ultraviolet spectrum of mycomycin methyl ester exhibited absorption peaks at 267 and 281 mμ of approximately equal intensity, ε 70,000.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66; CH_3O, 14.62. Found: C, 79.47; H, 5.82; CH_3O, 14.34.

Because of its low water solubility, mycomycin methyl ester could only be assayed in very dilute solutions. However, under these conditions, the activity was that calculated from its mycomycin content.

Mycomycin methyl ester (212 mg., 1.0 millimole) was hydrogenated in 30 ml. of ethyl acetate at atmospheric pressure and 27° over 200 mg. of previously reduced Adams platinum oxide catalyst. The hydrogenation was complete after 60 minutes with a consumption of 179 ml. of hydrogen (S.T.P.) or 8.0 millimoles. The catalyst was removed by filtration and the solvent removed by distillation at reduced pressure. A light yellow, oily residue (228 mg.) was obtained. The oil possessed the same infrared absorption spectrum as methyl *n*-tridecanoate. Saponification of hydrogenated mycomycin methyl ester (200 mg.) with 1.0 *N* sodium hydroxide gave after acidification a crystalline solid (165 mg.), m.p. 39–40°, identified as *n*-tridecanoic acid.

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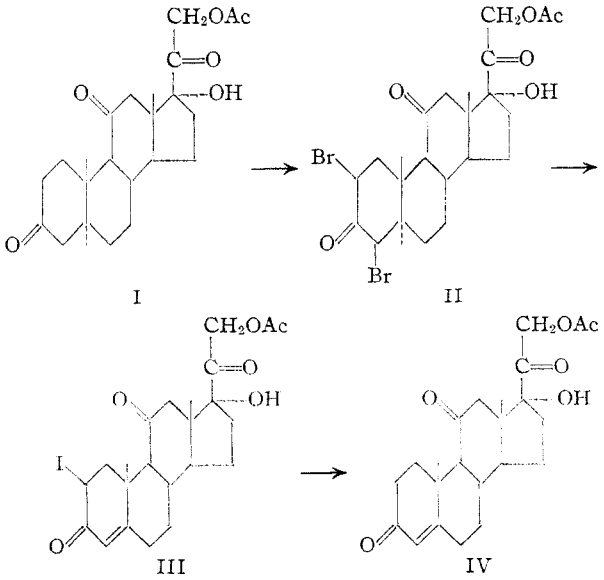
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Allopregnan-17α,21-diol-3,11,20-trione-21-acetate

BY EUGENE P. OLIVETO, CORINNE GEROLD AND E. B. HERSHBERG

Allopregnan-17α,21-diol-3,11,20-trione-21-acetate (I) has been prepared by two different procedures: (a) direct hydrogenation of cortisone acetate (IV) in neutral solution using palladium on charcoal catalyst and (b) hydrogenation of cortisone acetate enol ether (V) in neutral solution with palladium-on-charcoal catalyst, followed by hydrolysis of the intermediate enol ether VI. No evidence was obtained for the formation of compounds of the normal series in either process.

Recent reports[1] have outlined the synthesis of cortisone acetate from steroidal sapogenins, ergosterol, stigmasterol, and similar $\Delta^{5,6}$-steroids, which are potentially more abundant than the bile acids now used. In the course of each of these newer syntheses the 5,6-double bond is reduced to give the allo configuration of the A–B rings in the common intermediate, allopregnan-17α,21-diol-3,-11,20-trione-21-acetate (I). The conversion of this compound to cortisone acetate involves the formation of the 2,4-dibromide (II), followed by treatment with sodium iodide to form the 4-double bond, and to replace the 2-bromine with iodine. Removal of the iodine by reduction with bisulfite yields cortisone acetate (IV).



While no yields have as yet been stated for these halogenation–dehalogenation reactions, they are reported[1a] to be lower than those previously obtained with analogous reactions[2] in the androstane series (*ca.* 60%).

In order to study this important reaction in the cortisone series and to avoid carrying out the lengthy synthesis using incompletely described reactions to prepare I from sapogenins, ergosterol, or similar steroids, we decided to begin with cortisone acetate which was more readily available. This was transformed into allopregnan-17α,21-diol-3,11,20-trione-21-acetate by two different routes. In the first and more obvious method, that of direct hydrogenation, the literature gave no clear-cut picture on the likely course of the reduction of this 3-keto-Δ^4-system. Thus, cholestenone[3] yields coprostanone on reduction with palladium in ether, testosterone and androstendione[4] give androstane compounds and progesterone[5] gives almost equal amounts of pregnane and allopregnane derivatives.

Evidently, no generalizations can be drawn from the above examples with respect to the proportion of isomers which will be obtained in a specific case and the nature of the products is dictated by the remainder of the molecule. Tishler and co-workers[1b] hydrogenated cortisone acetate with palladium-in-methanol containing potassium hydroxide to obtain allopregnan-17α,21-diol-3,11,20-trione in unspecified yield. However, besides causing hydrolysis of the 21-acetate group, the alkali may also cause secondary reactions on the sensitive ketol side-chain.

We have found that good yields of the desired allopregnane product (I), may be obtained by hy-

(1) For leading references, *cf.* (a) G. Rosenkranz, C. Djerassi, R. Yashin and J. Pataki, *Nature*, **168**, 28 (1951); (b) J. M. Chemerda, E. M. Chamberlain, E. H. Wilson and M. Tishler, THIS JOURNAL, **73**, 4052 (1951).

(2) G. Rosenkranz, St. Kaufmann, J. Pataki and C. Djerassi, *ibid.*, **72**, 1046 (1950); G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *ibid.*, **72**, 4077 (1950).

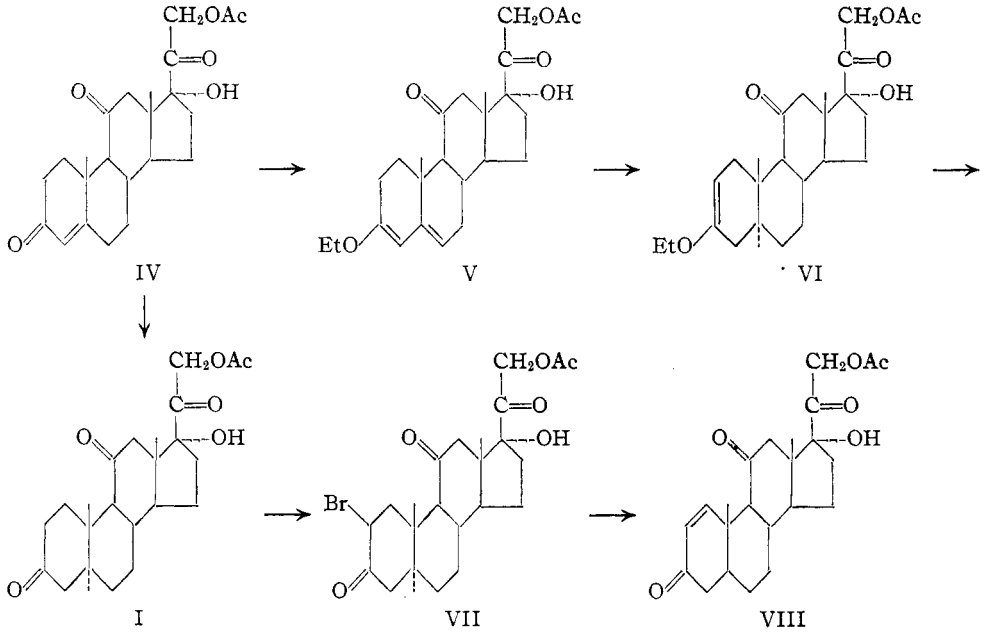
(3) H. Grasshof, *Z. physiol. Chem.*, **223**, 249 (1934).

(4) A. Butenandt, K. Tscherning and G. Hanisch, *Ber.*, **68**, 2097 (1935).

(5) A. Butenandt and G. Fleischer, *ibid.*, **68**, 2094 (1935).

drogenation of cortisone acetate in neutral solution using tetrahydrofuran or ethyl acetate as the solvent and palladium-on-charcoal catalyst. No evidence was obtained for the presence of the *cis* A–B ring isomer, pregnan-17α,21-diol-3,11,20-trione-21-acetate.

The second method for the preparation of I is an extension of the work of Inhoffen, Stoeck, Kolling and Stoeck.[6] These workers found that upon hydrogenation of cholestenone enol ether with palladium in a neutral solvent only the 5,6-double bond cluded any studies on it. We found it preferable to treat the crude hydrogenation product with 50% aqueous acetic acid which hydrolyzed the enol ether and gave the desired allopregnan-17α,21-diol-3,11,-20-trione-21-acetate (I) in approximately 65% yield after crystallization. Chromatography of the crude product over silica gel did not indicate the presence of appreciable amounts of other compounds. There was a marked depression of melting point when I was mixed with pregnan-17α,21-diol-3,11,20-trione-21-acetate.



was reduced and gave a *trans* A–B ring fusion. Hydrolysis of the intermediate 3-ethoxy-Δ^2-cholestene gave cholestanone in 50–60% yield. However, later attempts[7] to repeat this sequence of reactions on the enol ether of 3-keto-12α-acetoxy-Δ^4-cholenic acid methyl ester gave only 20–30% of the 3-ketoallocholanic acid, together with the 3-ketocholanic acid and the 3-ethoxycholanic acid derivatives.

In order to repeat these reactions in the cortisone series, cortisone acetate was converted into its enol ether (V) in 75–80% yield using the method of Julian.[8] Hydrogenation was carried out in ethyl acetate solution using palladium-on-charcoal catalyst. The absorption of hydrogen ceased after the addition of slightly more than one mole. In some instances the intermediate 3-ethoxy-Δ^2-allopregnen-17α,21-diol-11,20-dione-21-acetate[9] (VI) (ethyl enol ether of allopregnan-17α,21-diol-3,11,20-trione-21-acetate) could be isolated, but its instability and the ease of its conversion to the parent ketone pre-

Monobromination of I dissolved in either acetic acid or methylene chloride–*t*-butanol mixture gave the 2-bromide (VII) in 50–60% yield. Recrystallization of the latter from ethyl acetate, methanol or methylene chloride–ether gave solvates in each case. The monobromide was dehydrohalogenated by refluxing for one hour with collidine to give Δ^1-allopregnen-17α,21-diol-3,11,20-trione-21-acetate (VIII). It is interesting to note that the semicarbazide procedure for the introduction of the double bond in α-bromoketones[10] gave a complex mixture, even under conditions where 4-bromopregnan-17α,-21-diol-3,11,20-trione-21-acetate is smoothly converted to cortisone acetate.

Our Δ^1-allopregnene compound had λ_{max} 227 mμ, log ε 4.00. These values are in good agreement[11] with those for other Δ^1-allo compounds, and with Δ^1-pregnen-17α,21-diol-3,11,20-trione-21-acetate[12] previously reported. However, Kaufmann and Pataki[13] in preparing the same compound, Δ^1-allopregnen-17α,21-diol-3,11,20-trione-21-acetate, report the abnormally high log ε 4.24 at λ_{max} 228 mμ. This is even higher than most ε values reported for Δ^4-3-keto compounds which, however, have their maxima at a different wave length.

(6) H. H. Inhoffen, G. Stoeck, G. Kolling and U. Stoeck, *Ann.*, **568**, 52 (1950).

(7) H. H. Inhoffen, G. Kolling, G. Koch and I. Nebel, *Ber.*, **84**, 361 (1951).

(8) P. Julian, E. Meyer, W. Karpel and W. Cole, THIS JOURNAL, **73**, 1982 (1951).

(9) The position of the double bond is inferred from the work of Inhoffen (ref. 6) who proved that the product obtained by hydrogenation of cholestenone enol ether was the 3-ethoxy-Δ^2-cholestene by addition of bromine and formation of 2-bromocholestanone. Similar experiments on VI gave a bromide, which, based on melting point, rotation and infrared spectra, was crude VII.

(10) V. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951); B. Koechlin, T. Kritchevsky and T. F. Gallagher, *ibid.*, **184**, 393 (1950); E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(11) C. Djerassi and C. R. Scholz, THIS JOURNAL, **69**, 2404 (1947); *cf.* H. Dannenberg, *Abhandl. preuss. Akad. Wiss.*, **21**, 3 (1939).

(12) V. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

(13) S. Kaufmann and J. Pataki, *Experientia*, **7**, 260 (1951).

Experimental[14]

3-Ethoxy-$\Delta^{3,5}$-pregnadien-17α,21-diol-11,20-dione-21-acetate (V) (3-Ethyl Enol Ether of Cortisone Acetate).—The enolization was carried out according to the directions of Julian[8] for similar materials, except that the reaction time was reduced to 15 min. Thus, 10.00 g. of cortisone acetate was allowed to react with 10.7 ml. of ethyl orthoformate, 0.54 ml. of anhydrous ethanol, 54 ml. of anhydrous dioxane and 2.7 ml. of dioxane containing 0.134 ml. of concentrated sulfuric acid at 31°. The reaction was stopped by the addition of 5.4 ml. of pyridine and after concentration under reduced pressure, 27 ml. of methanol was added. There was obtained 8.18 g. (77%) of pale yellow product, m.p. 180–188°, $[\alpha]^{23}D$ +21.1° (dioxane) λ_{max} 242, log ϵ 4.27.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.60; H, 8.06.

Sarett, Feurer and Folkers[15] prepared this compound from cortisone acetate in ethanol–benzene solution using HCl as the catalyst. Their material had $[\alpha]D$ +28°, m.p. 177–182°. No yield was reported and a repetition of the process in this Laboratory gave about 25% of V.

3-Ethoxy-Δ^2-allopregnen-17α,21-diol-11,20-dione-21-acetate (VI).—A solution of 10.00 g. of V in 200 ml. of C.P. ethyl acetate was hydrogenated at atmospheric pressure and room temperature, using 1.00 g. of 5% palladium-on-charcoal as catalyst.[16] The hydrogenation required 8 hours and ceased after the absorption of 1 mole of hydrogen. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure. The crystalline residue was recrystallized from ether, yielding two crops, 3.43 g., m.p. 163–165°, $[\alpha]^{22}D$ +82.0° (acetone) and 3.89 g., m.p. 132–139°, and the infrared spectrum indicated that the two crops were identical. The ultraviolet spectrum of the first crop material showed general transmission. The compound was very unstable, and attempts to obtain correct analyses for carbon and hydrogen were unsuccessful.

The residues from the ether recrystallizations were found to yield I on merely treating with acetic acid at room temperature or on recrystallization from acetone, as evidenced by identical infrared spectra. The preferred method of hydrolysis, that of warming the material for 15 min. with 50% acetic acid, also gave I from the recrystallized samples.

Allopregnan-17α-21-diol-3,11,20-trione-21-acetate (I). A.—A solution of 7.00 g. of V in 150 ml. of C.P. ethyl acetate was hydrogenated at atmospheric pressure and room temperature, using 0.70 g. of 5% palladium-on-charcoal[16] as catalyst. The hydrogenation required 5 hours, and ceased after the absorption of 1 mole. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was taken up in 125 ml. of glacial acetic acid with heating, and 125 ml. of water was added to the warm solution. After 15 min. on the steam-bath, the solution was cooled and chilled and the resulting crystals were collected with suction; yield 4.56 g., m.p. 223–227°. Dilution of the filtrate with water yielded an additional 1.19 g., m.p. below 200°. Extraction of the aqueous solution with methylene chloride afforded 1.10 g. of crystalline material. The three portions of material were combined, dissolved in methylene chloride, and chromatographed on 100 g. of silica gel. Elution with 5% methanol in methylene chloride gave 6.51 g. of material over ten fractions of 80-ml. volume each. All ten fractions melted above 200°. This material upon recrystallization from acetone gave 4.25 g. (65%) of I, m.p. 223–226°. A sample recrystallized once more for analysis melted at 229–231°, $[\alpha]^{23}D$ +93.2° (chloroform); lit.[1a] m.p. 235–237°, $[\alpha]^{20}D$ +89° (chloroform) +78° (acetone); m.p.[13] 228–230°, $[\alpha]^{20}D$ +78° (acetone).

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 67.95; H, 8.10.

An ultraviolet spectrum showed no peak. The infrared spectrum confirmed the structure, and was different from that of pregnan-17α,21-diol-3,11,20-trione-21-acetate. A mixture m.p. with the latter was 210–213°.

B.—A solution of 2.00 g. of cortisone acetate in 200 ml. of C.P. ethyl acetate was hydrogenated at atmospheric pressure and room temperature using 0.20 g. of 5% palladium-on-charcoal[16] as catalyst. The hydrogenation was very slow and was allowed to proceed overnight, whereupon the hydrogen uptake was 20% above that required for 1 mole. After filtration and evaporation of the solvent under reduced pressure, the residue melted at 200–210°. Recrystallization from acetone gave two crops of I: 1.15 g., m.p. 225–227°, and 0.27 g., m.p. 222–225° (total, 70%). Mixture melting points with material prepared from the hydrogenation of the enol ether in A showed no depression.

2-Bromoallopregnan-17α,21-diol-3,11,20-trione-21-acetate (VII). A.—A solution of 1.00 g. of I in 20 ml. of methylene chloride and 10 ml. of *t*-butanol was treated with a solution of 0.40 g. of bromine in 5 ml. of methylene chloride and 5 ml. of *t*-butanol. When the bromine color had discharged, 1.5 hours later, the methylene chloride was removed under reduced pressure. Crystals began to form in the remaining *t*-butanol solvent, and the suspension was poured into water. The bromide was collected, washed with water, and dried. It was recrystallized from a mixture of methylene chloride and ether to give 0.74 g. (62%); m.p. 181–183° dec., $[\alpha]^{23}D$ +106.0° (chloroform), +100.9° (acetone). Analysis indicated methylene chloride of solvation:

Anal. Calcd. for $C_{23}H_{31}O_6Br \cdot {}^1/_2CH_2Cl_2$: apparent Br, 26.80. Found: Br, 26.88, 26.40. Recrystallization from (a) methanol and (b) ethyl acetate also gave solvates. *Anal.* (a) Calcd. for $C_{23}H_{31}O_6Br \cdot CH_3OH$: Br, 15.51. Found: Br, 15.63. (b) Calcd. for $C_{23}H_{31}O_6Br \cdot CH_3CO_2C_2H_5$: Br, 13.98. Found: Br, 13.53; lit.[12] m.p. 196.5–200°, $[\alpha]D$ +98.1° (acetone).

B.—To a solution of 1.5 g. of I in 50 ml. of glacial acetic acid was added a solution of 630 mg. of bromine in 10 ml. of acetic acid as rapidly as the bromine color was discharged. Addition was complete in 1.5 minutes. Addition of water precipitated 1.15 g. of crude bromide. Recrystallization from methanol gave 0.9 g. (50%) of pure 2-bromide.

Δ^1-Allopregnen-17α,21-diol-3,11,20-trione-21-acetate (VIII).—To 50 ml. of refluxing collidine was added 900 mg. of 2-bromide, and the heating was continued for 1 hour. Chloroform and water were added, and the organic layer was washed several times with 10% sulfuric acid, and then with water until neutral. After drying over anhydrous calcium sulfate, the organic layer was evaporated under reduced pressure and the residue was crystallized from aqueous methanol; weight 0.35 g. (47%), m.p. 229–231°, $[\alpha]^{21}D$ +135.4° (acetone), λ_{max} 227 mμ, log ϵ 4.00.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.88; H, 7.51. Found: C, 68.60; H, 7.75. Literature[13] m.p. 231–234°, $[\alpha]D$ +128.6° (acetone), λ_{max} 228 mμ, log ϵ 4.24.

BLOOMFIELD, NEW JERSEY RECEIVED NOVEMBER 19, 1951

(14) All m.ps. are corrected. All rotations were taken in a one-decimeter tube at a concentration of 1%. We are indebted to Mr. Edwin Conner and his staff for the micro-analytical data, and to Dr. Wm. Tarpley and his staff for the infrared spectra and interpretations.

(15) L. H. Sarett, M. Feurer and K. Folkers, THIS JOURNAL, **73**, 1777 (1951).

(16) Commercially available from Baker and Co., Inc., Newark, N. J.