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Note

5- and 4-(D-lyxofuranosyl)pyrazoles: a new type of pyrazole *C*-nucleoside

Manuel Gómez-Guillén and José María Lassaletta Simon

Departamento de Química Orgánica "Profesor García González", Universidad de Sevilla, Apartado de Correos No. 553, 41071 Seville (Spain)

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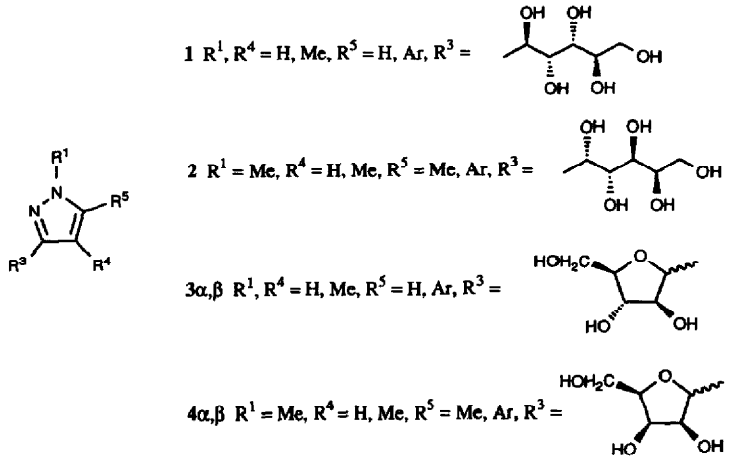
C-Nucleosides and their analogues constitute targets in organic synthesis because of their biological and pharmacological properties. A convenient route to this type of compound involves the well-known acid-catalysed cyclodehydration of polyhydroxyalkyl chains bonded to heterocycles[1–8]. Thus, in the presence of trifluoroacetic acid as catalyst, 3-(D-*manno*- or D-*galacto*-pentitol-1-yl)pyrazole (**1** or **2**) was dehydrated[9,10] to give 3-(D-arabinofuranosyl)- (**3**) or 3-(D-lyxofuranosyl)-pyrazole (**4**), respectively, in moderate to good yields. To the best of our knowledge, 1-substituted pyrazole *C*-nucleosides having the sugar moiety at C-5 or C-4 have not yet been described and we now report their preparation.

The starting compounds used for the cyclodehydration were 1-methyl (or phenyl)pyrazole derivatives having a D-*galacto*-pentitol-1-yl chain at C-5 (**5** and **6**) or at C-4 (**7**). These compounds were prepared[11] by deacetylation of the respective penta-*O*-acetyl derivatives (**8–10**) obtained[11] by the reaction of aldehyde methyl (or phenyl)hydrazones with the readily available 3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy-1-nitro-D-*galacto*-hept-1-enitol.

Heating of aqueous solutions of **5–7** severally with an excess of CF_3CO_2H led to the (D-lyxofuranosyl)pyrazole derivatives **11–13**, respectively, as α,β-mixtures or, for **13**, a unique product. The furanoid character of **11–13** was shown by the consumption of only 1 mol of periodate, as observed[10] for the 3-substituted analogues **4**. The α,β-ratios found (NMR data) were 60:40 for **11** and 65:35 for **12**, in agreement with the greater steric hindrance expected for the β-D-lyxofuranosyl than for the α isomers. Configurations were assigned on the basis of the chemical shifts of the H-1′ resonances and the $J_{1',2'}$ values. Thus, the δ values for the H-1′ resonances of the α isomers **11**α and **12**α (4.87 and 4.71 ppm,

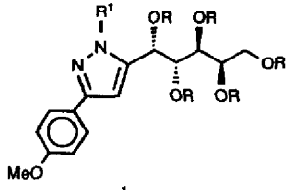
Correspondence to: Profesor M. Gómez-Guillén, Departamento de Química Orgánica "Profesor García González", Universidad de Sevilla, Apartado de Correos No. 553, 41071 Seville, Spain.



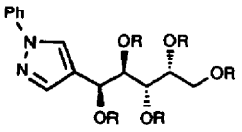
respectively) were lower than those for the corresponding β isomers **11**β and **12**β (5.07 and 4.93 ppm, respectively), as described[12,13] for D-lyxofuranose derivatives, and the $J_{1',2'}$ values for **11**α and **12**α (8.3 and 8.6 Hz, respectively) were outside the range reported[13] for *cisoid* protons, whereas those for **11**β and **12**β were much lower (4.7 and 5.2 Hz, respectively). For **13**, H-1′ gave a signal at δ 4.92 (d, $J_{1',2'}$ 4.4 Hz) that allowed the β configuration to be assigned tentatively. The reason why only the β anomer of **13** is formed may be the marked decrease of steric hindrance in comparison with **11**β and **12**β, due to the absence of a substituent at position 3 or 5 of the pyrazole ring, i.e., adjacent to the *C*-nucleosidic bond.

The triacetate (**14**) of **11**α had a $J_{1',2'}$ value of 7.1 Hz which confirmed the α-D-furanoid structure.

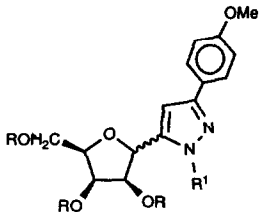
The fragmentation pattern observed in the mass spectra of **11**–**13** was similar to those described[9,10,14] for other *C*-nucleosides. For **11**β, **12**α, and **12**β, the base peak corresponded to M^+, but the ion $[B + CHOH]^+$, where B connotes the pyrazole moiety, also had a high abundance and, for **13**, was the base peak. The



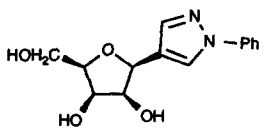
5 R¹ = Me, R = H
6 R¹ = Ph, R = H
8 R¹ = Me, R = Ac
9 R¹ = Ph, R = Ac



7 R = H
10 R = Ac



11α,β R^1 = Me, R = H
12α,β R^1 = Ph, R = H
14α R^1 = Me, R = Ac



13

mass spectrum of the triacetate **14** showed features similar to those of the spectra of other acetylated *C*-nucleosides[14,16,17].

EXPERIMENTAL

General methods.—Solvents were evaporated in vacuo at < 45°C. Melting points were determined with a Gallenkamp MFB-595 apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. IR spectra were recorded with a Perkin–Elmer 299 spectrometer for films or KBr discs. The ^1H and ^{13}C NMR spectra were recorded with a Varian XL-200 spectrometer. EI-mass spectra (70 eV) were obtained with a Kratos MS-80 RFA instrument with the ion-source at 200°C. The composition of molecular ions was confirmed by accurate mass measurements at a resolving power of ~ 10 000 (10% valley). Consumption of periodate was determined by a method based on that of Fleury and Lange[18].

Cyclodehydration of the (pentitol-1-yl)pyrazoles **5–7**.—To a warm solution of **5–7** (0.75 mmol) severally in water (20–40 mL) was added CF_3CO_2H (0.5–0.6 mL), and the mixture was boiled under reflux for 48–96 h, then concentrated. The residue was subjected to column chromatography (10:1 CH_2Cl_2–MeOH) on Silica Gel 60 (Merck, 63–200 μm).

3-(p-Anisyl)-5-(α- and β-D-lyxofuranosyl)-1-methylpyrazole (**11α** *and* **11β**).—Application of the general procedure to **5** (0.25 g) afforded **5** (96 mg, 38%) and a mixture (120 mg, 51%) of **11α** and **11β** (60:40, ^1H NMR data), which was resolved by preparative TLC (5:1 CH_2Cl_2–MeOH) on Silica Gel PSC-60 F_{254} s (Merck).

Compound **11α** (66 mg, 28%) had mp 146–147 °C (from MeOH); $[\alpha]_D^{24}$ + 31° (*c* 1, pyridine); ν_{max} 3320 (OH), 1610 (phenyl), 1570 (pyrazole C=N), and 1515 cm^{-1} (phenyl). NMR data: ^1H [$(CD_3)_2SO + D_2O$], δ 7.77 (d, 2 H, $J_{o,m}$ 8.6 Hz, *m*-H), 7.05 (d, 2 H, *o*-H), 6.72 (s, 1 H, H-4), 4.87 (d, 1 H, $J_{1',2'}$ 8.3 Hz, H-1′), 4.35 (dd, 1 H, $J_{2',3'}$ 4.0 Hz, H-2′), 4.2 (m, 2 H, H-3′,4′), 3.90 (s, 3 H, Me-1), 3.85 (s, 3 H, MeO), 3.76 (dd, 1 H, $J_{4',5'a}$ 5.0, $J_{5'a,5'b}$ 11.4 Hz, H-5′a), and 3.64 (dd, 1 H, $J_{4',5'b}$ 5.9 Hz, H-5′b); ^{13}C [$(CD_3)_2SO$], δ 159.5 (C-4 of *p*-anisyl), 149.1 (C-3), 144.6 (C-5), 127.1, 126.3 (C-1,2 of *p*-anisyl), 114.8 (C-3 of *p*-anisyl), 101.5 (C-4), 81.8, 77.3, 74.2,

71.7 (C-1′/4′), 60.8 (C-5′), 55.8 (MeO), and 37.4 (Me-1). Mass spectrum: *m/z* 322 (1%, $[M+2]^+$), 321 (9, $[M+1]^+$), 320 (37, M^+), 302 (1, $[M-H_2O]^+$), 231 (12, $[BCH_2CHOH]^+$), 230 (35, $[BCH_2CHO]^+$), 217 (25, $[BCHOH]^+$), 216 (51, $[BCHO]^+$), 201 (51, $[BCH_2]^+$), 189 (7, $[B+2]^+$), and 187 (12, $[B]^+$). Periodate consumption, 0.99 mol. Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 60.00; H, 6.29; N, 8.74. Found: C, 59.83; H, 6.40; N, 8.66.

Conventional treatment of **11α** (50 mg) with pyridine (0.5 mL) and acetic anhydride (0.5 mL) for 48 h at 0°C, with preparative TLC (10:1 ether–hexane) of the product on Silica Gel PSC-60 F_{254} s, gave the 2,3,5-triacetate **14** (60 mg, 86%), isolated as a colourless syrup; $[\alpha]_D^{25}$ + 63° (*c* 1, $CHCl_3$); ν_{max} 1740 (ester C=O), 1605 (phenyl), 1570 (pyrazole C=N), 1510 (phenyl), and 900 cm^{-1} (pyrazole ring bending). NMR data ($CDCl_3$): ^1H, δ 7.64 (d, 1 H, $J_{o,m}$ 8.9 Hz, *m*-H), 6.88 (d, 1 H, *o*-H), 6.42 (s, 1 H, H-4), 5.65 (dd, 1 H, $J_{2',3'}$ 4.6, $J_{3',4'}$ 4.5 Hz, H-3′), 5.59 (dd, 1 H, H-2′), 5.12 (d, 1 H, $J_{1',2'}$ 7.1 Hz, H-1′), 4.53 (ddd, 1 H, $J_{4',5'a}$ 6.6, $J_{4',5'b}$ 5.5 Hz, H-4′), 4.31 (dd, 1 H, $J_{5'a,5'b}$ 11.6 Hz, H-5′a), 4.22 (dd, 1 H, H-5′b), 3.91 (s, 3 H, Me-1), 3.80 (s, 3 H, MeO), 2.15, 2.05, and 2.03 (s, 9 H, 3 Ac); ^{13}C, δ 170.5, 169.5, 169.4 (3 CH_3CO), 159.2 (C-4 of *p*-anisyl), 150.0 (C-3), 139.9 (C-5), 126.6, 125.7 (C-1, 2 of *p*-anisyl), 113.8 (C-3 of *p*-anisyl), 101.0 (C-4), 76.3, 74.4, 72.5, 71.0 (C-1′/4′), 62.0 (C-5′), 55.1 (MeO), 36.9 (Me-1), 20.6 and 20.4 (3 CH_3CO). Mass spectrum: (*a*) *m/z* 448 (4%, $[M+2]^+$), 447 (21, $[M+1]^+$), 446 (84, M^+), 404 (9, $[M-CH_2{=}C{=}O]^+$), 386 (3, $[M-AcOH]^+$), 285 (3, $[M-AcOH-AcO-CH_2{=}C{=}O]^+$), 284 (4, $[M-2\,AcOH-CH_2{=}C{=}O]^+$), 267 (100, $[M-3\,AcOH+H]^+$), 217 (19, $[BCHOH]^+$), 216 (17, $[BCHO]^+$), 201 (11, $[BCH_2]^+$), 189 (3, $[B+2]^+$), and 187 (4, $[B]^+$); (*b*) *m/z* 446.1694 (calcd for $C_{22}H_{26}N_2O_8$: 446.1689).

Compound **11β** was isolated as a colourless syrup (43 mg, 18%); $[\alpha]_D^{25}$ + 14° (*c* 1, pyridine); ν_{max} 3300 (OH), 1610 (phenyl), 1565 pyrazole C=N), and 1510 cm^{-1} (phenyl). NMR data: ^1H [$(CD_3)_2SO + D_2O$], δ 7.77 (d, 2 H, $J_{o,m}$ 8.9 Hz, *m*-H), 7.05 (d, 2 H, *o*-H), 6.69 (s, 1 H, H-4), 5.07 (d, 1 H, $J_{1',2'}$ 4.7 Hz, H-1′), 4.42 (dd, 1 H, $J_{2',3'}$ 5.0, $J_{3',4'}$ 6.2 Hz, H-3′), 4.35 (dd, 1 H, H-2′), 4.04 (m, 1 H, $J_{4',5'a}$ 3.8, $J_{4',5'b}$ 5.4 Hz, H-4′), 3.92 (s, 3 H, Me-1), 3.88 (s, 3 H, MeO), and 3.7 (m, 2 H, H-5′a,5′b); ^{13}C [$(CD_3)_2SO$], δ 159.1 (C-4 of *p*-anisyl), 148.6 (C-3), 142.2 (C-5), 126.7 (C-1,2 of *p*-anisyl), 114.6 (C-3 of *p*-anisyl), 103.3 (C-4), 80.1, 75.4, 72.2, 72.0 (C-1′/4′), 60.5 (C-5′), 55.6 (MeO), and 37.6 (Me-1). Mass spectrum: (*a*) *m/z* 322 (3%, $[M+2]^+$), 321 (19, $[M+1]^+$), 320 (100, M^+), 302 (2, $[M-H_2O]^+$), 231 (13, $[BCH_2CHOH]^+$), 230 (20, $[BCH_2CHO]^+$), 217 (53, $[BCHOH]^+$), 216 (51, $[BCHO]^+$), 201 (25, $[BCH_2]^+$), 189 (18, $[B+2]^+$), and 187 (11, $[B]^+$); (*b*) *m/z* 320.1423 (calcd for $C_{16}H_{20}N_2O_5$: 320.1373). Periodate consumption, 0.90 mol.

3-(p-Anisyl)-5-(α- and β-D-lyxofuranosyl)-1-phenylpyrazole (**12α** *and* **12β**).—Application of the general procedure to **6** (0.30 g) gave **6** (0.12 g, 40%) and a mixture (0.13 g, 45%) of **12α** and **12β** (65:35, ^1H NMR data), which was resolved by TLC as described for **11α** and **11β**.

Compound **12α** (76 mg, 26%) was isolated as a colourless syrup, $[\alpha]_D^{23}$ + 36° (*c* 1, $CHCl_3$); ν_{max} 3300 (OH), 1605, 1590 (phenyl), 1570 (pyrazole C=N), 1510 and 1495

cm^{-1} (C=C and C=N aromatic). NMR data: ^1H [$(CD_3)_2SO + D_2O$], δ 7.90 (d, 2 H, $J_{o,m}$ 8.9 Hz, *m*-H of *p*-anisyl), 7.8–7.5 (m, 5 H, Ph), 7.14 (s, 1 H, H-4), 7.11 (d, 2 H, *o*-H of *p*-anisyl), 4.71 (d, 1 H, $J_{1',2'}$ 8.6 Hz, H-1'), 4.53 (dd, 1 H, $J_{2',3'}$ 4.0 Hz, H-2'), 4.2 (m, 2 H, H-3',4'), 3.89 (s, 3 H, MeO), 3.72 (dd, 1 H, $J_{4',5'a}$ 5.0 $J_{5'a,5'b}$ 11.4 Hz, H-5'a), and 3.58 (dd, 1 H, $J_{4',5'b}$ 6.0 Hz, H-5'b); ^{13}C [$(CD_3)_2SO$], δ 159.6 (C-4 of *p*-anisyl), 151.1 (C-3), 144.5 (C-5), 139.5 (C-1 of Ph), 129.7, 128.4, 127.1 (C-2,3,4 of Ph), 125.8, 125.2 (C-1,2 of *p*-anisyl), 114.7 (C-3 of *p*-anisyl), 103.4 (C-4), 81.6, 77.4, 73.2, 71.4 (C-1'/4'), 60.6 (C-5'), and 55.6 (MeO). Mass spectrum: (*a*) *m/z* 384 (4%, $[M + 2]^+$), 383 (25, $[M + 1]^+$), 382 (100, M^+), 364 (6, $[M - H_2O]^+$), 293 (19, $[BCH_2CHOH]^+$), 292 (41, $[BCH_2CHO]^+$), 279 (69, $[BCHOH]^+$), 278 (44, $[BCHO]^+$), 263 (34, $[BCH_2]^+$), 251 (11, $[B + 2]^+$), and 249 (10, $[B]^+$); (*b*) *m/z* 382.1510 (calcd for $C_{21}H_{22}N_2O_5$: 382.1529). Periodate consumption, 0.95 mol.

Compound **12**β was isolated as a syrup (20 mg, 14%), $[\alpha]_D^{25} + 15°$ (*c* 1, $CHCl_3$); ν_{max} 3300 (OH), 1610, 1590 (phenyl), 1575 (pyrazole C=N), 1515 and 1495 cm^{-1} (C=C and C=N aromatic). NMR data: ^1H [$(CD_3)_2SO + D_2O$], δ 7.86 (d, 2 H, $J_{o,m}$ 8.8 Hz, *m*-H of *p*-anisyl), 7.7–7.5 (m, 5 H, Ph), 7.10 (d, 2 H, *o*-H of *p*-anisyl), 7.06 (s, 1 H, H-4), 4.93 (d, 1 H, $J_{1',2'}$ 5.2 Hz, H-1'), 4.35 (dd, 1 H, $J_{2',3'}$ 4.9, $J_{3',4'}$ 5.9 Hz, H-3'), 4.21 (dd, 1 H, H-2'), 3.98 (ddd, 1 H, $J_{4',5'a}$ 4.2, $J_{4',5'b}$ 5.4 Hz, H-4'), 3.91 (s, 3 H, MeO), 3.81 (dd, 1 H, $J_{5'a,5'b}$ 11.3 Hz, H-5'a), and 3.70 (dd, 1 H, H-5'b); ^{13}C [$(CD_3)_2SO$], δ 159.2 (C-4 of *p*-anisyl), 150.4 (C-3), 142.7 (C-5), 139.7 (C-1 of Ph), 129.5, 128.3, 126.8 (C-2,3,4 of Ph), 125.9, 125.3 (C-1,2 of *p*-anisyl), 114.4 (C-3 of *p*-anisyl), 105.4 (C-4), 80.5, 74.5, 72.1, 71.7 (C-1'/4'), 60.1 (C-5'), and 55.4 (MeO). Periodate consumption, 0.97 mol. Mass spectrum: *m/z* 382.1515 (calcd for $C_{21}H_{22}N_2O_5$: 382.1529).

4-(β-D-Lyxofuranosyl)-1-phenylpyrazole (**13**).—Application of the general procedure to **7** (0.22 g) gave **7** (64 mg) and **13** (0.12 g, 58%); mp 120–122 °C (from MeOH); $[\alpha]_D^{25} + 11°$ (*c* 1, pyridine); ν_{max} 3480, 3250 (OH), 1600 (phenyl), 1575, 1565 (pyrazole C=N), 1500 (phenyl), and 900 cm^{-1} (pyrazole ring bending). NMR data: ^1H [$(CD_3)_2SO + D_2O$], δ 8.47 (s, 1 H, H-5), 8.0–7.3 (m, 5 H, Ph), 7.83 (s, 1 H, H-3), 4.92 (d, 1 H, $J_{1',2'}$ 4.4 Hz, H-1'), 4.46 (dd, 1 H, $J_{2',3'}$ 4.9, $J_{3',4'}$ 6.7 Hz, H-3'), 4.11 (dd, 1 H, H-2'), 4.00 (ddd, 1 H, $J_{4',5'a}$ 4.0, $J_{4',5'b}$ 4.9 Hz, H-4'), and 3.8–3.6 (m, 2 H, H-5'a,5'b); ^{13}C [$(CD_3)_2SO$], δ 141.4 (C-3), 139.9 (C-1 of Ph), 129.7 (C-3 of Ph), 127.0, 126.0 (C-4 of Ph and C-5), 121.4 (C-4), 118.1 (C-2 of Ph), 80.0, 74.7, 72.3, 72.1 (C-1'/4'), and 60.2 (C-5'). Mass spectrum: *m/z* 277 (1%, $[M + 1]^+$), 276 (7, M^+), 258 (50, $[M - H_2O]^+$), 187 (5, $[BCH_2CHOH]^+$), 186 (12, $[BCH_2CHO]^+$), 173 (100, $[BCHOH]^+$), 172 (12, $[BCHO]^+$), 157 (41, $[BCH_2]^+$), 145 (5, $[B + 2]^+$), and 143 (1, $[B]^+$). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.79; H, 5.91; N, 9.96.

ACKNOWLEDGMENTS

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