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1,3:4,6-Dimethylene-D-mannitol

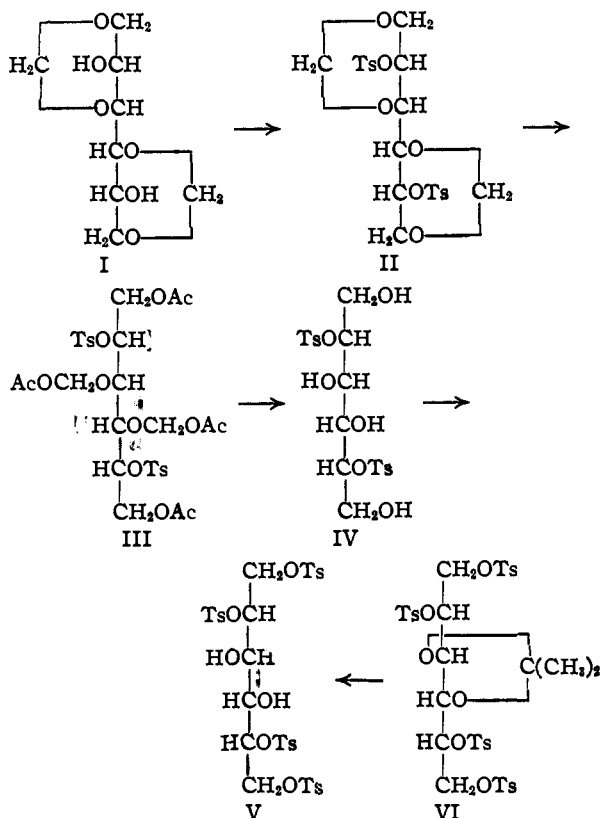
BY HEWITT G. FLETCHER, JR., AND HARRY W. DIEHL

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Acetolysis of the ditosyl ester of the dimethylene-D-mannitol which is formed by the methylenation of D-mannitol affords a diacetoxymethylidiacetylditosyl-D-mannitol which, upon acidic hydrolysis, yields a ditosyl-D-mannitol. Lead tetraacetate oxidation of this ester shows it to be 2,5-ditosyl-D-mannitol; further tosylation converts it into the known 1,2,5,6-tetratosyl-D-mannitol. From this evidence it is concluded that the diacetal is 1,3:4,6-dimethylene-D-mannitol. A practical method for the preparation of 1,3:4,6-dimethylene-D-mannitol from 1,3:2,5:4,6-trimethylene-D-mannitol is described and 2,5-ditosyl-D-mannitol further characterized through the preparation of its tetraacetate and tetrabenzoate.

In 1943 Haskins, Hann and Hudson¹ showed that the condensation of D-mannitol with formaldehyde in the presence of hydrochloric acid gives, in addition to the long known 1,3:2,5:4,6-trimethylene-D-mannitol²⁻⁴ a dimethylene-D-mannitol melting at 204-208°⁵ and rotating $[\alpha]^{20}_D -91.0^\circ$ in water. Since this substance was stable to the action of periodic acid and gave a ditosyl ester which could not be induced to react with sodium iodide, it was tentatively assigned the structure of 1,3:4,6- or 1,3:5,6-dimethylene-D-mannitol. Subsequently it was observed⁶ that this dimethylene-D-mannitol, when treated with formaldehyde and concentrated hydrochloric acid, gives 1,3:2,5:4,6-trimethylene-D-mannitol more rapidly than either 2,5-methylene-D-mannitol or D-mannitol itself and this observation was interpreted as supporting the 1,3:4,6-dimethylene-D-mannitol (I) structure. Further and conclusive evidence has now been found to confirm this structure.

That the dimethylene-D-mannitol was of the expected molecular size was demonstrated through determination of the molecular weight of its ditosyl ester (II), a substance first prepared by Haskins, Hann and Hudson.¹ Acetolysis of this ester with a mixture of acetic anhydride, acetic and sulfuric acids³ gave a crystalline diacetoxymethylidiacetylditosyl-D-mannitol (III) which was then hydrolyzed with methanolic hydrogen chloride to yield a crystalline ditosyl-D-mannitol (IV). The structure of this latter compound was determined by two independent methods. The first proof was obtained by oxidation with lead tetraacetate; on a molar basis the substance consumed one mole of oxidant without liberating formaldehyde. Of the nine isomeric ditosyl-D-mannitols only the 2,5-isomer (IV) would be expected to behave thus. The second proof was obtained through further tosylation of the diester; there was obtained a tetratosyl-D-mannitol which was found to consume one mole of lead tetraacetate without the formation of formaldehyde and to be identical with a sample of authentic 1,2,5,6-tetratosyl-D-mannitol (V) prepared *via* the acid hydrolysis of 3,4-isopropylidene-1,2,5,6-tetratosyl-D-mannitol (VI).⁶ The diester



was, therefore, 2,5-ditosyl-D-mannitol (IV); it was further characterized through the preparation of its tetraacetate and tetrabenzoate.

Since the methylenation of 2,5-ditosyl-D-mannitol (IV) readily gave the original 1,3:4,6-dimethylene-2,5-ditosyl-D-mannitol (II) it follows that the tosyl groups did not shift in the two-stage hydrolysis of II to IV and that the original cyclic acetal is 1,3:4,6-dimethylene-D-mannitol (I). This structure is analogous to that of the diethylidene-D-mannitol of Bourne, Bruce and Wiggins⁷; while the evidence here adduced does not exclude the 1,4:3,6-structure the latter is unlikely both on steric grounds and in view of experience with the cyclic acetals as summarized in the generalizations of Hann and Hudson⁴ and of Ness, Hann and Hudson.⁸

As mentioned earlier, Ness, Hann and Hudson⁸ showed that 1,3:4,6-dimethylene-D-mannitol could

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

(8) A. T. Ness, R. M. Hann and C. S. Hudson, *THIS JOURNAL*, **70**, 765 (1948).

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

(2) M. Schulz and B. Tollens, *Ann.*, **239**, 21 (1896).

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

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

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

be methylenated to 1,3:2,5:4,6-trimethylene-D-mannitol. In the course of the present research it was found that this reaction, as might be expected, is readily reversible and that the preparation of 1,3:4,6-dimethylene-D-mannitol from 1,3:2,5:4,6-trimethylene-D-mannitol is fully as satisfactory as from D-mannitol itself.

It is interesting to note that while the 2,5-methylene ring in 1,3:2,5:4,6-trimethylene-D-mannitol is most stable to acetolysis⁹ it is least stable to hydrolysis by aqueous acid. Bourne, Bruce and Wiggins⁷ have similarly observed that the hydrolysis of 1,3:2,5:4,6-triethylidene-D-mannitol leads to the formation of 1,3:4,6-diethylidene-D-mannitol.

Experimental

1,3:4,6-Dimethylene-D-mannitol (I) from 1,3:2,5:4,6-trimethylene-D-mannitol.—1,3:2,5:4,6-Trimethylene-D-mannitol (167 g., recrystallized from dioxane, m.p. 232–234°) was dissolved in a mixture of 334 ml. of concentrated hydrochloric acid and 334 ml. of water and the solution boiled under reflux for five hours. Upon cooling, 28.8 g. of unchanged 1,3:2,5:4,6-trimethylene-D-mannitol was recovered. The filtrate was concentrated *in vacuo* to a sludge and the latter dissolved in 235 ml. of hot water. After cooling, the solution deposited 6.1 g. more 1,3:2,5:4,6-trimethylene-D-mannitol (21% recovery); it was then filtered through decolorizing carbon and reconcentrated *in vacuo* to a stiff sirup. From its solution in 220 ml. of absolute alcohol this residue deposited 29.0 g. of crude 1,3:4,6-dimethylene-D-mannitol (m.p. 194–203°). Concentration of the mother liquor afforded a second crop which, upon recrystallization, gave 3.4 g. more 1,3:4,6-dimethylene-D-mannitol (total yield 26%, based on the 1,3:2,5:4,6-trimethylene-D-mannitol not recovered⁹) and 7.88 g. of crude D-mannitol. Recrystallized from isopentyl acetate, the combined crops melted at 205–206° and showed in water a rotation of -90.8° (*c* 3.5).

For the preparation of the ditosyl ester it was found more convenient to use the crude 1,3:4,6-dimethylene-D-mannitol as isolated since the purification of the latter is time-consuming and involves considerable loss.

3,4-Diacetoxymethyl-1,6-diacetyl-2,5-ditosyl-D-mannitol (III).—Ten grams of pure, powdered 1,3:4,6-dimethylene-2,5-ditosyl-D-mannitol,¹⁰ prepared as described by Haskins, Hann and Hudson¹ (m.p. 147–148°, $[\alpha]_D^{20} -37.9^\circ$ in chloroform) was dissolved in a chilled, freshly-made solution of 1 ml. of concentrated sulfuric acid in a mixture of 35 ml. of acetic anhydride and 15 ml. of glacial acetic acid. After 65 minutes at 20° the mutarotation of the solution was essentially complete; 2 ml. of benzene was added to facilitate subsequent crystallization and the mixture was poured on finely chipped ice. A gentle stream of air was passed through the mixture for one hour; at no time was the temperature allowed to rise above 0°. Repeated washing of the precipitated sirup with fresh ice water gave, after several hours, a filterable mass of crystalline material which weighed 17.4 g. Recrystallization at -5° from 2 parts of methanol containing 2 ml. of benzene gave 10.6 g. (68%) of clear prisms melting at 42–43° and showing in chloroform $+71.1^\circ$ (*c* 0.78). Further recrystallization failed to change these values.

When first prepared this substance could only be crystallized from a medium containing benzene. A chloroform solution of the compound gave with aqueous ammoniacal nickel cyanide the bluish-white crystals characteristic of the clathrate compound $\text{Ni}(\text{CN})_2 \cdot \text{NH}_3 \cdot \text{C}_6\text{H}_6$,¹¹ confirming the suspicion that benzene of crystallization was present.

(9) If the 1,3:2,5:4,6-trimethylene-D-mannitol which is formed as a by-product in the preparation of 1,3:4,6-dimethylene-D-mannitol from D-mannitol (*cf. ref. 1*) is hydrolyzed in the above fashion, an overall yield of 15% of 1,3:4,6-dimethylene-D-mannitol may be obtained from D-mannitol.

(10) Determination of the molecular weight of this substance by the Rast method gave a value of 458; the theoretical value is 515.

(11) K. A. Hofmann and H. Arnoldi, *Ber.*, **39**, 339 (1906); H. M. Powell and J. H. Reynet, *Nature*, **163**, 566 (1949).

Anal. Calcd. for $\text{C}_{30}\text{H}_{38}\text{O}_{16}\text{S}_2 \cdot \text{C}_6\text{H}_6$: C, 54.26; H, 5.57; S, 8.05; C_6H_6 , 9.80. Found: C, 53.95; H, 5.61; S, 8.29; loss of weight *in vacuo* at 57°, 9.57.

The benzene addition compound is soluble in acetone, methanol and ether at room temperature, insoluble in pentane and water. When dissolved in methanolic hydrogen chloride the compound afforded a solution giving a strongly positive Schiff test.

In the course of subsequent work, 3,4-diacetoxymethyl-1,6-diacetyl-2,5-ditosyl-D-mannitol was obtained in crystalline, solvent-free form. Recrystallized from 1.5 parts of methanol, the material melted at 75–76° and rotated in chloroform $+80.0^\circ$ (*c* 0.79). Thereafter, either form of the substance could be obtained at will and they were found to be mutually interconvertible. At room temperature the instability of the compound is marked by the appearance of the odor of acetic acid within a few hours.

2,5-Ditosyl-D-mannitol (IV).—Twenty grams of powdered, solvent-free 3,4-diacetoxymethyl-1,6-diacetyl-2,5-ditosyl-D-mannitol was dissolved in 760 ml. of 0.6962 *N* methanolic hydrogen chloride and the resulting solution observed polarimetrically at 20°. After about three hours mutarotation had ceased; the solution was diluted with 50 ml. of water and concentrated *in vacuo* (40° bath) to a volume of about 50 ml. The crystalline mass removed by filtration and dried in the air (12.7 g., 93%) melted at 125–126°; recrystallization from three parts of ethyl acetate failed to change this melting point. In chloroform the pure product showed -2.5° (*c* 0.79).

Anal. Calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_{10}\text{S}_2$: C, 48.97; H, 5.34; S, 13.07. Found: C, 49.40; H, 5.45; S, 13.08.

The structure of the above ditosylhexitol was revealed by quantitative oxidation with lead tetraacetate using the procedure of Hockett and McClenahan.¹² The ester (0.4957 g.) was dissolved in glacial acetic acid, the solution treated with 50.0 ml. of 0.1307 *N* lead tetraacetate (in the same solvent) and the whole made up to a volume of 100 ml. After 21 hours at room temperature, titration of an aliquot of the solution showed that 0.985 mole of oxidant had been consumed per mole of compound used. The remaining solution was diluted with 25 ml. of water and *ca.* 7 ml. distilled over into 5 ml. of a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. No precipitate was formed in one hour. In a parallel experiment D-mannitol ($1/2$ the molal quantity of the ditosyl-D-mannitol used above) gave a copious precipitate of formaldehyde 2,4-dinitrophenylhydrazone.

1,3:4,6-Dimethylene-2,5-ditosyl-D-mannitol (II) from 2,5-ditosyl-D-mannitol (IV).—One-half gram of 2,5-ditosyl-D-mannitol, dissolved in 2 ml. of glacial acetic acid, was treated with 1 ml. of 37% formalin and 1 ml. of concentrated hydrochloric acid and the resulting solution held at 45°. After 18 hours the crystalline mass which had formed was washed with alcohol and dried *in vacuo*: 0.35 g. (67%), m.p. 145–148°. After one recrystallization from 4 ml. of alcohol the product melted at 148–149° either alone or in admixture with authentic 1,3:4,6-dimethylene-2,5-ditosyl-D-mannitol.

1,3,4,6-Tetraacetyl-2,5-ditosyl-D-mannitol.—One-half gram of 2,5-ditosyl-D-mannitol was acetylated with acetic anhydride in pyridine solution to give 0.7 g. of crude product which, after recrystallization from a mixture of chloroform and pentane, yielded 0.6 g. (89%) of product melting at 101–102°. Further recrystallization from chloroform-pentane failed to change this melting point; the pure product showed in chloroform $+39.0^\circ$ (*c* 0.70).

Anal. Calcd. for $\text{C}_{28}\text{H}_{34}\text{O}_{14}\text{S}_2$: C, 51.05; H, 5.20; S, 9.73. Found: C, 50.77; H, 5.27; S, 9.68.

1,3,4,6-Tetrabenzoyl-2,5-ditosyl-D-mannitol.—One gram of 2,5-ditosyl-D-mannitol was benzoylated with a mixture of 2 ml. of benzoyl chloride and 10 ml. of pyridine in the usual manner to give a crude crystalline product which, recrystallized from 100 parts of methanol, afforded 1.6 g. (87%) of rectangular prisms melting at 147–148° and showing in chloroform $+83.4^\circ$ (*c* 0.65). Further recrystallizations from a mixture of 2-butanone and pentane failed to change these constants.

Anal. Calcd. for $\text{C}_{48}\text{H}_{42}\text{O}_{14}\text{S}_2$: C, 63.56; H, 4.67; S, 7.07. Found: C, 63.41; H, 4.88; S, 7.22.

(12) R. C. Hockett and W. S. McClenahan, *This Journal*, **61**, 1667 (1939).

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 Koffler 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 $C_{24}H_{40}O_{14}S_4$: 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 tetracetate 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.

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[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

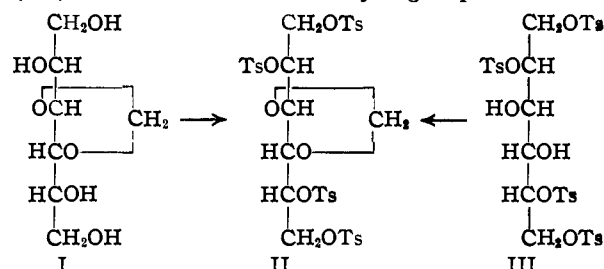
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The methylenation of D-mannitol with formaldehyde and hydrochloric acid gives (in addition to 1,3:2,5:4,6-trimethylene-D-mannitol and 1,3:4,6-dimethylene-D-mannitol) 3,4-methylene-D-mannitol, 1,3-methylene-D-mannitol and 1,4-anhydro-2,3-methylene-D-mannitol. 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 $[\alpha]^{20}_D +41.6^\circ$ (H₂O),⁵ a second monomethylenehexitol of m.p. 127–128° and $[\alpha]^{20}_D -38.7^\circ$ and a substance of m.p. 120–121° and $[\alpha]^{20}_D -52.1^\circ$ (H₂O) which gave analytical values corresponding to an anhydromethylenehexitol. Each of these will now be discussed in turn.

The Dextrorotatory Monomethylenehexitol 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).^{4,5} Evidence that tosyl groups do not



migrate during methylenation was adduced in the preceding paper⁴ 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-mannitol⁷ and 3,4-cyclohexylidene-D-mannitol.⁸

While a 3,4-methylene-D-mannitol is not to be expected in the light of the generalizations of Hann and Hudson³ and of Ness, Hann and Hudson⁹ 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-

(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. Brilline, *J. Chem. Soc.*, 786 (1950).

(9) A. T. Ness, R. M. Hann and C. S. Hudson, *ibid.*, **70**, 765 (1943).