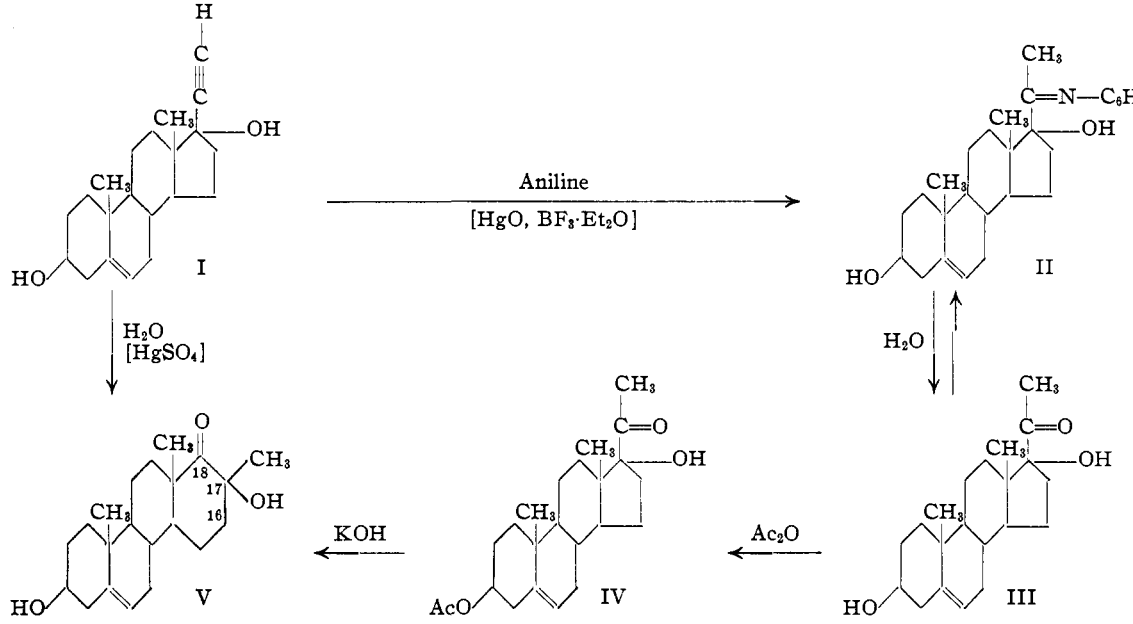
[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

The Preparation of Δ^5-Pregnenediol-3,17-one-20 from Δ^5-17-Ethynyl-androstenediol-3,17

BY HOMER E. STAVELY

The transformation of Δ^5-17-ethynyl-androstenediol-3,17 (I) into the hydroxy ketone III has been studied by Ruzicka and Meldahl,[1] who added acetic acid to the acetylene bond and then saponified the resulting acetate. An identical compound was obtained by Stavely[2] by the direct hydration of the acetylene compound in the presence of mercuric sulfate.



Degradation studies by Ruzicka, *et al.*,[3] have revealed the very noteworthy fact that this product cannot have the expected structure III. Oxidation of the corresponding acetylated and hydrogenated hydroxy ketone (presumed to have the side chain structure of III) led to a keto acid without the loss of any carbon atoms, instead of giving the expected acetate of *trans*-androsterone. To explain this unlooked for result Ruzicka proposed that in the preparation of substance III from the corresponding 17-ethynyl compound a rearrangement into a structure V had occurred, which readily explains the oxidation into the keto acid. Although the formulation of the compound V may be hypothetical in its details, there is not much doubt that a transformation of a five-membered into a six-membered ring must have occurred. The name chrysopregnane is now proposed for the parent hydrocarbon of the series to express the relationship to chrysene as well as to pregnane. Compound V should then be named Δ^5-3,17-dihydroxy-18-keto-chrysopregnene.

Since the appearance of an article by Loritsch and Vogt,[4] who condensed 1-heptyne and 3-octyne with aniline in the presence of ether–boron fluoride and mercuric oxide catalysts, and split the anils into the corresponding ketones, the reaction has been applied by me to ethynylandrostenediol (I). While this work was in progress Goldberg and Aeschbacher[5] described in a preliminary form an anil obtained by the condensation of the same compounds, using mercuric chloride as a catalyst. It seems certain that their anil is identical with the one described in this paper.

The anil (II) seems to be hydrolyzed on standing in aqueous methanol, although the reaction is not complete even on prolonged heating. Apparently an equilibrium between ketone and anil

(1) Ruzicka and Meldahl, *Helv. Chim. Acta*, **21**, 1760 (1938).
(2) Stavely, THIS JOURNAL, **61**, 79 (1939).
(3) Ruzicka, Gätzi and Reichstein, *Helv. Chim. Acta*, **22**, 626 (1939).
(4) Loritsch and Vogt, THIS JOURNAL, **61**, 1462 (1939).
(5) Goldberg and Aeschbacher, *Helv. Chim. Acta*, **22**, 1188 (1939).

is established. Separation of the ketone III from the mixture was difficult, but after acetylation it was possible to remove the sparingly soluble anil acetate and obtain both products in pure form. Since ketone IV is not identical with the acetate of the chrysopregnane ketone V, it was probable that the acetate of Δ^5-pregnenediol-3,17-one-20 (III) had been obtained. In order to prove this assumption the acetate IV was oxidized with chromic acid and from the neutral fraction was isolated the acetate of dehydroandrosterone as the semicarbazone. When saponification of the acetoxy group of IV was attempted by heating with methyl alcoholic potassium hydroxide, the alcohol obtained was identical with Δ^5-3,17-dihydroxy-18-keto-chrysopregnene (V). In view of the rearrangement of IV to V, it seems remarkable that Reichstein[6] can subject the 3-acetates of his natural adrenal steroids with 17-hydroxyl and 17-acetyl groups, such as his substance L, to alkali saponification without a similar rearrangement. However, he points out[7] that all pregnane derivatives obtained by the interaction of ethylmagnesium bromide or acetylene with 17-ketoandrostane compounds belong to the same series (precipitated by digitonin), designated as the 17(α)-series; whereas natural adrenal steroids belong to the 17(β)-series (not precipitated by digitonin). Therefore, it would seem that only members of the 17(α)-series are susceptible to rearrangement into chrysopregnane compounds. The anil II and the ketone IV appear to be sensitive to dilute acid also. By splitting the anil with dilute acid and acetylating, a product was isolated which is not identical with IV or with the acetate of V. The influence of both acid and alkali on these compounds is being more extensively investigated.

Experimental

Δ^5-Pregnenediol-3,17-one-20-anil (II).—A mixture of 1 g. of Δ^5-17-ethynyl-androstenediol-3,17, 500 mg. of mercuric oxide, 0.3 cc. of ether–boron fluoride catalyst,[8] and 5.0 cc. of dry aniline was allowed to stand at room temperature for a week. The excess aniline was then removed by steam distillation, and the flask was cooled and saturated with hydrogen sulfide. The next morning the mixture was thoroughly extracted with ether, the ether washed with water, dried over sodium sulfate, evaporated to dryness and the residue crystallized from aqueous methanol; yield, 500 mg., m. p. 148°, $[\alpha]^{23}D$ −196 ± 2.0° (12.3 mg. in 2.0 cc. chloroform, 1 dm. tube, α^{23} −1.20).

Anal.[9] Calcd. for $C_{27}H_{37}O_2N$: C, 79.56; H, 9.15. Found: C, 79.61; H, 9.60.

Using mercuric chloride as a catalyst,[5] a better yield was obtained by working up the reaction mixture as above, instead of by the method used by Goldberg and Aeschbacher.

Δ^5-Pregnenediol-3,17-one-20 (III).—From the aqueous methanol mother liquor of the anil crystallization, after standing for about ten days, another crop of crystals was isolated. After purification the substance analyzed for Δ^5-pregnenediol-3,17-one-20, sinters at 158°, m. p. 161–163°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.71. Found: C, 75.60; H, 9.61.

Δ^5-3-Acetoxypregnenol-17-one-20 Oxime from (III).—Fifty milligrams of Δ^5-pregnenediol-3,17-one-20 was acetylated in pyridine and acetic anhydride overnight. The solvents were removed in a vacuum and the residue heated with 50 mg. of hydroxylamine hydrochloride, 50 mg. of potassium acetate and 10 cc. of ethanol for two hours. Water was then added, the precipitate filtered, washed with water, dried, and recrystallized from benzene–petroleum ether; m. p. 254–256°.

Anal. Calcd. for $C_{23}H_{35}O_4N$: C, 70.92; H, 9.08. Found: C, 71.15; H, 9.29.

Separation of Δ^5-3-Acetoxypregnenol-17-one-20 (IV) from Δ^5-3-Acetoxypregnenol-17-one-20-anil.—Two grams of the crude anil II was refluxed with aqueous methanol for twenty-eight hours. The products crystallized on cooling, but melted over a 30° range and were a mixture. The crystals were dried and acetylated by standing at room temperature overnight in pyridine and acetic anhydride. The solvents were removed in a vacuum and the residue dissolved in a large volume of methanol. On cooling 700 mg. of beautiful crystals separated, m. p. 232–234° after recrystallizing twice from methanol–ether. The mother liquors yielded 200 mg. more; $[\alpha]^{24}D$ −176 ± 2.0° (13.0 mg. in 2.0 cc. of chloroform, 1 dm. tube, α^{24} −1.14).

Anal. Calcd. for $C_{29}H_{39}O_5N$: C, 77.46; H, 8.75; N, 3.13. Found: C, 77.60; H, 8.68; N, 3.39.

The mother liquors were concentrated to a small volume and the Δ^5-3-acetoxypregnenol-17-one-20 precipitated by addition of water. After drying, the precipitate was crystallized as beautiful needles from benzene–petroleum ether; yield, 520 mg.; m. p. 196–198°; $[\alpha]^{23}D$ −61 ± 1.5° (9.2 mg. in 2.0 cc. chloroform, 1 dm. tube, α^{23} −0.28).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.16. Found: C, 74.06; H, 9.24.

Oxidation of Δ^5-3-Acetoxypregnenol-17-one-20 (IV) to 3-Acetoxydehydroandrosterone.—To 100 mg. of Δ^5-3-acetoxypregnenol-17-one-20 in 4.0 cc. of glacial acetic acid, 43 mg. of bromine in acetic acid (1 mole) was added dropwise with cooling. Chromic oxide, 170 mg. dissolved in acetic acid, was added and the mixture allowed to stand for twenty hours at room temperature. Since no oxida-

(6) Reichstein and Gätzi, *Helv. Chim. Acta*, **21**, 1497 (1938), etc.

(7) Reichstein and Gätzi, *ibid.*, **21**, 1185 (1938).

(8) Hennion, Hinton and Nieuwland, THIS JOURNAL, **55**, 2858 (1933).

(9) Analyses herein reported are by Mr. J. F. Alicino, Fordham University.

tion was apparent, the flask was heated to 45° for four hours. Methanol was added to destroy excess chromic acid, then 200 mg. of zinc dust, and the mixture heated on the steam-bath for one hour. The solution was concentrated in a vacuum. After addition of water, it was extracted with ether. The ether extract was washed with 1 *N* potassium hydroxide and with water, dried over sodium sulfate, and evaporated to dryness. The residue weighed 45 mg. It was refluxed with semicarbazide hydrochloride and potassium acetate in ethanol for an hour, water was added, the precipitate filtered, washed with water and ether, and recrystallized several times from chloroform–ethanol. Seventeen milligrams of pure 3-acetoxydehydroandrosterone semicarbazone was obtained, m. p. 275–278°. A mixed m. p. with an authentic specimen showed no depression.

Anal. Calcd. for $C_{22}H_{35}O_3N_3$: C, 68.18; H, 8.59. Found: C, 67.90; H, 8.88.

Δ^5-3-Acetoxypregnenol-17-one-20 Oxime from (IV).—The oxime was prepared from the ketone in the usual manner. It was crystallized from benzene–petroleum ether, m. p. 253–256°; mixed m. p. with the 3-acetoxy oxime prepared from the Δ^5-pregnenediol-3,17-one-20 isolated directly from the products of the anil hydrolysis showed no depression.

Anal. Calcd. for $C_{23}H_{35}O_4N$: C, 70.92; H, 9.08; N, 3.60. Found: C, 70.71; H, 9.21; N, 3.79.

Rearrangement of Δ^5-3-Acetoxypregnenol-17-one-20 (IV) to Δ^5-3,17-Dihydroxy-18-keto-chrysopregnene (V).—Fifty milligrams of Δ^5-3-acetoxypregnenol-17-one-20 was refluxed with 3% methanolic potassium hydroxide for two hours. The alkali was neutralized with carbon dioxide, the solution concentrated, and water added. The precipitate was filtered, washed with water, and crystallized in beautiful hexagonal prisms from acetone, m. p. 278–280°; $[\alpha]^{22}D$ −104° (9.8 mg. in 2.0 cc. dioxane, 1 dm. tube, α^{22} −0.51). A mixed m. p. with Δ^5-3,17-dihydroxy-18-keto-chrysopregnene prepared by the direct hydration of Δ^5-17-ethynyl-androstenediol-3,17[2] showed no depression. The specific rotations of the two substances were the same.

Summary

Δ^5-17-Ethynyl-androstenediol-3,17 and aniline have been condensed in the presence of ether–boron fluoride and mercuric oxide catalysts to form Δ^5-pregnenediol-3,17-one-20-anil.

The anil is partially hydrolyzed by contact with water to form Δ^5-pregnenediol-3,17-one-20. The acetate of this substance has been oxidized to 3-acetoxydehydroandrosterone, thus proving its pregnane structure.

By saponification of Δ^5-3-acetoxypregnenol-17-one-20 with methyl alcoholic potassium hydroxide a rearranged product is obtained for which the name Δ^5-3,17-dihydroxy-18-keto-chrysopregnene is proposed. The substance is identical with the ketone obtained by the direct hydration of Δ^5-17-ethynylandrostenediol-3,17.

NEW BRUNSWICK, N. J. RECEIVED DECEMBER 13, 1939

[CONTRIBUTION FROM THE BIOCHEMISTRY DEPARTMENT OF THE UNIVERSITY OF OKLAHOMA MEDICAL SCHOOL]

The Isolation of Keturonic Acids. II[1,2]

BY L. T. CREWS, J. P. HART AND M. R. EVERETT

The authors are reporting the isolation of crystalline brucine salts of keturonic acids prepared by oxidation of *l*-xylose, *l*-arabinose and *d*-glucosamine, together with a new type of oxidation product, an anhydride of a dicarbonyl sugar, from oxidized levoglucosan. Brucine keturonates also have been prepared from oxidized *α-d*-glucoheptose and *l*-fucose but to date these salts have not been separated completely from accompanying non-reducing substances. Ultimate analysis and melting point determinations of the reported preparations are given in Table I and other properties of these substances in Table II.

Experimental

Oxidation of the 1% carbohydrate solutions, preparation of the mixed barium salts, and isolation of the crystalline brucine salts were conducted according to the general methods of Hart and Everett.[2] Yields of mixed barium salts from 4-g. quantities of the carbohydrates were as follows: *l*-xylose, 4.1 g.; *l*-arabinose, 3.0 g.; and *d*-glucosamine hydrochloride, 1.7 g. Reducing barium salts could not be obtained from oxidized levoglucosan solutions but during concentration of the barium salt solution *in vacuo* the substance designated as ketolevoglucosan crystallized directly. Non-reducing barium salts could be precipitated from the mother liquor by the addition of acetone.

Brucine-*l*-xyloketuronate.—A solution of this salt was prepared from 3.75 g. of the mixed barium salts obtained from oxidized *l*-xylose. The reducing brucine salt began to crystallize during concentration of the solution *in vacuo*. After two hours in the refrigerator it was filtered off, washed with alcohol and ether and dried in a desiccator. The yield was 2.5 g. The salt was recrystallized from water.

Brucine-*l*-araboketuronate.—A solution of this salt was prepared from 2.9 g. of the mixed barium salts obtained

(1) Aided by a grant from the Research Appropriation of the University of Oklahoma Medical School.

(2) For previous paper in this series see THIS JOURNAL, **61**, 1822 (1939).