



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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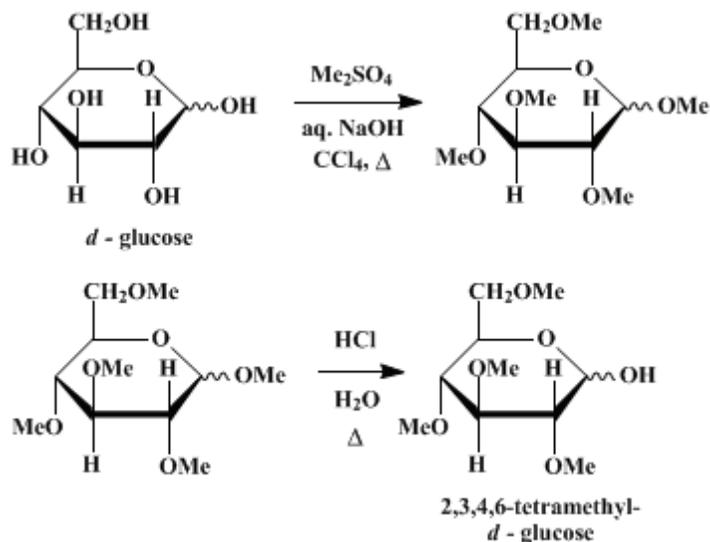
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 3, p.800 (1955); Vol. 20, p.97 (1940).

2,3,4,6-TETRAMETHYL-*D*-GLUCOSE

[*D*-Glucose, 2,3,4,6-tetramethyl-]



Submitted by Edward S. West and Raymond F. Holden.

Checked by W. W. Hartman and A. J. Schwaderer.

1. Procedure

This preparation must be carried out in a hood having good ventilation. [Methyl sulfate](#) has a high vapor pressure in spite of its high boiling point and is very poisonous. [Ammonia](#) is a specific antidote and should be kept on hand to destroy any of the ester accidentally spilled. It is advisable to wash the hands in dilute [ammonium hydroxide](#) frequently.

In a 2-l. distilling flask immersed in a 4-l. water bath are placed 25 g. (0.14 mole) of anhydrous [glucose](#) ([Note 1](#)) and 15 ml. of water. The flask is fitted with a cork through which passes a strong mechanical stirrer ([Note 2](#)) and a dropping tube connected by rubber tubing and a screw clamp to a 500-ml. reservoir flask. The side tube of the flask is connected to a water condenser, fitted with a suction flask, from which fumes are led to a flue by a piece of tubing. The temperature of the water bath is raised to 55° , and the [glucose](#) is brought into solution with rapid stirring, which is maintained throughout the process. A mixture of 90 ml. (120 g., 9.5 moles) of [methyl sulfate](#) and 125 ml. of [carbon tetrachloride](#) is added from the reservoir as quickly as possible to the flask. The clamp is closed, and 400 ml. (580 g.) of 40% (by weight) [sodium hydroxide](#) is placed in the reservoir. The alkali is admitted to the flask at the rate of 1 drop in 2 seconds for 5 minutes, then 1 drop per second for 5 minutes, and then 3 drops per second until the distillation of [carbon tetrachloride](#) slackens or ceases. This is usually accomplished in 15–20 minutes and after the addition of 70–90 ml. of alkali. The heat of reaction generally maintains the proper temperature of 50 – 55° throughout this stage without the necessity of heating the water bath externally. The remainder of the alkali is added as quickly as possible, and the bath temperature raised to and maintained at 70 – 75° . Then 160 ml. (208 g., 1.65 moles) of [methyl sulfate](#) is placed in the reservoir immediately and added at the rate of 3–4 drops per second (slower if the mixture foams seriously).

After all the [methyl sulfate](#) has been added, the bath is boiled for 30 minutes with continued stirring. The contents of the flask are cooled, diluted with sufficient water to dissolve most of the separated [sodium sulfate](#), and extracted four times with 150-ml. portions of [chloroform](#); the [chloroform](#) and water layers are separated carefully. The combined [chloroform](#) extracts ([Note 3](#)) are placed in a 2- or 3-l. distilling flask (with condenser attached) with 400 ml. of 2 *N* [hydrochloric acid](#), and the [chloroform](#) is

removed by distillation. A rapid current of steam is then passed through the solution for 1 hour, care being taken to maintain the volume approximately constant by heating the flask. Five grams of **Norite** is added to the hot solution, which is then cooled and filtered. The filtrate is saturated with **sodium sulfate** and extracted four times with 150-ml. portions of **chloroform**. The combined **chloroform** extracts are dried with **sodium sulfate**, 1 g. of **Norit** is added, and the mixture is filtered. The **chloroform** is removed as completely as possible in a boiling water bath without vacuum and finally at the water pump. The heavy syrup is treated with 40–50 ml. of petroleum ether (30–60°) and shaken for a short time, whereupon it sets to a mass of crystals. After cooling in an ice bath for 30 minutes, the crystals are filtered, washed with a little cold petroleum ether, and dried over **calcium chloride** under reduced pressure. The yield is 15–18 g. (46–55%) (**Note 3**). The specific rotation, $[\alpha]_D^{26}$, in water was found to be about +79–79.5°, when $c = 4$; a drop of 15% **ammonia** was added to speed equilibration, and the readings were made 1 hour after the solution was prepared in a 2-dm. tube.

The slightly impure product is recrystallized from petroleum ether (b.p. 30–60°) containing 0.5% of anhydrous **ether** in a continuous extractor, using 100 ml. of solvent per 6–7 g. of compound. One crystallization is generally sufficient to give a pure product. The specific rotation of pure **tetramethyl-d-glucose** prepared by this method is approximately $[\alpha]_D^{20} +81.3^\circ$ (**Note 4**).

2. Notes

1. α -Methylglucoside may be methylated in the same way as **glucose**, using four-fifths of the reagents and hydrolyzing the tetramethyl- α -methylglucoside (contained in the **chloroform** solution) for 3 hours instead of the 1 hour required for the mixture of α - and β -tetramethyl-methylglucosides obtained directly from **glucose**. **Tetramethylglucose** prepared in this way may show the correct rotation without recrystallization.

2. The stirrer consists of a 3/16-in. Monel rod formed into a 1-in. flattened loop at one end for stirring. The stirrer is passed through a closely fitting 3/8 by 5 in. brass bearing with a packing nut at the lower end, the top of the bearing being countersunk to facilitate oiling with heavy engine oil. This metal stirrer permits much more vigorous stirring (which is essential) than the ordinary glass apparatus.

3. The tetramethylmethylglucosides may be isolated from the **chloroform** solution by drying with **sodium sulfate**, distilling off the **chloroform**, and then vacuum-distilling the syrup. The distillation can be easily carried out in a distilling flask (100-ml.) filled with glass wool (which effectively prevents bumping) and having a low side arm. The glass wool materially lowers the distilling temperature. The mixture of α - and β -glucosides (approximately 85% β form) and the pure α form distil at about 88–90°/0.15 mm. under the above conditions, and they constitute the entire distillate after the solvent has been removed. The specific rotation, $[\alpha]_D$, lies between +9° and +12°, depending upon the proportion of isomers in the distillate; for the pure α form it is 151°/25°. The refractive index is 1.4445²⁰ for the α,β mixture and 1.4460²⁰ for the pure α isomer.

4. The correct value for any temperature between 5° and 37° may be calculated from the equation $[\alpha]_D^T = 85 - 0.1846t$. The melting point of the compound varies according to the proportion of α and β isomers present. After prolonged digestion with petroleum ether, the α isomer predominates and the melting point rises. A sample of the product recrystallized once melted at 90–93°, and after five recrystallizations it melted at 98°, without change in the optical rotation.

3. Discussion

Tetramethyl-d-glucose has been prepared by the action of **methyl iodide** and **silver oxide** on **methylglucoside**,¹ by the action of **methyl sulfate** and alkali on both **methylglucoside** and **glucose**,² and also by hydrolysis of various methylated polysaccharides, for example **methyl decamethyl maltotrioxide**.³

This preparation is referenced from:

- **Org. Syn. Coll. Vol. 3, 798**

1. Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903).
 2. Haworth, *J. Chem. Soc.*, **107**, 8 (1915); **113**, 188 (1918).
 3. Sugihara and Wolfrom, *J. Am. Chem. Soc.*, **71**, 3357 (1949).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

petroleum ether

α -Methylglucoside

tetramethyl- α -methylglucoside

methyl decamethyl maltotrioside

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

silver oxide (20667-12-3)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

Norite,
Norit (7782-42-5)

ammonium hydroxide (1336-21-6)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

glucose (492-62-6)

D-Glucose, 2,3,4,6-tetramethyl-,
2,3,4,6-Tetramethyl-D-glucose (7506-68-5)

Tetramethylglucose,

tetramethyl-d-glucose

methylglucoside

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