amount of water required stoichiometrically. An excess of water permits rapid oxidation.

6. The possible relationship between this phenomenon and the observed passivity of hemoglobin is discussed.

BALTIMORE 18, MD. RECEIVED APRIL 22, 1946

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

The Partial Synthesis of Dehydrocorticosterone Acetate

BY LEWIS HASTINGS SARETT

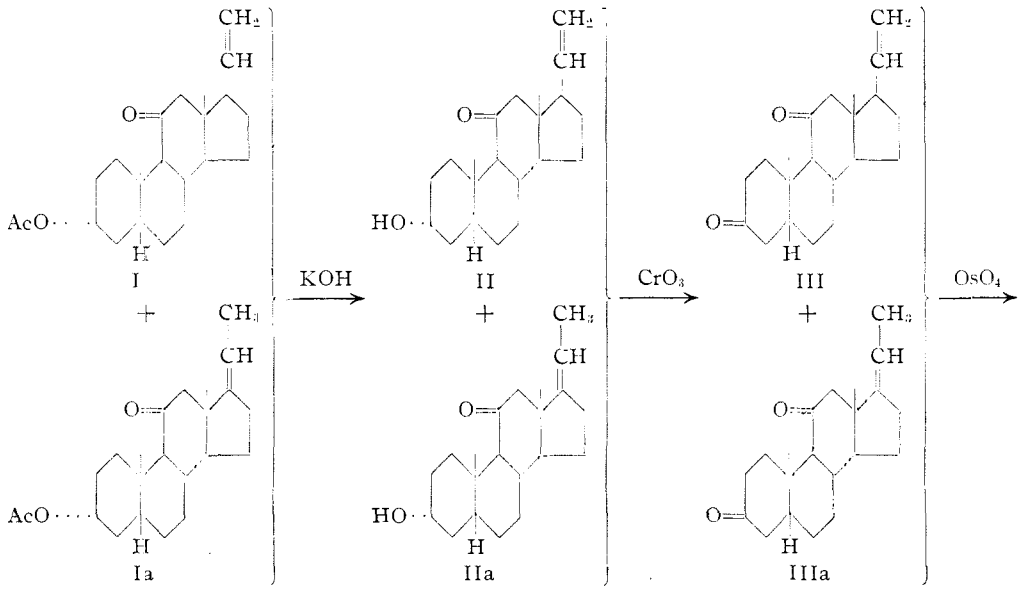
Dehydrocorticosterone, a member of the adrenal cortical hormone group, was first isolated from cortical extracts by Kendall and co-workers.[1] Its partial synthesis from desoxycholic acid has been accomplished by Lardon and Reichstein.[2] This synthesis employs the reaction of a 3-acetoxy-11-keto-*etio*-cholanic acid chloride with diazomethane as a means of introducing the required ketol side chain. This has also been accomplished by lead tetraacetate oxidation.[3]

The availability of $\Delta^{17,20}$- and $\Delta^{20,21}$-3(α)-acetoxy-11-ketopregnenes[4] has now made possible the utilization of another method for constructing the ketol side chain.

The crude crystalline mixture of $\Delta^{17,20}$- and $\Delta^{20,21}$-3(α)-acetoxy-11-ketopregnenes (I and Ia), obtained by the method previously described[4] was saponified to the corresponding mixture of 3(α)-hydroxy-11-ketopregnenes (II and IIa), which upon oxidation with chromic acid afforded the corresponding mixture of 3,11-diketopregnenes (III and IIIa). Hydroxylation with osmium tetroxide by the method of Criegee[5] gave a mixture of pregnanedioldiones from which the pair of isomeric 20,21-diols could immediately be separated. This was effected by subjecting the mixture to mild esterification with succinic anhydride followed by separation of the acidic from the neutral fraction.

The neutral fraction consisted essentially of a pregnanediol-17,20-dione-3,11,[6] (IV), which was best isolated as the readily crystalline 20-acetate, (V). The structure of this dioldione was shown to be that given by formula IV through chromic acid oxidation. Two products were obtained, *etio*-cholanetrione-3,11,17 (VII) and pregnanol-17-trione-3,11,20 (VI). VII could also be obtained by oxidation of *etio*-cholanol-3(α)-dione-11,17.[4]

The $\Delta^{4,5}$-unsaturated derivative of IV was also prepared. Bromination of V gave 4-bromopregnandiol-17,20-dione-3,11 acetate-20 (XXI) as the crystalline alcohol complex. Refluxing this product with pyridine gave pregnene-4-diol-17,20-dione-3,11 acetate-20 (XXII), saponification of



(1) Mason, Myers and Kendall, *J. Biol. Chem.*, **114**, 613 (1936).

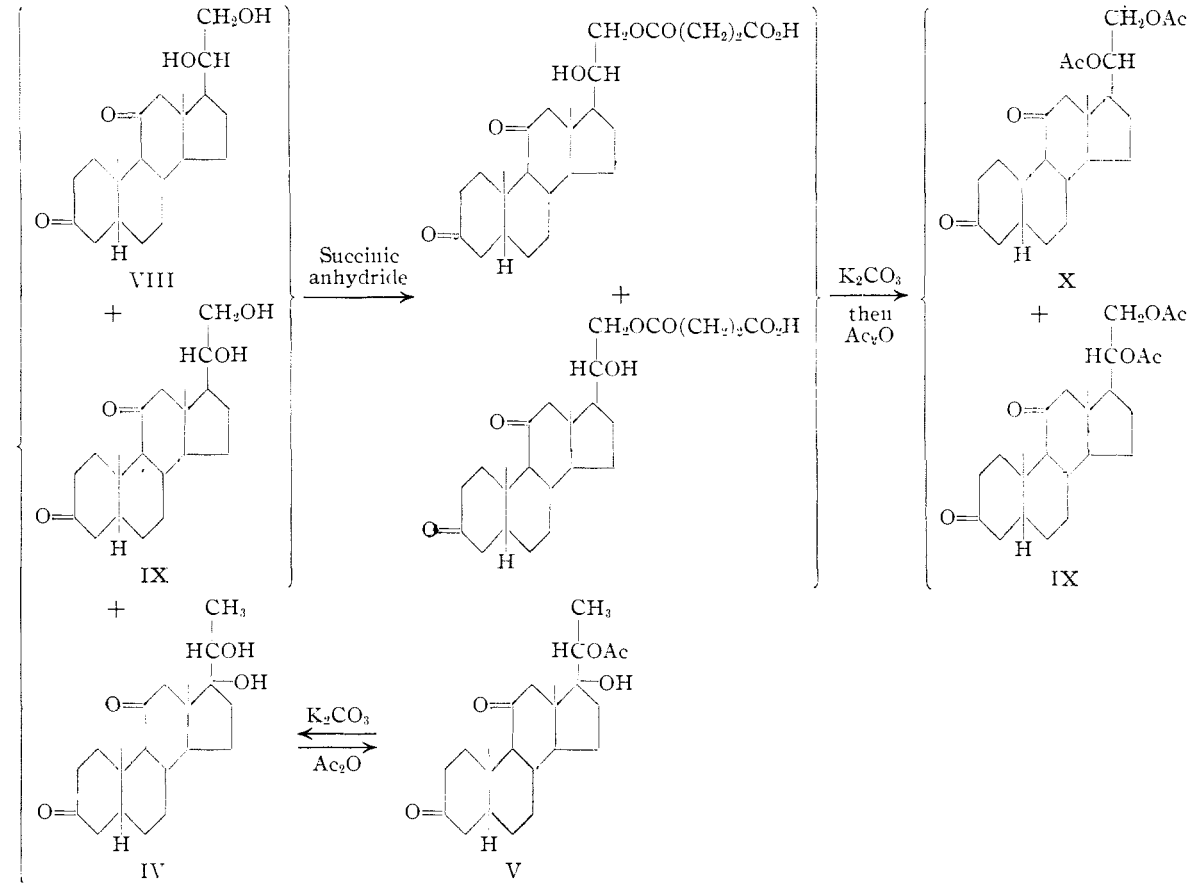
(2) Lardon and Reichstein, *Helv. Chim. Acta*, **26**, 747 (1943).

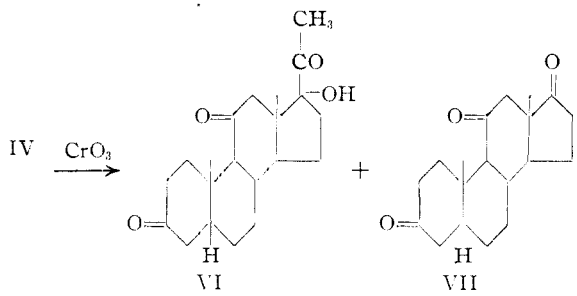
(3) *E. g.* von Euw, Lardon and Reichstein, *ibid.*, **27**, 1287 (1944).

(4) Sarett, *J. Biol. Chem.*, **162**, 591 (1946).

(5) Criegee, *Ann.*, **522**, 75 (1936); Criegee, Marchand and Wannowius, *ibid.*, **550**, 99 (1942).

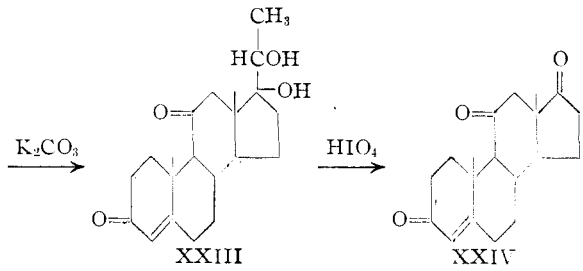
(6) The stereochemical configuration of this compound has not yet been determined.

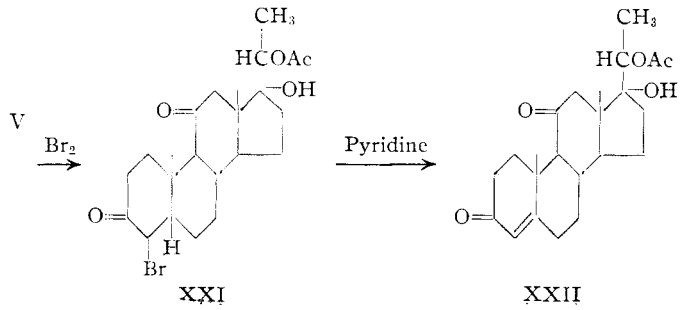




which afforded the free diol (XXIII) obtained as the crystalline hydrate. A sample of XXIII was oxidized with periodic acid and yielded, as expected, adrenosterone (XXIV).

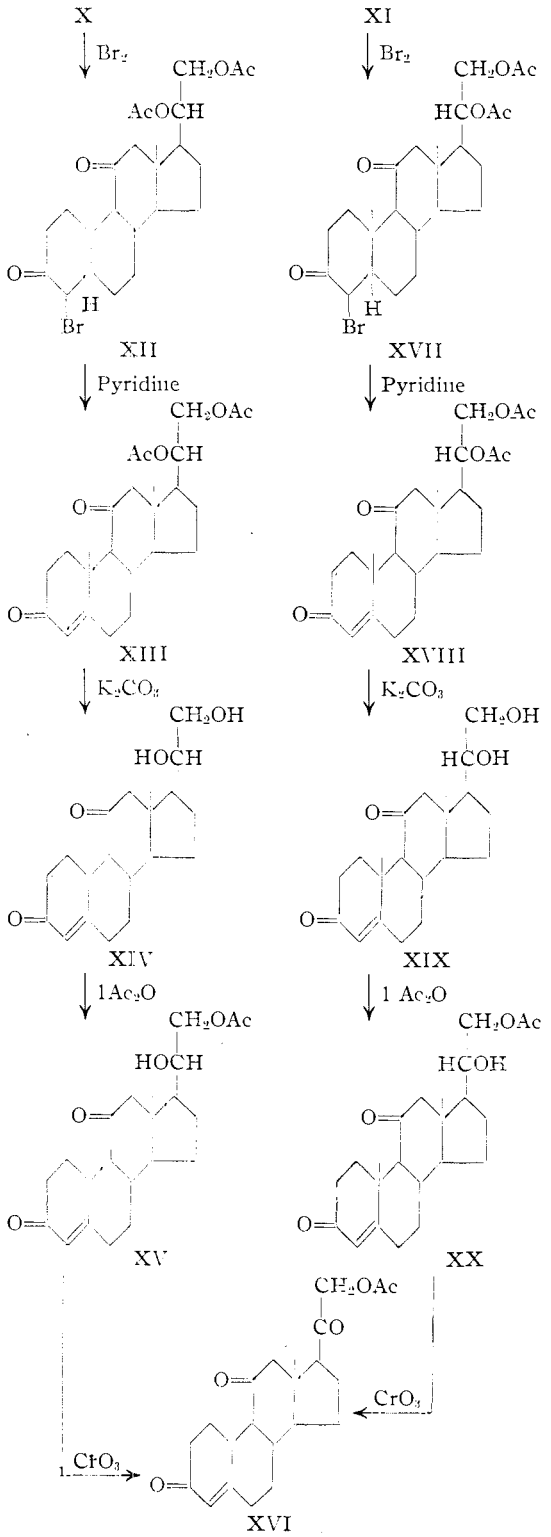
The acid succinate fraction, the separation of which was described above, was saponified and





gave a mixture of the two isomers, pregnanediol-20(α and β),21-dione-3,11 (VIII + IX). Separation was achieved by acetylation followed by chromatography. Since, unfortunately, the respective dioldiones (VIII and IX) and their corresponding acetates (X and XI) could not easily be related stereochemically to compounds of known conventional configuration at C-20, the arbitrary assignment of 20(α) was made to VIII and X, 20(β) to IX and XI.

The bromination of X led to the corresponding 4-bromopregnanediol-20(α),21-dione-3,11 diacetate (XII) which could not be obtained crystalline. Refluxing the crude bromoketone with pyridine gave crude crystalline pregnene-4-diol-20-(α),21-dione-3,11 diacetate (XIII), the separation of which from a small amount of X was best achieved by saponification to the free dioldione (XIV) and recrystallization of the latter from water. Reacetylation afforded the pure diacetate which melted at 153–154°.



When a dioxane solution of XIV was treated with one mole of acetic anhydride and pyridine[4,7] and the product then chromatographed, pregnene-4-diol-20(α),21-dione-3,11 acetate-21 (XV) could be obtained in 25% yield. The partial acetylation of both XIV and XIX was found to be considerably less selective than that of the corresponding 17(β),20(β),21-trihydroxy compound.[4] When XV was oxidized with chromic acid, a good yield of dehydrocorticosterone acetate[8] (XV) was obtained.

The isomeric pregnanedioldione diacetate (XI) was then submitted to the series of reactions described above. Bromination gave a non-crystalline bromoketone (XVII) which was refluxed with pyridine. The unsaturated ketone (XVIII), after several recrystallizations, had the constant melting point 207–208° and $[\alpha]^{20}D$ + 170° (acetone). Formula XVIII (or the isomeric structure XIII) has been shown to represent the diacetate of a naturally occurring adrenal cortical compound, "Substance T."[9] Although no direct comparison of XVIII with "Substance T" could be made and, in addition, physical data on the latter compound are incomplete,[10] the structural evidence adduced for "Substance T" and for the unsaturated ketone XVIII demonstrates that they are identical.

Saponification of XVIII gave pregnene-4-diol-20(β),21-dione-3,11 (XIX), which melted at 223.5–224.5° and had $[\alpha]^{20}D$ + 176° (acetone). Partial acetylation afforded the 21-monoacetate (XX) in 40% yield, oxidation of which gave dehydrocorticosterone acetate (XVI).

Experimental[11]

All melting points are corrected.
Rotations were taken in acetone, c = 1.0.
Absorption spectra were taken in alcohol.

Pregnanediol-17,20-dione-3,11 Acetate-20 (V).—A solution of 14.6 g. of crude mixture of $\Delta^{17,20}$- and $\Delta^{20,21}$-pregnenol-3(α)-one-11 acetate in 100 cc. of 1.1 *N* methanolic potassium hydroxide was refluxed for thirty minutes. The solution was concentrated *in vacuo* to a small volume, water was added and the organic material taken up in ether. The ethereal solution was washed twice with water, then concentrated to dryness on the steam-bath. The

(7) *Cf.* Prins and Reichstein, *Helv. Chim. Acta*, **25**, 300 (1942).

(8) An authentic sample for comparison was kindly furnished us by Dr. E. C. Kendall of the Mayo Clinic, Rochester, Minnesota.

(9) Reichstein and von Euw, *Helv. Chim. Acta*, **22**, 1222 (1939).

(10) Reichstein and von Euw, ref. 19, give m. p. 212–213° for the diacetate, m. p. *ca.* 210° for the crude glycol; no rotations are given.

(11) To Mr. W. A. Bastedo, Jr., and to Mrs. R. C. Anderson the author is indebted for the absorption spectra determinations and to Messrs. R. N. Boos, L. Rosalsky, E. Thornton, W. K. Humphrey J. H. McGregor and Miss J. Cheng for all microanalyses.

residue (12.2 g.) was a pale yellow oil which consisted of a crude mixture of $\Delta^{17,20}$- and $\Delta^{20,21}$-pregnenol-3(α)-one-11.

This material was then dissolved in 1200 cc. of glacial acetic acid, the solution cooled to 16° and treated over a period of 45 minutes with a solution of 6.0 g. of chromic acid in 120 cc. of acetic acid and 120 cc. of water. The solution was stirred mechanically during the addition. After an additional hour at 16°, 16.0 g. of anhydrous sodium sulfite was added and the solution stirred until excess chromic acid was destroyed. The acetic acid was then removed *in vacuo*, the residue taken up in ether, and the ether layer washed successively with water, dilute potassium carbonate and again with water. Upon evaporation of the ethereal solution, 9.65 g. of crude $\Delta^{17,20}$- and $\Delta^{20,21}$-pregnanedione-3,11 was obtained as a yellow oil.

This material was dissolved in 50 cc. of absolute ether to which was added a solution of 8.0 g. of osmium tetraxide in 50 cc. of absolute ether. After the addition of 2.4 cc. of pyridine the mixture was permitted to stand for one hour at room temperature and thirty-six hours at 0°. The precipitated osmium complex was filtered off and washed with a mixture of ether and petroleum ether. After drying at room temperature it weighed 15.5 g.

This material was then hydrolyzed by refluxing for three and one-half hours with a mixture of 53 g. of sodium sulfite, 350 cc. of 95% alcohol and 240 cc. of water. The solution was cooled to 35°, filtered and the residue extracted twice with 200-cc. portions of alcohol. The filtrate was concentrated *in vacuo* to 50 cc., 50 cc. of water was added and the suspension extracted thrice with 200-cc. portions of chloroform. The chloroform layer was washed twice with a small volume of water, then concentrated to dryness *in vacuo*. The yellowish residue weighed 9.05 g.

This mixture of glycols was then dissolved in 25 cc. of pyridine at 95°. To the hot solution was added 5.0 g. of succinic anhydride. After the solution was heated on the steam-bath for fifteen minutes, 5.0 cc. of water was added, the solvent removed *in vacuo* and the residue taken up in 300 cc. of chloroform. The chloroform solution was washed with water, then with dilute hydrochloric acid, and finally extracted with a 10% aqueous solution of potassium carbonate. Because of partial emulsification the separation was imperfect and therefore the chloroform layer was shaken with two additional portions of dilute carbonate and the aqueous alkaline extracts were likewise shaken twice with fresh portions of chloroform. The combined chloroform solutions were then washed with water and concentrated to dryness *in vacuo*. The residue weighed 3.6 g. ("Neutral fraction").

The combined aqueous carbonate solutions were carefully acidified with dilute hydrochloric acid and the precipitated acids taken up in chloroform. The washed chloroform solution was concentrated to dryness *in vacuo* and gave 7.2 g. of gummy residue ("Acid fraction," see below).

The 3.6 g. of "neutral fraction" described above was acetylated by heating on the steam-bath for half an hour with 5 cc. of pyridine and 5 cc. of acetic anhydride. The solution was then cooled and treated with water. A crystalline product was obtained which weighed 2.9 g. and melted at 155–175°. After several recrystallizations from benzene–alcohol and from ethyl acetate, a product was obtained which melted at 218–224° with partial loss of solvent. After drying *in vacuo* at 130° for one hour the pregnanediol-17,20-dione-3,11 acetate-20 (V) melted at 228–230° and was distinctly hygroscopic. It had $[\alpha]_D$ + 75°. A sample for analysis was recrystallized from absolute toluene.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 70.73; H, 8.78. Found: C, 71.03; H, 9.20.

Pregnanediol-20(α),21-dione-3,11 Diacetate (X) and Pregnanediol-20(β),21-dione-3,11 Diacetate (XI).—The 7.2 g. of crude hemisuccinate ("acid fraction," described above) was saponified by dissolving in a mixture of 150 cc. of methanol and 50 cc. of water containing 7.5 g. of potassium carbonate and 1.5 g. of sodium hydroxide. After standing overnight at room temperature, the solution was concentrated *in vacuo* to a small volume, the gummy precipitate taken up in chloroform, the chloroform solution washed with water and concentrated to dryness. The residual diol mixture weighed 5.17 g.

This product was dissolved in a mixture of 10 cc. of acetic anhydride and 10 cc. of pyridine and heated on the steam-bath for thirty minutes. Water was then added, the solvents removed *in vacuo* and the residue taken up in benzene, washed successively with dilute hydrochloric acid, dilute potassium carbonate and with water. Concentration of the benzene solution to a small volume, followed by addition of petroleum ether to turbidity gave 2.3 g. of a crystalline precipitate which melted at 166–177°. This product was taken up in benzene and chromatographed over a column of 40 g. of alumina (acid washed, activated at 150°). The fractions from absolute ether to 6:4 ether–chloroform gave pregnanediol-20(α),21-dione-3,11 diacetate (X) while the succeeding fractions gave IV. The fractions consisting of the diacetate X were combined and weighed 1.44 g. After recrystallization from ethyl acetate–petroleum ether this diacetate had m. p. 181°, $[\alpha]_D$ + 45°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; CH_3CO—, 19.9. Found: C, 69.42; H, 8.58; CH_3CO—, 18.1.

The diacetate mother liquors after separation of the 2.3 g. of X was diluted with petroleum ether and chromatographed. The fractions from 1:9 petroleum ether–ether to 6:4 ether–chloroform gave after several recrystallizations from ether and from dilute acetone 1.15 g. of pregnanediol-20(β),21-dione-3,11 diacetate (XI), m. p. 174.5–175.0°, $[\alpha]^{20}D$ + 74°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; CH_3CO—, 19.9. Found: C, 69.63; H, 8.53; CH_3CO—, 18.5.

Pregnanediol-20(α),21-dione-3,11 (VIII) and Pregnanediol-20(β),21-dione-3,11 (IX).—A solution of 500 mg. of pregnanediol-20(α),21-dione-3,11 diacetate (m. p. 181°) was treated with a solution of 300 mg. of potassium carbonate and 650 mg. of potassium bicarbonate in 10 cc. of water. The mixture was warmed for a few minutes to prevent crystallization of the diacetate and then permitted to stand at room temperature for twenty-two hours. The methanol was then removed *in vacuo* and the aqueous mixture extracted thrice with chloroform. The chloroform extracts were washed with water and concentrated to dryness *in vacuo*. The residue was recrystallized from acetone–ether and melted at 182–183°, $[\alpha]^{20}D$ + 68.5°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.25. Found: C, 72.39; H, 9.22.

Analogous saponification of a sample of pregnanediol-20(β),21-dione-3,11 diacetate (m. p. 174.5–175.0°) gave pregnanediol-20(β),21-dione-3,11 (IX), m. p. 167.5–168.0°, $[\alpha]^{20}D$ + 61.5°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.25. Found: C, 72.46; H, 9.28.

Pregnene-4-diol-20(α),21-dione-3,11 (XIV).—A solution of 703 mg. of pregnanediol-20(α),21-dione-3,11 diacetate (X) in 2.8 cc. of glacial acetic acid was treated with 276 mg. of bromine in 2.8 cc. of acetic acid. The mixture was permitted to stand at room temperature until decolorization ensued (two minutes) and was then poured into water. The bromoketone was extracted with chloroform, the chloroform solution was washed with bicarbonate and then with water and finally concentrated to dryness *in vacuo*. The colorless amorphous residue consisted of 4-bromo-pregnanediol-20(α),21-dione-3,11 diacetate (XII).

The crude bromoketone (840 mg.) was dissolved in 35 cc. of pyridine and the solution refluxed for ten hours. The pyridine was removed *in vacuo*, the residue taken up in chloroform, washed successively with dilute hydrochloric acid, dilute bicarbonate and water, then concentrated to dryness. The residue was dissolved in 5 cc. of benzene and then treated with 50 cc. of absolute ether. The flocculent precipitate was filtered and the filtrate concentrated to dryness. The residue was crystallized from a small volume of cold methanol, giving 203 mg. of

crude diacetate, m. p. 130–139°, contaminated with X. The product could not be readily purified by recrystallization or chromatography. Hence it was saponified by dissolving in 7 cc. of methanol and treating with a solution of 200 mg. of potassium carbonate and 300 mg. of potassium bicarbonate in 3 cc. of water. After standing at room temperature overnight, the mixture was concentrated *in vacuo* and the aqueous suspension then extracted with chloroform. The chloroform solution was washed with water and concentrated to dryness. The residue was almost entirely dissolved in 25 cc. of boiling water. The aqueous solution was decanted from small blobs of amorphous material and cooled. The crystals were filtered and the product recrystallized from water. A final recrystallization from acetone–ether gave 75 mg. of pregnene-4-diol-20(α),-21-dione-3,11 (XIV), m. p. 194–195°; $[\alpha]^{20}D$ + 176.5°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.78; H, 8.81. Found: C, 72.68, 73.05; H, 8.36, 8.68.

The pure diacetate (XIII) was prepared by warming the diol on the steam-bath with pyridine–acetic anhydride for fifteen minutes. It was recrystallized from dilute alcohol and had m. p. 153.5–154.5°, $[\alpha]^{20}D$ + 133°.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.66; H, 7.99; λ max. = 237.5 mμ; $E^{1}_{1\%}$ = 403.

Pregnene-4-diol-20(β),21-dione-3,11 Diacetate (XVIII) (Reichstein's Substance T Diacetate).—The bromination of 663 mg. of pregnanediol-20(β),21-dione-3,11 diacetate (XI) was carried out in the same manner as described for X. An amorphous bromoketone (XVII) was obtained which, after treatment with pyridine and removal of ether insoluble material, gave 418 mg. of crude product. This was recrystallized successively from ether, methanol (thrice) and finally from a small volume of acetone. The pure pregnene-4-diol-20(β),21-dione-3,11 diacetate (XVIII) so obtained had m. p. 207–208°, $[\alpha]^{20}D$ + 170°. Additional recrystallization from acetone or ethyl acetate failed to raise the melting point; λ max. = 237.5 m; $E^{1}_{1\%}$ = 357.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.95. Found: C, 69.74; H, 7.79.

Pregnene-4-diol-20(β),21-dione-3,11 (XIX) (Reichstein's Substance T).—The carbonate–bicarbonate saponification of XVIII was accomplished as described above for XIII. The pregnene-4-diol-20(β),21-dione-3,11 was purified by recrystallization from acetone and had m. p. 223.5–224.5°, $[\alpha]^{20}D$ + 176°. The substance was slightly hygroscopic and was dried at 130° for one hour before analysis.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.78; H, 8.81. Found: C, 73.41; H, 9.08.

Pregnene-4-diol-20(α),21-dione-3,11 Acetate-21 (XV).—A solution of 60 mg .of pregnene-4-diol-20(α),21-dione 3,11 in 1 cc. of absolute dioxane was concentrated to dryness *in vacuo* to remove moisture. The residue was dissolved in 0.42 cc. of absolute dioxane containing 23.6 mg. of dry pyridine and 27.4 mg. of redistilled acetic anhydride (1.31 moles). The mixture was allowed to stand at room temperature for sixty hours. The solvents were then removed *in vacuo*, the crystalline residue dissolved in a minimum volume of chloroform and then diluted with benzene and petroleum ether. The solution was then chromatographed over 1.5 g. of alumina. The fractions eluted with ether and 8.2 ether–chloroform consisted of diacetate. The subsequent fractions down to 2:8 ether–chloroform gave crystals of pregnene-4-diol-20(α),21-dione-3,11 acetate-21, which after recrystallization from acetone and then from methanol weighed 14 mg. and melted at 221–227°.

Pregnene-4-diol-20(β),21-dione-3,11 Acetate-21 (XX).—Pregnene-4-diol-20(β),21-dione-3,11 (90 mg.) was partially acetylated (1.21 moles of acetic anhydride) in the same manner as described above for XIV. The product was chromatographed and a total of 36 mg. of recrystallized monoacetate was obtained. It melted at 161.5–162.5°.

Pregnene-4-ol-21-trione-3,11,20 Acetate (Dehydrocorticosterone Acetate) (XVI). (a) From Pregnene-4-diol-20(β),21-dione-3,11 Acetate-21.—To a solution of 36 mg. of XX in 3.3 cc. of acetic acid was added a solution of 18 mg. of chromic acid in 0.33 cc. of acetic acid and 0.37 cc. of water. After standing at 18° for eighty minutes, the solution was treated with sufficient solid sodium sulfite to destroy the excess chromic acid and then concentrated to a small volume *in vacuo*. The addition of water gave 29.5 mg. of crystalline product, which after recrystallization from methanol melted at 182.5–183.5°. The mixed melting point with an authentic sample of dehydrocorticosterone acetate showed no depression; $[\alpha]^{20}D$ + 215 ± 3°; $\lambda_{max.}$ = 237.5 mμ, $E^{1}_{1\%}$ = 386.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.47; H, 7.83. Found: C, 71.20; H, 7.80.

(b) From Pregnene-4-diol-20(α),21-dione-3,11 Acetate-21.—The oxidation of XV (14 mg.) in a similar manner gave 11 mg. of dehydrocorticosterone acetate, m. p. 180–181.5°. A mixed melting point with an authentic sample gave no depression. Both samples of synthetic dehydrocorticosterone gave the characteristic heavy precipitate with Tollens reagent.

Pregnanediol-17,20-dione-3,11 (IV).—A suspension of 1.80 g. of pregnanediol-17,20-dione-3,11 acetate-20 in 180 cc. of methanol was treated with a solution of 1.8 g. of potassium bicarbonate and 0.9 g. of potassium carbonate in 30 cc. of water. The mixture was refluxed for forty-five minutes and the resulting solution then permitted to stand at room temperature for forty hours. The solution was concentrated *in vacuo* to a small volume, the oily precipitate taken up in chloroform, washed with water and concentrated to dryness. The residue was recrystallized several times from ethyl acetate and melted at 186–187°, $[\alpha]^{20}D$ + 47°. A sample recrystallized from acetone–ether was solvated and melted with decomposition at 150°. A sample for analysis was recrystallized from ethyl acetate and dried at 100° for two hours.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.25. Found: C, 72.69; H, 9.50.

Pregnanol-17-trione-3,11,20 (VI) and *etio*-Cholanetrione-3,11,17 (VII).—A solution of 300 mg. of pregnanediol-17,20-dione-3,11 in 30 cc. of acetic acid was treated dropwise with a solution of 150 mg. of chromic acid in 3 cc. of water. After standing at room temperature for three and one-half hours the mixture was treated with sufficient sodium sulfite to reduce the excess oxidizing agent and then concentrated to a small volume *in vacuo*. The residue was diluted with water and extracted with chloroform. The chloroform layer was washed with dilute sodium carbonate, then with water and concentrated to dryness *in vacuo*. The residue was chromatographed over 8 g. of acid washed alumina; the fractions from absolute ether to 1:1 ether–chloroform could all be crystallized by triturating with a few drops of warm water. These fractions were combined and crystallized from dilute methanol and then from ether. A total of 160 mg. of pure *etio*-cholanetrione-3,11,17, m. p. 134–135°, was obtained; $[\alpha]^{20}D$ + 155°. A mixed melting point with the *etio*-cholanetrione prepared by oxidation of *etio*-cholanol-3(α)-dione-11,17 (see below) showed no depression.

The chromatographic fractions from 1:1 ether–chloroform to pure chloroform were combined (78 mg.) and crystallized from ethyl acetate. Recrystallization from acetone–petroleum ether and dilute acetone gave pure pregnanol-17-trione-3,11,20, m. p. 204.5–205.5°, $[\alpha]^{20}D$ + 75°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.78; H, 8.81. Found: C, 72.64, 72.82; H, 8.51, 8.79.

***etio*-Cholanetrione-3,11,17 from *etio*-Cholanol-3(α)-dione-11,17.**—A solution of 19.5 mg. of *etio*-cholanol-3(α)-dione-11,17 in 2 cc. of acetic acid was treated with 10 mg. of chromic acid in 0.18 cc. of water. After standing at room temperature for one hour, the solution was treated with a little dilute sodium sulfite and concentrated to a small volume *in vacuo*. Water was added to turbidity and the mixture left in the icebox overnight. The crystalline product was separated and recrystallized from a small volume of cold dilute methanol. The long needles which were obtained melted at about 60°, apparently with loss of

solvent. Recrystallization from absolute ether gave pure material, m. p. 133.5–134.5°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.66. Found: C, 75.59; H, 8.70.

Pregnene-4-diol-17,20-dione-3,11 Acetate-20 (XXII).—A solution of 860 mg. of pregnanediol-17,20-dione-3,11 acetate-20 in a mixture of 3 cc. of chloroform and 3 cc. of acetic acid was treated with 370 mg. of bromine in 3 cc. of acetic acid. After a few minutes the bromine was consumed. The mixture was then poured into chloroform and washed successively with water, dilute potassium carbonate and again with water. The chloroform was removed *in vacuo*, leaving crude bromo ketone as a gel. Trituration with a small volume of absolute alcohol gave 709 mg. of 4-bromopregnanediol-17,20-dione-3,11 acetate-20 (XXI) which melted at 150–155° (loss of alcohol of crystallization).

This bromoketone was refluxed for eight hours with 20 cc. of pyridine. The product was worked up as usual (see above), and finally crystallized from a small volume of ether. A first crop of 189 mg. of prisms was obtained which melted at 194–200°. Recrystallization from benzene gave fluffy solvated crystals which melted at 104° (loss of solvent) and remelted at 215–218°. A final recrystallization from chloroform–ether gave unsolvated material, m. p. 219–220°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.09; H, 8.31. Found: C, 70.97; H, 8.02.

Pregnene-4-diol-17,20-dione-3,11 (XXIII).—A solution of 64 mg. of pregnene-4-diol-17,20-dione-3,11 acetate-20 in 5 cc. of methanol and 2 cc. of water containing 60 mg. of potassium bicarbonate and 100 mg. of potassium carbonate was permitted to stand at room temperature overnight. The solution was acidified with 3 drops of acetic acid, concentrated *in vacuo* and extracted with chloroform. The chloroform solution was washed with water and concentrated to dryness. The residue was triturated with a little water giving the crystalline hydrate. Two recrystallizations from water gave a product of m. p. 107–110° ($-H_2O$). For analysis the hydrate was dried in a weighing pig at 110° for two hours.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.78; H, 8.81. Found: C, 72.42; H, 8.61.

Adrenosterone from XXIII.—A solution of 90 mg. of crude pregnanediol-17,20-dione-3,11 (prepared by hydrolysis of 106 mg. of crude acetate of m. p. 201–211°) in 2 cc. of aqueous 80% methanol was treated with 100 mg. of periodic acid. After five hours the solution was diluted with water and extracted with chloroform. The washed chloroform extract was concentrated to dryness and the residue chromatographed. The fractions from absolute ether to 1:1 ether–chloroform were combined and recrystallized twice from alcohol. Adrenosterone was thus obtained in characteristic platelets, m. p. 219–221°. No depression was observed in admixture with an authentic sample.

Acknowledgment.—The author wishes to express his appreciation to Dr. Everett S. Wallis of Princeton University and to Dr. Karl Folkers and Dr. Randolph T. Major for their active association with this work.

Summary

Hydroxylation of a mixture of pregnene-17- and pregnene-20-dione-3,11 with osmium tetroxide gives both of the possible 20,21-glycols and one of the possible 17,20-glycols. From each of these compounds the corresponding $\Delta^{4,5}$-pregnene-diol-diones was prepared. Acetylation of the C-21 hydroxyl group in the 20,21-glycols followed by oxidation gave dehydrocorticosterone acetate.

RAHWAY, NEW JERSEY RECEIVED JULY 18, 1946

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Studies in Pyrane Chemistry

BY G. FORREST WOODS AND HERMAN SANDERS

It has been found that 2,3-dihydropyrane is the precursor of a number of very reactive and versatile substances. R. Paul[1] observed that 2,3-dihydropyrane reacts readily with bromine to yield 2,3-dibromotetrahydropyrane and that this latter substance is relatively unstable. For instance, distillation thereof yields in part 1,5-epoxy-2-bromo-1-pentene with the elimination of hydrogen bromide, while hydrolysis of this substance leads to the hemi-acetal of 2-bromo-5-hydroxypentanal which does not appear to form any carbonyl derivatives. In his latest report which had just been obtained[2] is described the reaction of 2,3-dihydropyrane with chlorine. The product of this reaction is 2,3-dichlorotetrahydropyrane. He also observed that 2,3-dichlorotetrahydropyrane reacts with methyl alcohol in the presence of sodium methylate to form 2-methoxy-3-chlorotetrahydropyrane.

This study concerns the reaction of 2,3-dibromotetrahydropyrane (I) with alcohol, and the products derivable therefrom. The difference in the reactivity of the two bromine atoms of this substance was most noticeable. Alcoholysis of the bromine atom on the carbon adjacent to the oxygen linkage was readily accomplished in cold alcohol–sodium alcoholate or alcohol saturated with dry ammonia. The product of this reaction was 2-alkoxy-3-bromotetrahydropyrane (II). Under these conditions the second bromine atom was completely inert.

The more drastic treatment of refluxing 2-alkoxy-3-bromotetrahydropyrane with alcoholic potassium hydroxide led to the elimination of a molecule of hydrogen bromide with the formation of the corresponding 2-alkoxy-Δ^3-dihydropyrane (III). Reduction of 2-ethoxy-Δ^3-dihydropyrane with Adams catalyst afforded 2-ethoxytetrahydropyrane (IV) which, since it is an acetal was readily cleaved by mild acid hydrolysis. That these structures were correct was shown by the identity of the 2,4-dinitrophenylhydrazone of the acid hydrolysis product of 2-ethoxytetrahydropyrane with the 2,4-dinitrophenylhydrazone

(1) R. Paul, *Bull. soc. chim.*, [5] **1**, 1307 (1934).

(2) R. Paul, *Comp. rend.*, **218**, 122 (1944); *C. A.*, **40**, 2447 (1946).