ment benzoin was recovered but no benzoic acid was obtained. Benzoin (0.200 g.) in xylene treated with methyl Grignard reagent in isoamyl ether, and subsequently treated with oxygen as outlined above gave 0.001 g. of benzoic acid.

Thanks are due Miss Joan Romeyn for the microanalyses.

Summary

1. A solution of dimethylmagnesium in dioxane has been prepared under conditions which suggest that its dioxanate has a limited solubility in ether.

2. Upon reaction with benzoin, dimethylmagnesium shows such a preferential reaction with hydroxyl groups that an ene-diol magnesium salt seems to be formed.

3. The reaction of dimethylmagnesium with enolizable ketones indicates that this substance is less reactive toward carbonyl than is methylmagnesium iodide.

TORONTO, CANADA RECEIVED FEBRUARY 27, 1939

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

A New Approach to the Synthesis of Aldehydo Sugars

BY CHARLES D. HURD AND EDWARD M. FILACHIONE

Methods for the synthesis of aldehydo sugars, developed in recent years, involve these final steps in the various processes: (a) reaction of a thioacetal function with mercuric chloride, or with mercuric chloride and cadmium carbonate, (b) removal of oxime or semicarbazone configurations by means of nitrous acid, (c) scission of a glycol function with lead tetraacetate, (d) catalytic hydrogenation of an aldonyl chloride

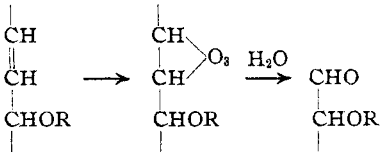
$$\mathrm{ROCH_2(CHOR)_4CH(SEt)_2 \longrightarrow ROCH_2(CHOR)_4CHO}$$

$$\mathrm{AcOCH_2(CHOAc)_4CH{=}NOH \longrightarrow AcOCH_2(CHOAc)_4CHO}$$

$$\mathrm{BzOCH_2CHOBzCHOHCHOHCHOBzCH_2OBz \longrightarrow 2BzOCBzCHOBzCHO}$$

$$\mathrm{AcOCH_2(CHOAc)_4COCl \longrightarrow AcOCH_2(CHOAc)_4CHO}$$

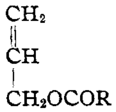
In the present work, another approach was studied involving ozonolysis of a carbon-to-carbon double bond



$$\begin{array}{c} | \\ \mathrm{CH} \\ \| \\ \mathrm{CH} \\ | \\ \mathrm{CHOR} \\ | \end{array} \longrightarrow \begin{array}{c} | \\ \mathrm{CH} \\ | \\ \mathrm{CH} \\ | \\ \mathrm{CHOR} \\ | \end{array}\!\!>\mathrm{O_3} \xrightarrow{\mathrm{H_2O}} \begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{CHOR} \\ | \end{array}$$

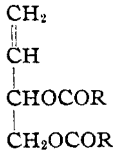
The unsaturated compounds selected for study were of two types, namely, those with a terminal vinyl group and those possessing cyclic unsaturation as in glucal.

Originally, it was planned to test three types possessing a terminal vinyl group (I–III), for which the starting points, respectively, were glycerol, *meso*-erythritol and mannitol. Glycerol was converted into allyl alcohol (for I) by the formic acid reaction, and erythritol into erythrol (for II) by the same general procedure.



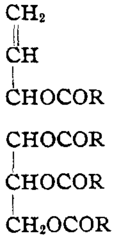
$$\begin{array}{c} \mathrm{CH_2} \\ \| \\ \mathrm{CH} \\ | \\ \mathrm{CH_2OCOR} \end{array}$$

I



$$\begin{array}{c} \mathrm{CH_2} \\ \| \\ \mathrm{CH} \\ | \\ \mathrm{CHOCOR} \\ | \\ \mathrm{CH_2OCOR} \end{array}$$

II

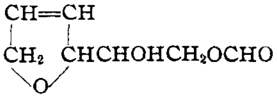


$$\begin{array}{c} \mathrm{CH_2} \\ \| \\ \mathrm{CH} \\ | \\ \mathrm{CHOCOR} \\ | \\ \mathrm{CHOCOR} \\ | \\ \mathrm{CHOCOR} \\ | \\ \mathrm{CH_2OCOR} \end{array}$$

III

This type of reaction was not successful, however, when applied to the conversion of mannitol into the vinyltetrol related to III. This confirms the results of earlier workers,[1] who obtained a furan type of ring closure rather than production of terminal ethylenic unsaturation. The products identified were 2-vinyl-2,5-dihydrofuran, mannitan tetraformate and isomannide diformate.

In the present work additional data were obtained on this subject. A sirup was produced at 140° in the reaction between mannitol and formic acid from which mannitol triformate was obtainable in 20% yields. Vacuum distillation of the sirup yielded a water-insoluble distillate, half of which appeared to be a substance with the following structure or one closely related to it.



$$\begin{array}{l} \mathrm{CH{=}CH} \\ |\quad\;\;\; | \\ \mathrm{CH_2\ CHCHOHCH_2OCHO} \\ \;\;\diagdown_{\mathrm{O}}\diagup \end{array}$$

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[1] Henninger, *Ber.*, **7**, 264 (1876); Fauconnier, *Compt. rend.*, **100**, 914 (1885); von Romburgh and Van der Berg, *Proc. Acad. Sci. Amsterdam*, **25**, 235 (1922); *C. A.*, **17**, 1214 (1923).

The ozonolytic cleavage of allyl benzoate into benzoylglycolaldehyde was found to proceed smoothly.

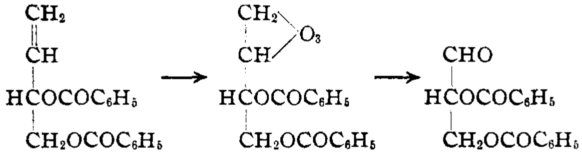
$C_6H_5COOCH_2—CH=CH_2 \longrightarrow C_6H_5COOCH_2—CH=O$

Considerable oxidation to benzoylglycolic acid was observed when water alone was taken for hydrolysis of the ozonide, but this oxidation was preventable in large measure if 20% pyruvic acid solution was used as the hydrolyzing medium. It consumed the hydrogen peroxide normally formed during hydrolysis of the ozonide

$CH_3COCOOH + H_2O_2 \longrightarrow CH_3COOH + CO_2 + H_2O$

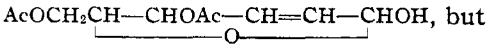
Allyl acetate, studied similarly, was found to yield glycolaldehyde chiefly, not acetylglycolaldehyde. In this reaction hydrolysis occurred at both the ozonide and the ester functions.

When the ozonide of erythrol dibenzoate was hydrolyzed with pyruvic acid solution, there was formed a 70% yield of dibenzoylglyceraldehyde and a 20% yield of dibenzoylglyceric acid.

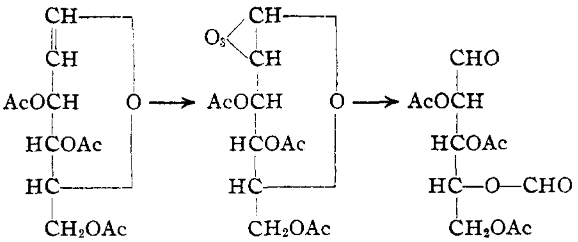


The ozonolysis of glucals is related to the above, but there is no experimental record of the formation of aldehydo sugars in such reactions. Fischer, Bergmann and Schotte[2a] ozonized triactylglucal in acetic acid. They obtained an arabinose acetate from which the acetyl groups were hydrolyzed and the *d*-arabinose characterized as the *p*-bromophenylosazone. The ozonide of diacetylxylal,[2d] prepared in acetic acid, was converted to 2,3-diacetyl-*d*-threose in 78% yield by decomposition with zinc dust. No search for formic acid was made in either of these studies.

No identification of the tetrose residue was made following ozonolysis of diacetyl-ψ-glucal,[2c] $AcOCH_2CH—CHOAc—CH=CH—CHOH$, but glyoxal was obtained in small yields as the osazone.



Schematically, hydrolysis of the ozonide of triacetylglucal should yield an aldehydo pentose if none of the ester groups were removed by concurrent hydrolysis. Three of the four hydroxyls would be blocked by acetate radicals and the other hydroxyl by a formate radical.



In an article by Bergmann, Schotte and Leschinsky[2b] it was stated but without accompanying experimental evidence that trimethylarabinose monoformate was obtained by ozonolysis of trimethylglucal. This production of an aldehydo sugar is at variance with the non-formation of similar substances from triacetylglucal, diacetyl-ψ-glucal, or diacetylxylal.

Accordingly, triacetylglucal was reinvestigated, the medium for the ozonization being carbon tetrachloride so that both formic and acetic acid residues, if detached during hydrolysis of the ozonide, might be recognized. It was demonstrated that no aldehydo sugar was obtainable, for not only was the formate group removed but an acetate radical as well during the process of heating with water to hydrolyze the ozonide. The evidence consisted in direct determination of the volatile acids, and in an acetyl analysis of the chloroform-soluble sirup. The latter was a mixture of di- and triacetylarabinose.

Experimental Part

Reagents.—Allyl benzoate was synthesized from allyl alcohol and benzoyl chloride following Perkin's directions.[3] It boiled at 122–123° (24 mm.).

Triacetylglucal was synthesized by adding tetraacetylglucosyl bromide into a vigorously-stirred mixture of zinc dust in 50% aqueous acetic acid solution.[4] Erythrol (3-butene-1,2-diol) was made by Urion's method[5] from *meso*-erythritol and 80% formic acid. Distillation at 24 mm. (93–98°) following the initial reaction period at 130–150° gave a 57% yield of erythrol monoformate. Hydrolysis of the latter with barium hydroxide and subsequent distillation gave rise to erythrol, b. p. 95–97° (16 mm.), in 67% yield.

Erythrol Dibenzoate.—A solution of 8.3 g. (0.094 mole) of erythrol in 25 cc. of anhydrous pyridine was added slowly to a solution of 37 g. (0.26 mole) of benzoyl chloride in 15 cc. of pyridine. The flask was kept at 10–15° during the addition, then it was heated on the steam-bath for one hour. Water was added. After four hours the ester layer was extracted with ether, the ether solution washed with dilute hydrochloric acid, sodium bicarbonate solution, dilute sodium hydroxide, followed immediately by a dilute hydrochloric acid wash. The ether layer was dried

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(2) (a) Fischer, Bergmann and Schotte, *Ber.*, **53**, 520 (1920); (b) Bergmann, Schotte and Leschinsky, *ibid.*, **56**, 1054 (1923); (c) Bergmann and Freudenberg, *ibid.*, **64**, 158 (1931); (d) W. Freudenberg, *ibid.*, **65**, 168 (1932).

(3) Perkin, *J. Chem. Soc.*, **69**, 1226 (1896).

(4) Fischer, *Ber.*, **47**, 196 (1914).

(5) Urion, *Ann. chim.*, [11] **1**, 33 (1934).

and the solvent evaporated. The oily residue was distilled, b. p. 235–237° (19 mm.). It was redistilled at 6 mm., b. p. 199–200°; $n^{20}D$ 1.5512. The yield was 23.4 g., or 76%.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.94; H, 5.45; C_6H_5CO, 71.0. Found: C, 72.65; H, 5.29; C_6H_5CO, 70.3.

Reactions with Ozone

An ozonizer of the Henne[6] type was employed which delivered 3 to 10% by weight of ozone in the oxygen stream. Between 5–10 g. of the unsaturated acetate or benzoate was dissolved in 75–100 cc. of carbon tetrachloride at 0° and ozone passed into the solution until a 10% excess had been used. The ozonides of allyl benzoate and erythrol dibenzoate remained in solution in the carbon tetrachloride, whereas triacetylglucal ozonide separated.

To hydrolyze the ozonides it was found safer to surround the flask with a stout wire gauze and to add water directly to the mixture of ozonide and carbon tetrachloride. Then the latter was distilled off, after which the hydrolysis was completed at 100°. In some experiments the carbon tetrachloride was removed before addition of water but the method was abandoned following a violent explosion when it was applied to the ozonide of allyl benzoate.

Hydrolysis of Ozonides by Pyruvic Acid Solution.—Fifty cc. of a 20% aqueous solution of pyruvic acid was added to the ozonide from 5 g. of unsaturated ester. The mixture was heated to 80° to remove the carbon tetrachloride, then to 100° whereupon a lively evolution of gas took place because of the reaction of the pyruvic acid with hydrogen peroxide. The evolution of gas lasted only half an hour and served as a convenient index of completion of the reaction.

Triacetylglucal.—The ozonide from 10 g. (0.0368 mole) of triacetylglucal was hydrolyzed with water. The aqueous hydrolysate was distilled under diminished pressure, yielding a residual sirup and an acidic distillate. Three-fourths of the latter was shown to contain 0.0427 mole of total acid of which 0.0219 mole was formic acid by permanganate titration. Acetic acid, by difference, was 0.0208 mole. In terms of the entire distillate, this indicates 0.029 mole of formic acid and 0.028 mole of acetic.

Toluene was added to and distilled from the "residual sirup" to dry the sirup completely. The residue (7.1 g.) was taken up in 100 cc. of chloroform, and 5.2 g. of it was extracted by three washings with water. The 1.9 g. of material which remained in the chloroform was a mixture of di- and triacetylarabinose. It contained 42.7% acetyl (calcd. for di- and triacetyl, respectively, 36.8 and 46.7%). That only acetyl groups were present was confirmed by hydrolysis and Duclaux analysis.

Allyl Acetate.—The ozonide from 10 g. (0.1 mole) of this ester was hydrolyzed with 100 cc. of water in half an hour. Five cc. of the aqueous solution was treated with phenylhydrazine in acetic acid. An oil separated which solidified and melted at 165–167°. It was glyoxal osazone.

Distillation of the remainder of the aqueous solution under diminished pressure produced a distillate which contained 0.106 equivalent of acid (acetic). The residue of glycolaldehyde and glycolic acid solidified on standing overnight.

Allyl Benzoate.—The ozonide from 10 g. (0.062 mole) of the ester was hydrolyzed with 100 cc. of water. The oil which separated on cooling contained benzoylglycolaldehyde (2.6 g., 25%) and benzoylglycolic acid (5.2 g., 47%). The oil was dissolved in ether and the acid removed therefrom by bicarbonate extraction. The benzoylglycolic acid melted[7] at 111–112° and gave a neutral equivalent of 180.9 (theoretical value, 180). For identification of the benzoylglycolaldehyde, it was converted into two new derivatives.

The 2,4-Dinitrophenylhydrazone, $C_6H_5COOCH_2CH{=}N{-}NHC_6H_3(NO_2)_2$.—The aldehyde was added to a hot, saturated solution of 2,4-dinitrophenylhydrazine in 50% aqueous acetic acid. A yellow solid separated immediately which, after several recrystallizations from ethyl acetate, melted at 186–187°.

Anal. Calcd. for $C_{15}H_{12}O_6N_4$: N, 16.27. Found: N, 16.22.

The *p*-Nitrophenylhydrazone.—This was prepared by adding the aldehyde to a saturated alcohol solution of the hydrazine, heating on the steam-bath for one minute, adding two drops of concentrated hydrochloric acid, then adding water to turbidity. The solid which separated was recrystallized from alcohol–water solution. It melted at 155–156°.

Anal. Calcd. for $C_{15}H_{13}O_4N_3$: N, 14.04. Found: N, 13.92.

Allyl Benzoate (pyruvic acid method).—The ozonide from 5 g. of allyl benzoate was hydrolyzed with 50 cc. of a 20% solution of pyruvic acid in water. The oil which separated was worked up as in the previous method. The yield of benzoylglycolaldehyde was 2.9 g. or 56%. About 3.7 g. of crude benzoylglycolic acid was obtained.

The aldehyde was dried thoroughly by distilling benzene away from it; then it was crystallized from petroleum ether at 0°. The crystalline needles melted at 28–30°. Aoyama[8] reported 32–34° as the m. p.

Erythrol Dibenzoate (pyruvic acid method).—To the ozonide from 5.4 g. of the dibenzoate was added 50 cc. of a 20% aqueous solution of pyruvic acid and then heated till gas evolution ceased (forty-five minutes). The oil was extracted with ether and the small quantity of acid was removed by washing with sodium bicarbonate solution. A 70% yield (3.8 g.) of dibenzoyl-*dl*-glycerose was obtained on evaporation of the ether solution. After crystallization from petroleum ether, the m. p. was 55–56°.

Anal. (by M. A. Pollack) Calcd. for $C_{17}H_{14}O_5$: C, 68.43; H, 4.73. Found: C, 68.56; H, 4.88.

Dibenzoyl-*d*-glycerose[9] is known (m. p. 80°; semicarbazone, m. p. 133°), but the racemic dibenzoylglycerose is new. Some of it was heated for a few minutes with a saturated alcohol solution of 2,4-dinitrophenylhydrazine. Yellow crystals of dibenzoyl-*dl*-glycerose 2,4-dinitrophenylhydrazone separated promptly. They were recrystallized from a mixture of alcohol and ethyl acetate; m. p. 151–152°.

Anal. (Dumas method) Calcd. for $C_{23}H_{18}O_8N_4$: N, 11.7. Found: N, 11.9.

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[6] Henne, This Journal, **51**, 2676 (1929).

[7] Brigl and Grüner, *Ber.*, **65**, 641 (1932).

[8] Aoyama, *J. Pharm. Soc. Japan*, **539**, 27 (1927); *C. A.*, **22**, 4469 (1928).

[9] Brigl and Grüner, *Ber.*, **66**, 931 (1933).

Dibenzoyl-*dl*-glyceric Acid.—Acidification of the above sodium bicarbonate solution yielded 1.6 g. of oil which solidified after a few days. For purification it was titrated in alcohol–water with barium hydroxide solution. The barium salt was collected on a filter and purified by crystallization from hot water. The acid was regenerated by adding dilute sulfuric acid to a supersaturated solution of the salt in water. (The salt formed supersaturated solutions easily.) The acid was ether extracted and crystallized from a mixture of toluene and petroleum ether. The crystals melted at 88–89°.

Anal. (by M. A. Pollack) Calcd. for $C_{17}H_{14}O_6$: C, 64.95; H, 4.49. Found: C, 64.31; H, 4.54.

Mannitol Triformate

Formic acid was distilled off slowly from a mixture of 20 g. of mannitol and 50 cc. of 80% formic acid. An oil-bath at 140° was used. Finally, all of the formic acid was removed by heating *in vacuo*. The residual sirup was taken up in 200 cc. of acetone and cooled to 0°. Five grams of crystals separated, m. p. 94–103°. Two recrystallizations brought the m. p. to 108–111°; $[\alpha]^{24}_{\mathrm{D}}$ 10.4° in acetone.

Anal. Calcd. for $C_6H_{11}O_3(OCHO)_3$: C, 40.58; H, 5.30; sapon. equiv., 88.6. Found: C, 40.36; H, 5.42; sapon. equiv., 92.2.

Mannitol and Formic Acid.—The sirup from 52 g. of mannitol and 150 cc. of formic acid, which was prepared at 140° as outlined above, was pyrolyzed in a Claisen flask at a bath temperature of 205–210° and a pressure of 0.6 to 3 mm. Twenty-three grams of dark colored distillate was obtained. Redistillation gave these fractions, A to E: (g., °C., mm., n^{23}_{D}) A, 3.2, to 40°, 18 mm.; B, 7.4, 90–115°, 6; C, 2, 120–130°, 0.2, 1.4960; D, 1.0, 130–140°, 0.7, 1.4943; E, 1.6, 140–160°, 0.7–1.8, 1.4947.

Fraction A, b. p. 104–107° at atmospheric pressure, was half formic acid. The remainder was probably 2-vinyl-2,5-dihydrofuran. Fractions C–E were not studied, other than to demonstrate the partial insolubility in water and the absence of formate groups by the negative test with mercuric oxide.

Fraction B, on redistillation, yielded 2.7 g. of liquid, b. p. 135–142° at 17 mm., $[\alpha]^{24}_{\mathrm{D}}$ −32.9° in chloroform. It was insoluble in water, soluble in ether, chloroform and sodium hydroxide solution. It reacted strongly toward permanganate solution and toward bromine in carbon tetrachloride. A positive test for formic acid was obtained when the liquid was boiled with dilute acid and then treated with mercuric oxide.

Anal. Calcd. for $C_6H_9O_2$ (OCHO): C, 53.14; H, 6.38; sapon. equiv., 158. Found: C, 53.51; H, 6.47; sapon. equiv., 153.

Summary

The syntheses of benzoylglycolaldehyde (A) and dibenzoyl-*dl*-glycerose (B) by the ozonolysis of allyl benzoate and erythrol dibenzoate, respectively, demonstrate that aldehydo modifications of sugars may be prepared by the general method of ozonolytic cleavage of the appropriate unsaturated benzoate. Some dibenzoyl-*dl*-glyceric acid, hitherto unprepared, was formed concurrently with B. 2,4-Dinitrophenylhydrazones of A and B were satisfactory derivatives, as was the *p*-nitrophenylhydrazone of A. Benzoic esters were preferable to acetic esters because of the susceptibility of the latter to hydrolysis. The ozonolysis of allyl acetate yielded glycolaldehyde instead of acetylglycolaldehyde. Similarly, triacetylglucal ozonide gave rise to a mixture of di- and triacetylarabinose instead of 2,3,5-triacetyl-4-formylarabinose.

The concurrent oxidation of aldehydes to acids during hydrolysis of the ozonides was prevented in large measure by the use of 20% pyruvic acid as a hydrolyzing medium.

Mannitol triformate was obtained by interaction of mannitol and formic acid at 140°. Vacuum distillation at higher temperatures yielded a levorotatory monoformate of dihydrofurylethanediol.

EVANSTON, ILLINOIS RECEIVED FEBRUARY 24, 1939