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Note

Reaction of 2-amino-2-deoxy-D-*glycero*-L-*gluco*-heptose with cyanamide

PILAR ARECES BRAVO*, JUAN IGNACIO FERNANDEZ GARCIA-HIERRO,
Department of Organic Chemistry, University of Extremadura, 06071 Badajoz (Spain)

JOSE FUENTES MOTA,
Department of Organic Chemistry, Faculty of Chemistry, University of Seville, 41071 Seville (Spain)

AND JUAN ANTONIO GALBIS PEREZ
Department of Organic and Pharmaceutic Chemistry, Faculty of Pharmacy, University of Seville, 41071 Seville (Spain)

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We have described the preparation of some glycitolylthioimidazoles[1,2] which are useful intermediates in the syntheses of acyclic *C*-nucleosides[3,4]. In order to obtain 2-aminoimidazole derivatives, 2-amino-2-deoxy-D-*glycero*-L-*gluco*-heptose[5] (**1**) was treated with cyanamide, and the crystalline hydrochloride of the 2-imino-imidazolidine derivative (**2**) was obtained. The u.v. spectrum of **2** contained no absorption band above 200 nm, and the ^{1}H- and ^{13}C-n.m.r. spectra (see Experimental) agree with the bicyclic structure **2**. A similar compound has been prepared[6] from 2-amino-2-deoxy-D-*glycero*-L-*manno*-heptose.

Conventional treatment of **2** with pyridine–acetic anhydride and washing with acid gave the hexa-acetate **3**, the structure of which was supported by spectroscopic data and established by conversion into **4** and the tetra-acetate **5**, previously obtained[7] from **1** and silver cyanate.

When the crude product of the reaction of **1** and cyanamide was subjected to flash chromatography and the fraction with R_F 0.21 was treated with pyridine–acetic anhydride, the hexa-acetates **3** and **6** were obtained. The ratio **3**:**6** depended on the work-up procedure. The fraction with R_F 0.21 may have contained a mixture of **2** and deacetylated **6**; when this mixture was acetylated, both hexa-acetates were obtained but, on treatment with acid, the imino group of acetylated **2** was hydrolyzed to give **3**, as the major product. If the crude mixture of acetylated products was concentrated, **6**, crystallised from ethanol, was the major product.

The structure of **6** was supported by its elemental analysis and spectroscopic data. The acetylation must have occurred on N-1 because of the higher basicity of

*Author for correspondence.

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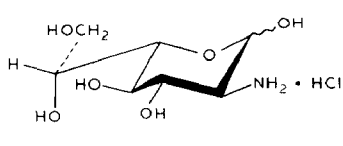
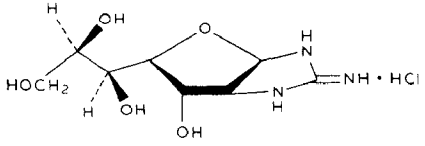
the endocyclic nitrogen[8,9] and the smaller steric hindrance of N-1. The ^{13}C-n.m.r. (decoupled and attached proton test[10]) spectra at 23° contained six signals in the range 115–144 p.p.m., which were assigned to C-2,4,5 of aminoimidazole (**6**) and iminoimidazoline (**7**) components of the equilibrium (see Experimental). When the ^{13}C-n.m.r. spectrum was recorded at 37°, the signals coalesced.

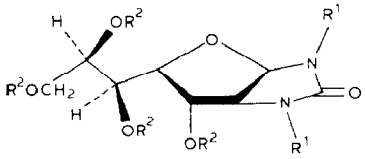
The $^3J_{H,H}$ values for **3** and **5** showed[11] that a conformation close to ^4E and $^4T_0$ preponderated for a solution in chloroform. The side chain showed a *P* major conformation[12]. Compounds **6** and **7** exist in a conformational equilibrium between the $^4G^-$ and *P* conformations.



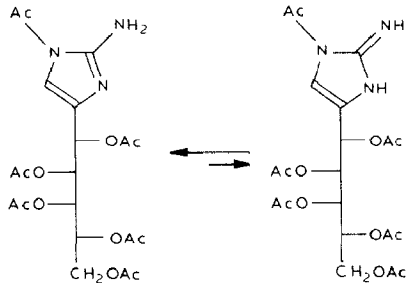
1



2



3 $R^1 = R^2 = Ac$
4 $R^1 = R^2 = H$
5 $R^1 = H, R^2 = Ac$



6 7

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 cell). I.r. spectra (KBr discs) were recorded with a Perkin–Elmer 399 spectrophotometer and u.v. spectra with a Beckmann 25 instrument. ^{1}H-N.m.r. spectra were recorded with a Varian XL-200 (200 MHz) spectrometer. Assignments were confirmed by double resonance, and overlapping signals were resolved by incremental addition of Eu(fod)$_3$. ^{13}C-N.m.r. spectra were recorded with Bruker WP-80-SY (20.15 MHz) and Varian XL-200 (50.3 MHz) spectrometers. Proton-decoupled APT[10] spectra and "off resonance" spectra were used to assist in signal assignments. T.l.c. was conducted on Silica Gel GF_{254} (Merck) with 1:1 chloroform–methanol, and detection with u.v. light and iodine vapour. Flash column chromatography[13] was performed on Silica Gel 60 (230–400 mesh, Merck) with chloroform–methanol.

1,2-Dideoxy-β-D-glycero-L-gluco-*heptofurano*[*2,1*-d]*imidazolidin-2-imine hydrochloride* (**2**). — A solution of 2-amino-2-deoxy-D-*glycero*-L-*gluco*-heptose hydrochloride[5] (**1**; 5.3 g, 21.2 mmol) in water (20 mL) was treated with cyanamide (1.3 g, 36 mmol) and neutralized with 5M sodium hydroxide. The mixture was stirred for 7 h at 60°, then kept at room temperature for 12 h, and concentrated to dryness under diminished pressure. The solid residue was extracted with boiling methanol (3 × 25 mL), the combined extracts were concentrated, and the residue was subjected to flash chromatography. The fraction containing the component with R_F 0.21 was concentrated to give a syrup which was crystallized from methanol to give **2** (2.14 g, 38%). Recrystallization from methanol gave a product with m.p. 165–166°, $[\alpha]_D^{19}$ +41°, $[\alpha]_{578}^{19}$ +46°, $[\alpha]_{546}^{19}$ +53°, $[\alpha]_{436}^{19}$ +97°, $[\alpha]_{365}^{19}$ +166° (*c* 0.5, pyridine); ν_{max} 3400–3220 (NH, OH), 1685, 1630, and 1565 cm^{-1} (guanidine group). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 9.60, 9.25 (2 bs, each 1 H, 2 NH), 8.60 (b, 2 H, C=NH_2^+), 6.33 (d, 1 H, $J_{1',2'}$ 6.1 Hz, H-1'), 6.02 (b, 1 H, OH), 5.20–5.05 (m, 2 H, 2 OH), 4.90 (b, 1 H, OH); ^{13}C, δ 158.8 (C=N), 85.5 (C-1'), 79.3 (C-4'), 73.7 (C-3'), 71.2 (C-6'), 66.6 (C-2', C-5'), 62.8 (C-7').

Anal. Calc. for $C_8H_{16}ClN_3O_5$: C, 35.63; H, 5.99; N, 15.68. Found: C, 35.92; H, 6.19; N, 15.65.

1,3-Diacetyl-(3,5,6,7-tetra-O-*acetyl-1,2-dideoxy-β*-D-glycero-L-gluco-*heptofurano)*[*2,1*-d]*imidazolidin-2-one* (**3**). — A solution of **2** (1.30 g, 5.51 mmol) in pyridine (7 mL) was treated with acetic anhydride (7.30 mL) for 2 days at room temperature, then poured into ice–water (200 mL), and extracted with chloroform (2 × 180 mL). The combined extracts were washed successively with M hydrochloric acid (2 × 200 mL) and saturated aqueous sodium hydrogencarbonate (2 × 200 mL), dried ($MgSO_4$), and concentrated. The syrupy residue crystallized from ethanol–water to give **3** (1.0 g, 42%), m.p. 137–138° (from ethanol), $[\alpha]_D^{22}$ +1.1°, $[\alpha]_{578}^{22}$ +1.2°, $[\alpha]_{546}^{22}$ +1.4°, $[\alpha]_{436}^{22}$ +2.8°, $[\alpha]_{365}^{22}$ +5.7° (*c* 1.2, pyridine); $\lambda_{max}^{96\%\ EtOH}$ 250 nm (ε_{mM} 4.0); ν_{max} 1775, 1750, 1720, 1700 (C=O ester), and 1250–1210 cm^{-1} (C–O–C). N.m.r. data: ^1H ($CDCl_3$), δ 6.26 (d, 1 H, $J_{1',2'}$ 6.7 Hz, H-1'), 5.62 (d, 1 H, $J_{3',4'}$ 2.7 Hz, H-3'), 5.38 (m, 1 H, H-6'), 5.27 (dd, 1 H, $J_{5',6'}$ 3.0, $J_{4',5'}$ 10.1 Hz, H-5'), 4.49 (d, 1 H, $J_{2',3'}$ 0 Hz, H-2'), 4.29 (dd, 1 H, $J_{6',7'}$ 5.0, $J_{6',7''}$ 6.1 Hz, H-7'), 3.97 (dd, 1 H, H-4'), 3.95 (dd, 1 H, $J_{7',7''}$ 12.0 Hz, H-7''), 2.08 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.01 (s, 6 H, 2 OAc), 2.56 and 2.52 (2 s, each 3 H, 2 NAc); ^{13}C [$(CD_3)_2SO$], δ 170.2, 170.1 (2 C=O ester), 169.5 (2 C=O ester), 169.3, 168.7 (2 C=O amide), 151.0 (N–CO–N), 82.7 (C-1'), 76.5 (C-4'), 73.1 (C-3'), 70.2 (C-6'), 67.1 (C-5'), 62.3 (C-2'), 60.9 (C-7'), 24.4, 24.3 (2 NAc), 20.4 (OAc), 20.3 (2 OAc).

Anal. Calc. for $C_{20}H_{26}N_2O_{12}$: C, 49.38; H, 5.38; N, 5.75. Found: C, 49.40; H, 5.34; N, 5.67.

1,2-Dideoxy-β-D-glycero-L-gluco-*heptofurano*[*1,2*-d]*imidazolidin-2-one* (**4**). — A solution of **3** (0.308 g, 0.63 mmol) in methanol (6 mL) was treated with methanolic 2M sodium methoxide (0.1 mL) at room temperature for 30 min, then concentrated. Crystallization of the residue from methanol gave **4** (0.120 g, 51%), m.p. 180–182° (lit[7]. m.p. 182–184°), $[\alpha]_D^{19}$ +52° (*c* 1, water); ν_{max} 3600–3000 (NH, OH), 1695, 1660 cm^{-1} (urea).

3,5,6,7-Tetra-O-acetyl-1,2-dideoxy-β-D-glycero-L-gluco-heptofurano[1,2-d]-imidazolidin-2-one (**5**). — Conventional treatment of **4** with pyridine–acetic anhydride gave **5** (40%), m.p. 170–171° (from aqueous 96% ethanol); lit.[7] m.p. 166–168°, $[\alpha]_D^{19}$ +28° (*c* 1, chloroform); ν_{max} 3400–3100 (NH), 1740, 1710 cm^{-1} (C=O ester). N.m.r. data: ^1H ($CDCl_3$), δ 7.65, 7.08 (2 bs, each 1 H, 2 NH), 5.65 (dd, 1 H, $J_{1',NH}$ 1.2, $J_{1',2'}$ 6.6 Hz, H-1'), 5.25 (m, 1 H, H-6'), 5.20 (dd, 1 H, $J_{5',6'}$ 2.6, $J_{5',4'}$ 9.3 Hz, H-5'), 5.02 (d, 1 H, $J_{3',4'}$ 2.6, $J_{3',2'}$ 0 Hz, H-3'), 4.22 (dd, 1 H, $J_{7',6'}$ 4.6, $J_{7',7''}$ 12.0 Hz, H-7'), 4.07 (dd, 1 H, $J_{2',NH}$ 2.2 Hz, H-2'), 3.92 (dd, 1 H, $J_{7'',6'}$ 6.6 Hz, H-7''), 2.04, 2.00, 1.98, 1.97 (4 s, each 3 H, 4 OAc); ^{13}C [$(CD_3)_2SO$], δ 169.6, 168.9 (4 C=O ester), 160.4, (C=O urea), 86.4 (C-1'), 75.0 (C-4'), 74.3 (C-3'), 69.2 (C-5'), 67.1 (C-6'), 61.6 (C-2'), 61.0 (C-7'), 20.3, 20.1 (4 OAc).

1-Acetyl-2-amino-4-(1,2,3,4,5-penta-O-acetyl-D-galacto-pentitol-1-yl)imidazole (**6**). — A solution of **1**[5] (2.5 g, 10 mmol) in water (10 mL) was treated with cyanamide (0.65 g, 18 mmol) and neutralized with sodium hydrogencarbonate. The mixture was stirred for 7 h at 60°, then concentrated to a syrup which was extracted with boiling methanol (3 × 25 mL). The combined extracts were concentrated to an oil that was subjected to flash chromatography. The fractions with R_F 0.21 were concentrated and the water was removed by repeated evaporation with ethanol under diminished pressure. The resulting dry syrup (1 g) was treated with acetic anhydride (10 mL) and pyridine (10 mL) for 24 h at room temperature. The mixture was concentrated to a syrup which was treated with water (40 mL) and stored at ~5°. Recrystallization from ethanol gave **6** (1.56 g, 32%), m.p. 156–158°, $[\alpha]_D^{19}$ +66°, $[\alpha]_{578}^{23}$ +70°, $[\alpha]_{546}^{23}$ +79°, $[\alpha]_{436}^{23}$ +144°, $[\alpha]_{365}^{23}$ +246° (*c* 0.5, pyridine); $\lambda_{max}^{96\%\ EtOH}$ 245 nm (ε_{mM} 18.0); ν_{max} 3500–3100 (NH), 1740 (C=O ester), 1650 (C=O amide), 1215 cm^{-1} (C–O–C). N.m.r. data ($CDCl_3$): ^1H, δ 9.10 (bs, 2 H, NH_2), 6.75 (s, 1 H, H-5), 6.01 (bs, 1 H, $J_{1',2'}$ 2.6 Hz, H-1'), 5.46 (m, 2 H, $J_{2',3'}$ 8.3, $J_{3',4'}$ 2.3 Hz, H-2',3'), 5.23 (m, 1 H, H-4'), 4.27 (dd, 1 H, $J_{4',5'}$ 5.0, $J_{5',5''}$ 11.7 Hz, H-5'), 3.87 (dd, 1 H, $J_{4',5''}$ 7.3 Hz, H-5''), 2.23 (s, 3 H, NAc), 2.11, 2.08, 2.04 (3 s, each 3 H, 3 OAc), 2.02 (s, 6 H, 2 OAc); ^{13}C (23°), δ 170.2, 169.9, 169.6, 169.4 (5 C=O ester), 169.0 (C=O amide), 143.8, 142.4 (C-2, C-4 both of **6**; these assignments can be interchanged), 132.5 (C-2 of **7**), 122.5 (C-5 of **6**), 120.6 (C-4 of **7**), 115.4 (C-5 of **7**), 69.3, 67.8, 67.5 (C-2',3',4'), 64.1 (C-1'), 61.6 (C-5').

Anal. Calc. for $C_{20}H_{27}N_3O_{11}$: C, 49.52; H, 5.60; N, 8.65. Found: C, 49.38; H, 5.69; N, 8.59.

From the mother-liquors, **3** (0.3 g, 6%) was obtained as a minor product. When the mixture of acetylated products was poured into ice–water and extracted with chloroform, and the extract was washed successively with M hydrochloric acid and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated, **3** crystallized as a major product (35%) and **6** was detected only by t.l.c.

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REFERENCES

1 J. A. GALBIS PEREZ, P. ARECES BRAVO, F. REBOLLEDO VICENTE, J. I. FERNANDEZ GARCIA-HIERRO, AND J. FUENTES MOTA, *Carbohydr. Res.*, 176 (1988) 97–106.
2 J. FUENTES MOTA, J. I. FERNANDEZ GARCIA-HIERRO, P. ARECES BRAVO, F. REBOLLEDO VICENTE, AND J. A. GALBIS PEREZ, *Nucleosides Nucleotides*, 7 (1988) 457–477.
3 J. FUENTES MOTA, P. ARECES BRAVO, F. REBOLLEDO VICENTE, J. I. FERNANDEZ GARCIA-HIERRO, AND J. A. GALBIS PEREZ, *Nucleosides Nucleotides*, 3 (1984) 115–121.
4 F. GARCIA GONZALEZ, J. A. GALBIS PEREZ, J. I. FERNANDEZ GARCIA-HIERRO, AND J. FERNANDEZ-BOLAÑOS, *An. Quim.*, 75 (1979) 1002–1004.
5 J. A. GALBIS PEREZ, R. M. PINTO CORRALIZA, E. ROMAN GALAN AND M. GOMEZ GUILLEN, *An. Quim.*, 75 (1979) 387–391.
6 J. FERNANDEZ-BOLAÑOS AND M. ALAIZ BARRAGAN, unpublished results.
7 J. A. GALBIS PEREZ, P. TURMO FERNANDEZ, AND F. ZAMORA MATA, *Carbohydr. Res.*, 163 (1987) 132–135.
8 J. A. JOULE AND G. F. SMITH, *Heterocyclic Chemistry*, 2nd edn., Van Nostrand Reinhold, London, 1978.
9 M. D. COBURN AND P. N. NEWMAN, *J. Heterocycl. Chem.*, 7 (1970) 1391–1395.
10 S. L. PATT AND J. M. SHOOLERY, *J. Magn. Reson.*, 46 (1982) 536–539.
11 B. COXON, *Methods Carbohydr. Chem.*, 6 (1972) 513–539.
12 D. HORTON AND J. D. WANDER, *J. Org. Chem.*, 39 (1974) 1859–1863.
13 W. C. STILL, M. KAHN, AND A. MITRA, *J. Org. Chem.*, 43 (1978) 2923–2925.