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THE STEREOSELECTIVE REPLACEMENT OF HYDROXYL GROUPS BY CHLORINE, USING THE MESYL CHLORIDE–*N*,*N*-DIMETHYLFORMAMIDE REAGENT*†

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ABSTRACT

The mesyl chloride–*N*,*N*-dimethylformamide reagent, previously described as selective for the replacement of primary hydroxyl groups by chlorine, has been shown to cause extensive, but selective, chlorination at secondary positions of glycopyranosides, particularly in the disaccharide series. Thus, reaction with methyl β-maltoside gave initially the 6,6′-dichloro derivative **2**, which was then fairly rapidly transformed into the 3,6,6′-trichloro derivative **4**. Further reaction, but at a slower rate, gave the 3,4′,6,6′-tetrachloro derivative **6**. As anticipated, inversion of configuration accompanied reaction at positions C-3 and C-4′, indicating that the chlorine substituents were introduced by an S_N2 mechanism. Benzyl β-cellobioside reacted to give a more-complex mixture from which the 6,6′-di-, 3′,6,6′-tri-, 3,6,6′-tri-, 4′,6,6′-tri-, 3,3′,6,6′-tetra-, and 3,4′,6,6′-tetra-chloro derivatives were isolated, after acetylation. Similarly, methyl glycopyranosides gave products of secondary chlorination, although the reaction proceeded less readily. Methyl α-D-glucopyranoside and methyl α-D-galactopyranoside gave the 4,6-dichloro-galactopyranoside and -glucopyranoside, respectively. On the other hand, methyl β-D-glucopyranoside gave a 2:1 mixture of methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside and methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside. Structural elucidation of these chlorinated derivatives was based mainly on mass spectrometry and 220-MHz ^1H n.m.r. spectroscopy.

INTRODUCTION

Halogeno derivatives of carbohydrates[2] are of wide synthetic utility, since the halogeno substituents may be employed as leaving groups in nucleophilic displacement reactions[3], or they may be reductively removed to give deoxy sugars[4]. A variety of reagents have been reported for the direct replacement of a hydroxyl group in carbohydrate derivatives by a chloro substituent. The first such reagent was reported

*Dedicated to Dr. Horace S. Isbell, in honour of his 75th birthday.

†Part IV of 'The Chemistry of Maltose' (for Part III see ref. 17) and Part II of 'The Chemistry of Cellobiose and Lactose' (for Part I see R. S. Blatt, L. Hough and A. C. Richardson, *Carbohyd. Res.*, 32 (1974) C4.

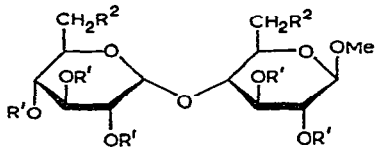
in 1921 by Helferich and his co-workers[5] who showed that both primary and secondary hydroxyl groups were replaced by chlorine upon reaction of certain glycosides with sulphuryl chloride. Later, Jones and his co-workers[6], who exploited this reaction as a synthetic tool, showed that the chloro substituent was introduced by an S_N2 displacement of the first-formed chlorosulphonyloxy group by chloride anion. More recently, reagents such as trisphenyloxymethylphosphonium iodide[7], triphenylphosphine in conjunction with carbon tetrahalides[8], *N*-halosuccinimides[9], or halogen[10], aryl isocyanates in the presence of hydrogen chloride[11], and mesyl chloride in *N*,*N*-dimethylformamide[12] have been reported to effect similar transformations. However, the use of trisphenyloxymethylphosphonium iodide and the triphenylphosphine-based reagents have been reported to cause rearrangements in certain cases[13,14].

The mesyl chloride–*N*,*N*-dimethylformamide reagent was reported by Evans *et al.*[12] as a means of selectively replacing primary hydroxyl groups of hexopyranosides by chlorine. However, when this reaction was applied to disaccharide derivatives, we found that reaction was more extensive than originally claimed, and we now report on these findings.

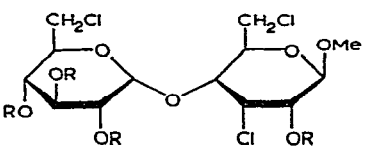
RESULTS

In extending our studies of the chemistry of maltose[15–17], methyl 6,6′-dichloro-6,6′-dideoxy-β-maltoside (**2**) was required. However, when methyl β-maltoside (**1**) was treated with mesyl chloride in *N*,*N*-dimethylformamide[12] under the conditions reported as being optimal for the chlorination of methyl β-D-glucopyranoside at C-6 (10 moles of mesyl chloride per hexopyranosyl unit and 65°), we found that a mixture of products was formed (t.l.c.). The major component was the desired dichloride **2**, but there was also a substantial amount of a faster-moving derivative, isolated as its acetate **5**, which was shown to be the trichloro derivative **4**. Variation of the reaction conditions indicated that, under milder conditions, a slower-moving component was present, probably the 6- or 6′-chloromaltoside, but conditions were not found which favoured the sole formation of the 6,6′-dichloromaltoside **2**; in all experiments, the trichloro derivative **4** appeared before the starting material had been consumed. The use of a larger proportion of mesyl chloride (15 moles per hexopyranosyl unit) and a longer reaction time (8 days) resulted in a substantial increase in the amount of the trichloride **4**, and the appearance of another faster-moving component, the tetrachloride **6**. The reaction mixture was processed by decomposition of the excess mesyl chloride by the addition of 1-propanol, evaporation to dryness, and acetylation. A facile fractional crystallisation from ethanol afforded the trichloride as its tetraacetate **5** in 46% yield. Further crystallisation of the mother liquors gave the faster-moving component in 8% yield, which was shown to be methyl 2-*O*-acetyl-3,6-dichloro-3,6-dideoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl)-β-D-allopyranoside (**7**) by comparison with the product formed from the reaction of methyl β-maltoside with sulphuryl chloride[15]. The yield of the tetrachloride **7** was raised to 20% when the reaction temperature was increased to 100°

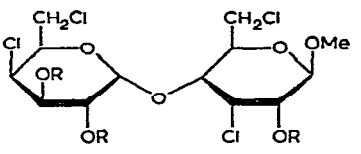
and the reaction time decreased to 24 h, but the yield of **5** was decreased slightly (37%). After the isolation of the tri- and tetra-chlorides, chromatographic fractionation of the mother liquors afforded the 6,6′-dichloromaltoside as the pentaacetate **3**,



1 $R^1 = H$, $R^2 = OH$
2 $R^1 = H$, $R^2 = Cl$
3 $R^1 = Ac$, $R^2 = Cl$

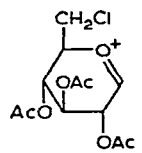


4 R = H
5 R = Ac

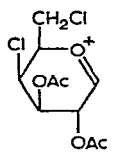


6 R = H
7 R = Ac

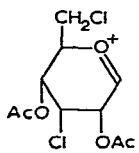
The mass spectrum (Table II) of the 6,6′-dichloromaltoside **3** showed, as expected[18], fragments due to cleavage of the two bonds leading from the interglycosidic oxygen atom at *m/e* 307 (**8**) and 279 (**11**), in a ratio of 4:1*. The oxycarbonium ion **8** fragmented in the usual way, showing the sequential loss of (*i*) acetic acid, (*ii*) acetic acid or ketene, (*iii*) ketene or acetic acid, (*iv*) carbon monoxide, and (*v*) hydrogen chloride. The ion **11** lost either acetic acid (*m/e* 219) or hydrogen chloride (*m/e* 243). No molecular ion was observed, but fragments of low intensity were noted at *m/e* 507 and 483, corresponding to ions **16** ($M^+ - OAc\cdot - HCl$) and **15** ($M^+ - OAc\cdot - HOAc$), of which an analogue of the former had been noted[15] in the mass spectrum of **7**. The 220-MHz ^1H n.m.r. spectrum of **3** was largely first-order (Table I), and the chemical shifts were in close agreement with those of other related methyl β-maltosides[16,17].



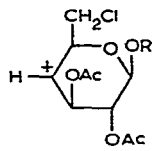
8 (*m/e* 307)



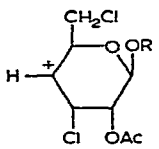
9 (*m/e* 283)



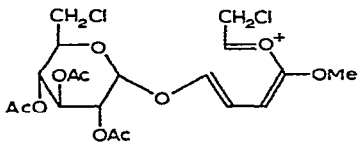
10 (*m/e* 283)



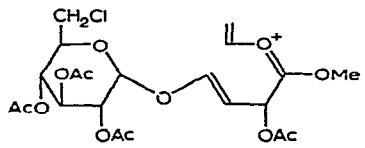
11 R = Me (*m/e* 279)
12 R = CH_2Ph (*m/e* 355)



13 R = Me (*m/e* 255)
14 R = CH_2Ph (*m/e* 331)



15 (*m/e* 483)



16 (*m/e* 507)

*It is probable that the cleavage of the C-4–O-4 bond occurs indirectly by initial cleavage of the C-1′–C-2′ bond (see ref. 15).

TABLE I

FIRST-ORDER ^{1}H N.M.R. PARAMETERS (τ VALUES) IN BENZENE-d_6 AT 220 MHz

	5	3	19	20	21	22	23	24
H-1	5.27 *d*	5.85 *d*	5.66 *m*	5.61 *m*	5.70 *d*	4.91 *d*	4.80 *d*	4.96 *m*
H-2	5.03 *dd*	4.96 *t*	4.73 *m*	4.64 *m*	4.75 *m*		4.68 *dd*	4.82 *m*
H-3	5.32 *t*	4.68 *t*				4.68 *t*	4.59 *t*	
H-4	6.04 *dd*	6.08 *t*	6.32		6.34 *m*	6.12 *dd*	6.26 *dd*	6.10 *m*
H-5	6.15 *dt*	7.30 *dt*	−7.05 *m*	6.93 *m*	7.06 *m*	6.04 *m*	~5.9 *m*	
H-6a	6.51 *dd*	6.38 *dd*		6.27 *dd*	6.46 *m*	6.45 *m*	6.28 *dd*	6.40 *dd*
H-6b	6.68 *dd*	6.6 *m*					6.38 *dd*	6.53 *dd*
H-1′	4.97 *d*	4.50 *d*	5.70 *d*	5.11 *d*	5.79 *d*	6.02 *d*	5.13 *d*	6.06 *d*
H-2′	5.07 *dd*	5.04 *dd*	4.92 *t*	5.20 *dd*	4.50 *t*	4.77 *m*	4.97 *dd*	4.41 *t*
H-3′	4.24 *t*	4.21 *t*	4.73 *m*	4.85 *t*	5.07 *dd*		4.93 *t*	5.11 *dd*
H-4′	4.78 *t*	4.68 *t*	4.94 *t*	5.05 *dd*	5.59 *dd*	5.27 *t*	5.35 *dd*	5.88 *dd*
H-5′	5.78 *m*	5.84 *m*	6.32–	5.98 *m*	6.83 *dt*	~6.8 *m*	~5.9 *m*	6.92 *dt*
H-6′a	6.58 *m*	6.6 *m*	7.05 *m*	6.64 *dd*	6.67 *m*	6.75 *m*	6.66 *dd*	6.68 *dd*
H-6′b				6.77 *dd*			6.81 *dd*	7.03 *dd*
$J_{1,2}$	8.0	7.8			7.5	8.2	8.0	
$J_{2,3}$	3.5	9.5				3.0	2.8	
$J_{3,4}$	3.0	9.3				3.0	2.8	
$J_{4,5}$	8.8	9.3			~9	9.4	9.2	
$J_{5,6a}$	4.5	3.2		2.0	~5		2.5	<1.5
$J_{5,6b}$	3.5				~5		5.0	<1.5
$J_{6a,6b}$	−12.0	−12.0		−12.0			−12.0	−12.0
$J_{1',2'}$	4.0	4.0	8.5	8.0	7.5	8.0	8.0	8.0
$J_{2',3'}$	10.5	10.5	9.5	2.9	10.0		3.5	10.0
$J_{3',4'}$	10.0	9.5	9.5	2.9	4.0	9.2	3.5	4.2
$J_{4',5'}$	9.8	~10	9.5	9.5	~1.5	9.2	9.6	~2
$J_{5',6'a}$		~4		~2	~5		~3	7.0
$J_{5',6'b}$		~4		4.5	~5		8.0	5.0
$J_{6'a,6'b}$				−12.0			−12.0	−12.0

Similarly, the mass spectrum of the trichloride **5** (Table II) contained fragments resulting from the cleavage of the bonds leading from the interglycosidic oxygen atom. The fragment **8** at *m/e* 307 (1 Cl)† arose from the non-reducing ring§, which therefore contained a single chlorine substituent. The ion then fragmented in exactly the same way as described above for that obtained from the 6,6′-dichloride **3**, suggesting that the chloro substituent was at the 6′-position. The fragment **13**, arising from the reducing ring, was less intense than that due to the non-reducing moiety and appeared at *m/e* 255 (2 Cl), and subsequent fragmentation occurred by the loss of either acetic

†Indicates number of chlorine atoms, as inferred from the isotope peaks.

§The term "reducing ring" refers to the ring which was the reducing ring in the parent disaccharide. The term "non-reducing ring" accordingly refers to the other sugar moiety.

TABLE II

MASS-SPECTRAL DATA BASED ON ^{35}Cl (ISOTOPE FRAGMENTS OMITTED)

m/e		3	5	19	20	21	22	23	24	27	30	32	34	37
587	M—CH_2Ph			0.2										
563					0.2	0.1								
543	M—Cl		0.05											
523	M—OCH_2Ph							1.1						
507	**16**	0.3												
483	**15**	0.1	0.3											
355	**12**			0.8	1.6	0.5								
331	**14**						0.4	1.3	0.4					
307	**8**	8.3	12.7	27			41				7.3			
283	**9 or 10**				43	11.0		89	14	1.0		0.5	0.1	35
279	**11**	2.0									2.2[a]		1.0[a]	
265	M—CH_2Cl									0.5			0.2	
255	**13**		0.7							2.5[a]		1.5[a]		0.01[a]
247	8—HOAc	3.1	3.7	9.0	0.7		14	1.8			1.6			
243	11—HCl	1.3												
223	9/10—HOAc		0.7		4.3	27		0.9	18	15		1.5		7.5
219	11—HOAc	2.1	0.2[e]							40[b]	4.0[c]	50[b]	7.0[b]	10[b]
205	8—HOAc—CH_2CO	10	12.7	35	11.0		56	11.2			9.5		0.2	
195	13—HOAc		0.4							20[c]		20[c]		2.5[e]
187	8—2×HOAc	9	13	22	5.0		45	7.1			11.3			
181						4.3			2	10		0.7		2.5
163	10—2×HOAc					0.3		1.8						
145		30	30	60	18	4.4	76	20	4	4.1	25.6	1.5	1.0	1.0
117		8.2	8.8	9.0	6.0	2.1	14	10	1.4	40	14.3	0.5	30	25

[a]M—OAc, [b]M—Cl—HOAc, [c]M—OAc—HOAc, [d]M—Cl, [e]13–HCl

acid or hydrogen chloride to give *m/e* 195 and 219, respectively. As in the mass spectrum of **3**, the low-intensity ion **15** (M^+—$Cl^\cdot$—HOAc) was noted at *m/e* 438.

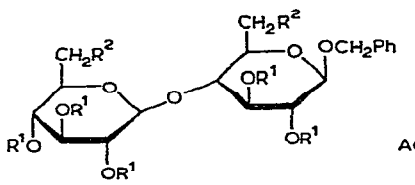
The position of the chlorine atoms in the 3,6,6′-trichloride **5** was indicated by its 220-MHz ^1H n.m.r. spectrum. Comparison of the spectrum with that of the 6,6′-dichloride **3** indicated that the resonance positions of the protons in the non-reducing ring had been unaltered except for the H-1′ resonance, which had undergone a diamagnetic shift of 0.47 p.p.m. On the other hand, the resonances due to the reducing-ring protons had been markedly perturbed (Table I). Significantly, the paramagnetic shifts experienced by H-1 and H-5 (0.58 and 1.15 p.p.m., respectively) were characteristic[16] of the deshielding influence of a *syn*-axial chlorine atom at C-3. This was confirmed by the appearance of the H-3 resonance as a narrow triplet (*J* values ~3 Hz) at τ 5.32, and by the H-2 and H-4 resonances which appeared as double doublets (*J* values ~3 and ~9 Hz).

The results obtained with methyl β-maltoside prompted us to investigate the reaction of benzyl β-cellobioside[19] (**17**) with this reagent. Initially, the reaction was carried out for 7 days at 70° with 25 moles of mesyl chloride. After processing in the usual way, which included acetylation, a mixture of products was obtained which initially appeared to be composed of four components (t.l.c.). However, when the mixture was fractionated by chromatography on silica gel, at least seven components were detected.

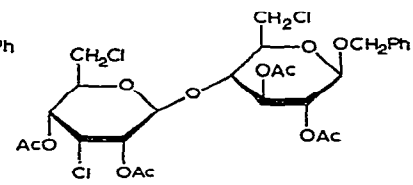
The first fraction eluted from the column moved as a single component in several t.l.c. solvent systems, and was obtained as a crystalline solid in 16% yield. Elemental analysis indicated that it was a trichloro derivative. However, the ^1H n.m.r. spectrum showed that it was a 3:2 mixture of two isomeric trichlorides; in particular, the acetate region of the spectrum exhibited eight resonances consisting of two sets of four lines. Fractional crystallisation of the mixture afforded the pure, crystalline components, although their total recovery was only 25%.

The mass spectra of the two isomers (Table II) each contained relatively intense fragments at *m/e* 283 due to the oxycarbonium ion resulting from the non-reducing ring. The isotope patterns indicated the presence of two chlorine atoms in the non-reducing ring in each isomer. In both spectra, a low-intensity fragment was observed at *m/e* 355 due to the reducing ring, which, from the isotope pattern, contained only a single chlorine atom. The position of the chlorine atoms in the non-reducing moiety was indicated by the subsequent fragmentation of the *m/e* 283 ions. In the spectrum of one isomer, this ion lost acetic acid to give an even more-intense fragment at *m/e* 223 (ratio 1:2.5), which then underwent sequential loss of ketene (*m/e* 181) and hydrogen chloride (*m/e* 145). This behaviour is characteristic[18,20] of acetoxyl groups at C-3′ and C-2′, and therefore the chlorine atoms were placed at C-4′ and C-6′. Consequently, this isomer was characterised as benzyl 2,3-di-*O*-acetyl-6-chloro-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (**21**). Confirmation was provided by the 220-MHz ^1H n.m.r. spectrum of **21**. Comparison of the spectrum with that[21] of benzyl β-cellobioside hepta-acetate (**18**) (Table I) indicated that (*i*) no configurational changes had occurred

in the reducing ring; (*ii*) a slight upfield shift of the H-6 and H-6′ resonances had occurred, indicating the location of chlorine atoms at these positions; (*iii*) the non-reducing ring possessed the *galacto* configuration, by the appearance of the H-4′ and H-3′ resonances as narrow and wide double-doublets, respectively.



17 $R^1 = H$, $R^2 = OH$
18 $R^1 = Ac$, $R^2 = OAc$
19 $R^1 = Ac$, $R^2 = Cl$



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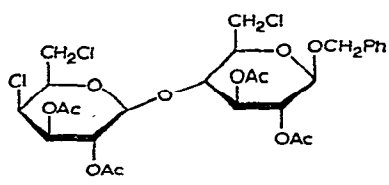

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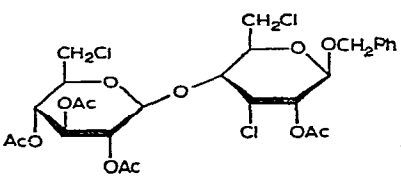

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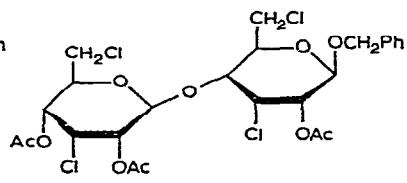

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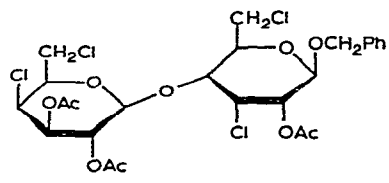

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The structure of the other isomeric trichloride was deduced in a similar manner. The *m/e* 283 fragment lost both acetic acid (*m/e* 223) and hydrogen chloride (*m/e* 247), but both ions were of low intensity (Table II), indicating the lack of an acetoxyl group at C-3′. This result suggested that the isomer was the 3′,6,6′-trichloride **20**, which was confirmed from its 220-MHz ^{1}H n.m.r. spectrum, using arguments similar to those described above. In this case, the H-3′ resonance appeared as a narrow triplet, and H-4′ as a wide double-doublet (Table I).

The second fraction from the column initially appeared to be homogeneous, but showed three components on careful t.l.c. There was insufficient material to achieve a preparative separation, but in a later experiment the fastest-moving component was isolated and shown to be the 3,6,6′-trichloride (**22**).

The third fraction eluted from the column was isolated crystalline in 25% yield, and elemental analysis indicated that it was a dichloro derivative. The mass spectrum, with an intense fragment at *m/e* 307 (1 Cl, **8**) due to the non-reducing ring, and a less-intense fragment **12** at *m/e* 355 (1 Cl) due to the reducing moiety, showed that each ring possessed only one chlorine substituent. Fragmentation of the former ion proceeded identically with that from methyl 6,6′-dichloro-6,6′-dideoxy-β-maltoside penta-acetate (**3**), which suggested the presence of a 6′-chlorine substituent. The 220-MHz ^{1}H n.m.r. spectra of the dichloride and benzyl β-cellobioside hepta-acetate (**18**) were closely similar, except for an upfield shift of the signals for the

hydrogen atoms at C-6 and C-6′ (Table I), indicating that the product was benzyl 6,6′-dichloro-6,6′-dideoxy-β-cellobioside penta-acetate (**19**).

The final fraction from the column was an isomeric dichloro derivative obtained in 5% yield. The mass spectrum (see Experimental) contained an intense fragment at *m/e* 307 (1 Cl), indicating that the non-reducing ring contained a single chlorine substituent. The successive loss of acetic acid and ketene to give fragments *m/e* 247 and 205 suggested the presence of acetoxyl groups at C-2′ and C-3′. A fragment of very low intensity at *m/e* 355 might have been due to the reducing ring. The n.m.r. spectrum (see Experimental) could not be interpreted in terms of any of the possible dichlorides, although the presence of H-1 and H-1′ resonances very close to each other at τ 5.68 and 5.79 indicated the absence of an axial chlorine substituent at C-3 or C-3′, which would have deshielded the appropriate H-1 by at least 0.5 p.p.m.[15]. The characterisation of this compound must await further studies.

A more vigorous reaction of benzyl β-cellobioside with the reagent (30 moles at 70° for 11 days) afforded, after the same work-up procedure as before, a complex mixture which differed from that obtained previously and from which six fractions were obtained.

The first fraction was a pure, crystalline tetrachloro derivative, isolated in 4% yield. The mass spectrum showed an intense fragment **10** at *m/e* 283 (2 Cl) for the non-reducing ring and a fragment **14** of low intensity at *m/e* 331 (2 Cl) for the reducing ring, showing an equal distribution of chlorine between the two rings. The former ion underwent further fragmentation with the loss of either acetic acid or hydrogen chloride to give low-intensity ions at *m/e* 223 (2 Cl) and 247 (1 Cl) (ratios of *m/e* 283, 247, and 223 = 89:1.8:0.9). This suggested the absence of an acetoxyl group at C-3′, and therefore the chlorine atoms were located at C-3′ and C-6′ on the non-reducing ring. Hence, the compound was identified as benzyl 2-*O*-acetyl-3,6-dichloro-3,6-dideoxy-4-*O*-(2,4-di-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-allopyranosyl)-β-D-allopyranoside (**23**), which was confirmed by the ^{1}H n.m.r. data (Table I).

The second fraction constituted less than 1% yield and, since t.l.c. indicated that it was a mixture of at least two components, it was not further investigated. Likewise, the third fraction was not homogeneous, but in this case crystallisation afforded the pure, major component in 1.4% yield. Elemental analysis indicated that it was a tetrachloro derivative and the mass spectrum, which contained an intense species **9** at *m/e* 283 (2 Cl), showed that the non-reducing ring contained two of the four chlorine substituents. The fragment at *m/e* 331 (2 Cl) originated from the reducing ring, showing that this also had two chlorine substituents. In contrast to the 3,3′,6,6′-tetrachloro analogue **23**, the fragment at *m/e* 283 (**9**) readily lost acetic acid, giving an intense fragment at *m/e* 223 (2 Cl) which was indicative of the presence of a 3-acetoxy substituent. The subsequent loss of ketene to give *m/e* 181 indicated the presence of an acetyl group at C-2′. These facts, supported by the 220-MHz ^{1}H n.m.r. data (Table I), identified the compound as benzyl 2-*O*-acetyl-3,6-dichloro-3,6-dideoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-β-D-galactopyranosyl)-β-D-allopyranoside (**24**).

The fourth (and major) fraction was shown to be a mixture of the 3′,6,6′- and 4′,6,6′-trichloro derivatives, **20** and **21**, respectively, which had been obtained in much smaller yield under the less-vigorous reaction conditions described above.

The fifth fraction was obtained crystalline in 3% yield, and t.l.c. indicated that it corresponded to the fastest-moving component in the second fraction of the previous experiment (see above). The compound was shown to be a trichloro derivative (elemental analysis), and the intense fragment at *m/e* 307 (1 Cl) in its mass spectrum showed that only one chlorine atom was attached to the non-reducing ring. The subsequent fragmentation of this ion indicated that it was **8** with the chlorine at the primary position. The presence of a low-intensity fragment at *m/e* 331 (2 Cl) confirmed that the reducing ring contained two chlorine substituents. These results implied that the compound was the 3,6,6′-trichloride **22**, which was verified by its ^{1}H n.m.r. spectrum at 220 MHz. In particular, the appearance of the signal for H-3 as a narrow triplet (*J* values 3 Hz) and that for H-4 as a double doublet (*J* 9.4 and 3 Hz) were diagnostic of inversion of configuration at C-3.

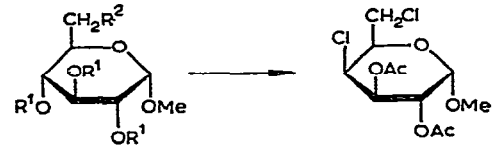
The sixth fraction (9.5% yield) was shown to be the 6,6′-dichloride **19** by direct comparison with the product from the previous experiment. When benzyl β-cellobioside (**17**) was treated in the usual way with sulphuryl chloride in pyridine, a mixture of the two tetrachlorides **23** and **24** and the two trichlorides **20** and **21** was formed, although the overall recovery of products was only 20%.

In view of the promising results obtained with the above disaccharide derivatives, it seemed worthwhile to re-examine the selectivity of the reagent with simple hexopyranosides under more-forcing conditions than those used by Evans *et al.*[12].

Reaction of methyl α-D-glucopyranoside (**25**) with 30 moles of mesyl chloride at 70° rapidly gave the 6-chloride which was slowly transformed into another component. After 10 days, the reaction mixture was worked up in the usual way and the product acetylated. Fractionation of the mixture by chromatography on silica gel afforded, in the first fractions, methyl 2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (**27**) in 8% yield, which was identified by comparison with an authentic specimen obtained from the action of sulphuryl chloride on the α-glucoside[3,22]. Later fractions contained the 6-chloride **26** in 44% yield. At higher temperatures, the yield of **27** was increased to at least 19%, but the overall recovery of products from this reaction was low, suggesting extensive decomposition.

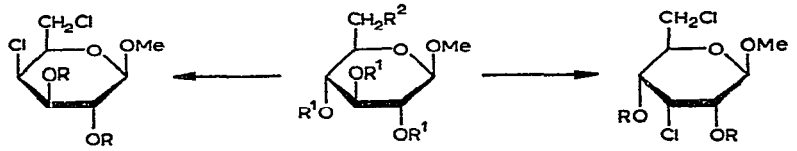
When the reaction was repeated with methyl β-D-glucopyranoside (**28**) under similar conditions for 90 h, a mixture of three products was formed which was fractionated chromatographically. The fastest-moving component, a dichloro derivative, was isolated in 31% yield and gave physical data (m.p. and $[\alpha]_D$) similar to those[23] of methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**33**). Corroboration of this identification was afforded by the ^{1}H n.m.r. spectrum, which showed two low-field resonances: a narrow H-3 triplet at τ 4.88 (*J* values 2.5 Hz) and the H-1 doublet at τ 4.94 (*J* 7.5 Hz).

The second fraction from the column afforded an isomeric dichloro derivative (15%) which was identified as methyl 4,6-dichloro-4,6-dideoxy-β-D-galacto-



25 $R^1 = H$, $R^2 = OH$
26 $R^1 = Ac$, $R^2 = Cl$

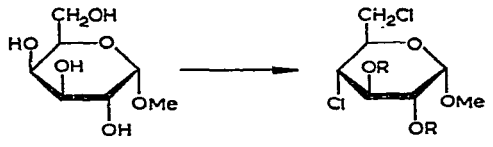
27



31 R = H
32 R = Ac

28 $R^1 = H$, $R^2 = OH$
29 $R^1 = H$, $R^2 = Cl$
30 $R^1 = Ac$, $R^2 = Cl$

33 R = H
34 R = Ac



35

36 R = H
37 R = Ac

pyranoside (**31**) by comparison with an authentic specimen[24]. The mass spectrum of the diacetate **32** showed an ion at *m/e* 283 (2 Cl), which fragmented with the loss of acetic acid to give a more-intense ion at *m/e* 223 (2 Cl), indicating the presence of a 3-acetoxy group, and the subsequent loss of ketene from *m/e* 223 to give *m/e* 181 was indicative of a 2-acetoxy group.

The final fractions afforded methyl 6-chloro-6-deoxy-β-D-glucopyranoside (**29**, 15%), which had been previously obtained under the milder conditions used by Evans *et al.*[12].

Similarly, application of the same reaction conditions to methyl α-D-galactopyranoside (**35**) afforded the known[24] methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside (**36**) in 37% yield.

DISCUSSION

Evans *et al.*[12] suggested that chlorination by the mesyl chloride–*N*,*N*-dimethylformamide reagent proceeded by initial attack of the alcohol on the iminium salt $Me_2\overset{+}{N}{=}CHOMs\ Cl^-$, to give the formiminium ester $Me_2\overset{+}{N}{=}CHOR\ Cl^-$, which then either underwent hydrolysis to give the formic ester, or nucleophilic attack by

chloride anion to give the chloride. It was further suggested that the rate-limiting step in the chlorination was the formation of the initial iminium salt ($Me_2\overset{+}{N}$=CHOMs Cl^-) and that the rate of the subsequent, nucleophilic displacement reaction did not affect the overall rate for the reaction. This was supported by the observation that the addition of lithium chloride to the reaction mixture failed to accelerate the formation of chlorinated products. Prior to the work of Evans *et al.*[12], related chlorinations had been achieved with *N,N*–dimethylformamide–*p*-tolylsulphonyl chloride[25], and with dimethylchloroformiminium chloride[26] ($Me_2\overset{+}{N}$=CHCl Cl^-), but in one example only (2-propanol) has chlorination been achieved at a secondary position[27]. However, in related work, Stevens *et al.*[28] were able to demonstrate that pyrolysis of a closely related imino-ester hydrochloride salt of an optically active 2-butanol afforded the corresponding chloride with inversion of configuration.

The present results show conclusively that the reaction proceeds with inversion of configuration at chiral centers, and that it only occurs at secondary positions where the steric and electronic factors, as outlined by Richardson[29], are favourable for an S_N2 reaction. Hence, in methyl β-maltoside (**1**), we have observed reaction at C-3, but not at C-3′ which is hindered by the axial C-1 substituent. Subsequently, chlorination is observed at C-4′, although the rate of reaction is much less. In many respects, this is somewhat surprising since selective acylation studies have indicated that C-3 is the most sterically hindered position in the maltoside[16], and it seems unexpected that an S_N2 transition state should form more readily at this position than at C-4′. Similarly, we[30] and others[31] have also observed that nucleophilic displacements occur more readily at C-6 than at C-6′, although the latter is more readily esterified[31] and etherified[32]. These observations suggest that steric factors, which are important in acylation reactions, may not be so significant in displacement reactions, which are more sensitive to polar effects. For benzyl β-cellobioside (**17**), displacement reactions are predictable at C-3, C-3′, C-4′, C-6, and C-6′, but reaction at either C-3′ or C-4′ will impede subsequent reaction at the other position because of the vicinal-axial effect[29]. However, in this example, reaction at C-3′ and C-4′ seems to be more favourable than that at C-3 because both the 3′,6,6′- and 4′,6,6′-trichlorides, **20** and **21**, are present in substantial amounts, whereas the 3,6,6′-trichloride **22** was isolated in only low yield. The greater rate of chlorination at C-4′ is surprising, since in related studies we have found that 4′-sulphonic esters of benzyl β-cellobioside are more sluggish towards nucleophilic displacement reactions than are 4′sulphonates of methyl β-maltoside, which has been attributed to the β-anomeric configuration of the non-reducing ring[21].

The reaction of methyl α-D-glucopyranoside and methyl β-D-galactopyranoside with mesyl chloride proceeded in a manner analogous to that of their reaction with sulphuryl chloride[24,33], but the β-D-glucopyranoside **28** appeared to react differently with the two reagents. The mesyl chloride–*N,N*-dimethylformamide reagent afforded both the 4,6- and 3,6-dichlorides, **31** and **33**, respectively, in a ratio of 1:2, whereas reaction with sulphuryl chloride was reported to give only the 4,6-dichloride **31**. This

unexpected difference prompted us to re-investigate the reaction of **28** with sulphuryl chloride. A mixture of two products was obtained which were separated with difficulty to give the expected 4,6-dichloride **31** as the major product and the 3,6-dichloride **33** as the minor component.

In conclusion, it may be noted that the mesyl chloride–*N,N*-dimethylformamide reagent appears to have a selectivity similar to that of the sulphuryl chloride–pyridine reagent. However, the latter reagent reacts very rapidly with carbohydrate substrates, giving maximal chlorination even at very low temperatures, so that less-chlorinated intermediates are not usually isolated. The main advantage of the mesyl chloride reagent seems to be that reaction proceeds more slowly, so that intermediate chlorinated species are isolable, and in certain situations this reagent may possess considerable synthetic utility.

EXPERIMENTAL

Concentrations were performed under diminished pressure. Melting points were determined on a Kofler microscope hot-stage and are uncorrected. Rotations were determined on a Perkin–Elmer 141 automatic polarimeter in a 1-dm tube at 20–25°, and unless otherwise stated chloroform was used as the solvent. T.l.c. was performed on Merck 7731 silica gel, with detection by 5% ethanolic sulphuric acid. Dry-column chromatography, using the technique of Hough *et al.*[34] was employed for preparative separations, except that the mixture was first dissolved in a suitable, volatile solvent and the solution treated with a little Merck 7734 silica gel. The mixture was then evaporated to dryness *in vacuo*, using a rotary evaporator, until a free-flowing powder was obtained, which was then applied to the top of the dry-packed column of silica gel and eluted in the usual way. Anhydrous *N,N*-dimethylformamide was prepared by distillation under diminished pressure from calcium hydride. ^{1}H n.m.r. spectra were measured on either a Perkin–Elmer R-12B spectrometer at 60 MHz, or on a Varian HA-100 spectrometer at 100 MHz. Selected regions of the n.m.r. spectra, usually τ 4–7, were then redetermined at 220 MHz, using a Varian HR-220 spectrometer. Tetramethylsilane was used as an internal standard. Mass spectrometry was carried out on an AEI MS-30 spectrometer at 70 eV.

*Reaction of glycosides with mesyl chloride–*N,N*-dimethylformamide: general procedure.* — A solution of the glycoside in anhydrous *N,N*-dimethylformamide (10–15 ml per g of glycoside) was cooled to 0°, and mesyl chloride (20–30 mol.) was added dropwise during 0.5 h. The mixture was then stirred at the stated temperature (oil bath) with protection from atmospheric moisture. The reaction mixture was processed by the addition of an excess of 1-propanol and then evaporated to dryness*. The dark residue was then treated with an excess of acetic anhydride in pyridine, and the acetylated products were isolated, in the usual way, by decomposition with water followed by extraction into dichloromethane, if necessary. Preliminary purification

*In some early experiments, the product was treated with sodium methoxide at this point, in order to hydrolyse any formic esters present. Subsequently, this step was found to be superfluous.

of the dark reaction-product was achieved by allowing a solution of the product in dichloromethane to percolate through a column containing a 1:1 (v/v) mixture of silica gel and charcoal (6–7 g per g of the starting glycoside). The products were eluted from the column with ether containing sufficient dichloromethane (usually 10%) to prevent crystallisation of the products at the exit of the column. The eluate obtained in this way was pale orange-yellow and was then subjected further to fractionation, as described in the individual sections.

Chlorination of methyl β-maltoside (**1**). — Anhydrous methyl β-maltoside[15] (**1**, 4 g) was treated with *N*,*N*-dimethylformamide (48 ml) and mesyl chloride (24.4 ml, 30 equiv.) at 65° for 8 days, and processed as above. The eluate from the silica–charcoal column was evaporated to a crystalline residue which was recrystallised twice from ethanol to give methyl 2-*O*-acetyl-3,6-dichloro-3,6-dideoxy-4-*O*-(2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-α-D-glucopyranosyl)-β-D-allopyranoside (**5**) (3 g, 46%), m.p. 202–204°, $[\alpha]_D$ +88.5° (Found: C, 43.2; H, 5.4; Cl, 18.9. $C_{21}H_{32}Cl_3O_{12}$ calc.: C, 43.25; H, 5.5; Cl, 18.3%).

Evaporation of the filtrates to dryness and recrystallisation of the residue from ethanol gave methyl 2-*O*-acetyl-3,6-dichloro-3,6-dideoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl)-β-D-allopyranoside (**7**) (0.5 g, 8%), m.p. 158–160°, $[\alpha]_D$ +114° (*c* 1.4), identical with an authentic specimen[15] having m.p. 161–162°, $[\alpha]_D$ +119°.

Chromatographic fractionation of the mother liquors on silica gel afforded, in variable yield (7–25%), methyl 2,3-di-*O*-acetyl-6-chloro-6-deoxy-4-*O*-(2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-α-D-glucopyranosyl)-β-D-glucopyranoside (**3**), m.p. 180–182°, $[\alpha]_D$ +58° (*c* 2.2) (Found: C, 45.9; H, 5.8; Cl, 11.8. $C_{23}H_{34}Cl_2O_{14}$ calc.: C, 45.6; H, 5.6; Cl, 11.75%).

Similar results were obtained when the reaction was conducted at 95° for 19 h, and these conditions gave the best yield of the trichloride **5**. At 100° for 24 h, a 37% yield of **5** was obtained along with 20% of the tetrachloride **7** and only a trace of the dichloride **3**.

Chlorination of benzyl β-cellobioside (**17**). — (*a*). Reaction of **17**[19] (4 g) with mesyl chloride (17 ml, 25 equiv.) and *N*,*N*-dimethylformamide (40 ml) at 70° for 7 days gave, after processing in the usual way, a crude, brown solid, which t.l.c. (cyclohexane–ethyl acetate, 2:1) indicated to be a mixture of four components of which two were major components. The mixture was fractionated on a dry column of silica gel, in the usual manner, using light petroleum–ethyl acetate (5:2).

The first fraction contained a major component that was obtained initially as a syrup which solidified on the addition of light petroleum. A single precipitation from chloroform with light petroleum afforded a white powder (0.95 g, 16%) which was homogeneous on t.l.c. in various solvent systems and had m.p. 129–139° (Found: C, 49.1; H, 5.2; Cl, 16.2. $C_{27}H_{33}Cl_3O_{12}$ calc.: C, 49.4; H, 5.0; Cl, 16.25%). However, the n.m.r. spectrum of the product (mainly the acetate region) indicated that it was a mixture of two tetra-acetates in the ratio of 3:2. A 0.5-g sample of the mixture was carefully recrystallised twice from chloroform–light petroleum to give needles,

m.p. 170–176°, which after two further recrystallisations gave benzyl 2,3-di-*O*-acetyl-6-chloro-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (**21**) (53 mg), m.p. 183–185° (crystal transition, 176°), $[\alpha]_D$ −27° (*c* 1) (Found: C, 49.5; H, 5.4%). The filtrates from the first two recrystallisations were combined and evaporated to dryness, and the residue was recrystallised three times from chloroform–light petroleum to give benzyl 2,3-di-*O*-acetyl-6-chloro-6-deoxy-4-*O*-(2,4-di-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-allopyranosyl)-β-D-glucopyranoside (**20**) (75 mg), m.p. 151–154° (crystal transition, 143°), $[\alpha]_D$ −54° (*c* 1) (Found: C, 49.2; H, 5.0%).

The second component (0.13 g) from the column was obtained as a syrup which solidified on the addition of light petroleum. Although homogeneous on t.l.c. with cyclohexane–ethyl acetate (2:1), three components were detected after multiple development with chloroform. This mixture was not investigated further, although one of the components was isolated pure in a subsequent reaction [see (*b*)].

The third fraction, which contained the other major component, afforded a crystalline residue which was recrystallised from chloroform–light petroleum to give benzyl 2,3-di-*O*-acetyl-6-chloro-6-deoxy-4-*O*-(2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (**19**) (1.6 g, 25%), m.p. 204–206°, $[\alpha]_D$ −48° (*c* 1) (Found: C, 51.5; H, 5.4; Cl, 10.6. $C_{29}H_{36}Cl_2O_{14}$ calc.: C, 51.25; H, 5.3; Cl, 10.5%).

The fourth fraction was evaporated to dryness to give a crystalline mass, which was twice recrystallised from chloroform–light petroleum to give a dichloro derivative (0.3 g, 5%) of unknown structure (see Discussion), m.p. 195.5–198°, $[\alpha]_D$ −43° (*c* 0.6) (Found: C, 51.1; H, 5.5; Cl, 10.45%).

N.m.r. data (220 MHz, benzene-d_6): τ 4.58 (1 H, *t*, *J* 7.8 and 9.5), 4.80 (1 H, *t*, *J* 9.3 Hz), 4.86 (1 H, *t*, *J* 9.0 Hz), 5.09 (1 H, *t*, *J* ~9 Hz), 5.17 (1 H, *d*, *J* 12.5 Hz, PhCH_A), 5.49 (1 H, *d*, *J* 12.5 Hz, PhCH_B), 5.68 (1 H, *d*, *J* 8.0 Hz, H-1 or H-1′), 5.79 (1 H, *d*, *J* 7.5 Hz, H-1 or H-1′), 6.16 (1 H, *d*, *J* 1.5 Hz), 6.35 (1 H, *dt*, *J* 1.5 and ~9 Hz), 6.49 (2 H, *m*), 6.59 (1 H, *t*, *J* ~9 Hz), 6.75–7.1 (4 H, *m*), 8.12 (6 H, *s*, 2AcO), 8.20 (6 H, *s*, 2AcO), 8.35 (3 H, *s*, AcO).

Mass-spectral data: *m/e* 531 (2 Cl, 0.2%), 511 (2 Cl, 0.1%), 485 (2 Cl, 0.1%), 421 (1 Cl, 0.2%), 307 (1 Cl, 15%), 247 (1 Cl, 5%), 205 (1 Cl, 20%), 187 (1 Cl, 15%), 145 (1 Cl, 45%), 91 (100%).

(*b*). The above reaction was repeated using mesyl chloride (20.4 ml, 30 equiv.) and *N*,*N*-dimethylformamide (65 ml) at 70° for 11 days, and the mixture was then processed as above to give a more-complex mixture as indicated by t.l.c. The mixture was fractionated on a dry column of silica gel, using light petroleum–ethyl acetate (3:1).

The first component to be eluted was benzyl 2-*O*-acetyl-3,6-dichloro-3,6-dideoxy-4-*O*-(2,4-di-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-allopyranosyl)-β-D-allopyranoside (**23**) (0.25 g, 4%), m.p. 146.5–148° (from ethyl acetate–light petroleum), $[\alpha]_D$ −53° (*c* 1) (Found: C, 47.7; H, 5.1; Cl, 22.5. $C_{25}H_{30}Cl_4O_{10}$ calc.: C, 47.5; H, 4.75; Cl, 22.5%).

The next product to be eluted was a mixture of two minor components (0.07 g) as indicated by t.l.c. in chloroform (multiple development). This mixture was not further investigated.

The third component was obtained as a syrup which was shown by t.l.c. (chloroform) to be a mixture of two components, one major and the other minor. The syrup ultimately crystallised and was twice recrystallised from chloroform–light petroleum to give the major component, namely, benzyl 2-*O*-acetyl-3,6-dichloro-3,6-dideoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-β-D-galactopyranosyl)-β-D-allopyranoside (**24**) (84 mg, 1.4%), m.p. 157.5–160.5°, $[\alpha]_D$ −18.5° (*c* 0.6) (Found: C, 47.7; H, 4.9; Cl, 22.4. $C_{25}H_{30}Cl_4O_{10}$ calc.: C, 47.5; H, 4.75; Cl, 22.5%).

The fourth component was obtained as a syrup which solidified on the addition of light petroleum (2.5 g, 41%), and was shown by its t.l.c. mobility and its n.m.r. spectrum to be a mixture of the two trichloro derivatives **20** and **21** obtained in section (*a*).

The fifth component also solidified on the addition of light petroleum. T.l.c. [cyclohexane–ethyl acetate (2:1)] indicated it to have a mobility similar to that of the second fraction containing three components obtained in section (*a*). However, a closer examination of it by t.l.c., using chloroform as eluent, showed that it was homogeneous and corresponded to the faster-moving of the three components in the previous mixture. Two recrystallisations from chloroform–light petroleum gave benzyl 2-*O*-acetyl-3,6-dichloro-3,6-dideoxy-4-*O*-(2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-β-D-glucopyranosyl)-β-D-allopyranoside (**22**) (0.18 g, 3%), m.p. 194–195.5°, $[\alpha]_D$ −50° (*c* 1) (Found: C, 49.3; H, 5.1; Cl, 16.3. $C_{27}H_{33}Cl_3O_{12}$ calc.: C, 49.4; H, 5.0; Cl, 16.25%).

The sixth fraction crystallised on evaporation, and recrystallisation from chloroform–light petroleum afforded the 6,6′-dichloro derivative **19** (0.6 g, 9.5%), m.p. and mixture m.p. 202–204°, which was identical with the third fraction obtained in section (*a*).

Chlorination of methyl α-D-glucopyranoside (**25**). — Reaction of the glucoside (4 g) with mesyl chloride (30.4 ml, 30 equiv.) and *N*,*N*-dimethylformamide (65 ml) at 70° for 10 days gave, after processing in the usual way, a dark syrup. T.l.c. [cyclohexane–ethyl acetate (3:1)] revealed two components which were separated in the usual way by dry-column chromatography on silica gel with light petroleum–ether (5:2). The faster-moving component was obtained as a pale-yellow syrup which, on decolorisation with charcoal in chloroform, afforded methyl 2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (**27**) (0.52 g, 8.2%), m.p. 103.5–105° (from 2-propanol) (mixture m.p. 103–104°), $[\alpha]_D$ +190° (*c* 1); lit.[35] m.p. 104–106°, $[\alpha]_D$ +188°.

The fractions containing the slower-moving component were concentrated to a solid which was recrystallised twice from chloroform–light petroleum to give methyl 2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-α-D-glucopyranoside (**26**) (3.1 g, 44%), m.p. 96.5–98.5°, $[\alpha]_D$ +159° (*c* 1, pyridine); lit.[36] m.p. 98–99°, $[\alpha]_D$ +164°.

When the reaction was repeated at 95° for 7 days, the chloro- and dichloro-glycosides were obtained in yields of 7 and 19%, respectively.

Chlorination of methyl β-D-glucopyranoside (**28**). — The glycoside (5 g) was treated with mesyl chloride (37.8 ml, 30 equiv.) at 95° for 90 h, and the mixture processed in the usual way to give a mixture of three major components (t.l.c.; ether–light petroleum, 2:1). The two faster-moving components were very close together and could only be resolved by careful t.l.c., thereby making preparative separation very difficult. However, *O*-deacetylation (sodium methoxide) gave a mixture of three products (t.l.c.; chloroform–ethanol, 6:1) which were more readily separable and were subjected to careful column chromatography on a dry-packed column of silica gel (150 g) with dichloromethane–ethanol (20:1).

The first fractions from the column gave a crystalline product which was recrystallised from chloroform–light petroleum to give methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**33**) (1.5 g, 31%), m.p. 163–164°, $[\alpha]_D$ −54° (*c* 0.6) (Found: C, 36.8; H, 5.5; Cl, 31.2. $C_7H_{12}Cl_2O_4$ calc.: C, 36.4; H, 5.2; Cl, 30.75%). Lit.[23] m.p. 162–163°, $[\alpha]_D$ −43°.

Acetylation of **33** in the usual way (acetic anhydride–pyridine) gave the syrupy diacetate **34** which was used for spectroscopic studies.

The second fraction gave a crystalline residue which was recrystallised from chloroform–light petroleum to give methyl 4,6-dichloro-4,6-dideoxy-β-D-galacto-pyranoside (**31**) (0.7 g, 15%), m.p. 152–153°, $[\alpha]_D$ −14° (*c* 0.5), +7° (*c* 1.4, water), identical to an authentic specimen prepared by the sulphuryl chloride method of Jennings and Jones[22]; lit.[22] m.p. 154°, $[\alpha]_D$ +16° (water)*.

Acetylation in the usual way afforded the diacetate **32** (75%), m.p. 119–120°, $[\alpha]_D$ +33° (*c* 0.6) (Found: C, 42.1; H, 5.0; Cl, 22.4. $C_{11}H_{16}Cl_2O_6$ calc.: C, 41.9; H, 5.1; Cl, 22.55%).

The third fraction was crystalline, and recrystallisation from ethyl acetate–light petroleum gave methyl 6-chloro-6-deoxy-β-D-glucopyranoside (**29**) (0.8 g, 15%), m.p. 157–159°, $[\alpha]_D$ −48° (*c* 1, water); lit.[37] m.p. 157–159°, $[\alpha]_D$ −49°.

The triacetate **30**, prepared in the usual way, had m.p. 138–139°, $[\alpha]_D$ +5.5° (*c* 2.4); lit.[37] m.p. 141°, $[\alpha]_D$ −9.8° (pyridine).

Chlorination of methyl α-D-galactopyranoside (**35**). — The anhydrous glycoside (3 g) was dissolved in *N,N*-dimethylformamide (50 ml), treated with mesyl chloride (23.5 ml, 20 equiv.) at 100° (bath) for 4 days, and then processed in the usual way. The syrupy product was *O*-deacetylated in the usual way (sodium methoxide) to give a mixture composed of a single major product and several minor products. The mixture crystallised and was recrystallised from dichloro methane–isopropyl ether to give methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside (**36**) (1.3 g, 37%), m.p. 122–124°, $[\alpha]_D$ +128° (c 1.25) (Found: C, 36.5; H, 5.7; Cl, 31.1. $C_7H_{12}Cl_2O_4$ calc.: C, 36.4; H, 5.2; Cl, 30.75%). Lit.[24] m.p. 119–121°, $[\alpha]_D$ +121° (water).

*In a personal communication, Professor J. K. N. Jones has acknowledged an error in the original paper and has kindly supplied this revised value.

Acetylation of **36** in the usual way was carried out on a very small scale only for mass spectrometry.

Reaction of methyl β-D-glucopyranoside (**28**) *with sulphuryl chloride.*† — A solution of the β-glucoside (2 g) in anhydrous pyridine (40 ml) and dichloromethane (40 ml) was cooled to −78° (solid carbon dioxide–acetone bath), and sulphuryl chloride (5.2 ml) was added slowly. The mixture was then stored at −78° for 2 h and thereafter allowed to rise to room temperature during 3 h. After a further 2.5 h, t.l.c.* (chloroform–ethanol, 6:1) indicated the presence of two products, one major and the other minor. The reaction mixture was then poured into methanolic sodium iodide (50 ml), and the resulting red solution was evaporated to a syrup which, after two co-distillations with toluene, was fractionated on a dry-packed column of silica gel. Elution with dichloromethane removed iodine and other fast-moving, non-carbohydrate impurities. Careful elution with dichloromethane–ethanol (20:1) then achieved a partial separation of the two products. The first few fractions contained the faster-moving, minor component, and later fractions were mixtures of this compound with the slower-moving component. The mixed fractions were rechromatographed on a dry-packed column with dichloromethane–ethanol (50:1), and complete separation of the two products was achieved.

The fractions (from both columns) containing the faster-moving compound only were combined and evaporated to a yellow syrup, which was further purified by passage through a short column of silica gel with dichloromethane–ethanol (20:1); this removed some coloured impurities. Evaporation of the pure fractions from this column gave a small quantity of a crystalline compound (~0.05 g). Recrystallisation from ethyl acetate–light petroleum gave methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**33**) as a microcrystalline solid, m.p. 160–163.5° [from 145°, a slow, crystal transition (giving highly refractive, rod-like crystals) was noted], identical (i.r., mixture m.p., and t.l.c. mobility) with the sample already described.

The pure fractions containing the slower-moving, major product were evaporated to a yellow, crystalline mass which, after decolorisation with charcoal in chloroform, followed by recrystallisation from chloroform–light petroleum, gave methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside (**31**) as white needles (0.25 g, 10%), m.p. 152–153.5° (120°, crystal transition), $[\alpha]_D$ +6° (*c* 1, water), identical with the sample already described.

Reaction of benzyl β-cellobioside (**17**) *with sulphuryl chloride.* — A stirred solution of benzyl β-cellobioside (**17**, 2 g) in a mixture of dichloromethane (40 ml) and anhydrous pyridine (15 ml) was cooled to −78° (bath) and slowly treated with

*For t.l.c., a small aliquot of the reaction mixture was mixed with an equal volume of methanolic sodium iodide in order to remove chlorosulphate groups.

†*Note added in proof May 28th, 1974.* Recently D. M. Dean, W. A. Szarek and J. K. N. Jones (*Carbohyd. Res.*, 33 (1974) 383) have reported the same reaction. They obtain considerably better yields of the 3,6- and 4,6-dichlorides (50 and 22% respectively) after 2 h at ambient temperature. However, they note that yields decrease markedly with longer reaction times, which might explain our considerably lower yields.

sulphuryl chloride (6 ml). The mixture was then stirred at −78° for 1.5 h, stored thereafter at −40° for 24 h and at 0° for 17 h, and poured into ice-cold 0.5M sulphuric acid (50 ml) contained in a separating funnel. The organic layer was separated and the remaining aqueous phase further extracted with dichloromethane. The combined organic extracts were washed well with aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$). The extracts were then evaporated to dryness, and the resulting syrup was dissolved in a mixture of methanol and dichloromethane. Addition of sodium iodide, surprisingly, did not liberate iodine, suggesting the absence of chlorosulphates. The mixture was then quickly passed through a dry-packed column of silica gel with methanol–dichloromethane (1:1), and the eluate was evaporated to a thick, yellow syrup, which was thoroughly dried *in vacuo* over phosphorus pentaoxide. The resulting solid was acetylated in the usual way (pyridine–acetic anhydride) to give a yellow solid containing three components (t.l.c.; cyclohexane–ethyl acetate, 2:1). The mixture was fractionated by chromatography on a dry-packed column with light petroleum–ethyl acetate (3:1).

The component eluted first crystallised on the addition of light petroleum, and two recrystallisations from ethyl acetate–light petroleum gave the 3,3′,6,6′-tetrachloride **23** (0.2 g, 7%), m.p. 146–148.5°, identical (i.r. and mixture m.p.) with the product already described.

The second fraction was evaporated to a syrup which crystallised on the addition of light petroleum. Recrystallisation from chloroform–light petroleum gave the 3,4′,6,6′-tetrachloride **24** (0.18 g, 6%), m.p. 159.5–162°, identical (i.r. and mixture m.p.) with the product already described.

The third fraction was evaporated to a syrup that solidified on the addition of light petroleum (0.2 g, 7%). T.l.c. (cyclohexane–ethyl acetate, 2:1) indicated that it was the mixture of 3′,6,6′- and 4′,6,6′-trichloro derivatives, **20** and **21**, respectively, previously encountered in the mesyl chloride–*N*,*N*-dimethylformamide reaction. The composition of the mixture was confirmed by its ^1H n.m.r. spectrum, which showed that the two components were present in approximately equal amounts. The mixture was not further fractionated.

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REFERENCES

1 Preliminary communication: R. G. EDWARDS, L. HOUGH, A. C. RICHARDSON, and E. TARELLI, *Tetrahedron Lett.*, (1973) 2369.
2 J. E. G. BARNETT, *Advan. Carbohyd. Chem.*, 22 (1967) 177.
3 B. T. LAWTON, W. A. SZAREK, AND J. K. N. JONES, *Chem. Commun.*, (1969) 787; *Carbohyd. Res.*, 15 (1970) 397.
4 S. HANESSIAN, *Advan. Carbohyd. Chem.*, 21 (1966) 143; B. T. LAWTON, W. A. SZAREK, and J. K. N. JONES, *Carbohyd. Res.*, 14 (1970) 255.

5 B. HELFERICH, *Ber.*, 54 (1921) 1082; B. HELFERICH AND J. F. LEETE, *ibid.*, 62 (1929) 1549.
6 S. S. ALI, T. J. MEPHAM, I. M. E. THIEL, E. BUNCEL, AND J. K. N. JONES, *Carbohyd. Res.*, 5 (1967) 118, and earlier papers; E. BUNCEL, *Chem. Rev.*, 70 (1970) 323.
7 J. P. H. VERHEYDEN AND J. G. MOFFATT, *J. Org. Chem.*, 35 (1970) 2868, 2319, and earlier references cited therein.
8 D. BRETT, I. M. DOWNIE, J. B. LEE, AND M. F. S. MATOUGH, *Chem. Ind. (London)*, (1969) 1017; C. R. HAYLOCK, L. D. MELTON, K. N. SLESSOR, AND A. S. TRACEY, *Carbohyd. Res.*, 16 (1971) 375; J. P. H. VERHEYDEN AND J. G. MOFFATT, *J. Org. Chem.*, 37 (1972) 2289.
9 M. M. PONPIPOM AND S. HANESSIAN, *Carbohyd. Res.*, 18 (1971) 342; S. HANESSIAN, M. M. PONPIPOM, AND P. LAVALLÉE, *ibid.*, 24 (1972) 45; S. HANESSIAN AND P. LAVALLÉE, *ibid.*, 28 (1973) 303.
10 K. HAGA, M. YOSHIKAWA, AND T. KATO, *Bull. Chem. Soc. Jap.*, 43 (1970) 3922.
11 A. KLEMER AND G. MERSMANN, *Carbohyd. Res.*, 22 (1972) 425.
12 M. E. EVANS, L. LONG, JR., AND F. W. PARRISH, *J. Org. Chem.*, 33 (1968) 1074.
13 J. B. LEE AND M. M. EL SAWI, *Chem. Ind., (London)*, (1960) 839.
14 N. K. KOCHETKOV, A. I. USOV, AND K. S. ADAMYANTS, *Tetrahedron*, 27 (1971) 549.
15 P. L. DURETTE, L. HOUGH, AND A. C. RICHARDSON, *Carbohyd. Res.*, 31 (1973) 114.
16 P. L. DURETTE, L. HOUGH, AND A. C. RICHARDSON, *J. Chem. Soc. Perkin I*, (1974) 88.
17 P. L. DURETTE, L. HOUGH, AND A. C. RICHARDSON, *J. Chem. Soc. Perkin I*, (1974) 97.
18 N. K. KOCHETKOV AND O. S. CHIZHOV, *Advan. Carbohyd. Chem.*, 21 (1966) 69; N. K. KOCHETKOV, O. S. CHIZHOV, AND N. V. MOLODTSOV, *Tetrahedron*, 24 (1968) 5587.
19 G. JAYME AND W. DEMMIG, *Chem. Ber.*, 93 (1960) 356.
20 L. HOUGH, A. K. PALMER, AND A. C. RICHARDSON, *J. Chem. Soc. Perkin I*, (1973) 784.
21 R. G. EDWARDS, Ph. D. thesis, Univ. London, 1973; R. G. EDWARDS, L. HOUGH AND A. C. RICHARDSON, forthcoming publication.
22 H. J. JENNINGS AND J. K. N. JONES, *Can. J. Chem.*, 40 (1962) 1408.
23 E. H. WILLIAMS, W. A. SZAREK AND J. K. N. JONES, *Can. J. Chem.*, 49 (1971) 796.
24 J. K. N. JONES, M. B. PERRY, AND J. C. TURNER, *Can. J. Chem.*, 38 (1960) 1122.
25 J. D. ALBRIGHT, E. BENZ, A. E. LANZILOTTI, AND L. GOLDMAN, *Chem. Commun.*, (1965) 413; S. NOGUCHI, K. MORITA, AND M. NISHIKAWE, *Chem. Pharm. Bull.*, 8 (1960) 563.
26 S. HANESSIAN AND N. R. PLESSAS, *J. Org. Chem.*, 34 (1969) 2163.
27 H. EILINGSFELD, M. SEEFELDER, AND H. WEIDINGER, *Chem. Ber.*, 96 (1963) 2671.
28 C. L. STEVENS, D. MORROW, AND J. LAWSON, *J. Amer. Chem. Soc.*, 77 (1955) 2341.
29 A. C. RICHARDSON, *Carbohyd. Res.*, 10 (1969) 395.
30 E. TARELLI, unpublished observation.
31 R. T. SLEETER AND H. B. SINCLAIR, *J. Org. Chem.*, 35 (1970) 3804.
32 M. L. WOLFROM AND K. KOIZUMI, *J. Org. Chem.*, 32 (1967) 656.
33 P. D. BRAGG, J. K. N. JONES, AND J. C. TURNER, *Can. J. Chem.* 37 (1959) 1412.
34 L. HOUGH, A. K. PALMER, AND A. C. RICHARDSON, *J. Chem. Soc. Perkin I*, (1972) 2513.
35 C. K. LEE, Ph.D. Thesis, University of Reading, 1973.
36 B. HELFERICH, W. KLEIN, AND W. SCHAFER, *Ber.*, 59 (1926) 79.
37 B. HELFERICH AND A. SCHNEIDMULLER, *Ber.*, 60 (1927) 2002.