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REACTIONS OF SUGAR CHLOROSULFATES

PART VIII. D-RIBOSE AND ITS DERIVATIVES

S. S. ALI, T. J. MEPHAM, (MISS) I. M. E. THIEL, E. BUNCEL, AND J. K. N. JONES
(Department of Chemistry, Queen's University, Kingston, Ontario (Canada)
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INTRODUCTION

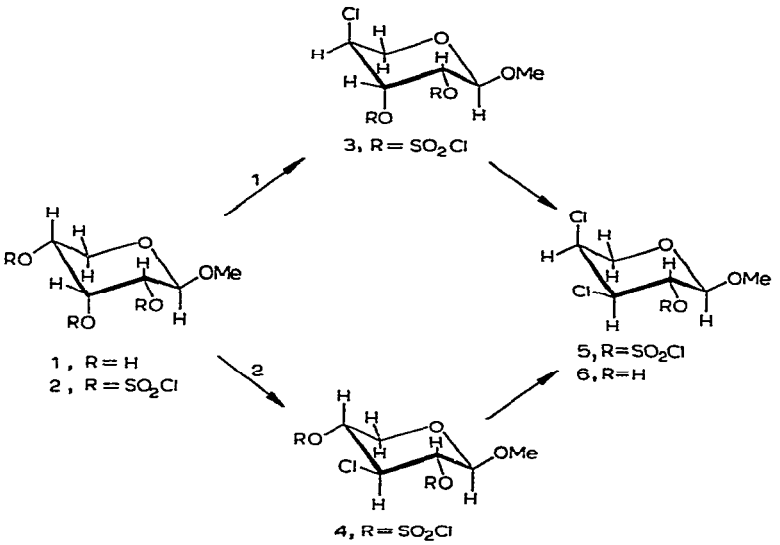
The displacement of the chlorosulfate (OSO_2Cl) group by chloride ion has been shown to occur at C-4 and at C-3 of chlorosulfate derivatives in hexopyranosides with inversion of configuration[1,2], which is in accord with a bimolecular nucleophilic displacement (S_N2) mechanism. Chlorosulfates of the pentopyranose series have been investigated to a lesser extent, but the available evidence shows that displacement of OSO_2Cl at C-4 proceeds with inversion here also. On the other hand, no example has yet been recorded of chlorosulfate displacement at C-3 of a pentopyranose derivative (see, however, ref. 3). The present work reports on such a displacement, and provides evidence of the stereochemistry of the process.

RESULTS AND DISCUSSION

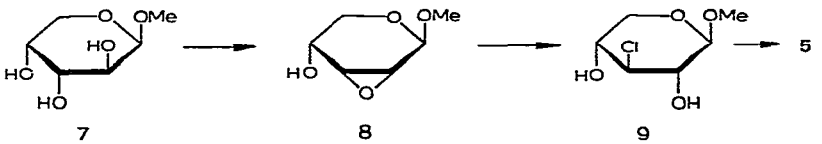
Methyl β-D-ribopyranoside (**1**) on treatment with sulfuryl chloride and pyridine in chloroform solution yields the tri(chlorosulfate) (**2**). Treatment of the latter with chloride ion results in replacement of two of the chlorosulfate groups and formation of a product that may be formulated as methyl 3,4-dichloro-3,4-dideoxy-α-L-arabinopyranoside 2-chlorosulfate (**5**), on the assumption that inversion of configuration has taken place at C-3 and C-4. In addition to providing structural proof of the stereochemistry of the process, it would be of interest to know whether the intermediate, monosubstituted product is **3** or **4**, formed by substitution at C-4 or C-3 (reactions 1 and 2), respectively. No monochloro-deoxy compound could, in fact, be isolated.

The stereochemistry of the substitution process was elucidated as follows. Methyl β-D-arabinopyranoside (**7**) was converted into methyl 2,3-anhydro-β-D-ribopyranoside (**8**) *via* the 2-*p*-toluenesulfonic ester of **7**. The anhydro ring of **8** is known[4] to be opened, by hydrogen bromide, with preponderant formation of a β-D-xyloside derivative. In the present work, this reaction (with hydrogen chloride) gave methyl 3-chloro-3-deoxy-β-D-xyloside (**9**) which, as expected[5], was unaffected by sodium periodate solution. Treatment of **9** with sulfuryl chloride and pyridine hydrochloride yielded the same dichlorodideoxy mono(chlorosulfate) (**5**) as had been obtained from **2**, even when the reaction was carried out under very mild conditions. Dechlorosulfation of the product **5** yielded a methyl dichlorodideoxypentoside (**6**), which may be formu-

lated as methyl 3,4-dichloro-3,4-dideoxy-α-L-arabinopyranoside on the expectation[1,2] that substitution at C-4 had occurred with inversion of configuration. The methyl

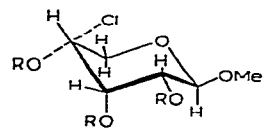


glycoside **6** could be hydrolyzed with difficulty to yield the crystalline reducing sugar which consumed 1 mole of periodate/mole rapidly and yielded formic acid slowly, presumably because of slow hydrolysis of the formic ester.



The mild conditions under which **9** is converted, *via* the 2,4-di(chlorosulfate), into **5** suggest that formation of **5** from **2** proceeds *via* intermediate **4**, rather than **3**. Indeed, it could be argued that, had substitution first occurred at C-4, the axially oriented chlorine of **3** would deactivate the neighbouring chlorosulfate group at C-3 towards further substitution, as had been observed previously[2,6] in related cases. However, the following discussion, based on conformational considerations, differentiates satisfactorily between the two alternatives (reactions 1 and 2). The transition state of the S_N2 displacement process in the pyranose series may be represented by the chairlike structures[7,8] **10** and **11**. The transition state for substitution at C-4, [**10**, and the end-on representation (**10a**) from a viewpoint along the C-4–C-3 bond] possesses considerable strain as a result of steric interaction between the near-eclipsed, adjacent, chlorosulfate groups. On the other hand, the transition state (**11**, **11a**) (or the equivalent of **11a** from a viewpoint along the C-3–C-2 bond) for substitution at C-3 is free from such unfavorable interactions and will, therefore, be of lower potential energy, thus

favoring this reaction path. A similar argument shows that further substitution at C-4 of **4** can take place without introduction of such unfavorable interactions in the transition state of the process; hence, this reaction will also occur readily.



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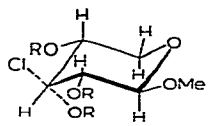

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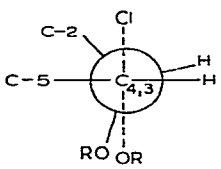
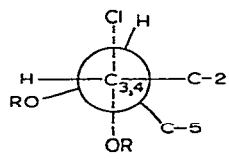
$R = SO_2Cl$



10a



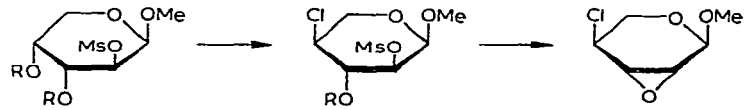
11a

D-Ribose, with sulfuryl chloride and pyridine, yielded a crystalline D-ribopyranosyl chloride 2,3,4-tri(chlorosulfate). The n.m.r. spectrum of this compound in acetonitrile with external tetramethylsilane as standard, shows the following features. The resonance farthest downfield is attributed to H-1 and appears as an ill-defined doublet at τ 3.71 with a width at half-height of 3 Hz. The narrow splitting shows that H-1 and H-2 are not *trans*-diaxial, and the rather complex appearance of the H-1 signal can be explained on the basis of long-range coupling with H-5e. Hall* has recently observed this effect in similar ribopyranosyl compounds. The H-3 signal, at τ 4.36, is a very sharp triplet with coupling constants of 3.6 Hz. The H-2 and H-4 signals appear together as a highly complex multiplet, upfield from the H-3 signal, at τ 4.76. The two H-5 signals, centered at τ 5.75, appear as the AB part of an ABX pattern. These spectral characteristics strongly indicate that the compound is the β-D anomer in the *1C*(D) conformation. A closely similar n.m.r. spectrum was obtained by Horton and Turner[9] for tri-*O*-acetyl-β-D-ribopyranosyl bromide; these authors also concluded that the compound under study exists in the *1C*(D) conformation.

It seemed of interest also to study the effect of substitution at C-2 of methyl β-D-arabinopyranoside on the process of chlorosulfate displacement. The 2-methanesulfonic ester **12** was prepared for this purpose and converted into the 3,4-di(chlorosulfate) derivative **13** with sulfuryl chloride and pyridine. The latter, on treatment with pyridinium chloride, yielded methyl 4-chloro-4-deoxy-2-*O*-(methylsulfonyl)-α-L-xyloside 3-chlorosulfate (**14**) which, on dechlorosulfation, produced methyl 4-chloro-4-deoxy-2-*O*-(methylsulfonyl)-α-L-xyloside (**15**). Base converted this substance mainly into methyl 2,3-anhydro-4-chloro-4-deoxy-α-L-lyxoside (**16**), which also can be obtained by the reaction of sulfuryl chloride and pyridinium chloride with methyl 2,3-

*Personal communication from Professor L. D. Hall.

anhydro-β-D-ribopyranoside (**8**), thus proving that, in **13**, it was the chlorosulfate group at C-4, and not the one at C-3, that had been displaced by chloride. Presumably, the chlorosulfate residue at C-3 of **13** is not displaced, because of an unfavorable diaxial interaction between an incoming chloride ion and the axial methoxyl group at C-1.



12, R = H
13, R = SO_2Cl

14, R = SO_2Cl
15, R = H

16

EXPERIMENTAL

General. — Melting points were determined on a Kofler Hot Stage and are uncorrected. Solutions were concentrated under diminished pressure at 50°, or below, with a rotary evaporator.

Paper chromatograms were made by the descending method with Whatman No. 1 filter paper and the following solvent systems (v/v): (a) 18:3:1:4 ethyl acetate–acetic acid–formic acid–water, (b) 3:1:1 butyl alcohol–ethanol–water, and (c) 5:3:3:1 butyl alcohol–pyridine–benzene–water. The sugars were detected on the chromatograms by using alkaline silver nitrate spray[10] or *p*-anisidine hydrochloride spray followed by application of heat[11]. Chlorosulfate derivatives of sugars were detected by the specific butyl alcohol–aniline–pyridine spray reagent followed by heating[12]. Sugar epoxides were detected[13] by spraying with a solution of sodium iodide and Methyl Red in butyl alcohol and heating the paper chromatogram for a few minutes at 140°.

Thin-layer chromatograms were made by the ascending technique on glass plates that had been coated with silica gel G and dried at 150–160° for 2 h. The following solvent systems were used: (d) 10:1 benzene–methanol, (e) 20:1 benzene–methanol, and (f) 2:1 benzene–isopropyl alcohol. The sugars were detected by spraying the plates with 5% sulfuric acid in ethanol followed by heating them in an oven at 110°.

Deionization of solutions was effected by passing them through Amberlite IR-120 (H^+) cation-exchange resin and Duolite A-4 anion-exchange resin.

I.r. spectra were measured with a Perkin–Elmer Model 21 spectrophotometer by using either a 5% (w/v) chloroform solution of the compound or a potassium bromide pellet containing 0.8% of the substance.

Methyl β-D-ribopyranoside tri(chlorosulfate) (**2**). — Methyl β-D-ribopyranoside (**7**, 21.4 g) was converted into the tri(chlorosulfate) (**2**, 13.2 g) in the usual way[2]. The product had m.p. 151–152°, $[\alpha]_D^{20}$ −63° (*c* 1.1, methanol).

Anal. Calc. for $C_6H_9Cl_3O_4S_3$: C, 15.7; H, 1.98; Cl, 23.1; S, 21.0. Found: C, 15.7; H, 1.87; Cl, 23.1; S, 20.6.

Reaction of methyl β-D-ribopyranoside tri(chlorosulfate) (**2**) *with an excess of pyridine hydrochloride.* — Compound **2** (13.2 g) in chloroform (250 ml) containing pyridine hydrochloride (13.2 g, 4 moles) was heated for 2 days under reflux. The

crystalline product **5**, isolated in the usual way[2], was recrystallized from aqueous acetone; yield 4.5 g (52%), m.p. 130°, $[\alpha]_D^{20}$ +49° (*c* 3.0, methanol), R_F 0.76 [t.l.c., solvent (f)].

Anal. Calc. for $C_6H_9Cl_3O_5S$: C, 24.05; H, 3.01; Cl, 35.6; S, 10.7. Found: C, 24.2; H, 2.83; Cl, 36.2; S, 10.9. The compound gave a positive test for the $-OSO_2Cl$ group.

*Methyl 3,4-dichloro-3,4-dideoxy-α-*L*-arabinoside* (**6**). — Compound **5** (4.1 g) was dechlorosulfated by treating it in methanol (100 ml) in the presence of calcium carbonate (12 g) with one drop of N sodium iodide. After 6 h, the reaction was complete (t.l.c.). The solution was filtered and deionized, and the ash-free solution evaporated to yield crystals that were recrystallized from acetone–petroleum ether (b.p. 35–60°). The product (1.4 g, 51%) had m.p. 108°, $[\alpha]_D^{27}$ +88° (*c* 1.0, methanol), R_F 0.63.

Anal. Calc. for $C_6H_{10}Cl_2O_3$: C, 35.9; H, 4.98, Cl, 35.3. Found: C, 36.0; H, 4.78; Cl, 35.5.

*3,4-Dichloro-3,4-dideoxy-*L*-arabinose.* — The methyl L-arabinoside derivative **6** (680 mg) was heated in 4N sulfuric acid (60 ml) for 36 h, after which time hydrolysis was complete (t.l.c.). The solution was neutralized (barium carbonate), and the product (300 mg, 47%) was isolated in the usual way. It had m.p. 123°, $[\alpha]_D^{22}$ +167–174° (*c* 0.17, water, 25 h), R_F 0.48.

Anal. Calc. for $C_5H_8Cl_2O_3$: C, 32.1; H, 4.28; Cl, 38.0. Found: C, 32.2; H, 4.22; Cl. 38.0. Attempts to make a phenylosazone failed.

*Periodate oxidation of 3,4-dichloro-3,4-dideoxy-*L*-arabinose.* — A sample of the sugar (9 mg) was oxidized with aqueous sodium metaperiodate in the usual manner. Found (moles of periodate reduced/mole of formic acid produced in given time): 6 min, 0.477/0.04; 35 min, 0.996/0.00; 220 min, 0.954/0.5.

*β-*D*-Ribopyranosyl chloride 2,3,4-tri(chlorosulfate).* — D-Ribose (25 g) in dry pyridine (40 ml) and dry chloroform (100 ml), cooled to −70°, was treated with sulfuryl chloride (26 ml) to give a syrupy product that crystallized on standing. The compound was recrystallized from aqueous ethanol, yield 5 g (11%), m.p. 132°, $[\alpha]_D$ −108° (*c* 0.8, chloroform).

Anal. Calc. for $C_5H_6Cl_4O_{10}S_3$; C, 12.95; H, 1.29; Cl, 30.6; S, 20.8. Found: C, 13.0; H, 1.26; Cl, 30.8; S, 20.6.

The product gave a positive test for $-OSO_2Cl$ groups, and its infrared spectrum (in $CHCl_3$) exhibited strong absorption bands at 1435 and 1200 cm^{-1}.

When a portion of the compound was treated in methanol with aqueous sodium iodide in the presence of calcium carbonate at 20°, dechlorosulfation occurred. The only sugar detectable in solution after this procedure was D-ribose.

*Methyl 3-chloro-3-deoxy-β-*D*-xylopyranoside* (**9**). — A solution of **8** (4 g) in acetone (600 ml) containing 5N hydrochloric acid (16 ml) was refluxed for 4 h. The reaction was then complete (t.l.c.). The solution was neutralized (lead carbonate), and the product, crude **9**, was isolated in the usual way. Analysis (t.l.c.) indicated the presence of a major component (**9**) and a minor component, presumably the methyl 2-chloro-2-deoxy-D-arabinoside.

Methyl 2,4-di-O-acetyl-3-chloro-3-deoxy-β-D-xylopyranoside. — Crude **9** (0.5 g) was acetylated with a mixture of pyridine (6 ml) and acetic anhydride (3 ml). After 21 h, the crystalline product was isolated in 62% yield. It was recrystallized from ethanol–water, and had m.p. 116–117°, $[\alpha]_D$ −50° (*c* 1.2, chloroform).

Anal. Calc. for $C_{10}H_{15}ClO_6$: C, 45.0; H, 5.7; Cl, 13.3. Found: C, 45.3; H, 5.6; Cl, 13.0.

The i.r. spectrum was in agreement with this structure.

Conversion of **9** *into* **5.** — Substance **9** (2 g) was dissolved in a mixture of pyridine (4.5 ml) and chloroform (16 ml), and treated with sulfuryl chloride (2.5 ml) for 2 h at −70°. The reaction mixture was then warmed to 25° and, after 4 h at this temperature, was diluted with chloroform; the product was isolated in the usual manner. The recrystallized compound (m.p. 130–131°, 54% yield) was identical in all respects with **5** obtained from methyl β-D-ribopyranoside.

Attempted conversion of **9** *into* **4** ($R = SO_2Cl$). — Compound **9** in pyridine–chloroform solution was treated with sulfuryl chloride, as in the above experiment, but, following the 2-h period at −70°, the temperature was raised only to −20°; monitoring by t.l.c. over 6 h showed that reaction proceeded to only a very small extent and that mostly starting material was present. The temperature was then raised to 0° and, after 8 h, the product was isolated as previously described; it was identified as **5**.

Methyl 2-O-(methylsulfonyl)-β-D-arabinoside 3,4-di(chlorosulfate) (**13**). — Compound **12** (10 g) was dissolved in dry pyridine (15 ml) and chloroform (50 ml), and the mixture was treated with an excess of sulfuryl chloride (10 ml) at −70°. The product was isolated after 6 h, yield 81%, m.p. 110–111°, $[\alpha]_D^{20}$ −161° (*c* 3.3, chloroform). The i.r. spectrum showed the presence of the OSO_2Cl group[14].

Anal. Calc. for $C_7H_{12}Cl_2O_{11}S_3$: C, 19.1; H, 2.7; Cl, 16.2; S, 21.9. Found: C, 19.2; H, 3.0; Cl, 16.0; S, 21.8.

Methyl 4-chloro-4-deoxy-2-O-(methylsulfonyl)-α-L-xyloside 3-chlorosulfate (**14**). — The above di(chlorosulfate) (14 g) was dissolved in chloroform (250 ml), and an excess of pyridine hydrochloride (11 g) was added to the solution, which was then boiled for 5 h. The product, isolated in the usual way, was recrystallized from methanol; yield 76%, m.p. 99–100°, $[\alpha]_D^{20}$ −38° (*c* 5.4, chloroform).

Anal. Calc. for $C_7H_{12}Cl_2O_8S_2$: C, 23.4; H, 3.3; Cl, 19.8; S, 17.8. Found: C, 23.7; H, 3.7; Cl, 19.5; S, 17.7.

Prolonged reaction with pyridine hydrochloride failed to cause any further substitution of chlorosulfate by chlorine in **14**.

Methyl 4-chloro-4-deoxy-2-O-(methylsulfonyl)-α-L-xyloside (**15**). — The above chlorosulfate **14** (4 g) was dechlorosulfated in the usual way, and the product (2.5 g, 76%) was recrystallized from methanol. It was homogeneous by t.l.c. and had m.p. 119–120°, $[\alpha]_D$ −74° (*c* 3.25, chloroform). The i.r. spectrum showed the absence of $-OSO_2Cl$, and the presence of -OH.

Anal. Calc. for $C_7H_{13}ClO_6S$: C, 32.2; H, 5.0; Cl, 13.6; S, 12.3. Found: C, 32.0; H, 5.0; Cl, 13.6; S, 12.6.

Methyl 2,3-anhydro-4-chloro-4-deoxy-α-L-lyxoside (**16**). — Compound **15** (2 g) was dissolved in methanol (60 ml), and sodium methoxide (2 g) was added to the solution. After 24 h at 20°, the reaction was complete (t.l.c.), and the product was isolated in the usual way. The product was a mixture, both components giving a positive test for an anhydro ring (Methyl Red–sodium iodide spray). The major component was isolated by t.l.c., and was found to be identical with methyl 2,3-anhydro-4-chloro-4-deoxy-α-L-lyxoside (see below).

Methyl 2,3-anhydro-β-D-ribopyranoside (**8**, 2g) was dissolved in a mixture of dry pyridine (3.5 ml) and chloroform (9 ml) cooled to −70°, and sulfuryl chloride (2.1 ml) was added. After 4 h, the reaction was complete (t.l.c.), and the product, a syrup (1.4 g), was isolated. It was purified by distillation, b.p. 40°/15 mm; it had $[\alpha]_D$ −84° (*c* 4.2, in chloroform). The compound **16** was pure by t.l.c. and was free from -OSO_2Cl and -OH groups (i.r.).

Anal. Calc. for $C_6H_9ClO_3$: C, 43.8; H, 5.5; Cl, 21.6. Found: C, 43.9; H, 5.4; Cl, 21.7.

Attempts to prepare the intermediate methyl 2,3-anhydro-β-D-ribopyranoside 4-chlorosulfate were unsuccessful. Cleavage of the ring of **8** by hydrogen chloride yielded a complex mixture of products.

ACKNOWLEDGMENTS

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SUMMARY

The course of the reaction of methyl β-D-ribopyranoside (**1**) with sulfuryl chloride and pyridinium chloride is described. Compound **1** may readily be converted into the 2,3,4-tri(chlorosulfate) (**2**) which, with chloride ion, yields methyl 3,4-dichloro-3,4-dideoxy-α-L-arabinopyranoside 2-chlorosulfate (**5**). A consideration of conformational aspects of the substitution process suggests that the 3-chlorosulfate group of **1** is first displaced by chloride and that substitution then occurs at C-4. This conclusion is supported by a reaction series in which 3-chloro-3-deoxy-β-D-xylopyranoside was synthesized and converted into **5**. The stereochemical outcome at C-3 of **2** during the substitution process is also proved thereby.

The reaction of D-ribose with sulfuryl chloride yielded a D-ribopyranosyl chloride tri(chlorosulfate) which, on the basis of n.m.r. evidence, is described as the β-D anomer in the *1C*(D) conformation.

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