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Note

Reaction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside with ethanolamine and 1,4,7,10-tetraoxa-13-azacyclopentadecane

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Chiral crown derivatives have gained importance for the resolution of racemates and as ligands in ion-selective electrodes[1]. We have reported several crown ethers where the chirality originated from a monosaccharide moiety[2–5] and now report on novel sugar-azacrown ethers obtained from methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**1**).

Rigid *trans*-fused bicyclic derivatives of 2,3-anhydropyranosides react regioselectively during nucleophilic ring-opening[6]. Thus, according to the Fürst–Plattner rule, the anhydroallose derivative **1** will yield mainly 2-substituted *altro* derivatives on reaction with amines[7], the 3-substituted *gluco* derivatives being minor products.

Reaction of **1** with ethanolamine (2-aminoethanol) gave 71% of **2** but, with 1,4,7,10-tetraoxa-13-azacyclopentadecane, the crown derivatives **3** and **4** were obtained in yields of 31 and 27%, respectively, and 25% of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was detected. The structures of **2–5** were established on the basis of ^{1}H- and ^{13}C-n.m.r. data (Tables I and II). The ^{13}C–^{1}H heteronuclear shift-correlated experiments[8] indicated that the previous[9] assignment of ^{13}C resonances for C-2 and C-3 should be reversed. The value (0.8 Hz) of $J_{1,2}$ for methyl 4,6-*O*-benzylidene-α-D-altropyranoside significantly differs from that (3.6 Hz) of the *gluco* isomer[10]. Thus, **2** ($J_{1,2}$ 0.9 Hz) has the *altro* configuration. A 2-substituted

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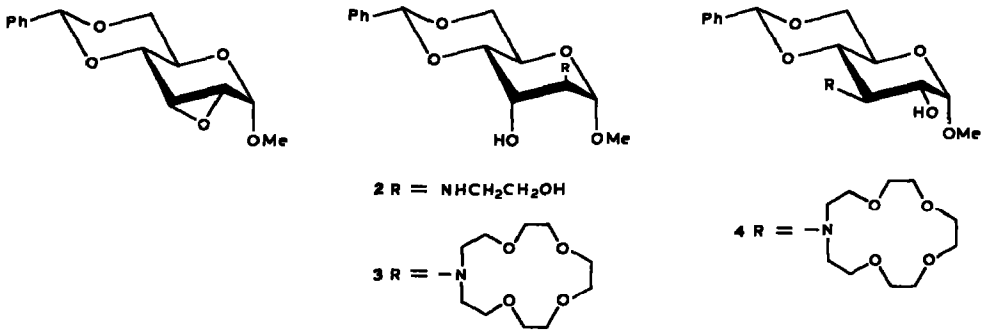

altrose structure is also indicated by the H-2 signal, which appears at highest field (2.99 p.p.m.), and the $J_{2,3} = J_{3,4} = 2.9$ Hz coupling constants also support the altroside structure. The $J_{1,2}$ value (3.6 Hz) for **4** is characteristic for methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[10]. As a consequence of the 3-deoxy-3-azacrown structure, H-3 is the most shielded proton. The *gluco* structure is also supported by $J_{2,3} = J_{3,4} = 10.3$ Hz, which indicates that the 2,3-substituents are equatorial. The ^{1}H chemical shift data for the two products formed by the reaction of **1** with phthalimide[11] were quite different from our data, due to the anisotropic effect of the imide carbonyl groups, but the *J* values were similar. However, the assignments[11] of C-2 and C-5 in the *gluco* isomer, and C-3 and C-5 in the *altro* isomer, should be reversed.

The ^{13}C-n.m.r. data for **2–4** further supported the structures assigned on the basis of data[12] for methyl 4,6-*O*-benzylidene-α-D-gluco- (**5**) and -altro-pyranoside (**6**). Significant up-field shifts were observed for the C-2,3,4,5 signals of **6**. The

TABLE I

^{1}H-N.M.R. DATA FOR **1–4**

Compound	*Chemical shifts (δ)*								
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*H-7*	*MeO*
1	4.87	3.46	3.50	3.93	4.17	3.66	4.22	5.56	3.45
2	4.63	2.99	4.07	3.82	4.17	3.77	4.29	5.58	3.40
3	4.77	3.07	[a]	3.88	4.16	3.75	4.28	5.61	3.37
4	4.81	3.56[b]	3.19	3.62[b]	3.81	3.6[b]	4.21	5.44	3.39
	Coupling constants (Hz)								
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$^2J_{6,6'}$		
1	2.8	4.3	1.4	9.1	10.3	5.0	10.3		
2	0.9	2.9	2.9	9.8	10.1	5.1	10.1		
3	~0.7	2.1	3.2	10.0	10.0	5.0	10.2		
4	3.6	10.3	10.3	9.2	10.2	4.7	10.1		

[a]Overlapped with other signals. [b]Evaluated from the 2D C,H-COSY spectrum.

TABLE II

^{13}C-N.M.R. CHEMICAL SHIFT DATA FOR **1–6**[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	C_{ipso}	C_{ortho}	C_{meta}	C_{para}	CH_3O
1	95.27	53.07	50.65	77.82	60.00	68.85	102.69	137.13	126.26	128.26	123.17	55.80
2	101.4	60.51	68.41	76.71	58.40	69.14	102.26	137.22	126.21	128.20	129.07	55.57
3	101.7	65.77	66.47	77.32	57.65	63.28	102.00	137.25	126.02	128.13	128.93	55.13
4	99.99	68.26	62.18	78.27	63.45	69.23	100.97	137.40	125.85	128.08	128.75	55.11
5	99.69	73.27	71.02	80.91	60.96	68.62	101.6	136.74	126.14	128.13	128.98	55.40
6[b]	101.6	69.6	68.8	76.0	57.8	68.8	101.8					55.0

[a]P.p.m., measured in $CDCl_3$ at 100 MHz. [b]Data taken from ref. 12.

assignments were proved for **2** and **4** by ^{13}C–^{1}H heteronuclear shift-correlated spectroscopy[8] (data not shown). The only characteristic difference between **6** and **2** is at C-2. The up-field shift (9 p.p.m.) of the signal for C-2 in **2** reflects the effect[11,13–15] of replacing OH by N. Relative to the C-2 signal for **2**, that for **3** is shifted down-field by 5 p.p.m., reflecting the effect of the secondary and tertiary nitrogen substituents, respectively. A 2-p.p.m. up-field shift was observed for the signal of C-3 in **3** due to the substitution, as was a down-field shift of 2 p.p.m. for the signal for C-4 caused by the δ-steric effect[16].

A comparison of the ^{13}C data for **5** and **4** shows that the signal for C-3 is shifted up-field (9 p.p.m.) due to the OH → N substitution. The CH_2NCH_2 methylene causes different up-field shifts of the signals for C-2 and C-4 (5.01 and 2.64 p.p.m., respectively), indicating preponderant conformations where both NCH_2 groups are *gauche* to C-2 but only one is *gauche* to C-4 around the C-3–NCH_2 bond.

The reaction of **1** with the bulky azacrown ether does not accord with the Fürst–Plattner rule, probably because of the bulk of the nucleophile. Thus, the reaction of **1** with ammonia and methylamine yields[17] 91% and 86%, respectively, of the 2,3-diaxial products. With ethanolamine, the yield declines to 71%. The ratios of diaxial and diequatorial products is 15:1 in the reaction with azide ion[18], but 3:1 in the reaction with phthalimide[11].

EXPERIMENTAL

General. — Melting points were obtained with a Büchi apparatus and are uncorrected. Microanalyses were performed in the Microanalytical Laboratory of the Institute. N.m.r. measurements were carried out on solutions in $CDCl_3$ with Bruker AM-400 and JEOL FX-100 spectrometers operating at 9.2 and 2.3 tesla, respectively. The ^{13}C–^{1}H heteronuclear shift-correlated maps were produced with the aid of a pulse sequence devised for elimination of the proton–proton couplings[8].

*Methyl 4,6-O-benzylidene-2-deoxy-2-hydroxyethylamino-α-*D*-altropyranoside* (**2**). — A mixture of freshly distilled ethanolamine (10.0 g) and **1** (4.0 g) was heated for 6 h at 140° under argon and then cooled to 90°, and water (30 mL) was added with stirring. The mixture was stored at room temperature to give **2** (3.5 g, 70.7%), m.p. 160–162°, $[\alpha]_D^{20}$ +63° (*c* 1.1, methanol).

Anal. Calc. for $C_{16}H_{23}NO_6$: C, 59.07; H, 7.13; N, 4.30. Found: C, 59.48; H, 7.18; N, 4.43.

*Reaction of methyl 2,3-anhydro-4,6-O-benzylidene-α-*D*-allopyranoside* (**1**) *with 1,4,7,10-tetraoxa-13-azacyclopentadecane.* — A mixture of 1,4,7,10-tetraoxa-13-azacyclopentadecane (1.6 g) and **1** (3.0 g) was heated for 16 h at 180° under argon. The mixture was cooled and diluted with methanol, the unreacted **1** was removed, the filtrate was concentrated, and the residue was eluted from a column (30 × 400 mm) of Kieselgel (100 g) with toluene–methanol (3:2) to give, first, methyl 4,6-*O*-benzylidene-2-deoxy-2-(1,4,7,10-tetraoxa-13-azacyclopentadecanyl)-

α-D-altropyranoside (**3**; 1.1 g, 31.7%), isolated as a yellow syrup, $[\alpha]_D^{20}$ +45° (*c* 1.2, chloroform), R_F 0.59 (Kieselgel 60; toluene–ethanol–ammonia, 6:6:1). Mass spectrum: *m/z* 484 (M^+).

Anal. Calc. for $C_{24}H_{37}NO_9$: C, 59.62; H, 7.66; N, 2.89. Found: C, 59.60; H, 7.38; N, 2.71.

Eluted second was methyl 4,6-*O*-benzylidene-3-deoxy-3-(1,4,7,10-tetraoxa-13-azacyclopentadecanyl)-α-D-glucopyranoside (**4**), isolated as yellow syrup (0.95 g, 27.4%), $[\alpha]_D^{20}$ +39° (*c* 1.2, chloroform), R_F 0.32. Mass spectrum: *m/z* 483 (M^+).

Anal. Found: C, 59.94; H, 7.51; N, 2.69.

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