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Partial Synthesis of Compounds Related to Adrenal Cortical Hormones. XVI. Preparation of Cortisone and Related Compounds[1]

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A procedure for the partial synthesis of cortisone acetate and its 21-desoxy analog has been described. The key reaction was the formation of a tertiary alcohol at C-17 in the α-configuration, accomplished by perbenzoic acid oxidation of the dienol triacetate of 3α-hydroxypregnane-11,20-dione in which only the 17,20-enol double bond was oxidized. Mild alkaline hydrolysis converted the intermediate 20-acetoxy-17,20-epoxy steroid to 3α,17α-dihydroxypregnane-11,20-dione. Bromination at C-21 was effected in chloroform solution and the halogen was replaced by hydroxyl with dilute alkali. Oxidation with N-bromoacetamide yielded 17,21-dihydroxypregnane-3,11,20-trione and, after acetylation, this substance was brominated at C-4 and dehydrobrominated by means of semicarbazide to yield cortisone acetate.

In the synthesis of the most active adrenal cortical hormones, two major chemical problems have been encountered. These were the introduction of an 11-oxygen function and the elaboration of ketol or dihydroxyacetone side chains in 11-oxygenated as well as 11-desoxysteroids. The first and more important of these two problems was solved initially by Reich and Reichstein[2] who prepared 11-ketocholanic acid, an investigation that culminated in 1943 with the first synthesis of an 11-oxygenated cortical hormone, 11-dehydrocorticosterone.[3] Subsequently, a series of methods for the preparation of 11-oxygenated steroids from desoxycholic acid were described by Gallagher,[4] Kendall,[5] Wallis,[6] Wintersteiner[7] and their associates; more recently Tishler[8] and Fieser[9] and their co-workers have prepared 11-ketosteroids from starting materials lacking any oxygen in ring C.

The original procedure for the preparation of the ketol side chain devised by Steiger and Reichstein[10] formed an essential portion of the synthesis of dehydrocorticosterone. More difficulty has been encountered with the preparation of the dihydroxyacetone side chain. Von Euw and Reichstein[11] in the partial synthesis of Reichstein's "Substance S," described the first procedure for the preparation of this structural feature of the cortical hormones. Since that time a series of methods for the preparation of the dihydroxyacetone side chain have been developed.[12] For the most part these have been applied only to the hormones lacking an 11-oxygen function. Sarett[13] was the first investigator to utilize a new synthesis of the dihydroxyacetone side chain in conjunction with a steroid containing an 11-keto group; his investigations resulted in the first synthesis of cortisone (Kendall's compound E).

In preceding papers of this series,[12d] we have described a simple and efficient synthesis of the dihydroxyacetone side chain of highly active adrenocortical hormones and in a preliminary communication[14] demonstrated the applicability of this synthesis to the preparation of cortisone. The key reaction was the formation of a tertiary alcohol at C-17 in the natural or α-orientation by the reaction of perbenzoic acid with an enol ester of an 11-oxygenated 20-ketosteroid followed by hydrolysis to yield an 11,20-diketo-17α-hydroxysteroid. The present report describes the details of this synthesis of cortisone.

Upon treatment with acetic anhydride in the presence of *p*-toluenesulfonic acid 3α-hydroxypregnane-11,20-dione (I) was converted to the dienol triacetate II. Epoxidation of II with perbenzoic acid yielded the monoepoxy triacetate III (17α,20-epoxy-$\Delta^{9,11}$-pregnene-3α,11,20-triol triacetate) in which only the side chain double bond was oxidized. Mild alkaline hydrolysis readily removed all three ester groups and opened the epoxide to yield 3α,17α-dihydroxypregnane-11,20-dione (IV). Proof for the structure of IV was provided not only by the subsequent reactions leading to cortisone but also by oxidation of the 3-monoacetate of IV with chromic acid to 3α-acetoxyetiocholane-11,17-dione.

The interesting differential reaction of the two enol esters may be ascribed to the very marked hindrance of an unsaturated bond from C-9 to C-11 resulting not only from the steric influence of the two angular methyl groups but from the 11-acetoxy group as well. The compound II is considered to have the nuclear unsaturated bond extending from C-9 to C-11 rather than from C-11 to C-12 because the dienol triacetate formed only the monoepoxide III with perbenzoic acid. It is well known that $\Delta^{11,12}$-bile acids and related compounds react readily with perbenzoic acid to form epoxides while $\Delta^{9,11}$-derivatives are attacked more slowly by this reagent. The screening influence of the enol acetoxy group cannot be neglected, however, and because of this factor the formulation of II is provisional. The side chain enol reacted vigorously with the oxidant as expected from the behavior of analogous compounds lacking 11-oxygen functions. It was possible, as in the earlier examples, to isolate the

(1) This investigation was supported by grants from the Jane Coffin Childs Memorial Fund for Medical Research, the Lillia Babbitt Hyde Foundation, Teagle Foundation, the National Cancer Institute, United States Public Health Service and the Anna Fuller Fund.

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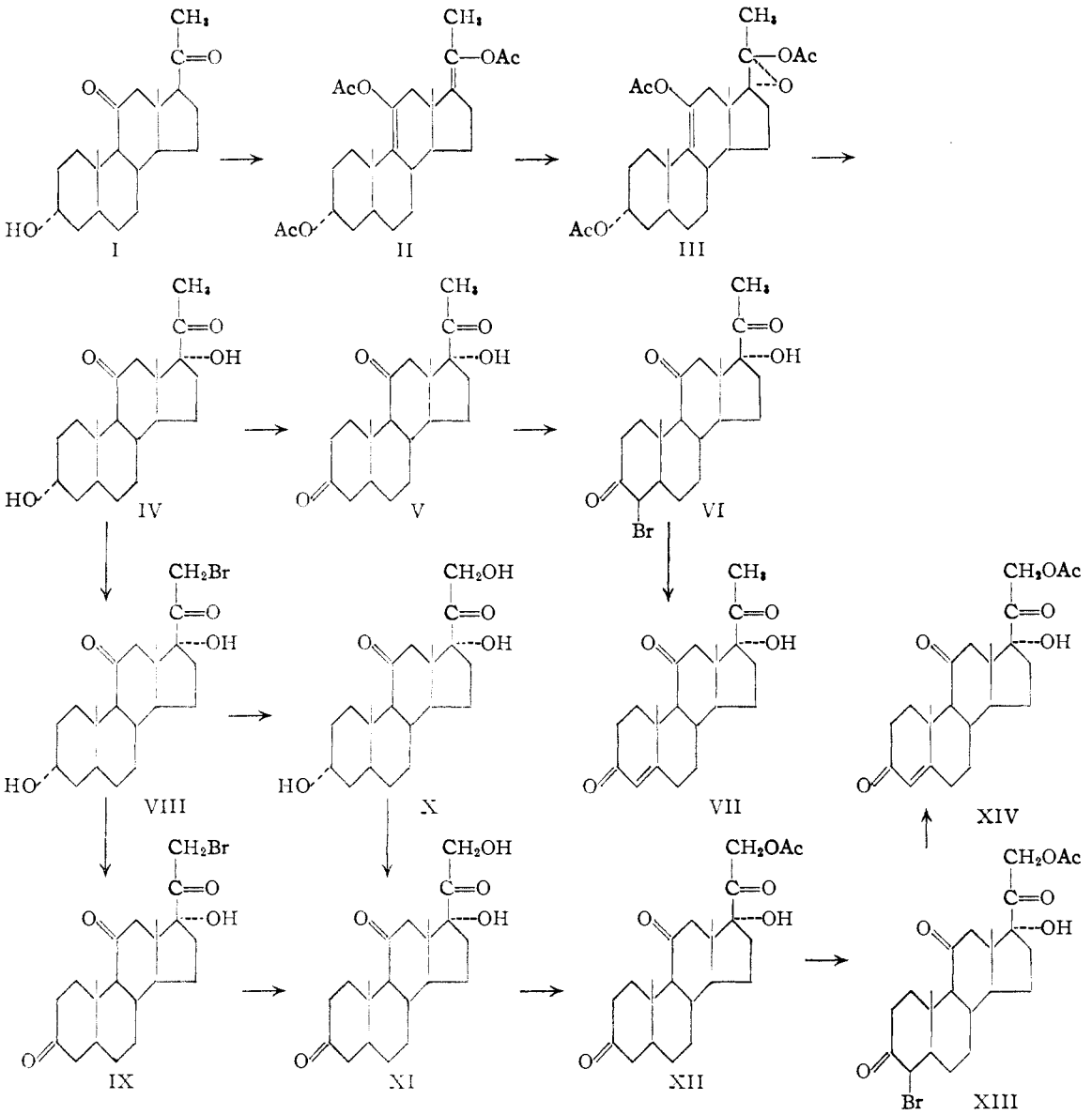

epoxide (III) and from its properties to demonstrate the nature of the reaction.

In agreement with earlier results from this Laboratory, bromination of 3α,17α-dihydroxypregnane-11,20-dione (IV) at C-21 was readily achieved in chloroform solution without protection of the C-3 hydroxyl group and 3α,17α-dihydroxy-21-bromopregnane-11,20-dione (VIII) was obtained in good yield. This bromination step on first inspection appears to present some complication since there are two carbonyl groups in the molecule, each capable of substitution on an α carbon. However, the reaction at C-21 proved to be far more facile than bromination of C-12 and the desired product was obtained without serious contamination with dibrominated products. There was probably some bromine substitution on C-12 as evidenced by the presence in the mother liquors of products from which all the halogen was not readily removed by alkaline hydrolysis but this was minor in amount and did not affect the yield appreciably. The 21-bromo compounds in which the halogen is adjacent to the 17,20-ketol structure are, as a class, relatively sensitive products and for preparation purposes it is preferable to proceed with their further transformation and to purify at a later stage. Rigorous purification of VIII is accompanied by unnecessary loss of product and storage of the partially purified product leads to a certain amount of decomposition. The same is true for 21-bromo-17α-hydroxypregnane-3,11,20-trione (IX) and in this instance also exhaustive purification is inadvisable.

Oxidation of the C-3 hydroxyl group was carried out upon either 3α,17α-dihydroxy-21-bromopregnane-11,20-dione (VIII) or 3α,17α,21-trihydroxypregnane-11,20-dione (X) by means of N-bromoacetamide in aqueous *t*-butanol solution. Oxidation of X gave superior yields, probably because the halogenated steroid IX underwent decomposition in the course of purification. It is possible, too, that the N-bromoacetamide caused substitution of halogen in the bromo triketone IX thus adversely affecting the yield. In any event, because it is desirable to replace the C-21 halogen at the earliest

possible stage and because of the superior yield in the oxidation, the sequence VIII → X → XI is preferable. An alternative procedure was the replacement of the C-21 halogen by an acetoxy group by heating with potassium acetate in acetone; this offered no particular advantage over the present series of reactions and was therefore not explored in detail.

The final stage in the synthesis of cortisone was accomplished with the introduction of the double bond at 4,5. Bromination of 17α-hydroxy-21-acetoxypregnane-3,11,20-trione (XII) yielded the 4-bromo derivative XIII. The dehydrobromination of XIII as the semicarbazone was carried out by the procedure of Koechlin, Kritchevsky and Gallagher,[15] a modification of the Mattox-Kendall reaction.[16] The effectiveness of this procedure has been demonstrated in the synthesis of Reichstein's "Substance S" and similar results were obtained with the 11-oxygenated analog. Thus the whole sequence of reactions previously applied to 11-desoxy adrenal cortical hormones has been shown to be equally effective in the synthesis of 11-oxygenated hormones of the cortisone type.

Because of considerable interest in comparison of the biological activity of analogs of cortisone in the amelioration of rheumatoid arthritis, we prepared the 21-desoxy derivative (VII) of cortisone for a study of its effect in man. Oxidation of 3α,17α-dihydroxypregnane-11,20-dione (IV) with N-bromoacetamide gave the 17α-hydroxypregnane-3,-11,20-trione(V) in good yield. Bromination of V yielded predominantly the 4-bromo derivative VI despite the presence of the reactive methylene group at C-12 and the reactive methyl group at C-21. Dehydrobromination of VI with pyridine or with 2,4-dinitrophenylhydrazine yielded 17α-hydroxy-Δ^4-pregnene-3,11,20-trione (VII). The compound was supplied to Dr. Randall Sprague of the Mayo Foundation and was found ineffective in an arthritic who responded favorably to cortisone.

Experimental[17]

$\Delta^{9,11;17,20}$-Pregnadiene-3α,11,20-triol Triacetate (II).—The dienol triacetate (II) was prepared essentially according to the procedure of Marshall, *et al.*[12d] After chromatography on alumina and recrystallization from ethyl acetate, needles, m.p. 200–201°; $[\alpha]^{23}D$ +105° (chloroform) were obtained.

Anal. Calcd. for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35; sapn. equiv., 153. Found: C, 70.80; H, 8.21; sapn. equiv., 155.

17α,20-Epoxy-$\Delta^{9,11}$-pregnene-3α,11,20-triol Triacetate (III).—Six and four-tenths grams of amorphous $\Delta^{9,11;17,20}$-pregnadiene-3α,11,20-triol triacetate (II) was dissolved in 30 ml. of 2.2 *M* perbenzoic acid in benzene with intermittent brief cooling and the solution was stored at room temperature for 2 hours. After dilution with ether, extraction with base and water, and evaporation of the solvent, a crystalline product III was obtained; recrystallization from ethyl acetate formed needles melting at 195–196°; $[\alpha]^{25}D$ +77.0° (chloroform).

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07; sapn. equiv., 158. Found: C, 68.16; H, 8.16; sapn. equiv. 159.

3α,17α-Dihydroxypregnane-11,20-dione (IV) (preparative procedure).—Acetic anhydride was slowly distilled from a solution containing 7 g. of 3α-acetoxypregnane-11,20-dione (I) and 1.8 g. of *p*-toluenesulfonic acid monohydrate for five hours. At the end of the reaction the volume of the solution was about 20 ml. Ether was added and the solution was extracted with very cold 5% sodium hydroxide solution and with ice-water. The ether with most of the remaining acetic anhydride was distilled off and the residual acetic anhydride was removed in a good vacuum. The brown sirup was dissolved in 50 ml. of a 2 *M* solution of perbenzoic acid in benzene. After one hour ether was added and the solution was extracted with dilute alkali and with water, and the solvent was removed. Without isolation of the epoxide, the reaction product was saponified in 1 liter of 0.25 *N* sodium hydroxide in 50% ethanol at room temperature for 40 minutes. The saponification product was a white crystalline solid and on recrystallization from benzene, 4.96 g. of product was obtained as plates melting 198–201°. After recrystallization from ethyl acetate, three crops of 3α,17α-dihydroxypregnane-11,20-dione (IV) were isolated; 3.3 g., m.p. 203–204°; 0.9 g., m.p. 200–201° and 0.49 g., m.p. 196–200° (72% yield). The first crop was recrystallized without elevation of the melting point, $[\alpha]^{23}D$ +65.8° (acetone). Sarett recorded[13b] for this compound m.p. 207–208°; $[\alpha]D$ +68.5° (acetone). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 71.43; H, 9.60. Found: C, 71.40; H, 9.56.

3α-Acetoxy-17α-hydroxypregnane-11,20-dione.—This compound was prepared from IV with acetic anhydride and pyridine at room temperature. It was recrystallized from petroleum ether–acetone, m.p. 202–204°, $[\alpha]^{30}D$ +81° (acetone). Recorded[13b] m.p. 208–209°; $[\alpha]D$ +84° (acetone).

3α-Acetoxyetiocholane-11,17-dione.—Eighty-five mg. of 3α-acetoxy-17α-hydroxypregnane-11,20-dione was dissolved in 2.0 ml. of acetic acid and 160 mg. of chromic oxide in 5 ml. of 90% acetic acid was added. After five hours at room temperature the neutral oxidation product was isolated in the usual way. Thirty mg. of irregular prisms melting 154–157° was obtained. There was no depression of the melting point upon admixture with an authentic sample of 3α-acetoxyetiocholane-11,17-dione; the infrared spectrum was likewise identical with the authentic sample.

3α-Formoxy-17α-hydroxypregnane-11,20-dione.—A solution of 3.2 g. of 3α,17α-dihydroxypregnane-11,20-dione (IV) in 200 ml. of benzene and 40 ml. of formic acid (98–100%) was distilled for 15 minutes and then 120 ml. of benzene and 16 ml. of formic acid were added. The distillation was continued for 30 minutes, the residue was diluted with ether and the product isolated in the usual way. After recrystallization from ethanol fine needles were obtained m.p. 115–125°, which sintered and lost weight on drying at 100° *in vacuo;* after drying for five hours at 100° the product melted 133–137° and the melt on cooling solidified and then melted 143–145°, $[\alpha]^{23}D$ +75.6° (acetone). The product held solvent tenaciously and poor analyses were obtained.

17α-Hydroxypregnane-3,11,20-trione (V).—To a solution of 4.47 g. of 3α,17α-dihydroxypregnane-11,20-dione in 50 ml. of *t*-butanol, 3 ml. of water and 3 ml. of pyridine, was added 4.5 g. of hydrated N-bromoacetamide (equivalent by titration to 3.6 g. of anhydrous product) and the solution was stored overnight at room temperature. The solution was diluted with a large volume of ether and worked up in the usual way. Three crops, total weight 3.77 g., m.p. 202–204°, were obtained after crystallization from ethyl acetate together with 600 mg. of amorphous product. The amorphous material was dissolved in glacial acetic acid and 1 g. of zinc dust added and the mixture was stored overnight at room temperature. Ether was added and the product isolated in the usual way. An additional 283 mg. of pure V was obtained. The purest sample of 17α-hydroxypregnane-3,11,20-trione (V) melted 203–204°; $[\alpha]D$ +41° ($CHCl_3$). Sarett reported[13b] m.p. 205–206°.

17α-Hydroxy-4-bromopregnane-3,11,20-trione (VI) and 17α-Hydroxy-Δ^4-pregnene-3,11,20-trione (VII).—To a solution of 4.25 g. of V in 65 ml. of glacial acetic acid 14.2 ml. of a glacial acetic acid 3.4 *M* bromine solution was added. The solution was completely decolorized as rapidly as it could be added. The solution was poured into a large volume of 1:1 ether–ethyl acetate and the product isolated in the usual way. Crystallization afforded 2.00 g., $[\alpha]D$ +72.3°

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(16) V. R. Mattox and E. C. Kendall, *ibid.*, **188**, 287 (1951).

(17) All melting points were determined in capillary tubes and are corrected.

(chloroform) in the first crop. Addition of ethyl acetate yielded a total of 1.115 g. of VI in three successive crops with $[\alpha]_D$ +72° (chloroform). The bromoketone VI upon heating with anhydrous pyridine at 110° for 16 hours was converted to Δ^4-pregnene-3,11,20-trione (VII), m.p. 235–236°, $[\alpha]_D$ +187° (chloroform) in 53% yield. Reported[13b] m.p. is 236–239°. The same product in similar yield was obtained upon dehydrobromination with 2,4-dinitrophenylhydrazine followed by cleavage with pyruvic acid.

3α,17α-Dihydroxy-21-bromopregnane-11,20-dione (VIII).—To a solution of 2.254 g. of 3α,17α-dihydroxypregnane-11,20-dione (IV) dissolved in 45 ml. of reagent grade chloroform 27.51 ml. of 0.247 *M* bromine in reagent chloroform was added. The solution was diluted with 500 ml. of chloroform and was washed with 5% sodium hydroxide and water. The product VIII was obtained white and crystalline after removal of the chloroform *in vacuo* at low temperature. After recrystallization from ethyl acetate to constant melting point, 2.25 g. of plates was obtained, m.p. 178–179.5°; $[\alpha]^{25}_D$ +70° (chloroform). After five more recrystallizations the melting point was still 178.5–179.5°.

Anal. Calcd. for $C_{21}H_{31}O_4Br$: C, 59.01; H, 7.31; Br, 18.70. Found: C, 59.36; H, 7.60; Br, 17.76 and 17.55.

The residues were almost completely crystalline and a considerable amount of starting material could be obtained by debromination with zinc in acetic acid at room temperature. The yield of the bromo compound, m.p. 178.5–179.5°, was 81% of theory without regard for recovered starting material.

3α,17α,21-Trihydroxypregnane-11,20-dione (X).—A solution of 436 mg. of 3α,17α-dihydroxy-21-bromopregnane-11,20-dione (VIII) in 200 ml. of 95% ethanol was flushed with nitrogen and 200 ml. of 0.1 *N* sodium hydroxide solution was added at room temperature. After ten minutes the solution was acidified, diluted with ether, and the ether washed with small amounts of 5% sodium hydroxide and 5% sodium chloride solution. After removal of the solvent, 270 mg. of X crystallized slowly from ethyl acetate–methanol as heavy rectangular prisms, m.p. 191–192°. Recrystallization from ethyl acetate raised the m.p. to 195–196.5°; $[\alpha]^{31}_D$ +69° (acetone). The yield was 73% of theory.

17α-Hydroxy-21-acetoxypregnane-3,11,20-trione (XII) (a) From X.—A solution of 107 mg. (0.294 mM.) of 3α,17α,21-dihydroxypregnane-11,20-dione (X), m.p. 191–192°, in 3 ml. of *t*-butanol was stored at 10° for five hours with 82.8 mg. of N-bromoacetamide (0.598 mM.) and 0.1 ml. of water. At that time, 0.297 mM. of the oxidizing agent had been consumed and the solution was diluted with ethyl acetate and washed with 5% sodium hydroxide solution and with water. The solvent was removed and the white crystalline residue was acetylated with pyridine and acetic anhydride at room temperature to yield 113 mg. of yellow crystalline product. By chromatography and recrystallization from ethyl acetate, 25 mg. of 17α-hydroxy-21-acetoxypregnane-3,11,20-trione, m.p. 230–231°; $[\alpha]_D$ +82° (acetone) and 60 mg. of m.p. 228–230° (71% yield) were obtained. The products were identical in all respects (m.p. of mixture, rotation and infrared spectrum) with an authentic sample[13b] from Dr. Sarett.

(b) From VIII.—A solution of 0.99 g. of 3α,17α-dihydroxy-21-bromopregnane-11,20-dione (VIII) in 25 ml. of *t*-butanol containing 646 mg. of N-bromoacetamide and 3 ml. of water was stored for 18 hours at 10°. After the usual isolation procedure the white crystalline reaction product was hydrolyzed in 1 liter of 0.05 *N* sodium hydroxide in 50% ethanol for ten minutes in a nitrogen atmosphere. The crystalline reaction product was acetylated at room temperature with acetic anhydride and pyridine and after recrystallization from ethyl acetate 486 mg. of m.p. 221–224° and 313 mg. of crude crystalline mother liquor were obtained. After repeated recrystallization from ethyl acetate and chromatography of the mother liquors on silica gel, 312 mg., m.p. 230–231°, and 162 mg., m.p. 228–230°, of XII were obtained. These products did not depress the melting point of an authentic sample on admixture and their infrared spectra were identical with that of the authentic sample. The over-all yield was 51%.

17α-Hydroxy-21-bromopregnane-3,11,20-trione (IX).—To a solution of 620 mg. of 3α,17α-dihydroxy-21-bromopregnane-11,20-dione (VIII) in 16 ml. of *t*-butanol was added 420 mg. of N-bromoacetamide and 2 ml. of water. After storage overnight at 10°, ethyl acetate was added and the solution was washed with 5% sodium hydroxide and with dilute sodium chloride solution. The reaction product was crystalline and after recrystallization from ethyl acetate, chunky dense prisms of IX were obtained, m.p. 215° (decomposition) $[\alpha]^{25}_D$ +77.7° (chloroform).

17α-Hydroxy-21-acetoxy-4-bromopregnane-3,11,20-trione (XIII).—Three-tenths ml. of a 0.257 *M* bromine solution in acetic acid was added dropwise to a solution of 308 mg. of 17α-hydroxy-21-acetoxypregnane-3,11,20-trione (XII) in 10 ml. of acetic acid. The bromination was continued with 2.88 ml. of 0.251 *M* bromine in acetic acid solution buffered with an equimolar amount of sodium acetate. When the substitution was completed ethyl acetate was added and the solution was washed thoroughly with dilute sodium chloride solution, dilute sodium hydroxide and again with dilute brine. The solvent was removed at low temperature and the crystalline residue was recrystallized from ethyl acetate. The pure product XIII melted at 196–199° with decomposition; $[\alpha]^{27}_D$ +103° (chloroform). Previous results had demonstrated that it was more advantageous to reduce the residual product with zinc and recycle rather than to attempt purification by recrystallization. The yield of pure XIII in several experiments was from 50 to 60% without regard for recovered starting material.

17α-Hydroxy-21-acetoxy-Δ^4-pregnene-3,11,20-trione (XIV), **Cortisone Acetate.**—A solution containing 692 mg. of 17α-hydroxy-21-acetoxy-4-bromopregnane-3,11,20-trione (XIII), 480 mg. of semicarbazide hydrochloride and 480 mg. of anhydrous sodium acetate in 125 ml. of 98% acetic acid was heated at 70° for two hours in an atmosphere of nitrogen. At that time 7 ml. of pyruvic acid in 14 ml. of water was added and the temperature of the solution was maintained at 70° for an additional two hours. The solution was cooled, diluted with ethyl acetate and extracted thoroughly with dilute sodium hydroxide solution and with 5% sodium chloride solution. Evaporation of the solvent gave 589 mg. of cortisone acetate which after crystallization from acetone yielded 469 mg. (81%) of long plates, m.p. 245–246°; $[\alpha]^{29}_D$ +186° (acetone); +218° (chloroform), ϵ_{2380} 16,100 (ethanol). The product was identical in all respects with the purest authentic compound.

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