[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORY, PIONEERING RESEARCH DIVISION, QUARTERMASTER RESEARCH AND ENGINEERING CENTER, U. S. ARMY]

Methyl 2,6-Di-*O*-methylsulfonyl-α-D-glucopyranoside and New Syntheses of 3,4-Di- and 3,4,6-Tri-*O*-methyl-D-glucose[1]

A. K. MITRA,[2] D. H. BALL, AND L. LONG, JR.

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Methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside has been prepared by partial mesylation of methyl α-D-glucopyranoside. The crystalline di-*O*-nitro and di-*O*-methyl derivatives are described. Saponification of the latter with aqueous alkali afforded crystalline methyl 3,4-di-*O*-methyl-α-D-glucoside, hydrolysis of which gave 3,4-di-*O*-methyl-D-glucose. Treatment of methyl 2,6-di-*O*-mesyl-3,4-di-*O*-methyl-α-D-glucoside with sodium methoxide in boiling methanol effected direct replacement of the 6-mesyloxy group by methoxide and methyl 3,4,6-tri-*O*-methyl-α-D-glucoside was formed. It gave a crystalline 2-*O*-mesyl derivative and was characterized by hydrolysis to 3,4,6-tri-*O*-methyl-D-glucose.

The variation in reactivities of the hydroxyl groups of carbohydrates has been recognized for many years.[3] In general, primary hydroxyl groups are more readily etherified and esterified than secondary hydroxyl groups and triphenylmethyl chloride in particular has been used extensively to "block" the former.[4] Sulfonylation appears to be less specific than "tritylation" but selective "tosylation" and "mesylation"[5] of primary hydroxyl groups have been described many times. 6-*O*-Tosyl esters of glucose[6] and of methyl α- and β-D-glucopyranosides,[7] the 6,6′-di-*O*-tosyl ester of methyl β-cellobioside[8] and 1,6-di-*O*-tosyl-D-fructose[9] have been prepared. The corresponding mesyl esters are also known.[10-13] Of the secondary hydroxyl groups, that at C_2 of an aldose or an aldoside is unusually reactive and methyl α-D-glucopyranoside has been converted to the 2,6-di-*O*-benzoyl[14] and 2,6-di-*O*-palmitoyl[15] derivatives. Dimolar tosylation of free D-glucose also gave predominantly a 2,6-di-*O*-tosyl derivative.[16] Methyl α-D-galactopyranoside may also be partially tosylated to give the 2,6-di-*O*-tosyl ester.[17]

In conjunction with an investigation of partially mesylated sucrose derivatives,[18] the mesylation of methyl α-D-glucopyranoside was examined in this laboratory. Helferich and Gnüchtel[11] and, more recently, Cramer *et al.*,[19] treated methyl α-D-glucopyranoside with one molar equivalent of mesyl chloride at −20°. No crystalline material was isolated from the reaction product but, after acetylation, crystalline methyl 2,3,4-tri-*O*-acetyl-6-*O*-mesyl-α-D-glucoside was obtained in good yield (Cramer *et al.*[19] reported 67%). The reaction conditions described by these authors were followed and the mesylation product was examined by paper chromatography. The chromatograms indicated that, in addition to a mono-esterified derivative, considerable amounts of methyl α-D-glucopyranoside and of di- and triesterified derivatives were present. The relative amounts of these constituents were not appreciably affected by lowering the reaction temperature to −40°. The molar ratio of mesyl chloride to glucoside was increased and when 2.3 or more, no starting material or mono-substituted products were observed. The product appeared to be mainly a di-*O*-mesyl glucoside together with smaller amounts of higher substituted glucosides.

From the reaction of methyl α-D-glucopyranoside with 2.2 moles of mesyl chloride, a crystalline methyl di-*O*-mesyl-α-D-glucoside (I) was isolated in 51% yield. By analogy with previous work,[14,15] the mesyl groups were thought to be at C_2 and C_6 of the glucopyranoside and this was confirmed by

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(2) Present address: Division of Food Technology, Jadavpur University, Calcutta 32, India.

(3) J. M. Sughihara, *Advances in Carbohydrate Chem.*, **8**, 1 (1953).

(4) B. Helferich, *Advances in Carbohydrate Chem.*, **3**, 79 (1948).

(5) "Trityl" = triphenylmethyl; "tosyl" = *p*-tolylsulfonyl; "mesyl" = methylsulfonyl.

(6) E. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946).

(7) J. Compton, *J. Am. Chem. Soc.*, **60**, 395 (1938).

(8) J. Compton, *J. Am. Chem. Soc.*, **60**, 1203 (1938).

(9) W. T. J. Morgan and T. Reichstein, *Helv. Chim. Acta*, **21**, 1023 (1938).

(10) B. Helferich, H. Dressler, and R. Griebel, *J. prakt. Chem.*, **153**, 285 (1939).

(11) B. Helferich and A. Gnüchtel, *Ber.*, **71**, 712 (1938).

(12) B. Helferich and F. von Stryk, *Ber.*, **74**, 1794 (1941).

(13) L. Vargha, O. Fehér, T. Horváth, L. Toldy, and J. Kuszmann, *Acta Chim. Acad. Sci. Hung.*, **25**, 361 (1960).

(14) T. Lieser and R. Schweizer, *Ann.*, **519**, 271 (1935); *Naturwissenschaften*, **23**, 131 (1935).

(15) J. Asselineau, *Bull. soc. chim. France*, 937 (1955).

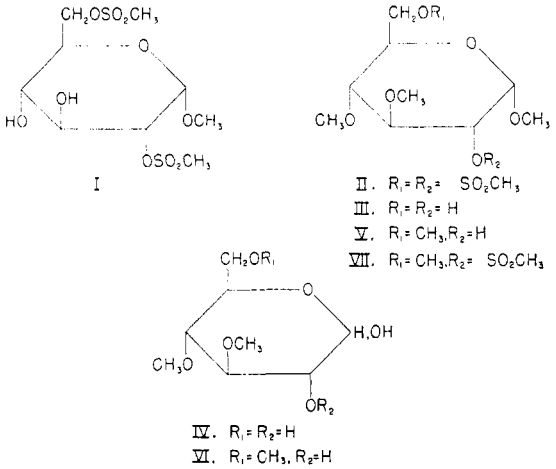
(16) E. Hardegger, R. M. Montavon, and O. Jucker, *Helv. Chim. Acta*, **31**, 1863 (1948).

(17) P. A. Rao and F. Smith, *J. Chem. Soc.*, 229 (1944).

(18) A. K. Mitra and L. Long, Jr., 135th Meeting of the American Chemical Society, Boston, Mass., 1959; Abstracts of Papers, 10D; 136th Meeting of the American Chemical Society, Atlantic City, N. J., 1959, Abstracts of Papers, 19D.

(19) F. Cramer, H. Otterbach, and H. Springmann, *Chem. Ber.*, **92**, 384 (1959).

methylation followed by alkaline saponification and acid hydrolysis to 3,4-di-*O*-methyl-D-glucose (IV). Methylation of I by the procedure of Kuhn *et al.*[20] afforded crystalline methyl 2,6-di-*O*-mesyl-3,4-di-*O*-methyl-α-D-glucoside (II) in 91% yield. Treatment of II with boiling aqueous sodium hydroxide removed the mesyl groups and gave, after distillation, methyl 3,4-di-*O*-methyl-α-D-glucoside (III) in 64% yield. Acid hydrolysis of III yielded 3,4-di-*O*-methyl-D-glucose (IV), which was further characterized as the crystalline anilide. The overall yield of IV from methyl α-D-glucopyranoside was approximately 25%; a considerable improvement on previous syntheses.[21,22]



Acetylation and benzoylation of I gave products which failed to crystallize, but with fuming nitric acid in acetic anhydride the crystalline dinitrate was formed.

When aqueous methanol was used as solvent in the saponification of II, the sulfur-free product contained two components. After acid hydrolysis, two spots were obtained on paper chromatograms, the slower moving corresponding to 3,4-di-*O*-methyl-D-glucose. The faster moving component had the mobility expected for a tri-*O*-methyl hexose. When II was treated with sodium methoxide in anhydrous methanol, III was not formed and the sulfur-free product after distillation analyzed for a methyl tri-*O*-methyl hexoside (V). This compound crystallized when cooled to 0° and acid hydrolysis afforded 3,4,6-tri-*O*-methyl-D-glucose (VI), proving that V is methyl 3,4,6-tri-*O*-methyl-α-D-glucoside. Treatment of V with mesyl chloride in pyridine gave methyl 2-*O*-mesyl-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (VII).

The direct nucleophilic displacement of a primary mesyloxy group by methoxide ion does not appear to have been observed previously in the carbohydrate field, although displacements have been effected by a wide variety of anions.[23] Taylor and Kent[24] found that when 1,2:3,4-di-*O*-isopropylidene-6-*O*-mesyl-α-D-galactose was treated with potassium fluoride in methanol at 150°, the product(s) contained methoxyl groups as well as the anticipated fluorine and when 1,6-anhydro-3,4-*O*-isopropylidene 2-*O*-mesyl-β-D-galactose was treated with these reagents, the axial C_2-mesyloxy group was displaced, with inversion, by methoxide. The product did not contain fluorine and was characterized as 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-methyl-β-D-talose.[25]

The comparatively mild conditions under which we observed displacement at C_6 may indicate that the sulfonyl group at C_2 exerts an effect and it is hoped that future work will clarify this point.

EXPERIMENTAL

Solutions were concentrated under reduced pressure at 40° unless otherwise stated. Melting points were determined on a Kofler micro hot stage and optical rotations were measured at 24° ±1°. Paper chromatography was carried out by the descending method on Whatman No. 1 filter paper using the solvent systems (a) butan-1-ol–ethanol–water (3:1:1), (b) butan-1-ol–pyridine–water (10:3:3), or (c) butan-1-ol–pyridine–water–benzene (5:4:3:1). Sugars were located on chromatograms either by the *p*-anisidine hydrochloride spray[26] or by the silver nitrate and alkali sprays.[27]

The microanalyses were done by Mr. C. DiPietro of this laboratory and Dr. S. M. Nagy of the Massachusetts Institute of Technology.

Methyl 2,6-di-O-mesyl-α-D-glucopyranoside (I). Dry methyl α-D-glucopyranoside (38.8 g., 0.20 mole) was dissolved in dry pyridine (300 ml.). The solution was cooled to −40° in a dry ice–acetone bath and mesyl chloride (50 g., 0.44 mole) was added during 7 hours. The solution was maintained at approximately −40°. The reaction mixture was stored overnight (15 hours) at −20° and was then allowed to warm up to room temperature. Pyridine hydrochloride was removed by filtration and was washed with acetone. The combined filtrate and washings were concentrated to a sirup which was taken up in ethanol-toluene and reconcentrated at 60° to remove most of the pyridine. The resultant clear yellow sirup was diluted with water (200 ml.), the solution was extracted with chloroform (3 × 50 ml.), and the aqueous phase was cooled. Colorless crystals formed in clusters and were collected by filtration, washed with ice-cold water, and dried. Yield 35.5 g., 51%. Recrystallization from water afforded colorless needles, m.p. 146–147°, $[\alpha]_D$ +118° (*c* 2.01 in water).

Anal. Calcd. for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.20. Found: C, 30.81; H, 5.19; S, 17.80.

Treatment of this compound at 0° with fuming nitric acid in acetic anhydride afforded a quantitative yield of a crystalline dinitrate. After three recrystallizations from ethanol, colorless prisms were obtained, m.p. 127–128°.

(20) R. Kuhn, H. Trischmann, and I. Löw, *Angew. Chem.*, **67**, 32 (1955).

(21) J. Dewar and G. Fort, *J. Chem. Soc.*, 496 (1944).

(22) D. J. Bell and G. D. Greville, *J. Chem. Soc.*, 1902 (1950).

(23) R. S. Tipson, *Advances in Carbohydrate Chem.*, **8**, 107 (1953).

(24) N. F. Taylor and P. W. Kent, *J. Chem. Soc.*, 872 (1958).

(25) P. W. Kent, D. W. A. Farmer, and N. F. Taylor, *Proc. Chem. Soc.*, 187 (1959).

(26) L. Hough, J. K. N. Jones, and W. H. Wadman, *J. Chem. Soc.*, 1702 (1950).

(27) W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950).

Anal. Calcd. for $C_9H_{16}N_2O_{14}S_2$: C, 24.55; H, 3.66; S, 14.56. Found: C, 25.03; H, 3.69; S, 14.63.

Methyl 2,6-di-O-mesyl-3,4-di-O-methyl-α-D-glucoside (II). A solution of I (15 g.) in dry dimethyl formamide (150 ml.) was cooled to 0°. Methyl iodide (30 ml.) and silver oxide (40 g.) were added and the mixture was shaken mechanically at 0° in the dark for 2 days. Solids were removed by filtration and were extracted repeatedly with chloroform. The combined filtrate and extracts were cooled to 0° and again filtered to remove a white solid. The clear pale yellow filtrate was concentrated to a sirup which crystallized from ethanol. The crystals were collected by filtration, washed with ethanol, and air-dried. Yield 14.8 g., 91%. Recrystallization from methanol afforded colorless prisms, m.p. 134.5–135.5°, $[\alpha]_D$ +104° (*c* 2.0 in chloroform).

Anal. Calcd. for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94; OCH_3, 24.60. Found: C, 34.74; H, 5.98; S, 17.05; OCH_3, 24.61.

Methyl 3,4-di-O-methyl-α-D-glucopyranoside (III). To a solution of II (3.0 g.) in boiling water (75 ml.) contained in a 300 ml. Erlenmeyer flask made from borate-free glass (Corning 7280)[28] was added a solution of sodium hydroxide (4.0 g.) in water (25 ml.) and the mixture was boiled under reflux for 4 hours. An oil separated on addition of the alkali but the solution was homogeneous after *ca.* 30 minutes. The straw-colored solution was allowed to cool and was then deionized by passage down columns of ion-exchange resins, Dowex 50W-X8 (H), and Amberlite IR 45 (OH). The neutral effluent was concentrated to a sirup which was taken up in chloroform, dried (Na_2SO_4), and reconcentrated to a sirup. Distillation at 120–130° (bath temp.)/5–6 microns afforded a thick, colorless sirup (1.37 g., 64%) which was induced to crystallize. Two recrystallizations from ether-hexane afforded large prisms, m.p. 53.5–55.5°, $[\alpha]_D$ +179° (*c* 4.44 in chloroform).

Anal. Calcd. for $C_6H_9O_3(OCH_3)_3$: C, 48.64; H, 8.16; OCH_3, 41.89. Found: C, 48.72; H, 8.13; OCH_3, 42.35.

3,4-Di-O-methyl-D-glucose (IV). The glycoside III (0.25 g.) was hydrolyzed with N hydrochloric acid at 100°. The optical rotation was determined at intervals and was constant after 4 hours. The hydrolyzate was neutralized by passage down a column of Amberlite ion-exchange resin IR 45 (OH). Concentration of the effluent afforded a sirup which was taken up in ethyl acetate and dried (K_2CO_3). Concentration afforded a crystalline solid (0.18 g.) which was recrystallized twice from ethyl acetate to give 3,4-di-*O*-methyl-α-D-glycopyranose, m.p. 114–118.5°, $[\alpha]_D$ +80.0° (6 min.) → +76.0° (7 hours, const., *c* 5.0 in water).

Treatment of IV with 1.3 equivalents of redistilled aniline in boiling ethanol for 3 hours, followed by evaporation of solvent, gave a crystalline residue. Recrystallization from *n*-butanol-heptane gave colorless needles of *N*-phenyl-(3,4-di-*O*-methyl-β-D-glucosyl)amine, m.p. 171–173°, $[\alpha]_D$ −102° (12 min.) → −19° (80 hours, const., *c* 1.72 in ethanol). Bell and Greville[22] reported $[\alpha]_D$ −106° in ethanol with no mutarotation.

Methyl 3,4,6-tri-O-methyl-α-D-glucopyranoside (V). A solution of II (5.0 g.) in anhydrous methanol (500 ml.) containing sodium (10 g.) was boiled under reflux with exclusion of moisture for 24 hours. The solution was then allowed to cool, precipitated sodium methylsulfonate was removed by filtration, and the colorless filtrate was deionized by passage down a column of mixed bed ion-exchange resin, Amberlite MB 3. Concentration of the effluent afforded a sirup which was taken up in chloroform, dried (Na_2SO_4), and reconcentrated. The sirup was distilled; b.p. 65–70°/5 microns (bath temp. 100–110°). The distillate (2.32 g., 75%) crystallized when cooled to 0° and had m.p. 21.5–23.5° (capillary), $[\alpha]_D$ +158° (*c* 4.0 in water).

Anal. Calcd. for $C_6H_8O_2(OCH_3)_4$: C, 50.83; H, 8.53; OCH_3, 52.53. Found: C, 50.48; H, 8.49; OCH_3, 52.89. The glycoside gave one peak on the gas chromatograph.

Methyl 2-O-mesyl-3,4,6-tri-O-methyl-α-D-glucoside (VII). To a solution of V (0.47 g., 0.002 mole) in dry pyridine (5 ml.), cooled to 0°, was added mesyl chloride (0.25 g., 0.0022 mole) and the solution was stored overnight at 0°. The solution was allowed to come to room temperature and was then concentrated to a white solid which was redissolved in an ethanol-toluene mixture and reconcentrated to remove most of the pyridine. The solid residue was extracted with boiling ether, the extracts were filtered through charcoal and Celite, and concentrated to a sirup which readily crystallized. Recrystallization from ether-heptane afforded large prisms (0.58 g., 92%), m.p. 70–70.5°, $[\alpha]_D$ +118° (*c* 5.0 in chloroform).

Anal. Calcd. for $C_7H_{10}O_4S(OCH_3)_4$: C, 42.03; H, 7.05; S, 10.20; OCH_3, 39.49. Found: C, 42.10; H, 7.14; S, 10.45; OCH_3, 39.68.

3,4,6-Tri-O-methyl-D-glucose (VI). The glycoside V (0.20 g.) was hydrolyzed with *N* hydrochloric acid at 100°. The optical rotation was determined at intervals and was constant after 4 hours. The hydrolyzate was then neutralized by passage down a column of Amberlite ion-exchange resin IR 45 (OH) and the effluent was concentrated to a sirup which was extracted with ether. The extracts were filtered through charcoal and reconcentrated. On paper chromatograms, the product (0.15 g.) gave one spot indistinguishable from authentic 3,4,6-tri-*O*-methyl-D-glucose. The sirup crystallized when seeded and, after two recrystallizations from isopropyl ether, had m.p. 91–94.5°, not depressed by admixture with authentic 3,4,6-tri-*O*-methyl-β-D-glucose, $[\alpha]_D$ +46° (5 min.) → +76° (6 hours, const., *c* 2.0 in water).[29]

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(28) In previous experiments, it was found that the product was contaminated with silica when the saponification was carried out in Pyrex flasks.

(29) R. L. Sundberg, C. M. McCloskey, D. E. Rees, and G. H. Coleman, *J. Am. Chem. Soc.*, **67**, 1080 (1945).