

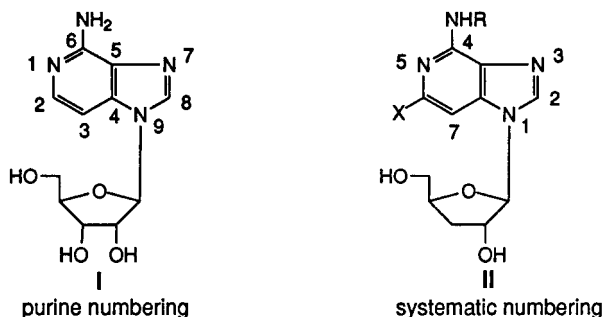
## Synthesis of New 3'-Deoxyribonucleosides Employing the Acid-Catalyzed Fusion Method

by Rosaria Volpini, Emidio Camaioni, Stefano Costanzi, Sauro Vittori, and Gloria Cristalli\*

Dipartimento di Scienze Chimiche, Università di Camerino, I-62032 Camerino

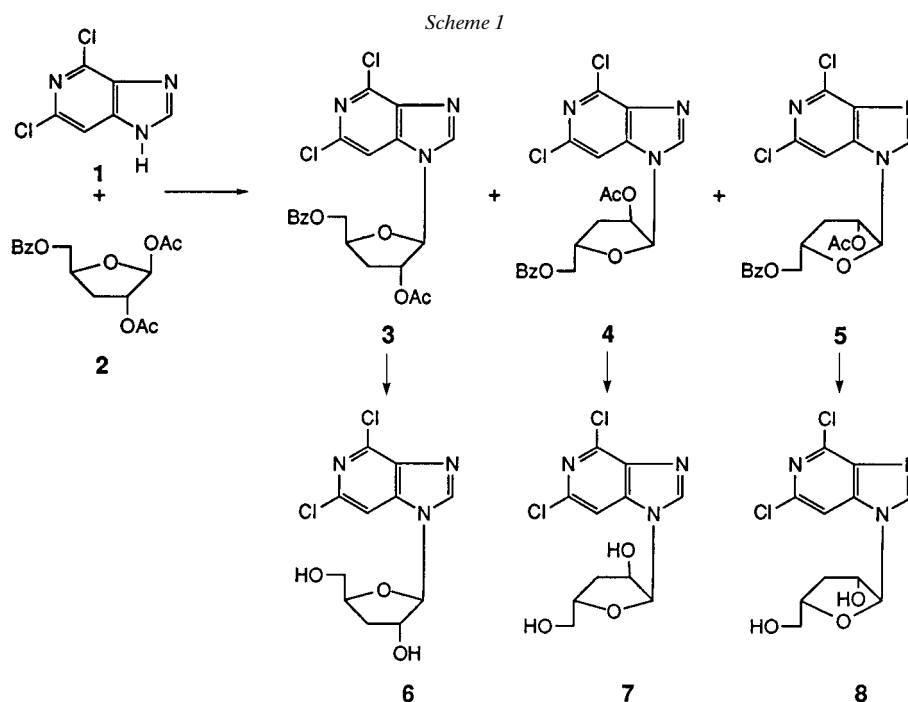
Coupling of 4,6-dichloro-1*H*-imidazo[4,5-*c*]pyridine (2,6-dichloro-3-deaza-9*H*-purine) (**1**) with 1,2-*O*-diacetyl-5-*O*-benzoyl-3-deoxy- $\beta$ -D-ribofuranose (**2**), employing the acid-catalyzed fusion method, is reported (*Scheme 1*). The condensation reaction was regioselective and gave the three *N*<sup>1</sup>-glycosylation products **3–5**, whereas no *N*<sup>3</sup>-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  $\beta$ -D- and  $\alpha$ -D-anomeric *N*<sup>1</sup>-(3'-deoxyribo)nucleosides, respectively. The third derivative **8** proved to be the  $\alpha$ -D-anomer of a 3'-deoxyarabinonucleoside deriving from epimerization at C(2) of the sugar. The 2-chloro- and *N*<sup>6</sup>-substituted derivatives **9**, **11**, and **13** of 3'-deoxy-3-deazaadenosine (**10**) and of its  $\alpha$ -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].



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 activities, *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-deoxy-ribose 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- $\beta$ -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  $\beta$ -D- and  $\alpha$ -D-anomeric *N*<sup>1</sup>-(3'-deoxyribo)nucleosides **3** and **4**, respectively, and a third isomer identified as the  $\alpha$ -D-anomer **5** of *N*<sup>1</sup>-(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%.



The glycosylation site and the anomeric configuration were assigned on the basis of UV data and <sup>1</sup>H-NMR spectra, including 1D <sup>1</sup>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  $\beta$ -D-configuration. On the other hand, saturation of H–C(1') of compound **7** gives rise to a NOE at the H<sub>a</sub>–C(3') signal (1.0%), while there is none at H–C(4'), establishing the  $\alpha$ -D-configuration. Similarly, irradiation of H–C(1') of **8** gives a NOE of 0.9% at the H<sub>a</sub>–C(3') signal and none at H–C(4'), establishing the  $\alpha$ -D-configuration. Saturation of both H–C(2') and H–C(4') of **8** produces a NOE at the H<sub>b</sub>–C(3') signal (3.1 and 2.9%, resp.), demonstrating that the sugar moiety is a deoxyarabinose derivative.

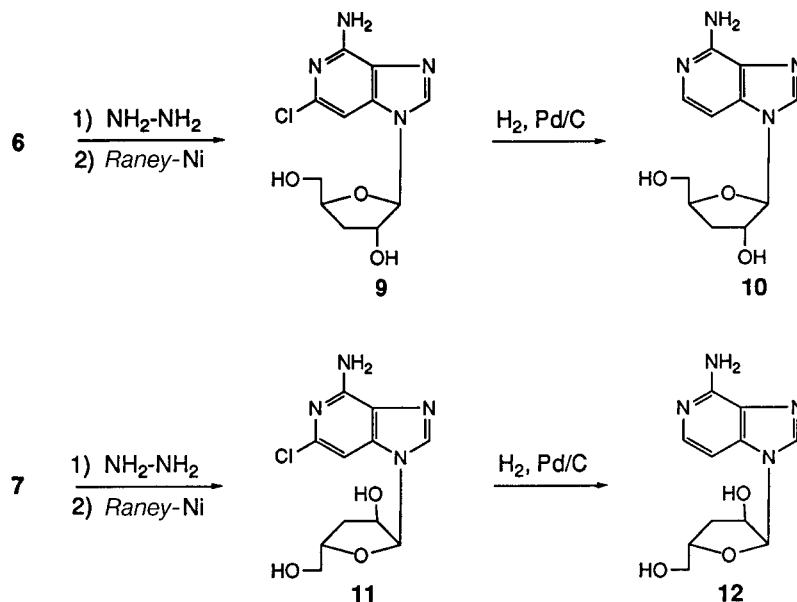
Table. NOE Data [%] of Imidazo[4,5-c]pyridine Nucleosides in (*D*<sub>6</sub>)DMSO at 23°

	Irradiated proton	Observed NOE [%]
<b>6</b>	H–C(1')	H–C(2) (9.2), H–C(7) (17.8), H–C(4') (and H–C(2')) (6.0)
<b>7</b>	H–C(1')	H–C(2) (4.2), H–C(7) (6.7), H–C(2') (6.8), H <sub>a</sub> –C(3') (1.0)
<b>8</b>	H–C(1')	H–C(2) (4.2), H–C(7) (6.5), H–C(2') (2.0), H <sub>a</sub> –C(3') (0.9)
	H–C(4')	H–C(2) (1.7), H–C(7) (1.4), H <sub>b</sub> –C(3') (2.9)
	H–C(2')	H–C(2) (3.0), H–C(7) (3.0), H–C(1') (2.1), H <sub>b</sub> –C(3') (3.1)

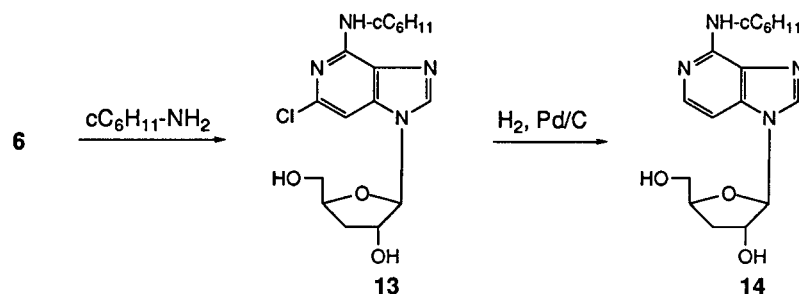
Treatment of **6** or **7** with hydrazine hydrate gave the corresponding crude hydrazino intermediates which were refluxed in the presence of *Raney*-Ni catalyst to afford the 4-amino-6-chloro-1-(3-deoxy- $\beta$ -D- and - $\alpha$ -D-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridines (**9** and **11**, 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 1*N* NaOH afforded the target compound **10** and its anomer **12**, respectively. The structure of **10** was confirmed by comparing its <sup>1</sup>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- $\beta$ -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. <sup>1</sup>H-NMR Spectra: Varian-VXR-300 spectrometer;  $\delta$  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-1H-imidazo[4,5-c]pyridine (**1**) [12] (250 mg, 1.33 mmol), 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy- $\beta$ -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<sub>3</sub>/MeOH 98:2).

1-(2-*O*-Acetyl-5-*O*-benzoyl-3-deoxy- $\beta$ -D-ribofuranosyl)-4,6-dichloro-1H-imidazo[4,5-c]pyridine (**3**): Yield 52%.  $R_f$  0.62. UV (EtOH): 259(8600), 273(7500). <sup>1</sup>H-NMR ((D<sub>6</sub>)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<sub>20</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>5</sub> (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- $\alpha$ -D-ribofuranosyl)-4,6-dichloro-1H-imidazo[4,5-c]pyridine (**4**): Yield 24%.  $R_f$  0.52. UV (EtOH): 259(8500), 273(7400). <sup>1</sup>H-NMR ((D<sub>6</sub>)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<sub>20</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>5</sub> (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- $\alpha$ -D-arabinofuranosyl)-4,6-dichloro-1H-imidazo[4,5-c]pyridine (**5**): Yield 14%.  $R_f$  0.57. UV (EtOH): 259(8600), 273(7500). <sup>1</sup>H-NMR ((D<sub>6</sub>)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<sub>20</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>5</sub> (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- $\beta$ -D-ribofuranosyl)-1H-imidazo[4,5-c]pyridine (**6**), 4,6-Dichloro-1-(3-deoxy- $\alpha$ -D-ribofuranosyl)-1H-imidazo[4,5-c]pyridine (**7**), and 4,6-Dichloro-1-(3-deoxy- $\alpha$ -D-arabinofuranosyl)-1H-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<sub>3</sub>/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). <sup>1</sup>H-NMR ((D<sub>6</sub>)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<sub>11</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub> (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). <sup>1</sup>H-NMR ((D<sub>6</sub>)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<sub>11</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub> (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).  $^1\text{H-NMR}$  ( $(\text{D}_6)$ 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  $\text{C}_{11}\text{H}_{11}\text{Cl}_2\text{N}_3\text{O}_3$  (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- $\beta$ -D-ribofuranosyl)-1H-imidazo[4,5-*c*]pyridine (**9**) and 4-Amino-6-chloro-1-(3-deoxy- $\alpha$ -D-ribofuranosyl)-1H-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  $\text{O}_2$ -free  $\text{H}_2\text{O}$  (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).  $^1\text{H-NMR}$  ( $(\text{D}_6)$ DMSO): 1.79–1.98 (*m*, 1 H–C(3')); 2.07–2.25 (*m*, 1 H–C(3')); 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*,  $\text{NH}_2$ ); 6.99 (*s*, H–C(7)); 8.37 (*s*, H–C(2)).  $^{13}\text{C-NMR}$  ( $(\text{D}_6)$ 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  $\text{C}_{11}\text{H}_{13}\text{ClN}_4\text{O}_3$  (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).  $^1\text{H-NMR}$  ( $(\text{D}_6)$ 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*,  $\text{NH}_2$ ); 6.87 (*s*, H–C(7)); 8.11 (*s*, H–C(2)).  $^{13}\text{C-NMR}$  ( $(\text{D}_6)$ 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  $\text{C}_{11}\text{H}_{13}\text{ClN}_4\text{O}_3$  (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- $\beta$ -D-ribofuranosyl)-1H-imidazo[4,5-*c*]pyridine (**10**) and 4-Amino-1-(3-deoxy- $\alpha$ -D-ribofuranosyl)-1H-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 ( $\text{CHCl}_3/\text{MeOH}$  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 ( $\text{H}_2\text{O}$ ): 262 (9800).  $^1\text{H-NMR}$  ( $(\text{D}_6)$ DMSO): 1.80–1.98 (*m*,  $\text{H}_b$ –C(3')); 2.08–2.27 (*m*,  $\text{H}_a$ –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*,  $\text{NH}_2$ ); 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  $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_3$  (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 ( $\text{H}_2\text{O}$ ): 262 (10200).  $^1\text{H-NMR}$  ( $(\text{D}_6)$ 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*,  $\text{NH}_2$ ); 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  $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_3$  (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- $\beta$ -D-ribofuranosyl)-1H-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 ( $\text{CHCl}_3/\text{MeOH}$  98:2) to give a colorless solid which was crystallized from MeCN: **13** (150 mg, 75%). M.p. 130° (dec.). UV (EtOH): 282 (16700).  $^1\text{H-NMR}$  ( $(\text{D}_6)$ 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  $\text{C}_{17}\text{H}_{23}\text{ClN}_4\text{O}_3$  (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- $\beta$ -D-ribofuranosyl)-1H-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 ( $\text{CHCl}_3/\text{MeOH}$  92:8) gave a colorless solid which was crystallized from MeCN: **14** (35 mg, 58%). M.p. 200° (dec.). UV (EtOH): 275 (14800).  $^1\text{H-NMR}$  ( $(\text{D}_6)$  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  $\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_3$  (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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Received June 19, 1998