

AN IMPROVED SYNTHESIS OF DL-GLYCERALDEHYDE

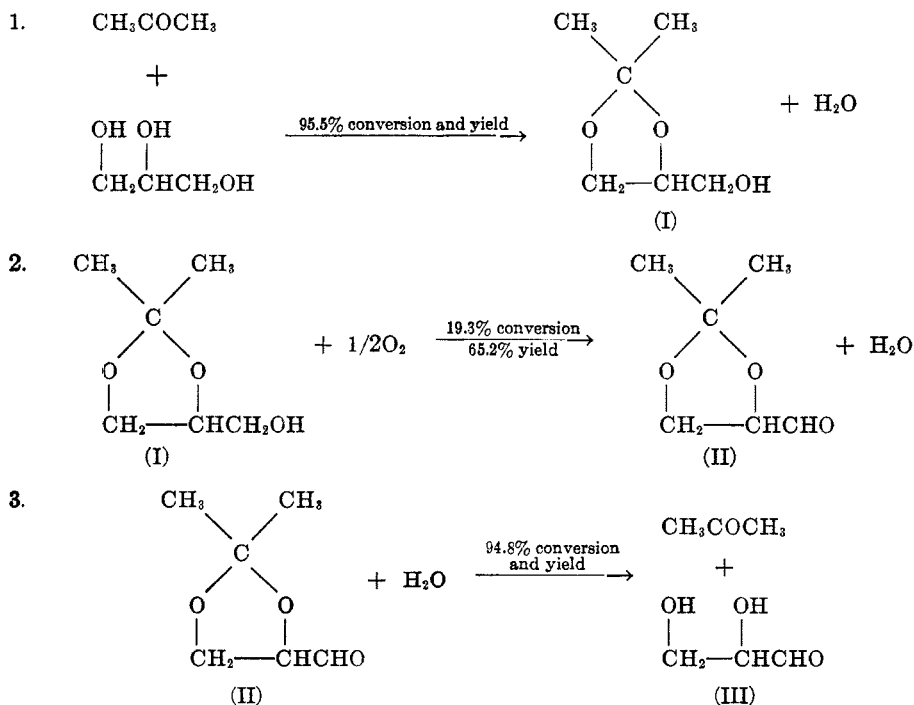
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Announcement (1) that DL-glyceraldehyde (III) might be an effective inhibitor of dental caries prompted attempts in these laboratories to find an attractive method for its synthesis. It is the purpose of this paper to report the synthesis which was developed during this work.

The best literature method for the synthesis of DL-glyceraldehyde appears to be that of Organic Syntheses (2), in which acrolein is prepared by dehydrating glycerol and then is converted to β -chloropropionaldehyde diethyl acetal, which is dehydrochlorinated to acrolein diethyl acetal. The latter is oxidized with potassium permanganate to give DL-glyceraldehyde diethyl acetal, which is hydrolyzed with dilute acid to yield DL-glyceraldehyde. The method is cumbersome, and the over-all conversion from glycerol to DL-glyceraldehyde is only 6.6%.

Our synthesis is a three-step procedure in which the over-all conversion (based on reactants charged) from glycerol to DL-glyceraldehyde is 17.5% and the over-all yield (based on reactants consumed) is 59%. The new method involves protecting two of the hydroxyl groups of glycerol by ketal formation, catalytically air-oxidizing the resulting monohydric alcohol to the corresponding aldehyde, and hydrolyzing the product to form glyceraldehyde.



The method is based on the demonstration by Fischer (3) and by Hibbert and Morazain (4) that the reaction product of acetone and glycerol is the 1,2-adduct, 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane (I). This material was synthesized in 95.5% conversion and yield by a modification of the method of Newman and Renoll (5). The stirring and the filtration of neutralized catalyst were omitted and 0.005% sulfuric acid catalyst was employed instead of 0.5% *p*-toluenesulfonic acid. Methylene chloride was used as the water carrier instead of petroleum ether in order to minimize the fire hazard.

Air oxidation of (I) (Step 2) has not been reported previously. The product, 2,2-dimethyl-4-formyl-1,3-dioxolane (II), has been synthesized by Baer and Fischer (6), and its acid-catalyzed hydrolysis was carried out by Baer, Grosheintz, and Fischer (7) without isolation of either the reactant or the product. It has now been found that the hydrolysis (Step 3) can be carried out without a catalyst; this procedure greatly simplifies the isolation of pure glyceraldehyde.

EXPERIMENTAL PART

Source of materials. Two grades of glycerol were tested as received from Colgate-Palmolive-Peet Co. Water-white U.S.P. glycerol gave poorer results than yellow, high-gravity glycerol (minimum specific gravity, 1.2620 at 15.6°/15.6°). A C.P. grade of acetone from Carbide and Carbon Chemicals Corp. was used as received. C.P. concentrated sulfuric acid and methylene chloride were products of E. I. duPont de Nemours and Co., Inc. Anhydrous sodium formate was purchased from Mallinckrodt Chemical Works, and the absolute alcohol used was the U.S.P. grade from U. S. Industrial Chemicals, Inc. Electrolytic hydrogen of 99.9% purity was purchased from Paschall Oxygen Co., and compressed air was obtained in cylinders from Air Reduction Sales Co. The latter company provided deoxidized, oil-pumped, and dried nitrogen. Distilled water was used at all times.

2,2-Dimethyl-4-hydroxymethyl-1,3-dioxolane (I). A mixture of 900 g. of yellow high-gravity glycerol, 2 liters of acetone, 1 liter of methylene chloride, and 0.1 cc. of concentrated sulfuric acid was refluxed continuously for 55 hours under a 3' × 1" Fenske packed column. The column's head was adjusted to withdraw the water of reaction and return the methylene chloride layer as reflux. At the end of the processing time, 0.5 g. of sodium formate was added and the mixture was distilled in a grease-free all-glass Vigreux column. The product (I) was distilled rapidly at 189–190.5° at atmospheric pressure. The conversion to distilled product was 94.4%; a sixty-eight hour run gave 95.5% conversion. The product was redistilled at atmospheric pressure prior to use in the oxidation step.

The boiling point of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane is 188–189°/760 mm., or 80.5–80.8°/11 mm. Its refractive index at 25° is 1.4326, and the specific gravity of the colorless oil is 1.055 at 25°.

Although the reaction mixture for Step 1 was originally heterogeneous, stirring was found unnecessary. Yellow, high-gravity glycerol repeatedly gave conversions of greater than 90%, while the best conversion obtained with water-white U.S.P. glycerol was 88%. Attempts were made to hasten the reaction by using larger quantities of sulfuric acid catalyst. However, the reaction was no faster and the yield became lower as the quantity of catalyst was increased. In the absence of a catalyst the reaction was too slow to be practical.

2,2-Dimethyl-4-formyl-1,3-dioxolane (II). The Pyrex glass converter (Fig. 1) was equipped with an unpacked spiral tube to preheat the gases and a section packed with 4–6 mesh quartz for vaporizing and preheating (I). The quartz had been digested with nitric acid at 100°, washed with water, and ignited at 700°. Several chromel-alumel thermocouples were located in the catalyst bed. The reactor, which was enclosed in an electric furnace with automatic temperature control, was placed behind a steel barricade. No explosions occurred. The liquid feed was either dropped into the converter from an ungreased dropping-funnel,

or pumped with a brass and bronze bellows pump (Precision Scientific Co., #9000) through copper tubing. Nitrogen and air were metered and introduced through glass tubing connected with washed gum rubber tubing. The gases were purified by passage over dehydrated Davison silica gel at room temperature.

The catalyst was prepared by impregnating tabular alumina with aqueous silver nitrate. A solution of 50 g. of silver nitrate in 36 cc. of distilled water was added to 100 cc. of 8-14 mesh Alorco T-61 tabular alumina with stirring. Excess solution was drained off by spreading the solid particles on filter paper and the catalyst was dried for four hours in a 110° oven.

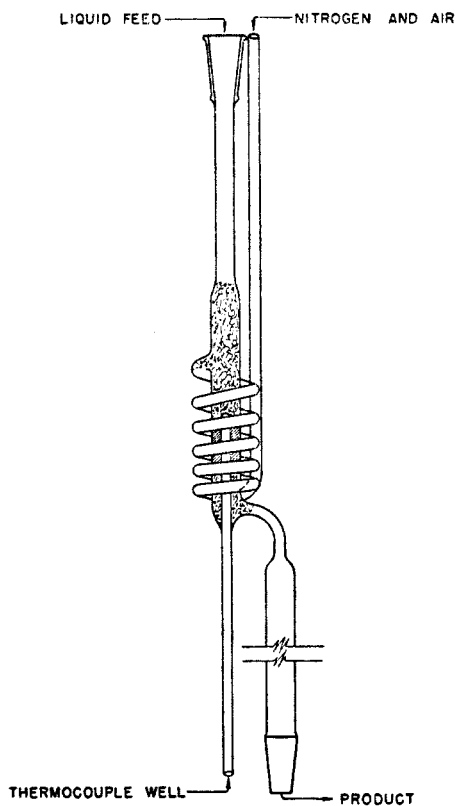


FIGURE 1. CONVERTER FOR OXIDATION REACTION

The catalyst (8 cc.) was reduced in place with a nitrogen-hydrogen mixture and finally with pure hydrogen at 350°. After hydrogen had been displaced from the apparatus with nitrogen, oxidation was started using air as the oxidizing agent. After the reaction started it was necessary to dilute the air with added nitrogen to keep the maximum catalyst temperature at about 410°. The reactor effluent was cooled and the condensate was collected. Uncondensed gas was passed through Dry Ice traps prior to metering and analysis with an Orsat apparatus.

In one experiment a total of 772 cc. (815 g.) of (I) was oxidized at a hot spot temperature of about 410°, using an average space velocity (cc. gas, calculated at STP/cc. catalyst/hr.) of 1475 hr.⁻¹ for (I), an average air space velocity of 3500 hr.⁻¹ and an average nitrogen space velocity of 3600 hr.⁻¹. The total condensate, which weighed 879.2 g., was kept cold overnight and was then distilled through a 3' × 1" Vigreux column, starting at 100 mm. pressure.

After the removal of water, 204.8 g. of crude 2,2-dimethyl-4-formyl-1,3-dioxolane (II) was distilled at 93–114° at 102–108 mm., followed by 556.5 g. of recovered (I) boiling at 76.5–80°/10 mm. The residue weighed 25.4 g. The crude product was redistilled, giving 154.8 g. of pure (II) and 18 g. of starting material. Thus the conversion to pure (II) was 19.3%, and the yield was 65.2%. The straw-yellow product boiled at 74°/50 mm., and a freshly distilled sample had a refractive index at 25° of 1.4189. The refractive index and the viscosity increased with the age of the sample, probably due to trimerization. A purified sample had a total carbonyl number (8) of 841 (theory 876). The catalyst showed a life of 13–44.5 hours. The longer life was demonstrated using recovered (I) that was recycled after two redistillations. Dow-Corning (silicone) stopcock grease seemed to destroy the activity of the catalyst. For this reason no grease was allowed to come in contact with (I), either in the still or in the oxidation apparatus. Instead, the alcohol itself was used as the lubricant for ground glass joints and stopcocks in the purification and oxidation apparatus.

The nitrogen-air mixture entering the converter ordinarily contained about 10% oxygen; the off-gas usually analyzed about 1% oxygen, 1–5% carbon dioxide, and 0.3–2% carbon monoxide.

DL-Glyceraldehyde (III). To 200 cc. of water at 10° was added 49.5 g. of freshly distilled 2,2-dimethyl-4-formyl-1,3-dioxolane (II). The temperature spontaneously rose to 20°. In this experiment an attempt was made to carry out the hydrolysis at room temperature, removing the acetone at 50 mm. pressure. However, the reaction was not complete at room temperature and was finished by refluxing for 3.5 hours at a bath temperature of 40–60°. The water was evaporated from the solution at room temperature and low pressure. Three days later most of the water had been removed, leaving a thick colorless syrup containing some crystals. An equal volume of absolute ethanol was added. Five days later the crystals were removed by vacuum filtration and washed with absolute alcohol. The conversion to the first crop of crystals was 53.6%. The filtrate was evaporated at room temperature and low pressure; additional absolute alcohol was added occasionally. Two weeks after the first filtration a second filtration was carried out, yielding an additional quantity of finely powdered, crystalline, white *DL*-glyceraldehyde, and after three more weeks a third crop was collected. The total conversion to the three crops was 92%. A similar experiment resulted in 94.8% conversion to crystalline glyceraldehyde.

In the hydrolysis step, water: 2,2-dimethyl-4-formyl-1,3-dioxolane ratios ranging from 10:1 to 30:1 all gave good results. Also, it was possible to carry out the reaction at 100° at atmospheric pressure, instead of at 50–60° and 50 mm. For example, a 75.3% conversion to crystalline product was obtained in an experiment in which the water:aldehyde ratio was 10:1 and in which the processing conditions were 93–100° at atmospheric pressure for 36 minutes. Another experiment at 100° for 30 minutes gave an 84% conversion. When the water and aldehyde were mixed and allowed to stand overnight prior to heating, only one hour at 50–60°/50 mm. was required instead of 3.5 hours.

When (II) was mixed with water, the mixture was yellow and heterogeneous for about fifteen seconds and then became colorless and homogeneous. During this time the temperature rose, sometimes to 65°.

The white dimeric crystals of *DL*-glyceraldehyde were small and grew very slowly, from either the syrup or its ethanol solution. The yield of crystals was diminished by overheating of the glyceraldehyde, especially in the absence of a diluent. For this reason the glyceraldehyde was not heated above room temperature after the hydrolysis of (II) was completed.

The final product was washed with absolute alcohol and dried at room temperature under reduced pressure. The melting point of *DL*-glyceraldehyde, when determined in a capillary tube, depended on the rate of heating. For example the melting point of a particular sample fell from 142–142.4° to 134.8–136° when the heating rate was decreased. Various samples of *DL*-glyceraldehyde melted at temperatures between 167.3° and 185.4° on a Dennis melting point bar (Parr Instrument Co., Model MPB); this technique is known to give higher melting points than the capillary tube method with heat-sensitive substances.

The identity of the glyceraldehyde was confirmed by a mixed melting point with a

sample of DL-glyceraldehyde supplied by Prof. L. S. Fosdick of Northwestern University. In the same bath at the same time, the authentic sample melted at 132.5–133.2°, the experimental sample at 132.5–133.1°, and the mixture at 132–133° (uncorr.). The total carbonyl number (8) of a synthetic product was 639 ± 2 (theory, 623) for a duplicate determination.

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SUMMARY

In a new three-step synthesis of DL-glyceraldehyde from glycerol, two of the hydroxyl groups are protected by ketal formation with acetone. The product is then catalytically oxidized with air to the corresponding aldehyde, which is hydrolyzed to glyceraldehyde without the use of a catalyst. The over-all conversion and yield are 17.5% and 59%, respectively.

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