[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. XIV. STUDIES IN THE SERIES OF THE ADRENAL CORTICAL HORMONES: DEHYDRATION OF 6β,21-DIACETOXYALLOPREGNANE-5-OL-3,20-DIONE[1]

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As the final step in a series of reactions, Ehrenstein (1, 2) reported the dehydration of 6β,21-diacetoxyallopregnane-5-ol-3,20-dione (I) with dry hydrogen chloride in chloroform. The resulting product (m.p. 84–88°; $[\alpha]_D^{27.2}$ +114.3° in acetone) was interpreted (2) to be 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate [6β,21-diacetoxy-Δ^4-pregnene-3,20-dione] (II). The evidence of the present paper indicates that this conclusion is erroneous.

The recent interest in cortisone and related steroids necessitated a repetition of the earlier work so as to obtain for physiological testing additional amounts of the 6-hydroxy-11-desoxycorticosterone 6,21-diacetate. As has been discussed elsewhere (2), the stereochemical structure of 6β,21-diacetoxyallopregnane-5-ol-3,20-dione (I) can be considered sufficiently proven, especially with regard to the configurations at carbon atoms 5 and 6. In the previous experiments (1) the solvent used for the dehydration of I was chloroform (C. P. Baker) which was dried over calcium chloride and redistilled before use. It cannot be stated with certainty that it was alcohol-free. The temperature of the reaction was in the neighborhood of +2°. When the experiment was repeated, the dehydration of I was carried out by chance in completely alcohol-free chloroform at a much lower temperature (−15° to −20°). This did not lead to the formation of the expected substance melting at 84–88°. Instead, another α,β-unsaturated ketone with a melting point of 123–125° resulted. This observation necessitated a reinvestigation of the dehydration reaction. As will be subsequently proven the two compounds are epimers. The lower-melting product is 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV) whereas the higher-melting substance is 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate (II).

The solvent influences the configuration of the product obtained by the dehydration. On treating I with dry hydrogen chloride in ordinary chloroform

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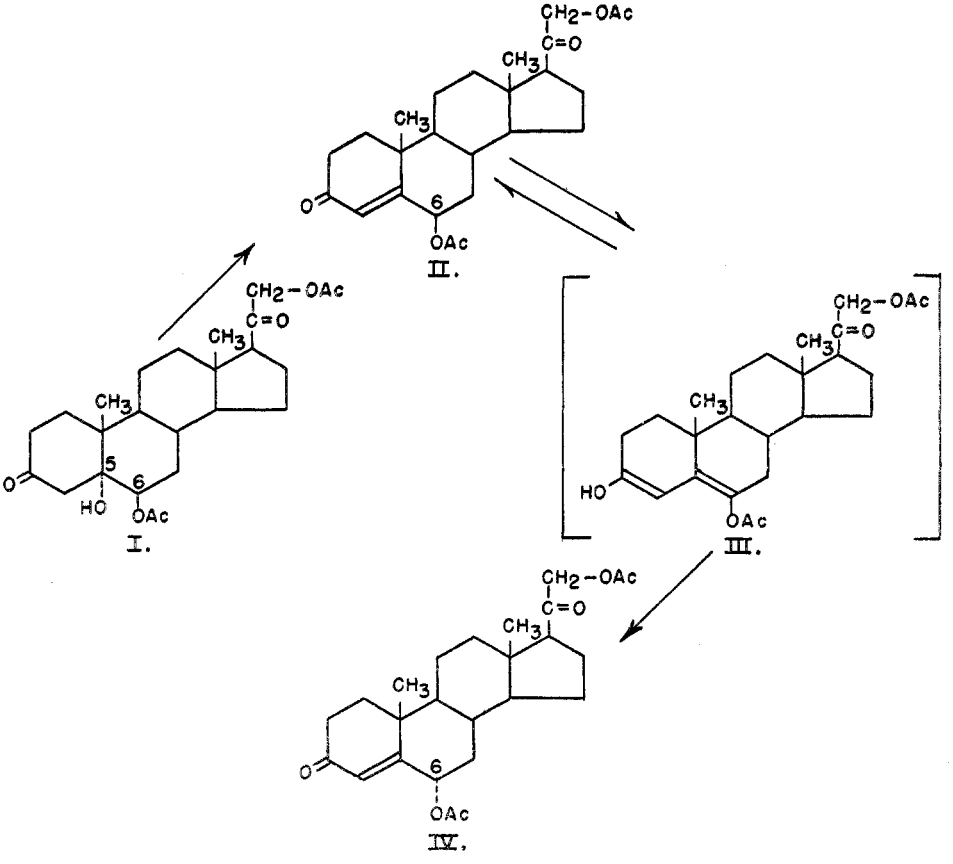
Presented before the Biological Chemistry Section at the Miniature Meeting of the Philadelphia Section of the American Chemical Society, January 18, 1951 [*cf.* Herzig and Ehrenstein, Abstracts of Papers, Fourth Meeting-in-Miniature, Philadelphia Section of the American Chemical Society, p. 15 (1951)] and before the American Society of Biological Chemists at the 35th annual meeting of the Federation of American Societies for Experimental Biology in Cleveland, Ohio, April 29–May 3, 1951 [Read by title *cf.* Ehrenstein and Herzig, *Federation Proc.*, **10**, 179, 476 (1951)].

(*i.e.*, containing 0.7% ethanol) at varying temperatures, the lower melting α-compound (IV) was exclusively obtained. If alcohol-free chloroform was used, the configuration of the final product depended on the temperature of the reaction. When conducted between +3° and +5°, the experiment yielded predominantly the α-isomer. When performed between −15° and −20°, the reaction gave a mixture from which the higher-melting β-isomer (II) was obtained by direct crystallization. On conducting the reaction between +3° and +7° in



carbon tetrachloride, *i.e.*, in a solvent of low polarity, a fair yield of the β-compound (II) resulted. As has been demonstrated in a previous publication (3), 3-keto-5-hydroxy steroids can be readily dehydrated with the aid of Girard's Reagent T. On applying this procedure to I, the higher-melting β-epimer (II) was obtained as the main product of the reaction. These observations and further data (*vide infra*) suggested that the higher-melting product is the thermodynamically unstable epimer with the acetoxy group at carbon atom 6 in the original β-position (II).[2] In agreement with this assumption it was possible to

[2] For pertinent thermodynamic considerations *cf.* (4).

rearrange the β-epimer into the lower-melting α-epimer by treatment with dry hydrogen chloride in a solution of either chloroform or carbon tetrachloride containing 0.7% of ethanol. Epimerization in the 17-position was ruled out, because 11-desoxycorticosterone acetate, when subjected to the same treatment, yielded unchanged starting material. It is considered plausible that the enolic form III is the intermediate in the rearrangement of II to IV.

COMPOUND	M.P., °C.	λ_{max}^{alc} mμ	ϵ_{max}	$[\alpha]_D$
6β-Hydroxy-11-desoxycorticosterone 6,21-diacetate (II)	125–127	236	15,950	+109.6°
6α-Hydroxy-11-desoxycorticosterone 6,21-diacetate (IV)	84–86	238	15,910	+136.9°

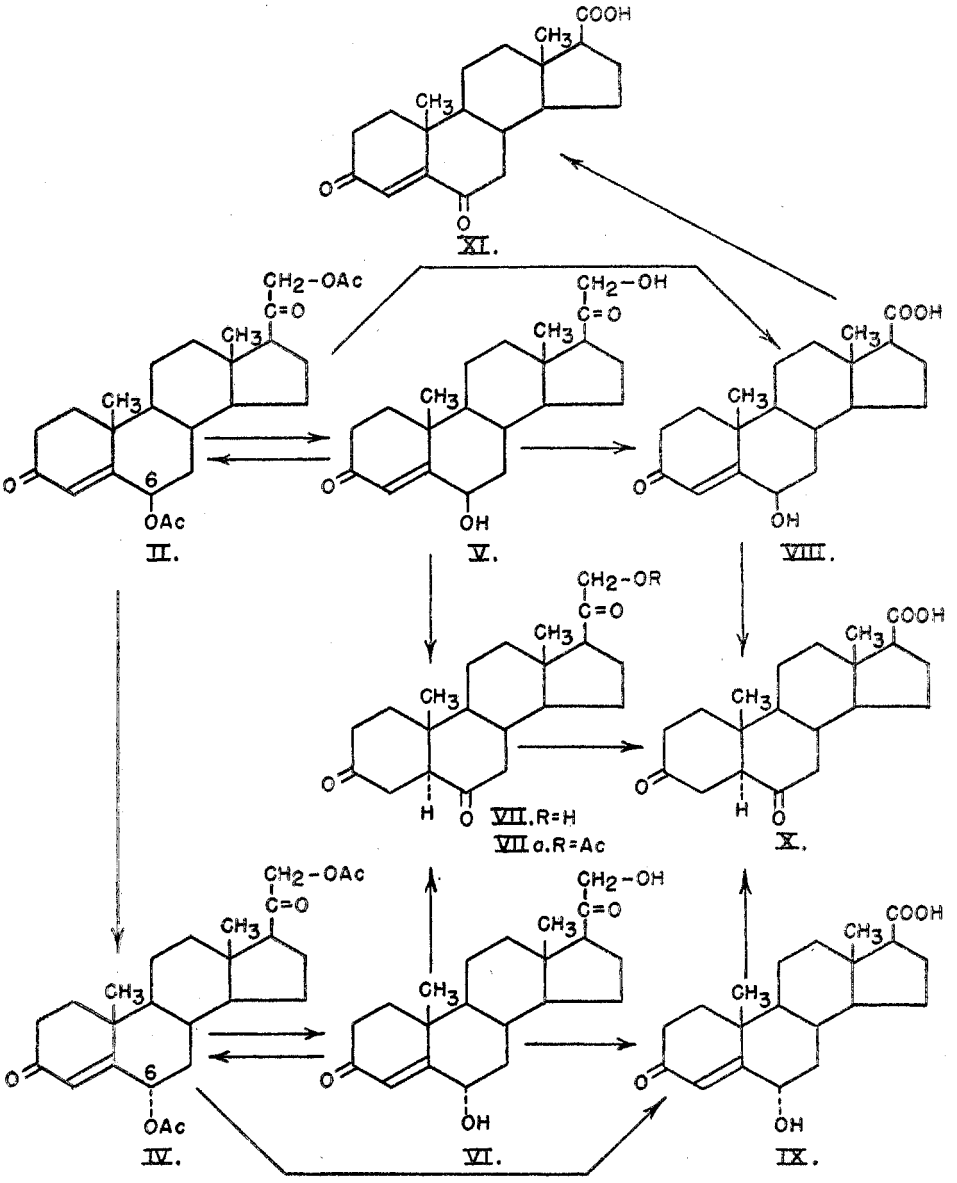
The physical constants of the two epimers (*vide supra*) appear to be in agreement with the assigned structures.

The infrared spectra were determined (in CS_2) through the courtesy of Dr. Konrad Dobriner and Mrs. Phyllis Humphries of the Sloan-Kettering Institute for Cancer Research in New York. In the fingerprint region (1200–850 cm^{-1}) the spectra of II and IV are completely different, thus confirming that these two substances are distinct compounds. In both products the spectrum shows the presence of a double bond at 3080 cm^{-1}. In the carbonyl region there is absorption at 1755–1750 cm^{-1} and 1734 cm^{-1}, indicating a 21-acetoxy-20-ketone grouping. An increased intensity of the 1755–1750 cm^{-1} band indicates the presence of an additional acetate group. Both compounds exhibited a shift of the conjugated carbonyl absorption from 1674 cm^{-1} to 1688 cm^{-1}. This shift is in the same direction as found with 2-acetoxy-Δ^4-3-ketones where the conjugated carbonyl absorption is shifted from 1674 cm^{-1} to 1700 cm^{-1}. The infrared spectra will be more fully discussed in a future publication by Dobriner, *et al.*

Further support for the structures of II and IV is given by the following chemical reactions. Attempts were made to deacetylate II under various experimental conditions. On treating II in absolute ethanol with 2.2 equivalents of potassium hydroxide under nitrogen at room temperature for 45 minutes, a smooth saponification occurred leading to an excellent yield of 6β-hydroxy-11-desoxycorticosterone (V).[2a] Reacetylation of V gave the starting material (II), proving that no rearrangement had taken place. In another experiment a methanol-water (4:3) solution of II was refluxed with potassium bicarbonate for 90 minutes. This furnished only a small yield of V and, in addition, some allo-

[2a] In a private communication from Dr. W. J. Haines and Dr. E. D. Nielson, of the Upjohn Research Laboratories, Kalamazoo, Michigan, it was reported that 6β-hydroxy-11-desoxycorticosterone has also been produced enzymatically by incubating 11-desoxycorticosterone with hog adrenal brei. The identity of this product with V, above, was established in collaboration with Dr. Dobriner and Mrs. Humphries of the Sloan-Kettering Institute where the diacetate was found to possess an infrared spectrum identical to that of II, above. Details of this enzymatic conversion will be presented in a future publication from the Upjohn Labratories.

pregnane-21-ol-3,6,20-trione (VII).[3] On refluxing II in methanol-water (1:10) with 3.2 equivalents of potassium hydroxide for one hour, only VII was isolated.



The experiments indicate that in an aqueous alkaline medium V is unstable and rearranges to VII.

Similar reactions were carried out in the α-series. Treatment of IV in absolute

[3] For assignment of the "allo" configuration at carbon atom 5 *cf. e.g.*, (2), p. 221.

ethanol with 2.2 equivalents of potassium hydroxide under nitrogen at room temperature for 45 minutes gave a good yield of 6α-hydroxy-11-desoxycorticosterone (VI). Reacetylation of VI gave the starting material (IV), proving that in this instance also no rearrangement had taken place. Unlike the β-series refluxing of IV with aqueous alcoholic alkali did not furnish VII, but yielded VI exclusively. The rearrangement of VI into VII was accomplished either by heating VI above the melting point or by treatment with glacial acetic acid plus a small amount of sulfuric acid. In the latter case there was also some oxidative cleavage resulting in the formation of some 3,6-diketoetioallocholanic acid (X) (*vide infra*). The trione VII was characterized by its acetate (VIIa).

COMPOUND	M.P., °C.	λ_{max}^{alc} mμ	ϵ_{max}	$[\alpha]_D$
6β-Hydroxy-11-desoxycorticosterone (V).....	190–192	235	13,730	+62.6°
6α-Hydroxy-11-desoxycorticosterone (VI).....	166–168	240	15,230	+139.7°

Velluz (5) observed that the determination of the saponification equivalent of a ketol acetate, *e.g.*, 11-desoxycorticosterone acetate or 21-acetoxy-Δ^5-pregnene-3β-ol-20-one, with ethanolic potassium hydroxide gave results exceeding the theoretical, even when the saponification was carried out at room temperature for only 30–60 minutes. It was found that in each of the named examples there were consumed three moles of potassium hydroxide and one mole of atmospheric oxygen. The reaction proceeds as follows: (a) $\overset{\overset{17}{\diagdown}}{}CHCOCH_2OAc + KOH \rightarrow \overset{\overset{17}{\diagdown}}{}CHCOCH_2OH + AcOK$; (b) $\overset{\overset{17}{\diagdown}}{}CHCOCH_2OH + O_2 + 2KOH \rightarrow \overset{\overset{17}{\diagdown}}{}CHCOOK + HCOOK + 2H_2O$. The reaction was studied in this laboratory and found to be reproducible in the above two instances. The consumption of oxygen can be followed quantitatively. It proceeds at a rapid rate at room temperature and comes to a standstill after the uptake of exactly one mole.

On the basis of this work, II was treated with 4.2 moles of potassium hydroxide (Calc'd: 4 moles, *i.e.*, 2 moles for the saponification of the acetate groups, 2 moles for the oxidative cleavage) in absolute ethanol at room temperature under oxygen. The reaction proceeded smoothly and furnished an almost quantitative yield of the etio acid, *i.e.*, 3-keto-6β-hydroxy-Δ^4-etiocholenic acid (VIII). The identical acid was obtained by the oxidation of V with periodic acid. In a like manner, application of the method of Velluz to IV gave an excellent yield of 3-keto-6α-hydroxy-Δ^4-etiocholenic acid (IX). The same acid resulted from the oxidation of VI with periodic acid. By oxidation with chromic

COMPOUND	M.P., °C.	λ_{max}^{alc} mμ	ϵ_{max}	$[\alpha]_D$
3-Keto-6β-hydroxy-Δ^4-etiocholenic acid (VIII)	232–234	238	12,250	+64.6°
3-Keto-6α-hydroxy-Δ^4-etiocholenic acid (IX)...	207–209	239	17,060	+56.2°
3,6-Diketo-Δ^4-etiocholenic acid (XI).....	240–242	248	13,060	+9.5°

acid, VIII was transformed into 3,6-diketo-Δ^4-etiocholenic acid (XI). The ultraviolet absorption spectrum is in agreement with the assigned structure.

3,6-Diketoetioallocholanic acid (X), which was briefly mentioned earlier (*vide supra*), has been secured by three clearly defined reactions, namely (a) the rearrangement of VIII in aqueous alkali, (b) the rearrangement of IX in glacial acetic acid containing a trace of sulfuric acid, and (c) the oxidation of VII with periodic acid. The rearrangements (a) and (b) are analogous to those leading to VII from V and VI respectively. The reaction mechanisms of some of the described rearrangements will be discussed in a future publication.

In the light of the present findings it will be necessary to reinvestigate a number of analogous reactions previously reported from this laboratory. Dehydration with dry hydrogen chloride in alcohol-free (?) chloroform of 6β-acetoxyallopregnane-5-ol-3,20-dione (6) led to a crystalline product interpreted to be 6β-acetoxyprogesterone (2). On repeating the experiment, supposedly under identical conditions, an amorphous α,β-unsaturated ketone of the same composition was obtained which resisted all attempts at crystallization. It was considered an "amorphous modification" of the same compound (7). It now appears probable that slight differences of the solvent existed in the dehydration experiments and that, therefore, this might be an analogous case of epimerism. The configuration of either of the two products cannot be deduced without additional experimental work. In a like manner, dehydration with dry hydrogen chloride in alcohol-free (?) chloroform of 6β-acetoxyandrostane-5-ol-3,17-dione (1) yielded a single crystalline compound to which was assigned the structure of 6β-acetoxy-Δ^4-androstene-3,17-dione (2). Depending on the character of the solvent, one would expect also in this instance the formation of two epimeric products. Since so far only one compound has been obtained, its configuration at carbon atom 6 remains uncertain.

EXPERIMENTAL[3a]

The melting points were determined with the Fisher-Johns melting point apparatus. The readings are sufficiently near the true melting points so that no corrections have been made. The microanalyses were carried out by Dr. E. W. D. Huffman, Denver 2, Colo. The starting material, 6β,21-diacetoxyallopregnane-5-ol-3,20-dione (I) was prepared as described previously. The yields and properties of the intermediates and the final product (I) were in agreement with the earlier observations (1, 2).

6β-Hydroxy-11-desoxycorticosterone 6,21-diacetate [6β,21-diacetoxy-Δ^4-pregnene-3,20-dione] (II) and 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate [6α,21-diacetoxy-Δ^4-pregnene-3,20-dione] (IV) from 6β,21-diacetoxyallopregnane-5-ol-3,20-dione (I). A. By the action of dry hydrogen chloride in chloroform. Except for the variations of temperature and characteristics of the solvent, these experiments (*a*, *b*, *c*, *d*) were performed under identical conditions as follows: Through a solution of 30 mg. of starting material (I) in 10 cc. of chloroform of quoted purity was passed under anhydrous conditions at the quoted temperature a moderate stream of dry hydrogen chloride for a period of 1½ hours. After the addition of 30 cc. of water, the solution was washed with two 10-cc. portions of ice-cold *N* sodium carbonate and two 15-cc. portions of water. After drying over sodium sulfate and subsequent removal of the solvent the crude reaction product resulted.

[3a] The 21-acetoxypregnenolone, used for preparing the starting material in this investigation, was kindly donated by Dr. C. R. Scholz of Ciba Pharmaceutical Products, Summit, N. J.

a. Solvent: Chloroform Merck Reagent (containing 0.7% alcohol), redistilled. Temperature of reaction: Between −15° and −20°. Yield: 28.6 mg. of resin. Recrystallized from acetone-petroleum ether; colorless needles; wt. 15 mg.; m.p. 77–80°. Renewed crystallization gave 12 mg. (42%) of m.p. 80–83°. Identified by mixture m.p. as 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV).

b. Solvent: Same as under a. Temperature of reaction: Between +3° and +6°. Yield: 28.4 mg. of resin. Recrystallized as under *a*; colorless needles; wt. 22 mg.; m.p. 78–81°. Renewed crystallization gave 18 mg. (63%) of m.p. 81–83°. Identified by mixture m.p. as 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV).

c. Solvent: Alcohol-free chloroform (*i.e.*, Chloroform Merck Reagent, successively shaken with conc'd sulfuric acid and water, dried over calcium chloride, and redistilled). Temperature of reaction: Between −15° and −20°. Yield: 29.4 mg. of resin, subsequently purified by chromatography [Aluminum oxide-Brockmann; Activity II (8)]. Isolated, in the order of elution: Several consecutive resinous fractions, total wt. 15.6 mg., probably consisting of mixtures of 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV) and the corresponding 6β-epimer (II). One crystalline fraction, wt. 5.4 mg., after recrystallization from acetone-petroleum ether, wt. 4.5 mg., m.p. 123–125°; identified by mixture m.p. as 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate (II).

d. Solvent: Same as under c. Temperature of reaction: Between +3° and +5°. Yield: 26.8 mg. of crystalline material; recrystallized from acetone-petroleum ether; colorless needles, wt. 14.4 mg., m.p. 81–83°. Identified by mixture m.p. as 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV).

B. By the action of dry hydrogen chloride in a solution of carbon tetrachloride. Through 15 mg. of starting material (I) in 15 cc. of dry carbon tetrachloride (Merck Reagent) was passed under anhydrous conditions a moderate stream of dry hydrogen chloride for one hour (temperature between +3° and +7°). The solvent and hydrogen chloride were removed *in vacuo*, leaving 16.4 mg. of a resin. Recrystallization from acetone-petroleum ether, after two days' standing in the refrigerator, gave 8.5 mg. of stout colorless needles, m.p. 122–125°, identified by mixture m.p. as 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate (II).

C. Under the influence of Girard's Reagent T. To 35.1 mg. of starting material (I) in 0.7 cc. of absolute ethanol was added 79.9 mg. of Girard's Reagent T and 0.04 cc. of glacial acetic acid. After refluxing this mixture on a water-bath for one hour and subsequent cooling, the Girard compound was decomposed with 2 cc. of 6 *N* hydrochloric acid and 5 cc. of water. The mixture was allowed to stand for three hours at room temperature. Then additional water was added and the resulting precipitate extracted with ether, followed by successive washing of the extract with 0.1 *N* sodium bicarbonate and water. After drying with sodium sulfate and evaporation of the solvent, 25.8 mg. of resinous ketonic material resulted which was chromatographed over 2 g. of alkali-free aluminum oxide.[4] The main fraction of the chromatogram, resulting from a benzene-ether (3:2) eluate, was crystalline; wt. 15.4 mg.; m.p. 117–119°. Recrystallized from acetone-petroleum ether; wt. 10.1 mg.; m.p. 125–127°; identified by mixture m.p. as 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate (II).

Characterization of 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate (II). A satisfactory yield of this substance somewhat unexpectedly resulted from an experiment in which 2.56 g. of 6β,21-diacetoxyallopregnane-5-ol-3,20-dione (I), dissolved in 150 cc. of dry alcohol-free chloroform, was treated with hydrogen chloride at about −10° for three hours. Chromatography of the reaction product over 65 g. of alkali-free aluminum oxide[4] (diam. of column: 3.3 cm.) gave, on evaporating the eluates (petroleum ether-benzene, 2:3; benzene; benzene-ether, 1:1; ether), four consecutive crystalline fractions; total wt. 1.80 g.; m.p. between 121 and 126°. Repeatedly recrystallized from acetone-petroleum ether; colorless

[4] One part of Alumina Adsorption (Fisher), 80–200 mesh, was placed in an adsorption column and slowly washed with two parts of a 9:1 mixture of methanol-glacial acetic acid. The material was subsequently washed acid free with methanol and dried in an oven at a temperature of 200° for four hours.

stout needles; wt. 1.26 g.; m.p. 125–127°. [From a late eluate (ether-methanol, 3:2) resulted 0.42 g. of an additional crystalline substance; m.p. 170–171° (details *vide infra*).] The crystals of II turn yellow upon exposure to light. The color change is reversible in the dark. $[\alpha]_D^{16}$ +109.57° (15.67 mg. in 2.0 cc. of chloroform; *l*, 2 dm.; α +1.72°); $[\alpha]_D^{25.5}$ +98.45° (21.21 mg. in 2.0 cc. of acetone; *l*, 1.5 dm.; α +1.57°). The ultraviolet absorption spectrum is that of an α,β-unsaturated ketone (λ_{max}^{alc} 236 mμ; ϵ, 15,950). For infrared spectrum see theoretical part. A sample was dried *in vacuo* over P_2O_5 at 80° prior to analysis.

Anal. Calc'd for $C_{25}H_{34}O_6$ (430.52): C, 69.73; H, 7.96.

Found: C, 69.88; H, 8.05.

On adding conc'd sulfuric acid to this substance, fluorescence is observed almost immediately. The fluorescence intensifies on standing and the originally yellow solution turns red.

2,4-Dinitrophenylhydrazone. To 5 mg. of II in 1 cc. of methanol was added 1 cc. of a 1% solution of 2,4-dinitrophenylhydrazine. The brick-red precipitate was filtered after 5 minutes standing and recrystallized from methanol-water; 3.5 mg.; red crystals; m.p. 170–172°.

Rearrangement of 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate (II) to 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV). Rearrangement by heating was unsuccessful. Thus 10 mg. of II was kept at 140–145° in a glass tube sealed under a high vacuum for 30 minutes. Recrystallization of the resulting glass from acetone-petroleum ether gave 7.5 mg. of colorless needles; m.p. 123–125°; identical with starting material.

The following two experiments were conducted identically except for the carbon tetrachloride used: Through 15 mg. of II in 15 cc. of carbon tetrachloride was passed a moderate stream of dry hydrogen chloride at +3° to +7° for 45 minutes under anhydrous conditions. The solvent was removed *in vacuo* (oil-pump) at room temperature and the residue recrystallized from acetone-petroleum ether. The first experiment, using dry redistilled carbon tetrachloride (Merck Reagent), gave 15.7 mg. of resinous residue; recrystallized, wt. of crystals: 12.2 mg. (81%); m.p. 125–126°; identified by mixture m.p. as II (starting material). In the second experiment the redistilled carbon tetrachloride (Merck Reagent) contained 0.1 cc. of absolute ethanol (*i.e.*, alcohol content approx. 0.7%). Wt. of resinous residue: 15.5 mg.; recrystallized, wt. of crystals: 10.1 mg. (67%); m.p. 83–85°; identified by mixture m.p. as 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV).

The rearrangement was also performed in redistilled chloroform (Merck Reagent, containing approx. 0.7% of ethanol). Through 75 mg. of II in 30 cc. of chloroform was passed a moderate stream of dry hydrogen chloride at +3° to +7° for 1½ hours under anhydrous conditions. The solution was washed neutral with *N* sodium carbonate and water, then dried with sodium sulfate, and brought to dryness. Recrystallization of the resinous residue (74.5 mg.) from acetone-petroleum ether gave 57.2 mg. (76%) of colorless needles; m.p. 84–86°; identified by mixture m.p. as IV. In another, similarly conducted experiment, 51.5 mg. of II gave 45.3 mg. (88%) of crystalline IV. Desoxycorticosterone acetate, when subjected to the same experimental conditions yielded approx. 90% of unchanged starting material.

Characterization of 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV). Several ways of preparing this compound have been described (*vide supra*). The pooled non-crystalline fractions resulting from various attempts at dehydrating I were subjected to further purification by chromatography (alkali-free[4] aluminum oxide). This furnished, in the order of eluting, additional quantities of IV (benzene-petroleum ether, 1:1), II (benzene), and the by-product of m.p. 170–172° (ether) (*vide supra*). The melting point of pure 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV) is 84–86°. $[\alpha]_D^{19.5}$ +136.9° (14.71 mg. in 2.0 cc. of chloroform; *l*, 2 dm.; α +2.01°); $[\alpha]_D^{25.6}$ +120.78° (18.69 mg. in 2.0 cc. of acetone; *l*, 1.5 dm.; α +1.69°); lit. (1) $[\alpha]_D^{27.2}$ +114.3° (acetone). The ultraviolet absorption curve is that of an α,β-unsaturated ketone (λ_{max}^{alc} 238 mμ; ϵ, 15,910). For infrared spectrum see theoretical part. A sample was dried *in vacuo* over P_2O_5 at 60° prior to analysis.

Anal. Calc'd for $C_{25}H_{34}O_6$ (430.52): C, 69.73; H, 7.96.

Found: C, 69.39; H, 8.10.

The color reaction with conc'd sulfuric acid is identical with that observed with the β-isomer (II) (*vide supra*).

2,4-Dinitrophenylhydrazone. To 5 mg. of IV in 1 cc. of methanol was added 1 cc. of a 1% solution of 2,4-dinitrophenylhydrazine. The light-red precipitate was filtered after 5 minutes' standing and recrystallized from methanol-water; 3.2 mg.; orange crystals; m.p. 191–192°.

By-product of the dehydration: 3β,6β,21-Triacetoxyallopregnane-5-ol-20-one. The substance (*vide supra*) was recrystallized from ether-petroleum ether; stout crystals; m.p. 170–172°. The product was identified by a mixture m.p. with an authentic sample (1, 2) and by analysis. $[\alpha]_D^{19.5}$ −0.28° (13.95 mg. in 2.0 cc. of chloroform; *l*, 2 dm.; α −0.004°); lit. (1) $[\alpha]_D^{26.1}$ +3.5° (acetone). A sample was dried *in vacuo* over P_2O_5 at 80°.

Anal. Calc'd for $C_{27}H_{40}O_8$ (492.59): C, 65.81; H, 8.19.

Found: C, 65.77; H, 8.20.

6β-Hydroxy-11-desoxycorticosterone [Δ⁴-*Pregnene-6β,21-diol-3,20-dione*] (*V*) *from 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate* (*II*). *Method A:* This procedure provides satisfactory yields if followed in detail. Nitrogen was freed from any oxygen by passage through two flasks containing Fieser's solution (9, p. 395), a solution of lead acetate, and finally through a tube filled with calcium chloride. Nitrogen-saturated ethanol was prepared by evacuating a flask containing ethanol and then admitting oxygen-free nitrogen. This was repeated three times. A solution of potassium hydroxide in nitrogen-saturated absolute ethanol was prepared under an atmosphere of oxygen-free nitrogen. A vial containing the 6,21-diacetate was inserted in the alcoholic alkali without mixing and, after thorough flushing of apparatus with oxygen-free nitrogen, the diacetate was permitted to dissolve. Subsequently a moderate stream of oxygen-free nitrogen was passed through the apparatus during the whole course of the reaction. Contact with air was permitted only after acidification of the reaction mixture. In a typical experiment, 32.2 mg. of potassium hydroxide (2.1 equiv.) was dissolved in 10.5 cc. of nitrogen-saturated absolute ethanol. Under nitrogen 113.4 mg. of 6,21-diacetate (II) was dissolved. The mixture was kept at room temperature for 45 minutes. After acidification with 0.2 cc. of 10% sulfuric acid, the ethanol was removed *in vacuo*. To the residue was added 20 cc. of water and the flocculent precipitate was extracted with ether. The ether layer was washed twice with *N* sodium carbonate and twice with water. No acid material could be secured from the carbonate phase. From the ether extract there resulted, after drying with sodium sulfate, 83.0 mg. (91%) of neutral crystalline material, m.p. 180–185°. Recrystallization from acetone-petroleum ether yielded 71.4 mg. (78%) of colorless needles; m.p. 190–192°. $[\alpha]_D^{21.1}$ +62.63° (11.23 mg. in 2.0 cc. of chloroform; *l*, 1.51 dm.; α +0.53°). The ultraviolet absorption curve is that of an α,β-unsaturated ketone (λ_{max}^{alc} 235 mμ; ε, 13,730). A sample was dried at 90° *in vacuo* over P_2O_5 prior to analysis.

Anal. Calc'd for $C_{21}H_{30}O_4$ (346.45): C, 72.76; H, 8.72.

Found: C, 72.62; H, 8.63.

On adding conc'd sulfuric acid to this substance, the crystals turned red immediately and, on dissolving, a greenish fluorescent solution resulted which turned red after some standing. On acetylating with pyridine (1 cc.)—acetic anhydride (0.5 cc.) at room temperature overnight, the substance (25.6 mg.) was converted into a product of m.p. 124–125° which was identical with the original 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate (II).

Method B: To 104.6 mg. of the 6,21-diacetate (II) in 4 cc. of methanol was added 114.8 mg. of potassium bicarbonate in 3 cc. of water. The mixture was refluxed on a water-bath for 1½ hours and was then diluted with water to three times the original volume. The precipitate was extracted with ethyl acetate and the extract washed with water and dried over sodium sulfate. Evaporation of the solvent yielded 104.2 mg. of a partly crystalline yellowish resin (neutral). No acid material resulted from the alkaline phase after acidification. Recrystallization of the neutral fraction from ethanol gave 18.5 mg. of shiny needles; m.p. 190–192°; identified by mixture m.p. as 6β-hydroxy-11-desoxycorticosterone (V) (*vide method*

A). From the mother liquors there resulted by fractional crystallization 3 mg. of colorless needles, m.p. 196–200°, which gave a depression of the m.p. when mixed with the before mentioned product. It was identified by mixture m.p. determination as allopregnane-21-ol-3,6,20-trione (VII) (*vide infra*). Experimental evidence indicated that the combined mother liquors contained appreciable, additional quantities of the latter product.

6α-Hydroxy-11-desoxycorticosterone [Δ^4-*Pregnene-6α,21-diol-3,20-dione*] (*VI*) *from 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate* (*IV*). *Method A:* The detailed experimental conditions were identical with those of the alcoholysis of 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate (II), *Method A* (*vide supra*). To 12.3 mg. of potassium hydroxide (2.2 equiv.) in 16.5 cc. of nitrogen-saturated absolute ethanol was added under nitrogen 45 mg. of 6,21-diacetate (IV). After keeping the mixture at room temperature for 45 minutes, 0.4 cc. of 10% sulfuric acid and 10 cc. of water was added and the mixture was freed from alcohol *in vacuo*. The flocculent precipitate was extracted with ethyl acetate and the extract washed with *N* sodium carbonate and water. After drying with sodium sulfate, evaporation of the solvent yielded 36 mg. of crystalline material which, upon recrystallization from acetone-petroleum ether gave 29.6 mg. (82%) of colorless needles of m.p. 166–168°. $[\alpha]_D^{18}$ +139.7° (10.18 mg. in 2.0 cc. of chloroform; *l*, 2 dm.; α +1.42°). The ultraviolet absorption spectrum is that of an α,β-unsaturated ketone. (λ_{max}^{alc} 240 mμ; ε, 15,230). A sample was dried *in vacuo* over P_2O_5 at 90° prior to analysis.

Anal. Calc'd for $C_{21}H_{30}O_4$ (346.45): C, 72.76; H, 8.72.
Found: C, 72.35; H, 8.76.

On adding conc'd sulfuric acid to this substance, the crystals and the resulting solution remained colorless for about 5 minutes. The solution then gradually turned markedly fluorescent and, after about 3 hours, a pink color was observed. On acetylating with pyridine (0.5 cc.)–acetic anhydride (0.2 cc.) at room temperature the substance (1 mg.) was converted into colorless needles (0.9 mg.) of m.p. 83–85°, identified by mixture m.p. determination as 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV).

Method B: The 6,21-diacetate (IV) (10 mg.) in 0.5 cc. of methanol was diluted with 30 cc. of water and, after the addition of 2.8 mg. of potassium hydroxide (2.2 equiv.) in 1 cc. of water, the mixture was kept on a boiling-water bath for 1½ hours. An initial slight turbidity disappeared within 5 minutes. The solution was then made acid to Congo Red with 10% sulfuric acid and extracted with ethyl acetate. Extraction of the resulting solution with *N* sodium carbonate failed to yield acidic material. After drying over sodium sulfate, evaporation of the ethyl acetate gave 7.5 mg. (93%) of neutral crystalline material which on recrystallizing from acetone-petroleum ether gave 4.6 mg. (57%) of colorless needles; m.p. 162–164°; identified by mixture m.p. determination as 6α-hydroxy-11-desoxycorticosterone (VI).

Method C: To 4 mg. of 6,21-diacetate (IV) in 1 cc. of methanol was added 0.03 cc. of 1.04 *N* sodium hydroxide (approx. 2.2 equiv.). The slightly turbid mixture was left at room temperature without special precautions (*i.e.*, exposed to air) for two hours. It was then diluted with 5 cc. of a saturated solution of sodium chloride and extracted with ethyl acetate. After drying with sodium sulfate the solvent was evaporated leaving 3.1 mg. of a neutral residue. Recrystallization from acetone-petroleum ether gave 2.7 mg. (88%) of colorless needles of m.p. 161–163°; identified by mixture m.p. determination and the ultraviolet absorption spectrum (λ_{max}^{alc} 240 mμ) as 6α-hydroxy-11-desoxycorticosterone (VI). A similar experiment was conducted in ordinary methanol (*i.e.*, containing some water) with 4.2 equiv. of potassium hydroxide at room temperature in the presence of oxygen; time of reaction: 1¾ hours. Only traces of acid material were obtained; the yield of the 6α-hydroxy-11-desoxycorticosterone (VI) was 92%.

Allopregnane-21-ol-3,6,20-trione (*VII*). *A. From 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate* (*II*). To 50 mg. of the 6,21-diacetate (II) in 2 cc. of methanol was added 20.8 mg. of potassium hydroxide (3.2 equiv.) in 1 cc. of methanol. Subsequently 30 cc. of water was added which caused a flocculent precipitate to appear. The latter went almost completely into solution on heating the mixture on a water-bath for one hour. After saturation with

sodium chloride, the mixture was extracted with ethyl acetate. The organic solvent phase was washed with water, dried with sodium sulfate, and evaporated to dryness; yield: 42.7 mg. of essentially neutral crystalline material. Only traces of a resinous acid fraction were secured after acidification of the alkaline phase. On recrystallizing the neutral product twice from ethanol, 16.7 mg. of crystals, m.p. 196–200°, was obtained. The compound was characterized by the 21-acetate (VIIa) (*vide infra.*).

B. From 6α-hydroxy-11-desoxycorticosterone (VI). a. By heating above the melting point. Two milligrams of VI was kept at 170–173° in a tube sealed under a high vacuum for 30 minutes. The resulting greenish fluorescent resin was recrystallized twice from acetone-petroleum ether; m.p. 195–198°; no depression of m.p. when mixed with product obtained under *A*.

b. By treatment with glacial acetic acid in the presence of sulfuric acid. To 5 mg. of VI in 0.5 cc. of glacial acetic acid was added one drop of 10% sulfuric acid in glacial acetic acid and the mixture allowed to stand at room temperature overnight. It was then made slightly alkaline with *N* sodium carbonate and subsequently extracted with ethyl acetate. The solvent was washed with water, dried with sodium sulfate, and evaporated; yield: 1.5 mg. of neutral material; recrystallized from acetone-petroleum ether, m.p. 191–193°; identified by mixture m.p. determination as allopregnane-21-ol-3,6,20-trione (VII). The aqueous alkaline solution was made acid to Congo Red and then extracted with ethyl acetate. The solvent was washed with water, dried with sodium sulfate, and evaporated to dryness; yield: 2.8 mg. of crystalline acid material; recrystallized from acetone-petroleum ether: 1.5 mg. of colorless needles, m.p. 261–263°; identified by mixture m.p. determination as 3,6-diketocholallocholanic acid (X) (*vide infra*).

21-Acetoxyallopregnane-3,6,20-trione (VIIa). The allopregnane-21-ol-3,6,20-trione (VII) as secured by procedure *A* (*vide supra*) was acetylated with pyridine-acetic anhydride at room temperature in the usual fashion. The resulting crude acetylation product was purified by chromatography [Al_2O_3-Brockmann; Activity III (8)]. The acetate was eluted by benzene and benzene-ether (3:2). Recrystallization gave colorless crystals of m.p. 193–195° $[\alpha]_D^{28.5}$ +73.76° (9.32 mg. in 2.0 cc. of chloroform; *l*, 1.51 dm.; α +0.52°). A sample was dried at 80° *in vacuo* over P_2O_5 prior to analysis.

Anal. Calc'd for $C_{23}H_{32}O_5$ (388.48): C, 71.07; H, 8.33.

Found: C, 70.97; H, 8.31.

3-Keto-6β-hydroxy-Δ⁴-etiocholenic acid (VIII). A. From 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate (II) by treatment with oxygen in alcoholic alkali. A 2 cc. glass vial containing 105.5 mg. of II in 1 cc. of absolute ethanol was carefully placed without mixing into a 50-cc. ground joint flask containing 58.6 mg. of potassium hydroxide (4.3 equiv.) in 5 cc. of absolute ethanol. The flask was attached to an apparatus similar to those used for hydrogenations. After thoroughly flushing the system with oxygen, the solutions were mixed. Absorption of oxygen began at a rapid rate and came to a standstill after about 25 minutes (Calc'd for 1 mole of O_2 at 756.7 mm. of Hg and 21°: 5.93 cc. Observed absorption: 6.2 cc.[5]). After completion of the oxidative cleavage, the reaction mixture was immediately poured into four times its volume of water and the resulting solution extracted with ether. Only traces of resinous neutral material were obtained from this ethereal phase. The alkaline aqueous solution was acidified to Congo Red with 10% sulfuric acid and the flocculent precipitate extracted with ether. After washing with water, drying with sodium sulfate, and evaporating the solvent, 89.3 mg. of slightly yellowish crystalline acid material, m.p. 223–227°, was isolated. Recrystallization from acetone-petroleum ether gave 63.3 mg. (78%) of m.p. 232–234°. $[\alpha]_D^{25.5}$ +64.58° (13.35 mg. in 2.0 cc. of chloroform; *l*, 1.51 dm.; α +0.65°). The ultraviolet absorption curve is that of an α,β-unsaturated ketone (λ_{max}^{al} 238 mμ; ε, 12,250). A sample was dried at 80° over P_2O_5 prior to analysis.

Anal. Calc'd for $C_{20}H_{28}O_4$ (332.42): C, 72.26; H, 8.49.

Found: C, 72.30; H, 8.45.

[5] Corrected: 7.6 cc. (actually observed) − 1.4 cc. (blank expt.) = 6.2 cc.

On adding conc'd sulfuric acid to this substance the crystals turned brown and, on dissolving, a greenish fluorescent solution resulted which turned dark yellow after three hours' standing.

B. From 6β-hydroxy-11-desoxycorticosterone (V) by treatment with periodic acid. To 7.0 mg. of V in 3 cc. of methanol was added 22 mg. of periodic acid ($HIO_4 \cdot 2H_2O$) in 0.5 cc. of water. The mixture was kept at room temperature overnight and then poured into water. The precipitate was extracted with ether and the ethereal solution washed with three 5-cc. portions of *N* sodium carbonate. Only traces of neutral material were obtained from the ether. The combined carbonate phases were acidified with 10% sulfuric acid and the acid extracted with ether. After washing the ether layer, drying with sodium sulfate, and evaporating, 5.8 mg. of a crystalline acid residue resulted. By recrystallizing it twice from aqueous methanol, 3.5 mg. of colorless needles, m.p. 230–232°, was obtained. There was no depression of the m.p. when mixed with the product described under *A*.

3-Keto-6α-hydroxy-Δ⁴-etiocholenic acid (IX). A. From 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate (IV) by treatment with oxygen in alcoholic alkali. To 25 mg. of IV in 5 cc. of absol. ethanol was added 12.5 mg. of potassium hydroxide (4.2 equiv.) dissolved in 0.2 cc. of absol. ethanol. The mixture was kept under oxygen at room temperature for 1½ hours and, after the subsequent addition of 30 cc. of water, was extracted with ethyl acetate. The solvent layer yielded only traces of resinous neutral material. The alkaline phase was made acid to Congo Red with 10% sulfuric acid and the crystalline precipitate extracted with ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated to dryness; yield: 18 mg. (95%) of crystalline acidic material, m.p. 202–206°. Recrystallization from acetone-petroleum ether gave 15.2 mg. of stout needles of m.p. 207–209°. $[\alpha]_D^{21}$ +56.2° (8.99 mg. in 2.0 cc. of chloroform; *l*, 2 dm.; α +0.51°). The ultraviolet absorption curve supports the structure of an α,β-unsaturated ketone ($\lambda_{max}^{a.c.}$ 239 mμ; ε, 17, 060). A sample was dried[6] to constant weight *in vacuo* over P_2O_5 at 90°.

Anal. Calc'd for $C_{20}H_{28}O_4$ (332.42): C, 72.26; H, 8.49.

Found: C, 71.92; H, 8.47.

On adding conc'd sulfuric acid to this substance, some fluorescence developed which gradually increased during the first 15 minutes. After about three hours' standing the solution assumed a light yellow color.

B. From 6α-hydroxy-11-desoxycorticosterone (VI) by treatment with periodic acid. To 13.6 mg. of VI in 0.5 cc. of methanol, water was gradually added until a slight turbidity appeared. Thereafter 25 mg. of periodic acid ($HIO_4 \cdot 2H_2O$) was added. Fine colorless needles began to appear after about 15 minutes. They were filtered after one hour's standing at room temperature, washed with water, and dried; yield: 12.7 mg.; m.p. 204–207°. Recrystallizing twice from acetone-petroleum ether gave 8.5 mg. of m.p. 207–209°. There was no depression of the m.p. when mixed with the product described under *A*.

3,6-Diketoetioallocholanic acid (X). A. From 3-keto-6β-hydroxy-Δ⁴-etiocholenic acid (VIII) by treatment with aqueous alkali. To 9.5 mg. of VIII in 2.19 cc. of 0.1056 *N* sodium hydroxide (2.2 equiv.) was added 2.5 cc. of water and the mixture was heated on a water-bath for one hour. After cooling to room temperature, it was made acid to Congo Red with hydrochloric acid and the resulting crystalline precipitate extracted with ether. Washing the ethereal solution with water, drying over sodium sulfate, and evaporation to dryness yielded 8.9 mg. of crystalline material, m.p. 236–237°. After recrystallizing twice from acetone-petroleum ether, 6.5 mg. of crystals, m.p. 262–264° resulted. Examination in the ultraviolet gave no evidence of the presence of starting material. $[\alpha]_D^{25.5}$ +23.71° (9.55 mg. in 2.0 cc. of chloroform; *l*, 1.51 dm.; α +0.17°). A sample was dried at 80° *in vacuo* over P_2O_5 prior to analysis.

Anal. Calc'd for $C_{20}H_{28}O_4$ (332.42): C, 72.26; H, 8.49.

Found: C, 72.01; H, 8.71.

B. From 3-keto-6α-hydroxy-Δ⁴-etiocholenic acid (IX) by treatment with glacial acetic acid in the presence of sulfuric acid. To 2.5 mg. of IX in 0.5 cc. of glacial acetic acid was added

[6] Special drying required (10).

one drop of a 10% solution of sulfuric acid in glacial acetic acid. After standing at room temperature overnight, the mixture was neutralized with *N* sodium carbonate and then diluted with some water. Extraction with ether yielded no neutral material. Subsequent acidification with 10% sulfuric acid yielded an acid precipitate which was extracted with ether. After washing with water and drying with sodium sulfate, the ethereal solution yielded 2.3 mg. of resinous material which, on recrystallizing twice from acetone-petroleum ether, gave 1.2 mg. of crystals, m.p. 262–264°. There was no depression of the m.p. on mixing this substance with the product described under *A*.

C. From allopregnane-21-ol-3,6,20-trione (VII) by treatment with periodic acid. To 3 mg. of VII in 1 cc. of methanol was added 12 mg. of periodic acid ($HIO_4 \cdot 2H_2O$) in 0.5 cc. of water containing a trace of sulfuric acid. The reaction mixture was kept at room temperature overnight, then diluted with 5 cc. of water and extracted with ethyl acetate. After washing with two 5-cc. portions of *N* sodium carbonate, the solvent layer yielded only traces of neutral material. The combined carbonate washings were made acid to Congo Red with 10% sulfuric acid and the resulting precipitate extracted with ether. After washing with water and drying over sodium sulfate, the ethereal solution gave 3.1 mg. of resinous acid material which, on recrystallizing twice from methanol-water, yielded 1.7 mg. of colorless needles, m.p. 260–263°. There was no depression of the m.p. when the substance was mixed with the product described under *A*.

3,6-Diketo-Δ^4-etiocholenic acid (XI). A total of 50.3 mg. of 3-keto-6β-hydroxy-Δ^4-etiocholenic acid (VIII) was dissolved in 2 cc. of glacial acetic acid. To this was added slowly 0.21 cc. (the equiv. of 1.2 atoms of oxygen) of a solution of 2.454 g. of chromium trioxide in 100 cc. of 90% acetic acid. After keeping the mixture at room temperature overnight, some methanol was added and the solution evaporated to dryness *in vacuo*. The residue was taken up in ethyl acetate and the resulting solution washed with water, dried over sodium sulfate, and taken to dryness. Recrystallization of the residue (yellowish solid; 41.7 mg.; m.p. 200–205°) from ethanol-water gave 27.5 mg. of yellowish crystals, m.p. 207–209°. Spectroscopic examination indicated that this product contained a moderate amount of starting material. It was subsequently found that the acetic acid used in this experiment possessed reducing properties. This probably accounts for the incompleteness of the oxidation. Hence 25 mg. of the crystalline product (m.p. 207–209°), dissolved in 1 cc. of glacial acetic acid, was reoxidized with 0.05 cc. (the equiv. of 0.5 atoms of oxygen) of the solution of chromium trioxide (*vide supra*). The reaction mixture was treated as in the original oxidation. The reaction product was a yellow crystalline mass which was recrystallized twice from methanol-water; 14.2 mg. of lemon yellow needles, m.p. 240–242°. The product is somewhat difficult to handle because of its electrostatic properties. There was a very pronounced depression of the m.p. when this substance was mixed with the starting material. $[\alpha]_D^{24.5}$ +9.51° (9.47 mg. in 2.0 cc. of chloroform; *l*, 1.51 dm.; α +0.068°). Ultraviolet absorption spectrum: λ_{max}^{alc} 248 mμ; ϵ, 13,060. A sample was dried *in vacuo* over P_2O_5 at 80° prior to analysis.

Anal. Calc'd for $C_{20}H_{26}O_4$ (330.41): C, 72.69; H, 7.94.
Found: C, 72.60; H, 7.90.

SUMMARY

1. Dehydration of 6β,21-diacetoxyallopregnane-5-ol-3,20-dione (I) furnishes 6β-hydroxy-11-desoxycorticosterone 6,21-diacetate [6β,21-diacetoxy-Δ^4-pregnene-3,20-dione] (II) (m.p. 125–127°) which can easily be rearranged to 6α-hydroxy-11-desoxycorticosterone 6,21-diacetate [6α,21-diacetoxy-Δ^4-pregnene-3,20-dione] (IV) (m.p. 84–86°). In earlier publications (1, 2) the latter, thermodynamically more stable epimer, was mistakenly considered to possess the 6β-configuration.

2. Treatment of II and IV with absolute ethanolic potassium hydroxide in

an atmosphere of nitrogen at room temperature gave good yields of 6β-hydroxy-11-desoxycorticosterone [Δ^4-pregnene-6β,21-diol-3,20-dione] (V) and 6α-hydroxy-11-desoxycorticosterone [Δ^4-pregnene-6α,21-diol-3,20-dione] (VI) respectively.

3. Procedures are discussed for the preparation of allopregnane-21-ol-3,6,20-trione (VII) by rearrangement of V and VI respectively.

4. On treating II and IV with absolute ethanolic potassium hydroxide in an atmosphere of oxygen at room temperature, exactly one mole of oxygen is consumed resulting in the practically quantitative formation of 3-keto-6β-hydroxy-Δ^4-etiocholenic acid (VIII) and 3-keto-6α-hydroxy-Δ^4-etiocholenic acid (IX) respectively. The latter acids were obtained also by the oxidation with periodic acid of V and VI respectively.

5. Procedures are presented for the preparation of 3,6-diketoetioallocholanic acid (X) by oxidation with periodic acid of VII or by rearrangement of VIII and IX respectively.

6. Previous publications (1, 2, 6, 7) are critically discussed.

PHILADELPHIA 4, PA.

REFERENCES

(1) EHRENSTEIN, *J. Org. Chem.*, **6**, 626 (1941).
(2) EHRENSTEIN, *J. Org. Chem.*, **13**, 214 (1948).
(3) EHRENSTEIN, BARBER, AND GORDON, *J. Org. Chem.*, **16**, 349 (1951).
(4) BARTON, *Experientia*, **6**, 316 (1950).
(5) VELLUZ, PETIT, PESEZ, AND BERRET, *Bull. soc. chim. France*, 123 (1947); [*Chem. Abstr.*, **41**, 5537 (1947)].
(6) EHRENSTEIN AND STEVENS, *J. Org. Chem.*, **5**, 318 (1940).
(7) EHRENSTEIN AND STEVENS, *J. Org. Chem.*, **6**, 908 (1941).
(8) BROCKMANN AND SCHODDER, *Ber.*, **74**, 73 (1941).
(9) FIESER, *Experiments in Organic Chemistry*, 2nd. ed., D. C. Heath and Company, New York, 1941.
(10) MILNER AND SHERMAN, *Ind. Eng. Chem., Anal. Ed.*, **8**, 427 (1936).