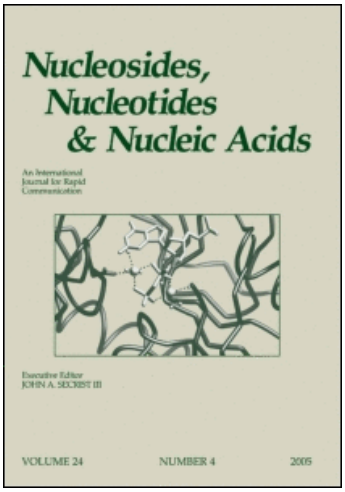

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SYNTHESIS OF 1,7-DIDEAZAPURINE RIBONUCLEOSIDES AND DEOXYRIBONUCLEOSIDES.

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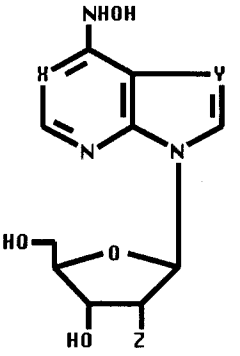
Abstract. The synthesis of hydroxylamino derivatives of 1,7-dideazaadenosine and of 1,7-dideaza-2'-deoxyadenosine, starting from 4-nitro-1H-pyrrolo[2,3-b]pyridine (**1**), is described. None of the synthesized compounds are substrates of adenosine deaminase and two of them (**3** and **18**) are weak inhibitors.

The growth-inhibitory effect and toxicity of 6-(hydroxylamino)purine and of its 9-ß-D-ribofuranosyl derivative (HAPR) are well established.[1,2] Clinical trials in patients with acute leukemia were impaired because HAPR is readily deaminated *in vivo* by the enzyme adenosine deaminase (ADA) with formation of inosine and free hydroxylamine which induces blood cell hemolysis.

In an effort to prepare cytotoxic compounds which are resistant to ADA, a series of 6-hydroxylamino purine and deazapurine nucleosides were recently synthesized and tested for their antitumor and adenosine deaminase inhibitory activity.[3] All the examined molecules displayed an *in vitro* activity comparable to that of the reference compounds HAPR and ara-A, their ID50 being in the micromolar range. Now we report the synthesis and ADA inhibitory activity of hydroxylamino derivatives of 1,7-dideazaadenosine and of 1,7-dideaza-2'-deoxyadenosine (Figure 1).



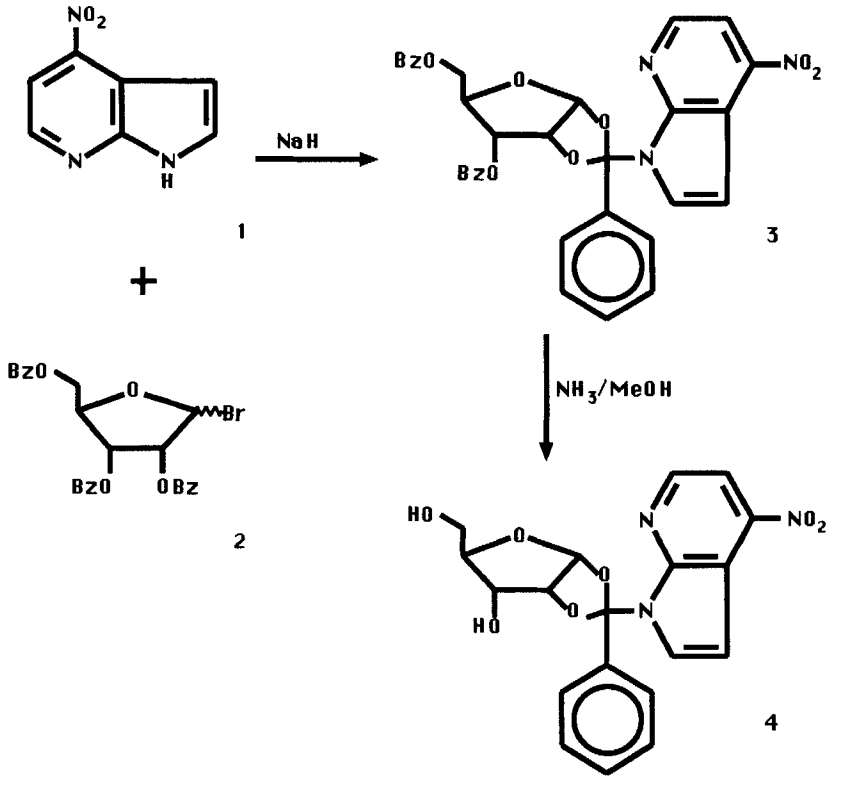
Comp.	X	Y	Z
HAPR	N	N	OH
15	CH	CH	OH
18	CH	CH	H

FIGURE 1

CHEMISTRY

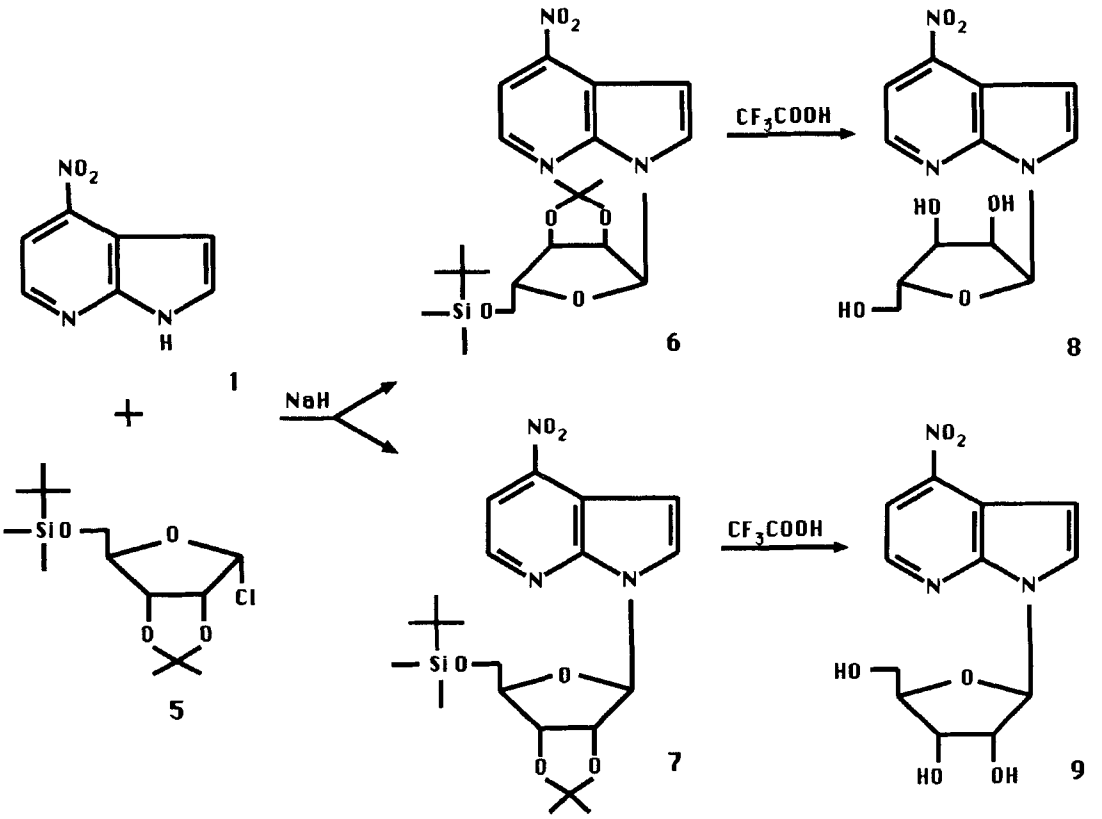
In order to synthesize the new nucleoside 4-nitro-1-β-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine, freshly prepared 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide (**2**)[4] was reacted with the sodium salt of 4-nitro-1H-pyrrolo[2,3-b]pyridine (**1**).[5] A nucleoside product **3** was isolated in 34% yield after silica gel column chromatography of the reaction mixture (Scheme I). The benzoyl blocking groups of **3** were removed by treatment with methanolic ammonia to give **4**. As already described by Revankar et al.[6] in the case of a pyrrole nucleoside, and by Cristalli et al.[7] in the case of pyrrolo[3,2-c]pyridine, ^{1}H NMR spectrum (phenyl protons at δ 7.43) and the elemental analysis of **4** indicated the presence of a benzoyl type group, whereas the IR spectrum failed to show any carbonyl stretching band. On the basis of this evidence and of the Revankar report, the structure of 1,2-O-{phenyl-1-[4-nitro-1H-(pyrrolo [2,3b]pyridinyl)]methylidene}-α-D-ribofuranose was assigned to **4** and 3,5-di-O-benzoyl-1,2-O-{phenyl-1-[4-nitro-1H(pyrrolo[2,3-b] pyridinyl)]methylidene}-α-D-ribofuranose was assigned to compound **3**.

Alternatively, freshly prepared 1-chloro-2,3-O-isopropylidene-5-O-(t-butyl)dimethylsilyl-α-D-ribofuranose (**5**)[8] was coupled with the sodium salt of **1** in dry acetonitrile at room temperature (Scheme II). The reaction mixture afforded, after separation by flash chromatography on silica gel column, the anomeric nucleosides 4-



SCHEME I

nitro-1-[2,3-O-isopropylidene-5-O-(t-butyldimethylsilyl)-D-ribofuranosyl]-1H-pyrrolo[2,3-b]pyridine (**6** and **7**) in the ratio 3:1. Deprotection of **6** and **7** with aqueous trifluoroacetic acid at room temperature gave 4-nitro-1-α-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (**8**) and 4-nitro-1-β-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (**9**). The ^{1}H NMR spectrum of blocked nucleosides **6** and **7** did not allow to distinguish whether they were α and β anomers or N-1 and N-7 isomers, the difference between the chemical shift of the two methyl signals of the isopropylidene group being 0.17 for **6** and 0.22 for **7**, both characteristic of β-configuration.[9] The configuration of compound **9** was assigned on the basis that reduction of nitro to amino group afforded the known nucleoside 4-amino-1-β-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (**16**).[5] The position of glycosylation of the isomeric nucleoside **8** was established



SCHEME II

as N-1 on the basis of the recent 2D $^{1}H,^{13}C$-correlation spectroscopy. In fact the 2D $^{1}H,^{13}C$-correlation spectroscopy exibited a long-range coupling between C-2 and H-1' of **8**, clearly indicating that the ribosylation occurred at N-1. Reduction of **8** afforded the nucleoside **14**. The UV spectra of amines **14** and **16** were very similar as expected for α and β anomers. In addition, the anomeric configuration of compounds **14** and **16** was assigned applying n.O.e. difference spectroscopy.[10] Saturation of H-1' of **14** resulted in n.O.e.s of the H-2' and H-3' signals (7.3 % and 2.0 %, respectively) while there was none at H-4' signal (Table I), establishing α-D-configuration. Saturation of H-1' of **16** yielded n.O.e.s of the H-2' and H-4' signals (1.3 % and 1.2 %, respectively) while there was none at H-3' signal (Table I), establishing β-D-configuration.

TABLE I: N.O.E.-data % of compounds **14** and **16** upon irradiation of H-1' (DMSO-d6, 25 °C, 300 MHz)

	H-2'	H-3'	H-4'	H-2
14	7.3	2.0	a	2.5
16	1.3	a	1.2	3.9

a: no detectable intensity enhancement (< 0.5%)

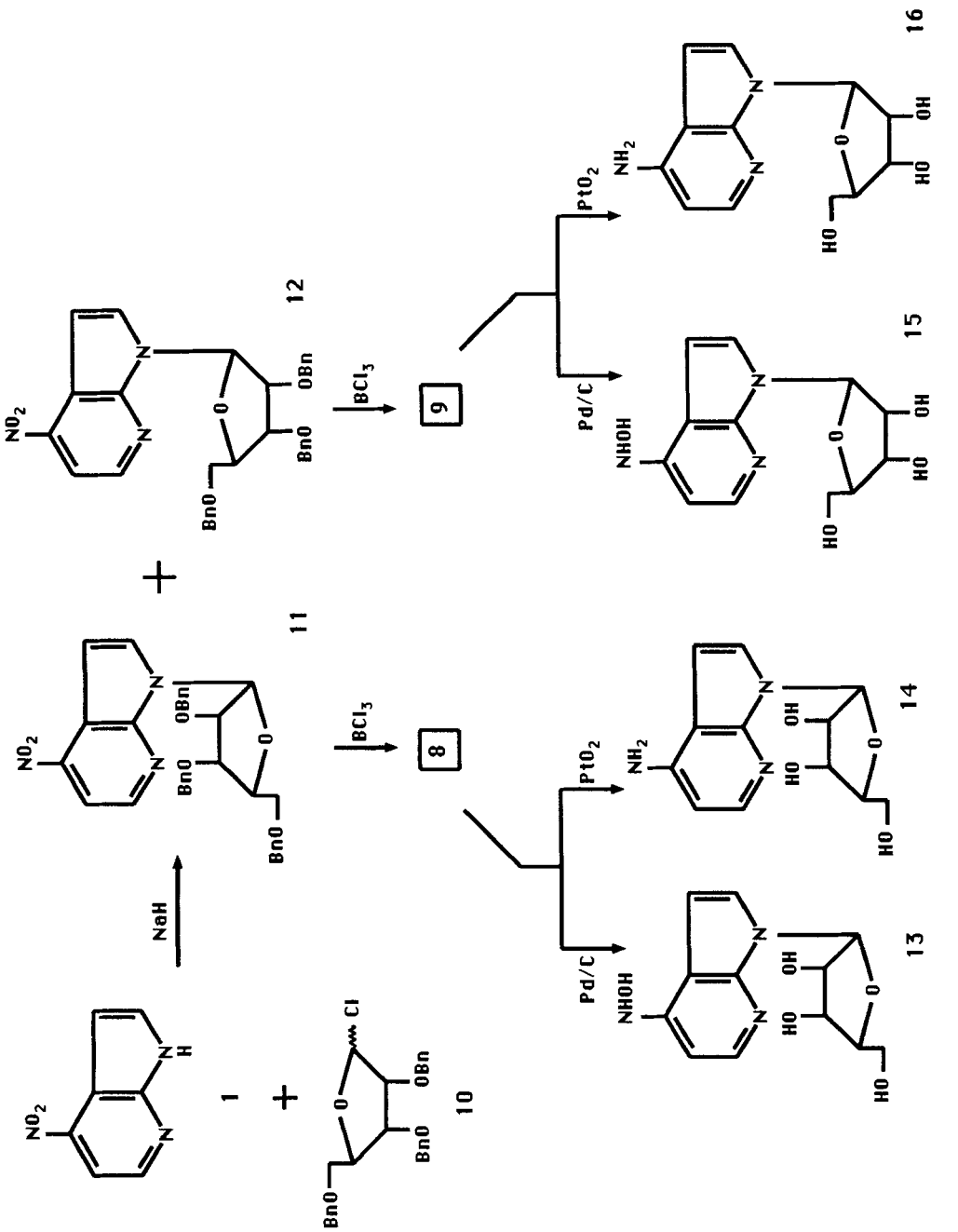
Furthermore n.O.e. effect was observed on H-2 when H-1' was irradiated, confirming N^1-glycosylation for both **14** and **16**. Therefore, on the basis of these data, **6** and **7** were assigned the α and β configuration, respectively.

In order to improve the yield in β anomer, the sodium salt of **1** was reacted with 1-chloro-2,3,5-tri-O-benzyl-D-ribofuranose (**10**)[11] in dry acetonitrile to give the α and β anomers **11** and **12** in the ratio 1:1 (86% total yield). Deprotection of the blocking groups of compounds **11** and **12** was accomplished by the treatment with BCl_3 at -70 °C to yield **8** (72%) and **9** (68%), respectively (Scheme III).

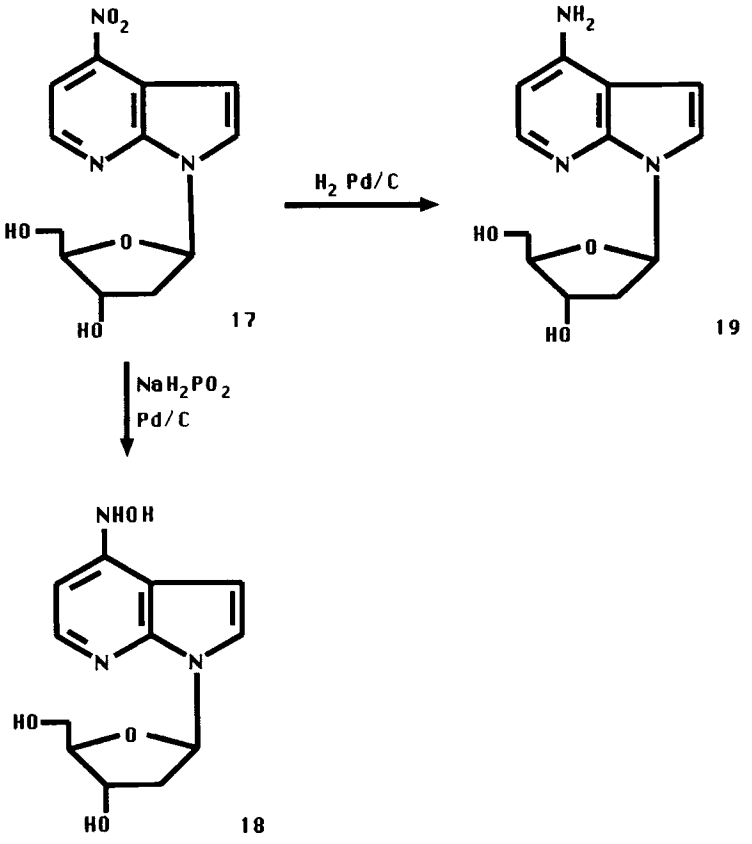
The usual reduction of nitro group with hydrogen and 10% Pd/C as catalyst did not afford the corresponding amino derivatives both in the case of **8** and **9**. In fact, hydrogenation of α and β anomers with 10% Pd/C at 30 psi yielded the corresponding hydroxylamino derivatives **13** and **15**.

The synthesis of 4-amino-1-β-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (**16**) was accomplished by reduction of **9** with hydrogen and PtO_2 at 45 psi for 6 h. Reduction of **8** with hydrogen and PtO_2 at 30 psi for 2.5 h gave the α anomer **14** (Scheme III).

In order to prepare the 4-hydroxylamino derivative of the corresponding 2'-deoxynucleoside, reduction of 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-4-nitro-1H-pyrrolo[2,3-b]pyridine (**17**)[12] was carried out in the same condition in which **9** furnished **15**. However, in the case of **17**, hydrogenation with 10% Pd/C at 30 psi yielded the amino derivative **19**.[12]



SCHEME III



SCHEME IV

The synthesis of 4-hydroxylamino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1H-pyrrolo[2,3-b]pyridine (**18**) was therefore accomplished by reduction of **17** with sodium hypophosphite and 5% Pd/C (Scheme IV).

BIOLOGICAL EVALUATION

The synthesized nucleosides were evaluated as substrates or inhibitors of adenosine deaminase from calf intestine.

None of them proved to be substrate for ADA, and in the ribofuranosyl series, only compound **3** yielded pattern of non competitive inhibition of the enzyme with $K_i = 1.1 \times 10^{-4}$.

In the deoxyribofuranosyl series, only the hydroxylamino derivative **18** was a weak inhibitor of ADA with Ki = 2.2 x 10^{-4}.

EXPERIMENTAL SECTION

Chemistry.

Melting points were determined with a Buchi apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Varian VXR 300 MHz spectrometer. UV spectra were recorded on a Perkin-Elmer Coleman 575 spectrophotometer. IR spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer. TLC were carried out on pre-coated TLC plates with silica gel 60 F-254 (Merck). For column chromatography, silica gel 60 (Merck) was used. Elemental analyses were determined on Carlo Erba model 1106 analyser.

3,5-Di-O-benzoyl-1,2-O-{phenyl-1-[4-nitro-1H-(pyrrolo[2,3-b]pyridinyl)]methylidene}-α-D-ribofuranose (3).

To a suspension of 1,63 g (10 mmol) of 4-nitro-1H-pyrrolo[2,3-b] pyridine (**1**)[5] in 50 mL of dry acetonitrile under an atmosphere of N_2 was added 470 mg of NaH (60% in oil), and the mixture was stirred at room temperature for 30 min. To the ice-cooled mixture was added a solution of 1-bromo-2,3,5-tri-O-benzoyl-D-ribofuranose (**2**)[4] (freshly prepared from 5,5 g, 11 mmol , of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose) in 10 ml of dry acetonitrile and the suspension was stirred at room temperature for 3 h. The reaction mixture was filtered to remove the insoluble material and the filtrate was concentrated to a residue which was chromatographed on a silica gel column. Elution with a gradient of cC_6H_{12}-EtOAc from 80:20 to 60:40 gave 1,54 g (31%) of **3** as a white solid and 0,5 g of starting material **1**: mp 129-132 °C; IR λ_{max} 1715 cm^{-1} (C=O); ^{1}H NMR (Me_2SO-d_6) δ 4.32 (m, 1H, H-4'), 4.55 (m, 2H, CH_2-5'), 5.28 (m, 1H, H-3'), 5.44 (m, 1H, H-2'), 6.54 (d, 1H, J= 4.2 Hz, H-1'), 7.03 (d, 1H, $J_{3,2}$= 3.6 Hz, H-3), 7.41-7.75 (br m, 10 H, H-Ph) 7.69 (d, 1H, $J_{2,3}$= 3.6 Hz, H-2), 7.95 (d, 1H, $J_{5,6}$= 5.4 Hz, H-5), 7.96 (m, 5H, H-Ph), 8.50 (d, 1H, $J_{6,5}$= 5.4 Hz, H-6). Anal. Calcd. for $C_{33}H_{25}N_3O_9$: C, 65.24; H, 4.15; N, 6.92. Found: C, 64.96; H, 4.10; N, 6.99.

1,2-O-{Phenyl-1-[4-nitro-1H-(pyrrolo[2,3b]pyridinyl)]methylidene}-α-D-ribofuranose (4).

A solution of 620 mg (1,02 mmol) of **3** in 50 mL of methanol saturated at 0 °C with ammonia was stirred at room temperature for 8 h. The reaction mixture was evaporated and the residue was flash chromatographed on a silica gel column eluting with $CHCl_3$-cC_6H_{12}-MeOH (50:49:1) to provide 100 mg (25%) of **4** as a chromatographically pure amber glass and 150 mg of starting material **1**: IR λ_{max} 1590 cm^{-1} (Ph); ^1H NMR (Me_2SO-d_6) δ 6.19 (d, 1H, H-1'), 7.09 (d, 1H, H-3), 7.43 (m, 5H, H-Ph), 7.91 (d, 1H, H-5), 8.11 (d, 1H, H-2), 8.42 (d, 1H, H-6). Anal. for $C_{19}H_{17}N_3O_7$: C, 57.14; H, 4.29; N, 10.52. Found: C, 57.37; H, 4.17; N, 10.36.

4-Nitro-1-[2,3-O-isopropylidene-5-O-(*tert*-butyldimethylsilyl)-α-D-ribofuranosyl]-1H-pyrrolo[2,3-b]pyridine (6)
4-Nitro-1-[2,3-O-isopropylidene-5-O-(*tert*-butyldimethylsilyl)-β -D-ribofuranosyl]-1H-pyrrolo[2,3-b]pyridine (7).

To a suspension of 0.50 g (3.1 mmol) of 4-nitro-1H-pyrrolo[2,3-b] pyridine (**1**)[5] in 20 mL of dry acetonitrile under an atmosphere of N_2 was added NaH (60% in oil, 150 mg) and the mixture was stirred at room temperature for 2 h. To the ice-cooled mixture was added 0,95 g (3,1 mmol) of freshly prepared 1-chloro-2,3-O-isopropylidene-5-O-(t-butyl)dimethylsilyl-α-D-ribofuranose (**5**)[7] in 15 mL of dry THF and the suspension was stirred at room temperature for 3 h. The reaction mixture was filtered through Celite to remove the insoluble material and the filtrate was concentrated to a residue which was used without further purification for the next reaction.

Analytical samples of **6** and **7** were obtained by flash chromatography on silica gel column eluting with cC_6H_{12}-EtOAc (90:10): (**6**) ^1H NMR (Me_2SO-d_6) δ 0.12 (s, 6H, 2 CH_3), 0.95 (s, 9H, tert-butyl), 1.24 and 1.41 (2s, 6H, isopropylidene CH_3), 3.84 (m, 2H, CH_2-5'), 4.38 (m, 1H, H-4'), 4.90 (m, 2H, H-2' and H-3'), 6.92 (d, 1H, J= 4.0 Hz, H-1'), 7.07 (d, 1H, $J_{3,2}$= 3.5 Hz, H-3), 7.97 (d, 1H, $J_{5,6}$= 5,3 Hz, H-5), 7.99 (d, 1H, $J_{2,3}$= 3.5 Hz, H-2), 8.52 (d, 1H, $J_{6,5}$= 5,3 Hz, H-6). Anal. for $C_{21}H_{31}N_3O_6Si$: C, 56.10; H, 6.95; N, 9.35. Found: C, 56.29; H, 6.77; N, 9.21.

(**7**): ^1H NMR (Me_2SO-d_6) δ 0.04 (s, 6H, 2 CH_3), 0.84 (s, 9H, tert-butyl), 1.34 and 1.56 (2s, 6H, isopropylidene CH_3), 3.74 (m, 2H, CH_2-

5'), 4.21 (m, 1H, H-4'), 4.97 (m, 1H, H-3'), 5.30 (m, 1H, H-2'), 6.49 (d, 1H, J= 4.0 Hz, H-1'), 7.12 (d, 1H, $J_{3,2}$= 3.5 Hz, H-3), 8.03 (d, 1H, $J_{5,6}$= 5,3 Hz, H-5), 8.17 (d, 1H, $J_{2,3}$= 3.5 Hz, H-2), 8.60 (d, 1H, $J_{6,5}$= 5,3 Hz, H-6). Anal. for $C_{21}H_{31}N_3O_6Si$: C, 56.10; H, 6.95; N, 9.35. Found: C, 56.24; H, 6.75; N, 9.18.

4-Nitro-1-α-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine(8) 4-Nitro-1-β-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (9).

Method A. To the residue obtained from the above reaction was added 20 mL of a solution of CF_3COOH-H_2O (1:1) and the mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted several times with EtOAc. The extracts were dried (Na_2SO_4) and evaporated at room temperature. The residue was chromatographed on a silica gel column eluting with $CHCl_3$-C_6H_6-MeOH (80:12:8) to give 227 mg (1,39 mmol) of unreacted **1**, 150 mg (30%) of **8** and 50 mg (10%) of **9** as chromatographically pure solids.

Method B. To a stirred solution of 25 mL of 1M BCl_3 in dry CH_2Cl_2 cooled at -70 °C was added dropwise 0.55 g (0,95 mmol) of **11** in 5 mL of dry CH_2Cl_2, and the reaction mixture was stirred at -70 °C for 2 h. The solvent was removed and the residue coevaporated several times with CH_2Cl_2 and then chromatographed on a silica gel column eluting with $CHCl_3$-C_6H_6-MeOH (80:12:8) to give 0.2 g (72%) of **8** as chromatographically pure solid.

Starting from 0,55 g (0,95 mmol) of **12** and using the same procedure 0,19 g (68%) of **9** was obtained.

(**8**): mp 139-142 °C; ^1H NMR (Me_2SO-d_6) δ 3.55 (m, 2H, CH_2-5'), 4.13 (m, 1H, H-4'), 4.21 (m, 1H, H-3'), 4.40 (m, 1H, H-2'), 6.76 (d, 1H, J= 5,3 Hz, H-1'), 7.05 (d, 1H, $J_{3,2}$= 3.6 Hz, H-3), 7.90 (d, 1H, $J_{5,6}$= 5,4 Hz, H-5), 8.23 (d, 1H, $J_{2,3}$= 3.6 Hz, H-2), 8.53 (d, 1H, $J_{6,5}$= 5,4 Hz, H-6). ^{13}C NMR (Me_2SO-d_6) δ 158.88 (C-8), 144.60 (C-4), 142.14 (C-6), 135.29 (C-2), 112.61 (C-9), 109.97 (C-5), 98.96 (C-3), 84.53 (C-1'), 83.78 (C-4'), 70.87 (C-3'), 70.65 (C-2'), 61.49 (C-5'). Anal. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.44; N, 14.23. Found: C, 48.51; H, 4.56; N, 14.52.

(**9**): mp 178-181 °C; ^1H NMR (Me_2SO-d_6) δ 3.64 (m, 2H, CH_2-5'), 3.95 (m, 1H, H-4'), 4.07 (m, 1H, H-3'), 4.24 (m, 1H, H-2'), 6.36 (d, 1H, J= 5,8

Hz, H-1'), 7.12 (d, 1H, $J_{3,2}$= 3.3 Hz, H-3), 8.01 (d, 1H, $J_{5,6}$= 5,5 Hz, H-5), 8.27 (d, 1H, $J_{2,3}$= 3.3 Hz, H-2), 8.58 (d, 1H, $J_{6,5}$= 5,5 Hz, H-6). Anal. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.44; N, 14.23. Found: C, 48.56; H, 4.60; N, 14.49.

4-Nitro-1-(2,3,5-tri-O-benzyl-α-D-ribofuranosyl]-1H-pyrrole[2,3-b]pyridine (11).

4-Nitro-1-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl]-1H-pyrrole[2,3-b]pyridine (12).

To a stirred suspension of 0.41 g (2.51 mmol) of **1**[5] in 15 mL of dry acetonitrile was added 125 mg of NaH (60% in oil, 5 mmol), and the mixture was stirred at room temperature for 1 h. A solution of 3.0 g (5,27 mmol) of 1-chloro-2,3,5-tri-O-benzyl-D-ribofuranose (**10**)[10] in dry acetonitrile was added dropwise and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was filtered to remove the insoluble material, and the filtrate was concentrated to a residue which was purified by flash chromatography over silica gel. Elution with cC_6H_{12}-AcOEt-C_6H_6 (80:7:13) gave 626 mg (44%) of the α isomer **11** and 600 mg (42%) of the β isomer **12** as chromatographically pure amber glass: (**11**) ^{1}H NMR (Me_2SO-d_6) δ 3.58 (m, 2H, CH_2-5'), 4.20-4.70 (m, 9H, H-2',3',4'and 3 CH_2), 6.89 (d, 1H, J= 6.0 Hz, H-1'), 6.98 (m, 2H, H-Ph), 7.03 (d, 1H, $J_{3,2}$= 3.6 Hz, H-3), 7.13-7.40 (m, 13H, H-Ph), 7.98 (d, 1H, $J_{5,6}$= 5,3 Hz, H-5), 8.28 (d, 1H, $J_{2,3}$= 3.6 Hz, H-2), 8.53 (d, 1H, $J_{6,5}$= 5,3 Hz, H-6). Anal. for $C_{33}H_{31}N_3O_6$: C, 70.08; H, 5.52; N, 7.43. Found: C, 70.37; H, 5.34; N, 7.19.

(**12**): ^{1}H NMR (Me_2SO-d_6) δ 3.70 (m, 2H, CH_2-5'), 4.25-4.70 (m, 9H, H-2',3',4' and 3CH_2), 6.55 (d, 1H, J= 5.8 Hz, H-1'), 6.98 (d, 1H, $J_{3,2}$= 3.7 Hz, H-3), 7.10-7.40 (m, 15H, H-Ph), 7.99 (d, 1H, $J_{5,6}$= 5,3 Hz, H-5), 8.03 (d, 1H, $J_{2,3}$= 3.7 Hz, H-2), 8.55 (d, 1H, $J_{6,5}$= 5,3 Hz, H-6). Anal. for $C_{33}H_{31}N_3O_6$: C, 70.08; H, 5.52; N, 7.43. Found: C, 70.42; H, 5.37; N, 7.21.

4-Hydroxylamino-1-α-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (13).

To a solution of 0.5 g (1,69 mmol) of **8** in 40 mL of MeOH was added of 0.25 g of 10% Pd/C, and the mixture was shaken with hydrogen at 30 psi for 75 min.

The catalyst was removed by filtration and the filtrate was evaporated to a residue which was chromatographed on a silica gel column. Elution with $CHCl_3$-MeOH (80:20) gave 0.23 g (49%) of **13** as a light yellow solid: mp 155-158 °C; ^1H NMR (Me_2SO-d_6) δ 3.52 (m, 2H, CH_2-5'), 4.02 (m, 1H, H-4'), 4.13 (m, 1H, H-3'), 4.24 (m, 1H, H-2'), 6.44 (d, 1H, $J_{3,2}$= 3.7 Hz, H-3), 6.54 (d, 1H, J= 5.05 Hz, H-1'), 6.56 (d, 1H, $J_{5,6}$= 4.9 Hz, H-5), 7.49 (d, 1H, $J_{2,3}$= 3.7 Hz, H-2), 7.91 (d, 1H, $J_{6,5}$= 5.4 Hz, H-6). 8.77 (s, 1H, NHOH), 9.33 (s, 1H, NHOH) Anal. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.59; H, 5.51; N, 14.65.

4-Amino-1-α-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (14).

To a solution of 0.5 g (1,69 mmol) of **8** in 40 mL of MeOH was added of 0.25 g of PtO_2, and the mixture was shaken with hydrogen at 30 psi for 2.5 h.

The catalyst was removed by filtration and the filtrate was evaporated to a residue which was flash chromatographed on a silica gel column. Elution with $CHCl_3$-C_6H_6-MeOH (65:22:13) gave 0.3 g (68%) of **14** as a light yellow solid: mp 183-186 °C; UV λ_{max} (MeOH) 229 nm (ε 17500), 273 (ε 13700), 291 (sh) (ε 12100), 301 (sh) (ε 9400); ^1H NMR (Me_2SO-d_6) δ 3.53 (m, 2H, CH_2-5'), 4.09 (m, 1H, H-4'), 4.13 (m, 1H, H-3'), 4.30 (m, 1H, H-2'), 6.32 (d, 1H, $J_{5,6}$= 6.0 Hz, H-5), 6.44 (d, 1H, J= 5,1 Hz, H-1'), 6.62 (d, 1H, $J_{3,2}$= 3.6 Hz, H-3), 7.46 (d, 1H, $J_{2,3}$= 3.6 Hz, H-2), 7.76 (d, 1H, $J_{6,5}$= 6.0 Hz, H-6). Anal. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.01; H, 5.57; N, 16.08.

4-Hydroxylamino-1-β-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (15).

To a solution of 0.5 g (1,69 mmol) of **9** in 40 mL of MeOH was added of 0.25 g of 10% Pd/C, and the mixture was shaken with hydrogen at 20 psi for 2 h.

The catalyst was removed by filtration and the filtrate was evaporated to give 0.44 g (89%) of **15** as a chromatographically pure solid: mp 177-181 °C (dec.). ^1H NMR (Me_2SO-d_6) δ 3.57 (m, 2H, CH_2-5'), 3.93 (m, 1H, H-4'), 4.12 (m, 1H, H-3'), 4.53 (m, 1H, H-2'), 6.03 (d,

1H, J= 6.5 Hz, H-1'), 6.48 (d, 1H, $J_{3,2}$= 3.7 Hz, H-3), 6.56 (d, 1H, $J_{5,6}$= 4.9 Hz, H-5), 7.37 (d, 1H, $J_{2,3}$= 3.7 Hz, H-2), 7.90 (d, 1H, $J_{6,5}$= 5.4 Hz, H-6). 8.81 (s, 1H, NHOH), 9.39 (s, 1H, NHOH). Anal. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.57; H, 5.49; N, 14.63.

4-Amino-1-β-D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (16).

To a solution of 0.5 g (1,69 mmol) of **9** in 40 mL of MeOH was added of 0.25 g of PtO_2, and the mixture was shaken with hydrogen at 45 psi for 6 h. The catalyst was removed by filtration and the filtrate was evaporated to a residue which was flash chromatographed on a silica gel column. Elution with $CHCl_3$-MeOH-cC_6H_{12}-NH_3 (66:19:14,5:0,5) gave 0.18 g (42%) of **16** as a pure solid: mp 247-250 °C (dec.) (lit.[5] mp 252-253 °C). UV λ_{max} (MeOH) 228 nm (ε 19100), 273 (ε 16000), 291 (ε 16500), 300 (sh) (ε 14300); ^{1}H NMR (Me_2SO-d_6) δ 3.56 (m, 2H, CH_2-5'), 3.90 (m, 1H, H-4'), 4.07 (m, 1H, H-3'), 4.55 (m, 1H, H-2'), 5.93 (d, 1H, J= 6.6 Hz, H-1'), 6.20 (d, 1H, $J_{5,6}$= 5.5 Hz, H-5), 6.55 (d, 1H, $J_{3,2}$= 3.6 Hz, H-3), 7.27 (d, 1H, $J_{2,3}$= 3.6 Hz, H-2), 7.69 (d, 1H, $J_{6,5}$= 5.5 Hz, H-6). Anal. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.03; H, 5.82; N, 16.12.

4-Hydroxylamino-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-1H-pyrrolo[2,3-b]pyridine (18).

To a suspension of 0.24 g (0.86 mmol) of 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-4-nitro-1H-pyrrolo[2,3-b]pyridine (**17**)[12] in 10 mL of THF under an atmosphere of N_2 was added 0.22 g (2.5 mmol) of NaH_2PO_2 in 5 mL of H_2O and 20 mg of 5% Pd/C . The reaction mixture was stirred under N_2 overnight and then the catalyst was removed, washed with methanol and the filtrate was concentrated to dryness. The residue was dissolved in methanol and the phosphorous salts were precipitated with EtOAc and removed by filtration. The filtrate was concentrated in vacuo and the residue chromatographed on a silica gel column eluting with $CHCl_3$-MeOH (87:13) to provide 0.10 g (45%) of **18** as a chromatographically pure solid; mp 278-280 °C (dec.). ^{1}H NMR (Me_2SO-d_6) δ 2.15 (m, 1H, H-2'), 2.59 (m, 1H, H-2"), 3.55 (m, 2H, CH_2-5'), 3.85 (m, 1H, H-4'), 4.37 (m, 1H, H-3'), 6.55 (m, 3H, H-1', H-3 and H-5), 7.39 (d, 1H, $J_{2,3}$= 3.8 Hz, H-2), 7.96 (d, 1H,

$J_{6,5}$= 5.6 Hz, H-6). 8.80 (s, 1H, NHOH), 9.38 (s, 1H, NHOH). Anal. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.58; H, 5.84; N, 15.56.

Enzyme Assay.

The method used for the determination of activity against adenosine deaminase has been described in a preceding paper.[13]

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REFERENCES

1) Giner-Sorolla, A.; Medrek, L.; Bendich, A. *J. Med. Chem.* **1966**, *9*, 143.
2) Burchenal, J.H.; Dollinger, M.; Butterbaught J.; Stoll, D.; Giner-Sorolla, A. *Biochem. Pharmacol.* **1967**, *16*, 423.
3) Cristalli, G.; Vittori, S.; Eleuteri, A.; Grifantini, M.; Volpini, R.; Lupidi, G.; Capolongo, L.; Pesenti, E. *J. Med. Chem.* **1991**, *34*, 2226.
4) Stevens, J.D.; Ness, R.K.; Fletcher, H.G. *J. Org. Chem.* **1968**, *33*,1806.
5) Antonini, I.; Claudi, F.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *J. Med. Chem.* **1982**, *25*, 1258.
6) Ramasamy, K.; Robins, R.K.; Revankar, G.R. *J. Heterocycl. Chem.* **1987**, *24*, 863.
7) Cristalli, G.; Franchetti, P.; Grifantini, M.; Nocentini, G.; Vittori, S. *J. Med. Chem.* **1989**, *32*, 1463.
8) Wilcox, C.S.; Otoski, R.M. *Tetrahedron Letters* **1986**, *27*, 1011.
9) Imbach, J.L.; Barascut, J.L.; Kam, B.L.; Rayner, B.; Tamby, C.; Tapiero, C. *J. Heterocycl. Chem.* **1973**, *10*, 1069.
10) Rosemeyer, H.; Toth, G.; Seela, F. *Nucleosides & Nucleotides* **1989**, *8*, 587.
11) Barker, R.; Fletcher, H.G. *J. Org. Chem.* **1961**, *26*, 4605.

12) Seela, F.; Gumbiowski, R. *Heterocycles* **1989**, *29*, 795.
13) Lupidi, G.; Cristalli, G.; Marmocchi, F.; Riva, F.; Grifantini, M. *J. Enzyme Inhib.* **1985**, *1*, 67.

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