pared from 70 g. of nitrosomethylurea.[27] After standing one hour in an ice-bath and one hour at room temperature, the solution was concentrated *in vacuo* to about two-thirds volume. The benzene solution was washed successively with small amounts of water, 1% sodium bicarbonate, water, 1% acetic acid, and water, with no significant loss of activity. The benzene was removed *in vacuo* leaving 56.98 g. of a solvent-free oil containing essentially all the activity. Bioautographs[15] confirmed the presence of the ester and the absence of free acid.

This ester (60.7 g.) was slurried in a minimal amount of *n*-heptane and introduced onto a column (8-cm. diameter) prepared from a slurry of 2400 g. activated alumina[2] in *n*-heptane. The bulk of the solids was eluted with increasing amounts of benzene in heptane. At a concentration of 50% benzene in heptane the activity was eluted.

Crystallization of Synthetic DL-α-Lipoic Acid.—The most potent of the alumina column fractions were pooled, and the solvent removed *in vacuo*. The oil was suspended in 500 ml. of 0.1 *N* potassium hydroxide and shaken continuously in an atomosphere of nitrogen for 16 hours at 25°. The alkaline solution was washed with 150 ml. of low-boiling petroleum ether in two portions. No activity was removed. The alkaline solution was acidified to *p*H 1, by adding 10 ml. of 6 *N* sulfuric acid, and extracted with 400 ml. of benzene in five portions. After washing with 25 ml. of water, the benzene contained 236,000,000 units. Evaporation *in vacuo* gave 2.485 g. of solvent-free yellow oil. The oil was extracted by slurrying with several small (10-ml.) portions of hot low-boiling petroleum ether, leaving a residue of 204 mg. of insoluble oil. The extract (50 ml.) was allowed to cool slowly. The resulting small yellow platelets (1.400 g.) were collected and dried. The mother liquor contained 910 mg. of a non-crystallizable oil. After two recrystallizations from low-boiling petroleum ether the product melted at 59–60° (cor.) and possessed one-half the biological activity on a weight basis of α-lipoic acid from natural sources.

The usual over-all yield to crystalline DL-α-lipoic acid (based on the crude bromolactone) was about 4%.

URBANA, ILLINOIS

(27) F. Arndt, *Org. Syntheses*, **2**, 461 (1948).

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

Steroids. XLI.[1] Synthesis of 11α,17α-Dihydroxyprogesterone and of 11α,17α,21-Trihydroxyprogesterone, the 11-Epimer of Kendall's Compound F[2]

BY J. ROMO, G. ROSENKRANZ, CARL DJERASSI[3] AND FRANZ SONDHEIMER

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Δ^{16}-Allopregnene-3β,11α-diol-20-one 3,11-diacetate (I) is converted by a nine-step synthesis to 11α,17α-dihydroxyprogesterone (Vb), and by a ten-step synthesis to 11α,17α,21-trihydroxyprogesterone (XII), the 11-epimer of Kendall's Compound F.

In view of the biological importance of 11β-hydroxylated hormones of the adrenal cortex, such as 11β,21-dihydroxyprogesterone (corticosterone) and 11β,17α,21-trihydroxyprogesterone (Kendall's compound F),[4] it was felt to be of interest to synthesize the 11α-hydroxy analogs of the various adrenal hormones in order to make them available for biological testing as hormone substitutes or antagonists. These compounds have very recently taken on special importance since they have been shown to be produced by the microbiological oxidation of the corresponding 11-desoxy derivatives.[5]

The chemical synthesis of 11α-hydroxyprogesterone, through the use of recently discovered methods[6] for the introduction of the 11α-hydroxy group into ring C unsubstituted steroids, has already been recorded.[7] We now wish to describe the synthesis of two more complex hormone analogs, that of 11α,17α-dihydroxyprogesterone (Vb), the 11α-hydroxy analog of 17α-hydroxyprogesterone,[8] and that of 11α,17α,21-trihydroxyprogesterone (XII),[9] the 11-epimer of Kendall's compound F.

The starting point for these syntheses was Δ^{16}-allopregnene-3β,11α-diol-20-one 3,11-diacetate (I), which has recently been obtained[10] by the side degradation of 22a-5α-spirostane-3β,11α-diol; the latter in turn had been derived from "diosgenin." Oxidation of I with alkaline hydrogen peroxide smoothly yielded the free 16α,17α-oxidoallopregnane-3β,11α-diol-20-one (IIb) as a low melting solid. It has already been shown[7] that a 3β,11α-diol of the 5α (allo) series may be preferentially oxidized at C-3 either with N-bromoacetamide or by the Oppenauer method, and the glycol IIb was oxidized by the latter procedure. The resulting 16α,17α-oxidoallopregnan-11α-ol-3,20-dione (IIIb), obtained in 75% yield, was acetylated at C-11 to furnish the acetate IIIa. Conversion of the latter to the bromohydrin with hydrogen bromide in

(1) Paper XL, F. Sondheimer and G. Rosenkranz, *Experientia*, in press.

(2) Presented in part at the Atlantic City Meeting of the American Chemical Society, Sept., 1952. A preliminary announcement of part of this work has appeared in *Chemistry and Industry*, 783, 834 (1952).

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

(4) *Cf.* H. Reich, D. H. Nelson and A. Zaffaroni, *J. Biol. Chem.*, **187**, 411 (1950).

(5) (a) D. H. Peterson and H. C. Murray, THIS JOURNAL, **74**, 1871 (1952); (b) O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 3711 (1952); (c) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, *ibid.*, **74**, 3962 (1952).

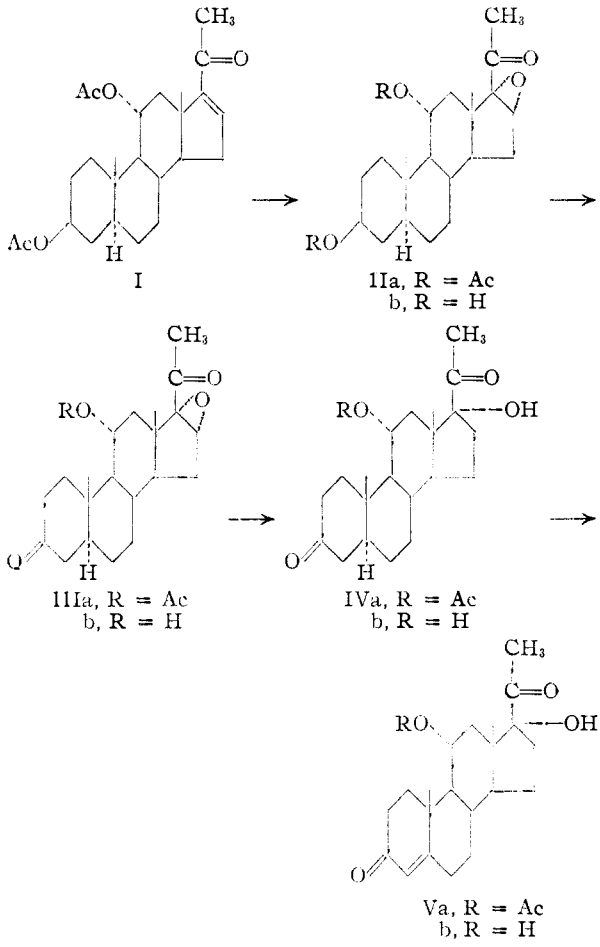
(6) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951); C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *ibid.*, **74**, 1712 (1952); F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952); C. Djerassi, O. Mancera, M. Velasco, G. Stork and G. Rosenkranz, *ibid.*, **74**, 3321 (1952).

(7) O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, 1066 (1952).

(8) J. J. Pfiffner and H. B. North, *J. Biol. Chem.*, **132**, 459 (1940); **139**, 855 (1941).

(9) After our work had been completed (*cf.* footnote 2), a preliminary communication by H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg (THIS JOURNAL, **74**, 4471 (1952)) appeared, in which an independent and different synthesis of the 11,21-diacetate of this compound is described, proceeding *via* intermediates of the 5β (normal) series. Moreover A. Lardon and T. Reichstein at the Colloquium on the "Synthesis and Metabolism of Adrenal Cortical Steroids" sponsored by the Ciba Foundation, London (July 7–10, 1952) announced the conversion of sarmentogenin to the 11,21-diacetate of XII, a synthesis which also proceeded *via* 5β (normal) compounds. This conversion has now been published (*Pharm. Acta Helv.*, **27**, 287 (1952)).

(10) C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, THIS JOURNAL, **74**, 3634 (1952).



acetic acid, followed by hydrogenolysis over a palladium-calcium carbonate catalyst (the Kendall[11] modification of the Julian[12] 17α-hydroxyl introduction) readily yielded the corresponding 17α-hydroxy compound, allopregnane-11α,17α-diol-3,20-dione 11-acetate (IVa), which could be saponified to the free glycol IVb. The double bond introduction into the monoacetate IVa was effected by the now standard method[13] of 2,4-dibromination with bromine in acetic acid, followed by treatment with sodium iodide and then with chromous chloride. The 11α,17α-dihydroxyprogesterone 11-acetate (Va) thus obtained was saponified with potassium carbonate to the free glycol Vb. The latter was alternatively obtained directly from the free "dihydroallo" glycol IVb by the above described double bond introduction, with the modification that the 2,4-dibromination was carried out in chloroform solution so as to prevent acetylation at C-11. The physical properties of 11α,17α-dihydroxyprogesterone (Vb) and of its 11-acetate (Va), were in good agreement with those reported[5c] for the microbiological products.

For the synthesis of the 11,21-diacetate (Xa) of 11α,17α,21-trihydroxyprogesterone, the above-described 16α,17α-oxidoallopregnane-3β,11α-diol-20-one (IIb) was reacetylated, and the resulting diacetate IIa was converted *via* the bromohydrin to the 17α-hydroxy compound by the method indicated above for the corresponding 3-ketone. The allopregnane-3β,11α,17α-triol-3,11-diacetate (VIa) thus produced in 83% yield proved to be identical with that prepared previously[10] by application of the Gallagher[14] enol acetate–peracid method to allopregnane-3β,11α-diol-20-one diacetate (obtained by the hydrogenation of I). Monobromination of VIa with bromine in acetic acid gave a crude 21-bromide, which without purification was transformed to the iodo-compound with sodium iodide, and thence with potassium acetate[15] into allopregnane-3β,11α,17α,21-tetrol-20-one 3,11,21-triacetate (VIIa).

It has recently been shown in these laboratories[7] that the diacetate of a 3β,11α-diol of the 5α series may be preferentially saponified at C-3 by means of a relatively small excess of potassium bicarbonate with heating. We have now found that this type of preferential reaction may be carried out more simply by means of excess potassium hydroxide at room temperature. When the triacetate VIIa was subjected to these latter conditions, only the 3- and 21-acetate groupings were affected, and the 11-monoacetate VIIb was obtained smoothly. Oxidation of the latter with N-bromoacetamide in aqueous *t*-butanol at 10° (*cf.* footnote 14c) followed by acetylation at C-21 then yielded allopregnane-11α,17α,21-triol-3,20-dione 11,21-diacetate (IXa). The Δ^4-double bond introduction into this compound was carried out by the method indicated above for the preparation of Va, but the final deiodination was carried out with sodium bisulfite. The 11α,17α,21-trihydroxyprogesterone 11,21-diacetate (Xa) thus obtained was found to be capable of existing in several polymorphic forms. The highest melting form agreed well in properties with those reported by the Schering group,[9] but only reasonably so with the microbiological product.[5c]

Since it was found that the final diacetate Xa could not easily be saponified to the free triol XII, the latter was prepared by the following route. The free epoxide IIb was subjected to the bromohydrin–palladium reduction method, and the resulting allopregnane-3β,11α,17α-triol-20-one (VIb) was monobrominated in chloroform solution. The crude 21-bromide was transformed by the successive action of sodium iodide and potassium acetate to allopregnane-3β,11α,17α,21-tetrol-20-one 21-monoacetate (VIIc), the structure of which was confirmed through chromium trioxide oxidation to the 3,11,20-triketone, "dihydroallocortisone" acetate (VIII), identical with an authentic specimen,[16] and through acetylation to the triacetate VIIa. On oxidation of VIIc with N-bromoacetamide in aqueous *t*-butanol, only the hydroxyl group at C-3 was affected (*cf.* footnote 7) and allopregnane-11α,17α,21-triol-3,20-dione 21-acetate (IXb) was formed. The Δ^4-double bond introduction was

(11) F. B. Colton, W. R. Nes, D. A. van Dorp, H. L. Mason and E. C. Kendall, *J. Biol. Chem.*, **194**, 235 (1952).

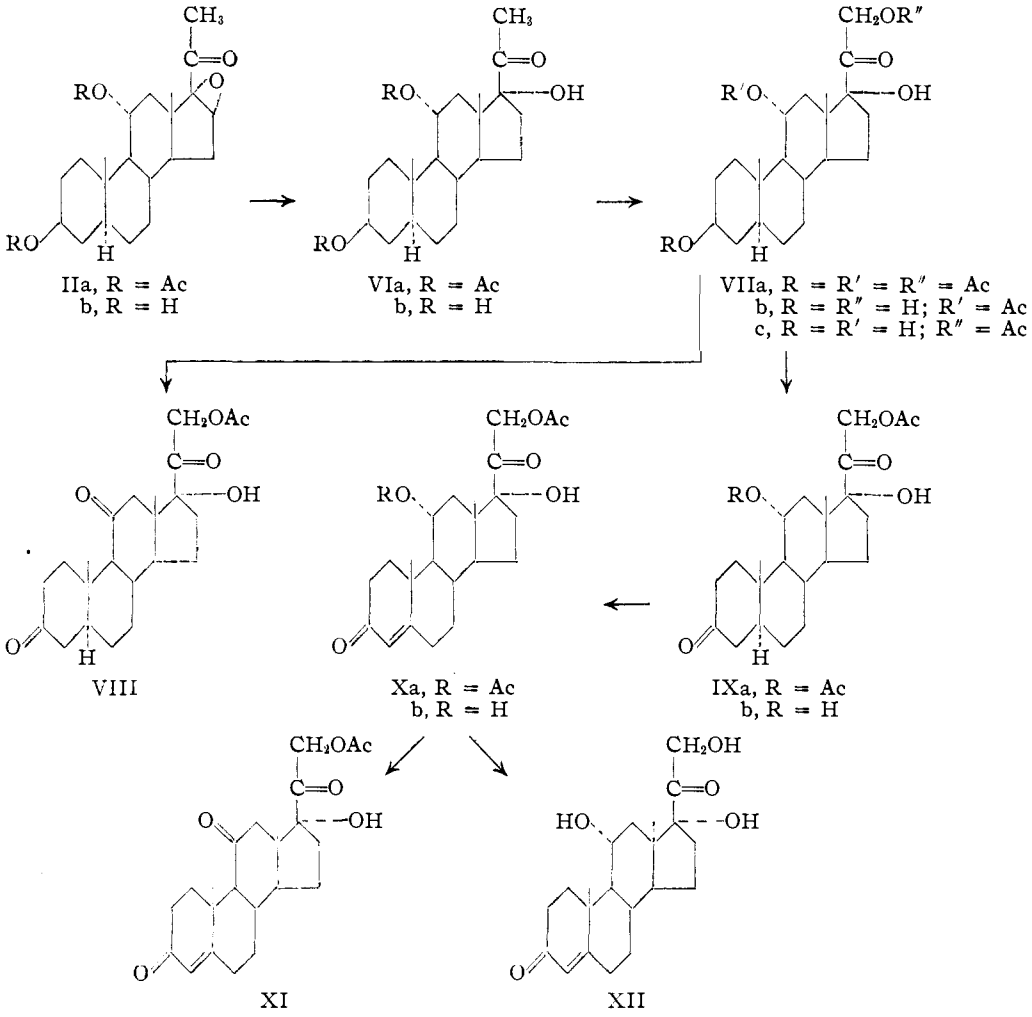
(12) P. L. Julian, E. W. Meyer, W. J. Karpel, *et al.*, THIS JOURNAL, **71**, 3574 (1949); **72**, 5145 (1950).

(13) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *ibid.*, **72**, 1077 (1950).

(14) (a) T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949); (b) THIS JOURNAL, **73**, 184 (1951); (c) **74**, 483 (1952).

(15) *Cf.* G. Rosenkranz, J. Pataki, S. Kaufmann, J. Berlin and C. Djerassi, *ibid.*, **72**, 4081 (1950).

(16) *Inter al.* C. Djerassi, G. Rosenkranz, J. Pataki and S. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952).



effected in the same way as with the 11-acetate IXa, except that the initial 2,4-dibromination was again carried out in chloroform solution so as to prevent acetylation at C-11. The 11α,17α,21-trihydroxyprogesterone 21-monoacetate (Xb) obtained in this way exhibited an indefinite melting point, but its structure was confirmed through acetylation to the above described diacetate Xa, and especially through the ready oxidation by means of chromium trioxide to cortisone acetate (XI).[17] Finally, on saponification with potassium bicarbonate, the monoacetate Xb yielded the free triol XII with physical properties in good agreement with those of the microbiological product,[5c] and identified by direct comparison with a specimen synthesized by an independent route.[18]

The compounds Vb and XII as well as 11α,21-dihydroxyprogesterone, the 11-epimer[19] of corticosterone, are being tested biologically and the results will be reported elsewhere.

(17) After completion of this work, Fried, *et al.*,[5c] independently reported the obtention of cortisone acetate through chromium trioxide oxidation of the monoacetate Xb. The latter had been prepared by the monoacetylation of XII (obtained microbiologically) but unfortunately no physical properties were given.

(18) F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL **75**, 1272 (1953).

(19) This compound has been synthesized by methods similar to those described above (O. Mancera, G. Rosenkranz, C. Djerassi and F. Sondheimer, to be published).

Experimental[20]

16α,17α-Oxidoallopregnane-3β,11α-diol-20-one (IIb).—To a stirred solution of 3 g. of Δ^{16}-allopregnene-3β,11α-diol-20-one diacetate[10] (I) in methanol (100 cc.), cooled in an ice-bath, was added dropwise simultaneously from two separatory funnels 6 cc. of 30% hydrogen peroxide and a solution of 4 g. of sodium hydroxide in 15 cc. of water, over the course of 15 minutes. After being cooled for another 30 minutes, the solution was set aside at room temperature overnight. It was diluted with water, extracted with chloroform, and the dried and evaporated extract was refluxed for 1 hour with a solution of potassium hydroxide (2 g.) in water (10 cc.) and methanol (150 cc.). Addition of water, extraction with chloroform and evaporation gave the diol IIb as an oil (2.2 g., 88%) which only slowly solidified. The analytical sample was crystallized from aqueous methanol and exhibited m.p. 98–100°, $[\alpha]^{20}D$ +30°, $\lambda_{max}^{CHCl_3}$ 1708 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.02; H, 9.03.

The diacetate IIa was prepared as above, but instead of being saponified, the residue after the peroxide oxidation was acetylated with pyridine (8 cc.) and acetic anhydride (8 cc.) for 1 hour on the steam-bath. It was obtained in 96% yield, and after crystallization from ether–pentane had m.p. 173–175°, $[\alpha]^{20}D$ ±0°, λ_{max}^{mull} 1720 and 1700 cm.$^{-1}$.

(20) All melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque for these measurements as well as for the infrared spectra, which were obtained on a Perkin–Elmer model 12C spectrometer with sodium chloride prism. Thanks are due to Srta. Amparo Barba and staff for the microanalyses.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.71; H, 8.68.

In earlier experiments this diacetate had m.p. 73–76°, and this proved to be an unstable polymorphic form.

16α,17α-Oxidoallopregnan-11α-ol-3,20-dione (IIIb).—A solution of 6 g. of the diol IIb (crude, uncrystallized) in 100 cc. of toluene was concentrated to 80 cc., cyclohexanone (60 cc.) was added, and 20 cc. was again distilled off. This solution together with 5 g. of aluminum isopropoxide in 25 cc. of toluene was refluxed for 45 minutes and then washed with dilute hydrochloric acid. The organic layer was distilled with steam, the residue extracted with ether, and the dried extract was evaporated. Crystallization from acetone–hexane yielded 4.5 g. (75%) of the dione IIIb with m.p. 195–197°. The analytical sample had m.p. 201–203°, $[\alpha]^{20}D$ +49°, $\lambda_{max}^{CHCl_3}$ 1710 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.80; H, 8.68.

The acetate IIIa (acetic anhydride–pyridine 1 hour, steam-bath) was crystallized from acetone–hexane and had m.p. 170–172°, $[\alpha]^{20}D$ +32°, $\lambda_{max}^{CHCl_3}$ 1720 and 1704 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.34; H, 8.45.

Allopregnane-11α,17α-diol-3,20-dione 11-Acetate (IVa).—To a solution of the above acetate IIIa (3.0 g.) in acetic acid (40 cc.) was added 2 cc. of acetic acid previously saturated with hydrogen bromide. The solution was allowed to stand at room temperature for 30 minutes and was then poured into ice-water. The solid product was collected, washed well with water, dissolved in 100 cc. of ethanol and shaken in hydrogen together with 6 g. of a 1.5% palladium-calcium carbonate catalyst for 16 hours. Removal of catalyst and solvent followed by crystallization of the residue from acetone–hexane gave 2.03 g. (67%) of IVa, m.p. 196–198°, $[\alpha]^{20}D$ −7°, $\lambda_{max}^{CHCl_3}$ 1724 and 1704 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.58; H, 9.08.

The free diol IVb was obtained by refluxing the acetate IVa (200 mg.) with potassium carbonate (400 mg.) dissolved in water (20 cc.) and methanol (50 cc.) for 1 hour. It had m.p. 228–230°, $[\alpha]^{20}D$ +5°, $\lambda_{max}^{CHCl_3}$ 1710 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.18; H, 9.15.

Δ^4-Pregnene-11α,17α-diol-3,20-dione (11α,17α-Dihydroxyprogesterone) (Vb). (a) From the Acetate IVa.—A solution of 0.90 g. (2.2 equivalents) of bromine in 10 cc. of glacial acetic acid was added dropwise during 10 minutes to a solution of 1.0 g. of the 11-monoacetate IVa in 20 cc. of acetic acid containing 8 drops of 4 *N* hydrogen bromide in acetic acid. The color was discharged rapidly. After 4 hours at room temperature, the mixture was poured into ice-water and the precipitated dibromo compound was collected, washed well with water, and dried. This product was refluxed for 20 hours with sodium iodide (5 g.) in dry acetone (80 cc.), and was then diluted with water. The product was extracted with ether, and this extract was washed with sodium thiosulfate solution and water, dried and evaporated under reduced pressure. The crude residue (λ_{max} 242 mμ, log ε 4.04), dissolved in 40 cc. of acetone, was treated in a carbon dioxide atmosphere with a solution of chromous chloride prepared[13] from 5 g. of chromic chloride. After 10 minutes at room temperature, water was added, and the product was extracted with ether. Chromatographic purification of the residue (λ_{max} 240 mμ, log ε 4.11) on alumina and crystallization of the fractions eluted with benzene–ether (3:1) from acetone–ether yielded 80 mg. of 11α,17α-dihydroxyprogesterone 11-monoacetate (Va), m.p. 204–206°. Further crystallization gave the analytical specimen, m.p. 206–208°, $[\alpha]^{20}D$ +72°, λ_{max} 240 and 296 mμ, log ε 4.25 and 2.22, respectively, $\lambda_{max}^{CHCl_3}$ 1728, 1704 and 1670 cm.$^{-1}$ and free hydroxyl band; reported for the microbiological oxidation product[5c]: m.p. 205–208°, $[\alpha]^{24}D$ +65°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.78; H, 8.59.

The free 11α,17α-dihydroxyprogesterone (Vb) was obtained by refluxing the 11-acetate (90 mg.) in methanol (20 cc.) with potassium carbonate (200 mg.) in water (10 cc.) for 1 hour. It exhibited m.p. 216–218°, $[\alpha]^{20}D$ +88°, λ_{max} 242 mμ, log ε 4.19, $\lambda_{max}^{CHCl_3}$ 1704 and 1660 cm.$^{-1}$ and free hydroxyl band; reported for the microbiological oxidation product[5c]: m.p. 219–221°, $[\alpha]^{23}D$ +87°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.57; H, 8.67.

(b) **From the Free Glycol IVb.**—The free glycol IVb (1.0 g.) dissolved in 80 cc. of C.P. chloroform containing 8 drops of 4 *N* hydrogen bromide in acetic acid was treated dropwise with a 10% solution of bromine in chloroform, until 2 equivalents of bromine had been added. Decolorization occurred very rapidly, and the solution was allowed to stand for 3 hours. It was then washed with water, dried, and evaporated, and the residue was treated with sodium iodide in acetone as described under (a). The crude iodo compound (λ_{max} 240 mμ, log ε 3.98%) dissolved in dioxane (30 cc.) was refluxed for 1 hour with a solution of sodium bisulfite (2 g.) in water (30 cc.). Addition of water, extraction with chloroform and chromatographic purification gave 130 mg. of 11α,17α-dihydroxyprogesterone, m.p. 205–208°, which on further purification through crystallization showed properties identical with those of the material prepared above. Identity was established through mixture melting point and infrared comparison.

Allopregnane-3β,11α,17α-triol-20-one 3,11-Diacetate (VIa).—The bromohydrin was prepared from 13 g. of 16α,17α-oxidoallopregnane-3β,11α-diol-20-one diacetate (IIa) in 120 cc. of glacial acetic acid and 15 cc. of a saturated solution of hydrogen bromide in acetic acid, as described above for the preparation of IVa. The collected and well-washed bromohydrin was hydrogenated in 1 l. of ethanol for 15 hours in the presence of 35 g. of the 1.5% palladium–calcium carbonate catalyst. Crystallization of the product from ether–pentane furnished 10.9 g. (83%) of the triol diacetate VIa, m.p. 179–181°, $[\alpha]^{20}D$ −21°, $\lambda_{max}^{CHCl_3}$ 1726 and 1704 cm.$^{-1}$ and free hydroxyl band. Identity with a sample prepared as described previously[10] was established through infrared comparison and mixture melting point.

Allopregnane-3β,11α,17α,21-tetrol-20-one 3,11,21-Triacetate (VIIa).—To a solution of 10.0 g. of the above diacetate VIa in 160 cc. of glacial acetic acid containing 1 cc. of acetic acid previously saturated with hydrogen bromide was added dropwise at room temperature during 15 minutes 36.8 cc. (1 equivalent) of a 10% solution of bromine in acetic acid. Decolorization was very rapid, and the mixture was allowed to stand for 30 minutes after the end of the addition. It was then poured into water, the product was extracted with ether, and the ether extract was washed with aqueous sodium bicarbonate solution and water, dried and evaporated. The crude 21-bromo compound was refluxed for 30 minutes with sodium iodide (5 g.) in acetone (500 cc.), potassium acetate (prepared from 20 g. of potassium bicarbonate and 12 g. of acetic acid) was added, and refluxing was continued for another 15 hours. Dilution with water, extraction with ether, washing of the extract with sodium thiosulfate solution and water, drying, evaporation and crystallization from ether–pentane yielded 7.1 g. (63%) of the triacetate VIIa with m.p. 197–198°, $[\alpha]^{20}D$ +25°, $\lambda_{max}^{CHCl_3}$ 1736 and 1720 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19. Found: C, 65.71; H, 8.33.

Allopregnane-3β,11α,17α,21-tetrol-20-one 11-Monoacetate (VIIb).—To an ice-cooled solution of 4.0 g. of the triacetate VIIa in 400 cc. of methanol was added an ice-cooled solution of 4 g. of potassium hydroxide in 20 cc. of water, in an atmosphere of nitrogen. The solution was allowed to attain room temperature and then to stand for 1 hour. It was acidified with acetic acid, concentrated to a small volume and diluted with water. Chloroform extraction, followed by crystallization from acetone–ether furnished 2.2 g. (66%) of the triol monoacetate VIIb with m.p. 229–232°, $[\alpha]^{20}D$ +2°, λ_{max}^{mull} 1700 cm.$^{-1}$ and free hydroxyl band.[21]

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88; acetyl, 10.29. Found: C, 67.56; H, 8.78; acetyl, 10.32.

Allopregnane-11α,17α,21-triol-3,20-dione 11,21-Diacetate (IXa).—To a solution of 3.5 g. of the above-described tetrol monoacetate VIIb in 59 cc. of *t*-butanol chilled to 10°

(21) The 11α-acetoxy group in this compound could not be detected in the infrared.

was added 1.61 g. (1.36 moles) of N-bromoacetamide and 4 cc. of water. The solution was allowed to stand at 10° for 5 hours, and was then diluted with water. The product was extracted with ether, the extract washed with sodium hydroxide solution and water, dried and evaporated. The residue was acetylated with pyridine and acetic anhydride for 30 minutes on the steam-bath. The diketone IXa was obtained by ether extraction, and was purified by direct crystallization from ether–hexane and by chromatography of the mother liquors. In this way a total of 1.6 g. (42%) was obtained with m.p. 197–199°, $[\alpha]^{20}D$ +48°, λ_{max}^{mull} 1736 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.61; H, 8.29.

Δ⁴-Pregnene-11α,17α,21-triol-3,20-dione 11,21-Diacetate (11α,17α,21-Trihydroxyprogesterone Diacetate) (Xa).—The diketone IXa (500 mg.) in acetic acid (40 cc.) containing 8 drops of acetic acid saturated with hydrogen bromide was dibrominated with 2 equivalents of bromine as described above for the preparation of Vb, method (a). The product was refluxed for 20 hours with 3 g. of sodium iodide in 100 cc. of dry acetone. The iodo compound (λ_{max} 242 mμ, log ε 4.12) isolated as described previously, dissolved in 50 cc. of dioxane was refluxed for 1 hour with a solution of 2 g. of sodium bisulfite in 20 cc. of water. Addition of water and ether extraction yielded a crude product (λ_{max} 240 mμ, log ε 4.00), which was purified by chromatography on alumina. The crystalline fractions eluted with benzene–ether (1:1) were pooled and crystallized from ether–pentane. This yielded 60 mg. of the diacetate Xa with m.p. 128–131°, λ_{max} 240 mμ, log ε 4.24. One recrystallization raised the m.p. to 132–134°, but two further crystallizations did not raise this value. However, a fifth crystallization gave material with m.p. above 200°, and this on recrystallization gave the analytical sample with constant m.p. 221–223°, $[\alpha]^{20}D$ +120°, λ_{max} 240 mμ, log ε 4.24, $\lambda_{max}^{CHCl_3}$ 1736, 1724 and 1670 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.10; H, 7.79.

In another experiment a sample with apparently constant m.p. 202–205° was obtained, but this on crystallization in the presence of a seed of the higher melting form was converted to it. This compound obviously can exist in several polymorphic forms: reported for the synthetic product[9]: m.p. 223.0–225.8°, $[\alpha]D$ +116° (dioxane), λ_{max} 240 mμ, log ε 4.23; for the microbiological product[5c]: m.p. 206–208°, $[\alpha]^{22}D$ +117°.

Allopregnane-3β,11α-triol-20-one (VIb).—To a solution of 12 g. of the free 16α,17α-oxidoallopregnane-3β,11α-diol-20-one (IIb) (crude uncrystallized) in 500 cc. of acetic acid was added 15 cc. of acetic acid saturated with hydrogen bromide. The solution was cooled in ice for 15 minutes and then left at room temperature for another 15 minutes. Water was added, the product was extracted with chloroform, and the extract was washed with water, dried and evaporated. The residue dissolved in 700 cc. of alcohol was shaken in hydrogen with 40 g. of a 1.5% palladium–calcium carbonate catalyst for 16 hours. The catalyst was removed by filtration, the solvent was evaporated, the residue was dissolved in chloroform and the solution was washed with water, dried and evaporated. Crystallization from acetone furnished 6.3 g. (52%) of the free triol VIb with m.p. 248–250°. Further crystallization yielded the analytical sample with m.p. 253–255°, $[\alpha]^{20}D$ −44°, λ_{max}^{mull} 1700 and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.18; H, 9.70.

Acetylation (acetic anhydride–pyridine, steam-bath, 1 hour) gave the 3,11-diacetate VIa, m.p. 180–182°, $[\alpha]^{20}D$ −22°, identical with the material described above, as evidenced by mixture melting point determination and infrared comparison.

Allopregnane-3β,11α,17α,21-tetrol-20-one 21-Monoacetate (VIIc).—To a solution of 6 g. of the triol VIb in 2 l. of C.P. chloroform containing 0.5 cc. of acetic acid previously saturated with hydrogen bromide was added over 15 minutes 1 equivalent of bromine as a 10% solution in chloroform. Decolorization occurred within a few minutes of the end of addition, and the solution was then allowed to stand for 1 hour. It was washed with water, dried, evaporated and the residue was refluxed with 3.5 g. of sodium iodide in 300 cc. of acetone for 30 minutes. Potassium acetate (prepared from 20 g. of potassium bicarbonate and 12 g. of acetic acid) was added, and refluxing was continued for 15 hours. Water was added and the product was extracted well with ether. Chromatographic purification on alumina and crystallization of the fractions eluted with benzene–ether (1:2) from benzene–pentane gave 3.2 g. (46%) of the tetrol monoacetate VIIc with m.p. 116–118°, $[\alpha]^{20}D$ +31°, λ_{max} 1736 and 1720 cm.$^{-1}$, and free hydroxyl band. This material was probably not quite pure and no satisfactory analysis could be obtained.

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 66.95; H, 8.96.

On acetylation (acetic anhydride–pyridine, steam-bath, 1 hour) the triacetate VIIa was obtained with m.p. 194–196°. Identity was established through mixture melting point determination and infrared comparison.

Allopregnane-17α,21-diol-3,11,20-trione 21-Acetate ("Dihydroallocortisone" Acetate) (VIII).—A solution of 400 mg. of the tetrol monoacetate VIIc in 10 cc. of acetic acid was oxidized with 400 mg. of chromium trioxide dissolved in 2 cc. of water for 1 hour at room temperature (after 15 minutes the product started to crystallize). Water was added, the solid product was collected and recrystallized from acetone. There was obtained 210 mg. with m.p. 224–226°, raised on further crystallization to 232–235°, $[\alpha]^{20}D$ +82° (acetone), $\lambda_{max}^{CHCl_3}$ 1736 and 1700 cm.$^{-1}$ and free hydroxyl band; reported[16]: m.p. 235–236°, $[\alpha]^{20}D$ +81° (acetone). Identity with an authentic specimen was established by mixture melting point determination and infrared comparison.

Allopregnane-11α,17α,21-triol-3,20-dione 21-Monoacetate (IXb).—A solution of 3 g. of the tetrol monoacetate VIIc in 60 cc. of *t*-butanol containing 5 cc. of water was oxidized with 3 g. of N-bromoacetamide for 16 hours at room temperature. Water was added, the product was extracted with ether, and the extract was washed with sodium hydroxide solution and water, dried and evaporated. Chromatography on alumina and crystallization from acetone–hexane furnished 1.5 g. (50%) of the dione IXb with m.p. 190–196°. The analytical sample had m.p. 195–197°, $[\alpha]^{20}D$ +50°, $\lambda_{max}^{CHCl_3}$ 1736, 1720 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.10; H, 8.57.

On acetylation (acetic anhydride–pyridine, steam-bath, 1 hour) the above described diacetate IXa with m.p. 196–198° was obtained. Identity was established by mixture melting point determination and infrared comparison. On admixture with the original monoacetate IXb a depression of *ca.* 20° was observed.

Δ⁴-Pregnene-11α,17α,21-triol-3,20-dione 21-Monoacetate (11α,17α,21-Trihydroxyprogesterone 21-Acetate) (Xb).—A solution of 1.5 g. of the triol monoacetate IXb in 100 cc. of C.P. chloroform containing 6 drops of acetic acid saturated with hydrogen bromide was treated with 2 equivalents of bromine as a 10% solution in chloroform. After 2 hours at room temperature, the solution was washed with water, dried, evaporated and the residue refluxed for 20 hours with 1.5 g. of sodium iodide in 100 cc. of acetone. The crude iodo compound (λ_{max} 244 mμ, log ε 3.98), isolated in the usual manner, was dissolved in 60 cc. of dioxane and refluxed with 1.5 g. of sodium bisulfite in 30 cc. of water for 1 hour. Chromatographic purification of the product on alumina gave 180 mg. of the acetate Xb with m.p. *ca.* 85–100°, $[\alpha]^{20}D$ +81°, λ_{max} 242 mμ, log ε 4.16, $\lambda_{max}^{CHCl_3}$ 1736, 1720, 1700 and 1658 cm.$^{-1}$ and free hydroxyl band. The analytical sample was prepared by crystallization from benzene–hexane, but the m.p. could not be sharpened, and the rotation and ultraviolet spectrum were unchanged.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.10; H, 8.20.

Acetylation (acetic anhydride–pyridine, steam-bath, 1 hour) yielded the above described diacetate Xa with m.p. 218–221°, $[\alpha]^{20}D$ +116°, λ_{max} 240 mμ, log ε 4.22. Identity was established through mixture melting point determination and infrared comparison.

Δ⁴-Pregnene-17α,21-diol-3,11,20-trione 21-Acetate (Cortisone Acetate) (XI).—A solution of 80 mg. of the monoacetate Xb in 3 cc. of acetic acid was oxidized with 50 mg. of chromium trioxide in 1 cc. of water for 5 minutes in an ice-bath and then for 1 hour at room temperature. Cortisone

acetate started to crystallize after 10 minutes, and was precipitated completely by addition of water. After crystallization from acetone it had m.p. 235–238°, $[\alpha]_D$ +178° (acetone), λ_{max} 238 mμ, log ε 4.16, $\lambda_{max}^{CHCl_3}$ 1736, 1700 and 1660 cm.$^{-1}$ and free hydroxyl band. Identity was established by mixture melting point determination and infrared comparison.

Δ^4-Pregnene-11α,17α,21-triol-3,20-dione (XII).—A solution of 35 mg. of the trihydroxyprogesterone monoacetate Xb in 4 cc. of methanol was hydrolyzed with 35 mg. of potassium bicarbonate in 1 cc. of water for 48 hours at room temperature.[22] Water was added and the product was extracted with chloroform. It was crystallized from acetone–ether, and then had m.p. 215–218°, $[\alpha]^{20}_D$ +110° (EtOH), λ_{max} 242 mμ, log ε 4.24, λ_{max}^{mull} 1700 and 1660 cm.$^{-1}$ and free hydroxyl band; reported for the microbiological product[6c]: m.p. 217–219°, $[\alpha]^{20}_D$ +117° (EtOH).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.37; H, 8.14.

A sample obtained by an independent route[18] had m.p. 209–211° and 216–219° (polymorphic forms), $[\alpha]^{20}_D$ +112° (EtOH), and there was no depression in melting point on admixture.

(22) *Cf.* T. Reichstein and J. v. Euw, *Helv. Chim. Acta*, **21**, 1183 (1938).

LAGUNA MAYRAN 413
MEXICO CITY 17, D. F.

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

Steroids. XLII. Steroidal Sapogenins. XXVI.[1] The Chemical Reduction of Δ^8-11-Keto and of Saturated 11-Keto Steroids. A New Approach to 11-Keto and 11α-Hydroxy Steroids[2]

BY FRANZ SONDHEIMER, O. MANCERA, G. ROSENKRANZ AND CARL DJERASSI[3]

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Δ^8-22a-5α-Spirosten-3β-ol-11-one propionate (I) was reduced by means of lithium in liquid ammonia to 22a-5α-spirostan-3β-ol-11-one (IIa), thus providing a new route to cortisone. When the reduction of I with lithium in ammonia was carried out in the presence of alcohol, 22a-5α-spirostan-3β,11α-diol (IIIa) resulted. The latter reducing conditions smoothly converted saturated 11-keto steroids to the corresponding 11α-hydroxy compounds. Thus IIa yielded IIIa, pregnan-3α-ol-11,-20-dione 20-ethylene ketal (VI) led to pregnane-3α,11α-diol-20-one 20-ethylene ketal (VII), and cortisone 3,20-diethylene ketal (X) gave the corresponding 11α-hydroxy compound XI; the latter was converted by treatment with *p*-toluenesulfonic acid and acetone to Δ^4-pregnene-11α,17α,21-triol-3,20-dione (XIIa), the 11-epimer of Kendall's compound F.

All the methods so far reported for the chemical introduction of an 11-keto or hydroxy group into ring C unsubstituted steroids[4] have proceeded *via* a $\Delta^{7,9(11)}$-diene, and thence *via* a derivative bearing oxygen substituents at C-7 as well as at C-11, from which the substituent at C-7 had to be removed subsequently. We now wish to describe the details[2] of a new method for effecting 11-oxygenation, which we have applied to the preparation of 22a-5α-spirostan-3β-ol-11-one (II) and 22α-5α-spirostane-3β,11α-diol (III), which proceeds directly from the $\Delta^{7,9(11)}$-diene to the 11-oxygenated derivative, no additional group being introduced at C-7. This method both with regards to the number of steps (seven from the Δ^5-3-ol, "diosgenin" in this case, or three from the $\Delta^{7,9(11)}$-diene) and overall yield appears to be superior to the other methods that have been published[4,5] for the chemical introduction of a C-11 oxygen function into $\Delta^{7,9(11)}$-dienes. Furthermore, in view of previously recorded transformations[6] the present work constitutes an alternate route to cortisone.

The starting point for the present method was Δ^8-22a-5α-spirosten-3β-ol-11-one propionate (I), which may easily be obtained in good yield from $\Delta^{7,9(11)}$ - 22a - 5α - spirostadien - 3β - ol[7] propionate through treatment with one mole of perbenzoic or permonophthalic acid, followed by rearrangement of the 9,11-oxide with boron trifluoride.[2] The saturation of the double bond in I was first carried out by means of catalytic hydrogenation. These experiments, as was anticipated, did not lead to the 11-keto steroid with the "natural" B/C ring junction (8β,9α), but gave rise to a series of interesting "abnormal" derivatives which are being investigated further.[8]

We next turned our attention to the chemical reduction of the Δ^8-11-one I, since this type of reduction might well lead to the most stable of the four possible dihydro products, *i.e.*, to the 8β,9α-compound (possessing the "natural" configuration) rather than the 8α,9β-isomer. Some of the usual

(1) (a) Steroids. XLI. J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, THIS JOURNAL, **75**, 1277 (1953). (b) Steroidal Sapogenins. XXV. H. Martínez, H. J. Ringold, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 239 (1953).

(2) This paper is to be regarded as "Introduction of the 11-Keto and 11α-Hydroxy Groups into Ring C Unsubstituted Steroids (Part 7)." A preliminary announcement of part of this work has been published (F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952)).

(3) Department of Chemistry, Wayne University, Detroit 1, Michigan.

(4) For recent reviews see L. Velluz, A. Petit and J. Matbieu, *Bull. soc. chim.*, 1 (1952); A. J. Birch, *Ann. Repts. on Progress Chem. (Chem. Soc. London)*, **48**, 204 (1951).

(5) At the same time that the preliminary announcement of this work appeared (footnote 2), E. Schoenewaldt, L. Turnbull, E. M. Chamberlin, D. Reinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda and M. Tishler (THIS JOURNAL, **74**, 2696 (1952)), independently described a method for introducing an 11-keto group both in the ergostane and in the spirostane series, which appears to be identical with ours.

(6) (a) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *ibid.*, **73**, 2396 (1951); (b) C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *ibid.*, **74**, 3634 (1952); (c) J. M. Chemerda, E. M. Chamberlin E. H. Wilson and M. Tishler, *ibid.*, **73**, 4052 (1951); (d) G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, **73**, 4055 (1951); (e) G. Rosenkranz, C. Djerassi, R. Yashin and J. Pataki, *Nature*, **168**, 28 (1951).

(7) G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951).

(8) An account of these hydrogenation experiments, together with the experimental details for preparing I from $\Delta^{7,9(11)}$-22a-5α-spirostadien-3β-ol, will be published separately. (C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, in press).