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Note

Synthesis of some β-D-glucopyranosides having a hydrophobic aglycon group terminated with a hydrophilic group

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Over the years, extensive studies on the transport of D-glucose in the small intestine of the hamster have shown it to have those kinetic characteristics that are commonly attributed to carrier transport[1–3]. Studies with other substrates have also been undertaken to obtain some information on the specificity of transport and, among these, a variety of D-glucosides has been shown to be actively transported by the D-glucose transport-system[4,5]. These D-glucosides appear to have lipid-soluble aglycon groups, and this property was tentatively interpreted[2] to indicate that lipid solubility of the aglycone may be a requisite for a D-glucoside to be translocated by the D-glucose transport-system. We have investigated this hypothesis by studying as substrates D-glucosides that have an alkyl chain in the range of 2–18 carbon atoms[6]. These studies have shown that D-glucosides that are insoluble in water owing to the chain length of the aglycon are nonetheless transported actively by the D-glucose transport-system when in the form of mixed micelles with sodium taurocholate. To extend these studies, we have synthesized β-D-glucosides having similar aglycon fatty-chains but with a hydroxyl group or a D-glucose moiety terminating the chain. In this paper, we report the methods of synthesis and characterization of these compounds. These syntheses were achieved by condensation of the appropriate diols with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of mercuric cyanide, and the resultant products were separated by chromatography on silica gel.

The Koenigs–Knorr reaction, modified by the addition of mercuric cyanide in nitromethane solution, leads to the formation of β-D- and α-L-linked glycosides[7–10] and, in some cases, α-D-linked glycosides have been isolated[11,12]. The acetylated D-glucosides and diglucosides reported here showed negative specific optical rotations (Tables I and II) and n.m.r. data (chloroform-*d*) for the anomeric protons (δ ~4.45–4.52, $J_{1,2}$ ~7.8–7.9 Hz) analogous with the data of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[13].

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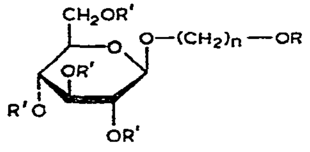
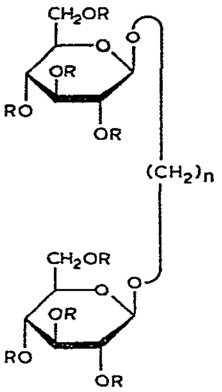
Condensation of the diols with an excess of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of mercuric cyanide resulted in a variety of products that were difficult to separate. The formation of some of these products may be explained by transesterification of an acetyl group of the carbohydrate residue to one of the hydroxyl groups of the diol, and the de-esterified carbohydrates may react further with the bromide present in excess to form a variety of disaccharides. However, a low proportion of bromide gave rise to only three or four major reaction products, and only one of them was probably the result of transesterification.



1 R = H, R′ = Ac, n = 4
2 R = R′ = Ac, n = 4
3 R = R′ = H, n = 4
4 R = H, R′ = Ac, n = 6
5 R = R′ = Ac, n = 6
6 R = R′ = H, n = 6



7 R = Ac, n = 4
8 R = H, n = 4
9 R = Ac, n = 6
10 R = H, n = 6

Condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with diols (1:4 molar ratio) in the presence of mercuric cyanide resulted in three types of compounds: (a) 4-hydroxybutyl (**1**) and 6-hydroxyhexyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**4**), where one hydroxyl group is linked and the other hydroxyl group remains free; (b) 4-acetoxybutyl (**2**) and 6-acetoxyhexyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**5**), where one hydroxyl group is transesterified with an acetyl group of the carbohydrate residue and the other hydroxyl group is linked to a 2,3,4,6-tetra-acetyl-β-D-glucopyranosyl residue; and (c) tetramethylene (**7**) and hexamethylene bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside) (**9**), where both hydroxyl groups are linked to a 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl residue.

Deacetylation of **1** and **2** with a catalytic amount of sodium methoxide gave 4-hydroxybutyl β-D-glucopyranoside (**3**), and of **4** and **5** gave 6-hydroxyhexyl β-D-glucopyranoside (**6**), respectively. Compounds **3** and **6** were identified by analytical, spectral, and optical data. Tetramethylene (**8**) and hexamethylene β-D-glucopyranoside (**10**) were obtained by deacetylation of **7** and **9**. Molecular-weight determinations, estimations of D-glucose and acetyl groups, i.r. spectra, and the data reported in Tables I and II are evidence for the structures shown.

TABLE I

PROPERTIES AND ANALYTICAL DATA OF THE COMPOUNDS FORMED IN THE REACTION OF 1,4-BUTANEDIOL WITH 2,3,4,6-TETRA-*O*-ACETYL-α-D-GLUCOPYRANOSYL BROMIDE

Properties and analytical data	*Compounds* 1	2	3	7	8
Yield (%)	12.5	14.4		10.0	
M.p. (°)	71–73	75–77	99–100	139–140	174–175
$[\alpha]^{24}_{D}$ (°)	−22.2	−20.0	−37.0	−30.0	−68.5
	(*c* 0.95)[a]	(*c* 0.95)[a]	(*c* 0.85)[b]	(*c* 0.95)[a]	(*c* 0.85)[b]
R_F (t.l.c.)	0.54[c]	0.16[c]	0.68[d]	0.40[c]	0.53[d]
Anal. Calc. for:	$C_{18}H_{28}O_{11}$	$C_{20}H_{30}O_{12}$	$C_{10}H_{20}O_{7}$	$C_{32}H_{46}O_{20}$	$C_{16}H_{30}O_{12}$
C	51.40	51.94	47.62	51.20	46.37
H	6.66	6.49	7.93	6.13	7.24
Mol. wt.	420	462		750	
Found:					
C	51.55	51.72	47.49	51.11	46.30
H	6.54	6.51	7.95	6.27	7.28
Mol. wt.	458	480		723	
D-Glucose[e] per mol	1	1	1	2	2

[a] In chloroform. [b] In methanol. [c] In 1:19 (v/v) methanol–benzene. [d] In 4:5:1 (v/v) butanol–acetone–water. [e] By the D-glucose oxidase method[17,18] after hydrolysis with M hydrochloric acid.

TABLE II

PROPERTIES AND ANALYTICAL DATA OF THE COMPOUNDS FORMED IN THE REACTION OF 1,6-HEXANEDIOL WITH 2,3,4,6-TETRA-*O*-ACETYL-α-D-GLUCOPYRANOSYL BROMIDE

Properties and analytical data	*Compounds* 4	5	6	9	10
Yield (%)	11.2	14.0		9.5	
M.p. (°)	58–60	63–65	105–107	118–120	138–140
$[\alpha]^{24}_{D}$ (°)	−20.5	−19.0	−35.0	−27.0	−54.5
	(*c* 0.95)[a]	(*c* 0.95)[a]	(*c* 0.85)[b]	(*c* 0.95)[a]	(*c* 0.85)[b]
R_F (t.l.c.)	0.58[c]	0.21[c]	0.76[d]	0.44[c]	0.62[d]
Anal. Calc. for:	$C_{20}H_{32}O_{11}$	$C_{22}H_{34}O_{12}$	$C_{12}H_{24}O_{7}$	$C_{34}H_{50}O_{20}$	$C_{18}H_{34}O_{12}$
C	53.75	53.87	51.43	52.44	48.87
H	7.14	6.93	8.57	6.43	7.69
Found:					
C	53.74	53.85	51.37	52.35	48.85
H	7.14	7.01	8.52	6.60	7.70
D-Glucose[e] per mol	1	1	1	2	2

[a,b,c,d,e] See footnotes to Table I.

EXPERIMENTAL

General methods. — Melting points were determined with a Gallenkamp melting-point apparatus. Optical rotations were measured with a Rudolph–Model 80 polarimeter. Infrared spectra were recorded with a Perkin–Elmer Model 237B spectrophotometer on potassium bromide pellets. The n.m.r. spectra were recorded with a Varian A-60A spectrometer for a solution in chloroform-*d*, with tetramethylsilane as internal standard. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J. Molecular weights were determined by the Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

T.l.c. was performed with 1:19 (v/v) methanol–benzene for acetylated compounds and 4:5:1 (v/v) butanol–acetone–water for deacetylated compounds on Silica gel G (Merck) precoated on glass plates. Generally, t.l.c. plates were sprayed with naphthorescorcinol–phosphoric acid[14,15] and then dried at 100–105° for a few min to give characteristic colors.

Reaction of 1,4-butanediol and 1,6-hexanediol with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide. — A stirred solution of 1,4-butanediol or 1,6-hexanediol (200 mmol) in 1:1 (v/v) nitromethane–benzene was boiled until ~50 ml of the solvent mixture had distilled to ensure complete dehydration and then cooled to room temperature. Mercuric cyanide (50 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (50 mmol) were added, and the reaction mixture was heated at reflux for 5 days at 60–70° with the exclusion of moisture. After being cooled, the reaction mixture was diluted with benzene (60 ml) and washed successively with a cold, saturated aqueous solution of sodium hydrogencarbonate and water, dried with anhydrous sodium sulfate, and concentrated *in vacuo*. On examination by t.l.c., the syrups obtained showed three majors spots for each reaction mixture, corresponding to **1**, **2**, and **7** for compounds derived from 1,4-butanediol, and **4**, **5**, and **9** for compounds derived from 1,6-hexanediol.

They were separated by column chromatography on columns (2.5 × 100 cm) of silica gel (60–200 mesh, Baker Chemical, Phillipsburg, N.J.) with 1:19 (v/v) methanol–benzene. The first 200 ml of eluate were discarded as it gave a negative test for carbohydrates. Fractions (500–600) of 7.0-ml volume were collected. The fractions containing materials that showed on t.l.c. an R_F similar to those of **1**, **2**, **4**, **5**, **7**, and **9** were pooled separately and dried *in vacuo*. Column chromatography was repeated until the products appeared to be homogeneous. The products were amorphous solids and the overall yield was 37%.

Deacetylation was performed with sodium methoxide[16] in dry methanol solution, and the solution was de-ionized by passage through a small column of methanol-washed Amberlite IR-120 (H^+) ion-exchange resin. The properties and analytical data are reported in Tables I and II.

ACKNOWLEDGMENTS

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