THE REACTION OF SULPHURYL CHLORIDE WITH GLYCOSIDES AND SUGAR ALCOHOLS. PART I[1]

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ABSTRACT

The reaction of sulphuryl chloride with methyl α-D-glucopyranoside, methyl 4,6-*O*-benzylidene-α-D-glucoside, methyl β-D-arabinopyranoside, D-mannitol, 2,5-*O*-methylene-D-mannitol, dulcitol, and sucrose is described.

INTRODUCTION

Helferich and his co-workers in a series of papers (1, 2, 3) described the action of sulphuryl chloride on methyl α- and methyl β-D-glucopyranoside, mannitol, and trehalose. They isolated crystalline products in which the hydroxyl groups had either been replaced by chlorine atoms or bridged by cyclic sulphate groups. The compound derived from methyl α-D-glucopyranoside was shown to contain 2 chlorine atoms and a cyclic sulphate group (1). The cyclic sulphate ring could be opened by treatment with base, and the sulphate group so formed hydrolyzed with hydrochloric or sulphuric acid to yield a dichloro-dideoxy hexose (2).

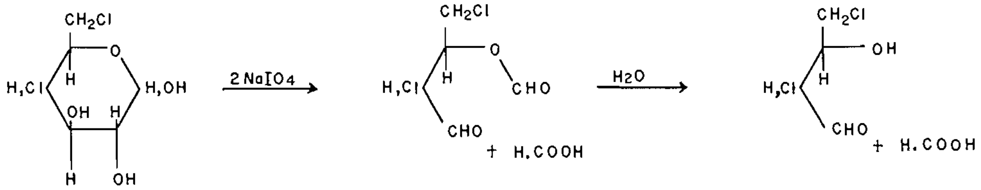
In the present work, this reaction was applied to glycosides and hexitols, and an attempt was made to determine the structure of the desulphated chloro-sugars.

The dichloro-dideoxy hexose from methyl α-D-glucopyranoside was prepared by Helferich's method (1). On periodate oxidation this compound (I) in 24 hours consumed 2 moles periodate and liberated 2 moles of formic acid.

Although all the periodate was consumed rapidly the second molecule of acid was liberated more slowly suggesting that hydrolysis of the formyl ester (II) was occurring. These results are only consistent with I being 4,6-dichloro-4,6-dideoxy hexose. Periodate oxidation of the methyl glycoside of I (0.87 mole periodate; 26 hours) substantiated this conclusion. Helferich had previously suggested that 1 chlorine atom was at $C_{(6)}$ because of the ease with which it could be removed by alkali (3).

The dichloro-dideoxy hexose was reduced with potassium borohydride. The dichloro-dideoxy hexitol was obtained as an impure syrup which rapidly consumed 1.56 moles periodate liberating 0.73 mole formic acid and formaldehyde (not estimated), which is only consistent with the assignment of chlorine atoms to $C_{(4)}$ and $C_{(6)}$.

The structure of the original compound is therefore probably methyl 4,6-dichloro-4,6-dideoxy-α-D-hexoside 2,3-sulphate. The elimination of the hydroxyl group at $C_{(4)}$ by the chlorine atom might occur with inversion of configuration to give the D-galactose configuration. This problem is now under investigation. The presence of a 2,3-sulphate



I

II

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group was also suggested by the isolation of an analogous methyl 4,6-*O*-benzylidene-α-D-glucoside 2,3-sulphate by the action of sulphuryl chloride on methyl 4,6-*O*-benzylidene-α-D-glucoside.

Hydrolysis of the cyclic sulphate derivative eliminated the methyl glycoside and benzylidene groups and gave glucose only, showing that removal of the sulphate group occurred without inversion of the hydroxyl groups on $C_{(2)}$ and $C_{(3)}$ unless the initial formation of the cyclic ester had also resulted in inversion.

Methyl β-D-arabinopyranoside was converted by sulphuryl chloride to a methyl monochloro-monodeoxy pentoside cyclic sulphate which could be desulphated to yield a monochloro-monodeoxy pentose. The results of periodate oxidation (2 moles periodate consumed with the liberation of 2 moles acid) indicated that the chlorine atom was located on $C_{(4)}$. Periodate oxidation (1.1 moles; 26 hours) of the methyl α-glycoside confirmed this. The monochloro-monodeoxy pentose gave a *p*-nitrophenylosazone without loss of chlorine showing that the chlorine atom was not on $C_{(1)}$ or $C_{(2)}$ of the pentose. The very probable structure of the original compound would therefore be methyl 4-chloro-4-deoxy-β-pentoside 2,3-sulphate.

Both dulcitol and D-mannitol readily give crystalline compounds with sulphuryl chloride and in both cases 4 chlorine atoms and a cyclic sulphate group are introduced. 2,5-*O*-Methylene-D-mannitol gave a trichloro-trideoxy-mono-*O*-methylene hexitol.

The cyclic sulphate ester of the mannitol derivative is very resistant to acid hydrolysis. Very little acetolysis of this compound occurred at 25° C, but appreciable hydrolysis of the sulphate group followed by acetylation occurred at 100° C. Deacetylation of the product then yielded a substance (contaminated with starting material) with a chromatographic mobility consistent with that of a tetrachloro-tetradeoxy hexitol. The impure product consumed 0.77 mole periodate (46 hours) suggesting that the sulphate group in the original compound bridged adjacent hydroxyl groups (presumably on $C_{(3)}$–$C_{(4)}$).

Sucrose yielded a product which appeared to be a mixture of di- and tri-chlorodeoxy sucrose disulphates. The structure of the glucose moiety is similar to that from methyl α-D-glucopyranoside since the same 4,6-dichloro-4,6-dideoxy hexose can be obtained from both. The remaining cyclic sulphate group and chlorine atom are located on the fructose portion of the molecule. The position of these groups was not determined since the vigorous conditions of hydrolysis necessary to cleave the interglycosidic linkage destroyed the fructose moiety, but it is probable by comparison with the anhydrides of sucrose (4), that the sulphate group spans $C_{(3')}$–$C_{(6')}$ or $C_{(1')}$–$C_{(4')}$ with the chlorine atom on $C_{(1')}$ or $C_{(6')}$ respectively.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler microheating stage. Optical rotations were measured at 24° C. All evaporations were carried out under reduced pressure.

General Method

Redistilled sulphuryl chloride (7 ml) was added to a mixture of pyridine (30 ml) and chloroform (100 ml), which had been dried over potassium hydroxide pellets and anhydrous sodium sulphate respectively. The temperature of the solution was maintained at 5° C while the glycoside or hexitol (4 g; dried over phosphoric oxide) was added with vigorous stirring. After 2 hours the reaction mixture was poured into ice water and the chloroform layer separated, well washed with water, and dried (sodium hydrogen carbonate). Concentration afforded a syrup which was decolorized with charcoal if necessary. Crystallization was spontaneous, but purification by extracting the product into ether was sometimes imperative.

Methyl α-D-Glucopyranoside

With sulphuryl chloride, methyl α-D-glucopyranoside gave long colorless needles (1.8 g) which, recrystallized from ether – light petroleum (40–60° C), had m.p. 104–105° C, $[\alpha]_D$ +140° (*c*, 1.99 in methanol). Analysis: Calc. for $C_7H_{10}O_6Cl_2S$: C, 28.7%, H, 3.4%; Cl, 24.2%; S, 10.9%. Found: C, 28.9%; H, 3.4%; Cl, 24.1%; S, 11.1%.

Methyl Dichloro-dideoxy Hexoside and Dichloro-dideoxy Hexose

The above compound (1.8 g) dissolved in methanol saturated with ammonia at 0° C (50 ml) was kept at room temperature for 24 hours. Concentration gave a partially crystalline syrup which was heated at 100° C for 14 hours with *N* sulphuric acid (50 ml). The acid was neutralized with barium carbonate and the solution deionized by passage through Amberlite IR-120 and Duolite A4 resin columns. The eluate was concentrated to a syrup (0.74 g) which slowly crystallized. An aqueous solution of the syrup was continuously extracted with chloroform. The chloroform extract on evaporation yielded crystals, m.p. 158° C, $[\alpha]_D$ +184° (*c*, 2.1 in water). Analysis: Calc. for $C_7H_{12}O_4Cl_2$: C, 36.3%; H, 5.2%; Cl, 30.7%. Found: C, 36.2%; H, 5.3%; Cl, 31.0%. On concentration of the aqueous solution white needle-shaped crystals were obtained. Recrystallized from ethanol–water, the dichloro-dideoxy hexose had m.p. 183–186° C (decomp.), $[\alpha]_D$ +132° (5 minutes) → 98° (equilibrium; 24 hours) (*c*, 0.69 in methanol). Analysis: Calc. for $C_6H_{10}O_4Cl_2$: C, 33.2%; H, 4.6%. Found: C, 33.6%; H, 4.7%.

The dichloro-dideoxy hexose (115 mg) was reduced for 1 hour with potassium borohydride (365 mg) in water (50 ml). Excess borohydride was destroyed with acetic acid, and after deionization with resin, the major component (R_f 0.56) *n*-butanol:ethanol: water = 3:1:1 was separated as a syrup (47 mg) on paper chromatograms, $[\alpha]_D$ 0° (*c*, 1.0 in water).

Methyl β-D-Arabinoside

Methyl β-D-arabinoside and sulphuryl chloride yielded colorless needles (1.6 g) which, recrystallized from ether – light petroleum (80–100° C), had m.p. 108.5° C, $[\alpha]_D$ −89° (*c*, 0.97 in methanol). Analysis: Calc. for $C_6H_9O_6SCl$: S, 13.1%; Cl, 14.5%. Found: S, 13.3%; Cl, 14.1%.

Methyl Monochloro-monodeoxy Pentoside and Monochloro-monodeoxy Pentose

Both were prepared from the compound derived from methyl β-D-arabinoside by treatment with methanolic ammonia followed by sulphuric acid as described above. The methyl pentoside crystallized as white needles which after recrystallization from ether – light petroleum (b.p. 60–80° C) had m.p. 102–104° C, $[\alpha]_D$ +119° (*c*, 2.25 in water). Analysis: Calc. for $C_6H_{11}O_4Cl$: C, 39.5%; H, 6.0%; Cl, 19.5%. Found: C, 39.6%; H, 6.2%; Cl, 19.8%. Monochloro-monodeoxy pentose had m.p. 128–131° C, $[\alpha]_D$ +57° (10 minutes) → 0° (equilibrium, 6 hours) (*c*, 0.98 in methanol). Analysis: Calc. for $C_5H_9O_4Cl$: C, 35.6%; H, 5.3%. Found: C, 35.8%; H, 5.8%.

The product (95 mg) in 50% acetic acid (2 ml) was added to *p*-nitrophenylhydrazine (0.3 g) in glacial acetic acid (2 ml) and heated at 100° C for 1 hour. Crystals of the *p*-nitrophenylosazone were precipitated. After they were washed with water and ether, they had m.p. 224° C. Analysis: Calc. for $C_{17}H_{17}O_6N_6Cl$: N, 13.7%; Cl, 8.7%. Found: N, 11.7%; Cl, 7.1%.

Methyl 4,6-O-Benzylidene-α-D-glucopyranoside

This reacted with sulphuryl chloride to give long colorless needles (2 g) which slowly darkened over a period of days with liberation of benzaldehyde. When recrystallized from chloroform – light petroleum it had m.p. 107° C (decomp.). A sodium fusion showed chlorine to be absent from the molecule. Analysis: Calc. for $C_{14}H_{16}O_8S$: S, 9.3%. Found: S, 9.0%. Treatment first with methanolic ammonia and then with sulphuric acid gave chromatographically homogeneous glucose which was characterized as its *p*-nitroanilide derivative, m.p. 186° C, $[\alpha]_D$ +192° (*c*, 0.85 in water).

D-*Mannitol*

With sulphuryl chloride, D-mannitol afforded needle-shaped crystals (1.5 g) which when recrystallized from chloroform – light petroleum had m.p. 105° C, $[\alpha]_D$ +88° (*c*, 2.84 in methanol). Analysis: Calc. for $C_6H_8O_4Cl_4S$: C, 22.6%; H, 2.5%; Cl, 44.7%; S, 10.0%. Found: C, 22.8%; H, 2.8%; Cl, 44.3%; S, 10.4%.

The compound (4.2 g) was heated at 95–100° C for $2\frac{1}{2}$ hours in acetic anhydride (30 ml) and sulphuric acid (1.5 ml). The dark brown solution was poured into ice water, which was then extracted with chloroform. The chloroform extract was washed with an aqueous sodium hydrogen carbonate solution, dried (anhydrous magnesium sulphate), and was concentrated to a syrup. Following decolorization with charcoal, the syrup was deacetylated with sodium methoxide at 5° C. Excess sodium methoxide was removed with carbon dioxide, and after dilution with water, the solution was continuously extracted with ether. Concentration of the ether extract afforded a syrup (0.9 g) which gave a single spot (R_f 0.79) with the periodate–anisidine spray (5) on chromatography in butan-1-ol:ethanol:water (3:1:1) solvent.

Mono-anhydro-trichloro-trideoxy Hexitol

The compound (2.7 g) obtained from mannitol was treated with methanolic ammonia and with sulphuric acid, as previously described, to yield colorless needles (0.6 g) m.p. 102° C, $[\alpha]_D$ 0° (*c*, 0.86 in methanol). Analysis: Calc. for $C_6H_9O_2Cl_3$: C, 32.8%; H, 4.1%; Cl, 48.5%. Found: C, 33.0%; H, 4.1%; Cl, 46.2%.

*2,5-O-Methylene-*D*-mannitol*

2,5-*O*-Methylene-D-mannitol and sulphuryl chloride yielded a crystalline product (1.1 g); when recrystallized from ethanol–water it had m.p. 116° C and $[\alpha]_D$ −42° (*c*, 1.73 in methanol). Analysis: Calc. for $C_7H_{11}O_3Cl_3$: C, 33.6%; H, 4.4%; Cl, 42.7%. Found: C, 33.7%; H, 4.3%; Cl, 42.9%. In the infrared a hydroxyl peak was obtained. The methylene group was not removed by treatment with *N*-sulphuric acid at 100° C for 5 hours.

Dulcitol

Dulcitol and sulphuryl chloride gave a crystalline product (1.4 g) m.p. 116° C. Analysis: Calc. for $C_6H_8O_4Cl_4S$: C, 22.6%; H, 2.5%; Cl, 44.7%; S, 10.0%. Found: C, 22.6%; H, 2.7%; Cl, 44.3%; S, 10.4%.

Sucrose

Sucrose (4 g) was dissolved in pyridine (80 ml) at the boiling point and the solution then cooled to 5° C. Chloroform (90 ml) was added and the slight precipitate produced was redissolved by the further addition of pyridine (10 ml). Sulphuryl chloride (7 ml) was added dropwise with stirring to the cooled solution (5° C). After 2 hours the liquid was poured into ice water, the chloroform layer washed with water and dried (magnesium sulphate). Concentration gave a syrup (2.9 g), and from a chloroform solution of this the product was precipitated by ether as a pale yellow solid, m.p. 94–99° C. Analysis: Calc. for $C_{12}H_{16}O_{13}S_2Cl_2$: S, 12.7%; Cl, 14.1%. Calc. for $C_{12}H_{15}O_{12}S_2Cl_3$: S, 12.3%; Cl, 20.4%. Found: S, 12.4%; Cl, 16.8%.

Hydrolysis (*N* sulphuric acid, 24 hours) gave a complex mixture of substances but mainly 4,6-dichloro-4,6-dideoxy hexose identical with that derived from methyl α-D-glucoside. After separation on a cellulose column using *n*-butanol:water (19:1) it had m.p. and mixed m.p. 186° C (decomp.). Calc. for $C_6H_{10}O_4Cl_2$: C, 33.2%; H, 4.6%; Cl, 32.7%. Found: C, 33.4%; H, 4.7%; Cl, 32.6%.

Compounds reacting with the resorcinol spray (ketoses) (6) were largely absent from the hydrolysis mixture.

TABLE I

Substance	Time of oxidation (hours)	Consumption of periodate (mole/molecule)	Acid production (mole/molecule)
Methyl dichloro-dideoxy hexoside	1.08	0.16	
	20	0.79	0.00
	26	0.87	
	43	1.13	0.00
Dichloro-dideoxy hexose	1	1.40	1.14
	4	2.05	1.89
	7	2.05	2.01
	24	2.09	1.96
Dichloro-dideoxy hexitol	1	1.49	
	5	1.56	0.73
	24	1.56	0.73
Methyl monochloro-monodeoxy pentoside	1.08	0.15	
	20	1.01	0.00
	26	1.10	
	43	1.22	0.00
Monochloro-monodeoxy pentose	1	1.62	1.09
	4	1.87	1.42
	7	1.87	1.42
	24	1.93	1.72
Tetrachloro-tetradeoxy hexitol	1	0.46	
	4	0.52	
	23	0.67	0.00
	46	0.77	0.00

Periodate Oxidation of Chloro-sugars

About 25 mg of the substance, accurately weighed, was dissolved in water (50 ml) and 0.3 *M* sodium metaperiodate (2 ml) added. Aliquots were removed at intervals and the consumption of periodate and the production of formic acid measured (7, 8). Dichloro-dideoxy hexitol gave formaldehyde (characterized as the dimedone complex, m.p. 188° C) (9) on periodate oxidation.

Mono-anhydro-trichloro-trideoxy hexitol was not attacked by periodate.

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