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Isomerization and Displacement Reactions in the Cyanopregnene Series. Synthesis of Cortisone 21-Methyl Ether

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20-Cyano-17-pregnene-3(α),21-diol-11-one has been found to undergo geometrical inversion under alkaline conditions accompanied by ether formation at position 21. This discovery has enabled the synthesis of 17-hydroxydehydrocorticosterone-21-methyl ether.

20-Cyano-17-pregnene-3(α),21-diol-11-one 3,21-diacetate (Ia) is deacetylated readily by brief treatment with methanolic alkali to give the corresponding diol (I).² It has been found that prolonged treatment of Ia with methanolic alkali leads to the formation of two new substances: A, m.p. 234–235° and B, m.p. 221–222°. Although the ultraviolet and infrared spectra of these substances clearly indicated the retention of the cyanoethylene system, their non-identity with 20-cyano-17-pregnene-3(α),21-diol-11-one (I) was demonstrated by mixed melting point comparison. The same two substances, A and B, were formed by reaction of the pure diol I with methanolic alkali. The proportion of the two products formed was found to depend on the length of time the reaction mixture was allowed to stand. Thus, when a solution of the diol I in 3% methanolic alkali was allowed to stand for 24 hours or longer, substance B, m.p. 221–222°, could be isolated in over 80% yield in addition to a small amount of substance A, m.p. 234–235°. When the reaction time was shortened to three or four hours, however, a mixture of substances A and B together with some unchanged starting material was obtained in which substance A, m.p. 234–235°, predominated.

It was suggested from the analytical data alone that substance B might be a configurational or positional isomer of the starting diol I having structure II or XI, respectively. It was found, however, that substance B formed only a monoacetate, m.p. 158–159° even after prolonged refluxing with acetic anhydride. This monoacetate derivative, moreover, exhibited no free hydroxyl band in the infrared spectrum thereby excluding structures II or XI for this substance. The possibility remained that the 21-hydroxyl group of the starting diol I had been replaced by a methoxyl group to give the methyl ether (III). Consistent with this consideration III should form a monoacetate possessing no free hydroxyl function. Structure III for substance B was confirmed by active hydrogen and methoxyl group determinations performed on III and its

monoacetate, respectively. Ozonolysis of III, furthermore, yielded the known 17-ketone (V),³ whereas hydroxylation with osmium tetroxide afforded pregnane-3(α),17(α),21-triol-11,20-dione 3-monoacetate 21-methyl ether (VII) (see below) in analogy with the conversion of I to dihydrocortisone (VI).²

In order to demonstrate that the 21-hydroxyl function of I had become displaced by a methoxyl group from the solvent, methanol, I was in turn treated with ethanolic alkali. In this case a new substance, m.p. 144–145°, was obtained together with the above-mentioned substance A, m.p. 234–235°. The analysis, ultraviolet and infrared spectra of the new product, m.p. 144–145°, agreed with the 21-ethoxy structure IV. The latter also formed a monoacetate, m.p. 139.5–140.3°, and the presence of an ethoxyl group was confirmed by Zeisel determination.

Substance A, m.p. 234–235°, was found to be the $\Delta^{17,20}$ -geometrical isomer of the starting diol I and is therefore to be formulated as II.⁴ Thus when the diol I was treated with alkali in aqueous dioxane, only II along with some unchanged I could be isolated. II formed a diacetate, m.p. 135°, still in possession of the cyanoethylene system and exhibiting no hydroxyl band in the infrared spectrum. The structure of II was confirmed by conversion of its 21-monoacetate through osmylation and oxidation to VI, identical with that obtained from the 21-monoacetate of I by the same sequence of reactions.⁵

It is interesting to note that II may be the intermediate product in the formation of III from I. As mentioned above, I is largely converted to II on short standing with methanolic alkali but gives III

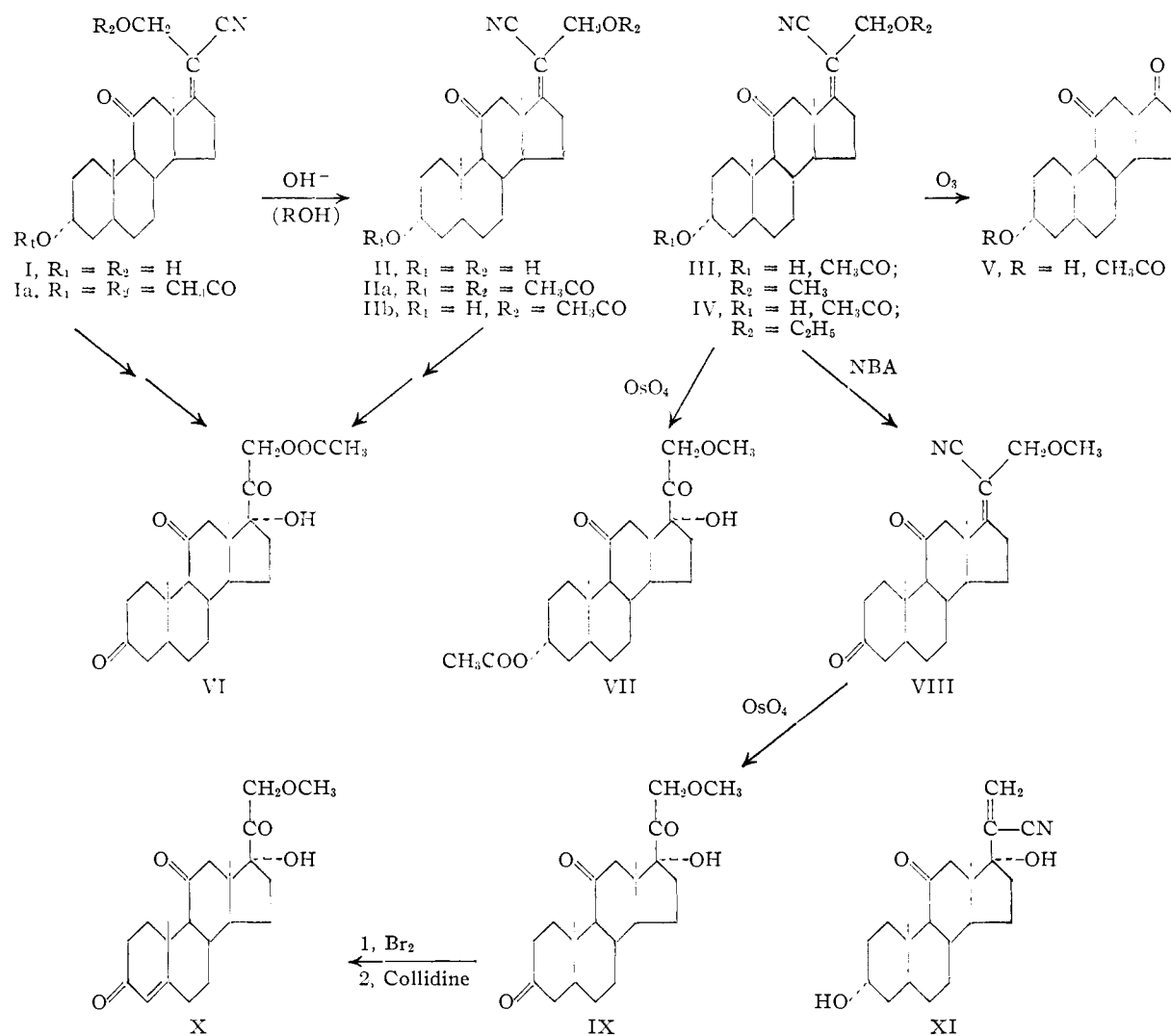
(3) L. H. Sarett, *J. Biol. Chem.*, **162**, 601 (1946).

(4) Inspection of the models of I and II indicates that in I there is a definite crowding of groups between C₁₂ and C₂₁ as well as a distinct restriction to free rotation of the C₂₁-hydroxymethylene group about the axis of the C₂₀-C₂₁ bond. In contrast thereto no apparent steric interference is offered to the linear —C=N group in II. It may therefore be concluded tentatively that II represents the more stable geometrical species and consequently is the configuration to be assigned to the predominant isomer arising from the base-catalyzed inversion.

(5) Private communication from Dr. R. E. Jones and Mr. S. A. Robinson of these laboratories.

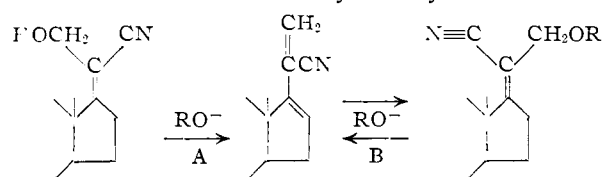
(1) (a) Huang-Minlon, 178 Sin Lo Road, Shanghai, China; (b) John Babcock, Upjohn Company, Kalamazoo, Mich.

(2) L. H. Sarett, *This Journal*, **70**, 1454 (1948).



in good yield after a longer reaction time. Furthermore, II is independently converted to III in over 80% yield on treatment with methanolic alkali under the same conditions for the conversion of I to III directly. Both isomers I and II as well as the 21-methoxy compound III are quite stable to acid since they could be recovered essentially unchanged after refluxing for two hours with hydrochloric acid in methanol.

The mechanics of the transformation of I to give II and III may be visualized reasonably as proceeding *via* base-catalyzed β -elimination to a cyano diene (see below) wherein the latter provides a unidirectionally activated system to further reaction with alkoxide ion to provide the configurationally more stable 21-substituted cyanoethylene.



Visualized in this manner path A becomes essentially irreversible with path B reversible. The above

interpretation gains some measure of support from the fact that I in the presence of hydroxide ion alone undergoes geometrical inversion whereas it is stable to acid; furthermore, the formation of 17-substituted derivatives was never realized. The relatively small differences in optical rotation of II, III and IV and their acetate derivatives in contrast to their marked difference in rotation as compared with I and its acetate derivative strongly indicate that II, III and IV are all in the same geometrical series.

The methoxycyanopregne (III) was converted into 17-hydroxydehydrocorticosterone 21-methyl ether (X) by oxidation with N-bromoacetamide to give the 3-keto derivative VIII followed by hydroxylation with osmium tetroxide to give the ketol IX and finally bromination and debromination. The structure of X was confirmed by analysis, methoxyl determination and spectroscopic examinations.

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Experimental

20-Cyano-17-pregnene-3(α),21-diol-11-one 3,21-Diacetate (Ia).¹—Five grams of 20-cyanopregnane-3(α),20,21-triol-11-one 3,21-diacetate¹ was dissolved in 17.5 cc. of pyridine. After cooling the solution to 0°, the solution was treated with 2.9 cc. of phosphorus oxychloride and allowed to stand overnight at room temperature. The mixture was poured into cold, dilute hydrochloric acid. After decantation of the dilute acid, the gum was triturated with water and dissolved in methanol. The solution was diluted with water until turbid and allowed to stand at 0–5° for four days. The cyanopregnene was filtered and recrystallized from a mixture of benzene and petroleum ether; weight 2.5 g., m.p. 105–107°, $[\alpha]^{25D} +51^\circ$ (*c* 1, acetone).

Anal. Calcd. for C₂₅H₃₅NO₅: C, 70.72; H, 7.99. Found: C, 70.97; H, 7.72.

20-Cyano-17-pregnene-3(α),21-diol-11-one 21-Methyl Ether (III) and 20-Cyano-17-pregnene-3(α),21-diol-11-one (II) from I.—To a solution of 12 g. of the diol (I, m.p. 260–262°) in 500 cc. of abs. methanol was added a solution of 18 g. of sodium hydroxide in 90 cc. of water. The reaction mixture was stoppered and swirled several times, then allowed to stand at room temperature for 48 hours. At the end of this time the reaction mixture was diluted with 1200 cc. of H₂O, the resulting crystalline precipitate was chilled overnight, filtered, washed with water until the washings were neutral, and dried on the steam-bath; yield 10.8 g., m.p. 210–213°. The crude product was dissolved in a minimum volume of 1:1 mixture of chloroform and benzene and chromatographed through a column of 160 g. of acid-washed alumina prepared in benzene.

Eluant	Eluate, g.	M.p. range, °C.
Benzene	Nothing	
Chloroform	9.35	216–221
Acetone	1.37	224–232

Recrystallization of the "chloroform fraction" from chloroform-petroleum ether (b.p. 90–115°) gave 8.65 g. of the 21-methoxycyanopregnene (III), m.p. 220–222°. Several recrystallizations of a small sample from the same solvent pair gave an analytical sample, m.p. 221–222°, $[\alpha]_D +46 \pm 1^\circ$ (*c* 1, acetone).

Anal. Calcd. for C₂₅H₃₅O₃N: C, 74.35; H, 8.95; N, 3.77. Found: C, 74.34; H, 8.85; N, 3.94.

Active Hydrogen.—Calcd., 1.0. Found: 1.1 (room temp.).

The methoxycyanopregnene (III) afforded only a monoacetate; 6 g. of III, 25 cc. of pyridine and 25 cc. of acetic anhydride were mixed, warmed for a few seconds, and allowed to stand stoppered overnight. The reaction mixture was diluted with water, allowed to stand for several hours, filtered, and the residue washed with water. Recrystallization from dilute methanol gave 6.5 g. of the acetate, m.p. 158–159°, $[\alpha]^{25D} +75^\circ$ (*c* 1, acetone).

Anal. Calcd. for C₂₅H₃₅O₄N: C, 72.37; H, 8.53; N, 3.39; CH₃O, 7.5; CH₃CO, 10.4. Found: C, 71.97; H, 8.40; N, 3.79; CH₃O, 6.6; CH₃CO, 11.63.

Recrystallization of the "acetone fraction" of the chromatograph from chloroform-petroleum ether (90–115°) gave 1.05 g. of II melting at 234–235°, $[\alpha]^{25D} +50^\circ$ (*c* 1, acetone).

Anal. Calcd. for C₂₅H₃₁O₃N: C, 73.91; H, 8.74; N, 3.92. Found: C, 74.16; H, 8.75; N, 4.08.

Treatment of 0.28 g. of II overnight in 1.5 cc. of acetic anhydride and 1.5 cc. of pyridine, followed by dilution with water, afforded 0.23 g. of a diacetate (IIa), which after recrystallization from methanol, melted at 134–135°, $[\alpha]^{25D} +80^\circ$ (*c* 1%, acetone).

Anal. Calcd. for C₂₆H₃₃O₅N: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.85; H, 8.06; N, 3.35.

20-Cyano-17-pregnene-3(α),21-diol-11-one 21-Methyl Ether (III) from II.—To a solution of 0.5 g. of II in 17.5 cc. of methanol was added a solution of 0.6 g. of sodium hydroxide in 1.5 cc. of water and 1 cc. of methanol. After standing for 24 hours at room temperature, the mixture was diluted with 80 cc. of water, chilled and filtered, to give 0.45 g., m.p. 209–212°. The crude material (0.30 g.) was dissolved in 10 cc. of chloroform and chromatographed through 12 g. of acid-washed alumina.

Eluant	Eluate, g.	M.p. range, °C.
Chloroform	0.269	218–221
Acetone	.021	228–234

Recrystallization (chloroform-petroleum ether) of the "chloroform fraction" gave 0.23 g., m.p. 221–222.5°, depressed with starting material but not depressed on admixture with III from I. Recrystallization of the "acetone fraction" from the solvent pair gave 0.014 g., m.p. 233–234°—not depressed with the starting material.

20-Cyano-17-pregnene-3(α),21-diol-11-one (II) from I in Dioxane.—To a solution of 1.0 g. of I in 50 cc. of dioxane was added a solution of 2.9 g. of sodium hydroxide in 55 cc. of water. After standing for four hours the mixture was diluted with 200 cc. of water and allowed to stand overnight at 0–5°. The precipitate was filtered and washed with water; weight 0.52 g. After recrystallization from chloroform the material melted at 262.5–264° and did not depress the melting point of the starting material I. The aqueous dioxane filtrate was evaporated and the residue recrystallized twice from chloroform, m.p. 231–233°—no depression with a sample of II.

Treatment of I, II and III with Hydrochloric Acid.—Both geometrical isomers (I and II) and the methoxycyanopregnene (III) were tested for stability to acid in the following manner: 0.1 g. of the compound was treated with a solution of 1 cc. of concentrated hydrochloric acid in 10 cc. of methanol for two hours at the temperature of reflux. In each case the starting material was recovered unchanged in over 90% yield by dilution with water.

20-Cyano-17-pregnene-3(α),21-diol-11-one 21-Acetate (IIb) from II.⁴—To a solution of II (20.0 g.) in 73.3 cc. of pyridine was added 5.75 cc. of acetic anhydride with swirling. The mixture was allowed to stand overnight at room temperature, diluted with benzene and the organic layer was washed with a solution containing 76.5 cc. of concentrated hydrochloric acid and 300 cc. of water, followed by 183 cc. of 3% potassium carbonate solution and 110 cc. of saturated sodium chloride. The benzene solution was dried and evaporated under reduced pressure. The solid residue was dissolved in 225 cc. of chloroform and the solution passed through a column of acid-washed alumina (112 g.) prepared in acetone and washed with chloroform. The column was eluted with 666 cc. of chloroform and finally with 666 cc. of acetone. The chloroform fraction was evaporated and the residue was recrystallized from a mixture of benzene, ether and petroleum ether. There was obtained 14.86 g. (66.5%) of IIb, m.p. 174.4–178°.

A sample was recrystallized twice from benzene for analysis, m.p. 180.6–181.6°, $[\alpha]^{25D} +45.3^\circ$ (*c* 1, acetone).

Anal. Calcd. for C₂₄H₃₃O₄N: C, 72.15; H, 7.88. Found: C, 72.35; H, 8.06.

Pregnane-17(α),21-diol-3,11,20-trione 21-Acetate (VI) from IIb.⁴—To a solution of 9.0 g. of IIb in 6.3 cc. of pyridine and 82 cc. of benzene was added 5.78 g. of osmium tetroxide. After standing for two days at room temperature the solvents were removed *in vacuo* and the residue dissolved in a mixture of 47.3 cc. of glacial acetic acid and 5.3 cc. of water. The solution was cooled to 10° and treated with a cold solution of 4.3 g. of chromic acid in 4.6 cc. of water and 41 cc. of glacial acetic acid followed by the addition of a solution of 2.1 cc. of concentrated sulfuric acid in 20 cc. of glacial acetic acid. After the mixture had stood for 40 minutes at 12–13° with frequent swirling, 40 cc. of methanol was added and the mixture was allowed to stand for an additional 30 minutes. The mixture was added, with stirring, to a suspension of 176 g. of potassium bicarbonate in 420 cc. of water and 50 cc. of ether. After distillation to remove the ether the residue was dissolved in 200 cc. of benzene and 280 cc. of methanol and stirred overnight with a mixture of 41.7 g. of sodium sulfite and 41.7 g. of potassium bicarbonate. The mixture was filtered and the cake washed extensively with chloroform. The filtrate was separated and the aqueous layer extracted with chloroform. The combined organic layers were dried and evaporated to dryness. The residue was treated with 10.5 cc. of acetic anhydride and 19 cc. of pyridine at 50° for five minutes and diluted with 750 cc. of water. The crude material was recrystallized from a mixture of ethyl acetate and ether to give 3.7 g. of VI, m.p. 225–227°, $[\alpha]^{25D} +82^\circ$ (*c* 1, acetone). This material did not depress the melting point of an authentic sample of VI.

Etiocholane-3(α)-ol-11,17-dione (V).—A solution of 2 g. of III ($R_1 = \text{CH}_3\text{CO}$) in 100 cc. of ethyl acetate was treated with a stream of 1.4% ozone until no further consumption was observed. To decompose the ozonide, 50 cc. of water was added and the mixture stirred for 0.5 hour at room temperature. After the ethyl acetate had been volatilized by stirring one hour on the steam-bath, the aqueous solution was thoroughly extracted with ether, which was washed with water, 5% sodium bicarbonate (until acidification no longer produced a turbidity), and water again, dried, and concentrated until crystals separated, crude yield 0.85 g.

The crude material was recrystallized fractionally from ether giving 0.32 g. of an unidentified substance of lactonic character, m.p. 186–187°, depressed with V.

Anal. Calcd. for $\text{C}_{21}\text{H}_{30}\text{O}_5$: C, 69.58; H, 8.34. Found: C, 69.31; H, 8.36.

In addition, there was obtained 0.35 g. of material which melted at 167–168°—no depression with an authentic sample of etiocholane-3(α)-ol-11,17-dione 3-acetate (V).

Eighty-two milligrams of this acetate was hydrolyzed by treatment with 4 cc. of 5% methanolic hydrochloric acid for two days. The solution was diluted with water, neutralized with sodium bicarbonate and concentrated *in vacuo*. After cooling, crystals were obtained, m.p. 188–189°—not depressed by admixture with an authentic sample of etiocholane-3(α)-ol-11,17-dione.

20-Cyano-17-pregnene-3(α),21-diol-11-one 21-Ethyl Ether (IV).—To 10 g. of I dissolved in 350 cc. of abs. ethanol a solution of 12 g. of sodium hydroxide in 50 cc. of water was added, and the atmosphere replaced by nitrogen. After standing at room temperature for 24 hours, the wine-red solution was neutralized with 2.5 *N* hydrochloric acid and diluted with 750 cc. of water. After chilling six hours, the crystalline product was collected on a filter, washed with water until the washings were neutral and dried *in vacuo* at 50°, 10 g., m.p. 101–130°.

The crude product was dissolved in chloroform–benzene (1:1) and chromatographed through a column containing 170 g. of acid-washed alumina prepared in benzene. Chloroform and chloroform–acetone (1:1) eluted 6.7 g. of a substance in the first fractions which crystallized when treated with methanol and melted between 90° and 105°. Continued elution with acetone removed 2.5 g. of oil. The crystalline material was recrystallized from acetone–petroleum ether (75–115°) several times until the constant melting point, 144–145°, was reached, weight 3 g., $[\alpha]^{25}_D +47^\circ$ (*c* 1, acetone).

Anal. Calcd. for $\text{C}_{24}\text{H}_{35}\text{O}_3\text{N}$: C, 74.76; H, 9.15; N, 3.63. Found: C, 74.75; H, 9.00; N, 3.92.

The monoacetate was prepared by treating overnight with pyridine–acetic anhydride and melted at 139.5–140.5° after recrystallization from alcohol, $[\alpha]^{25}_D +73.5^\circ$ (*c* 1, acetone).

Anal. Calcd. for $\text{C}_{26}\text{H}_{37}\text{O}_4\text{N}$: C, 73.03; H, 8.72; N, 3.27; $\text{C}_2\text{H}_5\text{O}$, 10.52. Found: C, 72.94; H, 8.72; N, 3.37; $\text{C}_2\text{H}_5\text{O}$, 8.20.

Pregnane-3(α),17(α),21-triol-11,20-dione 3-Acetate 21-Methyl Ether (VII).—To 1 g. of the cyanoacetate (III) in 1 cc. of pyridine and 10 cc. of benzene was added 1 g. of osmium tetroxide. After standing stoppered at room temperature for 6 days, the reaction mixture was stirred vigorously overnight with 40 cc. of methanol and a solution of 4 g. of sodium sulfite and 1.8 g. of sodium hydroxide in 60 cc. of water. The mixture was extracted seven times with chloroform and the combined chloroform extracts were washed with water until neutral, dried over sodium sulfate and the solvent removed *in vacuo*. The glassy residue (0.788 g.) was dissolved in 2 cc. of pyridine and acetylated with 2 cc. of acetic anhydride. After standing overnight, the anhydride was decomposed with 40 cc. of water and the aqueous solution was extracted six times with chloroform. The combined chloroform extracts were washed thoroughly with water, dilute hydrochloric acid and sodium bicarbonate solution, dried over sodium sulfate, and concentrated to 5 cc. This solution was placed on an alumina column prepared in benzene and eluted with chloroform. The first three crystalline fractions were combined and recrystallized from methanol (charcoal) giving 0.40 g. of VII, m.p. 198–

202°. Recrystallization from methanol for analysis raised the melting point to 201–202°.

Anal. Calcd. for $\text{C}_{24}\text{H}_{36}\text{O}_6$: C, 68.54; H, 8.63. Found: C, 68.42; H, 8.49.

20-Cyano-17-pregnene-21-ol-3,11-dione 21-Methyl Ether (VIII).—A solution containing 6 g. of III, 15 cc. of pyridine, 50 cc. of *t*-butyl alcohol, 2 cc. of water and 5.6 g. of *N*-bromoacetamide was stirred for 17 hours at room temperature in the dark. The reaction mixture was diluted with 180 cc. of water with stirring and cooling, filtered, and the precipitate washed with a small volume of water. The filter cake was dissolved, without drying, in 40 cc. of glacial acetic acid, and treated with 1.5 g. of zinc dust in several portions at 40°, filtered (charcoal), and diluted with 150 cc. of water; yield 5.6 g. (93%), m.p. 209–210°. One sample was recrystallized from dilute methanol for analysis, m.p. 209–211°, $[\alpha]^{25}_D +55^\circ$ (*c* 1, MeOH).

Anal. Calcd. for $\text{C}_{23}\text{H}_{31}\text{O}_5\text{N}$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.83; H, 8.37; N, 4.01.

Pregnane-17(α),21-diol-3,11,20-trione 21-Methyl Ether (IX).—Eight grams of VIII was dissolved in 100 cc. of benzene and 8 cc. of pyridine. After the addition of 9.6 g. of OsO_4 , the reaction mixture was stoppered and allowed to stand at room temperature for 5 days. The mixture was stirred for 24 hours with 160 cc. of chloroform, 200 cc. of methanol and 280 cc. of an aqueous solution containing 58 g. of sodium sulfite and 58 g. of potassium bicarbonate, filtered through Super-cel and washed extensively with chloroform. The filtrate was separated and the aqueous layer extracted with chloroform. The combined chloroform solution was washed thoroughly with sodium carbonate, dilute hydrochloric acid, and sodium bicarbonate, dried and concentrated to give 7.28 g. of an oil. Crystallization from acetone–petroleum ether (90–115°) gave 6.22 g. of dense prisms in two crops, m.p. 164–166°, $[\alpha]^{25}_D +76^\circ$ (*c* 1, MeOH).

Anal. Calcd. for $\text{C}_{22}\text{H}_{32}\text{O}_5$: C, 70.18; H, 8.57; CH_3O , 8.24. Found: C, 70.55; H, 8.51; CH_3O , 7.96.

17(α)-Hydroxydehydrocorticosterone 21-Methyl Ether (X).—To a solution of 2 g. of IX in 40 cc. of glacial acetic acid 1 cc. of 1 *N* hydrobromic acid in acetic acid was added. A solution of 5.31 mM. bromine and 5.31 mM. sodium acetate in 10.4 cc. of acetic acid was added at 25° from a dropping funnel at such a rate that each drop was decolorized. The mixture was diluted immediately with 400 cc. of water and extracted with chloroform. The chloroform solution was washed with water and sodium bicarbonate, dried, and concentrated to give an oil. Crystallization of a small amount of the oil from chloroform–petroleum ether (90–115°) gave crystals which decomposed near 185–187° depending on rate of heating; $[\alpha]^{25}_D +114^\circ$ (*c* 1, MeOH).

Anal. Calcd. for $\text{C}_{22}\text{H}_{31}\text{O}_5\text{Br}$: C, 58.02; H, 6.86; Br, 17.56. Found: C, 58.32; H, 6.61; Br, 17.46.

The oily bromination product was dried by distillation of benzene from it *in vacuo*, dissolved in redistilled collidine, and refluxed 0.5 hour under nitrogen. The collidine hydrobromide was removed by filtration, the dark filtrate was distilled *in vacuo*, and the residue was dissolved in chloroform. The chloroform solution was washed with water, dilute hydrochloric acid, and sodium bicarbonate, dried, filtered and distilled *in vacuo* at 25° to give an oil. The oil was dried by distilling benzene from it *in vacuo*, dissolved in a small amount of chloroform, and chromatographed through acid-washed alumina. The column was eluted with benzene, benzene–chloroform (10:1; 1:1; 1:9), pure chloroform and acetone. From the middle fractions (eluted with benzene–chloroform 1:1 and 1:9) a crude crystalline product (m.p. 227–240°) was isolated which, after repeated recrystallization from methanol (charcoal), melted at 250–253°; λ_{max} 2380 Å., *E%* 400. Infrared Spectrum: OH band at 2.84, 20-keto at 5.83, 11-keto at 5.89, conjugated 3-keto at 6.02 and conjugated double bond at 6.17 μ .

Anal. Calcd. for $\text{C}_{22}\text{H}_{30}\text{O}_5$: C, 70.56; H, 8.08; CH_3O , 8.28. Found: C, 70.73; H, 7.80; CH_3O , 8.09.

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