Note

Synthesis of substituted 2-phenoxyethyl β-D-glucopyranosides

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In previous reports [1–4], the synthesis and properties of several halogenoalkyl glycosides were discussed. We now report on the reaction of 2-bromoethyl tetra-*O*-acetyl-β-D-glucopyranoside with various mono-substituted phenols. The resulting glycosides were required for a comparison of their pharmacological activity with that of active phenoxy alcohols.

EXPERIMENTAL

General. — Infrared spectra were obtained on a Beckman IR-5A spectrophotometer. N.m.r. spectra were determined at 100 MHz on a Varian HA-100 spectrometer for solutions in $CDCl_3$ or D_2O, with tetramethylsilane or sodium 4,4-dimethyl-4-silapentane-1-sulphonate as internal standards. Optical rotations were measured with a Zeiss polarimeter, Type 58510. Melting points were determined with an Electrothermal apparatus. 2-Bromoethyl tetra-*O*-acetyl-β-D-glucopyranoside was prepared as previously reported[2]. The phenols used were commercial products (analytical grade), purified by vacuum distillation or recrystallization. The sodium phenoxides were prepared by adding to the phenol the theoretical quantity of aqueous sodium hydroxide, followed by evaporation. Alternatively, the stoichiometric quantity of the phenol was added to an ethanolic solution of sodium ethoxide and the resulting solution was used directly.

Syntheses of tetra-O-acetyl-β-D-glucopyranosides of substituted phenols. — On boiling a solution of 2-bromoethyl tetra-*O*-acetyl-β-D-glucopyranoside (5 mmoles) and the monosubstituted sodium phenoxide (7.5 mmoles) in ethanol (60 ml) for 32 h, condensation was complete. Good yields were also obtained by adding the equivalent quantity of alcoholic potassium hydroxide to an alcoholic solution of the phenol, followed by refluxing. The reaction mixtures were evaporated to dryness under diminished pressure and the residues, usually syrupy, were re-acetylated with acetic anhydride–pyridine. The acetates were isolated by the usual extraction procedure with chloroform. The compounds so prepared are listed in Table I.

TABLE I

SUBSTITUTED 2-PHENOXYETHYL β-D-GLUCOPYRANOSIDES AND THEIR TETRA-ACETATES

Substituent	*Yield* (%)	*M.p.* (*degrees*)	$[\alpha]_D^{20}$ (*degrees*)	*Found* (%)				*Formula*	*Calc.* (%)			
				C	*H*	*Cl*	*N*		*C*	*H*	*Cl*	*N*
Tetra-acetates												
Parent compound	31	85–86	−13.7	56.8	5.8			$C_{22}H_{28}O_{11}$	56.5	5.9		
o-Methyl	32	143–144	−9.9	57.3	6.2							
m-Methyl	42	133	−5.2	57.4	6.2			$C_{23}H_{30}O_{11}$	57.4	6.2		
p-Methyl	27.5	123–125	−2.8	57.4	6.4							
o-Nitro	68	114–115	−33.9	51.1	5.1		2.49					
m-Nitro	66.4	118.5–120	−16.2	51.3	5.3		2.7	$C_{22}H_{27}NO_{13}$	51.4	5.2		2.7
p-Nitro	76.1	119.5–121	−14.9	51.1	5.4		2.8					
o-Chloro[11]	54.3	90–92	−18.0									
m-Chloro	42.1	92–93	−20.3	52.8	5.3	6.8		$C_{22}H_{27}ClO_{11}$	52.5	5.4	7.0	
p-Chloro[11]	33.1	78	−19.1									
Deacetylated compounds												
o-Nitro	87	109	−9.9	48.5	5.5		4.0					
m-Nitro	80	115–116	−13.0	48.6	5.4		4.0	$C_{14}H_{19}NO_9$	48.7	5.5		4.0
p-Nitro	93	141–145	[a]	48.5	5.4		3.6					
o-Chloro[11]	85.3	Syrup	−17.2									
m-Chloro	80.9	74	−11.0	50.1	5.7	10.4		$C_{14}H_{19}ClO_7$	50.2	5.7	10.5	
p-Chloro, hemihydrate[11]	77.7	53	−16.1					$C_{14}H_{19}ClO_7 \cdot 0.5H_2O$				
Other compounds												
1,2-*O*-Ethylene-β-D-glucopyranose	variable	215–217	+58.0	46.6	6.9			$C_8H_{14}O_6$	46.6	6.8		
1,2-*O*-Ethylene-β-D-glucopyranose triacetate	94	125.5–127	+51.3	50.4	6.0			$C_{14}H_{20}O_9$	50.6	6.0		

[a]Optical rotation could not be measured because of coloured solution.

After many of these reactions, a second product, 1,2-*O*-ethylene-β-D-glucopyranose was isolated (see Table I), and further characterised as the triacetate.

Deacetylated compounds. — By treatment of the acetates with catalytic quantities of sodium methoxide[5], the D-glucosides described in Table I were prepared.

DISCUSSION

All the compounds prepared retained the β-D configuration, as indicated by the $[\alpha]_D$ values and by the presence of an i.r. band at ~900 cm^{-1} characteristic[4,6,7] of an axial H-1.

When the phenol carried an electron-donating substituent, such as methyl, the yield of glucoside was lower than when an electron-withdrawing substituent (*e.g.* nitro) was present. In the cresol series, the higher yield (42%) of *m*-isomer (*cf.* 32% for *o*- and 27.5% for *p*-isomer) is apparently related to the greater acidity of the corresponding phenol. Similarly with the other substituents, the yield is related to the acidity of the corresponding phenol.

The structure of 1,2-*O*-ethylene-β-D-glucopyranose was determined by i.r. and n.m.r. spectroscopic data, and by elemental analysis. The i.r. spectrum showed a peak at 890 cm^{-1} which is attributed[6] to H-1 in the sugar ring. The n.m.r. spectrum (and that of the triacetate) contained a doublet for H-1 at τ 5.55 ($J_{1,2}$ 8 Hz), characteristic of H-1 and H-2 in *trans*-diaxial positions, and a sextuplet at τ 6.60, assignable to cyclic ether protons[8]. The coupling constants of the latter peaks were distributed symmetrically between 8–9 and 3–4 Hz, indicating dihedral angles of ~180° and ~60° between the neighbouring protons of the $-CH_2-CH_2-$ grouping. These data are consistent with a dioxane ring in a chair conformation, and therefore with a 1,2-location of the ethylene substituent. A substance having very similar physical constants has been described by Höök and Lindberg[9] and by Helferich[10], who also assigned a bicyclic structure. The compound is undoubtedly formed by intramolecular dehydrohalogenation of the halogenoalkyl glycoside under alkaline conditions.

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