The final *p*H was 4.10. The entire ferment was extracted seven times with one-quarter volumes of chloroform to give 0.310 g. of crude product. Elution from a Florisil column with benzene gave 0.12 g. of crystalline product, m.p. 200–203° (yield 60%). Recrystallization from benzene gave a product with m.p. 205–207°, $[\alpha]^{25}D$ + 49.0 (lit.[11] gives m.p. 201–203°, $[\alpha]D$ +49.0°), infrared spectrum shows a band at 3600 cm.$^{-1}$ (hydroxyl), strong band at 1712 cm.$^{-1}$ (3,20-carbonyl) and bands near 900 and 850 cm.$^{-1}$ (epoxide).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.52; H, 8.39.

16α,17α - Epoxy - 11α - acetoxy - 5α - pregnane - 3,20 - dione (Vb).—Acetylation of Va with acetic anhydride in pyridine in the usual manner at room temperature gave Vb, crystals from methanol, m.p. 169–170.5°, $[\alpha]^{25}D$ +12.5 (lit.[11] gives m.p. 170–172°, $[\alpha]D$ +32°), infrared spectrum shows absence of hydroxyl, strong band at 1735 cm.$^{-1}$ (acetate), strong bands at 1712 cm.$^{-1}$ (3,20-carbonyl) and bands near 900 and 850 cm.$^{-1}$ (epoxide).

16α,17α - Epoxy - 5α - pregnane - 3,11,20 - trione (VI).—A solution of 0.2 g. of compound V in 5 ml. of glacial acetic acid was cooled to 14° and treated with a precooled solution of 0.1 g. of chromium trioxide in 2 ml. of 50% glacial acetic acid, which was added dropwise to the solution of V. The solution was allowed to come to room temperature over a period of 10 minutes, six volumes of water added and the resultant silvery plates filtered; yield 0.17 g., m.p. 180–190°. Crystallization from acetone gave the analytical sample, plates, m.p. 189–190.5°, $[\alpha]^{25}D$ +125°; infrared spectrum shows absence of hydroxyl bands, a broad strong band at 1710 cm.$^{-1}$ (3,11,20-carbonyl) and bands near 900 and 850 cm.$^{-1}$ (epoxide).

16α,17α - Epoxy - 5α - 3,11,20 - trione 3,20 - Dioxime (VII).—A solution of 0.1 g. of compound VI was prepared in 0.36 ml. of pyridine. To this solution were added 1.56 ml. of 95% ethanol and 0.1 g. of hydroxylamine hydrochloride. The solution was refluxed one hour. After dilution with water the product was given an ethereal extraction. The residue from ether was not crystalline.

Anal. Calcd. for $C_{21}H_{30}O_4N_2$: N, 7.48. Found: N, 7.54.

17α - Hydroxy - 5α - pregnane - 3,11,20 - trione (VIII).—A solution of 0.16 g. of the triketo-epoxide VI in 7.75 ml. of glacial acetic acid was cooled to 15°. To this solution was added 3.25 ml. of a solution prepared by adding 1 ml. of 48% hydrobromic acid to 5 ml. of glacial acetic acid. The mixture was allowed to stand at room temperature overnight. The solvent then was removed *in vacuo* at room temperature. The residue of crude bromohydrin was without purification dissolved in 25 ml. of 90% methanol and catalytically hydrogenated at 4 atmospheres pressure in the presence of 0.1 g. of a 10% palladium–calcium carbonate catalyst for 5 hours. Filtration of the catalyst, removal of the solvent *in vacuo*, and recrystallization from methanol gave plates, m.p. 262–263°, $[\alpha]^{25}D$ +60° (lit.[14] gives m.p. 259–262°, $[\alpha]D$ +44°); infrared spectrum (potassium bromide disk) shows a strong, bonded band at 3370 cm.$^{-1}$ (17-hydroxyl), a strong, broad band 1705–1690 cm.$^{-1}$ (3,11,20-carbonyl) and absence of the 900 and 850 cm.$^{-1}$ doublet.

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

Synthesis of 17α-Halo Analogs of Corticoids. 17α-Chloro- and 17α-Fluoro-4-pregnen-21-ol-3,11,20-trione Acetates

BY HERSHEL L. HERZOG, MARGARET JEVNIK GENTLES, HELEN M. MARSHALL AND E. B. HERSHBERG

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17α-Bromopregnan-3α-ol-11,20-dione acetate has been transformed into 17α-chloro-4-pregnen-21-ol-3,11,20-trione acetate and 17α-fluoro-4-pregnen-21-ol-3,11,20-trione acetate. The substitution of 17α-halogen for 17α-hydroxyl diminishes adrenocorticoid activity markedly as measured by the eosinophil test in the mouse.

In view of the interesting and therapeutically worthwhile effects which have been achieved sometimes by introduction of halogen, particularly fluorine, into corticosteroids,[1] we chose to study the effect of replacement of the 17α-hydroxyl group in cortisone by halogen. While methods have been described for the introduction of bromine at 17- which were conceivably applicable to chlorine,[2] no satisfactory system has been reported for introducing fluorine at this position. Since fluorine seemed to us the most interesting function, we investigated possible new routes for its introduction at 17-.

A recent Upjohn patent[3] contains a description of the synthesis of what was considered to be a 17,20-epoxy-20-cyano steroid, from the action of potassium cyanide in aqueous ethanol on 17α-bromopregnan-3α-ol-11,20-dione acetate (V). We felt that such a cyanoepoxide would afford any desired 17α-halo-20-ketosteroid by the action of the appropriate halogen acid.[3a] Accordingly, the procedure of the patent was repeated and the isolated products studied.

As it turned out, the reaction of cyanide ion with V is quite complex. Careful chromatography on Florisil of the water-precipitated, neutral fraction from the reaction, run essentially as described by Lincoln and Hogg, afforded four crystalline products of the same empirical formula (I, II, III and IV). All four displayed C–O–C bands, combined or split acetate and 11-ketone carbonyl bands, and nitrile bands in their infrared spectra. In addition, II and IV showed hydroxyl bands, while I and III were hydroxyl-free.

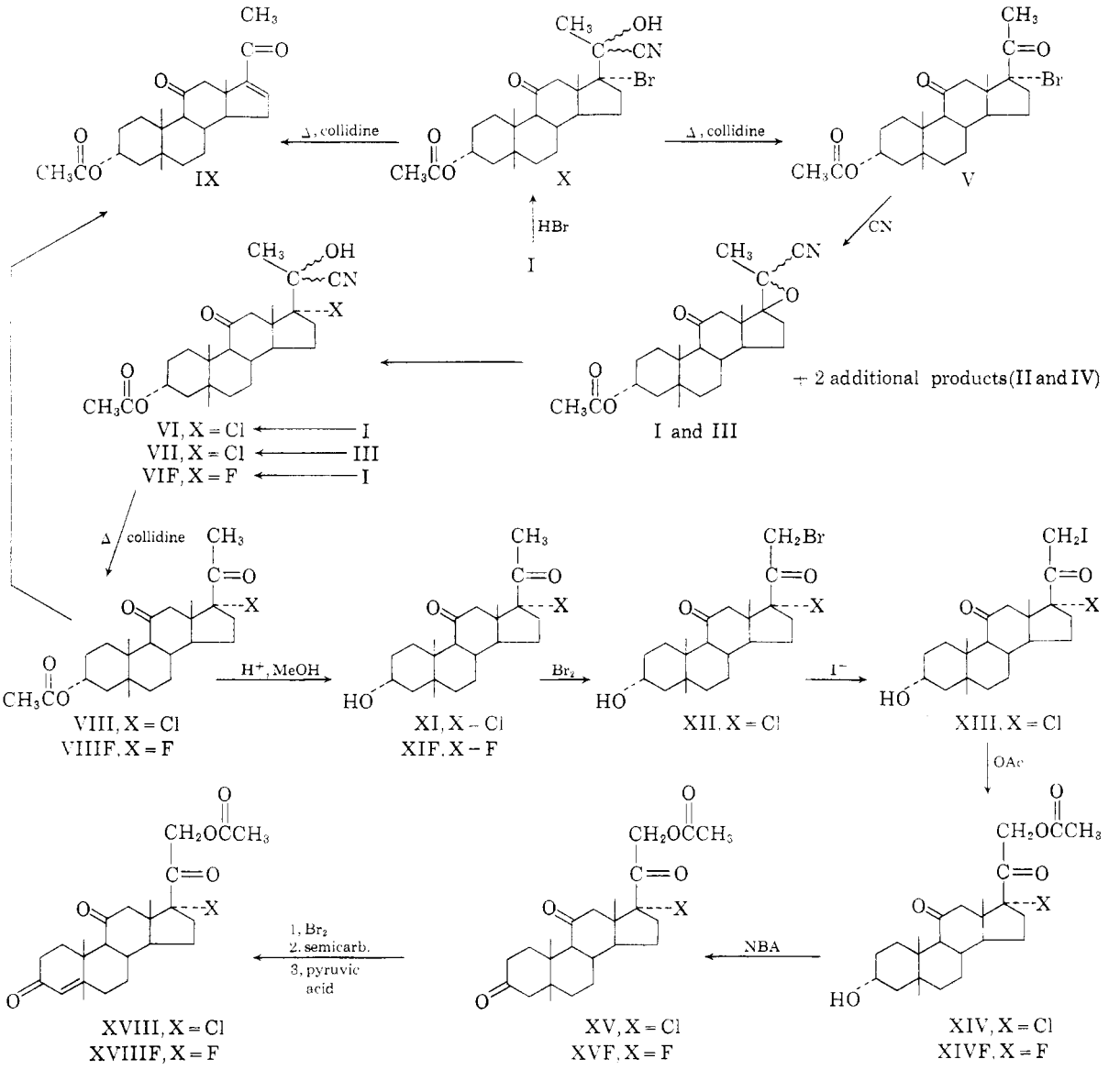
The action of hydrogen bromide in acetic acid on the principal product (I) afforded a crystalline bromohydrin (X), one mole of hydrogen bromide being taken up. The infrared spectrum of X displayed a hydroxyl band in addition to the bands observed initially in I. The stability of X was quite remarkable. Refluxing in acetone in the presence of *p*-toluenesulfonic acid or refluxing in xylene effected no change, X being recovered in

(1) J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957); J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *ibid.*, **78**, 4814 (1956); A. Bowers and H. J. Ringold, *ibid.*, **80**, 4423 (1958).

(2) Ch. R. Engel and H. Jahnke, *Can. J. Biochem. Physiol.*, **35**, 1047 (1957). Prof. Engel has kindly advised us that he and Dr. R. Deghenghi have independently carried out the synthesis of 17α-bromo- and 17α-chloro-4-pregnen-21-ol-3,11,20-trione 21-acetate.

(3) F. H. Lincoln and J. A. Hogg, U. S. Patent 2,813,860 (Nov. 19, 1957).

(3a) ADDED IN PROOF.—Professor Gilbert Stork has kindly informed us that he and his collaborators have described a general synthesis of α-haloketones from cyanoepoxides; G. Stork, W. S. Worrall and J. J. Pappas, THIS JOURNAL, in press.



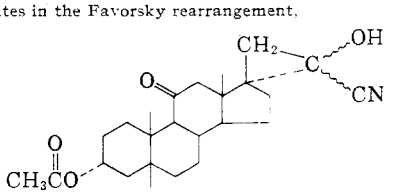
substantial yield. However, refluxing X briefly in collidine–toluene afforded V, identical in all respects with authentic material. Prolonged refluxing of X in collidine gave IX. Hence we concluded that Compound I has the proposed cyanoepoxide structure and that the cyanoepoxide may be opened by halogen acid in the fashion desired to afford the appropriate 17α-halocyanohydrins, and in turn 17α-halo-ketones.

Each of the four intermediates (I, II, III and IV) was then subjected, individually, to the action of hydrogen chloride in acetic acid. From I and III were isolated, in good yield, crystalline products of the empirical formula and in other respects consistent with the structures shown (VI and VII, respectively). When either VI or VII was refluxed briefly in collidine, the same chloroketone (VIII) was isolated, whose carbon skeleton was confirmed by dehydrohalogenation to IX under more vigorous conditions. Since the only asymmetric center destroyed in the respective sequences to VIII was that at 20-, we concluded that I and III are epimeric at 20-, as are also VI and VII. We have not assigned configuration at 20- in any of these compounds.

From the action of hydrogen chloride in acetic acid on II and IV no pure crystalline transformation products were isolated. Starting material was not recovered from II, and was recovered in 30% yield from IV. On the basis of the evidence at hand we are unable to assign reliable structures to II and IV.[4]

If the total, crude, neutral fraction from the action of potassium cyanide on V was subjected to

(4) Prof. D. H. R. Barton has suggested to us that II and IV may be intermediates in the Favorsky rearrangement,



which would be in agreement with the analytical and infrared data.

the action of hydrogen chloride in acetic acid, and the crude product therefrom, in turn, to the action of collidine, a 40–45% yield of VIII was obtained.

The conversion of VIII into 17α-chloro-4-pregnen-21-ol-3,11,20-trione 21-acetate (XVIII) then followed well-established paths, although a number of important modifications in the conventional reaction conditions were required. Hydrolysis of VIII to the 3-alcohol (XI) was carried out in aqueous methanolic hydrochloric acid. Reaction of XI with bromine in chloroform to give XII was sensitive to temperature. Good yields of crystalline bromide could only be obtained when the reaction was carried out at −10° overnight. The 21-bromine in XII was carefully displaced by iodide ion at 0° to give XIII, which was then acetoxylated at room temperature, thereby yielding XIV. Oxidation of XIV with N-bromoacetamide afforded the 3-ketone XV, which was then brominated at 4- and dehydrobrominated *via* the semicarbazone to give the desired 17α-chlorocorticoid XVIII.

From the action of anhydrous hydrogen fluoride in tetrahydrofuran on I there was obtained a fluorocyanohydrin (VIF) which was transformed into the 17α-fluoro-20-ketone VIIIF by collidine treatment. The total crude cyanoepoxide mixture was also transformed into VIIIF by this combination of steps. The 17α-fluoro group in VIIIF was quite stable to prolonged reflux in collidine in contrast with the 17α-chloro group in VIII which was dehydrohalogenated under the same conditions. The presence of the fluorine at 17- was unequivocally proved by polarographic titration of VIIIF.[5] The half-wave reduction potential was consistent with that expected for a fluoro group alpha to carbonyl which in this instance can only be at 17-. Wagner–Meerwein rearrangement of the methyl group from 13- is thereby excluded. From VIIIF the desired 17α-fluoro-4-pregnen-21-ol-3,11,20-trione 21-acetate (XVIIIF) was prepared *via* XIF and XVF, essentially the path employed for the chloro series.

Both XVIII and XVIIIF displayed insignificant adrenocorticoid action compared with cortisone, as measured in the mouse eosinophil test.[6]

Experimental[7]

Reaction of 17α-Bromopregnan-3α-ol-11,20-dione 3-Acetate (V) with Potassium Cyanide (Formation and Isolation of I, II, III and IV).—To a mixture of 2.51 g. of V[8] in 250 ml. of absolute ethanol was added a solution of 0.72 g. of potassium cyanide and 1.10 g. of potassium acetate in 100 ml. of water. The resulting mixture was agitated for 20 hours at 25°. A trace of unreacted starting material was removed by filtration and 1.0 l. of water was added to the filtrate. The resulting precipitate (1.13 g.), which had a negative Beilstein test, was suspended in hexane and placed on a column containing 100 g. of Florisil prepared with hexane. Fifty-five 50-ml. fractions were collected. Fractions 2–8 were eluted with 20% ether-in-hexane. Fractions 9–14 were eluted with 30% ether-in-hexane. Fractions 15–55 were eluted with 50% ether-in-hexane. Fractions 18–22 (0.280 g.) crystallized as hard needles, melting in the range 182–187. Recrystallization from ether–hexane afforded 0.181 g. of I, 20-cyano-17β,20-epoxypregnan-3α-ol-11-one acetate, m.p. 184–188°, $[\alpha]^{25}D$ +4.4° (dioxane); λ_{max}^{Nujol} 4.48 μ (C≡N), 5.80 μ (acetate carbonyl), 5.85 μ (11-carbonyl), 7.95 μ (C−O−C of acetate).

Anal. Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.13; H, 8.58; N, 3.42.

Fractions 23–29 melted broadly and in the range 150–235°. Fractions 25–29 were washed with hexane and combined (yield 0.060 g.). Crystallization from ether–hexane afforded 0.025 g. of II, m.p. 255–260° dec. with a phase change at 220–225°, $[\alpha]^{25}D$ −10.9° (dioxane); λ_{max}^{Nujol} 2.96 μ (OH), 4.50 μ (C≡N), 5.87 μ (combined 11-carbonyl and 3-acetate), 7.90 μ, 8.00 μ (C–O–C of acetate).

Anal. Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.29; H, 8.45; N, 3.61.

Fractions 29–32 were triturated with ether–hexane and the ether–hexane solution was decanted from the crystalline needles, m.p. 205–215°, which deposited. From the decantate there precipitated on standing additional needles of the same variety. A second decantation was carried out and from the mother liquor there was deposited a new crystalline variety as long, fine soft needles, m.p. 183–185°. Fractions 33–36 also melted in the range 183–185°. The two groups of fractions (0.100 g.), melting 183–185°, were pooled and crystallized from ether–hexane, yielding thereby III (0.033 g.), m.p. 187–190°, $[\alpha]^{25}D$ +26.9° (dioxane); λ_{max}^{Nujol} 4.46 μ (C≡N), 5.77 μ (acetate carbonyl), 5.88 μ (11-carbonyl), 8.00 μ (C−O−C of acetate). The infrared spectrum of III was different from that of I.

Anal. Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33; N, 3.51. Found: C, 71.86; H, 8.59; N, 3.68.

Fractions 41–54 after trituration with ether–hexane deposited solids (34 mg.) melting in the range 208–235°. Recrystallization from ether–hexane gave 0.015 g. of IV, m.p. 239–245° (no depression on admixture with II), $[\alpha]^{25}D$ +80.1° (dioxane); λ_{max}^{Nujol} 2.94 μ (OH), 4.50 μ (C≡N), 5.85 μ (combined acetate and 11-carbonyl), 7.85 μ (C–O–C of acetate). The infrared spectrum of IV was different from that of II.

Anal. Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33; N, 3.51: Found: C, 72.37; H, 8.56; N, 3.61.

In three subsequent experiments the yield of the initial, water-precipitated, neutral fraction varied between 80 and 85%.

Regeneration of V from I *via* X.—A solution of 0.224 g. of I in 5.5 ml. of glacial acetic acid was saturated with hydrogen bromide (anhyd.) at 19°. After 0.5 hour of standing at 19° the mixture was poured into aqueous sodium acetate. There was precipitated 0.246 g. of solid, which after crystallization from ether–hexane afforded 0.153 g. of X, 17α-bromo-20-cyanopregnane-3α,20-diol-11-one 3-acetate, m.p. 199–200° dec., $[\alpha]^{25}D$ −0.5° (dioxane); λ_{max}^{Nujol} 2.98 μ (OH), 5.78 μ (acetate carbonyl), 5.86 μ (11-carbonyl), 7.86 8.06μ (C–O–C of acetate).

Anal. Calcd. for $C_{24}H_{34}O_4NBr$: Br, 16.64; N, 2.92. Found: Br, 16.51; N, 2.88.

A solution of 0.050 g. of X in 1.0 ml. of toluene was treated with 0.58 ml. of a mixture of toluene and collidine which contained 0.028 g. of collidine per ml. of solution and the resulting solution was heated at reflux for one hour. The reaction mixture was concentrated to dryness at room temperature and the residual oil was taken up in ether. Hexane was then added to induce crystallization and there was isolated 0.024 g. of needles, m.p. 170–171°, which had a positive Beilstein test, showed no ultraviolet absorption in the range 220–350 mμ and had an infrared spectrum which was identical with that of V, which we employed as the original starting material.

Conversion of X into IX.—A solution of 0.036 g. of X in 1.0 ml. of collidine was heated at reflux for one hour. The cooled reaction mixture was diluted with ether, and the precipitated collidine hydrobromide was removed by filtration. The ethereal solution was washed free of collidine with dilute sulfuric acid and with water, was dried over magnesium sulfate and was concentrated to an oily residue. The residue was taken up in methanol and crystallization was induced by adding water. Thereby was isolated 0.017 g. of IX, 16-

(5) We are indebted to Mr. J. McGlotten for carrying out and interpreting the polarogram.

(6) R. S. Speirs and R. K. Meyer, *Endocrinol.*, **48**, 316 (1951); E. Rosemberg, *et al.*, *ibid.*, **54**, 363 (1954). We are indebted to Dr. Sibylle Tolksdorf for these measurements.

(7) All m.p.'s were taken in capillaries and are corrected. Analytical and optical data were obtained by the Physical Chemistry Department of the Schering Corporation. The infrared spectra were interpreted by Richard Wayne.

(8) N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

pregnen-3α-ol-11,20-dione acetate, m.p. 155–160°, λ_{max}^{MeOH} 235 mμ (ε 8,400), whose infrared spectrum was identical with that of an authentic sample.

Conversion of I into VIII *via* VI.—A solution of 0.250 g. of I in 4.0 ml. of glacial acetic acid was saturated with hydrogen chloride at 15°. After thirty minutes at 24° the reaction mixture was water precipitated affording thereby 0.250 g. of solid. Recrystallization from acetone–hexane gave 0.170 g. of VI, 17α-chloro-20-cyanopregnane-3α,20-diol-11-one 3-acetate, m.p. 218–219° dec., $[\alpha]^{25}D$ +20.7° (dioxane); λ_{max}^{Nujol} 2.99 μ (OH), 5.88 μ (combined carbonyl bands), 7.90 μ (C–O–C of acetate).

Anal. Calcd. for $C_{24}H_{34}O_4NCl$: C, 66.11; H, 7.84; N, 3.21; Cl, 8.13. Found: C, 65.83; H, 7.60; N, 3.58; Cl, 8.15.

A solution of 0.050 g. of VI in 1.0 ml. of toluene was treated with 0.67 ml. of a mixture of collidine and toluene which contained 0.0228 g. of collidine per ml. The resulting solution was heated at reflux for 1 hour, cooled to room temperature and diluted with ether. The ethereal solution was washed free of collidine, dried and concentrated. The residue was crystallized from aqueous methanol affording 0.0246 g. of VIII, 17α-chloropregnan-3α-ol-11,20 dione acetate, m.p. 156.5–157.5°, $[\alpha]^{25}D$ +22.3° (dioxane); λ_{max}^{Nujol} 5.80 μ (acetate carbonyl), 5.86 μ (11 and 20-carbonyl), 8.02 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{33}O_4Cl$: C, 67.55; H, 8.13; Cl, 8.67. Found: C, 67.84; H, 8.16; Cl, 8.81.

From the heating at reflux of 0.0338 g. of VI in 3.0 ml. of collidine for 2 hours there was isolated in the usual way 0.022 g. of VIII, m.p. 150–152°. A trace of 16,17-unsaturation was noted in the infrared spectrum, which was in other respects identical with that of VIII from the preceding experiment.

Conversion of III into VIII *via* VII.—By the method of the preceding experiment, 0.101 g. of III was converted into 0.052 g. of VII, m.p. 184–187°, $[\alpha]^{25}D$ +22.2° (dioxane); λ_{max}^{Nujol} 3.02 μ (OH), 5.87 μ (combined carbonyl bands), 7.88, 7.98 μ (C–O–C of acetate). The infrared spectrum was different from that of VI. A polymorphic variety of VII, m.p. 190–192°, with a different infrared spectrum has also been observed.

Anal. Calcd. for $C_{24}H_{34}O_4NCl$: C, 66.11; H, 7.84; N, 3.21. Found: C, 66.46; H, 7.84; N, 3.15.

A solution of 0.037 g. of VII in 2.0 ml. of collidine was heated at reflux for 1 hour. The reaction mixture was processed in the usual way and there was isolated 0.027 g. of VIII, m.p. 148–152°, which possessed an infrared spectrum identical with that of VIII prepared from VI.

Procedure for the Preparation of VIII from V without Isolation of Pure Intermediates.—The crude cyanoepoxide mixture (10.0 g.), prepared according to the first experiment in this article, was dissolved in 60 ml. of glacial acetic acid and the resulting solution was saturated with hydrogen chloride at 25°. After 0.5 hour longer at room temperature the mixture was water precipitated with 1800 ml. of water. The resulting solid was separated by filtration, washed free of acid with water and dried to constant weight.

The crude chlorocyanohydrin mixture was taken up in 200 ml. of toluene to which was then added 3.17 g. of collidine. The mixture was heated at reflux for one hour, cooled to room temperature and concentrated at room temperature to remove most of the toluene and part of the collidine. The residue was taken up in ether, washed free of collidine with dilute sulfuric acid, dried and concentrated to a resin. The resin was chromatographed over 150 g. of Florisil and VIII was eluted with 25% ether-in-hexane. The combined fractions afforded, after crystallization from methanol–water, 4.1–4.4 g. of VIII, with the previously noted constants.

Conversion of VIII into IX.—A solution of 0.50 g. of VIII in 2.0 ml. of collidine was heated at reflux for 18 hours. The reaction mixture was freed from collidine in the usual way and the steroidal residue was chromatographed over 7.0 g. of Florisil. Elution with 50% ether-in-hexane afforded, after recrystallization from aqueous methanol, 0.20 g. of IX, m.p. 159–164°. The product gave a negative Beilstein test and had an infrared spectrum which was identical with that from authentic IX.

Stability of X. (a) Reflux with Acetone.—A solution of 0.054 g. of X in 10.0 ml. of acetone containing 0.0055 g. of *p*-toluenesulfonic acid was heated at reflux for 15 minutes. From water precipitation was isolated 0.040 g. of X, m.p. 194–196° dec., having an infrared spectrum identical with that of the starting material.

(**b**) **Reflux in Xylene.**—A solution of 0.040 g. of X in 10.0 ml. of xylene was heated at reflux for 30 minutes. The xylene was removed by evaporation at room temperature and the solid residue was recrystallized from ether–hexane, affording thereby 0.015 g. of X, m.p. 194–196° dec., having an infrared spectrum identical with that of starting material.

Action of Hydrogen Chloride on IV.—A solution of 0.100 g. of IV in 5.0 ml. of glacial acetic acid was saturated with hydrogen chloride at 25° and allowed to stand for 1.5 hours. Water precipitation yielded 0.066 g. of solid, m.p. 220–230°, which gave a negative Beilstein test. From chromatography over Florisil and recrystallization of the solid fractions from ether–hexane 0.030 g. of IV, m.p. 245–250° (phase change at 225–230°), was isolated, having an infrared spectrum identical with that of starting material.

XI from VIII.—A solution of 2.00 g. of VIII in 20.0 ml. of methylene chloride, 59.0 ml. of methanol, 4.2 ml. of concentrated hydrochloric acid and 7.0 ml. of water was allowed to stand at room temperature for 64 hours. Excess water and methylene chloride were added and the layers were separated. The aqueous phase was extracted with methylene chloride and the extracts were combined with the original methylene chloride phase. The methylene chloride pool was washed free of acid with water, dried and concentrated to an oily residue. Crystallization from ether–hexane afforded 1.74 g. of XI, 17α-chloropregnan-3α-ol-11,20-dione, m.p. 145–147°. Further recrystallization did not change the m.p.; $[\alpha]^{25}D$ −10.7° (dioxane); λ_{max}^{Nujol} 2.90 μ (OH), 5.85–5.91 μ (broad 11- and 20-carbonyls).

Anal. Calcd. for $C_{21}H_{31}O_3Cl$: C, 68.74; H, 8.52; Cl, 9.66. Found: C, 68.54; H, 8.62; Cl, 9.49.

XIV from XI *via* XII and XIII.—A solution of 0.300 g. of XI in 50.0 ml. of chloroform saturated with hydrogen bromide was cooled to −12° with the aid of an ice–salt-bath contained in a Dewar flask. A solution of 0.142 g. of bromine in 5.0 ml. of chloroform was added, with stirring, in 1.0-ml. portions at the start of the reaction, after 45 minutes, after 3 hours, after 3.5 hours and after 4.25 hours, respectively. The temperature of reaction after the final addition was −11°. After 22 hours of reaction the contents of the flask had warmed to 10° and the solution no longer showed any coloration due to bromine. The solution was washed to neutrality with aqueous sodium acetate, dried and concentrated *in vacuo* to an oily residue. Crystallization from ether–hexane afforded 0.258 g. of XII, 17α-chloro-21-bromopregnan-3α-ol-11,20-dione, m.p. 160–163° (heavy dec. at 171°). Recrystallization raised the m.p. to 164–165°, $[\alpha]^{25}D$ +15.1° (dioxane); λ_{max}^{Nujol} 2.90 μ (OH), 5.80, 5.86, 5.92 μ (carbonyl bands).

Anal. Calcd. for $C_{21}H_{30}O_3ClBr$: Cl, 7.95. Found: Cl, 8.18.

Experiments conducted at 0° and at room temperature gave notably poorer yields of XII, and ultraviolet-absorbing by-products were formed in the latter case.

A solution of 0.300 g. of XII in 45.0 ml. of acetone was cooled to 0° and 0.111 g. of sodium iodide was added with agitation. After 1.5 hours at 0° with continued agitation the reaction mixture was diluted with water and extracted with methylene chloride. The extracts were washed with water, dried and concentrated to an oily residue *in vacuo*. Crystallization from methylene chloride–ether–hexane afforded 0.264 g. of XIII, 17α-chloro-21-iodopregnan-3α-ol-11,20-dione, m.p. 162–165° (iodine evolution 178–185°), $[\alpha]^{25}D$ +13.5° (dioxane).

Anal. Calcd. for $C_{21}H_{30}O_3ClI$: I, 25.75. Found: I, 26.80.

A solution of 1.00 g. of XIII in 200 ml. of acetone was treated with 1.20 g. of potassium acetate, and the mixture was stirred at 25° for 40 hours. The acetone was then removed *in vacuo;* the residue was taken up in methylene chloride, washed with water, dried and concentrated to a semi-crystalline residue. Chromatography of the residue on 25 g. of Florisil and elution with 50% ether–hexane afforded a series of solid fractions (0.587 g.) which upon crystallization from acetone–hexane gave 0.389 g. of XIV, 17α-chloropregnane-3α,21-diol-11,20-dione 21-acetate, m.p. 200–203°. A second crop of 0.085 g. melted at 180–190°. Further recrystallization raised the m.p. to 204–205.5°, $[\alpha]^{25}D$ +10.4° (dioxane); λ_{max}^{Nujol} 2.85 μ (OH), 5.74 μ (acetate car-

bonyl), 5.82 μ (20-carbonyl), 5.88 μ (11-carbonyl), 8.10 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{35}O_5Cl$: C, 65.00; H, 7.83; Cl, 8.34. Found: C, 65.37; H, 7.69; Cl, 8.26.

Acetoxylation at reflux for 5 hours or at room temperature for 23 hours afforded poorer yields of XIV. In the latter instance a portion of the unreacted 21-iodide XIII could be recovered.

XV from XIV.—A solution of 0.555 g. of XIV in 40.0 ml. of acetone was treated with 0.360 g. of N-bromoacetamide in 10.0 ml. of water at room temperature. The reaction mixture was then held in the refrigerator (ambient temp. 5°) for 4 hours. The product was precipitated by the addition of excess aqueous sodium sulfite. There was isolated thereby 0.502 g. of XV, 17α-chloropregnan-21-ol-3,11,20-trione acetate, m.p. 204–209°. An analytical sample purified by chromatography over Florisil and crystallization from acetone–hexane, melted at 210–213° dec., $[\alpha]^{25}D$ +13.4° (dioxane); λ_{max}^{Nujol} 5.70 μ (acetate carbonyl), 5.80 μ (20-carbonyl), 5.86 μ (3- and 11-carbonyl), 8.10 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{31}O_5Cl$: C, 65.31; H, 7.39; Cl, 8.39. Found: C, 65.54; H, 7.40; Cl, 8.26.

XVIII from XV.—To a solution of 0.300 g. of XV in 13.0 ml. of glacial acetic acid was added 0.86 ml. of a solution of bromine in acetic acid (which contained 0.669 g. of bromine in 5.0 ml. of glacial acetic acid) at 15°. The bromine color disappeared immediately. After 2 minutes of continued agitation, water was added and the product was extracted with methylene chloride. The extracts were washed free of acid with water, dried, concentrated to a small volume and diluted with hexane. The resulting slurry was chromatographed over 30.0 g. of Florisil and eluted with 25% methylene chloride in ether through 75% methylene chloride in ether. Recrystallization of the crystalline fractions afforded 0.215 g. of a 4-bromide as fine needles, m.p. 216–218° dec.

A solution of 0.202 g. of the bromide in 25.0 ml. of chloroform and 37.0 ml. of *t*-butyl alcohol was treated with 0.063 g. of semicarbazide under a carbon dioxide atmosphere at room temperature. After 40 minutes of agitation the solution had become quite yellow. After 110 minutes the solution was once again colorless. The reaction was allowed to proceed for a total of 4.5 hours and was then concentrated to a residue *in vacuo*. The residue was triturated with water and filtered, furnishing 0.177 g. of a powder, m.p. 215° dec., $\lambda_{max}^{methanol}$ 269 mμ (ε 21,800), 230–240 mμ (plateau) ε *ca.* 10,000.

A solution of 0.175 mg. of semicarbazone in 12.0 ml. of acetic acid and 6.0 ml. of water was treated under a carbon dioxide atmosphere with 0.063 g. of pyruvic acid (as 1.85 ml. of a solution of 0.867 g. of pyruvic acid made up to 25 ml. with acetic acid). The reaction mixture was agitated overnight at room temperature, then diluted with water and extracted with methylene chloride. The extracts were washed free of acid with water, dried and concentrated to a residue. Chromatography over 7.0 g. of Florisil and elution with 50% ether-in-hexane, with ether and with 25% methylene chloride in ether afforded a series of crystalline fractions which were recrystallized from acetone–ether–hexane to give 0.039 g. of XVIII, 17α-chloro-4-pregnen-21-ol-3,11-20-trione acetate, m.p. 135–138°, and a second crop, 0.028 g., m.p. 128°. Further recrystallization from ether–hexane gave XVIII, m.p. 141–143°, $[\alpha]^{25}D$ +100.6° (dioxane), $\lambda_{max}^{methanol}$ 237 mμ (ε 14,600); λ_{max}^{Nujol} 5.72 μ (acetate carbonyl), 5.78 μ (20-carbonyl), 5.86 μ (11-carbonyl), 6.02 μ (3-carbonyl), 6.20 μ (Δ^4), 8.14 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{29}O_5Cl$: C, 65.63; H, 6.95. Found: C, 65.75; H, 7.01.

VIF from I.—To a solution of 0.200 g. of I in 20 ml. of distilled chloroform was added at −78° c 6.0 ml. of a solution made from 0.268 g. of anhydrous hydrogen fluoride per ml. of tetrahydrofuran. The reaction mixture was allowed to warm to 0°, at which temperature it was held for 7.5 hours. The mixture was then precipitated into excess aqueous potassium bicarbonate and extracted with methylene chloride. The extracts were washed to neutrality, dried and concentrated, and the residual oil was crystallized from ether–hexane. There resulted 0.046 g. of VIF, 17α-fluoro-20-cyanopregnan-3α,20-diol-11-one 3-acetate, as the first crop, m.p. 219–223°, and 0.024 g. of second crop, m.p. 210–213°. Additional crystallization afforded VIF, m.p. 226–229°, $[\alpha]^{25}D$ +60° (dioxane); λ_{max}^{Nujol} 3.02 μ (OH), 5.78 μ (acetate carbonyl), 5.94 μ (11-carbonyl), and 8.08 μ (C–O–C of acetate).

Anal. Calcd. for $C_{24}H_{34}O_4NF$: C, 68.70; H, 8.17. Found: C, 68.79; H, 7.79.

Procedure for the Preparation of VIIIF from V without the Isolation of Pure Intermediates.—The crude cyanoepoxide mixture (10.0 g.), prepared according to the first experiment of this article, was suspended in 60.0 ml. of hydrogen fluoride–tetrahydrofuran (same concentration as preceding experiment) and the mixture was stirred for 18 hours at room temperature. Excess solid potassium bicarbonate was added to stop the reaction, the suspended solids were removed by filtration and the filtrate was concentrated to a residue. To the residue was then added 10.0 ml. of collidine and the resulting mixture was heated at reflux with agitation for 1 hour. The reaction mixture was then cooled, diluted with ether and aqueous sulfuric acid, and the ethereal layer was washed to neutrality, dried, filtered and concentrated.

A solution of the residue in the minimum amount of ether was chromatographed over 300 g. of Florisil and eluted with mixtures of ether and hexane. Crystalline fractions were collected with 25% ether and 50% ether. Those melting above 154° were pooled and crystallized from methanol–water affording thereby 3.39 g. of VIIIF, 17α-fluoropregnan-3α-ol-11,20-dione acetate, m.p. 156–157°, $[\alpha]^{25}D$ +133° (dioxane); λ_{max}^{Nujol} 5.78 μ (acetate carbonyl), 5.88 μ (11- and 20-carbonyl).

Anal. Calcd. for $C_{23}H_{33}O_4F$: C, 70.38; H, 8.47; F, 4.84. Found: C, 70.42; H, 8.54; F, 4.42.

A polymorph of VIIIF has been obtained, on crystallization from ether–hexane, which melted at 150–151°, $[\alpha]^{25}D$ +135° (dioxane).

Further elution of the aforedescribed chromatogram has on occasion, in the 100% ether fractions, afforded minor amounts of 16-pregnen-3α-ol-11,20-dione acetate (IX), m.p. 162–165°, λ_{max}^{MeOH} 235 mμ (ε 9,000); infrared spectrum identical with that of an authentic sample. It cannot be stated unequivocally that this was formed by dehydrofluorination in the collidine reaction since minor amounts of 17α-bromo derivative V, which might conceivably have escaped reaction with cyanide ion, would yield IX also.

VIF to VIIIF.—A solution of 0.020 g. of VIF in 0.2 ml. of collidine was heated at 140° for 1 hour. The isolation of VIIIF, carried out as before, afforded 0.009 g. of VIIIF, m.p. 150–152°, with an infrared spectrum identical with that obtained without isolation of VIF.

Hydrolysis of VIIIF to XIF.—To a solution of 2.0 g. of VIIIF in 30 ml. of methylene chloride and 100 ml. of methanol was added 6 ml. of concentrated hydrochloric acid in 10 ml. of water. After 72 hours at room temperature excess water was added, and the aqueous layer was extracted with methylene chloride. The combined extracts were washed with water, dried, concentrated and the residue was crystallized from methanol–water, affording 1.17 g. of XIF, 17α-fluoropregnan-3α-ol-11,20-dione, m.p. 124–126°, $[\alpha]^{25}D$ +122° (dioxane); λ_{max}^{Nujol} 2.98 μ (OH), 5.88 μ (11- and 20-carbonyl).

Anal. Calcd. for $C_{21}H_{31}O_3F$: C, 71.97; H, 8.92. Found: C, 71.68; H, 8.58.

The product XIF did not crystallize well from all runs and occasionally chromatography was required for isolation.

XIVF from XIF.—A solution of 1.38 g. of XIF in 150 ml. of distilled chloroform, which was saturated with anhydrous hydrogen bromide, was cooled to and held at −8° and a solution of 0.66 g. of bromine in 15 ml. of distilled chloroform was added with agitation in *ca.* 4.0-ml. portions at the start of the reaction and after 7 minutes, 12 minutes and 25 minutes. Stirring was continued for a total of 60 minutes, whereupon the mixture was poured into aqueous sodium acetate. The chloroform layer was washed to neutrality, dried and concentrated *in vacuo*. Hexane was added in two portions and the concentration was repeated twice. The crude bromide was taken up in 167 ml. of acetone, 1.67 g. of potassium acetate was added and the mixture was stirred at room temperature for 70 hours. The reaction mixture was concentrated to a residue *in vacuo*, water was added and the solid remaining (1.5 g.) was removed by filtration. Recrystallization from acetone–hexane afforded 0.99 g. of XIVF, 17α-fluoropregnane-3α,21-diol-11,20-dione 21-acetate, m.p. 190–191°. Chromatography and crystallization from acetone–hexane raised the m.p. to 196–197°, $[\alpha]^{25}D$ +127° (diox-

ane); λ_{max}^{Nujol} 2.88 μ (OH), 5.74 μ (acetate carbonyl), 5.78 μ (20-carbonyl), 5.85 μ (11-carbonyl), 7.82 and 8.00 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{33}O_5F$: C, 67.62; H, 8.14. Found: C, 67.74; H, 8.00.

XVF from XIVF.—To a solution of 1.64 g. of XIVF in 50 ml. of acetone and 15 ml. of water was added 1.3 g. of N-bromoacetamide. After 10 minutes agitation at room temperature, the reaction mixture was placed in the refrigerator for 4 hours. Then aqueous sodium sulfite was added, the precipitated solid was removed by filtration, washed with water, dried and crystallized from acetone–hexane affording 1.3 g. of XVF, 17α-fluoropregnan-21-ol-3,11,20-trione acetate, m.p. 208–209°, $[\alpha]^{25}D$ +134° (dioxane); λ_{max}^{Nujol} 5.70 μ (acetate carbonyl), 5.76 μ (20-carbonyl), 5.88 μ (3- and 11-carbonyl), 7.85 and 8.15 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{31}O_5F$: C, 67.95; H, 7.69. Found: C, 68.17; H, 7.73.

XVIIIF from XVF *via* a Crystalline 4-Bromide.—To a solution of 1.31 g. of XVF in 40 ml. of glacial acetic acid was added a solution of 0.43 g. of bromine in 10 ml. of acetic acid. The bromine color disappeared immediately, and a precipitate formed. The solid was separated by filtration and recrystallized from acetone–methylene chloride–hexane affording thereby 1.49 g. of 4-bromide, m.p. 219–222° dec., $[\alpha]^{25}D$ +135° (dioxane).

Anal. Calcd. for $C_{23}H_{30}O_5FBr$: Br, 16.47. Found: Br, 16.66.

To a solution of 0.5 g. of 4-bromide in 85 ml. of freshly distilled chloroform and 42.5 ml. of *t*-butyl alcohol was added, under a carbon dioxide atmosphere, 0.154 g. of semicarbazide. Agitation was continued for 80 minutes. The reaction mixture was warmed gently after 1 hour of agitation, whereupon the suspended solid dissolved completely leaving a bright yellow solution. The color discharged in 20 minutes and a haze returned. The reaction mixture was then stored at room temperature for 18 hours, concentrated *in vacuo*, and the residue was triturated with water, separated by filtration and dried. There resulted 0.425 g. of crude solid, which gave no Beilstein test and showed λ_{max}^{MeOH} 269 mμ (ϵ 20,100).

To a solution of 0.57 g. of crude semicarbazone in 67 ml. of acetic acid and 13.5 ml. of water was added 1.35 ml. of 99% pyruvic acid. The mixture was heated at reflux with agitation for 15 minutes, cooled, and excess water was added. The product was extracted from the aqueous phase with methylene chloride and the extracts were washed, dried, concentrated and chromatographed over Florisil. A series of fractions, from 50% ether–hexane and 100% ether eluates, melting 224–227° were pooled and recrystallized from acetone–hexane affording XVIIIF, 17α-fluoro-4-pregnen-21-ol-3,11,20-trione acetate (0.170 g.), m.p. 226–226.5°; $[\alpha]^{25}D$ +245° (dioxane), λ_{max}^{MeOH} 238 mμ (ϵ 15,500); λ_{max}^{Nujol} 5.68 μ (acetate carbonyl), 5.72 μ (20-carbonyl), 5.85 μ (11-carbonyl), 5.98 μ (3-carbonyl), 6.18 μ (Δ^4), 8.14 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{29}O_5F$: C, 68.30; H, 7.23. Found: C, 68.03; H, 7.39.

BLOOMFIELD, N. J.

[CONTRIBUTION FROM LEDERLE LABORATORIES, A DIVISION OF THE AMERICAN CYANAMID CO.]

21-Acetoxy-16α,17α-epoxy-4-pregnene-3,20-dione as a Starting Material for the Synthesis of Triamcinolone

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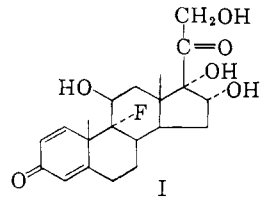
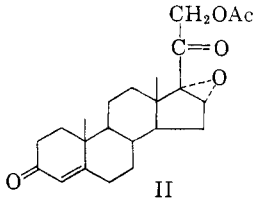
The conversion by several microbiological–chemical pathways of 21-acetoxy-16α,17α-epoxy-4-pregnene-3,20-dione(II) to 21-acetoxy-4,9(11),16-pregnatriene-3,20-dione (XII) and 16α,21-diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XVII) is described. Compounds XII and XVII are intermediates for the synthesis of triamcinolone.

A number of syntheses of the biologically important triamcinolone (I)[2] already have been reported.[3] Our research in this area has continued,



I



II

and we now wish to describe certain *formal* syntheses of triamcinolone (I) which utilize as a starting material 21-acetoxy-16α,17α-epoxy-4-pregnene-3,20-dione (II). This compound is readily available by several stages from diosgenin, and was described first by Julian and co-workers.[4]

In connection with the use of a 16α,17α-epoxy derivative, such as II, for the synthesis of the 16α,17α-diol-containing triamcinolone, it may be noted that previous reports[5] have already demonstrated that the 16α,17α-epoxy group in 16α,17α-epoxy 11α-hydroxyprogesterone may serve two functions. This group may be considered as a protective group for the C-16,17-double bond, the double bond being regenerated by the chromous chloride method of Cole and Julian.[6] The double bond may then be treated with a hydroxylating agent, such as osmium tetroxide, for the introduction of the desired 16α,17α-dihydroxy grouping. Secondly, the 16α,17α-epoxy group by means of the Romo procedure[7] may be converted directly into the 16α-acetoxy-17α-hydroxy moiety.

Key intermediates for the synthesis of triamcinolone (I) from the epoxy derivative II appeared to be triene XII and the 16α-acetoxy-17α-hydroxy-

(1) (a) Organic Chemical Research Section, (b) Biochemical Research Section.

(2) The trademark of the Lederle Laboratories, Division of American Cyanamid Co. for triamcinolone is Aristocort.

(3) (a) W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955); (b) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *ibid.*, **78**, 5693 (1956); (c) R. W. Thoma, J. Fried, S. Bonanno and P. Grabowich, *ibid.*, **79**, 4818 (1957); (d) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *ibid.*, **81**, 1689 (1959); (e) S. Bernstein and R. Littell, *J. Org. Chem.*, **24**, 429 (1958); and (f) R. E. Schaub, G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4962 (1959).

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