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Synthesis of some 2-*O*-(2-hydroxyalkyl) and 2-*O*-(2,3-dihydroxyalkyl) derivatives of cyclomaltoheptaose

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ABSTRACT

On alkylation of cyclomaltoheptaose with oxiranes, promoted by alkali of low concentration, substitution at secondary positions, particularly at O-2, is favoured. The reaction has been used to prepare the 2-*O*-[(*R*)- and (*S*)-2-hydroxypropyl], 2-*O*-(2-hydroxy-2-methylpropyl), 2-*O*-[(*R*)- and (*S*)-2,3-dihydroxypropyl], and 2-*O*-[(*R*)- and (*S*)-2,3-dihydroxy-2-methylpropyl] derivatives. Each of these derivatives is less soluble in water than cyclomaltoheptaose, and their complexes with toluene, in contrast to that of cyclomaltoheptaose, are well soluble in water.

INTRODUCTION

Alkylation of cyclomaltoheptaose (**2**) with propylene oxide in alkaline, aqueous solution gives mixtures of 2-*O*-hydroxypropyl derivatives, which may be used as host molecules for lipophilic drugs and thus increase their solubility in water[1]. Their methylated derivatives have been used as stationary phases for g.l.c.[2]. The distribution of substituents between different molecules of these 2-*O*-hydroxypropyl derivatives has been determined by plasma-desorption mass spectrometry[3], and the distribution between the 2-, 3-, and 6-positions in the α-D-glucopyranosyl residues by methylation analysis[4,5]. It was observed[5] that the relative reactivities at the primary and secondary positions depended on the concentration of alkali. Thus, high and low concentrations of alkali favoured the alkylation of primary and secondary positions, respectively. The 2-position was more reactive than the 3-position, but the reactivity of the latter increased when O-2 was alkylated.

When a low concentration of alkali was used with an excess of cyclomaltoheptaose, O-2 was preferentially alkylated, and these conditions were used to prepare pure 2-*O*-[(*R*)- and (*S*)-2-hydroxypropyl]cyclomaltoheptaose[6]. We now report on the synthesis of some analogous 2-*O*-alkyl derivatives, using different oxiranes.

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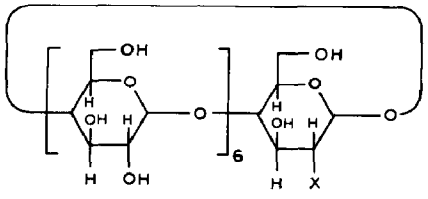
RESULTS AND DISCUSSION

The following oxiranes were used: (*R*)- (**1a**) and (*S*)-propylene oxide (**1b**) (as reported[6]), 2-methyl-1,2-epoxypropane (**1c**), (*R*)- (**1d**) and (*S*)-2,3-epoxy-1-propanol (**1e**) [(*R*)- and (*S*)-glycidol], and (*R*)- (**1f**) and (*S*)-2-methyl-2,3-epoxy-1-propanol (**1g**) [(*R*)- and (*S*)-2-methylglycidol]. The alkylations were promoted by 0.38M sodium hydroxide, and the molar ratio of cyclomaltoheptaose to the oxirane was ~1:0.75. The starting material (**2**) and its 2-*O*-alkyl derivatives (**2a–2g**) were not very soluble in water (Table I) and crystallised from the reaction mixture after acidification. On stirring with

TABLE I

Solubilities and association constants of the mono-2-*O*-alkylated cyclomaltoheptaoses



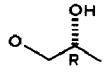
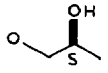
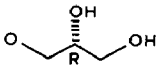
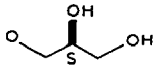
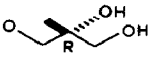
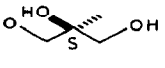
Substance	*Substituent X*	*Solubility (%)*		K_{assoc} *with phenolphthalein* ($\times 10^{-4}$ M^{-1})
		In water	*In water with excess of toluene*	
2	OH	1.80	0.20	2.17
2a		0.75	1.55	2.30
2b		0.32	0.57	2.40
2c		0.29	0.42	2.10
2d		1.54	2.22	2.55
2e		1.19	2.08	2.75
2f		0.66	1.05	2.73
2g		0.35	0.62	2.79

TABLE II

Yields on synthesis and some properties of the mono-2-*O*-alkylated cyclomaltoheptaoses

Substance	*Yield (%)*	*Recovered starting material (%)*	*M.p. (dec.)*	R_F *(degrees)*	*F.a.b.-m.s. (positive ion)*
2	–	–	280	0.18	–
2a	5.2	93	290	0.27	1193.5[a]
2b	4.7	94	292	0.27	1193.2[a]
2c	3.0	92	297	0.31	1229.3[b]
2d	7.0	79	295	0.18	1231.4[b]
2e	9.8	77	298	0.18	1231.6[b]
2f	3.5	85	289	0.24	1245.5[b]
2g	5.3	79	289	0.24	1245.7[b]

[a] $[M + H]^+$. [b] $[M + Na]^+$.

water and toluene, each derivative formed a complex, but, whereas that of **2** crystallised, the others stayed in solution. This situation facilitated the isolation of the 2-*O*-alkyl derivatives, which were recovered from the aqueous solution and purified by crystallisation from water. The yields of the pure substances were low (3–5%, Table II), but most of the starting material (80% or more) was recovered as its complex with toluene.

The purity of the products was investigated by methylation analyses[5] (Table III). Compounds **2d–2g** each gave only two alditol derivatives, formed from unsubstituted and 2-*O*-substituted D-glucopyranosyl residues, respectively, in the molar proportions ~6:1. The alditol derivatives were identified from their e.i.-mass spectra, which, *inter alia*, showed the typical fragments a and *m/z* 233, obtained on fission between C-2 and C-3 as indicated in **3**. On methylation analysis of **2c**, which had been alkylated with 2-methyl-1,2-epoxypropane, no 2-methoxy-2-methylpropyl derivative was detected but only the acetylated 3,6-di- and 2,3,6-tri-*O*-methyl-D-glucitol derivatives (6 and 94 mole%, respectively) were obtained. The 2-methoxy-2-methylpropyl group, which contains a tertiary ether grouping, was eliminated during the hydrolysis with acid. On

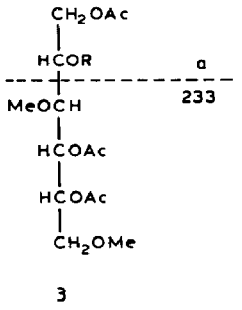
TABLE III

Methylation analysis of **2a–2g**

Substance	S_0[a]	S_2[a]	*D.s.*[b]	*Fragment a*[c]	$[M + Na]^+_{Calc.}$	$[M + Na]^+_{Found}$
2a	85.6	14.4	1.01	175	–	–
2b	86.5	13.5	0.95	175	–	–
2c	–	–	–	–	1523.8	1524.4
2d	88.0	12.0	0.84	205	1539.8	1540.3
2e	84.9	15.1	1.05	205	1539.8	1540.3
2f	87.1	12.9	0.91	219	1553.8	1554.4
2g	87.1	12.9	0.91	219	1553.8	1554.4

[a] Molar percentages of acetylated 2,3,6-tri-*O*-methyl- and 2-*O*-alkyl-3,6-di-*O*-methyl-D-glucitol, respectively. [b] Average number of substituents per cyclomaltoheptaose unit. [c] *m/z* of fragment a (see formula **3**).

f.a.b.-m.s., each methylated product, however, gave the expected $[M + Na]^+$ ion after mixing with sodium acetate. Otherwise, they each gave an ion with 5 mass units less, probably the $[M + NH_4]^+$ ion. For some samples, traces of ions derived from unsubstituted and/or disubstituted products were also observed.



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Samples **2a–2g** gave single spots in t.l.c., but the (*R*) and (*S*) derivatives were not separated (Table II). The purity was further confirmed by ^{252}Cf plasma-desorption m.s., by which the $[M + Na]^+$ ions of the mono-*O*-alkyl derivatives, but no other ions, were detected. The ^1H-n.m.r. spectra of **2a–2g** contained, *inter alia*, signals at δ 5.21–5.25 (1 H, $J_{1,2}$ 3–4 Hz) and 5.07–5.08 (6 H, $J_{1,2}$ 3–4 Hz), assigned to H-1 of the substituted and unsubstituted α-D-glucopyranosyl residues, respectively (*cf.*, Fig. 1A). In other respects, the spectra were in agreement with the postulated structures.

Each of the derivatives **2a–2g** was less soluble in water than cyclomaltoheptaose (Table I). In the crystal structure of **2b**[7], the 2-hydroxypropyl group of one molecule is inserted into the cavity of an adjacent molecule, leading to tightly packed chains in the crystal lattice. This arrangement is probably a common feature for this group of substances and accounts for their low solubilities. The (*S*) forms were less soluble in water than the (*R*) forms. An additional methyl group decreased the solubility and an additional hydroxyl group had the opposite effect. The solubility of each of the 2-*O*-alkyl derivatives was enhanced by complex formation with toluene. That a complex has formed was confirmed by ^1H-n.m.r. spectroscopy. The spectrum of a solution of **2a** in D_2O, when compared with a spectrum of the same solution which had been stirred with toluene (Fig. 1), showed that a 1:1 complex had been formed, and the significant shift of the H-5 signals is typical for such complexes[8]. The cavity in the cyclomaltoheptaose moiety was filled in the complex, so that the 2-*O*-substituent of an adjacent molecule could not be accommodated, and this may explain why the complexes, unlike the cyclomaltoheptaose–toluene complex, did not crystallise. In order to check the influence of the 2-*O*-substituent on the complexation ability in **2a–2g**, their association constants with phenolphthalein[9] were measured and compared with that of **2** (Table I). The values were not substantially different, which indicated that the alkyl group did not significantly hinder the association of this guest molecule.

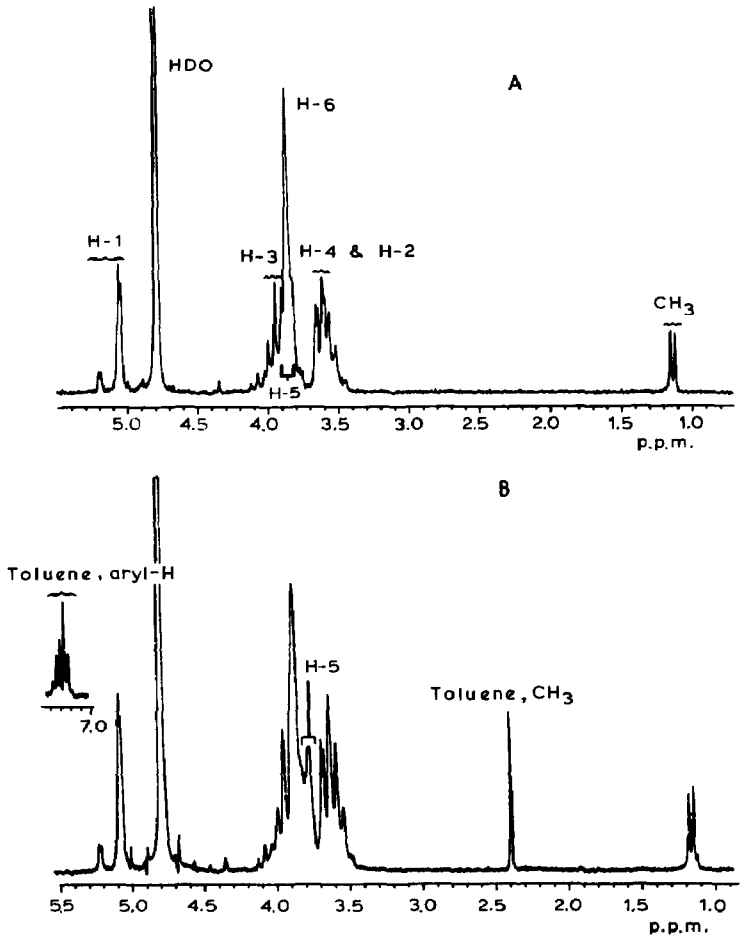

Fig. 1. *A*, ^{1}H-N.m.r. spectrum of 2-*O*-[(*R*)-2-hydroxypropyl]cyclomaltoheptaose (**2a**); *B*, ^{1}H-n.m.r. spectrum of the complex between **2a** and toluene.

When cyclomaltohexaose and cyclomalto-octaose were treated with (*S*)-propylene oxide under conditions similar to those used for cyclomaltoheptaose, the 2-[(*S*)-2-hydroxypropyl] derivatives did not precipitate together with the starting material after acidification. The unreacted starting material was precipitated on treatment with cyclohexane and *p*-cymene, respectively. The crude material obtained on concentration of the mother liquors contained mainly mono-2- and 3-*O*-alkyl derivatives, as revealed by methylation analysis.

EXPERIMENTAL

General methods. — N.m.r. spectra for solutions in D_2O were determined at 24° with a Varian XL 200 instrument. The HDO signal, at δ 4.80, was used as internal reference. A JEOL SX102 instrument and a thioglycerol matrix were used for f.a.b-m.s. T.l.c. was performed on silica gel, using 1-propanol–water–ethyl acetate–conc. ammonia (6:3:1:1). Methylation analyses were performed as described[5]. Association constants with phenolphthalein were determined as devised by Vikmon[9]. Solubilities were determined by concentration of a defined volume of a solution, saturated at 22°, and weighing of the dried residue.

Alkylation of cyclomaltoheptaose. — In a typical experiment, a mixture of cyclomaltoheptaose (53 g, 40.6 mmol) and 3-methyl-1,2-epoxypropane (**1c**; 2.2 g, 30 mmol) in aqueous 0.38M sodium hydroxide (200 mL) was stirred at 0° for 10 h, then at room temperature for 60 h. The mixture was neutralised with 5M hydrochloric acid, the precipitate was collected, the filtrate was dialysed for 7 h against distilled water and then concentrated to 25 mL, and the precipitate was collected. A suspension of the combined solids in water (500 mL) was stirred overnight with toluene (50 mL), the solid (49 g) was collected, and the filtrate was concentrated to dryness. The product was crystallised from water to give **2c** (1.7 g, 3.0%).

The other 2-*O*-alkylcyclomaltoheptaoses were prepared in an analogous manner and the relevant data are given in Table II. The elemental analyses of **2a–2g** were not very good, as these substances contain non-stoichiometric amounts of water which is difficult to remove by drying.

Hydroxypropylation of cyclomaltohexaose and cyclomalto-octaose. — A mixture of cyclomaltohexaose (222 g, 0.21 mmol) and (*S*)-propylene oxide (8.3 g, 0.14 mmol) in aqueous 0.38M sodium hydroxide (800 mL) was kept at 0° for 10 h, then at room temperature for 9 h, neutralised with 5M hydrochloric acid, and filtered. The filtrate was concentrated to 200 mL, dialysed for 6 h, diluted to 550 mL, stirred with cyclohexane (60 mL) for 24 h, and filtered. The filtrate was concentrated to 130 mL, stirred with cyclohexane (30 mL), and filtered. The filtrate was decolorised with Norite (9 g), then concentrated to dryness, and residual water was removed by codistillation with anhydrous ethanol. The amorphous product (6.2 g, 2.6%) was characterised by methylation analysis, which indicated an average d.s. of 0.88 and 2- and 3-mono-*O*-alkylated α-D-glucopyranosyl residues in the ratio 1:0.7.

The reaction between cyclomalto-octaose and (*S*)-propylene oxide was performed in an analogous manner, except that *p*-cymene was used for the precipitation of the starting material. The amorphous product (4.1%) had d.s. 0.97, and contained, in addition to 2- and 3-substituted α-D-glucopyranosyl residues, also low percentages of 2-*O*-[2-(*S*)-1-hydroxypropyl], 6-*O*-[(*S*)-2-hydroxypropyl], and 2,3-di-*O*-[(*S*)-2-hydroxypropyl] residues.

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