Absorption Spectra.—The ultraviolet absorption spectra of A (maxima: λ 231 mμ, log ε 4.54; λ 254, log ε 4.49; λ 294, log ε 3.81), B (maxima: λ 244, log ε 4.54; λ 307, log ε 3.87), I (maxima: λ 244, log ε 4.56; λ 307, log ε 3.85) and 6,7-dimethoxy-1-phenylnaphthalene[19] (maxima: λ 238, log ε 4.80; λ 290, log ε 3.94) were determined in ethanolic solution in the region 218–320 mμ with a Beckman spectrophotometer, model DU. Preliminary infrared absorption spectra were obtained on Nujol mulls of A and B in the range 2–13 μ by means of a Baird Associates infrared spectrophotometer using a sodium chloride prism. Similar Nujol pastes for A, B, benzene, guaiacol, phenol and α-naphthol were run in a Beckman IR-2 Spectrophotometer only in the range 8–13 μ, where significant differentiation between A and B had previously appeared.

Miscellaneous Reactions of Crude Stobbe Product (V and VI). Hydrolysis.—A mixture of 13.7 g. of the crude Stobbe ethyl half ester (mixed V and VI), 70 ml. of ethanol, 100 ml. of water, and 49 g. of barium hydroxide octahydrate was refluxed in an atmosphere of nitrogen for 3 hours. After partial distillation of the mixture, the residue was cooled, acidified with dilute hydrochloric acid and extracted with ether. The residue obtained on evaporation of the ethereal extract crystallized from ethyl acetate–petroleum ether (b.p. 97–120°) to yield 9 g. (72%, assuming the half ester was pure) of **3-carboxy-4-(3-methoxyphenyl)-4-phenyl-3-butenoic acid**, m.p. 148–153°. Repeated fractional acidification of an alkaline solution of the diacid followed by crystallization of the precipitate from the same solvent-pair produced clusters of needles, m.p. 166–167°.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.19; H, 5.28.

(19) W. N. Howell and A. Robertson, *J. Chem. Soc.*, 587 (1936).

The *p*-**toluidine derivative**, prepared from the crude diacid according to the same procedure as for the Stobbe methyl half ester, formed fine faintly pink needles from ethanol, m.p. 155–156°, undepressed on admixture with the previously obtained *p*-toluidine derivative VII.

Reduction of Stobbe Diacid.—A solution of 12 g. of crude Stobbe diacid in 300 ml. of 2.5% aqueous sodium hydroxide was treated with 320 g. of 4% sodium amalgam, added over a period of 12 hours in an atmosphere of carbon dioxide. After several hours the mixture was filtered and acidified with dilute hydrochloric acid. The precipitate crystallized from water as minute prisms; yield 11.9 g. (94%) of **3-carboxy-4-(3-methoxyphenyl)-4-phenylbutanoic acid monohydrate**, m.p. 79–80° (rapid heating).

Anal. Calcd. for $C_{18}H_{18}O_5 \cdot H_2O$: C, 65.07; H, 6.07. Found: C, 64.97; H, 6.16.

The *p*-**toluidine derivative**, prepared according to previous directions, formed faintly pink prisms from ethanol, m.p. 175–176°, assigned the structure of 1-(4-tolyl)-3-[phenyl-(3-methoxyphenyl)-methyl]-2,5-pyrrolidinedione.

Anal. Calcd. for $C_{25}H_{23}O_3N$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.96; H, 6.36; N, 3.86.

Acknowledgments.—We gratefully acknowledge the assistance of Mr. Edward Schulz who determined the infrared spectra and helped in the interpretation thereof, and of the Graduate School of Indiana University for a grant-in-aid to enable one of us (L. H. K.) to initiate work on this project.

EUGENE, OREGON

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Aldehydes Derived from Cortisone and Hydrocortisone[1]

BY W. J. LEANZA, J. P. CONBERE, E. F. ROGERS AND K. PFISTER 3RD

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The aldehydes derived from cortisone and hydrocortisone have been synthesized and derivatives prepared therefrom. The syntheses, physical properties and biological activities of these compounds are reported.

As part of a program of systematic variation of the functional groups of cortisone and hydrocortisone, it was desirable to obtain the corresponding 21-aldehydes. These syntheses have been accomplished and details of the preparation of the aldehydes, their derivatives and related compounds form the context of this paper.

Treatment of cortisone (I) with *p*-toluenesulfonyl chloride in pyridine without cooling the reaction mixture yielded a 21-pyridinium salt which could be isolated either as the chloride IV or the tosylate V. Under similar conditions, hydrocortisone (II) yielded only the 21-pyridinium chloride VI. When the reaction with cortisone was carried out with cooling, the 21-chloro analog III could be isolated. Heating III in pyridine converted it to the pyridinium chloride IV.

The nitrones VII and VIII were prepared from the respective pyridinium salts with *p*-nitrosodimethylaniline.[2] Hydrolysis of the respective nitrones to cortisone-21-aldehyde hydrate (IX) and hydrocortisone aldehyde hydrate (X) was accomplished with dilute acid.

(1) Portions of this work were presented in a preliminary communication: E. F. Rogers, W. J. Leanza, J. P. Conbere and K. Pfister 3rd, THIS JOURNAL, **74**, 2947 (1952).

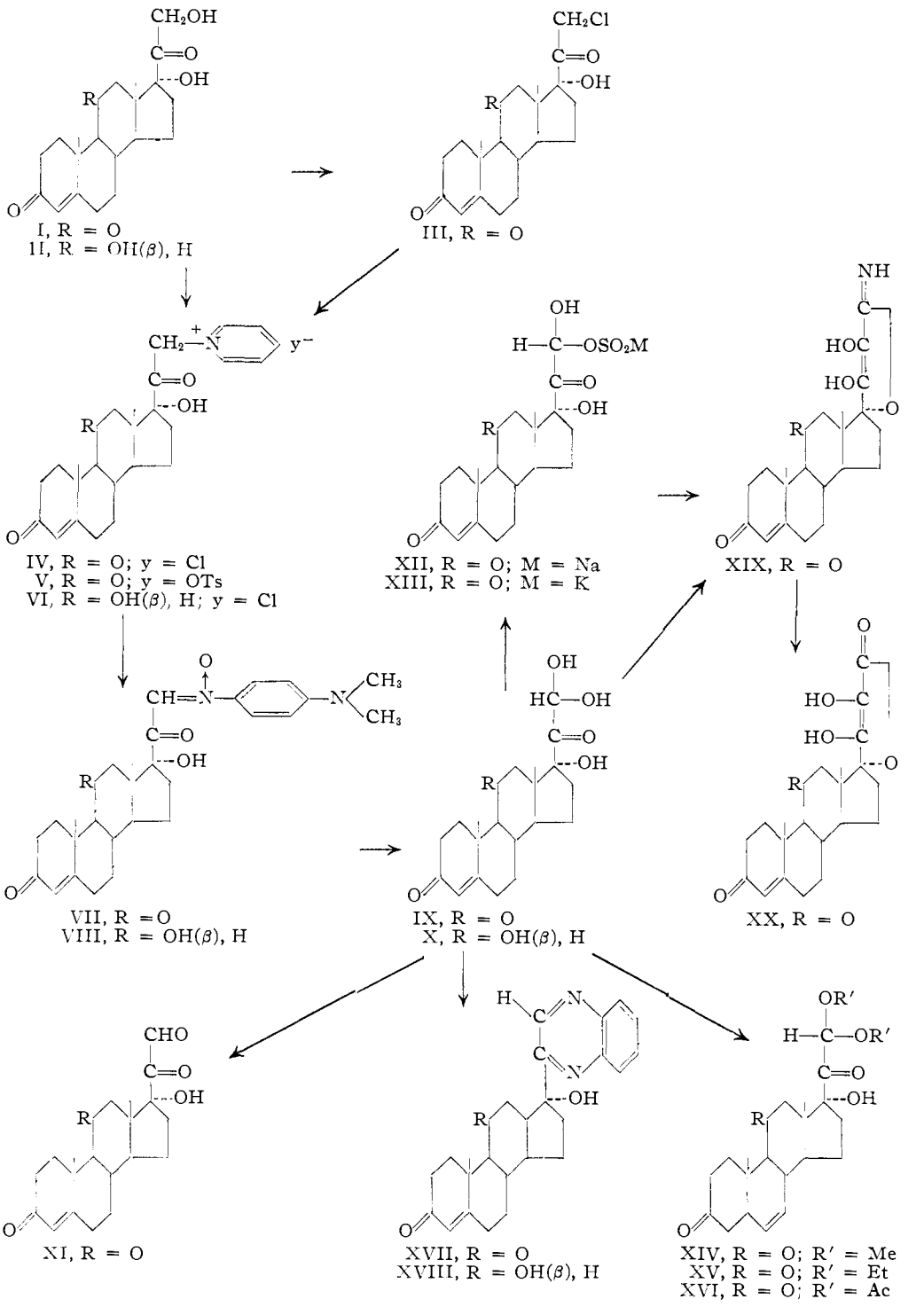
(2) F. Krönke, *Ber.*, **71B**, 2583 (1938).

The ultraviolet absorption spectra of cortisone aldehyde hydrate (IX) (λ_{max}^{MeOH} 238 mμ, E_M 15,700) and hydrocortisone aldehyde hydrate (X) (λ_{max}^{MeOH} 242 mμ, E_M 16,000) closely resemble those of cortisone and hydrocortisone. Anhydrous cortisone aldehyde (XI), obtained by heating the hydrate IX *in vacuo*, was a yellow solid which had an additional band in anhydrous chloroform at 450 mμ (E_M 36). Fleisher and Kendall[3] have shown that steroids with a glyoxal side chain, as well as methyl glyoxal, possess this band. It appears from the molecular weight data that cortisone aldehyde may have partially polymerized during the dehydration. This is in agreement with the suggestion of Reich and Reichstein[4] that Δ^5-3-hydroxy-20-ketopregnene-21-al exists as a polymer in the anhydrous state.

Chemically the aldehyde hydrates react as typical glyoxals. Positive Schiff and silver mirror tests were observed. They form bisulfite addition products (XII, XIII), acetals (XIV, XV) and diacetates (XVI) in the usual manner. The quinoxalines (XVII, XVIII) are the best derivatives for characterization purposes. They are formed in

(3) G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 573 (1951).

(4) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939).



high yield, have distinct melting points and characteristic absorption spectra.

Cortisone aldehyde hydrate (IX), or its bisulfite addition product XII upon treatment with potassium cyanide yielded an iminolactone which could be hydrolyzed to the lactone with dilute acid in a manner analogous to the synthesis of ascorbic acid from xylosone.[5,6] The structure of the iminolactone and lactone have been established as XIX and XX by elemental analyses and correlation of their absorption spectra with similar compounds in the sugar series. The iminolactone XIX has in addition to the absorption at 238 mμ, which is characteristic of the steroid, an absorption at 286 mμ (E_M 14,900); imino-gluco-ascorbic acid has an absorption at 272 mμ (E_M 17,000).[6] The lactone XX has an absorption at 242 mμ (E_M 22,400) which approximates the total absorption of the parent ster-

(5) W. N. Haworth and E. L. Hirst, *Helv. Chim. Acta*, **17**, 520 (1934).

(6) W. N. Haworth, E. L. Hirst, J. K. N. Jones and F. Smith, *J. Chem. Soc.*, 1192 (1934).

oid (E_M 15,700) plus the absorption of ascorbic acid at 245 mμ (E_M 7,500).[7] In addition to the ultraviolet spectral evidence, infrared spectral analyses showed the absence of any free hydroxyl group at 2.8 μ, but did reveal bonded hydroxyl bands at 3.28 μ and 3.70 μ. Titration of the lactone XX with iodine was analogous to the titration of ascorbic acid.[7]

In contrast to the case with desoxycorticosterone aldehyde,[4] which had only one-twentieth of the activity of the parent steroid, the aldehyde hydrates derived from cortisone and hydrocortisone were approximately as active as the parent hormones in the liver glycogen deposition assay.[8] They also caused adrenal atrophy and thymus involution similar to that which resulted upon administration of the parent hormones. Schneider[9] has shown that cortisone aldehyde hydrate (IX) can be enzymatically reduced *in vitro* to cortisone.

In addition to the aldehyde hydrates IX and X, the nitrones VII and VIII, bisulfite addition compounds XII and XIII and the diacetate XVI were active in the liver glycogen deposition assay. On the other hand, the 21-chloro compound III, the pyridinium salts IV, V and VI, the acetals XIV and XV, the iminolactone XIX and the lactone XX were inactive in this assay.

Acknowledgments.—The authors wish to thank Drs. C. C. Porter, R. H. Silber and C. A. Winter for the biological testing, Mr. F. A. Bacher and his associates for the spectral data and Mr. R. N. Boos and his associates for the elemental analyses reported herein.

Experimental

The Reaction of Cortisone with *p*-Toluenesulfonyl Chloride and Pyridine. A. Δ⁴-17α-Hydroxy-3,11,20-triketopregnene-21-pyridinium Chloride (IV).—To a solution of 12.0 g. (0.033 mole) of cortisone in 100 ml. of anhydrous pyridine was added 7.5 g. (0.039 mole) of *p*-toluenesulfonyl chloride. The solution was warmed gently for a few minutes and set aside overnight at room temperature to crystallize. The mixture was poured into 300 ml. of acetone and the precipitate collected and washed with acetone to yield 12.0 g. (78.5%) of analytically pure Δ⁴-17α-hydroxy-3,11,20-triketopregnene-21-pyridinium chloride (IV), m.p. 290–291° dec., $[\alpha]^{25}D$ +231° (*c* 2, methanol).

Anal. Calcd. for $C_{21}H_{32}ClNO_4$: C, 68.18; H, 7.04. Found: C, 68.13; H, 7.17.

After concentrating the filtrate and washings to a sirup under reduced pressure, trituration of the residue with 50 ml. of acetone yielded 7.0 g. of a mixture of *p*-toluenesulfonic acid, the 21-pyridinium chloride IV and the 21-pyridinium tosylate V.

B. Δ⁴-17α-Hydroxy-3,11,20-triketopregnene-21-pyridinium Tosylate (V).—Cortisone (3.6 g., 0.01 mole) was allowed to react with *p*-toluenesulfonyl chloride and pyridine in the same manner as above and the reaction mixture was pumped to dryness on the steam-bath at 1 mm. pressure. After washing with acetone the residue was crystallized from methanol–95% ethanol to yield 3.3 g. (56%) of the 21-pyridinium tosylate V, m.p. 290–295° dec.

Anal. Calcd. for $C_{28}H_{39}NO_7S$: C, 66.75; H, 6.62. Found: C, 66.60; H, 6.82.

C. Δ⁴-17α-Hydroxy-3,11,20-triketopregnene 21-Chloride (III).—A solution of 2.4 g. (0.0067 mole) of cortisone in 10 ml. of anhydrous pyridine was cooled to 15° and 1.4 g. (0.007 mole) of *p*-toluenesulfonyl chloride was added. The mixture was kept in a water-bath at 10–15° for one hour with occasional shaking. After standing overnight at room temperature, the precipitate was collected and washed with methanol. The damp cake was triturated with 30 ml. of boiling methanol to extract any quaternary salt, leaving 1.0 g. (46%) of the insoluble 21-chloride III as a fine powder, m.p. 243–245° dec.

Anal. Calcd. for $C_{21}H_{27}ClO_4$: C, 66.57; H, 7.18; Cl, 9.36. Found: C, 66.33; H, 7.25; Cl, 9.04.

The mother liquor and methanol extract yielded 0.9 g. of the pyridinium chloride IV.

The 21-chloride III was readily converted to the quaternary chloride IV by warming with pyridine for a few minutes.

Δ⁴-11β,17α-Dihydroxy-3,11-diketopregnene-21-pyridinium Chloride (VI).—A solution of 2.5 g. (0.0069 mole) of hydrocortisone and 1.6 g. (0.0083 mole) of *p*-toluenesulfonyl chloride in 13.5 ml. of anhydrous pyridine was heated to 60° and then allowed to stand overnight at room temperature. After cooling in an ice-bath, the solid was collected and washed well with acetone. The air-dried product weighed 2.1 g., m.p. 295–296° dec., $[\alpha]^{25}D$ +233° (*c* 2, methanol). Concentration of the filtrate and washings and trituration of the residue with acetone yielded a second crop of 0.2 g., m.p. 295–296° dec. Recrystallization from methanol–ether did not change the melting point of either crop.

Anal. Calcd. for $C_{26}H_{34}ClNO_4$: C, 67.88; H, 7.45. Found: C, 67.37; H, 7.16.

Δ⁴-17α-Hydroxy-3,11,20-triketopregnene-21-(*p*-dimethylaminophenyl)-nitrone (VII).—The 21-pyridinium chloride IV (3.6 g., 0.007 mole) and *p*-nitrosodimethylaniline (1.2 g., 0.008 mole) were dissolved in 100 ml. of methanol and 65 ml. of water with gentle warming and a solution of 0.75 g. (0.0075 mole) of potassium bicarbonate in 10 ml. of water was added. A rapid color change from green to reddish-brown occurred and after several hours at room temperature with intermittent shaking red plates or yellow needles precipitated. The product was collected, washed with water until the washings were colorless, and air-dried to yield 3.5 g. (90%) of the nitrone, m.p. 189–190° dec.

Anal. Calcd. for $C_{29}H_{36}N_2O_5$: C, 70.70; H, 7.37; N, 5.69. Found: C, 71.07; H, 7.43; N, 5.48.

Δ⁴-11β,17α-Dihydroxy-3,20-diketopregnene-21-(*p*-dimethylaminophenyl)-nitrone (VIII) was obtained in the same manner from the 21-pyridinium chloride VI in 83% yield as yellow needles, m.p. 186–188° dec.

Anal. Calcd. for $C_{29}H_{38}N_2O_5$: C, 70.43; H, 7.75; N, 5.67. Found: C, 69.79; H, 7.82; N, 6.03.

Δ⁴-17α-Hydroxy-3,11,20-triketopregnene-21-al Hydrate (Cortisone-21-aldehyde Hydrate) (IX).—A suspension of 2.8 g. of the nitrone VII in 800 ml. of ether was shaken with 100 ml. of 1.8 *N* hydrochloric acid until all the solid had dissolved. The layers were separated and the aqueous layer re-extracted with three 200-ml. portions of ether. The ether layers were combined and washed with 100 ml. each of 2 *N* hydrochloric acid, water, 5% sodium bicarbonate and water, dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was dissolved in 60 ml. of warm acetone and 160 ml. of water added while the temperature was raised to 70°. After the addition of 0.3 g. of charcoal, another 60 ml. of water was added and the whole kept at 70° for 10 minutes, allowed to cool to 50° and filtered. The filtrate was concentrated under reduced pressure to 30 ml. to yield 1.5 g. (70%) of air-dried fine needles. The aldehyde hydrate lost water when heated over 100° and melted in a capillary tube with decomposition at about 225°. Between soft glass slides on a Fisher–Johns micromelting point block decomposition occurred between 170° and 190°. An analytical sample was dried at room temperature at 1 mm. pressure for four hours, $[\alpha]^{25}D$ +182° (*c* 2, methanol), λ_{max}^{MeOH} 238 mμ, $E_{1\,cm}^{1\%}$ 418.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.01; H, 7.75.

Δ⁴-17α-Hydroxy-3,11,20-triketopregnene-21-al (XI).—The aldehyde hydrate IX was heated at 110° (1 mm.) for 18 hours to yield the anhydrous aldehyde XI as a yellow powder, $\lambda_{max}^{CHCl_3}$ 238 mμ, $E_{1\,cm}^{1\%}$ 437; $\lambda_{max}^{CHCl_3}$ 450 mμ, $E_{1\,cm}^{1\%}$ 1.07, molecular weight 575 ± 20 (ebullioscopically in acetonitrile).

(7) R. W. Herbert, E. L. Hirst, E. G. V. Percival, R. J. W. Reynolds and F. Smith, *J. Chem. Soc.*, 1270 (1933).

(8) Details of the assay procedure of Drs. C. C. Porter and R. H. Silber are included in a forthcoming article by J. P. Conbere and E. F. Rogers, "Esters of Cortisone."

(9) J. J. Schneider, THIS JOURNAL, **75**, 2024 (1953).

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.36; H, 7.31. Found: C, 70.09; H, 7.52.

Crystallization of the anhydrous aldehyde from acetone–water reconverted it to the hydrate IX.

Δ^4-11β,17α-Dihydroxy-3,20-diketopregnene-21-al hydrate (X) was prepared in the same manner as the cortisone analog IX in 76% yield, m.p. 155–160° dec., $[\alpha]^{25}D$ +155° (*c* 2, methanol), λ_{max}^{MeOH} 244 mμ, $E_{1\,cm}^{1\%}$ 423.

Anal. Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.45; H, 7.89.

Δ^4-17α-Hydroxy-3,11,20-triketopregnene-21-al Sodium Bisulfite Compound (XII).—A solution of 2.26 g. (0.0060 mole) of the aldehyde hydrate IX in 50 ml. of methanol was treated with a solution of 0.66 g. (0.0063 mole) of sodium bisulfite in 50 ml. of water. The methanol was distilled and the water removed *in vacuo* until a gel formed. The whole was lyophilized to a light powder which was dissolved in 200 ml. of boiling alcohol and filtered through Supercel. Concentration of the filtrate *in vacuo* to 10 ml. caused crystals to form which were collected, washed with ethanol and air-dried to give 2.4 g. (84%) of product, m.p. 191–192° dec. An analytical sample was dried at 60° (1 mm.) for two hours, $[\alpha]^{25}D$ +170° (*c* 2, methanol); λ_{max}^{MeOH} 238 mμ, $E_{1\,cm}^{1\%}$ 342; $\lambda_{max}^{H_2O}$ 245 mμ, $E_{1\,cm}^{1\%}$ 354.

Anal. Calcd. for $C_{21}H_{27}NaO_8S$: C, 54.53; H, 5.89. Found: C, 54.64; H, 5.85.

The dried product absorbed approximately 1.5 moles of water when exposed to the air and was 12% soluble in water at 23°.

Δ^4-17α-Hydroxy-3,11,20-triketopregnene-21-al Potassium Bisulfite Compound (XIII).—To a solution of 0.80 g. (0.0036 mole) of potassium metabisulfite in 60 ml. of water was added a solution of 2.26 g. (0.0060 mole) of the aldehyde hydrate IX in 30 ml. of methanol. Upon distillation of the methanol a granular precipitate formed which was collected and air-dried. The product (2.0 g., 68%) melted at 237–240° with decomposition and was 0.5% soluble in water, $[\alpha]^{24}D$ +165° (*c* 0.4, water); $\lambda_{max}^{H_2O}$ 245 mμ, $E_{1\,cm}^{1\%}$ 349.

Anal. Calcd. for $C_{21}H_{27}KO_8S$: C, 52.70; H, 5.69; K, 8.17. Found: C, 53.13; H, 5.33; K, 7.87.

Δ^4-17α-Hydroxy-21,21-dimethoxypregnene-3,11,20-trione (XIV).—A solution of the aldehyde hydrate (IX) (0.20 g.) in 15 ml. of 2% anhydrous hydrogen chloride in methanol was allowed to stand for two hours at room temperature. After the addition of 500 ml. of ether, the solution was poured into an excess of sodium bicarbonate solution. The ether layer was separated, washed with sodium carbonate solution and water, dried over sodium sulfate and concentrated to a sirup which solidified on scratching. Recrystallization from ether yielded 0.10 g. of fine needles, m.p. 142°, $[\alpha]^{25}D$ +176° (*c* 2, methanol); λ_{max}^{MeOH} 240 mμ, $E_{1\,cm}^{1\%}$ 387.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.36; H, 8.01.

Δ^4-17α-Hydroxy-21,21-diethoxypregnene-3,11,20-trione (XV) was prepared in the same manner as XIV, but was more difficult to obtain in a crystalline form. The ethereal solution was filtered through alumina, concentrated and chilled in a Dry Ice-bath. The addition of petroleum ether precipitated an amorphous solid which was collected and crystallized from ether, m.p. 77°, $[\alpha]^{25}D$ +165° (*c* 2, methanol); λ_{max}^{MeOH} 238 mμ, $E_{1\,cm}^{1\%}$ 372.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.47; H, 8.39. Found: C, 69.48; H, 8.52.

Δ^4-17α-Hydroxy-21,21-diacetoxypregnene-3,11,20-trione (XVI).—A solution of 2.0 g. of the aldehyde hydrate IX in 10 ml. of acetic anhydride and 1 ml. of pyridine was allowed to stand at room temperature for two days, at which time the initially yellow solution was practically colorless. The excess acetic anhydride was hydrolyzed with 20 ml. of 50% acetic acid and the solution concentrated *in vacuo* to a sirup. Trituration with 40 ml. of water gave a solid which was air-dried. The crude product was dissolved in 30 ml. of hot amyl acetate, charcoaled, concentrated to 7 ml. and cooled to give a precipitate which was collected, washed with 30% amyl acetate in ether, ether, and air-dried. The solid, 0.95 g. (40%), melted at 169–170°, $[\alpha]^{25}D$ +99° (*c* 2, methanol); λ_{max}^{MeOH} 238 mμ, $E_{1\,cm}^{1\%}$ 321. A second crop of 0.3 g., m.p. 167–169°, was obtained by concentrating the filtrate.

Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01. Found: C, 65.18; H, 7.30.

Δ^4-17α-Hydroxy-11-ketoandrostene-17β-(2-quinoxaline) (XVII).—To a solution of 0.20 g. (0.0005 mole) of the aldehyde hydrate IX in 5 ml. of methanol was added 0.08 g. (0.0008 mole) of sodium bisulfite in 30 ml. of water. The reaction mixture was heated on the steam-bath for five minutes and the methanol removed under reduced pressure. The residue was dissolved in 10 ml. of water and treated with 0.080 g. (0.0007 mole) of *o*-phenylenediamine in 5 ml. of hot water. After heating on the steam-bath for 30 minutes the reaction mixture was cooled and the solid collected and air-dried at 100°. The crude product, 0.18 g., m.p. 233–235° dec., was recrystallized from methanol to give plates, m.p. 242–243° dec.; λ_{max}^{MeOH} 238 mμ, $E_{1\,cm}^{1\%}$ 1045; λ_{max}^{MeOH} 319 mμ, $E_{1\,cm}^{1\%}$ 185.

Anal. Calcd. for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02. Found: C, 75.53; H, 7.03.

Δ^4-11β,17α-Dihydroxyandrostene-17β-(2-quinoxaline) (XVIII) was prepared by the same procedure as XVII. The product melted at 274–276° dec.; λ_{max}^{MeOH} 237 mμ, $E_{1\,cm}^{1\%}$ 985; λ_{max}^{MeOH} 318 mμ, $E_{1\,cm}^{1\%}$ 185.

Anal. Calcd. for $C_{27}H_{32}N_2O_3$: C, 74.97; H, 7.46. Found: C, 74.72; H, 7.53.

$\Delta^{4,20}$-17α,20,21-Trihydroxy-3,11-diketopregnadiene-22-carboximino-17-lactone (XIX).—A solution of 2.23 g. (0.006 mole) of the aldehyde hydrate (IX) and 0.66 g. (0.0063 mole) of sodium bisulfite in 60 ml. of 50% aqueous methanol in a nitrogen atmosphere was cooled in an ice-bath. The addition of a solution of 0.45 g. (0.0069 mole) of potassium cyanide in 20 ml. of water caused the formation of a white precipitate. After standing at room temperature for 15 minutes, the mixture was acidified to congo paper with dilute hydrochloric acid. The methanol was evaporated under reduced pressure and the precipitate collected. Recrystallization from boiling methanol gave 1.7 g. (74%) of crystalline product which decomposed at 255° in a capillary, $[\alpha]^{25}D$ +97° (*c* 1, methanol); λ_{max}^{MeOH} 238 mμ, $E_{1\,cm}^{1\%}$ 439; λ_{max}^{MeOH} 286 mμ, $E_{1\,cm}^{1\%}$ 383. Titration of a 0.05-g. sample with 0.01 *M* iodine to the starch–iodide end-point requires 25 ml. of reagent. The "ene-diol" oxidation theoretically required 26 ml.

Anal. Calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.22; H, 7.38; N, 3.20.

$\Delta^{4,20}$-17α,20,21-Trihydroxy-3,11-diketopregnadiene-22-carboxy-17-lactone (XX).—The iminolactone XIX (2.0 g.) was dissolved in 100 ml. of acetic acid and 75 ml. of water and heated in an atmosphere of carbon dioxide at 85–90° for 18 hours. The solution was concentrated to 50 ml. *in vacuo* and 10 ml. of 2.5 *N* hydrochloric acid added. The concentration was continued to dryness and the granular residue was dissolved in hot ethanol and again concentrated to dryness. The product was crystallized under carbon dioxide from aqueous methanol to yield 1.0 g. (50%) of white crystals which decomposed at 260–265°, $[\alpha]^{25}D$ +45° (*c* 2, methanol); λ_{max}^{MeOH} 242 mμ, $E_{1\,cm}^{1\%}$ 578 (E_M 22,400). The infrared spectrum showed absorption at 3.28 μ and 3.70 μ.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.79. Found: C, 68.63; H, 6.50.

RAHWAY, NEW JERSEY