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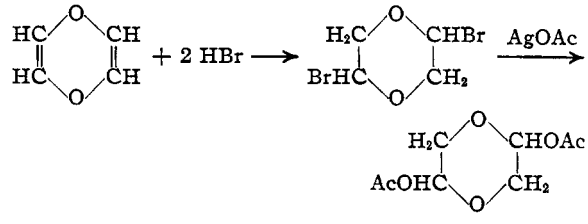
The Structure of Glycolaldehyde Dimer

BY R. K. SUMMERBELL AND LEO K. ROCHEN

Glycolaldehyde, the simplest hydroxyaldehyde, was shown by Fenton and Jackson[1] to exist in both the monomeric and dimeric states. Various derivatives of glycolaldehyde, as well as a number of related compounds, are found as dimers.[2-9] Emil Fischer[10] proposed a dioxane structure for the dimer of benzoylcarbinol methylacetal, and for a number of years it was the accepted structure for this and similar types of compounds. McClelland[11] in 1911 offered a four-atom unstable heterocyclic ring as a possible structure. H. O. L. Fischer[4] evidently did not accept the dioxane structure in 1927 as he designated glycolaldehyde and its derivatives by ethylene oxide structures with the added statement that they were dimeric. Bergmann[12] returned to the dioxane structures in 1929, and no evidence has been presented since then which causes one to question the commonly accepted thesis that the dimeric compounds are dioxane derivatives. On the other hand, no one has ever demonstrated that these compounds can be synthesized using a dioxane nucleus as the starting material. The preparation of dioxadiene,[13] and the reaction of the latter with hydrogen chloride to yield 2,5-dichlorodioxane indicated the possibility of a series of synthetic reactions which would constitute more definite proof of the structure of the derivatives of dimeric glycolaldehyde.

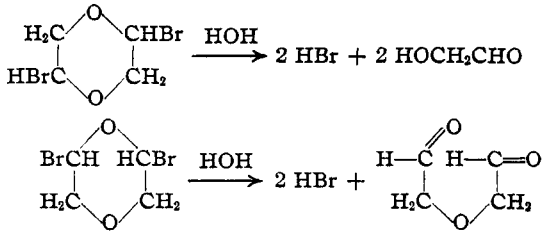
It was found that dry hydrogen bromide adds to the double bonds of dioxadiene to form 2,5-dibromodioxane which may be treated with silver acetate in dry toluene to yield 2,5-diacetoxydioxane.



Glycolaldehyde dimer diacetate was synthesized according to Fischer[4] and it proved to be identical with the 2,5-diacetoxydioxane prepared from dioxadiene through the 2,5-dibromodioxane. Both samples have the same melting point, and a mixed melting point showed no depression. The dimeric glycolaldehyde bromide synthesized by Fischer's method was found to be identical with 2,5-dibromodioxane. Inasmuch as Fischer's bromide is actually 2,5-dibromodioxane, and his acetate is 2,5-diacetoxydioxane, the inference is very strong that dimeric glycolaldehyde is 2,5-dihydroxydioxane.

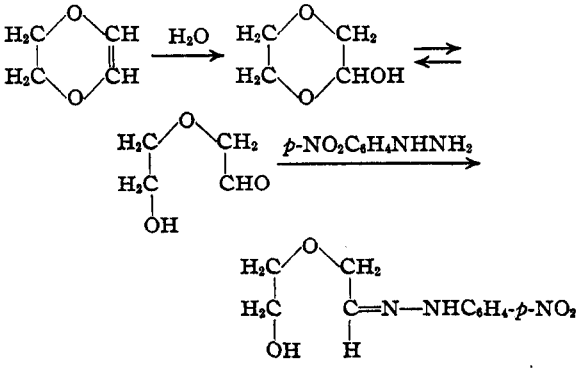
(1) Fenton and Jackson, *J. Chem. Soc.*, **75**, 575 (1899).
(2) Gehrke and Kohler, *Ber.*, **64B**, 2700 (1931).
(3) Bergmann and Miekeley, *ibid.*, **54B**, 2150 (1921).
(4) Fischer and Taube, *ibid.*, **60B**, 1704 (1927).
(5) Bergmann and Ludewig, *Ann.*, **436**, 173 (1924).
(6) Bertrand, *Compt. rend.*, **129**, 341 (1899).
(7) Nef, *Ann.*, **335**, 257 (1904).
(8) Fischer and Mildbrand, *Ber.*, **57B**, 707 (1924).
(9) Fischer and Taube, *ibid.*, **59B**, 857 (1926).
(10) E. Fischer, *ibid.*, **28**, 1161 (1895).
(11) McClelland, *J. Chem. Soc.*, **99**, 1827 (1911).
(12) Bergmann and Miekeley, *Ber.*, **62B**, 2297 (1929); *ibid.*, **64B**, 803 (1931).
(13) Summerbell and Umhoefer, THIS JOURNAL, **61**, 3020 (1939).

Hydrogen bromide could add to dioxadiene to give either 2,5- or 2,6-dibromodioxane. The 2,6-compound should hydrolyze to yield one mole of diglycolaldehyde, while the 2,5-compound should yield two moles of glycolaldehyde.



Treatment of the hydrolyzed solution with *p*-nitrophenylhydrazine might be expected to yield either one mole of the dihydrazone of diglycolaldehyde or two moles of glyoxal osazone. The weight and properties of the precipitate corresponded to two moles of the osazone.

Attempts to prepare the unknown dihydrazone of diglycolaldehyde for comparison with the above product were not successful. Ozonolysis of 2,5-dihydrofuran and subsequent hydrolysis in a reducing atmosphere yielded no isolatable diglycolaldehyde. Attempts to prepare the hydrazone without isolating the aldehyde resulted in the formation of glyoxal *p*-nitrophenylosazone. The question is thus raised as to whether the failure to isolate the dihydrazone of diglycolaldehyde constitutes sufficient proof of the structure of 2,5-dibromodioxane. Since diglycolaldehyde was not available, the related compound obtained from the hydrolysis of dioxene was studied. The *p*-nitrophenylhydrazone of 5-hydroxy-3-oxapentanal was readily isolated.



Refluxing the above hydrazone with excess *p*-nitrophenylhydrazine in 25% acetic acid resulted in the *p*-nitrophenylosazone, indicating that the ether linkage in this type of compound may be broken by such reagents. The hydrazone is converted to the osazone of glyoxal by heating in the presence of hydrogen ions, but seems to be rather stable to refluxing in the presence of water. Unusual reactivity toward the Grignard reagent of ether linkages beta to an aldehyde have been observed by Drake and co-workers,[14] but they report no difficulty in isolating hydrazones. Their compounds differ from those under study in that the ethers contained only one beta oxygen atom.

Although the hydrolysis experiments do not constitute complete proof of the positions occupied by the bromine in dibromodioxane, the synthetic work coupled with that of H. O. L. Fischer does fix these positions. If dimeric glycolaldehyde contains a dioxane ring, it seems much more probable that it is 2,5-dihydroxydioxane rather than the 2,6-isomer. Our synthetic experiments show two of the derivatives of dimeric glycolaldehyde to be dioxane derivatives. Therefore, the substituents must be in the 2,5-positions.

Experimental

2,5-Dibromodioxane.—Dioxadiene was prepared from 2,3,5,6-tetrachlorodioxane by the method of Summerbell and Umhoefer.[13] At ice-bath temperatures dry hydrogen bromide was passed into a solution of 2.26 g. (0.026 mole) of dioxadiene in 50 cc. of dry chloroform. At the end of one hour, the source of hydrogen bromide was removed and the mixture filtered rapidly. The solid was placed temporarily in the refrigerator, while the filtrate was put in a vacuum desiccator to facilitate further crystallization. As soon as crystals appeared, the mixture was placed in the refrigerator for three hours, after which the solid was filtered quickly. The combined solids weighed 6.0 g., which represents a 93.7% yield of crude dibromodioxane. The solid was dissolved in the minimum amount of chloroform necessary to effect solution at room temperature. The solution was then placed in a salt–ice-bath and the chloroform evaporated under vacuum until crystallization occurred. The fine white needles were filtered quickly and air dried. The crystals do not melt, but darken at 104–106° and decompose completely at 134°.

Anal. Calcd. for $C_4H_6O_2Br_2$: Br, 65.01. Found: Br, 64.85.

Thirty cc. of distilled water was added to 0.0416 g. of the dibromodioxane and the mixture heated over the steam-bath for two hours with occasional stirring. To the cooled solution was then added 0.35 g. of *p*-nitrophenylhydrazine hydrochloride in 50 cc. of a 25% acetic acid solution. The mixture was heated on a steam-bath for one hour and the red precipitate filtered and washed with water, alcohol and ether in succession. The precipitate was dried at 110° to constant weight, 0.1122 g.; calculated weight, for two equivalent moles of *p*-nitrophenylosazone of glyoxal, 0.1102 g.; calculated weight, assuming product to be *p*-nitrophenylhydrazone of diglycolaldehyde, 0.0625 g.

(14) Drake, Duvall, Jacobs, Thompson and Sonnichsen, THIS JOURNAL, **60**, 73 (1938).

Glycolaldehyde dimer dibromide was prepared according to the method of Fischer.[4] Because of instability, the proof of identity with 2,5-dibromodioxane was difficult. Both samples darkened at 104° and decomposed completely at 134°, and a mixture of the two showed the same characteristics. Their crystal structures, long white rectangles, appeared to be identical under the microscope. Paralleling the hydrolysis procedure for 2,5-dibromodioxane, the treatment of the glycolaldehyde dimer dibromide resulted as follows: weight of dibromide hydrolyzed, 0.0730 g.; weight of precipitate, 0.1895 g.; calculated weight for two equivalent moles of *p*-nitrophenylosazone of glyoxal, 0.1829 g.; calculated weight, assuming product to be *p*-nitrophenylhydrazone of diglycolaldehyde, 0.1108 g.

2,5-Diacetoxydioxane.—A mixture of 3.0 g. of 2,5-dibromodioxane, 80 cc. of dry toluene, and 5.0 g. of silver acetate was shaken for twelve hours. The mixture was filtered, and the precipitate washed with 20 ml. of dry toluene. The filtrates were combined and evaporated under reduced pressure at 40°. The residue was recrystallized from absolute ethyl alcohol, yielding white needles melting at 151–154°. The material was recrystallized several times from absolute ethyl alcohol and finally melted at 157–158°. A mixed melting point with a sample of glycolaldehyde dimer diacetate[4] showed no depression.

Attempted Synthesis of *p*-Nitrophenylhydrazone of Diglycolaldehyde.—(a) A solution of 1.1 g. of 2,5-dihydrofuran[15] in 25 cc. of glacial acetic acid was ozonized twelve hours. At the end of that time, a sample of the solution did not decolorize a solution of bromine in acetic acid. The acetic acid solution of the ozonide was diluted with an equal volume of water, and 10 g. of zinc dust was added as well as traces of silver nitrate and hydroquinone. The mixture was then refluxed over a steam-bath for four hours. The hydrolyzed solution was filtered, and the filtrate diluted with an equal volume of water, thus making it approximately a 25% acetic acid solution. To it was added a solution of 5.5 g. of *p*-nitrophenylhydrazine hydrochloride dissolved in 100 cc. of 25% acetic acid. An immediate precipitation of a red, flocculent solid occurred. The mixture was digested on the steam-bath for two hours, cooled to room temperature, and filtered. The solid was then washed successively with water, alcohol, acetone and ether; the yield of the solid was 1.3 g. After successive recrystallizations from alcohol and pyridine, the small red needles melted at 304–306° (uncor.). An alcoholic sodium hydroxide solution of the substance gave a blue color. The same color test is given by the *p*-nitrophenylosazone of glyoxal, which melts at 311°[16] (cor.).

(b) The following experiment was carried out with the hope of isolating the free dialdehyde. A solution of 2.2 g. of 2,5-dihydrofuran in 50 cc. of dry carbon tetrachloride was ozonized for twelve hours. Hydrolysis was carried out according to the method of Hurd and Filachione.[17] To the solution of the ozonide was added 50 cc. of a 20% pyruvic acid solution. The carbon tetrachloride was distilled off, and the mixture slowly heated to 100° on a steam-bath and maintained at that temperature until the evolution of carbon dioxide ceased. The cold solution was extracted with 100 cc. of ether and the ether solution washed free of acid with sodium bicarbonate solution. The ether extract was dried over sodium sulfate and the ether removed by distillation. There was practically no residue.

5-Hydroxy-3-oxapentanal *p*-Nitrophenylhydrazone

(a) **Preparation.**—Dioxene was prepared by the method of Summerbell and Umhoefer.[18] A mixture of 2 g. of dioxene, 2 drops of concentrated hydrochloric acid and 25 cc. of water was refluxed over a steam-bath for one hour. To the cooled solution was added a cold solution of 2.6 g. of *p*-nitrophenylhydrazine hydrochloride in 100 cc. of water. The resulting orange solid was filtered and recrystallized from 50% ethyl alcohol. The product consisted of orange needles melting at 142°; the yield was 5.1 g. of the hydrazone or 56.6%.

Anal. Calcd. for $C_{10}H_{13}O_4N_3$: N, 17.56. Found: N, 17.78.

(b) **Oxidation.**—A mixture of 0.1821 g. (0.00076 mole) of the above hydrazone, 0.3814 g. (0.0018 mole) of *p*-nitrophenylhydrazine hydrochloride, and 100 cc. of a 25% acetic acid solution was refluxed for five hours. The mixture turned from the original yellow orange to red in thirty minutes. The mixture was cooled, filtered and washed with 95% ethyl alcohol. The air dried red residue weighed 0.1561 g. Theoretical weight of the glyoxal osazone was 0.2205 g. The red solid was twice recrystallized from pyridine, yielding short red needles, m. p. 310° (uncor.). The substance gave a blue color with alcoholic sodium hydroxide, a typical reaction of *p*-nitrophenylosazone of glyoxal. A mixed melting point with the known osazone showed no depression. In a similar experiment the mixture was refluxed for ten hours, and the yield increased to 96%.

(c) **Autoöxidation.**—A mixture of 0.5853 g. of the hydrazone in 80 cc. of 25% acetic acid was refluxed for four hours. The mixture was then cooled and filtered. The red solid weighed 0.1798 g. The theoretical weight of the osazone was 0.2329 g. This was calculated on the assumption that one-third of the hydrazone was needed as oxidizing agent, and another third to supply the extra hydrazine for osazone formation.

A mixture of 0.200 g. of the hydrazone and 50 cc. of water was refluxed for three hours. The residue, when filtered and dried, weighed 0.186 g., and was still orange in color. Alcoholic sodium hydroxide showed a deep red color when treated with the solid. There was no evidence of conversion to the osazone in this experiment where hydrogen ions were absent.

A mixture of 1.46 g. of the hydrazone, 50 cc. of water and one drop of concd. hydrochloric acid was refluxed for two hours. The mixture was cooled, and the red precipitate filtered: wt. 0.416 g.; calcd., 0.5805 g. The precipitate gave the typical blue color of glyoxal osazone when treated with alcoholic sodium hydroxide.

5-Hydroxy-3-oxapentanal 2,4-Dinitrophenylhydrazone.—Two grams of dioxene was hydrolyzed as previously described and the resulting solution treated with a solution of 3.5 g. of 2,4-dinitrophenylhydrazine hydrochloride in dilute acetic acid. The resulting solid was filtered off and recrystallized from 50% alcohol to yield yellow orange needles melting at 136°.

(15) Henninger, *Ann. chim. phys.*, [6] **7**, 211 (1886).

(16) Wohl and Neuberg, *Ber.*, **33**, 3107 (1900); F. G. Fischer, *Ann.*, **464**, 85 (1928).

(17) Hurd and Filachione, THIS JOURNAL, **61**, 1156 (1939).

(18) Summerbell and Umhoefer, *ibid.*, **61**, 3016 (1939).

Anal. Calcd. for $C_{10}H_{12}O_6N_4$: N, 19.72. Found: N, 19.61.

Summary

1. Compounds identical with derivatives of dimeric glycolaldehyde have been prepared from dioxadiene.

2. The dioxane structure for dimeric glycolaldehyde and its derivatives is given synthetic experimental confirmation.

3. Attempts to prepare diglycolaldehyde or its *p*-nitrophenylhydrazone were unsuccessful under the conditions studied.

4. Hydrolysis of dioxene results in the formation of an aldehyde, probably 5-hydroxy-3-oxapentanal, of which the *p*-nitrophenylhydrazone and the 2,4-dinitrophenylhydrazone have been isolated.

5. Ether bonds beta to a functional group may be split by comparatively mild reagents. Hydrogen ions seem to be particularly important.

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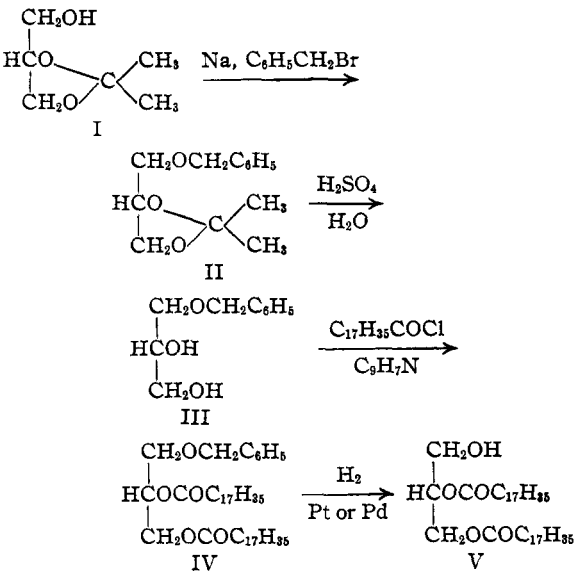
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

Optically Active α,β-Diglycerides

BY JOHN C. SOWDEN AND HERMANN O. L. FISCHER

In previous publications from this Laboratory, it has been shown that the enantiomorphic 1,2-acetone-glycerols[1,2] are convenient starting materials for the synthesis of optically active α-monoglycerides,[3] α-glycerophosphates,[4] and mixed acid triglycerides.[3] The methods involved in preparing these glycerol derivatives were such that no change in configuration could occur and the steric relationship of the products to *d*- and *l*-acetone-glycerol, and hence to *d*- and *l*-glyceraldehyde, was known.

A method has now been developed whereby these same starting materials, the stereoisomeric acetone-glycerols, may be employed to prepare optically active α,β-diglycerides of known configuration. The synthesis of *d*-α,β-distearin from *d*(+)-acetone-glycerol, represented in formulas I to V, illustrates the reactions involved.



The sequence of the above reactions is such that the asymmetry of the substituted glycerol molecule is maintained throughout.

The benzyl group was introduced, I → II, by the reaction of benzyl chloride or benzyl bromide with the sodium salt of *d*(+)-acetone-glycerol, a reaction which had been reported previously for racemic acetone-glycerol by Lorenz Ach.[5] In order to demonstrate that the reaction with sodium had no racemizing effect, the known α'-methyl ether of *d*(+)-acetone-glycerol[6] was also prepared through the sodium salt, and found to be of good optical purity. The benzyl ether is especially suitable for the preservation of the asymmetry of the glycerol molecule, since in contrast to the trityl ether, for instance, it is relatively stable toward acid and alkali but can be cleaved readily by catalytic hydrogenation to produce the original alcohol group.[7] Moreover, to avoid racemization, the free α,β-diglycerides must at no time be subjected to the action of mineral acids, since these have been observed to cause migration of aliphatic residues in β-substituted mono- and diglycerides.[8] Since the

(1) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).
(2) E. Baer and H. O. L. Fischer, THIS JOURNAL, **61**, 761 (1939).
(3) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 475 (1939).
(4) E. Baer and H. O. L. Fischer, *ibid.*, **128**, 491 (1939); **135**, 321 (1940).
(5) German Patent 403,050 (*cf. Chem. Zentr.*, **96**, I, 293 (1925)).
(6) H. O. L. Fischer and E. Baer, *Naturwiss.*, **36**, 588 (1937).
(7) K. Freudenberg, W. Dürr and H. Hochstetter, *Ber.*, **61**, 1735 (1928); H. O. L. Fischer and B. Gohlke, *Helv. Chim. Acta*, **31**, 1130 (1933).
(8) E. Fischer, *Ber.*, **53**, 1621 (1920); M. Bergmann and N. M. Carter, *Z. physiol. Chem.*, **191**, 211 (1930); D. T. Jackson and C. G. King, THIS JOURNAL, **55**, 678 (1933).