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

Steroids. LVI.[1] C-6 Oxygenated Derivatives of Cortical Hormones

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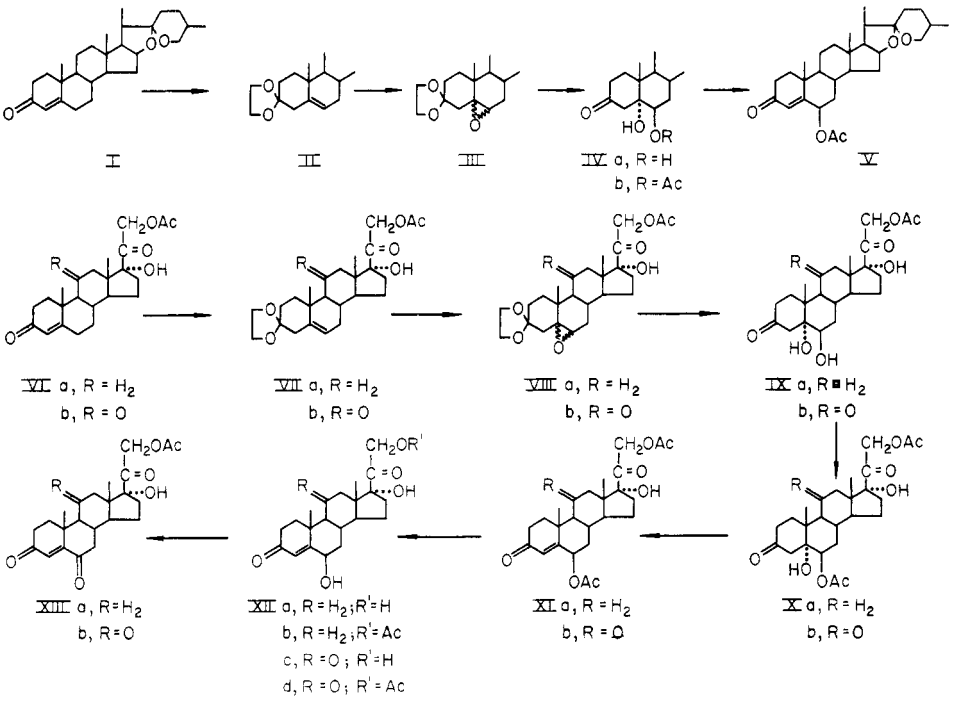
Reichstein's substance S 21-acetate VIa on ketal formation, followed by perbenzoic acid oxidation to VIIIa, perchloric acid hydration to IXa, acetylation, dehydration to XIa and saponification, furnished 6β-hydroxy-substance S (XIIa). Chromic acid oxidation of the 21-monoacetate XIIb yielded 6-keto-substance S 21-acetate (XIIIa). A similar reaction sequence led from cortisone 21-acetate (VIb) to 6β-hydroxycortisone (XIIc) and to 6-ketocortisone 21-acetate (XIIIb). The practicability of the route was first demonstrated in the 22a-spirostane series (I → V).

Recently we have been interested in making available 6β-hydroxylated hormones for biological testing, and the preparation in these laboratories of a number of such hormone analogs by two different methods has already been reported.[1,2] Now we wish to describe the synthesis of two more complex members of this series, 6β-hydroxy-substance S (XIIa)[3] and 6β-hydroxycortisone (XIIc), as well as of the corresponding 6-keto derivatives (as the 21-acetates XIIIa and XIIIb).

For the preparation of these substances it was convenient to utilize the Δ^4-3-ketones (substance S 21-acetate (VIa) and cortisone 21-acetate (VIb)) as starting materials. We have described a procedure for transforming Δ^4-3-ketones to the corresponding 6β-hydroxy compounds, by peracid oxidation of the enol acetates,[1] but this method has been found to proceed poorly with substances containing the 17α,21-diol-20-one system. All previous routes to 6β-hydroxy-Δ^4-3-ketones had employed as starting materials the Δ^5-3β-hydroxy compounds, but the latter are not available in the 11-oxygenated series. For these reasons, in order to prepare the required C-6 oxygenated derivatives of substance S and cortisone, it was necessary to develop another method to introduce the 6β-hydroxy grouping into Δ^4-3-ketones.

The fact that conversion of a Δ^4-3-ketone to the 3-cycloethylene ketal results in a shift of the double bond from the Δ^4- to the Δ^5-position is now well substantiated,[4] and such ketals (type II) previously have been transformed to C-6 oxygenated derivatives of the saturated series.[4a,c] These transformations form the basis of the present synthesis of 6β-hydroxy-Δ^4-3-ketones. The feasibility of the route was first demonstrated with the ketal II derived from Δ^4-22a-spirosten-3-one (I). Perbenzoic acid oxidation led to the 5ξ,6ξ-oxide (III)[5] which on treatment with mineral acids (preferably perchloric acid[4c]) at room temperature afforded 22a-spiro-



(1) Paper LV, J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954).

(2) C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954).

(3) This compound XIIa has previously been prepared by the microbiological oxidation of Reichstein's substance S by means of *Rhizopus arrhizus* [(a) D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, H. C. Murray, H. M. Leigh, A. Weintraub and L. M. Reineke, THIS JOURNAL, **75**, 412 (1953)]. In addition a chemical synthesis of the 6,21-diacetate XIa has been mentioned recently [(b) C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1587 (1952), there footnote 8].

(4) *Inter al.*, (a) E. Fernholz and H. E. Stavely, Abstracts of the 102nd Meeting of the American Chemical Society, Atlantic City, N. J., 1941, 39 M; (b) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952); (c) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(5) *Cf.* references 4a and 4c for the corresponding reaction in the cholesterol series. Treatment of 3β- and 3α-hydroxy-Δ^5-steroids as well as their acetates with peracids results in a mixture of α- and β-oxides (L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, pp. 221–223; P. A. Plattner, A. Fürst, F. Koller and H. H. Kuhn, *Helv. Chim. Acta*, **37**, 258 (1954)) and a similar mixture may result with the present 3-ethylenedioxy-Δ^5-compound. Since both possible oxides would be expected to yield the same 3-keto-5α,6β-diol in the next step (*cf.* L. F. Fieser and M. Fieser, and Plattner, *et al.*, this ref.) no special attempt was made to purify the bulk of the material at this stage.

stan-3-one-5α,6β-diol (IVa), hydration of the oxide function being accompanied by regeneration of the 3-keto grouping. Acetylation yielded the 6-monoacetate IVb, which on dehydration with hydrogen chloride in alcohol-free chloroform,[3b,6] or less efficiently with thionyl chloride in refluxing pyridine,[7] furnished the same Δ^4-22a-spirosten-3-one-6β-ol acetate (V) as had been obtained previously by two different methods.[1]

All the steps in the sequence leading from II to V were carried out at room temperature or below, and none of the reaction conditions employed were expected to cause attack of a 17α-hydroxy-20-keto-21-acetoxy side chain. In fact, when the reaction sequence involving ketal formation, perbenzoic acid oxidation, perchloric acid hydration, C-6 acetylation and hydrogen chloride dehydration, was applied to Reichstein's substance S 21-acetate (VIa), 6β-hydroxy-substance S 6,21-diacetate (XIa) was obtained smoothly *via* the intermediates VIIa,[8] VIIIa,[5] IXa and Xa. Saponification with potassium hydroxide yielded the free triol XIIa with properties in fair agreement with those of the microbiological product.[3a] Each of the six steps in the sequence leading from substance S 21-acetate VIa to 6β-hydroxy-substance S XIIa proceeded in satisfactory yield, the over-all conversion being 32%. Partial acetylation of XIIa afforded the 21-monoacetate XIIb,[3a] which on oxidation at C-6 with chromic acid furnished 6-keto substance S 21-acetate (XIIIa).

In analogous fashion, cortisone 21-acetate (VIb) was transformed *via* the intermediates VIIb,[8] VIIIb,[5] IXb, Xb and XIb to 6β-hydroxycortisone (XIIc) in 35% over-all yield. Preferential acetylation at C-21 furnished the 21-monoacetate XIId, which on chromic acid oxidation afforded 6-ketocortisone 21-acetate (XIIIb).

It has been demonstrated[1,2,3b,6,9a]: that introduction of a 6β-hydroxy or 6β-acetoxy grouping into 3-keto-Δ^4-steroids lowers the position of maximum ultraviolet absorption by 4–5 mμ (to *ca.* 236 mμ) and the intensity (ϵ) by about 3000 (to 13,000–14,000). This effect is shown in the spectrum of 6β-hydroxy-substance S (XIIa) (λ_{max} 236 mμ, ϵ 13,800) and of its 6,21-diacetate XIa (λ_{max} 236 mμ ϵ 13,200). The introduction of an 11-keto grouping into 3-keto-Δ^4-steroids (as well as into 3-keto-Δ^1-steroids and 20-keto-Δ^{16}-steroids) has also been shown to effect a hypsochromic shift of 3–5 mμ.[9b,10] 6-Hydroxycortisone (XIIc) and the 6,21-diacetate XIb would therefore be expected to absorb about 8–9 mμ lower than a 3-keto-Δ^4-steroid unsubstituted at C-6 or C-11 and the observed values (232 mμ) fully bear out this expectation. Similarly, whereas 6-keto-substance S 21-acetate (XIIIa) exhibits ultraviolet absorption typical of a Δ^4-3,6-dione (λ_{max} 250 mμ),[2,9c] a hypsochromic shift of 5 mμ is shown in the spectrum of 6-ketocortisone 21-acetate (XIIIb) (λ_{max} 245 mμ).

The 6-oxygenated derivatives of substance S and of cortisone described in this paper are being tested for their biological properties, and the results will be reported later.

Experimental[11]

3-Ethylenedioxy-Δ^5-22a-spirostene (II).—A mixture of 10.0 g. of Δ^4-22a-spirosten-3-one,[12] 250 cc. of dry benzene and 50 cc. of ethylene glycol containing 0.3 g. of *p*-toluenesulfonic acid was refluxed with stirring for 18 hr., a water separator being employed. The mixture was washed with sodium bicarbonate solution and water, dried and evaporated nearly to dryness. Addition of hexane yielded 8.9 g. (80%) of the ketal, m.p. 240–242° (not raised on crystallization from chloroform–methanol), $[\alpha]_D$ −63° (chloroform containing a drop of pyridine), no appreciable absorption in the ultraviolet.[13]

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 75.97; H, 9.51.

3-Ethylenedioxy-5ξ,6ξ-oxido-22a-spirostane (III).—The above ketal (8.0 g.) was dissolved in 60 cc. of chloroform containing 1.15 equivalents of perbenzoic acid. After 5 hours at room temperature all the peracid had been consumed. The solution was washed with sodium bicarbonate solution and water, dried and evaporated. The residual oil crystallized on trituration with methanol to yield 4.44 g. of the crude oxide with m.p. 185–195°, $[\alpha]_D$ −102°. A small sample was crystallized repeatedly from chloroform–methanol and furnished a specimen of presumably one pure epimer as shiny plates, m.p. 222–224°.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.91; H, 9.25.

22a-Spirostan-3-one-5α,6β-diol (IVa).—Aqueous perchloric acid (8 cc. of a 3 *N* solution) was added to a solution of 2.30 g. of the crude oxide (III) (m.p. 185–195°) in 25 cc. of tetrahydrofuran, and the mixture was stirred for 3 hours at room temperature. The crystalline precipitate which had formed during the first few minutes was then collected. Crystallization of this material from acetone–hexane furnished 0.66 g. of the diol-one with m.p. 253–255°. The filtrate was poured into water, the precipitate was collected, washed, dried and chromatographed on 30 g. of neutral alumina. The fractions eluted with chloroform were crystallized from acetone–hexane to yield a further 0.75 g. of the diol-one IVa with m.p. 255–259° (total yield 1.41 g., 65%). The analytical sample showed m.p. 264–266°, $[\alpha]_D$ −70°, no appreciable absorption in the ultraviolet, ν_{max}^{mull} 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.51; H, 9.39.

Substitution of dilute sulfuric for perchloric acid in the

(6) P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951).

(7) B. Ellis and V. A. Petrow, *J. Chem. Soc.*, 1078 (1939).

(8) Previous synthesis of the 3-cycloethylene ketal of substance S 21-acetate: (a) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953) (69% yield); of the ketal of cortisone 21-acetate: R. Antonucci, *et al.*, *loc. cit.* (74% yield); (b) J. M. Constantin, A. C. Haven and L. H. Sarett, THIS JOURNAL, **75**, 1716 (1953) (76% yield). We have found these compounds to be formed most conveniently by the interchange reaction with 2-methyl-2-ethyl-1,3-dioxolane in the presence of *p*-toluenesulfonic acid [H. J. Dauben, B. Löken and H. J. Ringold, THIS JOURNAL, **76**, 1359 (1954)]; under these conditions the ketals precipitate directly from the reaction mixture in *ca.* 90% yield.

(9) L. Dorfman, *Chem. Revs.*, **53**, 72 (1953), (a) Table 12; (b) Table 11; (c) Table 8.

(10) The hypsochromic shift exerted by the 11-keto grouping is also apparent in the $\Delta^{4,6}$-dien-3-one series. Thus, whereas a variety of ring C-unsubstituted $\Delta^{4,6}$-dien-3-ones show λ_{max} 284 mμ (*cf.* F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5932 (1953), Table I), 6-dehydrocortisone (an 11-keto-$\Delta^{4,6}$-dien-3-one) and its 21-acetate exhibit λ_{max} 280–281 mμ (V. R. Mattox, E. L. Woroch, G. A. Fleisher and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952)).

(11) Melting points are uncorrected. Unless noted otherwise rotations were determined (at 20°) in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Miss P. Revaque (Mrs. P. Lopez) 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 due to Miss A. Barba (Mrs. A. Gonzalez) for the microanalyses and to Miss C. Velasco for skillful technical assistance.

(12) R. E. Marker, T. Tsukamoto and D. L. Turner, THIS JOURNAL, **62**, 2525 (1940).

(13) Since completion of this work S. Bernstein, R. Littell and J. H. Williams (*J. Org. Chem.*, **18**, 1418 (1953)) have described the preparation of the ketal II (m.p. 235.5–239°, $[\alpha]^{29}_D$ −98°) in 68% yield.

hydration step resulted in a markedly poorer yield of product.

22a-Spirostan-3-one-5α,6β-diol 6-Monoacetate (IVb).—The diol-one IVa (1.28 g.) was treated overnight with 4 cc. of pyridine and 4 cc. of acetic anhydride at room temperature. Addition of water followed by collection and drying of the precipitate afforded 1.25 g. of the monoacetate with m.p. 245–247°. Crystallization from acetone–hexane gave a sample with m.p. 253–255°, $[\alpha]_D$ −90°, $\nu_{max}^{CHCl_3}$ 1736 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.17; H, 9.04.

Δ⁴-22a-Spirosten-3-one-6β-ol Acetate (V).—Dry hydrogen chloride gas was bubbled through a solution of 250 mg. of the monoacetate IVb in 100 cc. of ice-cooled chloroform (previously washed with concentrated sulfuric acid to remove alcohol) for 3 hours. The solution was washed with sodium carbonate solution and water, dried and evaporated. Crystallization from acetone–hexane furnished 160 mg. (66%) of the 6β-acetoxy-Δ⁴-3-ketone (V) with m.p. 200–205°. A further purified sample exhibited m.p. 208–210°, $[\alpha]_D$ +46°, λ_{max} 236 mμ, log ε 4.13, $\nu_{max}^{CHCl_3}$ 1736 and 1674 cm.$^{-1}$, no free hydroxyl band. Identity with samples (m.p. 209–211°, $[\alpha]_D$ +48°) prepared by two different routes[1] was established through mixture m.p. and infrared comparison.

An alternative dehydration procedure[7] involved refluxing 200 mg. of the monoacetate IVb with 2 cc. of pyridine and 0.07 cc. of thionyl chloride for 10 minutes. Addition of water and ether, washing the organic layer with dilute hydrochloric acid, sodium carbonate solution and water, drying and evaporation left a residue, which on crystallization from acetone–methanol afforded 55 mg. (29%) of the 6β-acetoxy-Δ⁴-3-ketone (V) with m.p. 205–207°. The material was identical with that obtained by hydrogen chloride dehydration as evidenced by mixture m.p. determination and infrared comparison.

3-Ethylenedioxy-Δ⁵-pregnen-20-one-17α,21-diol 21-Acetate (VIIa).—A mixture of 14.0 g. of Δ⁴-pregnene-3,20-dione-17α,21-diol (Reichstein's substance S) 21-acetate (IVa), 150 cc. of 2-methyl-2-ethyl-1,3-dioxolane and 400 mg. of *p*-toluenesulfonic acid was heated to boiling and distilled for 1 hour, 100 cc. of distillate being collected in this time (the product began to precipitate after a few minutes of boiling). The mixture was cooled, the precipitate was collected and washed with cold methanol. In this way 13.8 g. (89%) of the ketal VIIa with m.p. 273–276°, $[\alpha]_D$ +3° (pyridine) no appreciable absorption in the ultraviolet, was obtained (reported m.p. 266–270°, $[\alpha]^{29}D$ −10° (pyridine)[8a]).

3-Ethylenedioxy-5ξ,6ξ-oxidopregnan-20-one-17α,21-diol-21-Acetate (VIIIa).—The aforementioned ketal (12.0 g.) was dissolved in 1500 cc. of chloroform and mixed with a chloroform solution containing 9.5 g. (2.5 equivalents) of perbenzoic acid. After 60 hours at room temperature the solution was washed with sodium carbonate solution and water, dried and evaporated. One crystallization from chloroform–hexane yielded 10.5 g. (84%) of the crude oxide VIIIa, m.p. 265–280°, $[\alpha]_D$ +22° (pyridine), no appreciable absorption in the ultraviolet, which was suitable for the subsequent step. Two further crystallizations of a small sample yielded a product with m.p. 287–295°, which may still be a stereoisomeric mixture.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.81; H, 8.25.

Allopregnane-3,20-dione-5α,6β,17α,21-tetrol 21-Monoacetate (IXa).—The oxido-ketal VIIIa (10.10 g., m.p. 265–280°, finely ground) was suspended in 300 cc. of acetone, 20 cc. of 1.5 *N* aqueous perchloric acid was added, and the mixture was stirred at room temperature for 16 hours. After being cooled in ice, the precipitate was collected and washed with cold acetone. The resulting tetrol monoacetate IXa weighed 3.90 g. and exhibited m.p. 272–274°. The filtrate was concentrated under vacuum nearly to dryness, diluted with saturated ammonium chloride solution, and the precipitate was collected, dried and crystallized from chloroform–hexane. In this way another 3.82 g. (total 7.72 g., 81%) of product with m.p. 270–275° was obtained. The analytical sample was crystallized from acetone, m.p. 279–280°, $[\alpha]_D$ +53° (ethanol), no appreciable absorption in the ultraviolet, ν_{max}^{mull} 1736, 1718 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.61; H, 8.27.

Allopregnane-3,20-dione-5α,6β,17α,21-tetrol 6,21-Diacetate (Xa).—Monoacetate (6.0 g.) was heated on the steam-bath with 15 cc. of acetic anhydride and 20 cc. of pyridine for 1 hour, and was then diluted with water. The precipitate was extracted with chloroform and the organic solution was washed with acid and base, dried and evaporated. Crystallization of the residue from acetone–benzene furnished 6.1 g. (92%) of the diacetate, m.p. 187–191°. The analytical sample exhibited m.p. 194–196°, $[\alpha]_D$ +5°, ν_{max}^{mull} 1736, 1718 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{36}O_8$: C, 64.63; H, 7.81. Found: C, 65.04; H, 8.04.

Δ⁴-Pregnene-3,20-dione-6β,17α,21-triol (6β-Hydroxy-Substance S) 6,21-Diacetate (XIa).—Dry hydrogen chloride was passed for 3 hours through an ice-cooled solution of 6.0 g. of the diacetate Xa in 900 cc. of dry alcohol-free chloroform. The solution was then washed with sodium carbonate solution and water, dried and evaporated. Trituration of the residue with ether afforded 3.06 g. of the dehydrated product with m.p. 183–187°. An additional 0.63 g. (total 3.69 g., 64%) of m.p. 185–187° was obtained by chromatography of the mother liquors on alumina. The analytical sample was crystallized from acetone–hexane, m.p. 192–193°, $[\alpha]_D$ +64°, λ_{max} 236 mμ, log ε 4.12, ν_{max}^{mull} 1736, 1718, 1702 and 1676 cm.$^{-1}$ and free hydroxyl band (reported m.p. 191–192°, $[\alpha]^{26}D$ +62°, for a synthetic product[3b]; m.p. 192–195°, $[\alpha]^{23}D$ +63°, for a microbiological product[3a]).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 66.89; H, 7.85.

Δ⁴-Pregnene-3,20-dione-6β,17α,21-triol (6β-Hydroxy-Substance S) (XIIa).—A solution of 1.13 g. of potassium hydroxide in 2 cc. of water and 10 cc. of methanol was added to an ice-cooled solution of 3.0 g. of the unsaturated diacetate XIa in 100 cc. of methanol, under a nitrogen atmosphere. The mixture was allowed to stand at room temperature for 1 hour, and was then acidified with acetic acid and concentrated to dryness in vacuum. The crystalline residue was diluted with saturated ammonium chloride solution, and the precipitate was collected, washed with water, dried and crystallized from acetone–hexane. The resulting 6β-hydroxy-substance S weighed 2.17 g. (89%) and showed m.p. 231–233° dec., $[\alpha]_D$ +53° (ethanol), λ_{max} 236 mμ, log ε 4.14, ν_{max}^{mull} 1700 and 1672 cm.$^{-1}$ and free hydroxyl band (reported for a microbiological product m.p. 230–233°, $[\alpha]^{25}D$ +58.5° (ethanol)[3a]).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 70.08; H, 8.72.

Δ⁴-Pregnene-3,20-dione-6β,17α,21-triol 21-Monoacetate (XIIb).—A solution of 500 mg. of 6β-hydroxy-substance S (XIIa) in 5 cc. of dry pyridine was cooled to −10° and treated with 155 mg. (1.1 equivalents) of acetic anhydride. After being kept for 18 hours at −10°, the solution was diluted with water and the precipitate so obtained was collected, washed with dilute hydrochloric acid and water, dried and crystallized from acetone–benzene. The resulting 21-monoacetate XIIb weighed 380 mg. and exhibited m.p. 255–257° (reported[3a] m.p. 258–260°).

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.10; H, 7.81.

Δ⁴-Pregnene-3,6,20-trione-17α,21-diol (6-Keto-Substance S) 21-Acetate (XIIIa).—6β-Hydroxy-substance S 21-monoacetate (240 mg.) in 5 cc. of C.P. acetic acid was treated dropwise at room temperature with 43 mg. (1.1 equivalents) of chromic acid previously dissolved in 0.4 cc. of water and 1.6 cc. of acetic acid. After 1 hour at room temperature the solution was diluted with water and the product was extracted with ethyl acetate. Crystallization from acetone–hexane furnished 190 mg. of 6-keto-substance S 21-acetate (XIIIa), m.p. 197–198°, $[\alpha]_D$ +10°, λ_{max} 250 mμ, log ε 4.05, $\nu_{max}^{CHCl_3}$ 1736, 1718, 1700 and 1688 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.69; H, 7.78.

3-Ethylenedioxy-Δ⁵-pregnene-11,20-dione-17α,21-diol 21-Acetate (VIIb).—A mixture of 10.0 g. of Δ⁴-pregnene-3,11,-

20-trione-17α,21-diol (cortisone) 21-acetate (VIb), 150 cc. of 2-methyl-2-ethyl-1,3-dioxolane and 400 mg. of *p*-toluenesulfonic acid was heated to boiling and distilled slowly. After a few minutes an almost homogeneous solution resulted, but a few minutes later a copious precipitate appeared. After 1.5 hours (75 cc. of distillate collected) the mixture was cooled in ice, and the precipitate was collected and washed with cold methanol to yield 10.44 g. (94%) of the ketal VIIb, m.p. 268–272°, $[\alpha]_D$ +49° (pyridine), no appreciable absorption in the ultraviolet (reported m.p. 267–268.5°, $[\alpha]^{29}_D$ +46° (pyridine)[8a]; m.p. *ca.* 264–274°, $[\alpha]^{26}_D$ +51.5° (pyridine)[8b]).

3-Ethylenedioxy-5ξ,6ξ-oxidopregnane-11,20-dione-17α,21-diol 21-Acetate (VIIIb).—The ketal VIIb (10 g.), dissolved in 1500 cc. of chloroform, was treated at room temperature with a chloroform solution containing 7.6 g. (2.5 equivalents) of perbenzoic acid for 60 hours. The precipitate which had formed was then collected to furnish 3.62 g. of the oxide VIIIb with m.p. above 300°. The filtrate was washed with sodium carbonate solution and water, dried and evaporated. Crystallization of the residue from chloroform–hexane afforded another 4.27 g. (total 7.89 g., 76%) of the oxide with m.p. above 300°. A small sample was recrystallized from the same solvent pair and yielded a specimen, m.p. above 300°, $[\alpha]_D$ +62° (pyridine), no appreciable absorption in the ultraviolet, ν^{mull}_{max} 1744, 1736, 1718 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41. Found: C, 64.62; H, 7.41.

Allopregnane-3,11,20-trione-5α,6β,17α,21-tetrol 21-Monoacetate (IXb).—A suspension of 7.8 g. of the finely ground oxide VIIIb in 300 cc. of acetone containing 20 cc. of 1.5 *N* aqueous perchloric acid was stirred at room temperature for 18 hours. The mixture was cooled in ice and the precipitate was collected to yield 4.09 g. of the tetrol monoacetate IXb, m.p. 278–280°. Concentration of the filtrate under vacuum nearly to dryness and addition of saturated ammonium chloride solution yielded 1.43 g. of product with m.p. 278–280° by filtration. Extraction of the aqueous filtrate with chloroform, removal of solvent and crystallization from acetone–hexane afforded another 0.31 g. (total 5.83 g., 79%) of the tetrol monoacetate with m.p. 276–278°. The analytical sample exhibited m.p. 279–280°, $[\alpha]_D$ +67° (ethanol), no appreciable absorption in the ultraviolet, ν^{mull}_{max} 1744, 1736, 1718 and 1702 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{32}O_8$: C, 63.28; H, 7.39. Found: C, 62.88; H, 7.39.

Allopregnane-3,11,20-trione-5α,6β,17α,21-tetrol 6,21-Diacetate (Xb).—This compound was prepared in the usual way from 5.60 g. of the tetrol monoacetate IXb, 15 cc. of acetic anhydride and 20 cc. of pyridine (steam-bath, 30 minutes). Chloroform extraction and crystallization from acetone–benzene yielded 5.58 g. (91%) of the diacetate, m.p. 222–223°, $[\alpha]_D$ +34°, ν^{mull}_{max} 1740, 1718 and 1702 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{34}O_9$: C, 62.75; H, 7.16. Found: C, 62.58; H, 7.43.

Δ^4-Pregnene-3,11,20-trione-6β,17α,21-triol (6β-Hydroxycortisone) 6,21-Diacetate (XIb).—The dehydration of 5.5 g. of the tetrol diacetate Xb in 450 cc. of alcohol-free chloroform with hydrogen chloride was carried out as described above in the 11-desoxo series. Trituration with ether afforded 4.1 g. (77%) of the unsaturated diacetate, m.p. 237–239°. Crystallization from acetone–benzene led to the analytical sample, m.p. 241–243°, $[\alpha]_D$ +128°, λ_{max} 232 mμ, log ϵ 4.13, ν^{mull}_{max} 1736, 1718, 1700 and 1676 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01. Found: C, 64.95; H, 7.36.

Δ^4-Pregnene-3,11,20-trione-6β,17α,21-triol (6β-Hydroxycortisone) (XIIc).—6β-Hydroxycortisone diacetate (3.50 g.) in 200 cc. of ice-cold methanol was allowed to stand under nitrogen for 1 hour at room temperature with 1.28 g. of potassium hydroxide previously dissolved in 2 cc. of water and 10 cc. of methanol. The solution was then acidified with 2 cc. of acetic acid, concentrated in vacuum to *ca.* 15 cc. and diluted with 150 cc. of water. Further concentration (to *ca.* 100 cc.) removed most of the remaining methanol and caused the separation of a dark yellow resin which adhered to the sides of the flask. The almost clear water solution was decanted and cooled in ice, whereupon 2.51 g. (88%) of 6β-hydroxycortisone separated as small flat needles with m.p. 225–228°. Crystallization from methanol–ether afforded the analytical specimen, m.p. 236–238°, $[\alpha]_D$ +117° (ethanol), λ_{max} 232 mμ, log ϵ 4.14, ν^{mull}_{max} 1700 and 1674 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.04; H, 7.79.

Δ^4-Pregnene-3,11,20-trione-6β,17α,21-triol 21-Monoacetate (XIId).—This compound was prepared from 500 mg. of 6β-hydroxycortisone (XIIc) and 160 mg. (1.2 equivalents) of acetic anhydride in 3 cc. of pyridine at −10°, as described above for the 11-desoxo derivative XIIb. After addition of water, the product was extracted with ethyl acetate (3 50-cc. portions), and the organic extract was washed with small volumes of dilute hydrochloric acid, sodium bicarbonate solution and water, dried and evaporated. Chromatographic purification on 25 g. of neutral alumina, and crystallization of the fractions eluted with ether–chloroform from acetone–benzene, afforded 215 mg. of the 21-monoacetate XIId with m.p. 246–248°, ν^{mull}_{max} 1736, 1718, 1700 and 1674 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.97; H, 7.38.

Δ^4-Pregnene-3,6,11,20-tetrone-17α,21-diol (6-Ketocortisone) 21-Acetate (XIIIb).—The oxidation of 170 mg. of 6β-hydroxycortisone 21-monoacetate (XIId) in 5 cc. of C.P. acetic acid was carried out with 32.5 mg. (1.2 equivalents) of chromic acid dissolved in 2 cc. of 80% aqueous acetic acid for 1 hour at room temperature. Addition of water followed by exhaustive extraction with ethyl acetate and crystallization from acetone–hexane yielded 115 mg. of 6-ketocortisone 21-acetate with m.p. 204–206°. The analytical sample was obtained by crystallization from methanol and acetone–hexane, and exhibited m.p. 210–212°, $[\alpha]_D$ +115°, λ_{max} 245 mμ, log ϵ 4.04, $\nu^{CHCl_3}_{max}$ 1736, 1718, 1700 and 1688 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.65; H, 6.75.

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