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

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ABSTRACT

The structures of methyl 4,6-dichloro-4,6-dideoxy-α-D-hexoside and methyl "4-chloro-4-deoxy-β-pentoside" (I) have been investigated. The desulphation reaction leading to the formation of the latter compound is described. Replacement of the hydroxyl group at $C_{(4)}$ by a chlorine atom in both compounds is shown to have occurred with inversion of configuration.

INTRODUCTION

In Part I (1) the product of the reaction of sulphuryl chloride with methyl α-D-glucopyranoside was shown to be probably methyl 4,6-dichloro-4,6-dideoxy-α-D-hexoside 2,3-sulphate which on desulphation gave methyl 4,6-dichloro-4,6-dideoxy-α-D-hexoside (I). It was possible that the replacement of the hydroxyl group at $C_{(4)}$ by the chlorine atom had occurred with inversion of configuration to give the galactose configuration.

This problem was investigated using a synthetic route to a methyl 4,6-dichloro-4,6-dideoxy-α-D-hexoside of known configuration. Methyl 4-chloro-4-deoxy-α-D-glucopyranoside was synthesized by the method of Buchanan (2). Reaction with sulphuryl chloride and subsequent desulphation gave a complex mixture from which was isolated methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside (II) which was found to be different from that obtained from the reaction of sulphuryl chloride with methyl α-D-glucopyranoside (I). It was found that II consumed periodate extremely slowly (1.04 moles, 167 hours) and this bore some resemblance to the parent methyl 4-chloro-4-deoxy-α-D-glucopyranoside which was oxidized under somewhat similar conditions (1.03 moles, 170 hours) (3, 3*a*). Accordingly the chlorine atom at $C_{(4)}$ of I was placed in the galactose configuration since this was the only position in which I and II differed.

Further evidence as to the configuration at $C_{(4)}$ of I was obtained when the reaction of sulphuryl chloride with methyl α-D-galactopyranoside was examined. Desulphation of the fully substituted product gave a complex mixture from which was isolated a methyl dichloro-dideoxy-α-D-hexoside identical with II.

Compound I did not react with sodium hydroxide, whereas II lost approximately 1 equivalent of chlorine under the same conditions probably to give I*b*. It was found that methyl 3-chloro-3-deoxy-α-D-gulopyranoside, with sodium hydroxide, lost chlorine to give methyl 3,4-anhydro-α-D-galactopyranoside (I*a*) in good yield. These findings were related to the configurations of the chlorine atom at $C_{(4)}$ and the hydroxyl group at $C_{(3)}$ in I and II, and it was concluded that a trans configuration was necessary for the elimination of chlorine from $C_{(4)}$ to take place.

Since the threo configuration was retained in I at $C_{(2)}$ and $C_{(3)}$ during desulphation (1) and the $C_{(3)}$ and $C_{(4)}$ hydroxyl group and chlorine atom were cis disposed it was concluded that I possessed the galactose configuration and that elimination of hydroxyl at $C_{(4)}$ by chlorine had occurred with inversion of configuration.

Accordingly I would be methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside, and the fully substituted compound from which it was obtained by desulphation would be methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-sulphate.

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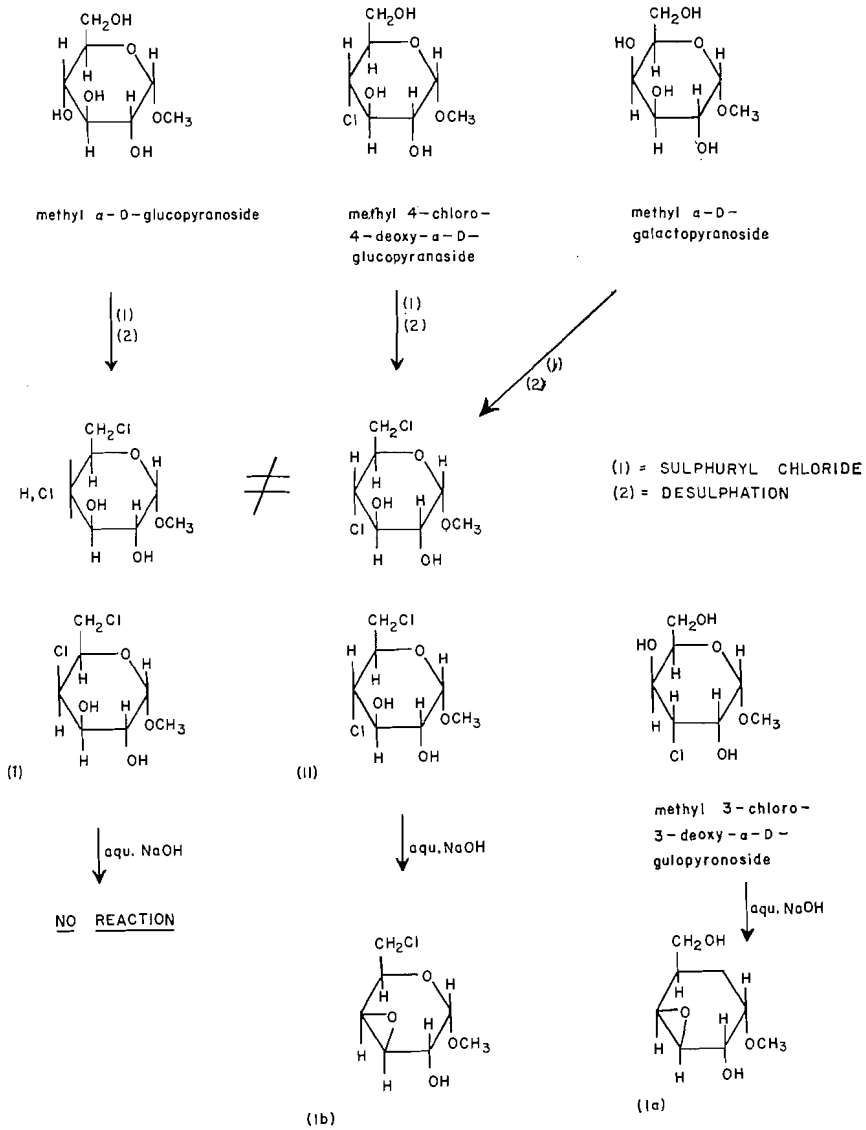
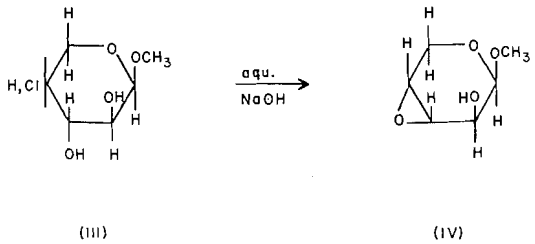
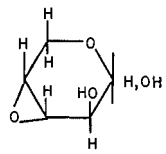


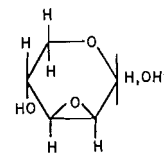
The monochloro monodeoxy pentoside (III) from methyl β-D-arabinopyranoside possessed the chlorine atom at $C_{(4)}$ (1). On treatment of III with sodium hydroxide, chlorine was eliminated, presumably with the formation of the anhydro pentoside (IV).



On hydrolysis IV gave two pentoses, D-lyxose and xylose. (The latter was not completely characterized as only a small amount was produced.) The structure of IV was therefore very probably as written, namely, methyl 3,4-anhydro-β-D-arabinopyranoside. As shown previously, elimination of chlorine under the influence of sodium hydroxide occurred when the chlorine atom and hydroxyl group involved were trans to one another. Since the configuration of the hydroxyl groups on $C_{(2)}$ and $C_{(3)}$ did not change on desulphation (1) and $C_{(3)}$ and $C_{(4)}$ groups were trans, III possessed the L-xylose configuration and was therefore methyl 4-chloro-4-deoxy-α-L-xylopyranoside. The fully substituted compound from which III was obtained by desulphation also possessed the L-xylose configuration and was methyl 4-chloro-4-deoxy-α-L-xylopyranoside 2,3-sulphate. The desulphation of the latter compound was investigated more fully. In addition to methyl 4-chloro-4-deoxy-α-L-xylopyranoside and 4-chloro-4-deoxy-L-xylose, five other compounds were isolated in small amount from the desulphated mixture. They were: two anhydro pentoses, D-lyxose, xylose, and D-arabinose. One anhydro pentose (V) gave on hydrolysis xylose and lyxose, while the other (VI) gave xylose and arabinose which were identified chromatographically because the pentoses were present in too small an amount to be completely characterized in this instance.



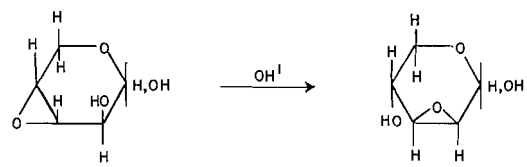
V(3,4-anhydro-D-arabinose)



VI(2,3-anhydro-D-lyxose)

Very probably V and VI gave rise to D-lyxose, xylose, and D-arabinose during the second stage of desulphation (treatment with 2 *N* sulphuric acid). The mechanism of formation of VI is less certain but a possible explanation is outlined below.

An apparently anomalous reaction is proposed in the conversion of methyl 3,4-anhydro-β-D-arabinopyranoside 2-sulphate (a postulated reaction intermediate) to methyl 2,3-anhydro-β-D-lyxopyranoside by 2 *N* sulphuric acid. Reactions of the type V $\rightarrow$ VI are



(V) (VI)

known to occur, under the influence of alkali (4), but not in an acid medium. However, no free ionic sulphate could be detected after the first stage of desulphation (treatment with methanolic ammonia) and the sulphate residue remaining on $C_{(2)}$ would presumably prevent migration of the epoxide ring from $C_{(3)}$–$C_{(4)}$ to $C_{(2)}$–$C_{(3)}$. Therefore the migration was presumed to occur in the second stage in which the sulphate residue was removed (treatment with 2 *N* sulphuric acid).

The initial reaction in the desulphation, the cleavage of the cyclic sulphate ring with

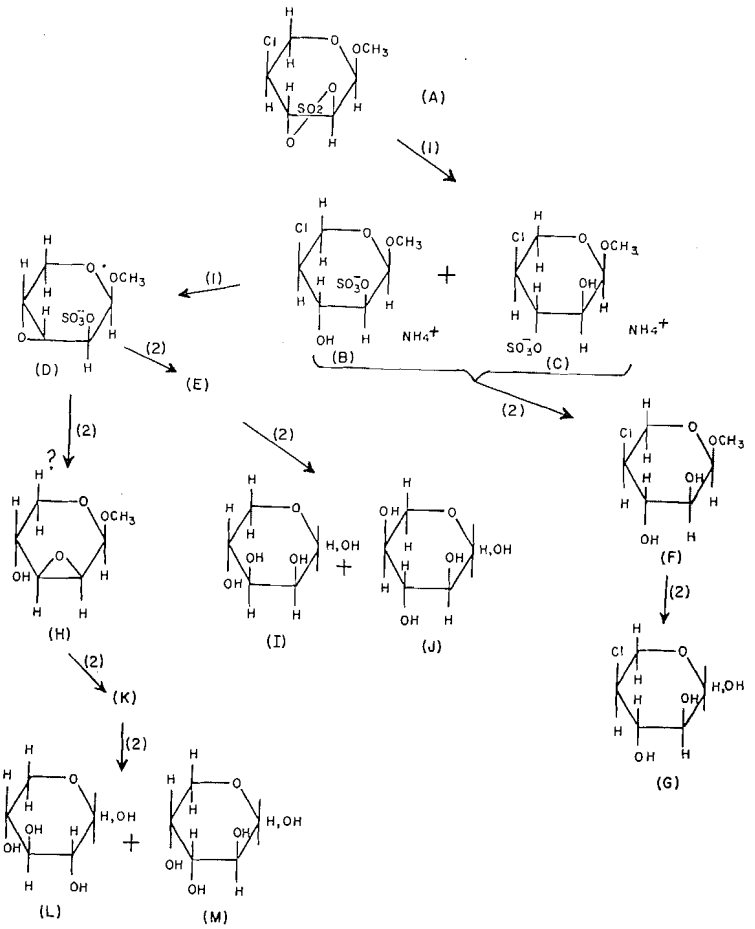


FIG. 1. The desulphation of methyl 4-chloro-4-deoxy-α-L-xyloside 2,3-sulphate (A).
LEGEND: First stage of desulphation ($MeOH/NH_3$) (1).
Second stage of desulphation (2 *N* H_2SO_4) (2).
(B) and (C) Ammonium salts of opened sulphate ring. (D) 3,4-Anhydro-β-D-arabinose 2-sulphate. (E) 3,4-Anhydro-D-arabinose. (F) Methyl 4-chloro-4-deoxy-L-xylose. (G) 4-Chloro-4-deoxy-L-xylose. (H) 2,3-Anhydro-β-D-lyxoside. (I) D-Lyxose. (J) L-Xylose. (K) 2,3-Anhydro-D-lyxose. (L) D-Xylose. (M) D-Arabinose.

ammonia, very probably gave two compounds ((B) and (C) in diagram). The ratio of (B) to (C) was not known, but it was unlikely that a very high proportion of (B) was present, as chlorine would then have been eliminated by the methanolic ammonia due to the trans configuration of the chlorine atom on $C_{(4)}$ and the hydroxyl group on $C_{(3)}$.

An analogous sequence of reactions leading to the formation of complex mixtures would be expected to occur with all those fully substituted derivatives containing a chlorine atom trans to an adjacent potential secondary hydroxyl group, and this was found to be the case (see above) with methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside 2,3-sulphate. The corresponding derivative from methyl α-D-glucopyranoside, possessing the galactose configuration, gave only methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (I) and 4,6-dichloro-4,6-dideoxy-D-galactose on desulphation.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler microheating stage. All evaporations were carried out under reduced pressure. Optical rotations were measured in water at 21±3° C unless otherwise stated. Paper chromatograms were run using a descending flow (5) and Whatman No. 1 paper in the following solvent systems:

(*a*) butan-1-ol:ethanol:water (3:1:1),
(*b*) butan-1-ol:pyridine:water (10:3:3),
(*c*) ethyl acetate:acetic acid:formic acid:water (18:3:1:4).

Reaction of Sulphuryl Chloride with Methyl 4-Chloro-4-deoxy-α-D-glucopyranoside

The chloro sugar was obtained as a syrup contaminated with a small amount of methyl 3-chloro-3-deoxy-α-D-gulopyranoside, by the method of Buchanan (2). The syrup (0.5 g) gave with sulphuryl chloride a pale yellow syrup (0.388 g) containing sulphur and chlorine. On desulphation first with methanolic ammonia and then with 2 *N* sulphuric acid in the usual manner (1) a complex mixture was obtained (0.180 g) which consisted of seven components of R_f values 0.19, 0.21, 0.40, 0.48, 0.73, 0.78, 0.81, in solvent (*a*). Alkaline silver nitrate spray (6) was used to detect the sugars. An aqueous solution of the mixture was continuously extracted with chloroform for 24 hours. The chloroform extract on evaporation gave a syrup (43 mg) which crystallized. The syrup contained the three components R_f 0.73, R_f 0.78, R_f 0.81, of which the component R_f 0.78 was the major one. The syrupy crystals were recrystallized twice from chloroform/light petroleum (60°–80° C) to give white needles of melting point 119–121° C and $[\alpha]_D$ +121° (*c*, 1.8). Analysis: Calc. $C_7H_{12}O_4Cl_2$: C, 36.4%; H, 5.2%. Found: C, 37.0%; H, 5.3%.

Periodate Oxidation of the Methyl Dichloro-dideoxy-α-D-hexoside Prepared from Methyl 4-Chloro-4-deoxy-α-D-glucopyranoside

The oxidation was carried out at 25° C, using a small sample (8.5 mg) of the compound in distilled water (25 ml) containing 0.3 *M* sodium metaperiodate (1 ml). The results are shown below and are compared with those of Buchanan (3) for methyl 4-chloro-4-deoxy-α-D-glucopyranoside.

TABLE I

Substance	Time of oxidation (hours)	Consumption of periodate (mole/molecule)	Acid production (mole/molecule)
Methyl dichloro-dideoxy-α-D-hexoside	3.8	0.195	
	10	0.310	
	24.5	0.415	
	167	1.04	
	243	1.07	0.00
Methyl 4-chloro-4-deoxy-α-D-glucopyranoside	20	0.42	
	40	0.58	Not reported
	170	1.03	
	212	1.06	

Reaction of Sulphuryl Chloride with Methyl α-D-Galactopyranoside

Methyl α-D-galactopyranoside was prepared by the method of Dale and Hudson (7), purified by recrystallization from hot absolute ethanol, and dried *in vacuo* at 40° C. With sulphuryl chloride, methyl α-D-galactopyranoside (5 g) gave a brown syrup (3.7 g)

which contained chlorine and sulphur (sodium fusion). The syrup could not be obtained crystalline.

Desulphation of the syrup with methanolic ammonia and 2 *N* sulphuric acid gave a mixture (0.73 g) containing four components of R_f values 0.12, 0.22, 0.42 (major component), 0.71 (solvent (*a*); alkaline silver nitrate and anisidine hydrochloride (8) sprays). An aqueous solution of the mixture was continuously extracted with chloroform for 24 hours. The chloroform extract on evaporation gave a colorless syrup (0.3 g). On nucleation with the methyl dichloro-dideoxy-α-D-hexoside which had been prepared from methyl 4-chloro-4-deoxy-α-D-glucopyranoside (see above) rapid crystallization occurred.

When recrystallized from chloroform/light petroleum (60°–80° C) the crystals had a melting point of 119–121° C, mixed melting point with the above compound 119–121° C, $[\alpha]_D$ +122° (*c*, 1.9) and were therefore identical with that compound. Analysis: Calc. for $C_7H_{12}O_4Cl_2$: Cl, 30.7%. Found (Schöniger combustion method (9)): Cl, 30.4%.

The Reaction of Chloro Sugars with Sodium Hydroxide

The Methyl 4,6-Dichloro-4,6-dideoxy-α-D-hexoside from Methyl α-D-Glucopyranoside (1)

The hexoside (150 mg) was dissolved in water (25 ml) and phenolphthalein was added. The solution was then titrated with 0.232 *N* sodium hydroxide solution. No sodium hydroxide was neutralized even after 4 hours at 40° C. The solution was deionized with resin and the eluate concentrated to a crystalline mass (151 mg). The crystals had a melting point of 156–158° C and mixed melting point with the starting material, 156–158° C. Analysis: Calc. for $C_7H_{12}O_4Cl_2$: Cl, 30.7%. Found: starting material, 31.0%; product, 31.4%.

The Methyl Dichloro-dideoxy-α-D-hexoside from Methyl α-D-Galactopyranoside

The hexoside (m.p. 119–121° C, 0.875 mg) was dissolved in distilled water (1 ml) and sodium hydroxide solution (1 ml of 0.01 *N*) was added. The solution was allowed to stand for 6 hours at room temperature, then neutralized exactly with 0.01 *N* sulphuric acid, using screened methyl red – methylene blue indicator. To the neutralized solution was added neutralized mercuric oxycyanide solution (5 ml of 2% solution) and the resultant alkaline solution titrated to exact neutrality with 0.01 *N* sulphuric acid. The titer was 0.330 ml, which corresponded to the elimination of 0.88 mole chlorine per molecule of hexoside. The titration mixture was deionized with resin and examined on paper chromatograms. Three components were observed of R_f values 0.04 (faint), 0.38 (major component), 0.71 (faint co-chromatographing with starting material) (solvent (*a*), alkaline silver nitrate spray).

The Methyl 3-Chloro-3-deoxy-α-D-gulopyranoside (2)

The gulopyranoside (164 mg) was dissolved in water (25 ml) and titrated with sodium hydroxide (0.232 *N*) as described above. The solution took up 1 equivalent (3.31 ml) of sodium hydroxide over a period of 72 hours at 40° C and was then evaporated to dryness. The residue was extracted three times with 100-ml portions of boiling ether. The combined ether extracts on evaporation gave a syrup (101 mg, 74%) which rapidly crystallized. The crystals had a melting point of 117–118° C undepressed on admixture with an authentic specimen of methyl 3,4-anhydro-α-D-galactopyranoside (m.p. 117.5–118.5° C).

The Methyl 4-Chloro-4-deoxy-β-pentoside from Methyl β-D-Arabinopyranoside (1)

The pentoside (67 mg) was dissolved in water (3.0 ml) and sodium hydroxide solution

(0.45 ml of 0.232 *N*) was added. The change in optical rotation was followed at intervals up to 5 hours.

TABLE II

Time of reaction (hours)	$[\alpha]_D$
0	+108°
0.25	+82°
0.50	+73°
1.0	+72°
1.75	+63°
4.0	+61°
5.0	+59°

The slight excess of sodium hydroxide remaining after 8 hours was neutralized with nitric acid, the solution evaporated to dryness, and the residue extracted with ether. The extract on evaporation gave a colorless syrup (47 mg), while the residue gave a positive test for ionic chloride. The syrup gave one main spot, R_f 0.53 (solvent (*a*)), on paper chromatograms. The syrup was heated with 2 *N* sulphuric acid at 100° C for 14 hours, neutralized with barium carbonate, filtered, and deionized with resin. The eluate was concentrated to a colorless syrup (30 mg) which consisted of xylose and lyxose as shown by paper chromatograms, and paper electrophoresis in pH 9.5 borate buffer at 2500 volts for 40 minutes. An attempted separation of the pentoses using phenol saturated with water as the chromatographic solvent (10) with a descending flow on Whatman 3MM paper was unsuccessful. The pentoses were separated by paper electrophoresis under the conditions mentioned above. The lyxose (10 mg) $[\alpha]_D$ −18° (*c*, 1) was characterized by its rate of movement on chromatograms and as its phenyl osazone, m.p. 158–161° C, unchanged on admixture with authentic D-lyxose (xylose) phenylosazone (11). The xylose could not be satisfactorily characterized due to its small amount (ca. 2 mg).

The Desulphation of Methyl 4-Chloro-4-deoxy-β-pentoside 2,3-Sulphate (1)

The desulphated mixture (0.9 g) was separated on a cellulose column using butan-1-ol: water (19:1). Besides methyl 4-chloro-4-deoxy-β-pentoside and 4-chloro-4-deoxy pentose, four other fractions were isolated: Fraction I, a syrup (53 mg) with R_f 0.44 (in solvent (*a*)) was obtained. On hydrolysis with sulphuric acid it gave xylose and lyxose, identified by paper chromatography and paper electrophoresis: Fraction II was a syrup (15 mg) with R_f 0.39 (solvent (*a*)). On hydrolysis it gave xylose and arabinose, identified by paper chromatography and paper electrophoresis. Fraction III was a syrup (78 mg) with R_f 0.24 (solvent (*a*)). This fraction consisted of xylose and lyxose as shown by paper chromatograms and paper electrophoresis. A partial separation was achieved on a column of Dowex 50W sulphuric acid resin (86×2.2 cm, 8% cross-linked with divinyl benzene, 200–400 mesh, barium salt form). The lyxose was obtained pure, and characterized as its *p*-toluene sulphonhydrazone (12), m.p. 152–153° C, which did not depress the melting point of authentic D-lyxose *p*-toluene sulphonhydrazone (141° C). The xylose could not be completely characterized. Fraction IV, syrupy crystals (51 mg), R_f 0.214 (solvent (*a*)), consisted of D-arabinose as shown by paper chromatograms. It was contaminated with some water-insoluble material and had $[\alpha]_D$ −74° (5 minutes) → −66° (8 hours) (*c*, 0.4 in methanol). It was characterized as the benzoyl hydrazone, m.p. 190–195° C, undepressed on admixture with authentic D-arabinose benzoyl hydrazone, m.p. 190–195° C (13).

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