity (total yield quantitative).

(b) **From the Hydroxy Acid VIIIa.**—A solution of 458 mg. of VIIIa, m.p. 291–294°, in 25 cc. of absolute methanol was treated for 15 hr. at 0° with 25 cc. of 2.4% ethereal diazomethane. The excess diazomethane was destroyed with acetic acid and the solvents were removed *in vacuo*. Crystallization of the resulting oil (492 mg.) from ether–hexane afforded 336 mg. of ester VIIa, m.p. 160–163.5°, and 62 mg. of a less pure sample melting at 155.5–158°. Recrystallization raised the m.p. to 167–168°; admixture with the ester obtained as described under (a) did not depress the m.p.

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.77; H, 9.38.

Reacetylation.—The hydroxy ester VIIa (125 mg.) was treated with 3 cc. of acetic anhydride in 5 cc. of pyridine for 15 hr. at room temperature, and the mixture was worked up in the usual manner, yielding 130 mg. of the diacetate VIIb, m.p. 156–159°. Recrystallization from methanol raised the m.p. to 160–160.5°; the m.p. was not depressed upon admixture with authentic VIIb.

Methyl 3α,12α-Dihydroxy-17α-methyletianate (VII).—A solution of 10.211 g. of methyl ester VIIb in 300 cc. of 5.6% methanolic potassium hydroxide was refluxed for 4 hr. and worked up in the usual manner, yielding 8.446 g. of VII, m.p. 95–105°/148–150° (double m.p.). Recrystallization for analysis from ether–hexane afforded prisms, m.p. 152–152.5°, $[\alpha]^{22}D$ 42.3° (*c* 0.79 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.63; H, 9.80.

Methyl 3α,12α-Dihydroxy-17α-methyletianate-3-methylsuccinate (VIId).—Dihydroxy ester VII (8.446 g.) was heated for 2.5 hr. in 100 cc. of pyridine with 11.85 g. of succinic anhydride. The mixture was worked up in the usual manner and afforded the colorless crystalline **hemisuccinate VIIc**, which was treated in 500 cc. of absolute ether and 50 cc. of absolute methanol with 150 cc. of a 2% ethereal diazomethane solution at 0°. After 10 minutes the excess diazomethane was destroyed with acetic acid and the solvents were removed. The residue, 11.14 g. of needles, m.p. 122.5–124°, was recrystallized three times from ether–hexane for analysis; m.p. 127–128°, $[\alpha]^{24}D$ 66.1° (*c* 1.07 in $CHCl_3$).

Anal. Calcd. for $C_{27}H_{42}O_7$: C, 67.75; H, 8.85. Found: C, 67.69; H, 8.85.

3α,12α-Dihydroxy-17α-methyletianic Acid (VIII).—In a sealed tube, 2 g. of methyl ester VIIb was heated with 80 cc. of a 6.7% methanolic potassium hydroxide solution for 48 hr. at 168–170°. The product was diluted with water and acidified. Chloroform extraction afforded 1.565 g. of a crystalline material, m.p. 273–275.5°. It was recrystallized three times from acetone for analysis, m.p. 280–280.5°, $[\alpha]^{26}D$ 48.8° (*c* 1.35 in dioxane).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.07, 71.73; H, 9.67, 9.71.

Remethylation and Reacetylation.—Acid VIII (100 mg.) was methylated with diazomethane in the usual manner, and the dry crude dihydroxy ester VII was refluxed for 1 hr. with 5 cc. of acetic anhydride in 10 cc. of pyridine. Chromatography of the resulting product (150 mg.) on 4 g. of aluminum oxide and recrystallization from methanol of the petroleum ether–benzene (1:1,1:4), benzene and benzene–ether (4:1) fractions afforded 104 mg. of the diacetoxy ester VIIb, m.p. 157–159° (81%), identified by a mixed m.p. with an authentic sample.

3α-Hydroxy-12α-acetoxy-17α-methyletianic Acid (VIIIa) from Dihydroxy Acid VIII.—Dihydroxy acid VIII (1.565 g., m.p. 273–275.5°) was dissolved in 18 cc. of pyridine and refluxed with 9 cc. of acetic anhydride for 1.5 hr. The product was taken to dryness *in vacuo* and the crude **acid anhydride IX** was dissolved in 60 cc. of methanol and refluxed for 1 hr. with 1.5 g. of potassium carbonate in 20 cc. of water. The reaction mixture was poured into 600 cc. of 2 *N* sulfuric acid and the crystalline precipitate was filtered off and was dried. Thus, 1.73 g. of the **acetoxy acid VIIIa**, m.p. 291–294°, was obtained (98.6%). A sample was recrystallized three times from acetone for analysis; m.p. 302–303°, not depressed upon admixture with VIIIa obtained from the acid fraction of the rearrangement reaction.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.05; H, 9.05.

Methyl 3-Oxo-12α-acetoxy-17α-methyletianate (Xa).—To a solution of 9 g. of methyl 3α-hydroxy-12α-acetoxy-17α-methyletianate (VIIa) in 417 cc. of acetic acid was added 2.47 g. of chromic acid in 24 cc. of 90% acetic acid. The mixture was stored at room temperature for 15 hr., then poured into 4 l. of ice-water. After addition of sodium bisulfite, the solution was extracted with ether, the organic layer was washed with water, iced sodium carbonate solution and water and was dried. Evaporation of the solvent afforded 8.47 g. of foamy material crystallizing upon moistening with ether, m.p. 144.5–146.5° (94.6% yield). Five recrystallizations from ether–hexane gave coarse prisms, m.p. 148.5–149°, $[\alpha]^{22}D$ 108.5° (*c* 0.95 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.41; H, 8.84.

Methyl 3-Oxo-12α-hydroxy-17α-methyletianate (X).—A solution of 6.475 g. of acetoxy ester Xa in 165 cc. of 6.5% methanolic potassium hydroxide was refluxed for 2 hr. and worked up in the usual manner. Thus was obtained 5.576 g. of crystalline hydroxy ester X, m.p. 129.5–131.5° (96%

yield). Recrystallization from ether–hexane gave 3.766 g. of crystals, m.p. 134–135°. Chromatographic purification of the mother liquors and subsequent recrystallization afforded another 600 mg. of the same product. A sample was recrystallized three times for analysis; long needles, m.p. 136.5–137°, $[\alpha]^{22}D$ 53.2° (*c* 0.997 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.02; H, 9.48.

Methyl 3-Oxo-12α-tosyloxy-17α-methyletianate (Xb).—A solution of 4.363 g. of hydroxy keto ester X and of 5.05 g. of *p*-toluenesulfonyl chloride in 39 cc. of pyridine was heated for 3.5 days at 50–55°. The reaction mixture was poured into iced *N* hydrochloric acid and the organic product was extracted with ether. The ethereal solution was washed with iced hydrochloric acid, cold sodium bicarbonate solution and with water. After drying, the solvent was removed and the yellow residue (6.63 g.) was dissolved in 5–10 cc. of acetone and covered with 15 cc. of ether. Thus, 4.45 g. (73.1%) of crystalline tosylate Xb, m.p. 141.5° dec., was obtained. Chromatography of the mother liquors (2.084 g.) on 60 g. of aluminum oxide and recrystallization of the petroleum ether–benzene (1:1, 1:4), benzene and benzene ether (95:5,4:1,1:1) eluates gave another crop of 936 mg. (15.7%) of Xb, m.p. 138–141° dec. A sample was recrystallized three times from ether for analysis; m.p. 141.5–142° dec., $[\alpha]^{22}D$ 55.5° (*c* 0.951 in $CHCl_3$), λ_{max}^{EtOH} 226 mμ (log ε 4.1).

Anal. Calcd. for $C_{29}H_{40}O_6S$: C, 67.41; H, 7.8; S, 6.2. Found: C, 67.53; H, 7.79; S, 6.35.

(XVIII) Methyl Δ⁴-3-Oxo-12α-tosyloxy-17α-methyletienate.—To a solution of 5.486 g. of tosylate Xb in 55 cc. of glacial acetic acid were added, at room temperature, 3 drops of a 25% hydrogen bromide solution in acetic acid and subsequently, dropwise and with stirring, 1.68 g. of bromine in 21.1 cc. of acetic acid. After completion of the addition, the mixture was stirred for 15 minutes and then poured into water. The usual ether extraction afforded a dark yellow, amorphous **bromide XIV** (7.2 g.), which resisted all attempts of crystallization and which was used for the subsequent reaction without further purification. The product was dissolved in 180 cc. of absolute chloroform and 267 cc. of dry *t*-butyl alcohol, and the air was displaced with carbon dioxide. To this mixture was added 1.59 g. of semicarbazide base, the flask was again flushed with carbon dioxide, sealed and shaken repeatedly. The usual color changes were observed.[20] After 2 hr. the solvents were removed *in vacuo* at 40–50°. The residue was dissolved in 110 cc. of ethanol and the semicarbazone XVIIIa precipitated with water. Filtration afforded 7.6 g. of white, solid **semicarbazone XVIIIa**, m.p. 140° dec. The adduct was hydrolyzed at room temperature and in a carbon dioxide atmosphere with 151 cc. of acetic acid, 54 cc. of water and 13 cc. of 1.66 *N* aqueous pyruvic acid. The product was poured into water, the mixture was extracted with ether, the organic solution was washed with iced 2 *N* sodium carbonate solution, cold dilute hydrochloric acid and water and was dried. The solvent was reduced to 100 cc. and the tosylate XVIII crystallized by addition of small quantities of acetone and hexane. Thus, 3.027 g. (55.4%) of unsaturated **tosylate XVIII**, m.p. 147–147.5° dec., was obtained. A sample was recrystallized four times for analysis; colorless prisms, m.p. 155.5–156° dec., $[\alpha]^{20}D$ 88.1° (*c* 0.657 in $CHCl_3$), λ_{max}^{EtOH} 229 mμ (log ε 4.44), shoulder at 242 mμ (log ε 4.2).

Anal. Calcd. for $C_{29}H_{38}O_6S$: C, 67.68; H, 7.44; S, 6.23. Found: C, 67.70; H, 7.29; S, 6.15.

Chromatography and recrystallizations of the mother liquors of the above described crystallizations gave another 580 mg. (10.6%) of tosylate XVIII, m.p. 137–141° dec.

Methyl Δ⁴,¹¹-3-Oxo-17α-methyletiadienate (XXII).—A solution of 1.28 g. of tosylate XVIII, m.p. 147–147.5° dec., in 8.5 cc. of freshly distilled collidine was heated at 155° for 15 hr. in a nitrogen atmosphere. The mixture was poured into water and extracted with ether. The organic solution was washed with iced dilute sulfuric acid, cold sodium bicarbonate solution and with water and was dried. The solvent was removed and the residue, a dark brown oil (1.088 g.), was chromatographed on 30 g. of aluminum oxide. The petroleum ether–benzene, benzene and benzene–ether eluates gave clear oils with positive tetranitromethane reactions. The fractions were, however, not homogeneous, as evidenced by their optical rotations, varying from 35 to 68°. By rechromatography a separation in colorless and yellow oils was achieved. Part of the colorless fractions (710 mg.) became darker during prolonged contact with the atmosphere. Repeated rechromatography of the colorless fractions gave 261 mg. of a homogeneous colorless oil, eluted by petroleum ether–benzene; positive tetranitromethane reaction, $[\alpha]^{23}D$ 73° (*c* 0.54 in $CHCl_3$), λ_{max}^{EtOH} 239 mμ (log ε 4.27). A sample was sublimed twice for analysis.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.93; H, 8.75.

Methyl Δ⁴,¹¹-3-Oxo-17α-methyletiadienate-3-dinitro-(2,4)-phenylhydrazone (XXIIa).—A solution of 1.915 g. of tosylate XVIII, m.p. 147–151° dec., in 13 cc. of freshly distilled collidine was heated at 149° for 18 hr. The product was worked up as described above, and there was obtained 1.515 g. of a dark brown oil which was chromatographed on 45 g. of aluminum oxide. The petroleum ether–benzene, benzene and benzene–ether (4:1, 1:1) fractions (together 1 g.) consisted of a clear oil, giving a positive tetranitromethane test. One petroleum ether–benzene fraction (100 mg.) was well dried and was subsequently dissolved in 5 cc. of absolute ethanol; to the solution 250 mg. of 2,4-dinitrophenylhydrazine in 25 cc. of absolute ethanol and 2 cc. of concentrated hydrochloric acid in 30 cc. of absolute ethanol were added at room temperature. After 20 hr., red crystals which had started to form after 15 minutes were filtered off and were washed with ethanol. There were obtained 82 mg. of crystals, m.p. 203–206.5°. The product was recrystallized, once from ether, once from ethanol and once from ethanol–acetone, m.p. 223–225°.

Anal. Calcd. for $C_{28}H_{34}O_6N_4$: C, 64.35; H, 6.56; N, 10.72. Found: C, 64.22; H, 6.43; N, 10.71.

The yield of the dinitrophenylhydrazone from the other chromatogram fractions was unsatisfactory.

Hydrolysis.—A solution of 37 mg. of the dinitrophenylhydrazone XXIIa, m.p. 207–210°, in 7.4 cc. of acetone was refluxed with 0.19 cc. of concentrated hydrochloric acid.[21] After cooling, there was added 185 mg. of stannous chloride in 0.74 cc. of hydrochloric acid and 1.1 cc. of water; the mixture was allowed to stand for 24 hr. at room temperature and was then extracted with ether. The organic solution was washed with dilute hydrochloric acid and with water and was dried. Removal of the solvent gave 33 mg. of an amorphous material which was chromatographed on 1 g. of aluminum oxide. Petroleum ether–benzene eluted 26 mg. of a colorless oil (XXII), λ_{max}^{EtOH} 239 mμ (log ε 4.2).

Attempted Transformation of Methyl Δ⁴,¹¹-3-Oxo-17α-methyletiadienate (XXII) to 11-Dehydro-17α-methylprogesterone (III).—Following the procedure described by Julian and co-workers,[31] 220 mg. of the unsaturated keto ester XXII, $[\alpha]^{23}D$ 73°, was subjected to the action of ethyl orthoformate, in order to be converted to the **ethyl enol ether XXIII**. The crude reaction product appeared as a yellow oil which resisted attempts of crystallization; $[\alpha]^{24}D$ −111° (*c* 1.0 in pyridine), λ_{max}^{EtOH} 241 mμ (log ε 3.9). The crude product was heated in a sealed tube with 15 cc. of 6.9% methanolic potassium hydroxide. The usual working up gave 105 mg. of yellow-brownish acid material, which was purified by treatment with charcoal and by fractional precipitations. Thus, 94 mg. of a light yellow oil, λ_{max}^{EtOH} 238 mμ (log ε 3.93), (compare **acid XXIV**) was obtained. To a solution of 72 mg. of this acid in 3 cc. of absolute benzene was added at 0° oxalyl chloride (0.6 cc.) in absolute benzene (1.5 cc.). The mixture was shaken at frequent intervals at room temperature. After an hour the solvents were removed *in vacuo* at 15–20° and the crude **acid chloride** (compare XXIVa) was dissolved in 3 cc. of absolute benzene. This solution was added to ethereal dimethylcadmium, prepared from 900 mg. of cadmium chloride and methylmagnesium bromide, formed in turn by the reaction of 210 mg. of magnesium with methyl bromide. The reaction mixture was refluxed for 1 hr. and, after cooling, the excess of dimethylcadmium was destroyed by addition of 10% acetic acid. The usual working up afforded 84 mg. of a neutral oil. Preliminary chromatographic purification gave 21 mg. of a clear oil, showing in the ultraviolet a broad absorption maximum between 236 and 239 mμ (log ε 3.5). In another run there was obtained 240 mg. of crude acid XXIV in the

(31) P. L. Julian, E. W. Karpel and W. Cole, THIS JOURNAL, **73**, 1982 (1951).

form of a brownish solid, m.p. 130–145°, from 241 mg. of keto ester XXII. The acid was transformed, without purification, through its acid chloride to 110 mg. of methyl ketone (compare III). By repeated chromatography 20 mg. of a homogeneous oil, eluted by petroleum ether–benzene, was obtained. Precipitation from acetone with hexane gave an amorphous solid, m.p. 126–133°. The product was sublimed at 130° in high vacuum. The resulting amorphous ketonic material (compare III), λ_{max}^{EtOH} 238 mμ (log ε 4.2), was used entirely for preliminary biological tests, indicating high luteoid activity.

Methyl 3-Oxo-12α-acetoxy-17α-methyletianate-3-ethylene-ketal (XI).—A solution of 9.0 g. of the keto ester Xa in 200 cc. of absolute benzene was refluxed with 20 cc. of ethylene glycol and 100 mg. of *p*-toluenesulfonic acid for 6 hr., with continuous removal of water. The usual working up afforded 9.825 g. of the ketal XI, m.p. 163–167° (98%). A sample was recrystallized twice from ether–hexane for analysis; prisms, m.p. 176–176.5°, $[\alpha]^{23}D$ 109° (*c* 1.35 in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.68; H, 8.75.

Hydrolysis.—A solution of 390 mg. of the ketal XI in 13 cc. of methanol and 24 cc. of ethanol was refluxed for 30 minutes with 8.7 cc. of 8.5% sulfuric acid. The usual working up and crystallization of the crude reaction product from ether–hexane gave 350 mg. of the keto ester Xa, m.p. 145–147°. The m.p. was not depressed upon admixture with authentic Xa.

3-Oxo-12α-hydroxy-17α-methyletianic Acid (XII).—In a sealed tube, 9.825 g. of ketal XI, m.p. 163–167°, was heated with 200 cc. of a 6.8% methanolic potassium hydroxide solution for 48 hr. at 168–170°. The reaction mixture was diluted with 615 cc. of ethanol and was refluxed for 30 minutes with 161 cc. of 13.5% sulfuric acid. The excess solvents were removed to a large extent *in vacuo* at 30–40°, and the acid was precipitated with water. Extraction with ether afforded 7.8 g. of acid XII, m.p. 242–244° (quantitative yield). Recrystallization from acetone raised the m.p. to 245.5–246.5°, fine needles, $[\alpha]^{26}D$ 73.8° (*c* 1.07 in $CHCl_3$).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.21; H, 9.57.

Remethylation and Reacetylation.—A sample of acid XII (109 mg.) was methylated with diazomethane in the usual manner. The resulting product was acetylated by being refluxed with 5 cc. of acetic anhydride in 10 cc. of pyridine for 1 hr. The reaction product (150 mg.) was chromatographed on 4 g. of aluminum oxide. Petroleum ether–benzene (1:1,1:4), benzene and benzene–ether (4:1) afforded 78 mg. of keto ester Xa, m.p. 148.5–149°, and 48 mg. melting between 143 and 146° (91%). The m.p. was not depressed by admixture with authentic keto ester Xa. A sample was recrystallized for analysis, m.p. 148.5–149°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.09; H, 8.86.

3-Oxo-12α-acetoxy-17α-methyletianic Acid (XIIa). (a) **By Acetylation of the Hydroxy Acid XII.**—A solution of 2.93 g. of the hydroxy acid XII in 27 cc. of pyridine was refluxed for 1.5 hr. with 13.5 cc. of acetic anhydride. The product was taken to dryness *in vacuo* and the residue, crude **anhydride XIII**, was dissolved in 90 cc. of methanol and 20 cc. of benzene and was refluxed for 1 hr. with 2.25 g. of potassium carbonate in 15 cc. of water. The mixture was diluted with water and the neutral fraction was removed by extraction with ether. Upon acidification of the alkaline layer a crystalline precipitate formed. After 20 minutes, 2.57 g. of **acid XIIa**, m.p. 230–231° (78%), was separated by filtration. A sample was recrystallized three times from acetone for analysis; long needles, m.p. 234–236°, $[\alpha]^{23}D$ 117° (*c* 0.425 in $CHCl_3$).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.46; H, 8.65.

(b) **By Oxidation of 3α-Hydroxy-12α-acetoxy-17α-methyletianic Acid (VIIIa).**—A solution of 818 mg. of acid VIIIa, m.p. 295–301°, in 39 cc. of acetic acid was treated for 15 hr. with 230 mg. of chromic acid in 2.3 cc. of 90% acetic acid. A few cc. of methanol was added to destroy the excess oxidizing agent and the acid was precipitated by addition of water and was separated by filtration. The greenish precipitate was dissolved in acetone, filtered through anhydrous sodium sulfate and the solvent was removed. Thus, 606 mg. of acid XIIa, m.p. 220–227° (74%), was obtained. Recrystallization from acetone raised the m.p. to 234–236°; it was not depressed upon admixture with acid obtained as described under (a).

Methylation.—A sample of the keto acid XIIa (105 mg.) was methylated with diazomethane in the usual manner. By chromatography of the reaction product there was obtained 94 mg. of keto ester Xa, m.p. 144–148.5°, not depressed upon admixture with authentic Xa.

3-Oxo-12α-acetoxy-17α-methyletianic Acid Chloride (XVa).—To a suspension of 773 mg. of dry acetoxy acid XIIa, m.p. 230–231°, in 35 cc. of absolute benzene was added at 0°, with stirring, a solution of 6.1 cc. of oxalyl chloride in 29 cc. of absolute benzene. After a period of 3 min. all the acid had dissolved. The mixture was stored at room temperature for 1.5 hr. and was subsequently taken to dryness *in vacuo* at 20–30°; the product, representing crude acid chloride XVa, was dried three times with absolute benzene and was employed without further purification for the following reaction with dimethylcadmium.

3,20-Dioxo-12α-acetoxy-17α-methylpregnane (XVIa).—Cleaned and dried magnesium shavings (1.94 g.) were covered with 30 cc. of absolute ether and subjected in the usual manner to the action of 15 cc. of methyl bromide. To the thus prepared Grignard solution were added portionwise and with stirring 8.08 g. of dried cadmium chloride and 70 cc. of absolute ether. The mixture was refluxed for 1 hr. with vigorous stirring and was subsequently filtered. To the filtrate was added, with stirring, a solution of the above described acid chloride XVa in 35 cc. of absolute ether. The mixture was refluxed for 1 hr. and subsequently the excess dimethylcadmium was destroyed by careful addition of 10% aqueous acetic acid in the cold. The product was extracted with ether, and the ethereal solution was washed with cold dilute sulfuric acid, sodium carbonate solution and water and was dried. The solvent was removed and the resulting clear oil (870 mg.) was chromatographed on 25 g. of aluminum oxide. The petroleum ether–benzene (1:1, 1:4), benzene and benzene–ether (4:1) elutions afforded 420 mg. (54%) of prisms, m.p. 154–155°, and 24 mg. (3%), melting between 139 and 143°. The product was recrystallized four times from hexane for analysis, m.p. 162–163°, $[\alpha]^{22}D$ 94° (*c* 0.88 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.39; H, 9.45.

The following benzene–ether fractions of the chromatogram eluted 110 mg. of a substance which gave after recrystallization from ether–hexane fluffy needles melting at 155.5–156°, $[\alpha]^{22}D$ 94.6° (*c* 0.956 in $CHCl_3$). Found: C, 75.75; H, 10.34. The product was not further investigated.

In another run, 390 mg. of diketone XVIa was obtained from 651 mg. of keto acid XIIa (60.2% yield).

3,20-Dioxo-12α-hydroxy-17α-methylpregnane (XVI). (a) **From 3,20-Dioxo-12α-acetoxy-17α-methylpregnane (XVIa).**—A solution of 3.05 g. of the acetoxy diketone XVIa in 90 cc. of 6.8% methanolic potassium hydroxide was refluxed for 4 hr. The usual working up gave 2.622 g. of crystalline hydroxy diketone XVI, m.p. 144–146° (96.5% yield). The product was recrystallized three times from ether–hexane for analysis; needles, m.p. 150.5°, $[\alpha]^{21}D$ 43.6° (*c* 1.17 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.36; H, 9.78.

(b) **From 3-Oxo-12α-hydroxy-17α-methyletianic Acid (XII).**—To a suspension of 240 mg. of hydroxy acid XII, m.p. 245–246°, in 12 cc. of absolute benzene was added at 0° a solution of 2.1 cc. of oxalyl chloride in 10 cc. of absolute benzene. The mixture was shaken at frequent intervals for 1.5 hr. and subsequently the product was taken to dryness as described above. This crude **acid chloride XV** was dissolved in 30 cc. of absolute ether and added to an ethereal solution of dimethylcadmium, prepared as described above, from 2.75 g. of cadmium chloride, 0.66 g. of magnesium and 5 cc. of methyl bromide. The reaction mixture was refluxed with vigorous stirring for 1 hr. and then worked up as described previously. There was obtained 203 mg. of a neutral oil which was chromatographed on 3 g. of aluminum oxide. Benzene and benzene–ether (4:1, 1:1) eluted 93 mg. of crude hydroxy diketone XVI, m.p. 134–139° (39% yield). The following chromatogram fractions (125 mg.),

which were only in part crystalline, were dissolved in 4 cc. of pyridine and were acetylated by being refluxed for 1.5 hr. with 2 cc. of acetic anhydride. The product was taken to dryness *in vacuo* and chromatographed on 3 g. of aluminum oxide. Petroleum ether–benzene (1:1, 1:4) eluted 41 mg. of the acetoxy diketone XVIa, m.p. 142–150° (14.3% from XII), and 6 mg. of very impure diketone XVIa.

3,20-Dioxo-12α-tosyloxy-17α-methylpregnane (XVIb).—A solution of 2.622 g. of hydroxy diketone XVI, m.p. 144–146°, and of 3.15 g. of *p*-toluenesulfonyl chloride in 25 cc. of pyridine was heated for 4 days at 52°. The reaction mixture was poured into iced *N* hydrochloric acid and the mixture was extracted with ether. The ethereal solution was washed with iced hydrochloric acid, iced sodium bicarbonate solution and water. The solution was dried and subsequently refluxed for 20 minutes with 300 mg. of charcoal, then filtered over sodium sulfate and the solvent was removed. The residue (4.0 g.) consisted of a slightly yellow oil exhibiting the ultraviolet peak at 226 mμ, typical of a tosylate. It crystallized partly from methanol after 10 hr. Recrystallization afforded 1.66 g. (43.8%) of the tosylate XVIb, m.p. 64–72° dec. The substance retains methanol and is very unstable. A sample of 130 mg. was recrystallized from 3 cc. of methanol (12 hours at −10°) and afforded 30 mg. of crystals, m.p. 78–79.5° dec., $[\alpha]^{22}D$ 39° (*c* 0.95 in $CHCl_3$), λ_{max}^{EtOH} 226 mμ (log ε 3.93).

Anal. Calcd. for $C_{29}H_{40}O_5S \cdot CH_3OH$: C, 67.64; H, 8.27; S, 6.02. Found: C, 67.68; H, 8.31; S, 5.51.

Δ¹¹-3,20-Dioxo-17α-methylpregnene (XVII).—Tosylate XVIb (438 mg.), m.p. 64–72°, was chromatographed on 45 g. of slightly alkaline aluminum oxide. Elutions were made with 250-cc. fractions of petroleum ether–benzene (1:4), benzene, benzene–ether (4:1), ether and ethyl acetate. The first two fractions crystallized poorly from hexane. The rest of the eluates were amorphous. The total eluate (300 mg.) was rechromatographed in an analogous way on 30 g. of aluminum oxide. There was obtained 263 mg. of a crystalline material. The non-crystalline ether and ethyl acetate fractions (75 mg.) were rechromatographed on 7.5 g. of aluminum oxide and afforded 17 mg. of the same crystalline material. All the crystalline fractions showed no ultraviolet absorption typical of a tosyl group and gave a positive tetranitromethane test. The crude crystalline material, obtained in 88.5% yield, was rechromatographed on 10 g. of aluminum oxide. There was obtained 224 mg. of XVII, m.p. 137–142° (72% yield). Recrystallization from hexane gave 118 mg., m.p. 142–144°. The product was recrystallized three times from hexane for analysis, prisms, m.p. 150–150.5°, $[\alpha]^{21}D$ 22.5° (*c* 0.79 in $CHCl_3$), γ_{max}^{KBr} 3010 cm.$^{-1}$ (C–H stretching, double bond), 1716 cm.$^{-1}$ (3-ketone), 1691 cm.$^{-1}$ (17-methyl-20-ketone), 721 cm.$^{-1}$ (Δ¹¹).

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.42; H, 10.01.

Analogous results were obtained when crude, non-crystalline tosylate XVIb or the mother liquors of the crystallization of XVIb were chromatographed on slightly alkaline aluminum oxide. Furthermore, the three consecutive chromatograms, each with an approximate ratio of aluminum oxide to tosylate of 100:1, could be replaced by a single chromatogram with a corresponding ratio of 300–450:1.

Δ⁴-3,20-Dioxo-12α-hydroxy-17α-methylpregnene (XXI).—To a solution of 180 mg. of the hydroxy diketone XVI, m.p. 150.5°, in 8.2 cc. of glacial acetic acid were added at 10°, dropwise and with stirring, 2 drops of a 25% hydrogen bromide solution in acetic acid and subsequently 6.4 cc. of a 0.1 *M* bromine solution in acetic acid. The mixture was stirred for another 30 minutes and then worked up in the usual fashion. Thus, 270 mg. of amorphous crude **bromide XIX** was obtained. The product was treated, as described above, with 96 mg. of semicarbazide base in 9.6 cc. of absolute chloroform and 16 cc. of dry *t*-butyl alcohol. The usual working up afforded 211 mg. of **semicarbazone XX**, m.p. 205° dec., λ_{max}^{EtOH} 270 mμ (log ε 4.4). The product was hydrolyzed in the usual manner with 7 cc. of acetic acid and 2.5 cc. of water in the presence of 0.6 cc. of 1.66 *N* pyruvic acid. The amorphous reaction product (180 mg.) was chromatographed on 3.5 g. of aluminum oxide. Benzene and benzene–ether eluted 96 mg. of mostly crystalline material which showed a positive Beilstein test. The product was dissolved in 2 cc. of acetic acid and 0.2 cc. of water and was treated for 1 hr. at 100° with 190 mg. of zinc dust. The usual working up afforded 82 mg. of a substance which was chromatographed on 2 g. of aluminum oxide. Petroleum ether–benzene (1:4), benzene and benzene–ether eluted 52 mg. of crystals (30% yield from XVI), m.p. 156–162°. One recrystallization from ether–hexane afforded 44 mg. of **hydroxy diketone XXI**, m.p. 163–166°. The product was recrystallized twice for analysis, m.p. 164–166°, $[\alpha]^{24}D$ 100° (*c* 0.862 in $CHCl_3$), λ_{max}^{EtOH} 241 mμ (log ε 4.2).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.79; H, 9.34.

Δ⁴-3,20-Dioxo-12α-tosyloxy-17α-methylpregnene (XXIa).—To a solution of 500 mg. of diketo tosylate XVIb in 5 cc. of acetic acid were added at room temperature 1 drop of a 25% HBr solution in acetic acid and subsequently, with stirring, 2 cc. of a 0.5 *M* bromine solution in acetic acid. After approximately 1 cc. of the bromine solution had been added the mixture at first turned green upon the addition of new bromine solution and was decolorized only a few moments later. At the end of the bromine addition a light green color persisted. After five minutes, 80 cc. of water was added and the precipitate was separated by filtration. There was obtained 600 mg. of **bromide XIXa**, m.p. 91–93°, which could not be recrystallized. According to Kendall's method,[20] the bromide was dissolved in 15.5 cc. of absolute chloroform and 26 cc. of *t*-butyl alcohol. The solution was shaken with 150 mg. of semicarbazide base in a carbon dioxide atmosphere. After 2 hr. the solvents were removed *in vacuo* at 40°. The residue was dissolved in 20 cc. of ethanol and the **semicarbazone XXa** was precipitated with 80 cc. of water. There was obtained 508 mg. of a nearly colorless powder, m.p. 140–144° dec., λ_{max}^{EtOH} 227 mμ (log ε 4.4) and 269 mμ (log ε 4.4). The semicarbazone was hydrolyzed at room temperature in a carbon dioxide atmosphere for 16 hr. with 12.5 cc. of acetic acid, 1.1 cc. of 1.66 *N* pyruvic acid and 4.5 cc. of water. Ether extraction afforded 450 mg. of a slightly yellow oil, λ_{max}^{EtOH} 229 mμ (log ε 4.28) (crude XXIa). The product was chromatographed on 13.5 g. of aluminum oxide. Petroleum ether–benzene (1:4) elutions afforded 7 mg. of III, m.p. 129–140°, showing a positive tetranitromethane test and absorbing in the ultraviolet at 238–239 mμ (log ε 4.05) (compare also below). Further elutions with petroleum ether–benzene (1:4), benzene and benzene–ether (4:1) gave 151 mg. of a mixture of XXIa and III. Benzene–ether (4:1, 1:1) eluted 63 mg. of the tosylate XXIa, m.p. 126–133°. Recrystallization from ether–hexane afforded prismatic crystals, m.p. 137° dec., $[\alpha]^{22}D$ 82° (*c* 0.77 in $CHCl_3$), λ_{max}^{EtOH} 229 mμ (log ε 4.25), shoulder at 242 mμ.

Anal. Calcd. for $C_{29}H_{38}O_5S$: C, 69.85; H, 7.68; S, 6.43. Found: C, 69.78; H, 7.62; S, 6.38.

11-Dehydro-17α-methylprogesterone (III).—Tosylate XXIa (44 mg.) was chromatographed twice on 5 g. of slightly alkaline aluminum oxide. Petroleum ether–benzene (1:4) and benzene eluted 18 mg. of III, m.p. 128–139° (61%), showing a positive tetranitromethane test. Two recrystallizations from hexane afforded fine needles, m.p. 140.5–141°, $[\alpha]^{22}D$ 170° (*c* 0.57 in $CHCl_3$), λ_{max}^{EtOH} 239 mμ (log ε 4.23); γ_{max}^{nujol} 1692 cm.$^{-1}$ (17-methyl-20-ketone), 1674 and 1615 cm.$^{-1}$ (Δ⁴-3-ketone-doublet), 860 cm.$^{-1}$ (Δ⁴-3-ketone), 718 cm.$^{-1}$ (Δ¹¹-double bond).

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.92; H, 9.17.

On the other hand, when a solution of 717 mg. of tosylate XXIa in 10 cc. of *o*-xylene and 4 cc. of collidine was refluxed for 24 hr., according to the method described by Meystre, *et al.*,[5c,18] an amorphous product was obtained (443 mg.). Repeated chromatography yielded only non-crystalline fractions. An attempt to purify the fractions showing a positive tetranitromethane test and an absorption peak at 238 mμ (115 mg.) through a semicarbazone adduct was likewise unsuccessful.

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