1,2,5,6-Tetratosyl-D-mannitol (V).—One gram of 2,5-ditosyl-D-mannitol, dissolved in 10 ml. of pyridine, was treated with 1.71 g. of tosyl chloride and the resulting solution left at room temperature for 4.5 hours. The solution was then cooled and diluted with a mixture of ice and methylene dichloride. After washing the organic layer successively with water, 3 *N* sulfuric acid and saturated aqueous sodium bicarbonate it was dried with sodium sulfate and concentrated *in vacuo*. From its solution in 18 ml. of warm absolute ethanol the residue afforded spherical masses of fine needles (1.92 g., 118%) melting at 140–142° and showing in chloroform −15.4° (*c* 1.0). After three recrystallizations from alcohol the product (0.8 g., 49%) melted at 143–144° and rotated −16.7° in chloroform (*c* 1.17). Further recrystallizations from alcohol and from dioxane–pentane failed to change these constants. On a Kofler hot stage the substance melted at 144–145°; when mixed with a sample of authentic 1,2,5,6-tetratosyl-D-mannitol (m.p. 143–145°)[6] a melting point of 143–145° was obtained.

Anal. Calcd. for $C_{34}H_{38}O_{14}S_4$: C, 51.11; H, 4.79; S, 16.05. Found: C, 51.30; H, 4.99; S, 16.13.

A sample of the compound was treated with lead tetraacetate in a fashion similar to that described above for 2,5-ditosyl-D-mannitol; one mole of the substance was found to consume 1.03 moles of oxidant.

Acknowledgment.—The authors wish to thank Professor P. Karrer for the gift of a sample of authentic 1,2,5,6-tetratosyl-D-mannitol. They also wish to express their indebtedness to Dr. William C. Alford, Mrs. Evelyn G. Peake, Miss Paula M. Parisius and Miss Mary Jean Stockton for analytical determinations incident to this research.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY]

New Methylene Derivatives of D-Mannitol and 1,4-Anhydro-D-mannitol

BY HEWITT G. FLETCHER, JR., AND HARRY W. DIEHL

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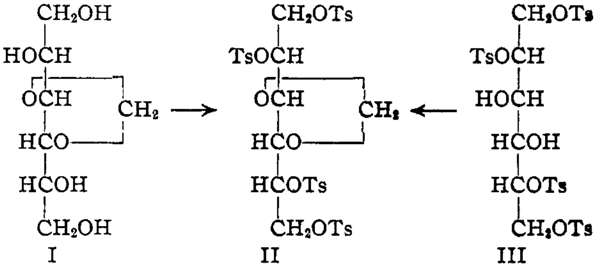
The methylenation of D-mannitol with formaldehyde and hydrochloric acid gives (in addition to 1,3:2,5:4,6-trimethylene-D-mannitol and 1,3:4,6-dimethylene-D-mannitol) 3,4-methylene-D-mannitol, 1,3-methylene-D-mannitol and 1,4-anhydro-2,3-methylene-D-mannitol. The product reported in the literature as 1,6-dibenzoylmethylene-D-mannitol is now shown to be a derivative of 2,4-methylene-D-mannitol.

In the course of the methylenation of D-mannitol with formaldehyde and hydrochloric acid there were obtained, in addition to the long-known 1,3:2,5:4,6-trimethylene-D-mannitol[1,2,3] and the 1,3:4,6-dimethylene-D-mannitol whose structure is the subject of the preceding paper,[4] low yields of a monomethylenehexitol of m.p. 124–125°[5] and $[\alpha]^{20}D$ +41.6° (H_2O),[5] a second monomethylenehexitol of m.p. 127–128° and $[\alpha]^{20}D$ −38.7° and a substance of m.p. 120–121° and $[\alpha]^{20}D$ −52.1° (H_2O) which gave analytical values corresponding to an anhydromethylenehexitol. Each of these will now be discussed in turn.

The Dextrorotatory Monomethylene-hexitol of M.p. 124–125°.—Molecular weight determinations showed this substance to be monomeric while reaction with formaldehyde in the presence of hydrochloric acid converted it to the known 1,3:2,5:4,6-trimethylene-D-mannitol; the compound is therefore a monomethylene-D-mannitol and its physical constants show it to differ from the 2,5-methylene-D-mannitol of Ness, Hann and Hudson.[2] Upon treatment with sodium metaperiodate the substance consumed two molar equivalents of oxidant and liberated two moles of formaldehyde but no formic acid; of all the various possible isomers only 3,4-methylene-D-mannitol (I) would be expected to behave in this fashion. Reaction with trityl chloride readily gave a ditrityl ether. Unequivocal proof of the structure of the cyclic acetal as 3,4-methylene-D-mannitol (I) was obtained through its crystalline tetratosyl ester (II) which proved to be identical with the product obtained on methylenation of 1,2,5,6-tetratosyl-D-mannitol (III).[4,6] Evidence that tosyl groups do not migrate during methylenation was adduced in the preceding paper[4] where the conversion of 2,5-ditosyl-D-mannitol to 1,3:4,6-dimethylene-2,5-ditosyl-D-mannitol was described. It is evident, therefore, that the new dextrorotatory monomethylene-D-mannitol is analogous to the ketals 3,4-isopropylidene-D-mannitol[7] and 3,4-cyclohexylidene-D-mannitol.[8]


I II III

While a 3,4-methylene-D-mannitol is not to be expected in the light of the generalizations of Hann and Hudson[3] and of Ness, Hann and Hudson[9] it should be noted that, under all experimental conditions investigated, this product was obtained in relatively small yield.

The Levorotatory Monomethylenehexitol of M.p. 127–128°.—As was the case with the preceding isomer, this monomethylenehexitol had the ex-

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(1) M. Schulz and B. Tollens, *Ann.*, **289**, 21 (1896).

(2) A. T. Ness, R. M. Hann and C. S. Hudson, THIS JOURNAL, **65**, 2215 (1943).

(3) R. M. Hann and C. S. Hudson, *ibid.*, **66**, 1909 (1944).

(4) H. G. Fletcher, Jr., and H. W. Diehl, *ibid.*, **74**, 3797 (1952).

(5) Melting points cited are corrected. Rotations are specific rotations for the D-line of sodium at 20°; concentration is expressed in grams of substance per 100 ml. of solution.

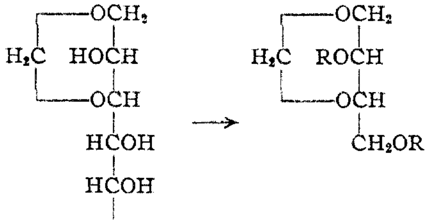
(6) P. Karrer and P. C. Davis, *Helv. Chim. Acta*, **31**, 1611 (1948).

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

(8) E. J. Bourne, W. M. Corbett and D. Brilinne, *J. Chem. Soc.*, 786 (1950).

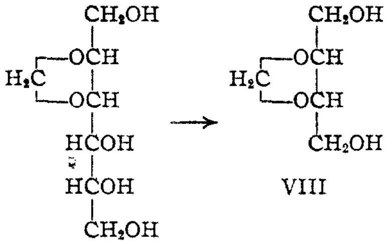
(9) A. T. Ness, R. M. Hann and C. S. Hudson, *ibid.*, **70**, 765 (1948).

pected molecular weight and could readily be converted to 1,3:2,5:4,6-trimethylene-D-mannitol; also like the preceding isomer it was not identical with the known 2,5-methylene-D-mannitol.[2] Oxidation with sodium metaperiodate gave one molar equivalent each of formic acid and formaldehyde while two moles of oxidant were consumed. If only the seven sterically reasonable isomeric monomethylene-D-mannitols (*i.e.*, those containing C_3O_2, C_4O_2 and C_5O_2 rings) be considered, it is evident that the levorotatory substance is either 1,3-methylene-D-mannitol (IV) or 2,3-methylene-D-mannitol (VII). Upon oxidation and subsequent reduction the first of these structures should yield 1,3-methylene-L-erythritol (V, synonym: 2,4-methylene-D-erythritol), an asymmetric structure, while the second structure would lead to 2,3-methylene-erythritol (VIII), a *meso* structure. When the levorotatory methylene-D-mannitol was oxidized with sodium metaperiodate and the strongly reducing product hydrogenated, there was obtained a levorotatory, amorphous product. Although efforts to obtain the latter in crystalline form failed, it gave, when treated with phenyl isocyanate an optically active crystalline derivative which possessed the correct analysis for 1,3-methylene-2,4-bis-(phenylcarbamyl)-L-erythritol (VI). The levorotatory methylenehexitol is, therefore, 1,3-methylene-D-mannitol (IV); it was further characterized through its tetraacetate, tetrabenzoate and tetratosylate. 1,3-Methylene-D-mannitol (IV) represents the structure which would be predicted by the use of the generalizations mentioned above[8,9] and is analogous to the 1,3-ethylidene-D-mannitol which Bourne, Bruce and Wiggins[10] obtained through the hydrolysis of 1,3:2,5:4,6-triethylidene-D-mannitol.



IV

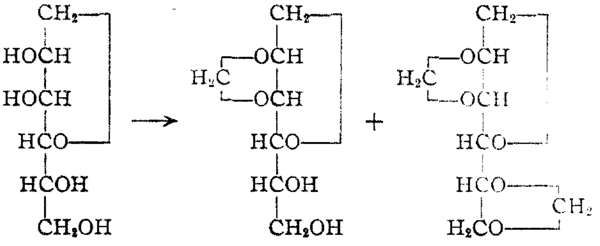
V, R = H
VI, R = OCNHC$_6$H$_5$



VII

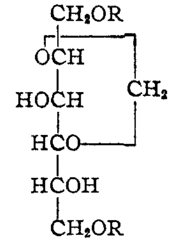
VIII

The Anhydromethylenehexitol of M.p. 120–121°.—The third product obtained through the action of a hot mixture of formalin and hydrochloric acid on D-mannitol was subjected to the action of sodium metaperiodate. On a molar basis it consumed one mole of oxidant and liberated one mole of formaldehyde. In view of these facts and of the known conversion of D-mannitol to 1,4(= 3,6)-anhydro-D-mannitol by boiling hydrochloric acid,[11,12] it appeared highly probable that the substance was 1,4-anhydro-2,3-methylene-D-mannitol (X). Such, indeed, proved to be the case; methylenation of 1,4-anhydro-D-mannitol (IX) yielded an anhydromethylene-D-mannitol identical with that obtained directly from D-mannitol. In addition, there was also obtained from 1,4-anhydro-D-mannitol a dimethylene derivative, 1,4-anhydro-2,3:5,6-dimethylene-D-mannitol (XI). Isopropylidene derivatives of 1,4-anhydro-D-mannitol analogous to X and XI have been reported by Foster and Overend.[12] 1,4-Anhydro-2,3-methylene-D-mannitol (X) was characterized by a crystalline diacetate.

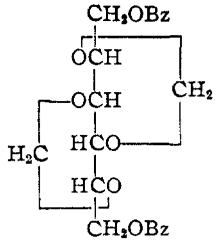


IX X XI

The 1,6-Dibenzoyl-methylene-D-mannitol of Haworth and Wiggins.—In 1944 Haworth and Wiggins[13] reported that the methylenation of 1,6-dibenzoyl-D-mannitol yields a 1,6-dibenzoylmethylene-D-mannitol and a 1,6-dibenzoyl-2,3,4,5-dimethylene-D-mannitol.[14] While the monomethylene derivative was not further investigated, other researches[15–17] adduced a somewhat involved, indirect proof that the dimethylene derivative is 1,6-dibenzoyl-2,4:3,5-dimethylene-D-mannitol (XIV).



XII, R = benzoyl
XIII, R = H



XIV

If this assignment of structure is correct and if the monomethylene derivative is the precursor of the dimethylene it would be expected that the former is 1,6-dibenzoyl-2,4-methylene-D-mannitol (XII). This has now been shown to be the case. Debenzoylation of XII gave a crystalline monomethylene-D-mannitol (XIII) of m.p. 108–109° and $[\alpha]^{20}\text{D}$ +25.9° (H_2O) which was not identical with either 2,5-methylene-D-mannitol[2] or the 3,4-methylene-D-mannitol described above. That it was 2,4- rather than 2,3-methylene-D-mannitol was

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(10) E. J. Bourne, G. T. Bruce and L. F. Wiggins, *J. Chem. Soc.*, 2708 (1951).

(11) R. Montgomery and L. F. Wiggins, *ibid.*, 2204 (1948).

(12) A. B. Foster and W. G. Overend, *ibid.*, 680 (1951).

(13) W. N. Haworth and L. F. Wiggins, *ibid.*, 58 (1944).

(14) This substance had previously been prepared by W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, 65, 67 (1943).

(15) W. N. Haworth, W. G. M. Jones, M. Stacey and L. F. Wiggins, *J. Chem. Soc.*, 61 (1944).

(16) W. N. Haworth and W. G. M. Jones, *ibid.*, 65 (1944).

(17) W. G. M. Jones and L. F. Wiggins, *ibid.*, 364 (1944).

shown by the fact that it consumed one, rather than two, molar equivalents of periodate and, of course, furnished no formic acid. The identification of the substance of Haworth and Wiggins as 1,6-dibenzoyl-2,4-methylene-D-mannitol (XII) lends support, therefore, to the assignment of structure XIV to 1,6-dibenzoyldimethylene-D-mannitol.[18]

It is to be noted that both the 3,4-methylene-D-mannitol (I) mentioned earlier and the 2,4-methylene-D-mannitol (XII) are readily converted to 1,3:2,5:4,6-trimethylene-D-mannitol when treated with formaldehyde and hydrochloric acid despite the fact that neither of these methylene-D-mannitols possesses a ring structure which is carried over into the trimethylene derivative. This fact strongly emphasizes the lability of methylene rings under acid conditions and shows that such reactions cannot be used as a basis for structure assignments.[19] However, it may be significant that under comparable conditions 1,3-methylene-D-mannitol (IV) began to give a precipitate of 1,3:-2,5:4,6-trimethylene-D-mannitol in an appreciably shorter time than did either 3,4-methylene-D-mannitol (I) or 2,4-methylene-D-mannitol (XIII).

Experimental

3,4-Methylene-D-mannitol (I).—Two hundred grams of D-mannitol was treated with formaldehyde and hydrochloric acid precisely as described by Haskins, Hann and Hudson[20] for the preparation of 1,3:4,6-dimethylene-D-mannitol. After removal of the di- and trimethylene-D-mannitols as was done by these authors, the residual mother liquors were concentrated *in vacuo* to a stiff sirup and dissolved in 3:1 absolute alcohol–ether. The 13.3 g. of crystalline material which was deposited proved to be largely unchanged D-mannitol. From the mother liquor there was subsequently obtained 16.0 g. of a crude, crystalline product. From its solution in 100 ml. of absolute alcohol this latter afforded 3.2 g. (1.5%) of crude 3,4-methylene-D-mannitol melting at 122–124°. One further recrystallization from 8 parts of absolute alcohol gave elongated prisms which melted at 124–125° and showed +41.6° in water (*c* 0.77).

Anal. Calcd. for $C_7H_{14}O_6$: mol. wt., 194; C, 43.29; H, 7.27. Found: mol. wt., 189[21]; C, 43.29; H, 7.41.

A sample (213.6 mg.) of 3,4-methylene-D-mannitol in aqueous solution was treated with 5.0 ml. of 0.5 *M* sodium metaperiodate and the solution diluted to 25 ml. with water. After 24 hours at room temperature analysis showed the consumption of 1.99 molar equivalents of oxidant with no change in acidity.

A quantitative estimation of the amount of formaldehyde liberated on periodate oxidation of 27.4 mg. of the substance was made using the method of Jeanloz.[22] The yield of formaldehyde dimethone corresponded to 2.16 moles of formaldehyde.

1,3:2,5:4,6-Trimethylene-D-mannitol from 3,4-Methylene-D-mannitol (I).—3,4-Methylene-D-mannitol (207.8 mg.) was dissolved in a mixture of 37% formalin (0.4 ml.) and concentrated hydrochloric acid (0.4 ml.) and held at 50°. Needle-shaped crystals were observed to be forming after 75 minutes; when a total of three days had elapsed, the mass of crystalline material was cooled, filtered, washed with water and dried at 100°. The product (209.8 mg., 90%) melted at 230–232°; when mixed with authentic 1,3:2,5:-4,6-trimethylene-D-mannitol it melted at 232–234°. In chloroform a rotation of −103.9° (*c* 0.77) was observed; Ness, Hann and Hudson[2] reported a value of −104.2°.

3,4-Methylene-1,6-ditrityl-D-mannitol.—A mixture of 0.7548 g. of 3,4-methylene-D-mannitol and 2.1678 g. of pure trityl chloride was shaken with 7 ml. of anhydrous pyridine until dissolved. After standing at 100° for one hour the reaction mixture was cooled and diluted with 3 ml. of water. The precipitated sirup was washed with three successive 3-ml. portions of water and then dissolved in *ca.* 40 ml. of warm methanol. Two grams (*ca.* 73%) of minute clusters of needles melting at 78–82° was obtained. Recrystallized from aqueous methanol they melted indefinitely at about 80° and proved to be a hydrate which rotated +8.8° in methanol (*c* 1.02).

Anal. Calcd. for $C_{45}H_{42}O_6 \cdot 1.5H_2O$: C, 76.57; H, 6.43; H_2O, 3.83. Found: C, 76.50; H, 6.79; H_2O, 3.99.

Attempts to crystallize the ditrityl ether in anhydrous form failed. On standing for a few hours in the air, however, the hydrous material effloresced and then melted at 116–120°.

Anal. Calcd. for $C_{45}H_{42}O_6$: C, 79.62; H, 6.24. Found: C, 79.46; H, 5.93.

3,4-Methylene-1,2,5,6-tetratosyl-D-mannitol (II). (a) **From 3,4-Methylene-D-mannitol (I).**—Two grams of 3,4-methylene-D-mannitol was dissolved in 15 ml. of pyridine and the solution treated with 9.0 g. of tosyl chloride. After two days at room temperature the excess tosyl chloride was decomposed with ice, the precipitated sirup dissolved in chloroform and washed successively with cold water, 3 *N* sulfuric acid and aqueous sodium bicarbonate. After drying with sodium sulfate the solution was concentrated *in vacuo* to a stiff sirup. From its solution in 200 ml. of methanol this material deposited 4.33 g. (52%) of thin hexagonal plates melting at 95°. After three recrystallizations from 95% ethanol the product melted at 99–103° and rotated +9.9° in chloroform (*c* 1.11).

Anal. Calcd. for $C_{35}H_{38}O_{14}S_4$: C, 51.84; H, 4.72; S, 15.81. Found: C, 51.90; H, 4.69; S, 15.57.

(b) **From 1,2,5,6-Tetratosyl-D-mannitol (III).**—A solution of 6.0 g. of 1,2,5,6-tetratosyl-D-mannitol and 6.0 g. of *s*-trioxane in 30 ml. of glacial acetic acid was cooled in an ice-bath while 4 g. of hydrogen chloride was passed in. After 5 days at 50° the reaction mixture was cooled, diluted with chloroform and washed successively with water and aqueous sodium bicarbonate. Moisture was removed with sodium sulfate, the solution concentrated *in vacuo* and the sirupy residue dissolved in 190 ml. of warm 95% ethanol. The clear prisms (1.41 g., 23%) which deposited melted at 97–101°; subsequent fractions proved to be mixtures of product with starting material. Recrystallization of the first crop, first from methanol and then from ethanol, gave 1.02 g. of material melting at 99–102°; mixed with 3,4-methylene-1,2,5,6-tetratosyl-D-mannitol prepared in (a) above it melted at 99–103°.

1,3-Methylene-D-mannitol (IV).—Two hundred grams of D-mannitol was dissolved in a mixture of 100 ml. of 37% formalin and 200 ml. of concentrated hydrochloric acid and the solution boiled under reflux for two hours. The reaction mixture was concentrated *in vacuo* until it became solid through the formation of crystalline material. Absolute alcohol (225 ml.) was added and the mass boiled under reflux for ten minutes. Unchanged D-mannitol (36.8 g.) was then removed by filtration; on standing at room temperature for two hours the mother liquor deposited 58 g. more D-mannitol. Concentration of the mother liquor afforded a third fraction (31.5 g., m.p. 135–150°) which proved to be a mixture of D-mannitol and 1,3:4,6-dimethylene-D-mannitol. The fourth fraction (7.4 g., m.p. 115–130°), deposited on standing, was fractionated from six parts of dioxane to give 2.7 g. of crude 3,4-methylene-D-mannitol (m.p. 119–121°) and 3.3 g. of crude 1,3-methylene-D-mannitol, m.p. 105–110°. The main mother liquor, concentrated to a heavy sirup and dissolved in 75 ml. of dioxane gave a fifth fraction (34.0 g., m.p. 75–90°). This was boiled with three parts of absolute alcohol and the in-

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[18] This evidence equally supports the 2,4:3,5-structure for a variety of 2,3,4,5-dimethylene derivatives in the D-glucitol and L-iditol series inasmuch as these substances have been correlated with 2,4:3,5-dimethylene-D-mannitol. See refs. 14, 15 and 16.

[19] Contrariwise, it is not safe to assume that the ring structures of mono- and dicyclic acetals formed by the hydrolysis of tricyclic acetals represent ring structures in the latter although such, however, is doubtless often the case. In the preceding paper (ref. 4), for instance, acid hydrolysis of 1,3:2,5:4,6-trimethylene-D-mannitol was shown to give 1,3:4,6-dimethylene-D-mannitol.

[20] W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **65**, 67 (1943).

[21] This value was determined by the isothermal distillation method. See E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941); R. Signer, *Ann.*, **478**, 246 (1930).

[22] R. Jeanloz, *Helv. Chim. Acta*, **27**, 1509 (1944).

soluble D-mannitol removed to give a filtrate which afforded, first, 3.5 g. of crude 1,3-methylene-D-mannitol (m.p. 120–125°) and then 11 g. of semi-solid material. Solution of this latter in 20 ml. of dioxane gave 3.4 g. of crude 3,4-methylene-D-mannitol (m.p. 105–110°); addition of ether to the mother liquor led to the isolation of 9.0 g. of impure 1,3-methylene-D-mannitol (m.p. 105–110°).

The combined crops of crude 1,3-methylene-D-mannitol (15.8 g., 7.9%) were extracted with 5 parts of pyridine at room temperature (to remove D-mannitol), the extract filtered through carbon and concentrated to a thick sirup. From 5 parts of dioxane there was obtained 9.5 g. of product melting at 125–126° and showing −37.1° in water; recrystallization from 4 parts of alcohol gave material melting at 127–128° and showing in water a rotation of −38.7° (*c* 0.60). Further recrystallization failed to change these constants.

Anal. Calcd. for $C_7H_{14}O_6$: mol. wt., 194; C, 43.29; H, 7.27. Found: mol. wt., 184[21]; C, 43.47; H, 7.36.

A sample (207.5 mg.) of 1,3-methylene-D-mannitol in aqueous solution was treated with 5.0 ml. of 0.5 *M* sodium metaperiodate and the solution diluted to 25 ml. with water. After 24 hours at room temperature analysis showed that 2.00 mole equivalents of oxidant had been consumed while 0.98 mole equivalent of formic acid had been liberated. Quantitative estimation of the formaldehyde produced on periodate oxidation was made on a 27.1-mg. sample of the methylenhexitol. The amount of formaldehyde dimethone obtained corresponded to the liberation of 1.07 moles of formaldehyde per mole of methylenehexitol.

1,3:2,5:4,6-Trimethylene-D-mannitol from 1,3-Methylene-D-mannitol (IV).—1,3-Methylene-D-mannitol (200.1 mg.) was treated with 37% formalin and hydrochloric acid just as described above for the 3,4-isomer. Within one hour the reaction mixture became solid through the formation of crystals; after three days there was obtained 194.6 mg. (87%) of trimethylene-D-mannitol melting at 232–233° either alone or in admixture with authentic material.

2,4,5,6-Tetraacetyl-1,3-methylene-D-mannitol.—One-half gram of 1,3-methylene-D-mannitol was acetylated with pyridine and acetic anhydride in the usual manner to give 0.8 g. (86%) of crystalline material melting at 143–144°. Repeated crystallization from alcohol gave quadrilateral plates of the same melting point which showed in chloroform −2.73° (*c* 0.63).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.65; H, 6.29.

2,4,5,6-Tetrabenzoyl-1,3-methylene-D-mannitol.—1,3-Methylene-D-mannitol (300 mg.) was benzoylated with benzoyl chloride in pyridine in the usual fashion. From methanol there was obtained 840 mg. (89%) of crystalline material melting at 112–113°. Crystallization from 6 parts of absolute alcohol gave 720 mg. of irregular plates melting at 120–121°; further recrystallization failed to change this value. The pure product showed a rotation of +14.8° in chloroform (*c* 0.76).

Anal. Calcd. for $C_{35}H_{30}O_{10}$: C, 68.84; H, 4.95. Found: C, 69.11; H, 4.98.

2,4,5,6-Tetratosyl-1,3-methylene-D-mannitol.—Two grams of 1,3-methylene-D-mannitol was tosylated with 10 g. of tosyl chloride in pyridine in the usual manner to give from alcohol 3.4 g. (41%) of crude product melting at 125–130°. Two recrystallizations from 35 to 50 parts of absolute alcohol afforded material melting at 136–137°. Further purification through flowing chromatography on alumina gave fine needles from ethanol melting at 138–141° and showing +3.3° in chloroform (*c* 2.14).

Anal. Calcd. for $C_{35}H_{38}O_{14}S_4$: C, 51.84; H, 4.72; S, 15.81. Found: C, 52.12; H, 4.64; S, 15.70

1,3-Methylene-2,4-bis-(phenylcarbamyl)-L-erythritol (VI) **from 1,3-Methylene-D-mannitol** (IV).—Five grams of 1,3-methylene-D-mannitol, dissolved in 50 ml. of water, was cooled and treated with 11.017 g. of sodium metaperiodate. After one hour at room temperature 2.16 g. of sodium bicarbonate was added to the solution and it was then concentrated *in vacuo* at 45° (bath) to a dry crystalline mass. Extraction of this mass with successive portions (50, 50, 25 ml.) of warm absolute ethanol afforded a solution which was treated with *ca.* 10 g. of freshly prepared Raney nickel and then shaken at room temperature under 40 p.s.i. of hydrogen for two hours. After removal of the nickel and concentration *in vacuo* there was obtained a levorotatory sirup (3.66 g.) which gave a negative Fehling test and which could not be induced to crystallize. Attempts to obtain a crystalline benzoate, *p*-nitrobenzoate and tosylate failed. A sample (2.7976 g.) of the sirup was dissolved in 20 ml. of pyridine, treated with 10 ml. of phenyl isocyanate and the solution held at 50° for one hour. The reaction mixture was then cooled and concentrated *in vacuo*, finally at 80° and < 0.1 mm. pressure. From its solution in 200 ml. of absolute alcohol this material gave 3.18 g. of triphenylisocyanuric acid melting at 282–283° either alone or in admixture with an authentic sample.[23] On standing, the mother liquor deposited, first, 70 mg. more triphenylisocyanuric acid, then 920 mg. of crude material and finally 1.66 g. (23% based on the 1,3-methylene-D-mannitol) of 1,3-methylene-2,4-bis-(phenylcarbamyl)-L-erythritol (VI) melting at 188–190°. After two recrystallizations from methanol this product melted at 189–190° and showed in chloroform (*c* 1.86) a rotation of −47.7°. Further recrystallization failed to change these constants.

Anal. Calcd. for $C_{19}H_{20}O_6N_2$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.53; H, 5.59; N, 7.65.

1,4-Anhydro-2,3-methylene-D-mannitol (X) **from D-Mannitol.**—A mixture of 100 g. of D-mannitol, 100 ml. of 37% formalin and 200 ml. of concentrated hydrochloric acid was boiled under reflux for seven hours, cooled and filtered to remove 5.5 g. of 1,3:2,5:4,6-trimethylene-D-mannitol. The mother liquor, concentrated *in vacuo* to a semi-solid mass, was warmed with 100 ml. of absolute alcohol. After removal of 0.2 g. more 1,3:2,5:4,6-trimethylene-D-mannitol, the solution was seeded to give 17.6 g. of 1,3:4,6-dimethylene-D-mannitol. Concentration of the mother liquor *in vacuo* followed by solution of the sirupy residue in a mixture of 62 ml. of absolute alcohol and 12 ml. of ether gave 15.6 g. of a mixture of D-mannitol and 1,3:4,6-dimethylene-D-mannitol. Addition of ether to the mother liquors afforded 29 g. of crude material which proved to be a mixture of D-mannitol and 3,4-methylene-D-mannitol. The mother liquor was then concentrated to a sirup and diluted with 10 ml. of absolute alcohol; the addition of ether gave 2.48 g. (2.6%) of nearly pure 1,4-anhydro-2,3-methylene-D-mannitol. Recrystallization raised the melting point to 120–121°; the needle-shaped crystals rotated −52.1° in water (*c* 0.76). The substance sublimed readily at 110° under a pressure of 0.005 mm.

Anal. Calcd. for $C_7H_{12}O_5$: C, 47.72; H, 6.87. Found: C, 47.84; H, 6.89.

A sample of the anhydromethylenhexitol (181.4 mg.) dissolved in a few ml. of water was treated with 5.0 ml. of *ca.* 0.5 *M* sodium metaperiodate and the resulting solution diluted with water to 25 ml. After 20 hours analysis showed the consumption of 1.02 molar equivalents of oxidant, the *p*H having remained constant. Oxidation of a 49.3-mg. sample followed by isolation of formaldehyde as its dimethone indicated the formation of 1.16 molar equivalents of formaldehyde.

1,4-Anhydro-2,3:5,6-dimethylene-D-mannitol (XI) **and 1,4-Anhydro-2,3-methylene-D-mannitol** (X) **from 1,4-Anhydro-D-mannitol** (IX).—One gram of 1,4-anhydro-D-mannitol, prepared through the hydrolysis of its dibenzoate[24] was dissolved in a mixture of 2 ml. of 37% formalin and 2 ml. of concentrated hydrochloric acid and the solution left at 50° for three days. After cooling, the solution was concentrated *in vacuo* to a stiff sirup which was distilled *in vacuo* (0.5 mm. and 150°) to give a sirup which rapidly crystallized to a solid melting at 51–55°. From *ca.* 1 ml. of water this distillate afforded 200 mg. (17%) of needles melting at 55–57°. Recrystallization from water gave pure 1,4-anhydro-2,3:5,6-dimethylene-D-mannitol melting at 57–58° and rotating −40.7° in water (*c* 0.62).

Anal. Calcd. for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.06; H, 6.47.

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(23) A. W. Hofmann [*Ber.*, **18**, 764 (1885)] discovered that phenyl isocyanate is converted to this cyclic trimer on heating with potassium acetate or any of several other salts including sodium formate. Doubtless this latter salt, arising from the oxidation of carbon 5 of 1,3-methylene-D-mannitol, was present in the crude 1,3-methylene-L-erythritol and served as catalyst for the conversion of phenyl isocyanate to triphenylisocyanuric acid.

(24) R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, R. M. Goepp, Jr., and S. Soltzberg, THIS JOURNAL, **68**, 930 (1946).

The aqueous mother liquor from which the 1,4-anhydro-2,3:5,6-dimethylene-D-mannitol had been removed was concentrated *in vacuo* to a sirup and treated with 25 ml. of carbon tetrachloride. About 1 ml. of the solvent was boiled off to remove traces of water; on cooling, fine needles separated: 80 mg. (7.5%), m.p. 109–117°. After recrystallization from 0.4 ml. of absolute ethanol the product melted at 120–121° either alone or in admixture with 1,4-anhydro-2,3-methylene-D-mannitol as prepared above. A rotation of −51.3° was observed in water (*c* 0.98).

5,6-Diacetyl-1,4-anhydro-2,3-methylene-D-mannitol.—One-half gram of 1,4-anhydro-2,3-methylene-D-mannitol was acetylated with acetic anhydride in pyridine in the usual fashion to give 0.51 g. (69%) of product melting at 87–88°; recrystallization from 6 parts of absolute alcohol failed to change this melting point. In chloroform the ester rotated −43.1° (*c* 0.80).

Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.76; H, 6.20. Found: C, 50.76; H, 6.14.

2,4-Methylene-D-mannitol (XIII) from 1,6-Dibenzoyl-2,4-methylene-D-mannitol (XII).—Fifteen grams of 1,6-dibenzoyl-2,4-methylene-D-mannitol (m.p. 156–157°, $[\alpha]^{20}D$ +23.4° in chloroform), prepared in 20 to 29% yield from 1,6-dibenzoyl-D-mannitol using the procedure of Haworth and Wiggins,[18] was suspended in a mixture of 50 ml. of chloroform and 150 ml. of absolute methanol. When 5 ml. of 1 *N* barium methylate was added solution was rapid; after two hours at room temperature the reaction mixture was passed through a column (3.2 × 30 cm.) of Amberlite IR-120[25] and the neutral barium-free effluent concentrated *in vacuo* to a volume of *ca.* 25 ml. A faint turbidity and slight color were removed by filtration through decolorizing carbon and the solution, after treatment with two drops of pyridine, concentrated *in vacuo* at 45–50° (bath) to a sirup which crystallized spontaneously. From 19 ml. of warm absolute alcohol there was obtained 6.18 g. (88%) of needles melting at 108–109°. Successive recrystallization from absolute alcohol and from dioxane failed to change this value; the pure 2,4-methylene-D-mannitol showed a rotation of +25.9° in water (*c* 2.04).

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 43.55; H, 7.27.

A sample (206.2 mg.) of the 2,4-methylene-D-mannitol, dissolved in a small amount of water, was treated with 5.0 ml. of *ca.* 0.5 *M* sodium metaperiodate and the resulting solution diluted with water to 25 ml. After 17 hours at room temperature analysis showed that 1.07 molar equivalents of oxidant had been consumed and that no acid had been formed.

1,3:2,5:4,6-Trimethylene-D-mannitol from 2,4-Methylene-D-mannitol (XIII).—A sample (212.7 mg.) of pure 2,4-methylene-D-mannitol was dissolved in a mixture of 0.45 ml. of 37% formalin and 0.45 ml. of concentrated hydrochloric acid and the solution kept at 50°. The formation of crystals was first observed after 105 minutes. After 5 days at 50° there was obtained 206.5 mg. (86%) of well-formed needles melting at 229–232°; mixed with authentic 1,3:2,5:4,6-trimethylene-D-mannitol they melted at 232–233°.

1,3,5,6-Tetrabenzoyl-2,4-methylene-D-mannitol.—One gram of 2,4-methylene-D-mannitol was benzoylated in the usual fashion with benzoyl chloride and pyridine. From *ca.* 50 ml. of absolute alcohol there was obtained 2.9 g. (42%) of product melting at 100–101°; after recrystallization from 17 parts of absolute alcohol the product melted at 101–103° and showed −83.8° in chloroform (*c* 2.15).

Anal. Calcd. for $C_{35}H_{30}O_{10}$: C, 68.84; H, 4.95. Found: C, 68.74; H, 5.03.

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BETHESDA, MARYLAND

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[25] A product of the Resinous Products and Chemical Co., Washington Square, Philadelphia 5, Pa.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Friedel–Crafts Reaction with Disubstituted Ethylene Oxides. III. The Rearrangement of α,α-Dimethylbibenzyl

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d,l-2,3-Diphenylbutane was shown to be converted to the *meso* isomer in the presence of anhydrous aluminum chloride or concentrated sulfuric acid. Both neophyl chloride and benzyldimethylcarbinyl chloride yield a mixture of α,α-dimethyldibenzyl and *meso*-2,3-diphenylbutane when condensed with aluminum chloride and benzene. In order to obtain information concerning the mechanism of the rearrangement, α,α-dimethyldibenzyl has been treated with aluminum chloride using both chlorobenzene and toluene as solvents. The solvent has been shown to participate in the rearrangement indicating that the reaction was intermolecular and probably preceded by cleavage of the α,α-dimethyldibenzyl molecule. Mechanisms consistent with the experimental data are presented.

The rearrangement of α,α-dimethyldibenzyl in benzene solution to *meso*-2,3-diphenylbutane by aluminum chloride and the formation of this isomer from both isobutylene dibromide and benzyldimethylcarbinol in benzene in the Friedel–Crafts reaction has been reported[2] previously. The present work presents some additional cases of this rearrangement as well as the results of studies on the mechanism of these rearrangements.

The relationship between *d,l*- and *meso*-2,3-diphenylbutane was investigated. It was found that the *d,l*-isomer is readily converted to the *meso* form when treated with aluminum chloride in benzene solution; the extent of conversion is dependent on the temperature and amount of aluminum chloride used. The results of these experiments are given in Table I.

TABLE I

ISOMERIZATION OF *d,l*-2,3-DIPHENYLBUTANE

(Time of reactions two hours.)

Expt.[a]	$AlCl_3$, moles	*t*, °C.	Yield of *meso* isomer, %
1	0.2	5–10	0
2	2.0	5–10	10.4
3	2.0	26–8	32

[a] Using one mole of the *d,l*-isomer and 20 moles of benzene.

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[1] Taken in part from a dissertation presented by Willard T. Somerville to the Graduate Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1950.

[2] W. T. Somerville and P. E. Spoerri, THIS JOURNAL, **72**, 2185 (1950).