Anal. Calcd. for $C_{23}H_{36}O_6$: C, 70.37; H, 9.24. Found: C, 70.25; H, 9.41.

Pregnane-17α,20β-diol-3,11-dione 20-Acetate (X). (a).—A solution of 1.20 g. of 3,3-dimethoxypregnane-17α-ol-11,20-dione (VII) in 40 ml. of C.P. methanol was added to a solution of 1.2 g. of sodium borohydride in 4 ml. of water. The mixture was allowed to stand at room temperature (24°) for three hours and then processed as before. Hydrolysis of the dimethoxy group followed by acetylation as described above yielded 1.17 g., m.p. 183–190°. Recrystallization from ethanol gave two crops: 0.61 g., m.p. 215–222°, and 0.06 g., m.p. 251–253°. A mixture m.p. of the second crop with pregnane-11β,17α,20β-triol-3-one 20-acetate showed no depression, and the infrared spectra were identical. A second crystallization of the first crop yielded 0.52 g. of X solvated with ethanol, m.p. 222–224°, $[\alpha]^{25}D$ +59.5° (acetone); reported[10] m.p. 222–224°.

Anal. Calcd. for $C_{23}H_{34}O_6 \cdot C_2H_5OH$: C, 68.77; H, 9.23. Found: C, 68.66; H, 9.61.

(b).—A solution of 0.50 g. of pregnane-11β,17α,20β-triol-3-one 20-acetate in 75 ml. of C.P. acetone and 7.5 ml. of water was cooled to 3° and treated with 0.35 g. of N-bromoacetamide. After 18 hours at 3°, a solution of 1 g. of sodium sulfite in a minimum amount of water was added and the acetone was removed under reduced pressure. The concentrated suspension was diluted with water and the solid collected with suction weighed 0.48 g., m.p. 218–220°. Recrystallization from ethanol gave 0.42 g., m.p. 223–225°, $[\alpha]^{26}D$ +59.6° (acetone). A mixture m.p. with the sample prepared in (a) showed no depression.

3,3-Dimethoxypregnane-11,20-dione (XII).—A solution of 1.00 g. of pregnane-3,11,20-trione (XI) in 40 ml. of C.P. methanol was treated with 1.00 g. of selenium dioxide and allowed to stand 2 days at room temperature. The solution was made alkaline by the addition of 1 g. of potassium hydroxide in methanol, and poured into water. Filtration yielded 0.85 g. of material melting at 136–143°. Recrystallization from hexane gave 0.75 g., m.p. 140–142°, $[\alpha]^{25}D$ +130.4° (chloroform).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.48; H, 9.85.

Pregnan-20β-ol-3,11-dione 20-Acetate (XVI).—A solution of 1.70 g. of 3,3-dimethoxypregnane-11,20-dione in 80 ml. of C.P. methanol containing 0.2 g. of potassium hydroxide was added to a solution of 3.40 g. of sodium borohydride in 8 ml. of water. After refluxing for 16 hours, the solution was cooled and worked up as previously described. The dimethoxy group was hydrolyzed by treatment with 50% acetic acid and the residue was acetylated, again as described previously in the formation of X. This material was taken up in 100 ml. of C.P. acetone and 20 ml. of water. The solution was cooled to 3° and 1.78 g. of N-bromoacetamide was added. After 3 hours at 3°, the solution was poured into 1 l. of water containing 3 g. of sodium sulfite. Filtration yielded 1.43 g. of solid melting at 150–170°. This material was taken up in C.P. benzene and chromatographed on 17 g. of Florisil (100/200 mesh). Elution with benzene gave 0.96 g. of material, m.p. 165–198°. Two recrystallizations from methanol yielded 0.49 g., m.p. 201–203°, $[\alpha]^{25}D$ +66.6° (acetone); reported[11] m.p. 201–203°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.56; H, 9.45.

(10) L. H. Sarett, THIS JOURNAL, **71**, 1169 (1949).

(11) L. H. Sarett, *ibid.*, **71**, 1165 (1949).

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Steroidal Cyclic Ketals. XI.[1] The Conversion of 11-*epi*-Hydrocortisone into Hydrocortisone

BY WILLIAM S. ALLEN, SEYMOUR BERNSTEIN AND RUDDY LITTELL

RECEIVED JULY 1, 1954

11-*epi*-Hydrocortisone (I) by use of a modified procedure was converted into its 3,20-bis-ethylene ketal (II) in over 70% yield. The latter was selectively oxidized at the C-11-hydroxyl group by chromium trioxide–pyridine complex to afford in 89% yield the bis-ethylene ketal (IIIa) of cortisone. Reduction of IIIa with sodium borohydride in tetrahydrofuran and aqueous sodium hydroxide, followed by acid hydrolysis gave in 72% yield (from IIIa) hydrocortisone (V). These transformations established a four step process for the conversion of 11-*epi*-hydrocortisone (I) into hydrocortisone (V) in 45–50% yield.

The facile conversion of Reichstein's Substance S into 11-*epi*-hydrocortisone (I) by microbiological hydroxylation is now well established.[2] This remarkable transformation with the subsequent conversion (70%) of I into cortisone acetate[2] constituted one of the most direct syntheses of the latter.

However, the preparation in good yield of hydrocortisone (V) from 11-*epi*-hydrocortisone (I), has presented a more complex problem.[3] An obvious solution would appear in the utilization of cortisone as an intermediate prepared as indicated. Two methods have been described for the conversion of cortisone (from its acetate) into hydrocortisone.[4] Both entailed selective protection of the C-3 and 20-carbonyl groups of cortisone by either semicarbazone[4a] or ethylene ketal[4b] formation. The intermediate was reduced with a metal hydride, and the reduction product in turn was converted into hydrocortisone acetate[4a] or hydrocortisone.[4b] These processes afforded low yields, and were only of academic interest.

Subsequently, Fried and Sabo[5] announced an essentially five-step synthesis of hydrocortisone acetate from 11-*epi*-hydrocortisone (I) *via* 9-dehydro-Reichstein's Substance S acetate ($\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate).[6]

(1) Paper X, S. Bernstein, Milton Heller and Stephen M. Stolar, THIS JOURNAL, **76**, 5674 (1954).

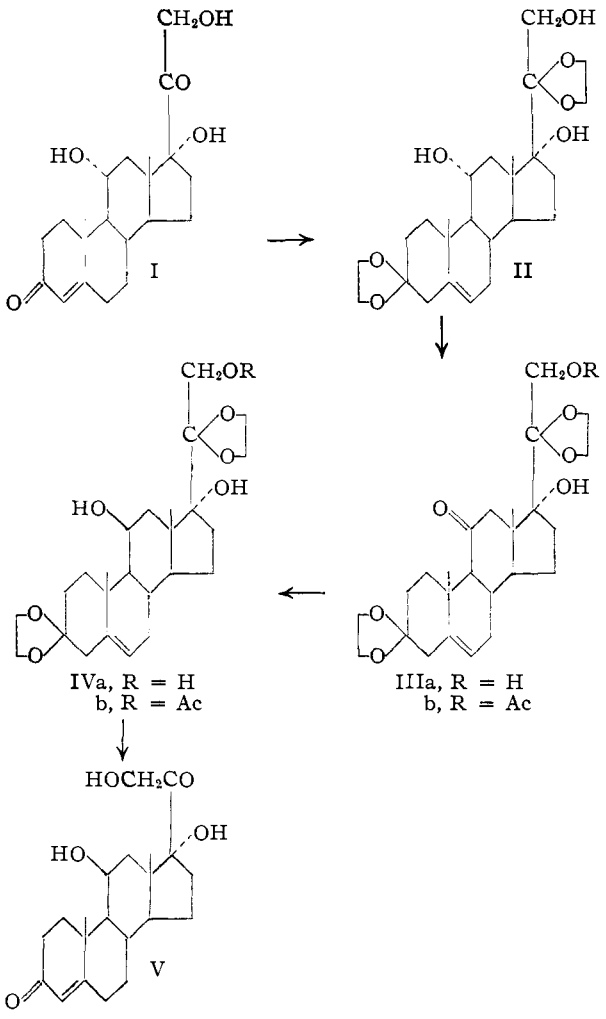
(2) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769 (July 8, 1952); D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, H. C. Murray, H. M. Leigh, A. Weintraub and L. M. Reineke, THIS JOURNAL, **75**, 412 (1953); J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, *ibid.*, **74**, 3962 (1952); F. W. Kahnt, C. Meystre, R. Neher, E. Vischer and A. Wettstein, *Experientia*, **8**, 422 (1952).

(3) Model substance work recently carried out in this Laboratory [S. Bernstein, R. Lenhard and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954)] has indicated that any Walden inversion approach for the conversion of 11-*epi*-hydrocortisone (I) into hydrocortisone (V) would be difficult.

(4) (a) N. L. Wendler, Huang-Minlon and M. Tishler, THIS JOURNAL, **73**, 3818 (1951); (b) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(5) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

(6) This compound has been prepared in this Laboratory by an independent route from the bis-ethylene ketal IVb of hydrocortisone acetate [S. Bernstein, R. Littell and J. H. Williams, *ibid.*, **75**, 4830 (1953); see also R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, *ibid.*, **75**, 4722 (1953)].



This pathway was investigated to avoid the use of ketone protective groupings. No over-all yield was given, and full evaluation of this process must await the detailed publication of the Squibb investigators.

We wish here to report on a number of experiments which have an important bearing on the problem of converting 11-*epi*-hydrocortisone (I) into hydrocortisone (V). An outstanding feature of this work is that the bis-ethylene ketal III of cortisone, the key intermediate in our previously described[4b] hydrocortisone synthesis, may be synthesized without proceeding through cortisone itself. Thus, we have succeeded in by-passing the cortisone ketalization step which was the principal deterrent to the exploitation of such a pathway to hydrocortisone (V).

It has been found that 11-*epi*-hydrocortisone (I) may be directly converted in good yield into its 3,20-bis-ketal II, which was identical in all respects with the product prepared by the reduction of the bis-ethylene ketal III of cortisone with either lithium aluminum hydride[4b] or lithium–liquid ammonia–alcohol.[7] Two related methods have been studied for the preparation of the bis-ethylene ketal II of 11-*epi*-hydrocortisone from its free steroid I. By use of the conventional Salmi[8] method (benzene, ethylene glycol and *p*-toluenesulfonic acid) a 63% yield of the desired product was readily obtained. By use of a modified procedure the yield was increased to over 70%. This new procedure[9] does not require benzene. A mixture of the steroid, ethylene glycol (large excess to serve both as reactant and solvent) and *p*-toluenesulfonic acid was stirred and distilled under reduced pressure (about 2 mm.) at a slow rate for about 5 hours. These conditions gave a distillation temperature of about 80°, and ethylene glycol and water codistilled. The ethylene glycol which distilled was not replaced. During the course of the reaction, the desired bis-ketal II separated.

This modified procedure has also been successfully applied to progesterone and cortisone acetate, and in both cases significant increases in yield were observed. However, it appeared not to offer any advantage over the conventional method when applied to cortisone (free alcohol), and Reichstein's Substance S (free alcohol).

The bis-ethylene ketal II of 11-*epi*-hydrocortisone was in turn treated with chromium trioxide–pyridine complex,[10] and the compound was *selectively* oxidized at the C-11-hydroxyl group to afford in 89% yield the bis-ethylene ketal IIIa of cortisone. The product was in addition converted into its acetate IIIb.

Thus a new relay to the bis-ethylene ketal IIIa of cortisone was established and, consequently, it was decided to reinvestigate its conversion into hydrocortisone (V). The reduction of the bis-ketal IIIa in tetrahydrofuran with lithium aluminum hydride has been reported to give the bis-ethylene ketal IVa of hydrocortisone in 58% yield.[4b] The simultaneous elaboration of the 11α-epimer II was found to be of low but significant percentage (8% crude). The actual amount of the 11α-epimer formed in this reduction has been estimated by use of paper chromatographic techniques, and was found to be practically identical with that reported, *i.e.*, about 7%.[11]

For several reasons (yield, safety hazard, etc.) the lithium aluminum hydride reduction was unsatisfactory and, consequently, our attention was directed to a study of this reduction with sodium borohydride under a variety of conditions.[12] The

(7) S. Bernstein, R. Littell and J. H. Williams, THIS JOURNAL, **75**, 1481 (1953).

(8) E. Salmi, *Ber.*, **71**, 1803 (1938); E. Salmi and V. Rannikko, *ibid.*, **72**, 600 (1939).

(9) We are indebted to Dr. J. R. McCormick of our Chemical Production Section for the conception and early development of this modification.

(10) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(11) The amount of 11α-epimer was determined in the following manner. The reduction mixture was hydrolyzed with dilute sulfuric acid[4b] to yield a mixture of free steroids, which was then examined by paper chromatography according to I. E. Bush [*Biochem. J.*, **50**, 370 (1952)]. The chromatography was carried out on untreated Whatman No. 1 paper with a benzene (2):water(1):methanol(1) solvent system; and was allowed to run for about 3 hours. The steroids were detected with an alkaline Blue Tetrazolium spray. It was assumed that the amount of free steroid determined represented very closely the amount of the ketal derivative formed in the reduction.

(12) For the reduction of a C-11-carbonyl group with sodium borohydride, see H. Heymann and L. F. Fieser, THIS JOURNAL, **73**, 5252 (1951); H. L. Herzog, M. A. Jevnik and E. B. Hershberg, *ibid.*, **75**, 269 (1953); E. P. Oliveto, T. Clayton and E. B. Hershberg, *ibid.*, **75**, 486 (1953); and E. P. Oliveto and E. B. Hershberg, *ibid.*, **75**, 488 (1953).

reduction of IIIa to the bis-ethylene ketal IVa of hydrocortisone may be performed in about 90% yield with an exceedingly large excess of sodium borohydride in a mixture of tetrahydrofuran and aqueous sodium hydroxide.[13] The reduction mixture was refluxed for 20–40 hours dependent on the amount of excess sodium borohydride employed. Paper chromatographic studies[11] indicated the formation of about 2% of the 11α-epimer II. It is interesting to note that the amount of the 11α-epimer formed was less than that observed with lithium aluminum hydride.

The determination of the m.p. of the bis-ethylene ketal IVa of hydrocortisone has presented a minor problem. This compound reported[4b] to melt at 184–186° (from acetone–petroleum ether) has been found to have variable melting points dependent on the method of crystallization. A melting point as high as 211–214° has been obtained for a preparation crystallized from methanol–ether. Therefore, to evaluate more definitely the yield in this reduction, the product was converted into its acetate IVb, where no m.p. difficulties were encountered. In one run, the over-all yield of IVb from the 11-keto-bisketal (IIIa) was 85%. This was highly indicative of about a 90% yield of the 11β-compound in the reduction.

In a previous publication[14] it was pointed out that in the reduction of a C-11-carbonyl group, frontal attack is possible, and that the course of the reduction is dependent on both steric and energetic factors. The lower yield of the 11α-epimer with sodium borohydride may possibly be related to the fact that sodium borohydride is a less potent reducing agent than lithium aluminum hydride.[15]

From a preparative viewpoint, it was found expedient, in light of the small amount of 11α-epimer, to hydrolyze the crude reduction product with dilute sulfuric acid for the removal of the ketal protective groups. In this manner there was obtained a 72% over-all yield of hydrocortisone (V) from the bis-ethylene ketal IIIa of cortisone.

Summarily, the four-step conversion of 11-*epi*-hydrocortisone (I) into hydrocortisone (V) was accomplished in an over-all yield of 45–50%.

Experimental

Melting Points.—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

Optical Rotations.—The sample was dissolved in the stated solvent to make a 2-ml. solution, and the rotation was determined in a 1-dm. semi-micro tube at wave length 5893 Å. (D).

Absorption Spectra.—The ultraviolet spectra were determined in absolute alcohol with a Beckman spectrophotometer (Model DU). The infrared spectra (Nujol mulls) were determined with a Perkin–Elmer spectrophotometer (Model 21).

Bis-ethylene Ketal of 11-*epi*-Hydrocortisone (Δ^5-Pregnene-11α,17α,21-triol-3,20-dione 3,20-Bis-ethylene Ketal) (II). A.—11-*epi*-Hydrocortisone (I, 0.65 g.) in 30 ml. of benzene was treated with 3.5 ml. of ethylene glycol and 19 mg. of *p*-toluenesulfonic acid monohydrate in the manner previously described[16] (3.5 hours reflux). During the course of the reaction, the bis-ketal II separated. The mixture was cooled, and treated with 0.5 ml. of 2% alcoholic potassium hydroxide solution, and a small amount of acetone. The crystals were collected, and washed with acetone; 438 mg. of practically pure II, m.p. 295–297°.

The mother liquor was evaporated under reduced pressure to a small volume. Water and salt were added, and the mixture was extracted with ethyl acetate. Evaporation gave a white powder which was slurried with acetone, and filtered. In this manner an additional 74 mg. of II was obtained, m.p. 293–295°; 63% yield.[17]

In another run, the product was recrystallized to constant m.p. from methanol–acetone–ethyl acetate, m.p. 300–301°; $[\alpha]^{24}D$ −32° (14.6 mg., pyridine, αD −0.23°). Infrared absorption analysis showed complete identity with an authentic sample; lit.[4b,7] m.p. 299–301°, $[\alpha]^{25}D$ −31° (pyridine); m.p. 300–301°, $[\alpha]^{26}D$ −36° (pyridine).

B.[18]—A mixture of 10 g. of 11-*epi*-hydrocortisone (I) (m.p. 221–224°), 270 ml. of ethylene glycol and 310 mg. of *p*-toluenesulfonic acid monohydrate was stirred and distilled at a slow rate over a period of 5 hours at about 2 mm. pressure. This gave a distillation temperature of 80 ± 2°. The reaction mixture was made alkaline with alcoholic potassium hydroxide, and was poured into water. The precipitated product was collected by filtration and was washed with a copious quantity of water, 10.9 g., m.p. 272–279° (fraction 1). The mother liquor was extracted with ethyl acetate. Evaporation and an acetone slurry of the residue afforded 0.82 g., m.p. 285–291°, λ_{max} 242 mμ ($E^{1\%}_{1\,cm.}$ 19) (fraction 2).

Fraction 1 was slurried with acetone, and gave 8.8 g. of II, m.p. 282–287°; negative ketol test; λ_{max} 241–245 mμ ($E^{1\%}_{1\,cm.}$ 11). Its infrared absorption spectrum compared well with that of an authentic sample. The mother liquor was combined with fraction 2, and by slurry treatments with acetone and ethyl acetate three additional fractions of II were obtained; 0.31 g., m.p. 294–298° (trace absorption for α,β-unsaturated ketone); 0.20 g., m.p. 291–295°, λ_{max} 240–242 mμ ($E^{1\%}_{1\,cm.}$ 17); and 0.17 g., m.p. 288–293°, λ_{max} 240 mμ ($E^{1\%}_{1\,cm.}$ 17). The yield of II was 76% based on material which showed an extinction coefficient of $E^{1\%}_{1\,cm.}$ 17 or less.

A portion of the main fraction was recrystallized from dimethylformamide–water, and ethyl acetate–methanol, m.p. 299–301°. Its infrared absorption spectrum was identical with that of an authentic sample.

Bis-ethylene Ketal of Progesterone (Δ^5-Pregnene-3,20-dione 3,20-Bis-ethylene Ketal).[18]—A mixture of 15 g. of progesterone, 300 ml. of ethylene glycol and 450 mg. of *p*-toluenesulfonic acid monohydrate was stirred and distilled at a slow rate over a period of 2 hours at 1.5 mm. pressure with a still-head temperature of 77–81°. The solution became turbid in 30 minutes, and crystals separated in 45 minutes. A purple color developed after 1 hour. The reaction mixture was made alkaline with alcoholic potassium hydroxide, and poured into an equal volume of cold water. The solid was collected and washed with a copious quantity of water; 18.9 g., m.p. 165–171°. Recrystallization from acetone afforded 12.5 g., m.p. 180–183°. Its infrared absorption spectrum was identical with that of an authentic sample. The mother liquor on concentration afforded two additional fractions, 2.6 g., m.p. 177–180°, and 0.36 g. (from acetone–methanol), m.p. 173–176°; 79% yield (based on two principal fractions); lit.[19] m.p. 181–182°, 67% yield (based on material melting at 178–182°).

Ethylene Ketal of Cortisone Acetate (Δ^5-Pregnene-17α,-21-diol-3,11,20-trione 21-Acetate 3-Ethylene Ketal).[18]—A mixture of 9.5 g. of cortisone acetate, 200 ml. of ethylene glycol and 300 mg. of *p*-toluenesulfonic acid monohydrate was stirred and distilled over a period of 4.25 hours at about 1–2 mm. pressure. During this time the reaction mixture temperature was 72–81°, and the still-head temperature was 60–80°. It was made alkaline with alcoholic potassium hydroxide and was poured into water. The solid was collected, and dried; 9.25 g. (88% "crude" yield), m.p. 260–265°, no selective absorption in the ultraviolet. Recrystallization from pyridine–water gave 8.2 g., m.p. 268–271°,

(13) D. A. Lyttle, E. H. Jensen and W. A. Struck, *Anal. Chem.*, **24**, 1843 (1952), have observed the increased stability of sodium borohydride solution upon the addition of alkali.

(14) S. Bernstein, R. H. Lenhard and J. H. Williams, *J. Org. Chem.*, **18**, 1166 (1953).

(15) S. W. Chaikin and W. G. Brown, THIS JOURNAL, **71**, 122 (1949).

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

(17) The stated yields are for preparations of sufficient purity for further transformations.

(18) This preparation was carried out by Stephen M. Stolar.

(19) R. Antonucci, S. Bernsteiu, R. Lenhard, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

78% yield; lit.[4b] m.p. 267–268.5°; 64% yield (based on material melting at 265–267°).

Bis-ethylene Ketal of Cortisone (Δ^5-Pregnene-17α,21-diol-3,11,20-trione 3,20-Bis-ethylene Ketal) (IIIa).—Chromic anhydride (150 mg.) was added to chilled pyridine (15 ml.), and the mixture was allowed to warm to room temperature. A solution of II (250 mg.) in pyridine (20 ml.) was added, and the mixture was allowed to stand at room temperature for 20 hours. It was poured into 50 ml. of water containing 0.7 g. of sodium bicarbonate. The mixture was steam-distilled for about 0.5 hour, and the product was extracted with ethyl acetate. The extract was washed with water, dried and evaporated under reduced pressure. This afforded 220 mg. (89% yield) of slightly impure IIIa, m.p. 230–237°, with previous softening. Recrystallization from acetone–petroleum ether (b.p. 64–66°) gave 80 mg., m.p. 241–245°. An additional 116 mg., m.p. 238–241°, was obtained from the mother liquor. Infrared analysis showed identity with an authentic sample of the bis-ethylene ketal of cortisone.

In another run the crude bis-ketal was exhaustively recrystallized from acetone–petroleum ether (Skellysolve B), and acetone. This gave pure IIIa; m.p. 245.5–248.5°, $[\alpha]^{24}D$ −8° (20.5 mg., chloroform, αD −0.085°). Infrared analysis showed complete identity with an authentic sample; lit.[4b] m.p. 234–238.5°, $[\alpha]^{26}D$ −8° (chloroform).

Anal.[20] Calcd. for $C_{25}H_{36}O_7$ (448.54): C, 66.94; H, 8.04. Found: C, 66.92; H, 7.77.

Bis-ethylene Ketal of Cortisone Acetate (Δ^5-Pregnene-17α,21-diol-3,11,20-trione 21-acetate 3,20-Bis-ethylene Ketal) (IIIb).—The free steroid (IIIa) (m.p. 245.5–248.5°) was acetylated in the usual manner; m.p. 226.5–228.5°; $[\alpha]^{24}D$ ±0° (21.6 mg., chloroform, αD −0.03°). Its infrared spectrum was identical with that of an authentic sample; lit.[4b] m.p. 226.5–228°; $[\alpha]^{31}D$ ±0° (chloroform).

Reduction of the Bis-ethylene Ketal IIIa of Cortisone with Sodium Borohydride.[21]—A mixture of 1.05 g. (0.0023 *M*) of IIIa, 1.25 g. (0.033 mole) sodium borohydride, 40 ml. of tetrahydrofuran, 3.5 ml. of 5% sodium hydroxide solution and 3.5 ml. of water was refluxed for 20 hours. With additional water, the mixture was refluxed for 0.5 hour more. The tetrahydrofuran was removed under reduced pressure, and the residual mixture was extracted with ethyl acetate. Evaporation under reduced pressure gave a glass which was dissolved in ether. Concentration gave a white powder; 653 mg., m.p. 186–215°. The mother liquor on evaporation afforded about 380 mg. of a glass.

Both fractions were combined, and acetylated at room temperature with 3 ml. of acetic anhydride and 5 ml. of pyridine. In this manner there was obtained 979 mg. of the acetate-bis-ketal IVb, m.p. 197–199°, 85% yield from cortisone bis-ketal (IIIa). Its infrared absorption spectrum was identical with that of an authentic sample.

Melting Point Determination of the Bis-ethylene Ketal IVa of Hydrocortisone.—Cortisone bis-ketal (IIIa) was reduced with sodium borohydride in the manner described above. In this run the product was extracted with chloroform. Evaporation gave a glass which on crystallization from acetone–petroleum ether afforded IVa, m.p. 186–210°. A portion of this material was recrystallized from methanol–ether, m.p. 211–214° with previous melt at 140–141°, and resolidification.

The remainder of IVa was acetylated. Recrystallization of the crude product from acetone–ether gave pure IVb, m.p. 207–209°; $[\alpha]^{25}D$ −27.1° (αD −0.33°, 24.36 mg., chloroform); lit.[5] m.p. 199–201°, $[\alpha]^{27}D$ −26° (chloroform).

A sample of the pure acetate IVb was saponified with 2% alcoholic potassium hydroxide, and the free steroid bis-ketal IVa was recrystallized once from acetone–ether, m.p. 170–200°.

In another hydrolysis, the free steroid bis-ketal IVa was recrystallized from acetone–petroleum ether, m.p. 181–183°.

Conversion of the Bis-ethylene Ketal IVa of Cortisone to Hydrocortisone (V).—A mixture of 1 g. (0.0022 mole) of cortisone bis-ketal (IIIa, m.p. 244–247°), 40 ml. of tetrahydrofuran, 0.50 g. (0.013 mole) of sodium borohydride, 3.5 ml. of 5% sodium hydroxide and 3.5 ml. of water was refluxed for 40 hours. The mixture was worked up in chloroform to yield 1.03 g. of a clear glass. This product in about 50 ml. of methanol was treated with 5 ml. of 8% (v./v.) sulfuric acid, and was refluxed for 50 minutes. Water (50 ml.) was added to the cooled mixture, and the methanol was removed under reduced pressure. The residual mixture was neutralized with 14 ml. of a saturated sodium bicarbonate solution, and was extracted with 500 ml. of chloroform. Evaporation gave a crystalline residue which melted at 207–210°. Recrystallization from acetone–petroleum ether afforded 514 mg. of hydrocortisone (V), m.p. 217.5–219°. An additional 65 mg. of V was obtained from the mother liquor, m.p. 212–215°; 72% yield from IIIa.

PEARL RIVER, NEW YORK

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

(21) In another reduction with 3 g. of the bis-ketal IIIa, there was isolated 9 mg. of impure bis-ethylene ketal IIa of 11-*epi*-hydrocortisone, m.p. 266–270°. The identification of this material was confirmed by infrared analysis. It should be noted that the sample of IIIa employed here was obtained directly from cortisone prepared from "Merck" cortisone acetate. Hence the possibility of trace impurities of IIa in the starting material was eliminated.

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY]

Application of the Favorskii Rearrangement to the Preparation of A-Norsteroids

BY BILL B. SMITH[1] AND HAROLD R. NACE

RECEIVED JULY 15, 1954

Treatment of 2α-bromocholestan-3-one with sodium ethoxide gave, in about 72% yield, a one-to-one mixture of 2- and 3-carbomethoxy-A-norcholestane, and in about 6% yield, dimethyl 2,3-*seco*-cholestane-2,3-dioate. Treatment of the esters with phenylmagnesium bromide, followed by dehydration, gave the corresponding diphenylethylenes. Ozonization of each of these gave 2- and 3-keto-A-norcholestane, respectively, thus establishing the structures of the rearrangement products.

Changes in the basic carbon skeleton of a steroid may cause striking changes in its physiological activity. For example, converting the A or D ring to the next higher homolog may result in increased or decreased activity.[2] It was therefore felt that the development of a method for the preparation of A-norsteroids, in high yield, would be of interest.

Among the various methods available for ring contraction, the Favorskii rearrangement appeared to offer interesting possibilities, especially since the required starting compound, 2α-bromocholestan-3-one, was readily available. Extension of the method to other steroids should be possible since α-bromoketo steroids are generally available.

Treatment of 2α-bromocholestan-3-one[3] with sodium ethoxide in refluxing ethanol yielded, after saponification of the reaction mixture, a mixture of acids, which was converted to a mixture of methyl esters for ease in handling.

(1) Abstracted from the Ph.D. Thesis of Bill B. Smith, Brown University, 1953. Research Corporation Fellow, 1951–1952; Brown University Fellow, 1952–1953.

(2) *Cf.* L. F. Fieser and M. Fieser, "The Chemistry of Natural Products Related to Phenanthrene," third edition, Reinhold Publishing Corp., New York, N. Y., 1949, Chap. 4.

(3) (a) A. Butenandt and A. Wolf, *Ber.*, **68B**, 2091 (1935); (b) E. J. Corey, THIS JOURNAL, **75**, 4832 (1953).