Koenigs–Knorr Reactions. Part 1. Effects of a 2-*O*-Acetyl Substituent, the Promoter, and the Alcohol Concentration on the Stereoselectivity of Reactions of 1,2-*cis*-Glucopyranosyl Bromide

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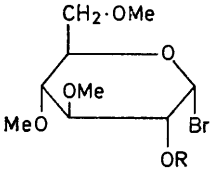
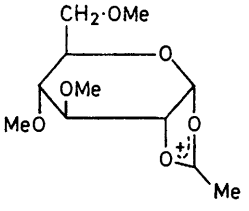
Koenigs–Knorr reactions of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl bromide and the 2-*O*-acetyl analogue with cyclohexanol, with various promoters in the customary solvents, were investigated at 23 °C. The promoters employed were silver(I) oxide with iodine in chloroform, mercury(II) oxide with mercury(II) bromide in chloroform, cadmium carbonate in toluene, and mercury(II) cyanide in benzene–nitromethane (1 : 1 v/v). Primary emphasis was on reactions having an alcohol (ROH) to glucosyl halide (RBr) molar ratio of 3 : 1 at a glucosyl halide concentration of *ca.* 6.5 × 10^{-2}M. In addition, mercury cyanide-promoted reactions employing 10 : 1 and 30 : 1 molar ratios of ROH to RBr were studied. The 2-*O*-acetylglucosyl bromide selectively afforded the β-glucoside (95—98% of the glucosidic products) in all the reactions. In contrast, reactions of the 2-*O*-methylglucosyl bromide were less selective (53—91% β-glucoside), and the selectivity was dependent on the promoter and the alcohol concentration. The selectivity for β-glucoside formation was greatest in the silver oxide system and least in the cadmium carbonate system. In the mercury cyanide system, selectivity for β-glucoside formation increased as the alcohol concentration was increased.

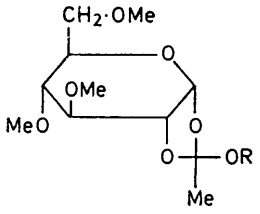
THE Koenigs–Knorr reaction,[1] in which a substituted glycosyl halide reacts with an alcohol, phenol, or substituted glycose has been employed for the preparation of numerous glycosides and oligosaccharides.[2-7] However its usefulness has been limited because of the lack of steric control over the reaction. The primary reason for this is the complex way in which the steric course of the reaction is influenced by various factors,[8] including, in addition to the configuration of the glycosyl halide, the nature of the C-2 substituent, the alcohol concentration, and the promoter ('acid acceptor'). The purpose of this investigation was to determine the effect of a 2-*O*-acetyl substituent, the alcohol concentration, and the promoter system on the stereoselectivity of reactions of 1,2-*cis*-glucopyranosyl bromide. To this end, reactions of 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide (I) and its 2-*O*-methyl analogue (II) with cyclohexanol and various promoters in the customary solvents were investigated at 23 °C. The promoter and solvent systems employed were: silver(I)



(I) R = Ac
(II) R = Me



(III)



(IV) R = Et
(V) R = Pr^{i}
(VI) R = cyclohexyl

[1] W. Koenigs and E. Knorr, *Ber.*, 1901, **34**, 957.
[2] W. L. Evans, D. D. Reynolds, and E. A. Talley, *Adv. Carbohydrate Chem.*, 1951, **6**, 27.
[3] L. J. Haynes and F. H. Newth, *Adv. Carbohydrate Chem.*, 1955, **10**, 207.
[4] J. Conchie, G. A. Levvy, and C. A. Marsh, *Adv. Carbohydrate Chem.*, 1957, **12**, 157.
[5] E. A. Talley, *Methods Carbohydrate Chem.*, 1963, **2**, 337.
[6] H. M. Flowers, *Methods Carbohydrate Chem.*, 1972, **6**, 474.
[7] W. G. Overend, in 'The Carbohydrates,' ed. W. Pigman and D. Horton, 2nd edn., Academic Press, New York, 1972, vol. IA, p. 279.
[8] C. Schuerch, *Accounts Chem. Res.*, 1973, **6**, 184.

oxide–iodine [5] in chloroform, mercury(II) oxide–mercury(II) bromide [9] in chloroform, mercury(II) cyanide [6] in benzene–nitromethane (1 : 1 v/v), and cadmium carbonate [10] in toluene.

RESULTS AND DISCUSSION

The analyses of the glucosidic products from the reactions conducted are presented in the Table. All the reactions of the 2-*O*-acetyl derivative (I) occurred with a high degree of stereoselectivity; the mole fraction of β-anomer (n_β) in the glucosidic products was 0.95—0.98. In contrast, reactions of the 2-*O*-methyl derivative (II) occurred with lower and varied degrees of selectivity (n_β 0.53—0.92). The selectivity of the 2-*O*-methylglucosyl bromide (II) reactions was extremely dependent on both the promoter system and the alcohol concentration. These data indicate that the effect of a 2-*O*-acetyl substituent dominates the effect of either the promoter or the alcohol concentration.

Glucoside analyses for reactions of 3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromides (*ca.* 6.5 × 10^{-2}M) with cyclohexanol at 23 °C

		Glucosyl bromide			
		2-OAc (I)		2-OMe (II)	
Promoter [a]	ROH : RBr : Promoter (mole ratio)	n_β [b]	Glucosides (%)	n_β [b]	Glucosides (%)
Ag_2O [c]	3 : 1 : 1	0.98	85	0.91	95
HgO [d]	3 : 1 : 1	0.96	84	0.81	91
$CdCO_3$ [e]	3 : 1 : 1	0.98	98	0.53	100
$Hg(CN)_2$ [f]	3 : 1 : 1	0.95	91	0.71	100
$Hg(CN)_2$ [f]	10 : 1 : 1	0.95	98	0.81	100
$Hg(CN)_2$ [f]	30 : 1 : 1	0.96	99	0.88	100

[a] Powdered Drierite was employed as a desiccant in each reaction. [b] Mole fraction of β-anomer in the glucosidic products. [c] Iodine (*ca.* 1.2 × 10^{-2}M) employed as co-catalyst; solvent, chloroform. [d] Mercury(II) bromide (*ca.* 3.0 × 10^{-3}M) employed as co-catalyst; solvent, chloroform. [e] Solvent, toluene. [f] Solvent, benzene–nitromethane (1 : 1 v/v).

The results are consistent with those of earlier investigations which have shown that reactions of 1,2-*cis*-glycosyl halides having a 2-*O*-acyl substituent generally occur with a high degree of inversion at C-1,[2,5,11] whereas the stereoselectivity of reactions of 1,2-*cis*-glycosyl halides having a 'non-participating' C-2 substituent is extremely variable.[12–14] It has been postulated that the effect of a 2-*O*-acyl substituent on the stereoselectivity of 1,2-*cis*-glycosyl halide reactions is due to direct participation of the substituent through formation of a relatively stable dioxolanylium ion, *e.g.* (III), which guides the incoming nucleophile into the 1,2-*trans*-position.[11] However, evidence against reaction of the nucleophile at the anomeric carbon atom of the dioxolanylium ion (III) being important has been obtained for both hydrolyses [15] and alcoholyses [16,17] of the 1,2-*O*-(1-alkoxyethylidene)-3,4,6-tri-*O*-methyl-α-D-gluco-pyranoses (IV) and (V), even though (III) is an important intermediate. Another potential explanation for the high degree of stereoselectivity of the 2-*O*-acetylglucosyl bromide (I) reactions is that the intermediate dioxolanylium ion (III) reacts with the cyclohexanol to form the orthoester (VI). Even though the mechanism is uncertain, it is known that 1,2-(alkyl orthoacetates) of D-glucose can selectively yield the alkyl 2-*O*-acetyl-β-D-glucopyranoside.[18] Thus, if the reaction system contains weak acids such as hydrogen cyanide in the mercury cyanide-promoted reaction or carbonic acid in the cadmium carbonate-promoted reaction, or if neutralization of the hydrogen bromide generated is not sufficiently rapid, the orthoester (VI) could be formed and subsequently generate the β-glucoside.

The lower yields of glucosides observed in the silver oxide- and mercury oxide-promoted reactions may have been due, in part, to hydrolysis. If desiccation is not rapid and efficient, water produced by neutralization of the hydrogen bromide by silver oxide or mercury oxide could compete with the alcohol for the glucosyl bromide (and orthoester [15]) resulting in formation of reducing sugars rather than the preferred glucosides. In addition, the yield of glucosides was significantly lower for the silver oxide- and mercury oxide-promoted reactions of the 2-*O*-acetylglucosyl bromide (I) than for the analogous reactions of the 2-*O*-methyl derivative (II). This indicates the formation, and partial stabilization, of the orthoester (VI) in the reaction of (I). The analytical procedure did not include analysis of (VI), which would not be stable to direct g.l.c. analysis.[15] A substantial amount of an orthoester has been isolated from a reaction of a 1,2-*cis*-*O*-acetylglucosyl bromide with a secondary alcohol promoted by mercury bromide and mercury oxide in similar solvents.[19] Thus, it is possible that mercury oxide, and potentially silver oxide,[20] may

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[10] R. B. Conrow and S. Bernstein, *J. Org. Chem.*, 1971, **36**, 863.
[11] L. Hough and A. C. Richardson, in 'Rodd's Chemistry of Carbon Compounds,' ed. S. Coffey, 2nd edn., Elsevier, Amsterdam, 1967, vol. IF, p. 327.
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[19] G. F. Rudie and L. R. Schroeder, in preparation.
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have partially stabilized any orthoester (VI) formed in the 2-*O*-acetylglucosyl bromide (I) reaction, and thereby lowered the yield of glucosides.

Formation of the α-glucoside from the 2-*O*-methylglucosyl bromide (II) is only possible if the bromine atom is not present to shield the α-side of the anomeric carbon atom. Therefore, the formation of cyclohexyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside from (II) is indicative of either bromide exchange to form the β-glucosyl bromide or formation of a carbocation. Since the promoters used in this investigation should act as anion acceptors, the extent of ion exchange should be minimal, and formation of the cyclohexyl α-glucoside should be primarily indicative of carbocation formation.

Previous investigations have shown that the promoter may influence the stereoselectivity of a Koenigs–Knorr reaction. For example, reactions conducted in the presence of silver salts have generally been found to be stereoselective, whereas the results of those with mercuric salts have been varied.[6,7] The data in the Table show that the stereoselectivity of the reactions of 2-*O*-methylglucosyl bromide (II) was significantly dependent on the promoter system. The mole fraction of β-anomer in the glucosidic products (n_β) ranged from 0.91 for the silver oxide-facilitated reaction to 0.53 for that with cadmium carbonate. The influence of the promoter system is complex and may be due to the nature of the promoter,[21] the solvent, or a combination of both.[22] Under the conditions of the present study, the stereoselectivity decreased as a function of the promoter system in the order: $Ag_2O > HgBr_2–HgO > Hg(CN)_2 > CdCO_3$.

The effect of the alcohol concentration on the stereoselectivity of the mercury cyanide-promoted reactions of both glucosyl halides was investigated (Table). There was no apparent dependence of the glucoside configuration on the alcohol concentration for reactions of the 2-*O*-acetylglucosyl bromide (I). However, for reactions of the 2-*O*-methyl derivative (II), the mole fraction of β-anomer in the glucosidic products (n_β) increased from 0.71 to 0.88 as the cyclohexanol concentration was increased tenfold. The dependence on the cyclohexanol concentration indicates that the intermediate glucopyranosyl carboxonium ion was partially shielded by the departing anion, or that the ions existed as an ion pair. As the alcohol concentration was increased, the probability that a nucleophilic substitution would occur before the anion had time to dissociate completely from the carbocation increased because the availability of the alcohol to react with the carbocation increased. Thus, the relative importance of shielding of the α-side of the carbocation increased as the alcohol concentration increased, and resulted in an increase in the selectivity of the reactions of 2-*O*-methylglucosyl bromide (II) for β-glucoside formation.

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[22] G. Wulff and G. Röhle, *Chem. Ber.*, 1972, **105**, 1122.
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EXPERIMENTAL

M.p.s were determined with a Thomas–Hoover capillary apparatus and are corrected. Polarimetric measurements were made with a Perkin-Elmer 141 MC polarimeter. Elemental analyses were performed by Chemalytics, Inc. ^{1}H N.m.r. spectra were determined with a Varian A-60A spectrometer at normal probe temperature with tetramethylsilane as internal standard and $CDCl_3$ as solvent. T.l.c. was performed on microscope slides coated with silica gel G; methanolic sulphuric acid (5 : 1 w/w) with charring was used for component detection.

G.l.c. analyses were performed on a Varian Aerograph 1200-1 instrument equipped with a hydrogen flame ionization detector and a Honeywell Electronic 16 recorder with a disc integrator. Conditions were: (A) 20% Carbowax 20M TPA on 60—80 mesh HMDS Chromosorb W (5 ft × 0.125 in o.d. stainless steel); column temp. 155 °C; N_2 21 ml min^{-1}; injector 205 °C; detector 265 °C; and (B) 5% SE-30 on 60—80 mesh Chromosorb W (10 ft × 0.125 in o.d. stainless steel); column temp. 160 ⟶ 220 °C at 1° min^{-1}; N_2 16 ml min^{-1}; injector 205 °C; detector 265 °C.

2-O-*Acetyl*-3,4,6-*tri*-O-*methyl*-α-D-*glucopyranosyl Bromide* (I).— 1,2-Di-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranose [15] (7.0 g) was stirred with 1,2-dichloroethane (220 ml) saturated with hydrogen bromide (15.5 g) for 8 min, and poured into stirred ice–water. After 10 min, the solution was extracted with chloroform (3 × 100 ml). The extracts were washed with saturated aqueous sodium hydrogen carbonate and water, dried ($CaCl_2$), and concentrated *in vacuo* to yield the *bromide* (I), pure by t.l.c. (di-isopropyl ether) and ^{1}H n.m.r. analysis, as a syrup (6.7 g, 91%); $[\alpha]_D$ +250° (*c* 1.0 in $CHCl_3$); δ ($CDCl_3$) 6.65 (1 H, d, $J_{1,2}$ 4.0 Hz, H-1), 4.65 (1 H, m, $J_{2,3}$ *ca.* 9 Hz, H-2), and 2.15 (3 H, s, OAc). The large positive specific optical rotation, the small value of $J_{1,2}$, and the low-field position of the H-1 signal are indicative of the α-D-configuration.

2,3,4,6-*Tetra*-O-*methyl*-α-D-*glucopyranosyl Bromide* (II).— 1-*O*-Acetyl-2,3,4,6-tetra-*O*-methyl-D-glucopyranose [23] (7.0 g) was treated with hydrogen bromide in dichloroethane as described for the preparation of (I). The pure *bromide* (II) [as determined by t.l.c. (benzene–ethyl acetate, 1 : 1 v/v)] and ^{1}H n.m.r. analyses, was obtained as a syrup (6.1 g, 86%); $[\alpha]_D$ +244° (*c* 1.1 in $CHCl_3$); δ ($CDCl_3$) 6.58 (1 H, d, $J_{1,2}$ 3.5 Hz, H-1). The large positive specific optical rotation, the small value of $J_{1,2}$, and the low-field position of the H-1 signal are indicative of the α-D-configuration.

Cyclohexyl 2,3,4,6-*Tetra*-O-*methyl*-α-D-*glucopyranoside*.— Cyclohexyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside [24] (5.0 g) was deacetylated with methanolic sodium methoxide,[25] and methylated in *NN*-dimethylformamide (50 ml) with methyl iodide (15 ml) and silver oxide (25 g) [26] to yield the *tetra*-O-*methylglycoside* as a syrup (3.5 g, 95%), purified by distillation at 0.05 mmHg through a 10 cm Vigreux column. The distillate had $[\alpha]_D$ +148° (*c* 1.0 in $CHCl_3$); δ ($CDCl_3$) 5.06 (1 H, d, $J_{1,2}$ 3.5 Hz, H-1) (Found: C, 60.6; H, 9.6. $C_{16}H_{30}O_6$ requires C, 60.3; H, 9.5%).

Cyclohexyl 2,3,4,6-*Tetra*-O-*methyl*-β-D-*glucopyranoside*.— Compound (VIII) was prepared from cyclohexyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside [27] (8.0 g) by deacetyl-

[24] L. R. Schroeder, J. W. Green, and D. C. Johnson, *J. Chem. Soc.* (*B*), 1966, 447.
[25] A. Thompson, M. L. Wolfrom, and E. Pacsu, *Methods Carbohydrate Chem.*, 1963, **2**, 215.
[26] R. M. Rowell, *Carbohydrate Res.*, 1972, **23**, 417.
[27] L. R. Schroeder and J. W. Green, *J. Chem. Soc.* (*C*), 1966, 530.

ation and subsequent methylation as for the preparation of (VII). The *glycoside* (5.4 g, 91%) was purified by silica gel (Sargent–Welch, 60—200 mesh) chromatography with chloroform–acetone (16 : 1, v/v) as eluant and subsequent distillation at 0.05 mmHg through a 10 cm Vigreux column. The distillate had $[\alpha]_D$ −27° (*c* 1.1 in $CHCl_3$); δ ($CDCl_3$) 4.34 (1 H, d, $J_{1,2}$ 7.0 Hz, H-1) (Found: C, 60.6; H, 9.5%).

Cyclohexyl 2-O-*Acetyl*-3,4,6-*tri*-O-*methyl*-α- *and* -β-D-*glucopyranosides*.—3,4,6-Tri-*O*-methyl-D-glucopyranose [15] (26.4 g) was dissolved in cyclohexanol (130 ml) and acetyl chloride (5 ml). After 3 days of mild heating, t.l.c. (benzene–methanol, 5 : 1 v/v) indicated that glycoside formation was complete. The solution was diluted with chloroform (400 ml), washed with water, dried ($CaCl_2$), and concentrated *in vacuo* to a syrup which was acetylated with acetic anhydride–pyridine [28] (180 ml; 1 : 2 v/v) to yield a mixture of (IX) and (X) (33.3 g, 81%), separated by silica gel (Sargent–Welch, 60—200 mesh) chromatography with chloroform–ethyl acetate (20 : 1 v/v) as eluant.

The fractions containing pure α-*anomer*, as determined by g.l.c. [conditions (B)], were combined, concentrated *in vacuo*, and distilled at 0.05 mmHg. The distillate had $[\alpha]_D$ +162° (*c* 1.0 in $CHCl_3$); δ ($CDCl_3$) 5.13 (1 H, d, $J_{1,2}$ 3.8 Hz, H-1), 4.64 (1 H, m, $J_{2,3}$ *ca.* 9 Hz, H-2), and 2.08 (3 H, s, OAc) (Found: C, 59.0; H, 8.9. $C_{17}H_{30}O_7$ requires C, 58.9; H, 8.7%).

The fractions containing pure β-*anomer* were combined, concentrated *in vacuo*, and crystallized from petroleum (b.p. 30—60 °C); m.p. 58—59 °C; $[\alpha]_D$ −25° (*c* 0.9 in $CDCl_3$); δ ($CDCl_3$) 4.40 (1 H, d, $J_{1,2}$ *ca.* 8 Hz, H-1) and 2.08 (3 H, s, OAc) (Found: C, 59.1; H, 9.0%).

n-Butyl 2,3,4,6-*Tetra*-O-*methyl*-β-D-*glucopyranoside*.—n-Butyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside [27] (57.4 g) was methylated with dimethyl sulphate as described for the preparation of methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside [23] to yield the *tetra*-O-*methylglucoside* as a syrup (32.2 g, 78%), purified by distillation at 0.05 mmHg. The distillate had $[\alpha]_D$ −29° (*c* 1.0 in $CHCl_3$) (Found: C, 57.2; H, 9.5. $C_{14}H_{28}O_6$ requires C, 57.5; H, 9.6%).

Solvents and Reagents.—Cyclohexanol,[24] chloroform,[29] nitromethane,[30] benzene,[30] and toluene,[30] were purified according to published procedures. The silver, mercury, and cadmium compounds were dried *in vacuo* at 100 °C for 24 h and stored in a vacuum desiccator (Drierite).

Reaction Procedures.—All glassware was dried at 100 °C for 24 h prior to use. The reactions were conducted in a constant temperature room (23 °C) in tightly sealed, 100 ml, round-bottom flasks wrapped with aluminium foil. The reagents, solvents, and glassware were thermally equilibrated overnight before use. The reaction mixtures were stirred continuously to prevent the promoters from settling out.

Cyclohexanol was weighed into a 10 ml volumetric flask, diluted to volume with solvent, and transferred to the reaction flask. The volumetric flask was again filled to volume with solvent, which was transferred to the reaction flask. The internal standard (n-butyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside) was weighed into a second 10 ml volumetric flask, diluted to volume with solvent, and transferred to the reaction flask. The volumetric flask was again filled to volume with solvent which was then transferred to the reaction flask. The promoters and powdered Drierite were weighed and transferred to the reaction flask. The system was stirred for 1 h prior to addition of the glucosyl bromide. The glucosyl bromide was weighed into a 5 ml volumetric flask, diluted to volume with solvent, and transferred to the reaction flask. The volumetric flask was rinsed with 5.0 ml of solvent, which was transferred to the reaction flask. Finally, iodine, if used, was transferred to the reaction flask.

T.l.c. (di-isopropyl ether) was used to determine whether the reaction was complete. Samples from the reactions of the 2-*O*-acetylglucosyl bromide (I) were analysed directly. Samples from the reactions of the 2-*O*-methylglucosyl bromide (II) were treated with silver nitrate (3%) in acetone–water (19 : 1 v/v) to convert the bromide (II) into 2,3,4,6-tetra-*O*-methyl-D-glucose prior to analysis.

Quantitative Analysis.—When reaction was complete, the solution was filtered (Celite) and the residue was rinsed with chloroform. The filtrates were washed as follows: Ag_2O–I_2 reactions, 5% $Na_2S_2O_3$ and water; HgO–$HgBr_2$ reactions, 20% KI and water; $CdCO_3$ and $Hg(CN)_2$ reactions, $NaHCO_3$ and water. Each aqueous phase was back-extracted with chloroform. The combined chloroform extracts were dried ($CaCl_2$) and concentrated *in vacuo*. Each sample was treated with pyridine–propanoic anhydride (*ca.* 1.5 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 × 15 ml). The extracts were washed [N-H_2SO_4 (10 ml), sat. $NaHCO_3$ (10 ml), and H_2O (10 ml)]. In each case the aqueous phase was back-extracted with a comparable volume of chloroform. The chloroform solutions were then combined for the subsequent wash. The final chloroform solution was concentrated *in vacuo* and the residue was dissolved in chloroform (1—2 ml) for g.l.c. analysis. Conditions (A) were employed to analyse the reactions of the 2-*O*-methylglucosyl bromide (II); conditions (B) for those of the 2-*O*-acetyl analogue (I).

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