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Note

Some derivatives of 6-amino-6-deoxy-D-gluconic acid that are precursors for the synthesis of polyamides

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Polyamides, polyesters, and polyurethanes have several biomedical applications (surgical sutures, membranes, superficial coverings, and drug-delivery systems). As a first step in the synthesis of polyamides from sugar derivatives, we now report the preparation of derivatives of 6-amino-6-deoxy-D-gluconic acid that are precursors of bifunctional monomers for linear polycondensations.

Various 6-amino-6-deoxy-D-aldonic acids and some of their derivatives have been described[1]. 6-Amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-gluconic acid (**1**) has been prepared[2] (~ 14% overall yield) in six steps from 6-azido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. A more convenient synthesis starts from methyl α-D-glucopyranoside (**7**), selective 6-tosylation of which followed by treatment with sodium azide in *N*,*N*-dimethylformamide gave **8**[3]. The azido group was not reduced to an amino group until the last step because of its stability towards acidic and weakly basic conditions, and also against oxidation[4]. Treatment of **8** with methyl iodide–potassium hydroxide in methyl sulphoxide gave the tri-*O*-methyl derivative **9**, acid hydrolysis of which followed by oxidation[5] with acetic anhydride–methyl sulphoxide gave 6-azido-6-deoxy-2,3,4-tri-*O*-methyl-D-glucono-1,5-lactone (**11**).

Opening of the lactone ring in **11** and methylation of HO-5 was carried out with methyl iodide–potassium hydroxide–tetrahydrofuran to give 6-azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-gluconic acid (**2**, 97%), characterised as the methyl ester **3**. Hydrogenation of **2** in hydrochloric acid gave 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-gluconic acid (**1**, 30% from **7**), which was transformed into the *N*-(*tert*-butoxycarbonyl) pentachlorophenyl (**5**) and *p*-nitrophenyl (**6**) esters suitable for polymerisation after removal of the *N*-protecting groups.

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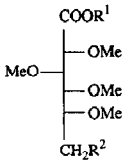
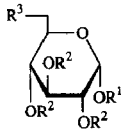
EXPERIMENTAL

General.–Solutions were concentrated in vacuo at $< 40°$. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured at 20 $\pm 5°$ with a Perkin–Elmer 141 polarimeter (10-cm cell). TLC was performed on Silica Gel 60 F_{254} (Merck) with detection by UV light or charring with H_2SO_4. Flash-column chromatography was performed as described[6]. FT-IR spectra (films or KBr discs) were recorded with a Michelson 100 spectrometer. ^{1}H-NMR spectra were recorded with Bruker WP-80-SY (^{1}H, 80.13 MHz; ^{13}C, 20.15 MHz) and Varian XL-200 (^{1}H, 200 MHz) spectrometers. Mass spectra were obtained using a Kratos MS80RFA instrument. Compounds characterised by exact mass were shown to be pure by TLC and NMR spectroscopy.

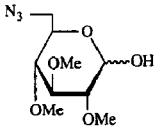
*6-Azido-6-deoxy-1,2,3,4-tetra-*O*-methyl-α-*D*-glucopyranoside* (**9**).—To a solution of **8**[3] (0.219 g, 1 mmol) in dry Me_2SO (2 mL) was added freshly pulverised KOH (0.67 g, 12 mmol) and MeI (0.4 mL, 6 mmol). The mixture was stirred for 4 h at room temperature, then poured into water, and extracted several times with CH_2Cl_2. The combined extracts were concentrated and the residue was distilled (81°/0.3 mbar) to give **9** (0.24 g, 93%), bp 81°/0.3 mbar as an oil that crystallised on storage; mp 38–40° (from aq 50% EtOH), $[\alpha]_D$ +139° (*c* 1.6, $CHCl_3$); ν_{max} 2101



1 R^1 = H, R^2 = NH_2·HCl
2 R^1 = H, R^2 = N_3
3 R^1 = Me, R^2 = N_3
4 R^1 = H, R^2 = NHBoc
5 R^1 = C_6Cl_5, R^2 = NHBoc
6 R^1 = p-$C_6H_4NO_2$, R^2 = NHBoc



7 R^1 = Me, R^2 = H, R^3 = OH
8 R^1 = Me, R^2 = H, R^3 = N_3
9 R^1 = R^2 = Me, R^3 = N_3



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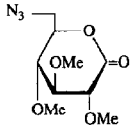

11

cm^{-1} (N_3). NMR data ($CDCl_3$): ^1H, δ 4.74 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 3.74–3.27 (m, 4 H, H-2/5), 3.54, 3.47, 3.44, 3.36 (4 s, 12 H, 4 OMe), 3.12 (dd, 1 H, $J_{5,6a}$ 3.4, $J_{6a,6b}$ – 9.3 Hz, H-6a), 2.97 (dd, 1 H, $J_{5,6b}$ 8.5, H-6b); ^{13}C, δ 51.5 (C-6), 55.2, 58.8, 60.3, 60.6 (4 OMe), 70.0, 80.5, 81.9, 83.4 (C-2/5), 97.6 (C-1).

Anal. Calcd for $C_{10}H_{19}N_3O_5$: C, 45.97; H, 7.23; N, 16.08. Found: C, 46.19; H, 7.24; N, 15.86.

*6-Azido-6-deoxy-2,3,4-tri-*O*-methyl-*D*-glucopyranose* (**10**).—A solution of **9** (5.0 g, 19.15 mmol) in 2 M HCl (500 mL) was heated for 7 h at 100°, then extracted with CH_2Cl_2 (7 × 100 mL). The combined extracts were washed with satd aq $NaHCO_3$ and water, dried, and concentrated. Column chromatography (2:1 hexane–EtOAc) of the residue gave **10** (1.35 g, 76%), isolated as an oil (α,β-ratio 2:1); ν_{max} 3391 (OH), 2106 cm^{-1} (N_3). NMR data ($CDCl_3$): ^1H, δ 5.35 (d, $J_{1,2}$ 3.5 Hz, H-1α), 4.62 (d, $J_{1,2}$ 7.7 Hz, H-1β), 4.00–3.36 (m, 4 H, H-2/5), 3.65, 3.57, 3.56 (3 s, 9 H, 3 OMe), 3.27–2.95 (m, 2 H, H-6a,6b); ^{13}C, δ 53.2 (C-6α,6β), 60.5, 62.1, 62.4 (3 OMe), 71.5, 81.9, 83.7, 84.7 (C-2/5α), 92.3 (C-1α), 75.8, 81.9, 86.5, 87.9 (C-2/5β), 98.8 (C-1β).

Anal. Calcd for $C_9H_{17}N_3O_5$: C, 43.72; H, 6.93; N, 16.99. Found: C, 43.91; H, 6.92; N, 16.94.

*6-Azido-6-deoxy-2,3,4-tri-*O*-methyl-*D*-glucono-1,5-lactone* (**11**).—A solution of **10** (1.7 g, 6.8 mmol) in Me_2SO (21 mL, 300 mmol) was treated with acetic anhydride (14 mL, 150 mmol) at room temperature overnight. Cool water (40 mL) was added, the oil which precipitated was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 40 mL). The oil and extracts were combined and concentrated. Column chromatography (2:1 hexane–EtOAc) of the residue gave **11** (1.45 g, 87%), isolated as an oil, $[\alpha]_D$ +133° (*c* 1, $CHCl_3$); ν_{max} 2106 (N_3), 1761 cm^{-1} (C=O). NMR data ($CDCl_3$): ^1H, δ 4.40 (ddd, 1 H, $J_{4,5}$ 9.1, $J_{5,6a}$ 3.0, $J_{5,6b}$ 4.3 Hz, H-5), 3.78 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 3.61–3.25 (m, 4 H, H-3,4,6a,6b), 3.48, 3.44 (2 s, 9 H, 3 OMe); ^{13}C, δ 50.3 (C-6), 57.4, 58.0 (3 OMe), 75.4, 77.5, 78.6, 81.7 (C-2/5), 166.7 (C-1). Mass spectrum: *m/z* 245.10324 (calcd for $C_9H_{15}N_3O_5$: 245.10220).

*6-Azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-*D*-gluconic acid* (**2**).—To a solution of **11** (0.49 g, 2 mmol) in dry tetrahydrofuran (3 mL) was added freshly pulverised KOH (0.67 g, 12 mmol) and MeI (0.5 mL, 7.8 mmol). The mixture was stirred in the dark at room temperature for 24 h, then poured into water, stirred for 6 h, and extracted with CH_2Cl_2. The aqueous phase was acidified (pH 4–5) and extracted with CH_2Cl_2. The combined extracts were concentrated to give **2** (0.54 g, 97%) as an oil, $[\alpha]_D$ +27° (*c* 2.4, $CHCl_3$); ν_{max} 3505 (OH), 2102 (N_3), 1733 cm^{-1} (C=O). NMR data ($CDCl_3$): ^1H, δ 9.33 (s, 1 H, COOH), 4.00 (d, 1 H, $J_{2,3}$ 4.7 Hz, H-2), 3.80–3.20 (m, 5 H, H-3/6), 3.55, 3.53, 3.48, 3.46 (4 s, 12 H, 4 OMe); ^{13}C, δ 50.1 (C-6), 57.4, 59.2, 60.6 (4 OMe), 79.4, 79.5, 80.8, 81.8 (C-2/5), 173.3 (C-1). Mass spectrum: *m/z* 221.1028 (calcd for $C_9H_{17}O_6^+$: 221.1025) and 189.0765 (calcd for $C_8H_{13}O_5^+$: 189.07629).

*Methyl 6-azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-*D*-gluconate* (**3**).—A mixture of **11** (0.49 g, 2 mmol), KOH (0.67 g, 12 mmol), 18-Crown-6 (0.05 g), and MeI (1 mL,

15.7 mmol) in tetrahydrofuran (3 mL) was treated as described above. The resulting mixture was partitioned between water and CH_2Cl_2, and the organic layer was concentrated. Column chromatography (4:1 hexane–EtOAc) of the residue gave **3** (0.34 g, 59%), isolated as an oil, $[\alpha]_D$ +22° (*c* 1.3, $CHCl_3$); ν_{max} 2101 (N_3), 1750 cm^{-1} (C=O). NMR data ($CDCl_3$: ^1H, δ 4.15–3.30 (m, 6 H, H-2/6), 3.80, 3.51, 3.47, 3.46 (4 s, 15 H, 5 OMe); ^{13}C, δ 50.5 (C-6), 51.7, 57.5, 58.7, 60.4, 60.5 (5 OMe), 79.8, 80.6, 81.1, 81.9 (C-2/5), 170.8 (C-1). Mass spectrum (CI): *m/z* 292 ($M^+ + 1$), 231.1222 (calcd for $C_9H_{17}N_3O_4^+$: 231.1219), and 203.0928 (calcd for $C_9H_{15}O_5^+$: 203.09194).

Anal. Calcd for $C_{11}H_{21}N_3O_6$: C, 45.35; H, 7.26; N, 14.42. Found: C, 45.06; H, 7.14; N, 14.08.

*6-Amino-6-deoxy-2,3,4-5-tetra-*O*-methyl-*D*-gluconic acid hydrochloride* (**1**).—A solution of **2** (0.25 g, 0.9 mmol) in 2 M HCl (1.6 mL) was hydrogenated (20 psi) at room temperature in the presence of 10% Pd–C (0.03 g). After 4 h, the mixture was filtered, the insoluble material was washed with water, and the combined filtrate and washings were concentrated under diminished pressure. The residue was crystallised from EtOH to give **1** (0.24 g, 92%), mp 202–204°, $[\alpha]_D$ +33° (*c* 1.2, H_2O); lit.[2] mp 204–205°, $[\alpha]_D$ +29.8 ±1° (H_2O).

*6-(*tert*-Butoxycarbonylamino)-6-deoxy-2,3,4,5-tetra-*O*-methyl-*D*-gluconic acid* (**4**). —To a suspension of **1** (6.2 g, 21.55 mmol) in acetonitrile (180 mL) was added di-*tert*-butyl dicarbonate (4.7 g, 21.55 mmol) and triethylamine (3 mL). The mixture was stirred for 24 h at room temperature, then concentrated under diminished pressure, and the residue was treated with a mixture of water and CH_2Cl_2. The organic phase was washed with water (30 mL), dried ($MgSO_4$), and concentrated to give **4** (6.4 g, 84%), mp 138–140° (from EtOH), $[\alpha]_D$ +16° (*c* 1.3, $CHCl_3$); ν_{max} 3333 (OH, NH), 1763 (C=O), 1706, 1530 cm^{-1} (CONH). NMR data ($CDCl_3$): ^1H, δ 9.81 (s, 1 H, COOH), 5.04 (bs, 1 H, NH), 4.10–3.20 (m, 6 H, H-2/6), 3.55, 3.51, 3.41 (3 s, 12 H, 4 OMe), 1.46 (s, 9 H, 3 Me); ^{13}C, δ 28.4 (3 Me), 40.0 (C-6), 57.2, 59.1, 60.7 (4 OMe), 79.6 (*C*Me), 80.1, 80.2, 80.3, 82.2 (C-2/5), 156.4 (CONH), 172.7 (C-1).

Anal. Calcd for $C_{15}H_{29}NO_8$: C, 51.27; H, 8.32; N, 3.98 Found: C, 51.58; H, 8.54; N, 4.09.

*Pentachlorophenyl 6-(*tert*-butoxycarbonylamino)-6-deoxy-2,3,4,5-tetra-*O*-methyl-*D*-gluconate* (**5**).—To a stirred solution of **4** (0.13 g, 0.369 mmol) in dry EtOAc (2 mL) was added pentachlorophenol (0.104 g, 0.39 mmol) and dicyclohexylcarbodiimide (0.081 g, 0.39 mmol). After 24 h, the solid formed was collected and washed with EtOAc, and the combined filtrate and washings were concentrated. Column chromatography (30:20:1 hexane–CH_2Cl_2–2-propanol) of the residue gave **5**, isolated as an oil (0.155 g, 70%), $[\alpha]_D$ +27° (*c* 2.4, $CHCl_3$); ν_{max} 3345, 3360 (NH), 1786 (C=O), 1705, 1506 cm^{-1} (CONH). NMR data ($CDCl_3$): ^1H, δ 4.86 (bs, 1 H, NH), 4.42 (d, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 3.88 (dd, 1 H, $J_{3,4}$ 5.4 Hz, H-3), 3.80–3.30 (m, 4 H, H-4/6), 3.62, 3.54, 3.42 (3 s, 12 H, 4 OMe), 1.45 (s, 9 H, 3 Me); ^{13}C, δ 28.4 (3 Me), 39.8 (C-6), 57.4, 59.5, 60.6, 61.2 (4 OMe), 79.3 (*C*Me), 80.4, 81.6, 81.8

(C-2/5), 127.6, 131.8, 132.2, 144.2 (aromatic), 156.0 (CONH), 167.0 (C-1). Mass spectrum: *m/z* 597.0326 (calcd for $C_{21}H_{28}Cl_5NO_8^+$: 597.0257), 523.9598 (calcd for $C_{17}H_{19}Cl_5NO_7^+$: 523.9601), 434.9117 (calcd for $C_{14}H_{12}Cl_5O_5^+$: 434.9126), 390.8888 (calcd for $C_{12}H_8Cl_5O_4^+$: 390.8865).

Anal. Calcd for $C_{21}H_{28}Cl_5NO_8$: C, 42.06; H, 4.71; Cl, 29.56; N, 2.33. Found: C, 42.44; H, 4.87; Cl, 29.35; N, 2.60.

p-*Nitrophenyl 6-(*tert*-butoxycarbonylamino)-6-deoxy-2,3,4,5-tetra*-O-*methyl*-D-*gluconate* (**6**).—Compound **4** (2.68 g, 7.62 mmol) was reacted with *p*-nitrophenol, as described for pentachlorophenol. Column chromatography (1:2 ether–hexane) of the product gave **6** (2.55 g, 71%), mp 54–56° (from 2-propanol), $[\alpha]_D$ +18° (*c* 1.1, $CHCl_3$); ν_{max} 3387 (NH), 1776 (C=O), 1705, 1515 (CONH), 1615, 1591 cm^{-1} (aromatic). NMR data ($CDCl_3$): ^1H, δ 8.27, 7.33 (2 d, 4 H, aromatic), 4.92 (bs, 1 H, NH), 4.31 (d, 1 H, $J_{2,3}$ 3.7 Hz, H-2), 3.90–3.20 (m, 5 H, H-3/6), 3.58, 3.55, 3.48, 3.42 (4 s, 12 H, 4 OMe), 1.44 (s, 9 H, 3 Me); ^{13}C, δ 28.3 (3 Me), 40.1 (C-6), 57.4, 59.0, 60.5 (4 OMe), 79.2 (*C*Me), 80.0, 80.2, 80.4, 82.3 (C-2/5), 122.3, 125.1, 145.6, 155.2 (aromatic), 156.1 (CONH), 168.2 (C-1).

Anal. Calcd for $C_{21}H_{32}N_2O_{10}$: C, 53.38; H, 6.83; N, 5.93. Found: C, 53.37; H, 6.85; N, 5.89.

ACKNOWLEDGMENT

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