drated salt was −10.8° in water (*c*, 1.6; *l*, 4), equivalent to −13.9 ± 0.4° for the anhydrous salt (*c*, 1.2). The rotation of the hydrated strontium salt was +23.3° in an excess of *N* hydrochloric acid (*c*, 1.9; *l*, 4), equivalent to +45.6 ± 0.4° for the liberated dibasic acid (*c*, 0.98).

Anal. Calcd. for $C_5H_6O_6Sr \cdot 4H_2O$: C, 18.66; H, 4.38; Sr, 27.23; H_2O, 22.39. Found: C, 18.76; H, 4.52; Sr, 27.05; H_2O (dried at 130° *in vacuo*), 22.47.

The authors express their indebtedness to Dr. C. Jelleff Carr, of the University of Maryland School of Medicine, for his generous gift of synthetic styracitol; to Dr. and Mrs. George Tunell, of the Geophysical Laboratory of the Carnegie Institution of Washington, for their measurements of the polygalitol crystals; and to Dr. Arthur T. Ness, of this Laboratory, for carrying out the microanalyses. One of the authors (N. K. R.) desires to thank the Chemical Foundation, of New York, for a Research Associateship which he held while completing a portion of this research.

Summary

1. An improved method has been described for the isolation of polygalitol from *Polygala Senega*, L.

2. The identity of aceritol and polygalitol has been confirmed by crystallographic examination.

3. Polygalitol and styracitol have been oxidized by periodic acid, followed by bromine water and strontium carbonate, to strontium D-hydroxymethyldiglycolate. Polygalitol and styracitol have thus been proved to possess the same 1,5-ring; the D-configuration of polygalitol follows from the known D-configuration of styracitol.

BETHESDA, MD. RECEIVED OCTOBER 28, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

2,3,4,5-Dimethylene-D-mannitol and a Second Dimethylene-D-mannitol

BY W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

In a study of the products that result from the condensation of formaldehyde with D-mannitol in the presence of strong hydrochloric acid, we have isolated the known trimethylene-D-mannitol (m. p. 227°, $[\alpha]_D$ −103.9° in chloroform)[1] and a new substance, the analysis of which shows that it is a dimethylene-D-mannitol (m. p. 204–208°, $[\alpha]^{20}D$ −91.0° in water).

Trimethylene-D-mannitol and a New Dimethylene-D-mannitol from Formaldehyde, D-Mannitol and Concentrated Hydrochloric Acid.—A solution of 100 g. of D-mannitol in a mixture of 100 cc. of 37% formaldehyde and 100 cc. of concentrated hydrochloric acid was heated on the steam-bath for forty-five minutes; the reaction mixture was cooled and the precipitated trimethylene-D-mannitol (47 g., 39%) was separated by filtration, and upon recrystallization from 100 parts of 50% alcohol it was obtained in needles which melted sharply at 232° (cor.) and rotated $[\alpha]^{20}D$ −104.0° in chloroform (*c*, 2.2)[2] in agreement with the recorded values of Schulz and Tollens. The strongly acid filtrate remaining after the separation of the trimethylene-D-mannitol was neutralized with 64 g. of sodium carbonate and the solution was concentrated *in vacuo;* the crystalline residue was extracted with hot absolute alcohol and as the extract cooled it deposited tufts of plates which, after recrystallization from 8 parts of alcohol, melted at 204–208° (cor.) and rotated $[\alpha]^{20}D$ −91.0° in water (*c*, 0.9). The yield was 14.3 g. (12.6%).

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.47; H, 6.82.

No dimethylene-D-mannitol has been reported previously, but Micheel[3] has established the structure for a 1,6-di-iodo-2,3,4,5-dimethylene-D-mannitol and some derivatives of it; our first effort was therefore directed toward determining whether our dimethylene-D-mannitol is to be regarded as the corresponding diacetal in Micheel's series of compounds. A test showed that the dimethylene-D-mannitol (m. p. 204–208°) was not oxidized by per-iodic acid, which proves that the substance contains no α-glycol grouping; the possibility of its belonging in Micheel's series of compounds was therefore not excluded. A decisive answer to the question was obtained through the preparation, by structurally interpretable syntheses, of the hitherto unknown 2,3,4,5-dimethylene-D-mannitol; the properties of this substance (m. p. 139° (cor.); $[\alpha]^{20}D$ + 71.1° in water) show that the two dimethylene-D-mannitols are different compounds. In naming them we designate the one of melting point 139° as 2,3,4,5-

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[1] Schulz and Tollens, *Ann.*, **289**, 21 (1896).

[2] All of the crystalline compounds described in the experimental part were recrystallized to constant melting point and specific rotation, $[\alpha]^{20}D$; *c* is the concentration in grams in 100 cc. of solution; the tube length was 4 dm.

[3] Micheel, *Ann.* **496**, 93 (1932).

dimethylene-D-mannitol, according to its proved structure, but leave unspecified the choice between the 2,3:4,5 and 2,4:3,5 arrangements of its acetal rings. Micheel considers the 2,3:4,5 arrangement the more probable one in his series of compounds; although we leave this matter open it can be stated positively that the same arrangement holds in the 2,3,4,5-dimethylene-D-mannitol as in Micheel's compounds, as will be shown in the continuation. The isomeric substance, of m. p. 204–208° and $[\alpha]^{20}\mathrm{D}$ $-$ 91.0°, will be designated provisionally as the second dimethylene-D-mannitol.

1,6-Dibenzoyl-2,3,4,5-dimethylene-D-mannitol.—A suspension of 25 g. of 1,6-dibenzoyl-D-mannitol[4] in a mixture of 50 cc. of absolute dioxane and 25 cc. of 37% formaldehyde was cooled to 0° and saturated with dry hydrochloric acid gas. The reaction mixture was agitated at 5° for one hour to complete the solution of the dibenzoate and after standing for a further eighteen hours at 5° it was poured into 500 cc. of ice-water and extracted with chloroform; the washed and dried chloroform extract was concentrated *in vacuo* to dryness and the resulting crystalline mass was dissolved in warm alcohol; upon cooling, the solution deposited 14.6 g. (55%) of 1,6-dibenzoyl-2,3,4,5-dimethylene-D-mannitol. The compound was recrystallized from 10 parts of alcohol in the form of prisms melting at 120–122° (cor.) and rotating $[\alpha]^{20}\mathrm{D}$ +47.5° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35; C_6H_5-CO, 50.7. Found: C, 63.90; H, 5.39; C_6H_5CO, 50.6.

2,3,4,5-Dimethylene-D-mannitol.—A solution of 2.0 g. of 1,6-dibenzoyl-2,3,4,5-dimethylene-D-mannitol in 50 cc. of chloroform was cooled in an ice-bath and 5 cc. of 0.1 *N* sodium methylate solution was added. The mixture was allowed to stand at 5° for eighteen hours and the solvent removed by concentration *in vacuo;* the crystalline residue was extracted with ether to remove methyl benzoate and then dissolved in 10 cc. of boiling alcohol. The diacetal, which deposited from the alcoholic solution as it cooled, was recrystallized from 5 parts of alcohol and formed small prisms. The yield was 0.85 g. (85%). The compound melted at 139° (cor.) and rotated $[\alpha]^{20}\mathrm{D}$ +71.1° in water (*c*, 0.9).

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.80; H, 6.95.

1,6-Diacetyl-2,3,4,5-dimethylene-D-mannitol.—A mixture of 1.0 g. of 2,3,4,5-dimethylene-D-mannitol, 0.25 g. of fused sodium acetate and 4 cc. of acetic anhydride was heated on the steam-bath for one hour and then poured upon crushed ice. The precipitated diacetate (1.0 g.) was separated by filtration and the acetic acid filtrate was neutralized and extracted with chloroform; the extract, upon concentration, gave a further 0.4 g. of product, the total yield being quantitative. The substance was recrystallized from 5 parts of alcohol in the form of elongated prisms, which melted at 105–106° (cor.) and rotated $[\alpha]^{20}\mathrm{D}$ +98.3° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25; CH_3-CO, 29.7. Found: C, 49.73; H, 6.31; CH_3CO, 29.8.

The 2,3,4,5-dimethylene-D-mannitol (m. p. 139°) was converted to a 1,6-di-iodo-2,3,4,5-dimethylene-D-mannitol through the following customary reactions: 2,3,4,5-dimethylene-D-mannitol → 1,6-ditosyl-2,3,4,5-dimethylene-D-mannitol → 1,6-di-iodo-2,3,4,5-dimethylene-D-mannitol, and the last named substance was found to be identical with the di-iodo compound of Micheel's series; the structure of this substance, in so far as it is disclosed by the name, is thus firmly established by the agreeing results of two independent methods of synthesis. This di-iodo compound was then reduced by hydrogen and Raney nickel to Micheel's 1,6-didesoxy-2,3,4,5-D-mannitol, and the acid hydrolysis of the latter substance gave his 1,6-didesoxy-D-mannitol, though the yield was low, apparently because of the occurrence of reactions of undetermined nature accompanying the hydrolytic release of formaldehyde. Finally, we have verified the 1,6-didesoxy structure by the oxidation of 1,6-didesoxy-D-mannitol with periodic acid; it was found through the oxidation of 5 mg. of the substance according to the directions of Nicolet and Shinn[5] that each mole of it generated one and nine-tenths moles of acetaldehyde, corresponding to the theoretical two moles to be expected by the equation

$$CH_3(CHOH)_4CH_3 + 3HIO_4 = 2CH_3CHO + 2HCOOH + H_2O + 3HIO_3$$

a result which proves in this independent way that methyl groups occupy the terminal (1 and 6) positions in the didesoxy-D-mannitol.

1,6-Ditosyl-2,3,4,5-dimethylene-D-mannitol.—This derivative was obtained in quantitative yield by the action of tosyl chloride in pyridine solution upon 2,3,4,5-dimethylene-D-mannitol. It was recrystallized from 7 parts of chloroform by the addition of 7 parts of petroleum ether as rod-like prisms melting at 164–165° (cor.) and rotating $[\alpha]^{20}\mathrm{D}$ +68.1° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{22}H_{26}O_{10}S_2$: C, 51.35; H, 5.09. Found: C, 51.02; H, 5.09.

1,6-Di-iodo-2,3,4,5-dimethylene-D-mannitol.—A solution of 2.0 g. of 1,6-ditosyl-2,3,4,5-dimethylene-D-mannitol and 3.0 g. of sodium iodide in 50 cc. of acetone was heated for two hours at 100° in a pressure bottle. The cooled reaction mixture was filtered to remove the precipitated sodium tosylate and the crystalline residue, obtained by concentration of the filtrate, was washed with water to remove excess sodium iodide and recrystallized from 6 parts of dioxane. The yield was 1.6 g. (98%). The compound crystallized in octahedra which melted at 196–197° (cor.)

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(4) Brigl and Grüner, *Ber.*, **65**, 642 (1932); Müller, *ibid.*, **65**, 1055 (1932).

(5) Nicolet and Shinn, *J. Biol. Chem.*, **138**, 91 (1941); THIS JOURNAL, **63**, 1456 (1941).

and rotated $[\alpha]^{20}_{\mathrm{D}}$ +49.7° in chloroform (*c*, 0.8), in close agreement with Micheel's recorded values of 194–195° and $[\alpha]^{16}_{\mathrm{D}}$ +50.0° in chloroform.

Anal. Calcd. for $C_8H_{12}O_4I_2$: C, 22.55; H, 2.84. Found: C, 22.79; H, 2.99.

1,6-Didesoxy-2,3,4,5-dimethylene-D-mannitol.—A suspension of 3.0 g. of 1,6-di-iodo-2,3,4,5-dimethylene-D-mannitol and 1.0 g. of Raney nickel in a mixture of 50 cc. of methyl alcohol and 15 cc. of 10% methyl alcoholic sodium hydroxide solution was agitated vigorously at about 25° while hydrogen under a slight positive pressure was introduced. In thirty minutes 336 cc. (theory, 316 cc., S. T. P.) of hydrogen was taken up and no further absorption occurred in the second half hour. The catalyst was removed by filtration and the alkaline methanol solution was neutralized by a current of carbon dioxide and then concentrated *in vacuo* to dryness. The solid was extracted with three 10-cc. portions of ether and upon evaporation of the solvent the reduction product deposited in a yield of 1.0 g. The substance was recrystallized from 5 parts of petroleum ether (b. p. 30–65°) and formed prisms which melted at 59–60° (cor.) and rotated $[\alpha]^{20}_{\mathrm{D}}$ +54.9° in chloroform (*c*, 0.8). Micheel[3] reported a melting point of 60° and a specific rotation $[\alpha]^{18}_{\mathrm{D}}$ of +54.8° in chloroform for the 1,6-didesoxy-2,3,4,5-dimethylene-D-mannitol which he obtained by the action of molecular silver in toluene solution at 165–170° on 1,6-di-iodo-2,3,4,5-dimethylene-D-mannitol.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.07; H, 8.17.

1,6-Didesoxy-D-mannitol.—The hydrolysis of 1.0 g. of 1,6-didesoxy-2,3,4,5-dimethylene-D-mannitol with 10 cc. of boiling 10% hydrochloric acid was incomplete in ten hours and even after seventeen hours it was possible to isolate only 0.04 g. (5%) of 1,6-didesoxy-D-mannitol from the hydrolysis solution; further hydrolysis failed to yield more crystalline material. The 1,6-didesoxy-D-mannitol was recrystallized by solution in absolute alcohol and the addition of ether, and formed small prisms which melted at 147–148° (cor.) and rotated $[\alpha]^{20}_{\mathrm{D}}$ −22.5° in water (*c*, 0.7). Micheel reported a melting point of 148° and a rotation $[\alpha]^{18}_{\mathrm{D}}$ −17.6 in chloroform (*c*, 1.02); our compound was not soluble in chloroform at this concentration.

Anal. Calcd. for $C_6H_{14}O_4$: C, 47.98; H, 9.40. Found: C, 48.04; H, 9.40.

Determination of the Acetaldehyde Produced in the Oxidation of 1,6-Didesoxy-D-mannitol by Per-iodic Acid.—A sample of 4.993 mg. of 1,6-didesoxy-D-mannitol was oxidized by per-iodic acid and the acetaldehyde produced was determined by the procedures described by Nicolet and Shinn.[5] The consumption of 0.02 *N* iodine (6.30 cc.) corresponded to 0.0630 millimole of acetaldehyde, equivalent to 1.90 moles of acetaldehyde per mole of 1,6-didesoxy-D-mannitol. As previously mentioned, the expected production of acetaldehyde was 2.00 moles.

The structure of the second dimethylene-D-mannitol (m. p. 204–208°) has not been determined, but some evidence related to the question has been obtained. First, it is not oxidized by per-iodic acid, as has been mentioned. Second, it forms a ditosyl-dimethylene-D-mannitol, and it has not been possible to replace these tosyl groups by iodine through heating the compound with sodium iodide and acetone at 100°, or even at 140° with sodium iodide and acetic anhydride, a combination of reagents which we find to be more effective for this substitution in the case of other tosyl compounds. These results lead us to the tentative assumption that the two free hydroxyl groups in this second dimethylene-D-mannitol are secondary hydroxyls and that they are not contiguous. Should this be the case, the additional factor of the symmetry of the mannitol molecule limits the possible structure of the second dimethylene-D-mannitol to that of 1,3:4,6- or 1,3:5,6-dimethylene-D-mannitol.

Diacetate of the Second Dimethylene-D-mannitol.—The dimethylene-D-mannitol (m. p. 204–208°) was acetylated in the usual manner with sodium acetate and acetic anhydride and its diacetate was obtained in good yield in the form of prisms melting at 166° (cor.) and rotating $[\alpha]^{20}_{\mathrm{D}}$ −64.4° in chloroform (*c*, 0.9).

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25; CH_3CO, 29.7. Found: C, 49.82; H, 6.28; CH_3CO, 29.6.

Dibenzoate of the Second Dimethylene-D-mannitol.—The benzoylation of 2.0 g. of the dimethylene-D-mannitol in pyridine solution by benzoyl chloride, yielded 4.0 g. (quantitative) of a dibenzoate which, upon recrystallization from 30 parts of alcohol, formed elongated prisms melting at 180° (cor.) and rotating $[\alpha]^{20}_{\mathrm{D}}$ +9.5° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35; C_6H_5CO, 50.7. Found: C, 64.00; H, 5.42; C_6H_5CO, 50.9.

Ditosylate of the Second Dimethylene-D-mannitol.—This derivative was obtained in a yield of 82% by the action of tosyl chloride in pyridine solution upon the diacetal. It was recrystallized from 25 parts of alcohol as plates melting at 147° (cor.) and rotating $[\alpha]^{20}_{\mathrm{D}}$ −37.3° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{22}H_{26}O_{10}S_2$: C, 51.35; H, 5.09. Found: C, 51.70; H, 5.06.

We are indebted to Dr. A. T. Ness for performing the microchemical analyses and to Dr. B. H. Nicolet and Mr. L. A. Shinn, of the Bureau of Dairy Industry, U. S. Department of Agriculture, for assistance in the acetaldehyde determinations.

Summary

A dimethylene-D-mannitol is described and the method of its synthesis shows it to be 2,3,4,5-dimethylene-D-mannitol. It has been converted to 1,6-di-iodo-2,3,4,5-dimethylene-D-mannitol, which is found to be identical with the substance of same name which Micheel has described. This di-iodo derivative has been converted to the

known 1,6-didesoxy-2,3,4,5-dimethylene-D-mannitol and 1,6-didesoxy-D-mannitol; the latter substance yields the expected quantity of acetaldehyde on oxidation with per-iodic acid, a result which confirms the 1,6-didesoxy structure.

A second dimethylene-D-mannitol, so named provisionally, has been found in the mother liquor of the trimethylene-D-mannitol that results from the condensation of D-mannitol with formaldehyde under strongly acidic conditions. Evidence is presented which indicates that this isomer is either 1,3:4,6- or 1,3:5,6-dimethylene-D-mannitol.

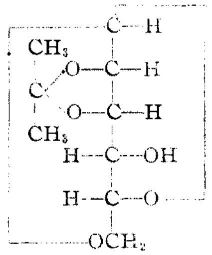
Bethesda, Md. Received October 23, 1942

[Contribution from the Division of Chemistry, National Institute of Health, U. S. Public Health Service]

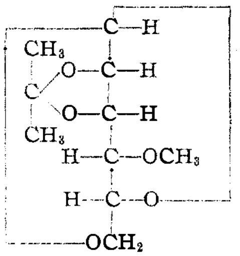
Crystalline 4-Methyl-D-mannose and Some of its Derivatives

By W. T. Haskins, Raymond M. Hann and C. S. Hudson

Pacsu and Trister[1] have recently prepared crystalline 2-methyl-D-mannose. This substance, in amorphous form, was first obtained by Pacsu and Kary[2] and thought to be 4-methyl-D-mannose, but subsequent studies,[3] which have now resulted in its crystallization as mentioned, show it to be the 2-methyl derivative. It was recently stated[4] that 4-methyl-D-mannose (III) has been prepared in this Laboratory through the complete acid hydrolysis of the methylation product (II) of 2,3-isopropylidene-D-mannosan<1,5>β<1,6> (I). The present paper describes the new sugar and some of its derivatives. Crystalline 4-methyl-D-mannose is an alpha form, since its aqueous solution at 20° shows a change in specific rotation from an initial value of +34° to an equilibrium value of +22.6°; the mutarotation constant, calculated for a unimolecular reaction, is 0.020 at 20°, which corresponds closely to that of D-mannose, for which the values 0.019[5] and 0.017[6] have been reported. A solution of the sugar in 1 N hydrochloric acid at 20° attained an equilibrium rotation $[\alpha]^{20}\text{D}$ + 22.4° within five minutes, but on heating the acid solution for one hour at 98° the rotation decreased to +18.5°, and this value was not changed on further heating; this rotation is close to that of +17.7° observed when 2,3-isopropylidene-4-methyl-D-mannosan <1,5>β<1,6> is hydrolyzed by 1 N hydrochloric acid at 98° and is also in agreement with the final value, namely, +18.7°, obtained when 4-methyl-α-methyl-D-mannopyranoside is completely hydrolyzed by 0.05 N hydrochloric acid at 98°; these agreeing results suggest that solutions of the sugar are converted by the action of the hydrochloric acid into an equilibrium mixture of the sugar and a substance of more negative rotation, possibly the sugar anhydride. The sugar yields a crystalline methylglycoside, which is doubtless a pyranoside of alpha configuration because its specific rotation (+83.9° in water) is more positive than the initial or the equilibrium rotation of the sugar, and furanose forms are not possible for this sugar. The difference in the molecular rotations of the glycoside ($[M]^{20}\text{D}$ +17,470) and the alpha form of the sugar ($[M]^{20}\text{D}$ +6600) is +10,870, which conforms with the fairly agreeing ($a_{\text{me}} - a_{\text{OH}}$) values that are known for many sugars and



2,3-Isopropylidene-D-mannosan<1,5>β<1,6>
(I)



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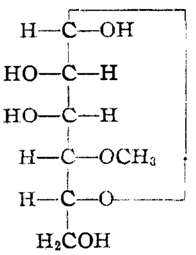
(II)



4-Methyl-α-D-mannose
(III)

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[1] Pacsu and Trister, This Journal, 63, 925 (1941).

[2] Pacsu and Kary, *Ber.*, 62, 2811 (1929).

[3] Levene, Meyer and Raymond, *J. Biol. Chem.*, 91, 498 (1931); Pacsu, *Ber.*, 65, 51 (1932).

[4] Knauf, Hann and Hudson, This Journal, 63, 1449 (1941).

[5] Hudson and Sawyer, *ibid.*, 39, 475 (1917).

[6] Isbell and Pigman, *J. Research Natl. Bur. Standards*, 18, 180 (1937).