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Note

A reinvestigation of the reaction of methyl β-D-glucopyranoside with sulfuryl chloride*

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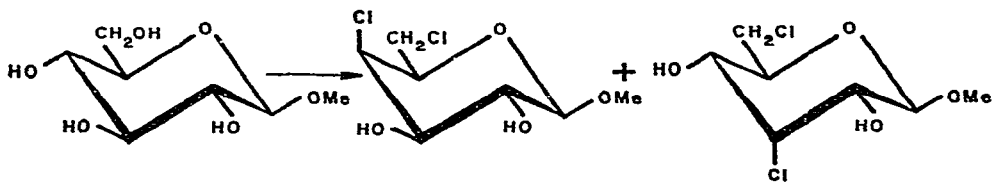
The reaction of sulfuryl chloride (SO_2Cl_2) with carbohydrates containing free hydroxyl groups has become a well-established method for the preparation of chlorodeoxy sugars[1–3]. The process[4–6] involves the initial formation of chlorosulfate groups, followed by bimolecular displacement of certain of these by chloride ion liberated during the chlorosulfation The displacement occurs only at those centers where the steric and polar factors[3,7] are favorable for an SN2 reaction. Thus, for example, treatment of methyl α-D-glucopyranoside with sulfuryl chloride and pyridine in chloroform solution, and isolation of the product at room temperature, gave methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-di(chlorosulfate), which was dechlorosulfated by using sodium iodide to afford a high yield of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside[4,5,8]. In this example, the lack of substitution by chloride ion of the intermediate chlorosulfonyloxy group at C-3 is attributed to the presence of the β-*trans*-axial methoxyl group at C-1, also, a chlorosulfonyloxy group at C-2 is deactivated to nucleophilic substitution by chloride ion[3,7]. On this basis it would be expected that methyl β-D-glucopyranoside (**1**), having the methoxyl group at C-1 in equatorial orientation, would afford, under the same conditions, not only methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside 2,3-di(chlorosulfate) but also methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside 2,4-di(chlorosulfate); however, in 1965 only the isolation of crystalline methyl 6-chloro-



1 **2** **3**

*Part VIII in the series "Synthesis and Reactions of Chlorodeoxy Sugars".

6-deoxy-β-D-glucopyranoside 2,3,4-tri(chlorosulfate) (in 10% yield) was reported[6], and it was stated that t l c indicated that "the non-crystalline material was mainly the 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside derivative" It was also reported that treatment of the crystalline product with pyridinium chloride in chloroform for 12 h at 50°, followed by dechlorosulfation of the resultant material, and then acid-catalyzed hydrolysis, gave 4,6-dichloro-4,6-dideoxy-D-galactose and two minor components whose structures were not elucidated Thus, in the early work[6], the formation of a 3,6-dichloro-3,6-dideoxy compound was not explicitly established The present report describes the results of a reinvestigation of the reaction of methyl β-D-glucopyranoside (**1**) with sulfuryl chloride.

Compound **1** was treated with sulfuryl chloride in a mixture of pyridine and chloroform for 2 5 h in a Dry Ice–acetone bath, and the reaction mixture was then stirred for 2 h at room temperature Dechlorosulfation of the resultant syrup by using sodium iodide afforded a product from which methyl 4.6-dichloro-4,6-dideoxy-β-D-galactopyranoside (**2**) and methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**3**) were isolated by column chromatography in yields of 22% and 50%, respectively The melting points and specific rotations obtained for **2** and **3** accorded with some literature values (see Experimental section) Moreover, the structural assignments were corroborated by the observation that compound **2** is periodate-vulnerable whereas compound **3** is periodate-resistant It is noteworthy that **2** and **3** were obtained in lower yields if the sulfuryl chloride reaction-mixture was stirred at room temperature for longer periods of time, after 3 days, the presence of the dichloro-dideoxy derivatives could not be observed by t l c

In an earlier publication[2], a synthesis of the biologically significant sugar, paratose (3,6-dideoxy-D-*ribo*-hexose), was described, by way of hydrogenation of methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**3**) Compound **3** was obtained in that work by a somewhat laborious route starting from methyl 4,6-*O*-benzylidene-β-D-glucopyranoside and involving two separate reactions with sulfuryl chloride Clearly, the formation of **3** in good yield from methyl β-D-glucopyranoside (**1**), as described in the present report, makes available a very facile method for the preparation of paratose

Very recently, Hough and Richardson and their coworkers[9] reported that the reaction of methyl β-D-glucopyranoside (**1**) with methanesulfonyl chloride in *N*,*N*-dimethylformamide gives methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**3**) in 10% yield, in addition to the expected[10] methyl 6-chloro-6-deoxy-β-D-glucopyranoside The formation of chlorodeoxy derivatives by this reaction is presumed to involve nucleophilic attack by an alcohol (ROH) on the iminium salt ($Me_2N^+=CHOSO_2CH_3)Cl^-$, derived from methanesulfonyl chloride and *N*,*N*-dimethylformamide, to give an intermediate $Me_2N^+=CHOR$, which is then attacked by chloride ion. Thus, the isolation of compound **3** in the British work[9] and in that described in the present report clearly indicates the feasibility of nucleophilic displacement at C-3 in the β-D-glucopyranoside series

EXPERIMENTAL

General methods — Melting points were determined on a Fisher–Johns apparatus and are uncorrected Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter at 23 ±3° T l c was performed with Silica Gel G as the adsorbent in the following solvent systems (v/v)· (*A*) 3 1 pentane–ethyl acetate; (*B*) 3 1 ethyl acetate–chloroform Unless otherwise stated, the developed plates were air-dried, and compounds were located by heating the plates at about 150° after they had been sprayed with a 10% aqueous sulfuric acid solution containing 1% cerium sulfate and 1 5% molybdic acid Column chromatography was performed on Silica Gel 60 (70–230 mesh, E Merck, Darmstadt, Germany)

Reaction of methyl β-D-glucopyranoside (1) *with sulfuryl chloride* — To a mixture, cooled in a Dry Ice–acetone bath, of methyl β-D-glucopyranoside (5 0 g, 26 mmoles) in dry pyridine (20 ml) and chloroform was added, dropwise with stirring, sulfuryl chloride (13 ml, 170 mmoles) over a period of 30 min The reaction mixture was stirred for a further 2 h at the low temperature, and then for 2 h at room temperature The mixture was poured into ice and water, and the chloroform layer was separated, the aqueous solution was extracted several times with chloroform The combined chloroform solutions were washed with sodium hydrogen carbonate solution and then with water Concentration of the dried (sodium sulfate) chloroform solution gave a syrup (13 5 g) which was revealed by t l c (solvent *A*) to consist of two major components, having R_F 0 62 and R_F 0 78, and some minor components, the two major components were detected also with aniline–pyridine in *n*-butanol[11], a spray reagent for sugars containing a chlorosulfate group

To a stirred solution of the syrup in methanol was added sodium hydrogen carbonate (75 g) and then, dropwise, sodium iodide (0 55 g) in methanol, the progress of the dechlorosulfation was monitored by t l c (solvent *A*) At the end of the reaction, the mixture was filtered through Celite, and the filtrate was concentrated The residue was shown by t l c (solvent *B*) to contain two new, major components having R_F 0 40 and R_F 0 53 These two components were isolated by column chromatography, with solvent *B* as eluant, and were identified as methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside (2), yield 1 28 g (22%), and methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (3), yield 2 98 g (50 2%), respectively, recrystallization of each sample from chloroform–petroleum ether (b p. 60–80°) afforded **2** in 21% yield and **3** in 48% yield Compound **2** had m p 154–154 5° and $[\alpha]_D$ +8° (*c* 0 8, water), lit [4] m p 154°, $[\alpha]_D$ −8° (*c* 0 8, water) Compound **3** had m p 164–165° and $[\alpha]_D$ −54° (*c* 0 6, chloroform), lit , m p 163–164° (ref 9), 162–163° (ref 2), 154–156° (ref 12), $[\alpha]_D$ −54° (chloroform) (ref 9), −43° (*c* 0 6, chloroform) (ref 2), −45° (*c* 0 6, chloroform) (ref 12)

Aqueous solutions of compounds **2** and **3** were each treated with 2 molar equiv. of sodium metaperiodate and kept overnight at room temperature T l c (solvent *B*) did not reveal any change in the case of the 3,6-dichloro-3,6-dideoxy derivative **3**,

however, in the case of the 4,6-dichloro-4,6-dideoxy derivative **2**, some starting material and two faster-moving components were shown to be present

In a separate experiment, methyl β-D-glucopyranoside (**1**) was treated with sulfuryl chloride as already described except that the reaction mixture was stirred for 21.5 h at room temperature After dechlorosulfation of the resultant product, compounds **2** and **3** were isolated by column chromatography in yields of 18% and 15%, respectively In a third experiment, the sulfuryl chloride reaction-mixture was stirred for 3 days at room temperature; the presence of the two major components, observed in the first experiment, could not be detected by t l c in this case, and no change was observed by t l c on treatment of the resultant product with sodium iodide in methanol

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