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A Synthesis of 2,4,6-Trimethylglucose

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Researches on 2,4,6-trimethylglucose formed part of a wider investigation carried out in this Laboratory some years ago. The major researches led to ambiguous results, but we have been asked by Professor Freudenberg to publish this synthesis, to which reference has already been made in the footnote of a previous communication.[1]

The most obvious method of approach to derivatives of 2,4,6-trimethylglucose is through a compound in which position 3 is occupied by a stable group of atoms. The non-labile nature of the *p*-toluenesulfonyl group had long been recognized and 3-*p*-toluenesulfonyl-diacetone-glucose was accordingly chosen as a suitable starting material. Attempts to methylate the sirupy 3-*p*-toluenesulfonyl-β-methylglucoside, obtained from 3-*p*-toluenesulfonyl-diacetone-glucose as described in the practical part of this paper, led, however, to unfortunate results, direct methylation being followed by unexpected decomposition and an indirect method being rendered difficult by steric hindrance. An alternative route was, however, available. The 3-*p*-toluenesulfonyl-diacetone-glucose was converted to a mixture of the corresponding α- and β-methylglucosides by boiling with methyl alcohol containing hydrogen chloride and this mixture, unlike the pure β-methylglucoside, reacted readily with the methylating reagents. The α-form of 3-*p*-toluenesulfonyl-2,4,6-trimethylmethylglucoside was separated in the crystalline state and is here described for the first time. Unfortunately, the β-form could not be isolated from the mixture and, as it was this form that was required for identification purposes, another method of preparation had to be employed.

2-Monomethyl-β-methylglucoside was treated with benzaldehyde and converted to the corresponding benzylidene compound. Its constitution was determined by methylation of a small sample from which a good yield of the well-known 2,3-dimethyl-benzylidene-β-methylglucoside was obtained. The main bulk reacted with *p*-toluenesulfonyl chloride with difficulty, giving a crystalline derivative in which the *p*-toluenesulfonyl group must necessarily occupy position 3. This, after removal of the benzylidene residue and methylation of the sirup so obtained, was converted into a crystalline substance with the composition of a mono-*p*-toluenesulfonyl-trimethylmethylglucoside, its method of preparation leaving no doubt as to the positions occupied by the various groups. It was shown to be identical with the crystals obtained by treating the 2,4,6-trimethyl-β-methylglucoside (referred to in our previous paper) with *p*-toluenesulfonyl chloride. This trimethyl-glucose had been obtained from sucrose and, although good reasons had been advanced by Haworth[2] to show that the methyl groups occupied positions 2,4,6, its constitution had not been established definitely.

Experimental

3 - *p* - Toluenesulfonyl - triacetyl - β - methylglucoside.—3-*p*-Toluenesulfonyl-diacetone-glucose was hydrolyzed by boiling in 8.55% concentration with acetonitrile containing 20% by volume of 0.1 *N* hydrochloric acid for two hours, when the rotation became constant at +49.9°. The solution was neutralized with barium carbonate, evaporated to dryness at 80° (if drying is continued too long, decomposition occurs) and the product acetylated with excess of acetic anhydride and pyridine. Two and one-half grams of starting material yielded 3 g. of product which partly crystallized, giving 1.2 g. of crystals melting at 170–171° and having $[\alpha]_D$ in chloroform +8.7° for *c*, 5.075,[3] and 1.8 g. of sirup having $[\alpha]_D$ in chloroform +42.6° for *c*, 5.482. On treatment with 25% of hydrobromic acid in glacial acetic acid, ether and benzene in the usual manner, the rotation of the crystals rose to +170.0° and of the sirup to +141.5°, indicating that the sirup contained a fair amount of compound in the γ-form. The product was converted to the β-methylglucoside by reaction with methyl alcohol and silver carbonate. From 19.1 g. of total acetylated material, 8.9 g. of the pure β-methylglucoside,[3] m. p. 134–136°, and 1.7 g. of less pure, m. p. 125–128°, were obtained.

The products were deacetylated with sodium methylate in a mixture of benzene and methyl alcohol at the temperature of the room. The system was neutralized with a few drops of glacial acetic acid and evaporated to dryness at 40°. The sirup, so obtained, was treated with silver oxide and methyl iodide. During the methylation, however, decomposition seemed to occur.

3 - *p* - Toluenesulfonyl - 4,6 - benzylidene - β - methylglucoside.—One and three-tenths grams of 3-*p*-toluenesulfonyl-β-methylglucoside, obtained as described above, was treated with benzaldehyde and zinc chloride for twenty

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[1] Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

[2] Haworth, *J. Chem. Soc.*, 273 (1926).

[3] Freudenberg, *Ber.*, **55**, 929 (1922).

hours and the product was recrystallized from absolute alcohol as prisms melting at 174–176° with decomposition and having $[\alpha]_D$ in chloroform −93.3° for *c*, 5.653. It was almost insoluble in hot and cold alcohol but soluble in other solvents. Calcd. for $C_{21}H_{24}O_8S$: OCH_3, 7.2. Found: OCH_3, 6.4.

On attempted methylation, the melting point merely rose to 179–182°. As it was shown later that the methylated compound melted at 135–136°, it was assumed that methylation had been prevented by steric hindrance.

3 - *p* - Toluenesulfonyl - 2,4,6 - trimethyl - α - methylglucoside.—3 - *p* - Toluenesulfonyl - diacetone - glucose was boiled with methyl alcohol containing 2% of hydrogen chloride. The following changes in rotation occurred:

0.5 hour	5 hours	6.5 hours
−21.3	+15.9	+17.9

In the last two calculations, allowance was made for change in concentration due to the loss of the acetone groups. The solution was neutralized and the product was isolated in the usual manner. Methylation with silver oxide followed until the refractive index became constant at 1.4999. On standing, the product partly crystallized; the crystals were isolated from the sirup and, after recrystallization, melted at 123–124° with $[\alpha]_D$, in chloroform, +53.6° for *c*, 2.64. Calcd. for $C_{17}H_{18}O_8S$: OCH_3, 31.8. Found: OCH_3, 31.6.

4,6 - Benzylidene - 2 - methyl - β - methylglucoside.—On treating 6.4 g. of 2-methyl-β-methylglucoside with benzaldehyde and zinc chloride, 6.1 g. of crystalline benzylidene compound, m. p. 169–171°, was isolated. After recrystallization from absolute alcohol, the product separated in needles, m. p. 170–171°, and having $[\alpha]_D$ in chloroform −69.2° for *c*, 4.1826. It was fairly soluble in acetone, chloroform and hot alcohols but insoluble in ether, petroleum ether and cold alcohols. Calcd. for $C_{15}H_{20}O_6$: OCH_3, 20.9. Found: OCH_3, 21.4.

4,6 - Benzylidene - 2,3 - methyl - β - methylglucoside.—Sixth-tenths gram of the substance was twice methylated and the product recrystallized from alcohol, 0.4 g. of crystals, melting at 132–135°, being obtained. The melting point was unchanged on admixture with an authentic specimen of benzylidene-2,3-dimethyl-β-methylglucoside.

4,6 - Benzylidene - 3 - *p* - toluenesulfonyl - 2 - methyl-β-methylglucoside.—Two and seven-tenths grams of benzylidene-2-methyl-β-methylglucoside was treated twice with *p*-toluenesulfonyl chloride and 3.79 g. of crude product was isolated (a yield of 94% of the theoretical amount). After being twice recrystallized from absolute alcohol, the crystals separated in large prisms, melting at 135–136°. It was almost insoluble in hot alcohols, petroleum ether and ether, sparingly soluble in benzene and soluble in other solvents. Calcd. for $C_{22}H_{26}O_8S$: OCH_3, 13.7. Found: OCH_3, 13.9.

2,4,6 - Trimethyl - 3 - *p* - toluenesulfonyl - β - methylglucoside.—The benzylidene residue was hydrolyzed in a manner already described. The following changes in $[\alpha]_D$ occurred:

Min.	0	30	50	70	95
$[\alpha]_D$	−84.5	−43.0	−30.0	−21.2	−13.1
Min.	120	140	160	215	
$[\alpha]_D$	−12.7	−10.9	− 9.7	− 8.4	

In the last four values, allowance was made for change in concentration.

The product was isolated and methylated until there was no further change in the refractive index. After recrystallization from absolute alcohol, the fully methylated substance separated as cubes melting at 103–104°, soluble in all solvents, except cold alcohol, petroleum ether and water, and showing $[\alpha]_D$ in chloroform +1.9 for *c*, 5.068. It proved to be identical in melting point, mixed melting point and rotation with the product obtained by the *p*-toluenesulfonation of the supposed 2,4,6-trimethyl-β-methylglucoside already described.[1]

In conclusion, the authors wish to express their thanks to Principal Sir James C. Irvine, LL.D., D.C.L., F.R.S., for his constant and kindly interest in the work and for much valuable criticism and advice.

Summary

2-Monomethyl-β-methylglucoside was converted to 2,4,6-trimethyl-3-*p*-toluenesulfonyl-β-methylglucoside and shown to be identical with the compound obtained on *p*-toluenesulfonation of the supposed 2,4,6-trimethyl-β-methylglucoside (referred to in a previous communication), thus establishing the constitution of this compound. In addition, the following new compounds are described: 3-*p*-toluenesulfonyl-4,6-benzylidene-β-methylglucoside, 3-*p*-toluenesulfonyl-2,4,6-trimethyl-α-methylglucoside, 4,6-benzylidene-2-methyl-β-methylglucoside, 4,6-benzylidene-3-*p*-toluenesulfonyl-2-methyl-β-methylglucoside.

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