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Note

Synthesis of cyclohexakis- and cycloheptakis-(1 → 4)-(7-amino-6,7-dideoxy-α-D-*gluco*-heptopyranosyl), homoanalogues of 6-amino-6-deoxy-cyclomaltooligosaccharides

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Cyclomaltooligosaccharides (cyclodextrins), in which primary hydroxyl groups are replaced by amine functionalities are of interest since protonation of the amine may affect the selectivity of their complexing ability [1]. Interaction with membranes, in relation with their use as carrier agents in biological and medicinal fields may also be modified, and 6-aminodeoxycyclodextrins have been shown less haemolytic as compared to their hydroxylated natural precursor [2]. Changes in the geometry of such polar groups with respect to the cyclodextrin cavity, as with homoanalogues of 6-amino-6-deoxy-cyclomaltooligosaccharides, are thus of interest.

Acyl-protected cycloheptakis-(1 → 4)-(7-amino-6,7-dideoxy-α-D-*gluco*-heptopyranosyl) (**9**) was prepared earlier [3] by catalytic hydrogenation, over platinum oxide, of the corresponding urononitrile **4** followed by acetylation of the resulting product. The rather modest yield of this conversion (23%) is howewer an impediment for further utilization, such as deprotection of **9** to **8**, which had not previously been attempted. In an effort to find a more direct access to **8**, which could be generalized to other types of cyclomaltooligosaccharides, an alternative reduction scheme of cyclopyranosidurononitriles **3** and **4** was devised. In the meantime, **3** and **4** were conveniently prepared by nucleophilic displacement

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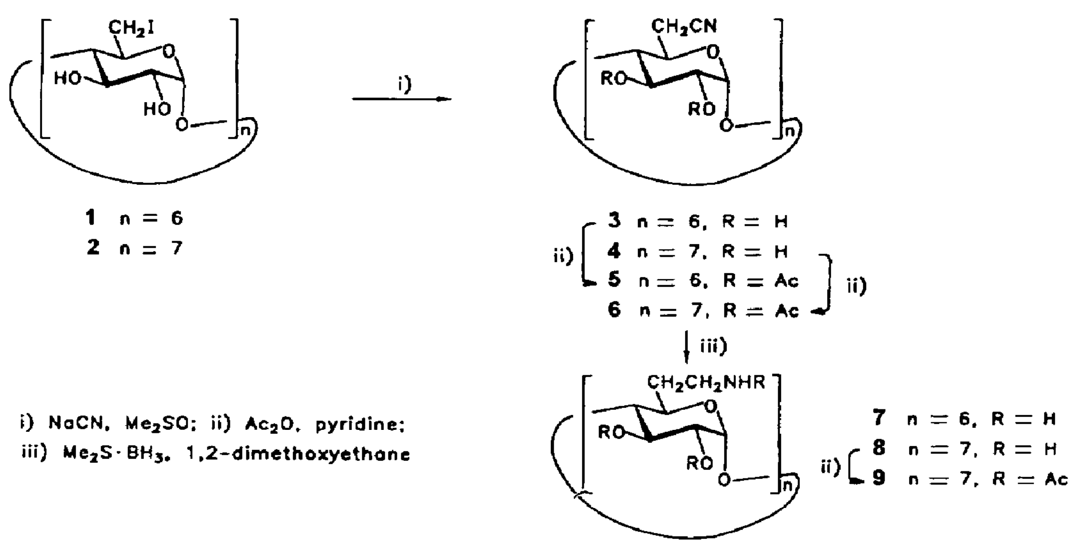

Scheme 1.

of either 6-deoxy-6-iodocyclomaltooligosaccharides (**1** or **2** [4], respectively) with sodium azide instead of lithium azide [3] in dimethyl sulfoxide, affording **3** and **4** in 86% yield.

The borane–dimethyl sulfide complex has already been used for the reduction of aromatic carboxylic acids and nitriles [5]. A main advantage of this commercialy available, stable source of borane is its solubility in a wide variety of solvents, and this makes it attractive for compounds of limited solubility in alkyl-ether solvents (such as tetrahydrofuran) commonly used in hydroboration reactions. When applied to acetylated nitriles **5** and **6** [3] in 1,2-dimethoxyethane, the reaction with dimethyl sulfide–borane proceeded smoothly and, after 1 day at 40°C, amines **7** and **8** were obtained in almost quantitative yields and isolated as their crystalline hydrochlorides. Proof of the structures for both compounds rely on the characteristic low-field ^{13}C NMR signals for C-6 and C-7 at ~28.6, and 37.0–37.2, ppm respectively. The cyclomaltoheptaose homoanalogue **8** was further correlated to its known [3] 7-acetamido-2,3-di-*O*-acetyl derivative **9** by acetylation with pyridine–acetic anhydride (see Scheme 1).

1. Experimental

Materials and methods.—The borane–methyl sulfide complex (Aldrich, Milwaukee, USA) contained ~5% excess methyl sulfide; the BH_3 concentration was ~10.0–10.2 M. Melting points were measured in capillary tubes with a Büchi 535 apparatus and are corrected. Microanalyses were performed under Ar by the Service Central de Microanalyse du CNRS (Solaize), for samples prepared in sealed tubes after drying under vacuum (60°C, 70 Pa, 24 h). ^{13}C NMR spectra were recorded at 50 MHz with a Bruker WP-200 apparatus in Me_2SO-d_6 (39.6 ppm), $CDCl_3$ (77.2 ppm) or D_2O (internal acetone at 31.1 ppm). FABMS (Cs, acceleration potential 8 kV) was measured in the positive-ion mode with a VG ZAB-SEQ instrument using glycerol–thioglycerol–aq 10% AcOH as the liquid matrix.

*Cyclohexakis(1 → 4)-(α-*D*-*gluco*-heptopyranosyl)urononitrile* (**3**).—To a stirred solution of hexakis(6-deoxy-6-iodo)cyclomaltohexaose [4] (**1**, 10 g, 6.13 mmol) in Me_2SO

(50 mL) was added NaCN (2 g, 40.8 mmol). The solution was stirred for 1 day at 80°C, and then cooled and DMF (200 mL) and a mixed bed ion-exchange resin (Amberlite MB-6113, 100 mL, previously washed with MeOH) were added. The suspension was stirred for 10 min, and then filtered and the filtrate was concentrated under diminished pressure. The residue was dispersed in EtOH, recovered from the suspension by centrifugation, and dried (5.4 g, 86%); mp 215–216°C, $[\alpha]_D$ +64.7° (*c* 0.97, Me_2SO). ^{13}C NMR (Me_2SO): δ 118.7 (CN); 102.3 (C-1); 86.1 (C-4); 72.7, 71.9, 67.3, (C-2,3,5); 21.3 (C-6). Anal. Calcd for $C_{42}H_{54}N_6O_{24}$: C, 49.12; H, 5.26, N, 8.19; . Found: C, 49.25; H, 5.41; N, 8.08.

*Cycloheptakis(1 → 4)-(α-*D-gluco-*heptopyranosyl)urononitrile* (**4**).—The procedure used for **3** was applied to the preparation of **4**, starting from heptakis(6-deoxy-6-iodo)cyclomaltoheptaose [4] (**2**, 10 g, 5.25 mmol) in Me_2SO (50 mL) to which was added NaCN (2 g, 40.8 mmol). The resulting **4** (5.4 g, 86%) had mp 277–278°C (dec); $[\alpha]_D$ +140° (*c* 1, DMF); lit. [3] mp 276–278°C (dec), $[\alpha]_d$+138° (*c* 0.7, DMF). ^{13}C NMR (Me_2SO): δ 118.4 (CN); 102.7 (C-1); 85.9 (C-4); 72.7, 72.4, 67.6, (C-2,3,5); 21.6 (C-6).

*Cyclohexakis(1 → 4)-(2,3-di-O-acetyl-α-*D-gluco-*heptopyranosyl)urononitrile* (**5**).—To crude **3** (4.7 g, 4.58 mmol) in pyridine (25 mL) was added Ac_2O (25 mL) and a catalytic amount of 4-dimethylaminopyridine. The solution was left for 2 days at room temperature, and then concentrated under diminished pressure with addition of MeOH (3×25 mL). The residue was dissolved in CH_2Cl_2 (200 mL), washed successively with H_2SO_4 (2 N), aq satd $NaHCO_3$ and water, and dried (Na_2SO_4). Solubilization in acetone and the addition of EtOH yielded crystalline **5** (6.10 g, 87%); mp 199–200°C, $[\alpha]_D$+100° (*c* 1.34, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.4 and 170.3 (2 CH_3CO) 117.3 (CN); 96.6 (C-1); 79.6 (C-4); 70.1, 69.9, 66.0, (C-2,3,5); 22.3 (C-6); 20.8 (CH_3CO). Anal. Calcd for $C_{66}H_{78}N_6O_{36}$: C, 51.76; H, 5.10; N, 5.49. Found: C, 51.53; H, 5.18; N, 5.11.

*Cyclohexakis(1 → 4)-(7-amino-6,7-dideoxy-α-*D-gluco-*heptopyranosyl)hydrochloride* (**7**).—To the crude acetylated nitrile **5** (1 g, 3.92 mmol) in anhyd 1,2-dimethoxyethane (40 mL), the commercial borane–methyl sulfide complex (4 mL, ~40 mmol) was gradually added with a syringe and the stirred solution was kept at 40°C for 1 day. After cooling to room temperature, MeOH (10 mL) was added, and the soln stirred for 1 day before the addition of water (10 mL). Concentration under diminished pressure led to a residue which was dissolved in water and neutralized with HCl (1 M, ~2 mL). The freeze-dried residue was dissolved in water and crystallized from water–MeOH (686 mg, 83%, hygroscopic); mp 125°C (dec); $[\alpha]_D$ +105.8° (*c* 1.04, H_2O). FABMS: 1051.7 (97, $[MH-6\,HCl]^+$); ^{13}C NMR (D_2O): δ 102.1 (C-1); 84.7 (C-4); 74.0, 72.5, 70.7 (C-2,3,5); 37.0 (C-7); 28.6 (C-6). Anal. Calcd for $C_{42}H_{78}N_6O_{24}\cdot 4\,H_2O$, 6 HCl: C, 37.58; H, 6.86; N, 6.26; Cl, 15.88. Found: C, 37.55; H, 6.86; N, 5.80; Cl, 13.47.

*Cycloheptakis(1 → 4)-(7-amino-6,7-dideoxy-α-*D-gluco-*heptopyranosyl)hydrochloride* (**8**).—The foregoing reduction procedure used to obtain **7** was applied to the preparation of **8**, starting from the acetylated nitrile **6** (0.51 g, 0.29 mmol, obtained from **4** according to Ref. [3]) to which the commercial borane–methyl sulfide complex (2 mL, 20 mmol) was added. The resulting amine hydrochloride crystallized from MeOH–water (0.40 g, 95%, hygroscopic); mp 205°C (dec); $[\alpha]_D$ +74.4° (*c* 1.07, H_2O). FABMS: 1226.9 (80, $[MH-7HCl]^+$); ^{13}C NMR (D_2O): δ 102.3 (C-1); 84.4 (C-4); 73.7, 72.9, 70.7 (C-

2,3,5); 37.2 (C-7); 28.6 (C-6). Anal. Calcd for $C_{49}H_{91}N_7O_{28} \cdot 4\,H_2O$, 7 HCl: C, 37.87; H, 6.38; N, 6.31; Cl, 16.0. Found: C, 37.87; H, 6.32; N, 6.30; Cl, 14.2.

*Cycloheptakis[(1 → 4)-(7-acetamido-2,3-di-O-acetyl-6,7-dideoxy-α-*D-gluco*-heptopyranosyl]hydrochloride* (**9**).—The crude amine, resulting from the borane–methyl sulfide reduction of **6**, was freeze-dried from its aqueous solution. To the foamy residue (300 mg), pyridine (3 mL), Ac_2O (3 mL), and a catalytic amount of 4-dimethylaminopyridine were added, and the solution was left for 2 days at room temperature. Concentration of the mixture under reduced pressure, with the addition of MeOH (3×3 mL), left a residue which was dissolved in CH_2Cl_2 (20 mL), washed successively with H_2SO_4 (2 M), aq satd $NaHCO_3$ and water, and then dried (Na_2SO_4). Concentration resulted in a white crystalline solid which was recrystallised from CH_2Cl_2–hexane (200 mg, 38.4%); mp 183–184°C, $[\alpha]_D$ +35° (*c* 1.3, $CHCl_3$); lit. [3] mp 183–186°C, $[\alpha]_D$+38° (*c* 1, $CHCl_3$).

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