"β"-3-Ketobisnor-4-cholenic Acid (VII) from the Oxidation of the "β"-Ketoaldehyde (V).—A solution of 1.09 g. of the "β"-ketoaldehyde in 20 ml. of benzene and 20 ml. of glacial acetic acid was cooled to 0–4° and, while stirring, a solution of 0.25 g. of chromic acid anhydride in 1 ml. of water and 20 ml. of glacial acetic acid was added dropwise during 10 minutes. The oxidation was allowed to proceed for 1 hour while cooling in an ice-bath and 10 ml. of methanol was added. The mixture was diluted with water, extracted with ether, washed with water and 10% sodium hydroxide to the point of removal of the insoluble sodium salt of the acid. This sodium salt was recovered by centrifugation, washed well with ether, and the free acid recovered by treatment with 20% sulfuric acid. The "β"-ketoacid (0.77 g.) melted at 260–265° (dec.) and after recrystallizing from methylene chloride–methanol melted at 268–270° (dec.) and did not depress the decomposition point of the known acid[1,7]; $[\alpha]^{24}\mathrm{D}$ ($CHCl_3$) +60°.

From the neutral ether solution after the removal of the acid fraction there was obtained 0.20 g. of recovered "β"-ketoaldehyde.

"β"-3-Ketobisnor-4-cholenic Acid Methyl Ester (IX).—The "β"-ketoacid (0.92 g.) (prepared as described above) in 10 ml. of methylene chloride and 2 ml. of methanol was added to a cold solution of methylene chloride containing an excess of diazomethane. After standing 2 hours in an ice-bath the solvent was evaporated and the residue dissolved in ether, washed with water, and dried over sodium sulfate. The solvent was evaporated and the crystalline residue upon recrystallizing from acetone gave long prisms, m.p. 178°, $[\alpha]^{24}\mathrm{D}$ +72°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.43; H, 9.85.

"α"-3-Ketobisnor-4-cholenic Acid (VIII) from the Oxidation of the "α"-Ketoaldehyde.—The "α"-ketoaldehyde (VI) (3.28 g.) was oxidized with chromic acid as described above. The alkali solution containing the soluble salts, upon making acid with 20% sulfuric acid, gave an acid fraction weighing 1.40 g. and melting at 210–215°. From methanol a first crop of "β"-ketoacid was obtained, m.p. 260–265°. The filtrate upon concentration and dilution with water gave the "α"-ketoacid which after three further crystallizations from benzene–Skellysolve C formed needles melting at 220–222°, $[\alpha]^{24}\mathrm{D}$ +109°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.68; H, 9.34. Found: C, 76.21; H, 9.01.

"α"-3-Ketobisnor-4-cholenic acid methyl ester (X) was prepared in the same manner as the "β"-ketoacid methyl ester. From dilute acetone it crystallized in needles, m.p. 119–121°, $[\alpha]^{22}\mathrm{D}$ +98°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.15; H, 9.36.

KALAMAZOO, MICHIGAN

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

The Synthesis of 11-Hydroxylated Cortical Steroids. 17-Hydroxycorticosterone[1]

BY N. L. WENDLER, R. P. GRABER, R. E. JONES AND M. TISHLER

RECEIVED JANUARY 11, 1952

The synthesis of 17-hydroxycorticosterone (Compound F) from 20-cyano-17-pregnene-21-ol-3,11-dione is described.

17-Hydroxycorticosterone[2] was first isolated from adrenal cortex in 1937 by Reichstein[3] and shortly thereafter by Mason, Hoehn and Kendall.[4] Recent studies[5] have indicated that this substance possesses therapeutic activity similar to Cortisone; consequently the need for a practical synthesis of this compound was suggested.

The biosynthesis of 17-hydroxycorticosterone from Reichstein's Substance S has been demonstrated using techniques of perfusion in the isolated beef adrenal gland[6] and incubation with adrenal homogenates.[7,8] This same transformation has also been effected by employing the enzyme system associated with the insoluble cellular constituents of the adrenal cells.[9]

We have synthesized 17-hydroxycorticosterone starting with 20-cyano-17-pregnene-21-ol-3,11-dione (Ia), prepared previously in connection with the synthesis of Cortisone from the bile acids.[10] This cyanopregnene as its 21-acetate (I) was converted with methyl or ethyl orthoformate to the corresponding 3-dialkyl ketal (II) and (IIa), respectively. The dimethyl ketal was found to possess superior crystallizing properties and could be isolated in a direct yield of 80–85%.

Hydrolysis of II with bicarbonate afforded the 21-hydroxy ketal (III) nearly quantitatively. The latter was reduced with lithium borohydride at 25° or preferably with sodium borohydride at 65–70° to produce IV, which was acid-hydrolyzed without isolation to give crystalline 20-cyano-17-pregnene-11(β),21-diol-3-one (V) in 80% yield based on the 21-acetoxy ketal (II).

Attempts to convert 20-cyano-17-pregnene-21-ol-3,11-dione (Ia) directly to the 3-dimethyl ketal (III) were without substantial success. Similar efforts aimed at the direct employment of II in the hydride reduction were equally unrewarding. The failure of Ia, in an early phase of this work, to give a crystalline ketal derivative suggested masking the 3-carbonyl group as the semicarbazone (IX). Reduction of IX with lithium borohydride and removal of the semicarbazone grouping afforded the desired 20-cyano-17-pregnene-11,21-diol-3-one (V) in substantial yield.[11]

Hydroxylation of Va with osmium tetroxide yielded 4,5-dihydro-17-hydroxycorticosterone-21-acetate (VI). Bromination of the latter followed by dehydrobromination with semicarbazide ace-

[1] A preliminary announcement of this work was reported in a Communication to the Editor, THIS JOURNAL, **72**, 5793 (1950).

[2] This substance has been variously designated Reichstein's "Substance M" and Kendall's "Compound F." "Hydrocortisone" was suggested as a generic name for 17-hydroxycorticosterone by Dr. E. C. Kendall in a paper presented before the American Academy of Orthopaedic Surgeons at Chicago, Illinois, in January, 1951.

[3] Reichstein, *Helv. Chim. Acta*, **20**, 953 (1937).

[4] Mason, Hoehn and Kendall, *J. Biol. Chem.*, **124**, 459 (1938).

[5] Hench, Kendall, Slocumb and Polley, *Arch. Int. Med.*, **85**, 545 (1950).

[6] Hechter, Jacobsen, Jeanloz, Levy, Marshall, Pincus and Schenker, *Arch. Biochem.*, **25**, 457 (1950).

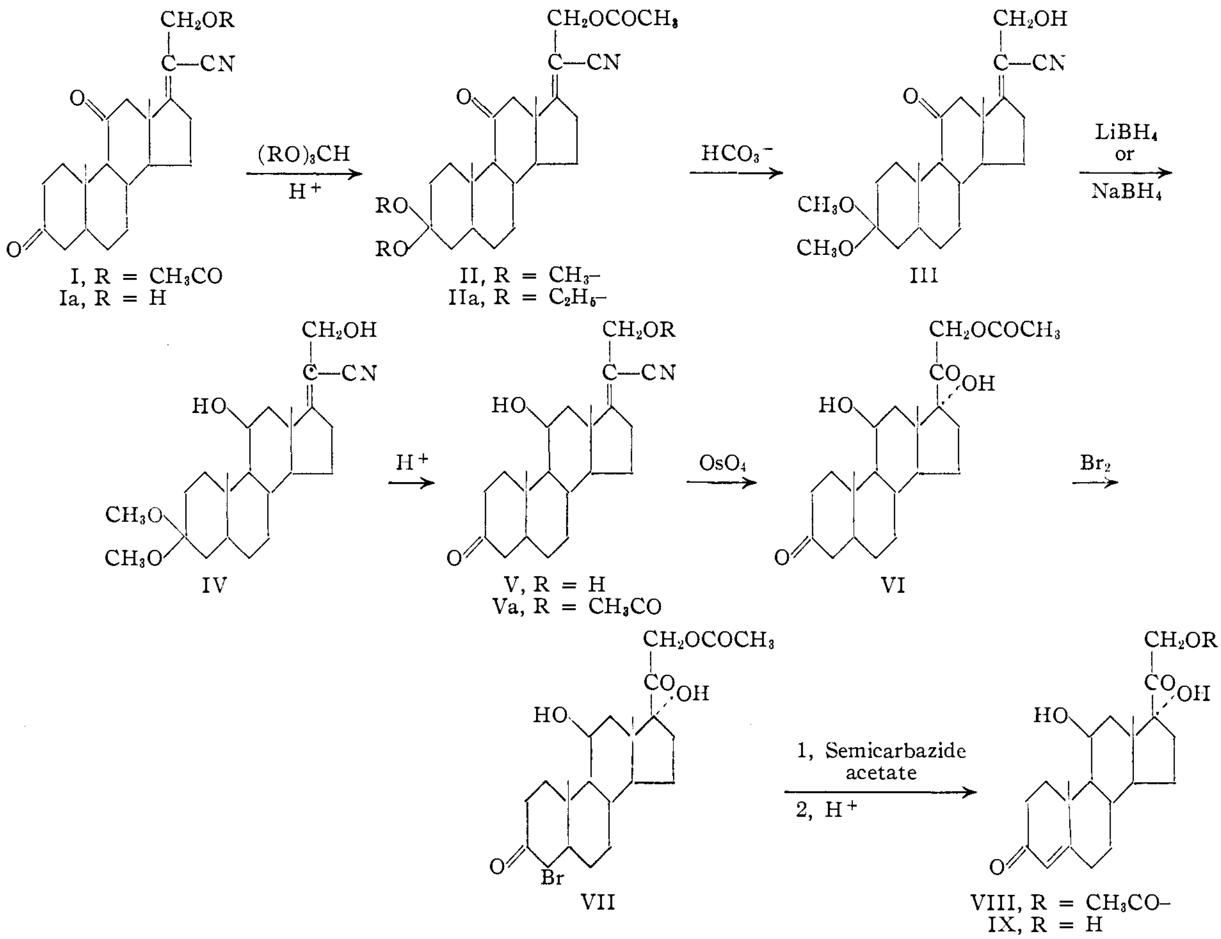
[7] McGinty, Smith, Wilson and Worrel, *Science*, **112**, 506 (1950).

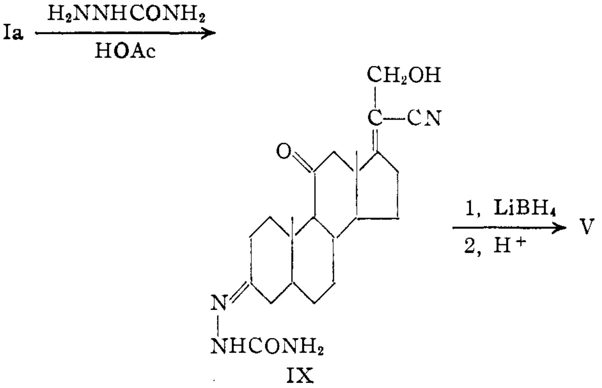
[8] Kahnt and Wettstein, *Helv. Chim. Acta*, **34**, 1790 (1951).

[9] Sweat, THIS JOURNAL, **73**, 4056 (1951).

[10] Sarett, *ibid.*, **70**, 1454 (1948).

[11] Reference to this work has already been cited. *Cf.* Wendler, Huang-Minlon and Tishler, *ibid.*, **73**, 3818 (1951).





tate[12] and removal of the semicarbazone grouping gave 17-hydroxycorticosterone-21-acetate (VIII).

Experimental[13]

3,3-Dimethoxy-20-cyano-17-pregnene-21-ol-11-one-21-acetate (II).—A mixture of 15.9 g. of methyl orthoformate (0.15 mole), 190 ml. of dry benzene, 0.48 g. of methanol (0.015 mole) and 0.225 g. of concentrated sulfuric acid (10 small drops) was warmed on the steam-bath with vigorous swirling until a homogeneous solution was produced. To this warm solution was added 39.75 g. of 20-cyano-17-pregnene-21-ol-3,11-dione-21-acetate (I) (0.10 mole), m.p. 194–196.5°. The acetate dissolved readily on swirling and the resulting light brown solution was heated for four hours at 70–75°. The solution was then cooled to room temperature and 5.0 ml. of pyridine was added to quench the acid. The benzene solution was diluted with 250 ml. of ether and washed with one 250-ml. portion of 5% aqueous sodium bicarbonate, one 150-ml. portion of water and one 150-ml. portion of saturated salt solution. The organic layer was dried over magnesium sulfate, filtered and the solvents were removed *in vacuo* to give a partially crystalline buff-colored residue which weighed 44.35 g. (100%). One recrystallization from methanol containing 0.1% of pyridine afforded 36.35 g. (81.9%) of the ketal, m.p. 163.5–168° (dec.) with previous softening at 162°, $\lambda_{\max}^{\text{methanol}}$ 2225 Å., $E_{1\,\text{cm.}}^{1\%}$ 335. A sample prepared for analysis by recrystallization from methanol containing 0.1% of pyridine was obtained as colorless prisms, m.p. 172.5–175.5° (dec.), $\lambda_{\max}^{\text{methanol}}$ 2225 Å., $E_{1\,\text{cm.}}^{1\%}$ 328, $[\alpha]^{23}\text{D}$ +9.0 (*c* 1.22, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{37}O_5N$: C, 70.40; H, 8.41; N, 3.16; OCH_3, 13.99. Found: C, 70.78; H, 8.34; N, 3.26; OCH_3, 13.50.

20-Cyano-17-pregnene-21-ol-3,11-dione (Ia) was recovered from the ketal mother liquor as follows. The methanol solution was concentrated *in vacuo* to *ca.* 60 ml., 3.80 ml. of concentrated hydrochloric acid added and the mixture allowed to stand at room temperature overnight. The solution was again concentrated *in vacuo* to a volume of *ca.* 25 ml., maintaining the temperature below 30°. Addition of 150 ml. of water caused the separation of a granular crystalline solid which was removed by filtration, washed free of acid with water, and dried, weight 6.12 g., m.p. 243–254° (dec.) with previous softening. Recrystallization from acetone gave a first crop which weighed 4.54 g., m.p. 262–265.5° (dec.), and a second crop which weighed 0.61 g., m.p. 253–259° (dec.); the m.p.'s of these samples were undepressed on admixture with authentic Ia.

3,3-Diethoxy-20-cyano-17-pregnene-21-ol-11-one-21-acetate (IIa).—The diethyl ketal was prepared from 3.97 g. of I by the procedure described above for the dimethyl ketal. The solution was heated for two hours at 72–74°, cooled to

---

[12] Koechlin, Kritchevsky and Gallagher, *J. Biol. Chem.*, **184**, 393 (1950); also Djerassi, THIS JOURNAL, **71**, 1003 (1949); Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

[13] All melting points are corrected.

room temperature and 0.5 g. of sodium bicarbonate added followed by 15 ml. of 5% sodium bicarbonate solution. The organic layer was diluted with ether, separated from the aqueous layer, washed several times with water, once with saturated salt solution, and dried over anhydrous sodium sulfate. After filtration of the dried solution and removal of the solvents *in vacuo*, there was obtained a buff-colored partly crystalline residue. Trituration with 1:1 ether:petroleum ether (b.p. 30–60°) gave 2.97 g. (63%) of needles, m.p. 129–132° with previous softening. Several recrystallizations from ether raised the m.p. to 142.4–143.6°, $\lambda_{\text{max}}^{\text{methanol}}$ 2225 Å., $E^{1\%}_{1\text{ cm.}}$ 307, $[\alpha]^{23}\text{D}$ +14.5° (*c* 1.0, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{41}O_5N$: C, 71.30; H, 8.76; N, 2.97. Found: C, 71.41; H, 8.59; N, 3.22.

3,3-Dimethoxy-20-cyano-17-pregnene-21-ol-11-one (III).—A 36.30-g. sample of the 21-acetoxy ketal (II) (0.0818 mole), m.p. 163.5–168° (dec.), was dissolved in 250 ml. of purified tetrahydrofuran. To this solution was added 1000 ml. of methanol, 250 ml. of water and 163.6 ml. of 1.0 *M* aqueous potassium bicarbonate solution (0.1636 mole). The clear solution was allowed to stand at room temperature for 64 hours and then concentrated *in vacuo* to *ca.* 600 ml., maintaining the temperature at about 35°. The resulting suspension of buff-colored, granular crystalline material was diluted with 150 ml. of water and filtered. The residue was washed with three 40-ml. portions of water and dried *in vacuo* to afford 33.70 g. of the 21-hydroxy ketal (III), m.p. 179–181° (dec.) with previous softening at 177°, $\lambda_{\text{max}}^{\text{methanol}}$ 2225 Å., $E^{1\%}_{1\text{ cm.}}$ 322. Although the product was dried to constant weight at room temperature, a Karl Fischer determination showed it to contain 5.34% of water. The water content of a series of preparations varied from 5 to 7%, and the m.p.'s varied in the range 167–189° (dec.). A sample prepared for analysis by recrystallization from methanol–ether was obtained as fine needles, m.p. 183.5–184° (dec.), $\lambda_{\text{max}}^{\text{methanol}}$ 2225 Å., $E^{1\%}_{1\text{ cm.}}$ 357.

Anal. Calcd. for $C_{24}H_{35}O_4N$: C, 71.79; H, 8.79; OCH_3, 15.46. Found: C, 71.96; H, 8.60; OCH_3, 14.79.

An alternate procedure for the hydrolysis is as follows. To a solution of 44.4 g. of the 21-acetoxy ketal (0.10 mole), m.p. 152.5–158° (dec.), in 150 ml. of purified tetrahydrofuran was added 750 ml. of methanol and 200 ml. of 1.0 *M* aqueous potassium bicarbonate solution (0.20 mole). A heavy precipitate of colorless crystalline material separated. This mixture was heated rapidly to boiling and reflux maintained for 15 minutes, during which the solid rapidly dissolved to give a clear light brown solution. The solution was then quickly cooled to below 35° and the tetrahydrofuran and methanol removed *in vacuo*. The granular crystalline material which separated was isolated as described above and weighed 41.79 g., m.p. 175–178.5° (dec.) with previous softening at 174.5°. This residue also contained 5–7% water.

20-Cyano-17-pregnene-11(β),21-diol-3-one (V). (a) From **3,3-Dimethoxy-20-cyano-17-pregnene-21-ol-11-one** (III).—To a solution of 41.79 g. of crude 21-hydroxy ketal (III) from the above second procedure in 900 ml. of purified tetrahydrofuran was added 300 ml. of water, 4.0 ml. of 2.5 *N* sodium hydroxide (0.01 mole) and 16.8 g. of sodium borohydride (0.445 mole). The hydride dissolved readily and the mixture separated into two layers. The mixture was heated under reflux for two hours, cooled to room temperature and treated portionwise with 150 ml. of aqueous acetic acid containing 27.9 g. of glacial acetic acid (0.465 mole) to decompose the excess hydride. The initial vigorous evolution of gas subsided rapidly and then the tetrahydrofuran was removed *in vacuo*. The resulting suspension of pale yellow, gummy oil was diluted with 390 ml. of saturated salt solution and the organic material extracted with one 600-ml. portion and two 125-ml. portions of ethyl acetate. The combined extracts were washed with one 200-ml. portion of saturated salt solution, one 300-ml. portion of 5% aqueous sodium bicarbonate solution, again with one 300-ml. portion of saturated salt solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to constant weight.

The pale yellow amorphous residue was dissolved in 600 ml. of acetone and to this solution was added 90 ml. of water and 6.0 ml. of 2.5 *N* hydrochloric acid. After standing at room temperature for 1.5 hours, 100 ml. of 5% aqueous sodium bicarbonate solution was added and the acetone removed *in vacuo*. The suspension of pale buff-colored crystalline material thus obtained was diluted with 250 ml. of saturated salt solution and an additional 50 g. of solid salt added. After standing for several hours at room temperature with occasional swirling the salt had dissolved. The product was then removed by filtration, washed with three 100-ml. portions of water and dried *in vacuo*. The crude product weighed 34.45 g. (96.4%), m.p. 185–190° with previous softening at 184° (on cooling, the melt partially resolidified and remelted at 207–210°), $\lambda_{\text{max}}^{\text{methanol}}$ 2225 Å., $E^{1\%}_{1\text{ cm.}}$ 354. One recrystallization from acetone–ether gave 26.45 g. (74.0%) of short needles, m.p. 218–219° (softened 204°, partly melted 205–207°, then resolidified), $\lambda_{\text{max}}^{\text{methanol}}$ 2225 Å., $E^{1\%}_{1\text{ cm.}}$ 394. A second crop weighing 2.91 g., m.p. 196–201° with previous softening at 195°, was obtained by concentrating the mother liquor to a small volume and diluting with ether; two recrystallizations of this material gave an additional 1.87 g. (5.2%), m.p. 217–220° (partly melted 206–207°, then resolidified), $\lambda_{\text{max}}^{\text{methanol}}$ 2225 Å., $E^{1\%}_{1\text{ cm.}}$ 392. An analytical sample prepared by recrystallization from aqueous acetone melted at 217.5–220.5° (partly melted 207–210°, then recrystallized in a different crystal form), $\lambda_{\text{max}}^{\text{methanol}}$ 2225 Å., $E^{1\%}_{1\text{ cm.}}$ 396, $[\alpha]^{25}\text{D}$ +24.4° (*c*, 1.03, acetone).

Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74. Found: C, 74.12; H, 8.73.

(b) From **20-Cyano-17-pregnene-21-ol-3,11-dione Semicarbazone (IX)**.—A 20.0-g. sample of 20-cyano-17-pregnene-21-ol-3,11-dione was dissolved in 300 ml. of warm acetic acid and a solution of 12.55 g. of semicarbazide hydrochloride and 12.55 g. of anhydrous sodium acetate in 28 ml. of water and 72 ml. of acetic acid was added. This solution was then warmed at 65–70° for 2.5 hours during which a small amount of granular crystalline material separated. The mixture was then concentrated *in vacuo* under nitrogen to a thick slurry which was diluted with 200 ml. of water and filtered. The residue was washed twice with water and dried *in vacuo* to afford the crude semicarbazone in nearly quantitative yield. One recrystallization from chloroform–methanol gave 20.2 g. of feathery needles, m.p. 238–240° (dec.). An analytical sample prepared by recrystallization from methanol melted at 244–245° (dec.).

Anal. Calcd. for $C_{23}H_{32}O_3N_4$: N, 13.58. Found: N, 13.47.

For the reduction of the 11-keto-3-semicarbazone, a solution of 8.25 g. (0.02 mole) of the semicarbazone, m.p. 238–240° (dec.), in 1050 ml. of dry purified tetrahydrofuran was added with stirring over a period of one-half hour to a solution of 4.85 g. (0.223 mole) of lithium borohydride in 150 ml. of dry purified tetrahydrofuran. The reaction mixture was maintained at 25° during the addition. Stirring was continued for an additional hour at 25° and for 15 minutes while the mixture was cooled in ice. The excess lithium borohydride was decomposed by slow addition of 300 ml. of aqueous acetic acid containing 63.7 ml. of glacial acetic acid over a 15- to 20-minute period. The clear colorless solution was concentrated *in vacuo* to remove substantially all of the tetrahydrofuran and the oil which separated was removed by three extractions with chloroform. The combined extracts were washed twice with water, once with 5% aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the chloroform *in vacuo* gave a buff-colored amorphous residue weighing 7.0 g.

The residue of crude 11(β)-hydroxy-3-semicarbazone in a mixture of 35 ml. of glacial acetic acid, 17.5 ml. of water, 15.9 g. of anhydrous sodium acetate and 14 ml. of 90% pyruvic acid (17.1 g.) was heated at 75–85° under nitrogen for 3.5 hours. The cooled mixture was then diluted with 280 ml. of water and the organic material extracted with four portions of chloroform. The combined extracts were washed twice with water, twice with aqueous sodium bicarbonate, again with water, dried and concentrated *in vacuo* to give 6.10 g. of buff-colored amorphous solid. A solution of this material in acetone–ether deposited 2.30 g. of granular crystals, m.p. 214–217.5° (softened 202°, melted 203–206°, then resolidified), undepressed on admixture with material prepared *via* the dimethyl ketal.

20-Cyano-17-pregnene-11(β),21-diol-3-one-21-acetate (Va).—A 35.75-g. sample of V, m.p. 217.8–221°, was dissolved in 715 ml. of warm acetic anhydride and 57.2 ml. of dry pyridine added. This mixture was warmed for one-half hour at 65°, then cooled to room temperature and 143 ml. of water added with cooling. After the hydrolysis of the acetic anhydride was substantially complete, an additional 2685 ml. of water was added slowly with stirring and cooling. Colorless needles separated readily and after cooling at 0–5° for one hour, the suspension was filtered and the product washed with water until free of acid, weight 38.65 g. (96.8%), m.p. 178.5–181° with previous softening at 177.5°. A sample for analysis prepared by recrystallization from acetone–ether melted at 180.5–182.5°, $\lambda_{\max}^{\text{methanol}}$ 2225 Å., $E_{1\text{ cm.}}^{1\%}$ 370, $[\alpha]^{25}\text{D}$ +34.1° (c, 0.95, acetone).

Anal. Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.22; H, 8.18; N, 3.72.

This substance was occasionally obtained as a lower melting modification, m.p. 170–171.5°.

Pregnane-11(β),17(α),21-triol-3,20-dione-21-acetate (VI).—To a solution of 2.675 g. (0.0105 mole) of crystalline osmium tetroxide in a mixture of 39.0 ml. of dry benzene and 2.96 ml. (0.037 mole) of dry pyridine was added 3.995 g. (0.010 mole) of the acetate (Va), m.p. 177.8–181°. The mixture was stored at room temperature for 65 hours at which time it was nearly black and contained a heavy cake of dark-colored, crystalline osmium complex. The solid was brought into solution by the addition of 273 ml. of chloroform and 1.4 g. of Filtercel added followed by the dropwise addition of 8.7 ml. of concentrated hydrochloric acid over a 15-minute period with vigorous stirring. After stirring for three hours the light brown curdy precipitate containing the osmium was removed by filtration and the residue washed with four 40-ml. portions of hot chloroform.

The light brown benzene–chloroform solution was separated from the aqueous layer, washed once with water, and then stirred vigorously with 200 ml. of 5% aqueous potassium carbonate solution for one hour. Finally the brown aqueous potassium carbonate layer was separated from the benzene–chloroform solution and the latter washed with two 40-ml. portions of water and dried over anhydrous magnesium sulfate. The crystalline residue obtained by filtration and removal of the solvents *in vacuo* weighed 4.035 g. (99.3%) m.p. 206–218° with previous softening at 205°. Two recrystallizations from acetone–petroleum ether (b.p. 30–60°) afforded 3.24 g. (79.7%) of heavy prismatic needles, m.p. 216–217° with slight previous softening. A sample prepared for analysis by recrystallization from acetone–petroleum ether (b.p. 30–60°) melted at 217.6–219.8°, $[\alpha]^{25}\text{D}$ +86.6 (c 1.05, acetone).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.20; H, 8.19.

4-Bromo-pregnane-11(β),17(α),21-triol-3,20-dione-21-acetate (VII).—To a stirred solution of 10.0 g. (0.0246 mole) of the acetate VI in 240 ml. of glacial acetic acid was added 5.89 ml. of 1.0 N hydrogen bromide in glacial acetic acid. A solution of 21.6 ml. of 2.187 N bromine in acetic acid (0.0236 mole) containing 23.2 ml. of 1.0 N sodium acetate in acetic acid (0.0232 mole) was added rapidly over a period of about three minutes; the bromine color was completely discharged at this point. Finally, an additional 5.89 ml. of 1.0 N sodium acetate in acetic acid was added followed by 240 ml. of water. Crystallization was induced by seeding. After stirring for one hour at room temperature and two hours in an ice-bath, the crystalline product was removed by filtration, washed once with 50% aqueous acetic acid and dried *in vacuo* to give 5.42 g. (45.4%) of colorless needles, $[\alpha]^{25}\text{D}$ +97.8° (c 0.935, acetone). The m.p.'s of various samples prepared in this manner varied over the range of 165–180° with decomposition and evolution of gas and depended to a large measure on the rate of heating and the temperature at which they were introduced into the bath. A sample recrystallized several times from acetone–petroleum ether (b.p. 30–60°) had the m.p. 190.4–191.6° (dec. and evolution of gas), $[\alpha]^{25}\text{D}$ +99.0 (c 1.0, acetone). Since it was found that the second crops obtained by further dilution of the aqueous acetic acid mother liquors melted in the range 110–160° and had specific rotations of *ca.* 80°, the quality of the product was based in practice solely on the specific rotation.

17-Hydroxycorticosterone-21-acetate (VIII).—A three-necked flask fitted with a stirrer, thermometer and a dropping funnel were so connected that the flask and funnel could be evacuated and filled with nitrogen simultaneously. In the flask was placed a solution of 5.0 g. (0.0103 mole) of the 4-bromoketone (VII) in 233 ml. of glacial acetic acid and in the funnel a solution of 3.465 g. (0.0311 mole) of semicarbazide hydrochloride and 3.80 g. (0.0463 mole) of anhydrous sodium acetate in 16 ml. of water and 750 ml. of glacial acetic acid. The apparatus was flushed several times with oxygen-free nitrogen and then the solution in the funnel was added to the solution in the flask. This mixture was heated at 65–67° for two hours. At the end of this time, the solution was cooled to room temperature, 47.65 g. of anhydrous sodium acetate and 46.6 ml. of 90% aqueous pyruvic acid were added and the mixture heated at 70–72° under nitrogen for an additional four hours. At the conclusion of this reaction period 2000 ml. of water was added and the volume of the resulting solution reduced to *ca.* 170 ml. *in vacuo*. The suspension of solid was diluted with 670 ml. of water, filtered, and the product washed with water and dried to give 3.00 g. (72.1%) of granular prisms, m.p. 210.5–214.0°. One recrystallization from ethyl acetate afforded 2.31 g. (55.6%) of 17-hydroxycorticosterone-21-acetate as prisms, m.p. 218–221.5°, $\lambda_{\max}^{\text{methanol}}$ 2420 Å., $E_{1\text{ cm.}}^{1\%}$ 380, $[\alpha]^{25}\text{D}$ +157.5° (c 1.0, dioxane); a series of preparations, all of which gave the correct analysis for carbon and hydrogen, showed $\lambda_{\max}^{\text{methanol}}$ 2420 Å., $E_{1\text{ cm.}}^{1\%}$ in the range 374–393.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.52; H, 7.88.

A mixed m.p. of synthetic VIII with an authentic sample of Compound F acetate was not depressed; comparative *infrared* spectra of the two samples were identical in all respects.

17-Hydroxycorticosterone (IX).—The acetate (VIII) was hydrolyzed by essentially the procedure (b) described above for the hydrolysis of the 21-acetoxy ketal (II) to give crude 17-hydroxycorticosterone in 95% yield, m.p. 209–215° (dec.) with previous softening and sintering at 200°, $\lambda_{\max}^{\text{methanol}}$ 2420 Å., $E_{1\text{ cm.}}^{1\%}$ 428. One recrystallization from acetone–ethyl acetate gave a 74–75% first crop yield of small prisms, m.p. 215.5–221° (dec.) with slight previous softening, $\lambda_{\max}^{\text{methanol}}$ 2420 Å., $E_{1\text{ cm.}}^{1\%}$ 443, $[\alpha]^{24}\text{D}$ +163° (c, 0.89, CH_3OH).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.63; H, 8.26.

Acknowledgments.—The authors wish to acknowledge the capable technical assistance of Mr. H. B. Arnold and the excellent contributions to the development of this synthesis made by Mr. S. M. Miller.

RAHWAY, NEW JERSEY