Vitamin A alcohol (10.5 mg.) was treated in exactly the same manner.

Behavior of Vitamin A Methyl Ether with *p*-Toluenesulfonic acid

1. In a Molar Ratio of 218 to 1 (Fig. 3).—A solution of 26 micrograms of *p*-toluenesulfonic acid monohydrate in 20 cc. of benzene was dried by distillation of 10 cc. of benzene. To this solution crystalline vitamin A methyl ether (8.9 mg.) was added and the solution refluxed for thirty minutes after which it was cooled in ice, and then poured onto cold saturated sodium bicarbonate contained in a separatory funnel. The benzene solution was washed well with the bicarbonate solution and then three times with cold water, dried over anhydrous sodium sulfate, filtered and concentrated. After the last traces of benzene were removed as above, an ultraviolet absorption curve was run on the residual oil.

Crystalline vitamin A alcohol (8.5 mg.) was run under identical conditions.

2. In a Molar Ratio of 92 to 1 (Fig. 4).—Vitamin A methyl ether (9.4 mg.) was treated with 65 micrograms of *p*-toluenesulfonic acid monohydrate exactly as in (1) above. Definite anhydro formation is indicated in the spectrophotometric curve.

Vitamin A acetate (10.6 mg.) under identical conditions was little affected.

Summary

1. Crystalline vitamin A methyl ether has been prepared by the action of dimethyl sulfate on the lithium salt of the alcohol.

2. Crystalline vitamin A methyl ether has a provisional biological potency of 3,500,000 U. S. P. XII units per gram.

3. The behavior of vitamin A methyl ether under dehydration conditions has been studied and a comparison is made between the stability of the vitamin A alcohol, ether and acetate under these conditions.

KALAMAZOO 99, MICHIGAN RECEIVED JUNE 23, 1947

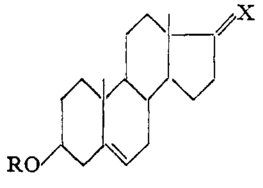
[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF SYNTEX S. A.]

Mercaptols of 17-Keto Steroids

BY L. NORYMBERSKA, J. NORYMBERSKI AND A. OLALDE

In a recent paper by Hauptmann[1] the reaction of estrone acetate with ethanedithiol was reported. Since the reactions of 17-keto steroids with mercaptans have been the object of investigation in our laboratory for a considerable period of time, we wish to communicate some of the results obtained.[2]

By condensation of dehydroisoandrosterone acetate (II) with benzyl and ethyl mercaptan in the presence of fused zinc chloride and anhydrous sodium sulfate, we were able to prepare the respective mercaptols III and V.



I. $R = H, X = O$
II. $R = CH_3CO, X = O$
III. $R = CH_3CO, X = (C_6H_5CH_2S)_2$
IV. $R = H, X = (C_6H_5CH_2S)_2$
V. $R = CH_3CO, X = (C_2H_5S)_2$
VI. $R = H, X = (C_2H_5S)_2$
VII. $R = CH_3CO, X = H_2$
VIII. $R = H, X = H_2$

Acid hydrolysis of dehydroisoandrosterone acetate dibenzylmercaptol (III) led to the formation of dehydroisoandrosterone (I); alkaline hydrolysis to dehydroisoandrosterone dibenzylmercaptol (IV); boiling with cadmium carbonate and mercuric chloride in acetone or acetic acid solution to dehydroisoandrosterone acetate (II); hydrogenolysis with Raney nickel to desoxo-dehydroisoandrosterone acetate (VII).

The last-mentioned reaction is of some special interest: Butenandt and Surányi[3] and recently Heard and McKay[4] described the Wolff–Kishner reduction of dehydroisoandrosterone semicarbazone and the product obtained has been proved to consist of a hard to separate mixture of desoxo-dehydroisoandrosterone, etiocholan-3(α)-ol and androstan-3(β)-ol. On the other hand, by hydrogenolysis of the dibenzylmercaptol, as well as of the diethylmercaptol of dehydroisoandrosterone acetate (III and V, respectively) with Raney nickel, we have obtained the pure desoxo-dehydroisoandrosterone acetate (VII) in excellent yield and by its saponification the desoxo-dehydroisoandrosterone (VIII).

Acknowledgment.—The microanalyses have been carried out by L. N. at the microanalytical laboratory of the Escuela Nacional de Ciencias Biológicas, Instituto Politecnico Nacional, with the kind permission of Dr. P. Hope, to whom we wish to express our thanks for his obligingness. Dr. G. Rosenkranz of our laboratory we thank for his kind interest in this work.

Experimental

Dibenzylmercaptol of Dehydroisoandrosterone Acetate (III).—A mixture of 15 g. of dehydroisoandrosterone acetate, 15 cc. of benzylmercaptan, 10 cc. of dioxane and 15 g. of anhydrous sodium sulfate is ice-cooled and 15 g. of freshly fused and pulverized zinc chloride is added.

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[1] Hauptmann, THIS JOURNAL, **69**, 562 (1947).

[2] Further communications on this subject will be reported soon.

[3] Butenandt and Surányi, *Ber.*, **75**, 591 (1942).

[4] Heard and McKay, *J. Biol. Chem.*, **165**, 677 (1946).

The mixture solidifies in few minutes and is kept at room temperature overnight. The reaction product is extracted with chloroform, the chloroform solution washed with water, dried over sodium sulfate and evaporated. The residue crystallizes from a mixture of chloroform and methanol in the form of prismatic plates, m. p. 148–149°, yield 20 g. (78.5%).

Anal. Calcd. for $C_{35}H_{44}O_2S_2$: C, 74.95; H, 7.91. Found: C, 74.81; H, 7.95.

Diethylmercaptol of Dehydroisoandrosterone Acetate (V).—The preparation proceeds in the manner described above for dibenzylmercaptol. The crude product crystallizes from acetone, m. p. 147–149°.

Anal. Calcd. for $C_{25}H_{40}O_2S_2$: C, 68.76; H, 9.23. Found: C, 69.00; H, 9.33.

Acid Hydrolysis of the Dibenzylmercaptol Acetate (III).—One hundred milligrams of the compound (III) is refluxed for one hour with 5 cc. of dioxane, 5 cc. of methanol and 0.4 cc. of concentrated hydrochloric acid. The warm solution is diluted with water and the precipitated needles are filtered off, m. p. 138–140°. The product gives no depression with dehydroisoandrosterone.

Alkaline Hydrolysis of the Dibenzylmercaptol Acetate (III).—One and one-tenth grams of the compound (III) is dissolved in 10 cc. of dioxane and a solution of 0.5 g. of sodium hydroxide in 20 cc. of methanol is added. The dibenzylmercaptol of dehydroisoandrosterone is precipitated by dilution with water and recrystallized from acetone; prismatic needles, m. p. 185–186°.

Anal. Calcd. for $C_{33}H_{42}OS_2$: C, 76.40; H, 8.16. Found: C, 76.48; H, 8.31.

Acetylation of the compound with acetic anhydride in pyridine at room temperature gives the original acetate.

Reaction of the Dibenzylmercaptol Acetate (III) with Mercuric Chloride and Cadmium Carbonate.—Two-hundred-fifty milligrams of the compound (III), 300 mg. of mercuric chloride and 400 mg. of cadmium carbonate are refluxed in 10 cc. of acetone and 1 cc. of water for eight hours. The inorganic salts are filtered off, the crude reaction product purified by adsorption on activated alumina, the benzene fraction yielding crystals of dehydroisoandrosterone acetate of the melting point 165–166°. The resulting dehydroisoandrosterone acetate may be isolated from the crude product by recrystallization from methanol if the reaction is carried out in acetic acid instead of acetone.

Desoxo-dehydroisoandrosterone Acetate (VII).—To a suspension of 40 g. of Raney nickel[5] in 120 cc. of methanol is added a solution of 4 g. of dibenzylmercaptol of dehydroisoandrosterone acetate in 120 cc. of acetone and the mixture is refluxed for two hours. The nickel is filtered off, washed with methanol, the filtrate evaporated and the residue (2 g., m. p. 86–91°) recrystallized from methanol, yielding leaflets of constant melting point, 96–97°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.56; H, 10.03.

Hydrogenolysis of the diethylmercaptol (V) is carried out in the same manner and gives an identical product.

Desoxo-dehydroisoandrosterone (VIII).—Nine-tenths gram of the acetate (VII) is refluxed with 1 g. of potassium hydroxide in 20 cc. of methanol for one hour. The hot solution is diluted with water until the first crystals appear and the mixture is cooled to complete the precipitation; long needles, m. p. 136–137°. Repeated recrystallization from aqueous methanol or from hexane does not change the melting point.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.16; H, 11.16; $[\alpha]_D$ −75.8° (in dioxane).

Summary

1. The dibenzylmercaptol and the diethylmercaptol of dehydroisoandrosterone acetate have been prepared; conditions are described under which the selective hydrolysis of either the acetyl or mercaptol group may be carried out.

2. Desoxo-dehydroisoandrosterone and its acetate have been prepared by the hydrogenolysis of the mercaptols of dehydroisoandrosterone acetate with Raney nickel and the advantages of this method over the Wolff–Kishner reduction for this particular case have been shown.

[5] The Raney nickel was prepared according to Mozingo, *et al.*, THIS JOURNAL, **65**, 1477 (1943).

MEXICO CITY, MEXICO RECEIVED JULY 31, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MEAD JOHNSON AND COMPANY]

Pyrazine Chemistry. III. Derivatives of 3-Amino-5,6-dimethylpyrazinoic Acid

BY RUDOLPH C. ELLINGSON AND ROBERT L. HENRY

3-Amino-5,6-dimethylpyrazinoic acid[1] can be obtained in excellent yield by the alkaline hydrolysis of 6,7-dimethyllumazine. The decarboxylation of this acid according to a modification of the described method[1] gives 2-amino-5,6-dimethylpyrazine (I) in good yield.

Bromination of I gives 2-amino-3-bromo-5,6-dimethylpyrazine (II). The structure of II was established by amination to the hitherto unknown diamine (III) followed by conversion of the diamine by reaction with glyoxal into the unknown 2,3-dimethylpyrazinopyrazine (IV). The structure of IV was established by its synthesis from diacetyl and the known 2,3-diaminopyrazine.[2] This series of reactions proves that in II the bromine atom is in position 3.

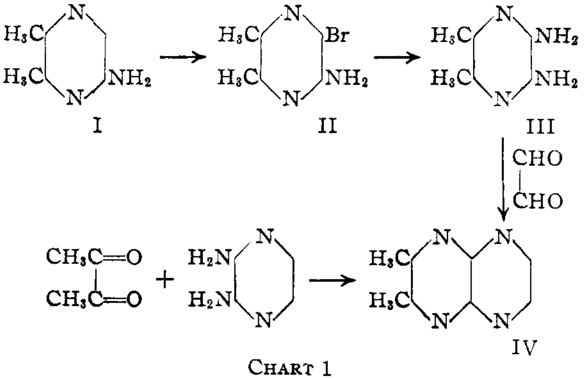

CHART 1

Condensation of III with diacetyl gave tetramethylpyrazinopyrazine. 2,3-Dimethylpyrazinopyrazine and tetramethylpyrazinopyrazine are

[1] Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 802 (1945).

[2] McDonald and Ellingson, *ibid.*, **69**, 1034 (1947).