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LIMITATIONS OF THE AMINONITRILE SYNTHESIS. NEW PRODUCTS FROM D-GLUCOSE, D-GALACTOSE, AND D-MANNOSE

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ABSTRACT

The reaction of aldoses with an excess of amine and hydrogen cyanide can yield a series of cyclic and acyclic compounds in addition to the expected α-aminoaldononitriles. The nature of these unexpected products depends on the specific reaction conditions and on the structure of the aldose. Thus, the α-aminoheptononitriles formed from D-glucose, D-galactose, and D-mannose can be transformed into 2-alkylamino-1,4-anhydro-2-deoxy-1-imino(or alkylimino)heptitols (**1–6**), N^1-alkyl-2-alkylamino-2-deoxyheptonamidines (**10a** and **10c**), or *N*-alkyl-2-alkylamino-2-deoxyheptonamides (**11a–11c, 12c,** and **13a–13c**), depending on the reaction conditions.

INTRODUCTION

The aminonitrile synthesis of 2-amino-2-deoxyaldoses[1] from aldoses has been applied to the preparation of 2-amino- and 2-alkylamino-2-deoxyheptoses from hexoses[2–5]. 2-Alkylamino-2-deoxyheptononitriles[6–8] are intermediates in these syntheses, and can be prepared by reaction of an aldose with an excess of alkylamine in dry ethanol or methanol with the subsequent addition of dry hydrogen cyanide. However, under these conditions, abnormal products have been obtained sometimes. We now report on the structure of these unexpected products and the conditions for their formation, in order to establish the scope and limitations of the aminonitrile synthesis.

RESULTS AND DISCUSSION

The reaction of D-galactose with an excess of ethylamine and dry hydrogen cyanide in dry methanol did not yield the expected aminonitrile **7a**, but gave 1,4-anhydro-2-deoxy-2-ethylamino-1-ethylimino-D-*glycero*-L-*gluco*-heptitol (**1**). Compound **1** lacked i.r. absorption for nitrile but showed the characteristic absorption[9]

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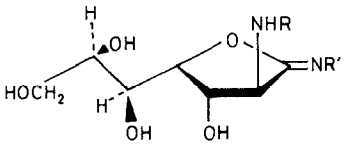
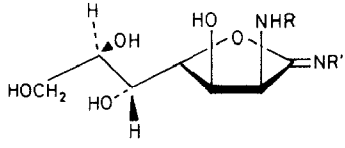
of the imine group at 1695 cm^{-1}, and its ^1H-n.m.r. spectrum revealed two different ethyl groups. Likewise, the reaction of D-mannose and ethylamine or benzylamine gave the 1,4-anhydroheptitols **3** and **4**. Compound **4** was also prepared by the reaction of 2-benzylamino-2-deoxy-D-*glycero*-D-*talo*-heptononitrile (**9b**) with benzylamine in dry methanol, but when a similar reaction was carried out with the D-*glycero*-L-*gluco* (**9a**) and D-*glycero*-D-*ido* (**9c**) isomers, the heptonamidines **10a** and **10c**, respectively, were obtained.

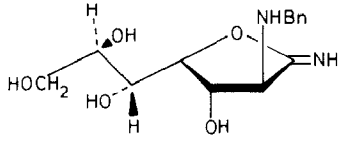


1 R = R' = Et
2 R = Et, R' = H



3 R = R' = Et
4 R = R' = Bn
5 R = Bn, R' = H

The formation of these products can be explained by the addition of the amine to C-1 of the imine **19** formed by cyclisation of the aminonitrile **18**, or by nucleophilic addition of the amine to **18** and subsequent cyclisation of the resulting amidine **20**. Elimination of ammonia from the intermediate **21** then gives the 1,4-anhydro-1-iminoheptitol **22**. Compounds with structures similar to that of **19** have been prepared by Kuhn *et al.*[10–12] by treatment of the aminonitriles with bases. We have also prepared compounds of this type by boiling methanolic solutions of 2-alkylamino-2-deoxyheptononitriles. Thus, from the aminonitriles **7a, 9b**, and **9c**, the products **2, 5**, and **6** have been obtained.



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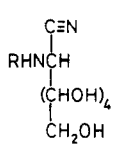
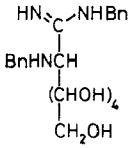


7 R = Et
8 R = Pr
9 R = Bn



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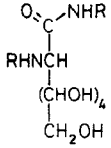
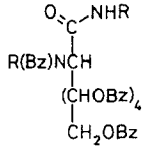


11 R = Et
12 R = Pr
13 R = Bn

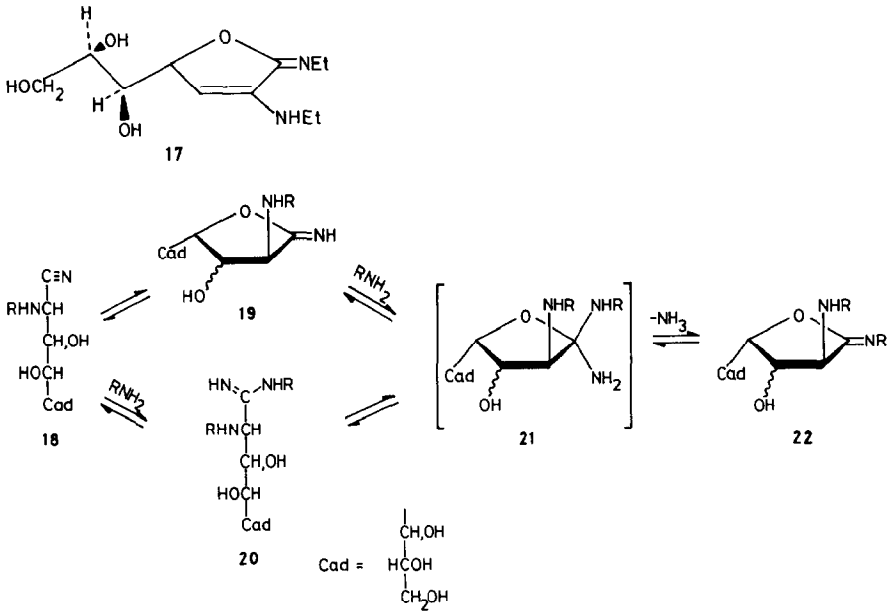


14 R = Et
15 R = Pr
16 R = Bn

Configurations
a D-*glycero*-L-*gluco*
b D-*glycero*-D-*talo*
c D-*glycero*-D-*ido*

The structures proposed for these new compounds are supported by their elemental analyses and physical properties. The ring size of the cyclic compounds is consistent with the observed rotatory powers in agreement with Hudson's lactone rule[13], which has been applied previously to this type of compound[12].

When a methanolic solution of **1** was boiled for a short time, dehydration occurred to give 1,4-anhydro-2-deoxy-2-ethylamino-1-ethylimino-D-*lyxo*-hept-2-enitol (**17**), the structure of which was proved by elemental analyses and spectral data. Thus, **17** had (*a*) λ_{max} 261 nm (**1** had no absorption maximum above 200 nm), (*b*) i.r. bands at 1680 and 1640 cm^{-1}, characteristic of α,β-unsaturated imines, and (*c*) a ^{1}H-n.m.r. doublet at δ 5.34 (*J* 1.9 Hz) for the olefinic proton on C-3.



Reaction of D-glucose with hydrogen cyanide and an excess of ethylamine, propylamine, or benzylamine gave the *N*-alkyl-2-alkylamino-2-deoxyheptonamides **11c, 12c**, and **13c**, respectively. Compound **13c** was also obtained by hydrolysis of **10c** in aqueous methanol. When D-galactose was treated with an excess of benzylamine and hydrogen cyanide, the aminonitrile **9a** crystallised immediately, but, on heating, **9a** was converted into the *N*-benzyl-2-benzylamino-2-deoxy-D-*glycero*-L-*gluco*-heptonamide (**13a**). Compound **13a** was also obtained by the reaction of **9a** and benzylamine in aqueous methanol or by the hydrolysis of **10a**. In a similar way, the hydrolysis of the 2-alkylamino-1,4-anhydro-2-deoxy-1-iminoheptitols **1, 3**, and **4** yielded the heptonamides **11a, 11b**, and **13b**, respectively. The structures of these compounds were supported by their elemental analyses and spectral data, and confirmed by the preparation of the hexabenzoates **14c, 15c, 16a, 16b**, and **16c**. The configuration at C-2 of the heptonamides was confirmed[14] by the

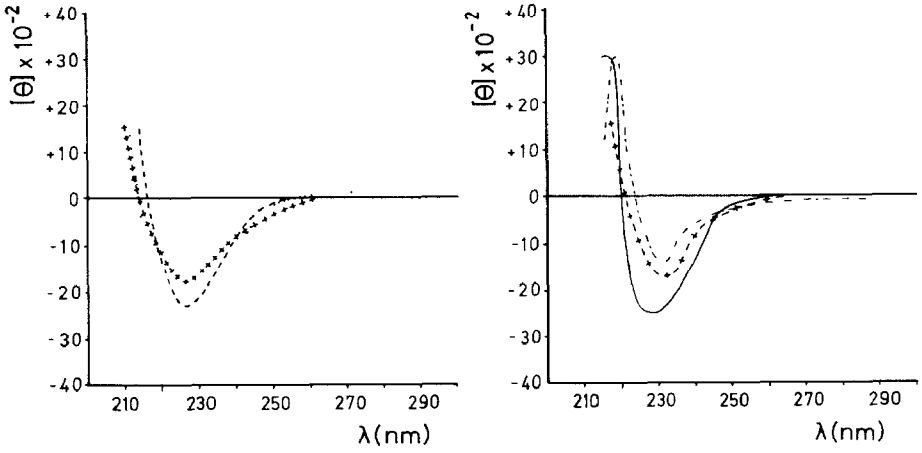
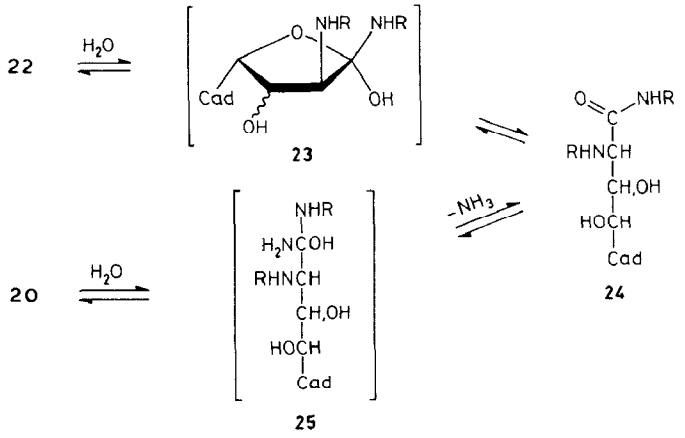


Fig. 1. C.d. spectra of compounds **11a** (– – –), **11c** (+ + + +), **12c** (· · ·), **13a** (– · – · –), **13b** (+ – + –), and **13c** (——).



negative Cotton effect in their c.d. spectra (Fig. 1). These compounds are formed by the sequences **22**→**23**→**24** and **20**→**25**→**24**.

Thus, in the reactions of aldoses with hydrogen cyanide and an excess of amine, the α-aminoaldononitriles are the products only if they crystallise immediately. If they stay in solution, they are converted into one of the cyclic or acyclic compounds described above. The nature of the products depends on the reaction conditions and on the relative solubilities of the various possible products. By adding dry hydrogen cyanide to a methanolic solution of the glycosylamine, previously isolated, good yields of the aminonitriles **18** can be obtained, by avoiding the excess of amine and the presence of water which are necessary for their conversion into the "abnormal" products.

EXPERIMENTAL

General methods. — Solutions were concentrated *in vacuo* at <40°. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter (10-cm, 5-mL cell). P.c. (ascending) was performed on Whatman No. 1 paper, using 1-butanol–pyridine–water (1:1:1) and detection with silver nitrate–sodium hydroxide. I.r. spectra (KBr discs) were recorded with a Perkin–Elmer 399 spectrophotometer, and u.v. spectra with a Pye–Unicam SP8-250 instrument. ^{1}H-N.m.r. spectra (90 MHz, 35.5°, internal Me_4Si) were recorded with a Perkin–Elmer R-32 spectrometer, and coupling constants were measured directly from the spectra recorded at a 300-Hz sweep-width. Assignments were confirmed by double-resonance experiments. The ^{13}C-n.m.r. spectrum (90 MHz, internal Me_4Si) of **11c** was recorded with a Bruker HX-90-E spectrometer. C.d. spectra were recorded with a Jobin–Yvon Dichrographe III spectropolarimeter.

1,4-Anhydro-2-deoxy-2-ethylamino-1-ethylimino-D-glycero-L-gluco-*heptitol* (**1**). — To a suspension of D-galactose (10.0 g, 55.6 mmol) in methanol (50 mL) was added ethylamine (10 mL, 150 mmol), and the mixture was stirred until dissolution was complete. Dry hydrogen cyanide (5 mL) was then added, and the mixture was kept for 2 h at room temperature and for 24 h at ~0°, and then concentrated under reduced pressure. A solution of the syrupy residue in methanol was concentrated and the process was repeated with dry ethanol. The residue was crystallised from dry ethanol to give **1** (2.43 g, 19%), m.p. 127–129°, $[\alpha]_D^{22}$ −45°, $[\alpha]_{578}^{22}$ −46°, $[\alpha]_{546}^{22}$ −52°, $[\alpha]_{436}^{22}$ −88°, $[\alpha]_{365}^{22}$ −138° (*c* 1, pyridine); ν_{max} 3600–3100 (NH, OH) and 1695 cm^{-1} (C=N). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 3.17 (q, 2 H, CH_2 ethylimino), 2.68 (q, 2 H, CH_2 ethylamino), 1.05 (t, 3 H, *J* 7.0 Hz, Me), and 1.03 (t, 3 H, *J* 7.0 Hz, Me).

Anal. Calc. for $C_{11}H_{22}N_2O_5$: C, 50.37; H, 8.45; N, 10.68. Found: C, 50.44; H, 8.73; N, 11.00.

1,4-Anhydro-2-deoxy-2-ethylamino-1-ethylimino-D-glycero-D-talo-*heptitol* (**3**). — To a suspension of D-mannose (10.0 g, 55.6 mmol) in methanol (50 mL) was added ethylamine (10 mL, 150 mmol), and the mixture was stirred until dissolution was complete. Dry hydrogen cyanide (5 mL) was then added, and the mixture was kept for 2 h at room temperature and for 3 days at 0°, and then concentrated under diminished pressure. The resulting syrup was crystallised from the minimum quantity of dry ethanol to give **3** (6.35 g, 44%), m.p. 159–161° (from methanol), $[\alpha]_D^{18}$ −42.5°, $[\alpha]_{578}^{18}$ −44.5°, $[\alpha]_{546}^{18}$ −50.5°, $[\alpha]_{436}^{18}$ −87°, $[\alpha]_{365}^{18}$ −140.5° (*c* 0.5, pyridine); ν_{max} 3600–3000 (NH, OH) and 1690 cm^{-1} (C=N).

Anal. Calc. for $C_{11}H_{22}N_2O_5 \cdot H_2O$: C, 47.13; H, 8.63; N, 9.99. Found: C, 47.41; H, 8.35; N, 10.09.

1,4-Anhydro-2-benzylamino-1-benzylimino-2-deoxy-D-glycero-D-talo-*heptitol* (**4**). — (*a*) To a suspension of D-mannose (10.0 g, 55.6 mmol) in methanol (70 mL) was added benzylamine (17 mL, 150 mmol), and the mixture was stirred until dis-

solution was complete. Dry hydrogen cyanide (5 mL) was then added, and the mixture was kept for 2 h at room temperature and for 24 h at ~0°, and then concentrated under diminished pressure. The product (12.1 g, 56%) was recrystallised from methanol to give **4**, m.p. 151–153°, $[\alpha]_D^{18}$ −23°, $[\alpha]_{578}^{18}$ −25°, $[\alpha]_{546}^{18}$ −29.5°, $[\alpha]_{436}^{18}$ −51.5°, $[\alpha]_{365}^{18}$ −85.5° (*c* 0.5, pyridine); ν_{max} 3620 and 3600–3000 (NH, OH), 1710 (C=N), 1630 (H_2O), 1605, 1585, 750, 730, and 700 cm^{-1} (phenyl).

Anal. Calc. for $C_{21}H_{26}N_2O_5 \cdot H_2O$: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.40; H, 6.73; N, 6.98.

(*b*) To a suspension of 2-benzylamino-2-deoxy-D-*glycero*-D-*talo*-heptononitrile[2] (**9b**; 5.0 g, 16.9 mmol) in methanol (55 mL) was added benzylamine (3 mL, 26.9 mmol), and the mixture was stirred for 2 days at room temperature and then for 5 min at 70°. After cooling for 3 h at 0°, **4** (4.38 g, 67%) was obtained.

N[1]-*Benzyl-2-benzylamino-2-deoxy*-D-glycero-L-gluco-*heptonamidine* (**10a**). — To a suspension of 2-benzylamino-2-deoxy-D-*glycero*-L-*gluco*-heptononitrile[6] (**9a**; 5.0 g, 16.9 mmol) in methanol (40 mL) was added benzylamine (3 mL, 26.9 mmol), and the mixture was stirred overnight at room temperature and then at 70° until dissolution was complete. After several hours, **10a** (3.02 g, 46%) was collected and recrystallised from methanol, to give material having m.p. 130–132°, $[\alpha]_D^{19}$ −26°, $[\alpha]_{578}^{19}$ −26.5°, $[\alpha]_{546}^{19}$ −30.5°, $[\alpha]_{436}^{19}$ −52.5°, $[\alpha]_{365}^{19}$ −83° (*c* 0.5, pyridine); ν_{max} 3560 and 3500–3000 (NH, OH), 1605 (C=N), 750, 735, 710, and 695 cm^{-1} (phenyl).

Anal. Calc. for $C_{21}H_{29}N_3O_5$: C, 62.51; H, 7.24; N, 10.41. Found: C, 62.52; H, 7.49; N, 10.16.

After storage of the mother liquors for several days at ~5°, **13a** (0.53 g, 8%) was obtained, m.p. 194–196°.

N[1]-*Benzyl-2-benzylamino-2-deoxy*-D-glycero-D-ido-*heptonamidine* (**10c**). — To a suspension of 2-benzylamino-2-deoxy-D-*glycero*-D-*ido*-heptononitrile[6] (**9c**; 3.0 g, 10.1 mmol) in methanol (24 mL) was added benzylamine (1.8 mL, 16.1 mmol), and the mixture was stirred until dissolution was complete (~5 h) and then concentrated under diminished pressure. The resulting, crude, crystalline product was washed twice with ether, and then triturated with methanol (5 mL). Recrystallisation from methanol gave **10c** (3.0 g, 77%), m.p. 112–114°, $[\alpha]_D^{18}$ −28°, $[\alpha]_{578}^{18}$ −29.5°, $[\alpha]_{546}^{18}$ −33°, $[\alpha]_{436}^{18}$ −56.5°, $[\alpha]_{365}^{18}$ −89.5° (*c* 0.5, pyridine); ν_{max} 3600–3000 (NH, OH), 1660 (C=N), 740, 725, and 690 cm^{-1} (phenyl).

Anal. Calc. for $C_{21}H_{29}N_3O_5 \cdot CH_3OH$: C, 60.67; H, 7.64; N, 9.65. Found: C, 60.64; H, 7.84; N, 9.95.

1,4-Anhydro-2-deoxy-2-ethylamino-1-ethylimino-D-lyxo-*hep-2-enitol* (**17**). — A solution of **1** (2.0 g, 8.2 mmol) in methanol was boiled under reflux for 5 min, and then cooled to room temperature, to give **17**. Recrystallisation from methanol gave needles (0.60 g, 33%), m.p. 141–143°, $[\alpha]_D^{22}$ +87°, $[\alpha]_{578}^{22}$ +91.5°, $[\alpha]_{546}^{22}$ +107°, $[\alpha]_{436}^{22}$ +214°, $[\alpha]_{365}^{22}$ +420.5° (*c* 1, pyridine); λ_{max}^{EtOH} 261 nm (ε_{mM} 15.10); ν_{max} 3500–3100 (NH, OH), 1680 (C=N), 1640 (C=C), 1505 (NH), and 855 cm^{-1} (C=N). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 5.32 (d, 1 H, $J_{3,4}$ 1.9 Hz, H-3), 4.89 (dd, 1 H, $J_{4,5}$ 6.7

Hz, H-4), 4.60–4.40 (m, 3 OH), 4.58 (m, 1 H, H-6), 3.80–3.10 (m, 4 H, H-5,7,7′ and NH), 3.27 (q, 2 H, CH_2 ethylimino), 2.92 (q, 2 H, CH_2 ethylamino), 1.10 (t, 3 H, *J* 7.3 Hz, Me), and 1.08 (t, 3 H, *J* 7.3 Hz, Me).

Anal. Calc. for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47. Found: C, 54.11; H, 8.30; N, 11.22.

1,4-Anhydro-2-deoxy-2-ethylamino-1-imino-D-glycero-L-gluco-*heptitol* (**2**). — A suspension of 2-deoxy-2-ethylamino-D-*glycero*-L-*gluco*-heptononitrile[7] (**7a**; 2.0 g, 8.5 mmol) in methanol (10 mL) was boiled under reflux for 15 min, and then stored for 2 days at 0°, to give **2** (0.78 g, 39%). Recrystallisation from methanol gave needles, m.p. 112–114°, $[\alpha]_D^{22}$ −86°, $[\alpha]_{578}^{22}$ −89.5°, $[\alpha]_{546}^{22}$ −101°, $[\alpha]_{436}^{22}$ −172.5°, $[\alpha]_{365}^{22}$ −271° (*c* 1, pyridine); ν_{max} 3600–3000 (NH, OH) and 1665 cm^{-1} (C=N).

Anal. Calc. for $C_9H_{18}N_2O_5 \cdot CH_3OH$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.20; H, 8.18; N, 10.30.

1,4-Anhydro-2-benzylamino-2-deoxy-1-imino-D-glycero-D-talo-*heptitol* (**5**). — A suspension of 2-benzylamino-2-deoxy-D-*glycero*-D-*talo*-heptononitrile[2] (**9b**; 5.0 g, 16.9 mmol) in methanol (20 mL) was boiled under reflux for 30 min, and then stored at room temperature, to give **5** (0.65 g, 13%). Recrystallisation from methanol gave material having m.p. 113–115°, $[\alpha]_D^{16}$ −67.5°, $[\alpha]_{578}^{16}$ −70°, $[\alpha]_{546}^{16}$ −79.5°, $[\alpha]_{436}^{16}$ −136.5°, $[\alpha]_{365}^{16}$ −216.5° (*c* 0.5, pyridine); ν_{max} 3600–3000 (NH, OH), 1665 (C=N), 740, and 695 cm^{-1} (phenyl).

Anal. Calc. for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.53; H, 6.95; N, 9.18.

1,4-Anhydro-2-benzylamino-2-deoxy-1-imino-D-glycero-D-ido-*heptitol* (**6**). — A suspension of 2-benzylamino-2-deoxy-D-*glycero*-D-*ido*-heptononitrile[6] (**9c**; 2.4 g, 8.5 mmol) in methanol (13 mL) was boiled under reflux for 1 h, and then stored at ~5°, to give **6** (0.44 g, 18%), m.p. 117–119°, $[\alpha]_D^{18}$ −25.5°, $[\alpha]_{578}^{18}$ −27°, $[\alpha]_{546}^{18}$ −31°, $[\alpha]_{436}^{18}$ −51°, $[\alpha]_{365}^{18}$ −79.5° (*c* 0.5, pyridine); ν_{max} 3600–3000 (NH, OH), 1645 (C=N), 1595, 740, and 695 cm^{-1} (phenyl).

Anal. Calc. for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 57.02; H, 6.86; N, 9.72.

N-*Benzyl-2-benzylamino-2-deoxy*-D-glycero-L-gluco-*heptonamide* (**13a**). — (*a*) To a suspension of D-galactose (10.0 g, 55.6 mmol) in methanol (100 mL) was added benzylamine (25 mL, 223.6 mmol), and the mixture was stirred until dissolution was complete. Dry hydrogen cyanide (5 mL) was then added and crystalline 2-benzylamino-2-deoxy-D-*glycero*-L-*gluco*-heptononitrile[6] (**9a**) separated immediately. The resulting suspension was stirred at ~60° until dissolution was complete, and then concentrated. Ethanol was repeatedly evaporated from the syrupy residue to give **13a** as a white solid (9.8 g, 44%). Recrystallisation from ethanol gave needles, m.p. 194–196°, $[\alpha]_D^{21}$ −1°, $[\alpha]_{578}^{21}$ −1°, $[\alpha]_{546}^{21}$ −1.5°, $[\alpha]_{436}^{21}$ −3°, $[\alpha]_{365}^{21}$ −4.5° (*c* 0.5, pyridine); c.d. data (MeOH, *c* 0.4 mg/mL): 250 ($[\theta]$0), 240 (−600), 235 (−1,068), 231 (−1,468), 228 (−1,135), 225 (−534), 223 (0), 222 (+668), 218 (+2,940), and 215 (+1,200); ν_{max} 3600–3000 (NH, OH), 1615 (Amide I), 1545 (Amide II), 1490, 750, 730, and 695 cm^{-1} (phenyl). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 8.41 (m, 1 H, CONH) and 7.31 (s, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{28}N_2O_6$: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.65; H, 6.75; N, 6.66.

(*b*) To a suspension of 2-benzylamino-2-deoxy-D-*glycero*-L-*gluco*-heptononitrile[6] (**9a**; 5.0 g, 16.9 mmol) in aqueous 98% methanol (40 mL) was added benzylamine (3 mL, 26.9 mmol). The mixture was stirred for 15 h at room temperature and then at ~45° until dissolution was complete, and stored at room temperature to give **13a** (2.5 g). Concentration of the mother liquors gave more **13a** (total yield, 4.9 g, 72%).

(*c*) A suspension of **10a** (0.25 g, 2.3 mmol) in aqueous 75% methanol (4 mL) was kept at 90° until dissolution was complete, and then for a further 15 min. The resulting solution, when left at room temperature, gave **13a** (0.1 g, 38%).

3,4,5,6,7-Penta-O-benzoyl-N-benzyl-2-(N-benzylbenzamido)-2-deoxy-D-glycero-L-gluco-*heptonamide* (**16a**). — Conventional treatment of **13a** (1.2 g, 3.0 mmol) in pyridine (25 mL) at 0° with benzoyl chloride (3.1 mL, 27.0 mmol) gave **16a** (2.9 g, 95%). The purified product (2.0 g, 62%) had m.p. 92–94° (from ethanol–water), $[\alpha]_D^{15}$ −3°, $[\alpha]_{578}^{15}$ −3.5°, $[\alpha]_{546}^{15}$ −16°, $[\alpha]_{436}^{15}$ −28.5°, $[\alpha]_{365}^{15}$ −47° (*c* 1, chloroform); ν_{max} 3395 (NH), 1715 (C=O benzoate), 1670 (C=O benzamide), 1620 (C=O heptonamide), 1515 (NH), and 710 cm^{-1} (phenyl).

Anal. Calc. for $C_{63}H_{52}N_2O_{12}$: C, 73.53; H, 5.09; N, 2.72. Found: C, 73.25; H, 5.20; N, 2.78.

2-Deoxy-N-*ethyl-2-ethylamino*-D-glycero-L-gluco-*heptonamide* (**11a**). — A suspension of **1** (0.7 g, 2.7 mmol) in aqueous 90% ethanol (7 mL) was boiled under reflux for 10 min. The resulting solution was kept at room temperature to give **11a** (0.37 g, 46%), m.p. 176–178°, $[\alpha]_D^{21}$ −6°, $[\alpha]_{578}^{21}$ −6.5°, $[\alpha]_{546}^{21}$ −7.5°, $[\alpha]_{436}^{21}$ −16.5°, $[\alpha]_{365}^{21}$ −36° (*c* 0.6, pyridine); c.d. data (MeOH, *c* 0.26 mg/mL): 225 ([θ]0), 250 (−142), 240 (−783), 235 (−1,494), 230 (−2,100), 225 (−2,313), 223 (−1,990), 220 (−1,280), 216 (0), and 214 (+1,495); ν_{max} 3600–3000 (NH, OH), 1620 (Amide I), and 1545 cm^{-1} (Amide II). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 7.87 (t, 1 H, J_{NH,CH_2} 6.0 Hz, CONH), 3.14 (m, 2 H, CH_2 ethylamide), 2.47 (m, 2 H, CH_2 ethylamine), 1.03 (t, 3 H, *J* 7.2 Hz, Me), and 0.98 (t, 3 H, *J* 7.2 Hz, Me).

Anal. Calc. for $C_{11}H_{24}N_2O_6 \cdot H_2O$: C, 44.29; H, 8.78; N, 9.39. Found: C, 44.19; H, 8.55; N, 9.32.

N-*Benzyl-2-benzylamino-2-deoxy*-D-glycero-D-talo-*heptonamide* (**13b**). — A suspension of **4** (0.25 g, 0.65 mmol) in aqueous 67% methanol (3 mL) was processed as described for the preparation of **11a**. After several recrystallisations of the product (0.16 g, 61%) from ethanol, it gave needles, m.p. 174–176°, $[\alpha]_D^{13}$ −25°, $[\alpha]_{578}^{13}$ −26°, $[\alpha]_{546}^{13}$ −29.5°, $[\alpha]_{436}^{13}$ −49°, $[\alpha]_{365}^{13}$ −75° (*c* 0.5, pyridine); c.d. data (MeOH, *c* 0.5 mg/mL): 260 ([θ]0), 250 (−374), 240 (−747), 235 (−1,628), 231 (−1,735), 229 (−1,495), 225 (−1,094), 220 (0), 218 (+1,308), and 215 (+2,000); ν_{max} 3600–3000 (NH, OH), 1630 (Amide I), 1530 (Amide II), 1595, 1490, 740, 730, and 695 cm^{-1} (phenyl). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 8.39 (m, 1 H, CONH) and 7.30 (s, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{28}N_2O_6$: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.52; H, 6.93; N, 7.19.

*3,4,5,6,7-Penta-*O*-benzoyl-*N*-benzyl-2-(*N*-benzylbenzamido)-2-deoxy-*D*-glycero-*D*-talo-heptonamide* (**16b**). — Benzoylation of **13b** (0.3 g, 0.74 mmol) gave **16b** (0.73 g, 96%). The purified product (0.33 g, 43%) had m.p. 73–75° (from ethanol–water), $[\alpha]_D^{16}$ +1°, $[\alpha]_{578}^{16}$ +1.5°, $[\alpha]_{546}^{16}$ +1°, $[\alpha]_{436}^{16}$ −3°, $[\alpha]_{365}^{16}$ −19° (*c* 1, chloroform); ν_{max} 3400 (NH), 1725 (C=O benzoate), 1680 (C=O benzamide), 1635 (C=O heptonamide), 1520 (NH), and 710 cm^{-1} (phenyl).

Anal. Calc. for $C_{63}H_{52}N_2O_{12}$: C, 73.53; H, 5.09; N, 2.72. Found: C, 73.21; H, 5.35; N, 3.03.

*2-Deoxy-*N*-ethyl-2-ethylamino-*D*-glycero-*D*-talo-heptonamide* (**11b**). — A suspension of **3** (5.9 g, 22.5 mmol) in aqueous 93% methanol (70 mL) was boiled under reflux for 15 min and then concentrated under diminished pressure, and the syrupy residue was crystallised from ethanol. Recrystallisation of the product (4.4 g, 69%) from methanol gave **11b**, m.p. 159–160°, $[\alpha]_{578}^{35}$ −20°, $[\alpha]_{546}^{35}$ −24.5°, $[\alpha]_{436}^{35}$ −37.5°, $[\alpha]_{365}^{35}$ −49° (*c* 0.2, pyridine); ν_{max} 3600–3000 (NH, OH), 1640 (Amide I), and 1540 cm^{-1} (Amide II). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 7.86 (t, 1 H, J_{NH,CH_2} 6.0 Hz, CONH), 3.17 (m, 2 H, CH_2 ethylamide), 2.50 (m, 2 H, CH_2 ethylamine), 1.03 (t, 3 H, *J* 7.2 Hz, Me), and 0.99 (t, 3 H, *J* 7.2 Hz, Me).

Anal. Calc. for $C_{11}H_{24}N_2O_6$: C, 47.13; H, 8.63; N, 9.99. Found: C, 47.29; H, 8.63; N, 9.75.

*N-Benzyl-2-benzylamino-2-deoxy-*D*-glycero-*D*-ido-heptonamide* (**13c**). — (*a*) To a suspension of D-glucose (10.0 g, 55.6 mmol) in methanol (70 mL) was added benzylamine (17 mL, 150 mmol), and the mixture was stirred for 12 h at room temperature, and then at ~40° until dissolution was complete. Dry hydrogen cyanide (5 mL) was added, and the mixture was kept for 2 h at room temperature and overnight at 0°, and then concentrated under diminished pressure. A solution of the resulting syrup in methanol was concentrated to dryness and the residue was crystallised from methanol (3.3 g, 15%). Several recrystallisations from ethanol gave **13c** as needles, m.p. 155–157°, $[\alpha]_D^{20}$ −3°, $[\alpha]_{578}^{20}$ −3.5°, $[\alpha]_{546}^{20}$ −4°, $[\alpha]_{436}^{20}$ −8.5°, $[\alpha]_{365}^{20}$ −17° (*c* 1, pyridine); c.d. data (MeOH, *c* 0.43 mg/mL): 250 ([θ]0), 240 (−1,263), 235 (−2,033), 230 (−2,464), 228 (−2,526), 225 (−2,250), 222 (−1,140), 220 (0), 218 (+2,800), and 215 (+3,020); ν_{max} 3500–3000 (NH, OH), 1620 (Amide I), 1550 (Amide II), 1600, 1490, 750, 730, and 695 cm^{-1} (phenyl). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 8.39 (t, 1 H, J_{NH,CH_2} 6.0 Hz, CONH) and 7.29 (s, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{28}N_2O_6$: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.50; H, 7.07; N, 7.01.

(*b*) A suspension of **10c** (0.25 g, 0.65 mmol) in aqueous 67% methanol (3 mL) was boiled under reflux for 15 min, and then concentrated at room temperature to give **13c** (0.09 g, 34%) after processing as in (*a*).

*3,4,5,6,7-Penta-*O*-benzoyl-*N*-benzyl-2-(*N*-benzylbenzamido)-2-deoxy-*D*-glycero-*D*-ido-heptonamide* (**16c**). — Benzoylation of **13c** (1.2 g, 3.0 mmol) gave **16c** (3.1 g). Two recrystallisations of the crude product from ethanol gave needles (2.6 g, 83%), m.p. 170–172°, $[\alpha]_D^{20}$ −0.5°, $[\alpha]_{578}^{20}$ −1°, $[\alpha]_{546}^{20}$ −1.5°, $[\alpha]_{436}^{20}$ −7°,

$[\alpha]_{365}^{20}$ −24° (*c* 1, chloroform); ν_{max} 3320 (NH), 1725 and 1710 (C=O benzoate), 1680 (C=O benzamide), 1635 (C=O heptonamide), 1540 (NH), and 700 cm^{-1} (phenyl). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.20–6.70 (m, 40 H, 8 Ph), 7.44 (m, 1 H, CONH), 6.86 (d, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ <1 Hz, H-3), 6.25–6.00 (m, 2 H, H-4,5), 5.97 (m, 1 H, H-6), 4.86 (dd, 1 H, $J_{6,7}$ 3.8, $J_{7,7'}$ −13.0 Hz, H-7), 4.81 (d, 1 H, H-2), 4.57 (dd, 1 H, $J_{6,7'}$ 5.4 Hz, H-7'), and 4.70–3.80 (m, 4 H, CH_2 benzylamide and benzylamine).

Anal. Calc. for $C_{63}H_{52}N_2O_{12}$: C, 73.53; H, 5.09; N, 2.72. Found: C, 73.52; H, 5.16; N, 2.48.

2-Deoxy-N-*ethyl-2-ethylamino*-D-glycero-D-ido-*heptonamide* (**11c**). — To a suspension of D-glucose (50.0 g, 0.28 mol) in methanol (200 mL) was added ethylamine (50 mL, 0.75 mol), and the mixture was stirred until dissolution was complete. Dry hydrogen cyanide (25 mL) was then added and the mixture was kept for 4 days at room temperature to give **11c** (13.3 g). The mother liquors yielded more **11c** (total yield, 40.0 g, 51%). Recrystallisation from ethanol gave needles, m.p. 154–156°, $[\alpha]_D^{20}$ −13.5°, $[\alpha]_{578}^{20}$ −14.5°, $[\alpha]_{546}^{20}$ −16.5°, $[\alpha]_{436}^{20}$ −12°, $[\alpha]_{365}^{20}$ −58.5° (*c* 0.5, pyridine); c.d. data (MeOH, *c* 0.4 mg/mL): 260 ([θ]0), 250 (−370), 240 (−810), 235 (−1,249), 230 (−1,596), 227 (−1,804), 224 (−1,619), 220 (−970), 214 (0), and 210 (+1,642); ν_{max} 3500–3000 (NH, OH), 1630 (Amide I), and 1535 cm^{-1} (Amide II). N.m.r. data (Me_2SO-d_6): ^{1}H, δ 7.87 (t, 1 H, J_{NH,CH_2} 6.0 Hz, CONH), 3.17 (m, 2 H, CH_2 ethylamide), 2.47 (m, 2 H, CH_2 ethylamine), 1.03 (t, 3 H, *J* 7.2 Hz, Me), and 0.98 (t, 3 H, *J* 7.2 Hz, Me); ^{13}C, δ 176.5 (s, carbonyl), 77.1, 76.6, 75.5, 73.3, and 67.9 (5 d, C-2,3,4,5,6), 67.3 (t, C-7), 45.7 (t, CH_2 ethylamide), 37.2 (t, CH_2 ethylamine), 19.0 (q, Me ethylamide), and 18.7 (q, Me ethylamine).

Anal. Calc. for $C_{11}H_{24}N_2O_6$: C, 47.13; H, 8.63; N, 9.99. Found: C, 46.95; H, 8.83; N, 10.04.

3,4,5,6,7-Penta-O-*benzoyl-2-deoxy*-N-*ethyl-2-(*N-*ethylbenzamido)*-D-glycero-D-ido-*heptonamide* (**14c**). — Benzoylation of **11c** (1.0 g, 3.6 mmol) gave **14c** (3.3 g). The purified product (1.2 g, 38%) had m.p. 88–90° (from ethanol–water), $[\alpha]_D^{22}$ −9.5°, $[\alpha]_{578}^{22}$ −10°, $[\alpha]_{546}^{22}$ −12°, $[\alpha]_{436}^{22}$ −24.5°, $[\alpha]_{365}^{22}$ −49.5° (*c* 0.5, chloroform); ν_{max} 3320 (NH), 1710 (C=O benzoate), 1665 (C=O benzamide), 1620 (C=O heptonamide), 1520 (NH), and 705 cm^{-1} (phenyl). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.10–7.05 (m, 30 H, 6 Ph), 7.45 (m, 1 H, CONH), 6.97 (d, 1 H, $J_{2,3}$ 10.2, $J_{3,4}$ <1 Hz, H-3), 6.20–5.98 (m, 2 H, H-4,5), 5.93 (m, 1 H, H-6), 4.86 (dd, 1 H, $J_{6,7}$ 2.8, $J_{7,7'}$ −12.3 Hz, H-7), 4.58 (dd, 1 H, $J_{6,7'}$ 3.9 Hz, H-7'), 4.54 (d, 1 H, H-2), 3.50–2.95 (m, 4 H, CH_2 ethylamide and ethylamine), 1.02 (t, 3 H, *J* 7.1 Hz, Me), and 0.81 (t, 3 H, *J* 7.1 Hz, Me).

Anal. Calc. for $C_{53}H_{48}N_2O_{12}$: C, 70.34; H, 5.35; N, 3.10. Found: C, 70.32; H, 5.37; N, 3.05.

2-Deoxy-N-*propyl-2-propylamino*-D-glycero-D-ido-*heptonamide* (**12c**). — (*a*) To a suspension of D-glucose (10.0 g, 55.6 mmol) in methanol (90 mL) was added propylamine (12.5 mL, 150 mmol), and the mixture was stirred at ~45° until dis-

solution was complete. Dry hydrogen cyanide (5 mL) was then added, and the mixture was kept for 4 h at room temperature and for 3 days at 0°, and then concentrated under diminished pressure. The resulting syrup was crystallised from ethanol–acetone to give **12c** (5.1 g, 30%). Several recrystallisations from ethanol gave needles, m.p. 145–147°, $[\alpha]_D^{20}$ −9°, $[\alpha]_{578}^{20}$ −9.5°, $[\alpha]_{546}^{20}$ −11.5°, $[\alpha]_{436}^{20}$ −23°, $[\alpha]_{365}^{20}$ −44° (*c* 1, pyridine); c.d. data (MeOH, *c* 0.26 mg/mL): 270 ([θ] +78), 255 (0), 250 (−117), 240 (−1,252), 230 (−3,640), 228 (−3,757), 224 (−3,640), 220 (−2,583), 214 (0), and 212 (+1,526); ν_{max} 3600–3000 (NH, OH), 1635 (Amide I), and 1540 cm^{-1} (Amide II). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 7.86 (t, 1 H, J_{NH,CH_2} 6.0 Hz, CONH), 3.11 (t, 2 H, $J_{CH_2CH_2}$ 7.5 Hz, NCH_2 propylamide), 2.40 (t, 2 H, $J_{CH_2CH_2}$ 7.5 Hz, NCH_2 propylamine), 1.40 (m, 4 H, $NCH_2CH_2CH_3$ propylamide and propylamine), and 0.84 (t, 6 H, *J* 7.5 Hz, Me propylamide and propylamine).

Anal. Calc. for $C_{13}H_{28}N_2O_6$: C, 50.63; H, 9.15; N, 9.08. Found: C, 50.46; H, 9.37; N, 9.14.

(*b*) To a suspension of 2-deoxy-2-propylamino-D-*glycero*-D-*ido*-heptononitrile[8] (**8c**; 5.0 g, 20.1 mmol) in methanol (40 mL) was added propylamine (4.0 mL, 37.6 mmol), and the mixture was stirred at room temperature until dissolution was complete, and then stored at 0° to give **12c** (1.4 g, 23%).

3,4,5,6,7-Penta-O-benzoyl-2-deoxy-N-propyl-2-(N-propylbenzamido)-D-glycero-D-ido-heptonamide (**15c**). — Benzoylation of **12c** (1.0 g, 3.3 mmol) gave **15c** (3.1 g). The purified product (2.9 g, 96%) had m.p. 90–92° (from ethanol–water), $[\alpha]_D^{19}$ −9.5°, $[\alpha]_{578}^{19}$ −10°, $[\alpha]_{546}^{19}$ −11.5°, $[\alpha]_{436}^{19}$ −23.5°, $[\alpha]_{365}^{19}$ −47.5° (*c* 1, chloroform); ν_{max} 3400–3300 (NH), 1715 (C=O benzoate), 1670 (C=O benzamide), 1620 (C=O heptonamide), 1520 (NH), and 710 cm^{-1} (phenyl). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.20–7.05 (m, 30 H, 6 Ph), 7.50 (m, 1 H, CONH), 7.00 (d, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ <1 Hz, H-3), 6.25–6.00 (m, 2 H, H-4,5), 5.95 (m, 1 H, H-6), 4.88 (dd, 1 H, $J_{6,7}$ 3.8, $J_{7,7'}$ −12.5 Hz, H-7), 4.58 (dd, 1 H, $J_{6,7'}$ 5.8 Hz, H-7′), 4.53 (d, 1 H, H-2), 3.40–2.85 (m, 4 H, NCH_2 propylamide and propylamine), 1.60–1.10 (m, 4 H, $NCH_2CH_2CH_3$ propylamide and propylamine), 0.83 (t, 3 H, *J* 7.3 Hz, Me), and 0.40 (t, 3 H, *J* 6.5 Hz, Me).

Anal. Calc. for $C_{55}H_{52}N_2O_{12}$: C, 70.80; H, 5.62; N, 3.00. Found: C, 70.54; H, 5.44; N, 2.80.

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