Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.4; H, 9.9. Found: C, 74.2; H, 9.7.

2,3,17-Trihydroxyandrostane. (a).—The total product including the mother liquors from the above reaction was dissolved in 50 cc. of *n*-propyl alcohol and reduced by adding 5 g. of sodium. When this had dissolved, water was added, the product extracted with ether and the residue crystallized from methanol, m. p. 261–264°. It did not precipitate with alcoholic digitonin.

Anal. Calcd. for $C_{19}H_{32}O_3$: C, 74.0; H, 10.5. Found: C, 74.0; H, 10.4.

(b).—To a solution of 500 mg. of androstenol-17 in 50 cc. of acetic acid at 100° was added 5 cc. of hydrogen peroxide. The product was worked up as described for 2,3-dihydroxyandrostanone. It was crystallized from methanol to give a melting point of 264°. It gave no depression in melting point when mixed with the product obtained in the former case.

2,3,17-Trihydroxyandrostane Triacetate.—A solution of 100 mg. of the triol was refluxed with 3 cc. of acetic anhydride for thirty minutes. After cooling the crystalline product was filtered and recrystallized from methanol, m. p. 188°. Upon hydrolysis of this product the original triol, m. p. 264°, was obtained.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.1; H, 8.8. Found: C, 69.0; H, 8.7.

Summary

Upon treatment of Δ^2-cholestene with hydrogen peroxide, 2,3-cholestanediol is obtained. In a similar manner Δ^2-androstenone-17 gave androstanone-17-diol-2,3, which upon reduction with sodium gave 2,3,17-androstanetriol identical to the product obtained by treatment of Δ^2-androstenol-17 with hydrogen peroxide.

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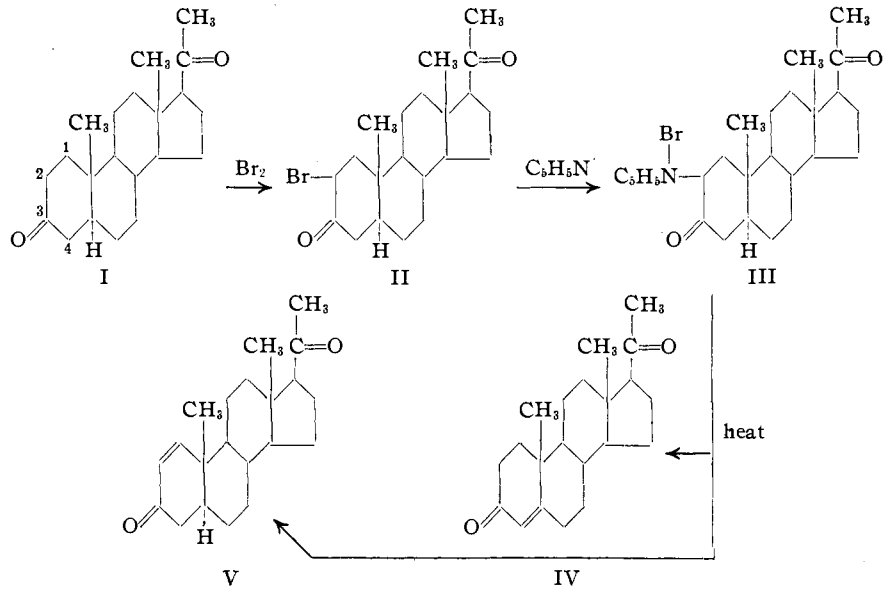
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXV. Progesterone from *allo*-Pregnanedione

BY RUSSELL E. MARKER, EUGENE L. WITTLE AND LOUIS PLAMBECK, JR.

One of the properties of steroids of the *allo*-series (H at C-5 *trans* to methyl at C-10) possessing a carbonyl group at C-3 is that bromination takes place almost exclusively at position C-2 (II) of the sterol molecule, while those of the coprostane series (H at C-5 *cis* to methyl at C-10) brominate almost exclusively at C-4.[1] When these latter C-4 bromides are refluxed with pyridine they suffer a splitting of hydrogen bromide from the molecule to form α,β-unsaturated ketones of the type (IV). In contrast to this, C-2 bromides under the same conditions form stable pyridine salts (III).



Recently Ruzicka[2] has shown that when the pyridine salt of 2-bromocholestanone is decomposed by dry distillation, a mixture of products is formed in which the most readily isolated compound is cholestenone and not the expected $\Delta^{1,2}$-*allo*-cholestenone. In this reaction a shift of the double bond from $\Delta^{1,2}$ to $\Delta^{4,5}$ has taken place. In the present work this reaction has been studied with *allo*-pregnanedione and a similar shift has been found to take place.

Treatment of 2-bromo-*allo*-pregnanedione (II) with pyridine forms the stable pyridine salt (III). Dry distillation of this salt at reduced pressure gave a mixture from which two substances, pro-

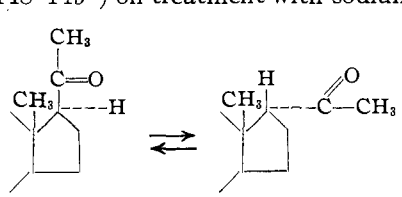
(1) Butenandt and Mamoli, *Ber.*, **68**, 1854 (1935); Butenandt and Wolff, *ibid.*, **68**, 2091 (1935).

(2) Ruzicka, Plattner, and Aeschbacher, *Helv. Chim. Acta*, **21**, 870 (1938).

gesterone (IV) and $\Delta^{1,2}$-*allo*-pregnenedione (V), were isolated by fractional crystallization. The more soluble fraction was found to be identical with progesterone, whereas the less soluble fraction gave a product melting at 208–210°, which from its reactions and mode of formation has the probable structure of $\Delta^{1,2}$-*allo*-pregnenedione (V). These two products were obtained in the pure state in approximately equal quantities. Upon further investigation of the intermediate fractions only these two products could be obtained. They appear to crystallize in a molecular combination which is separated only with difficulty.

Butenandt and Mamoli[3] treated 2-bromo-*allo*-pregnanedione with potassium acetate at 180° and obtained a very low yield of an α,β-unsaturated diketone melting at 140°, which from the mode of its formation and its absorption spectrum was thought to be $\Delta^{1,2}$-*allo*-pregnenedione (V). While this compound and the one we have obtained may be polymorphous forms of the same substance, it has not been possible to obtain a melting point other than 208–210° for our product. This product has all the properties expected for $\Delta^{1,2}$-*allo*-pregnenedione. It gives a depression in melting point with *allo*-pregnanedione, a dioxime, and an orange *bis*-2,4-dinitrophenylhydrazone indicative of the α,β-unsaturation. Catalytic reduction with platinum oxide gave a quantitative yield of *allo*-pregnanediol-3(β),20(β) which was identical with the known product. Partial reduction gave *allo*-pregnanol-3(β)-one-20 which upon oxidation gave *allo*-pregnanedione. As Butenandt did not thoroughly characterize his product, it may be possible that his diketone is stereoisomeric at some point with $\Delta^{1,2}$-*allo*-pregnenedione.

During the course of this work we have had occasion to prepare iso-*allo*-pregnanedione, a product which is isomeric at C-17 with normal *allo*-pregnanedione. It was found that this could be obtained in low yield by the isomerization of *allo*-pregnanedione by sodium methylate or methyl alcoholic potassium hydroxide. The compound (m. p. 148–149°) on treatment with sodium methylate reverts largely to the original *allo*-pregnanedione. This product was previously prepared by Butenandt and Mamoli[4] (m. p. 134–135°) by the oxidation of iso-*allo*-pregnanol-3-one-20.



We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous help and assistance in various phases of this work.

Experimental Part

2-Bromo-*allo*-pregnanedione Pyridine Salt.—A solution of 3.8 g. of 2-bromo-*allo*-pregnanedione, m. p. 199–201°, in 15 cc. of dry pyridine was heated for three hours under reflux. The pyridine salt precipitated after the first few minutes of heating. The solution was cooled, diluted with 15 cc. of ligroin and the salt was filtered off with suction and washed with ligroin. The pyridine salt is very soluble in alcohols but difficultly soluble in acetone. It was crystallized by dissolving in a very small amount of methyl alcohol and adding acetone, followed by cooling; yield 3.6 g., m. p. 300–302° dec.

Anal. Calcd. for $C_{26}H_{36}O_2NBr$: C, 65.8; H, 7.7. Found: C, 64.8; H, 7.7.

Decomposition of the Pyridine Salt.—In a 500-cc. retort was placed 10.6 g. of the pyridine salt of 2-bromo-*allo*-pregnanedione. The retort was joined to a receiver having a side-arm tube connected to a vacuum pump. The system was placed under a pressure of 10 mm. and the retort was heated carefully with a free flame to decompose the salt and distill the product into the receiver. The distillation required about fifteen minutes and was continued until only a small tarry residue remained in the retort. The distillate was extracted from the flask with hot alcohol and the alcohol solution evaporated to dryness. The residue was distilled in a molecular still and the fraction distilling at 100–160° was collected. A small residue remained. The distilled product was taken up in acetone and the solution was concentrated to 50 cc. and cooled. The solid which separated was filtered and found to melt at 165–185°. Crystallization of this mixture from acetone or ethyl acetate gave a pure product melting at 208–210°.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 79.9; H, 9.6.

The acetone filtrate from the initial crystallization was evaporated to dryness and the residue was dissolved in 25 cc. of alcohol. The solution was cooled overnight and the solids were filtered off. The alcoholic filtrate was diluted with 5 cc. of water, cooled and the solid again filtered off. This filtrate was again diluted with 5 cc. of water and cooled. The crystals which were obtained in this manner were recrystallized from dilute alcohol and dilute acetone. They melted at 126–127° and gave no depression in melting point when mixed with an authentic sample of progesterone.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.5; H, 9.9.

The above two products are the only substances which could be isolated. Absorption of the intermediate fractions on a column of aluminum oxide followed by elution

(3) Butenandt and Mamoli, *Ber.*, **68**, 1847 (1935).

(4) Butenandt and Mamoli, *Ber.*, **68**, 1850 (1935).

with benzene and ligroin gave an additional quantity of the two products.

A mixture of equal quantities of $\Delta^{1,2}$-*allo*-pregnenedione, m. p. 208–210°, and progesterone, m. p. 126–128°, gave a melting point range of 125–195°.

The product, m. p. 208–210°, obtained in the above reaction gave a depression in melting point with *allo*-pregnanedione (200°) to 193–196°.

Upon treatment with hydroxylamine hydrochloride and sodium acetate in alcohol, it gave a dioxime which was crystallized from dilute acetone, m. p. 248–250°.

Anal. Calcd. for $C_{21}H_{32}O_2N_2$: C, 73.2; H, 9.4. Found: C, 72.8; H, 9.7.

The Reduction of $\Delta^{1,2}$-*allo*-Pregnenedione.—A suspension of 500 mg. of Adams platinum oxide catalyst in a solution of 100 mg. of $\Delta^{1,2}$-*allo*-pregnenedione in 50 cc. of ethyl alcohol was shaken with hydrogen at 3 atmospheres and room temperature for six hours. The solution was filtered, evaporated to dryness and the residue was crystallized from dilute methyl alcohol to yield 70 mg. of *allo*-pregnanediol-3(β),20(β), m. p. 192–194°. This gave no depression in melting point with the known product.

A suspension of 400 mg. of partially inactivated platinum catalyst in a solution of 200 mg. of $\Delta^{1,2}$-*allo*-pregnenedione and 75 cc. of ethyl alcohol was shaken with hydrogen at 3 atmospheres for seven hours. The solution was filtered from the catalyst and evaporated to dryness. The product was crystallized from acetone to give *allo*-pregnanol-3(β)-one-20, m. p. 194°. It gave no depression in melting point when mixed with an authentic sample.

Oxidation of a portion of this compound with chromic anhydride gave *allo*-pregnanedione, m. p. 200–202°. This gave no depression in melting point with the known product, but gave a depression in melting point with $\Delta^{1,2}$-*allo*-pregnenedione.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.1.

An acetate prepared by refluxing a portion of *allo*-pregnanol-3(β)-one-20 with an excess of acetic anhydride, after crystallization melted at 144°. It gave no depression in melting point with the known *allo*-pregnanol-3(β)-one-20-acetate, m. p. 144°.

Iso-*allo*-pregnanedione.—A solution of 3 g. of *allo*-pregnanedione in 250 cc. of 5% methyl alcoholic potassium hydroxide was refluxed for two hours and then cooled and diluted with water. The product was extracted with ether and the solution was washed thoroughly with water and evaporated to dryness. The residue was crystallized from acetone to give 2 g. of crude *allo*-pregnanedione. The filtrate was evaporated to dryness and the residue was crystallized from dilute acetone to give a further small quantity of impure *allo*-pregnanedione. The mother liquor on evaporation gave a solid melting at 130–145° which on recrystallization gave iso-*allo*-pregnanedione, m. p. 148–149°; yield 50 mg.

This same product was obtained by isomerization of *allo*-pregnanedione with sodium methylate in methyl alcohol. Recrystallization gave no change in melting point.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.4; H, 10.2.

This compound gave a depression in melting point to 128-140° when mixed with a small quantity of *allo*-pregnanedione. Treatment with refluxing acetic anhydride for one-half hour caused very little change and the major product which was recovered was the original, m. p. 147–149°.

Isomerization to *allo*-Pregnanedione.—A solution of 25 mg. of iso-*allo*-pregnanedione, m. p. 148–149°, in 25 cc. of methyl alcohol containing 500 mg. of dissolved sodium was refluxed for two hours. The solution was diluted with water and the product was extracted with ether. The ether solution was washed with water and evaporated and the residue was crystallized from methyl alcohol to give *allo*-pregnanedione, m. p. 198–200°.

Summary

The destructive distillation of the pyridine salt of 2-bromo-*allo*-pregnanedione gave a mixture of products from which progesterone and an isomeric product $\Delta^{1,2}$-*allo*-pregnenedione were isolated. Isomerization of *allo*-pregnanedione gave iso-*allo*-pregnanedione which could be isomerized back to the original.

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