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Note

Preparation of 2-amino-2-deoxy-3,4,5,6-tetra-*O*-methyl-D-gluconic acid hydrochloride, an intermediate in the preparation of polypeptide-type polyamides

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Carbohydrate-based polyamides are of interest as biomaterials. We have reported[1] the synthesis of some derivatives of 6-amino-6-deoxy-D-gluconic acid that are precursors for the synthesis of linear polyamides. Attempts to use 2-amino-2-deoxy-D-gluconic acid and its 4,6-*O*-benzylidene derivative in the synthesis of polypeptides were not successful due to interference by the hydroxyl groups[2]. We now report the preparation of 2-amino-2-deoxy-3,4,5,6-tetra-*O*-methyl-D-gluconic acid hydrochloride (**1**) and its transformation into 4-(D-*arabino*-tetramethoxybutyl)-1,3-oxazolidine-2,5-dione (**2**), which is an active monomer for polymerisation reactions.

The synthesis of **1** started from 2-acetamido-2-deoxy-D-glucose (**3**). Methylation of **3** with methyl sulphate–sodium hydroxide in carbon tetrachloride[3] gave 40% of **4**, but the use of methyl iodide–potassium hydroxide in dry *N*,*N*-dimethylformamide[4] gave a yield of 65%. Hydrolysis of **4** with hydrochloric acid[3] gave the hydrochloride **5**, which reacted with di-*tert*-butyl dicarbonate in chloroform to afford **6** (90%). The phthalimido derivative **8** was also prepared (67.5%) by the reaction of **5** with phthalic anhydride–acetic anhydride[5] and 1-*O*-deacetylation of the product **7**. Oxidation of **6** with pyridinium chlorochromate gave the lactone **9** (85%). The lactone **10** was also obtained (95.6%) by oxidation of **8** with acetic anhydride–methyl sulphoxide. Opening of the lactone ring in **9** and methylation of HO-5 was effected with methyl iodide–potassium hydroxide–tetrahydrofuran followed by hydrolysis of the N-Boc group with hydrochloric acid to afford **1**. Treatment of **10** under similar conditions was unsuccessful.

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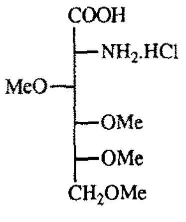
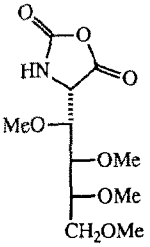


1



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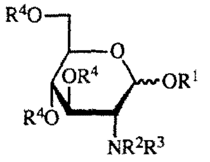
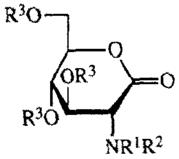
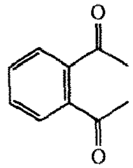


3 R^1=R^2=R^4=H, R^3=Ac
4 R^1=R^4=Me, R^2=H, R^3=Ac
5 R^1=R^2=R^3=H, R^4=Me
6 R^1=R^2=H, R^3=Boc, R^4=Me
7 R^1=Ac, R^2, R^3=Phth, R^4=Me
8 R^1=H, R^2, R^3=Phth, R^4=Me



9 R^1=H, R^2=Boc, R^3=Me
10 R^1, R^2=Phth, R^3=Me

Phth =



Treatment of **1** with trichloromethyl chloroformate in dry tetrahydrofuran gave the *N*-carboxyanhydride **2** which could be polymerised, to give polyamides of molecular weight of 10000 (GPC).

EXPERIMENTAL

General methods.—Unless stated otherwise, these were as described[1]. NMR spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si), unless otherwise specified, using a Bruker WP-80-SY, Varian XL-200, or Bruker AMX-500 spectrometer. All reactions were monitored by TLC.

Methyl 2-acetamido-2-deoxy-3,4,6-tri-O-methyl-α,β-D-glucopyranoside (**4**).—To an ice-cold solution of 2-acetamido-2-deoxy-D-glucose (**3**, 12 g) in dry DMF (200 mL) was added freshly powdered KOH (27 g), 18-Crown-6 (0.54 g), and MeI (27 mL). The resulting suspension was stirred vigorously at room temperature overnight, then diluted with CH_2Cl_2 (200 mL), filtered through diatomaceous earth, and concentrated first at 40°C/15 mmHg, then at 0.1 mmHg. A solution of the residue in CH_2Cl_2 (300 mL) was washed with water, dried, and concentrated, and the residue was crystallised from EtOAc to afford **4** (8.45 g, 65%); mp 174–175°C (lit.[3] mp 192°C).

2-tert-*Butoxycarbonylamino-2-deoxy-3,4,6-tri-*O*-methyl-α,β-*D*-glucopyranose* (**6**).—To a stirred suspension of 2-amino-2-deoxy-3,4,6-tri-*O*-methyl-D-glucose hydrochloride[3] (**5**; 0.5 g, 1.8 mmol) in $CHCl_3$ (7 mL) containing triethylamine (0.25 mL, 1.89 mmol) was added di-*tert*-butyl dicarbonate (0.41 g, 1.89 mmol), and stirring was continued for 24 h. The mixture was diluted with $CHCl_3$, washed with water, and concentrated. The solid residue was recrystallised from MeOH–H_2O to afford **6** (0.52 g, 90%); mp 150–151°C, $[\alpha]_D^{22}$ +81° (*c* 1, $CHCl_3$); ν_{max} 1698 (NH–CO–O) and 1246 cm^{-1} (C–N). NMR data: ^1H (80 MHz), δ 5.15 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1α), 4.85 (d, 1 H, $J_{1,2}$ 9.2 Hz, H-1β), 1.45 (s, 18 H, 2 CMe_3); ^{13}C (20.15 MHz), α anomer: δ 92.38 (C-1), 54.88 (C-2), 82.50 (C-3), 80.09 (C-4), 75.41 (C-5), 77.00 (C-6), 155.75 (C=O), 60.09 and 59.01 (3 OMe), and 28.35 (CMe_3). Mass spectrum: *m/z* 322 $(M+H)^+$. Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.35. Found: C, 52.44; H, 8.50; N, 4.15.

2-tert-*Butoxycarbonylamino-2-deoxy-3,4,6-tri-*O*-methyl-*D*-glucono-1,5-lactone* (**9**).—A solution of **6** (0.63 g, 1.97 mmol) in dry CH_2Cl_2 (10 mL) was stirred with 3A molecular sieves (5.91 g) for 10 min, then pyridinium chlorochromate (2.12 g, 9.85 mmol) was added. The mixture was stirred at room temperature in the dark for 5 h, then diluted with ether, filtered through a column of silica gel G containing $CaSO_4$ (10%), and concentrated to give **9** as a colourless oil (0.53 g, 85%); $[\alpha]_D^{22}$ +66° (*c* 1.56, CH_2Cl_2); ν_{max} 1760 cm^{-1} (lactone C=O). ^{13}C-NMR data (20.15 MHz): δ 168.92 (C-1), 56.03 (C-2), 78.58 (C-3/4), 82.10 (C-5), 70.82 (C-6), 59.17, 59.56, and 59.98 (3 OMe), 28.18 (CMe_3), 155.47 (NCOO), and 80.46 (*C*Me_3). Mass spectrum: *m/z* 319.1648 (calcd for $C_{14}H_{27}NO_7$: 319.1630).

*1-*O*-Acetyl-2-deoxy-3,4,6-tri-*O*-methyl-2-phthalimido-α,β-*D*-glucopyranose* (**7**).—A suspension of **5** (0.25 g, 1 mmol) in DMF (1.4 mL) containing triethylamine (0.35 mL, 2.5 mmol) and phthalic anhydride (0.22 g, 1.5 mmol) was stirred at room temperature for 30 min, and then heated at 70°C for 15 min. Anhydrous sodium acetate (0.20 g, 1.5 mmol) and acetic anhydride (0.38 mL, 4 mmol) were added quickly, and the mixture was stirred at 100°C for 5 h, then cooled, and poured into ice–water (20 mL). A solution of the gummy mass in CH_2Cl_2 (50 mL) was washed with water, aq 10% $NaHCO_3$, and water, then concentrated. TLC (2:1 ether–light petroleum) of the syrupy residue revealed a major product (R_f 0.35). Flash-column chromatography with the same solvent system afforded **7** (0.37 g, 95.7%), isolated as an oil, α,β-ratio 1:3; $[\alpha]_D^{22}$ +94° (*c* 1, CH_2Cl_2); ν_{max} 1717 (C=O) and 1240 cm^{-1} (OAc). NMR data: ^1H (200 MHz), β anomer: δ 7.90–7.70 (m, 4 H, aromatic), 6.26 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 3.57, 3.44, and 3.42 (3 s, each 3 H, 3 OMe), and 1.96 (s, 3 H, OAc); ^{13}C (20.15 MHz), β anomer: δ 167.94 (phthalimide C=O), 133.95, 131.48, and 123.34 (aromatic), 91.24 (C-1), 54.53 (C-2), 81.18 (C-3), 76.15 (C-4), 73.60 (C-5), 70.68 (C-6), 60.10, 59.50, and 59.04 (3 OMe), and 20.66 (OAc). Mass spectrum: *m/z* 393.1436 (calcd for $C_{19}H_{23}NO_8$: 393.1423).

*2-Deoxy-3,4,6-tri-*O*-methyl-2-phthalimido-α,β-*D*-glucopyranose* (**8**).—A solution of **7** (0.39 g, 1 mmol) in dry MeOH (5 mL) was treated with methanolic 0.2 M NaOMe (0.15 mL) for 30 min. The mixture was deionised with Amberlite IR-120 (H^+) resin and concentrated. Flash-column chromatography (4:1 ether–light petroleum) of the solid residue (0.33 g) afforded **8** (0.24 g, 67.5%); mp 139–140°C; $[\alpha]_D^{22}$ +108° (*c* 0.54, CH_2Cl_2); ν_{max} 3443 cm^{-1} (OH). NMR data: ^1H (500 MHz), β anomer: δ 7.90–7.70 (m, 4 H, aromatic), 5.27 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 4.03 (dd, 1 H, $J_{2,3}$ 11.0 Hz, H-2), 4.17 (dd, 1 H, $J_{3,4}$ 8.8 Hz, H-3), 3.53, 3.40, and 3.38 (3 s, each 3 H, 3 OMe); α anomer: δ 5.29 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.36 (dd, 1 H, $J_{2,3}$ 11.5 Hz, H-2), and 4.50 (dd, 1 H, $J_{3,4}$ 8.8 Hz, H-3); ^{13}C (20.15 MHz), β anomer: δ 168.42 (C=O), 134.13, 131.95, and 123.48 (aromatic), 93.17 (C-1), 57.55 (C-2), 80.81 (C-3), 80.46 (C-4), 75.01 (C-5), 71.54 (C-6), 60.16, 59.75, and 59.20 (3 OMe). Mass spectrum: *m/z* 334 $(M - OH)^+$. Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.98. Found: C, 57.55; H, 6.43; N, 3.47.

*2-Deoxy-3,4,6-tri-O-methyl-2-phthalimido-*D*-glucono-1,5-lactone* (**10**).—A solution of **8** (0.5 g, 1.4 mmol) in Me_2SO (4 mL) and acetic anhydride (4 mL) was kept overnight at room temperature, then poured into ice–water (25 mL). Recrystallisation of the product (0.47 g, 95.6%) from EtOH gave **10**; mp 135–136°C; $[\alpha]_D^{22}$ +10.4° (*c* 1, CH_2Cl_2); ν_{max} 1750 cm^{-1} (lactone C=O). NMR data: ^1H (500 MHz): δ 7.90–7.70 (m, 4 H, aromatic), 4.83 (d, 1 H, $J_{2,3}$ 10.6 Hz, H-2), 4.29 (dt, 1 H, $J_{5,6}$ 8.8 Hz, H-5), 4.09 (dd, 1 H, $J_{3,4}$ 10.5 Hz, H-3), 3.74 (t, 1 H, $J_{4,5}$ 9 Hz, H-4), 3.70 (dd, 1 H, H-6a), 3.66 (dd, 1 H, H-6b), 3.57, 3.41, and 3.40 (3 s, each 3 H, 3 OMe); ^{13}C (20.15 MHz): δ 167.00 (phthalimide C=O), 165.80 (C-1), 134.24, 131.59, and 123.48 (aromatic), 52.81 (C-2), 79.20, 79.02, and 78.59 (C-3/5), and 70.52 (C-6). Mass spectrum: *m/z* 349.1177 (calcd for $C_{17}H_{19}NO_7$: 349.1161). Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.53; H, 5.29; N, 4.05.

*2-Amino-2-deoxy-3,4,5,6-tetra-O-methyl-*D*-gluconic acid hydrochloride* (**1**).—To a solution of **9** (0.57 g, 1.78 mmol) in dry tetrahydrofuran (12 mL) was added freshly pulverised KOH (0.4 g, 7.13 mmol), 18-Crown-6 (0.05 g, 0.19 mmol), and MeI (0.4 mL, 6.28 mmol). The mixture was stirred at room temperature for 3 h, then diluted with CH_2Cl_2, and washed with water. The aqueous layer was acidified (pH 4–5) with concd HCl and extracted with $CHCl_3$, and the extract was concentrated. To a solution of the oily residue (0.4 g) in EtOAc (4 mL) was added 4 M HCl (1 mL), and the mixture was stirred at room temperature overnight to afford **1** (0.25 g, 48.7%); mp 178–180°C; $[\alpha]_D^{22}$ 0° (*c* 1, MeOH); ν_{max} 1622 (NH_3^+) and 1737 cm^{-1} (COO^-). ^{13}C NMR data [20.15 MHz, $(CD_3)_2SO$]: δ 169.02 (C-1), 53.25 (C-2), 79.91, 79.19, and 78.92 (C-3/5), 69.89 (C-6), 60.19, 59.55, 58.21, and 56.69 (4 OMe). Mass spectrum: *m/z* 252 $(M + H)^+$. Anal. Calcd for $C_{10}H_{22}NClO_6 \cdot H_2O$: C, 39.28; H, 7.91; N, 4.58. Found: C, 39.33; H, 8.11; N, 4.59.

*4-*D-arabino*-Tetramethoxybutyl-1,3-oxazolidine-2,5-dione* (**2**).—To a suspension of **1** (0.26 g, 0.93 mmol) in dry tetrahydrofuran (14 mL) was added trichloromethyl chloroformate (0.14 mL, 1.28 mmol; 40% excess) and active carbon (≈ 3 mg). The mixture was stirred at 55°C for 4 h, then diluted with dry tetrahydrofuran, filtered through diatomaceous earth, and concentrated. The semi-solid residue crystallised when treated with light petroleum to give **2** (0.24 g, 95%); mp 88–89°C; $[\alpha]_D^{22}$ +6.6° (*c* 0.5, $CHCl_3$); ν_{max} 1856, 1797 (C=O), and 920 cm^{-1} (C–O–C). ^{13}C NMR data (20.15 MHz): δ 170.00 (C-5), 152.18 (C-2), 80.05 (C-1′/3′), 70.50 (C-4′), 60.53, 59.54, and 59.08 (4 OMe), and 58.70 (C-4). Mass spectrum: *m/z* 278 $(M+H)^+$. Anal. Calcd for $C_{11}H_{19}NO_7$: C, 47.65; H, 6.90; N, 5.05. Found: C, 47.91; H, 7.19; N, 4.83.

Polymerisation of **2**.—A solution of **2** (0.23 g, 0.83 mmol) in dry DMF (0.5 mL) containing triethylamine (0.03 mL) was stirred under N_2 at room temperature for 2 days. The polymer was precipitated by adding ether (30 mL), filtered off, and dried; mp 90–184°C; intrinsic viscosity, 0.2 dL/g (in dichloroacetic acid at 25°C); $\overline{M}_w$ 10000 (determined by GPC); ν_{max} 1670 (Amide I) and 1510 cm^{-1} (Amide II). ^{13}C NMR data (20.15 MHz): δ 170.18 (C=O), 53.40 (C-2), 81.07 and 80.09 (C-3/5), 71.02 (C-6), 60.73, 60.16, 58.94, and 57.43 (4 OMe). Anal. Calcd for $C_{10}H_{19}NO_5 \cdot 0.5\ H_2O$: C, 49.57; H, 8.32; N, 5.77. Found: C, 49.51; H, 8.08; N, 6.55.

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