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Note

Syntheses of 2-amino- and 2-(benzylamino)-2-deoxyheptonic acids

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Carbohydrate α-amino acids are interesting not only because they may be regarded as analogs of the sugar moiety of the polyoxins[1], but also because, by reaction with nitrous acid, they yield anhydro sugars that are useful intermediates in the synthesis of *C*-nucleosides.

We now report the preparation of new 2-benzylamino-2-deoxyheptonic acids (**2**) by hydrolysis of the 2-(benzylamino)-2-deoxyheptononitriles having the D-*glycero*-L-*gluco* (**1a**), D-*glycero*-D-*ido* (**1c**), and D-*glycero*-D-*talo* (**1e**) configurations, already described in earlier studies on the aminonitrile synthesis of 2-amino-2-deoxyheptoses[2]. The hydrolytic reactions were conducted by heating aqueous solutions of the nitriles, and, in all instances, the epimerization of C-2 took place. In this way, the six 2-(benzylamino)-2-deoxyheptonic acids **2a**–**2f** were obtained.

Small proportions of *N*-benzylheptonamides (**5**) were formed as by-products. In the hydrolysis of **1a** and **1e**, they were isolated, and characterized by comparison of their properties with those of authentic samples[3]; in the case of **1c**, the amide was only detected by t.l.c. These products may have been formed by hydrolysis of the amidines resulting from addition, to the aminonitrile, of benzylamine that might be liberated by partial decomposition of the aminonitrile during the hydrolysis.

By hydrogenolysis of the benzyl group of compounds **2**, the 2-amino-2-deoxyheptonic acids (**3**) were obtained. Compound **3a** was also synthesized by oxidation of 2-amino-2-deoxy-D-*glycero*-L-*gluco*-heptose[2] (**4a**).

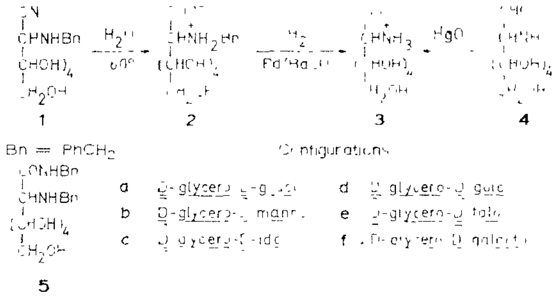

TABLE I

SPECIFIC OPTICAL ROTATIONS OF COMPOUNDS **2** AND **3**, AND THEIR SODIUM SALTS: CONFIGURATION OF C-2

Compounds	$[\alpha]_D$ *(degrees)*		*Difference*	*Configuration*
	Sodium salt	*Free acid*	*(salt — acid)*	*of C-2*[a]
2a	−47.1	−13.5	−33.6	*S*
2b	+10.0	+8.0	+9.2	*R*
2c	−14.0	−10.3	−3.7	*S*
2d	+9.2	−7.3	+16.5	*R*
2e	−9.8	+2.4	−12.2	*S*
2f	+0.4	−5.0	+5.4	*R*
3a	+1.1	+11.1	−10.0	*S*
3b	+4.9	−6.2	+11.1	*R*
3c	−6.2	+4.4	−10.6	*S*
3d	0.0	−17.2	+17.2	*R*
3e	−3.4	+3.2	−6.6	*S*
3f	−6.6	−13.0	+6.4	*R*

[a]See ref. 4.

The proposed structures of the new compounds **2** and **3** are in accord with their elemental analyses and physical properties (including u.v. and i.r. spectra). The configurations of C-2 were assigned on the basis of the optical rotations of the acids and their sodium salts (see Table I), according to Levene's rule[4], which states that, if the configuration of C-2 is as in 2-amino-2-deoxy-D-gluconic acid [namely, (*R*)], the difference between the optical rotation of the salt and that of the free acid (salt — acid) has a positive value; but, if the configuration is as in 2-amino-2-deoxy-D-mannonic acid [that is, (*S*)], this difference has a negative value.

EXPERIMENTAL

General methods. — Solutions were evaporated *in vacuo* at temperatures below 50°. Melting points were determined with a Gallenkamp apparatus, and are uncorrected. Optical rotations were measured at 20 ±2° with a Perkin–Elmer 141 polarimeter (10-cm, 5-mL cell) for solutions in 0.1M NaOH, including the change in optical rotation on acidification with two drops of 12M HCl. I.r. spectra (KBr discs) were recorded with a Perkin–Elmer 399 spectrophotometer, and u.v. spectra with a Pye–Unicam SP8-250 instrument. Paper chromatography was performed on Whatman No. 1 paper, by the ascending technique, with 1:1:1 1-butanol–pyridine–water as the eluant, and silver nitrate–sodium hydroxide or ninhydrin as the indicator.

2-(Benzylamino)-2-deoxy-D-glycero-L-gluco-*heptonic* (**2a**) *and 2-(benzylamino)-2-deoxy*-D-glycero-L-manno-*heptonic* (**2b**) *acids*. — A solution of 2-(benzylamino)-2-deoxy-D-*glycero*-L-*gluco*-heptononitrile[5] (**1a**; 5.0 g, 16.87 mmol) in water (60 mL) was heated for 2 h at 60°. During the reaction, a crystalline precipitate separated, and was filtered off, successively washed with methanol and acetone, and dried (0.54 g, R_F 0.94); this product was identified as *N*-benzyl-2-(benzylamino)-2-deoxy-D-*glycero*-L-*gluco*-heptonamide[3] (**5a**). The filtrate was evaporated under diminished pressure, and methanol was repeatedly added to, and evaporated from, the resulting syrup, to give a solid residue (3.7 g, 69%) (R_F 0.50). Several recrystallizations from water afforded pure **2a** (0.93 g), m.p. 229–231° (dec.), $[\alpha]_D$ 47.1°, $[\alpha]_{578}$ 49.4°, $[\alpha]_{546}$ −55.5°, $[\alpha]_{436}$ 89.8°, $[\alpha]_{365}$ −133.5° (*c* 1, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ 13.5°, $[\alpha]_{578}$ −14.5°, $[\alpha]_{546}$ 16.1°, $[\alpha]_{436}$ 25.0°, $[\alpha]_{365}$ −33.5°; $\lambda_{max}^{H_2O}$ 205 and 261 nm (ε_{mM} 8.40 and 1.20); ν_{max} 3600–2400 (OH, NH_2^+), 1605 (NH_2^+), 1530 and 1400 (COO^-), 1495, 740, and 695 cm^{-1} (phenyl).

Anal. Calc. for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found. C, 53.25; H, 6.63; N, 4.20.

Concentration of the mother liquors gave **2b**; after several recrystallizations from water–ethanol, yield: 0.13 g; m.p. 205–207° (dec.), $[\alpha]_D$ +10.0°, $[\alpha]_{578}$ +10.2°, $[\alpha]_{546}$ +11.0°, $[\alpha]_{436}$ +16.0°, $[\alpha]_{365}$ +20.2° (*c* 1, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ +0.8°, $[\alpha]_{578}$ +0.8°, $[\alpha]_{546}$ +0.8°, $[\alpha]_{436}$ 0.0°, $[\alpha]_{365}$ −1.9°; $\lambda_{max}^{H_2O}$ 204 and 255 (ε_{mM} 8.60 and 0.32); ν_{max} 3650–2400 (OH, NH_2^+), 1600 and 1375 (COO^-), 1495, 745, and 695 cm^{-1} (phenyl).

Anal. Calc. for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found: C, 52.93; H, 6.69; N, 4.29.

*2-(Benzylamino)-2-deoxy-*D-glycero-D-gulo-*heptonic* (**2d**) *and 2-(benzylamino)-2-deoxy-*D-glycero-D-ido-*heptonic* (**2c**) *acids*. — A solution of 2-(benzylamino)-2-deoxy-D-*glycero*-D-*ido*-heptononitrile[5] (**1c**; 5.0 g, 16.87 mmol) in water (45 mL) was heated for 2 h at 60°. Paper chromatography revealed the formation of *N*-benzyl-2-(benzylamino)-2-deoxy-D-*glycero*-D-*ido*-heptonamide (**5c**; R_F 0.94), identified by comparison with an authentic sample[3]. The reaction mixture was evaporated to a syrup; methanol was repeatedly added, and evaporated, to give a solid residue (2.6 g, 49%; R_F 0.50). Several recrystallizations from water afforded pure **2d** (1.96 g): m.p. 180–182° (dec.), $[\alpha]_D$ +9.2°, $[\alpha]_{578}$ +9.2°, $[\alpha]_{546}$ +8.5°, $[\alpha]_{436}$ +9.5°, $[\alpha]_{365}$ +10.6° (*c* 1, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ −7.3°, $[\alpha]_{578}$ −7.8°, $[\alpha]_{546}$ −8.9°, $[\alpha]_{436}$ −15.7°, $[\alpha]_{365}$ 26.8°, $\lambda_{max}^{H_2O}$ 204 and 255 nm (ε_{mM} 8.50 and 0.25); ν_{max} 3650–2200 (OH, NH_2^+), 1625 (NH_2^+), 1570 and 1400 (COO^-), 1490, 755, and 700 cm^{-1} (phenyl).

Anal. Calc. for $C_{14}H_{21}NO_7 \cdot 0.5\ H_2O$: C, 51.85; H, 6.84; N, 4.32. Found. C, 51.93; H, 6.58; N, 4.23

Concentration of the mother liquors gave **2c**; after several recrystallizations from water–acetone, yield: 0.53 g; m.p. 163–165° (dec.). $[\alpha]_D$ 14.0°, $[\alpha]_{578}$ −15.0°, $[\alpha]_{546}$ −17.2°, $[\alpha]_{436}$ 28.8°, $[\alpha]_{365}$ 42.6° (*c* 1, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ 10.3°, $[\alpha]_{578}$ 10.6°, $[\alpha]_{546}$ 12.1°, $[\alpha]_{436}$ −19.8°, $[\alpha]_{365}$ −29.1°; $\lambda_{max}^{H_2O}$ 203 and 255 nm (ε_{mM} 8.80 and 0.32); ν_{max} 3600–2300 (OH, NH_2^+), 1600 (NH_2^+, COO^-), 1410 (COO^-), 1490, 745, and 690 cm^{-1} (phenyl).

Anal. Calc. for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found: C, 53.28; H, 7.00; N, 4.55.

*2-(Benzylamino)-2-deoxy-*D-glycero-D-talo-*heptonic* (**2e**) *and 2-(benzylamino)-2-deoxy-*D-glycero-D-galacto-*heptonic* (**2f**) *acids.* — A solution of 2-(benzylamino)-2-deoxy-D-*glycero*-D-*talo*-heptononitrile[2] (**1e**; 5.0 g, 16.87 mmol) in water (55 mL) was heated for 2 h at 60°. During the reaction, a crystalline precipitate separated (0.53 g, R_F 0.94); it was filtered off, and identified as *N*-benzyl-2-(benzylamino-2-deoxy-D-*glycero*-D-*talo*-heptonamide[3] (**5e**). The filtrate was evaporated under diminished pressure, and the resulting syrup was treated by repeated addition and evaporation of methanol, to give a solid residue (3.9 g, 73%) (R_F 0.50). Several recrystallizations from water afforded pure **2e** (2.2 g); m.p. 189–191° (dec.), $[\alpha]_D$ −9.8°, $[\alpha]_{578}$ −10.0°, $[\alpha]_{546}$ −11.4°, $[\alpha]_{436}$ −20.6°, $[\alpha]_{365}$ −33.4° (*c* 0.5, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ +2.4°, $[\alpha]_{578}$ +2.4°, $[\alpha]_{546}$ +2.6°, $[\alpha]_{436}$ +3.6°, $[\alpha]_{365}$ +5.2°; $\lambda_{max}^{H_2O}$ 203 and 255 nm (ε_{mM} 8.40 and 0.24); ν_{max} 3600–2000 (OH, NH_2^+), 1620 (NH_2^+, COO^-), 1370 (COO^-), 1490, 745, and 700 cm^{-1} (phenyl).

Anal. Calc. for $C_{14}H_{21}NO_7 \cdot 0.5\ H_2O$: C, 51.85; H, 6.84; N, 4.32. Found: C, 51.76; H, 6.84; N, 4.17.

Concentration of the mother liquors gave **2f**; after several recrystallizations from water–acetone, yield 0.65 g; m.p. 175–177° (dec.), $[\alpha]_D$ +0.4°, $[\alpha]_{578}$ +0.4°, $[\alpha]_{546}$ +0.4°, $[\alpha]_{436}$ −1.4°, $[\alpha]_{365}$ −6.0° (*c* 0.5, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ −5.0°, $[\alpha]_{578}$ −5.4°, $[\alpha]_{546}$ −6.8°, $[\alpha]_{436}$ −11.4°, $[\alpha]_{365}$ −21.2°; $\lambda_{max}^{H_2O}$ 203 and 255 nm (ε_{mM} 7.70 and 0.26); ν_{max} 3600–2100 (OH, NH_2^+), 1600 (NH_2^+), 1580 and 1380 (COO^-), 1490, 745, and 700 cm^{-1} (phenyl).

Anal. Calc. for $C_{14}H_{21}NO_7 \cdot H_2O$: C, 50.44; H, 6.95; N, 4.20. Found: C, 50.24; H, 6.85; N, 4.05.

2-Amino-2-deoxyheptonic acids (**3**): *general procedure.* — A solution of the 2-(benzylamino)-2-deoxyheptonic acid (**2**; 1.0 g, 4.4 mmol) in water (100 mL) was hydrogenated at atmospheric pressure in the presence of 10% palladium-on-barium sulfate (0.4 g). Paper chromatography showed the formation of **3** (R_F 0.20), and, after 5 days, the spot of **2** (R_F 0.50) had disappeared completely. The mixture was filtered, and the filtrate evaporated to a solid that was successively washed with cold water and methanol. In other cases, the solution was concentrated to ~10 mL, and the product was obtained crystalline by addition of methanol.

*2-Amino-2-deoxy-*D-glycero-L-gluco-*heptonic* acid (**3a**). — (*a*) The product (**3a**) was obtained from **2a** by the general procedure described; yield: 93%; m.p. 236–238° (dec.) (from water), $[\alpha]_D$ +1.1°, $[\alpha]_{578}$ +1.2°, $[\alpha]_{546}$ +1.5°, $[\alpha]_{436}$ +2.8°, $[\alpha]_{365}$ +5.6° (*c* 1, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ +11.1°, $[\alpha]_{578}$ +11.6°, $[\alpha]_{546}$ +13.4°, $[\alpha]_{436}$ +26.2°, $[\alpha]_{365}$ +48.3°; ν_{max} 3600–2500 (OH, NH_3^+), 2200, 1610, and 1530 (NH_3^+), 1570 and 1395 cm^{-1} (COO^-).

Anal. Calc. for $C_7H_{15}NO_7 \cdot H_2O$: C, 34.57; H, 7.05; N, 5.76. Found: C, 34.49; H, 7.29; N, 5.71.

(*b*) To a stirred solution of 2-amino-2-deoxy-D-*glycero*-L-*gluco*-heptose hydrochloride (**4a**; 4.0 g, 16.33 mmol) in water (200 mL) at 100° was added yellow mercuric oxide (10.6 g). After 45 min at 95–100° with stirring, the mixture was cooled and filtered; the filtrate was treated with hydrogen sulfide, the precipitate filtered off and the filtrate concentrated until crystallization was observed. An equal volume of hot methanol was added, and the product isolated; it was identified as **3a** by its i.r. spectrum and by mixed m.p.

2-Amino-2-deoxy-D-glycero-L-manno-*heptonic acid* (**3b**). — Compound **3b** was prepared from **2b**, according to the general procedure; yield: 59%; m.p. 184–186° (dec.) (from water–methanol), $[\alpha]_D$ +4.9°, $[\alpha]_{578}$ +5.2°, $[\alpha]_{546}$ +5.7°, $[\alpha]_{436}$ +9.3°, $[\alpha]_{365}$ +13.3° (*c* 1, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ −6.2°, $[\alpha]_{578}$ −6.4°, $[\alpha]_{546}$ 7.6°, $[\alpha]_{436}$ −15.4°, $[\alpha]_{365}$ 29.9°; ν_{max} 3600–2500 (OH, NH_3^+), 2100, 1650, and 1520 (NH_3^+), 1650 and 1415 cm^{-1} (COO^-).

Anal. Calc. for $C_7H_{15}NO_7$: C, 37.34; H, 6.71; N, 6.22. Found: C, 37.05; H, 7.02; N, 6.13.

2-Amino-2-deoxy-D-glycero-D-ido-*heptonic acid* (**3c**). — Compound **3c** was obtained from **2c**; yield: 89%; m.p. 213–215° (dec.) (from water–methanol), $[\alpha]_D$ −6.2°, $[\alpha]_{578}$ −6.6°, $[\alpha]_{546}$ −7.4°, $[\alpha]_{436}$ 11.6°, $[\alpha]_{365}$ 16.0 (*c* 0.5, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ +4.4°, $[\alpha]_{578}$ +4.6°, $[\alpha]_{546}$ +5.4°, $[\alpha]_{436}$ +12.4°, $[\alpha]_{365}$ +26.6°; ν_{max} 3600–2400 (OH, NH_3^+), 1620 and 1480 (NH_3^+), 1575 and 1395 cm^{-1} (COO^-).

Anal. Calc. for $C_7H_{15}NO_7$: C, 37.34; H, 6.71; N, 6.22. Found: C, 37.19; H, 7.09; N, 6.27.

2-Amino-2-deoxy-D-glycero-D-gulo-*heptonic acid* (**3d**). — Compound **3d** was prepared from **2d**; yield: 96%; m.p. 155–157° (dec.) (from water–methanol), $[\alpha]_D$ 0.0°, $[\alpha]_{578}$ 0.0°, $[\alpha]_{546}$ 0.0°, $[\alpha]_{436}$ 1.0°, $[\alpha]_{365}$ 2.8 (*c* 1, 0.1M NaOH); after acidification with 12M HCl. $[\alpha]_D$ −17.2°, $[\alpha]_{578}$ −18.0°, $[\alpha]_{546}$ 20.7°, $[\alpha]_{436}$ −47.5°, $[\alpha]_{365}$ 60.4°; ν_{max} 3600–2400 (OH, NH_3^+), 2070, 1620, and 1530 (NH_3^+), 1570 and 1410 cm^{-1} (COO^-).

Anal. Calc. for $C_7H_{15}NO_7 \cdot H_2O$: C, 34.57; H, 7.05; N, 5.76. Found: C, 34.63; H, 7.40; N, 5.62.

2-Amino-2-deoxy-D-glycero-D-talo-*heptonic acid* (**3e**). — Compound **3e** was obtained from **2e**; yield: 98%; m.p. 223–225° (dec.) (from water–methanol), $[\alpha]_D$ −3.4°, $[\alpha]_{578}$ −4.0°, $[\alpha]_{546}$ −4.8°, $[\alpha]_{436}$ −8.8°, $[\alpha]_{365}$ 16.0 (*c* 0.5, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ +3.2°, $[\alpha]_{578}$ +3.2°, $[\alpha]_{546}$ +3.4°, $[\alpha]_{436}$ +4.6°, $[\alpha]_{365}$ +5.2°; ν_{max} 3600–2400 (OH, NH_3^+), 2040, 1630, and 1490 (NH_3^+), 1585 and 1415 cm^{-1} (COO).

Anal. Calc. for $C_7H_{15}NO_7$: C, 37.34; H, 6.71; N, 6.22. Found: C, 37.07; H, 7.04; N, 6.11.

2-Amino-2-deoxy-D-glycero-D-galacto-*heptonic acid* (**3f**). — Compound **3f** was prepared from **2f**; yield: 96%; m.p. 221–223° (dec.) (from water–methanol), $[\alpha]_D$ −6.6°, $[\alpha]_{578}$ 6.8°, $[\alpha]_{546}$ −8.0°, $[\alpha]_{436}$ −15.8°, $[\alpha]_{365}$ 29.0 (*c* 1, 0.1M NaOH); after acidification with 12M HCl: $[\alpha]_D$ 13.0°, $[\alpha]_{578}$ −13.6°, $[\alpha]_{546}$ −15.8°, $[\alpha]_{436}$ 30.4°, $[\alpha]_{365}$ −55.0°; ν_{max} 3600–2800 (OH, NH_3^+), 2040, 1630, and 1520 (NH_3^+), 1590 and 1385 cm^{-1} (COO^-).

Anal. Calc. for $C_7H_{15}NO_7 \cdot H_2O$: C, 34.57; H, 7.05; N, 5.76. Found: C, 34.44; H, 7.04; N, 5.52.

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