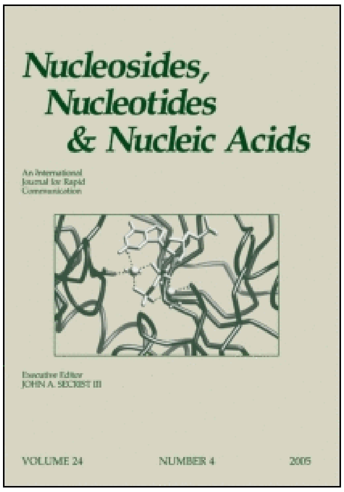

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NEW ACYCLIC *C*-NUCLEOSIDES OF THE IMIDAZOLE

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ABSTRACT.- Acid catalyzed isomerization of 1-aryl-(1,2-dideoxy-*D*-*glycero*-β-*L*-*gluco*-heptofuranose)[1,2-*d*]-2-imidazolines (**4**) yields 1-aryl-4-(*D*-*galacto*-pentitol-1-yl)imidazoles (**8**) which can be also obtained by reductive desulphuration of 1-aryl-2-benzylthio-4-(*D*-*galacto*-pentitol-1-yl)imidazoles (**6**). Compounds (**4**) were obtained by desulphuration with Raney nickel from 1-aryl-(1,2-dideoxy-*D*-*glycero*-β-*L*-*gluco*-heptofuranose)[1,2-*d*]-imidazolidine-2-thiones (**1**) or 1-aryl-2-benzylthio-(1,2-dideoxy-*D*-*glycero*-β-*L*-*gluco*-heptofuranose)[1,2-*d*]-2-imidazolines (**2**).

In studies on the synthesis of the *C*-nucleosides analogs, we have recently described[1,2] the preparation of some thiolglucitylimidazoles (**1**,**2**,**3**). We now report the reductive desulphuration with Raney nickel of these compounds to give new carbohydrate derivatives of the imidazole which by acid catalyzed isomerization can become acyclic *C*-nucleosides.

In this way, the desulphuration of compounds **1** or **2** yields the 1-aryl-(1,2-dideoxy-*D*-*glycero*-β-*L*-*gluco*-heptofuranose)[1,2-*d*]-2-imidazolines (**4**), whose structures were assigned on the basis of their elemental analyses, spectral data (u.v., i.r., p.m.r. and m.s.) and oxidative titration with sodium periodate, that produced 1 mol of formic acid per mol of substance, in accord with the proposed furanoid structures. The p.m.r. spectra of the acetylated derivatives **5** are also in agreement with these structures. Compounds **5** were obtained by desulphuration with Raney nickel of **3**. Deacetylation of **5** gives **4** in good yields.

Trifluoroacetic acid catalyzed isomerization of **4** yields the 1-aryl-4-(*D*-*galacto*-pentitol-1-yl)imidazoles (**8**) through their trifluoroacetate salts (**7**); the structure of **8** were demonstrated by elemental analyses and spectral data (u.v. and i.r.). The presence of the penta-

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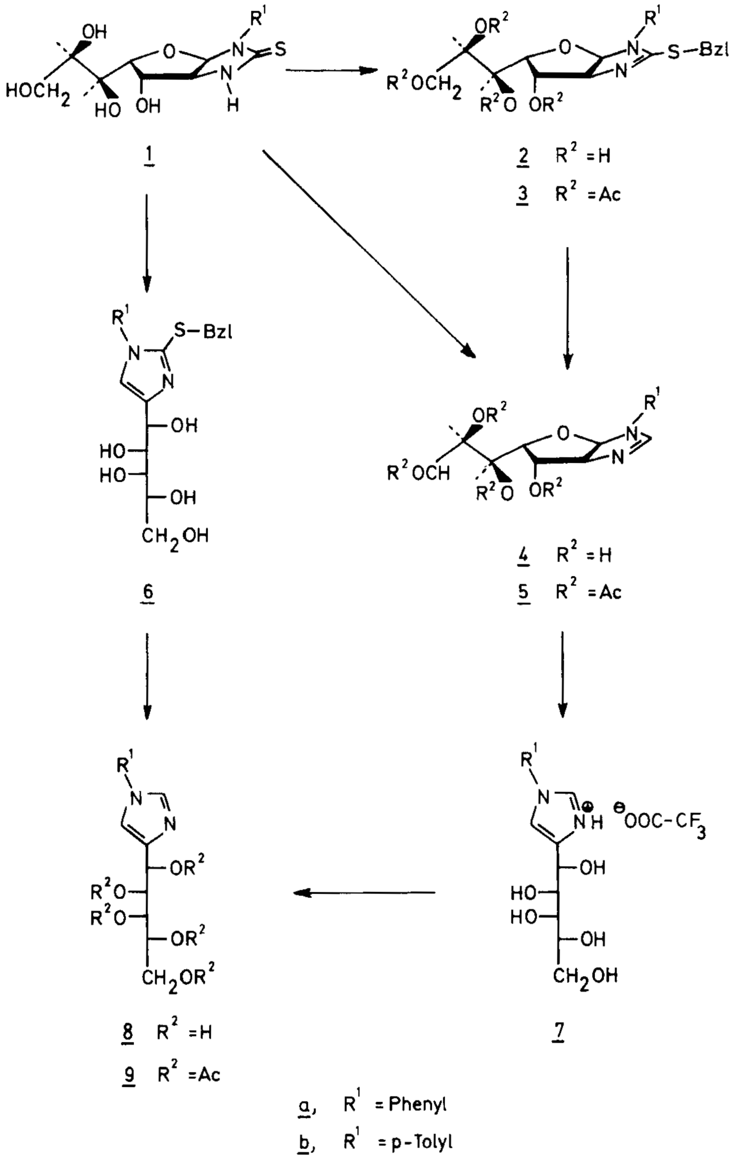

hydroxypentyl chain was proved by periodate oxidation, showing a periodate consumption of 4 mol per mol of substance. The structures of 8 were also proved by preparation of their pentaacetate derivatives 9. The coupling constants between the chain protons of 9 demonstrated the preponderance of the conformation having the planar, zig-zag arrangement of carbon atoms 1'-5', as others acyclic sugars derivatives with D-*galacto* configuration[3,4]. No unfavorable, parallel 1,3-interaction[5] of acetoxyl groups is present in this arrangement. Compounds 8 were also obtained by reductive desulphuration of 6 previously described[2].

EXPERIMENTAL

General methods.- Solutions were concentrated *in vacuo* at temperatures below 40°. 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 cell). I.r. spectra (KBr discs) were recorded with Beckman IR-33 and Perkin Elmer 399 spectrophotometers, and u.v. spectra with a Beckman 25 instrument. P.m.r. spectra (90 MHz, internal Me_4Si) were recorded with a Perkin Elmer R-32 spectrometer, and coupling constants were measured directly from spectra recorded at 300 Hz sweep-width. Assignments were confirmed by double-resonance and displacement of signals with $Eu(fod)_3$ experiments. The mass spectra was registered with a MS-30 AEI spectrometer operated at an ionizing voltage of 70 eV. T.L.C. was performed on silica gel GF_{254} (Merck) with ethyl acetate-ethanol 3:1 and detection with u.v. light and iodine vapour. Consumption of periodate and formic acid produced were determined as previously described[6,7,8].

1-Phenyl-(1,2-dideoxy-D-glycero-β-L-gluco-heptofuranose)[1,2-d]-2-imidazoline (4a).- a)A solution of 2a[2] (1.5 g, 3.6 mmol) in 90% ethanol (30 ml) was treated with Raney nickel (15 ml), and the mixture was boiled under reflux, with stirring for 5 minutes. Then, the catalyst was filtered off, and the solution evaporated until a foam, that was crystallized from ethanol (0.16 g, 20%). Recrystallized from ethanol, m.p. 96-97°, $[\alpha]_D^{22}$ -220° (*c* 0.6, pyridine); $\lambda_{max}^{H_2O}$ 256 nm (ε 14,000); ν_{max} 3420-3300 (OH), 1500 (C=C aromatic)cm^{-1}. P.m.r. data (DMSO-d_6): δ 7.97 (1H, d, $^4J_{2,2'}$ 1.5 Hz, H-2), 7.45-7.15 (5H, m , C_6H_5) and 5.95 (1H, d, $^3J_{1',2'}$6 Hz, H-1')ppm. MS m/e (%): 295 (1, M^+ + H), 294 (8, M^+), 203 (14), 185 (4), 173 (5), 157 (14), 145 (40), 144 (83), 143 (4), 117 (32), 104 (21), 77 (58), 31 (100).

Anal. Calc. for $C_{14}H_{18}N_2O_5 \cdot C_2H_5OH$: C, 56.46; H, 7.11; N, 8.24. Found: C, 56.51; H, 7.16; N, 8.44. Formic acid produced: 0.83 mol.

b) A solution of 1a[1] (1 g, 3 mmol) in 90% ethanol (20 ml) was treated with Raney nickel (10 ml) and the mixture was boiled and stirred under reflux for 10 minutes. Then, the catalyst was filtered off and the solution was treated as it was described in a) (0.46 g, 65%).

1-Phenyl-(3,5,6,7-tetra-O-acetyl-1,2-dideoxy-D-glycero-β-L-gluco-heptofuranose)[1,2-d]-2-imidazoline (5a).- A solution of 3a[2] (0.84 g, 1.4 mmol) in ethanol (17 ml) was treated with Raney nickel (8.5 ml), and the mixture was boiled under reflux for 3 minutes. Then the catalyst was filtered off and the resulting solution concentrated, crystallizing 5a (0.41 g, 62%). Recrystallized from ethanol-water, m.p. 144-146°; $[\alpha]_D^{16}$ -150.4°, $[\alpha]_{578}^{16}$ -159.0°, $[\alpha]_{546}^{16}$ -184.1°, $[\alpha]_{436}^{16}$ -351.7°, $[\alpha]_{365}^{16}$ -656.8° (c 0.53, pyridine); ν_{max} 2975, 2950 and 2880 (C-H), 1730 (C=O), 1500 and 1450 (C=C aromatic), 1220 (C-O-C) cm^{-1}. P.m.r. data (Cl_3CD): δ 7.63 (1H, d, $^4J_{2,2'}$2.0 Hz,H-2), 7.50-7.05 (5H, m, C_6H_5), 5.95 (1H, d, $^3J_{1',2'}$6.3 Hz,H-1'), 5.60-5.30 (3H, m,H-3', H-5' and H-6'), 4.65 (1H, dd, $^3J_{2',3'}$0.0 Hz, H-2'), 4.35 (1H, dd, $^3J_{6',7'}$4.6 Hz, $^2J_{7',7''}$ 11.4 Hz, H-7'), 4.10-3.78 (1H, m, H-4'), 3.92 (1H, dd, $^3J_{6',7''}$6.8 Hz, H-7"), 2.10 (3H, s, OAc), 2.02 (6H, s, OAc), 1.70 (3H, s, OAc).

Anal. Calc. for $C_{22}H_{26}N_2O_9$: C, 57.13; H, 5.62; N, 6.06. Found: C, 57.32; H, 5.84; N, 6.36.

A solution of 5a (0.1 g, 0.21 mmol) in methanol (1 ml) was treated with 4-5 drops of a solution of sodium methoxide. The mixture was neutralized with 1 M HCl and a precipitate of ionic salts was filtered off. Then, the solution was concentrated and the syrupy residue was crystallized from ethanol. The solid obtained was identified as 4a (0.04 g, 70%).

1-p-Tolyl-(1,2-dideoxy-D-glycero-β-L-gluco-heptofuranose)[1,2-d]-2-imidazoline (4b).- a) A solution of 2b[2](0.94 g, 2.18 mmol) in 90% ethanol (20 ml) was treated with Raney nickel (9.5 ml). The mixture was boiled and stirred under reflux for 7 minutes. Then the catalyst was filtered off and the solution was evaporated to a foam, which by solution in methanol-acetone 1:9 give 4b after 12 hours in the refrigerator (0.28 g, 42%). Recrystallization from methanol-acetone, m.p. 120-122°; $[\alpha]_D^{20}$ -234.5°, $[\alpha]_{578}^{20}$ -246.3°, $[\alpha]_{546}^{20}$ -286.7°, $[\alpha]_{436}^{20}$ -567.6°, $[\alpha]_{365}^{20}$ -1140.7° (c 0.67, pyridine); $\lambda_{max}^{H_2O}$ 260 nm (ε 13,800); ν_{max} 3500-3000 (OH), 2920 and 2860 (C-H), 1500 (C=C aromatic) cm^{-1}. MS m/e (%): 309 (2, M^+ + H), 308 (10, M^+), 217 (10), 199 (3), 187 (5), 171 (12), 159 (34), 158 (83), 157 (7), 118 (17), 91 (37), 32 (100).

Anal. Calc. for $C_{15}H_{20}N_2O_5 \cdot CH_3OH$: C, 56.47; H, 7.05; N, 8.23. Found: C, 56.31; H, 6.74; N, 8.65. Formic acid produced: 0.9 mol.

b) Compound 4b was also synthetized from 1b[1] (0.87 g, 2.5 mmol) by a similar procedure as in 4a. The product 4b (0.49 g, 63%) was recrystallized from methanol-acetone 1:9.

1-p-Tolyl-(3,5,6,7-tetra-O-acetyl-1,2-dideoxy-D-glycero-β-L-gluco-heptofuranose)[1,2-d]-2-imidazoline (5b).- Compound 5b was synthetized from 3b[2] (1 g, 1.6 mmol) by similar procedure to the used in the synthesis of 5a. Recrystallization of 5b (0.274 g, 36%) from ethanol, m.p. 173-174°;

$[\alpha]_D^{17}$ -156.0°, $[\alpha]_{578}^{17}$ -165.5°, $[\alpha]_{546}^{17}$ -190.9°, $[\alpha]_{436}^{17}$ -362.9°, $[\alpha]_{365}^{17}$ -679.4° (*c* 0.585, pyridine); ν_{max} 2970, 2940 and 2880 (C-H), 1730 (C=O), 1570 and 1450 (C=C aromatic), 1215 (C-O-C) cm^{-1}. P.m.r. data (Cl_3CD): δ 7.56 (1H, d, $^4J_{2,2'}$2.0 Hz, H-2), 7.25-6.92 (4H, m, C_6H_4), 5.90 (1H, d, $^3J_{1',2'}$6.3 Hz, H-1'), 5.60-5.30 (3H, m, H-3', H-5', H-6'), 4.63 (1H, dd, $^3J_{6',7'}$4.5 Hz, $^2J_{7',7''}$11.4 Hz, H-7'), 4.07-3.80 (1H, m, H-4'), 3.92 (1H, dd, $^3J_{6',7''}$7.2 Hz, H-7"), 2.31 (3H, s, CH_3), 2.10 (3H, s, OAc), 2.01 (6H, s, OAc), 1.75 (3H, s, OAc).

Anal. Calc. for $C_{23}H_{28}N_2O_9$: C, 57.98; H, 5.88; N, 5.88. Found: C, 58.20; H, 6.15; N, 6.14.

The deacetylation reaction of 5b was made by a similar procedure to the used in 5a; this process give 4b (67%).

4-(D-Galacto-pentitol-1-yl)-1-phenylimidazole (8a).- a) A solution of 6a[2] (1.7 g, 4 mmol) in 90% ethanol (31 ml) was treated with Raney nickel (17 ml) and the mixture was boiled and stirred under reflux for 10 minutes. Then, the catalyst was filtered off and the solution concentrated under diminished pressure. The resulting crystals were collected (0.7 g, 58%). Recrystallization from water gave 8a, m.p. 191-192°; $[\alpha]_D^{22}$ -19.5° (*c* 0.53, dimethylformamide); $\lambda_{max}^{H_2O}$ 236nm (ε 10,000); ν_{max} 3270 (OH), 3010 (C-H aromatic), 2930, 2910 and 2870 (C-H aliphatic), 1595, 1505 and 1460 (C=C aromatic) cm^{-1}.

Anal. Calc. for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.12; N, 9.52. Found: C, 57.04; H, 6.46; N, 9.56. Periodate consumption: 4.05 mol.

b) A solution of 4a (0.3 g, 1 mmol) in ethanol (3 ml) was treated with trifluoroacetic acid (0.45 ml) and boiled under reflux for 30 minutes. The trifluoroacetate of 8a crystallized very quickly (0.1 g, 24%). Recrystallized fron ethanol-water 1:1, m.p. 194-196°; $[\alpha]_D^{26}$ -13.3°, $[\alpha]_{578}^{26}$ -14.9°, $[\alpha]_{546}^{26}$ -19.2°, $[\alpha]_{436}^{26}$ -34.2° (*c* 0.57, pyridine); ν_{max} 3280 (OH), 1655 (C=O), 1595 and 1535 (C=C aromatic) cm^{-1}.

Anal. Calc. for $C_{16}H_{19}N_2O_7F_3$: C, 47.05; H, 4.65; N, 6.86. Found: C, 46.65; H, 4.26; N, 6.63.

The trifluoroacetate (0.06 g, 0.14 mmol) was dissolved in the smallest volume of water and neutralized with 0.1 *M* NaOH, to yield 8a (0.022 g, 52%).

4-(Penta-O-acetyl-D-galacto-pentitol-1-yl)-1-phenylimidazole (9a).- Conventional treatment of a suspension of 8a (0.25 g, 0.85 mmol) in pyridine (2.3 ml) and acetic anhydride (1.5 ml, 15.9 mmol) gave 9a (0.35 g, 83%). Recrystallized from ethanol, m.p. 157-158°, $[\alpha]_D^{22}$ + 50.1°, $[\alpha]_{578}^{22}$

+ 52.2°, $[\alpha]^{22}_{546}$ + 59.7°, $[\alpha]^{22}_{436}$ + 106.4°, $[\alpha]^{22}_{365}$ + 175.4° (*c* 0.52, pyridine); $\lambda^{96\%\ \mathrm{EtOH}}_{\max}$ 238 nm (ε 7,500); $\nu_{\max}$ 1730 (C=O), 1585 and 1500 (C=C aromatic), 1230 (C-O-C) cm^{-1}. P.m.r. data (Cl_3CD): δ 7.78 (1H, d, $^4J_{2,5}$ 1.2 Hz, H-2), 7.60-7.27 (5H, m, C_6H_5), 7.23 (1H, sb, H-5), 6.10 (1H, d, $^3J_{1',2'}$ 3.0 Hz, H-1'), 5.69 (1H, dd, $^3J_{2',3'}$ 8.9 Hz, H-2'), 5.52 (1H, dd, $^3J_{3',4'}$ 2.3 Hz, H-3'), 5.34 (1H, m, H-4'), 4.34 (1H, dd, $^3J_{4',5'}$ 4.9 Hz, $^2J_{5',5''}$ 11.6 Hz, H-5'), 3.95 (1H, dd, $^3J_{4',5''}$ 7.6 Hz, H-5"), 2.14 (6H, s, OAc), 2.08 (3H, s, OAc), 2.04 (6H, s, OAc).

Anal. Calc. for $C_{24}H_{28}N_2O_{10}$: C, 57.13; H, 5.59; N, 5.55. Found: C, 57.27; H, 5.82; N, 5.41.

4-(D-galacto-pentitol-1-yl)-1-p-tolylimidazole (*8b*).- a) A solution of *6b*[2] (2 g, 4.6 mmol) in 90% ethanol (40 ml) was treated with Raney nickel (20 ml) and the mixture was boiled and stirred under reflux for 9 minutes. Then, the catalyst was filtered off and the solution evaporated to give crystalline *8b* (1.03 g, 72%). Recrystallized from ethanol-water 1:6, m.p. 199-201°; $[\alpha]^{20}_{D}$ -12.4°, $[\alpha]^{20}_{578}$ -12.2°, $[\alpha]^{20}_{546}$ -14.5°, $[\alpha]^{20}_{436}$ -26.5°, $[\alpha]^{20}_{365}$ -46.4° (*c* 0.55, dimethylsulphoxide); $\lambda^{H_2O}_{\max}$ 238 nm (ε 10,000); $\nu_{\max}$ 3190-3320 (OH), 1600, 1515 and 1480 (C=C aromatic) cm^{-1}.

Anal. Calc. for $C_{15}H_{20}N_2O_5$: C, 58.44; H, 6.49; N, 9.09. Found: C, 58.12; H, 6.56; N, 8.92. Periodate consumption: 3.9 mol.

b) A solution of *4b* (0.2 g, 0.64 mmol) in ethanol (2 ml) was treated with trifluoroacetic acid (0.3 ml) and boiled under reflux for 30 minutes. The trifluoroacetate of *8b* crystallized very quickly (0.09 g, 32%). Recrystallization from ethanol-water 1:1, m.p. 201-202°; $[\alpha]^{19}_{D}$ -2.7°, $[\alpha]^{19}_{578}$ -3.9°, $[\alpha]^{19}_{546}$ -5.8°, $[\alpha]^{19}_{436}$ -10.5° (*c* 0.53, pyridine); $\nu_{\max}$ 3280 (OH), 2900 and 2800 (C-H), 1630 (C=O), 1590, 1510 and 1480 (C=C aromatic) cm^{-1}.

Anal. Calc. for $C_{17}H_{21}N_2O_7F_3$: C, 48.44; H, 4.97; N, 6.63. Found: C, 48.85; H, 4.91; N, 6.81.

The trifluoroacetate (0.041 g, 0.097 mmol) was dissolved in the smallest volume of water and neutralized with 0.1 *M* NaOH to yield *8b* (0.023 g, 56%).

4-(Penta-O-acetyl-D-galacto-pentitol-1-yl)-1-p-tolylimidazole (*9b*).- A suspension of *8b* (0.25 g, 0.57 mmol) in pyridine (2 ml) was treated with acetic anhydride (1.5 ml, 15.9 mmol). The mixture was kept to room temperature for 12 h and then in the refrigerator for 12 h more. The solution was poured into ice-water (60 ml) and the precipitate was filtered off, washed with cold water and dried, (0.41 g, 97%). Recrystallization from ethanol gave *9b*, m.p. 157-158°; $[\alpha]^{20}_{D}$ + 50.20°, $[\alpha]^{20}_{578}$+52.2°,

$[\alpha]_{546}^{20}$ + 60.2°, $[\alpha]_{436}^{20}$ + 108.3°, $[\alpha]_{365}^{20}$+ 179.7° (c 0.68, pyridine); $\lambda_{max}^{96\%\ EtOH}$ 240 nm (ε 11,500); ν_{max} 1730 (C=O), 1600, 1510 and 1430 (C=C aromatic), 1230 (C-O-C)cm^{-1}. P.m.r. data (Cl_3CD): δ 7.73 (1H, d, $^4J_{2,5}$ 1.1 Hz, H-2), 7.24 (4H, s, C_6H_4), 7.20 (1H, d, H-5), 6.09 (1H, d, $^3J_{1',2'}$ 3.0 Hz, H-1'), 5.68 (1H, dd, $^3J_{2',3'}$ 9.1 Hz, H-2'), 5.50 (1H, dd, $^3J_{3',4'}$ 2.3 Hz, H-3'), 5.33 (1H, m, H-4'), 4.33 (1H, dd, $^3J_{4',5'}$ 4.6 Hz, $^2J_{5',5''}$ 11.2 Hz, H-5'), 3.94 (1H, dd, $^3J_{4',5''}$ 6.9 Hz, H-5''), 2.40 (3H, s, CH_3), 2.14 (6H, s, OAc), 2.08 (3H, s, OAc), 2.03 (6H, s, OAc).

Anal. Calc. for $C_{25}H_{30}N_2O_{10}$: C, 57.91; H, 5.79; N, 5.40. Found: C, 57.96; H, 6.01; N, 5.38.

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