THE CHARACTERIZATION OF TRI-*O*-TOSYL SUCROSE[1]

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ABSTRACT

Tri-*O*-tosyl sucrose was synthesized by the action of *p*-tolylsulphonyl chloride upon sucrose in pyridine, and the tosyl groups were shown by methylation to be mainly (84%) located on the three primary hydroxyl groups.

INTRODUCTION

Hockett and Zief (1) prepared sulphonyl esters of sucrose by reaction with methane sulphonyl (mesyl) chloride or *p*-tolyl-sulphonyl (tosyl) chloride in pyridine solution. Although none of the products were isolated in crystalline form, analytical values were recorded for the tri-*O*- and octa-*O*-mesyl and tosyl sucrose derivatives. Tosyl and mesyl compounds undergo a large number of important reactions (2) so thorough characterization of the trisubstituted sucrose was considered to be desirable.

Tri-*O*-tosyl sucrose was prepared by Hockett and Zief's method (1). Complete methylation to tri-*O*-tosyl-penta-*O*-methyl sucrose was obtained by a single treatment with methyl iodide and silver oxide in dimethylformamide solution (3). Detosylation and subsequent hydrolysis gave a mixture of tri-*O*-methyl glucose, di-*O*-methyl fructose, and di-*O*-methyl glucose. A small amount (5%) of tri-*O*-methyl fructose was also present.

The methyl ethers of glucose were characterized by conversion to 2,3,4-tri-*O*-methyl-*N*-phenyl-D-glucosylamine and 2,4-di-*O*-methyl-*N*-*p*-nitrophenyl-D-glucosylamine respectively.

The di-*O*-methyl fructose was chromatographically identical with 3,4-di-*O*-methyl fructose. The measured rotation was lower than the quoted value (4) but this was probably due to the presence of an optically inactive impurity derived from the filter paper on which the sugar was fractionated. The identity of the fructose methyl ether was confirmed as 3,4-di-*O*-methyl-D-fructofuranose by periodic acid oxidation followed by bromine oxidation to dimethylsuccinic acid and the isolation of crystalline (−)-D-dimethoxysuccinamide formed by the action of ammonia on the methyl ester (5).

The isolation of 2,4-di-*O*-methyl-D-glucose from the hydrolysis mixture suggests that some undermethylation had occurred. In glucose the hydroxyl group at $C_{(3)}$ is less reactive than that at $C_{(2)}$, $C_{(4)}$, or $C_{(6)}$ (9), and 2,4-di-*O*-methyl glucose would result from undermethylation.

This sugar might arise through the formation of a 3,6-anhydro ring on the glucose residue of sucrose during methylation. But no 2,4-di-*O*-methyl-D-glucose was formed from methyl 2,4-di-*O*-methyl-3,6-anhydro α-D-glucoside when the latter was submitted to the conditions of hydrolysis used for the methylated sucrose derivative. The infrared spectrum of the methylated sucrose showed that hydroxyl groups were absent. However, it has been observed in these laboratories that incompletely methylated polysaccharides which had been submitted to the Kuhn methylation procedure in dimethylformamide (3) gave an infrared spectrum without hydroxyl peaks, and yet gave amounts of sugars which indicated that methylation was incomplete. This phenomenon is as yet unexplained.

The tri-*O*-tosyl sucrose consisted mainly therefore of $6,1^1,6^1$-tri-*O*-tosyl sucrose. This

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[1] *Manuscript received November 10, 1958.*
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Can. J. Chem. Vol. 37 (1959)

result is in agreement with the results of Lemieux and Barrette (6), who found that the trianhydro sucrose derived from the above compound was different from that obtained from $4,1^1,6^1$-tri-*O*-tosyl sucrose, which had been prepared from $2,3,6,3^1,4^1$-penta-*O*-acetyl sucrose (7). This structure is also supported by the isolation of a sirupy di-iodo-di-deoxy-mono-*O*-tosyl sucrose pentaacetate from the action of sodium iodide (8) on tri-*O*-tosyl sucrose pentaacetate. The iodine atoms are probably located on the $C_{(6)}$ of both fructose and glucose moieties, the tosyl group on fructose-$C_{(1)}$ remaining unsubstituted. In agreement with this, Lemieux and Barrette (6) obtained only a mono-iodo derivative from $4,1^1,6^1$-tri-*O*-tosyl sucrose.

It is probable that the tri-*O*-tosyl sucrose is not pure. However the high yield (89%) of di-iodo-di-deoxy-mono-*O*-tosyl sucrose pentaacetate (analysis indicates 94% purity) that was prepared from it shows that at least 84% of the preparation must have tosyl groups on $C_{(6)}$ and $C_{(6^1)}$. Since no other tri-*O*-methyl glucoses were found, which would be the case if other tri-*O*-tosyl sucroses were present, the preparation is probably purer than the above figure. The chromatography solvent used (*n*-butanol : ethanol : water, 3 : 1 : 1) resolved 2,3,4-tri-*O*-methyl-D-glucose (R_f 0.62) from 2,3,6-tri-*O*-methyl- (R_f 0.59) and 3,4,6-tri-*O*-methyl-D-glucose (R_f 0.58). Complete separation from 2,4,6-tri-*O*-methyl-D-glucose (R_f 0.61) was not obtained but since tosylation at $C_{(3)}$ of sucrose is unlikely (9) it is probable that this methylated sugar was not present.

Reduction of $6,1^1,6^1$-tri-*O*-tosyl sucrose with lithium aluminum hydride gave $6,6^1$-dideoxy sucrose (cf. 6), which was cleaved by invertase to 6-deoxy-D-glucose and D-rhamnoketose.

EXPERIMENTAL

Paper chromatograms were developed in the solvent system: *n*-butanol : ethanol : water (3 : 1 : 1). Reducing sugars were detected by *p*-anisidine hydrochloride and a resorcinol spray reagent was used for the specific detection of ketoses (10). Melting points are uncorrected and were determined on a Kofler microheating stage.

Tri-O-tosyl Sucrose

This was prepared by Hockett and Zief's method (1) and had $[\alpha]_D^{17}$ +41.3° (*c*, 2.06 in chloroform). Anal. Calc. for $C_{33}H_{40}O_{17}S_3$: S, 11.9%. Found: S, 11.5%.

Methylation of Tri-O-tosyl Sucrose

Tri-*O*-tosyl sucrose (7.3 g), dried over phosphoric oxide, was dissolved in dimethylformamide (120 ml), which had been distilled from barium oxide, and methyl iodide (45 ml). Silver oxide (45 g) was added portionwise with vigorous stirring, the temperature was not permitted to rise above 35°. After 7 hours, the mixture was filtered, the precipitate was washed with dimethylformamide (2×50 ml), and then chloroform (50 ml), and the combined liquids were poured into 1% aqueous sodium cyanide (500 ml). The aqueous layer was shaken with chloroform, which was then added to the chloroform layer and the combined solutions were washed well with water, dried (sodium carbonate), and concentrated to a sirup (5.33 g) $[\alpha]_D^{24}$ +49.5° (*c*, 4.05 in chloroform). The product showed no hydroxyl peaks in its infrared spectrum. Anal. Calc. for $C_{38}H_{50}O_{17}S_3$: OMe, 17.8%. Found: OMe, 20.7%. The high value for methoxyl suggests contamination of the product with dimethylformamide.

Detosylation of the Methylated Sucrose

The sirup (5.2 g) in 85% aqueous methanol (200 ml) was stirred with 4% sodium amalgam (125 g) for 18 hours. After filtration and neutralization with solid carbon dioxide, the solution was concentrated to a solid which was extracted with boiling chloroform (3×150 ml). The extract afforded a sirup (2.6 g) which on concentration did not give a solution in water or 50% aqueous ethanol sufficiently clear for optical rotation measurements.

Hydrolysis and Separation of the Methyl Sugars

The methylated sucrose (2.6 g) was hydrolyzed with 0.01 *N* sulphuric acid (150 ml) at 100° for 1½ hours. After neutralization the resulting mixture (2.4 g) was examined on paper chromatograms. With *p*-anisidine, tri-*O*-methyl glucose (R_f 0.62), di-*O*-methyl fructose (R_f 0.52), and di-*O*-methyl glucose (R_f 0.48) were detected. The resorcinol spray showed the presence of a small amount of a further component, tri-*O*-methyl fructose, having an identical R_f value to the tri-*O*-methyl glucose which previously masked it.

The mixture of sugars was fractionated on a cellulose column (30×3 cm) using methyl ethyl ketone : water azeotrope as solvent (7). A complete separation of the component sugars was not obtained so the fractions were combined to give a tri-*O*-methyl hexose fraction (0.75 g) and a di-*O*-methyl hexose fraction (1.2 g).

The tri-*O*-methyl hexose fraction was dissolved in 0.35% methanolic hydrogen chloride (25 ml) and the rotation was followed until equilibrium was reached (22 hours). After neutralization with silver oxide and removal of the silver ions with hydrogen sulphide, tri-*O*-methyl glucose (R_f 0.65) was separated on sheet paper chromatograms from a small amount of tri-*O*-methyl methyl fructofuranoside. The di-*O*-methyl hexose fraction was similarly fractionated into di-*O*-methyl glucose (R_f 0.49) and di-*O*-methyl methyl fructofuranoside (R_f 0.66).

Characterization of the Methyl Sugars

Tri-*O*-methyl hexose (280 mg) was refluxed with redistilled aniline (110 mg) in ethanol (10 ml). Removal of the ethanol under reduced pressure initiated crystallization. After recrystallization from ether – light petroleum (60–80°), the colorless needles had m.p. and mixed m.p. 144°–146° with authentic 2,3,4-tri-*O*-methyl-*N*-phenyl-D-glucosylamine. Anal. Calc. for $C_{15}H_{23}O_5N$: OMe, 31.3%. Found: OMe, 30.9%.

The di-*O*-methyl hexose (202 mg), having $[\alpha]_D$ +54° (*c*, 2.0 in water), was refluxed for 3 hours with *p*-nitroaniline (164 mg) in ethanol (5.5 ml) and acetic acid (5 drops). The reaction mixture was concentrated to a smaller volume and cooled to 5°. The light-brown precipitate was washed with ethanol and recrystallized as pale yellow crystals from ethyl acetate, m.p. 251°, $[\alpha]_D^{24}$ −250° (*c*, 0.38 in pyridine). Anal. Calc. for $C_{14}H_{20}O_7N_2$: OMe, 18.9%. Found: OMe, 19.9%. 2,4-Di-*O*-methyl-*N*-*p*-nitrophenyl-D-glucosylamine has m.p. 250°–251° $[\alpha]_D$ −252° (pyridine) (11).

The di-*O*-methyl methyl fructofuranoside was hydrolyzed (0.05 *N* H_2SO_4; 2 hours; 100°) to yield di-*O*-methyl-D-fructose (0.57 g), $[\alpha]_D$ −45° (*c*, 2.64 in water). Anal. Calc. for $C_8H_{16}O_6$: OMe, 29.7%. Found: OMe, 28.3%. Di-*O*-methyl fructose (160 mg) in 1.15 *M* periodic acid (5 ml) was kept at 25° for 3 days. The solution was freed from iodine by extraction with carbon tetrachloride. Barium chloride (0.5 g) and excess barium carbonate were added, and after filtration, enough bromine was added to give a saturated solution. After 2 days, excess bromine was removed by aeration, hydrobromic acid by lead carbonate, and lead ions with hydrogen sulphide. The solution was filtered and the filtrate was concentrated to a solid which was then refluxed overnight with 4% methanolic hydrogen chloride. Excess hydrogen chloride was removed with lead carbonate, as above, and the filtrate was concentrated to a solid. Chloroform extraction of the solid and subsequent evaporation of the solvent yielded a sirup (40 mg) which was dissolved in methanolic ammonia (3 ml) and kept at 0°. After 6 days, white crystals (15 mg) of (−)-D-di-methoxysuccinamide were deposited, $[\alpha]_D$ −94° (*c*, 0.60 in water), m.p. and mixed m.p. 275° (capillary tube) with authentic (−)-D-dimethoxysuccinamide. The compound showed maxima in the infrared at 3330 (s), 3150 (s), 2910 (w), 1637 (s), 1425 (s), 1341 (m), 1314 (w), 1210 (m), 1193 (m), 1139 (m), 1100 (s), 1023 (m), 881 (m), 825 (w), 805 (m), 705 (m) cm^{-1} and gave an identical infrared spectrum to authentic (−)-D-dimethoxysuccinamide.

Reaction of Sodium Iodide with Tri-O-tosyl Sucrose

Tri-*O*-tosyl sucrose pentaacetate (2.0 g) was heated at 110° for 2 hours with sodium iodide (5 g) in acetone (5 ml). The reaction mixture was poured into chloroform and after filtration was washed well with water containing sodium thiosulphate (5%) and sodium hydrogen carbonate (5%). After drying ($CaCl_2$), concentration of the chloroform extract gave sirupy mono-*O*-tosyl-di-iodo-di-deoxy sucrose pentaacetate (1.7 g) $[\alpha]_D^{19}$ +40° (*c*, 3.8 in chloroform). Anal. Calc. for $C_{39}H_{36}O_{16}I_2S$: I, 26.5%. Found: I, 24.9%.

Reduction of Tri-O-tosyl Sucrose

Tri-*O*-tosyl sucrose was reduced (10 hours) with $LiAlH_4$ at the boiling point of tetrahydrofuran. Following destruction of excess hydride with moist ethyl acetate and deionization of the solution with ion-exchange resin, 6,6¹-dideoxy sucrose was isolated as a chromatographically homogeneous, crisp solid (R_f 0.32), $[\alpha]_D^{19}$ +49.7° (*c*, 1.27 in water). Anal. Calc. for $C_{12}H_{22}O_9$: CMe, 9.7%. Found: CMe, 9.2%.

Dideoxy sucrose was completely hydrolyzed by invertase (48 hours) to give two compounds which cochromatographed with authentic rhamnoketose and 6-deoxy glucose.

ACKNOWLEDGMENT

The authors wish to thank the Sugar Research Foundation, Inc., for a grant.

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