been confirmed by the behavior of the substance toward lead tetraacetate. The dianhydromannitol described by Brigl and Grüner as "2,4,3,5-dianhydromannitol" has been shown by us to be identical with isomannide, and the structure of the latter has been shown to be either 1,5,3,6- or 1,4,3,6-dianhydromannitol. Several derivatives of these anhydrides described by Brigl and Grüner have been reprepared and their structural assignments corrected. Two new compounds have been prepared: 5,6-benzylidene-1,4-anhydromannitol and ditritylisomannide.

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WILMINGTON, DEL.
RECEIVED JANUARY 29, 1946

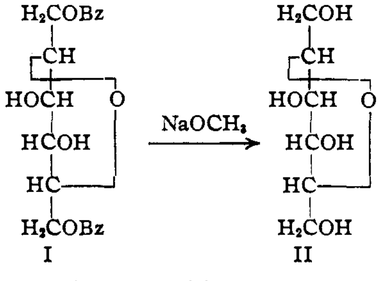
[CONTRIBUTION FROM THE SUGAR RESEARCH FOUNDATION LABORATORY, DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, AND THE RESEARCH DEPARTMENT, ATLAS POWDER COMPANY]

Hexitol Anhydrides.[1] The Structure of the "2,5-Anhydromannitol" of Brigl and Grüner[2] (2,5-Anhydrosorbitol)

BY R. C. HOCKETT,[3] MORRIS ZIEF[3] AND R. MAX GOEPP, JR.[3]

In an earlier paper of this series,[4] we described a repetition of the anhydridization of 1,6-dibenzoylmannitol according to the procedure of Brigl and Grüner[5] and indicated that we succeeded in obtaining the same three products described by the German workers. However, the structures assigned to two of these products were altered as a result of our investigations.[1,4]

The third product described by Brigl and Grüner was considered by them to be 2,5-monoanhydro-1,6-dibenzoylmannitol (I). A substance of this structure should be oxidized by lead tetraacetate according to theory, since it contains an unsubstituted pair of hydroxyl groups in a vicinal relation. Nevertheless the German authors described the compound as inactive toward lead tetraacetate. Because of its behavior when oxidized by permanganate, they nevertheless considered the structure assignment to be appropriate and ascribed the inactivity toward lead tetraacetate to the fact that the free hydroxyl groups bear a *trans* relation to each other in space.



I II

However, when we subjected our sample of the same compound to lead tetraacetate oxidation under the standard conditions used in this Laboratory for rate-of-oxidation measurements,[6] we found that oxidation does occur (Fig. 1). One molar equivalent of oxidant is consumed at a low rate of speed, exactly according to the prediction of theory. The very much more rapid oxidation of 1,4-anhydromannitol or of methyl α-D-mannofuranoside is plotted for comparison.

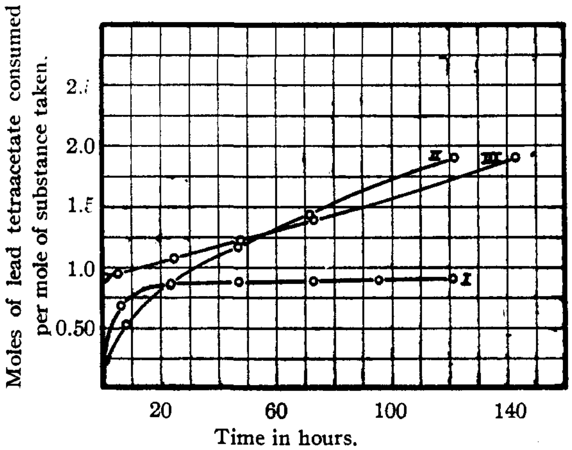


Fig. 1.—Oxidation of 2,5-monoanhydro-1,6-dibenzoylmannitol and 2,5-monoanhydromannitol: I, 2,5-monoanhydro-1,6-dibenzoylmannitol (2,5-monoanhydro-1,6-dibenzoylsorbitol); II, 2,5-monoanhydromannitol (2,5-monoanhydrosorbitol); III, methyl α-D-mannofuranoside.

The benzoyl groups of the compound were removed by sodium methylate to produce a sirupy mannitan (II). On oxidation under standard conditions, a less useful curve was obtained since the reaction rate did not diminish sharply after consumption of one molar equivalent of oxidant (Fig. 1). It was ascertained, however, that no significant quantity of formaldehyde is produced by the oxidation of the debenzoylated substance. Reference to the table indicating predicted be-

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(1) The previous paper of this series, THIS JOURNAL, **68**, 930 (1946).

(2) Most of the material in this paper was presented before the Division of Sugar Chemistry and Technology of the American Chemical Society at the Cleveland Meeting in April, 1944.

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(4) Hockett, Fletcher, Sheffield, Goepp and Soltzberg, THIS JOURNAL, **68**, 930 (1946).

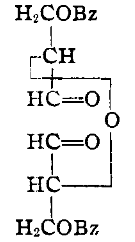
(5) Brigl and Grüner, *Ber.*, **66**, 1945 (1933); **67**, 1582 (1934).

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

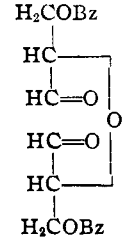
havior of mannitans on lead tetraacetate oxidation,[4] shows that only four are expected to produce no formaldehyde: 1,4 (3,6); 1,5 (2,6); 1,6 and 2,5. The first two of these are already known[4] and are not identical with the substance under study. The 1,6 ring is very unlikely because it would contain two *cis* glycol structures and certainly give a much higher initial oxidation rate as well as a larger total consumption of oxidant. Similar considerations also eliminate all possible sorbitan structures except the 2,5, when these structures are considered as possibilities on account of the probability of a Walden inversion during anhydridization.[7]

We therefore consider the ring assignment of Brigl and Grüner to be correct as well as the position of the benzoyl groups in the initial product, since they would prevent oxidation by lead tetraacetate if located elsewhere.

However, it seemed to us very unlikely on theoretical grounds that an anhydridization could occur involving two secondary hydroxyl groups attached to asymmetric carbon atoms without Walden inversion of one or the other. If an inversion occurred either at carbon two, or carbon five, the product would be a 2,5-anhydro-sorbitol instead of an anhydro-D-mannitol. It appeared also that the question of whether or not inversion occurs should be easy to answer experimentally since the oxidation product obtained by cleaving a 2,5-anhydromannitol at the 3,4-position ought to be optically active whereas the cleavage product from 2,5-anhydrosorbitol should be internally compensated. The same relation holds also for the 1,6-dibenzoates.



Product from
1,6-dibenzoyl-
2,5-anhydromannitol
Active



Product from
1,6-dibenzoyl-
2,5-anhydrosorbitol
Inactive

The product formed by lead tetraacetate fission was isolated in crystalline form as a dihydrate and found to have the composition predicted in the formulations given above. Two per cent. solutions were optically inactive to the D line of sodium in ethyl alcohol, acetic acid and chloroform. A 3.055% solution in 95% ethyl alcohol was inactive also to five other spectrum lines when observed in a two-decimeter tube.

We therefore conclude that the compound is inactive and that it must be 2,5-anhydrosorbitol rather than 2,5-anhydromannitol.

It was somewhat surprising that no derivative of this substance, presumed to be a dialdehyde, could be obtained with phenylhydrazine, 2,4-dinitrophenylhydrazine or methone reagent. In view of its failure to react with aldehyde reagents, it is probably not wise for us to commit ourselves to any assertion that this hydrated oxidation product contains aldehyde groups as such, and the name tentatively assigned should not be construed as descriptive of the actual structure, which may be elucidated by further work. The observed lack of optical activity requires that the substance be either a *meso* or D,L compound, so that the assignment of sorbitan configuration to the parent anhydro compound is valid, regardless of the actual structure of the oxidation product.

Vargha and Puskas[8] have reported an entirely analogous oxidation of 1,6-ditosyl-2,5-anhydro-L-iditol for the purpose of determining whether a Walden inversion occurred at carbon five during the course of preparation. The isolation of an optically active dialdehyde indicated that their product was actually an iditol derivative rather than a sorbitol anhydride.

Experimental

"2,5-Monoanhydromannitol" (2,5-Monoanhydrosorbitol).—One gram of 2,5-monoanhydro-1,6-dibenzoylmannitol (prepared according to the directions of Brigl and Grüner[8]) was suspended in 25 cc. of chloroform cooled to 0°. At 0°, 10 cc. of 0.1 *N* sodium methylate solution in methanol was added, whereupon the solid dissolved readily. The solution was kept at 4° for eighteen hours and was then concentrated *in vacuo* at 40° to a gummy product. The gum was difficultly soluble in chloroform, very soluble in absolute ethyl alcohol and water. The gum was dissolved in 15 cc. of water and the water layer was extracted three times with 25-cc. portions of ether to remove methyl benzoate. The aqueous layer was separated and concentrated *in vacuo* at 40° to a colorless semi-solid. Absolute ethyl alcohol (15 cc.) was added and concentration *in vacuo* was repeated. The addition of absolute ethyl alcohol and concentration *in vacuo* was repeated twice more but no crystalline material was obtained. The colorless semi-solid was dried at 65° in a vacuum oven for two hours.

Anal.[9] Calcd. for $C_6H_{12}O_5$: C, 43.9; H, 7.3. Found: C, 44.7; H, 6.7.

Determination of Formaldehyde.—"2,5-Monoanhydro-1,6-dibenzoylmannitol" (2,5-monoanhydro-1,6-dibenzoylsorbitol) (0.11 g.) dissolved in 5 cc. of glacial acetic acid was dropped on an excess of lead tetraacetate (0.4 g.) in an apparatus so arranged that a stream of dry air could be passed through the mixture, sweeping out formaldehyde through a vertical condenser that returned acetic acid to the reaction vessel. The exit gases were caught in an 8-inch test-tube containing 40 cc. of 2 *N* hydrochloric acid saturated with 2,4-dinitrophenylhydrazine. With careful heating no acetic acid was carried over into the receiver. After distillation for forty-five minutes, the 2,4-dinitrophenylhydrazine solution remained perfectly clear.

1,4-Sorbitan (0.0577 g.) under the same conditions produced within thirty minutes a 55% yield of formaldehyde 2,4-dinitrophenylhydrazone, melting at 161–162°. 2,5-Monoanhydrosorbitol, when treated similarly, produced a trace of formaldehyde equivalent to 3.5% of one molar equivalent. This formaldehyde was identified as the 2,4-

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(7) *Cf.* Hockett, Conley, Yusem and Mason, THIS JOURNAL, **68**, 922 (1946).

(8) Vargha and Puskas, *Ber.*, **76**, 859 (1943).

(9) Analysis by Mrs. Elaine Spencer, at M.I.T.

dinitrophenylhydrazone, melting at 162–163°. The quantity was not considered significant.

3,3′-Dibenzoyl-2,2′-di-(D-glyceraldehyde) Ether Dihydrate.—A solution of 50 cc. of glacial acetic acid containing 1 g. (0.0027 mole) of 2,5-monoanhydro-1,6-dibenzoylsorbitol and 1.8 g. (0.0041 mole) of lead tetraacetate was allowed to stand at room temperature for twenty-four hours. The mixture was then treated with hydrogen sulfide and the precipitate of lead sulfide was removed. The filtrate was aerated to remove hydrogen sulfide and was treated with 1 *N* potassium hydroxide solution until the first signs of permanent turbidity persisted upon shaking. The solution, still acid to litmus, was put away in the refrigerator. Long, colorless needles were deposited overnight. The crystals were filtered off, dissolved in a little ethyl alcohol, and precipitated by the careful addition of water to incipient turbidity. Two more recrystallizations from alcohol and water yielded colorless needles melting at 124–126° (cor.).

In another experiment the filtrate, after removal of lead sulfide, was concentrated *in vacuo* at 40° to a thin sirup. Water (40 cc.) was added followed by the careful addition of alcohol. Upon vigorous shaking the sirup disappeared and a colorless, crystalline product was deposited. Recrystallization was effected from a mixture of benzene and petroleum ether. Colorless, feathery needles, melting at 124–126°, which did not depress the melting point of the previous compound were obtained. The yield was 0.68 g. or 61%. No derivatives could be obtained with methone reagent, phenylhydrazine or 2,4-dinitrophenylhydrazine. Two per cent. solutions of the compound in ethyl alcohol, glacial acetic acid and chloroform exhibited no rotation. A molecular weight determination by freezing-point depression of benzene gave a value of 386 (calcd. 406). This measurement is sufficiently accurate to show that cleavage of the original substance into fragments did not occur.

Anal.[10] Calcd. for $C_{20}H_{22}O_9$: C, 59.11; H, 5.41. Found: C, 59.0, 59.2; H, 5.24, 5.09.

The rotations observed at all wave lengths utilized were within the range of experimental error.

TABLE I

DISPERSION OF 3,3′-DIBENZOYL-2,2′-DI-(D-GLYCERALDEHYDE) ETHER DIHYDRATE

0.1222 g. dissolved in 4 cc. of 95% ethyl alcohol in a 2-decimeter tube (equivalent to 3.055 g. in 100 cc.)

Temperature = 31.5°

	Red	Yellow	Green	Green	Green	Blue
Metal	Cd	Na	Cu	Hg	Cu	Cd
Wave length	6438	5890, 96	5700	5461	5105	4800
Reading	0.01	0.00	0.00	0.00	0.02	0.01

Rates of Oxidation.—The acetic acid was prepared exactly as that described by Hockett, Dienes and Ramsden.[6] The standardized conditions described by them were used for the rate determinations.

Summary

The preparation of a compound previously designated by Brigl and Grüner as 2,5-monoanhydro-1,6-dibenzoylmannitol has been repeated by their method of direct anhydridization of 1,6-dibenzoylmannitol. By debenzoylation of this product we have obtained also a monoanhydrohexitol. The behavior of these compounds when oxidized by lead tetraacetate shows that the 2,5-ring is present, but the observation that the resulting 3,3′-dibenzoyl-2,2′-di-(D-glyceraldehyde) ether dihydrate is optically inactive in three solvents and toward six wave lengths of light proves that a Walden inversion occurred during anhydridization and that the anhydrohexitol must be 2,5-monoanhydrosorbitol rather than 2,5-anhydromannitol.

CAMBRIDGE, MASSACHUSETTS

RECEIVED JANUARY 29, 1946

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[10] Analysis by Mrs. C. K. Fitz, M. I. T.

[CONTRIBUTION FROM THE SUGAR RESEARCH FOUNDATION LABORATORY AND FROM THE DEPARTMENT OF CHEMISTRY MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Hexitol Anhydrides.[1] The Preparation and Proof of Structure of 1,5,3,6-Dianhydromannitol (Neomannide). The Structure of Isomannide[2]

BY R. C. HOCKETT[3] AND ELIZABETH L. SHEFFIELD

In the preceding paper of this series, it was shown that Fauconnier's crystalline "isomannide" is either 1,5,3,6- or 1,4,3,6-dianhydromannitol. Since styracitol has recently been shown to be 1,5-monoanhydromannitol[4] we considered this substance to be a suitable starting material for synthesis of the 1,5,3,6-dianhydride by a method analogous to that introduced by Fischer and Zach[5] for the preparation of methyl 3,6-anhydro-D-glucopyranoside.

The first two steps of this proposed synthesis had already been carried out successfully by Zervas and Papadimitriou,[4] who obtained a crystalline 6-tosyl-2,3,4-tribenzoylstyracitol. The presence of the tosyl group in the six position is indicated not only by the numerous analogous cases where selective tosylation has been carried out upon substances containing both primary and secondary hydroxyl groups,[6] but likewise by

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[1] The previous paper of this series, THIS JOURNAL, **68**, 935 (1946).

[2] The material in this paper is taken from a thesis submitted to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy by Elizabeth L. Sheffield in October, 1944. The paper was read before the Division of Sugar Chemistry and Technology at the New York meeting of the American Chemical Society in September, 1944.

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[4] Zervas and Papadimitriou, *Ber.*, **73**, 174 (1940); *cf.* Hockett and Conley, THIS JOURNAL, **66**, 464 (1944); *cf.* Richtmyer, Carr and Hudson, *ibid.*, **65**, 1477 (1943).

[5] Fischer and Zach, *Ber.*, **45**, 456, 2068 (1912); *cf.* Hockett, Nickerson and Reeder, THIS JOURNAL, **66**, 472 (1944).

[6] Compton, *ibid.*, **60**, 395 (1938); Hockett and Downing, *ibid.*, **64**, 2463 (1942); *cf.* Brigl and Grüner, *Ber.*, **65**, 641 (1932); also unpublished results.