[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY, AND THE PULP AND PAPER RESEARCH INSTITUTE OF CANADA]

D-Mannitol-1,2,3,5,6-pentanitrate

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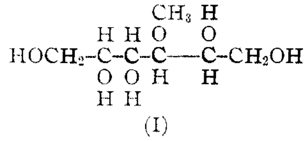
The crystalline D-mannitol pentanitrate known to be produced by the action of pyridine on the hexanitrate was shown to be the 1,2,3,5,6-derivative. The pentanitrate was stable to pyridine under conditions which cause selective partial denitration of D-mannitol hexanitrate. Methylation of the pentanitrate yielded a new compound, 4-methyl-D-mannitol pentanitrate, m.p. 111–112°, which was hydrogenated to the known 4-methyl-D-mannitol. The structure of the latter was confirmed by oxidation with periodate.

By passing dry ammonia gas into an ethereal solution of mannitol hexanitrate, Tichanowitsch[2] obtained a white crystalline solid resembling the hexanitrate in crystal form and sensitivity to shock and heat and capable of reduction to mannitol by ammonium sulfide. A report[3] that the crystals reduced Fehling solution was not confirmed by later workers[4,5] who showed definitely that the substance was a pentanitrate of mannitol, m.p. 81–82°, that the yield could be improved from 35% to 80 or 90% by replacing the ethereal solution of ammonia by pyridine, and that the pentanitrate could also be obtained in poor yield by a controlled nitration of mannitol. The vasodilatory action and solubility were studied[5] but no attempt to determine the detailed structure of the pentanitrate was made.[4] Since pyridine or other alkaline reagents appear to promote either a generalized degradation or a specific reaction with carbohydrate nitrates,[6,7,8] it seemed desirable to locate the position in the pentanitrate from which the nitrate group had been removed. The present article shows that the pentanitrate was the 1,2,3,5,6-derivative (structure II) and that this substance was stable to the further action of pyridine.

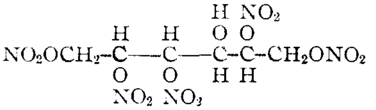
Preliminary experiments showed that the action of alcoholic pyridine on D-mannitol hexanitrate was slow and incomplete, but the action of pyridine alone produced a 73% yield of the pentanitrate with the correct elementary composition and melting point. The specific rotation, determined apparently for the first time, was $[\alpha]^{20}\mathrm{D}$ +43.6° in ethanol. Since both the hexanitrate and the pentanitrate gave 93% yields of crystalline D-mannitol when hydrogenated over a palladized charcoal catalyst,[9] and since the consumption of hydrogen was correct at 2.5 moles for each nitrate group removed, the partial denitration had caused no inversion or other change in the molecule. Details of these hydrogenations were similar to those described in the Experimental portion for the methylated pentanitrate. Methylation of the pentanitrate with silver oxide and methyl iodide gave a 66% yield of a new methyl mannitol pentanitrate, m.p. 111–112° and with a rotation of +39.8° in ethanol. Another Kuhn hydrogenation[9] gave a high yield of a crystalline monomethyl mannitol hydrate which after some difficulty was obtained in an anhydrous state, m.p. 134–135°, $[\alpha]^{20}\mathrm{D}$ +16.4° in water. When oxidized with aqueous potassium periodate, the monomethyl derivative yielded 1.76 moles of formaldehyde and 1.01 moles of formic acid. The high formaldehyde yield proved that the 1,2- and the 5,6-positions of the mannitol were unsubstituted and that the original compound was therefore either 3- or 4-monomethyl mannitol. Consideration of the structure (I) shows that these two particular position isomers are identical. The melting point and specific rotation of the 3(or 4)-monomethylmannitol, and also those of its crystalline pentaacetate, agreed with those of authentic samples synthesized in an independent way of Haskins, Hann and Hudson.[10] A mixed melting point of the 3(or 4)-monomethylmannitol with the authentic sample was not depressed.



$$\begin{array}{cccccc} & & & \mathrm{CH_3} & \mathrm{H} & \\ & \mathrm{H} & \mathrm{H} & \mathrm{O} & \mathrm{O} & \\ \mathrm{HOCH_2}- & \mathrm{C}- & \mathrm{C}- & \mathrm{C}\text{——} & \mathrm{C} & -\mathrm{CH_2OH} \\ & \mathrm{O} & \mathrm{O} & \mathrm{H} & \mathrm{H} & \\ & \mathrm{H} & \mathrm{H} & & & \end{array}$$

(I)

Since no case of wandering of nitrate or methyl groups from one hydroxyl group to another in a carbohydrate has ever been reported,[11] the mannitol pentanitrate had an unsubstituted hydroxyl group on the third or fourth position, or had the structure (II). It is probable that similar selective denitrations of other carbohydrate polynitrates may be encountered in the future.



$$\begin{array}{cccccc} & & & \mathrm{H} & \mathrm{NO_2} & \\ & \mathrm{H} & \mathrm{H} & \mathrm{O} & \mathrm{O} & \\ \mathrm{NO_2OCH_2}- & \mathrm{C}\text{——} & \mathrm{C}\text{——} & \mathrm{C}- & \mathrm{C} & -\mathrm{CH_2ONO_2} \\ & \mathrm{O} & \mathrm{O} & \mathrm{H} & \mathrm{H} & \\ & \mathrm{NO_2} & \mathrm{NO_2} & & & \end{array}$$

(II)

Experimental

Specific rotations were determined at 20° for the D line of sodium and with the use of 2-dm. or 4-dm. observation tubes. All evaporations were conducted under diminished pressure from a bath at not more than 50° and all products were recrystallized to constant melting point. To minimize risk and damage in the event of a detonation, no more than a few grams of mannitol hexa- or pentanitrate were stored or handled in a dry condition at one time.

D-Mannitol Hexanitrate.—Pure D-mannitol melting correctly at 166–167° and having a specific levorotation of −0.53° in water (*c*, 7.00), was nitrated in 5-g. lots as described by Patterson and Todd.[12] The hexanitrate melted

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(2) Tichanowitsch, *Z. chem. Pharm.*, 482 (1864); *J. Fortschritte Chem.*, 582 (1864).

(3) Vignon and Gerin, *Compt. rend.*, **133**, 515 (1901).

(4) Wigner, *Ber.*, **36**, 794 (1903).

(5) Marshall and Wigner, *Brit. Med. J.*, **2**, 1231 (1902).

(6) Gladding and Purves, THIS JOURNAL, **66**, 76 (1944).

(7) Giannini, *Gazz. chim. ital.*, **54**, 79 (1924).

(8) Kenyon and H. LeB. Gray, THIS JOURNAL, **58**, 1422 (1936).

(9) Kuhn, *ibid.*, **68**, 1761 (1946).

(10) Haskins, Hann and Hudson, *ibid.*, **65**, 70 (1943). The writer wishes to thank Dr. C. S. Hudson for having this mixed melting point determined.

(11) Bacon and Bell, *J. Chem. Soc.*, 1869 (1939).

(12) Patterson and Todd, *ibid.*, 2876 (1929).

correctly at 111–112°, had the correct nitrogen content and a specific rotation in ethanol of +43.1° (*c*, 2.13). The recorded values were $[\alpha]^{22}_{5790}$ + 45.8° and $[\alpha]^{22}_{4916}$ + 66.1°.[12]

D-Mannitol-1,2,3,5,6-pentanitrate.—Five grams of the hexanitrate dissolved almost immediately in 30 g. of pure pyridine at 25° to give a clear, colorless solution which rapidly turned yellow and commenced to evolve brown fumes. External cooling kept the temperature below 35° during the initial vigorous reaction, which lasted about 1 hour. After standing overnight at room temperature, the solution was poured into 300 ml. of water and the colorless precipitate of the pentanitrate was recovered on a sintered glass funnel, was thoroughly washed with water and then dried to constant weight in an evacuated desiccator. This drying was essential because traces of pyridine otherwise remained; yield 3.27 g. or 73%. Recrystallization from aqueous ethanol gave the pure product as silk-like, colorless needles with the correct melting point of 81–82°,[4] the correct nitrogen content and with a specific rotation in alcohol of +43.6° (*c*, 4.426).

The compound did not reduce Fehling solution, dissolved readily in methanol, ether and acetone and was insoluble in water, petroleum ether, benzene and chloroform.

In preliminary experiments, 2 g. of an original 5 g. of the hexanitrate was recovered unchanged after having been heated under reflux for one hour with 50 ml. of ethanol containing 1.7 ml. of pyridine; 3 g. of the hexanitrate, similarly heated with 15 ml. of ethanol and 4.0 ml. of pyridine, gave only a 13.7% yield of the pentanitrate. These preparations were similar to that preferred by Wigner[4] but the high yields he claimed could not be duplicated.

4-Methyl-D-mannitol Pentanitrate.—D-Mannitol pentanitrate, 2.19 g., was heated under reflux for 2 hours with acetone, 5 ml.; methyl iodide, 5 ml.; Drierite, 10 g.; and dry silver oxide, 10 g. The sirup recovered by filtration and evaporation soon crystallized. Recrystallization from aqueous ethanol gave 1.50 g. (66%) of the pure product as long colorless needles melting at 111–112° and with a specific dextrorotation of 39.8° in alcohol (*c*, 1.505).

Anal. Calcd. for $C_6H_8(OCH_3)(NO_3)_5$: N, 16.6; OCH_3, 7.4. Found: N, 16.3, 16.9 (micro-Kjeldahl); OCH_3, 7.5, 7.5.

The substance was soluble in alcohol, ether, dioxane and acetone but was insoluble in water.

4-Methyl-D-mannitol.—The corresponding pentanitrate, 0.99 g., was dissolved in 10 ml. of 1,4-dioxane and the solution was diluted with 30 ml. of ethanol and 10 ml. of water. One gram of palladized charcoal, prepared by the method of Hartung[13] was added and the mixture was shaken at room temperature with 32 p.s.i. pressure of hydrogen.[9] The pressure decreased to a constant value within 35 minutes and the drop corresponded to the consumption of 10.8 moles of hydrogen per mole of starting material. Evaporation of the filtered solution, which was free from nitrate by the diphenylamine test, yielded 0.605 g. of a sirup which crystallized after being dried *in vacuo*. After one recrystallization from ethanol–pentane the product melted at 83–84° with frothing. Haskins and co-workers[10] quoted m.p. 86–87° for a monohydrate. After drying to constant weight at 56° *in vacuo*, however, the substance had m.p. 113–114° and had a specific dextrorotation in water of 15.5°. Two more recrystallizations from ethanol–pentane failed to alter this melting point.

Anal. Calcd. for a hemihydrate $C_7H_{16}O_6 \cdot {}^1/_2H_2O$: OCH_3, 15.1. Found: OCH_3, 14.8, 15.0.

Recrystallization of the supposed hemihydrate from isoamyl alcohol gave a 68% yield of pure anhydrous 4-methyl-D-mannitol, with m.p. 134–135° and specific rotation in water 16.4° (*c*, 2.00). Haskins and co-workers[10] reported m.p. 133–134° and specific rotation of +16.7° in water (*c*, 2.0) for their product.

Acetylation of 4-methylmannitol with acetic anhydride and pyridine gave a 98% yield of the corresponding pentaacetate, which was recrystallized as quadratic plates whose melting point, 85–86°, and specific rotation, +35.8° in chloroform (*c*, 0.85), checked those reported by Haskins, Hann and Hudson.[10]

4-Methyl-D-mannitol and Potassium Metaperiodate.—A 0.101-g. sample of the methylmannitol was oxidized with aqueous potassium metaperiodate as described by Halsall, Hirst and Jones.[14] Aliquots of 10 ml. were withdrawn at intervals, excess periodate was destroyed by adding pure ethylene glycol, and the formic acid liberated was titrated with 0.01 *N* barium hydroxide solution. A calibrated Beckman *p*H meter was used and blanks were run. After 2, 4, 6 and 24 hours, 0.85, 0.98, 1.01 and 1.01 moles of formic acid were found per mole of 4-methylmannitol. A similar experiment with D-mannitol itself revealed 2.50, 2.65, 2.81 and 2.96 moles of formic acid after 2, 24, 168 and 336 hours of oxidation.

Two 10- to 12-mg. samples of 4-methyl-D-mannitol were oxidized with 0.3 *M* periodic acid and the formaldehyde produced was isolated according to Reeves[15] as the crystalline dimedon compound, m.p. 190°; found, 1.77 and 1.75 moles per mole of 4-methyl-D-mannitol, in circumstances where mannitol itself yielded 1.97 and 2.00 moles.

Stability of 4-Methyl-D-mannitol Pentanitrate to Pyridine.—The pure pentanitrate, 0.5 g., was dissolved in 3 ml. of pure pyridine and after standing overnight at room temperature the solution was diluted with 30 ml. of water. The colorless, crystalline precipitate weighed 0.455 g. (91%) and its m.p. of 81–82° was not depressed by admixture with an authentic sample of the original pentanitrate.

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(13) Hartung, THIS JOURNAL, **50**, 3372 (1928).

(14) Halsall, Hirst and Jones, *J. Chem. Soc.*, 1427 (1947).

(15) Reeves, THIS JOURNAL, **63**, 1476 (1941).