C-NUCLEOSIDES. 15.[1] NOVEL RING TRANSFORMATION OF 6-HYDROXY-6-(2,3,5-TRI-O-BENZOYL-β-D-RIBOFURANOSYL)-2,6-DIHYDROPYRAN-3-ONE WITH AMIDINES TO IMIDAZOLE

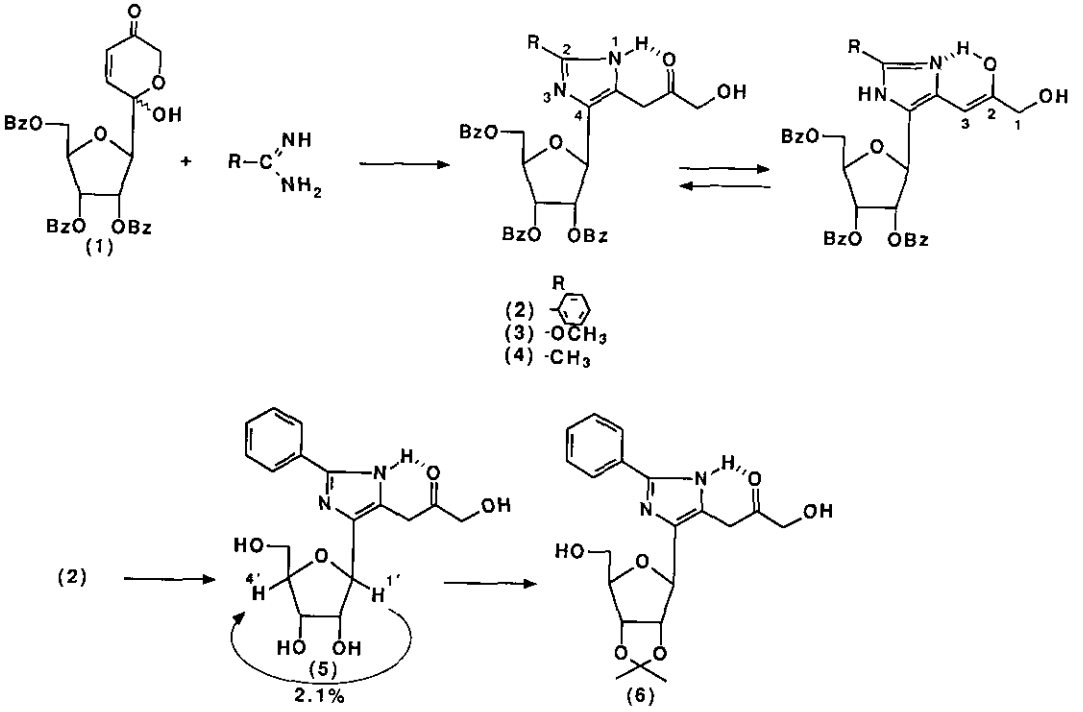
Isamu Maeba*, Kazuya Osaka, and Chihiro Ito
Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468, Japan

Abstract —— The novel ring transformation of 6-hydroxy-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,6-dihydropyran-3-one (1) with amidines to imidazole is described. Treatment of 1 with benzamidine afforded 3-[2-phenyl-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (2) in 53% yield. ^{1}H and ^{13}C nmr spectra of 2 accounted for the contribution of tautomeric structure. Deprotection of 2 with methanolic sodium hydroxide afforded 3-[2-phenyl-4-(β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (5) in 35% yield. Treatment of 1 with O-methylisourea afforded 2-methoxyimidazole (3) in 27% yield. Treatment of 1 with acetamidine afforded 2-methylimidazole (4) in 10% yield. However, debenzoylation of 3 and 4 with alkaline did not afforded the deprotected imidazole C-nucleosides.

The imidazole skeleton is found in several naturally occurring compounds which include the amino acid histidine, histamine, and purines.[1] A number of reviews[2] have presented some imidazole nucleoside and nucleotide chemistry or biochemistry. However, only a few reports have dealt with the preparation of imidazole C-nucleoside analogues.[3] In our studies on the preparation of new C-nucleosides by ring transformation of 6-hydroxy-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,6-dihydropyran-3-one (1), we have described the synthesis of pyrrole,[4] quinoxaline,[5] and lumazine[6] C-nucleosides. In this paper, we describe the novel ring transformation of 1 with amidines to imidazole ring.

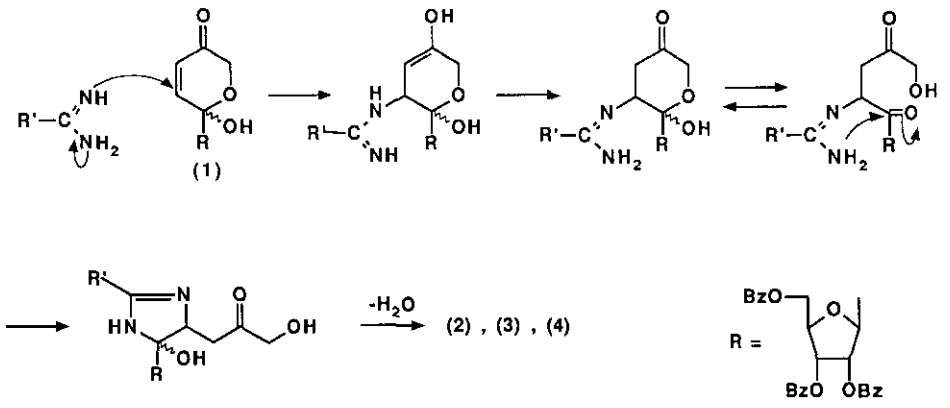
The condensation of 1 with benzamidine hydrochloride in the presence of sodium carbonate was carried out in chloroform at room temperature, followed by chromatographic purification of the product gave 3-[2-phenyl-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (2) in 53% yield. The structure of 2 was established by ^{1}H and ^{13}C nmr and mass spectra. In particular, the 270 MHz ^{1}H nmr spectrum featured a singlet at δ 3.93 (decrease in the signal intensity on the addition of deuterium oxide) and a doublet at 4.21 (J=6.1 Hz) for the side chain

methylene protons, and a doublet at δ 5.34 (J=4.4 Hz) attributed to the anomeric hydrogen atom of the ribofuranose moiety. In the C-H COSY and DEPT spectra, the methylene carbon atom of position 3 is not visible. The missing signal may be attributed to exchange occurring between tautomeric forms (Scheme 1).[7] The removal of the sugar protecting groups in 2 was readily accomplished with methanolic sodium hydroxide to afford 3-[2-phenyl-4-(β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (5) in 35% yield. The stereochemistry of 5 was determined by a nuclear Overhauser effect experiment. Irradiation of the 1'-H signal (δ 4.81) in 5 gave a 2.1% enhancement of the signal at δ 3.98 assignable to the 4'-H. Moreover, the isopropylidene acetal (6) was synthesized using p-toluenesulfonic acid in acetone. Its ^{1}H nmr spectrum showed two singlets at δ 1.35 and 1.61 (Δδ=0.26 ppm; a value of less than 0.10 ppm would be expected in the case of an α anomer).[8] This showed the β-ribofuranoside configuration had been preserved during the condensation reaction.



Scheme 1

O-Methylisourea hydrogen sulfate was also successfully condensed with **1** to afford 3-[2-methoxy-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (**3**) in 27% yield. Next, treatment of **1** with acetamidine acetate gave a 10% yield of 3-[2-methyl-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazolyl}-2-oxo-1-propanol (**4**). Debenzoylation of **3** and **4** with alkaline did not afford the deprotected imidazole C-nucleosides. We think that the formation of imidazoles *2*, *3*, and *4* proceeds by the *similar mechanism for formation* of quinoxalines in a previous paper.[5] The outline of the reaction mechanism is shown in Scheme 2.



Scheme 2

EXPERIMENTAL

Mass spectra were taken on a Hitachi *M-80* instrument by direct *insertion at 70 eV; fast-atom* bombardment (fab) mass spectra were run on a JMS-HX 110. ^{1}H Nmr spectra were measured with a JNM-GX-270 and a GX-400 (JEOL) spectrometer, with tetramethylsilane as internal standard. ^{13}C Nmr spectra were recorded on a JEOL JNM-FX-100 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as internal standard. Analytical thin-layer chromatography (tlc) was performed on glass plates coated with a 0.5-mm layer of silica gel GF_{254} (Merck). The compounds were detected by uv light (254 nm). Column chromatography was performed on silica gel C-200 (74-149 μm, Wakogel).

3-[2-Phenyl-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (2). To a solution of **1** (631.4 mg, 1.1 mmol) in chloroform (5 ml) at 0°C was added benzamidine hydrochloride hydrate (730.8 mg, 4.5 mmol) and sodium carbonate (479.7 mg, 4.5 mmol) during 10 min. The mixture was stirred at room temperature for 24 h. Water was added, and the mixture was extracted with chloroform, and dried over magnesium sulfate. The extracts, on evaporation, afforded a yellow oil which was chromatographed over a column of silica gel with chloroform-methanol (99:1) as eluent, to give **2** (394.6 mg, 52.8%) as a colorless syrup; ^{1}H nmr [$(CD_3)_2SO$] δ 3.93 (2 H, s, 3-H), 4.21 (2 H, d, J=6.1 Hz, 1-H), 4.55-4.68 (3 H, m, 4'- and 5'-H), 5.24 (1 H, t, J=6.1 Hz, OH), 5.34 (1 H, d, J=4.4 Hz, 1'-H), 6.01 (1 H, t, J=4.4 Hz, 2'-H), 6.11 (1 H, t, J=4.4 Hz, 3'-H), 7.34-8.30 (20 H, m, ArH), 12.41 (1 H, s, NH) [addition of D_2O caused the signals at δ 5.24 and 12.41 to disappear, that at δ 4.21 to sharpen, and that at δ 3.93 decrease in signal intensity]; ^{13}C nmr ($CDCl_3$) δ 64.29, 67.92 (C-5' and -1), 72.49, 77.28, 80.50 (C-1', -2', -3' and -4'), 125.02-133.44 (Ar-C, imidazole C-4 and -5), 146.43 (imidazole C-2), 165.45, 167.26 (C=O), and 208.15 (C-2); ms (fab, nitrobenzyl alcohol as matrix) 661 (MH^+, 7%) (Found: MH^+ 661.2153. $C_{38}H_{33}N_2O_9$ requires 661.2186).

3-[2-Methoxy-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (3). This compound was prepared from **1**, O-methylisourea hydrogen sulfate, and sodium carbonate as described above for **2**: a colorless foam, 26.8%; ^{1}H nmr [$(CD_3)_2SO$] δ 3.77 (3 H, s, OCH_3), 4.14 (2 H, s, 3-H), 4.54-4.64 (5 H, m, 4'-, 5'- and 1-H), 5.15 (1 H, br s, OH), 5.20 (1 H, d, J=4.7 Hz, 1'-H), 5.83 (1 H, t, J=4.7 Hz, 2'-H), 5.96 (1 H, apparent t, J=4.7 Hz, 3'-H), 7.38-8.05 (15 H, m, ArH), 11.23 (1 H, s, NH)[addition of D_2O caused the signals at δ 5.15 and 11.23 to disappear]; ^{13}C nmr ($CDCl_3$) δ 56.34 (OCH_3), 64.41, 67.75 (C-5' and -1), 72.49, 77.34, 79.80 (C-1', -2', -3' and -4'), 128.36-133.27 (Ar-C, imidazole C-4 and -5), 153.86 (imidazole C-2), 165.39, 166.62 (C=O), and 207.80 (C-2); ms (fab, nitrobenzyl alcohol as matrix) 615 (MH^+, 7%) (Found: MH^+ 615.1935. $C_{33}H_{31}N_2O_{10}$ requires 615.1979).

3-[2-Methyl-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (4). This compound was prepared from **1**, acetamidine acetate, and sodium carbonate as described above for **2**: a colorless foam, 10%; ^{1}H nmr ($CDCl_3$) δ 2.02 (3 H, s, CH_3), 3.79 (2 H, s, 3-H), 4.23 (2 H, s, 1-H), 4.67-4.71 (3 H, m, 4'- and 5'-H), 5.34 (1 H, d, J=6.4 Hz, 1'-H), 5.54 (1 H, t, J=6.4 Hz, 2'-H), 5.78 (1 H, t, J=6.4 Hz, 3'-H), 7.37-8.13 (15 H, m, ArH); ^{13}C nmr ($CDCl_3$) δ 13.69 (CH_3), 64.29, 67.75 (C-5' and -1), 72.39, 79.97 (C-1', -2', -3' and -4'), 128.36-133.85 (Ar-C, imidazole C-4 and

-5), 144.74 (imidazole C-2), 165.39, 166.73 (C=O), and 207.92 (C-2); ms (fab, nitrobenzyl alcohol as matrix) 599 (MH^+, 19%) (Found: MH^+ 599.1984. $C_{33}H_{31}N_2O_9$ requires 599.2029).

3-[2-Phenyl-4-(β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (5). To a solution of **2** (61.1 mg, 0.09 mmol) in methanol (1 ml) was added 5% aqueous NaOH (0.5 ml, 0.63 mmol) at 0°C during 30 min, the mixture was rendered neutral with acetic acid and evaporated. The residue was chromatographed over a column of silica gel with chloroform-methanol (9:1) as eluent, to give **5** (11.4 mg, 35.4%) as a colorless foam; ^1H nmr (CD_3OD) δ 3.31 (2 H, s, 3-H), 3.76 (1 H, dd, J=2.9 and 12.1 Hz, 5'-H_a), 3.89 (1 H, dd, J=2.9 and 12.1 Hz, 5'-H_b), 3.98 (1 H, q, J=2.9 and 6.6 Hz, 4'-H), 4.12 (1 H, t, J=6.2 Hz, 2'-H), 4.25 (1 H, dd, J=6.2 and 6.6 Hz, 3'-H), 4.37 (2 H, s, 1-H), 4.81 (1 H, d, J=6.2 Hz, 1'-H), 7.36-7.84 (5 H, m, ArH); ^{13}C nmr (CD_3OD) δ 63.81, 69.26 (C-5' and -1), 72.90, 78.16, 78.96, 87.44 (C-1', -2', -3' and -4'), 127.23-134.32 (Ar-C, imidazole C-4 and -5), 148.44 (imidazole C-2), and 209.65 (C-2); ms (fab, glycerol as matrix) 349 (MH^+, 34%) (Found: MH^+ 349.1398. $C_{17}H_{21}N_2O_6$ requires 349.1400).

3-[2-Phenyl-4-(2,3-O-isopropylidene-β-D-ribofuranosyl)imidazolyl]-2-oxo-1-propanol (6). To a solutuon of **5** (11.4 mg, 0.03 mmol) in acetone (1.5 ml) was added acetone containing PTSA monohydrate (7 mg) and the mixture was allowed to stand at room temperature for 14 h. The reaction mixture was neutralized with saturated sodium hydrogen carbonate solution. Water was added, and the mixture was extracted with chloroform, and dried over magnesium sulfate. The extracts, on evaporation, afforded a yellow oil which was purified by preparative tlc with chloroform-methanol (99:1) as eluent, to give **6** (7.3 mg, 57.5%) as a colorless oil; ^1H nmr ($CDCl_3$) δ 1.35, 1.61 (each 3 H, each s, isopropylidene Me), 3.75 (1 H, dd, J=2.4 and 12.8 Hz, 5'-H_a), 3.79 (2 H, s, 3-H), 3.99 (1 H, dd, J=1.7 and 12.8 Hz, 5'-H_b), 4.34 (2-H, s, 1-H), 4.42 (1 H, apparent q, J=1.7 Hz, 4'-H), 4.85 (1 H, dd, J=3.7 and 6.1 Hz, 2'-H), 5.00 (1 H, d, J=3.7 Hz, 1'-H), 5.04 (1 H, dd, J=1.7 and 6.1 Hz, 3'-H), 7.33-7.76 (5 H, m, ArH); ^{13}C nmr ($CDCl_3$) δ 25.27, 27.44 (CH_3), 63.94, 67.86 (C-5' and -1), 80.21, 82.84, 86.35 (C-1', -2', -3' and -4'), 113.32 (isopropylidene $\underline{C}Me_2$), 122.62-135.96 (Ar-C, imidazole C-4 and -5), 146.78 (imidazole C-2), and 207.28 (C-2).

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REFERENCES

1 Part 14: I. Maeba, K. Osaka, N. Morisita, K. Fujioka, and C. Ito, J. Chem. Soc., Perkin Trans. 1, accepted.

2 L. B. Townsend, Chem. Rev., 1967, 67, 533; A. Yamazaki and M. Okutsu, J. Heterocycl. Chem., 1978, 15, 353.

3 J. A. G. Pérez, P. A. Bravo, F. R. Vicente, J. I. F. García-Hierro, and J. F. Mota, Carbohydr. Res., 1988, 176, 97; J. Igolen, T. Huynh Dinh, A. Kolb, and C. Perreur, Bull. Chem. Therap., 1972, 207; J. Igolen and T. Huynh Dinh, Chem. Commun., 1971, 1267.

4 I. Maeba, T. Takeuchi, T. Iijima, and H. Furukawa, J. Org. Chem., 1988, 53, 1401.

5 I. Maeba, K. Kitaori, Y. Itaya, and C. Ito, J. Chem. Soc., Perkin Trans. 1, 1990, 67.

6 I. Maeba, K. Kitaori, and C. Ito, J. Org. Chem., 1989, 54, 3927.

7 A. Rahman, "Nuclear Magnetic Resonance" Springer-Verlag, New York 1986, p. 135; A. Rahman, S. Malik, H. Cun-heng, and J. Clardy, Tetrahedron Lett., 1985, 26, 2759.

8 J. -L Imbach and B. L. Kam, J. Carbohydr. Nucleosides, Nucleotides, 1974, 1, 271.

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