# ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

## 11-Oxygenated Steroids. XIII. Synthesis and Proof of Structure of $\Delta^{1,4}$-Pregnadiene-17$\alpha$,21-diol-3,11,20-trione and $\Delta^{1,4}$-Pregnadiene-11$\beta$,17$\alpha$,21-triol-3,20-dione

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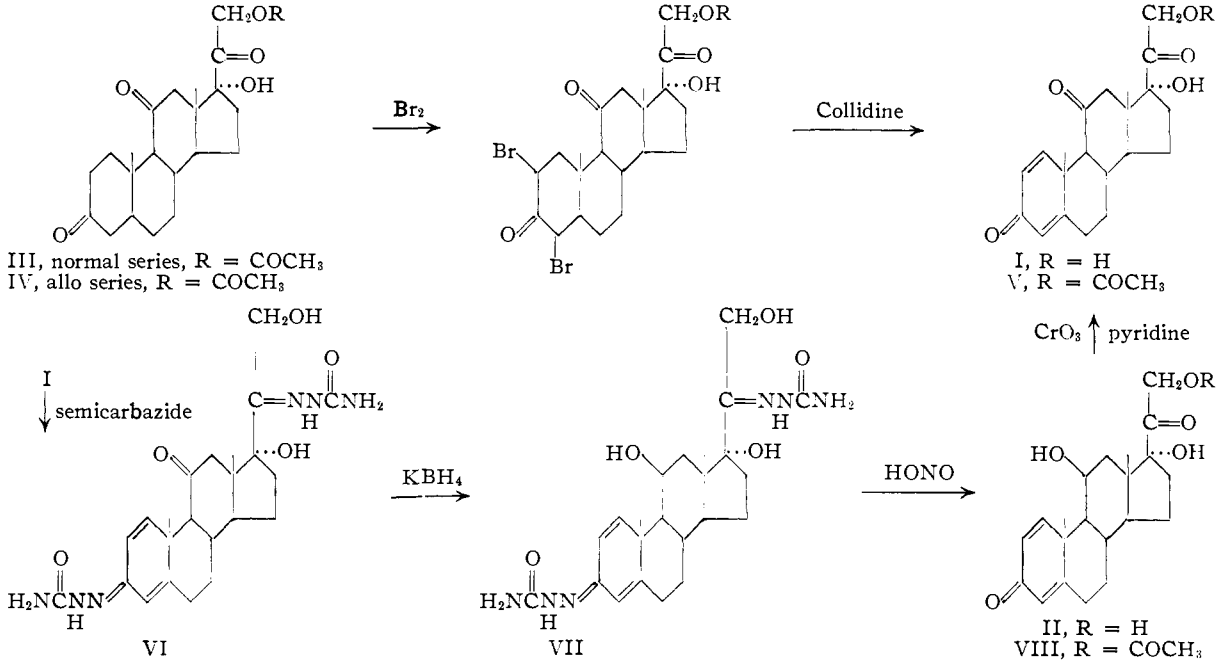
$\Delta^{1,4}$-Pregnadiene-17$\alpha$,21-diol-3,11,20-trione (I) has been synthesized from pregnane-17$\alpha$,21-diol-3,11,20-trione 21-acetate and from allopregnane-17$\alpha$,21-diol-3,11,20-trione 21-acetate. $\Delta^{1,4}$-Pregnadiene-11$\beta$,17$\alpha$,21-triol-3,20-dione (II) has been prepared from compound I. Degradation studies necessary to confirm the structures of both compounds I and II are described.

In recent reports the enhanced anti-inflammatory properties of $\Delta^{1,4}$-pregnadiene-17$\alpha$,21-diol-3,11,20-trione (I, Meticorten[2a]) and $\Delta^{1,4}$-pregnadiene-11$\beta$,17$\alpha$,21-triol-3,20-dione (II, Meticortelone[2b]) have been compared with those of cortisone and cortisol.[3a,b,c] These compounds were prepared from the readily available intermediates of cortical hormone synthesis, pregnane-17$\alpha$,21-diol-3,11,20-trione 21-acetate (III)[4] and allopregnane-17$\alpha$,21-diol-3,11,20-trione 21-acetate (IV).[5]




Dibromination[6] of III with bromine in acetic acid afforded a crude dibromide which was then dehydrobrominated by refluxing with collidine. From the dehydrobromination mixture there was isolated by chromatography, in 10–15% yield from III, $\Delta^{1,4}$-pregnadiene-17$\alpha$,21-diol-3,11,20-trione 21-acetate (V). By a similar procedure[7] IV also was converted to V. Hydrolysis of V with potassium bicarbonate in aqueous methanol gave I. The infrared spectra of both I and V displayed bands at approximately 6.00, 6.16 and 6.20 $\mu$, this triad being characteristic of the $\Delta^{1,4}$-diene-3-one grouping.[8]

The conversion of I into II followed, in principle,[9] the method of Wendler, Huang-Minlon and Tishler, for the conversion of cortisone to cortisol. Treatment of I with semicarbazide afforded the 3,20-bis-semicarbazone VI. The latter was reduced with potassium borohydride[10] to VII. At this point the conventional techniques of hydrolysis of semicarbazones were not adequate to meet the

(1) Deceased, Jan. 19, 1955.

(2) (a) Schering Corporation trademark for prednisone, formerly metacortandracin; (b) Schering Corporation trademark for prednisolone, formerly metacortandralone.

(3) (a) J. J. Bunim, M. M. Pechet and A. J. Bollet, *J. Am. Med. Assoc.*, **157**, 311 (1955); (b) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955); (c) ADDED IN PROOF.—E. Vischer, C. Meystre and A. Wettstein, *Helv. Chim. Acta*, **38**, 855 (1955), reported recently the preparation of I by the action of *Fusarium solani* on cortisone.

(4) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, THIS JOURNAL, **74**, 483 (1952).

(5) G. Rosenkranz, C. Djerassi, R. Yashin and J. Pataki, *Nature*, **168**, 28 (1951).

(6) C. Djerassi and G. Rosenkranz, *Experientia*, **7**, 93 (1951).

(7) G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin and C. Djerassi, THIS JOURNAL, **72**, 4081 (1950).

(8) J. Fried, R. W. Thoma and A. Klingsberg, *ibid.*, **75**, 5764 (1953).

(9) N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951).

(10) R. P. Graber and N. L. Wendler, U. S. Patent 2,628,966.

problem of hydrolyzing the semicarbazone of the $\Delta^{1,4}$-diene-3-ketone without otherwise disturbing the arrangement of the molecule. Demaecker and Martin[11] have described a method for the hydrolysis of 2,4-dinitrophenylhydrazones of $\Delta^{1,4}$-diene-3-ketones employing acetone and hydrochloric acid at room temperature for 15 days. With modifications of this technique (methanol also was present) we were unable to demonstrate the formation of II from VII. Subsequently we applied the same system to I and observed that in 24 hours at room temperature a good yield of a new product resulted. Since the infrared spectrum of this product showed that no hydroxyl groups were present and that strong C–O–C bands had appeared (the dienone and other carbonyl functions were apparently intact) we assigned to the new compound a structure analogous to that of the Mattox–Kendall rearrangement product of cortisone, namely, $\Delta^{1,4}$-pregnadiene-21-al-3,11,20-trione dimethyl acetal.[12a,b]

The hydrolysis of the semicarbazone groups of VII was finally accomplished, in about 5% yield, by treatment with nitrous acid, a procedure which apparently proceeds by a mechanism other than that of conventional hydrolytic methods.[13]

Acetylation of II with acetic anhydride in pyridine solution afforded VIII, which was in turn converted into V by oxidation with pyridine and chromic acid,[14] thus reaffirming the relationship between I and II.

The structures of I and II also were supported by degradation experiments. From the oxidation of I with sodium bismuthate[15] in aqueous acetic acid there resulted $\Delta^{1,4}$-androstadiene-3,11,17-trione (IX), whose infrared spectrum showed the characteristic bands for the $\Delta^{1,4}$-diene-3-one system, the 11-carbonyl group and the 17-carbonyl group. Dibromination of etiocholane-3,11,17-trione (X)[16] followed by collidine dehydrobromination gave IX, identical in all respects with the sample obtained *via* degradation of I. From the sodium bismuthate oxidation of II, $\Delta^{1,4}$-androstadiene-11$\beta$-ol-3,17-dione (XI) was obtained. Chromic acid oxidation of XI led to IX, identical with the previously described samples.

We wish to acknowledge the assistance of Miss Betty Blasko and Messrs. Peter Kabasakalian, Milton Yudis and Edward Townley in the interpretation of the infrared spectra.

## Experimental[17]

**$\Delta^{1,4}$-Pregnadiene-17$\alpha$,21-diol-3,11,20-trione 21-Acetate (V). A. From Pregnane-17$\alpha$,21-diol-3,11,20-trione 21-Acetate (III).**—To a stirred solution of 20.0 g. of III in 2 l. of glacial acetic acid at room temperature was added dropwise 16.8 g. of bromine in 100 ml. of acetic acid over a 30-minute period. Stirring was continued for four hours and then the pale yellow solution was poured into water. The resulting mixture was extracted with methylene chloride, the extracts were washed with water, dried over magnesium sulfate and concentrated to a residue *in vacuo*. Trituration of the residue with hexane and filtration of the solid afforded 28 g. of crude, pale yellow dibromide which was employed without further purification in the collidine dehydrobromination.

The crude dibromide was added all at once to 500 ml. of 2,4,6-collidine at reflux. After 30 minutes at reflux, the mixture was cooled and diluted with ten volumes of ether. The collidine hydrobromide which precipitated was removed by filtration, the filtrate was washed successively with dilute sulfuric acid and with water, and then dried over magnesium sulfate. The dried solution was concentrated to a residue of dark brown, amorphous solid (14.5 g.) which then was dissolved in ether–methylene chloride and chromatographed over a Florisil column (400 g.) prepared with ether. Elution with ether gave a series of crystalline fractions (m.p. > 200°) which were combined and recrystallized from acetone–hexane. There resulted 2.4 g. of V, m.p. 226–232° dec., $[\alpha]^{25}D$ +186° (dioxane), $\lambda_{max.}^{ethanol}$ 238 m$\mu$ ($\epsilon$ 16,100), $\lambda_{max.}^{Nujol}$ 2.98 $\mu$ (OH), 5.73 and 5.80 $\mu$ (20-carbonyl, 21-acetate interaction), 5.85 $\mu$ (11-carbonyl), 6.02, 6.16, 6.20 $\mu$ ($\Delta^{1,4}$-diene-3-one), 8.10 $\mu$ (21-acetate).

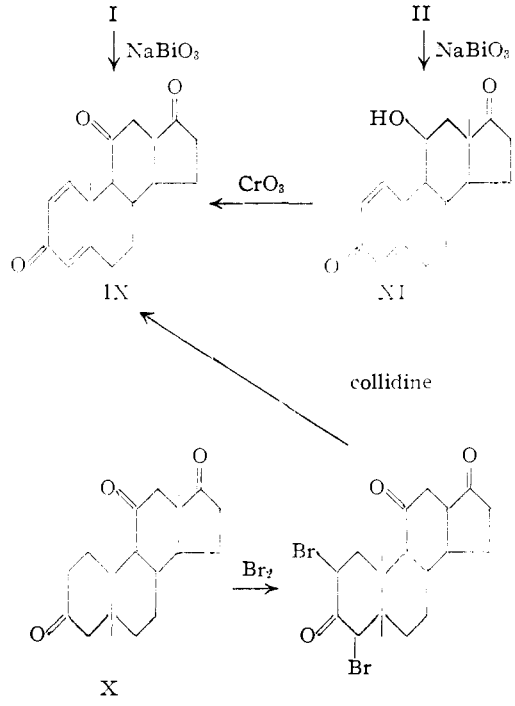
*Anal.* Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.82; H, 7.13.

Occasionally, samples of V, crystallized from the same solvents described previously, showed gross differences in the finger-print region of the infrared spectrum of a Nujol mull. Solution spectra were identical, however, and paper chromatographic analysis indicated that the samples in question were identical with authentic V, indicating polymorphism.

**B. From Allopregnane-17$\alpha$,21-diol-3,11,20-trione 21-Acetate (IV).**—2,4-Dibromoallopregnane-17$\alpha$-21-diol-3,11,-20-trione 21-acetate was prepared according to Rosenkranz and co-workers,[5] m.p. 130–135° dec., $[\alpha]^{25}D$ +92° (chloroform).

*Anal.* Calcd. for $C_{23}H_{30}O_6Br_2$: Br, 28.42. Found: Br, 28.20.

One gram of this dibromide was added to 15 ml. of refluxing 2,4,6-collidine and the mixture was refluxed for 30 minutes. The cooled mixture was diluted with ether and the collidine hydrobromide was removed by filtration. The ethereal solution was washed with dilute sulfuric acid




(11) J. Demaecker and R. H. Martin, *Nature*, **173**, 266 (1954).

(12) (a) V. R. Mattox, THIS JOURNAL, **74**, 4340 (1952); (b) D. Gould and E. B. Hershberg, *ibid.*, **75**, 3593 (1953).

(13) This technique will be described further in a later publication. See also S. Goldschmidt and W. Veer, *Rec. trav. chim.*, **66**, 238 (1947).

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

(15) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(16) H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile and E. B. Hershberg, THIS JOURNAL, **75**, 266 (1953).

(17) All m.p.'s are corrected. Analyses and optical data were obtained by the Microanalytical Department of these laboratories.

and with water until neutral. After drying, the solution was concentrated and chromatographed on Florisil prepared with ether. Elution with ether afforded a series of crystalline fractions, m.p. *ca.* 210–218° dec., with a total weight of 0.09 g. The infrared spectrum of the product was identical with that of the second mentioned polymorph (Nujol mull) described previously. Recrystallization from aqueous acetone gave colorless needles of V, m.p. 218–220°, $[\alpha]^{25}D$ +191° (dioxane), with the infrared spectrum (Nujol mull) of the first polymorph.

*Anal.* Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.70; H, 6.83.

**$\Delta^{1,4}$-Pregnadiene-17$\alpha$,21-diol-3,11,20-trione** (I).—To a solution of 0.120 g. of V in 3.3 ml. of methanol was added a solution of 0.032 g. of potassium bicarbonate in 0.5 ml. of water. The mixture was heated at reflux for about three minutes, cooled rapidly to room temperature and neutralized with dilute hydrochloric acid. The reaction mixture was diluted with water and extracted with methylene chloride. After drying, the extract was chromatographed on Florisil and the crystalline material obtained from the eluates with methylene chloride containing 1–5% methanol was recrystallized from acetone–hexane affording 50 mg. of I, m.p. 233–235° dec., $[\alpha]^{25}D$ + 172° (dioxane), $\lambda_{max}^{methanol}$ 238 m$\mu$ ($\epsilon$ 15,500), $\lambda_{max}^{Nujol}$ 3.04 $\mu$ (OH), 5.84 $\mu$ (11- and 20-carbonyls), 5.98, 6.16, 6.21 $\mu$ ($\Delta^{1,4}$-diene-3-one).

*Anal.* Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.35; H, 7.45.

**$\Delta^{1,4}$-Pregnadiene-11$\beta$,17$\alpha$,21-triol-3,20-dione** (II). **A. Formation of 3,20-Bis-semicarbazone VI of I.**—To a solution of 3.60 g. of I in 450 ml. of methanol was added a solution of 7.90 g. of semicarbazide hydrochloride in 40 ml. of water and 6.05 g. of pyridine. The reaction mixture was refluxed overnight, then 360 ml. of solvent was removed by distillation and 360 ml. of water was added. The reaction mixture was then cooled to 0° for one hour, the precipitate was removed by filtration and washed with water. There resulted 3.82 g. of tan amorphous solid (VI), m.p. 270–280° dec., $\lambda_{max}^{ethanol}$ 242, 293 m$\mu$ ($\epsilon_{242}$ 18,200, $\epsilon_{293}$ 22,100).

*Anal.* Calcd. for $C_{23}H_{32}O_5N_6$: N, 17.79. Found: N, 17.12.

**B. Reduction of the 11-Carbonyl Group of VI.**—A mixture of 5.90 g. of VI, 178 ml. of tetrahydrofuran, 90 ml. of water and 3.33 g. of potassium borohydride was refluxed overnight with stirring. The reaction mixture was cooled to room temperature and neutralized with acetic acid. Then 75 ml. of methanol and 75 ml. of water were added and the mixture was concentrated to a small volume *in vacuo*. The precipitated solid VII (5.08 g., m.p. > 350°) was collected on a filter.

**C. Nitrous Acid Cleavage of the Bis-semicarbazone VII to II.**—A solution of 1.0 g. of VII in 30 ml. of concentrated hydrochloric acid and 120 ml. of water was prepared at 23° under nitrogen. Over a 15-minute period, there then was added with stirring a solution of 0.51 g. of sodium nitrite in 5 ml. of water, the temperature being maintained at 23°. Stirring was continued for an additional 30 minutes and then 3 g. of urea in 6 ml. of water was added over an 8-minute period. Stirring was continued for an additional 15 minutes and then the reaction mixture was made neutral with 15% aqueous sodium hydroxide solution. The precipitate (0.210 g., m.p. > 270°) was collected by filtration, the filtrate was extracted thoroughly with methylene chloride, and the precipitate was leached with methylene chloride. The combined extracts were dried and chromatographed on Florisil. A series of fractions eluted with 2% methanol–methylene chloride was pooled and crystallized from acetone–hexane affording 0.035 g. (4.6%) of II, m.p. 225–228°. Recrystallization raised the m.p. to 240–241° dec., $[\alpha]^{25}D$ +102° (dioxane), $\lambda_{max}^{methanol}$ 243 m$\mu$ ($\epsilon$ 15,000), $\lambda_{max}^{Nujol}$ 2.96 $\mu$ (OH), 5.82 $\mu$ (20-carbonyl), 6.04, 6.19, 6.25 $\mu$ ($\Delta^{1,4}$-diene-3-one).

*Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.24; H, 8.13.

**21-Acetylation of $\Delta^{1,4}$-Pregnadiene-11$\beta$,17$\alpha$,21-triol-3,20-dione** (II).—A solution of 0.85 g. of II in 5 ml. of pyridine was treated with 3 ml. of acetic anhydride and the resulting solution was allowed to stand at room temperature overnight. Ice-water was then added, the precipitated solid was collected by filtration and recrystallized from acetone–hexane. There resulted 0.45 g. of VIII, m.p. 237–239° dec., $[\alpha]^{25}D$ +116° (dioxane), $\lambda_{max}^{methanol}$ 243 m$\mu$ ($\epsilon$ 15,000), $\lambda_{max}^{Nujol}$ 3.0 $\mu$ (OH), 5.71 and 5.78 $\mu$ (20-carbonyl, 21-acetate interaction), 6.04, 6.13 and 6.22 $\mu$ ($\Delta^{1,4}$-diene-3-one), 8.12 $\mu$ (21-acetate).

*Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.62; H, 7.78.

**Rearrangement of I in Acetone–Hydrochloric Acid.**—To a solution of 0.72 g. of I in 500 ml. of acetone and 150 ml. of methanol was added 20 ml. of concentrated hydrochloric acid. The temperature of the reaction mixture was maintained at 25° during the addition of the hydrochloric acid. After 24 hours at room temperature, the reaction mixture was neutralized with 15% aqueous sodium hydroxide solution, the precipitated salt was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. Water was added to the residue and the mixture was extracted with methylene chloride. The dried methylene chloride extracts were concentrated and hexane was added to induce crystallization. There resulted 400 mg. of $\Delta^{1,4}$-pregnadiene-21-al-3,11,20-trione dimethyl acetal, m.p. 157–159°, $[\alpha]^{25}D$ +200° (dioxane), $\lambda_{max}^{ethanol}$ 238 m$\mu$ ($\epsilon$ 14,900), $\lambda_{max}^{Nujol}$ 5.79 $\mu$ (20-carbonyl), 5.86 $\mu$ (11-carbonyl), 6.02, 6.17, and 6.23 $\mu$ ($\Delta^{1,4}$-diene-3-one), 8.30 $\mu$ (C-O-C of acetal).

*Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.38; H, 7.59.

**Oxidation of VIII to V.**—Following the procedure of Poos and co-workers[14] a slurry of 250 mg. of chromic acid in 10 ml. of pyridine was prepared. To this slurry at 0–5° was added a solution of 0.50 g. of VIII in 5 ml. of pyridine and the reaction mixture was stirred overnight at room temperature. Then 1 g. of sodium sulfite in 10 ml. of water was added and stirring was continued for two hours. The reaction mixture was diluted with water, acidified with hydrochloric acid and extracted with methylene chloride. The extracts were washed neutral with water, dried and concentrated to a small volume. Chromatography on Florisil and elution with 25% methylene chloride in ether afforded a series of crystalline fractions which were combined and crystallized from acetone–hexane. There resulted 290 mg. of V, m.p. 216–220°. Recrystallization raised the m.p. to 225–230°. The infrared spectrum of the product was identical with that of the first mentioned polymorph of V.

**Oxidation of II with Sodium Bismuthate.**—To a solution of 1.0 g. of II in 150 ml. of acetic acid was added 150 ml. of water and 18 g. of sodium bismuthate, and the resulting mixture was stirred overnight at room temperature. The sodium bismuthate was removed by filtration and both the filtrate and the precipitate were extracted with methylene chloride. The combined extracts were washed free of acetic acid with water, dried and concentrated to a small volume. Chromatography on Florisil and elution with ether afforded a series of crystalline fractions, m.p. 176–180°, which were pooled and recrystallized from methylene chloride–hexane. There resulted 0.5 g. of XI, m.p. 181–182°, $[\alpha]^{25}D$ +138° (acetone), $\lambda_{max}^{ethanol}$ 242 m$\mu$ ($\epsilon$ 15,200).

*Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.17; H, 8.13.

**Oxidation of XI to IX.**—To a solution of 0.06 g. of XI in 5 ml. of glacial acetic acid was added a solution of 0.015 g. of chromic acid in 0.5 ml. of water and 2 ml. of glacial acetic acid. The reaction mixture was allowed to remain at room temperature for three hours and was then poured into ice-water. The mixture was extracted with methylene chloride and the extracts were washed neutral with water. The dried solution was concentrated to a small volume and hexane was added to induce crystallization. There resulted 0.04 g. of IX, m.p. 195–196°, $[\alpha]^{25}D$ +230° (acetone), $\lambda_{max}^{ethanol}$ 239 m$\mu$ ($\epsilon$ 13,900), having an infrared spectrum identical with samples prepared from I and from X, and showing no depression in m.p. when mixed with samples derived from I or X.

*Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.24; H, 7.48.

**Oxidation of I with Sodium Bismuthate.**—To a solution of 1.0 g. of I in 150 ml. of acetic acid was added 150 ml. of water and 18 g. of sodium bismuthate, and the resulting mixture was stirred overnight at room temperature. Following the procedure described for isolating XI from the oxida-

tion of II, there was isolated 0.45 g. of IX, m.p. 193–195°, $\lambda_{max}^{Nujol}$ 5.72 $\mu$ (17-carbonyl), 5.85 $\mu$ (11-carbonyl), 6.01, 6.14, 6.22 $\mu$ ($\Delta^{1,4}$-diene-3-one). No depression in melting point was observed when this sample was mixed with IX from X.

**$\Delta^{1,4}$-Androstadiene-3,11,17-trione (IX) from X.**—To a solution of 4 g. of etiocholane-3,11,17-trione in 40 ml. of glacial acetic acid was added 2 drops of 0.28 *N* hydrogen bromide in acetic acid. The reaction mixture was cooled to 15°, and a solution of 5.1 g. of bromine in 20 ml. of acetic acid was added dropwise with stirring at such a rate that no build-up of bromine in the reaction mixture resulted. This required about 10 minutes. Stirring was continued for an additional 15 minutes, and then the reaction mixture was diluted with water and extracted with methylene chloride. The extracts were washed free of acid with water, dried and concentrated to a residue.

Trituration of the residue with ether afforded 2.92 g. of crystalline dibromide, m.p. 191–192° dec. Concentration of the ethereal solution gave an additional 1.75 g. of material, m.p. 189° dec.

Three grams of the dibromide was added to 90 ml. of boiling 2,4,6-collidine and reflux was continued for 25 minutes. The reaction mixture was diluted with ether and the precipitated collidine hydrobromide was removed by filtration. The filtrate was washed free of collidine with dilute sulfuric acid and then washed neutral with water. The dried solution was concentrated to a small volume and chromatographed on Florisil. A series of crystalline fractions, m.p. 180–192°, was eluted with 25% ether in hexane. Recrystallization from ether afforded 110 mg. of IX, m.p. 192.5–195°, $[\alpha]^{25}D$ +232° (acetone).

BLOOMFIELD, NEW JERSEY

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[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES RESEARCH DIVISION, AMERICAN CYANAMID CO.]

# Steroidal Cyclic Ketals. XV.[1,2] 17,21-Oxido-steroids. Part I. Preparation

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RECEIVED MARCH 14, 1955

Treatment of the ditosylate IIa of 11-*epi*-hydrocortisone bis-ethylene ketal with alkali resulted in a product which was assigned the structure, $\Delta^5$-pregnene-11$\alpha$-ol-3,20-dione-17$\alpha$,21-oxide 3,20-bis-ethylene ketal (IIIa). Solvolysis without Walden inversion occurred at C-11, and the derived oxygen anion at C-17 internally displaced the 21-tosyloxy group. Hydrolysis with dilute sulfuric acid gave $\Delta^4$-pregnene-11$\alpha$-ol-3,20-dione-17$\alpha$,21-oxide (IVa). Similar base-catalyzed cyclizations were performed on the 21-tosylates of the bis-ethylene ketals of Reichstein's substance S, cortisone and hydrocortisone. The cyclization also could be effected with lithium aluminum hydride as exemplified with the hydrocortisone derivative. Acid hydrolysis of these cyclized products (IIIc,d,e) afforded the desired 17$\alpha$,21-oxidocompounds (IVb,c), except in the case of the cortisone analog in which only the 3-ketal group was removed, and the 20-ketal-$\Delta^4$-3-one VIIa was obtained.

In conjunction with other work carried out in this Laboratory to determine the direction of elimination of C11-$\alpha$ and $\beta$-hydroxy-compounds,[3] $\Delta^5$-pregnene-11$\alpha$,17$\alpha$,21-triol-3,20-dione 11$\alpha$,21-di-(*p*-toluenesulfonate) 3,20-bis-ethylene ketal (IIa) was prepared in the usual fashion by tosylation of the bis-ethylene ketal Ia[4] of 11-*epi*-hydrocortisone. This compound proved to be difficult to prepare in a pure state[5]; its elemental analyses invariably were not completely satisfactory. Moreover the infrared absorption spectrum of the best sample obtained showed a weak, unexplained absorption in the carbonyl region at 1742 cm.$^{-1}$ (see Experimental). It was felt, however, that the material was of sufficient purity so that the conclusions drawn from ensuing experimentation were on a firm foundation. The ditosylate IIa was refluxed with 5% alcoholic potassium hydroxide for 4 hours to yield a new compound which contained no tosyl groups. This compound possessed *one* hydroxyl group which underwent facile acetylation.

It seemed that these facts could be accounted for best by the following reactions which are mechanistically sound. Firstly, solvolysis of the 11$\alpha$-tosyl group proceeded without Walden inversion.[6] The presence of an 11$\alpha$-hydroxyl group in the product was supported by the ease of acetylation. Secondly, under the basic conditions of the reaction, the derived anion at C-17 displaced the 21-tosyloxy group in the conventional manner[7] to form a 1,3-oxide as shown by the structure IIIa; the product of acetylation may be represented by the structure IIIb. Moreover, the infrared absorption spectrum of the latter showed no free hydroxyl groups. It is evident that, since the carbon–oxygen bond at C-17 was not involved in the reaction, the oxide formed may be designated as a 17$\alpha$,21-oxide. To demon-

(1) Paper XIV, S. Bernstein and R. H. Lenhard, THIS JOURNAL, **77**, 2233 (1955).

(2) Presented in part before the Organic Discussion Group at the Sixth Annual Meeting-in-miniature of the North Jersey Section, American Chemical Society, Newark, N. J., January 25, 1954.

(3) (a) S. Bernstein, R. Littell and J. H. Williams, THIS JOURNAL, **75**, 4830 (1953); (b) S. Bernstein, R. H. Lenhard and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954).

(4) (a) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *ibid.*, **18**, 70 (1953); (b) F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1282 (1953); (c) S. Bernstein, R. Littell and J. H. Williams, *ibid.*, **75**, 1481 (1953); (d) W. S. Allen, S. Bernstein and R. Littell, *ibid.*, **76**, 6116 (1954).

(5) A similar experience with a compound containing an 11$\alpha$-tosyloxy group bas been encountered previously in this Laboratory; see reference 3b.

(6) The mother liquors of this reaction were not investigated to determine the extent of the possible $\Delta^{9(11)}$ elimination product (*cf.* reference 3b). It should be noted here that non-inversion at C-11 can be explained by a SN1 mechanism (C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 341) which would be expected to operate in preference to a possible SN2 displacement (*cf.* L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 642) since in this case the $\beta$-face of the C-11 position is sterically hindered. Non-inversion might also be explained by displacement on sulfur (R–O–Ts → R–O–H) as postulated in a number of sugar examples (R. S. Tipson, *Advances in Carbohydrate Chem.*, **8**, 167 (1953)). This suggestion apparently was based on the reductive cleavage of tosyl esters with lithium aluminum hydride which has been observed to give displacement both on carbon and on sulfur depending upon the steric situation [H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949)]. Furthermore, there has been reported recently an interesting transformation, in which displacement on sulfur by base was described [G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgstahler, THIS JOURNAL, **75**, 384 (1953)]. Summarily, however, in the present case under discussion it was not possible *a priori* to establish which mechanism was applicable.

(7) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 9 and 59.