Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.76; neut. equiv., 266.0. Found: C, 71.70; H, 3.70; neut. equiv. (by titration), 265.2.

The methyl ester prepared by the methanol–sulfuric acid method, crystallized from dilute ethanol as needles, m.p. 139°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.3. Found: C, 72.51; H, 4.2.

4'-Methoxyflavone-6-carboxylic Acid.—A mixture of 2'-hydroxy-5'-carboxy-4-methoxychalcone (1 g.) dissolved in dry amyl alcohol (80 ml.) and selenium dioxide (1 g.), protected from moisture by a $CaCl_2$ guard-tube, was refluxed at 160–165° for 12 hours as before. On working it up similarly, the product obtained was dried and treated with benzene. The yellow solid that separated was collected and crystallized from ethanol as yellow granules, m.p. 328–330° dec., yield 0.3 g. It is soluble in hot acetic acid, sparingly so in hot ethanol, dissolves in $NaHCO_3$ with effervescence, and its sulfuric acid solution exhibits green fluorescence.

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.9; H, 4.05; neut. equiv., 296. Found: C, 68.7; H, 3.90; neut. equiv. (by titration), 298.4.

3'-Hydroxyflavone-6-carboxylic Acid.—2'-Hydroxy-5'-carboxy-3-hydroxychalcone (0.5 g.) in dry amyl alcohol (15 ml.) was treated with selenium dioxide (0.5 g.) at 150–160° for 12 hours, as above. The product isolated as above crystallized from acetic acid as reddish-brown crystals, m.p. 302° dec., yield 0.1 g. It dissolves in $NaHCO_3$ with effervescence and in alkali with yellow color.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.54. Found: C, 67.82; H, 3.35.

4'-Methoxyflavanone-6-carboxylic Acid.—2'-Hydroxy-5'-carboxy-4-methoxychalcone (0.5 g.) dissolved in ethanol (90 ml.) was mixed with hydrochloric acid (25 ml. 10%) when a slight precipitate was formed. It was dissolved by adding a little more ethanol, and the solution refluxed on steam-bath for nearly 50 hours, the excess of ethanol then distilled off and the residual liquid left at room temperature until a pale yellow solid separated which was collected and crystallized from ethanol, pale yellowish granules, m.p. 217°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.79; neut. equiv., 298. Found: C, 68.28; H, 4.81; neut. equiv. (by titration), 295.5.

Flavonol-6-carboxylic Acid.—2'-Hydroxy-5'-carboxychalcone (1 g.) was dissolved in ethanol (25 ml.) and sodium hydroxide solution (25 ml., 5%) added and the alkaline solution cooled in ice-bath; it turned red. To this solution, hydrogen peroxide (6 ml., 16.5%) was added. The reaction mixture was kept in ice-bath for 3 hours and then left at room temperature overnight for 24 hours. The red solution turned slowly to pale yellow. When it was diluted with ice-water and acidified (HCl 1:1) a yellow solid separated. This was collected, washed with water and crystallized from nitrobenzene as yellow needles, m.p. 313° dec. It gives Wilson's boric acid test and brown color with alcoholic ferric chloride. It dissolves in alkali with yellow color and is insoluble in acetone.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.1; H, 3.54; mol. wt., 282. Found: C, 68.0; H, 3.45%; mol. wt. (Ag salt method), 278.6.

The acetoxy derivative, prepared by acetic anhydride–NaAc method, crystallized from ethanol, pale yellow needles, m.p. 237–238°.

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.68; H, 3.70. Found: C, 66.48; H, 3.61.

4'-Methoxyflavonol-6-carboxylic Acid.—2'-Hydroxy-5'-carboxy-4-methoxychalcone (1 g.) was treated with hydrogen peroxide similarly as in the previous case. The product isolated as before, crystallized from nitrobenzene as yellow lustrous needles, m.p. 327° dec. It gives green fluorescence in concentrated sulfuric acid and dissolves in alkali with a yellow color.

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.4; H, 3.85; mol. wt., 312. Found: C, 65.3; H, 3.72; mol. wt. (Ag. salt method), 308.5.

The acetoxy derivative, prepared as before, crystallized from ethanol as lemon-yellow needles, m.p. 220°.

Anal. Calcd. for $C_{19}H_{14}O_7$: C, 64.4; H, 3.95. Found: C, 64.2; H, 3.78.

3'-Hydroxyflavonol-6-carboxylic Acid.—2',3-Dihydroxy-5'-carboxychalcone (0.5 g.) was subjected to hydrogen peroxide treatment as before. The product isolated similarly crystallized from ethanol as yellow needles, m.p. 311°.

Anal. Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.36. Found: C, 64.21; H, 3.17.

4'-Hydroxyflavonol-6-carboxylic Acid.—2'-Hydroxy-5'-carboxy-4-hydroxychalcone (0.5 g.) was treated with hydrogen peroxide as before. The product obtained similarly was collected and crystallized from dilute alcohol as pale yellow needles, m.p. 241°; in concentrated H_2SO_4 solution it gives pale green fluorescence.

Anal. Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.36. Found: C, 64.31; H, 3.40.

AHMEDABAD, INDIA

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF SCHERING CORPORATION]

11-Oxygenated Steroids. XI. The Synthesis of 17α-Hydroxycorticosterone (Compound F) 21-Acetate from Pregnane-11β,17α-diol-3,20-dione

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The conversion of pregnane-11β,17α-diol-3,20-dione to 17α-hydroxycorticosterone 21-acetate has been accomplished in several ways from the following intermediates: a, 3,3-dimethoxypregnane-11β,17α-diol-20-one; b, pregnane-11β,17α-diol-3,20-dione 3-ethylene ketal; c, 4-bromopregnane-11β,17α-diol-3,20-dione *via* the 3,20-bis-ethylene ketal; d, 4-bromopregnane-11β,17α-diol-3,20-dione *via* the 3-ethylene ketal.

The chemical synthesis of 17α-hydroxycorticosterone (Kendall's Compound F) has been accomplished from cortisone,[1] 20-cyano-Δ^{17}-pregnen-21-ol-3,11-dione,[2] Δ^4-pregnene-11α,17α,21-triol-3,20-dione (11-epi-17α-hydroxycorticosterone),[3] pregnane-3α,11α,17α-triol-20-one and pregnane-3α,17α-diol-11,20-dione[4] and from pregnane-3α,11β,17α-triol-20-one.[5] This paper describes

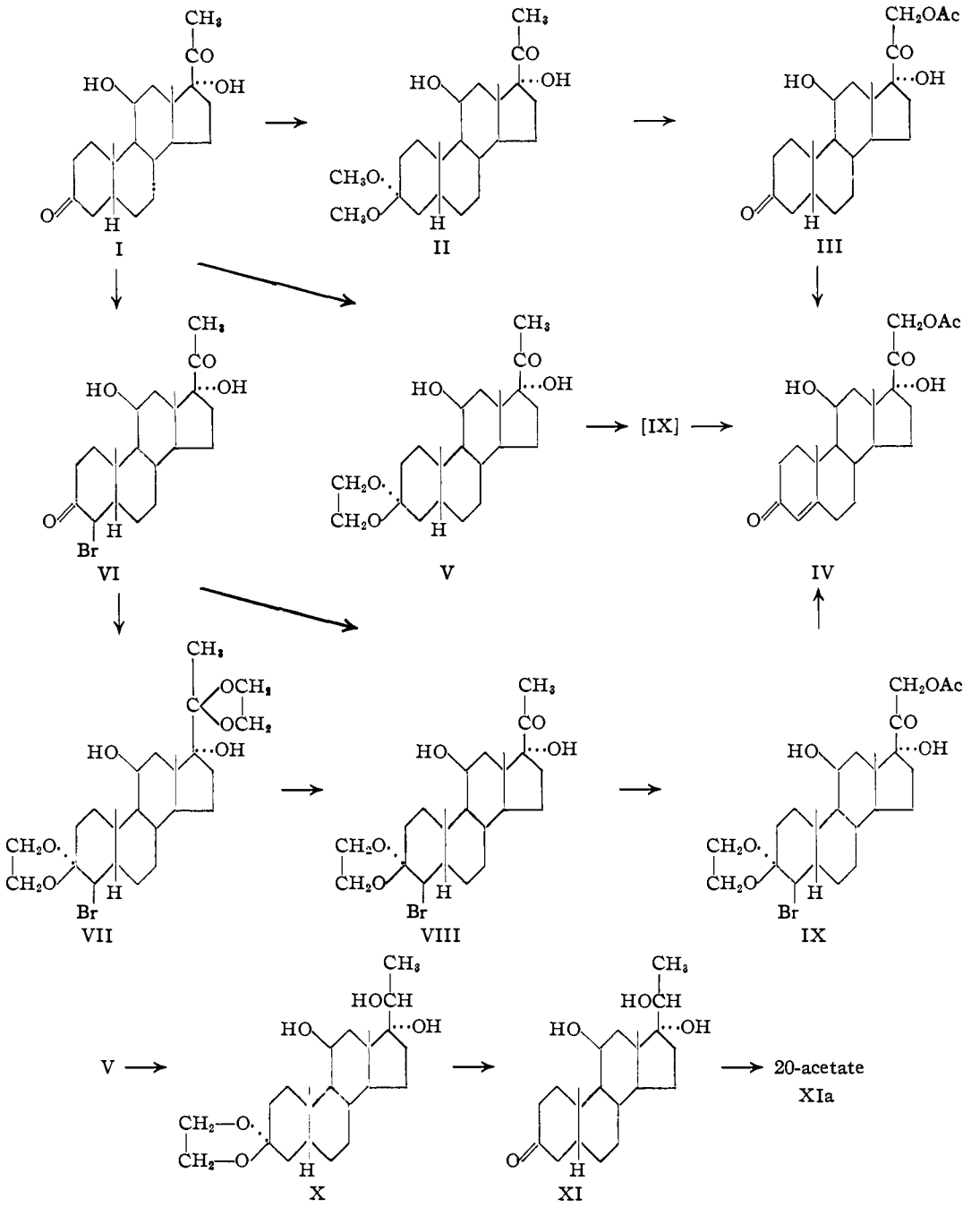
(1) (a) N. L. Wendler, Huang-Minlon and M. Tishler, THIS JOURNAL, **73**, 3818 (1951); (b) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. R. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(2) N. L. Wendler, R. P. Graber, R. E. Jones and M. Tishler, THIS JOURNAL, **74**, 3630 (1952).

(3) J. Fried and E. F. Sabo, *ibid.*, **75**, 2273 (1953).

(4) R. H. Levin, B. Magerlein, A. McIntosh, A. Hanze, G. Fonken, J. Thompson, A. Searcy, M. Scheri and E. Gutsell, *ibid.*, **75**, 502 (1953).

(5) E. P. Oliveto, C. Gerold and E. B. Hershberg, *Arch. Biochem. Biophys.*, **49**, 244 (1954).



the results of the investigation of several synthetic routes to 17α-hydroxycorticosterone 21-acetate (IV) from pregnane-11β,17α-diol-3,20-dione (I).[6] All of these involve the selective protection of a 3,20-diketone at C-3 in order to elaborate the cortical side-chain.

In a previous paper[7] we described the selective formation of 3,3-dimethyl ketals from 3,20-diones, including the preparation of 3,3-dimethoxypregnane-11β,17α-diol-20-one (II) from I. Bromination of II in chloroform with three moles of bromine, followed by acetoxylation at C-21 with potassium acetate in acetone, and subsqeuent dehalogenation with zinc and acetic acid (and possible concurrent ketal hydrolysis), gave a 38% yield of pregnane-11β,17α,21-triol-3,20-dione 21-acetate (4,5-dihydro F 21-acetate, III).

The conversion of III into 17α-hydroxycorticosterone 21-acetate (Compound F 21-acetate, IV) was accomplished by known procedures.[2]

The presence of the 3,3-dimethyl ketal (in II) rather than the 3-ketone (in I) apparently decreased the tendency to brominate in the A-ring, for pregnane-11β,17α-diol-3,20-dione (I) did not give any isolable 4,5-dihydro F 21-acetate (III)

(6) E. P. Oliveto, T. Clayton and E. B. Hershberg, THIS JOURNAL, **75**, 486 (1953).

(7) E. P. Oliveto, C. Gerold and E. B. Hershberg, *ibid.*, **76**, 6111 (1954).

upon bromination with varying quantities of bromine followed by treatment with potassium acetate. The use of more or less than three moles of bromine in the bromination of II gave less satisfactory results. This may be due to the fact that the dimethyl ketal does not deactivate sufficiently the A-ring to allow smooth bromination at C-21 with one or even two moles of bromine.[8] In addition, compound II was found to be unstable, reverting to I on standing at room temperature. This rapid reversal and hence inadequate protection may also explain why a large quantity of bromine had to be used in order to obtain a reasonable amount of bromination of C-21.

In the hope that another ketal at C-3 might give better results, pregnane-11β,17α-diol-3,20-dione 3-ethylene ketal (V) was prepared from I with ethylene glycol in the presence of selenium dioxide and chloroform diluent. Since this was the first instance in which a 3-ethylene ketal had been prepared by the selenium dioxide method,[7] the structure of V was proved by conversion to the known pregnane-11β,17α,20β-triol-3-one 20-acetate (XIa) *via* the sequence V → X → XI → XIa.

Although compound V was found to be stable, attempts to brominate it gave less satisfactory results than with III. Optimum results were obtained when two moles of bromine were used. The crude product obtained after bromination and acetoxylation apparently contained some 4-bromo-3-ethylene ketal. This was indicated by the isolation of a small amount of compound F 21-acetate (IV) upon subsequent treatment with semicarbazide in acetic acid in the presence of hydrogen bromide, followed by exchange with pyruvic acid.[9]

Two other synthetic routes were investigated starting with 4-bromopregnane-11β,17α-diol-3,20-dione (VI) which was prepared readily by the bromination of I. Treatment of VI with ethylene glycol in refluxing benzene in the presence of *p*-toluenesulfonic acid with the continuous azeotropic removal of water gave 4-bromopregnane-11β,17α-diol-3,20-dione 3,20-bis-ethylene ketal (VII) in 67% yield. Dehydration at C-11 was not appreciable even under these vigorous conditions.[10] Selective acidic hydrolysis[4] of the 20-ketal gave 4-bromopregnane-11β,17α-diol-3,20-dione 3-ethylene ketal (VIII) in 93% yield.

In an alternative scheme, the application of selective ketalization of 3-ketones by the use of selenium dioxide was extended to 4-bromo-3-ketones with the discovery that the reaction would proceed well in the presence of a strongly acidic catalyst. Thus VI gave VIII directly in 54% yield by the use of selenium dioxide, ethylene glycol and chloroform, with a catalytic amount of *p*-toluenesulfonic acid. Selenium dioxide alone gave very poor yields, while *p*-toluenesulfonic acid alone gave none of the expected product.

The more severe conditions which are necessary for room temperature ketal formation of VI are probably a consequence of the increased steric hindrance at C-3 due to the presence of the C-4 bromine atom.

Upon bromination and acetoxylation the product VIII obtained from either source gave 4-bromopregnane-11β,17α,21-triol-3,20-dione 3-ethylene ketal 21-acetate (IX) in 71% yield. Hydrolysis of the 3-ketal with sulfuric acid in warm acetic acid,[4] followed by treatment with semicarbazide and exchange with pyruvic acid, gave Compound F 21-acetate (IV) in 41% yield.

Experimental[11,12]

Pregnane-11β,17α,21-triol-3,20-dione 21-Acetate (III).—A solution of 13.96 g. (0.0353 mole) of 3,3-dimethoxypregnane-11β,17α-diol-20-one (II) in 280 ml. of C.P. chloroform was treated at 10–15° with a solution of 17.1 g. (0.107 mole) of bromine in 280 ml. of chloroform over a period of 15 minutes. After stirring an additional 15 minutes, 28 g. of anhydrous potassium acetate was added and the solvent was removed by distillation *in vacuo*. The residue was treated with 700 ml. of acetone and another 28 g. of potassium acetate and the mixture was refluxed with stirring for five hours. The acetone was distilled *in vacuo* and the residue was extracted by methylene chloride. The extract was washed with water, dried with magnesium sulfate and concentrated to dryness by distillation.

The residue was dissolved in 210 ml. of glacial acetic acid and treated with 28 g. of zinc dust with stirring at 50–60° for 15 minutes. Then 28 ml. of water was added, the reaction kept at 50–60° for another 20 minutes, cooled, filtered from the zinc and the filtrate was extracted with methylene chloride. The organic extract was washed with dilute sodium bicarbonate solution, water, dried over magnesium sulfate and concentrated to an oily residue. Trituration of the residue with ether gave 5.52 g. of crude III (38.5%), m.p. 193–196°.

A sample of crude III was chromatographed on Florisil. Elution with 50% benzene–ether, followed by two recrystallizations from ethyl acetate–hexane, gave III, m.p. 215–219°, which was converted to IV by the procedure of Wendler, *et al.*[2] The infrared spectrum of III was identical with an authentic specimen.[13]

Pregnane-11β,17α-diol-3,20-dione 3-Ethylene Ketal (V).—A mixture of 10.0 g. of pregnane-11β,17α-diol-3,20-dione (I), 10.0 g. of selenium dioxide, 150 ml. of ethylene glycol and 100 ml. of alcohol-free chloroform was stirred for 24 hours at 28°. The reaction mixture was poured into a solution of 20 g. of potassium carbonate in 1.5 l. of water and extracted with methylene chloride. The extract was washed with water, dried with magnesium sulfate, and upon evaporation left a solid residue weighing 11.06 g., m.p. 225–229°. Recrystallization from acetone–hexane gave 6.44 g. (56.9%) of V, m.p. 230.2–233.2°, $[\alpha]_D$ +28.2° (chl.). A second fraction of 3.30 g., m.p. 228–230°, was recrystallized and gave 2.52 g. (22.3%), m.p. 232.4–233.8°. Integration of the carbonyl region of the infrared spectrum showed the presence of only one ketone group.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.26; H, 9.67.

Pregnane-11β,17α,20β-triol-3-one (XI) and its 20-Acetate XIa.—A mixture of 0.5 g. of V, 1.0 g. of sodium borohydride, 40 ml. of methanol and 10 ml. of water was refluxed overnight. The solvent was removed by distillation, water was added and the precipitated solid was removed by filtration. The solid was dissolved in 20 ml. of 50% acetic acid, heated for 0.5 hour at 60°, poured into water, neutralized with sodium bicarbonate, and extracted with methylene chloride. The organic extract was washed with water, dried and evaporated to a residue. This was recrystallized twice from acetone–hexane to yield XI, m.p. 164.8–166.2°.

(8) The protection of a 3-ketone by ketal formation in order to permit bromination at C-21 was first reported by H. Inhoffen, U. S. Patent 2,409,043.

(9) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(10) *Cf.* R. P. Graber, A. C. Haven and N. L. Wendler, THIS JOURNAL, **75**, 4722 (1953).

(11) All melting points are corrected. All rotations are in a 1-dcm. tube at a concentration of about 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemical Departments of these laboratories.

(12) We wish to acknowledge the technical assistance of Mrs. F. E. Carlon.

(13) Kindly supplied by Dr. T. Stoudt, Merck and Co., Inc.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.09; H, 9.86.

The 20-acetate XIa melted at 262–264°; its infrared spectrum matched that of a sample prepared previously.[7]

17α-Hydroxycorticosterone 21-Acetate (IV) from V.—A solution of 10.0 g. (0.0254 mole) of V in 125 ml. of C.P. chloroform was treated at 10–15° with a solution of 8.2 g. (0.0513 mole) of bromine in 75 ml. of chloroform over a 20-minute period. After the addition of the bromine was complete, 8 g. of anhydrous potassium acetate was added and the solvent was removed by distillation *in vacuo*. The residue was treated with 250 ml. of acetone and another 20 g. of anhydrous potassium acetate, and the mixture was refluxed with stirring for five hours. The acetone was removed by steam distillation and the organic material was extracted into methylene chloride. The extract was washed with water, dried with magnesium sulfate and concentrated to dryness. The residue after evaporation was dissolved in 135 ml. of glacial acetic acid following which 4.33 g. of semicarbazide (0.0576 mole), 13.5 ml. of water and 10.8 ml. of a 10% solution of hydrogen bromide in glacial acetic acid were added. The reaction mixture was kept at about 70° for one hour under a carbon dioxide atmosphere and then poured into water. The solid thus obtained weighed 8.20 g., m.p. 165–250° dec., ϵ_{max} 17,700 at 270 mμ (ethanol).

A solution of 4.0 g. of this semicarbazone in 30 ml. of glacial acetic acid with 2.56 g. of 90% pyruvic acid, 7.2 g. of anhydrous sodium acetate and 20 ml. of water was refluxed for five minutes, diluted with water and extracted into methylene chloride. The extract was washed with sodium bicarbonate solution, and with water, then dried with magnesium sulfate and evaporated to dryness. The residue was chromatographed on 60 g. of Florisil. A fraction of 850 mg. eluted with 1% methanol in methylene chloride was crystallized from acetone–hexane to give 200 mg. of IV, m.p. 211.6–216.0° dec., ϵ_{max} 15,000 at 242 mμ (ethanol). The infrared spectrum was identical with an authentic sample of IV.

4-Bromopregnane-11β,17α-diol-3,20-dione 3,20-Bis-ethylene Ketal (VII).—A mixture of 8.26 g. of 4-bromopregnane-11β,17α-diol-3,20-dione (VI) with 826 ml. of benzene and 41.5 ml. of ethylene glycol was distilled to remove 83 ml. of distillate. Then 0.83 g. of *p*-toluenesulfonic acid was added and the two-phase solution was refluxed with stirring for four hours; 350 ml. of aqueous distillate was removed during this time by means of a Dean–Stark tube separatory device. The reaction mixture was cooled, neutralized with 0.5 g. of potassium hydroxide in methanol and the solution washed with water, dried over magnesium sulfate and concentrated to dryness *in vacuo*. The residue was triturated with ether to yield 4.66 g. (46.6%) of VII, m.p. 224–231°. Another 2.09 g. (21.0%), m.p. 219–225°, was obtained by concentration of the mother liquor. The infrared spectrum showed no carbonyl peaks. The analytical sample, recrystallized twice from ethyl acetate–hexane, melted at 240.0–241.4°, $[\alpha]_D$ +46.9° (acetone).

Anal. Calcd. for $C_{25}H_{39}O_6Br$: Br, 15.50. Found: Br, 15.42.

4-Bromopregnane-11β,17α-diol-3,20-dione 3-Ethylene Ketal (VIII). (A) From VII.—A solution of 2.58 g. of VII in 65 ml. of acetone was treated with a solution of 2.5 ml. of concentrated hydrochloric acid diluted to 13 ml. with water. After two hours at 23°, 300 ml. of water was added with stirring. There was obtained 2.20 g. (93.2%) of VIII, m.p. 182.5–183° dec. The sample prepared for analysis was recrystallized from ethyl acetate–hexane and melted at 186–187° dec., $[\alpha]_D$ +86.0° (acetone).

Anal. Calcd. for $C_{23}H_{35}O_5Br$: C, 58.60; H, 7.48. Found: C, 59.00; H, 7.55.

(B) From VI.—A mixture of 1.0 g. of VI with 1.0 g. of selenium dioxide, 0.1 g. of *p*-toluenesulfonic acid monohydrate, 10 ml. of ethylene glycol and 25 ml. of alcohol-free chloroform, was stirred at 25° for four days. Methylene chloride was added and the organic layer was washed with water, dilute sodium bicarbonate solution, and again with water, then dried over magnesium sulfate. The solvent was removed *in vacuo* at room temperature and the residue was triturated with ether. There was obtained 0.60 g. (54.3%) of VIII, m.p. 178–179° dec. The infrared spectrum was identical with VIII prepared from VII.

4-Bromopregnane-11β,17α,21-triol-3,20-dione 3-Ethylene Ketal 21-Acetate (IX).—A solution of 4.0 g. (0.0085 mole) of VIII in 240 ml. of C.P. chloroform was treated at 25° with a solution of 1.44 g. (0.0090 mole) of bromine in 80 ml. of chloroform over a period of 1.5 hours. After the addition of bromine was complete, 8 g. of anhydrous potassium acetate was added and the solvent was evaporated *in vacuo*. The residue was treated with another 8 g. of anhydrous potassium acetate, 60 mg. of potassium iodide, 252 ml. of acetone and 2.6 ml. of glacial acetic acid and was refluxed with stirring for 16 hours. The solvent was steam distilled and the solid which separated was collected by filtration. It was taken up in methylene chloride, washed with water, and dried over magnesium sulfate after which the solvent was removed *in vacuo* and the residue treated with ether. There was obtained 3.19 g. (71.3%) of IX, m.p. 206–208° dec. The sample for analysis was crystallized twice from acetone–hexane and melted at 216–217° dec., $[\alpha]_D$ +98.1° (acetone).

Anal. Calcd. for $C_{25}H_{37}O_7Br$: C, 56.71; H, 7.04. Found: C, 57.17; H, 7.10.

17α-Hydroxycorticosterone 21-Acetate (IV) from IX.—A mixture of 1.97 g. of IX, 20 ml. of glacial acetic acid, 6 ml. of water and 0.20 ml. of concentrated sulfuric acid, was heated at 70° for 1.5 hours with stirring, whereupon the solid gradually dissolved. The solution was cooled and 0.31 g. of sodium acetate was added. A solution of 0.57 g. of semicarbazide in 2 ml. of water was then added and the mixture was stirred at 25° for 30 minutes under a nitrogen atmosphere. Then 2 ml. of pyruvic acid was added, stirring was continued at 50° for 30 minutes, the flask was cooled and 2 g. of sodium acetate was added. The resulting solution was extracted with methylene chloride, washed with dilute sodium hydroxide solution and with water, and dried over magnesium sulfate. For the purpose of acetylation the methylene chloride solution was treated with 20 ml. of pyridine and 10 ml. of acetic anhydride and allowed to stand one hour at 25°. After this it was washed with dilute sulfuric acid, dilute sodium hydroxide and with water, and then dried over magnesium sulfate. The methylene chloride solvent was evaporated *in vacuo* and the residue triturated with ether and collected on a filter with suction. There was obtained 0.62 g. (41.2%) of IV, m.p. 215–218°, ϵ_{max} 14,600 at 242 mμ (ethanol). The infrared spectrum was identical with an authentic sample.

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