Synthesis of New 3′-Deoxyribonucleosides Employing the Acid-Catalyzed Fusion Method

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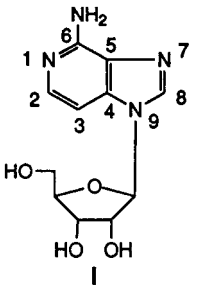
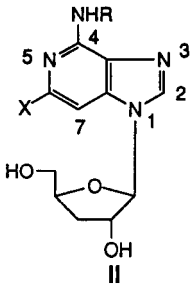
Coupling of 4,6-dichloro-1*H*-imidazo[4,5-*c*]pyridine (2,6-dichloro-3-deaza-9*H*-purine) (**1**) with 1,2-*O*-diacetyl-5-*O*-benzoyl-3-deoxy-β-D-ribofuranose (**2**), employing the acid-catalyzed fusion method, is reported (*Scheme 1*). The condensation reaction was regioselective and gave the three N^1-glycosylation products **3**–**5**, whereas no N^3-nucleosides were detected. Treatment of **3**–**5** with methanolic ammonia afforded the corresponding deprotected nucleosides **6**–**8**. Compounds **6** and **7** were assigned the structure of the β-D- and α-D-anomeric N^1-(3′-deoxyribo)nucleosides, respectively. The third derivative **8** proved to be the α-D-anomer of a 3′-deoxyarabinonucleoside deriving from epimerization at C(2) of the sugar. The 2-chloro- and N^6-substituted derivatives **9**, **11**, and **13** of 3′-deoxy-3-deazaadenosine (**10**) and of its α-D-anomer **12** can be obtained from these versatile synthons (*Schemes 2* and *3*).

Introduction. – 3-Deazaadenosine (c^3A, **I**) is an adenosine analogue endowed with a number of biological effects, probably mediated *via* interaction with multiple cellular targets. In the past, it has been shown that this nucleoside weakly interacts with A_1 adenosine receptors [1] and adenosine deaminase [2]. On the other hand, it is well-known that c^3A (**I**) is both an inhibitor and a substrate for *S*-adenosylhomocysteine hydrolase (AdoHcyase) [3], the enzyme which catalyzes the reversible hydrolysis of AdoHcy to L-homocysteine and adenosine. According to the fact that AdoHcyase is the key enzyme in methylation reactions depending on *S*-adenosylmethionine as the methyl donor, including those which are required for the maturation of viral mRNA [4], **I** has been reported to inhibit the replication of human immunodeficiency virus type 1 (HIV-1) [5]. In recent years, it was shown that exposure to **I** is a stimulus that initiates apoptotic cell death in human leukemia HL-60 cells [6]. Furthermore, c^3A analogues were reported to induce apoptosis in L1210 leukemia cells [7]. On the other hand, we have found that c^3A was inactive in inducing apoptosis in human peripheral blood mononuclear cells (PBMC), whilst its 2-chloro-2′-deoxy derivative triggered apoptosis in the same cell line [8].



I
purine numbering

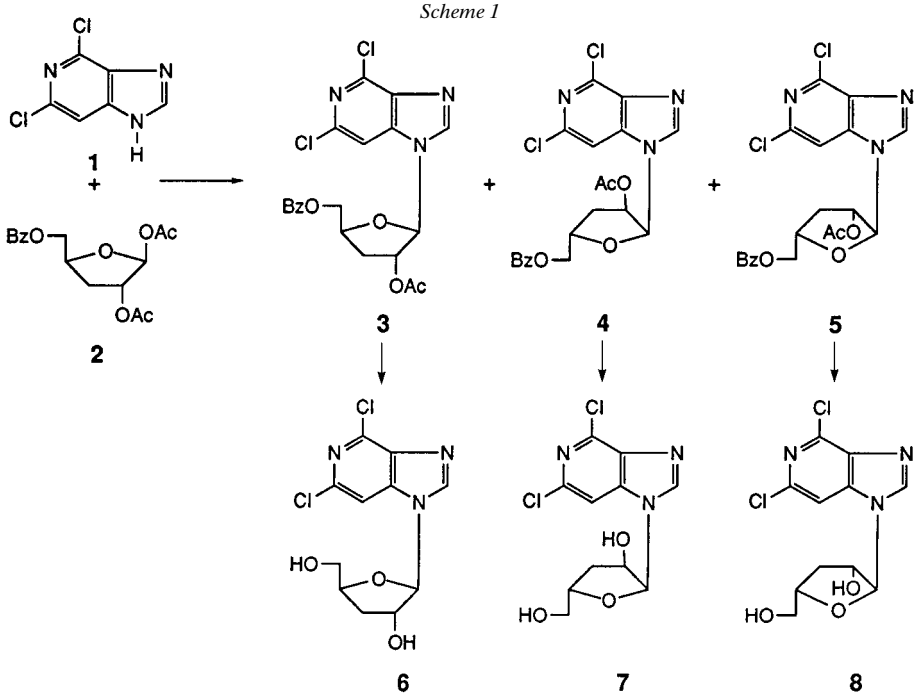


II
systematic numbering

These findings prompted us to select 3-deazapurine derivatives in an effort to synthesize deazanucleosides endowed with pharmacological activity. In particular, on the basis that 3′-deoxyribonucleosides exhibit a number of biological activites, *e.g.*, antifungal, antibacterial, antiparasitic, and anticancer activity [9], and a high affinity for adenotin [10][11], we coupled 2,6-dichloro-3-deazapurine (**1**) with the 3-deoxyribose derivative **2** to obtain compounds of the general formula **II**.

Results. – The 4,6-dichloro-1*H*-imidazo[4,5-*c*]pyridine (**1**) [12] was treated with 1,2-di-*O*-diacetyl-5-*O*-benzoyl-3-deoxy-β-D-ribofuranose (**2**) [13] in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH) at 160° *in vacuo* for 10 min (*Scheme 1*). The coupling gave a mixture of β-D- and α-D-anomeric N^1-(3′-deoxyribo)-nucleosides **3** and **4**, respectively, and a third isomer identified as the α-D-anomer **5** of N^1-(3′-deoxyarabino)nucleoside deriving from epimerization at C(2) of the sugar. A similar epimerization has been reported to occur under fusion reaction conditions in the case of ribose derivatives [14]. The total yield of nucleosides was 90%.

Scheme 1



The glycosylation site and the anomeric configuration were assigned on the basis of UV data and ^{1}H-NMR spectra, including 1D ^{1}H-NOE difference spectra, of the deprotected nucleosides **6**–**8**, obtained by reacting **3**–**5** with methanolic ammonia (*Scheme 1*).

The UV spectra of the three nucleosides **6**–**8** are essentially identical (see *Exper. Part*). Furthermore, a NOE at H–C(2) and H–C(7) upon saturation of H–C(1′) establishes N(1) as glycosylation site in all three cases [15] (see *Table*). Saturation of H–C(1′) of compound **6** results in a NOE at the H–C(4′) (and H–C(2′))

signal (6.0%), establishing the β-D-configuration. On the other hand, saturation of H–C(1′) of compound **7** gives rise to a NOE at the H_a–C(3′) signal (1.0%), while there is none at H–C(4′), establishing the α-D-configuration. Similarly, irradiation of H–C(1′) of **8** gives a NOE of 0.9% at the H_a–C(3′) signal and none at H–C(4′), establishing the α-D-configuration. Saturation of both H–C(2′) and H–C(4′) of **8** produces a NOE at the H_b–C(3′) signal (3.1 and 2.9%, resp.), demonstrating that the sugar moiety is a deoxyarabinose derivative.

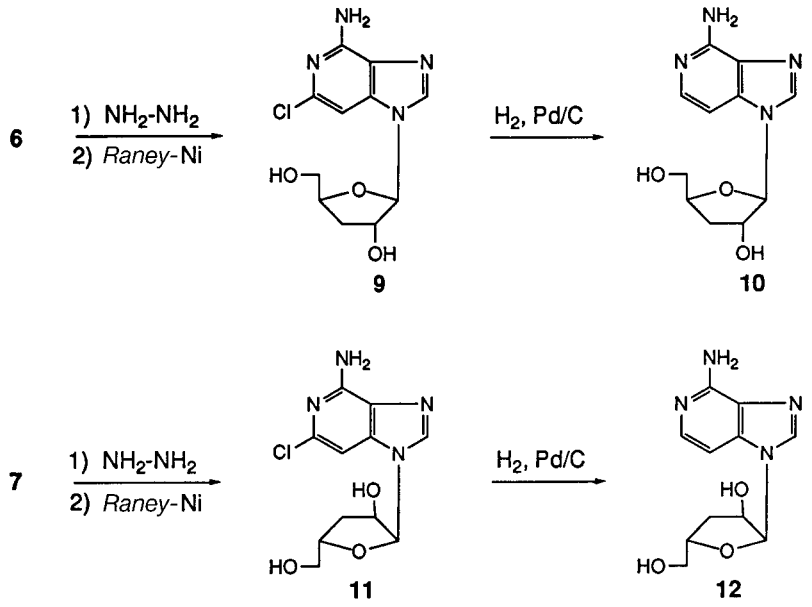
Table. *NOE Data* [%] *of Imidazo[4,5-c]pyridine Nucleosides in (D_6)DMSO at 23°*

	Irradiated proton	Observed NOE [%]
6	H–C(1′)	H–C(2) (9.2), H–C(7) (17.8), H–C(4′) (and H–C(2′)) (6.0)
7	H–C(1′)	H–C(2) (4.2), H–C(7) (6.7), H–C(2′) (6.8), H_a–C(3′) (1.0)
8	H–C(1′)	H–C(2) (4.2), H–C(7) (6.5), H–C(2′) (2.0), H_a–C(3′) (0.9)
	H–C(4′)	H–C(2) (1.7), H–C(7) (1.4), H_b–C(3′) (2.9)
	H–C(2′)	H–C(2) (3.0), H–C(7) (3.0), H–C(1′) (2.1), H_b–C(3′) (3.1)

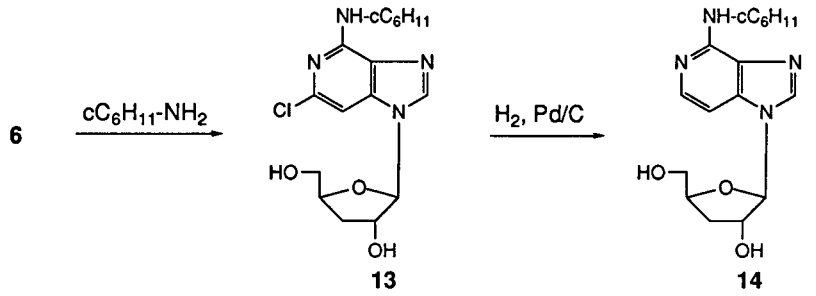
Treatment of **6** or **7** with hydrazine hydrate gave the corresponding crude hydrazino intermediates which were refluxed in the presence of *Raney*-Ni catalyst to afford the 4-amino-6-chloro-1-(3-deoxy-β-D- and -α-D-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridines (**9** and **11**, resp.), respectively (*Scheme 2*). Catalytic hydrogenolysis of the Cl-atom in **9** or **11** with 10% Pd/C in abs. EtOH and in the presence of 1N NaOH afforded the target compound **10** and its anomer **12**, respectively. The structure of **10** was confirmed by comparing its ^{1}H-NMR and UV spectra with those of the same compound synthesized by *Matsuda et al.*, starting from 3′-deoxyinosine [16].

Compound **6** was also treated with cyclohexylamine, at 105° for 16 h, and the obtained 6-chloro-4-(cyclohexylamino)-1-(3-deoxy-β-D-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine (**13**) was dechlorinated using the above mentioned conditions to give **14** (*Scheme 3*).

Scheme 2



Scheme 3



Experimental Part

1. *General*. M.p.: *Büchi* apparatus, uncorrected. UV Spectra: *Perkin-Elmer-Coleman-575* spectrophotometer. ^{1}H-NMR Spectra: *Varian-VXR-300* spectrometer; δ in ppm, J in Hz. TLC: TLC plates precoated with silica gel *60 F-254* (*Merck*). Flash chromatography (FC): silica gel *60* (*Merck*). Elemental analyses: *Carlo-Erba-1106* analyser, exper. values within $\pm 0.4\%$ of calc. values.

2. *Glycosylation of* **1** *with* **2**. An intimate mixture of 4,6-dichloro-1*H*-imidazo[4,5-*c*]pyridine (**1**) [12] (250 mg, 1.33 mmol), 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-ribofuranose (**2**) [13] (857 mg, 2.66 mmol) and TsOH (cat. amount) was heated at 160°. When the fusion started, *vacuum* from a water aspirator (25 Torr) was applied until bubbling ceased (5–10 min). The resulting solid was submitted to FC (silica gel, cyclohexane/AcOEt 7:3): mixture **3**–**5** (540 mg, 90%). Anal. samples of **3**, **4**, and **5** were obtained by prep. TLC ($CHCl_3$/MeOH 98:2).

*1-(2-*O*-Acetyl-5-*O*-benzoyl-3-deoxy-β-*D*-ribofuranosyl)-4,6-dichloro-1*H*-imidazo[4,5-*c*]pyridine* (**3**): Yield 52%. R_f 0.62. UV (EtOH): 259 (8600), 273 (7500). ^{1}H-NMR ((D$_6$)DMSO): 1.98–2.10 (*m*, 1 H–C(3′)); 2.15 (*s*, MeCO); 2.24–2.38 (*m*, 1 H–C(3′)); 4.45–4.80 (*m*, 2 H–C(5′), H–C(4′)); 5.59 (*d*, J = 6.1, H–C(2′)); 6.36 (*s*, H–C(1′)); 7.48–7.56 (*m*, 2 arom. H); 7.65–7.74 (*m*, 1 arom. H); 7.86–7.94 (*m*, 2 arom. H); 7.95 (*s*, H–C(7)); 8.72 (*s*, H–C(2)). Anal. calc. for $C_{20}H_{17}Cl_2N_3O_5$ (450.28): C 53.35, H 3.81, N 9.33; found: C 53.55, H 4.03, N 9.07.

*1-(2-*O*-Acetyl-5-*O*-benzoyl-3-deoxy-α-*D*-ribofuranosyl)-4,6-dichloro-1*H*-imidazo[4,5-*c*]pyridine* (**4**): Yield 24%. R_f 0.52. UV (EtOH): 259 (8500), 273 (7400). ^{1}H-NMR ((D$_6$)DMSO): 1.72 (*s*, MeCO); 2.42–2.58 (*m*, 2 H–C(3′)); 4.38–4.62 (*m*, 2 H–C(5′)); 5.01–5.15 (*m*, H–C(4′)); 5.59–5.70 (*m*, H–C(2′)); 6.67 (*d*, J = 4.0, H–C(1′)); 7.59–7.78 (*m*, 3 arom. H); 7.94 (*s*, H–C(7)); 8.03–8.10 (*m*, 2 arom. H); 8.71 (*s*, H–C(2)). Anal. calc. for $C_{20}H_{17}Cl_2N_3O_5$ (450.28): C 53.35, H 3.81, N 9.33; found: C 53.47, N 3.93, N 9.15.

*1-(2-*O*-Acetyl-5-*O*-benzyl-3-deoxy-α-*D*-arabinofuranosyl)-4,6-dichloro-1*H*-imidazo[4,5-*c*]pyridine* (**5**): Yield 14%. R_f 0.57. UV (EtOH): 259 (8600), 273 (7500). ^{1}H-NMR ((D$_6$)DMSO): 2.04 (*s*, MeCO); 2.05–2.14 (*m*, 2 H–C(3′)); 4.21–4.35 (*m*, 2 H–C(5′)); 4.91–4.93 (*m*, H–C(4′)); 5.18–5.20 (*m*, H–C(2′)); 6.71 (*s*, H–C(1′)); 7.61–7.78 (*m*, 3 arom. H); 7.94 (*s*, H–C(7)); 8.03–8.10 (*m*, 2 arom. H); 8.71 (*s*, H–C(2)). Anal. calc. for $C_{20}H_{17}Cl_2N_3O_5$ (450.28): C 53.35, H 3.81, N 9.33; found: C 53.45, H 3.90, N 9.17.

3. *4,6-Dichloro-1-(3-deoxy-β-*D*-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine* (**6**), *4,6-Dichloro-1-(3-deoxy-α-*D*-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine* (**7**), *and 4,6-Dichloro-1-(3-deoxy-α-*D*-arabinofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine* (**8**). To the mixture **3**–**5** (540 mg, 1.2 mmol), MeOH saturated at 0° with ammonia (40 ml) was added, and the mixture was allowed to stand at r.t. for 24 h. After evaporation, the residue was separated by FC ($CHCl_3$/MeOH 96:4): **6** (187 mg, 51%), **7** (82 mg, 23%), and **8** (45 mg, 13%) as amorphous solids.

Data of **6**: R_f 0.18. UV (EtOH): 259 (13400). ^{1}H-NMR ((D$_6$)DMSO): 1.81–1.97 (*m*, 1 H–C(3′)); 2.01–2.19 (*m*, 1 H–C(3′)); 3.50–3.65 (*m*, 1 H–C(5′)); 3.72–3.88 (*m*, 1 H–C(5′)); 4.36–4.52 (*m*, H–C(2′), H–C(4′)); 5.96 (*s*, H–C(1′)); 8.07 (*s*, H–C(7)); 8.84 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{11}Cl_2N_3O_3$ (304.13): C 43.44, H 3.65, N 13.82; found: C 43.58, H 3.77, N 13.65.

Data of **7**: R_f 0.10. UV (EtOH): 259 (13100). ^{1}H-NMR ((D$_6$)DMSO): 1.94–2.23 (*m*, 2 H–C(3′)); 3.38–3.65 (*m*, 2 H–C(5′)); 4.48–4.59 (*m*, H–C(2′)); 4.60–4.70 (*m*, H–C(4′)); 6.29 (*d*, J = 4.1, H–C(1′)); 7.89 (*s*, H–C(7)); 8.56 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{11}Cl_2N_3O_3$ (304.13): C 43.44, H 3.65, N 13.82; found: C 43.57, H 3.72, H 13.60.

Data of **8**: R_f 0.23. UV (EtOH): 259 (13600). ^{1}H-NMR ((D$_6$)DMSO): 1.79–1.86 (*m*, 1 H–C(3′)); 2.25–2.42 (*m*, 1 H–C(3′)); 3.45–3.60 (*m*, 2 H–C(5′)); 4.47–4.58 (*m*, H–C(4′)); 4.58–4.70 (*m*, H–C(2′)); 5.96 (*d*, *J* = 3.9, H–C(1′)); 7.96 (*s*, H–C(7)); 8.70 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{11}Cl_2N_3O_3$ (304.13): C 43.44, H 3.65, N 13.82; found: C 43.60, H 3.73, N 13.63.

4. *4-Amino-6-chloro-1-(3-deoxy-β-*D*-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine* (**9**) *and 4-Amino-6-chloro-1-(3-deoxy-α-*D*-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine* (**11**). Compound **6** or **7** (82 mg, 0.27 mmol) was stirred at r.t. for 5 h in the presence of hydrazine hydrate (5 ml). After evaporation, the hydrazino intermediate, *Raney*-Ni catalyst (200 mg), and O_2-free H_2O (10 ml) were refluxed for 1 h. The mixture was filtered, the filtrate evaporated, and the residue crystallized from MeCN: **9** (31 mg, 41%) or **11** (35 mg, 46%), resp., as chromatographically pure solids.

Data of **9**: M.p. 122–125°. UV (EtOH): 272 (13800). ^{1}H-NMR ((D$_6$)DMSO): 1.79–1.98 (*m*, 1 H–C(3′)); 2.07–2.25 (*m*, 1 H–C3′)); 3.49–3.63 (*m*, 1 H–C(5′)); 3.67–3.82 (*m*, 1 H–C(5′)); 4.30–4.48 (*m*, H–C(2′), H–C(4′)); 5.74 (*s*, H–C(1′)); 6.72 (*s*, NH$_2$); 6.99 (*s*, H–C(7)); 8.37 (*s*, H–C(2)). ^{13}C-NMR ((D$_6$)DMSO): 32.91 (C(3′)); 61.75 (C(5′)); 74.67 (C(2′)); 80.62 (C(4′)); 91.88 (C(1′)); 95.26 (C(7)); 125.60 (C(3a)); 138.86 (C(7a)); 139.96 (C(2)); 141.03 (C(6)); 151.27 (C(4)). Anal. calc. for $C_{11}H_{13}ClN_4O_3$ (284.70): C 46.41, H 4.60, N 19.68; found: C 46.61, H 4.73, N 19.48.

Data of **11**: M.p. 142–144°. UV (EtOH): 272 (13600). ^{1}H-NMR ((D$_6$)DMSO): 1.94–2.20 (*m*, 2 H–C(3′)); 3.38–3.61 (*m*, 2 H–C(5′)); 4.41–4.59 (*m*, H–C(2′), H–C(4′)); 6.08 (*d*, *J* = 4.0, H–C(1′)); 6.65 (*s*, NH$_2$); 6.87 (*s*, H–C(7)); 8.11 (*s*, H–C(2)). ^{13}C-NMR ((D$_6$)DMSO): 34.53 (C(3′)); 63.22 (C(5′)); 70.53 (C(2′)); 79.02 (C(4′)); 87.45 (C(1′)); 95.82 (C(7)); 125.07 (C(3a)); 139.78 (C(7a)); 140.67 (C(6)); 141.26 (C(2)); 151.09 (C(4)). Anal. calc. for $C_{11}H_{13}ClN_4O_3$ (284.70): C 46.41, H 4.60, N 19.68; found: C 46.65, H 4.70, N 19.51.

5. *4-Amino-1-(3-deoxy-β-*D*-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine* (**10**) *and 4-Amino-1-(3-deoxy-α-*D*-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine* (**12**). To **9** or **11** (30 mg, 0.1 mmol) in abs. EtOH (10 ml), 1N NaOH (1 ml) and a cat. amount of 10% Pd/C were added. The mixture was hydrogenated under 40 psi for 6 h. The catalyst was removed by filtration and the filtrate evaporated. Purification by prep. TLC ($CHCl_3$/MeOH 7:3) gave **10** (24 mg, 87%) or **12** (18 mg, 65%), resp., as colorless solids.

Data of **10**: M.p. 237° ([16]: 220–222°). UV (H_2O): 262 (9800): ^{1}H-NMR ((D$_6$)DMSO): 1.80–1.98 (*m*, H$_b$–C(3′)); 2.08–2.27 (*m*, H$_a$–C(3′)); 3.47–3.62 (*m*, 1 H–C(5′)); 3.63–3.78 (*m*, 1 H–C(5′)); 4.29–4.46 (*m*, H–C(4′), H–C(2′)); 5.78 (*s*, H–C(1′)); 6.18 (*s*, NH$_2$); 6.90 (*d*, *J* = 5.9, H–C(7)); 7.69 (*d*, *J* = 5.9, H–C(6)); 8.35 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{14}N_4O_3$ (250.26): C 52.79, H 5.64, N 22.39; found: C 52.91, H 5.72, N 22.17.

Data of **12**: M.p. 230° (dec.). UV (H_2O): 262 (10200). ^{1}H-NMR ((D$_6$)DMSO): 1.98–2.23 (*m*, 2 H–C(3′)); 3.35–3.63 (*m*, 2 H–C(5′)); 4.43–4.58 (*m*, H–C(4′), H–C(2′)); 6.10 (*d*, *J* = 4.1, H–C(1′)); 6.14 (*s*, NH$_2$); 6.82 (*d*, *J* = 5.9, H–C(7)); 7.66 (*d*, *J* = 5.9, H–C(6)); 8.10 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{14}N_4O_3$ (250.26): C 52.79, H 5.64, N 22.39; found: C 52.88, H 5.73, N 22.19.

6. *6-Chloro-4-(cyclohexylamino)-1-(3-deoxy-β-*D*-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine* (**13**). To **6** (162 mg, 0.53 mmol), cyclohexylamine (10 ml) was added, and the mixture was heated at 105° for 16 h. The exceeding amine was evaporated and the residue purified by FC ($CHCl_3$/MeOH 98:2) to give a colorless solid which was crystallized from MeCN: **13** (150 mg, 75%). M.p. 130° (dec.). UV (EtOH): 282 (16700). ^{1}H-NMR ((D$_6$)DMSO): 0.85–1.99 (*m*, 10 cyclohexyl H, 1 H–C(3′)); 2.04–2.23 (*m*, 1 H–C(3′)); 3.50–3.62 (*m*, 1 H–C(5′)); 3.68–3.82 (*m*, 1 H–C(5′)); 3.89–4.12 (*m*, 1 cyclohexyl H); 4.30–4.45 (*m*, H–C(2′), H–C(4′)); 5.75 (*d*, *J* = 2.0, H–C(1′)); 6.83 (*d*, *J* = 8.6, NH); 6.95 (*s*, H–C(7)); 8.37 (*s*, H–C(2)). Anal. calc. for $C_{17}H_{23}ClN_4O_3$ (366.85): C 55.66, H 6.32, N 15.27; found: C 55.80, H 6.47, N 15.14.

7. *4-(Cyclohexylamino)-1-(3-deoxy-β-*D*-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine* (**14**). As described in *Exper. 5*, with **13** (70 mg, 0.19 mmol), abs. EtOH (15 ml), 1N NaOH (2 ml), and a cat. amount of 10% Pd/C. Purification by FC ($CHCl_3$/MeOH 92:8) gave a colorless solid which was crystallized from MeCN: **14** (35 mg, 58%). M.p. 200° (dec.). UV (EtOH): 275 (14800). ^{1}H-NMR ((D$_6$) DMSO): 1.10–2.04 (*m*, 10 cyclohexyl H, 1 H–C(3′)); 2.06–2.27 (*m*, 1 H–C(3′)); 3.48–3.62 (*m*, 1 H–C(5′)); 3.64–3.78 (*m*, 1 H–C(5′)); 3.93–4.27 (*m*, 1 cyclohexyl H); 4.30–4.45 (*m*, H–C(2′), H–C(4′)); 5.77 (*d*, *J* = 2.1, H–C(1′)); 6.19 (*d*, *J* = 8.5, NH); 6.86 (*d*, *J* = 5.8, H–C(7)); 7.75 (*d*, *J* = 5.8, H–C(6)); 8.33 (*s*, H–C(2)). Anal. calc. for $C_{17}H_{24}N_4O_3$ (332.40): C 61.43, H 7.28, N 16.86; found: C 61.63, H 7.41, N 16.60.

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