the compound to be identical to that obtained in preparation A.

9α-Fluoro 11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (Ib).—Fifty flasks, each containing a beef extract, yeast extract, peptone and cerelose medium (100 ml.), were inoculated with 1% of an 8-hour growth of *Nocardia corallina* (ATCC 999). The flasks were placed on a reciprocating shaker and incubated at 28° for 17 hours when a solution of 9α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (XIId, 20 mg.) in methanol (2 ml.) was added to each flask. The fermentation was continued for 11 hours and the flasks then were harvested and their contents pooled. The beer was extracted with ethyl acetate (3 × 4 l.) and the combined extracts were washed with water and dried. The dried solvent was concentrated to a volume of 1 liter, treated with charcoal, and concentrated further until crystals (750 mg.) separated. This material was chromatographed on Celite using a partition system of cyclohexane (4 vols.), dioxane (5 vols.) and water (1 vol.) and the product (528 mg. after washing with a little ether) crystallized from acetone as small prisms, m.p. 286–287° dec., $[\alpha]^{25}D$ +62° (*c* 0.502, methanol), +41.5° (*c* 1.062, pyridine), λ_{max} 238 mμ (ε 15,100); ν_{max} 3509, 3401, 1709, 1667, 1618 and 1603 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{27}FO_5$ (378.43): C, 66.65; H, 7.19; F, 5,02. Found: C, 66.86; H, 7.40; F, 4.81.

The acetate, 16α-acetoxy 9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (Ic), was prepared by treating the triol Ib with acetic anhydride–pyridine overnight and it crystallized from ethyl acetate–petroleum ether as needles, m.p. 242–244°, $[\alpha]^{25}D$ +27.3° (*c* 0.768, methanol), λ_{max} 239 mμ (ε 16,200); ν_{max} 3509, 3413, 1736, 1695, 1672, 1629 and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}FO_6$ (420.46): C, 65.70; H, 6.95; F, 4.52. Found: C, 65.69; H, 7.17; F, 4.86.

The isopropylidene derivative, 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (XXI), prepared as for **XV** above, was obtained as needles, m.p. 307° dec., from ethyl acetate–petroleum ether: $[\alpha]^{25}D$ +102° (*c* 0.975), λ_{max} 238 mμ (ε 15,500); ν_{max} 3333, 1712, 1667, 1626, 1176, and 1059 cm.$^{-1}$ [lit.[10] m.p. 308–310° dec., $[\alpha]^{25}D$ +102° (*c* 1.0), λ_{max} 238 mμ (ε 15,500); ν_{max} 3344, 1709, 1661, 1621, 1603, 1379, 1374, 1171 and 1057 cm.$^{-1}$].

Anal. Calcd. for $C_{24}H_{31}FO_5$ (418.49): C, 68.88; H, 7.47; F, 4.54. Found: C, 69.01; H, 7.77; F, 4.54.

9α-Fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (XXI) and 9α-Fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4,6-pregnadiene-3,20-dione (XXII).—Ethyl oxalate (4.65 g.) was added to a solution of sodium methoxide (1.15 g.) in methanol (7.8 ml.) and the mixture was added to a solution of 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIb, 7.8 g.) in *t*-butyl alcohol (62.4 ml.). The reaction mixture was kept at room temperature for 24 hours and was then diluted with a large volume of petroleum ether. The yellow sodium salt which separated was filtered off, washed with ether, and dried. Starting material (3.4 g.), m.p. 240–244°, was obtained from the filtrate. A solution of this salt in water was acidified (congo red) with dilute hydrochloric acid (10%) and the precipitated light-yellow solid was collected, washed with water, and dried. The weight of dried product was 4 g.

The above product (620 mg.) and anhydrous potassium acetate (233 mg.) were dissolved in methanol (7.5 ml.) and the dark-green solution was cooled in an ice-bath. A solution of bromine (190 mg.) in methanol (2 ml.) was added dropwise (1 drop per second) to the stirred solution. When the addition was complete, methanolic sodium methoxide (1.5 ml., 1 *N*) and phenol (10 mg.) were added to the almost colorless solution and the mixture was heated under reflux on the steam-bath for 10 minutes. The cooled reaction mixture was poured into water and the product was filtered off, washed with water, and dried. The crude bromo compound weighed 540 mg.

The crude bromo product (3.5 g.) and *s*-collidine (70 ml.) were heated under reflux for 5 hours. The cooled reaction mixture was diluted with ether, filtered, and the filtrate was washed with dilute hydrochloric acid (3 *N*), water, and dried. The brown solid (2.085 g.), obtained by removal of solvent, was dissolved in benzene and chromatographed on neutral alumina (63 g.). The materials eluted with 75% ether in benzene, ether and 5% acetone in ether, were combined and crystallized from ethyl acetate–petroleum ether to give 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4,6-pregnadiene-3,20-dione as needles (790 mg.), m.p. 288–294° dec., $[\alpha]^{25}D$ +112° (*c* 0.981) λ_{max} 281 mμ (ε 23,800); ν_{max} 3448, 1712, 1658, 1621, 1587, 1081, 1055 and 1037 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}FO_5$ (418.49): C, 68.88; H, 7.47; F, 4.54. Found: C, 69.05; H, 7.68; F, 4.72.

The material eluted with 10% acetone in ether was crystallized from ethyl acetate to give 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione as plates (330 mg.), m.p. 308° dec., $[\alpha]^{25}D$ +103° (*c* 1.018, pyridine), λ_{max} 238 mμ (ε 15,400).

The compound XXI was identical to that prepared from 9α-fluoro-11β,16α-17α-trihydroxy-1,4-pregnadiene-3,20-dione (Ib).

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Studies in the Synthesis of Triamcinolone. The Ethoxalylation of 4,9(11),16-Pregnatriene-3,20-dione and 11α-Hydroxy-4,16-pregnadiene-3,20-dione

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Preferential 21-mono-ethoxalylation of the subject compounds (I and IX) was essentially unsuccessful. However, I and IX could be converted into 2,21-bis-ethoxalyl derivatives (IV and X, respectively). Bromine treatment of IV gave the corresponding dibromide V which, upon acetolysis followed by dehydrobromination, afforded 21-acetoxy-1,4,9(11),16-pregnatetraene-3,20-dione (VII). Bromine treatment of X gave dibromide XI which, on acetolysis followed by dehalogenation, produced 21-acetoxy-11α-hydroxy-4,16-pregnadiene-3,20-dione (XIII). Compounds VII and XIII previously have been converted into triamcinolone.

The important adrenocorticoid activity of 9α-fluoro-11β,16α,17α-21-tetrahydroxy-1,4-pregnadiene-3,20-dione[1] (Aristocort[2] triamcinolone) made it of interest to investigate the development of other syntheses for this valuable therapeutic agent.[3] An attractive starting material for this purpose

(1) S. Bernstein and co-workers, THIS JOURNAL, **78**, 5693 (1956); **81**, 4956 (1959).

(2) Aristocort is the Lederle Laboratories Division, American Cyanamid Co., trademark for triamcinolone.

(3) Other investigations concerning the development of new syntheses for triamcinolone are described in an accompanying paper.[4b] The general utility of 16α,17α-epoxy steroids for the synthesis of triamcinolone will be discussed in a forthcoming publication.[4a]

(4) (a) W. S. Allen, S. Bernstein, L. I. Feldman and M. J. Weiss, paper in preparation; (b) G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4968 (1959).

was 4,9(11),16-pregnatriene-3,20-dione (I) which can be obtained readily[5a] from the available and relatively cheap 16α,17α-epoxyprogesterone[5b]; triene I required only the introduction of a 21-acetoxy group to give an intermediate (III)[6] which already had been converted into triamcinolone.[1] Introduction of this group was undertaken *via* the ethoxalylation procedure first reported for a 21-acetoxylation by Ruschig.[7]

Thus, Compound I was treated in benzene solution with 1.7 molar equivalents of ethyl oxalate and 1.1 molar equivalents of sodium methoxide.[8,9] The crude sodium enolate, which was presumed to be the sodium salt of II, was then successively treated, without purification of the resulting intermediates, with iodine, sodium methoxide and sodium acetate to give the desired 21-acetoxytriene III. However, this product was obtained in very poor over-all yield (10%) and then only after arduous purification by partition chromatography.

Combustion analysis of the amorphous free ethoxalyl derivative, obtained by acidification of an aqueous solution of the crude sodium salt, indicated that the product contained substantial amounts of the bis-ethoxalyl derivative. The positions of the ethoxalyl groups were presumed to be C-21 and C-2 (structure IV).[10] In contrast, it is interesting to note that, under similar ethoxalylation conditions (1.1 molar equivalents of ethyl oxalate) 11-ketoprogesterone[9] is reported to undergo preferential mono-ethoxalylation at C-21 in good yield.[12] The amorphous bis-ethoxalylpregnatriene IV could be obtained consistently in 90% yield on treatment of triene I with 2.2 molar equivalents of sodium methoxide and 3.4 to 5.0 molar equivalents of ethyl oxalate.[11] Since an ethoxalyl group at C-2 was potentially convertible to a C_1–C_2 double bond, *via* a 2-bromo derivative,[11] it was reasonable to expect that IV could be converted into the 21-acetoxy-1,4,9(11),16-pregnatetraene-3,20-dione (VII)[13] from which the synthesis of triamcinolone already had been established.[1,13] Therefore, the transformation of IV into VII was investigated.

Reaction of the bis-ethoxalylpregnatriene IV with one molar equivalent of iodine followed by methoxide treatment gave an amorphous product which was presumed to be the 21-iodo-2-ethoxalyl derivative.[14] Conversion of this substance into the 21-acetoxypregnatetraene (VII) was attempted by the sequence: (1) acetolysis, (2) bromination, (3) deacylation and (4) dehydrobromination. This sequence was essentially unsuccessful, and the several intermediates could be obtained only in a crude state.

However, treatment of IV with two molar equivalents of bromine in methanol solution at 0° followed by de-ethoxalylation, gave a sirup which, after chromatography, afforded the crystalline 2,21-dibromo derivative V[16] in 37% yield. This dibromide also was obtained in a similar manner directly from the crude sodium salt of IV. Attempts to dehydrobrominate V to give a 1-dehydro-21-halo derivative by treatment with lithium chloride in dimethylformamide solution[17] or with γ-collidine gave unsatisfactory results. However, a preferential displacement of the C-21 bromine proved possible. Thus, reaction of dibromide V with excess potassium acetate in acetone at room temperature for three days gave an oily mixture which was resolved by chromatography into starting material V (29%) and the desired 21-acetoxy-2α-bromopregnatriene (VI) (51% conversion, 73% based on unrecovered V). A six-day potassium acetate treatment resulted in a 5% recovery of V, but only a 45% conversion yield of VI. Finally, dehydrobromination of the 21-acetoxy-2α-bromo derivative VI with γ-collidine afforded the desired 21-acetoxypregnatetraene (VII) in 46% yield. This product was identical with the material which already had been obtained[18] by selenium dioxide dehydrogenation of the 21-acetoxytriene (III).

The conversion of 21-acetoxypregnatetraene VII into triamcinolone requires the introduction of a 16α,17α-diol system and the elaboration of the ring C fluorohydrin. The diol introduction has been achieved by osmium tetroxide treatment of VII to give, after acetylation, 16α,21-diacetoxy-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione (VIII).[1,13] As an alternative to the osmium tetroxide procedure, the diol system was introduced by a potassium permanganate hydroxylation. This was effected by briefly (3 minutes) treating 21-acetoxypregnatetraene VII with potassium permanganate in acetone containing acetic acid to give a 45% yield of the 16α,17α-diol, which on acetylation gave VIII in 71% yield.[19]

(5) (a) S. Bernstein, J. J. Brown, L. I. Feldman and N. E. Rigler, THIS JOURNAL, **81**, 4956 (1959); (b) P. L. Julian, E. W. Meyer and I. Ryden, *ibid.*, **72**, 367 (1950).

(6) W. S. Allen and S. Bernstein, *ibid.*, **77**, 1028 (1955).

(7) H. Ruschig, *Ber.*, **88**, 878 (1955).

(8) J. A. Hogg and A. H. Nathan, U. S. Patent 2,683,724 (1954).

(9) J. A. Hogg and co-workers, THIS JOURNAL, **77**, 4436 (1955).

(10) Bis-etboxalylation of 11-ketoprogesterone gives the 2,21-disubstituted product.[11]

(11) J. A. Hogg and co-workers, THIS JOURNAL, **77**, 4438 (1955).

(12) Selective etboxalylation at C-21 also has been reported for 11β- and 11α-hydroxyprogesterone[9] and 16-dehydroprogesterone [A. H. Natban and J. A. Hogg, U. S. Patent 2,719,855 (1955)].

(13) L. L. Smith and H. Mendelsohn of the Chemical Process Improvement Department of these laboratories, unpublished work.

(14) It has been reported that a 21-etboxalyl derivative will react preferentially with iodine in the presence of a 2-etboxalyl group.[15] However, it should be noted that 2-etboxalyl-16α,17α-isopropylidenedioxy-4,9(11)-pregnadiene-3,20-dione reacts with 84–98% of one molar equivalent of iodine (see footnote 21 in ref. 4b) as determined by titration.

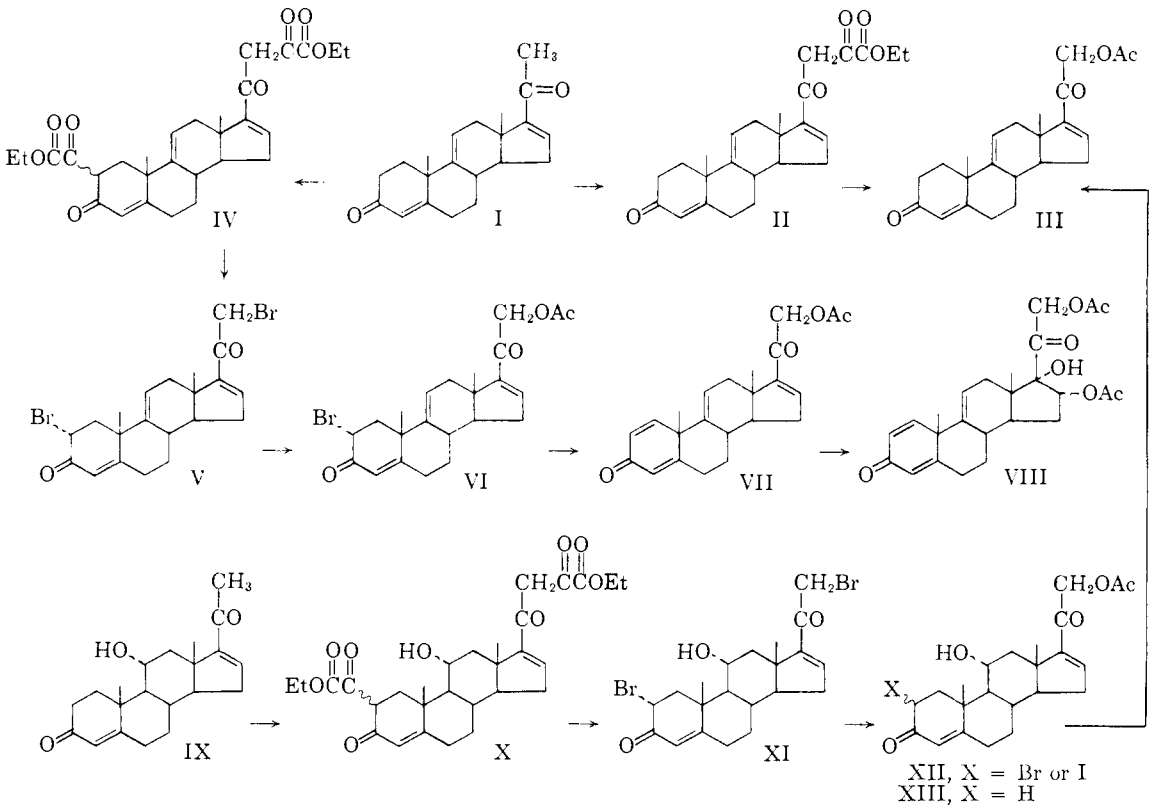
(15) A. H. Nathan and J. A. Hogg, U. S. Patent 2,730,537 (1956).

(16) Probably the 2-α epimer. Inasmuch as the mechanism of formation of this compound probably involves an intermediate carbanion for the de-etboxalylation step, it is reasonable to postulate that the bromine atom at C-2 has sufficient opportunity to assume the more stable equatorial (2-α) configuration see ref. 4b). However, it may be noted that a comparison of the infrared spectra of dibromide V and of monobromide VI with that of deoxytriene I and triene III, respectively, did not clearly show the shift in the position of the 3-carbonyl band usually resulting from the introduction of a 2α-bromo substituent [M. Fieser, M. A. Romero and L. F. Fieser, THIS JOURNAL, **77**, 3305 (1955); E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957)]. On the other hand, V and VI did not exhibit the bathochromic shift associated with a 2β-bromo-Δ⁴-3-ketone [B. Ellis and V. Petrow, *ibid.*, 1179 (1956)].

(17) R. P. Holysz, THIS JOURNAL, **75**, 4432 (1953).

(18) L. L. Smith and S. Fox of the Chemical Process Improvement Department of these laboratories, unpublished work.

(19) Potassium permanganate oxidation of a 16,17-double bond to give 16α,17α-diol has been reported by Petrow and co-workers (*J. Chem. Soc.*, 4373 (1955)]. The particular procedure used in our investigation was developed by L. L. Smith and M. Marx of the Chemical Process Improvement Department of these laboratories.



Another convenient starting material for this investigation was 11α-hydroxy-4,16-pregnadiene-3,20-dione (IX),[20] which is also readily available[4b] from 16α,17α-epoxyprogesterone. Conversion of IX into 21-acetoxytriene III was accomplished by 21-acetoxylation followed by introduction of the C_9–C_{11} double bond. Attempted 21-acetoxylation *via* preferential 21-mono-ethoxalylation of IX was apparently unsuccessful. Thus, treatment of IX by the reported mono-ethoxalylation conditions[8] gave a crude product, the combustion values for which were intermediate between those for a mono- and those for a bis-ethoxalyl derivative. Alkaline hydrolysis of this product did not afford a crystalline glyoxylic acid[8] and titration with standard iodine solution resulted in an uptake corresponding to 55% of one molar equivalent.[14] Although not conclusive by any means, these data led to an inference that the above preparation was a mixture possibly consisting of 21-ethoxalyl, 2-ethoxalyl and 2,21-bis-ethoxalyl derivatives of IX.[21] This conclusion was consistent with our observations concerning the ethoxalylation of triene I.

As an alternative, IX was treated under the bis-ethoxalylation conditions described above furnishing in 87–90% yield an amorphous product which was presumed to be crude 2,21-bis-ethoxalyl-11α-hydroxy-4,16-pregnadiene-3,20-dione (X). This on reaction with two molar equivalents of bromine, followed by de-ethoxalylation treatment, afforded a gum which was considered to contain a substantial amount of the corresponding 2α,21-dibromide (XI).[16] Crude XI then was converted into the desired 21-acetoxytriene III *via* the known 21-acetoxy-11α-hydroxy-4,16-pregnadiene-3,20-dione (XIII)[4a] in the described manner. Treatment of XI with sodium iodide and then potassium acetate gave an amorphous product which was assumed to be a mixture of the 2-iodo- and 2-bromo-21-acetoxy derivatives (XII). Without purification, this material was dehalogenated with chromous chloride[23] to give a crude preparation of XIII,[4a] which was converted into its crystalline 11α-tosylate, a previously[24] prepared compound. Treatment of this tosylate with sodium acetate in refluxing acetic acid afforded 21-acetoxytriene III as previously described.[4a] The over-all yield of III from IX by this procedure was 18%.

Acknowledgment.—We are indebted to Dr. S. Bernstein for suggesting the potential utility of progesterone oxide as a starting material for the synthesis of triamcinolone. We are grateful to Drs. N. Bohonos, L. Feldman and P. Shu and Mr. C. Pidacks of the Biochemical Research Section for generous supplies of 11α-hydroxy-16α,17α-epoxyprogesterone. We wish to thank Mr. W. S. Allen for technical advice, Mr. Anthony Pellicano of the Preparations Laboratory for the large scale preparation of certain intermediates and Mr. C. Pidacks and staff for the partition chromatography reported in this paper. Microanalyses were

(20) B. J. Magerlein, D. A. Lyttle and R. H. Levin, *J. Org. Chem.*, **20**, 1709 (1955).

(21) It has since been shown that under the same conditions progesterone reacts with ethyl oxalate to give a similar mixture of etboxalyl derivatives.[22]

(22) G. R. Allen, Jr., and M. J. Weiss, unpublished results.

(23) G. Rosenkranz and co-workers, *ibid.*, **72**, 4077 (1950).

(24) This compound was first prepared by V. Origoni and S. J. Fox of the Chemical Process Improvement Department of these laboratories.

done by Mr. L. Brancone and staff, and the spectroscopic and polarimetric determinations were done by Mr. W. Fulmor and staff.

Experimental[25]

Attempted Preparation of Sodium Salt of 21-Ethoxalyl-4,9(11),16-pregnatriene-3,20-dione (II).—A solution of 6.6 cc. of 1 *N* methanolic sodium methoxide (1.1 moles) in 40 cc. of anhydrous reagent benzene was freed from methanol by azeotropic distillation, the temperature of the distillate rising from 58 to 80°. To the sludge was added 1.37 cc. of redistilled ethyl oxalate (1.7 moles) and the resulting solution was added to a stirred solution of 1.85 g. of 4,9(11),16-pregnatriene-3,20-dione (I)[5] in 35 cc. of anhydrous reagent benzene.

In a few minutes the solution became turbid and an amorphous solid separated. The mixture, protected from moisture, was stirred for 2 hours; then 35 cc. of ether was added and stirring was continued for 1 hour. After a further 135 cc. of the anhydrous ether was added, stirring was continued for another hour and the mixture was filtered to yield 1.63 g. of yellow amorphous powder. The compound gave a deep red color with 1% alcoholic ferric chloride solution.

In another experiment, the yield was 2.1 g. Conversion to the free enolate was achieved from a solution of 250 mg. of the sodium enolate in 10 cc. of water by the addition of 5 cc. of 10% hydrochloric acid. This gave 166 mg. of an amorphous solid, the combustion values for which were between those calculated for a mono-ethoxalyl derivative II and those calculated for a bis-ethoxalyl derivative IV.

Anal. Calcd. For $C_{29}H_{34}O_8$ (bis): C, 68.22; H, 6.71; for $C_{25}H_{32}O_5$ (mono): C, 72.79; H, 7.82. Found: C, 69.12; H, 6.96.

Attempted Preparation of 21-Iodo-4,9(11),16-pregnatriene-3,20-dione.—To a stirred solution of 1.59 g. of the sodium salts of the above prepared mixture of ethoxalyl derivatives of 4,9(11),16-pregnatriene-3,20-dione in 25 cc. of absolute methanol cooled to −15 to −20° was added dropwise, during 1 hour, an absolute methanol solution (25 cc.) containing 935 mg. of iodine. After stirring for an additional hour, 3.95 cc. of 1 *N* methanolic sodium methoxide was added dropwise and stirring was continued at 0° for another hour. After the dropwise addition of 100 cc. of water, which caused a solid to separate, the mixture was kept at 0° for 24 hours. The buff-colored amorphous solid was collected on a filter and washed with water; yield 1.07 g. of crude iodo derivative.

21-Acetoxy-4,9(11),16-pregnatriene-3,20-dione (III). **A. From Crude 21-Iodo-4,9(11),16-pregnatriene-3,20-dione.**—A mixture of 300 mg. of the preceding crude preparation, which presumably contained some 21-iodo-4,9(11),16-pregnatriene-3,20-dione, 15 cc. of reagent acetone and a sludge prepared (in a mortar) from 1.6 g. of potassium bicarbonate and 0.96 cc. of glacial acetic acid was refluxed for 12 hours. After filtration, the solution was clarified with Norit activated carbon and evaporated to dryness leaving 266 mg. of a glass.

Extraction of the residue with hot benzene and evaporation as before afforded 150 mg. of a glass which gave a positive blue tetrazolium test. This glass was subjected to partition chromatography on Celite[26] in the following manner. The mobile phase consisted of three parts ethyl acetate and 2 parts petroleum ether (b.p. 90–100°), whereas the stationary phase consisted of three parts methanol and two parts water. Both phases were equilibrated with each other. The solid was dissolved in the stationary phase, slurried with Celite and the mixture added to the column. Chromatography was then initiated with the mobile phase and 10 fractions of 20 ml. volume each were collected. Fractions 4, 5 and 6 gave a single spot at 18.5 cm. on paper chromatographic analysis.[27]

Fractions 4, 5 and 6 on evaporation to dryness gave 90 mg. of a glass which could not be crystallized and was, therefore, rechromatographed as above, except that 5 parts of petroleum ether instead of 2 parts were used. Fraction 4 from the second column gave a single spot at 18.5 cm. and on evaporation afforded 43.3 mg. of product as a gum which crystallized from acetone–petroleum ether. Recrystallization from the same solvent pair gave material of m.p. 123–125°. Admixture of this material with authentic 21-acetoxy-4,9(11),-16-pregnatriene-3,20-dione[6] did not depress the melting point. The infrared spectra for the two samples were identical; ν_{max} 2920, 1760, 1680, 1440, 1380, 1240, 1220 cm.$^{-1}$.

B. From 21-Acetoxy-11α-*p*-toluenesulfonyloxy-4,16-pregnadiene-3,20-dione.—Using the procedure described previously,[4a] a solution of 1.500 g. of 21-acetoxy-11α-*p*-toluenesulfonyloxy-4,16-pregnadiene-3,20-dione (prepared as described below by tosylation of XIII), 1.500 g. of sodium acetate and 35 ml. of glacial acetic acid was allowed to reflux for three hours to give, after recrystallization from acetone-petroleum ether, 0.540 g. (55% yield) of long needles, m.p. 130–131°. A mixture of this material with an authentic sample[6] of the triene melted at 129–131°. The material had $[\alpha]^{24}D$ +189° (*c* 2.04, chloroform) and λ_{max}^{MeOH} 239 mμ (ε 26,500). Reported[6] values are $[\alpha]^{24}D$ +166° (chloroform) and λ_{max}^{EtOH} 239 mμ (ε 24,000). Moreover, the infrared spectra of this preparation and of an authentic sample were identical.

Sodium Salt of 2,21-Bis-ethoxalyl-4,9(11),16-pregnatriene-3,20-dione (IV).—A solution containing 144 cc. of 1 *N* methanolic sodium methoxide (2.2 moles) and 450 cc. of anhydrous reagent benzene was freed from methanol by azeotropic distillation, the temperature of the distillate rising from 58 to 80°. To the sludge was added 48 cc. (6 moles) of ethyl oxalate and the resulting solution was added to a stirred solution of 4,9(11),16-pregnatriene-3,20-dione[5] (I) (20 g.) in 400 cc. of anhydrous reagent benzene. In a few minutes the solution became turbid and an amorphous solid separated. The mixture, protected from moisture, was stirred for 2 hours, 600 cc. of ether then was added and stirring was continued for an additional hour. The yellow solid was filtered; yield 39.2 g. (109%).

2,21-Bis-ethoxalyl-4,9(11),16-pregnatriene-3,20-dione (IV).—A solution of 39.2 g. of sodium salt of 2,21-bis-ethoxalyl-4,9(11),16-pregnatriene-3,20-dione, prepared above, in 400 cc. of water was clarified by filtration, and then acidified with 100 cc. of 5% aqueous hydrochloric acid. The precipitated amorphous solid was collected and washed well with water; yield 29.9 g. (90% from triene I). In a pilot run, the yield of product was 288 mg. (74%) λ_{max}^{MeOH} 242 mμ (ε 16,900) and 315 mμ (ε 13,300), $\lambda_{max}^{0.1N\ NaOH}$ 249 mμ (ε 20,000) and 315 mμ (ε 10,400); ν_{max} 2940, 1740, 1440 and 1270 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{34}O_8$: C, 68.22; H, 6.71. Found: C, 68.31; H, 6.71.

2-Ethoxalyl-21-iodo-4,9(11),16-pregnatriene-3,20-dione.—To a stirred solution of 564 mg. of 2,21-bis-ethoxalyl-4,9-(11),16-pregnatriene-3,20-dione (IV) and 2 g. of anhydrous sodium acetate in 30 cc. of reagent methanol, cooled to −15° in an acetone–Dry Ice-bath, was added, dropwise, a solution of 9.33 cc. of absolute methanol containing 280 mg. of iodine. Stirring was continued for 3 hours. After this period an aliquot, titrated with 0.01 *N* sodium thiosulfate in the presence of starch indicator, showed a negligible amount of free iodine present in the solution.

After the addition of 2.26 cc. of 1 *N* methanolic sodium methoxide, stirring was continued at 0° for 1 hour and then the solution was neutralized with dilute acetic acid. The dropwise addition of 135 cc. of water precipitated an amorphous solid which was collected on the filter and washed well with water; yield 526 mg. (88%), λ_{max}^{MeOH} 242 mμ (ε 17,700), $\lambda_{max}^{0.1N\ NaOH}$ 228 mμ (ε 21,600) and λ_{max} 340 mμ (ε 7800), $\lambda_{max}^{0.1N\ HCl}$ 248 mμ (ε 17,700); ν_{max} 2960, 1740, 1650, 1600, 1440 and 1280 cm.$^{-1}$. This solid was presumed

(25) Melting points were determined in a capillary tube and are uncorrected. All infrared spectra were determined in potassium bromide disks. Ultraviolet spectra were determined on a Cary recording spectrophotometer and the infrared spectra were determined on a Perkin–Elmer spectrophotometer (model 21). The petroleum ether used was that fraction boiling at 60–70° unless otherwise specified. All concentrations were carried out under reduced pressure on the steam-bath.

(26) The adsorbent was specially treated Celite "545" which had been washed with 6 *N* hydrochloric acid, water, and finally with 3A alcohol, and then dried at 100°. Celite is the trademark of Johns-Manville Co. for diatomaceous silica products.

(27) This method was essentially that of I. E. Bush, *Biochem. J.*, **50**, 370 (1952). The chromatography was carried out on untreated Whatman No. 1 paper with a toluene–petroleum ether (b.p. 90–100°)–methanol–water (9:6:9.75:5.25) solvent system, and was allowed to run at 27° for two hours. The steroids were detected with an alkaline blue tetrazoleum spray.

to be 2-ethoxalyl-21-iodo-4,9(11),16-pregnatriene-3,20-dione.[14]

Anal. Calcd. for $C_{15}H_{29}O_5I \cdot 1H_2O$: C, 54.3; H, 5.64; I, 22.9. Found: C, 54.5; H, 5.39; I, 21.8.

2α,21-Dibromo-4,9(11),16-pregnatriene-3,20-dione (V).—A. To a stirred solution of 32.3 g. of 2,21-bis-ethoxalyl-4,9(11),16-pregnatriene-3,20-dione (IV), and 30 g. of anhydrous potassium acetate in 1300 cc. of reagent methanol (cooled to 0°) was added, dropwise during 25 minutes, 64 cc. of a carbon tetrachloride solution containing 20.3 g. of bromine. After 6 hours at 0°, there was added 400 mg. of phenol, then 60 cc. of 1 *N* methanolic sodium methoxide solution. After refluxing for 10 minutes, the solution was concentrated to half-volume. Dilution with 1500 cc. of water caused a gum to separate which was extracted with three 300-cc. portions of chloroform. The combined extracts, washed with water and dried with magnesium sulfate, were evaporated to dryness leaving 31 g. of a glass. The glass was dissolved in 200 cc. of reagent benzene and adsorbed on a silica gel column (500 g.). The product was eluted with 2500 cc. of 5% ether–benzene, and was crystallized from acetone–petroleum ether to give 11.1 g. (33%) of 2α,21-dibromo-4,9(11),16-pregnatriene-3,20-dione (V),[15] as an acetone solvate, m.p. 93–95° (gas). Recrystallization from acetone–petroleum ether afforded white crystals, m.p. 99–101° (gas.), $[\alpha]^{25}D$ +140° (2% in $CHCl_3$), λ_{max}^{MeOH} 242 mμ (ε 24,200); ν_{max} 2340, 1690, 1630, 1620, 1590 cm.$^{-1}$. Combustion analysis indicated solvation with 1.5 molar equivalents of acetone.

Anal. Calcd. for $C_{21}H_{24}O_2Br_2 \cdot 1.5C_3H_6O$: C, 55.2; H, 5.95; Br, 28.8. Found: C, 55.8; H, 5.95; Br, 29.5.

B. **From the Sodium Salt of the Bis-ethoxalylate IV.**—To a stirred solution of 4.62 g. of the disodium salt of 2,21-bis-ethoxalyl-4,9(11),16-pregnatriene-3,20-dione in 50 cc. of absolute methanol, cooled to 0° in an ice-bath, was added, dropwise, a solution of 8.45 cc. of carbon tetrachloride containing 2.68 g. of bromine. Stirring was continued at 0–5° for 6 hours. After standing at 5° for 24 hours, there was added 100 mg. of phenol, then 7.95 cc. of 2 *N* methanolic sodium methoxide. The solution was refluxed on the steam-bath for 10 minutes, then diluted with three volumes of water and extracted with three 100-cc. portions of methylene chloride. The combined extracts, washed with water and dried with magnesium sulfate, were evaporated to dryness leaving 4.5 g. of a glass. The glass was dissolved in 25 cc. of reagent benzene and adsorbed on a silica gel column (130 g.). The product was eluted with 1 l. of 5% ether–benzene to give 1.795 g. of a glass. Crystallization from acetone–petroleum ether afforded 1.07 g. (25%) of 2α,21-dibromo-4,9(11),16-pregnatriene-3,20-dione (V), m.p. 99–102° (gas).

21-Acetoxy-2α-bromo-4,9(11),16-pregnatriene-3,20-dione (VI).—A solution of 14.65 g. of 2α,21-dibromo-4,9(11),16-pregnatriene-3,20-dione (V) in 1100 cc. of reagent acetone was stirred for 72 hours at room temperature with a mixture (prepared in a mortar) of 73.5 g. of potassium bicarbonate and 44 cc. of glacial acetic acid. The mixture was diluted with 3 l. of water and extracted with three 500-cc. portions of methylene chloride. The combined extracts, washed with water and dried with magnesium sulfate, were evaporated to dryness, leaving 14 g. of a glass. The glass was dissolved in 50 cc. of benzene and adsorbed on a silica gel column (400 g.). Elution with 3 l. of 3% ether–benzene afforded 4.3 g. of crystalline material, m.p. 92–95° (gas) identified as the dibromide V by infrared and mixed m.p.

The product then was eluted with 3 l. of 10% ether–benzene and was crystallized from ether to give 6.4 g. (51% or 73% based on unrecovered V) of 21-acetoxy-2α-bromo-4,9(11),16-pregnatriene-3,20-dione (VI),[15] m.p. 168–172° dec. Recrystallization from acetone–petroleum ether afforded white crystals, m.p. 174–175° dec., $[\alpha]^{25}D$ +188° (1% in $CHCl_3$), λ_{max}^{MeOH} 250 mμ (ε 24,500); ν_{max} 1760, 1690, 1640, 1625, 1595, 1220 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{27}O_4Br$: C, 61.77; H, 6.09; Br, 17.87. Found: C, 61.98; H, 6.34; Br, 17.91.

21-Acetoxy-1,4,9(11),16-pregnatetraene-3,20-dione (VII).—A mixture of 2 g. of 21-acetoxy-2α-bromo-4,9(11),16-pregnatriene-3,20-dione (VI) and 10 cc. of γ-collidine was stirred at 155° in an oil-bath for 2.5 hours, solution being complete on warming. The cooled mixture was diluted with 100 cc. of ether and filtered from collidine hydrobromide (1.06 g.). The filtrate, washed with 8% sulfuric acid and then with water, was dried with magnesium sulfate and evaporated to dryness leaving 950 mg. (58%) of a glass. Crystallization from ether gave 757 mg. (46%) of product, m.p. 164–167°. Recrystallization from acetone–petroleum ether gave white crystals, m.p. 171–173°. This compound showed a single spot at 8 cm. on paper chromatographic analysis[28]; $[\alpha]^{25}D$ +114° (1% in $CHCl_3$), λ_{max}^{MeOH} 238 mμ (ε 24,000); ν_{max} 1750, 1680, 1630, 1610, 1580, 1240 cm.$^{-1}$. The infrared was identical with that of an authentic sample.[18]

Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.36; H, 7.36.

When the reaction was carried out at reflux temperature for one hour there was obtained 37% of product (596 mg.), m.p. 168–170°.

21-Acetoxy-16α,17α-dihydroxy-1,4,9(11)-pregnatriene-3,20-dione.—To a stirred solution of 500 mg. of 21-acetoxy-1,4,9(11),16-pregnatetraene-3,20-dione (VII) in 17.5 cc. of reagent acetone containing 0.15 cc. of acetic acid, cooled in an ice-bath, was added a solution of 236 mg. of potassium permanganate[19] in 12.5 cc. of 85% aqueous acetone. After 3 minutes, 2 cc. of 10% aqueous sodium bisulfite solution was added. The solution was filtered from salts and then concentrated to dryness to remove acetone. The residual mixture was diluted with 5 cc. of water and extracted with two 10-cc. portions of methylene chloride. The combined extracts, washed with aqueous sodium bicarbonate and dried with magnesium sulfate, were evaporated to dryness leaving 464 mg. (85%) of a glass. Crystallization from acetone–petroleum ether afforded 244 mg. (45%) of product, m.p. 202–205°. Recrystallization from the same solvents gave white crystals, m.p. 213–215°, $[\alpha]^{25}D$ +3.9° (±1°) (1% in MeOH), λ_{max}^{MeOH} 238 (ε 16,400); ν_{max} 1750, 1660, 1610, 1230 cm.$^{-1}$. The infrared spectrum was identical with that of an authentic sample.[13]

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.78; H, 7.18.

16α,21-Diacetoxy-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione (VIII).—To a solution of 89 mg. of 21-acetoxy-16α,17α-dihydroxy-1,4,9(11)-pregnatriene-3,20-dione in 2 cc. of reagent pyridine was added 0.25 cc. of acetic anhydride. After 18 hours at room temperature in a stoppered flask, the solution was diluted with 8 cc. of ice-water. The product was collected and washed with water; yield 70 mg. (71%), m.p. 194–196°. Recrystallization from acetone–petroleum ether afforded white needles, m.p. 200–201°, $[\alpha]^{25}D$ −2.9° (±1°) (1% in MeOH), λ_{max}^{MeOH} 238 (ε 16,400); ν_{max} 1750, 1730, 1670, 1630, 1610, 1230, 1070 cm.$^{-1}$. The infrared spectrum was identical with that of an authentic sample.[13]

Anal. Calcd. for $C_{25}H_{30}O_7$: C, 67.5; H, 6.83. Found: C, 68.09; H, 6.97.

Attempted Preparation of 21-Ethoxalyl-11α-hydroxy-4,16-pregnadiene-3,20-dione.—A solution of 1.1 ml. of 1 *N* methanolic sodium methoxide in 6 ml. of benzene was distilled until 3 ml. of distillate were collected. The cooled residue was treated with 0.23 ml. (1.7 mmoles) of ethyl oxalate during magnetic stirring; all solid dissolved. The solution then was treated with 0.328 g. (1.0 mmole) of 11α-hydroxy-4,16-pregnadiene-3,20-dione (IX). All solid dissolved to give a yellow solution from which an amorphous solid began separating within one minute. The mixture was stirred for two hours, diluted with 6 ml. of ether and stirred for an additional hour. The mixture then was diluted with an additional 18 ml. of ether and allowed to stir for one hour. The mixture was filtered to give 0.373 g. (83%) of crude sodio derivative.

The filtrate was taken to near dryness, and the residue was recrystallized from ethyl acetate–petroleum ether to give 32 mg. (10% recovery) of white needles, m.p. 174–176°. A mixture with the starting material IX melted at 175–178°.

The crude sodio derivative was dissolved in 10 ml. of water, and the slightly turbid solution was filtered through a bed of Celite. The clear yellow filtrate was treated with 2 ml. of 5% hydrochloric acid solution, and the precipitated solid was collected by filtration and washed with water to give 0.293 g. (68% yield) of ivory-colored solid. The material had λ_{max}^{MeOH} 242 mμ (ε 18,300), 315 mμ (ε 6500); λ_{max}^{HCl} 248 mμ (ε 20,000), 305 mμ (ε 4280); λ_{max}^{NaOH} 248 mμ (ε

(28) The chromatography was carried out on untreated Whatman No. 1 paper with a petroleum ether (b.p. 90–100°)–methanol–water (10:8:2) solvent system and was allowed to run at 27° for two hours. The steroids were detected with a blue tetrazolium spray.

19,300), 335 mμ (ε 8900)[29]; ν_{max}^{KBr} 3430, 1740, 1665, 1630 and 1225 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{25}H_{32}O_6$ (monoethoxalyl): C, 70.07; H, 7.53. Found: C, 67.18; H, 7.17.

This solid (250 mg., 0.5 mmole) was suspended in 15 ml. of benzene and 0.5 ml. of 1 *N* methanolic sodium methoxide was added. All solid dissolved immediately, and within one minute solid precipitated. The mixture was diluted with 10 ml. of ether and filtered to give 0.200 g. (76% yield) of the sodio derivative. This material gave a clear yellow solution with water; this solution gave a red color when treated with an alcoholic ferric chloride solution.

Anal. Calcd. for $C_{25}H_{31}O_6Na$ (monoethoxalyl): C, 66.64; H, 6.94; Na, 5.11. Found: C, 62.18; H, 6.69; Na, 5.93.

Attempted Preparation of 11α-Hydroxy-3,20-dione-4,16-pregnadiene-21-glyoxalic Acid.—A solution of 0.428 g. (1.0 mmole) of 21-ethoxalyl-11α-hydroxy-4,16-pregnadiene-3,20-dione and 2 ml. of 1 *N* potassium hydroxide in methanol was allowed to stand at room temperature for 45 minutes. The solution was diluted with 2 ml. of water and acidified with 5% hydrochloric acid solution. The precipitated amorphous solid was collected by filtration to give 0.386 g. (97% yield). This material gave a red color with alcoholic ferric chloride solution. The material had λ_{max}^{MeOH} 242 mμ (ε 17,100), 315 mμ (ε 6000); λ_{max}^{HCl} 248 mμ (ε 18,700), 305 mμ (ε 4200); λ_{max}^{NaOH} 248 mμ (ε 18,700), 335 mμ (ε 8600); ν_{max}^{KBr} 3430, 1740, 1665, 1630 and 1225 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{23}H_{28}O_6$ (monoethoxalyl): C, 68.98; H, 7.05. Found: C, 66.99; H, 7.36.

Attempted Preparation of 11α-Hydroxy-21-iodo-4,16-pregnadiene-3,20-dione.—A solution of 0.450 g. (1.0 mmole) of the presumed sodio salt of 21-ethoxalyl-11α-hydroxy-4,16-pregnadiene-3,20-dione in 5 ml. of methanol was chilled to −15° during magnetic stirring. A solution of 0.134 *M* iodine in methanol then was added dropwise until iodine was no longer absorbed; this required 4.10 ml. (0.55 mmole). Iodine then was added up to a total of 4.75 ml. of the solution. The solution was stirred for one hour, but the excess iodine had not been consumed. The excess iodine then was destroyed by titration with 1 *N* methanolic sodium methoxide; 0.65 ml. of this solution was required. An additional 0.55 ml. of 1 *N* methanolic sodium methoxide was put in and the solution stirred at 0° for one hour. Water (30 ml.) now was added dropwise over one hour and the mixture treated with 2 g. of sodium chloride and stirred at 0° for 2.5 hours. The mixture was filtered to give 0.262 g. of amorphous solid. It was not possible to crystallize this material nor to obtain satisfactory analyses.

2,21-Bis-ethoxalyl-11α-hydroxy-4,16-pregnadiene-3,20-dione (X).—A solution of 21 ml. of 1 *N* methanolic sodium methoxide in 100 ml. of benzene was distilled until 62 ml. of distillate was collected. The cooled residual mixture was treated with 0.500 g. (0.034 mole, 4.6 ml.) of ethyl oxalate during magnetic stirring; all solid dissolved immediately. A slurry of 3.28 g. (0.010 mole) of 11α-hydroxy-4,16-pregnadiene-3,20-dione (IX) in 50 ml. of dry benzene was added, an additional 10 ml. of benzene being used to aid in the transfer. All solid dissolved to give a yellow solution from which an amorphous solid began separating within one minute. Stirring was continued during 24 hours. The mixture then was diluted with 100 ml. of dry ether, and stirring was continued for an additional hour. The solid was collected by filtration and washed with 50 ml. of ether to give 5.73 g. (100% yield) of the disodium salt of 2,21-bis-ethoxalyl-11α-hydroxy-4,16-pregnadiene-3,20-dione (X) as crude amorphous yellow solid.

Anal. Calcd. for $C_{29}H_{34}O_9Na_2$: C, 60.83; H, 5.97; Na, 8.03. Found: C, 56.45, 56.06; H, 6.77, 6.35; Na, 7.68.

This solid was dissolved in 250 ml. of water to give a clear solution which was acidified with a 5% hydrochloric acid solution. The amorphous solid which precipitated was collected by filtration and dried under reduced pressure over phosphorus pentoxide to give 4.73 g. (90% yield). The material had λ_{max}^{MeOH} 244 mμ (ε 15,600) and 313 mμ (ε 12,900), λ_{max}^{NaOH} 250 mμ (ε 18,100) and 335 mμ (ε 20,100); a ν_{max} 3480, 1740, 1660 (inflection), 1627, 1264(broad) cm.$^{-1}$.[29]

Anal. Calcd. for $C_{29}H_{36}O_9$: C, 65.89; H, 6.87. Found: C, 63.48, 63.53; H, 6.78, 6.93.

20α,21-Dibromo-11α-hydroxy-4,16-pregnadiene-3,20-dione (XI).[16]—A solution of 4.582 g. (8.7 mmoles) of 2,21-ethoxalyl-11α-hydroxy-4,16-pregnadiene-3,20-dione (X), 3.500 g. (34.8 mmoles) of potassium acetate and 100 ml. of methanol was chilled in an ice-bath with continuous stirring. To this solution there was added over a period of one hour 30 ml. of 0.58 *M* bromine in carbon tetrachloride solution. The resulting yellow solution now was treated with 17.5 ml. of 1 *N* methanolic sodium methoxide. Some solid separated at this time. The mixture was distributed between 200 ml. of methylene chloride and 200 ml. of water. The organic solution was separated, washed with saturated saline solution, dried over magnesium sulfate and taken to dryness to give 4.126 g. of gummy residue. This material gave two blue tetrazolium-positive spots at 14.5 and 19.0 cm. on paper chromatography[27] and it had λ_{max}^{MeOH} 244 mμ (ε 14,400); ν_{max} 3480, 1750, 1677, 1627, 1582, 1241 and 1210 cm.$^{-1}$. The bands at 1750, 1241 and 1210 cm.$^{-1}$ suggested that this crude material contained some ethoxalyl-substituted steroid.

Anal. Calcd. for $C_{21}H_{26}Br_2O_3$: C, 51.87; H, 5.39; Br, 32.94. Found: C, 49.87; H, 5.39; Br, 27.59.

In other preparations of this material, attempts to crystallize it or to purify it by chromatography on silica gel were unsuccessful.

21-Acetoxy-11α-hydroxy-4,16-pregnadiene-3,20-dione (XIII).—A solution of 1.85 g. (0.012 mole) of sodium iodide in 100 ml. of acetone was added to 4.00 g. (8.2 mmoles) of 2α,21-dibromo-11α-hydroxy-4,16-pregnadiene-3,20-dione (XI). A solid began precipitating immediately; the mixture was warmed on the steam-bath for 15 minutes and filtered. The filtrate was allowed to reflux with continuous stirring for 18 hours with an intimately ground mixture of 21 g. of potassium bicarbonate and 12.5 ml. of glacial acetic acid. The mixture was distributed between 200 ml. of water and 300 ml. of methylene chloride. The organic layer was separated, washed with saturated sodium thiosulfate solution (250 ml.) and water (2 × 250 ml.), dried over magnesium sulfate and taken to dryness to give 2.92 g. of a glass.

This material was dissolved in 50 ml. of glacial acetic acid, and the solution was swept with carbon dioxide. While under carbon dioxide atmosphere, the solution was treated with 50 ml. of approximately 0.4 *N* chromous chloride solution during 15 minutes. The green solution was distributed between 100 ml. of water and 200 ml. of methylene chloride. The organic layer was separated, washed with water (2 × 100 ml.), saturated sodium bicarbonate solution (2 × 100 ml.) and again with water (2 × 100 ml.), and taken to dryness. The residue was dissolved in 100 ml. of ethyl acetate, dried over magnesium sulfate and taken to dryness to give 1.56 g. of a glass which had λ_{max}^{MeOH} 240 mμ (ε 20,900) and an infrared spectrum which was identical with that of an authentic sample.[4a]

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 68.86, 68.85; H, 8.30, 8.42.

21-Acetoxy-11α-*p*-toluenesulfonyloxy-4,16-pregnadiene-3,20-dione.[4a,24]—A solution of 1.500 g. (4.65 mmoles) of 21-acetoxy-11α-hydroxy-4,16-pregnadiene-3,20-dione (XIII) and 0.950 g. (5.00 mmoles) of *p*-toluenesulfonyl chloride in 17 ml. of pyridine was allowed to stand at 5° for 18 hours, the solution then was distributed between 100 ml. of water and 100 ml. of methylene chloride. The organic solution was washed with three 50-ml. portions of 5% hydrochloric acid solution and two 50-ml. portions of water, dried over magnesium sulfate and taken to dryness to give 2.17 g. of residue. This material was dissolved in the minimum quantity of benzene and adsorbed onto 50 g. of silica gel (column size: 2.8 × 20 cm.). The column was washed with 500 ml. of a 5% ether-in-benzene solution, and these washings were discarded. Elution with 3250 ml. of a 20% ether-in-benzene solution gave a small amount of glass which was discarded. The column then was washed with a 50% ether-in-benzene solution; 250-ml. fractions were collected. The material eluted in fractions 2–12 was combined and recrystallized from acetone–petroleum ether to give 1.789 g.

(29) For the acid and base spectra, a methanolic solution was diluted 1:1 with 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide, respectively.

(77% yield) of hard crystals, m.p. 158–160° dec. alone or in mixture with an authentic sample.[4a] The infrared spectra for the two samples were identical. The material had $[\alpha]^{24}D$ +71° (*c* 1.06, chloroform) and λ_{max}^{MeOH} 229 mμ (ε 30,800). Reported [4a] values are m.p. 158–159°, $[\alpha]^{25}D$ +69° (chloroform) and λ_{max}^{MeOH} 231 mμ (ε 31,400).

Anal.[4a] Calcd. for $C_{30}H_{36}O_5S$: C, 66.64; H, 6.71; S, 5.93. Found: C, 66.75; H, 6.89; S, 6.18.

Conversion of this compound to pregnatriene III is described above.

PEARL RIVER, N.Y.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Studies in the Synthesis of Triamcinolone. The Condensation of 16α,17α-Isopropylidenedioxy-4,9(11)-pregnadiene-3,20-dione with Ethyl Oxalate

BY GEORGE R. ALLEN, JR., AND MARTIN J. WEISS[1]

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Ethoxalylation of 16α,17α-isopropylidenedioxy-4,9(11)-pregnadiene-3,20-dione (XI), which was prepared from 16α,17α-epoxy-11α-hydroxyprogesterone (II), in the presence of a molar equivalent of sodium methoxide gave exclusively the 2-ethoxalyl derivative XVIII, which was converted by a six-step procedure into 9α-fluoro-11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (XXVII). The 9α-chloro analog of XXVII also was prepared. Bis-ethoxalylation of XI led to the preparation of the 2α,21-dibromide XXII. Attempts to convert XXII into 16α,21-diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione were unsuccessful.

The importance of 9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione (I)[2a] (Aristocort triamcinolone[2b]) as a therapeutic agent[3] made it desirable to explore other routes for the synthesis of this material.[4] An attractive starting point for a synthesis of I is 16α,17α-epoxy-11α-hydroxyprogesterone (II) which has been obtained from 16α,17α-epoxyprogesterone by fermentation with *Rhizopus nigricans*.[5] In the present paper we wish to describe the conversion of II into 16α,17α-dihydroxy-4,9(11)-pregnadiene-3,20-dione (X), and efforts to transform the latter material and certain of its derivatives into intermediates that have been utilized for the preparation of I.[9]

Our preparation of X was accomplished in the following manner. Reaction of II with methanesulfonyl (mesyl) chloride gave the 11α-mesyloxy derivative III from which 16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (IV) was prepared by elimination of the elements of methanesulfonic acid. This procedure, which is reported in the patent literature by Bergstrom,[11] in our hands has afforded a consistent over-all yield of 80%. The conversion of the 16α,17α-epoxy group of IV into a 16α,17α-diol system was accomplished by using the procedure of Romo and Romo de Vivar.[12] Reaction of the oxide IV with hydrogen bromide in glacial acetic acid gave the bromohydrin V in 62% yield. Acetylation of this material with acetic anhydride in the presence of *p*-toluenesulfonic acid afforded the enol diacetate VII in 95% yield. Treatment of VII with sodium acetate in refluxing acetic acid produced 16α-acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (IX) in 57% yield. This step, wherein the 16β-bromo group is displaced, involves participation of the neighboring 17-acetoxy group, presumably *via* an intermediate *ortho* ester type cation.[12] The diol acetate IX also was prepared by two variations of the above method. Reaction of the oxide IV with sodium iodide in glacial acetic acid gave in 69% yield the iodohydrin VI[13] which was converted into IX *via* the enol acetate VIII. Finally, IX also was obtained from 16α,17α-epoxy-11α-mesyloxyprogesterone (III). Reaction of this substance with hydrogen bromide in glacial acetic acid gave XII in almost quantitative yield. The bromohydrin XII was converted into the enol diacetate XIII which, without isolation, was treated with sodium acetate in refluxing acetic acid to give IX in 39% yield. Of the above three methods, the last gives the most satisfactory yield, whereas the method based on the iodohydrin VI gives the poorest. Hydrolysis of the diol acetate IX with 0.5 *N* hydrochloric acid gave 16α,17α,dihydroxy-4,9(11)-

(1) To whom inquiries concerning this paper should be addressed.

(2) (a) S. Bernstein, R. H. Lenbard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. 1. Feldman and R. H. Blank, THIS JOURNAL, **78**, 5693 (1956); **81**, in press (1959); (b) the trademark of American Cyanamid Co. for triamcinolone is Aristocort.

(3) L. Hellman, B. Zumoff, M. K. Schwartz, T. F. Gallagher, C. A. Berntsen and R. H. Freyberg, Abstracts of papers presented at the 3rd Interim Meeting of the American Rheumatism Association, Bethesda, Md., November 30, 1956.

(4) The original method for the preparation of I utilized 21-acetoxy-4,9(11),16-pregnatriene-3,20-dione[1,5] as the key intermediate. This latter substance has been prepared from 21-acetoxy-17α-hydroxyprogesterone (Reichstein's Substance S)[6] and the bis-ethylene ketal of cortisone acetate.[8] More recently, Fried and his co-workers have described the preparation of I from 9α-fluorohydrocortisone; this elegant procedure utilized microbiological fermentation to introduce the required 16α-hydroxy function.[7]

(5) W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955).

(6) W. S. Allen, S. Bernstein and R. Littell, *ibid.*, **76**, 6116 (1954).

(7) R. W. Thoma, J. Fried, S. Bonanno and P. Grabowich, *ibid.*, **79**, 4818 (1957).

(8) D. H. Peterson, P. D. Meister, A. Weintraub, L. M. Reineke, S. H. Eppstein, H. C. Murray and H. M. L. Osborn, *ibid.*, **77**, 1428 (1955).

(9) Other efforts to utilize 16α,17α-epoxy-11α-hydroxyprogesterone for the preparation of triamcinolone are the subject of an accompanying paper.[10] The general utility of 16α,17α-epoxy steroids for the synthesis of triamcinolone will be discussed in a forthcoming publication (W. S. Allen, S. Bernstein, L. I. Feldman and M. J. Weiss).

(10) R. E. Schaub, G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4962 (1959).

(11) C. G. Bergstrom, U. S. Patent 2,703,799.

(12) J. Romo and A. Romo de Vivar, *J. Org. Chem.*, **21**, 902 (1956).

(13) The opening of 16α,17α-oxides to yield iodohydrins has been reported by A. Ercoli and P. de Ruggieri [*Gazz. chim. ital.*, **84**, 479 (1954)].