Koenigs–Knorr Reactions. Part 3.[1] Mechanistic Study of Mercury(II) Cyanide Promoted Reactions of 2-*O*-Acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in Benzene–Nitromethane

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The kinetics and products of reactions of 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide (I) with cyclohexanol in the presence of $Hg(CN)_2$ in nitromethane–benzene (1 :1 v/v) at 10—25 °C were investigated by polarimetry, g.l.c., and ^1H n.m.r. The reactions exhibited a first-order kinetic dependence on the glucosyl bromide and $Hg(CN)_2$ concentrations, but the reaction rates were independent of the cyclohexanol concentration. Cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (IV) was the major final product (>90%) in reactions. The initial reaction is believed to involve rate-determining, $Hg(CN)_2$-assisted heterolysis of the carbon–bromine bond to form the glucopyranosyl carboxonium ion. Glucoside formation then results from reaction of the alcohol with the carboxonium ion as the ion pair, the dissociated carboxonium ion, or an intermediate orthoester, 1,2-*O*-(1-cyclohexyloxyethylidene)-3,4,6-tri-*O*-methyl-α-D-glucopyranose (III). The orthoester (III) was shown to selectively form the β-glucoside (IV) under the reaction conditions used. The mole fraction of orthoester (III) in the initial reaction products was always substantially greater than that of cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (V) and increased as the alcohol concentration decreased. Stereoselective formation of the β-glucoside (IV) in the overall reaction of the glucosyl bromide (I) is due to the fact that in those reactions of (I) which do not yield (IV) directly, α-glucoside (V) formation is minimized by preferential formation of the orthoester (III) which selectively forms the β-glucoside (IV).

THE steric course of Koenigs–Knorr reactions involving 1,2-*cis*-glycosyl halides has been found to be greatly influenced by the nature of the C-2 substituent. Reactions of 1,2-*cis*-glycosyl halides having a 2-*O*-acyl substituent generally proceed with a high degree of inversion of configuration at C-1,[2-4] whereas the steric

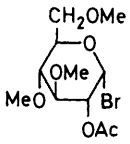
[1] Part 2, J. E. Wallace and L. R. Schroeder, *J.C.S. Perkin II*, 1976, 1632.

[2] W. L. Evans, D. D. Reynolds, and E. A. Talley, *Adv. Carbohydrate Chem.*, 1951, **6**, 27.

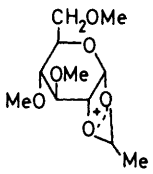
[3] E. A. Talley, *Methods Carbohydrate Chem.*, 1963, **2**, 337.

[4] L. Hough and A. C. Richardson, in ' Rodd's Chemistry of Carbon Compounds,' ed. S. Coffey, Elsevier, Amsterdam, 1967, 2nd edn., vol. I, part F, p. 327.

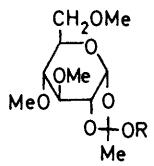
nature of the glycosidic products of the reactions of 1,2-*cis*-glycosyl halides having a 'non-participating' C-2 substituent is extremely variable.[5-7] In a previous study,[8] it was found that reactions of 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide (I) with cyclohexanol utilizing various promoters and alcohol concentrations selectively formed the 1,2-*trans*-glucoside. In contrast, similar reactions of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl bromide were less selective, and the selectivity was very dependent on the alcohol concentration and on the promoter employed.



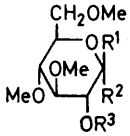
(I)



(II)



(III) R = C_6H_{11}
(X) R = Et



(IV) $R^1 = OC_6H_{11}, R^2 = H, R^3 = Ac$
(V) $R^1 = H, R^2 = OC_6H_{11}, R^3 = Ac$
(VI) $R^1 = OC_6H_{11}, R^2 = H, R^3 = H$
(VII) $R^1 = H, R^2 = OC_6H_{11}, R^3 = H$
(VIII) $R^1 = H, R^2 = OAc, R^3 = H$
(IX) $R^1 = H, R^2 = OH, R^3 = Ac$
(XV) $R^1, R^2 = H, OH, R^3 = H$
(XVII) $R^1 = OEt, R^2 = H, R^3 = COEt$
(XVIII) $R^1 = SPh, R^2 = H, R^3 = Ac$

It has been postulated [4] that the stereoselectivity of *cis*-2-*O*-acetylglycosyl halide [*e.g.* (I)] reactions arises because the acetoxy-group at C-2 participates in the reaction by formation of the cyclic 1,2-acetoxonium ion [*e.g.* (II)] which directs the incoming nucleophile into the 1,2-*trans*-position. However, reaction of an alcohol with the 1,2-acetoxonium ion should result in preferential formation of an orthoester [*e.g.* (III)] rather than the glycoside.[9,10] In a subsequent reaction, provided that the reaction conditions are suitable, the orthoester can selectively form 1,2-*trans*-glycosides.[10,11] Orthoesters have been reported as products in Koenigs–Knorr reactions of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide employing silver salts as promoters,[12,13] but it has not, to our knowledge, been demonstrated that orthoesters can act as important intermediates for glycoside formation in a Koenigs–Knorr reaction employing one of the typical promoters.

In this paper we report the results of a detailed study of the mercury(II) cyanide promoted reaction of 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide (I) with cyclohexanol in benzene–nitromethane (1 : 1 v/v). The mechanism of the reaction, particularly the potential contribution of an orthoester (III) intermediate to the stereochemistry of the reaction, was of interest.

RESULTS AND DISCUSSION

Orthoester Formation.—The average mole fraction of initial reactant accounted for by quantitative g.l.c. analysis of the carbohydrates as a function of time was 1.02 ($\sigma \pm 0.03$).

As illustrated in Figure 1, the initial products of the mercury(II) cyanide-promoted reaction of the glucosyl bromide (I) (RBr) with cyclohexanol (ROH) in benzene–nitromethane (1 : 1 v/v) were primarily cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (IV), cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (V), and 1,2-*O*-(1-cyclohexyloxyethylidene)-3,4,6-tri-*O*-methyl-α-D-glucopyranose (III). The concentration of the orthoester (III) increased as the glycosyl bromide (I) reacted, but when (I) was essentially depleted, the concentration of (III) decreased with a concurrent increase in the concentration of the β-glucoside (IV). Thus, part of the major reaction product, the 2-*O*-acetyl-β-glucoside (IV), was formed from the orthoester (III). The normalized mole fractions * of glucosidic products after the orthoester (III) had reacted completely were: cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (IV), 0.92; cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (V), 0.06; cyclohexyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside (VI), 0.01; and cyclohexyl 3,4,6-tri-*O*-methyl-α-D-glucopyranoside (VII), 0.01.

The data in Figure 1 were obtained by a procedure in which the orthoester (III), unstable to direct g.l.c. analysis, was analysed as its hydrolysis products,† 1-*O*-acetyl- (VIII) and 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranose (IX).[9] To obtain supporting evidence for formation of orthoesters in mercury(II) cyanide promoted reactions of the glucosyl bromide (I) with alcohols, the reactant and intermediate products of (I) with ethanol were isolated *in toto* and analysed by

* The mole fractions of glucosidic products are reported on a normalized basis because some hydrolysis products were always formed despite the extreme care taken to eliminate traces of water from the reaction systems. In this reaction *ca.* 5% of the initial reactants was accounted for as hydrolysis products. The hydrolysis products are believed to originate primarily from the orthoester (III) which will hydrolyse readily and in preference to forming glycosides.[9]

† The analytical procedure permitted differentiation between hydrolysis products formed during the reaction and those formed from the orthoester during analysis.

[5] T. Ishikawa and H. G. Fletcher, *J. Org. Chem.*, 1969, **34**, 563.
[6] C. Schuerch, *Accounts Chem. Res.*, 1973, **6**, 184.
[7] G. Wulff and G. Röhle, *Angew. Chem. Internat. Edn.*, 1974, **13**, 157.
[8] J. E. Wallace and L. R. Schroeder, *J.C.S. Perkin I*, 1976, 1938.
[9] L. R. Schroeder, D. P. Hultman, and D. C. Johnson, *J.C.S. Perkin II*, 1972, 1063.
[10] D. P. Hultman, Doctoral Dissertation, The Institute of Paper Chemistry, Appleton, 1970.
[11] C. A. Dykes, Doctoral Dissertation, The Institute of Paper Chemistry, Appleton, 1975.
[12] G. Wulff, G. Röhle, and U. Schmidt, *Chem. Ber.*, 1972, **105**, 1111.
[13] G. Wulff and G. Röhle, *Chem. Ber.*, 1972, **105**, 1122.

^{1}H n.m.r. (Figure 2). Ethanol was substituted for cyclohexanol because the broad multiplet from cyclohexyl

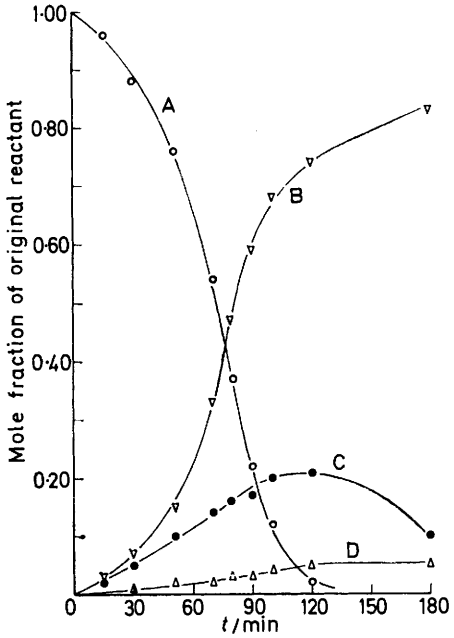


FIGURE 1 Reactant and product analyses for a reaction of the glucosyl bromide (I) (*ca.* 6.2 × 10^{-3}M) at 10 °C and an initial reactant mole ratio of 1 : 1 : 15 [bromide (I)–$Hg(CN)_2$–cyclohexanol]: A, glucosyl bromide (I); B, cyclohexyl 2-*O*-acetyl-β-glucoside (IV); C, orthoester (III); D, cyclohexyl 2-*O*-acetyl-α-glucoside (V). Powdered Drierite was used as a desiccant

ring protons masks the characteristic singlet of the dioxolan 2-methyl group of a 1,2-(alkyl orthoacetate) of D-glucopyranose. The singlet at δ 1.67 ($CDCl_3$) in Figure 2 is indicative of the dioxolan 2-methyl group of

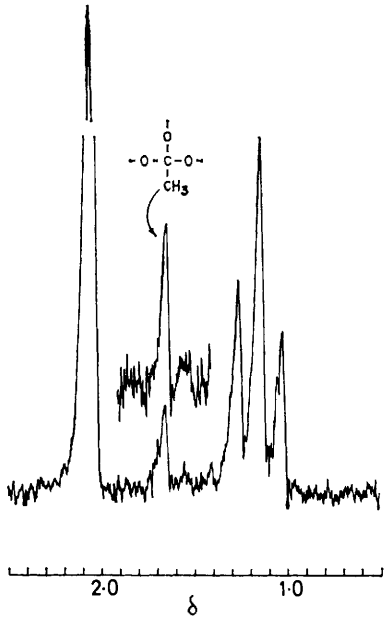


FIGURE 2 Partial n.m.r. spectrum ($CDCl_3$) of the reactant and products isolated from a mercury(II) cyanide-promoted reaction of the glucosyl bromide (I) with ethanol in benzene–nitromethane

1,2-*O*-(1-*exo*-ethoxyethylidene)-3,4,6-tri-*O*-methyl-α-D-glucopyranose (X).[9] Addition of known (X) to the sample increased the amplitude of the singlet while shaking the sample with acidic D_2O rapidly eliminated the singlet.

To determine the amount of orthoester (III) formed in a mercury(II) cyanide promoted reaction of (I) with cyclohexanol, mercury(II) oxide was added to the system to neutralize protic acids produced and thereby decrease the rate of conversion of the orthoester (III) into glycosides. Reactant and product mole fractions as a function of time are shown in Figure 3. In contrast to the unbuffered reaction (Figure 1), the mole fraction of orthoester (III) remained constant after the glucosyl bromide (I) was depleted. In addition, the orthoester (III) constituted *ca.* 45% of the reaction products, thus indicating its importance as an intermediate in glycoside

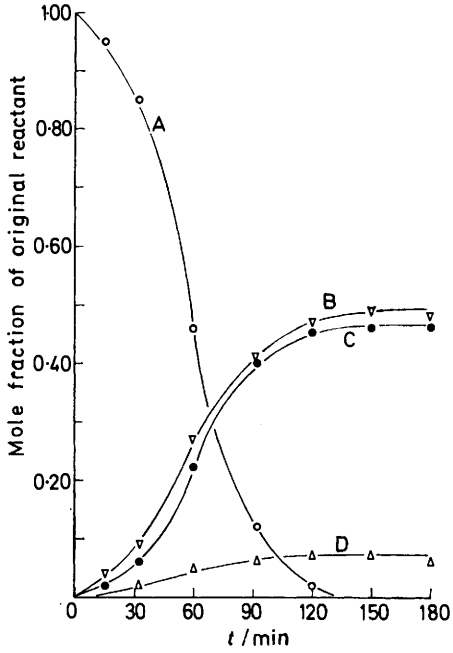


FIGURE 3 Reactant and product analyses for a mercury(II) oxide-buffered reaction of the glucosyl bromide (I) (*ca.* 5.4 × 10^{-3}M) at 10 °C and an initial reactant mole ratio of 1 : 1 : 2 : 15 [bromide (I)–$Hg(CN)_2$–HgO–cyclohexanol]: A, glucosyl bromide (I); B, cyclohexyl 2-*O*-acetyl-β-glucoside (IV); C, orthoester (III); D, cyclohexyl 2-*O*-acetyl-α-glucoside (V). Powdered Drierite was used as a desiccant

formation in the reaction of the glucosyl bromide (I) under these conditions.

The reaction of the orthoester (III) with cyclohexanol in benzene–nitromethane was also studied independently. Both $Hg(CN)_2$ and HBr were added to the system as catalysts. The reaction of (III) using only $Hg(CN)_2$ as a catalyst was extremely slow.[14] Therefore, HBr, which is formed when the glucosyl bromide (I) reacts with an alcohol, was used as a cocatalyst. A reaction of the orthoester (III) (*ca.* 5.0 × 10^{-3}M) at 10 °C and an initial reactant mole ratio of 1 : 1 : 1 : 15 [orthoester (III) : $Hg(CN)_2$: HBr : cyclohexanol] had a half-life of *ca.* 35 min. The normalized mole fractions of glucosidic products

were: cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (IV), 0.89; cyclohexyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside (VI), 0.06; and cyclohexyl 3,4,6-tri-*O*-methyl-α-D-glucopyranoside, 0.05. The product distribution further demonstrates that under the conditions of the glucosyl bromide (I) reactions, the orthoester (III) selectively forms the 2-*O*-acetyl-β-D-glucoside (IV).

Kinetic Analysis.—The initial rates of the glucosyl bromide (I) reactions, $(d[RBr]/dt)_{t=0}$, were determined (method of least squares) from the initial linear portions of plots of the concentration of the glucosyl bromide *versus* time, *e.g.* Figure 4. The concentration of the glucosyl bromide (I) was determined from polarimetric data and equation (1) [14,15] where [RBr] = the concen-

$$[RBr] = [RBr]_0 (\alpha_t - M)(\alpha_0 - M)^{-1} \quad (1)$$

tration of (I) at time t; $[RBr]_0$ = the initial concentration of (I); α_t = the optical rotation of the reaction system at time t; $\alpha_0 = \alpha_t$ at time zero (determined by extrapolation); $M = l(n_a[\alpha_a] + n_b[\alpha_b] + n_c[\alpha_c])M_G - [RBr]_0/1\,000$; l = the polarimeter cell length (dm); M_G = the gram-molecular weight of the anomeric glucosides, (IV) and (V), and the orthoester (III); n_a, n_b, and n_c = the mole fractions of the initial products accounted for by (V), (IV), and (III), respectively; and $[\alpha_a]$, $[\alpha_b]$, and $[\alpha_c]$ = the specific optical rotations of (V), (IV), and (III), respectively, in the reaction system. The values of n_a, n_b, and n_c were obtained by extrapolating the product mole ratios determined by g.l.c. analyses to zero time. The specific optical rotations of (III), (IV), and (V) were determined as a function of temperature in benzene–nitromethane (1 : 1 v/v).[14]

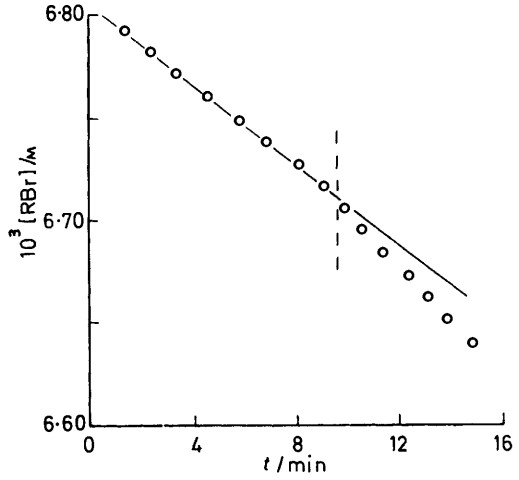


FIGURE 4 Initial reaction rate determination: 10 °C; 2-*O*-acetylglucosyl bromide (I), 5.79×10^{-3}M; $Hg(CN)_2$, 6.10×10^{-3}M. Initial slope = $(d[RBr]/dt)_{t=0} = 1.45 \times 10^{-7}$ mol l^{-1} s^{-1}

The reactions exhibited autocatalysis (*e.g.* Figure 3). As discussed previously [1], some potential catalysts which may be formed in a mercury(II) cyanide promoted reaction of a glycosyl bromide are HgBrCN, $HgBr_2$, HCN, HBr, and H^+. It was demonstrated that $HgBr_2$ is a more effective catalyst for the reaction of (I) under these conditions than $Hg(CN)_2$.[14]

The order of the reaction with respect to each reactant was calculated from initial reaction rates for series of reactions at 10 °C, in which the concentration of only

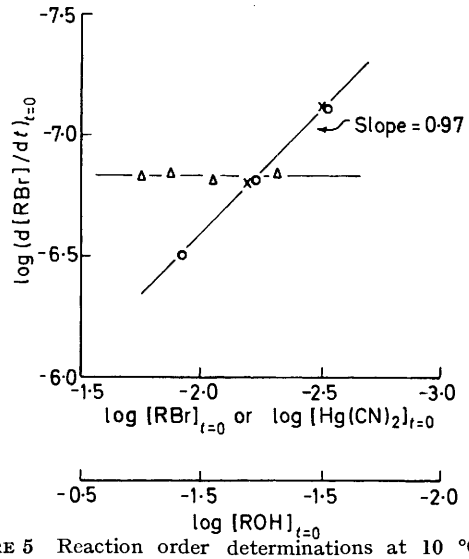


FIGURE 5 Reaction order determinations at 10 °C: ○, glucosyl bromide (I); ×, $Hg(CN)_2$; △, cyclohexanol (ROH)

one reactant was varied at a time. Plots of log $(d[RBr]/dt)_{t=0}$ *versus* log$[RBr]_{t=0}$, log$[Hg(CN)_2]_{t=0}$, and log$[ROH]_{t=0}$ are shown in Figure 5. Experimentally, the order of reaction with respect to both the glucosyl bromide (I) and $Hg(CN)_2$ was *ca.* 1.00. The reaction rate was independent of the cyclohexanol (ROH) concentration. Therefore, the initial rate of the reaction is described by equation (2), analogous to the rate expression determined for mercury(II) cyanide promoted

$$(d[RBr]/dt)_{t=0} = -k[RBr][Hg(CN)_2] \quad (2)$$

reactions of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl bromide (XI).[1]

The fact that the initial reactions of the glucosyl bromide (I) exhibit first-order kinetic dependence on both the glucosyl bromide (I) and $Hg(CN)_2$ concentrations, but are independent of the cyclohexanol concentration indicates, as with analogous reactions of (XI),[1] that the reactions occur by a mechanism in which heterolysis of the carbon–bromine bond is assisted by $Hg(CN)_2$ in the rate-determining step of the reaction. In a subsequent fast reaction the resultant glucopyranosyl carboxonium ion forms either glucosides (IV) or (V) or the orthoester (III). The mechanism by which $Hg(CN)_2$ assists in heterolysis of the carbon–bromine bond of (I) is unknown. However, at least two mechanisms can be envisaged for the reaction. $Hg(CN)_2$ may complex reversibly with the glucosyl bromide. In a unimolecular, rate-determining step the carbonium ion (R^+) would be formed from the complex [equation (3)].

[14] J. E. Wallace, Doctoral Dissertation, The Institute of Paper Chemistry, Appleton, 1975.

[15] L. R. Schroeder, J. W. Green, and D. C. Johnson, *J. Chem. Soc.* (*B*), 1966, 447.

Alternatively, the $Hg(CN)_2$ may assist in bond cleavage through a bimolecular rate-limiting step [equation (4)]. The existence of ions of the type HgX_3^-, as proposed for either mechanism is well established.[16,17]

$$RBr + Hg(CN)_2 \rightleftharpoons RBr{:}\ Hg(CN)_2 \overset{\text{slow}}{\rightleftharpoons} R^+ + BrHg(CN)_2^- \quad (3)$$

$$RBr + Hg(CN)_2 \overset{\text{slow}}{\rightleftharpoons} [R^{\delta+}\cdots Br^{\delta+}\cdots Hg(CN)_2]^{\ddagger}_{\text{Transition state}} \rightleftharpoons R^+ + BrHg(CN)_2^- \quad (4)$$

Initial rate constants for reactions of (I) were calculated from initial rates of reaction according to equation (2). Initial rate constants for several temperatures and the enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation are presented in Table 1. In comparison to analogous mercury(II) cyanide facilitated reactions of its 2-*O*-methyl analogue (XI),[1] the enthalpy of activation (14.5 kcal mol^{-1}) for reactions of the 2-*O*-acetyl glucosyl bromide (I) is *ca.* 5 kcal mol^{-1} greater. The greater energy required for heterolysis of the carbon–bromine bond of (I) relative to (XI) reflects in part the inductive effect of the 2-*O*-acetyl substituent which decreases the electron density at C-1. The entropy of activation (−18.4 cal mol^{-1} K^{-1}) for reactions of (I) is *ca.* 11 cal mol^{-1} K^{-1} greater than $\Delta S^{\ddagger}$ for reactions of (XI).[1] The reason for the greater $\Delta S^{\ddagger}$ for (I) is unknown. However, substituent changes within a series of similar compounds reacting by the same mechanism can effect changes in $\Delta S^{\ddagger}$ of this magnitude.[18]

TABLE 1

Initial rate constants and thermodynamic functions of activation

t/°C	10^3k/ l mol^{-1} s^{-1} [a]	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1} [b]
25	14.1		
20	8.84	14.5	−18.4
15	5.81		
10	3.82		

[a] Average of duplicate determinations. [b] Calculated for 20 °C.

Effect of Reactant Concentrations on the Product Distribution.—The effect of variation in the reactant concentrations on the distributions of the initial and final products of reactions of the glucosyl bromide (I) are summarized in Table 2. The distribution of the final products was essentially independent of variation in any of the reactant concentrations. All of the final product mixtures were similar and contained a high proportion of β-glucoside ($n_\beta \geq 0.93$).

The distribution of initial products was independent of the concentration of the glucosyl bromide (I) and $Hg(CN)_2$. However, the distribution of the initial products was significantly dependent on the concentration of cyclohexanol. As the alcohol concentration was increased, the initial mole fraction of β-glucoside (IV) (n_β) increased while those of the α-glucoside (V) (n_α) and the orthoester (III) (n_{OE}) decreased.

Reaction Mechanism.—The overall mechanism proposed to account for glucoside formation in mercury(II) cyanide promoted reactions of the 2-*O*-acetylglucosyl bromide (I) with cyclohexanol is shown in the Scheme. The rate-determining step in the reaction of (I), heterolysis of the carbon–bromine bond assisted by $Hg(CN)_2$, results in formation of a shielded carbonium ion, probably an ion pair (XII). The ion pair can either react directly with cyclohexanol to form the 2-*O*-acetyl-β-D-glucoside (IV) or it can dissociate to form a free carbonium ion (XIII). The free carbonium ion can react with the alcohol to form the 2-*O*-acetyl-β- (IV) and -α-glucoside (V) or form the 1,2-dioxolenium ion (II) by intramolecular reaction of the 2-acetoxy carbonyl oxygen atom with electron deficient C-1. Subsequent reaction of cyclohexanol with the 1,2-dioxolenium ion (II) results in formation of the orthoester (III). As the alcohol concentration is increased, the probability of it reacting with the ion pair (XII) before the ion pair can dissociate to the free carbonium ion (XIII) increases. Thus, as the alcohol concentration was increased (Table 2), the proportion of β-glucoside (IV) in the initial products increased, whereas the proportion of α-glucoside (V) and orthoester (III), which would be formed *via* the free glycosyl carboxonium ion (XIII), decreased.

The fact that the α-glucoside (V) and the orthoester (III) are initial products of the reaction indicates that some of the ion pairs do dissociate to form free carbonium ions. Halide exchange [equations (5) and (6)] could

TABLE 2

Effect of reactant concentrations on initial and final products at 10 °C

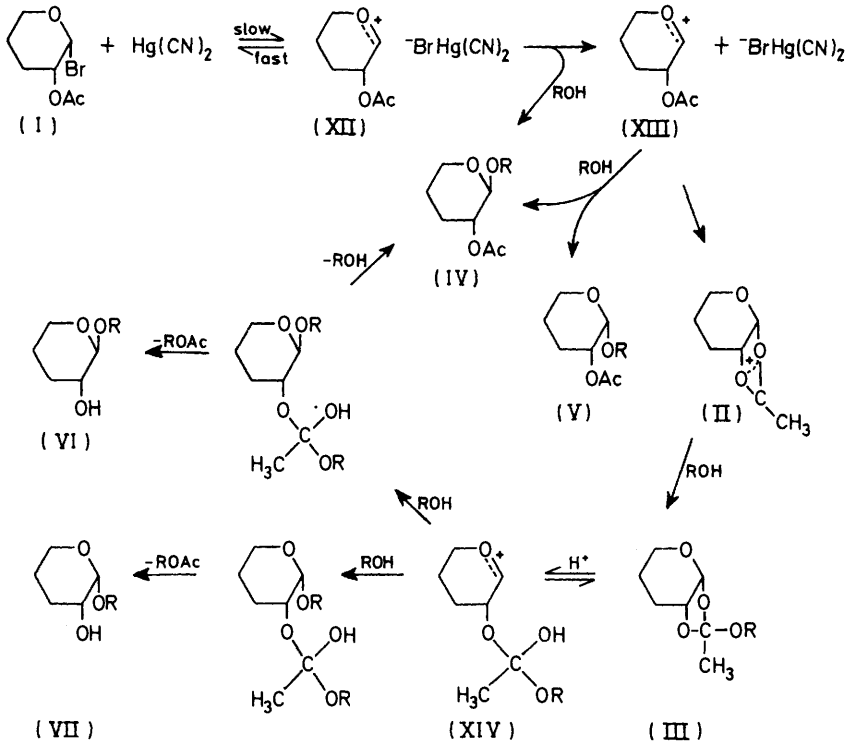
Variable	ROH:RBr:$Hg(CN)_2$ Mole ratio [a]	Initial products [b] n_{OE}	n_β	n_α	Final products [c,d] n_β	n_α
Cyclo-	7.5 : 1 : 1	0.53	0.39	0.08	0.93	0.07
hexanol	15 : 1 : 1	0.45	0.49	0.06	0.93	0.07
(ROH)	22.5 : 1 : 1	0.36	0.60	0.04	0.93	0.07
	30 : 1 : 1	0.23	0.73	0.04	0.94	0.06
$Hg(CN)_2$	15 : 1 : 0.5	0.44	0.50	0.06	0.95	0.05
	15 : 1 : 2	0.45	0.50	0.05	0.93	0.07
Glucosyl	15 : 0.5 : 1 [e]	0.47	0.48	0.05	0.94	0.06
bromide	15 : 1 : 1	0.45	0.49	0.06	0.93	0.07
(RBr)						

[a] 2-*O*-Acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide *ca.* 6×10^{-3}M. Benzene–nitromethane (1 : 1 v/v) solvent. [b] Mole fractions based on the orthoester and glucosidic products: n_{OE}, orthoester (III); n_β, 2-*O*-acetyl-β-glucoside (IV); and n_α, 2-*O*-acetyl-α-glucoside (V). The product distribution is corrected for hydrolysis products on the basis that the orthoester is the most readily hydrolysed species.[9] Obtained by extrapolating g.l.c. analysis data to time zero. [c] Product analyses after a minimum of 10 h reaction time. [d] Mole fractions based on the glucosidic products; hydrolysis products (VIII) and (IX) accounted for 12—17% of the final products in the undesiccated reactions. The mole fraction n_β includes (IV) plus the 2-hydroxy-β-glucoside (VI)(0.0—0.02); n_α includes (V) plus the 2-hydroxy-α-glucoside (VII) (0.0—0.02). [e] 2-*O*-Acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide *ca.* 3×10^{-3}M.

[16] G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1956, 1836.
[17] F. A. Cotton and G. Wilkinson, 'Advanced Inorganic Chemistry,' Interscience, New York, 1972, 3rd edn., p. 519.
[18] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.

potentially account for formation of the α-glucoside (V) [5,19] and the orthoester (III).[20] However, if halide exchange was totally responsible for formation of these compounds, the initial mole fractions of α-glucoside (V) (n_α) and the orthoester (III) (n_{OE}) in the products would be zero. This is definitely not the case (Table 2).

The orthoester subsequently forms glucosides selectively diverting the carbonium ion (XIII) from α-glucoside (V) formation to formation of the orthoester (III) which in turn selectively forms the β-glucoside (IV). The initial mole ratio of orthoester (III) to 2-*O*-acetyl-α-glucoside (V) was at least 5 : 1 in all of the reactions (Table 2). Preferential formation of the orthoester precursor, the 1,2-dioxolenium ion (II), relative



SCHEME Proposed mechanism for glucoside formation in mercury(II) cyanide promoted reactions of 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide with cyclohexanol in benzene–nitromethane (3-, 4-, and 5-substituents of the pyranoid rings are not shown)

(Scheme), the reaction being very selective for formation of the 2-*O*-acetyl-β-glucoside (IV) under these conditions.

$$\alpha\text{-ion pair} \overset{Br^-}{\rightleftharpoons} \beta\text{-ion pair} \quad (5)$$

$$\alpha\text{-glucosyl bromide} \overset{Br^-}{\rightleftharpoons} \beta\text{-glucosyl bromide} \quad (6)$$

Previous studies [10,11] indicate that acid-catalysed glucoside formation from the orthoester (III) involves formation of a carbonium ion at C-1 concurrent with formation of a 2-*O*-(1-cyclohexyloxy-1-hydroxyethyl) substituent (XIV) (Scheme). The alcohol reacts at C-1 to form glucosides, with formation of the β-anomer being preferred because of shielding by the departing orthoacid group. The orthoacid function at C-2 can yield either the 2-*O*-acetyl derivative of the glucoside or form cyclohexyl acetate leaving the hydroxy-group at C-2 unsubstituted.[9,11] However, the latter reaction must not be important under these reaction conditions since the 2-hydroxyglucosides (VI) and (VII) account for only a very small fraction of the glucosidic products.

The 2-*O*-acetyl substituent exerts its effect on the stereochemistry of the glucosyl bromide (I) reaction by to the α-glucoside (V) is probably due to the forced proximity of the carbonyl oxygen atom to the reaction centre of the carbonium ion (XIII).

EXPERIMENTAL

Analytical Methods.—M.p.s, elemental analyses, optical rotations, and n.m.r. spectra were determined as described previously.[8] T.l.c. was performed on silica gel G using methanolic sulphuric acid (5 : 1 w/w) spray with charring for component detection.

The g.l.c. instrument was described previously.[8] Analyses were performed with: (A) 5% SE-52 on 60—80 mesh Chromosorb W (5 ft × 0.125 in o.d. stainless steel column); column, 160—220 °C at 1° min^{-1}; N_2, 14 ml min^{-1}; injector, 205 °C; and detector, 265 °C; and (B) 5% SE-52 on 60—80 mesh Chromosorb W (10 ft × 0.125 in o.d. stainless steel column); column, 160 °C; N_2, 60 ml min^{-1}; injector, 205° C; and detector, 265 °C.

Solvents and Reagents.—Cyclohexanol,[15] ethanol,[21] methanol [21] were purified according to published procedures.

[19] T. J. Lucas and C. Schuerch, *Carbohydrate Res.*, 1975, **39**, 39.
[20] R. U. Lemieux and A. R. Morgan, *Canad. J. Chem.*, 1965, **43**, 2199.
[21] H. Lund and J. Bjerrum, *Ber.*, 1931, **64**, 210.

Benzene, nitromethane, thiophenol, and mercury(II) cyanide were purified as described previously.[1]

Compound Syntheses. General.—2-*O*-Acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide (I),[8] cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (IV),[8] cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (V),[8] 1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-3,4,6-tri-*O*-methyl-α-D-glucopyranose (X),[9] and 3,4,6-tri-*O*-methyl-D-glucopyranose (XV) [9] were prepared as described elsewhere.

3,4,6-*Tri*-O-*acetyl*-1,2-O-[1-(exo-*cyclohexyloxy*)*ethylidene*]-α-D-*glucopyranose* (XVI). Compound (XVI) was prepared in 69% yield by reacting tetra-*O*-acetyl-α-D-glucopyranosyl bromide [22] with cyclohexanol in the presence of tetraethylammonium bromide as described for the preparation of 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-α-D-glucopyranose.[9] The pure product was obtained by crystallization from isopropyl ether containing a trace of pyridine and had m.p. 82—83 °C, $[\alpha]_D$ +27.9° ($CHCl_3$) (Found: C, 56.1; H, 6.8. $C_{20}H_{30}O_9$ requires C, 55.8; H, 7.0%). The ^1H n.m.r. chemical shifts ($CDCl_3$) of the dioxolan 2-methyl protons, δ 1.73 (s) and the anomeric proton, δ 5.69 (d, $J_{1,2}$ 5.2 Hz), are indicative of the *exo*-cyclohexyloxy-configuration.[20]

1,2-O-[1-(exo-*cyclohexyloxy*)*ethylidene*]-3,4,6-*tri*-O-*methyl*-α-D-*glucopyranose* (III). Compound (III) was prepared by methylation of the *O*-acetyl analogue (XVI) with dimethyl sulphate as described for the preparation of 1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-3,4,6-tri-*O*-methyl-α-D-glucopyranose (X).[9] The crude product (93% yield) was purified by fractional distillation under reduced pressure (*ca.* 0.05 mmHg) through a 10 cm Vigreux column. The purified oil had $[\alpha]_D$ +37.4° ($CHCl_3$) (Found: C, 59.0; H, 8.6. $C_{17}H_{30}O_7$ requires C, 58.9; H, 8.7%), δ ($CDCl_3$) 1.68 (s, CH_3C), 5.63 (d, $J_{1,2}$ 5.2 Hz, H-1), 4.37 (m, $J_{2,3}$ 3.1 Hz, H-2), 3.41, 3.45, and 3.48 (3 × MeO), and 1.0—2.0 (m, cyclohexyl).

Cyclohexyl 3,4,6-*tri*-O-*methyl*-β-D-*glucopyranoside* (VI). Cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (IV) was deacetylated with sodium methoxide in methanol.[23] The solution was deionized (Amberlite MB-3) and concentrated *in vacuo* to an oil. The product, purified by fractional distillation through a 10 cm Vigreux column under reduced pressure (*ca.* 0.1 mmHg), crystallized during storage and had m.p. 48.5—50 °C, $[\alpha]_D$ −29.8° ($CHCl_3$) (Found: C, 58.9; H, 9.1. $C_{15}H_{28}O_6$ requires C, 59.2; H, 9.3%), δ ($CDCl_3$) 4.30 (d, $J_{1,2}$ 6.5 Hz, H-1), 3.04 (s, OH-2), 3.40, 3.53, and 3.65 (3 × MeO), and 1.2—2.0 (m, cyclohexyl).

Cyclohexyl 3,4,6-*tri*-O-*methyl*-α-D-*glucopyranoside* (VII). Cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (V) was deacetylated with sodium methoxide in methanol.[23] The solution was deionized (Amberlite MB-3) and concentrated *in vacuo* to an oil which had $[\alpha]_D$ +144° ($CHCl_3$) (Found: C, 59.0; H, 9.2. $C_{15}H_{28}O_6$ requires C, 59.2; H, 9.3%).

Ethyl 3,4,6-*tri*-O-*methyl*-2-O-*propanoyl*-β-D-*glucopyranoside* (XVII). Ethyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside [10] (2.0 g) was treated with propanoic anhydride–pyridine (12 ml; 1 : 2 v/v) for 24 h. The solution was stirred with ice–water for 0.5 h and extracted with chloroform (3 × 75 ml). The chloroform extracts were washed with 1N-H_2SO_4 (100 ml), saturated $NaHCO_3$ (100 ml), and water (50 ml), dried ($CaCl_2$), and concentrated *in vacuo* to an oil (2.1 g, 93%) which was distilled under reduced pressure (*ca.* 0.05 mmHg) in a Kontes short-path distillation apparatus. The distillate was crystallized from isopropyl ether and had m.p. 38—39 °C, $[\alpha]_D$ −20.5° ($CHCl_3$) (Found: C, 54.9; H, 8.5. $C_{14}H_{26}O_7$ requires C, 54.6; H, 8.4%).

Phenyl 2-O-*acetyl*-3,4,6-*tri*-O-*methyl*-1-*thio*-β-D-*glucopyranoside* (XVIII). 2-*O*-Acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide [9] (7.0 g) in chloroform (150 ml) was treated with thiophenol (54 g) in 1M methanolic sodium methoxide (250 ml). After 15 min the reaction was diluted with water (150 ml) and extracted with chloroform (3 × 150 ml). The extracts were washed with 10% Na_2CO_3 (3 × 250 ml) and water (250 ml), dried ($CaCl_2$), and concentrated *in vacuo* to an oil (7.2 g, 95%). The crude product was purified by chromatography on silica gel (Sargent–Welch; 60—200 mesh) using isopropyl ether as the eluant. Crystallization from light petroleum (b.p. 60—110 °C) yielded (XVIII), m.p. 68—69 °C, $[\alpha]_D$ −0.8° ($CHCl_3$) (Found C, 57.4; H, 6.6; S, 9.2. $C_{17}H_{24}O_6S$ requires C, 57.3; H, 6.8; S, 9.0%), δ ($CDCl_3$) 4.58 (d, $J_{1,2}$ *ca.* 10 Hz, H-1), 4.83 (m, H-2), 2.12 (s, OAc), and 7.1—7.7 (m, SC_6H_5).

Reaction Initiation.—Anhydrous conditions were imperative throughout the following procedures because of the sensitivity of the glucosyl bromide (I) and the orthoester (III) to hydrolysis. All glassware was dried at 180 °C for 24 h and stored in a vacuum desiccator (P_2O_5). Solvent transfers and weighing of compounds were conducted in a dry atmosphere.

Mercury(II) cyanide was weighed into a volumetric flask (50 ml). Anhydrous nitromethane (35 ml) was pipetted into the volumetric flask, and the mercury(II) cyanide was dissolved by refluxing the nitromethane. Subsequently, nitromethane (10 ml) was distilled from the flask to dry the system azeotropically. The flask was allowed to cool and weighed to determine the amount of nitromethane used in the reaction. For reactions of the glucosyl bromide (I), cyclohexanol was then weighed into the volumetric flask. If the reactions were analysed by g.l.c. only, the internal standard (XVII), Drierite, and mercury(II) oxide (when used) were also weighed into the cooled nitromethane. For the reaction of the orthoester (III), the orthoester, internal standard (XVII), and Drierite were weighed into the cooled nitromethane.

Anhydrous benzene (35 ml) was pipetted into a second volumetric flask (50 ml). Benzene (10 ml) was distilled from the flask to dry the system azeotropically. The flask was allowed to cool and weighed to determine the amount of benzene used in the reaction. For reactions of the glucosyl bromide (I), the bromide (I) was then weighed into the flask. If the reactions were analysed by g.l.c. only, Drierite was also weighed into the cooled benzene. For the reaction of the orthoester (III), cyclohexanol, HBr, and Drierite were weighed into the cooled benzene.

The two volumetric flasks were allowed to equilibrate thermally in a bath at the desired temperature for 30 min. A bent (45°) connecting tube was placed between the flasks and the contents of the two flasks were mixed together. Time zero for the reaction was taken to be the point at which mixing was begun. A sampling chamber [24] was attached to the flask containing the reaction solution to reduce the possibility of contamination by water during

[22] F. J. Bates, ' Polarimetry, Saccharimetry, and the Sugars,' U.S. Govt. Printing Office, Washington, 1942, p. 500.

[23] A. Thompson, M. L. Wolfrom, and E. Pacsu, *Methods Carbohydrate Chem.*, 1963, **2**, 216.

[24] D. P. Hultman, L. R. Schroeder, and F. C. Haigh, *J.C.S. Perkin II*, 1972, 1063.

sampling, and the flask was returned to the constant temperature bath.

Polarimetric Analysis.—The equipment and procedures used for polarimetric analyses were described previously.[1]

G.l.c. Analysis.—Samples (5.0 ml) taken of glucosyl bromide (I) reactions as a function of time were pipetted into a solution (0.38 ml) of thiophenol in 0.5M methanolic sodium methoxide (1 : 10 v/v) to quench the reaction by converting unchanged (I) to phenyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-1-thio-β-D-glucopyranoside (XVIII) and to stabilize any orthoester (III) present in the sample. Samples (5.0 ml) of completed reactions of (I) (minimum of 10 h reaction time) and samples (5.0 ml) of the orthoester (III) reaction were pipetted into triethylamine–toluene (2.0 ml; 3 : 7 v/v). For reactions which were also analysed by polarimetry the internal standard (XVI) was added to the sample prior to the work-up.

To differentiate between orthoester hydrolysis products [(VIII) and (IX)] formed deliberately in the analytical procedure [9] and (VIII) and (IX) resulting from hydrolysis of the glucosyl bromide and the orthoester during the reaction, each sample was analysed by two procedures.

Procedure (A). A portion (3.0 ml) of the sample was concentrated *in vacuo* to an oil and an aqueous solution of Bromocresol Purple indicator * (4 ml) was added. Sulphuric acid (N; 4 drops) was added and, after 3 min, 0.01N-NaOH was added to pH 5—7. Buffer (0.4 ml; 0.1M-K_2HPO_4–0.1M-KH_2PO_4) was added and the solution was concentrated *in vacuo* to an oil.

The sample was treated with pyridine–propanoic anhydride (*ca.* 2 ml; 1 : 1 v/v) at room temperature with occasional swirling for 24 h. Water (15 ml) was added and, after 15 min, the solution was extracted with chloroform (3 × 15 ml). The extracts were washed with 2N-HCl in saturated NaCl (10 ml), N-NaOH in 10% NaCl (10 ml), and water (10 ml). After each washing the aqueous phase was back-extracted with a comparable volume of chloroform. The chloroform solutions were then combined for the succeeding stage of the procedure. The resultant chloroform solution was concentrated *in vacuo* to an oil. If residual propanoic acid was noted, it was removed by adding several ml of water and reconcentrating. The sample was dissolved in chloroform and analysed by g.l.c.

The 1-*O*-acetyl- and 2-*O*-acetyl-3,4,6-tri-*O*-methyl-D-glucopyranose [(VIII) and (IX), monopropionates] determined by this procedure resulted from both hydrolysis of the glucosyl bromide and orthoester during the reaction and deliberate hydrolysis of the orthoester in the analytical procedure.

G.l.c. conditions (A) were used to analyse all samples. However, when samples had been treated with thiophenol in methanolic sodium methoxide, it was necessary to analyse for the monopropionates of the hydrolysis products [(VIII) and (IX)] using conditions (B). An extraneous compound originating from the thiophenol reagent had the same retention time as (VIII) and (IX) under conditions (A).

G.l.c. retention times (min) using conditions (A) were: (XVII) 12.0, (VIII) and (IX) (monopropionates) 14.5, (XV) (dipropionate) 19.2, (V) 27.0, (IV) 29.9, (VII) (monopropionate) 32.9, (VI) (monopropionate) 35.4, and (XVIII) 42.1. Retention times of (VIII) and (IX) (monopropionates) and (XVII) were 11.8 and 9.4 min, respectively, using conditions (B).

Procedure (B). A portion (2.0 ml) of the sample was concentrated *in vacuo* to an oil and treated with acetic anhydride–pyridine (*ca.* 2 ml; 1 : 2 v/v) at room temperature with occasional swirling for 24 h. Water (15 ml) was added and, after 15 min, the solution was extracted with chloroform (3 × 20 ml). The extracts were concentrated *in vacuo* to 1—2 ml and N-HCl (15 ml) was added. The mixture was shaken for 5—10 min and then extracted with chloroform (3 × 15 ml). The extracts were washed with N-NaOH in 10% NaCl (5 ml) and water (5 ml). After each washing the aqueous phase was back-extracted with chloroform (10 ml) and the chloroform solutions were combined for the succeeding step of the procedure. The final chloroform solution was concentrated *in vacuo* to an oil which was treated with propanoic anhydride–pyridine (*ca.* 2 ml; 1 : 2 v/v) and analysed by g.l.c. as described in procedure (A).

The monopropionates of (VIII) and (IX) determined by Procedure (B) result only from deliberate hydrolysis of the orthoester during the procedure.

The response factors required for quantitative g.l.c. were determined by subjecting synthetic mixtures of the necessary compounds to both analysis procedures.

N.m.r. Analysis.—Anhydrous nitromethane (25 ml) was pipetted into a volumetric flask (50 ml) containing $Hg(CN)_2$ (0.305 g). The mixture was refluxed to dissolve $Hg(CN)_2$. Ethanol (0.806 g) was weighed into the cooled solution. The solution was transferred to a volumetric flask (250 ml) and diluted with anhydrous nitromethane (75 ml). Anhydrous benzene (25 ml) was pipetted into a second volumetric flask (50 ml) and the glucosyl bromide (I) (0.333 g) was weighed into the solvent. The solution was transferred to a second volumetric flask (250 ml) and diluted with anhydrous benzene (75 ml). The above operations were performed in a dry atmosphere.

The two flasks were allowed to equilibrate thermally in a bath at 10 °C for 1 h. The contents of the two flasks were mixed together and a sample of the solution was transferred to a water-jacketted polarimeter cell at 10 °C. The remainder of the reaction solution was maintained in the bath. When the optical rotation of the reaction solution approached a constant value (*ca.* 90 min), thiophenol in 0.5M methanolic sodium methoxide (10 ml; 1 : 10 v/v) was added to the solution in the bath. The solution was concentrated to *ca.* 10 ml, filtered, washed with N-NaOH (2 × 10 ml) and water (10 ml), and dried ($CaCl_2$). The solution was treated with pyridine (2 ml) and concentrated *in vacuo* to an oil. The oil was dissolved in $CDCl_3$ (*ca.* 0.4 ml) and analysed by n.m.r.

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* Bromocresol Purple indicator (1.3 ml; Harleco; 0.04% solution) was diluted with water (100 ml).