Rotation.—0.0702 g. made up to 2.0 ml. with 95% ethanol at 35°: $\alpha^{35}D$ +1.3246°, *l* 1, $[\alpha]^{35}D$ +37.74°.

Dihydromonocrotaline Sulfite Hydrochloride (IX, as Hydrochloride).—A solution of 2.040 g. of monocrotaline sulfite hydrochloride in 65 ml. of 95% ethanol (distilled from Raney nickel) over 0.350 g. of catalyst consumed 108.6 ml. (S.T.P.) of hydrogen at an essentially constant rate of about 10 ml. (S.T.P.) per minute until the reduction stopped completely; required for one mole equivalent of hydrogen, 112.0 ml. (S.T.P.). The product was obtained in essentially quantitative yield as an oil which solidified upon trituration with anhydrous ether. After recrystallization from ethanol–ether it formed colorless needles, m.p. 185.8–186.2° (dec.).

Anal. Calcd. for $C_{16}H_{23}NO_7S \cdot HCl$: C, 46.88; H, 5.90; N, 3.42; S, 7.82. Found: C, 46.94; H, 5.88; N, 3.49; S, 7.64.

Rotation.—0.0701 g. made up to 2.0 ml. with 95% ethanol at 35°: $\alpha^{35}D$ −1.1125°, *l* 1; $[\alpha]^{35}D$ −31.74°.

Dihydromonocrotaline Sulfite (IX).—The reduction of a solution of 1.000 g. of monocrotaline sulfite in 25 ml. of ethanol over 0.150 g. of catalyst was stopped after one mole equivalent (60.3 ml., S.T.P.) had been consumed. The rate had decreased from about 5 ml./minute to less than 0.2 ml./minute and a trial run had shown that hydrogen would be absorbed at a decreasing rate until about two and one-half equivalents had been consumed. At this point the catalyst is apparently poisoned by traces of hydrogen sulfide arising from reduction of the sulfite ester group. The reduction product after one mole equivalent of hydrogen was absorbed was obtained as a crystalline solid after trituration with acetone. Upon recrystallization from ethanol–ether it formed long felted needles, m.p. 169.5–170° (dec.).

Anal. Calcd. for $C_{16}H_{23}NO_7S$: C, 51.46; H, 6.21; N, 3.75; S, 8.59. Found: C, 51.41; H, 6.39; N, 3.77; S, 8.86.

Rotation.—0.0713 g. made up to 2 ml. with water at 26°: $\alpha^{26}D$ +0.8450, *l* 1; $[\alpha]^{26}D$ +23.73°.

Lead Tetraacetate Oxidation of Monocrotaline.—A slurry of 3.25 g. of monocrotaline in 8 ml. of glacial acetic acid was treated with 4.35 g. (10% excess) of lead tetraacetate over a 5-minute period with external cooling to maintain the temperature below 15°. After standing at room temperature for 2 hours the reaction mixture was diluted with a solution of 1.5 g. of ammonium sulfate in 15 ml. of water and the precipitated lead sulfate removed by filtration. A solution of 1.81 g. of *o*-phenylenediamine dihydrochloride in 4 ml. of water was added to the filtrate and after about one minute 2-hydroxy-3-methylquinoxaline precipitated as fine matted needles; yield 1.3 g. (80%). The derivative was recrystallized from dilute acetic acid after preliminary treatment with Darco, m.p. 250.4–251.4°, not depressed upon admixture with an authentic sample, m.p. 250.8–251.4°, prepared from methyl pyruvate and *o*-phenylenediamine dihydrochloride in dilute aqueous acetic acid (reported m.p. 245°).[12]

Anal. Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.04; N, 17.49. Found: C, 67.24; H, 4.99; N, 17.55.

(12) O. Hinsberg, *Ann.*, **292**, 245 (1896).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. XXXVIII.[1] Synthesis of Allopregnane-3,11,20-trione-17α,21-diol (Dihydroallocortisone) from Allopregnan-3β-ol-11,20-dione

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Allopregnan-3β-ol-11,20-dione (Ia), the key intermediate of all the hitherto described C-11 oxygen introduction methods of plant steroids, was converted into allopregnane-3β,17α-diol-11,20-dione (Ib), by formation of the enol acetate followed by perbenzoic acid oxidation and saponification. Alternately, Δ^{16}-allopregnen-3β-ol-11,20-dione acetate (III) was transformed into the epoxide IV and thence by hydrogen bromide opening and debromination of the intermediate bromohydrin to the 17α-hydroxy derivative Ib. Bromination of Ib produced the 21-bromo compound Ic which upon treatment with potassium acetate led to allopregnane-3β,17α,21-triol-11,20-dione 21-acetate (Id) (Reichstein's Compound D monoacetate). Oxidation with N-bromoacetamide furnished the desired "dihydroallocortisone acetate (II)."

All of the recently described syntheses of cortisone from plant steroids (diosgenin,[3,4] ergosterol,[3] stigmasterol[3,4] and hecogenin[5]) proceed through allopregnan-3β-ol-11,20-dione (Ia). The further transformations of this substance to allopregnane-3,11,20-trione-17α,21-diol acetate (II) (dihydroallocortisone acetate) have been recorded in two recent Communications to the Editor[6,7] and the present paper is concerned with the description of the experimental details of this reaction sequence.

The introduction of the requisite 17α-hydroxy group into Ia was accomplished by two procedures. In the first, the 11,20-dione (Ia) was converted into the enol acetate which without isolation was oxidized with perbenzoic acid and saponified according to the general procedure of Kritchevsky and Gallagher[8] yielding allopregnane-3β,17α-diol-11,20-dione (Ib) without isolation of intermediates. The same reaction with isolation of intermediates has recently been recorded[9] in the case of pregnan-3α-ol-11,20-dione. The second synthesis of Ib involved an adaptation of Julian's method[10] to Δ^{16}-allopregnen-3β-ol-11,20-dione acetate (IIIb) which is the immediate degradation product[3,11] of 22a-5α-spirostan-3β-ol-11-one. Oxidation with alkaline hydrogen peroxide and reacetylation led to the oxide IV which was transformed with hydrogen bromide to the bromohydrin and directly debrominated with Raney nickel to afford after saponification allopregnane-3β,17α-diol-11,20-dione (Ib) identical

(1) Paper XXXVII, O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 3711 (1952).

(2) Department of Chemistry, Wayne University, Detroit, Michigan.

(3) E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951).

(4) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951).

(5) C. Djerassi, H. J. Ringold and G. Rosenkranz, *ibid.*, **73**, 5513 (1951).

(6) J. M. Chemerda, E. M. Chamberlain, E. H. Wilson and M. Tishler, *ibid.*, **73**, 4052 (1951).

(7) G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, **73**, 4055 (1951).

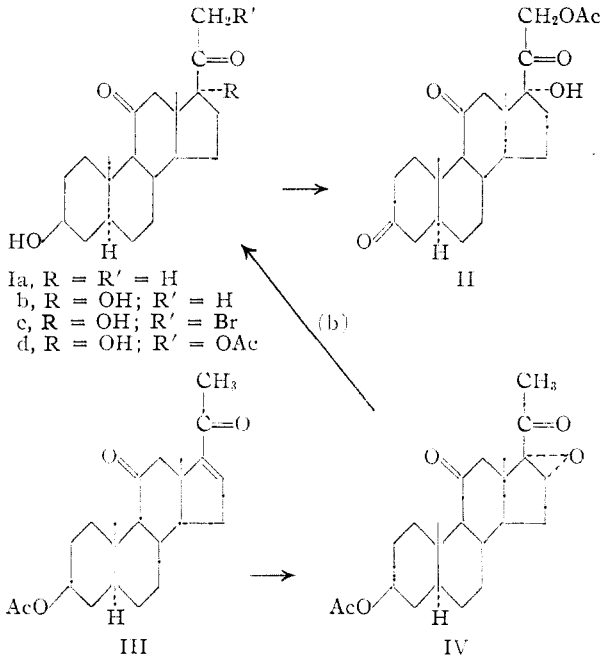
(8) T. H. Kritchevsky and T. F. Gallagher, *ibid.*, **73**, 184 (1951).

(9) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *ibid.*, **74**, 483 (1952).

(10) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

(11) C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *ibid.*, **74**, 3634 (1952).

with the product obtained by the first synthesis. Bromination at C-21 followed by iodide exchange and acetolysis[12] yielded allopregnane-3β,17α,21-triol-11,20-dione 21-monoacetate (Id), which was



identified with Reichstein's Compound D[13] through the 3,21-diacetate.[14] The above sequence of reactions constitutes the first partial synthesis of Reichstein's Compound D. The last step, oxidation of Reichstein's Compound D monoacetate (Id), was best accomplished by means of excess N-bromoacetamide in pyridine solution and the resulting "dihydroallocortisone acetate" (II) proved to be identical with an authentic sample prepared by catalytic hydrogenation[15] of cortisone acetate.

Experimental[16]

Allopregnane-3β,17α-diol-11,20-dione (Ib). (a) From Allopregnan-3β-ol-11,20-dione (Ia).—Allopregnan-3β-ol-11,-20-dione[4] (1.3 g.) was converted in the usual manner[8,9] (75 cc. of acetic anhydride, 0.75 g. of *p*-toluenesulfonic acid monohydrate, 4 hours) into the oily enol acetate (1.55 g.) which without isolation was treated directly with 30 cc. of a 0.246 *M* solution of perbenzoic acid in chloroform for 18 hours at room temperature at which point 1.2 equivalents of peracid had been consumed. The solution was diluted with ether, washed with sodium iodide solution, sodium thiosulfate solution, water, dried and evaporated. The residue was hydrolyzed by warming it at 50° for 1 hour with 1.5 g. of sodium hydroxide and 100 cc. of 80% methanol and the product was isolated by neutralization with acetic acid, concentration *in vacuo* to 20 cc., and dilution with a large volume of water. Recrystallization from acetone afforded colorless crystals with m.p. 272–274°, $[\alpha]^{20}D$ +67° (dioxane),[17] λ_{max}^{nujol} 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.44; H, 9.46.

(b) **From Δ16-Allopregnen-3β-ol-11,20-dione Acetate (III).**—To a cooled solution of 2.47 g. of III[11] in 300 cc. of methanol was added with stirring simultaneously from two dropping funnels 6 cc. of 30% hydrogen peroxide and 20 cc. of 5% sodium hydroxide solution and the mixture was kept in the ice-box for 20 hours. After addition of water, the precipitate was collected and directly acetylated by heating on the steam-bath for 1 hour with 10 cc. of pyridine and 5 cc. of acetic anhydride. Dilution with water, filtration and recrystallization from methanol furnished 2.03 g. of **16α,17α-oxidoallopregnan-3β-ol-11,20-dione acetate (IV)** with m.p. 236–238°, $[\alpha]^{20}D$ +72°, no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.37; H, 8.38.

A solution of 1.5 g. of the epoxide IV in 60 cc. of glacial acetic acid was treated for 15 minutes at 15° with 2.3 cc. of a 32% solution of hydrogen bromide in acetic acid and then diluted with water. The bromohydrin was filtered, air-dried at room temperature and then was refluxed for 5 hours in 60 cc. of ethanol with 20 g. of W-2 Raney nickel catalyst. After filtration of the catalyst, the filtrate was evaporated to dryness and the residue was recrystallized from methanol yielding 1.05 g. of **allopregnane-3β,17α-diol-11,20-dione 3-acetate** with m.p. 171–173°, $[\alpha]^{20}D$ +8°, $\lambda_{max}^{CHCl_3}$ 1720 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 70.74; H, 8.78. Found: C, 70.89; H, 8.83.

Alkaline saponification (1 hour refluxing with 1% methanolic sodium hydroxide solution) of the acetate proceeded in nearly quantitative yield and furnished the diol Ib with m.p. 273–274°, undepressed upon admixture with a specimen prepared according to (a), $[\alpha]^{20}D$ +63° (dioxane).

Allopregnane-3β,17α,21-triol-11,20-dione 21-Acetate (Reichstein's Compound D Monoacetate) (Id).—A solution of 1.5 g. of the diol Ib in 500 cc. of C.P. chloroform[18] was treated slowly at room temperature with a solution of 0.75 g. of bromine in 35 cc. of chloroform. Decolorization was complete after 25 minutes at which time the solution was washed well with dilute sodium bicarbonate, water, dried and evaporated. Trituration with ether afforded 1.2 g. of the **21-bromo derivative Ic** with m.p. 242–244° (dec.), $[\alpha]^{20}D$ +73° (dioxane) which was allowed to stand at room temperature for 30 minutes in 150 cc. of acetone with 2.0 g. of sodium iodide. The precipitated sodium bromide was filtered and the clear solution was refluxed for 8 hours with a mixture[12] of 30 g. of potassium bicarbonate and 18.5 cc. of glacial acetic acid. After concentration and dilution with water, the product was extracted with ethyl acetate, washed with sodium thiosulfate solution and water, dried and evaporated. Two recrystallizations from hexane–acetone furnished 0.8 g. of colorless crystals of Id with m.p. 235–237°, $[\alpha]^{20}D$ +66° (acetone).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.22; H, 8.73.

Allopregnane-3,11,20-trione-17α,21-diol 21-Acetate (Dihydroallocortisone Acetate) (II).—A solution of 200 mg. of the 21-monoacetate Id in 4 cc. of pyridine containing 68 mg. of N-bromoacetamide was allowed to stand at room temperature for 16 hours at which time a copious precipitate had formed. Filtration and washing with acetone yielded 170 mg. with m.p. 230–233°. One additional recrystallization raised the m.p. to 234–236°, undepressed upon admixture with a specimen prepared[15] from cortisone acetate, $[\alpha]^{20}D$ +78° (acetone), +89° (chloroform). The infrared spectrum was identical with that of an authentic sample.[15]

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.13; H, 7.63.

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(13) J. v. Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 1009 (1942).

(14) St. Kaufmann and J. Pataki, *Experientia*, **7**, 260 (1951).

(15) C. Djerassi, G. Rosenkranz, J. Pataki and St. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952.)

(16) Melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform solution. We are grateful to Srta. Paquita Revaque for the rotations and infrared spectra (Perkin-Elmer model 12C single beam spectrometer) and to Srta. Amparo Barba for the microanalyses. Thanks are due to Srta. Josefina Gatica for technical assistance.

(17) In the preliminary communication (ref. 7), the rotation was given by mistake as $[\alpha]^{20}D$ +76° rather than +67°.

(18) The use of chloroform as solvent in the bromination of steroids containing an unprotected 3-hydroxy group was introduced first by B. A. Kocchlin, T. H. Kritchevsky and T. F. Gallagher, THIS JOURNAL, **73**, 180 (1951).