Alternative Syntheses of Methylated Sugars. II.* 3,4,6-Tri-*O*-methyl-D-glucopyranose

P. KOVÁČ

Institute of Chemistry, Slovak Academy of Sciences, Bratislava 9

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3,4,6-Tri-*O*-methyl-D-glucopyranose has been synthesized by a new synthetic route starting from 4,6-di-*O*-methyl-α-D-glucopyranose. The intermediates of the synthesis are 1,2-*O*-isopropylidene-4,6-di-*O*-methyl-α-D-glucopyranose and 1,2-isopropylidene-3,4,6-tri-*O*-methyl-α-D-glucopyranose.

Partially methylated sugars are used for identification of the products of methylation analysis of polysaccharides. Although most of these compounds have already been synthesized new papers appear describing alternative syntheses of methylated sugars which are either less laborious or give better yields.

A review on older syntheses of 3,4,6-tri-*O*-methyl-D-glucopyranose was published by *Bourne* and *Peat* [1]. First workers who succeeded in preparation of this compound in crystalline state were *Sundberg et al.* [2]. They obtained 3,4,6-tri-*O*-methyl-D-glucopyranose as the result of a thirteen step synthesis in a reasonable yield (approximately 5.4% starting from D-glucose). Recently *Mitra et al.* [3] were able to prepare the title compound by a direct nucleophilic displacement of the 6-*O*-methylsulfonyl group in methyl-2,6-di-*O*-methylsulfonyl-3,4-di-*O*-methyl-α-D-glucopyranoside by methoxide ion and subsequent hydrolysis of the produced methyl-3,4,6-tri-*O*-methyl-α-D-glucopyranoside. So far, the above-mentioned synthesis is the shortest way for preparation of 3,4,6-tri-*O*-methyl-D-glucopyranose (four steps starting from methyl-α-D-glucopyranoside). Nevertheless, the paper [3] is not clear enough as to what yield of the final compound was obtained.

The present paper describes an alternative synthesis of 3,4,6-tri-*O*-methyl-D-glucopyranose.

Experimental

Melting points were determined on a Kofler hot stage. Optical rotations were determined with a Bendix—Ericsson authomatic polarimeter. Evaporations were done on a vacuum rotatory evaporator with a bath temperature 40°C.

The course of the reactions was monitored and the purity of the products was determined by thin-layer chromatography (TLC) on silica gel G coated plates (9 × 12 cm) irrigated with: *A*. chloroform—acetone 9 : 2, *B*. chloroform—methanol 6 : 1, *C*. chloroform—acetone 9 : 4. Solvent ratios are based on volumes. Sugar components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spots were visible.

* Part I: Methylfuranosides of 2-*O*-methyl-D-xylose, *Carbohyd. Res.*, in press.

Gas chromatography was carried out isothermally at 140°C using a Hewlett—Packard Research Gas Chromatograph Model 5750 G equipped with a thermal conductivity detector. The column (8 ft × 1/4 in. O.D.Al) packed with 5% XE-60 on Embacel AW was used. The carrier gas (hydrogene) flow rate was 70 ml/min. For trimethylsililation Tri-Sil Concentrate (Pierce Chemical Co) was used.

1,2-O-Isopropylidene-4,6-di-O-methyl-α-D-glucopyranose

To a suspension of 4,6-di-*O*-methyl-α-D-glucopyranose [4, 5] (10 g) in dry acetone (500 ml) fused zinc chloride was added followed by addition of 85% phosphoric acid (1 ml) and the reaction mixture was stirred at room temperature. The starting material went shortly into solution and after two hours TLC in the solvent system *A* showed the presence of the reaction product (R_F 0.4) only (4,6-di-*O*-methyl-α-D-glucopyranose stays in the solvent system *A* on the base line). The reaction mixture was neutralized with 50% sodium hydroxide, filtered, acetone evaporated and the residue dissolved in water. Thorough extraction of the water solution with chloroform gave, after drying with anhydrous sodium sulfate and evaporation, a syrup which solidified when kept in a refrigerator overnight. Crystallization from chloroform—heptane afforded long needles. M.p. 70—71°C; $[\alpha]_D^{24}$ +33.8 (c = 1, ethanol). Yield 10.2 g (85%).

For $C_{11}H_{20}O_6$ (248.27) calculated: 53.21% C, 8.12% H, 24.9% CH_3O; found: 53.28% C, 8.08% H, 25.0% CH_3O.

1,2-O-Isopropylidene-3,4,6-tri-O-methyl-α-D-glucopyranose

1,2-*O*-Isopropylidene-4,6-di-*O*-methyl-α-D-glucopyranose (5 g) was methylated in tetrahydrofurane (30 ml) with dimethylsulfate (5 ml) and sodium hydroxide (5 g) at 50°C. After thirty minutes TLC in the solvent system *A* revealed a complete conversion of the starting material into the reaction product (R_F 0.85). The reaction mixture was diluted with water, the organic solvent was removed and the alkaline solution was kept at 100°C for one hour to decompose the excess of the methylation agent. After having been cooled to room temperature the solution was extracted with chloroform, chloroform solution dried over anhydrous sodium sulfate and evaporated to dryness. The syrupy residue was vacuum distilled (110°C bath temperature, 0.3 Torr). The colourless oil thus obtained could not be induced to crystallize. $[\alpha]_D^{24}$ +42.5° (c = 1, ethanol). Yield 5 g (95%).

For $C_{12}H_{22}O_6$ (262.30) calculated: 54.95% C, 8.45% H, 35.5% CH_3O; found: 54.69% C, 8.39% H, 35.5% CH_3O.

3,4,6-Tri-O-methyl-D-glucopyranose

1,2-*O*-Isopropylidene group was removed by heating the solution of 1,2-*O*-isopropylidene-3,4,6-tri-*O*-methyl-α-D-glucopyranose (6 g) in water (100 ml) with Dowex 50W 100/200 mesh H^+ form (10 g) on a boiling water bath. After one hour of stirring TLC in solvent systems *B* and *C* showed the hydrolysis to be complete. The reaction product was in the solvent system *B* undistinguishable from a defined sample of 3,4,6-tri-*O*-methyl-α-D-glucopyranose (R_F 0.6). In the solvent system *C* the product, as well as the authentic sample, produced two clear but poorly separated spots (R_F 0.11 and 0.16). The ion exchange resin was filtered off and the water was removed, at the end by addition of benzene and ethanol. The thick syrup was stored in a refrigerator overnight whereupon

partial crystallization occured. A small amount of crystals was saved for seeding, the remaining syrup was dissolved in ether and the etheral solution diluted with pentane almost to turbidity. Chromatographically pure 3,4,6-tri-*O*-methyl-D-glucopyranose crystallized upon seeding. M.p. 64—68°C. Yield 4.5 g (88%). Recrystallization from diisopropylether gave pure α-form. M.p. 75.5—77.5°C; $[\alpha]_D^{24}$ +105° (2.5 min.) → +77.3° (6 hours const.; $c = 2$, water).

A small amount of 3,4,6-tri-*O*-methyl-α-D-glucopyranose was dissolved in pyridine, immediately trimethylsililated and gas chromatographed. One peak was eluted from the column (elution time 4.49 min.). The same compound was, prior to trimethylsililation, equilibrated by boiling of a water solution and gas chromatographed. Two peaks were eluted from the column (elution times 4.49 and 4.73 min., respectively).

For $C_9H_{18}O_6$ (222.23) calculated: 48.65% C, 8.16% H, 41.89% CH_3O; found: 48.61% C, 8.17% H, 41.90% CH_3O.

Discussion

4,6-Di-*O*-methyl-α-glucopyranose, which can be prepared in good yield according to known procedures [4, 5], has been shown to be a useful starting material for making 3,4,6-tri-*O*-methyl-D-glucopyranose.

Treatment of 4,6-di-*O*-methyl-α-D-glucopyranose with acetone, in the presence of zinc chloride under acidic conditions for two hours, resulted in complete disappearance of the starting material from the reaction mixture and afforded, in a good yield, crystalline 1,2-*O*-isopropylidene-4,6-di-*O*-methyl-α-D-glucopyranose. This substance, apart from being an indispensable intermediate of the presented synthesis, can serve as the parent compound for preparation of model compounds for investigation of certain derivatives of 1,2-*O*-isopropylidene-α-D-glucopyranose. The ratio of zinc chloride to the sugar component used for isopropylidenation of 4,6-di-*O*-methyl-α-D-glucopyranose was somewhat higher than usual [6]. It is noteworthy, that in attempting to synthesize 1,2-*O*-isopropylidene-4,6-di-*O*-methyl-α-D-glucopyranose by the copper sulfate—sulfuric acid method (or when lesser relative amount of zinc chloride was used) the conversion of the starting material was not complete even after 48 hours.

Methylation of 1,2-*O*-isopropylidene-4,6-di-*O*-methyl-α-D-glucopyranoside and subsequent hydrolysis of the produced tri-*O*-methyl derivative afforded 3,4,6-tri-*O*-methyl-D-glucopyranose. A mixture of ether—pentane was found to be favourable for obtaining a high yield of crystalline mixture of α- and β-anomers of 3,4,6-tri-*O*-methyl-D-glucopyranose (88.5%, m.p. 64—68°C). 3,4,6-Tri-*O*-methyl-α-D-glucopyranose (m.p. 75.5—77.5°C) was obtained by recrystallizing the first crystalline product from diisopropylether.

It was observed, by monitoring the course of the hydrolysis of 1,2-*O*-isopropylidene-3,4,6-tri-*O*-methyl-α-D-glucopyranose by thin-layer chromatography, that the product of the hydrolysis gave two spots. Since the same two spots were produced when the pure α-form was thin-layer chromatographed (fast spontaneous equilibration in solution), the phenomenon was accounted for the separation of α- and β-anomers of the free sugar. This explanation was supported by the result of gas chromatographic examination of the pure α-form. When a fresh solution of 3,4,6-tri-*O*-methyl-α-D-glucopyranose in pyridine was trimethylsililated one peak was eluted from the column. When the same substance was equilibrated, prior to trimethylsililation,

two peaks were eluted. The fact that α- and β-anomers of certain free sugars can be independantly visible on thin-layer plates does not appear to have been reported previously.

The initial specific rotation of 3,4,6-tri-*O*-methyl-α-D-glucopyranose ($[\alpha]_D^{24}$ +105°) is somewhat higher than *Sundberg et al.* [2] observed under the same conditions. Since the equilibrium value is practically the same as that of *Sundberg et al.* the higher initial value can be explained by the higher purity of the α-form obtained.

The synthetic procedure discussed above is very simple and affords the title compound in a high yield. Starting from 4,6-di-*O*-methyl-α-D-glucopyranose an overall yield of approximately 71% of 3,4,6-tri-*O*-methyl-D-glucopyranose was obtained. In various experiments starting from methyl-α-D-glucopyranoside *via* 4,6-di-*O*-methyl-α-D-glucopyranose overall yields between 16—22% were obtained.

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