# Lead Tetraacetate Oxidations in the Sugar Group. VI.[1] The Structures of Certain Di- and Tribenzoates of d-Sorbitol and d-Mannitol

By Robert C. Hockett and Hewitt G. Fletcher, Jr.[2]

In 1898, Einhorn and Hollandt[3] described a dibenzoyl mannitol prepared by the action of a limited amount of benzoyl chloride upon mannitol in pyridine solution. Some years later, Ohle and collaborators[4] assigned these benzoyl groups to the four and five positions since oxidation with neutral potassium permanganate yielded a product which they identified as dibenzoyl meso-tartaric acid. Brigl and Grüner[5] showed that this identification was erroneous and that the oxidation product is benzoylglycolic acid. Not only was the product compared directly with synthetic benzoylglycolic acid and dibenzoyl mesotartaric acid, but crystalline glycolic acid was isolated after debenzoylation. Since, moreover, the dibenzoylmannitol sample appeared to be a pure chemical individual and since the yield of benzoylglycolic acid was more than 50% of the theoretical, the benzoyl groups were assigned to the one *and* six positions.

$$
\begin{array}{c}
\text{H}_2\text{COBz} \\
| \\
\text{HOCH} \\
----|---- \\
\text{HOCH} \\
| \\
\text{HCOH} \\
----|---- \\
\text{HCOH} \\
| \\
\text{H}_2\text{COBz}
\end{array}
\longrightarrow
\begin{array}{c}
\text{COOH} \\
| \\
2\text{H}_2\text{COBz}
\end{array}
$$
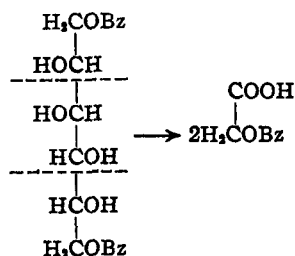
This structure implies that the primary hydroxyl groups are acylated much more rapidly than the more numerous secondary ones, an observation which is entirely in accord with many others to the same effect which have been made in recent years.[6]

In 1932, Alexander Müller[7] isolated a dibenzoyl-d-sorbitol by acylating d-sorbitol under similar conditions. It has been assumed without direct proof that this is also a 1,6-dibenzoate, because of the now general view that the primary alcohol groups will react first. A confirmation of this assumption is to be desired.

(1) Number V of this series, This Journal, **66**, 467 (1944).

(2) The material in this paper is taken from a thesis submitted by Hewitt G. Fletcher, Jr., to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy in September, 1942. Mr. Fletcher was Moore Fellow in Chemistry during 1941–1942.

(3) Einhorn and Hollandt, *Ann.*, **301**, 95 (1898); *cf.* Fischer, *Ber.*, **48**, 266 (1915).

(4) Ohle, *et al.*, *Ber.*, **62**, 2982 (1929).

(5) Brigl and Grüner, *ibid.*, **65**, 641 (1932).

(6) Compton, This Journal, **60**, 395 (1938); Cramer and Purves, *ibid.*, **61**, 3458 (1939); Hockett and Downing, *ibid.*, **64**, 2463 (1942).

(7) Müller, *Ber.*, **65**, 1055 (1932).

In a previous publication,[1] we have shown the behavior of open-chain polyalcohols when they are oxidized by lead tetraacetate under certain standard conditions. Similar oxidation of partially esterified polyalcohols should provide information concerning their structures very rapidly, easily and with samples on a micro scale. The observation of whether or not formaldehyde is produced and the number of moles of this aldehyde, is also carried out very easily and with very small samples.[8]

Fifteen isomeric d-sorbitol diesters are possible if the two substituent groups are identical. The table below shows how many moles of oxidant should be consumed by each in five to ten hours under standard conditions. It also shows the number of moles of formaldehyde to be expected from each.

| No. | Isomer | Moles of Pb(OAc)₄ used | Moles of HCHO produced |
|-----|--------|------------------------|------------------------|
| 1 | 1,2 | 3 | 1 |
| 2 | 1,3 | 2 | 1 |
| 3 | 1,4 | 2 | 1 |
| 4 | 1,5 | 2 | 0 |
| 5 | 1,6 | 3 | 0 |
| 6 | 2,3 | 2 | 1 |
| 7 | 2,4 | 1 | 1 |
| 8 | 2,5 | 1 | 0 |
| 9 | 2,6 | 2 | 0 |
| 10 | 3,4 | 2 | 2 |
| 11 | 3,5 | 1 | 1 |
| 12 | 3,6 | 2 | 1 |
| 13 | 4,5 | 2 | 1 |
| 14 | 4,6 | 2 | 1 |
| 15 | 5,6 | 3 | 1 |

These two experimental observations alone, will positively identify isomers no. 5, 8 and 10 since they give unique combinations of oxidant consumption and formaldehyde production. Three other combinations occur twice each so that in these six cases, the two experiments will limit the possible structures to two (4 and 9, 7 and 11, 1 and 15). Choice between the two alternatives will require further observations upon the oxidation products and this may not always be possible on a micro scale. Finally, the remaining combination occurs six times so that distinction of the corresponding isomers (2, 3, 6, 12, 13, 14) will be relatively difficult.

We succeeded in preparing a dibenzoyl-d-sorbitol with the properties reported by Müller. On oxidation it gave no trace of formaldehyde. Under standard conditions, it consumed just

(8) *Cf.* Criegee, *ibid.*, **64**, 260 (1931); *Ann.*, **495**, 211 (1932).

under three moles of oxidant in the critical time (Fig. 1). Therefore, $n - 1 = 3$ and $n = 4$ carbinol groups in an unbroken series. This behavior is very much like that of erythritol whose oxidation curve is plotted in Fig. 1 for comparison. Thus the 1,6 structure is confirmed.

As a by-product in the preparation of 1,6-dibenzoyl mannitol, Ohle and collaborators[4] obtained a tribenzoyl mannitol which melted at 162° and rotated[9] −18.0° in acetone ($C$, 1.721) or −44.0° in pyridine ($C$, 1.862). This compound was considered by Brigl and Gruner to be 1,2,6-tribenzoylmannitol[10] (which is identical with the 1,5,6 isomer). Their evidence is as follows: This tribenzoyl mannitol (I) combines with acetone to give a sirupy monoacetone derivative (II) whose one remaining hydroxyl group may be benzoylated to give the known 1,2;5,6-tetrabenzoyl-3,4-isopropylidene-D-mannitol (III). The structure of the last has been proved by the observation that it can be made by combining acetone with 1,2;5,6-tetrabenzoyl-D-mannitol (IV) whose structure in turn was proved by its nearly quantitative oxidation by lead tetraacetate to dibenzoyl-D-glyceric aldehyde.[11] These deductions are valid only if there is no shift of benzoyl groups.
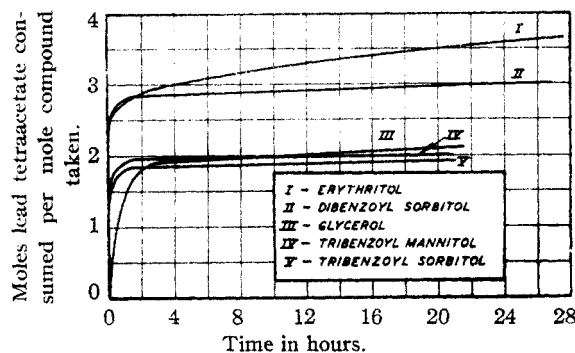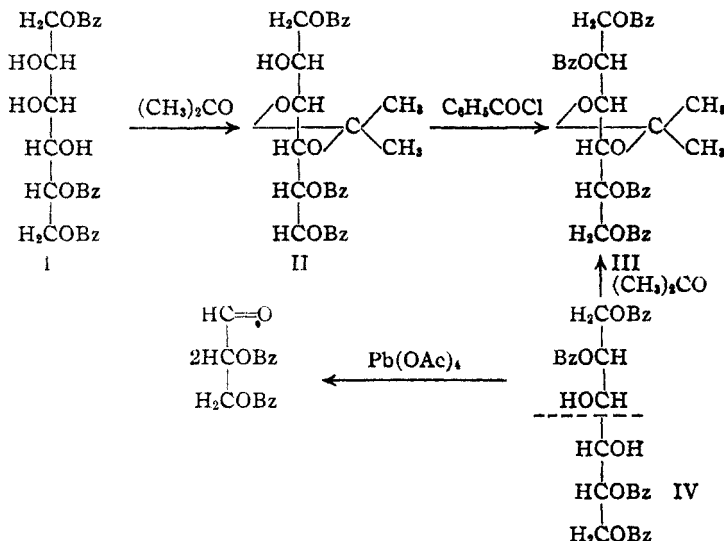


Fig. 1.

It should be noted that this evidence is not quite sufficient to *prove* the structure of the tribenzoyl-mannitol since a 2,5,6-tribenzoate could give the same reactions. The 1,2,6 structure is the more probable of the two possibilities since it is reasonable to suppose that the tribenzoate is formed by further acylation of the predominating 1,6-dibenzoyl-mannitol. However, an oxidation by lead tetraacetate under standard conditions can settle this point definitely since a 1,5,6 ester should behave like glycerol while a 2,5,6 ester would behave more like ethylene glycol. The

oxidation curve plotted on Fig. 1 shows unequivocally that the 1,5,6 (1,2,6) formulation is correct.

The following table, showing all the possible trisubstituted mannitols in which the three substituting groups are alike, indicates the lead tetraacetate consumption and the formaldehyde production to be expected of each. It will be noted that the isomer under discussion, No. 4, could be identified by these two observations alone since it is the only isomer which could consume two moles of oxidant without producing formaldehyde.

| No. | Isomer | Moles of Pb(OAc)₄ used | Moles of HCHO produced |
|---|---|---|---|
| 1 | 1,2,3 (4,5,6) | 2 | 1 |
| 2 | 1,2,4 (3,5,6) | 1 | 1 |
| 3 | 1,2,5 (2,5,6) | 1 | 0 |
| +4 | 1,2,6 (1,5,6) | 2 | 0 |
| 5 | 1,3,4 (3,4,6) | 1 | 1 |
| 6 | 1,3,5 (2,4,6) | 0 | 0 |
| 7 | 1,3,6 (1,4,6) | 1 | 0 |
| 8 | 1,4,5 (2,3,6) | 1 | 0 |
| 9 | 2,4,5 (2,3,5) | 0 | 0 |
| 10 | 2,3,4 (3,4,5) | 1 | 1 |

In the course of our repreparation of 1,6 dibenzoyl-D-sorbitol we obtained as a by-product, a small quantity of a tribenzoyl-D-sorbitol which apparently has not been described before. The possible number of trisubstituted D-sorbitols is twice as great as for trisubstituted mannitols since the sorbitol molecule is less symmetrical. These isomers are listed with their expected behavior.

| No. | Isomer | Moles of Pb(OAc)₄ used | Moles of HCHO produced |
|---|---|---|---|
| 1 | 1,2,3 | 2 | 1 |
| 2 | 1,2,4 | 1 | 1 |
| 3 | 1,2,5 | 1 | 0 |
| +4 | 1,2,6 | 2 | 0 |
| 5 | 1,3,4 | 1 | 1 |

(9) All rotations cited in this paper refer to specific rotations of the D line of sodium at 20° unless otherwise stated.

(10) Brigl and Grüner, *Ber.*, **66**, 931 (1933).

(11) Fischer, see ref. 3; Criegee, *Ber.*, **64**, 260 (1931); *Ann.*, **481**, 263 (1930).

| No. | Isomer | Moles of Pb(OAc)₄ used | Moles of HCHO produced |
|---|---|---|---|
| 6 | 1,3,5 | 0 | 0 |
| 7 | 1,3,6 | 1 | 0 |
| 8 | 1,4,5 | 1 | 0 |
| 9 | 1,4,6 | 1 | 0 |
| 10 | 1,5,6 | 2 | 0 |
| 11 | 2,3,4 | 1 | 1 |
| 12 | 2,3,5 | 0 | 0 |
| 13 | 2,3,6 | 1 | 0 |
| 14 | 2,4,5 | 0 | 0 |
| 15 | 2,4,6 | 0 | 0 |
| 16 | 2,5,6 | 1 | 0 |
| 17 | 3,4,5 | 1 | 1 |
| 18 | 3,4,6 | 1 | 1 |
| 19 | 3,5,6 | 1 | 1 |
| 20 | 4,5,6 | 2 | 1 |

No formaldehyde was obtained when tribenzoyl-D-sorbitol was oxidized and the consumption of oxidant was two moles at the critical time (Fig. 1). The structure therefore is limited to 4 or 10.

To distinguish between these two possibilities it is only necessary to determine whether this tribenzoate yields dibenzoyl-D-glyceric aldehyde or dibenzoyl-L-glyceric aldehyde on oxidation with lead tetraacetate.



Dibenzoyl-L-        Dibenzoyl-D-
1,2,6-Ester  glyceraldehyde    glyceraldehyde  1,5,6-Ester
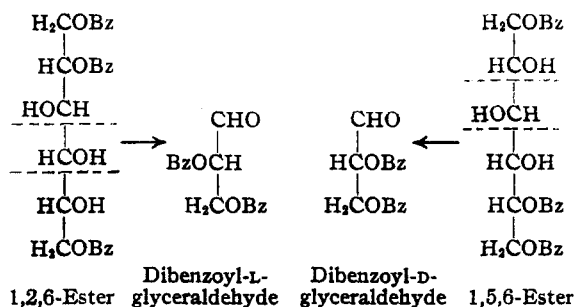
The D-form of this reference compound is well-known from the work of Brigl and Grüner[10] and has a rotation[9] of −35.6° in benzene. It follows that the L-form would rotate +35.6°. Since an oxidation by lead tetraacetate would be expected to destroy all other asymmetric centers and to yield the triose derivative almost quantitatively, it should suffice to oxidize a weighed sample of tribenzoyl hexitol with lead tetraacetate in a definite volume of benzene solution and to observe the final rotation attained. This plan was first tried out upon 1,2,6-tribenzoylmannitol which should yield dibenzoyl-D-glyceraldehyde mole for mole. The reading obtained was −0.21° in a 2-dm. tube as compared with −0.22° calculated. A similar oxidation was then performed upon an equal weight of tribenzoylsorbitol and a final rotation of +0.22° was recorded. This must be due to the L-form of dibenzoylglyceraldehyde and establishes the structure of the original compound as 1,2,6-tribenzoyl-D-sorbitol.

We wish to express our indebtedness to the Atlas Powder Company of Wilmington, Delaware, for samples of pure mannitol and sorbitol.

## Experimental

**1,6-Dibenzoyl-D-mannitol.**—Prepared as described by Brigl and Grüner,[8] our product was obtained in 29.1% yield and melted 182.3–183.3° (cor.).

**1,2,6-Tribenzoyl-D-mannitol.**—The alcoholic mother liquors from preparation of the 1,6-dibenzoate deposited crystals on standing in the refrigerator. Recrystallized from alcohol, these formed large needles melting sharply at 166.5–167.0° (cor.) and rotating⁹ −43.7° (C, 1.0096; pyridine). A melting point of 163° and rotation of −44° have been recorded.[4]

**1,6-Dibenzoyl-D-sorbitol.**—Thirty grams of pure sorbitol was dissolved in 600 cc. of pyridine at 80° and, after cooling to 10°, the rapidly stirred solution was treated with 36 cc. of benzoyl chloride added dropwise over the period of one and one-half hours. After two hours of standing at 20°, about two-thirds of the pyridine was removed under reduced pressure at 50° and the remaining solution was poured in a thin stream into 500 cc. of water with rapid stirring. Overnight in an ice-chest, the precipitated sirup became largely crystalline. Concentration of wash waters *in vacuo* yielded a few grams more material. The combined precipitates were dissolved in 120 cc. of boiling 95% alcohol which, on cooling, deposited 18.6 g. of crude 1,6-dibenzoylsorbitol. Recrystallization from 70 cc. of boiling alcohol gave 16.8 g. of white crystals melting at 142.2–143.2° (cor.); yield, 26.2%. They rotated +1.11° (C, 0.9006; pyridine). Müller[7] reported a melting point of 141° and a rotation in pyridine of +1.85°.

**1,2,6-Tribenzoyl-D-sorbitol.**—The combined mother liquors from the dibenzoate were treated with water to the turbid point. On standing first at room temperature and then in the ice-chest, there separated 8.8 g. of microcrystalline material which was much more soluble in alcohol than the dibenzoate. This product consisted of two or more difficultly-separable compounds (possibly the 1,5,6 isomer was present). By fractionation from hot toluene and then from chloroform, 2.8 g. of 1,6-dibenzoate was removed. The residue was recrystallized from alcohol several times by addition of water and attained a maximum melting point at 147.7–148.3° (cor.). The final yield was 0.125 g. The compound rotated −11.1° (C, 1.080; CHCl₃; 24.8°).

*Anal.* Calcd. for C₂₇H₂₆O₉: C, 65.58; H, 5.30. Found: C, 65.3, 65.5; H, 5.87, 5.67.

**Rates of Oxidation of 1,6-Dibenzoylsorbitol, 1,2,6-Tribenzoylsorbitol and 1,2,6-Tribenzoylmannitol.**—Exactly the conditions described by Hockett, Dienes and Ramsden[12] were used except that the molar concentration of samples was exactly twice the now-established standard of 0.0025 M. This difference in concentration has only a very small effect upon the oxidation rates of polyalcohols.

**Oxidation of 1,2,6-Tribenzoyl-mannitol to Dibenzoyl-D-glyceric-aldehyde.**—A sample of 0.0261 g. was suspended in 4.3415 g. of sulfur-free benzene saturated with water. With shaking 0.0521 g. (a 2.23 molar ratio) of crystalline lead tetraacetate was added. The mixture was shaken a minute and then left for twenty-four hours at room temperature. At 20°, the clear supernatant liquid then rotated −0.21° in a 2-dm. tube. A rotation of −0.22° would be expected if conversion to the glyceraldehyde ester was quantitative.

**Oxidation of 1,2,6-Tribenzoyl-sorbitol to Dibenzoyl-L-glyceric-aldehyde.**—A similar experiment was made using 0.0250 g. of tribenzoylsorbitol, 4.3434 g. of damp benzene and 0.0510 g. (2.28 molar ratio) of lead tetraacetate. At the end of thirty-six hours the supernatant liquid rotated +0.22° in a 2-dm. tube. Calculation, assuming quantitative oxidation to dibenzoyl-L-glyceraldehyde of specific rotation +35.6°, predicts +0.22°.

## Summary

1. The compounds previously described as

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

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 tetraace-

tate 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.

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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-sorbitol[2]

## 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.

Criegee[4] 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
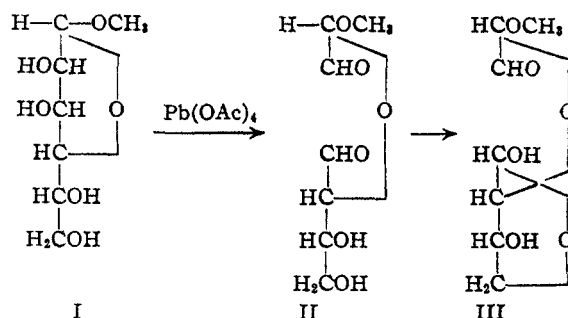


for attack while the group outside the ring is subject to free rotation around the carbon-to-carbon bonds and should be less readily attacked. A locked *trans* structure would represent the least reactive type of glycol.[6] Statistically, a great majority of the molecules should be cleaved inside the 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).