

cholesterols were extracted with ether; 820 g. was obtained from 1150 g. of crude material. This was converted into the acetate by boiling for one hour with three times excess of acetic anhydride. The excess acetic anhydride was removed by vacuum distillation. The acetates were boiled with 6 liters of 95% ethyl alcohol and the solution cooled to 5°. The precipitate was filtered and recrystallized, m. p. 101–104°. One more crystallization of the product gave pure cholesteryl acetate, m. p. 114°, which gave no depression in melting point when mixed with cholesteryl acetate prepared from pure cholesterol. The alcoholic mother liquors from the above crystallization were evaporated to dryness and hydrolyzed by means of alcoholic sodium hydroxide, giving a product consisting of approximately 90% of *epi*-cholesterol and 10% cholesterol. This mixture was then converted into the benzoate, and freed of cholesterol benzoate by crystallization from alcohol. The benzoate was then hydrolyzed and the *epi*-cholesterol crystallized from alcohol, m. p. 141.5°. Mixed with pure *epi*-cholesterol, m. p. 141.5°, it gave no depression in melting point, whereas when mixed with cholesterol, m. p. 147°, a depression of 19° was observed;  $[\alpha]^{20}_D -35.0^\circ$  in 1% alcohol.

*Anal.* Calcd. for  $C_{27}H_{46}O$ : C, 83.9; H, 12.0. Found: C, 83.9; H, 12.1.

**Action of Bromine on *epi*-Cholesteryl Acetate.**—To a solution of 100 mg. of *epi*-cholesteryl acetate in 3 cc. of ether was added a solution of 40 mg. of bromine in 5 cc. of acetic acid. A solid crystallized out. This was filtered and recrystallized from acetic acid, m. p. 110°. It gave a tetrabromocholestane.

*Anal.* Calcd. for  $C_{27}H_{43}Br_4$ : C, 47.2; H, 6.3. Found: C, 47.4; H, 6.7.

This bromide is different from the tetrabromide formed

from cholesterylene and bromine, giving a depression in melting point when mixed.

**Action of Hydrochloric Acid on *epi*-Cholesterol.**—A solution of 1 g. of *epi*-cholesterol in 30 cc. of alcohol containing 1 g. of hydrochloric acid was refluxed for sixteen hours. The insoluble oil was sublimed under high vacuum, then crystallized from alcohol, m. p. 76–77°, uncorr. Mixed with cholesterylene, m. p. 74–76°, prepared by the action of quinoline on cholesteryl chloride it gave no depression in melting point;  $[\alpha]^{20}_D -78.3^\circ$  compared to  $[\alpha]^{20}_D -80.0^\circ$  for authentic cholesterylene, concentration 1% in benzene.

When an attempt was made to prepare *epi*-allocholesterol by the addition of hydrochloric acid in the cold to an alcoholic solution of *epi*-cholesterol the same dehydration occurred, giving cholesterylene.

### Summary

A mixture of *cis*- and *trans*-3-carboxyandrostanone and its ethyl ester was prepared and found to produce oestrogenic activity in rats, but lacked male activity in the cock's comb test.

*epi*-Cholesterol and cholesterol can be separated into their components by crystallization of their acetates followed by crystallization of their benzoates. *epi*-Cholesterol on treatment with alcoholic hydrogen chloride forms cholesterylene. *epi*-Cholesterol acetate on treatment with bromine gives a tetrabromocholestane which is a different isomer from the product obtained by the action of bromine on cholesterylene.

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## The Mechanism of Carbohydrate Oxidation. XXII.<sup>1</sup> The Preparation and Reactions of Glyceraldehyde Diethyl Mercaptal

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During the course of our work on the synthesis of  $\beta$ -*D*-glucosidoglyceraldehyde derivatives<sup>2</sup> it seemed desirable to have available a monomeric glyceraldehyde derivative containing an unblocked hydroxyl group only on the third carbon atom. The following scheme was used in attempting to prepare such a derivative:

Glyceraldehyde diethyl mercaptal was prepared as a distillable oil by the usual procedure employed in preparing sugar mercaptals. It readily reacted with triphenylmethyl (trityl) chloride to form a crystalline trityl ether. From the

work of Helferich and his students<sup>3</sup> it appears probable that the compound prepared was 3-trityl glyceraldehyde diethyl mercaptal. A few exceptions to Helferich's rule concerning the preferential reaction of trityl chloride with primary alcohol groups have been found<sup>4</sup> but they do not invalidate the rule because of the vigorous reaction conditions employed in discovering them.

The 3-trityl glyceraldehyde diethyl mercaptal could be easily acetylated or benzoylated to give

(1) No. XXI of this series, *THIS JOURNAL*, **58**, 1890 (1936).

(2) H. W. Arnold and W. L. Evans, *ibid.*, **58**, 1890 (1936).

(3) B. Helferich, P. S. Speidel and W. Toeldte, *Ber.*, **56**, 766 (1923); B. Helferich, L. Moog and A. Jünger, *ibid.*, **58**, 872 (1925); B. Helferich, W. Klein and W. Schäfer, *Ann.*, **447**, 19 (1926).

(4) R. C. Hockett and C. S. Hudson, *THIS JOURNAL*, **53**, 4456 (1931); *ibid.*, **56**, 945 (1934).

crystalline products. All attempts to detritylate these compounds failed to give derivatives containing the free hydroxyl group on the third carbon atom. Various detritylation procedures were used. In each case the trityl ether was quantitatively cleaved, but the reaction product was a dark, gummy mass from which no definite compound could be isolated. Detritylation by catalytic hydrogenation<sup>5</sup> was not attempted since work by Dr. M. L. Wolf from in this Laboratory had shown that this procedure fails when applied to diethyl mercaptal derivatives, presumably because the catalyst becomes poisoned.

To show the analogy between the reactions of glyceraldehyde diethyl mercaptal and *d*-glucose diethyl mercaptal,<sup>6</sup> the glyceraldehyde diethyl mercaptal was acetylated. The product was subjected without purification to the hydrolytic action of mercuric chloride and cadmium carbonate in moist acetone to give a distillable oil whose properties corresponded to those reported by Fischer and Baer<sup>7</sup> for a monomeric glyceraldehyde diacetate which they prepared by a different procedure. Deacetylation of the oil gave a sirup which reacted with 2,4-dinitrophenylhydrazine in acid solution to yield the known 2,4-dinitrophenylhydrazone of glyceraldehyde. The oil likewise reacted with an acid solution of *p*-nitrophenylhydrazine under more drastic conditions to give a crystalline product which was apparently glyceraldehyde *p*-nitrophenylosazone acetate.

### Experimental Part

**Glyceraldehyde Diethyl Mercaptal.**—Fifteen grams of glyceraldehyde was placed in a glass-stoppered bottle; 13 cc. of ice-cold concentrated hydrochloric acid and 30 cc. of ice-cold diethyl mercaptan were added in rapid succession, and the stopper tightly closed. The mixture was shaken vigorously, the stopper being lifted occasionally to release pressure. A light yellow solution resulted after twenty-five minutes. The mixture was again cooled in an ice-salt bath and 100 cc. of ice water added. A heavy oil settled to the bottom of the bottle. This showed no tendency to crystallize after standing in ice for two hours. It was then separated from the remainder of the liquid, the aqueous layer being extracted twice with small volumes of chloroform. The oil and the combined extracts were dried over anhydrous sodium sulfate. Removal of the chloroform under reduced pressure left 22.5 g. of the oil. This was distilled *in vacuo*. After a small forerun, the bulk of the liquid distilled smoothly at 155–160° (bath, 185°) under a pressure of 3 mm. The fraction distilling

at this temperature weighed 15.0 g. The residue in the flask was a dark brown oil. Redistillation of the main fraction under 3 mm. pressure gave 13.2 g. of a light yellow oil boiling at 156–158° (bath, 180–185°). This corresponded to a yield of 40%. The oil is immiscible with water, but miscible with all common organic solvents.

*Anal.* Calcd. for  $C_7H_{16}O_2S_2$ : S, 32.66; mol. wt., 196. Found: S, 32.38; mol. wt. (ebullioscopic in benzene), 188.

The dark brown oil which remained from distillation deposited a small quantity of crystals (0.2 g.) after standing in the ice chest for several days. Recrystallization from ethyl alcohol gave small needles melting at 126–127.5° (corr.). The molecular weight as determined by the Rast method was 295. The analysis indicated a sulfur content of 10.6%. It seems probable that this compound is formed by the condensation of several molecules of the diethyl mercaptal.

**3-Trityl Glyceraldehyde Diethyl Mercaptal.**—A mixture of 5 g. of glyceraldehyde diethyl mercaptal, 8 g. of trityl chloride, and 50 cc. of anhydrous pyridine was allowed to stand in a stoppered flask at room temperature for forty-eight hours. At the end of this time it was filtered to remove a small quantity of trityl carbinol that had precipitated. The filtrate was then slowly dropped into one liter of rapidly stirred ice water. The product first separated as a thick sirup which crystallized entirely within an hour. The solid was filtered off and dried on porous porcelain. The weight of the crude product was 9.0 g. and the melting point was 96.5–98°. After three crystallizations from 80% alcohol, the melting point was constant at 100–101° (corr.). The weight was 5.2 g. corresponding to a yield of 55%. The compound is insoluble in water and petroleum ether, soluble in ethyl and methyl alcohol at the boiling point, and soluble in the common organic solvents at ordinary temperatures. If it is allowed to crystallize slowly from alcoholic solution, it forms large prismatic needles.

*Anal.* Calcd. for  $C_{26}H_{30}O_2S_2$ : S, 14.69. Found: S, 14.54.

**3-Trityl 2-Acetyl Glyceraldehyde Diethyl Mercaptal.**—A mixture of 1.72 g. of the trityl ether, 10 cc. of anhydrous pyridine and 10 cc. of purified acetic anhydride was allowed to stand in a stoppered flask at room temperature for twenty-four hours. The solution was then slowly dropped into 500 cc. of rapidly stirred ice water. After an hour, the product had become almost entirely crystalline. It was filtered off, washed with water, and dried on porcelain. After three recrystallizations from 95% ethyl alcohol, the melting point was constant at 93–94° (corr.). The weight of pure product was 1.50 g., corresponding to a yield of 80%. When the hot alcoholic solution was rapidly cooled, the compound crystallized in tiny needles.

*Anal.* Calcd. for  $C_{26}H_{30}O_3S_2(COCH_3)$ : acetyl, 2.08 cc. of 0.1 N NaOH per 100 mg.; S, 13.34. Found: acetyl, 2.03 cc., 2.05 cc.; S, 13.40. *Mol. wt.* Calcd. for  $C_{28}H_{32}O_3S_2$ : 480. Found: (cryoscopic in benzene), 458.

**3-Trityl 2-Benzoyl Glyceraldehyde Diethyl Mercaptal.**—1.42 g. of the trityl ether was dissolved in 10 cc. of anhydrous pyridine. The solution was cooled in ice and 4 cc. of ice-cold benzoyl chloride added. The mixture was allowed to stand in a stoppered flask at room temperature

(5) F. Micheel, *Ber.*, **65**, 262 (1932).

(6) M. L. Wolf from, *THIS JOURNAL*, **51**, 2188 (1929); **52**, 2464 (1930).

(7) H. O. L. Fischer and Erich Baer, *Ber.*, **65**, 345 (1932).

for twenty-four hours. It was then slowly dropped into 400 cc. of rapidly stirred ice water. After the mixture had stirred for one hour it was extracted with three successive 50-cc. volumes of chloroform. The chloroform solution was washed successively with water, dilute sulfuric acid, sodium bicarbonate solution and water. After drying over calcium chloride the solvent was removed by a warm air stream. The residue was recrystallized five times from absolute alcohol. The melting point had then become constant at 90–91° (corr.). The weight of the crystalline product was 1.70 g., corresponding to a yield of 97%. The solubility relationships are approximately the same as those of the corresponding acetyl compound. If allowed to crystallize slowly from alcohol, it forms long (1–2 cm.) prismatic needles.

*Anal.* Calcd. for  $C_{13}H_{14}O_6S_2$ : S, 11.82. Found: S, 12.01.

**Monomeric Glyceraldehyde Diacetate.**—8.94 g. of glyceraldehyde diethyl mercaptal and a mixture of 25 cc. of purified acetic anhydride and 25 cc. of anhydrous pyridine were allowed to stand in a stoppered flask for twenty-four hours at room temperature. The mixture was then poured into 500 cc. of ice water. After standing for several hours, this was extracted with five 50-cc. portions of chloroform. The chloroform solution was washed successively with water, dilute sulfuric acid, sodium bicarbonate solution and water. It was dried over calcium chloride. Removal of the solvent left a viscous yellow oil which could not be distilled under the conditions used (2 mm. pressure and bath temp. of 230°). No apparent decomposition took place at this temperature. The weight of the oil was 11.6 g., approaching the weight required if the theoretical quantity of mercaptal diacetate (12.7 g.) were formed. No analytical data were obtained for this compound. It was used directly in the attempt to prepare aldehydoglyceraldehyde diacetate.

After the manner of Wolfrom<sup>6</sup> the above oil and a mixture of 40.4 g. of mercuric chloride in 70 cc. of acetone, 45 g. of cadmium carbonate and 40 cc. of water were vigorously stirred, under mercury seal, for seventy-two hours at room temperature, small amounts of fresh cadmium carbonate being added at intervals. The solution was filtered over cadmium carbonate into a flask containing the same reagent. The solution was evaporated to complete dryness without removing the cadmium carbonate. The residue was repeatedly extracted with chloroform. Concentration of the chloroform solution *in vacuo* left a viscous yellow oil. This was vacuum distilled at a pressure of 3 mm. With a bath temperature of 180–190° a fraction weighing 4 g. distilled at 154–156°. The properties of this oil corresponded to those recorded by Fischer and Baer<sup>7</sup> for monomeric glyceraldehyde diacetate. It rapidly reduced Fehling's solution in the cold. A molecular weight determination (cryoscopic in benzene) gave a value of 168 (calcd., 174).

The following experiments were carried out to establish the identity of the compound. (1) One and one-half grams of the oil was allowed to stand overnight at 0° with 15 cc. of a saturated solution of ammonia in methyl alcohol.

The alcohol was removed *in vacuo* and the remaining sirup dissolved in 50 cc. of water. The solution was cooled in ice and a cooled solution of 1.5 g. of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid was added. Precipitation of a yellow crystalline solid began almost immediately, being complete within an hour. The precipitate was washed with water and dried. Recrystallization from 50% alcohol gave 1.0 g. of yellow needles melting at 155° (corr.). This corresponds to the melting point of glyceraldehyde-2,4-dinitrophenylhydrazone as recorded by Fischer and Baer.<sup>8</sup> The mixed melting point with an authentic sample prepared from glyceraldehyde according to the procedure of Fischer and Baer was likewise 155°.

(2) One and seven-tenths grams of *p*-nitrophenylhydrazine and 1.2 g. of the supposed aldehyde-glyceraldehyde diacetate in a mixture of 20 cc. of alcohol and 30 cc. of 3 *N* hydrochloric acid were heated on the water-bath for an hour and a half. Within a few minutes after beginning the heating a dark red precipitate began to form. Precipitation was complete within an hour. The precipitate was washed repeatedly with water and dried on porcelain. It weighed 1.2 g. Recrystallization from ethyl alcohol containing about 10% by volume of pyridine gave blood red needles which melted at 282–286° (block) with previous darkening at 235–240°. This compound is thought to be monoacetyl glyceraldehyde *p*-nitrophenylosazone.

*Anal.* Calcd. for  $C_{17}H_{16}O_6N_6$ : N, 21.0. Found: N, 20.8. Calcd. for  $C_{15}H_{14}O_6N_6(COCH_3)$ : acetyl, 2.50 cc. of 0.1 *N* NaOH per 100 mg. Found: acetyl, 2.60 cc.

### Summary

1. The diethyl mercaptal of glyceraldehyde has been prepared. It forms a crystalline trityl ether on reaction with trityl chloride. The trityl ether yields crystalline acetyl and benzoyl derivatives. Attempts to remove the trityl group from these compounds have been unsuccessful.

2. Acetylation of the glyceraldehyde diethyl mercaptal yields an oil which is apparently the diacetate. Treatment of this oil with mercuric chloride and cadmium carbonate in the presence of aqueous acetone yields a compound whose properties correspond to those of a monomeric glyceraldehyde diacetate. The compound reacts with *p*-nitrophenylhydrazine in acid solution to yield what is apparently monoacetyl glyceraldehyde *p*-nitrophenylosazone. This view is supported by our analytical data. Deacetylation of the diacetate yields a sirup which reacts with 2,4-dinitrophenylhydrazine to form glyceraldehyde 2,4-dinitrophenylhydrazone.

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(8) H. O. L. Fischer and Erich Baer, *Helv. Chim. Acta*, **17**, 622 (1934).