showed about 50 mole per cent. of 16-dehydro steroid. Both II and III were isolated as just described.

3β-Hydroxy-16α,17α-epoxy-5α-pregnane-12,20-dione (IV).—A 250-mg. sample of III was hydrolyzed for one hour in 50 ml. of boiling 0.5 *N* methanolic potassium hydroxide. The solution was neutralized, concentrated to 25 ml. and diluted with 15 ml. of water. Shiny leaflets, 221 mg., separated on cooling. These were recrystallized twice from aqueous methanol, m.p. 202–203° (sweating at 178°, partially melting at 190° and recrystallizing as spherulites), $[\alpha]_D$ +112°. The sample was air-dried. *Anal.* Calcd. for $C_{21}H_{30}O_4 \cdot H_2O$: C, 69.18; H, 8.85. Found: C, 69.45; H, 8.99. A sample recrystallized from acetone–hexane was extremely hygroscopic. Rigorous drying over phosphorus pentoxide at 110° did not remove all of the water of crystallization. *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 71.02; H, 8.94.

Acetates obtained earlier from II in alkaline media, as referred to in the previous experiment, yielded the same product on hydrolysis. Reacetylation in boiling acetic anhydride yielded III.

16β-Bromo-3β-acetoxy-17α-hydroxy-5α-pregnane-12,20-dione (V).[6]—A solution of 350 mg. of III in 5.4 ml. of glacial acetic acid was treated in the cold with 3.5 ml. of 48% hydrobromic acid in 26 ml. of acetic acid. After 30 minutes at 40° the mixture was precipitated in water. The product was fractionally crystallized giving some starting material and 218 mg. of V from which the analytical sample was obtained as transparent cubes from ether, m.p. 178.0–179.5°, $[\alpha]_D$ +30°; +45.7° (ethanol). *Anal.* Calcd. for $C_{23}H_{33}O_5Br$: C, 58.83; H, 7.08; Br, 17.02. Found: C, 58.95; H, 7.20; Br, 16.91.

Treatment of V, 103 mg., for 24 hours in 25 ml. of 0.5 *N* methanolic potassium hydroxide gave 94% of IV which was recrystallized from aqueous methanol yielding 41 mg. of flat, transparent needles, m.p. 202–203° (recrystallizing as spherulites at 190°), $[\alpha]_D$ +113°. This did not depress the melting point of the sample of IV described above.

3β,17α-Dihydroxy-16β-bromo-5α-pregnane-12,20-dione (VI).—3β-Hydroxy-16α,17α-epoxy-5α-pregnane-12,20-dione, 175 mg., was treated with hydrobromic acid in acetic acid as described above yielding 91% of VI. This was recrystallized from acetone–hexane and appeared as granular crystals, m.p. 168.5–170.0°, $[\alpha]_D$ +31°; +45.3° (ethanol). *Anal.* Calcd. for $C_{21}H_{31}O_4Br$: C, 59.00; H, 7.31. Found: C, 58.59; H, 7.09.

Acetylation of VI with boiling acetic anhydride gave V.

Reduction of 3β-Acetoxy-17α-hydroxy-16β-bromo-5α-pregnane-12,20-dione (V) to 3β-Acetoxy-5α-pregnane-12,20-dione (VII).—A solution of V, 279 mg. in 35 ml. of glacial acetic acid, was treated with 3 g. of zinc dust, portions being added at 30-minute intervals for 2 hours while stirring at 95° in a nitrogen atmosphere. The hot solution was filtered into cold water and the product isolated with ether. Evaporation of the washed and dried ether solution left a residue which was triturated with ether. The insoluble residue was then crystallized four times from acetone yielding irregular transparent prisms of VII, m.p. and m.m.p. with authentic sample[6] 195.5–197.0° (with sweating at 184°), $[\alpha]_D$ +140°. The analysis was correct and the total yield after reprocessing the mother liquors was 40%.

Hydrolysis of the acetate overnight in methanolic sodium hydroxide and recrystallization from acetone afforded 3β-hydroxy-5α-pregnane-12,20-dione crystallizing as elongated transparent prisms, m.p. 195.0–197.5°, $[\alpha]_D$ +164°. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.69; H, 9.59.

Reacetylation of the latter gave VII.

16α,17α-Epoxy-5α-pregnane-3,12,20-trione (VIII).—A solution of 650 mg. of sodium dichromate dihydrate in 15 ml. of glacial acetic acid was added over a 25-minute period to 225 mg. of IV in 60 ml. of 1:1 glacial acetic acid–benzene at 10°. After an hour an additional 325 mg. of oxidant in 5 ml. of solvent was added and the mixture allowed to stand 24 hours at 0°. The mixture was poured into cold, aqueous sodium bisulfite solution and extracted with ether. The washed and dried ether solution was evaporated and the residue triturated with more ether. The insoluble residue remaining was recrystallized four times from acetone; the elongated transparent prisms melted at 265.0–268.0° (sweating at 234° and becoming translucent at 239°, followed by slow growth of needles radiating from the crystalline mass at 247°) $[\alpha]_D$ +143°. *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.17; H, 8.30. Reworking the mother liquors brought the over-all yield to 40%.

3β-Acetoxy-16α-methoxy-5α-pregnane-12,20-dione (IX).—A solution was prepared under nitrogen containing 1 g. of potassium hydroxide in 50 ml. of methanol which had been freshly distilled in a nitrogen atmosphere. To this was added 0.50 g. of 3β-acetoxy-5α-pregn-16-ene-12,20-dione. After standing at 40° for 15 minutes, the whole was poured into 100 ml. of cold water containing 2 ml. of concentrated hydrochloric acid. The dry product, isolated by ether extraction, was reacetylated overnight in 10 ml. of pyridine and 10 ml. of acetic anhydride. The mixture of acetates remaining after ether extraction washing and removal of the ether weighed 0.44 g. and was an oil. This was chromatographed on 20 g. of silica gel, the desired product, 0.31 g. being eluted with 10% ether in benzene and crystallized from cyclohexane. The heavy rectangular plates melted at 144.0–145.2°, $[\alpha]_D$ +104° ($CHCl_3$). There was no appreciable absorption in the 225–245 mμ region. *Anal.* Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97; OCH_3, 7.67. Found: C, 71.31; H, 9.35; OCH_3, 7.22.

KNOXVILLE, TENNESSEE

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

Steroids. LX.[1] Synthesis of C-2 Oxygenated Derivatives of Reichstein's Substance S and of Cortisone

BY G. ROSENKRANZ, O. MANCERA AND FRANZ SONDHEIMER

RECEIVED JULY 26, 1954

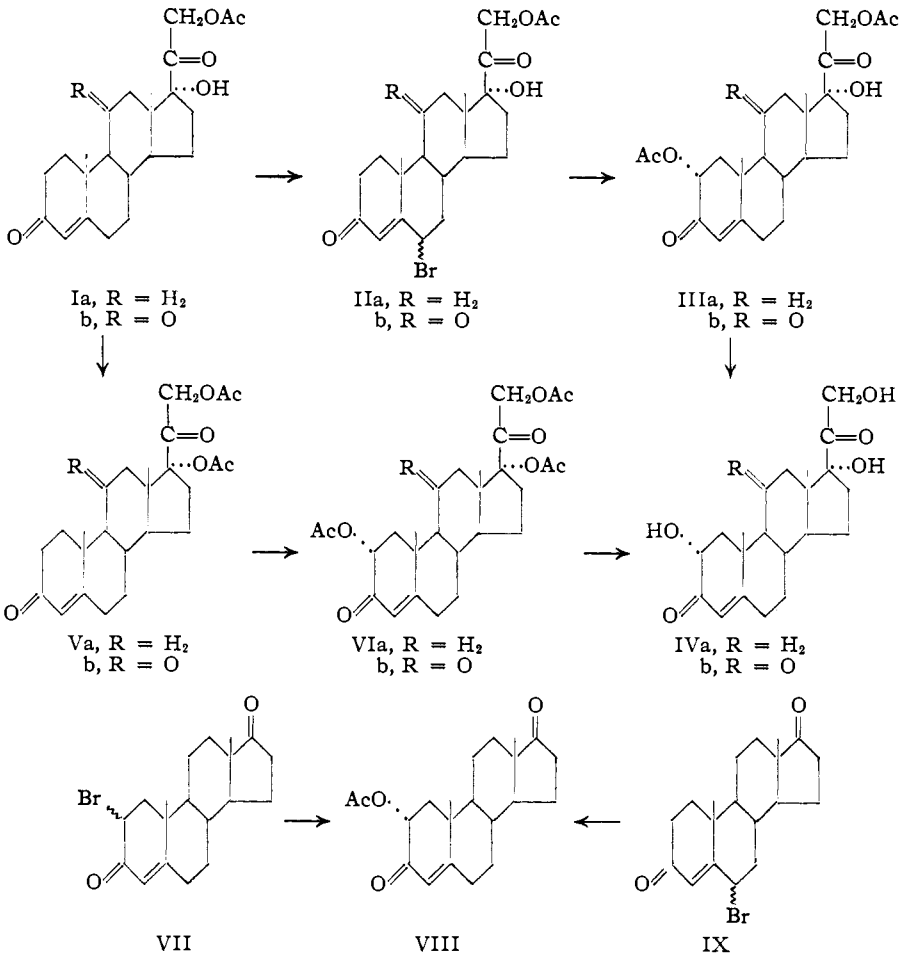
Syntheses of 2α-hydroxy-substance S (IVa) and 2α-hydroxy-cortisone (IVb), as well as of their 2,21-diacetates (IIIa and IIIb) and 2,17,21-triacetates (VIa and VIb), are described.

A number of hormone analogs bearing an α-hydroxy group at C-2 have previously been prepared by two different methods. The one involves direct acetoxylation of a Δ^4-3-ketone with lead tetraacetate,[2] followed by saponification of the resulting 2α- or 2β-acetoxy-Δ^4-3-ketone; the other involves acetolysis of a 6-bromo-Δ^4-3-ketone with potassium acetate,[2d,3] again followed by saponification. We now describe the employment of both these methods for the synthesis of 2α-hydroxy-substance S (IVa) and 2α-hydroxy-cortisone (IVb), as well as of their 2,21-diacetates (IIIa and IIIb) and 2,17,21-triacetates (VIa and VIb).

(1) Steroids. LIX, E. Batres, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 5171 (1954).

(2) (a) G. Ehrhart, H. Ruschig and W. Aumüller, *Angew. Chem.*, **52**, 363 (1939); *Ber.*, **72**, 2035 (1939); (b) T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939); (c) E. Seebeck and T. Reichstein, *ibid.*, **27**, 948 (1944); (d) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, THIS JOURNAL, **75**, 4712 (1953).

(3) (a) D. E. A. Rivett and E. S. Wallis, *J. Org. Chem.*, **15**, 35 (1950); (b) L. F. Fieser and M. A. Romero, THIS JOURNAL, **75**, 4716 (1953); (c) J. Herran, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 5531 (1954).



Substance S 21-acetate (Ia) had previously been converted by means of N-bromosuccinimide to the 6-bromo derivative IIa.[4] The latter on treatment with potassium acetate in boiling acetic acid furnished an acetoxy-substance S acetate, to which was assigned the 2α-acetoxy structure IIIa on the basis of analogous products obtained in other series.[3] The molecular rotation contribution of the new acetoxy grouping in IIIa supports this formulation (Table I).

In order to prepare 2-hydroxylated derivatives of substance S by the lead tetraacetate method,[2] it was necessary to protect the 17α-hydroxy group of substance S so as to prevent attack of the side-chain by the reagent. Consequently substance S 21-acetate (Ia) was converted to the 17,21-diacetate (Va) by means of boiling acetic anhydride, as had been described for cortisone 17,21-diacetate.[5] The diacetate Va was then allowed to react with lead tetraacetate in hot acetic acid and yielded the required 2α-hydroxy-substance S 2,17,21-triacetate (VIa) in 25% yield. The structure was confirmed by obtention of the same compound from substance S 17,21-diacetate (Va) through bromination at C-6 followed by treatment with potassium acetate, and by the molecular rotation contribution of the new acetoxy grouping in VIa (Table I).

Saponification of either the 2,21-diacetate IIIa or the 2,17,21-triacetate VIa with potassium hydroxide smoothly furnished the same 2α-hydroxy-substance S (IVa), which could be reacetylated to the 2,21-diacetate IIIa with acetic anhydride in pyridine.

In analogous fashion cortisone 21-acetate (Ib) was transformed to the 6-bromo derivative IIb[6] and thence by reaction with potassium acetate in boiling acetic acid to 2α-hydroxycortisone 2,21 - diacetate (IIIb). The corresponding 2,17,-21-triacetate VIb was prepared from cortisone 17,21-diacetate (Vb)[5] by means of lead tetraacetate, and free 2α-hydroxycortisone (IVb) was obtained from the diacetate IIIb by saponification with potassium hydroxide.

Fieser and Romero[3b] have suggested that the reaction of 6-bromo-Δ^4-3-ketone with potassium acetate, which yields the 2α-acetoxy-Δ^4-3-ketone, may proceed *via* the 2-bromo-Δ^4-3-ketone. We have now demonstrated that a 2-bromo-Δ^4-3-ketone under the acetolysis conditions employed does in fact furnish the 2α-acetoxy-Δ^4-3-ketone. 2-Bromo-Δ^4-androstene-3,17-dione (VII)[7] on treatment with potassium acetate in boiling acetic acid afforded 2α-acetoxy-androstene-3,17-dione (VIII) in comparable yield to that given by 6-bromo-Δ^4-androstene-3,17-dione (IX).[8]

In Table I are recorded the molecular rotation (M_D) values of the 2α-acetoxy-Δ^4-3-ketones and 2α-hydroxy-Δ^4-3-ketones described in this paper and previously. It can be seen that in all cases the introduction of a 2α-acetoxy grouping into a Δ^4-3-ketone results in a relatively small negative shift of the M_D, whereas the introduction of a 2α-hydroxy grouping causes a comparatively small positive shift.

(4) F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5932 (1953).

(5) Huang-Minlon, E. Wilson, N. L. Wendler and M. Tishler, *ibid.*, **74**, 5394 (1952).

(6) V. R. Mattox, E. L. Woroch, G. A. Fleisher and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952). These workers found that when 6-bromocortisone 21-acetate (IIb) is treated with semicarbazide in the presence of a high concentration of acetate ion, a substance is formed with λ_{max} 273 mμ in the ultraviolet. The compound responsible for this chromophore, for which the 6-hydroxycortisone 6,21-diacetate 3-semicarbazone structure had been considered, is presumably the 3-semicarbazone of 2α-hydroxycortisone 2,21-diacetate (IIIb)

(7) C. Djerassi and C. R. Scholz, *J. Org. Chem.*, **13**, 697 (1948).

(8) *Inter al.*, C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4534 (1950).

TABLE I

MOLECULAR ROTATION DATA OF 2α-ACETOXY- AND 2α-HYDROXY-Δ⁴-3-KETONES[a]

	M_D	M_D 2α-Acetoxy	M_D 2α-Hydroxy	Contribution of 2α-acetoxy group	Contribution of 2α-hydroxy group
Δ⁴-Cholesten-3-one	+340[b]	+290[2c]	.....	−50	.....
22a-Δ⁴-Spirosten-3-one	− 41[3c]	− 85[3c]	.....	−44	.....
Testosterone acetate	+317[2d]	+264[2d]	.....	−53	.....
Testosterone	+314[2d]	.....	+365[2d]	..	+51
Δ⁴-Androstene-3,17-dione	+566[c]	+502[d]	.....	−64	.....
Progesterone	+641[2d]	+610[2d]		−31	
	+601 (in ethanol)		+657 (in ethanol)[2d]		+56 (in ethanol)
Desoxycorticosterone acetate	+692[2d]	+662[2d]	.....	−30	.....
Substance S 17,21-diacetate	+288[d]	+278[d]	.....	−10	.....
Substance S 21-acetate	+554[f]	+544[d]	.....	−10	.....
Substance S	+381[c]	.....	+471[d]	..	+90
Cortisone 17,21-diacetate	+591[5]	+517[d]	.....	−74	.....
Cortisone	+738[e]	.....	+760	..	+22

[a] All rotations were determined at 20° in chloroform solution, unless specified otherwise. [b] A. Butenandt and A. Wolff, *Ber.*, 68, 2091 (1935). [c] Determined in these laboratories. [d] This paper. [e] A. Butenandt and J. Schmidt, *Ber.*, 67, 2088 (1934). [f] E. Batres, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, 76, 5171 (1954).

Experimental[9]

Δ⁴-Pregnene-2α,17α,21-triol-3,20-dione (2α-Hydroxy-substance S) 2,21-Diacetate (IIIa).—A solution containing 3.0 g. of 6-bromo-substance S 21-acetate (IIa)[4] and 12.0 g. of anhydrous potassium acetate in 75 cc. of glacial acetic acid was refluxed for 4 hours, cooled and poured into water. The precipitate was collected, washed well with water, dried and chromatographed on 120 g. of neutral alumina. The fractions eluted with benzene–ether (2:3) on crystallization from ether afforded 0.59 g. (21%) of the diacetate IIIa as small plates with m.p. 200–202° or 215–217° (Kofler block, different polymorphic forms), $[\alpha]_D$ +122°, M_D +544, $\lambda_{max.}$ 242 mμ, log ε 4.19, $\nu_{max}^{CHCl_3}$ 1736, 1718 and 1686 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.35; H, 7.68.

Δ⁴-Pregnene-2α,17α,21-triol-3,20-dione (2α-Hydroxy-substance S) Triacetate (VIa). (a) By Lead Tetraacetate Oxidation of Substance S 17,21-Diacetate (Va).—A solution of 5.0 g. of substance S 17,21-diacetate (m.p. 215–217°, $[\alpha]_D$ +67°, M_D +288, prepared by heating the 21-monoacetate with acetic anhydride as described for cortisone 17,21-diacetate[5]) and 7.75 g. of lead tetraacetate (90% pure) in 150 cc. of C.P. acetic acid containing 2.4 cc. of acetic anhydride was heated on the steam-bath for 4 hours, by which time all of the reagent had been consumed. The cooled solution was diluted with water, the product was extracted with chloroform and the organic layer was washed with sodium carbonate and water, dried and evaporated. Crystallization of the residue from chloroform–methanol furnished 1.41 g. (25%) of the 2,17,21-triacetate VIa as well-defined laths with m.p. 218–225°. The analytical specimen exhibited m.p. 229–231°, $[\alpha]_D$ +57°, M_D +278, $\lambda_{max.}$ 240 mμ, log ε 4.22.

Anal. Calcd. for $C_{27}H_{36}O_8$: C, 66.37; H, 7.43. Found: C, 66.83; H, 7.69.

(b) **By Acetolysis of 6-Bromo-substance S 17,21-Diacetate.**—A solution of 5.0 g. of substance S diacetate (Va) in 500 cc. of chlorobenzene and 560 cc. of carbon tetrachloride containing 1.3 cc. of pyridine was refluxed with 2.75 g. (1.2 equivalents) of N-bromosuccinimide for 15 minutes while being illuminated with two photospot lamps (General Electric Co., No. RSP 2) (*cf.* ref. 6). The resulting crude amorphous bromo compound was refluxed with 20 g. of anhydrous potassium acetate in 125 cc. of acetic acid and 10 cc. of acetic anhydride for 4 hours. Addition of water and extraction with chloroform, followed by chromatographic purification of the product on 150 g. of neutral alumina and crystallization of the fractions eluted with benzene–ether from chloroform–methanol, yielded 0.96 g. (17% over-all) of the triacetate VIa with m.p. 227–229°, $[\alpha]_D$ +59°. No depression in m.p. was observed on admixture with a sample prepared by method a.

Δ⁴-Pregnene-2α,17α,21-triol-3,20-dione (2α-Hydroxy-substance S) (IVa). (a) By Saponification of the 2,17,21-Triacetate VIa.—An ice-cold solution of 2.56 g. (4 equivalents) of potassium hydroxide in 50 cc. of dry methanol was added to 5.6 g. of the finely ground triacetate VIa suspended in 150 cc. of Dry Ice-cold methanol, and the mixture was stirred at 0° for 4 hours under nitrogen. At first a homogeneous solution resulted, but the product began to precipitate after *ca.* 3 hours. The mixture was acidified with 3 cc. of glacial acetic acid, evaporated to dryness under vacuum and diluted with saturated ammonium chloride solution. The precipitate was collected, washed with water and crystallized from methanol. The resulting 2α-hydroxy-substance S (IVa) weighed 3.08 g. (74%) and exhibited m.p. 215–217° (introduced at 210°). Further crystallization from acetone–hexane afforded the analytical sample as platelets with m.p. 219–221° (introduced at 215°; m.p. depends on rate of heating), $[\alpha]_D$ +130°, M_D +471, $\lambda_{max.}$ 242 mμ, log ε 4.19, ν_{max}^{mull} 1700 and 1670 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.31; H, 8.59.

2α-Hydroxy-substance S (IVa) on acetylation with acetic anhydride–pyridine (steam-bath, 1 hour) smoothly yielded the 2,21-diacetate IIIa with m.p. 200–202°, identified by mixture m.p. and infrared comparison.

(b) **By Saponification of the 2,21-Diacetate IIIa.**—A solution of 0.10 g. of potassium hydroxide in a little aqueous methanol was added to an ice-cold solution of 0.19 g. of the diacetate IIIa in 20 cc. of methanol. After being allowed to stand for 1 hour at room temperature under nitrogen, the solution was acidified with a few drops of acetic acid and the product was isolated as before. Crystallization from acetone–hexane furnished 0.11 g. of 2α-hydroxy-substance S with m.p. 219–220° (introduced at 215°), $[\alpha]_D$ +128°, identified with the material prepared from the triacetate VIa through mixture m.p. determination and infrared comparison.

Δ⁴-Pregnene-2α,17α,21-triol-3,11,20-trione (2α-Hydroxy-cortisone) 2,21-Diacetate (IIIb).—A solution of 4.8 g. of 6-bromocortisone 21-acetate (IIb)[6] and 19.2 g. of anhydrous potassium acetate in 120 cc. of glacial acetic acid was refluxed for 4 hours. The cooled solution was poured into water and the product was extracted with chloroform. Chromatographic purification on 200 g. of neutral alumina

(9) Melting points are uncorrected, unless noted otherwise. Rotations were determined (at 20°) in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We would like to thank Miss M. T. Cardenas for these measurements, as well as for the infrared spectra, which were determined on a Perkin–Elmer model 12C single beam spectrophotometer with sodium chloride prism. Thanks are also due to Mrs. A. Gonzalez for the microanalyses and to Miss C. Velasco for valuable technical assistance.

and crystallization of the fractions eluted with benzene–ether (1:1 and 1:3) from acetone–hexane furnished 0.58 g. (13%) of the diacetate IIIb as large shiny plates with m.p. 213–217° (Kofler, finely ground). The analytical sample was crystallized from acetone–ether or methanol and exhibited m.p. 218–220° (Kofler, finely ground), $\lambda_{max.}$ 237 mμ, log ε 4.22, $\nu_{max}^{CHCl_3}$ 1736, 1718, 1700 and 1686 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01. Found: C, 64.79; H, 7.16.

Δ⁴-Pregnene-2α,17α,21-triol-3,11,20-trione (2α-Hydroxycortisone) (IVb).—A solution of 152 mg. (2.5 equivalents) of potassium hydroxide in a few drops of water was added to a suspension of 500 mg. of the diacetate IIIb in 40 cc. of ice-cold methanol and the mixture was stirred at room temperature for 1 hour under nitrogen. The resulting solution was acidified with 1 cc. of acetic acid and evaporated to dryness under vacuum. The residual oil was diluted with saturated ammonium chloride solution, the product was extracted with chloroform and chromatographed on 25 g. of silica. The solid fractions eluted with ethyl acetate on crystallization from acetone–ether afforded 185 mg. of 2α-hydroxycortisone as small plates with m.p. 234–236° (introduced at 220°), $[\alpha]_D$ +202°, M_D +760, $\lambda_{max.}$ 237 mμ, log ε 4.21, ν_{max}^{mull} 1700 and 1670 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 66.42; H, 7.61.

Δ⁴-Pregnene-2α,17α,21-triol-3,11,20-trione (2α-Hydroxycortisone) Triacetate (VIb).—A solution containing 1.3 g. of cortisone 17,21-diacetate (Vb)[6] and 2.2 g. (1.5 equivalents) of lead tetraacetate (90% pure) in 50 cc. of C.P. acetic acid and 0.8 cc. of acetic anhydride was heated on the steam-bath for 5 hours. Addition of water, isolation with ether, crystallization of the product from acetone–hexane and chromatography of the mother liquors on alumina furnished a total of 0.33 g. (22%) of the triacetate VIb with m.p. 231–233°. The analytical specimen showed m.p. 243–244°, $[\alpha]_D$ +103°, M_D +517, $\lambda_{max.}$ 237 mμ, log ε 4.21, $\nu_{max}^{CHCl_3}$ 1736, 1718, 1700 and 1686 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{27}H_{34}O_9$: C, 64.53; H, 6.82. Found: C, 64.21; H, 6.68.

Δ⁴-Androsten-2α-ol-3,17-dione Acetate (VIII). (a) From 6-Bromo-Δ⁴-androstene-3,17-dione (IX).—A solution of 3 g. of 6-bromo-Δ⁴-androstene-3,17-dione[8] and 12 g. of anhydrous potassium acetate in 75 cc. of acetic acid was refluxed for 4 hours, cooled and poured into water. Isolation with ether and crystallization of the product from acetone–hexane afforded 0.58 g. (20%) of the 2α-acetoxy compound VIII with m.p. 200–203°. The analytical specimen exhibited m.p. 209–210°, $[\alpha]_D$ +146°, M_D +502, $\lambda_{max.}$ 241, log ε 4.21, $\nu_{max}^{CHCl_3}$ 1736 and 1684 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.97; H, 8.41.

(b) **From 2-Bromo-Δ⁴-androstene-3,17-dione (VII).**—The acetolysis reaction was carried out with 1.0 g. of 2-bromo-Δ⁴-androstene-3,17-dione[7] and 4 g. of potassium acetate in 25 cc. of acetic acid (refluxing for 4 hours). Crystallization of the product from ether–pentane furnished 0.12 g. (13%) of the 2α-acetoxy compound VIII with m.p. 201–204°. A further purified sample (m.p. 208–210°) was shown to be identical with one prepared by method a as evidenced by mixture m.p. determination and infrared comparison.

Saponification of 2α-Hydroxytestosterone Diacetate.—The complete saponification[2d] of 2α-hydroxytestosterone diacetate has been repeated with potassium carbonate in boiling aqueous methanol. The carefully purified product showed m.p. 170–171.5°, $[\alpha]_D$ +120° (reported[2d] m.p. 161–162°, $[\alpha]_D$ +120°).

A partial saponification at C-2 was carried out by adding an ice-cold solution of 1.8 g. of potassium hydroxide in 2 cc. of water and 10 cc. of methanol to a suspension of 5.0 g. of 2α-hydroxytestosterone diacetate in 100 cc. of ice-cold methanol. After 15 minutes stirring a homogeneous solution resulted, but the product then began to precipitate. After being allowed to stand at room temperature for a further 1 hour, the mixture was acidified with acetic acid, concentrated nearly to dryness and diluted with water. The precipitate on crystallization from acetone furnished 1.96 g. of 2α-hydroxytestosterone 17-monoacetate with m.p. 228–230°, λ_{max} 240 mμ, log ε 4.22, $\nu_{max}^{CHCl_3}$ 1718 and 1670 cm.$^{-1}$ and free hydroxyl band.[10]

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.52; H, 8.73.

(10) R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini [*cf.* THIS JOURNAL, in press] have kindly informed us that they have obtained this compound (m.p. 221–226°) by potassium bicarbonate saponification of the diacetate.

MEXICO CITY 17, D. F.

[JOINT CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO, THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY AND THE RESEARCH LABORATORIES OF SYNTEX S. A.]

Steroids. LXI.[1] Synthesis of 19-Nor-desoxycorticosterone, a Potent Mineralocorticoid Hormone[2]

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RECEIVED JULY 26, 1954

17-Nor-desoxycorticosterone (IVb), a substance exhibiting *ca.* twice the mineralcorticoid activity of desoxycorticosterone, has been synthesized by two routes.

It has recently been shown that removal of the C-19 methyl group from progesterone,[4] from 17-ethinyltestosterone[5] and from 17-methyltestosterone[5] in all cases results in increased hormonal activity. On the other hand, removal of the C-19 methyl group from testosterone considerably decreases the androgenic activity.[6,7] It was therefore of interest to make available for biological testing the C-19 nor-analogs of the adrenal cortical hormones, especially since it had been reported by Ehrenstein[8] that an amorphous 19-nor-desoxycorticosterone acetate isomer, obtained by degradation of strophanthidin, was biologically inactive. We now report upon the synthesis by two routes of 19-nor-desoxycorticosterone (IVb), which possesses the same configuration at all asymmetric centers as does desoxycorticosterone.

The first route utilized the previously described

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(3) (a) Universidad Nacional Autónoma de México; (b) Wayne University; (c) Syntex, S. A.

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