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Note

Preparation of amidine derivatives from 1-cyano-D-galactal

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Recently we described [3] the transformation of the cyano group of several 1-cyanoglycals [1,2] into various heterocycles in order to test them as glycosidase inhibitors. 1-Cyano-D-galactal triacetate (**1**) was also used by Banaszek for the synthesis of 3-deoxy-D-*lyxo*-2-heptulosaric acid derivatives [4]. As our comparative enzymatic investigations [5] required derivatives with some functionalities and heterocycles of basic character attached by a C–C bond to C-1 of D-galactal, syntheses of such compounds from **1** are reported now.

Since the use of amine derivatives as reagents was planned, deprotection of **1** in order to avoid possible interference by the ester groups was investigated first. Saponification in methanol under Zemplén conditions or in the presence of catalytic potassium cyanide at room temperature resulted in simultaneous removal of the acetyl groups and addition of methanol to the cyano group to give the imidate **3** as a highly crystalline solid (Scheme 1). This was in accordance with literature experience obtained with benzoylated ribofuranosyl cyanide [6], but contradicted the case of benzoylated rhamnopyranosyl cyanide where the cyano group remained intact [7] under similar treatment. Carrying out the Zemplén deprotection of **1** with ice-cooling [8] in a dilute solution gave 1-cyano-D-galactal (**2**) as the sole product.

It seemed interesting to apply this saponification to the galactopyranosyl cyanide **8** as well, because the deprotected **9** was previously made by using tedious separation methods [9,10]. Indeed, the low-temperature Zemplén deacetylation of **8** gave **9** as a chromatographically homogeneous crude product which crystallised spontaneously.

The enhanced reactivity of the imidate **3** relative to the nitrile **2** was then exploited. Thus, the reaction of **3** with ammonium chloride gave the amidine hydrochloride **4**, and with hydrazine hydrate the amidrazone **5** was obtained. With ethylenediamine, the

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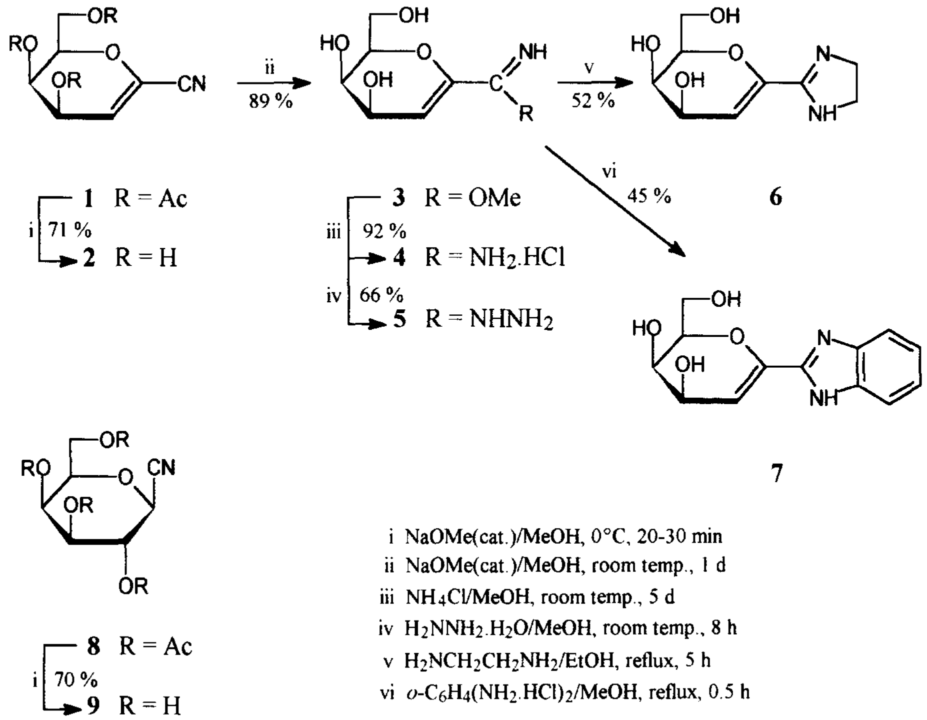

i NaOMe(cat.)/MeOH, 0°C, 20-30 min
ii NaOMe(cat.)/MeOH, room temp., 1 d
iii NH_4Cl/MeOH, room temp., 5 d
iv $H_2NNH_2.H_2O$/MeOH, room temp., 8 h
v $H_2NCH_2CH_2NH_2$/EtOH, reflux, 5 h
vi o-$C_6H_4(NH_2.HCl)_2$/MeOH, reflux, 0.5 h

Scheme 1.

imidazoline **6** crystallised from the reaction mixture. 1,2-Phenylenediamine did not react with **3**, but its dihydrochloride gave the benzimidazole **7**. This reaction, performed under essentially neutral conditions, may be an alternative synthesis for 2-glycosylbenzimidazoles using substrates with acid-sensitive groups. 2-(β-D-Ribofuranosyl)benzimidazole [11], the only example in the literature, was prepared from the corresponding 2,5-anhydroaldonic acid derivative in the presence of a strong mineral acid as catalyst (see also ref. [12]).

The rather large values of the long-range coupling constants ($^4J_{2,4}$ = 1.5–1.8, $^4J_{3,5}$ = 0.8–1.1 Hz) indicate that H-2 and H-4, as well as H-3 and H-5, are nearly coplanar in these D-galactal derivatives. Therefore $^4H_5$ is the preferred conformation, in accordance with previous observations [3].

1. Experimental

General methods.—Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at room temperature. NMR spectra were recorded with a Bruker WP 200 SY spectrometer (^{1}H, 200 MHz; ^{13}C, 50.3 MHz) for D_2O solutions [sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) internal standard] unless otherwise stated.

TLC was performed on DC-Alurolle, Kieselgel 60 F_{254} (Merck), and the plates were visualised by gentle heating. Solutions were concentrated in vacuo at 40–50 °C (water bath).

*2-Deoxy-*D-lyxo*-hex-1-enopyranosyl cyanide (2,6-anhydro-3-deoxy-*D-lyxo*-hept-2-enononitrile)* (**2**).—4,5,7-Tri-*O*-acetyl-2,6-anhydro-3-deoxy-D-*lyxo*-hept-2-enononitrile [1–3] (**1**; 1 g, 3.37 mmol) was dissolved in abs MeOH (100 mL) and the solution was cooled to 0 °C in an ice bath. Drops of 1 M methanolic NaOMe solution were added until the reaction mixture remained permanently basic (pH ~ 8). The mixture was kept at 0 °C and was monitored by TLC (7:3 $CHCl_3$–MeOH). The reaction was interrupted by the addition of dry Dowex 50-X8 (H^+ form) resin after ~ 20 min, when the chromatogram showed a single spot (R_f 0.46). After removal of the resin, the solution was evaporated to dryness and the residue crystallised from 2-propanol to give **2** (0.41 g, 71%); mp 121–123 °C; $[\alpha]_D$ −28° (*c* 1.69, H_2O); ^1H NMR: δ 5.91 (dd, 1 H, $J_{2,3}$ 2.3, $J_{2,4}$ 1.8 Hz, H-2), 4.71 (ddd, 1 H, $J_{3,4}$ 4.4, $J_{3,5}$ 1.1 Hz, H-3), 4.37 (dddd, 1 H, $J_{5,6a}$ 7.6 Hz, H-5), 4.16 (ddd, 1 H, $J_{4,5}$ 0.8 Hz, H-4), 4.02 (dd, 1 H, $J_{6a,6b}$ 12.1 Hz, H-6a), 3.94 (dd, 1 H, $J_{5,6b}$ 4.7 Hz, H-6b); ^{13}C NMR: δ 129.23 (C-1), 119.51 (C-2), 114.84 (CN), 80.20, 64.92, 64.40 (C-3,4,5), 61.70 (C-6). Anal. Calcd for $C_7H_9NO_4$ (171.1): C, 49.12; H, 5.30; N, 8.18. Found: C, 48.95; H, 5.32; N, 8.16.

*Methyl C-(2-deoxy-*D-lyxo*-hex-1-enopyranosyl)formimidate (methyl 2,6-anhydro-3-deoxy-*D-lyxo*-hept-2-enonimidate)* (**3**).—The nitrile **1** [1–3] (1 g, 3.37 mmol) was suspended in abs MeOH (8 mL) at room temperature and 1 M methanolic NaOMe solution was added dropwise until the reaction mixture remained permanently basic (pH ~ 8). The mixture was stirred at room temperature for 24 h during which time it became a clear solution and then crystallisation began. After keeping the flask in a refrigerator for at least half a day the crystals were filtered off to give **3** (0.61 g, 89%) which was sufficiently pure for further transformations. An analytical sample was obtained by recrystallisation from MeOH; mp 192–193 °C; $[\alpha]_D$ −64° (*c* 1.05, Me_2SO); ^1H NMR: δ 5.75 (dd, 1 H, $J_{2,3}$ 2.4, $J_{2,4}$ 1.8 Hz, H-2), 4.72 (ddd, 1 H, $J_{3,4}$ 4.5, $J_{3,5}$ 0.9 Hz, H-3), 4.30 (dddd, 1 H, $J_{5,6a}$ 7.7 Hz, H-5), 4.12 (ddd, 1 H, $J_{4,5}$ 0.8 Hz, H-4), 4.07 (dd, 1 H, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.97 (dd, 1 H, $J_{5,6b}$ 4.5 Hz, H-6b), 3.92 (s, 3 H, OMe); ^{13}C NMR (Me_2SO-d_6): δ 162.51 [*C*(=NH)OMe], 141.34 (C-1), 106.29 (C-2), 78.95, 64.31, 63.64 (C-3,4,5), 60.75 (C-6), 52.78 (OCH_3). Anal. Calcd for $C_8H_{13}NO_5$ (203.2): C, 47.28; H, 6.45; N, 6.89. Found: C, 47.09; H, 6.32; N, 6.75.

*C-(2-Deoxy-*D-lyxo*-hex-1-enopyranosyl)formamidine hydrochloride (2,6-anhydro-3-deoxy-*D-lyxo*-hept-2-enonamidine hydrochloride)* (**4**).—To a suspension of **3** (200 mg, 0.98 mmol) in abs MeOH (4 mL) was added NH_4Cl (56 mg, 1.04 mmol), and the mixture was stirred at room temperature for 5 days. The crystalline solid was then filtered off to give **4** (120 mg, 54%) in an analytically pure state. Concentration of the mother liquor afforded a further crop (85 mg, 38%); the compound did not melt till 360 °C, but gradually decomposed; $[\alpha]_D$ −23° (*c* 1.07, H_2O); ^1H NMR: δ 5.95 (dd, 1 H, $J_{2,3}$ 2.3, $J_{2,4}$ ~ 1.5 Hz, H-2), 4.68 (ddd, 1 H, $J_{3,4}$ 4.4, $J_{3,5}$ ~ 1.1 Hz, H-3), 4.32 (dddd, 1 H, $J_{5,6a}$ 7.7 Hz, H-5), 4.07 (ddd, 1 H, $J_{4,5}$ ~ 0.8 Hz, H-4), 3.98 (dd, 1 H, $J_{6a,6b}$ 12.1 Hz, H-6a), 3.89 (dd, 1 H, $J_{5,6b}$ 4.4 Hz, H-6b); ^{13}C NMR: δ 159.61 [*C*(=NH)NH_2], 141.21 (C-1), 112.14 (C-2), 79.85, 64.89, 64.18 (C-3,4,5), 61.74 (C-6). Anal. Calcd for $C_7H_{13}ClNO_4$ (224.6): C, 37.42; H, 5.83; N, 12.46. Found: C, 37.32; H, 5.90; N, 12.49.

*C-(2-Deoxy-*D-lyxo*-hex-1-enopyranosyl)formamidrazone (2,6-anhydro-3-deoxy-*D-lyxo*-hept-2-enonamidrazone)* (**5**).—To a suspension of **3** (500 mg, 2.46 mmol) in abs MeOH (5 mL) was added 98% N_2H_4 hydrate (0.15 mL, 3.09 mmol). The mixture was stirred at room temperature for 8 h, then kept in a refrigerator for 2 days. The precipitated solid was filtered off and recrystallised from MeOH to give **5** (331 mg, 66%); mp 172–173 °C; $[\alpha]_D$ +16° (c 1.13, H_2O); ^1H NMR: δ 5.31 (dd, 1 H, $J_{2,3}$ 2.2, $J_{2,4}$ 1.6 Hz, H-2), 4.58 (ddd, 1 H, $J_{3,4}$ 4.6, $J_{3,5}$ ~ 1 Hz, H-3), 4.17 (dddd, 1 H, $J_{5,6a}$ 7.8 Hz, H-5), 3.99 (ddd, 1 H, $J_{4,5} \leq 1$ Hz, H-4), 3.95 (dd, 1 H, $J_{6a,6b}$ 11.9 Hz, H-6a), 3.83 (dd, 1 H, $J_{5,6b}$ 4.5 Hz, H-6b); ^{13}C NMR (Me_2SO-d_6): δ 146.15 [C(=NH)NHNH$_2$], 142.31 (C-1), 99.61 (C-2), 78.50, 64.32, 64.30 (C-3,4,5), 60.94 (C-6). Anal. Calcd for $C_7H_{13}N_3O_4$ (203.2): C, 41.37; H, 6.44; N, 20.67. Found: C, 41.25; H, 6.33; N, 20.43.

*2-(2-Deoxy-*D-lyxo*-hex-1-enopyranosyl)-2-imidazoline* (**6**).—To a solution of **3** (520 mg, 3.04 mmol) in abs EtOH (10 mL) was added freshly distilled ethylenediamine (0.2 mL, 3.34 mmol), and the mixture was refluxed for 5 h. After cooling to room temperature the solid was filtered off and recrystallised from EtOH to give **6** (260 mg, 40%). A further crop (80 mg, 12%) was obtained from the mother liquor; the compound decomposed around 200 °C; $[\alpha]_D$ −39° (c 0.89, Me_2SO); ^1H NMR: δ 5.61 (dd, 1 H, $J_{2',3'}$ 2.3, $J_{2',4'}$ 1.8 Hz, H-2′), 4.71 (ddd, 1 H, $J_{3',4'}$ 4.5, $J_{3',5'}$ 0.8 Hz, H-3′), 4.29 (dddd, 1 H, $J_{5',6'a}$ 7.8 Hz, H-5′), 4.12 (ddd, 1 H, $J_{4',5'}$ 1 Hz, H-4′), 4.05 (dd, 1 H, $J_{6'a,6'b}$ 11.9 Hz, H-6′a), 3.95 (dd, 1 H, $J_{5',6'b}$ 4.5 Hz, H-6′b), 3.75 (br s, 4 H, $-CH_2CH_2-$); ^{13}C NMR (Me_2SO-d_6): δ 160.43 (C-2), 143.48 (C-1′), 105.63 (C-2′), 78.40, 64.16, 63.74 (C-3′,4′,5′), 60.63 (C-6′), 49.27 (C-4,5). Anal. Calcd for $C_9H_{14}N_2O_4$ (214.2): C, 50.46; H, 6.58; N, 13.07. Found: C, 49.85; H, 6.48; N, 12.65.

*2-(2-Deoxy-*D-lyxo*-hex-1-enopyranosyl)benzimidazole* (**7**).—A mixture of **3** (830 mg, 4.08 mmol) and 1,2-phenylenediamine dihydrochloride (760 mg, 4.19 mmol) in abs MeOH (17 mL) was refluxed under nitrogen in the dark for 0.5 h. The solvent was then evaporated, the residue was suspended in water (2–3 mL), and the suspension was made basic with concd aq NH_3. The precipitate was filtered off and recrystallised from water to give **7** (480 mg, 45%); mp 220–222 °C; $[\alpha]_D$ − 18° (c 1.08, Me_2SO); ^1H NMR (Me_2SO-d_6): δ 12.35 (br s, 1 H, NH), 7.6–7.5, 7.2–7.1 (2 m, 4 H, H-4,5,6,7), 5.75 (br s, 1 H, H-2′), 4.96 (d, 1 H, OH), 4.81 (dd, 1 H, OH), 4.69 (d, 1 H, OH), 4.48 (m, 1 H, H-3′), 4.08 (m, 1 H, H-5′), 3.93–3.65 (m, 3 H, H-4′,6′a,6′b); ^{13}C NMR (Me_2SO-d_6): δ 147.90 (C-1′), 143.58 (C-2,3a,7a), 123.46, 115.83 (C-4,5,6,7), 105.45 (C-2′), 79.35, 64.94, 64.65 (C-3′,4′,5′), 61.76 (C-6′). Anal. Calcd for $C_{13}H_{14}N_2O_4 \cdot 0.5\ H_2O$ (271.3): C, 57.55; H, 5.57; N, 10.32. Found: C, 57.18; H, 5.54; N, 10.23.

*β-*D*-Galactopyranosyl cyanide* (**9**).—2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl cyanide [13] (**8**; 1 g, 2.8 mmol) was dissolved in abs MeOH (120 mL) and the solution was cooled to 0 °C. Methanolic NaOMe solution (1 M) was added, and the mixture was kept at 0 °C and monitored by TLC as described for the preparation of **2**. Quenching by resin was effected when a single spot of R_f 0.39 (7:3 $CHCl_3$–MeOH) could be seen in TLC (~ 30 min). Workup as with **2** and crystallisation from 2-propanol gave **9** (0.37 g, 70%); mp 112–113 °C, ref. [9] 115–116 °C; $[\alpha]_D$ +73° (c 1.16, H_2O), ref. [9] +68.2° (c 0.88, H_2O); ^1H NMR: δ 4.42 (d, 1 H, $J_{1,2}$ 10 Hz, H-1), 4.09 (dd, 1 H, $J_{4,5} < 1$ Hz, H-4), 4.03 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 3.9–3.8 (m, 3 H, H-5,6a,6b), 3.75 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3); ^{13}C NMR: δ 120.25 (CN), 82.95, 75.96, 71.75, 71.52, 71.31 (C-1,2,3,4,5), 64.05 (C-6); the ^{13}C chemical shifts differ, in a regular manner, from those in ref. [9]. Anal. Calcd for $C_7H_{11}NO_5$ (189.2): C, 44.44; H, 5.86; N, 7.40. Found: C, 43.96; H, 6.01; N, 7.31.

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