Expeditious Syntheses of Imidazole *C*-Nucleosides (= *C*-Glycosylimidazoles) from Carbohydrates and Formamidine Acetate

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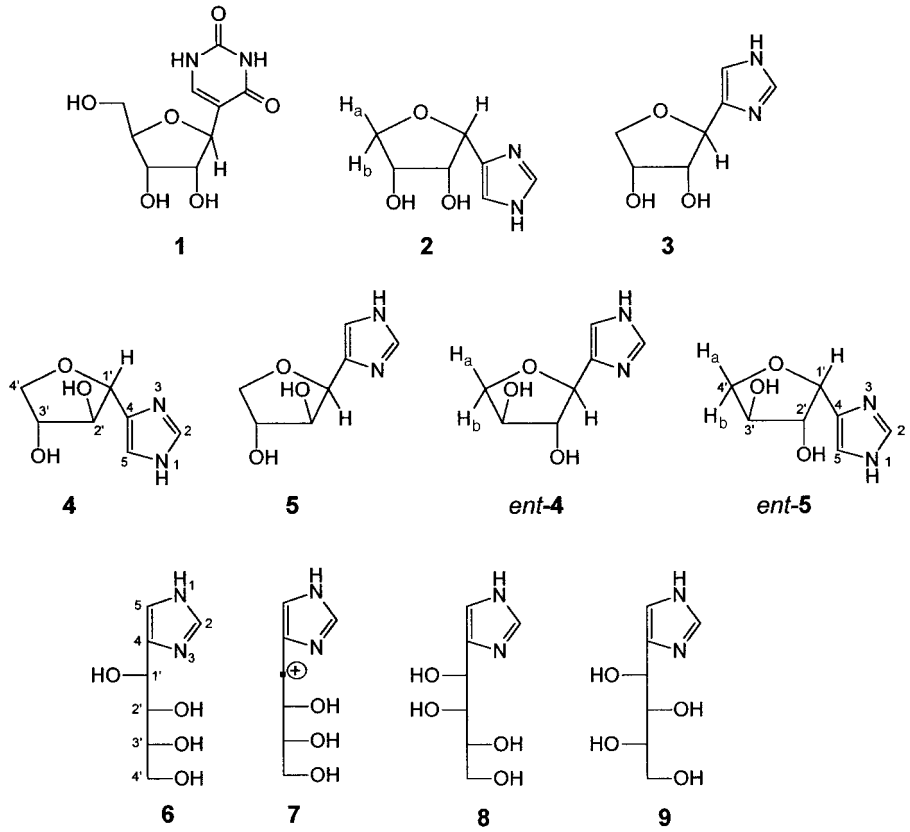
Pyrolysis of the neat hydrochloride salts of imidazolyl-tetritols **6**, **8**, and **9** led to the 4-glycofuranosyl-1*H*-imidazole anomer mixtures **2**/**3**, **4**/**5**, and *ent*-**4**/*ent*-**5**, respectively. The same pairs of *C*-nucleosides were also obtained in one-pot procedures by microwave irradiation of mixtures containing formamidine acetate (= formimidamide acetic acid salt), a few drops of H_2O, and the appropriate hexose or hexulose, *i.e.*, D-fructose (or D-glucose), D-galactose, and L-sorbose, respectively. Microwave irradiation clearly brought about sequential double condensation of formamidine with hexoses or hexuloses and acid-catalyzed intramolecular cyclization of the intermediate linear imidazolyl-tetritols.

Introduction. – Imidazoles are biologically important heterocyclic compounds. In particular, it has been demonstrated that naturally occurring imidazole *N*-nucleosides play a central role in purine biosynthesis [1][2]. From these latter observations, some scientists surmised that there should also be some potential utility for nucleoside antimetabolites based on a C–C linkage to the sugar moiety (*i.e.*, for *C*-nucleosides). Indeed, and not surprisingly ever since the discovery of pseudouridine (**1**), quite a few natural *C*-nucleosides could be isolated, some of which showed anticancer and antiviral activities [3].

Deredas and *Frankowski* described the synthesis of the two *erythro*-configured *C*-nucleosides **2** and **3** which were obtained as a mixture by heating the glycosyl-imidazole derivative **6** in acetic acid [4]. The formation of both *C*-nucleosides **2** and **3** is best explained by assuming protonation of the 'benzylic' OH–C(1′) of **6**, followed by formation of the corresponding secondary planar carbenium ion **7**, which is neutralized at once by the terminal primary-alcohol function *via* a non-stereoselective intramolecular ring closure.

In two previous reports, we described the synthesis of some linear imidazolyl-sugar derivatives – in particular of imidazolyl-alditols **6**, **8**, and **9** – by condensation of the corresponding hexoses with formamidine (= formimidamide) under ammonia atmosphere in a pressure vessel [5][6]. This procedure, albeit effective, is somewhat cumbersome since it requires the handling of liquid ammonia in an autoclave. We surmised that microwave activation could be as effective a method and would trigger the double condensation of formamidine with any carbohydrate at normal pressure [7]. We describe herein an expeditious one-pot synthesis of the *erythro*- and *threo*-configured *C*-nucleoside anomer pairs **2**/**3**, **4**/**5**, and *ent*-**4**/*ent*-**5** using microwave activation.



Results and Discussion. – *Pyrolysis of Some Imidazolyl-tetritol Hydrochloride Salts.* Heating the neat hydrochloride salt of 1-*C*-(1*H*-imidazol-4-yl)-D-*arabino*-tetritol (**6**) to 185–190° for a few minutes led to a mixture of the anomeric *C*-nucleosides **2** and **3**, both as hydrochlorides. Likewise, the hydrochloride salts of imidazolyl-D-*lyxo*-tetritol **8** and of imidazolyl-L-*xylo*-tetritol **9**, under the same experimental conditions, led to the hydrochloride salts of *C*-nucleosides **4**/**5** and *ent*-**4**/*ent*-**5**, respectively. The anomeric mixtures were percolated over an *Amberlite-CG-6000* (H^+) resin and then separated by column chromatography into the corresponding α- and β-D-anomers. The overall yield of *C*-nucleoside formation was between 53 and 70%, the ratio between α- and β-D-anomers being variable. These experiments represent an alternative to the procedure of *Deredas* and *Frankowski* in which imidazolyl-tetritol **6** was refluxed in glacial acetic acid to give the two anomeric *C*-nucleosides **2** and **3**, which were isolated as acetates (86% overall yield) [4].

Microwave-Induced Reaction of Hexoses and Hexuloses with Formamidine Acetate (= Formimidamide Acetic Acid Salt). – A mixture of a given hexose or hexulose, two equivalents of formamidine acetate, and a few drops of H_2O led to a dough which was submitted to microwave irradiation for 1.7–3 min. Irradiation for longer periods of time led to caramelization. The resulting brown reaction mixture was percolated over

an *Amberlite-CG-6000* (H^+) column and then purified and separated by two consecutive column chromatographies into the corresponding pair of anomeric *C*-nucleosides (see *Exper. Part*). With this expeditious procedure both D-fructose and D-glucose led to the same pair of the anomeric *erythro*-configured *C*-nucleosides **2** and **3**, D-galactose to the pair of the anomeric *threo*-configured *C*-nucleosides **4** and **5**, and L-sorbose to the pair of the anomeric *threo*-configured *C*-nucleosides *ent*-**4** and *ent*-**5**, the overall yield of *C*-nucleoside formation being modest (19–28%).

The microwave-induced twofold condensation of formamidine with the above cited four hexoses and hexuloses occurred as we had anticipated: after elimination of two molecules of H_2O, the resulting imidazolyl-tetritols obviously were formed as acetate salts. The imidazolyl-tetritols, occurring in their protonated form, underwent at once a microwave-induced (*i.e.*, a pyrolytic) intramolecular cyclization, identical to the cyclizations described above. The absence of any intramolecular pyrolytic reaction with non-protonated compound **6** could have been anticipated, since cyclization was supposed to occur only if the 'benzylic' cation **7** was formed after protonation of the secondary-alcohol function OH–C(1′), followed by expulsion of a H_2O molecule.

Structural Analyses. – Structure and configuration of all glycosyl-imidazoles could be ascertained unambiguously by ^{1}H- and by ^{13}C-NMR spectra (see *Tables 1* and *2*, resp.). The NMR patterns of the *C*-nucleosides **4** and *ent*-**4** were superimposable, as were those of **5** and *ent*-**5**. *Deredas* and *Frankowski* established the structure and configuration of **2** by an independent synthesis [4]. We ascertained the configuration of **2** by measuring nuclear *Overhauser* effects, and that of *ent*-**5** by long-range H,H-coupling-constant values.

Table 1. *^{1}H-NMR Spectra* (400 MHz, 300 K, CD_3OD) *of* **2**, **3**, ent-**4** *and* ent-**5**. δ in ppm, *J* in Hz.

	δ(H)	H–C	H–C	H_a–C	H_b–C	H–C	H–C	*J*	*J*	*J*	*J*	*J*	*J*
	H–C(1′)	(2′)	(3′)	(4′)	(4′)	(2)	(5)	(1′,2′)	(2′,3′)	(3′,4′a)	(3′,4′b)	(4′a,4′b)	(2,5)
2[a])	4.93	4.21	4.41	3.98	3.81	7.64	7.06	4.7	4.7	6.4	5.5	8.8	0.9
3[a])	4.71	4.23	4.27	4.22	3.79	7.68	7.09	7.2	4.8	4.8	2.7	9.5	1.1
ent-**4**[b])	5.18	4.25	4.45	3.83	4.32	7.77	7.17	3.3	1.4	1.4	4.4	10.1	> 0
ent-**5**[c])	4.70	4.19	4.15	3.91	4.07	7.66	7.07	3.6	2.2	2.2	4.5	9.5	1.1

[a]) The spectra of **2** and **3** are identical to those given by *Deredas* and *Frankowski* [4], except for δ of H–C(2′) of **2** which is reported to be at 4.74 ppm. [b]) In D_2O. [c]) $J(1',4') = 0.6$ and $J(2',4'a) = 0.7$.

Table 2. *^{13}C-NMR Spectra* (62.9 Hz, 300 K, CD_3OD) *of* **2**, **3**, ent-**4**, *and* ent-**5**

	C(1′)	C(2′)	C(3′)	C(4′)	C(2)	C(4)	C(5)
2	77.7	73.7	73.2	72.9	136.4	134.9	121.0
3	78.4	77.2	72.4	74.0	137.1	137.9	118.8
ent-**4**	77.9	79.2	78.4	74.5	136.3	134.3	120.5
ent-**5**	82.2	83.0	79.0	75.0	136.8	138.0	118.5

Irradiation of H–C(1′) of **2** led to NOEs at the resonances of H–C(2′) (10.9%), H–C(3′) (4.4%), and H_a–C(4′) (small but noticeable enhancement), and irradiation of H–C(3′) to NOEs at the resonances of H–C(2′) (5.6%), H–C(1′) (4.6%), and H_a–C(4′) (5.0%). The configuration of *ent*-**5** was established particularly by the occurrence of the W-type long-range coupling constants $^4J(1',4'a) = 0.6$ Hz and $^4J(2',4'a) = 0.7$ Hz.

Experimental Part

1. *General*. The H^+ exchange resin *Amberlite-CG-6000* was from *Rohm & Haas*. The microwave irradiation experiments were performed with a domestic multimode microwave oven *Whirlpool MO 100*. Flash chromatography (FC): silica gel *Merck 60* or *Fluka* (40–63 μm). Medium-pressure chromatography: silica gel *Merck LiChroprep Si 60* (15–25 μm). TLC: Al-roll silica gel *Merck 60*, HF_{254}. Optical rotations: *Schmidt-Haensch-Polartronic-Universal* polarimeter. IR Spectra (cm^{-1}): *Nicolet 205-FT*. ^1H- and ^{13}C-NMR Spectra: *Bruker-DSX-400* and *-AC-250* spectrometers; at 300 K; internal references for ^1H, CD_3OD (3.30 ppm) and sodium 3-(trimethylsilyl)(D_4)propanoate ((D_4)TSP; 0.00 ppm) in D_2O; internal reference for ^{13}C, CD_3OD (49.02 ppm); δ in ppm and J in Hz. MS and HR-MS (*m/z* (%)): *Varian-MAT-311* spectrometer, electron ionization; the spectra were recorded at the 'Centre Régional de Mesures Physiques de l'Ouest' at the University of Rennes. Microanalyses were carried out by the 'Service Central de Microanalyses' of the CNRS, F-69390 Vernaison.

2. *General Procedure 1* (*GP 1*): *Pyrolysis of Imidazolyl-tetritols*. The imidazolyl-tetritol **6**, **8**, or **9** (5 mmol) was dissolved in MeOH (*ca.* 40 ml) and 2N HCl (*ca.* 7 ml). The soln. was evaporated and the resulting hydrochloride salt pyrolyzed at 180–185° for 5–10 min. The residue was dissolved in H_2O and percolated over an *Amberlite-CG-6000* (H^+) column, first with H_2O, then with 5–15% aq. NH_3 soln. After evaporation, the mixture was purified by FC, which led to the separation of the corresponding pair of anomers.

3. *General Procedure 2* (*GP 2*): *Microwave-Induced Synthesis of* C*-Nucleosides from Hexoses or Hexuloses and Formamidine Acetate*. The mixture of a hexose or hexulose (10 mmol), formamidine acetate (2 equiv.), and drops of H_2O was kneaded to get a homogenous dough which was irradiated in a microwave oven at 350 W for 1.7–3 min. The brown mixture was taken up in H_2O and the soln. percolated over *Amberlite-CG-6000* (H^+) with H_2O and then with dil. aq. NH_3 soln., as described above (*GP 1*). After evaporation, the mixture was purified by column chromatography which led to the separation of the pairs of anomers.

4. *4,5-(α-*D*-Erythrofuranosyl)- and 4-(β-*D*-Erythrofuranosyl)-1*H*-imidazole* (= *1,4-Anhydro-1-*C*-(1*H*-imidazol-4-yl)-α-*D*- and -β-*D*-erythritol*, **2** and **3**, resp.). According to *GP 1*, the hydrochloride of imidazolyl-tetritol **6** (1.00 g, 4.45 mmol; neat) was heated for 10 min. FC ($CHCl_3$/MeOH/NH_4OH soln. 8 : 2 : 0.2) gave **2** (159 mg) and **3** (368 mg). Overall yield 70%.

According to *GP 2*, a mixture of D-fructose (2.00 g, 11.1 mmol) and formamidine acetate (2.31 g, 22.2 mmol), without addition of H_2O, was irradiated for 3 min. FC ($CHCl_3$/MeOH/NH_4OH soln. 8 : 2 : 0.25 → 7.5 : 2.5 : 0.25) gave **2** (115 mg) and **3**/**2** 77 : 23 (402 mg). Overall yield of **2** and **3** 27%.

According to *GP 2*, a mixture of D-glucose monohydrate (2.20 g, 11.1 mmol) and formamidine acetate (2.31 g, 22.2 mmol) was irradiated for 3 min. FC ($CHCl_3$/MeOH/NH_4OH soln. 8 : 2 : 0.25 → 7 : 3 : 0.5) gave **2** (132 mg) and **3**/**2** 86 : 14 (270 mg). Overall yield of **2** and **3** 21%. Anal. pure samples of **2** and **3** were obtained by medium-pressure chromatography (PrOH/H_2O/pyridine 90 : 10 : 0.2).

Data of **2**: Resin. $[\alpha]_D$ identical with the one reported [4]. ^1H- and ^{13}C-NMR: see *Tables 1* and *2* and [4].

Data of **3**: Resin. $[\alpha]_D = -84$ ($c = 1$, MeOH); [4]: $[\alpha]_D = -56.5$ ($c = 1.33$, MeOH). ^1H- and ^{13}C-NMR: see *Tables 1* and *2* and [4].

5. *4-(α-*D*-Threofuranosyl)- and 4-(β-*D*-Threofuranosyl)-1*H*-imidazole* (= *1,4-Anhydro-1-*C*-(1*H*-imidazol-4-yl)-α-*D*- and -β-*D*-threitol*; **4** and **5**, resp.). According to *GP 1*, the hydrochloride salt of **8** (2.22 g; 9.88 mmol) was pyrolyzed for 5 min at 180°. FC (PrOH/H_2O/pyridine 90 : 10 : 0.2) gave pure **5** (233 mg) followed by **4**/**5** 69 : 31 (660 mg). Overall yield of **4** and **5** 53%.

According to *GP 2*, a mixture of D-galactose (2.0 g, 11.1 mmol) and formamidine acetate (2.31 g, 22.2 mmol) was irradiated for 3 min. FC ($CHCl_3$/MeOH/NH_4OH soln. 8 : 2 : 0.5 → 7 : 3 : 0.5) gave **4**/**5** 12 : 88 (151 mg), followed by **4**/**5** 72:28 (210 mg). Overall yield of **4** and **5** 19%. Anal. pure samples of **4** and **5** were obtained by medium-pressure chromatography (PrOH/H_2O/pyridine 90 : 10 : 0.2).

Data of **4**: Yellowish resin. $[\alpha]_D = +32$ ($c = 1$, MeOH). IR, ^1H- and ^{13}C-NMR: identical with those of *ent*-**4**, see *Tables 1* and *2*.

Data of **5**: Colorless crystals (H_2O/PrOH). M.p. 157°. $[\alpha]_D = +65$ ($c = 1$, MeOH). IR, ^1H- and ^{13}C-NMR: identical with those of *ent*-**5**, see *Tables 1* and *2*. Anal. calc. for $C_7H_{10}N_2O_3$ (170.17): C 49.40, H 5.92, N 16.46; found: C 49.3, H 5.9, N 16.5.

6. *4-(α-*L*-Threofuranosyl)- and 4-(β-*L*-Threofuranosyl)-1*H*-imidazole* (= *1,4-Anhydro-1-*C*-(1*H*-imidazol-4-yl)-α-*L*- and -β-*L*-threitol*; *ent*-**4** and *ent*-**5**, resp.). According to *GP 1*, the hydrochloride salt of **9** (1.176 g, 5.23 mmol) was pyrolyzed for 8 min at 185°. FC (PrOH/H_2O/pyridine 9 : 1 : 0.05) gave *ent*-**5** with some *ent*-**4**, followed by *ent*-**4** with some *ent*-**5** (513 mg). Overall yield of *ent*-**4** and *ent*-**5** 58%.

According to *GP 2*, a mixture of L-sorbose (2.00 g, 11.1 mmol) and formamidine acetate (2.31 g, 22.2 mmol) was irradiated for 1.7 min. FC ($CHCl_3$/MeOH/NH_4OH soln. 8 : 2 : 0.25 → 7 : 3 : 0.25) gave *ent*-**4**/*ent*-**5**

7:93 (128 mg), followed by *ent*-**4**/*ent*-**5** 82:18 (374 mg). Overall yield of *ent*-**4** and *ent*-**5** 28%. Anal. pure samples of *ent*-**4** and *ent*-**5** were obtained by medium-pressure chromatography ($PrOH/H_2O$/pyridine 90:10:0.2).

Data of ent-**4**: Yellowish resin. $[\alpha]_D = -34$ ($c = 1$, MeOH). IR (KBr): 3400–3250, 2950, 2900, 1632, 1589, 1460–1444, 1348, 1308, 1213, 1086, 1059, 1034, 1006. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*. MS: 170 (5, M^+), 111 (7), 97 (100). HR-MS: 170.0687 (M^+, $C_7H_{10}N_2O_3^+$; calc. 170.06914).

Data of ent-**5**: Colorless crystals (MeOH/PrOH). M.p. 154–155°. $[\alpha]_D = -64$ ($c = 1$, MeOH). IR (KBr): 3350, 3250, 2925, 2875, 2700, 2350, 2325, 1583, 1500, 1453, 1360, 1330, 1284, 1203, 1159, 1087, 1070, 1035. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*. MS: 170 (5, M^+), 111 (46), 97 (100). HR-MS: 170.0687 (M^+, $C_7H_{10}N_2O_3^+$; calc.170.06914). Anal. calc. for $C_7H_{10}N_2O_3$ (170.17): C 49.40, H 5.92, N 16.46; found: C 49.3, H 5.8, N 16.3.

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