

1,6 - dibenzoyl - D - sorbitol, 1,6 - dibenzoyl - D - mannitol and 1,2,6-tribenzoyl-D-mannitol by other workers have been reprepared.

2. The assigned structures have been tested by oxidation of the compounds with lead tetraacetate under standard conditions and found correct.

3. A new tribenzoate of D-sorbitol has been described and its structure shown to be 1,2,6 by oxidation with lead tetraacetate.

CAMBRIDGE, MASS.

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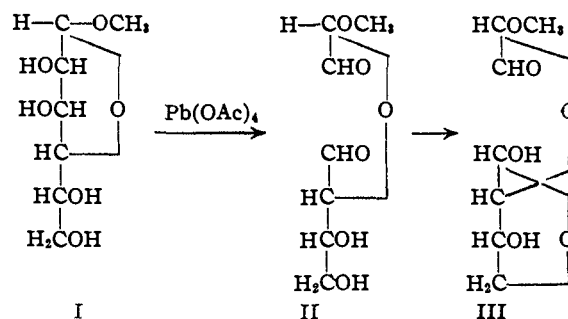
Lead Tetraacetate Oxidations in the Sugar Group. VII.¹ The Oxidation Rates of Ethyl β -D-Galactofuranoside, Methyl α -D-Mannofuranoside and 3,6-Anhydro-D-sorbitol²

BY ROBERT C. HOCKETT, MORTIMER H. NICKERSON AND WILLIAM H. REEDER, III

In previous publications,¹ we have described the behavior of two types of compounds toward lead tetraacetate in dry acetic acid under standard conditions: (1) polyalcohols with a six-membered glycoside or ether ring and (2) open-chain polyalcohols. We have also demonstrated the use of lead tetraacetate oxidations in establishing the structures of new compounds of these classes.³ Interest now centers upon the behavior of glycofuranosides and anhydroalcohols with a five-membered ether ring.

Criegee⁴ has already reported some work upon oxidation of furanosides and of aldonic acid gamma lactones by this agent. In particular, he has pointed out the impossibility of obtaining formaldehyde by the cleavage of hexo-pyranosides whereas certain furanosides will produce this easily identified aldehyde. He has also performed certain kinetic experiments and has assigned second-order rate constants to some of the reactions. However, since many lead tetraacetate oxidations have two or more distinct successive stages, we have found it instructive to record the oxidation rates in graphical form and have preferred to use a large excess of the oxidizing agent in order to render some of the reactions pseudo-unimolecular.

Hence, we have repeated the oxidation of methyl α -D-mannofuranoside under the conditions that have been established as standard in this Laboratory.⁵ An inspection of the structural formula (I) permits prediction of the type of curve to be expected, on the basis of generalizations previously stated.⁵ Thus, of the two glycol structures which can be attacked, the one inside the ring is held rigidly in a *cis* position favorable



for attack while the group outside the ring is subject to free rotation around the carbon-to-carbon bonds and should be less readily attacked. A locked *trans* structure would represent the least reactive type of glycol.⁶ Statistically, a great majority of the molecules should be cleaved inside the ring in the initial stage of reaction, to give the dialdehyde marked II. The latter, being a *gamma* hydroxy-aldehyde, would be expected to rearrange to a cyclic hemiacetal, establishing an equilibrium in which the proportion of open-chain isomer would be exceedingly small but finite.^{4,7} The cyclic hemiacetal itself should be unoxidized but the small proportion of free aldehyde present would account for a slow further oxidation.

The over-all prediction, therefore, is (1) the consumption of one molar equivalent of lead tetraacetate very rapidly, followed by a sharp break in the curve and a very much slower subsequent oxidation; (2) formation of only a trace of formaldehyde.⁴ The figure shows that the first prediction is very strikingly realized.

The predicted behavior of ethyl β -D-galactofuranoside is quite different. Examination of the structure shows two positions initially available for attack. Since the one inside the ring is locked in the unfavorable *trans* position, it appears that, statistically, most of the molecules would first be attacked outside the ring. This con-

(1) Number VI of this series, *THIS JOURNAL*, **66**, 469 (1944).

(2) This paper includes material from a thesis presented by Mortimer H. Nickerson to the Graduate School of the Massachusetts Institute of Technology in May, 1940, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. It was read before the Division of Organic Chemistry at the Detroit Meeting of the American Chemical Society, September, 1940.

(3) Hockett and Conley, *THIS JOURNAL*, **66**, 464 (1944).

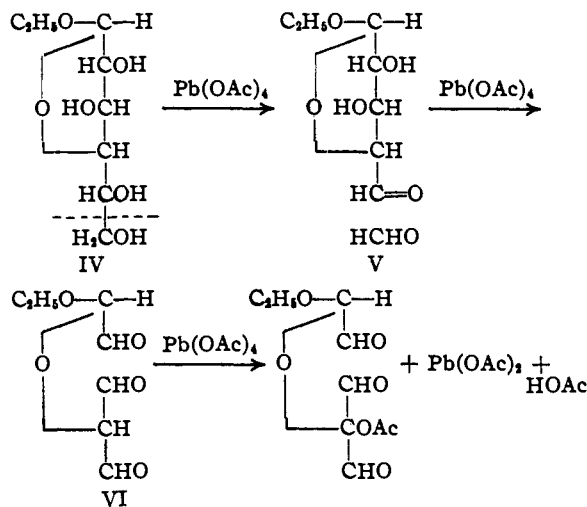
(4) Criegee, *Ann.*, **495**, 211 (1932).

(5) Hockett, Dienes and Ramsden, *THIS JOURNAL*, **65**, 1474 (1943).

(6) Cf. Criegee, *Ann.*, **507**, 159 (1933).

(7) Cf. Hockett and McClenahan, *THIS JOURNAL*, **60**, 2061 (1938).

ception leads to prediction of a nearly equi-molar production of formaldehyde along with an aldehyde V. The latter, having an unbroken ring, is



sterically impeded in forming a cyclic hemiacetal. Therefore, further oxidation may proceed at the 2,3 position to give a hypothetical trialdehyde VI in which one hydrogen should have an activity comparable to that of the alpha hydrogens in acetylacetone. The replacement of such alpha hydrogens by acetoxy under the action of lead tetraacetate is rapid enough to be observed under the conditions used (compare the oxidation curve for acetyl acetone Fig. 1). The over-all prediction, therefore, is (1) a relatively slow consumption of more than two molecular proportions of lead tetraacetate and (2) the production of an equi-molar quantity of formaldehyde. The figure shows confirmation of the first prediction and formaldehyde was found qualitatively.

A consideration of the possible aldohexofuranosides suggests that they may all fall into one or the other of two groups with respect to their oxidation behavior. All those with a *cis* structure inside the ring may be expected to act like methyl α -D-mannofuranoside while all containing a *trans* structure may very well give curves of the type observed for the ethyl β -D-galactofuranoside. Further experimentation will be required to substantiate this hypothesis. Criegee's observation that methyl β -D-glucoside produces formaldehyde is in accord with it.

The case of a ketohexofuranoside or of an aldopentofuranoside differs in that there is no glycol pair outside the ring. Therefore, formaldehyde should never be found and the two types (*cis* and *trans*) will both consume only one molar proportion of oxidant, differing markedly in rate. The fructose furanosides show this behavior.⁷

In 1912, Fischer and Zach⁸ described a crystalline 3,6-anhydro-D-sorbitol. This substance differs from a furanoside only in that the alkoxy

(8) Fischer and Zach, *Ber.*, **45**, 456, 2068 (1912); *cf.*, Ohle, von Vargha and Erlbach, *ibid.*, **61**, 1211 (1928).

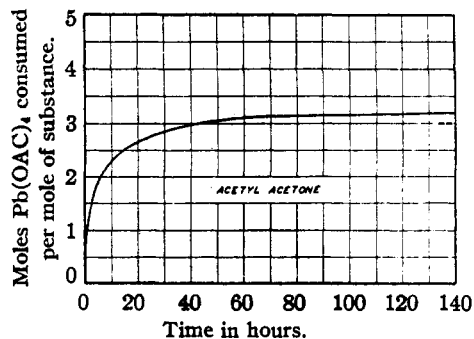


Fig. 1.

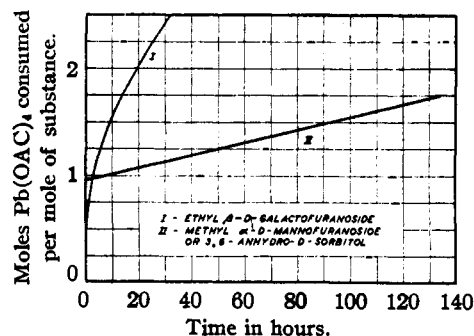


Fig. 2.—Oxidations in acetic acid containing less than 0.05% water: concentration of sample, 0.0025 molar; molar ratio of oxidant, 15.2/1.

group has been replaced by hydrogen. It might be expected to show an oxidation curve of the first type and to resemble the mannofuranoside closely. A close resemblance between the behavior of these two compounds would encourage us to apply the oxidation procedure in solving some of the many structural problems remaining in the little-known group of the anhydrides of polyalcohols.

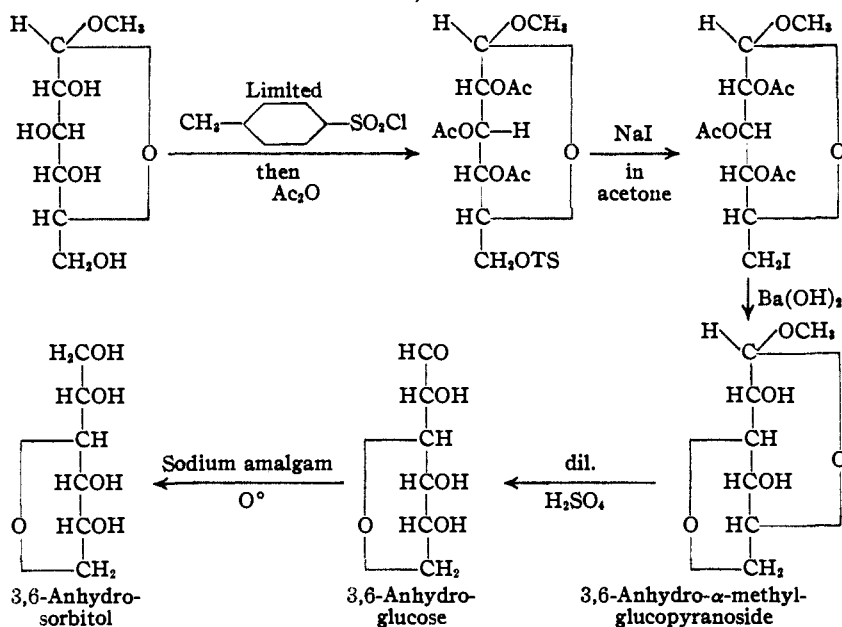
Fischer and Zach introduced the anhydro ring by treating methyl 6-deoxy-6-bromo-2,3,4-triacetyl- α -D-glucopyranoside with barium hydroxide. We preferred to use the corresponding iodo compound prepared as described by Compton,⁹ following Fischer's procedure in hydrolyzing the anhydroglucoside to the anhydro-glucose and in reducing the last with sodium amalgam to the anhydro-sorbitol.

The method of preparation eliminates any possibility of a Walden inversion at carbon atom number three during ether formation. Since there is no oxygen attached to the sixth carbon, the ether ring oxygen must be provided from the group upon carbon number three. Hence no bond of the third carbon atom has been broken and no inversion can have occurred. The structure of 3,6-anhydro-D-sorbitol, for the reasons enumerated, can be considered as established without question.

Oxidation of this sorbitan by lead tetraacetate under standard conditions, gave a curve identical

(9) Compton, *This Journal*, **60**, 398 (1938).

PREPARATION OF 3,6-ANHYDROSORBITOL



with that of methyl α -D-mannofuranoside within the limits of experimental error (Fig. 1).

We are very greatly indebted to Professor Eugene Pacsu of Princeton University for samples of the two furanosides, to Dr. Morris Zief of this Laboratory for repeating rate-of-oxidation measurements under more strictly anhydrous conditions and to Mr. Edward B. Weinberger, formerly of this Laboratory, for measuring the rate of oxidation of acetylacetone.

Experimental

Ethyl β -D-Galactofuranoside.¹⁰—This sample melted at $85\text{--}86^\circ$ and rotated¹¹ -102° (C , 0.500; H_2O).

Methyl α -D-Mannofuranoside.¹²—This sample melted at $118\text{--}119^\circ$ and rotated¹¹ $+108^\circ$.

Methyl 2,3,4-Triacetyl-6-*p*-toluenesulfonyl- α -D-glucopyranoside (M.H.N.).—The sirupy compound was prepared exactly as described by Compton⁹ from a 10-g. sample of methyl α -D-glucopyranoside.

Methyl 2,3,4-Triacetyl-6-deoxy-6-iodo- α -D-glucopyranoside (M.H.N.).—The entire sample of sirupy tosyl ester was treated with sodium iodide as described by Compton.⁹ Our product weighed 9 g., representing 40.5% of the theoretical yield from the methyl glucoside used. It melted $143\text{--}145^\circ$ and rotated¹¹ $+113.3^\circ$ (C , 0.94; CHCl_3).

3,6-Anhydro-D-glucose (M.H.N.).—The purification of methyl 3,6-anhydro- α -D-glucopyranoside was omitted in the present work.⁸ A sample of 20 g. of nearly pure methyl 6-deoxy-6-iodo-triacetyl- α -D-glucopyranoside was dissolved at the boiling point in 300 cc. of 50% (by vol.) ethanol. One hundred grams of barium hydroxide octahydrate, finely ground, was added and the mixture was heated under reflux for two hours. After cooling, filtration through carbon and evaporation to a sirup, the latter was extracted repeatedly with a 50:50 mixture of ethanol and ethyl acetate. The combined extracts were evaporated and

(10) Pacsu and Green, *THIS JOURNAL*, **59**, 1204 (1937).

(11) All rotations cited in this paper are specific rotations of the D line of sodium at 20° . Concentrations are expressed as grams per one hundred cc. of solution.

(12) Scattergood and Pacsu, *THIS JOURNAL*, **62**, 903 (1940).

the remaining sirup was dissolved in water. Barium ions were balanced out accurately with dilute sulfuric acid, hydriodic acid with silver carbonate, and dissolved silver with hydrogen sulfide. The filtered solution of methyl anhydroglucoside was concentrated nearly dry under diminished pressure, and then subjected to hydrolysis by solution in 50 cc. of 4.5% sulfuric acid and heating on a steam-bath for one hour and forty-five minutes. The sulfuric acid was balanced out with barium hydroxide and the filtered solution was concentrated to a sirup. When dissolved in a small volume of hot absolute ethanol and then cooled, the product separated in fine needles; yield 5.67 g. or 76% of theory. The anhydro-sugar melted $114\text{--}117^\circ$ and rotated¹¹ $+53.2^\circ$ (C , 0.73; H_2O).

3,6-Anhydro-D-sorbitol (M.H.N.).—Five grams of anhydro glucose dissolved in 50 cc. of water was subjected to

a rapid stream of carbon dioxide gas while 140 g. of sodium amalgam was added in successive 10-g. portions. The gas both served to keep the solution stirred and maintained the medium at the very slight alkalinity of a sodium bicarbonate solution. No cooling was used. By the time the last portion of amalgam was exhausted, only a faint reducing power toward Fehling solution remained. Mercury was separated and sodium bicarbonate was converted to sulfate by titration with dilute sulfuric acid (methyl orange). After filtration through carbon the solution was evaporated nearly dry under reduced pressure. The salts were extracted repeatedly with hot absolute ethanol and the combined, filtered extracts were concentrated to a sirup. This was redissolved in a minimum volume (30 cc.) of hot ethanol and ethyl acetate was added to incipient turbidity. Tabular crystals soon separated; yield, 3.85 g. Recrystallized from hot ethyl acetate, these melted at $108\text{--}109^\circ$.

Rate of Oxidation Measurements.—The samples were oxidized in solutions of the concentration adopted as standard by Hockett, Dienes and Ramsden,⁸ that is, 0.0025 molar with respect to sample and with a 15.2/1 molar ratio of oxidant to substance.

Detection of Formaldehyde.—The sample is dissolved in a small volume of water in a distilling flask and an excess of lead tetraacetate in acetic acid is added. After a few minutes, the water and acetic acid are distilled under reduced pressure into a receiver cooled in an ice and salt mixture. The distillate is then tested for formaldehyde by adding a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. If formaldehyde is present there occurs an almost instantaneous precipitation of the hydrazone, melting at 166° . This method is adaptable for either qualitative or quantitative determination.

Summary

1. The rates of oxidation of methyl α -D-mannofuranoside, ethyl β -D-galactofuranoside and 3,6-anhydro-D-sorbitol have been measured.

2. Correlations between structure and oxidation behavior have been pointed out.

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