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2,3,6-Trimethylglucose Diethyl Mercaptal and its Use in the Preparation of 2,3,6-Trimethylglucose

BY M. L. WOLFROM AND LOUIS W. GEORGES[1]

2,3,6-Trimethylglucose has been synthesized from *d*-glucose by Irvine and Rutherford,[2] but the procedure employed is rather laborious for preparative purposes. The trimethylglucose can also be obtained as a hydrolytic product of methylated cellulose, methylated starch and a number of methylated disaccharides. The free sugar is very sensitive and is difficult to isolate in good yield. We have found that it forms a well-crystallized and easily isolable diethyl mercaptal, from which the free sugar can be regenerated under mild conditions and can thus be prepared readily in good purity.

In the work herein reported, methylated cellulose has been used as a source of 2,3,6-trimethylglucose. Irvine and Hirst[3] prepared this trimethylglucose by the treatment of methylated cellulose under pressure with methanol containing hydrogen chloride, and subsequent hydrolysis of the glycosidic methyl group. Denham and Woodhouse,[4] who first obtained crystalline 2,3,6-trimethylglucose, prepared it from methylated cellulose by direct hydrolysis with fuming hydrochloric acid. Hess and Neumann[5] likewise prepared this trimethylglucose by the hydrolysis of methylated cellulose with fuming hydrochloric acid, purifying the product through its methylglycoside.

In our experiments, methylated cellulose was hydrolyzed with fuming hydrochloric acid at low temperatures and the diethyl mercaptal of 2,3,6-trimethylglucose was isolated directly from the acid solution. This was an extension of the work previously reported from this Laboratory[6] on the hydrolysis of cellulose with fuming hydrochloric acid and mercaptalation at various stages of the hydrolysis. The free sugar was then regenerated from its diethyl mercaptal by treatment with mercuric chloride in moist acetone in the presence of cadmium carbonate.[7]

2,3,6-Trimethylglucose diethyl mercaptal is a readily crystallizable substance and forms a crystalline dibenzoate. There are thus added two crystalline derivatives to the rather small number recorded for this sugar. The diethyl mercaptal offers promise as a characterizing derivative for 2,3,6-trimethylglucose. The diethyl mercaptal of tetramethylglucopyranose was also obtained. This was an oil which formed a crystalline monobenzoate.

Experimental

Preparation of Methylated Cellulose.[8]—Commercial acetone-soluble cellulose acetate (20 g.; CH_3CO, 40%)[9]

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[1] Du Pont Cellulose Research Fellow.

[2] J. C. Irvine and Jean K. Rutherford, THIS JOURNAL, **54**, 1491 (1932).

[3] J. C. Irvine and E. L. Hirst, *J. Chem. Soc.*, **123**, 518 (1923).

[4] W. S. Denham and Hilda Woodhouse, *ibid.*, **105**, 2357 (1914).

[5] K. Hess and F. Neumann, *Ber.*, **68**, 1360 (1935).

[6] M. L. Wolfrom and L. W. Georges, THIS JOURNAL, **59**, 282 (1937).

[7] M. L. Wolfrom, *ibid.*, **51**, 2188 (1929).

[8] We wish to acknowledge the assistance rendered by Messrs. M. E. Bernstein and R. D. Koons in the preparation of the methylated cellulose used in this work.

[9] Furnished through the courtesy of the du Pont Rayon Co., Waynesboro, Va. The viscosity of this material in 7% solution in acetone was 16.8 on the basis of an assigned viscosity of 100 for pure glycerol.

was methylated in one step to an approximate trimethyl cellulose according to the procedure employed by Haworth, Hirst and Thomas.[10] This method gave an average yield of 15 g. of the crude methylated product with a methoxyl content varying from 42 to 44%. This material was used without further purification in the subsequent hydrolytic experiments.

2,3,6-Trimethyl-*d*-glucose Diethyl Mercaptal.—Methyl cellulose (13.5 g.; OCH_3, 42–44%) was placed in a glass-stoppered pressure bottle and 200 cc. of fuming hydrochloric acid (d_4^{15} 1.202) added. Complete solution was effected by cooling to 0° and shaking. The solution, colored a pale amber, was allowed to stand at 4° for thirteen days. The solution had then acquired a dark-brown color which was removed by two treatments with Carboraffin, filtering each time through a layer of asbestos, previously treated with fuming hydrochloric acid. The final volume of the solution was adjusted with water to approximately 220 cc. and the solution divided into two 110-cc. portions for mercaptalation. Each portion was shaken mechanically for fifteen minutes at 0° with 14 cc. of purified ethyl mercaptan and was neutralized by pouring into a suspension of 107 g. of sodium bicarbonate in 170 cc. of water. During the neutralization a curdy precipitate formed. The mixture was kept overnight at ice-box temperature, filtered and dried in a vacuum desiccator over sodium hydroxide. The crude products from the two mercaptalations were combined and extracted with anhydrous ether. The ethereal extract was decolorized with Carboraffin, dried and the solvent removed; yield 10.5 g. of crystalline material. Pure material was obtained on recrystallization from petroleum ether (b. p. 65–110°); m. p. 71–72°; $[\alpha]^{29}$ $-15°$ (c, 3.8; $CHCl_3$).[11] The compound crystallizes in fine needles and is soluble in water, alcohol and the usual organic solvents.

Anal. Calcd. for $C_6H_9O_2(OCH_3)_3(SC_2H_5)_2$: S, 19.5; OCH_3, 28.3. Found: S (Carius), 19.3; OCH_3 (Kirpal and Bühn[12] method), 27.8.

Preparation of 2,3,6-Trimethyl-*d*-glucose from 2,3,6-Trimethyl-*d*-glucose Diethyl Mercaptal.—2,3,6-Trimethylglucose diethyl mercaptal (5.0 g.) was dissolved in acetone (30 cc.) containing water (0.8 cc.) and finely ground cadmium carbonate (4 g.) was added. A solution of mercuric chloride (16.0 g.) in acetone (30 cc.) was added gradually with mechanical stirring. The reaction was allowed to run at room temperature for twenty-four hours with occasional additions of fresh cadmium carbonate and acetone. The reaction mixture was then heated with stirring on a water-bath (40°) for fifteen minutes, filtered and the residue washed with acetone. The filtrate was concentrated in the presence of cadmium carbonate under reduced pressure at 35° to a viscous residue. This residue was extracted several times with warm chloroform until only a powder remained. The chloroform solution was filtered and then concentrated under reduced pressure at 35° to a sirup. The latter was dissolved in warm water and hydrogen sulfide passed into the cooled solution. The mercuric sulfide was removed by filtration, the filtrate aerated and the acid neutralized with solid sodium bicarbonate. The aqueous solution was then concentrated under reduced pressure at 40° to about one-third of the original volume. At this point inorganic salts began to separate and were removed by the addition of acetone to the solution and filtration. The filtrate was concentrated to a crystalline mass and the latter taken up in chloroform and the chloroform solution evaporated in a vacuum desiccator. The last traces of solvent were removed by stirring dry ether into the mass and evaporating under reduced pressure; yield, 2.6 g. The crystals so obtained were contaminated with a small amount of sirup, which was removed by two extractions with warm anhydrous ether; yield 2.0 g.; m. p. 104–108°. After one recrystallization from ordinary ether the melting point was 116–117°. Digestion of this material with cold, ordinary ether raised the melting point to 118–119°. The compound shows a downward mutarotation in aqueous solution and gave a final value after three and one-half hours of $[\alpha]^{26}$ $+68°$ (c, 1.7). The initial value after extrapolation to zero time was found to be $[\alpha]^{26}$ $+102°$. These constants identify the substance as 2,3,6-trimethylglucose of good purity.[13]

2,3,6-Trimethyl-*d*-glucose Diethyl Mercaptal 4,5-Dibenzoate.—2,3,6-Trimethylglucose diethyl mercaptal (1.0 g.) was benzoylated with pyridine (2 cc.) and benzoyl chloride (1 cc.) by standing at room temperature for twenty-four hours. Chloroform was added and the solution washed successively with 10% hydrochloric acid, aqueous sodium bicarbonate and water. The dried chloroform solution was concentrated under reduced pressure to a crystalline mass. Ether was added and the last traces of solvent removed under reduced pressure; yield 1.3 g. of crystalline material. The substance was obtained pure on recrystallization from ethanol; m. p. 115–116°; $[\alpha]^{23}$ $+61°$ (c, 4; $CHCl_3$). The compound crystallizes in glittering, elongated prisms and is soluble in ether, chloroform, acetone and benzene; is moderately soluble in alcohol; and is practically insoluble in water and petroleum ether.

Anal. Calcd. for $C_6H_7O_2(OCH_3)_3(COC_6H_5)_2(SC_2H_5)_2$: S, 11.9; C_6H_5CO, 39.1. Found: S, 11.6; C_6H_5CO,[14] 38.8.

2,3,4,6 - Tetramethyl - *d* - glucose Diethyl Mercaptal 5 - Benzoate.—Tetramethylglucopyranose[15] (3.0 g.) was dissolved in 30 cc. of concentrated hydrochloric acid (d^{15}_4 1.185) and the solution cooled to 0°. Ethyl mercaptan (6 cc.) was added and the mixture shaken at 0° for fifteen minutes, whereupon it was poured with stirring into a suspension of 30 g. of sodium bicarbonate in 75 cc. of water. The oily layer that separated was dissolved in chloroform and the mother liquor was extracted with chloroform. The combined extracts were dried, decolorized with Carboraffin and concentrated under reduced pressure to a thin sirup. Anhydrous ether was added and the solvent again removed under reduced pressure; yield 2.5 g. The sirup did not crystallize on standing for several weeks.

An amount of 2.5 g. of the sirupy tetramethylglucose diethyl mercaptal was benzoylated with pyridine (3 cc.) and benzoyl chloride (1.5 cc.) as described for the synthesis of

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[10] W. N. Haworth, E. L. Hirst and H. A. Thomas, *J. Chem. Soc.*, 821 (1931).

[11] All rotations are herein recorded to the D-line of sodium light.

[12] A. Kirpal and T. Bühn, *Ber.*, **47**, 1084 (1914).

[13] J. C. Irvine and E. L. Hirst, *J. Chem. Soc.*, **121**, 1213 (1922).

[14] P. Brigl and H. Muehlschlegel, *Ber.*, **63**, 1551 (1930).

[15] Acknowledgment is made to Mr. D. R. Husted for the tetramethylglucopyranose preparation.

2,3,6-trimethylglucose diethyl mercaptal 4,5-dibenzoate and the product was crystallized in the same manner; yield 2.2 g. Pure material was obtained on crystallization from methanol by the addition of water; m. p. 64–65°; $[\alpha]^{21}$ +33° (*c*, 3.7; $CHCl_3$).

Anal. Calcd. for $C_6H_7O(OCH_3)_4(COC_6H_5)(SC_2H_5)_2$: S, 14.4; C_6H_5CO, 23.5. Found: S (Carius), 14.2; C_6H_5CO,[14] 23.2.

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Summary

1. 2,3,6-Trimethyl-*d*-glucose diethyl mercaptal, its dibenzoate and the monobenzoate of 2,3,4,6-tetramethyl-*d*-glucose diethyl mercaptal have been synthesized in crystalline condition.

2. 2,3,6-Trimethyl-*d*-glucose may be prepared readily by the hydrolysis of methylated cellulose with fuming hydrochloric acid, isolation of the sugar as its diethyl mercaptal and subsequent removal of the ethylmercapto groups.

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The Cleavage of Diphenyl Ethers by Sodium in Liquid Ammonia. I. Ortho and Para Substituted Diphenyl Ethers

BY PAUL A. SARTORETTO AND FRANK J. SOWA

It has been found that a solution of sodium in liquid ammonia reacts vigorously and quantitatively with diphenyl ether. The reaction is complete when two atom equivalents of sodium is added to one mole equivalent of the ether. The products are mole equivalents of sodium phenate and benzene.

Conductivity experiments by Kraus[1] have shown that sodium is ionized in the medium of liquid ammonia, the metal being in equilibrium with sodium cations and electron anions. If reactivity involves sodium cations, a compound such as sodamide which is also ionized in liquid ammonia should cleave diphenyl ether; but it does not. Cleavage, therefore, involves either atomic sodium or the electron anions. Although there is no experimental proof favoring either, in a reduction of this type the electron anions are commonly thought of[2] as being the effective reagent. The mechanism of the reaction may be expressed as

$$\mathrm{ROR} + 2\mathrm{Na}^+ + 2\mathrm{e}^- \longrightarrow \mathrm{Re}^- + \mathrm{ROe}^- + 2\mathrm{Na}^+$$
$$\mathrm{Re}^- + \mathrm{NH_3} + \mathrm{Na}^+ \longrightarrow \mathrm{RH} + \mathrm{NH_2}^- + \mathrm{Na}^+$$

where (R) represents a phenyl group, and (e^-) an electron anion.

The purpose of this investigation was to use the above quantitative method to evaluate the effect of various substituents in the ortho and para positions. It was also employed to evaluate the effect of the ortho against the para position using the same substituent.

Experimental

For the preparation and physical properties of the substituted diphenyl ethers listed in Table I and used in this work the authors are indebted to John J. Verbanc for his assistance.

TABLE I

PHYSICAL PROPERTIES OF SOME DIPHENYL ETHERS

No.	Diphenyl ether	Yield, %	B. p., °C.	B. p., Mm.	M. p., °C.	Sp. gr., (25°C.)	n^{25}_D
1	*p*-Nitro-	80	200	15	56–58		
2	*o*-Nitro-	70	185	8			
3	*p*-Amino-	99	188	14	83.5		
4	*o*-Amino-	99	170	18	44		
5	*o*-Methoxy-	60	288	745	76		
6	*p*-Methoxy-	55	125	5		1.1133	1.5762
7	*o,p'*-Dimethoxy-	55	203	20	77		
8	*o*-Methyl-	58	101	5		1.0468	1.5695
9	*p*-Methyl-	67	114	6		1.0450	1.5697
10	*o,p'*-Dimethyl-	54	121	7		1.0299	1.5640
11	*o*-Carboxy-	58			112–114		
12	*p*-Carboxy-	45			141		

(1) and (2) prepared according to the method of Brewster and Groening, "Organic Syntheses," John Wiley and Sons, New York, Vol. XIV, p. 67. (3) and (4) by the reduction of the corresponding nitro compounds employing the method of Suter, THIS JOURNAL, **51**, 2583 (1929). (5) and (6) prepared by heating 252 g. of guaiacol, 56 g. of potassium hydroxide and 2 g. of copper catalyst to 150° until all of potassium hydroxide dissolved. The water was distilled, any guaiacol that steam distilled was replaced. After adding 137 g. of bromobenzene the mixture was heated on an oil-bath for two and one-half hours at 220–230°. *p*-Methoxydiphenyl ether prepared by same procedure except phenol was used in place of guaiacol and *p*-bromoanisole in place of bromobenzene. (7) Similar to preparation (5) using guaiacol and *p*-bromoanisole and heated on an oil-bath for three hours. (8),

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[1] Kraus, THIS JOURNAL, **30**, 1323 (1908).

[2] Franklin, "The Nitrogen System of Compounds," Am. Chem. Soc. Monograph, 1935, p. 50.