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Note

Synthesis of 1,2-diamino-1,2-dideoxy-D-*glycero*-L-*manno*- and -D-*glycero*-L-*gluco*-heptitol

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The 1,2-diamine group plays an important role in medicinal chemistry, *e.g.*, in antihistamines related to ethylenediamine[1] and in metal chelation[2,3]. However, the methods for preparing 1,2-diamino compounds, especially those with other functional groups in the molecule, are limited[4]. Thus, of the 1,2-diamino-1,2-dideoxyalditols, only the D-*gluco* and D-*manno* compounds are known and which were prepared by reduction of the corresponding phenylosazones[5]. These compounds may be useful as intermediates in the synthesis of *C*-nucleosides that may have interesting pharmacological properties[6].

We now report the synthesis of two epimeric 1,2-diamino-1,2-dideoxyheptitols from easily accessible compounds prepared from D-galactose. Thus, hydrogenation of 2-acetamido-1,2-dideoxy-1-nitro-D-*glycero*-L-*manno*-heptitol[7] gave 70% of 2-acetamido-1-amino-1,2-dideoxy-D-*glycero*-L-*manno*-heptitol (**2**), which was transformed into the dihydrochloride of the 1,2-diamine **3** and characterised as the hepta-acetyl derivative **4**. The C-2 epimer of **3** was obtained, by catalytic hydrogenation, from 3,4,5,6,7-penta-*O*-acetyl-2-benzylamino-2-deoxy-D-*glycero*-L-*gluco*-heptononitrile[8] (**8**). The synthesis of 1,2-diamines by catalytic hydrogenation of α-aminonitriles has not been applied extensively because of the low yields due to decomposition of the nitriles under the conditions of reaction. Average yields were obtained only when at least one *N*-alkyl substituent was present[9,10]. Reduction of **8** gave 65% of 1-acetamido-3,4,5,6,7-penta-*O*-acetyl-2-(*N*-benzylacetamido)-1,2-dideoxy-D-*glycero*-L-*gluco*-heptitol (**9**) that was converted into the 1,2-diamine isolated as the dihydrochloride **10**, and characterised as the hepta-acetyl derivative **11**.

Compounds **3** and **10** may be useful for the preparation of sugar derivatives that contain the 1,2-diamine moiety with control of the configuration on C-2, or for the preparation of acyclonucleosides. Thus, reaction of **3** with benzil gave the acyclic (2*S*)-2,3-dihydropyrazine-*C*-nucleoside **5**, which was transformed into the pyrazine derivative **7**. Likewise, **10** gave the (2*R*)-2,3-dihydropyrazine derivative **12** that was oxidised readily to the pyrazine derivative **7**, the major product of the reaction.

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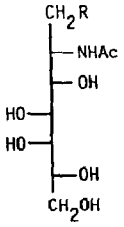

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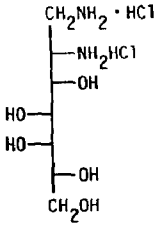
2 R = NH_2



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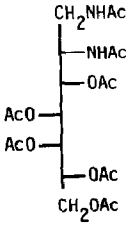

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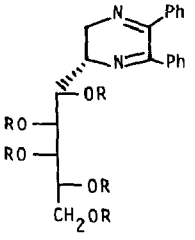
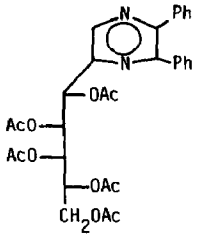


5 R = H
6 R = Ac



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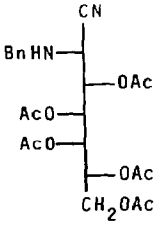

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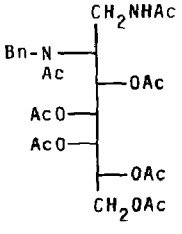

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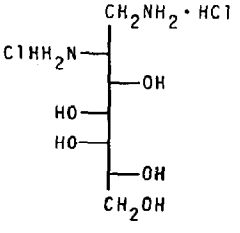

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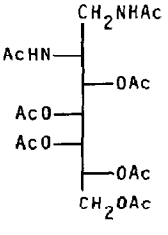

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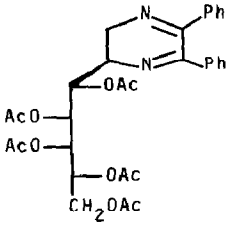

12

EXPERIMENTAL

General methods. — All melting points are uncorrected. Optical rotations were determined at 20–25° with a Perkin–Elmer 241 polarimeter (10-cm cell), and with an E. Hartnack polarimeter (2.5-cm cell). T.l.c. was performed on Sillica Gel 60 F_{254} (Merck) with detection by u.v. light or charring with sulfuric acid. Column chromatography was performed in the "flash" mode[11]. F.t.-i.r. spectra (KBr discs) were recorded with a Michelson 100 spectrometer. N.m.r. spectra were recorded with a Bruker WP-80-SY and a Varian XL-200 spectrometer. Mass spectra (e.i.) were obtained using a Kratos MS80RFA instrument. Compounds characterised by exact mass were shown to be pure by t.l.c. and n.m.r. analysis.

2-Acetamido-1-amino-1,2-dideoxy-D-glycero-L-manno-*heptitol* (**2**). — An aqueous solution (150 mL) of 2-acetamido-1,2-dideoxy-1-nitro-D-*glycero*-L-*manno*-heptitol[7] (9.8 g, 34.7 mmol) was hydrogenated (40 p.s.i.) at room temperature in the presence of Raney nickel (3.4 g). After 7 h, the mixture was filtered, then concentrated under reduced pressure, and the residue was crystallised from methanol to give **2** (6.1 g, 70%), m.p. 142–144°, $[\alpha]_D$ −1°, $[\alpha]_{578}$ −3.5°, $[\alpha]_{546}$ −6°, $[\alpha]_{436}$ −12°, $[\alpha]_{365}$ −17° (*c* 0.5, water); ν_{max} 3600–3100 (OH, NH), 1640, 1540 cm^{-1} (CONH). N.m.r. data (D_2O): ^1H, δ 1.93 (s, 3 H, NAc), 2.98 (dd, 1 H, $J_{1a,1b}$ −13.7, $J_{1b,2}$ 8.9 Hz, H-1b), 3.40 (dd, 1 H, $J_{1a,2}$ 4.2 Hz, H-1a), 4.17 (td, 1 H, $J_{2,3}$ 8.9 Hz, H-2), 3.20–4.0 (m, 6 H, H-3/7); ^{13}C, δ 23.4 ($NCOCH_3$), 42.4 (C-1), 50.1 (C-2), 64.4 (C-7), 69.8, 70.6, 70.9, 71.3 (C-3/6), 175.9 ($NCOCH_3$).

Anal. Calc. for $C_9H_{20}N_2O_6$: C, 42.85; H, 7.99; N, 11.10. Found: C, 42.50; H, 7.98; N, 10.92.

The hepta-acetyl derivative **4** had m.p. 116–118° (from ethanol), $[\alpha]_D$ +11°, $[\alpha]_{578}$ +11°, $[\alpha]_{546}$ +12°, $[\alpha]_{436}$ +21°, $[\alpha]_{365}$ +33° (*c* 1, chloroform); ν_{max} 3300, 3100 (NH), 1750 (CO), 1660, 1560 cm^{-1} (CONH). N.m.r. data ($CDCl_3$): ^1H, δ 1.93, 1.96 (2 s, 6 H, 2 NAc), 2.02, 2.07, 2.10, 2.10, and 2.13 (5 s, 15 H, 5 OAc), 3.15–3.40 (m, 2 H, H-1a,1b), 3.84 (dd, 1 H, $J_{7a,7b}$ −11.6, $J_{6,7b}$ 7.0 Hz, H-7b), 4.18 (m, 1 H, H-2), 4.27 (dd, 1 H, $J_{6,7a}$ 5.1 Hz, H-7a), 5.50–5.60 (m, 4 H, H-3/6), 6.30–6.53 (m, 2 H, 2 NH); ^{13}C, δ 20.5, 20.6 ($OCOCH_3$), 23.1 ($NCOCH_3$), 40.8 (C-1), 49.8 (C-2), 62.0 (C-7), 67.7, 67.9, 68.2, 70.3 (C-3/6), 169.7, 170.0, 170.2 ($OCOCH_3$), 171.1 ($NCOCH_3$). Mass spectrum: *m/z* 504.1934 (calc. for $C_{21}H_{32}N_2O_{12}$: 504.1955).

Anal. Calc. for $C_{21}H_{32}N_2O_{12}$: C, 50.00; H, 6.39; N, 5.55. Found: C, 49.83; H, 6.33; N, 5.60.

1,2-Diamino-1,2-dideoxy-D-glycero-L-manno-*heptitol dihydrochloride* (**3**). — A solution of **2** (10 g, 39.6 mmol) in 2M HCl (200 mL) was boiled under reflux for 1 h, then concentrated under diminished pressure. Ethanol was distilled several times from the residue to leave amorphous **3** (10 g, 89%; pure by n.m.r. analysis), $[\alpha]_D$ 0° (*c* 10, water), that was used directly in the preparation of **5**; ν_{max} 3680–2400 (OH and NH_3^+), 1620, 1500 cm^{-1} (NH_3^+). ^{13}C-N.m.r. data (D_2O): δ 39.6 (C-1), 52.9 (C-2), 64.2 (C-7), 69.2, 70.6, 70.8, 70.8 (C-3/6). Conventional acetylation of **3** gave **4**.

*(2S)-2-(*D-galacto-*Pentitol-1-yl)-5,6-diphenyl-2,3-dihydropyrazine* (**5**). — A solution of **3** (2.5 g, 8.8 mmol) in water was neutralised with $NaHCO_3$, and a solution of

benzil (1.85 g, 8.8 mmol) in ethanol (20 mL) was added. The resulting suspension was stirred at 50° for 2 days, then filtered to give **5**, which was washed with benzene. A second crop was obtained by concentrating the filtrate to a small volume (40% overall yield); ν_{max} 3345, 3240 (OH), 1666, 1644 cm^{-1} (C=N). ^{13}C-N.m.r. data [$(CD_3)_2SO$]: δ 47.8 (C-3), 56.2 (C-2), 63.3 (C-5'), 68.6, 69.5, 70.3, 70.7 (C-1'/4'), 127.5, 127.6, 127.8, 129.2, 137.5, 137.6 (Ph), 158.3, 159.8 (C-5,6).

The penta-acetate (**6**) of **5** had m.p. 122–124° (from ethanol), $[\alpha]_D$ −2°, $[\alpha]_{578}$ −6°, $[\alpha]_{546}$ −21°, $[\alpha]_{436}$ −277° (*c* 0.5, chloroform); ν_{max} 1753 (CO), 1635 cm^{-1} (C=N). N.m.r. data ($CDCl_3$): ^{1}H, δ 2.03, 2.03, 2.08, 2.15, and 2.16 (5 s, 15 H, 5 OAc), 2.80–3.45 (m, 2 H, H-3a,3b), 3.70–4.10 (m, 1 H, H-2), 3.88 (dd, 1 H, $J_{4',5'b}$ 7.0, $J_{5'a,5'b}$ −11.6 Hz, H-5'b), 4.33 (dd, 1 H, $J_{4',5'a}$ 5.0 Hz, H-5'a), 5.15–5.50 (m, 3 H), and 6.20 (dd, 1 H, *J* 1.5 and *J'* 9.7 Hz, H-1'/4'), 7.10–7.55 (m, 10 H, 2 Ph); ^{13}C, δ 20.6, 20.7 ($OCOCH_3$), 48.1 (C-3), 55.0 (C-2), 62.3 (C-5'), 67.5, 68.1, 68.3, 71.8 (C-1'/4'), 128.1, 128.4, 129.9, 137.2, and 137.5 (Ph), 159.6, 161.2 (C-5/6), 169.7, 169.9, 170.3, 170.5 ($OCOCH_3$). Mass spectrum: *m/z* 594.2258 (calc. for $C_{31}H_{34}N_2O_{10}$: 594.2214).

Anal. Calc. for $C_{31}H_{34}N_2O_{10}$: C, 62.62; H, 5.76; N, 4.71. Found: C, 62.83; H, 5.82; N, 4.68.

*2-(Penta-*O*-acetyl-*D*-galacto-pentitol-1-yl)-5,6-diphenylpyrazine* (**7**). — 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.34 g) was added to a solution of **6** (0.2 g, 0.34 mmol) in dry benzene (2 mL), the mixture was heated at 75° for 3.5 h, then filtered, and the solid collected was washed with benzene. The filtrate and washings were combined and chromatographed on neutral alumina (CH_2Cl_2) to give **7** slightly contaminated by partial deacetylated products which, on reacetylation, gave crude **7** (total yield 0.16 g, 80%). Recrystallisation from ethanol gave **7**, m.p. 170–172°, $[\alpha]_D$ +12°, $[\alpha]_{578}$ +9°, $[\alpha]_{546}$ +7°, $[\alpha]_{436}$ −28°, $[\alpha]_{365}$ −238° (*c* 0.3, chloroform); ν_{max} 1749 cm^{-1} (CO). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.85, 2.03, 2.07, 2.15, and 2.25 (5 s, 15 H, 5 OAc), 3.90 (dd, 1 H, $J_{4',5'b}$ 7.3, $J_{5'a,5'b}$ −11.5 Hz, H-5'b), 4.33 (dd, 1 H, $J_{4',5'a}$ 5.1 Hz, H-5'a), 5.35 (ddd, 1 H, $J_{3',4'}$ 1.9 Hz, H-4'), 5.58 (dd, 1 H, $J_{2',3'}$ 9.8 Hz, H-3'), 5.79 (dd, 1 H, $J_{1',2'}$ 2.0 Hz, H-2'), 6.16 (dd, 1 H, $J_{1',3}$ 0.5 Hz, H-1'), 7.20–7.60 (m, 10 H, 2 Ph), 8.50 (d, 1 H, H-3); ^{13}C, δ 20.2, 20.5, 20.6 ($OCOCH_3$), 62.1 (C-5'), 68.0, 68.1, 69.8, 72.1 (C-1'/4'), 128.2, 128.7, 129.6, 129.7, 138.3 (Ph), 139.6 (C-3), 148.6 (C-2), 151.9, 152.1 (C-5,6), 168.8, 169.6, 169.9, 170.0, 170.2 ($OCOCH_3$).

Anal. Calc. for $C_{31}H_{32}N_2O_{10}$: C, 62.83; H, 5.44; N, 4.73. Found: C, 62.64; H, 5.50; N, 4.60.

*1-Acetamido-3,4,5,6,7-penta-*O*-acetyl-2-(*N*-benzylacetamido)-1,2-dideoxy-*D*-glycero-*L*-gluco-heptitol* (**9**). — A mixture of 3,4,5,6,7-penta-*O*-acetyl-2-benzylamino-2-deoxy-*D*-*glycero*-*L*-*gluco*-heptononitrile[8] (**8**; 8.0 g, 15.8 mmol), anhydrous sodium acetate (3.0 g), and Raney nickel (16 g) in acetic anhydride (60 mL) was hydrogenated (900 p.s.i.) at room temperature for 3 days, then filtered, and the insoluble material was washed with methanol. The combined filtrate and washings were concentrated under diminished pressure and ethanol was distilled several times from the residue, which was then treated with water and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated, and the residue was crystallised from ethanol to give **9** (6.1 g, 65%),

m.p. 134–136°, $[\alpha]_D$ +135° (*c* 6.5, chloroform); ν_{max} 1690, 1654 cm^{-1} (CONH). N.m.r. data ($CDCl_3$): ^1H, δ 1.60, 1.71 (2 s, 6 H, 2 NAc), 2.03, 2.07, 2.09, 2.14, and 2.23 (5 s, 15 H, 5 OAc), 2.67 (ddd, 1 H, $J_{1b,2}$ 11.0, $J_{1b,NH}$ 5.5, $J_{1a,1b}$ −14.2 Hz, H-1b), 3.50 (ddd, 1 H, $J_{1a,2}$ 4.2, $J_{1a,NH}$ 6.4 Hz, H-1a), 3.62 (d, 1 H, *J* −15.9 Hz, PhC*H*), 3.82 (dd, 1 H, $J_{6,7b}$ 6.9, $J_{7a,7b}$ −11.6 Hz, H-7b), 4.17 (bt, 1 H, NH), 4.28 (dd, 1 H, $J_{6,7a}$ 5.2 Hz, H-7a), 4.49 (td, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 5.12 (ddd, 1 H, $J_{5,6}$ 1.7 Hz, H-6), 5.29 (dd, 1 H, $J_{3,4}$ 2.1 Hz, H-3), 5.33 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-5), 5.33 (d, 1 H, PhC*H*), 5.50 (dd, 1 H, H-4), 7.34 (m, 5 H, Ph); ^{13}C, δ 19.7 ($OCOCH_3$), 21.0, 21.6 ($NCOCH_3$), 37.8 (C-1), 44.4 ($PhCH_2$), 56.0 (C-2), 61.1 (C-7), 66.6, 66.9, 66.9, 67.4 (C-3/6), 127.6, 128.0, 128.8, 139.7 (Ph), 169.7, 170.0, 170.2 ($OCOCH_3$), 172.9 ($NCOCH_3$). Mass spectrum: *m/z* 594.2385 (calc. for $C_{28}H_{38}N_2O_{12}$: 594.2424).

Anal. Calc. for $C_{28}H_{38}N_2O_{12}$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.21; H, 6.38; N, 4.77.

1,2-Diamino-1,2-dideoxy-D-glycero-L-gluco-*heptitol dihydrochloride* (**10**). — A solution of **9** (2.40 g, 4.04 mmol) in 2M HCl (100 mL) was boiled under reflux for 2 h, then cooled to room temperature. 10% Pd/C (2.0 g) was added, the mixture was hydrogenated overnight, filtered, and concentrated, and ethanol was distilled several times from the residue to give amorphous **10** (1.1 g, 96%), $[\alpha]_D$ −4° (*c* 18, water); ν_{max} 3680–2400 (OH and NH_3^+), 1613, 1500 cm^{-1} (NH_3^+). ^{13}C-N.m.r. data (D_2O): δ 40.5 (C-1), 53.5 (C-2), 64.2 (C-7), 67.1, 70.6, 70.8, 72.7 (C-3/6).

Conventional acetylation of **10** gave **11**, m.p. 89–91° (from ethanol), $[\alpha]_D$ −11°, $[\alpha]_{578}$ −11°, $[\alpha]_{546}$ −13°, $[\alpha]_{436}$ −23°, $[\alpha]_{365}$ −38° (*c* 1.3, chloroform); ν_{max} 3390 (NH), 1747 (CO), 1659, 1550 cm^{-1} (CONH). N.m.r. data ($CDCl_3$): ^1H, δ 1.94 (s, 6 H, 2 NAc), 2.03, 2.10, 2.10, 2.12, and 2.14 (5 s, 15 H, 5 OAc), 3.17 (dt, 1 H, $J_{1a,1b}$ −13.7, $J_{1b,2}$ 4.2, $J_{1b,NH}$ 4.2 Hz, H-1b), 3.60 (ddd, 1 H, $J_{1a,2}$ 8.1, $J_{1a,NH}$ 9.2 Hz, H-1a), 3.84 (dd, 1 H, $J_{6,7b}$ 7.4, $J_{7a,7b}$ −11.6 Hz, H-7b), 4.18 (m, 1 H, H-2), 4.26 (dd, 1 H, $J_{6,7a}$ 4.9 Hz, H-7a), 5.03 (dd, 1 H, $J_{2,3}$ 7.2, $J_{3,4}$ 2.3 Hz, H-3), 5.25–5.34 (m, 2 H, H-5,6), 5.42 (dd, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 6.22 (bt, 1 H, *J* 9.2 Hz, NH), 6.50 (bd, 1 H, NH); ^{13}C, δ 20.4 ($OCOCH_3$), 22.8, 22.9 ($NCOCH_3$), 40.9 (C-1), 50.0 (C-2), 62.0 (C-7), 67.7, 68.1, 68.2, 69.5 (C-3/6), 169.6, 170.0, 170.2, 170.6, 170.9 (CO). Mass spectrum: *m/z* 504.1930 (calc. for $C_{21}H_{32}N_2O_{12}$: 504.1955).

Anal. Calc. for $C_{21}H_{32}N_2O_{12}$: C, 50.00; H, 6.39; N, 5.55. Found: C, 49.69; H, 6.32; N, 5.19.

(2R)-2-(Penta-O-*acetyl*-D-galacto-*pentitol-1-yl)-5,6-diphenyl-2,3-dihydropyrazine* (**12**). — Compound **10** (1.3 g) was reacted with benzil as described for **3**. After 2 days, the mixture was concentrated under diminished pressure, the residue was acetylated (Ac_2O/Py), and the resulting solid mixture (1.4 g) of **12** and the pyrazine **7** was subjected to chromatography (4:1 ethyl acetate–hexane). However, pure **12** was isolated in only a small amount (0.1 g) because it was oxidised quickly to **7**. N.m.r. data ($CDCl_3$): ^1H, δ 1.99, 2.01, 1.10, 2.13, and 2.18 (5 s, 15 H, 5 OAc), 3.40–3.70 (m, 2 H, H-3a,3b), 3.83 (dd, 1 H, $J_{4',5'b}$ 7.6, $J_{5'a,5'b}$ −11.7 Hz, H-5'b), 4.04 (m, 1 H, H-2), 4.30 (dd, 1 H, $J_{4',5'a}$ 4.4 Hz, H-5'a), 5.25–5.60 (m, 4 H, H-1'/4'), 7.20–7.60 (m, 10 H, 2 Ph); ^{13}C, δ 20.5, 20.8 ($OCOCH_3$), 47.1 (C-3), 55.2 (C-2), 62.4 (C-5'), 67.9, 68.1, 68.4, 69.5 (C-1'/4'), 128.0, 129.7, 137.3, 137.6 (Ph), 160.3, 161.3 (C-5,6), 169.7, 169.9, 170.2, 170.3 ($OCOCH_3$).

ACKNOWLEDGMENT

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