Experimental[6]

$\Delta^{3,5,7}$-Cholestatriene-3-ol Acetate.—A solution of 200 mg. of $\Delta^{4,6}$-cholestadiene-3-one[7] in 10 ml. of acetic anhydride and 20 ml. of acetyl chloride was refluxed for 6 hours, and evaporated *in vacuo*. The residue was treated with methanol which in turn was removed by evaporation *in vacuo*. The methanol treatment was repeated. One recrystallization from methanol afforded 0.18 g., m.p. 91–95°; $\lambda_{max}^{abs.\ alc.}$ 302–303, 316 and 331 mμ, ε13000, 15700 and 11000, respectively (59% *"spectroscopic"* yield based on ϵ_{316} 22000). Three further recrystallizations from methanol yielded 60 mg. (27% yield) of pure enol acetate, m.p. 101–102°; $\lambda_{max}^{abs.\ alc.}$ 302.5, 316 and 331 mμ, ε 17300, 21900 and 15300, respectively; $[\alpha]^{27}D$ −145° (7.2 mg., αD −0.51°). The m.p. was undepressed on admixture with the sample prepared from the $\Delta^{4,7}$-3-one. The infrared spectra were identical in all respects.

The first three mother liquors were combined, and evaporated *in vacuo* and gave an oily residue, $\lambda_{max}^{abs.\ alc.}$ 284–287 mμ (starting material?).

$\Delta^{3,5,7}$-Androstatriene-3,17β-diol-3-acetate-17-benzoate.—To a solution of 0.61 g. of $\Delta^{4,6}$-androstadiene-17β-ol-3-one benzoate[8] in 2 ml. of toluene was added 7 ml. each of acetic anhydride and acetyl chloride. The mixture was refluxed for 4 hours, and was worked-up as above; wt. 0.16 g. (from methanol), m.p. 154–156°; $\lambda_{max.}^{abs.\ alc.}$ 228, 302, 314 and 329 mμ, ε17600, 18200, 22000 and 15500, respectively, $[\alpha]^{27}D$ −71.4° (16 mg., αD −0.57°); 24% yield.

Anal.[9] Calcd. for $C_{28}H_{32}O_4$ (432.54): C, 77.75; H, 7.46. Found: C, 77.53; H, 7.69.

(6) All m.ps. are uncorrected, and were determined with uncalibrated Anschütz thermometers. Optical rotations were performed by solution of the sample in chloroform to make a 2 ml. solution, and were determined in a 1-dm. semi-micro tube.

(7) A. L. Wilds and C. Djerassi, THIS JOURNAL, **68**, 1719 (1946).

(8) C. Meystre and A. Wettstein, *Experientia*, **2**, 408 (1946).

(9) We wish to thank Mr. Samuel S. Modes for the microanalysis.

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Steroidal Cyclic Ketals. IV.[1] The Conversion of 11-Keto- to 11α-Hydroxysteroids. The Preparation of 11-*Epi*-hydrocortisone, and Δ^4-Androstene-11α-ol-3,17-dione

BY SEYMOUR BERNSTEIN, RUDDY LITTELL AND JAMES H. WILLIAMS

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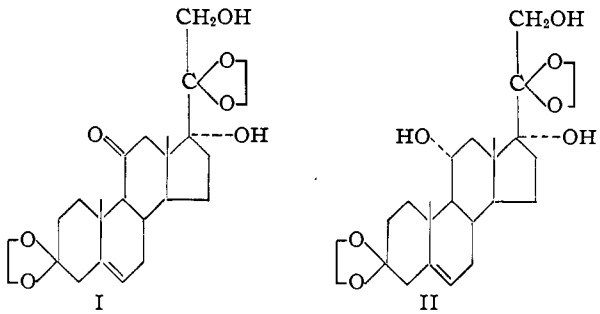
We have recently reported[1] that reduction of the diethylene ketal of cortisone (Δ^5-pregnene-17α,21-diol-3,11,20-trione-3,20-di-ethylene ketal) (I) in tetrahydrofuran with excess lithium aluminum hydride in ether produced not only the expected 11β-hydroxy compound (di-ethylene ketal of hydrocortisone) (58% yield), but also the 11α-hydroxy-compound (di-ethylene ketal of 11-*epi*-hydrocortisone) (II) (8% crude yield). Acid hydrolysis of the latter afforded 11-*epi*-hydrocortisone. This constituted the first time the 11α-epimer has been isolated and characterized in such a reduction. Moreover, the product itself was of interest as it differs solely from the physiologically important hydrocortisone by the configuration of the C-11 hydroxyl group.



(1) Paper III, R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, in press.

The microbiological preparation of 11-*epi*-hydrocortisone has been reported by Murray and Peterson,[2] and by Fried and co-workers.[3] Romo and co-workers[4] have announced the conversion of 11α-hydroxyprogesterone to 11-*epi*-hydrocortisone by incubation of the former with adrenal breis, as well as the chemical synthesis of 11-*epi*-hydrocortisone diacetate from Δ^{16}-allopregnene-3β,11α-diol-20-one diacetate. A closely related synthesis of 11-*epi*-hydrocortisone diacetate has been described by Hershberg and co-workers.[5] It is to be noted that neither the Syntex nor Schering groups have prepared chemically the free steroid, 11-*epi*-hydrocortisone.

In view of the need for a more facile preparation of 11-*epi*-hydrocortisone, and, in general, of 11α-hydroxy-Δ^4-3-ketosteroids, this Laboratory has undertaken a study of the reduction of 11-ketosteroids. While this work was in progress there appeared two publications[5,6] which have an important bearing on this problem. It was shown that reduction of an 11-keto group with sodium and propanol gave in good to excellent yields the corresponding 11α-hydroxy compound. In light of this work, we wish to record that this conversion has been accomplished independently in this Laboratory by use of lithium in liquid ammonia in the presence of alcohol.[7] Under these conditions, the diethylene ketal (I) of cortisone was transformed in 82% yield to the practically pure 11α-hydroxy compound (II). Compound II was identical with the material obtained in the lithium aluminum hydride reduction. Acid hydrolysis gave in 60% yield pure 11-*epi*-hydrocortisone.

This procedure, which involves protection of the reactive keto-groups as ethylene ketals followed by lithium–liquid ammonia–alcohol reduction of the 11-keto group, is apparently general, and has been applied successfully to adrenosterone. The latter was converted accordingly into Δ^4-androstene-11α-ol-3,17-dione.

Experimental[8]

Diethylene Ketal of 11-*epi*-Hydrocortisone (Δ^5-Pregnene-11α,17α,21-triol-3,20-dione-3,20-diethylene Ketal) (II).—

(2) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769 (July 8, 1952).

(3) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952).

(4) J. Romo, A. Zaffaroni, J. Hendrichs, G. Rosenkranz, C. Djerassi and F. Sondheimer, *Chemistry and Industry*, 783 (1952).

(5) H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, THIS JOURNAL, **74**, 4470 (1952).

(6) H. Heusser, R. Anliker and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952).

(7) This reduction procedure was suggested by the work of F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 2696 (1952).

(8) All m.ps. are uncorrected and were determined with uncalibrated Anschütz thermometers. All optical rotations are for 2 ml. of solution in the stated solvent and were determined in a 1-dm. semi-micro tube.

A stirred solution of I (0.85 g.) in 35 ml. of dioxane, 10 ml. of ether, 6 ml. of absolute alcohol and 150 ml. of liquid ammonia was treated portionwise with 1 g. of lithium metal. The mixture was stirred at room temperature for two hours when the excess ammonia had spontaneously evaporated. Extraction with ethyl acetate and evaporation *in vacuo* afforded about 900 mg. of white powder, m.p. 288–291°. The crude product was treated with 40 ml. of acetone, cooled and practically pure *II* was collected; wt. 700 mg., m.p. 297–298°, yield, 82%.

A 70-mg. sample recrystallized from methanol–acetone afforded 50 mg. of pure II, m.p. 300–301°. Admixture m.p. determination with an authentic sample[1] showed no depression; $[\alpha]^{26}D$ −36° (19.3 mg., pyridine, αD −0.35°).

11-*epi*-Hydrocortisone.—Compound II (0.4 g., m.p. 297–298°) in 30 ml. of methanol and 4 ml. of 8% (v./v.) sulfuric acid was hydrolyzed in the manner previously described.[1] This gave 193 mg. (60% yield) of pure 11-*epi*-hydrocortisone (recrystallized from acetone–petroleum ether, b.p. 64–66°), m.p. 214–216°, $[\alpha]^{25}D$ +116° (20.1 mg., absolute alcohol, αD +1.16°), $\lambda_{max.}^{abs.\ alc.}$ 241–242 mμ, ε 14,800. Admixture m.p. determination, and absorption analysis (infrared, and sulfuric acid chromogen spectra) showed identity with an authentic sample.[1]

Diethylene Ketal of Adrenosterone (Δ⁵-Androstene-3,11,-17-trione-3,17-diethylene Ketal).[9] **A.**—Adrenosterone[10] [λ_{max}^{nujol} 1730 cm.$^{-1}$ (17-keto), 1695 cm.$^{-1}$ (11-keto), 1660 cm.$^{-1}$ (3-keto), 1600 cm.$^{-1}$ (Δ⁴), 1258 cm.$^{-1}$ (weak absorption), no hydroxyl absorption][11] (0.3 g.) in 25 ml. of benzene was treated with 2.2 ml. of ethylene glycol and 9 mg. of *p*-toluenesulfonic acid monohydrate in the manner previously described[12] (reflux, 5.5 hours). The crude product was recrystallized from ether, and ether–petroleum ether (64–66°); wt. 0.12 g., m.p. 184.5–185.5°, $\lambda_{max}^{abs.\ alc.}$ none; λ_{max}^{nujol} 1695 cm.$^{-1}$ (11-keto), 1262 cm.$^{-1}$ (weak absorption), no hydroxyl absorption; $[\alpha]^{29}D$ −41° (13.5 mg., chloroform, αD −0.28°).

Anal.[13] Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 70.84; H, 8.28.

B.—In another run with 1 g. of adrenosterone, 50 ml. of benzene, 8 ml. of ethylene glycol and 30 mg. of *p*-toluenesulfonic acid monohydrate (reflux, 6 hours), there was obtained 0.93 g. (72%), m.p. 182–184°.

Δ⁵-Androstene-11α-ol-3,17-dione-3,17-di-ethylene Ketal.—The diketal of adrenosterone (0.68 g.) in 25 ml. of dioxane, 5 ml. of absolute alcohol and 140 ml. of liquid ammonia was treated with about 1 g. of lithium in the manner described above. Evaporation *in vacuo* of the ethyl acetate extract afforded 0.67 g. of a white powder, m.p. 196–210°. One recrystallization from acetone–petroleum ether (64–66°) gave 0.4 g. (58%), m.p. 217–220°. An aliquot (150 mg.) on further recrystallization gave 120 mg., m.p. 219.5–221°, λ_{max}^{nujol} 3450 cm.$^{-1}$ (11-hydroxy), 1259 cm.$^{-1}$ (weak absorption), no carbonyl absorption; $[\alpha]^{26}D$ −71° (25.5 mg., chloroform, αD −0.90°).

Anal. Calcd. for $C_{23}H_{34}O_5$ (390.50): C, 70.74; H, 8.78. Found: C, 70.98; H, 8.72.

Δ⁵-Androstene-11α-ol-3,17-dione-11-acetate-3,17-di-ethylene Ketal.—The free steroid (100 mg.) in pyridine was acetylated at room temperature, and afforded 53 mg. of acetate (recrystallized from acetone–methanol), m.p. 199–200°, λ_{max}^{nujol} 1718 cm.$^{-1}$ (11-acetoxy), 1252 cm.$^{-1}$ (strong absorption, 11-acetoxy), no hydroxyl absorption; $[\alpha]^{25}D$ −92° (12.2 mg., chloroform, αD −0.56°).

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.27; H, 8.25.

Δ⁴-Androstene-11α-ol-3,17-dione.—A solution of the 11α-ol-3,17-diketal (200 mg., m.p. 217–220°) in 5 ml. of glacial acetic acid was heated on the steam-bath, and was treated with 2 ml. of water. The heating was continued for 25 minutes when additional water was added. The mixture was cooled and neutralized with sodium bicarbonate solution. The crystals were collected and washed with water, 100 mg. (60%), m.p. 224–227°. Two recrystallizations from acetone–petroleum ether (64–66°) gave 65 mg., m.p. 227.5–229°, $\lambda_{max}^{abs.\ alc.}$ 241 mμ, ε 14,800; λ_{max}^{nujol} 3390 cm.$^{-1}$ (11-hydroxy), 1735 cm.$^{-1}$ (17-keto), 1645 cm.$^{-1}$ (3-keto), 1606 cm.$^{-1}$ (Δ⁴); $[\alpha]^{25}D$ +165° (11 mg., chloroform, αD +0.91°), $[\alpha]^{25}D$ +146° (11.5 mg., absolute alcohol, αD +0.84°); literature[2]: m.p. 226–227°, $[\alpha]^{24}D$ +162° (chloroform).

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(9) This preparation was carried out by Robert Lenhard.

(10) T. Reichstein, *Helv. Chim. Acta*, **20**, 953 (1937).

(11) We wish to thank William Fulmor for the infrared spectrograms.

(12) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(13) We wish to thank Louis M. Brancone, Samuel S. Modes and Edward B. Ruffing, Jr., for the microanalytical data.

The High Field Conductance of Aqueous Solutions of Glycine at 25°[1]

BY DANIEL BERG AND ANDREW PATTERSON, JR.

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The high field conductance of aqueous solutions of glycine, in the order of 0.1 to 1.6 molar, has been measured relative to hydrochloric acid at 25°. Two previous determinations of the high field conductance of glycine solutions have been reported.[2,3] These two sets of determinations are not in agreement with the observations reported herewith, and accordingly some discussion and explanation are in order. In this connection our results for a group of preliminary experiments on three separate samples of glycine are informative; these results are also presented briefly.

Experimental and Results

Both low and high field conductance measurements were carried out according to the procedure of Gledhill and Patterson[4] using a differential pulse transformer bridge circuit. The temperature control was to within 0.015°; the temperature of 25° was established with reference to a recently calibrated platinum resistance thermometer.

One conductance measurement was made on an unpurified stock sample of glycine. In this case the solid amino acid was added to the conductance cell with a spatula until a desired resistance was obtained. The concentration was determined to be approximately 0.12 molar by evaporating the water from a weighed portion of the solution and weighing the residue. The results obtained are shown as the lowest curve in Fig. 1. A second determination was made on a three-times recrystallized portion of the material originally employed. The glycine was recrystallized from conductivity water, filtered under suction, washed, and finally dried in a desiccator over sulfuric acid. The amount of material obtained was sufficient only to bring the cell resistance to approximately 3600 ohms, which was higher than desired. The concentration was approximately 0.6 molar. The results of the high field conductance determination on this solution are shown as the highest curve in Fig. 1. Because of the striking difference between these results and those obtained on the unpurified sample, approximately 10^{-5} mole of ammonium chloride was added to the liter of glycine solution in the conductance cell to bring the resistance to 1200.0 ohms and the high field conductance redetermined on the mixed electrolyte solution. The results are shown as curve C of Fig. 1. Finally, determinations were made on a once-recrystallized sample of Eastman ammonia-free glycine. The results of two determinations on the same solution are shown as curve B of Fig. 1. The concentration of the glycine solution was 1.644 molal, determined from the carefully weighed quantities of glycine and conductivity water used in preparation of the solution. In all cases a hydrochloric acid solution of appropriate resistance was used as reference solution.

(1) Contribution No. 1101 from the Department of Chemistry Yale University.

(2) M. Wien, *Phys. Z.*, **32**, 545 (1931).

(3) O. Blüh and F. Terenuink, *J. Chem. Phys.*, **18**, 1664 (1950).

(4) J. A. Gledhill and A. Patterson, *J. Phys. Chem.*, **56**, 999 (1952); also *Rev. Sci. Instr.*, **20**, 960 (1949).