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

Hexitol Anhydrides.[1] The Structure of Isosorbide, a Crystalline Dianhydrosorbitol[2]

BY R. C. HOCKETT,[3] H. G. FLETCHER, JR.,[3] ELIZABETH L. SHEFFIELD[3] AND R. MAX GOEPP, JR.[3]

A dianhydride of sorbitol was apparently first mentioned by Müller and Hoffmann in 1927.[4] By treating sorbitol with various dehydrating agents they obtained an amorphous material reported to boil at 157° at 3 mm. pressure. No crystalline product was obtained and no proof of homogeneity offered.

The first reported synthesis of a crystalline dianhydrosorbitol was made by Harden, who used the conditions described by Fauconnier[5] for the preparation of a crystalline dianhydromannitol which he had christened "isomannide." Harden's compound apparently was first described in the chemical literature by Bell, Carr and Krantz,[6] to whom samples were given (by R. M. G.) for physico-chemical studies. This dianhydrosorbitol was described as a crystalline substance melting at 60° and rotating[7] +46.5° (*c* 10.000, H_2O, 26°) (*cf.* experimental part).

Bell, Carr and Krantz found that, like Fauconnier's crystalline isomannide, Harden's dianhydrosorbitol does not enhance the conductivity of boric acid. Because of this similarity and the fact that the two substances were prepared by analogous methods, these authors suggested naming Harden's compound "isosorbide."[8] They also gave it a provisional structure as 1,4,3,6-dianhydrosorbitol without other evidence. In the present paper we present evidence which proves this structure.

We have found that crystalline isosorbide can be prepared very readily and in high yield by a minor modification of the Müller–Hoffmann method (experimental part).

Mathematically, there are forty-five possible structures for a sorbide. We reach the conclusion that the 1,4,3,6 structure is correct by the following reasoning and experimental observations:

1. The analysis of isosorbide fits the assumption that the molecule contains two ether rings, and has two free hydroxyl groups. The formation of a well-characterized dibenzoate melting at 101.8–102° (cor.) and rotating[7] + 25.6° (*c* 1.143, $CHCl_3$) supports this conclusion.

2. Isosorbide is not attacked by mild hydrolytic agents. The presence of ethylene oxide rings is therefore very unlikely. Twenty-four of the forty-five possible structures are thus eliminated. Of the remaining twenty-one, fourteen contain the very improbable four-membered rings.

Of the remaining seven, the 1,5,2,6; 1,4,2,6 and the 1,4,2,5 are sterically even less probable than those containing four-membered rings so that only four structures remain for consideration: the 1,4,3,6, the 1,5,3,6 and the somewhat more strained 1,6,2,5 and 2,5,3,6.

3. Isosorbide is not attacked by lead tetraacetate which shows that the two free hydroxyl groups are not adjacent. This observation eliminates the 1,6,2,5 structure, leaving only three possibilities: 1,4,3,6; 1,5,3,6; 2,5,3,6.

4. Isosorbide reacts only very slowly with triphenylchloromethane showing that the presence of a primary hydroxyl group is very unlikely[9] (Graph). This observation tends to eliminate the 2,5,3,6 structure leaving only two probable ones (1,4,3,6 and 1,5,3,6). The absence of primary hydroxyl groups is also indicated by the behavior of ditosylisosorbide (experimental part) when heated with sodium iodide under reflux in methyl isobutyl ketone solution.[10] Under these conditions no reaction occurs whereas methyl 6-tosyl-2,3,4-triacetyl-α-D-glucopyranoside reacts quantitatively to give the corresponding 6-iodo derivative.

Tipson and Cretcher[11] have shown that the *p*-toluenesulfonic acid esters of secondary alcohol groups in certain acyclic compounds will undergo the iodide replacement reaction when heated with sodium iodide in acetone solution for two hours at 100°. Levene and Mehltretter[12] also have replaced all the tosyloxy groups in tritosylglycerol

---

[1] Previous paper of this series, THIS JOURNAL, **68**, 922 (1946).

[2] Parts of the material in this paper are taken from theses 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 H. G. Fletcher, Jr., in September, 1942, and by Elizabeth L. Sheffield in October, 1944. A part of the material was contained in a paper read before the Division of Sugar Chemistry and Technology at the Detroit meeting of the American Chemical Society in April, 1943.

[3] Present addresses: R. C. Hockett, Sugar Research Foundation, 52 Wall St., New York, N. Y.; H. G. Fletcher, Jr., National Institute of Health, Bethesda, Md.; Elizabeth L. Sheffield, Massachusetts Institute of Technology, Cambridge, Mass.; R. Max Goepp, Jr., Atlas Powder Co., Wilmington, Del.

[4] Müller and Hoffmann, German Patent 488,602 (1927); U. S. Patent 1,757,468 (1930).

[5] Fauconnier, *Bull. soc. chim.*, (2) **41**, 119 (1884).

[6] Bell, Carr and Krantz, *J. Phys. Chem.*, **44**, 862 (1940).

[7] All rotations reported in this paper are specific rotations of the D line of sodium at 20°, unless otherwise specified. Concentrations are expressed in grams of substance in 100 cc. of solution.

[8] The term "mannide" was applied by Berthelot to an ill-characterized amorphous material that he obtained by the action of butyric acid on mannitol; Berthelot, *Ann. Chim.*, (3) **47**, 297 (1856). It is therefore suggested that the term "sorbide" be applied to the amorphous mixture prepared by Müller and Hoffmann, and that it be used as a generic name for the whole class of dianhydrosorbitols. The usage of Bell, Carr and Krantz for "isosorbide" is adopted here. A sample of crystalline isosorbide supplied by the Atlas Powder Company was used by Smith, Finkelstein and Smith, *J. Biol. Chem.*, **135**, 231 (1940), for renal excretion studies. In that paper it was called "sorbide."

[9] Hockett, Fletcher and Ames, THIS JOURNAL, **63**, 2516 (1941); *cf.* Hockett and Mowery, *ibid.*, **65**, 403 (1943).

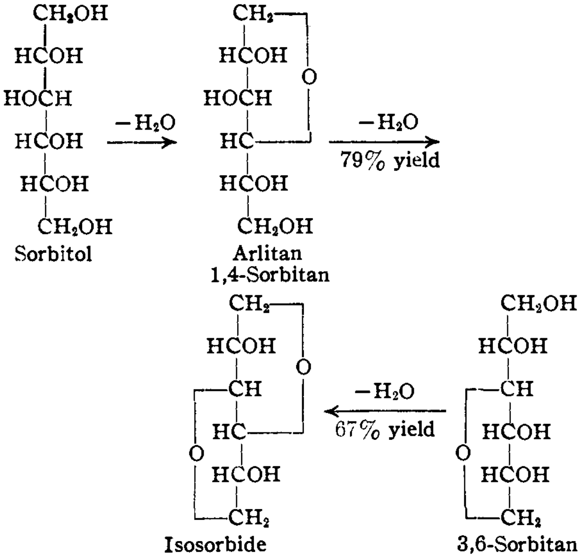
[10] Hockett, Zief and Goepp, *ibid.*,, **68**, 935 (1946).

[11] Tipson and Cretcher, *J. Org. Chem.*, **8**, 96 (1943).

[12] Levene and Mehltretter, *Enzymologia*, **4** II. 232 (1937).

by this method. Hence, the iodide replacement reaction cannot be considered to be confined to primary alcohol esters of *p*-toluenesulfonic acid. Ditosylisosorbide itself undergoes reaction slowly under more drastic conditions. Three to sixteen hours heating with sodium iodide in acetone at 120° converted this substance to a monoiodomonotosylisosorbide. The same product was formed by heating ditosyl sorbide with sodium iodide in acetonylacetone at 140° for three hours or in acetic anhydride at 140° for five hours. Complete replacement of both tosylate groups was not achieved.

5. Either 1,4-sorbitan[13] (arlitan) or 3,6-sorbitan,[14] when further treated by sulfuric acid under conditions similar to those employed for forming isosorbide directly from sorbitol, gives a 67–79% yield of isosorbide

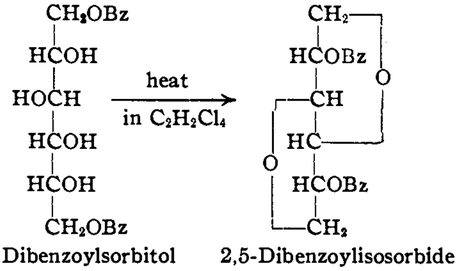


The simplest explanation of this observation is the hypothesis that isosorbide contains both the 1,4 and the 3,6 rings. Experiments with scale models show this to be a stable structure.

It might be argued that all rings are labile in the presence of sulfuric acid and tend to shift to the most stable sorbide structure regardless of the positions they occupied in the starting material. Against this view is the observation that polygalitol (1,5-sorbitan)[15] when similarly treated does not produce isosorbide.

In previous papers[13,14] we have shown that no Walden inversion occurs when 1,4-sorbitan or 3,6-sorbitan is formed. Hence it is concluded that isosorbide actually retains the sorbitol configuration. Subsequent work by Fletcher and Goepp has confirmed this view.[16]

In a previous paper[17] it has been shown conclusively that Müller's dibenzoylsorbitol is substituted in the 1 and 6 positions. When this substance is heated in boiling tetrachloroethane with a trace of *p*-toluenesulfonic acid,[18] it is converted into a mixture of two isomeric dibenzoylsorbides. One of these isomers is identical with the dibenzoate of isosorbide. If the ring structure of isosorbide is considered established, this observation indicates that the benzoyl groups have migrated during the catalyzed thermal anhydridization



The migration of benzoyl groups, under these conditions, in partially esterified polyalcohols invalidates the conclusions drawn by Brigl and Grüner[11] with respect to the structures of the mannitol anhydrides since these workers assumed *a priori* that the benzoyl groups remained in their original positions. This problem is the subject of the following paper.

Acknowledgments.—Our thanks are due to Dr. Morris Zief of the Massachusetts Institute of Technology for several experimental observations included in this paper. We also thank Dr. C. S. Hudson and Dr. Nelson K. Richtmyer of the National Institute of Health for a sample of polygalitol.

Experimental

The recommended procedure is as follows:

1,4,3,6-Dianhydrosorbitol (Isosorbide).—A sample of 15 g. of pure sorbitol (0.078 mole) is mixed with 0.25 g. of concentrated sulfuric acid in a 125-ml. distilling flask, and heated for one hour at an oil-bath temperature of 140–150° under a vacuum (aspirator). The black mixture is cooled, diluted with 200 cc. of water, treated with an excess of solid barium carbonate and filtered. After evaporation of water at reduced pressure, the residue is distilled at a pressure of 2 mm. and an oil-bath temperature between 160 and 175°. The pale yellow viscous distillate often solidifies in the receiver. The yield of crude product melting at 55.9–57.90° (cor.) is 9.85 or 82% g. of the theoretical.

When recrystallized twice from ethyl acetate, the compound is colorless, melts at 61.9–64.0° and rotates[7] +44.8° (*c* 2.22, 24.4°) +45.2° (*c* 3.5156, 20.5°) in water; +32.8° (*c* 2.47, 26.2°) in chloroform and +64.9° (*c* 2.32, 28.2°) in pyridine. The substance has a sharp, almost bitter, taste, is markedly hygroscopic and dissolves readily in water, alcohol, chloroform, dioxane and acetic acid. It is sparingly soluble in ethyl acetate, benzene, ether and acetone.

---

[13] Soltzberg, Goepp and Freudenberg, THIS JOURNAL, **68**, 919 (1945); Hockett, Conley, Yusem and Mason, *ibid.*, **68**, 922 (1945).

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

[15] Richtmyer, Carr and Hudson, THIS JOURNAL, **65**, 1477 (1943).

[16] Fletcher and Goepp, *ibid.*, **67**, 1042 (1945).

[17] Hockett and Fletcher, *ibid.*, **66**, 469 (1944); Müller, *Ber.*, **65**, 1058 (1932).

[18] Brigl and Grüner, *Ber.*, **66B**, 1945 (1934); *ibid.*, **67B**, 1582 (1935), applied this procedure to 1,6-dibenzoylmannitol to produce benzoylated anhydromannitols.

Isosorbide may be obtained in somewhat smaller yields but with fewer operations, by direct distillation from the sulfuric acid mixture after the removal of water is complete. It may also be prepared directly from commercial sorbitol sirups containing 15–30% water, by adding sulfuric acid, evaporating the water under reduced pressure, and heating the residue long enough to effect dehydration. Yields are only slightly lower in larger scale preparations.

2,5-Dibenzoyl-1,4,3,6-dianhydrosorbitol (from Isosorbide).—A sample of 12.09 g. of isosorbide (0.083 mole) was dissolved in 150 cc. of pyridine and the solution cooled in ice. A quantity of 20.7 cc. of benzoyl chloride (0.166 mole) was added slowly with constant stirring. When heat evolution had diminished, the mixture was heated on a steam-bath for fifteen minutes and then slowly poured into 600 cc. of cold water with stirring. The milky suspension first formed was left in a refrigerator until it resolved into a crystalline mass. Crystallized once from ethanol, large colorless needles weighing 22.0 g. were obtained; yield 75%. Again recrystallized, the needles melted 101.5–102.2° (cor.) and rotated[7] +23.1° (*c* 1.145, 25°, $CHCl_3$).

2,5-Dibenzoyl-1,4,3,6-dianhydrosorbitol (from 1,6-Dibenzoylsorbitol).—Twelve grams of 1,6-dibenzoylsorbitol (0.0285 mole) prepared as described elsewhere[15] was dissolved in 200 cc. (320 g.) of freshly distilled *sym*-acetylene tetrachloride together with 0.357 g. of pure *p*-toluenesulfonic acid monohydrate. The mixture was boiled gently under reflux for three hours, during which time water globules collected on the surface and a slight yellowing occurred. After cooling, the solvent was removed *in vacuo* at 50–55° and the residual sirup kept at this temperature and at 4 mm. pressure until ebullition ceased. The sirup was dissolved in about two volumes of alcohol and water was added to the point of turbidity. Crystallization began at once. After overnight standing at room temperature, the large, radially arranged prism clusters were filtered, washed and dried; yield 3.7 g. or 34% of the theoretical. The substance melted at 101.1–102.1° (cor.). Further crystallizations from ethanol raised the melting point to 101.8–102.0° (cor.) and a rotation[7] of +25.6° (*c* 1.143, 20.3°, $CHCl_3$). The substance is soluble in benzene and alcohol and insoluble in water, ether and petroleum ether. It is stable toward lead tetraacetate. The two samples of dibenzoylsorbide gave an undepressed melting point when mixed.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.4, 67.5; H, 5.51, 5.59.

An Isomeric Dibenzoylsorbide.—The mother liquors from the preparation just described were evaporated to a sirup which was taken up in about 0.75 cc. of alcohol. Water was added dropwise to turbidity and during thirty-six hours at room temperature, a crop of fine, silky needles separated. Repetition of this procedure gave a total of 0.95 g. of impure material. Recrystallized twice from 15 cc. of hot alcohol the needles showed a constant melting point of 125.8–126.3° (cor.) and rotated[7] +1.35° (*c* 1.109, 24.8°, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.3, 67.3; H, 5.63, 5.61.

Reaction of Isosorbide with Triphenylchloromethane.—Isosorbide (1.132 g. or 0.00768 mole) was dissolved in 50 cc. of pyridine and mixed, at a noted time, with a solution of 8.6168 g. of freshly prepared triphenylchloromethane in 50 cc. of pyridine. The optical changes occurring in the mixture were read in a two-decimeter tube at a temperature of 23–25° (The temperature was not under close control). For comparison, an equimolar sample of 1,4-anhydromannitol (as an analogous compound known to contain a primary hydrogen group) was similarly treated. The relative rates of reaction are shown graphically in Fig. 1.

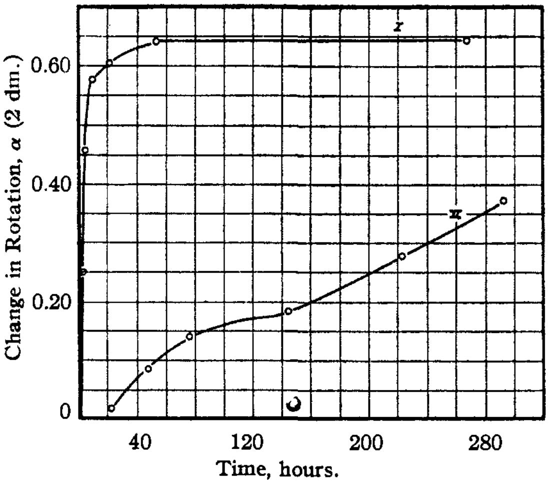


Fig. 1.—Reactions of anhydropolyols with triphenylchloromethane in pyridine solution: I, 1,4-anhydromannitol; II, isosorbide.

2,5-Ditrityl-1,4,3,6-dianhydrosorbitol (Ditritylisosorbide).—The solution used for the rate-of-reaction measurement was left at room temperature for about two and a half years. Water was then added dropwise to turbidity. Triphenylcarbinol separated and was removed by filtration. Further addition of water gave a precipitate which was crystallized from aqueous alcohol. After two recrystallizations, a colorless, microcrystalline product was obtained which softened at 85° and melted at 92–94° (uncor.). It rotated[7] +44.3° (*c* 0.38, 27°, $CHCl_3$).

Anal. Calcd. for $C_{44}H_{38}O_4$: C, 83.81; H, 6.03. Found: C, 83.8, 83.9; H, 6.17, 6.20.

2,5-Ditosyl-1,4,3,6-dianhydrosorbitol (Ditosylisosorbide).—Isosorbide (9.5 g., 0.065 mole) was dissolved in 75 cc. of pyridine. To this solution was added a solution of 26 g. (0.136 mole) of *p*-toluenesulfonyl chloride in 75 cc. of pyridine. The mixture, which evolved some heat, was kept for four hours and then heated on the steam-bath for one hour. After cooling, the mixture was poured on 500 g. of crushed ice. A precipitate was formed which became granular. It was filtered, washed many times with water (2–3 liters) and dried in a vacuum at 30° for six hours. Recrystallized from 200 cc. of methanol, 21 g. of crystalline ditosylsorbide was obtained; yield, 71% of the theoretical. The substance when pure melted from 98.3–99.6° (cor.) and rotated[7] +57.4° (*c* 1.068, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{22}S_2O_8$: S, 14.1. Found: S, 14.0, 13.8.

An identical tosyl ester of isosorbide has also been prepared from isosorbide obtained by debenzoylation of the dibenzoylisosorbide prepared by heating 1,6-dibenzoylsorbitol in acetylene tetrachloride.

X-Iodo-X′-tosyl-1,4,3,6-dianhydrosorbitol (X-Iodo-X′-tosyl-isosorbide).—This compound was formed by heating ditosylisosorbide with sodium iodide in acetone solution at 120° (sealed tube) for three to sixteen hours, in acetonylacetone at 140° for three hours, or in acetic anhydride at 140° for five hours.

Ditosylisosorbide (3 g., 0.0066 mole), sodium iodide (3 g., 0.020 mole) and acetic anhydride (30 cc.) were mixed and boiled under reflux. The mixture was then poured into 300 cc. of water. The precipitated oil was washed with three 100-cc. portions of fresh water and then dissolved in 250 cc. of ether. The ether solution was washed with ten 45-cc. portions of 1% sodium bicarbonate solution and two 45-cc. portions of 2% sodium thiosulfate solution and then was dried over anhydrous sodium sulfate. The residue left on evaporating the ether became crystalline when rubbed with 5 cc. of methanol. Three recrystallizations from 3–5 cc. portions of methanol gave white crystals melting at 90.8–91.3° (cor.). The melting point did not change after further crystallizations from methyl, ethyl or amyl alcohol. The yield after three crystallizations was 0.80 g. or 22% of the theoretical. The substance rotated[7] +52.73 (*c* 2.635, $CHCl_3$).

Anal. Calcd. for $C_{13}H_{15}O_6SI$: C, 38.1; H, 3.7; S, 7.8;

I, 30.8. Found: C, 37.8, 37.9; H, 3.6, 3.8; S, 7.71, 7.75; I, 31.1, 31.3.

While an almost complete replacement by iodide could be achieved by longer heating, no well-defined product was isolated.

Anhydridization of 1,4-Sorbitan (Arlitan).—Ten grams of 1,4-sorbitan was mixed with 0.5 g. of concentrated sulfuric acid and heated at 140° in an oil-bath for one hour. The liquid was then heated to 165–170° and evacuated to about 5 mm. pressure whereupon a nearly colorless liquid distilled. On seeding the distillate with isosorbide, immediate crystallization occurred. The crude product weighed 7.1 g. (79%); melted at 58–59° (cor.). After one recrystallization, it melted from 60–61° (cor.).

The preparation was successfully repeated with a sample of 0.5 g. of 1,4-sorbitan and one drop of sulfuric acid.

Anhydridization of 3,6-Sorbitan.—A sample of 0.83 g. of 3,6-anhydrosorbitol[14] was treated with two drops of concentrated sulfuric acid and heated in an oil-bath at 120–140° for three quarters of an hour. A light yellow liquid was formed. On reducing the pressure to 3 mm. and gradually raising the bath temperature to 160° a colorless liquid distilled. On being seeded with isosorbide, the distillate crystallized to a solid mass. The weight was 0.49 g. (67%) and the crude product melted from 59–60° (cor.).

Non-formation of Isosorbide by Anhydridization of 1,5-Sorbitan (Polygalitol).—A sample of 0.1469 g. of polygalitol was treated with one drop of concentrated sulfuric acid and heated in a bath at 145° for an hour in a small molecular still constructed from two test-tubes. The still was then evacuated to 2-mm. pressure and slowly warmed. A minute quantity of colorless sirup collected on the condenser. Dissolved in pyridine and treated with an excess (0.376 g.) of benzoyl chloride, this material gave a water-insoluble sirup which did not crystallize.

Pure sorbitol treated by the same micro technique readily yielded dibenzoylisosorbide identical with that described.

Summary

The crystalline dianhydrosorbitol discovered by Harden has been prepared by improved methods and its physical constants measured. The substance has been shown to contain the 1,4 and 3,6 anhydro rings and free secondary hydroxyl groups. The dibenzoate and di-*p*-toluenesulfonate have been described as well as a product formed from the latter by replacement of one tosylate group by iodide. It has been shown that isosorbide is formed by further anhydridization of either 1,4-sorbitan or 3,6-sorbitan but not from 1,5-sorbitan. The observation that 1,6-dibenzoylsorbitol is dehydrated directly to dibenzoylisosorbide in boiling acetylene tetrachloride indicates that benzoyl groups shift position under these conditions and invalidates the conclusions of Brigl concerning the structure of several mannitol anhydrides.

CAMBRIDGE, MASS.
WILMINGTON, DEL. RECEIVED JANUARY 29, 1946

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

Hexitol Anhydrides.[1] The Structures of the Anhydromannitols of Brigl and Grüner.[2] The Structure of Isomannide

BY R. C. HOCKETT,[3] H. G. FLETCHER, JR.,[3] ELIZABETH L. SHEFFIELD,[3] R. MAX GOEPP, JR.,[3] AND SOL SOLTZBERG[3]

Brigl and Grüner[4] have reported that when 1,6-dibenzoylmannitol is heated in boiling acetylene tetrachloride with a little *p*-toluenesulfonic acid as a catalyst, three transformation products are formed. To these compounds they assigned the following structures: A = 2,4-monoanhydromannitol 1,6-dibenzoate; B = 2,4,3,5-dianhydromannitol 1,6-dibenzoate; C = 2,5-monoanhydromannitol 1,6-dibenzoate.

In making these structure assignments, Brigl and Grüner assumed first of all that the benzoyl groups remain in their original positions during reaction. Since, however, we have recently shown that the benzoyl groups of the analogous 1,6-dibenzoylsorbitol shift their positions under the same conditions[1] it has seemed necessary to review the conclusions of these German workers with respect to the mannitol anhydrides.

A repetition of the experimental procedure described by these authors has yielded us three products whose physical constants agree with those reported. We have concluded, however, that the structures of the first two are actually these: A = 1,4-monoanhydromannitol 2,6 (or 3,6) dibenzoate; B = 1,4,3,6-dianhydromannitol 2,5-dibenzoate.

The third product (C) is discussed more fully in a later paper of this series.

The experimental observations and the chain of reasoning which led us to these structure assignments will be given in some detail since they represent general procedures capable of wide application.

---

[1] The previous paper of this series, THIS JOURNAL, **68**, 927 (1946).

[2] Parts of the material in this paper are taken from theses 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 H. G. Fletcher, Jr., in September, 1942, and by Elizabeth L. Sheffield in October, 1944. A part of the material was contained in a paper read before the Division of Sugar Chemistry and Technology at the Detroit meeting of the American Chemical Society in April, 1943.

[3] Present addresses: R. C. Hockett, Sugar Research Foundation, 52 Wall Street, New York, N. Y.; H. G. Fletcher, Jr., National Institute of Health, Bethesda, Maryland; Elizabeth L. Sheffield, Massachusetts Institute of Technology, Cambridge, Mass.; R. Max Goepp, Jr., and Sol Soltzberg, Atlas Powder Co., Wilmington, Del.

[4] (a) Brigl and Grüner, *Ber.*, **66B**, 1945–1949 (1933); (b) **67B**, 1582–1589 (1934); *cf.* Hockett and Fletcher, THIS JOURNAL, **66**, 469 (1944).