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Note

Stereoselectivity of Koenigs–Knorr syntheses of alkyl β-D-galactopyranoside and β-D-xylopyranoside peracetates promoted by mercuric bromide and mercuric oxide

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Koenigs–Knorr reactions employing mercuric oxide in conjunction with mercuric bromide as the acid acceptor–catalyst system were previously shown to provide efficient, high-yielding syntheses of alkyl β-D-glucopyranoside peracetates and perbenzoates[1]. In view of the uncertainty of the stereochemical course of Koenigs–Knorr reactions promoted by mercuric salts[2,3], we have questioned the stereoselectivity of the method for synthesis of glycosides of sugars other than D-glucose. We have also questioned whether or not the alcohol employed has a significant effect on the stereoselectivity of the reaction, as is the case for alcoholysis of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[4].

The necessity of preparing several anomeric pairs of alkyl D-galactopyranoside and D-xylopyranoside peracetates as reference compounds[5] provided an opportunity to investigate the stereoselectivity of mercuric oxide–mercuric bromide-facilitated Koenigs–Knorr syntheses employing peracetylated α-D-galactopyranosyl* and α-D-xylopyranosyl bromides.

Minor modifications of the original method[1], which make it more convenient to use, are reported.

RESULTS AND DISCUSSION

As indicated by the data in Table I, this modification of the Koenigs–Knorr reaction is very stereoselective for formation of the β anomer in preparations of alkyl glycopyranosides of D-galactose and D-xylose. The mole fraction (n_β) of β anomer in the glycosidic products was greater than 0.98 for all of the syntheses investigated. In addition, since t.l.c. and g.l.c. analyses of reaction-product mixtures indicated only

*During the course of this work, De Bruyne and van der Groen[6] reported syntheses of several alkyl β-D-galactopyranosides by this method. However, yield data and physical characteristics were not reported for the initial, peracetylated products, which were not crystallized.

TABLE I

ALKYL D-GLYCOPYRANOSIDE PERACETATES

Glycose	*Aglycon*	n_β[a]	*Yield*, %[b]	*Cryst. solvent*[c]	*m.p.* (°C)[d]	$[\alpha]_D$ (°), $CHCl_3$[d]	*Elemental analysis*[e]		*G.l.c. analysis*[f]	
							C, %	H, %	*Cond.*	T_r (*Rel.*, α/β)
Xylose	Methyl (β)	0.99	83	A	114–115 (115)[8]	−60.7 (−60.8)[8]			A	0.81
	Methyl (α)			B	85–86 (86–87)[9]	+119 (+120)[9]				
Xylose	Ethyl (β)	0.99	80	A	107–108 (106–107)[10]	−62.0 (−62)[10]			A	0.76
	Ethyl (α)			C	41–43 (38–39)[10]	+132 (+100)[10]	51.3 (51.3)	6.6 (6.6)		
Xylose	Propyl (β)	0.98	77	A	109–110 (108–109)[11]	−60.6 (−60.6)[11]			A	0.72
	Propyl (α)			C	59–61	+132	52.7 (52.8)	6.7 (7.0)		
Xylose	Butyl (β)	0.98	75	A	100–101 (100–101)[11]	−59.7 (−58.0)[11]			B	0.75
Xylose	2-Propyl (β)	0.98	71	A	122–123 (122–124)[11]	−63.5 (−62.5)[11]			A	0.75
	2-Propyl (α)			C	66–68	+144	52.8 (52.8)	7.0 (7.0)		
Xylose	Cyclohexyl (β)	0.99	77	A	116–118 (116–117)[12]	−56.0 (−55.2)[12]			D	0.78
	Cyclohexyl (α)			B	123–124	+140	57.2 (57.0)	7.4 (7.3)		
Galactose	Methyl (β)	0.99	75	A	96–97 (94–95)[13]	−14.3 (−14.5)[13]			C	0.80
	Methyl (α)			A	85–87 (85–86)[13]	+133 (+133)[13]				
Galactose	Ethyl (β)	0.99	79	B	86–88 (86–87)[14]	−15.1[g]	51.0 (51.1)	6.4 (6.4)	C	0.75
	Ethyl (α)			B	85–87 (85–86)[14]	+138 (+136)[14]				
Galactose	Propyl (β)	0.99	61	B	75–76	−13.5	52.4 (52.3)	6.6 (6.7)	C	0.74
	Propyl (α)			B	106–107	+138	52.4 (52.3)	6.9 (6.7)		
Galactose	Butyl (β)	0.99	68	B	58–59 (60–62)[15]	−13.6 (−13.8)[15]			E	0.75
	Butyl (α)			B	75–76	+137	53.4 (53.5)	7.0 (7.0)		
Galactose	2-Propyl (β)	0.99	60	B	59–61 (58–59)[14]	−15.7 (−9.0)[14]	52.4 (52.3)	6.6 (6.7)	C	0.76
	2-Propyl (α)			B	106–108	+150	52.5 (52.3)	7.0 (6.7)		
Galactose	Cyclohexyl (β)	0.99	73[h]		[i]	−12.8	55.6 (55.8)	7.0 (7.0)	F	0.80
	Cyclohexyl (α)			B	112–114	+148	55.9 (55.8)	7.1 (7.0)		

[a]Mole fraction of β anomer formed in the Koenigs-Knorr reaction; determined by g.l.c.; minimum value. [b]Isolated crystalline product. [c]A, ethanol; B, diisopropyl ether; C, ethanol by addition of petroleum ether (b.p. 30–60°). [d]Figures in parentheses are the values reported in the indicated literature references. [e]Figures in parentheses are the theoretical values. [f]All analyses employed injector, 225°; detector, 235°; and carrier gas (N_2), 25 ml/min at room temperature. The column temperatures (°C) were: A, 160; B, 175; C, 195; D, 200; E 205; and F, 215. The retention times ranged from ~11 to 26 min under these conditions. [g]$[\alpha]_D^{24}$ −32.4° (benzene); Fischer and Armstrong[16] reported $[\alpha]_D^{20}$ −29.8° (benzene). [h]Percentage recovery from silica gel column chromatography. [i]Syrup.

a small proportion (<1%, g.l.c.) of other, unidentified products, the actual yield of β-glycoside is essentially the same as n_β. The fact that the isolated yields are significantly lower than n_β (Table I) reflects the difficulties encountered in crystallizing the products. Nevertheless, the isolated yields of alkyl β-D-xylopyranoside peracetates appear to be significantly greater than yields reported for syntheses of these derivatives by other modifications of the Koenigs–Knorr reaction[10–12,17,18]. Isolated yields of the alkyl β-D-galactopyranoside peracetates, from the limited data available[14], appear to be comparable with those obtained from other Koenigs–Knorr methods.

The reactivity of the glycosyl halide does not appear to alter the stereoselectivity of the reaction under these conditions; the peracetylated α-D-galactosyl and α-D-xylosyl bromides are significantly different in reactivity[7] (see Experimental) yet the reactions of both halides approach stereospecificity for formation of the β-glycopyranoside. Also, within the series of alcohols employed, the particular alcohol does not affect the stereoselectivity of the reaction.

Many of the compounds prepared in this study have not, to our knowledge, been reported previously. In addition, for some of the derivatives, the physical characteristics differ from values reported in the literature. These compounds were characterized as follows. Elemental analyses for each of the glycosides were satisfactory (Table I). G.l.c. analyses (Table I) verified the anomeric purity, and the retention times were concordant with those of the indicated anomer. For the alkyl β-D-galactopyranoside peracetates, the negative specific optical rotations (Table I) and n.m.r. data ($CDCl_3$) for the anomeric protons (δ ~4.5–4.6, $J_{1,2}$ ~7 Hz), analogous with n.m.r. data for methyl tetra-*O*-acetyl-β-D-galactopyranoside[19], substantiated the assigned β configuration at the anomeric carbon atom. The anomeric configuration assigned to the alkyl α-D-glycopyranoside peracetates was confirmed by the large positive specific optical rotations (Table I) and n.m.r. data (D_2O) for the anomeric protons of the deacetylated analogs (α-D-xylopyranosides; δ ~4.9–5.0, $J_{1,2}$ ~2.5–3.0 Hz: α-D-galactopyranosides; δ ~4.9–5.1, $J_{1,2}$ <3.0 Hz).

n-Butyl tri-*O*-acetyl-α-D-xylopyranoside was the only glycoside of the twelve anomeric pairs that was not obtained pure, and no physical constants are reported for it in Table I. However, g.l.c. and n.m.r. data indicated that it had been formed.

EXPERIMENTAL

General methods. — Melting points were determined on a Thomas–Hoover capillary apparatus which was calibrated against known compounds. Polarimetric measurements were made on a Perkin–Elmer 141 MC polarimeter. Elemental analyses were performed by Chemalytics, Inc. N.m.r. spectra were determined with a Varian A-60A spectrometer at normal probe temperature employing sodium 2,2-dimethyl-2-silapentane-5-sulfonate and tetramethylsilane as internal standards in D_2O and $CDCl_3$ solutions, respectively. T.l.c. was performed on microscope slides coated with Silica Gel G (Brinkman Instruments, Inc.) utilizing methanolic sulfuric acid (5:1, wt) spray with subsequent charring for spot 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 Disk integrator. The column (2.5 ft × 0.125 inch o.d., stainless steel) was packed with a 1:1 mixture of 20% Apiezon M on 60–80 mesh Chromosorb W and 20% butanediol succinate on 60–80 mesh Chromosorb W. Analysis conditions are given in Table I. For quantitative calculations, the response factors for anomeric glycosides were assumed to be equal[4].

α-D-Glycopyranosyl bromide peracetates. — The *β*-D-glycopyranose peracetate[20,21] (30 g) in 1,2-dichloroethane (60 ml) was treated with hydrogen bromide in acetic acid (30–32%, 20 ml) at room temperature with occasional swirling for 1.5 h (D-galactose) or 0.75 h (D-xylose). The reactions were processed as described for the D-glucose analog[21], and crystallization from diisopropyl ether (60 ml) yielded products having physical constants in agreement with the literature[22–24]: tetra-*O*-acetyl-α-D-galactopyranosyl bromide, 79%, m.p. 83–85°, $[\alpha]_D^{20}$ +215° (chloroform); tri-*O*-acetyl-α-D-xylopyranosyl bromide, 77%, m.p. 101–102°, $[\alpha]_D^{25}$ +209° (chloroform).

Alkyl β-D-glycopyranoside peracetates. — Drierite (10–20 mesh, 20 g), yellow mercuric oxide (8.0 g), mercuric bromide (0.5 g), abs. chloroform[25] (150 ml), and the anhydrous alcohol[1] (50 ml) were stirred magnetically in a stoppered Erlenmeyer flask for 0.5 h. The α-D-glycopyranosyl bromide peracetate (18.0 g, D-galactose; 15.0 g, D-xylose) was added to the mixture and stirring was continued for 0.75 h (D-xylose) or 2.0 h (D-galactose). These reaction times are not necessarily optimal, but the reactions were complete.

The reaction mixture was filtered (Celite) and the residue was rinsed with chloroform (100 ml). The combined filtrates were washed with 20% aqueous potassium iodide (2 × 200 ml) and water (200 ml), dried (sodium sulfate), sampled for analyses by g.l.c. (n_β, Table I) and t.l.c. (diisopropyl ether); and concentrated *in vacuo* to a thick syrup. A sample of the syrup was dissolved in acetone–water (19:1, vol) containing silver nitrate (3%) and analyzed by t.l.c. (diisopropyl ether). Crystallization solvents, yields, and physical constants are recorded in Table I.

Cyclohexyl tetra-*O*-acetyl-*β*-D-galactopyranoside (5.5 g), which could not be crystallized, was purified (73% recovery) by dry-packed column chromatography on silica gel (2.5 × 100 cm, 135 g, Sargent–Welch, 60–200 mesh) with chloroform–ethyl acetate (6:1, vol) as the elution solvent. Residual solvent was removed under high vacuum (~0.05 mm Hg) at 60°.

Alkyl α-D-glycopyranoside peracetates. — Methyl α-D-glycopyranoside peracetates were obtained by acetylation of the respective glycosides (Pfanstiehl Laboratories, Inc.) with acetic anhydride in pyridine[20]. The remainder of the alkyl α-D-glycopyranoside peracetates were prepared by anomerization of the alkyl *β*-glycopyranoside peracetates with titanium tetrachloride[26]. Crystallization after conventional isolation of the product was generally difficult and tended to yield products having a short shelf-life. The syrup (~5 g) obtained by anomerization of each *β*-glycoside (6 g) was deacetylated with sodium methoxide in methanol[27],

concentrated *in vacuo*, refluxed in 0.3M NaOH (70 ml) for 2 h, and deionized by consecutive elution with distilled water (300 ml) through columns (50-ml burettes) of Amberlite IR-120 (H^+, 50 ml) and Amberlite MB-3 (H^+, OH^-; 50 ml). The effluent was concentrated to dryness *in vacuo*, and the product was acetylated with acetic anhydride in pyridine[20]. Several crystallizations were normally required to obtain a pure product, and yields, in general, were very low. Crystallization solvents and physical constants are given in Table I.

For n.m.r. analysis, a sample of each glycoside peracetate was deacetylated with sodium methoxide in methanol[27]. The solution was deionized with Amberlite MB-3, concentrated to dryness *in vacuo*, and the sample was dissolved* in deuterium oxide.

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REFERENCES

1 L. R. SCHROEDER AND J. W. GREEN, *J. Chem. Soc.*, (1966) 530.
2 W. G. OVEREND, in W. PIGMAN AND D. HORTON (Eds.), *The Carbohydrates*, Vol IA, 2nd ed., Academic Press, New York, 1972, p. 279.
3 H. M. FLOWERS, *Methods Carbohyd. Chem.*, 6 (1972) 474.
4 L. R. SCHROEDER, J. W. GREEN, AND D. C. JOHNSON, *J. Chem. Soc. B*, (1966) 447.
5 K. M. COUNTS AND L. R. SCHROEDER, in preparation.
6 C. K. DE BRUYNE AND G. VAN DER GROEN, *Carbohyd. Res.*, 25 (1972) 59.
7 F. H. NEWTH AND G. O. PHILLIPS, *J. Chem. Soc.*, (1953) 2904.
8 J. K. DALE, *J. Amer. Chem. Soc.*, 37 (1915) 2745.
9 R. L. WHISTLER, K. A. KIMMELL, AND D. F. DURSO, *J. Amer. Chem. Soc.*, 73 (1951) 3530.
10 L. ASP AND B. LINDBERG, *Acta Chem. Scand.*, 4 (1950) 1446.
11 C. K. DE BRUYNE AND F. G. LOONTIENS, *Nature*, 209 (1966) 396.
12 C. K. DE BRUYNE AND G. VAN DER GROEN, *Carbohyd. Res.*, 2 (1966) 173.
13 J. SWIDERSKI AND A. TEMERIUSZ, *Carbohyd. Res.*, 3 (1966) 225.
14 L. ASP AND B. LINDBERG, *Acta Chem. Scand.*, 4 (1950) 1386.
15 K. NISIZAWA, *Bull. Chem. Soc. Jap.*, 16 (1941) 155; *Chem. Abstr.*, 36 (1942) 430.
16 E. FISCHER AND E. F. ARMSTRONG, *Ber.*, 35 (1902) 3155.
17 B. HELFERICH AND W. OST, *Ber.*, 95 (1962) 2612.
18 R. HORI, *Yakugaku Zasshi*, 78 (1958) 523; *Chem. Abstr.*, 52 (1958) 17119a.
19 H. LIBERT, I. SCHUSTER, AND L. SCHMID, *Ber.*, 101 (1968) 1902.
20 M. L. WOLFROM AND A. THOMPSON, *Methods Carbohyd. Chem.*, 2 (1963) 211.
21 F. J. BATES AND ASSOCIATES, *Polarimetry, Saccharimetry, and the Sugars*, Circular C440, U.S. Gov. Printing Office, Washington, D.C., 1942.
22 J. CONCHIE AND G. A. LEVVY, *Methods Carbohyd. Chem.*, 2 (1963) 335.
23 D. H. BRAUNS, *J. Amer. Chem. Soc.*, 47 (1925) 1280.
24 B. CAPON, P. M. COLLINS, A. A. LEVY, AND W. G. OVEREND, *J. Chem. Soc.*, (1964) 3242.
25 D. D. REYNOLDS AND W. L. EVANS, *J. Amer. Chem. Soc.*, 60 (1938) 2559.
26 E. PACSU, J. JANSON, AND B. LINDBERG, *Methods Carbohyd. Chem.*, 2 (1963) 376.
27 A. THOMPSON, M. L. WOLFROM, AND E. PACSU, *Methods Carbohyd. Chem.*, 2 (1963) 215.

*The spectrum of cyclohexyl α-D-xylopyranoside was obtained with a heated solution, because of the low solubility of the compound at normal probe temperature.