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# TRANSFORMATIONS OF CELLOBIOSE DERIVATIVES INTO ANALOGUES OF LACTOSE*†

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ABSTRACT

The preparation of benzyl β-cellobioside 2,3,6,2′,3′-pentabenzoate (**2b**) via a 4′,6′-benzylidene acetal in 27% overall yield from cellobiose is described. This pentabenzoate has been utilised for conventional syntheses of the 6′-amino-, 4′-amino-, and 4′,6′-diamino-analogues of lactose, via the 4′,6′-dimesylate. In addition, reaction of the pentabenzoate **2b** with sulphuryl chloride initially afforded the 6′-chloro derivative, which was then slowly transformed into a mixture of the 4′,6′-dichloro-lactoside and an isomer in which the non-reducing ring of the disaccharide had been transformed into a 3′,6′-dideoxy-3′,6′-dichloro-gulopyranoside. The latter probably arose by neighbouring-group participation by the 3′-benzoyloxy group prior to the introduction of the secondary 3′-chloro substituent. The former dichloro compound was subsequently converted into 4′,6′-dideoxy-4′,6′-dichloro-lactose. It was found that the rate of nucleophilic displacement at C-4′ of a cellobioside was much lower than that for the corresponding α-linked disaccharide, maltose. Furthermore, nucleophilic displacement at C-4′ of a lactoside was accompanied by substantial elimination, to give the 4′-ene, together with some cleavage of the interglycosidic bond. The origins of these effects are discussed.

## INTRODUCTION

In recent years, we have studied the chemistry and chemical modification of the readily available disaccharides sucrose[2], trehalose[3], maltose[4], and lactose[1]; there exists a need to find alternative uses for the abundant disaccharides sucrose and lactose, whilst the less abundant, but readily available, disaccharides, trehalose and maltose, are potential precursors of analogues of biologically active compounds, for example, trehalosamine[5] and amicetin[6], respectively. We have now extended the studies to cellobiose, which is readily accessible by acetolysis of cellulose. Cellobiose has a close relationship to lactose, differing only in the chirality at C-4′, and could

*Dedicated to the memory of Professor J. K. N. Jones, F.R.S.

†Part VI of "The Chemistry of Cellobiose and Lactose". For Part V, see reference 1.

therefore serve as a starting point for synthesis of analogues of lactose. Because lactose is such an important compound in mammalian metabolism, including man[7], it was considered that the preparation of amino and halo derivatives might yield compounds having interesting biological properties.

Prior to 1973, few amino- or halo-analogues of lactose had been described, undoubtedly because of the complexity of such multifuctional molecules. However, at the conclusion of our work, Tejima *et al.*[8,9] described the synthesis of 6-acetamido-6-deoxy-lactose via benzyl 6-*O*-mesyl-β-lactoside hexa-acetate[8], 4′-acetamido-4′-deoxy-lactose (**13a**) from 1,6-anhydro-4′-*O*-tosyl-β-cellobiose penta-acetate[9], and 6′-acetamido-6′-deoxy-α-lactose and 4-*O*-β-D-idopyranosyl-D-glucopyranose from 1,6-anhydro-4′,6′-*O*-benzylidene-β-lactose[10].

## RESULTS AND DISCUSSION

In the chemical conversion of cellobiose into various lactoses, we selected benzyl β-cellobioside 2,3,6,2′,3′-pentabenzoate (**2b**) as a suitable intermediate, thus permitting the introduction of a variety of substituents at C-4′ and C-6′. In related studies, Kuzuhara and Emoto[11] utilised the corresponding penta-acetate, prepared via the 4′,6′-phenylboronate, but the overall yield of the penta-acetate was rather low. We proceeded by way of the 4′,6′-benzylidene acetal **3a**, which was prepared from benzyl β-cellobioside[12] (**2a**) in 73% yield[13]. Sequential benzoylation and mild acid hydrolysis with hydrochloric acid in a mixture of methanol and dichloromethane gave the required pentabenzoate **2b** in 51% overall yield from **2a**. Mesylation of the 4′,6′-diol **2b** was accomplished conventionally, except that much longer reaction-times were necessary for complete sulphonylation, the required 4′,6′-dimesylate **4b** being isolated crystalline in 73% yield. Interestingly, Hess and Hwang[14] encountered similar difficulties in trying to benzoylate benzyl 6′-*O*-trityl-β-cellobioside 2,3,6,2′,3′-pentabenzoate; benzoylation required 8 h at 100°, and tosylation for 7 days at 40° was unsuccessful.

For the synthesis of 6′-amino-6′-deoxy-lactose (**10a**), the 4′,6′-dimesylate **4b** was treated with sodium azide in hexamethylphosphoric triamide under conditions wherein only the primary sulphonyloxy group would be expected to undergo displacement, that is, for one h at 80°. This afforded the 6′-azide **5b** crystalline in 81% yield, the structure of which was supported by its 220-MHz $^1$H-n.m.r. spectrum (Table I). Subsequent treatment of the 6′-azido-4′-mesylate **5b** with sodium benzoate in hexamethylphosphoric triamide, in order to displace the remaining sulphonate group, was unusually slow, taking eight days of reaction at 80° for completion*.

The required 6′-azido-lactoside **18b** was isolated as an analytically pure syrup in 62% yield. Sequential deacetylation with sodium methoxide and hydrogenation with palladium-on-charcoal under acid conditions afforded syrupy 6′-amino-6′-deoxy-lactose (**10a**) as the hydrochloride in 73% yield. Acetylation of the amino-

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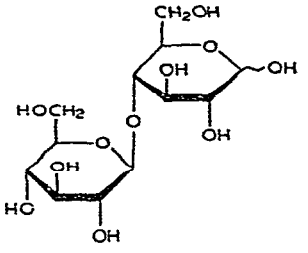
disaccharide **10a** afforded a mixture of two components (t.l.c.) that were separated by column chromatography. The least mobile was the required octa-acetate **11c**, but its n.m.r. spectrum indicated it to be a 4:1 mixture of the $\beta$- and $\alpha$-anomers, and these could not be further fractionated either by chromatography or by fractional crystallisation. The more-mobile component, isolated in only small amount, appeared also to be an $\alpha,\beta$ mixture, as indicated by n.m.r.-spectral doublets at $\tau$ 3.75 ($J$ 4 Hz) and $\tau$ 4.20 ($J$ 8 Hz). However, although the compound was isomeric with the foregoing



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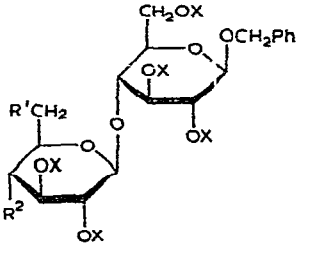
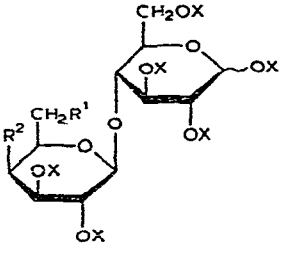
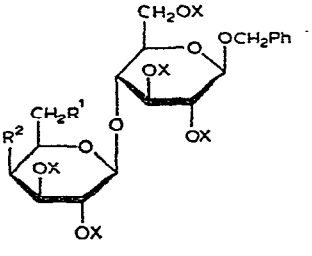


2 $R^1 = R^2 = OH$
3 $R^1, R^2 = -OCHPhO-$
4 $R^1 = R^2 = OMs$
5 $R^1 = N_3, R^2 = OMs$
6 $R^1 = OBz, R^2 = OMs$
7 $R^1 = Cl, R^2 = OH$
8 $R^1 = Cl, R^2 = OX$



9 $R^1 = R^2 = OX$
10 $R^1 = NH_3Cl, R^2 = OX$
11 $R^1 = NHAc, R^2 = OX$
12 $R^1 = OX, R^2 = NH_3Cl$
13 $R^1 = OX, R^2 = NHAc$
14 $R^1 = R^2 = NH_3Cl$
15 $R^1 = R^2 = NHAc$
16 $R^1 = R^2 = Cl$

a series, X = H
b series, X = Bz
c series, X = Ac



17 $R^1 = R^2 = OX$
18 $R^1 = N_3, R^2 = OX$
19 $R^1 = NH_2, R^2 = OX$
20 $R^1 = NHAc, R^2 = OX$
21 $R^1 = R^2 = N_3$
22 $R^1 = R^2 = NH_2$
23 $R^1 = R^2 = NHAc$
24 $R^1 = OX, R^2 = N_3$
25 $R^1 = OX, R^2 = NH_2$
26 $R^1 = OX, R^2 = NHAc$
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therefore serve as a starting point for synthesis of analogues of lactose. Because lactose is such an important compound in mammalian metabolism, including man[7], it was considered that the preparation of amino and halo derivatives might yield compounds having interesting biological properties.

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| 18b[a] | 21b[a] | 24b[a] | 27b[c] | 28[c] | 29[e] | 29[f] | 31[e] |
|---|---|---|---|---|---|---|---|
| 4.75d | 4.96d | 5.18d | 5.35d | 5.57d | 5.60m | 4.83d | ~5.4m |
| | 4.20dd | 4.40t[g] | 4.52dd | 4.01dd | 4.14m | 4.48dd | 4.18dd |
| | 3.98t | 4.26t | 4.35t | 4.15t | | 4.09t | 4.46t |
| | 5.47t | 5.70t | 5.82t | 5.75t | 5.80m | 5.33t | 6.24t |
| 5.77m | 5.98m | | 6.25m | 6.86m | 6.81m | | 6.62m |
| | | | | | 5.23dd | 5.02dd | ~5.4 |
| | | | | | 5.33d | 5.06dd | |
| 4.40d | 4.78d | 5.22d | 5.27d | 4.82d | 5.13d | 4.81d | |
| | 4.05dd | 4.19t | 4.18dd | 4.39dd | 4.33t | 4.30t | |
| | 4.13dd | 4.54dd | 4.85dd | 5.62t | 4.21t | 4.39t | |
| | 5.70dd | 5.86d | | 4.74dd | 4.58d | 4.18d | |
| 5.60t | 6.13t | | 6.44t | 5.93t | | | |
| | 7.02m | | 7.01m | 7.36m | 7.16d<br>7.41d | 7.24s | |
| 7.8 | 7.7 | 8.2 | 7.6 | 7.7 | | 8.2 | 7.7 |
| | 9.2 | 9.3 | 9.5 | 9.6 | | 9.8 | 9.5 |
| | 9.2 | 9.3 | 10.0 | 10.0 | | 9.8 | 9.5 |
| | 9.2 | 9.3 | 10.0 | 9.5 | | 9.8 | 9.5 |
| | | | | | 1.8 | 1.5 | |
| | | | | | 5.0 | 5.0 | |
| | | | | | −12.5 | −12.5 | |
| 7.8 | 7.7 | 8.2 | 7.5 | 7.8 | 4.2 | ~3 | |
| | 10.0 | 10.5 | 10.5 | 4.4 | 4.5 | 5.0 | |
| | 3.7 | 4.0 | 3.5 | 3.4 | 4.5 | 5.0 | |
| 1 | ~1 | ~1 | ~1 | ~1 | | | |
| 6 | ~6 | | | | | | |
| 6 | ~6 | | | | | | |
| | | | | | −14 | | |

derivative **15c**, the n.m.r. spectrum of which indicated the $\beta$-anomeric configuration ($J_{1,2}$ 7.5 Hz).

For the synthesis of 4′-amino-4′-deoxy-lactose (**12a**), the first step was displacement of the primary sulphonyloxy group of the 4′,6′-dimesylate **4b** by benzoate anion, which was achieved in hexamethylphosphoric triamide for 2 h at 80°. The resulting 4′-*O*-mesyl-hexa-benzoate **6b** was obtained crystalline in 74% yield, and on subsequent treatment with sodium azide in the same solvent afforded the crystalline 4′-azido-lactoside **24b** in 85% yield. The position and configuration of the azide substituent was indicated by the n.m.r. spectrum (Table I), in particular by the high-

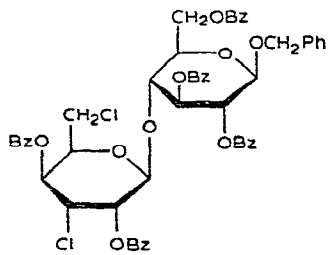
field position of the H-4′ resonance, which appeared as a double doublet exhibiting splittings of 4 and ~1 Hz, which is quite characteristic of H-4 of a galactoside[15]. *O*-Debenzoylation of the 4′-azide **24b** gave the crystalline 4′-azido-lactoside **24a** in 60% yield, and the latter was then hydrogenated as before to give 4′-amino-4′-deoxy-lactose (**12a**) as the syrupy hydrochloride in 63% yield. Acetylation of the amino-lactose with sodium acetate–acetic anhydride gave the crystalline octa-acetate **13c**. The n.m.r. spectrum of the octa-acetate, however, displayed two H-1 resonances, at $\tau$ 4.30 ($J$ 8.7 Hz) and at $\tau$ 3.75 ($J$ 3.6 Hz), in the ratio 4:1, assigned to the $\beta$ and $\alpha$ anomers, respectively.

Prolonged reaction (8 days) of the 4′,6′-dimesylate **4b** with sodium benzoate in hexamethylphosphoric triamide resulted in displacement of both sulphonyloxy groups by benzoate to give benzyl $\beta$-lactoside heptabenzoate (**17b**) in 48% yield. *O*-Debenzoylation of the heptabenzoate gave benzyl $\beta$-lactoside (**17a**), which on hydrogenolysis afforded a product having the correct optical rotation for $\beta$-lactose, but which melted 30° lower than authentic $\beta$-lactose. The sample was adequately characterised as lactose by acid hydrolysis to give glucose and galactose, and by the formation of $\beta$-lactose octa-acetate (**9c**), which was compared with an authentic specimen. It is possible that this sample of lactose could have been a molecular complex consisting mainly of the $\beta$-anomer with a little of the $\alpha$-anomer, as it is known that such complexes of the two anomers are formed under certain conditions[16].

The chlorination of benzyl $\beta$-cellobioside (**2a**) with mesyl chloride-*N*,*N*-dimethylformamide and with sulphuryl chloride has already been reported[17] and, in order to extend the range of chloro derivatives available, benzyl $\beta$-cellobioside 2,3,6,2′,3′-penta-benzoate (**2b**) was treated with sulphuryl chloride in pyridine for 2.5 h at −5°. An amorphous monochloro derivative was obtained in 43% yield, instead of the anticipated dichloride **27b**. Even though no attempt had been made to remove chlorosulphate groups, the compound possessed an hydroxyl group (i.r.), suggesting hydrolysis of the ester during the isolation procedure. The location of the chlorine substituent at the primary position was indicated by the 220-MHz n.m.r. spectrum, which showed that one pair of methylene hydrogen atoms resonated at higher field (1 p.p.m.) than the other pair (Table I). Furthermore, the hydroxyl group was located at C-4′ as the H-4′ resonance was observed at relatively high field ($\tau$ 6.50) as a triplet. The 6′-chloride **7b** was further characterised by benzoylation to give benzyl 6′-chloro-6′-deoxy-$\beta$-cellobioside hexabenzoate (**8b**).

Because of the sluggish reactivity of the 4′-hydroxyl group, or more precisely that of its chlorosulphate ,the reaction of the 4′,6′-diol **2b** with sulphuryl chloride was prolonged to 20 h, to afford a mixture of two compounds, one major and the other minor, neither of which was the mono-chloro derivative **7b** previously encountered. After chromatographic separation of the mixture, the two components were isolated in yields of 50 and 4.3% respectively. Elemental analysis of both products indicated that they were isomeric dichlorides, the mass spectra of which showed fragments at *m/e* 565 and 407 (2 Cl), arising from the reducing and non-reducing rings respectively, and which revealed that, in each compound, the chlorine atoms were located in the

non-reducing ring only. The subsequent fragmentation of the ions at *m/e* 407 was particularly significant. That of the major component underwent loss of benzoic acid to give an intense ion at *m/e* 285 (2 Cl), but the loss of the elements of HCl from *m/e* 407 was not observed. This provided strong evidence[17] that a benzoyl group was located at C-3′. On the other hand, the ion having *m/e* 407, which arose from the minor component, eliminated HCl and benzoic acid to give ions of relatively low intensity. These data showed that the two compounds differed in the pattern of substitution of the chlorine atoms in the non-reducing ring. It further indicated that the major product did not have a chlorine atom at C-3′, whereas the loss of HCl from the ion having *m/e* 407 in the minor product indicated that a chlorine atom might be located at C-3′. Accordingly, the major product was tentatively assigned the expected 4′,6′-dichloro structure **27b**, and the minor product was assigned the 3′,6′-dichloro structure **28**.

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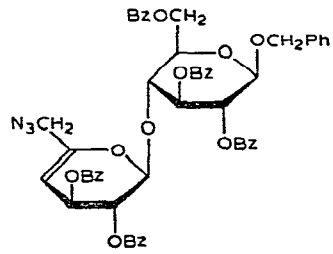


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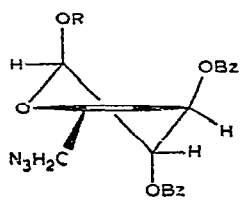


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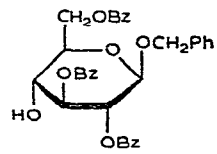


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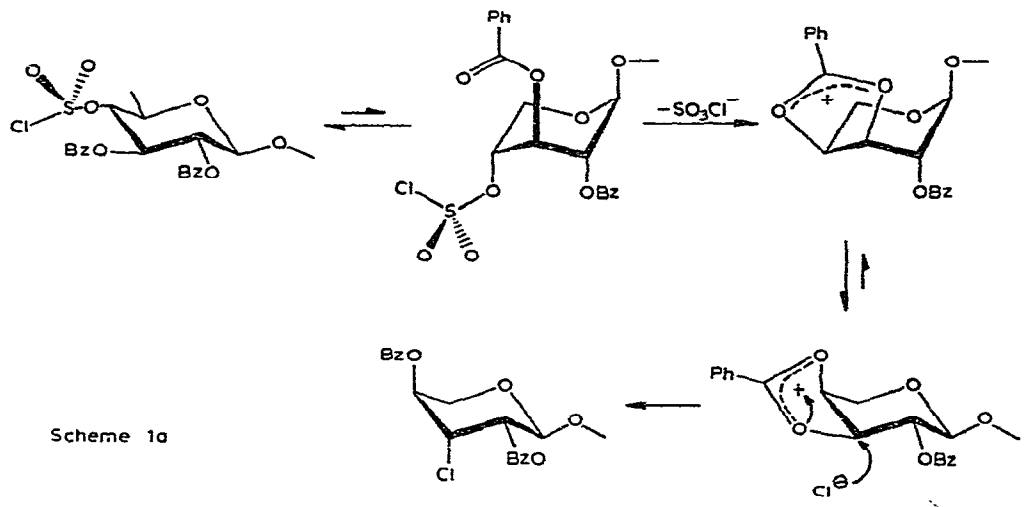
The 220-MHz n.m.r. spectra of the foregoing two products confirmed these tentative structural assignments. The spectrum of the major component **27b** showed the H-2′ resonance to be the lowest-field, methine-proton resonance ($\tau$ 4.18), which was consistent with its being deshielded by an axial chlorine atom at C-4′. Further evidence for the *galacto* configuration of the non-reducing ring was afforded by the H-3′ resonance, which appeared as a doublet of doublets at $\tau$ 4.85 showing splittings of 10 and 4 Hz. The high-field position (at $\tau$ 7.01) of a pair of methylene resonances was consistent with a $CH_2Cl$ grouping. Final confirmation of the structure was obtained by unequivocal synthesis of the 4′,6′-dichloride **27b** by the action of lithium

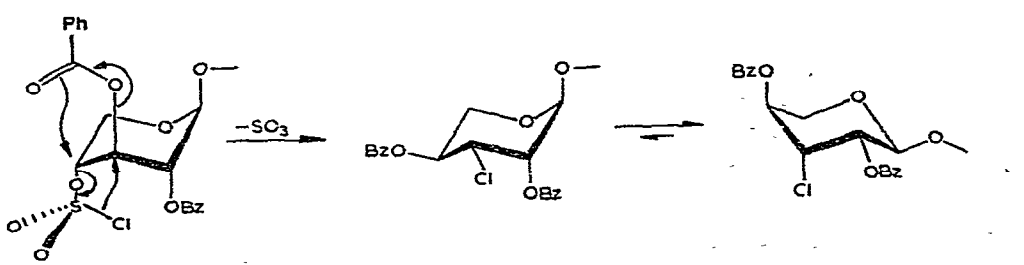
chloride on the corresponding 4′,6′-dimesylate **4b**, which afforded the 4′,6′-dichloro-lactoside **27b**, identical with the foregoing product, in high yield.

The n.m.r. spectrum of the minor product was very different from that of the major isomer, and was relatively free of overlapping resonances. Notably, the H-1 and H-1′ resonances were separated by 0.75 p.p.m., whereas in the 4′,6′-dichloride they were separated by only 0.08 p.p.m. This indicated[17] that the H-1′ resonance was being deshielded by an axial chlorine atom at C-3′. The H-1′, H-2′, H-3′, H-4′, and H-5′ resonances were readily assignable, and from the coupling constants ($J_{1,2}$ 7.8, $J_{2,3}$ 4.4, $J_{3,4}$ 3.4, and $J_{4,5}$ 1.0 Hz), it was possible to designate the non-reducing ring as a 3′,6′-dichlorogulopyranoside; consequently the minor product was benzyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,4-di-*O*-benzoyl-3,6-dichloro-3,6-dideoxy-β-D-gulopyranosyl)-β-D-glucopyranoside (**28**).

The 3′,6′-dichloride **28** must arise by neighbouring-group participation by the benzoyloxy group at C-3′ during the loss of the 4′-chlorosulphate group. The resulting 3′,4′-benzoxonium ion may then undergo nucleophilic ring-opening by attack of chloride anion at either C-3′ or C-4′ to give, respectively, the 3′,6′-dichloro-




Scheme 1a




Scheme 1b

gulopyranoside or the 4′,6′-dichloro-glucopyranoside. The fact that the 4′,6′-dichloro-*gluco*-isomer was not detected suggests that attack by chloride anion must take place predominantly at C-3′ to afford the *gulo* configuration (Scheme 1a). Alternatively, it is also conceivable that the migration of the 3′-benzoyloxy group may be synchronous with collapse of the chlorosulphonyloxy group and the stereospecific introduction of the chlorine of the chlorosulphonyloxy group (Scheme 1b).

*O*-Debenzoylation of the 4′,6′-dichloro-lactoside pentabenzoate **27b** with sodium methoxide gave the required benzyl 4′,6′-dichloro-4′,6′-dideoxy-β-lactoside (**27a**) in 63% yield, together with a minor product (~10–15%). The minor product was not characterised, but was thought to arise from incomplete de-esterification, as it is well known that the 6-benzoate of lactose is remarkably stable towards ester hydrolysis[18]. Hydrogenolysis of the 4′,6′-dichloro-lactoside **27a** gave 4′,6′-dichloro-4′,6′-dideoxy-lactose (**16a**) in 81% yield as an analytically pure glass. Acetylation of the dichloride afforded a crystalline, 15:85 mixture of the α- and β-hexa-acetates **16c** (n.m.r.). The structure of the dichlorolactose was also verified by acid hydrolysis, which gave only glucose and 4,6-dichloro-4,6-dideoxy-galactose, as indicated by paper-chromatographic examination of the hydrolysate.

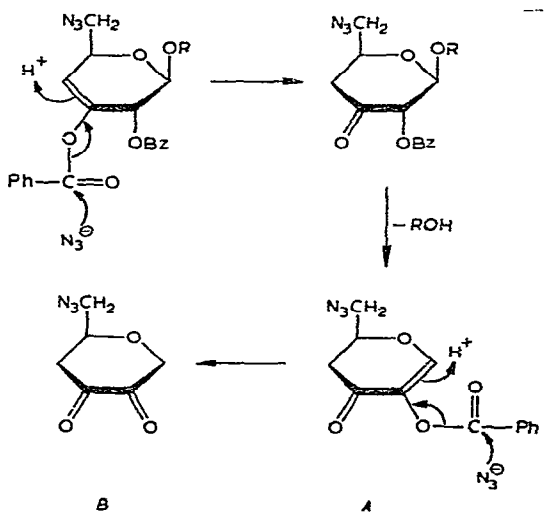
Displacement of the chlorine atoms of the 4′,6′-dichloro-lactoside pentabenzoate **27b** by azide anion, according to Lawton *et al.*[19], offered a route to 4′,6′-diamino-4′,6′-dideoxy-cellobiose. However, the dichloride **27b** underwent relatively slow reaction with sodium azide in hexamethylphosphoric triamide to give two products, in yields of 26 and 27% after chromatography.

The more-mobile compound contained only one azide group and no chlorine, as indicated by elemental analysis. The 220-MHz n.m.r. spectrum in benzene-$d_6$ showed an AB quartet centered at $\tau$ 7.28 that was consistent with a $CH_2N_3$ group attached to a carbon atom carrying no hydrogen atoms. This suggested that the primary chloro group had undergone normal displacement by azide, whereas the secondary chloro substituent had undergone elimination to give the 4′-ene, thus indicating that the product was the 6′-azido-4′-enoside **29**. The 220-MHz n.m.r. spectrum in acetone-$d_6$ was largely first-order, except for the hydrogen atoms at C-6′. The resonances of the reducing ring were readily assigned, and the chemical shifts and coupling constants indicated that this ring was unperturbed. In contrast, the resonances due to protons of the non-reducing ring indicated, in addition to the absence of an H-5′ resonance, that a gross conformational change had occurred. The observed coupling constants ($J_{1,2}$ ~3; $J_{2,3}$ 5.0; $J_{3,4}$ 5.0 Hz) suggested that the non-reducing ring adopted a conformation in which the substituents at C-1′, and C-2′ were axial and that at C-3′ was quasi-axial, as in the $^1H_2$ half-chair conformation **30**. This appears to be a further example of the effect, first described by Ferrier and Sankey[20], in which acyloxy groups adjacent to a double bond in a six-membered ring preferentially adopt a quasi-axial orientation instead of the seemingly more-stable quasi-equatorial position. This effect has since been observed by ourselves[21] and by other workers[22].

The less-mobile product of the azide displacement reaction unexpectedly did

not contain either chlorine or nitrogen, as indicated by elemental analysis, and its i.r. spectrum indicated the presence of an hydroxyl group ($\nu_{max}$ 3500 $cm^{-1}$). The 100-MHz n.m.r. spectrum of the compound showed that it could not be a disaccharide derivative, and was in fact a tribenzoate of benzyl β-D-glucopyranoside. The two lowest-field methine resonances (at τ 4.18 and 4.46) were clearly mutually coupled, as shown by the asymmetry of the two signals, and these were assigned to H-2 and H-3 respectively. Similarly a high-field triplet (τ 6.24) must have been the methine resonance of the hydrogen atom adjacent to the hydroxyl group. As the asymmetry of this resonance indicated that it must be coupled to H-5 (which resonated at τ 6.62), it was assigned to H-4. Consequently, the product was identified as benzyl 2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**31**).

We have recently encountered this behaviour with a closely related 4',6'-di-*O*-mesyl-lactoside[21], and believe that the elimination of the 4'-substituent gives both the 3'- and 4'-enes. The 3'-ene, which contains a more-labile, vinylic ester, undergoes loss of the acyl group, presumably by attack by azide anion at the carbonyl group. After tautomeric rearrangement of the resulting vinylic alcohol to the 3'-keto derivative, the aglycon is lost by β-elimination (Scheme 2). We have not detected the product or products arising from the non-reducing ring (*A* and/or *B*), but it is feasible that these are so volatile that they are lost during the course of the reaction or during the isolation.




Scheme 2.

## EXPERIMENTAL

*General methods.* — All evaporations were performed under diminished pressure. Melting points were determined on a Kofler hot-stage apparatus and are

uncorrected. Unless otherwise stated, specific rotations were measured in chloroform using a 1-dm tube at ambient temperature (~21 ±2°). Hexamethylphosphoric triamide was dried over calcium hydride and then distilled under diminished pressure. Light petroleum refers to a fraction having b.p. 60–80°.

*Benzyl 4-O-(β-D-glucopyranosyl)-β-D-glucopyranoside (benzyl β-cellobioside,* **2a**). — Perchloric acid (0.5 ml) was slowly added to a stirred suspension of dry cellobiose (**1**, 100 g) in glacial acetic acid (500 ml) and acetic anhydride (250 ml). After stirring at room temperature for 30 min, the solution became warm, and the disaccharide began to dissolve. After ~1.5 h, a crystalline, solid mass of octa-*O*-acetyl-β-cellobiose had precipitated. To this crystalline mass was added dichloromethane (400 ml), and the resulting solution was cooled in an ice bath, and 45% hydrogen bromide in glacial acetic acid (400 ml) was slowly added with stirring. When the addition was complete, the solution was stirred for 1 h at room temperature and then diluted with dichloromethane (250 ml). The mixture was then washed successively with water, aqueous sodium hydrogencarbonate, and water (1 l). The dichloromethane solution was dried (magnesium sulphate) and evaporated (bath 40°) to give hepta-*O*-acetyl-α-cellobiosyl bromide, which was not characterised, but immediately dissolved in benzyl alcohol (500 ml) containing dry mercuric acetate (70 g). The mixture was then heated with stirring for 2 h at 95°, and then poured into ethanol (3.5 l). The resulting white, crystalline, benzyl glycoside hepta-acetate was filtered off, dried as much as possible on a Buchner funnel, and the suspended in a solution prepared from sodium (2 g) in methanol (1 l). The mixture was stirred for 24–36 h at room temperature or until t.l.c. (2:1 ethyl acetate–methanol) indicated complete deacylation. Neutralisation with an excess of Amberlite IR-120($H^+$) resin, followed by decolourisation with charcoal and evaporation to dryness, gave benzyl β-cellobioside (**2a**, 65 g, 50%), m.p. 192.5–193° (from methanol–ether), $[\alpha]_D$ −37° (*c* 1, water). Lit.[12] m.p. 187°, $[\alpha]_D$ −36° (water).

*Benzyl 4-O-(4,6-O-benzylidene-β-D-glucopyranosyl)-β-D-glucopyranoside* (**3a**). — Benzyl β-cellobioside **2a** (80 g) was thoroughly dried and dissolved in benzaldehyde (800 ml); crushed zinc chloride (100 g) was added, and the mixture was stirred for 20 h at room temperature. The mixture was then poured slowly into a mixture of ice–water (3 l) and light petroleum (500 ml). Vigorous stirring of the mixture for 2 h gave a sticky white solid that was filtered off and washed successively with water (10 l), light petroleum (6 l), and ether (1 l). After drying *in vacuo* over $P_4O_{10}$ for 2 days at 60° the benzylidene acetal **3a** was obtained as a white powder (70 g, 73%) suitable for subsequent reactions. Precipitation of a small sample from ethanol with light petroleum gave a pure sample having m.p. 192–192.5°, $[\alpha]_D$ −46° (*c* 1, methanol). Lit.[13] m.p. 191°, $[\alpha]_D$ −47°.

*Benzyl 2,3,6-tri-O-benzoyl-4-O-(2,3-di-O-benzoyl-4,6-O-benzylidene-β-D-glucopyranosyl)-β-D-glucopyranoside* (**3b**). — The 4′,6′-benzylidene acetal **3a** (70 g) was dissolved in anhydrous pyridine (400 ml) and benzoyl chloride (85 ml) was added dropwise during 30 min. After stirring for 16 h at room temperature, the crude pentabenzoate (110 g, 78%) was isolated by precipitation with water and was suitable for subsequent steps. An analytical sample had m.p. 229–231° (from dichloro-

methane–ethanol), $[\alpha]_D$ +23° (*c* 1) (Found: C, 70.1; H, 5.2. $C_{61}H_{52}O_{16}$ calc.: C, 70.4; H, 5.0%).

*Benzyl 2,3,6-tri-O-benzoyl-4-O-(2,3-di-O-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranoside* (**2b**). — The crude pentabenzoate **3b** (110 g) was dissolved in boiling dichloromethane (600 ml), and methanol (800 ml), containing conc. hydrochloric acid (20 ml), was added. The solution was heated for 2 h under reflux, whereupon more acid (10 ml) was added and the reaction was continued until t.l.c. (4:1 chloroform–ethyl acetate) showed little or no starting material. (5–6 h more). The mixture was then cooled, neutralised (barium carbonate), and evaporated to a solid (100 g, 90%) that was dried *in vacuo* for 3 days. Recrystallisation from ethanol gave the 4′,6′-diol, m.p. 199.5–201.5°, $[\alpha]_D$ +45.5° (*c* 1.2) (Found: C, 68.0; H, 5.3. $C_{54}H_{48}O_{16}$ calc.: C, 68.05; H, 5.05%).

*Benzyl 2,3,6-tri-O-benzoyl-4-O-(2,3-di-O-benzoyl-4,6-di-O-mesyl-β-D-glucopyranosyl)-β-D-glucopyranoside* (**4b**). — A solution of the crude, but dry, 4′,6′-diol **2b** (100 g) in anhydrous pyridine (450 ml), was cooled in an ice-bath, and mesyl chloride (30 ml) was added dropwise. The solution was stored for 48 h at 0° or until t.l.c. (4:1 chloroform–ethyl acetate) indicated complete reaction. The mixture was then carefully poured into vigorously stirred ice–water and the resulting white precipitate was filtered off, washed well with water and ethanol, and then recrystallised twice from acetone–ethanol to give the 4′,6′-dimesylate as needles (85 g, 73%), m.p. 204–205°, $[\alpha]_D$ +57.5° (*c* 1) (Found: C, 60.5; H, 4.5. $C_{56}H_{52}O_{20}S_2$ calc.: C, 60.65; H, 4.7%).

*Benzyl 4-O-(6-azido-2,3-di-O-benzoyl-6-deoxy-4-O-mesyl-β-D-glucopyranosyl)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside* (**5b**). — The 4′,6′-dimesylate **4b** (5 g) was dissolved in anhydrous hexamethylphosphoric triamide (15 ml), and heated at 80° with sodium azide (5 g). When t.l.c. (2:1 cyclohexane–ethyl acetate) showed a single product to be present (~1 h), the mixture was poured into ice–water, and the resulting white precipitate was filtered off and washed with water. Two recrystallisations from acetone–ethanol gave the 6′-azido-4′-mesylate as fine needles (3.7 g, 81%), m.p. 204.5–205.5°, $[\alpha]_D$ +62° (*c* 1) (Found: C, 62.4; H, 4.8; N, 4.3. $C_{55}H_{49}N_3O_{17}S$ calc.: C, 62.55; H, 4.65; N, 4.0%).

*Benzyl 4-O-(6-azido-2,3,4-tri-O-benzoyl-6-deoxy-β-D-galactopyranosyl)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside* (**18b**). — The 6′-azido-4′-mesylate **5b** (10 g) was dissolved in anhydrous hexamethylphosphoric triamide (25 ml), sodium benzoate (5 g) was added, and the mixture was heated for 6 days at 80° whereupon t.l.c. (2:1 cyclohexane–ethyl acetate) showed the reaction to be virtually complete. The mixture was poured into ice–water and the resulting precipitate filtered off, washed with water and ethanol and decolourised with charcoal in acetone. The 6′-azido-lactoside was obtained as a foam (6.4 g, 62%), $[\alpha]_D$ +46.5° (*c* 1.1) (Found: C, 67.4; H, 4.8; N, 4.0. $C_{61}H_{51}N_3O_{16}$ calc.: C, 67.7; H, 4.7; N, 3.9%).

*4-O-(6-Amino-6-deoxy-β-D-galactopyranosyl)-D-glucopyranose hydrochloride (6′-amino-6′-deoxy-lactose hydrochloride)* (**10a**). — The 6′-azide **18b** (6 g) was dissolved

in a small volume of dichloromethane and 0.15M methanolic sodium methoxide (60 ml) added. The mixture was stirred for 2 days at room temperature and then neutralised [Amberlite IR-120($H^+$)], filtered, and the solution evaporated in the presence of silica gel. The resulting solid was chromatographed on a dry-packed column in the usual way[23], using initially light petroleum to remove methyl benzoate, and then 5:1 chloroform–methanol to elute the 6′-azido-lactoside **18a**, which was obtained as a clear syrup (2.1 g, 83%). A solution of this product (1 g) in 1% methanolic hydrogen chloride was hydrogenated over 5% palladium-on-charcoal at 50 lb.in$^{-2}$ for 17 h, whereupon t.l.c. (4:3:4 acetic acid–water–ethyl acetate), showed complete conversion into a slower-moving product. The mixture was filtered through Hyflo-Supercel, carefully concentrated to low volume, diluted with water (20 ml), concentrated again, and again diluted with water. This aqueous solution was then neutralised with methyldioctylamine (10% in chloroform). The aqueous phase, which gave positive tests with aniline hydrogen phthalate and ninhydrin spray-reagents, was evaporated to a hygroscopic glass of the 6′-amino-lactose hydrochloride, (0.63 g, 73%), $[\alpha]_D$ +43 (4 min) → +41° (24 h) (*c* 0.9, water) (Found: C, 37.3; H, 6.3; N, 3.6. $C_{12}H_{24}ClNO_{10}$ calc.: C, 38.15; H, 6.35; N, 3.7%).

*4-O-(6-Acetamido-2,3,4-tri-O-acetyl-6-deoxy-β-D-galactopyranosyl) 1,2,3,6-tetra-O-acetyl-α,β-D-glucopyranose* (**11c**). — The 6′-amine hydrochloride **10a** (0.4 g) was slowly added to a boiling solution of sodium acetate (0.8 g) in acetic anhydride (10 ml), and after a further 15 min at reflux, t.l.c. (15:1 chloroform–methanol) showed two products. The mixture was processed conventionally after 1 h, after no further change in composition had occurred. The resulting mixture was fractionated by dry-packed column chromatography[23], with 1:1 chloroform–ethyl acetate as eluant. The more-mobile component was not characterised, but was obtained as a powder from 2-propanol–light petroleum, m.p. 82–88°, $[\alpha]_D$ +47° (*c* 0.6) (Found: C, 49.85; H, 6.0; N, 2.3%). The 100-MHz $^1$H n.m.r. ($CDCl_3$) suggested that the compound was an anomeric mixture of α- and β-1-acetates because of the two low-field doublets at τ 3.75 ($J_{1,2}$ 4 Hz) and τ 4.2 ($J_{1,2}$ 8 Hz), but the spectrum did not show the presence of an acetamido-N–*H* resonance.

The slower-moving product was obtained as a fine powder from 2-propanol–light petroleum and shown by $^1$H n.m.r. to be the required acetamido hepta-acetate as a mixture of anomers, m.p. 103–107°, $[\alpha]_D$ +11° (*c* 0.8) (Found: C, 49.6; H, 6.0; N, 2.2. $C_{28}H_{39}NO_{18}$ calc.: C, 49.6; H, 5.75; N, 2.1%).

*Benzyl 4-O-(4,6-diazido-2,3-di-O-benzoyl-4,6-dideoxy-β-D-galactopyranosyl)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside* (**21b**). — A solution of the 4′,6′-dimesylate **4b** (10 g) in anhydrous hexamethylphosphoric triamide (25 ml) was mixed with sodium azide (10 g) and heated at 80° until t.l.c. (2:1 cyclohexane–ethyl acetate) showed complete conversion into a single product migrating faster than the intermediary 6′-azide **5b** (36–48 h). The mixture was poured into stirred ice–water and the resulting tan-coloured precipitate was filtered off, washed with water and ethanol, decolourised with charcoal in acetone, and recrystallised from acetone–ethanol giving the 4′,6′-diazide as fine needles, (7.0 g, 78%). One further recrystal-

lisation gave the analytical sample, m.p. 212–214°, $[\alpha]_D$ −25° (*c* ,1) (Found: C, 64.3; H, 4.8; N, 8.5. $C_{54}H_{46}N_6O_{14}$ calc.: C, 64.7; H, 4.6; N, 8.4%).

*Benzyl 4-O-(4,6-diazido-4,6-dideoxy-β-D-galactopyranosyl)-β-D-glucopyranoside* (**21a**). — The 4′,6′-diazido pentabenzoate **21b** (6 g) was dissolved in a small volume of dichloromethane and treated with a 0.01M sodium methoxide in methanol (50 ml). The solution was stirred for 2 days at room temperature, neutralised [Amberlite IR-120($H^+$)], filtered, and evaporated to a syrup. Several extractions of the syrup with boiling light petroleum, to remove methyl benzoate, gave a crystalline solid. Two recrystallisations from ethanol–light petroleum gave the 4′,6′-diazide as small needles, (2 g, 70%), m.p. 190–191.5°, $[\alpha]_D$ −62° (*c* 0.8, methanol) (Found: C, 47.3; H, 5.7; N, 17.4. $C_{19}H_{26}N_6O_9$ calc.: C, 47.3; H, 5.4; N, 17.4%).

*4-O-(4,6-Diamino-4,6-dideoxy-β-D-galactopyranosyl)-D-glucopyranose dihydrochloride* (*4′,6′-diamino-4′,6′-dideoxy-lactose dihydrochloride*, **14a**). — The 4′,6′-diazide **21a** (0.7 g) was dissolved in 1% methanolic hydrogen chloride (50 ml) and hydrogenated over 5% palladium-on charcoal at 50 lb.in$^{-2}$. After 5 h, the catalyst was replaced by another batch, and more hydrochloric acid (0.5 ml) was added. Hydrogenation was continued at 50 lb.in$^{-2}$ for 15 h, when t.l.c. (4:3:4 acetic acid–water–ethyl acetate) indicated complete conversion into a slower-moving product. The solution was then filtered through Hyflo-Supercel, carefully concentrated to low volume, diluted with water (20 ml), again concentrated, and again diluted with water. Finally this solution was concentrated to about 10 ml and conc. hydrochloric acid and ethanol were added. Storage at 0° for several days gave the crystalline dihydrochloride as a dihydrate (0.425 g, 71%), m.p. 110–118° (decomp.), $[\alpha]_D$ +30 (3 min) → +36° (27 h) (*c* 1.1, water) (Found: C, 32.2; H, 6.6; Cl, 15.7; N, 5.9. $C_{12}H_{26}Cl_2N_2O_9 \cdot 2H_2O$ calc.: C, 32.05; H, 6.7; Cl, 15.8; N, 6.2%).

The i.r. spectrum showed a band at 1690 cm$^{-1}$ indicative of hydration*. The disaccharide also gave positive aniline hydrogen phthalate and ninhydrin spray-tests for a reducing amino sugar.

*4-O-(4,6-Diacetamido-2,3-di-O-acetyl-4,6-dideoxy-β-D-galactopyranosyl)-1,2,3,6-tetra-O-acetyl-β-D-glucopyranose* (**15c**). — The 4′,6′-diamine dihydrochloride **14a** (0.125 g) was slowly added to a boiling solution of sodium acetate (0.2 g) in acetic anhydride (3 ml), and when the addition was complete the solution was heated at reflux. After 30 min, when t.l.c. (15:1 chloroform–methanol) showed reaction to be complete, the mixture was processed and purified by dry-packed column chromatography[23], eluting with 40:1 chloroform–methanol to give a syrup that separated from 2-propanol–light petroleum as a powder, m.p. 127–132°, $[\alpha]_D$ −10.4° (*c* 0.2) (Found: C, 49.5; H, 5.7; N, 4.25. $C_{28}H_{40}N_2O_{17}$ calc.: C, 49.7; H, 5.9; N, 4.15%).

*Benzyl 2,3,6-tri-O-benzoyl-4-O-(2,3,6-tri-O-benzoyl-4-O-mesyl-β-D-glucopyranosyl)-β-D-glucopyranoside* (**6b**). — The 4′,6′-dimesylate **4b** (11 g) was dissolved

*The position of this band, although it seems to be outside the normal limits for the presence of water of crystallisation (1615–1640 cm$^{-1}$), is in close agreement with an absorption band found for the dihydrate of α,α-trehalose, at 1690 cm$^{-1}$, which is not present in the spectrum of anhydrous α,α-trehalose).

in anhydrous hexamethylphosphoric triamide (30 ml), sodium benzoate (2.5 g) was added, and the mixture was heated for 2 h at 80°, when t.l.c. (1:1 cyclohexane–ethyl acetate) showed the presence of a single product. The mixture was poured into stirred ice–water, and the resulting white solid filtered off and washed with water. The product was difficult to crystallise, but the 4′-mesylate was eventually obtained as large, angular crystals (8.3 g, 74%), by dissolving it in dichloromethane and adding light petroleum gradually during the course of a week. A further recrystallisation gave an analytical sample, m.p. 195.5–197.5°, $[\alpha]_D$ +38° (*c* 0.8) (Found: C, 65.7; H, 5.0. $C_{62}H_{54}O_{19}S$ calc.: C, 65.6; H, 4.8%).

*Benzyl 4-O-(4-azido-2,3,6-tri-O-benzoyl-4-deoxy-β-D-galactopyranosyl)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside* (**24b**). — To a solution of the 4′-mesylate **6b** (8 g) in anhydrous hexamethylphosphoric triamide (20 ml) was added sodium azide (8 g), and the mixture was then heated for 20 h at 80°, when t.l.c. (2:1 cyclohexane–ethyl acetate) showed that the displacement was complete. The mixture was poured into stirred ice–water and the resulting precipitate filtered off, washed with water and ethanol; decolourised with charcoal in acetone, and recrystallised from acetone–ethanol to give white needles (6.5 g, 85%). A second recrystallisation gave an analytical sample of the 4′-azide m.p. 199–201°, $[\alpha]_D$ −20° (*c* 0.5) (Found: C, 67.65; H, 4.6; N, 4.2. $C_{61}H_{51}N_3O_{16}$ calc.: C, 67.7; H, 4.7; N, 3.9%).

*Benzyl 4-O-(4-azido-4-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside* (**24a**). — The monoazide **24b** (6 g) was dissolved in a small volume of dichloromethane and mixed with 0.15M methanolic sodium methoxide (60 ml). After stirring for 2 days at room temperature, the mixture was neutralised [Amberlite IR-120($H^+$)], filtered, and evaporated to a syrup that was extracted several times with boiling light petroleum to remove methyl benzoate. Crystallisation from methanol–dichloromethane gave the microcrystalline 4′-azido-lactoside (1.5 g, 60%), m.p. 277–279°, $[\alpha]_D$ −60° (*c* 0.5, methanol) (Found: C, 49.7; H, 6.0; N, 9.0. $C_{19}H_{27}N_3O_{10}$ calc.: C, 49.9; H, 5.9; N, 9.2%).

*4-O-(4-Amino-4-deoxy-β-D-galactopyranosyl)-D-glucopyranose hydrochloride (4′-amino-4′-deoxy-lactose hydrochloride*, **12a**), — The monoazide **24a** (1 g) was dissolved in 1% methanolic hydrogen chloride (60 ml) and hydrogenated over 5% palladium-on-charcoal at 50 lb.in$^{-2}$. After 4.5 h, the catalyst was replaced by another batch and hydrochloric acid (0.5 ml) was added. The hydrogenation was continued at 50 lb.in$^{-2}$ for 15 h, when t.l.c. (4:3:4 acetic acid–water–ethyl acetate) indicated completion. The catalyst was filtered off through Hyflo-Supercel and the yellow filtrate carefully concentrated to low volume. The solution was diluted with water (20 ml), again concentrated to low volume, and again diluted with water. This solution was neutralised with methyldioctylamine (10% in chloroform), and the resulting aqueous phase, which gave positive tests with aniline hydrogen phthalate and ninhydrin spray-reagents, was evaporated to an oil that gave the *4′-amine hydrochloride* as a hygroscopic foam (0.52 g, 63%) when evaporated from methanolic solution, $[\alpha]_D$ +21° (48 h) (*c* 1, water). A satisfactory analysis could not be obtained for this compound, probably because it was hygroscopic.

*4-O-(4-Acetamido-2,3,6-tri-O-acetyl-β-D-galactopyranosyl)-1,2,3,6-tetra-O-*

*acetyl-α,β-D-glucopyranose* (**13c**).— The thoroughly dried 4′-amine hydrochloride **12a** (0.3 g) was quickly added to a boiling solution of sodium acetate (0.25 g) in acetic anhydride (5 ml). When the addition was complete, the solution was gently boiled for 15 min, when t.l.c. (15:1 chloroform–methanol) showed the reaction to be complete. The mixture was processed and then purified by dry-packed column chromatography[23], eluting with 1:1 chloroform–ethyl acetate. The eluate was evaporated to a clear syrup (0.25 g, 46%) that gave the required *hepta-acetate* as a white powder from 2-propanol–light petroleum, m.p. 112–117°, $[\alpha]_D$ +5° (*c* 0.6) (Found: C, 49.5; H, 6.0; N, 1.9. $C_{28}H_{39}NO_{18}$ calc., C, 49.6; H, 5.8; N, 2.05%).

*Benzyl 2,3,6-tri-O-benzoyl-4-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-β-D-glucopyranoside* (**17b**). — The 4′,6′-dimesylate **4b** (5 g) was dissolved in anhydrous hexamethylphosphoric triamide, sodium benzoate (5 g) was added, and the mixture was heated for 8 days at 80°, at which time t.l.c. (1:1 cyclohexane–ethyl acetate) showed only one product. The mixture was poured into ice–water and the flocculent precipitate was filtered off and washed with water and light petroleum. The resulting grey solid was decolourised with charcoal in dichloromethane and evaporated to a foam that gave the *heptabenzoate* as a white powder from 2-propanol (2.5 g, 48%), m.p. 100–106°, $[\alpha]_D$ +33° (*c* 0.9) (Found, C, 70.2; H, 4.7. $C_{68}H_{56}O_{18}$ calc., C, 70.3; H, 4.8%).

*Benzyl 4-O-(β-D-galactopyranosyl)-β-D-glucopyranoside* (*benzyl β-lactoside*, **17a**). — The heptabenzoate **17b** (2 g) was de-esterified in the conventional way and the lactoside was obtained as an amorphous solid (0.35 g, 46%) from ethanol, m.p. 195–199.5°, $[\alpha]_D$ −17° (*c* 0.8, water) (Found, C, 52.5; H, 6.7. $C_{19}H_{28}O_{11}$ calc., C, 52.8; H, 6.5%). Lit.[24] m.p. 180°, $[\alpha]_D$ −18° (*c* 1.3, water) for the monohydrate.

*4-O-(β-D-Galactopyranosyl)-β-D-glucopyranose* (*β-lactose*, **9a**). — The lactoside **17a** (0.2 g) was dissolved in 1% methanolic hydrogen chloride (50 ml) and hydrogenated over 5% palladium-on-charcoal at 50 lb.in$^{-2}$. After 17 h, the mixture was diluted with water (25 ml) to dissolve the white precipitate that had formed, neutralised (barium carbonate), and filtered through Hyflo-Supercel. T.l.c. (2:1:3 acetic acid–water–ethyl acetate) of the filtrate showed a single product identical with authentic lactose. The filtrate was evaporated to a white solid that was recrystallised twice from aqueous methanol to give *β*-lactose (0.055 g, 35%) as small, triangular crystals, m.p. 223–226°, $[\alpha]_D$ +37 (5 min) → +54.5° (20 h) (*c* 0.6, water) (Found: C, 42.3; H, 6.55. $C_{12}H_{22}O_{11}$ calc.: C, 42.1; H, 6.4%). Lit.[25] m.p. 252°, $[\alpha]_D$ +35 → +55° ($H_2O$).

Attempts to crystallise authentic lactose from aqueous methanol so as to obtain a sample having the same physical constants as those of the foregoing synthetic lactose failed.

Hydrolysis of a small portion (10 mg) with boiling M sulphuric acid (1 ml) for 1.5 h gave only glucose and galactose, as indicated by paper chromatography on Whatman No. 1 filter paper, using 5:5:3:1 pyridine–ethyl acetate–acetic acid–water, with 11:40:6 pyridine–ethyl acetate–water in the bottom of the tank.

The *β*-octa-acetate **9c** was prepared in the usual way with a boiling solution of

sodium acetate in acetic anhydride, m.p. 87–89° (from chloroform–ethanol), $[\alpha]_D$ −4° (*c* 0.3) (Found: C, 49.7; H, 5.9. $C_{28}H_{38}O_{19}$ calc.: C, 49.6; H, 5.6%). Lit.[26] m.p. 90°, $[\alpha]_D$ −4.5° (*c* 0.8).

*Treatment of the 4′,6′-diol* **2b** *with sulphuryl chloride.* — (*a*) A solution of the dried 4′,6′-diol **2b** (3 g) in anhydrous pyridine (45 ml) was cooled to −5° in an ice–salt bath, and sulphuryl chloride (1.5 ml) was slowly added. The mixture was maintained for 2.5 h at −5° when t.l.c. (8:1 chloroform–ethyl acetate) showed a single product to be present. The mixture was poured into stirred ice–water and after 2 h the resulting yellow precipitate was filtered off. A solution of the crude product in chloroform was applied to the top of a dry column of silica gel, and eluted with chloroform; the carbohydrate fractions were combined and evaporated to a pale-yellow syrup. Attempted crystallisation from ethanol–dichloromethane gave a gelatinous mass which, after filtration, dried to a white powder of benzyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3-di-*O*-benzoyl-6-chloro-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (**7b**), (1.3 g, 43%), m.p. 95–100°, $[\alpha]_D$ +37° (*c* 0.5) (Found: C, 66.4; H, 5.0; Cl, 3.7. $C_{54}H_{47}ClO_{15}$ calc.: C, 66.8; H, 4.8; Cl, 3.7%).

Benzoylation of **7b** with benzoyl chloride–pyridine gave the 6-chloro hexabenzoate **8b** (91%), m.p. 253–255° (crystal transition at 228–230°) (from dichloromethane–ethanol), $[\alpha]_D$ −6° (*c* 0.15) (Found: C, 68.0; H, 4.9; Cl, 3.4. $C_{61}H_{51}ClO_{16}$ calc.: C, 68.1; H, 4.75; Cl, 3.3%).

(*b*) A solution of the dried 4′,6′-diol **2b** (20 g) in anhydrous pyridine (200 ml) was stirred at −35° in an acetone–solid carbon dioxide bath and sulphuryl chloride (35 ml) was slowly added. When the addition was complete, the reaction was allowed to warm up slowly to room temperature. After 2 h, t.l.c. (chloroform) showed a single product, migrating as the monochloride **7b**. However, after 20 h, t.l.c. (chloroform) showed two products, neither of which was identical to the 6′-chloride **7b**. The black, viscous mixture was processed by diluting with chloroform (500 ml), and filtering through a pad of silica gel and Hyflo-Supercel, which was subsequently washed well with chloroform. The combined filtrate and washings were evaporated to a red syrup, which was freed from traces of pyridine by evaporation from toluene and then from carbon tetrachloride. The resulting syrup crystallised slowly on addition of ethanol to give an almost pure sample (8.6 g, 41%) of the slower-moving, major product. Recrystallisation from ethanol–dichloromethane gave benzyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3-di-*O*-benzoyl-4,6-dichloro-4,6-dideoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (**27b**), m.p. 222–223°, $[\alpha]_D$ +52° (*c* 0.8) (Found: C, 65,6; H, 4.6; Cl, 7.0. $C_{54}H_{46}Cl_2O_{14}$ calc.: C, 65.5; H, 4.65; Cl, 7.2%).

The filtrate from the foregoing initial crystallisation was evaporated to dryness and fractionated by dry-packed column chromatography[23] on silica gel using 1:1 chloroform–light petroleum as eluant. This gave 0.9 g (4.3%) of the faster-moving, minor component, namely benzyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,4-di-*O*-benzoyl-3,6-dichloro-3,6-dideoxy-β-D-gulopyranosyl)-β-D-glucopyranoside (**28**) as an amorphous solid, m.p. 90–100°, $[\alpha]_D$ −5° (*c* 1) (Found: C, 65.4; H, 4.7; Cl, 7.4. $C_{54}H_{46}Cl_2O_{14}$

calc.: C, 65.5; H, 4.65; Cl, 7.2%). Further elution of the column afforded an additional 2 g (9.5%) of the 4',6'-dichloride **27b**.

*Benzyl 2,3,6-tri-O-benzoyl-4-O-(2,3-di-O-benzoyl-4,6-dichloro-4,6-dideoxy-β-D-galactopyranosyl)-β-D-glucopyranoside* (**27b**). — The 4',6'-dimesylate **4b** (0.5 g) was dissolved in anhydrous hexamethylphosphoric triamide, lithium chloride (0.5 g) was added, and the mixture was stirred for 5 days at 85°, when t.l.c. (2:1 cyclohexane–ethyl acetate) showed almost complete conversion into the required product. On pouring into ice–water, a white precipitate was obtained that was recrystallised from ethanol–dichloromethane giving the crude 4',6'-dichloride (0.38 g 85%), contaminated with impurities that were not removed by further recrystallisation. Dry-packed column chromatography[23] with 4:1 cyclohexane–ethyl acetate as eluant afforded, after two recrystallisations, the chromatographically pure 4',6'-dichloride, m.p. 223–225°, $[\alpha]_D$ +49° (*c* 0.7). The mixed m.p. and i.r. spectrum were identical with the major dichloride obtained as already described by the action of sulphuryl chloride on the diol **2b**.

*Benzyl 4-O-(4,6-dichloro-4,6-dideoxy-β-D-galactopyranosyl)-β-D-glucopyranoside* (**27a**). — The pentabenzoate **27b** (4 g) was cautiously debenzoylated with catalytic quantities of sodium methoxide in methanol. When reaction was complete (t.l.c.), the mixture was processed to give a syrup composed of two products, as shown by t.l.c. (6:1 chloroform–methanol); the slower-moving component was estimated to be present to the extent of 85%. Fractionation of the mixture by dry-packed column chromatography using 12:1 chloroform–methanol as eluant gave the major product, the required *dichloride*, as an amorphous solid (1.2 g, 63%), $[\alpha]_D$ −5° (*c* 0.8, water) (Found: C, 48.6; H, 5.5; Cl, 15.1. $C_{19}H_{26}Cl_2O_9$ requires C, 48.6; H, 5.55; Cl, 15.15%).

The minor product was obtained as a syrup that was not characterised.

*4-O-(4,6-Dichloro-4,6-dideoxy-β-D-galactopyranosyl)-D-glucopyranose* (*4',6'-dichloro-4',6'-dideoxy-lactose*, **16a**). — The dichloro-lactoside **27a** (0.5 g) was dissolved in 1% methanolic hydrogen chloride (50 ml) and hydrogenated over 5% palladium-on-charcoal at 50 lb.in$^{-2}$. After 3 h, t.l.c. (6:1 chloroform–methanol) showed the reaction to be complete, and the catalyst was filtered off through Hyflo-Supercel. The pale-yellow filtrate was carefully concentrated to low volume, and then diluted with water (20 ml), again concentrated, and again diluted with water. This solution was neutralised with methyldioctylamine (10% in chloroform). The neutralised, aqueous phase was decolourised with charcoal and evaporated to a clear glass of the *dichloro-lactose* (0.39 g, 81%), $[\alpha]_D$ +63 (5 min) → +59° (48 h) (*c* 0.8, water) (Found: C, 37.7; H, 6.0. $C_{12}H_{20}Cl_2O_9$ calc.: C, 38.0; H, 5.3%).

Hydrolysis of a small sample with boiling M sulphuric acid (2 ml) for 17 h and examination of the neutralised (lead carbonate) hydrolysate by paper chromatography with 40:11:19 1-butanol–ethanol–water, indicated that glucose and 4,6-dichloro-4,6-dideoxy-D-galactose* had been formed as the only two products.

*Prepared by hydrolysis of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside[27] under similar conditions to the foregoing.

A mixture (**16c**) of the α- and β-hexa-acetate was prepared in the usual way by using sodium acetate–acetic anhydride, and the product was isolated by precipitation with water. The resulting white, amorphous solid could not be crystallised, but gave the mixed *hexa-acetates* as a white powder from aqueous ethanol (0.18 g, 72%), m.p. 140–147°, $[\alpha]_D$ +34° (*c* 0.7) (Found: C, 45.6; H, 5.5; Cl, 11.3. $C_{24}H_{32}Cl_2O_{15}$ requires C, 45.6; H, 5.1; Cl, 11.3%).

*Reaction of benzyl 2,3,6-tri-O-benzoyl-4-O-(2,3-di-O-benzoyl-4,6-dichloro-4,6-dideoxy-β-D-galactopyranosyl)-β-D-glucopyranoside* (**27b**) *with sodium azide in hexamethylphosphoric triamide.* — A solution of the 4′,6′-dichloride **27b** (1 g) in anhydrous hexamethylphosphoric triamide (6 ml) containing sodium azide (1 g) was heated at 85°. After 2 days, t.l.c. (2:1 cyclohexane–ethyl acetate) showed two components, of which the faster-moving and the same mobility as the starting material. After a further 24 h, no change in the composition of this mixture was noted, and it was poured into stirred ice–water. The resulting brown solid was filtered off, air-dried on a Büchner funnel, and chromatographed on a dry-packed column[23] of silica gel, with 3:1 cyclohexane–ethyl acetate as eluant.

The first fraction eluted was evaporated to a syrup that crystallised on the addition of light petroleum. After decolourisation with charcoal in chloroform, it was recrystallised from chloroform–light petroleum to give benzyl 4-*O*-(6-azido-2,3-di-*O*-benzoyl-4,6-dideoxy-α-L-*threo*-hex-4-enopyranosyl)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**29**) (0.255 g, 26%), m.p. 167–173°, $[\alpha]_D$ +25° (*c* 0.9) (Found: C, 67.5; H, 4.6; N, 4.3. $C_{54}H_{45}N_3O_{14}$ requires C, 67.55; H, 4.7; N, 4.4%).

The second fraction was evaporated to a syrup that also crystallised on the addition of light petroleum. After decolourisation with charcoal in chloroform, it was recrystallised from chloroform–light petroleum to give *benzyl 2,3,6-tri-O-benzoyl-β-D-glucopyranoside* (**31**) (0.16 g, 27%), m.p. 145.5–147.5°, $[\alpha]_D$ +34° (*c* 0.9) (Found: C, 70.4; H, 5.0. $C_{34}H_{30}O_9$ requires C, 70.1; H, 5.15%).

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