Synthesis of 3,7-Dideaza-2′-deoxyadenosine and Related Pyrrolo[3,2-*c*]pyridine 2′-Deoxyribo- and 2′,3′-Dideoxyribonucleosides

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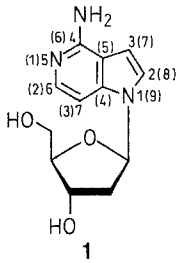
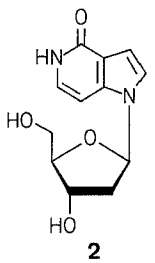
A number of new pyrrolo[3,2-*c*]pyridine 2′-deoxynucleosides including 3,7-dideaza-2′-deoxyadenosine **(1)**, 3,7-dideaza-2′-deoxyinosine **(2)**, and 3,7-dideaza-2′-deoxynebularin **(3)** were synthesized from 4,6-dichloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrrolo[3,2-*c*]pyridine **(10)**. The latter was obtained stereoselectively via solid-liquid phase-transfer glycosylation[1] of the nucleobase **7** with the halogenose **8**. Compound **10** was converted into the pyrrolo[3,2-*c*]pyridine 2′,3′-dideoxyribofuranoside **14** via a four-step deoxygenation procedure. From compound **14**, 3,7-dideaza-2′,3′-dideoxyadenosine **(4)** was obtained upon nucleophilic displacement of the 4-chloro substituent followed by reductive removal of the 6-chloro substituent. 3,7-Dideazapurine 2′-deoxynucleosides (1*H*-pyrrolo[3,2-*c*]pyridine 2′-deoxynucleosides) are extremely stable against acid or base.

In view of the chemotherapeutic and biological properties of deazapurine nucleosides[2] we have been looking for efficient syntheses of 3,7-dideazapurine (pyrrolo[3,2-*c*]pyridine) 2′-deoxynucleosides. These compounds are candidates not only for usage as antimetabolites in enzymatic reactions but also for incorporation into DNA. Due to the absence of two major DNA-binding sites (N-3 of purine in the minor and N-7 in the major groove of DNA) they can be used as probes for the study of DNA-protein interactions. Apart from this behavior, 3,7-dideazapurine 2′-deoxynucleosides are useful starting materials for the synthesis of 2′,3′-dideoxynucleosides with potential antiviral activity. In particular, 3,7-dideaza-2′,3′-dideoxyadenosine **(4)**, being isosteric to the anti-HIV active ddA **(5c)**,[3] may show such properties.



1

(in parentheses: purine numbering)



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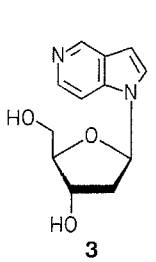

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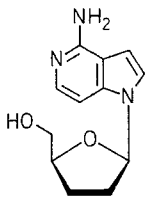

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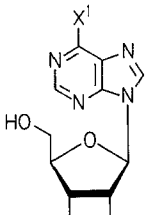
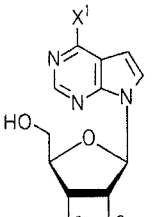


5 a-d

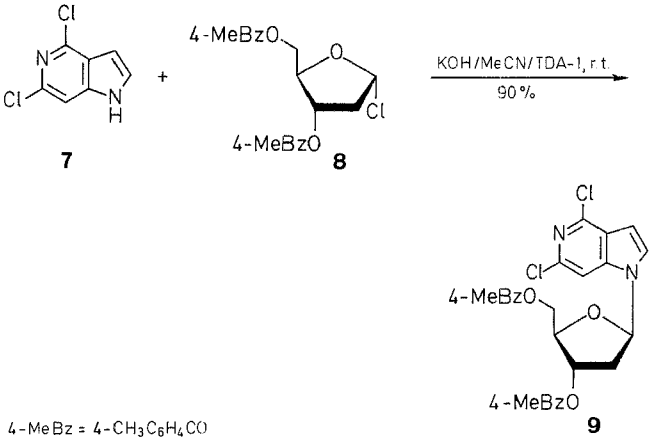


6 a-d

5	X^1	X^2	X^3	5	X^1	X^2	X^3	6	X^1	X^2	X^3	6	X^1	X^2	X^3
a	NH_2	H	OH	c	NH_2	H	H	a	NH_2	OH	OH	c	H	OH	OH
b	NH_2	OH	OH	d	H	OH	OH	b	NH_2	H	OH	d	H	H	OH

It was already shown that pyrrolo[2,3-*d*]pyrimidines can be stereoselectively glycosylated at N-7 using the halogenose **8** if the pyrrolo[2,3-*d*]pyrimidine anion is generated by the action of a strong base.[4] We have now employed solid-liquid phase-transfer glycosylation for the synthesis of pyrrolo[3,2-*c*]pyridine 2′-deoxynucleosides.[5,6] These compounds are not accessible by conventional glycosylation techniques which have been developed for purine nucleosides. The low nucleophilicity of the pyrrole N-atom directs glycosylation into the pyridine part of the molecule resulting in the exclusive formation of regioisomeric nucleosides.[7]

When we began with our studies the only described 2′-deoxynucleoside containing a 3,7-dideazapurine system was the dichloronucleoside **10**. Its protected precursor **9** had been obtained in 82% yield from the nucleobase **7**[8] by a sodium hydride-mediated reaction.[9] We glycosylated compound **7** with the halogenose **8**[10] in acetonitrile in the presence of the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1)[11] and a five-fold excess of powdered potassium hydroxide and thus obtained compound **9** in 90% yield.[5] As the cryptand chelates potassium ion the ring-fused pyrrolide anion is more nucleophilic in the presence of the chelating agent than in the form of its potassium or sodium salt. As a result, glycosylation occurs already within less than 15 min at ambient temperature. Reaction times of 2 h and elevated temperatures (50°C), as described for the sodium hydride-mediated reaction, are not necessary.



7 **8** **9**

4-MeBz = 4-$CH_3C_6H_4CO$

The reaction is stereoselective. Following the empirical rules of Nuhn et al.,[12] the small chemical shift difference of 4′-H and 5′-H in the ^{1}H-NMR spectrum of compound **9** suggested β-configuration. However, an unambiguous assignment was required to prove it.

NOE difference spectrometry has been employed for anomeric assignment of *C*-nucleosides.[13] This technique uses the NOEs of 4′-H in the β-series and of 3′-H in the α-series upon irradiation of

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the anomeric proton. We have now extended this method by testing it on a number of regular and modified nucleosides.[14] According to the NOE values of compound **10** (Table 1) 4'-H shows an enhancement of 1.9% and 2'-H of 6.4% upon irradiation of 1'-H whereas no enhancement was found for 3'-H.

Table 1. NOE-Data (%) of Compounds **4** and **10** upon Irradiation of 1'-H (DMSO-d_6; 23 °C)

Compound	2'-H_α	4'-H	2-H	7-H
4	6.4	2.6	2.6	10.3
10	6.4	1.9	3.6	13.0

This proved that the anomeric configuration of compound **10** and also of compound **9** is β. The position of glycosylation can also be deduced from this experiment. As 2-H and 7-H exhibit strong NOE values (Table 1) they must be in close proximity to 1'-H which is only the case if the sugar is attached to N-1. The ^{13}C-NMR data (Table 2) which are assigned on the basis of gated-decoupled spectra (Table 3) confirm this by the 4.3 Hz coupling of C-2 with the anomeric proton. A detailed conformational analysis will be published elsewhere.[15]

Compound **10**, obtained by deprotection of **9** with methanolic ammonia,[9] was used as starting material for a number of displacement reactions at the pyridine moiety as well as for deoxygenation of the 3'-hydroxy group. Catalytic hydrogenation of **10** in the presence of palladium on charcoal furnished crystalline 2'-deoxy-3,7-dideazanebularin (**3**), after chromatographic purification on an Amberlite XAD resin. Compound **3** is fluorescent and exhibits an emission maximum at $\lambda = 415$ nm upon irradiation at $\lambda = 268$ nm (aqueous solution). The emission maximum is bathochromically shifted as compared to 7-deaza-2'-deoxynebularin (**6d**; $\lambda_{max} = 403$ nm).[16]

Next, nucleophilic displacement reactions as depicted in the Scheme were carried out. Although it has been reported that nucleophilic substitution at pyrrolo[3,2-*c*]pyridines occurs only with difficulty[8] such substitution could be accomplished when

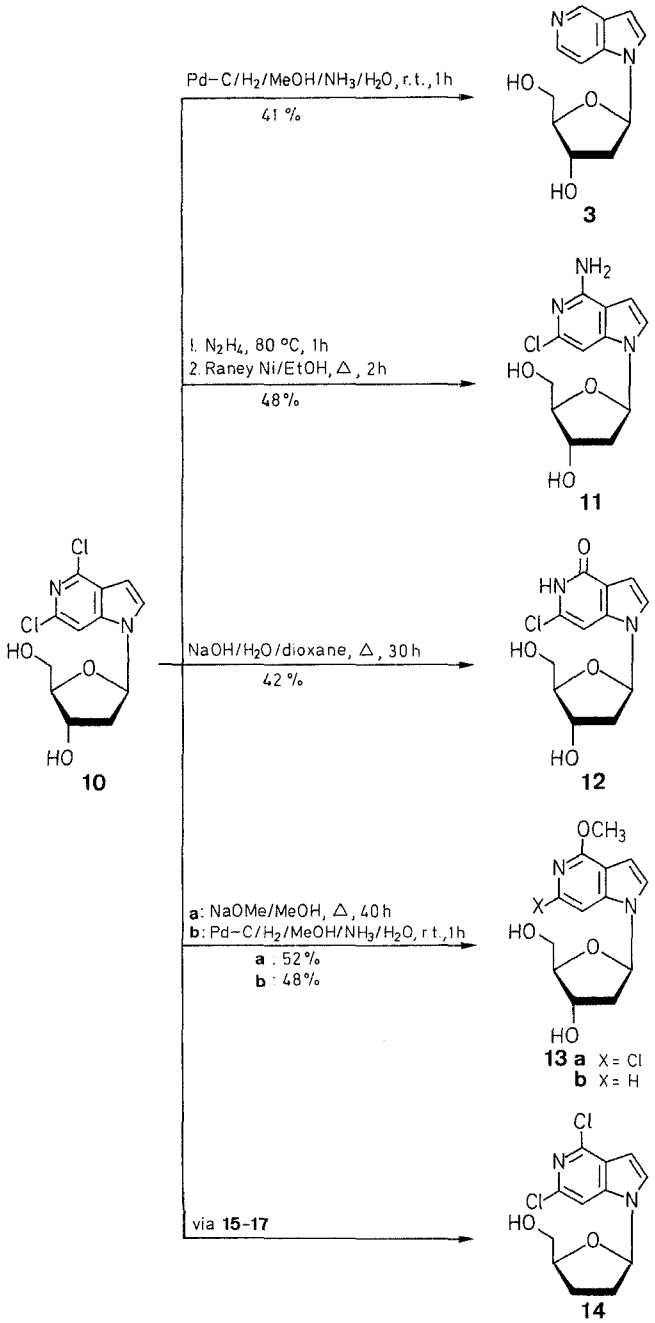

Table 2. ^{13}C-NMR Chemical Shifts of Pyrrolo[3,2-*c*]pyridine 2'-Deoxy- and 2',3'-Dideoxyribofuranosides[a,b]

Compound	C-2 (C-8)	C-3	C-3a (C-5)	C-4 (C-6)	C-6 (C-2)	C-7	C-7a (C-4)
1	122.5	101.5	110.7	153.7	139.7	96.9	140.0
2	122.0	104.6	115.9	159.6	127.8	93.8	139.0
3	126.9	101.7	125.5	143.3	140.6	105.9	139.2
4	122.2	101.1	110.7	153.6	139.5	97.0	139.7
7	129.4	100.2	122.5	140.2	138.9	106.3	142.2
9	129.7	102.0	123.1	140.6	140.0	106.1	142.4
10	129.7	101.3	123.1	140.4	139.7	106.1	142.0
11	123.5	101.6	109.6	152.9	141.0	95.1	141.4
12	123.2	104.1	114.0	158.7	129.1	94.9	139.2
13a	126.0	100.5	111.4	156.1	138.8	100.8	142.5
13b	124.8	100.4	112.2	157.8	137.8	101.7	141.2
14	129.3	101.0	123.0	140.4	139.5	105.9	141.7
15	129.1	101.3	123.2	140.5	139.8	106.2	142.3
16	128.9	101.8	123.1	140.6	140.1	106.3	142.4
17	128.8	100.9	123.2	140.5	139.6	106.3	142.3
18	123.1	101.3	109.6	152.9	140.9	95.0	141.1
5c	139.1		119.2	156.1	152.5		148.9

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	OCH_3	C=S	CDMT
1	84.5	[c]	70.8	87.1	62.0			
2	84.8	[c]	70.7	87.4	61.8			
3	84.6	[c]	70.8	87.3	61.9			
4	85.2	31.4	26.5	80.6	63.5			
9	81.7	36.8	74.9	85.6	64.2			
10	85.5	40.6	70.5	87.6	61.5			
11	84.7	[c]	70.6	87.2	61.8			
12	85.0	40.5	70.6	87.4	61.7			
13a	85.1	[c]	70.6	87.4	61.7	53.6		
13b	84.9	40.0	70.8	87.3	61.8	52.8		
14	86.0	31.9	25.8	81.4	62.8			
15	85.0[d]	[c]	70.1	85.5[d]	63.6	55.1		85.5[d]
16	84.2[d]	37.0	83.0[d]	85.6[d]	63.8	55.1	193.8	86.0[d]
17	85.8[d]	31.0	25.9	80.0	64.8	55.1		85.3[d]
18	85.3	31.5	26.3	80.7	63.3			
5c	84.5	31.8	25.7	81.8	63.0			

[a] In DMSO-d_6 relative to TMS.
[b] Purine numbering in parentheses.
[c] Superimposed by DMSO.
[d] Tentative assignment.

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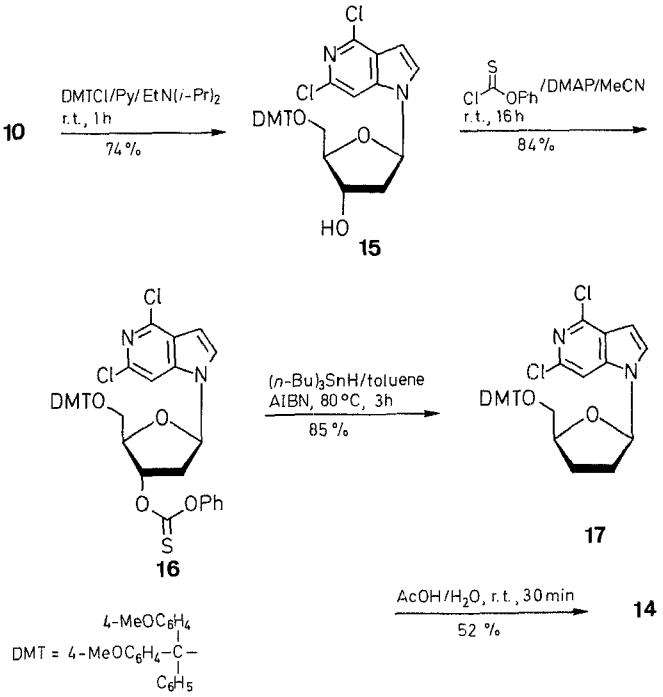
N-1 was substituted whereby pyrrolide anion formation was avoided. We were able to displace the 4-chloro substituent of **10** regioselectively by reaction of **10** with either 1 N sodium methoxide in methanol or 2 N sodium hydroxide–dioxane. The first reaction gave the 4-methoxy compound **13a** after 40 h heating and the second reaction gave **12** after 30 h heating. Both 2'-deoxynucleosides were isolated in crystalline form after desalting on an Amberlite XAD resin (**12**) or direct crystallization from methanol/water (**13a**).

Displacement of the 4-chloro substituent of **10** using ammonia failed. Even at elevated temperatures in a pressure bottle no reaction took place. To increase the reactivity of the nucleophile we then used hydrazine instead of ammonia at 80 °C; within 60 min, the 4-chloro substituent was selectively replaced by the hydrazino group. The reaction product was not isolated but was directly converted into the 4-amino compound **11** by treatment with Raney nickel in boiling ethanol. The ^{13}C-NMR data of the crystalline product **11** confirmed its structure (Table 2).

The chloro compounds **11**, **12**, and **13a** were converted into the 2'-deoxynucleosides **1**, **2**, and **13b**, respectively, by catalytic hydrogenation on palladium on charcoal. This demonstrates that the pyrrole ring of pyrrolo[3,2-*c*]pyridines is less sensitive towards hydrogenation than in pyrroles themselves. From nucleophilic displacement reactions it could also be concluded that these nucleosides are stable in alkaline solution. Purine nucleosides are nucleophilically ring-cleaved at the imidazole ring, followed by anomerization or even loss of the sugar moiety.[17] Compound **1** crystallizes from methanol but care has to by taken according to the pK_a value of this molecule. As can be seen from Table 4, protonation of **1** occurs already in alkaline solution: this behavior differs from that of the parent adenosine **5b**, in accordance with the higher electron density of pyrrolo[3,2-*c*]pyridines as compared to purines. A similar pk_a shift as found for the adenosine isoster **1** is observed for the corresponding nebularin derivative **3** (Table 4).

Recently, we have shown by ^{15}N-NMR spectrometry that the protonation site of 7-deaza-2'-deoxyadenosine (2'-deoxytubercidin, **6b**) is N-1 (purine numbering); the same was found for 2'-deoxyadenosine (**5a**).[18] As the pyrrol N-atom is less basic than that of the pyrimidine or pyridine part of the respective molecules, the protonation site of compound **1** should also be N-1 (purine numbering).

Considering the synthesis of a series of pyrrolo[3,2-*c*]pyridine 2',3'-dideoxyribofuranosides, compound **14** would be a versatile substrate for a number of displacement reactions. In a similar manner the 4-chloropyrrolo[2,3-*d*]pyrimidine 2',3'-dideoxyribofuranoside has already been used successfully.[19] We applied the Barton deoxygenation[20] to compound **10** to remove the 3'-hydroxy group. The 4,4'-dimethoxytrityl residue was introduced as 5'-protecting group, the protected compound **15** being isolated in 74% yield after flash chromatography. The position of tritylation was derived from the ^{13}C-NMR spectrum (Table 2). For deoxygenation, the 3'-hydroxy group was esterified by reaction with *O*-phenyl carbonochloridothioate[21] to give compound **16**. The latter was then subjected to deoxygenation by tributylstannane in toluene in the presence of 2,2'-azoisobutyronitrile (AIBN). Chromatographic work-up gave **17** from which the 4,4'-dimethoxytrityl (DMT) group was removed with acetic acid to give the dideoxynucleoside **14**.



The intermediates **15**–**17** of this four-step deoxygenation procedure did not crystallize, which was expected for 5'-DMT-protected nucleosides. However, compound **14**, crystallized from aqueous methanol. Apart from the characterization by microanalyses and ^{1}H-NMR spectra, ^{13}C-NMR data (Table 2) were recorded of all new compounds and assigned by the gated-decoupled mode.

Table 3. $J_{C,H}$ Coupling Constants of Compounds **3**, **10**, **11**, **12**, and **13a**[a]

$J_{C,H}$ (Hz)	3	10	11	12	13a
C-2, H-2	186.7	189.6	187.2	188.4	188.3
H-3	9.0	8.7	8.8	8.8	8.8
H-1'	4.4	4.3	4.2	4.7	4.1
C-3, H-3	175.8	180.2	175.6	176.0	177.9
H-2	7.5	7.6	7.5	7.5	7.6
C-3a, H-3		8.9		8.9	8.7
H-2	m[b]	4.5	m[b]	4.0	4.2
H-7		4.5		4.0	4.2
C-4, H-4	176.7				–
H-6	12.0	[c]	[c]	[c]	–
4-OCH_3	–				4.1
C-6, H-6	171.1	–	–		–
H-7	12.0	2.4	2.3	m[b]	2.6
C-7, H-7	164.5	174.4	172.3	175.0	173.0
H-6	8.9	–	–	–	–
C-7a, H-7			6.0		6.2
H-3	m[b]	m[b]	6.0	m[b]	6.2
H-1'			2.5		2.6

[a] In DMSO-d_6.
[b] Not resolved.
[c] Singlet.

Table 4. pK_a Values of Nucleosides

Compound	pK_a
Adenosine (**5b**)	3.5
7-Deazaadenosine (**6a**)	5.3
7-Deaza-2'-deoxyadenosine (**6b**)	5.3
3,7-Dideaza-2'-deoxyadenosine (**1**)	8.6
Nebularin (**5d**)	2.1
7-Deazanebularin (**6c**)	4.3
7-Deaza-2'-deoxynebularin (**6d**)	4.2
3,7-Dideaza-2'-deoxynebularin (**3**)	8.1

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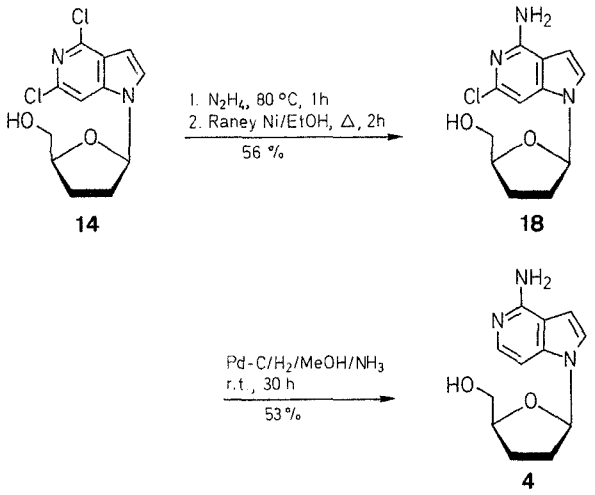
Compound **14** was subjected to a nucleophilic displacement reaction with hydrazine. This was directly followed by reduction of the hydrazino group employing Raney nickel catalyst to give **18**. Upon catalytic hydrogenation and crystallization (aqueous solution with traces of ammonia), 3,7-dideaza-2'-deoxyadenosine (**4**) was obtained. The NOE values of compound **4** were similar to those of compound **10** (Table 1). This demonstrates that NOE measurements are helpful in assigning the glycosylation position and in determining the anomeric configuration of 2',3'-dideoxynucleosides.



Although compounds **1** and **4** are protonated in alkaline solution their glycosylic bond is stable against hydrolysis in 1 N hydrochloric acid. This is different from 2'-deoxyadenosine (**5a**) or 2',3'-dideoxyadenosine (**5c**) which are rapidly hydrolyzed even in dilute hydrochloric acid (**5a**; $\tau/2 = 3.5$ min, 1 N HCl, 25 °C;[22] **5c**; $\tau/2 = 1.9$ min, 0.1 N HCl, 25 °C[23]).

Melting points were determined on a Linström apparatus (Wagner & Munz, Germany) and are not corrected. Microanalyses were performed by Mikroanalytisches Laboratorium Beller, Göttingen, Germany. UV spectra were measured on a 150-20-spectrometer (Hitachi, Japan). The pK_a values were determined spectrophotometrically in Teorell-Stenhagen buffer[24] at $\lambda = 295$ nm in the case of compound **3** and at $\lambda = 290$ nm in the case of compound **1**. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a AC-250-Bruker spectrometer.

Column chromatography was performed on silica gel 60 H (Merck, Darmstadt, FRG) and Amberlite XAD resin (Serva, Heidelberg, FRG). The columns were connected with a Uvicord S detector and an UltroRac II fraction collector (LKB Instruments, Sweden); solvent systems: A, CH_2Cl_2; B, CH_2Cl_2/EtOAc (99:1); C, CH_2Cl_2/EtOAc (97:3); D, CH_2Cl_2/acetone (99:1); E, CH_2Cl_2/acetone (95:5); F, CH_2Cl_2/MeOH (95:5); G, $CHCl_3$/MeOH (9:1); H, $CHCl_3$/MeOH (8:2); I, $CHCl_3$/MeOH/Et_3N (7:3:2). Acetonitrile and pyridine were distilled from CaH_2. TLC was carried out on silica gel plates Sil G-25 UV_{254} (Macherey-Nagel & Co, FRG); visualization was achieved by irradiation at $\lambda = 254$ nm.

4,6-Dichloro-1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-1*H*-pyrrolo[3,2-*c*]pyridine (9):

A solution of 4,6-dichloro-1*H*-pyrrolo[3,2-*c*]pyridine (**7**; 300 mg, 1.6 mmol) in anhydrous MeCN (35 mL) containing KOH (450 mg, 8.0 mmol) and the cryptand TDA-1[11] (30 mg, 0.1 mmol) is stirred at room temperature under N_2 for 30 min. The halogenose **8**[10] (625 mg, 1.6 mmol) is added and stirring is continued for 15 min. Unsoluble material is filtered off and the filtrate is evaporated under reduced pressure. The resultant oil is chromatographed on a silica gel column (8 × 4 cm; solvent C) to give product **9** as a colorless foam; yield: 762 mg (90%) (Lit.[9] 82%).

^{1}H-NMR (DMSO-d_6): $\delta = 2.37$, 2.41 (2 s, 6 H, 2 CH_3); 2.77 (m, 1 H, H-2'$_b$); 2.94 (m, 1 H, H-2'$_a$); 4.57 (m, 3 H, H-4', H-5'); 5.68 (m, 1 H, H-3'); 6.66 (pt, 1 H, H-1'); 6.71 (d, 1 H, $J = 3.5$ Hz, H-3); 8.00 (s, 1 H, H-7); and other aromatic protons.

4,6-Dichloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrrolo[3,2-*c*]-pyridine (10):

Compound **9** (500 mg, 0.93 mmol) is dissolved in a saturated (0 °C) solution of NH_3 in MeOH (30 mL). This solution is stirred at 50 °C for 12 h, then evaporated to dryness. The solid residue is dissolved in EtOH (100 mL) and adsorbed on silica gel 60 (2 g), and applied to the top of a silica gel column (10 × 4 cm, solvent G). From the main zone, compound **10** is isolated as a colorless oil which crystallizes from EtOH as colorless needles; yield: 101 mg (72%); mp 180 °C (Lit.[9] mp 173 °C).

^{1}H-NMR (DMSO-d_6): $\delta = 2.28$ (m, 1 H, H-2'$_b$); 2.43 (m, 1 H, H-2'$_a$); 3.56 (m, 2 H, H-5'); 3.85 (m, 1 H, H-4'); 4.38 (m, 1 H, H-3'); 5.02 (t, 1 H, $J = 5.2$ Hz, 5'-OH); 5.34 (d, 1 H, $J = 4.1$ Hz, 3'-OH); 6.42 (pt, 1 H, H-1'); 6.67 (d, 1 H, $J = 3.4$ Hz, H-3); 7.89 (d, 1 H, $J = 3.4$ Hz, H-2); 7.96 (s, 1 H, H-7).

4-Amino-6-chloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrrolo-[3,2-*c*]pyridine (11):

Compound **10** (460 mg, 1.52 mmol) is dissolved in anhydrous N_2H_4 (6 mL) and this solution is heated at 80 °C for 60 min. Hydrazine is then evaporated and the residue is coevaporated with EtOH (2 × 10 mL). The residue is dissolved in EtOH (40 mL), Raney nickel (2 g) is added, and the mixture is heated to reflux for 2 h with stirring. The catalyst is then filtered off and washed thoroughly with hot EtOH. The filtrate is evaporated to dryness and the residue is dissolved in MeOH (100 mL) and adsorbed on silica gel (2 g). The suspension of this silica gel in solvent G is applied to the top of a silica gel column (6 × 3 cm). Elution with solvent G affords product **11** as a colorless syrup. The product crystallizes from MeOH as tiny colorless crystals; yield: 207 mg (48%); mp 232 °C; TLC (solvent G): $R_f = 0.2$.

$C_{12}H_{14}ClN_3O_3$	calc.	C 50.80	H 4.97	N 14.81	Cl 12.50
(283.7)	found	50.91	5.05	14.75	12.53

UV (MeOH): λ_{max} (log ε) = 277 (4.17), 285 nm (4.14).

^{1}H-NMR (DMSO-d_6): $\delta = 2.20$ (m, 1 H, H-2'$_b$); 2.40 (m, 1 H, H-2'$_a$); 3.51 (m, 2 H, m, H-5'); 3.78 (m, 1 H, H-4'); 4.32 (m, 1 H, H-3'); 4.89 (t, 1 H, $J = 5$ Hz, 5'-OH); 5.26 (d, 1 H, $J = 4$ Hz, 3'-OH); 6.19 (pt, 1 H, H-1'); 6.55 (s, 2 H, NH_2); 6.64 (d, 1 H, $J = 3$ Hz, H-3); 6.83 (s, 1 H, H-7); 7.36 (d, 1 H, $J = 3$ Hz, H-2).

4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrrolo[3,2-*c*]pyridine (3,7-Dideaza-2'-deoxyadenosine, 1):

A solution of compound **11** (200 mg, 0.7 mmol) in MeOH (30 mL) containing MeOH/NH_3 (saturated at 0 °C; 0.4 mL) is hydrogenated in the presence of Pd/charcoal (50 mg, 10% Pd) at room temperature for 30 h. The catalyst is filtered off, and the filtrate is evaporated. Purification of the residue by flash chromatography (column 4 × 4 cm, solvent I) and crystallization from MeOH affords product **1** as colorless crystals; yield: 70 mg (40%); mp 205 °C; TLC (solvent I): $R_f = 0.4$.

$C_{12}H_{15}N_3O_3$	calc.	C 57.82	H 6.07	N 16.86
(249.3)	found	57.97	6.12	16.74

UV (MeOH): λ_{max} (log ε) = 271 nm (4.11).

^{1}H-NMR (DMSO-d_6): $\delta = 2.20$ (m, 1 H, H-2'$_b$); 2.42 (m, 1 H, H-2'$_a$); 3.51 (m, 2 H, H-5'); 3.80 (m, 1 H, H-4'); 4.32 (m, 1 H, H-3'); 4.91 (m, 1 H, 5'-OH); 5.32 (m, 1 H, 3'-OH); 6.08 (s, 2 H, NH_2); 6.23 (pt, 1 H, H-1'); 6.65 (d, 1 H, $J = 3$ Hz, H-3); 6.75 (d, 1 H, $J = 6$ Hz, H-7); 7.35 (d, 1 H, $J = 3$ Hz, H-2); 7.55 (d, 1 H, $J = 6$ Hz, H-6).

6-Chloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine (12):

A solution of compound **10** (400 mg, 1.32 mmol) in 2 N aq. NaOH (60 mL) containing 1,4-dioxane (5 mL) is heated to reflux for 30 h. The mixture is then neutralized with 2 N aq. HCl, filtered, and applied to an Amberlite-XAD-4 column (17 × 2 cm). The inorganic salt is eluted with H_2O and product **12** is eluted with MeOH. Crystallization from H_2O affords product **12** as colorless crystals; yield: 158 mg (42%); mp 242–243 °C; TLC (solvent H): $R_f = 0.5$.

$C_{12}H_{13}ClN_2O_4$	calc.	C 50.63	H 4.60	N 9.84	Cl 12.45
(284.7)	found	50.79	4.74	9.80	12.69

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UV (MeOH): λ_{max} (log ε) = 270 (4.05), 292 nm (3.97).

^{1}H-NMR (DMSO-d_6): δ = 2.22 (m, 1 H, H-2'$_b$); 2.38 (m, 1 H, H-2'$_a$); 3.53 (m, 2 H, H-5'); 3.80 (m, 1 H, H-4'); 4.33 (m, 1 H, H-3'); 4.96 (m, 1 H, 5'-OH); 5.29 (m, 1 H, 3'-OH); 6.22 (pt, 1 H, H-1'); 6.54 (d, 1 H, J = 3.3 Hz, H-3); 6.96 (s, 1 H, H-7); 7.38 (d, 1 H, J = 3.3 Hz, H-2); 11.81 (br, NH).

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl-4-oxo-4,5-dihydro-1*H*-pyrrolo-[3,2-*c*]pyridine (3,7-Dideaza-2'-deoxyinosine, 2):

To a solution of compound **12** (100 mg, 0.35 mmol) in MeOH (15 mL), conc. aq. NH_3 (0.5 mL) is added and the mixture is hydrogenated in the presence of Pd/charcoal (10% Pd, 15 mg) for 3 h (room temperature, normal pressure). The catalyst is filtered off and the filtrate is evaporated to dryness. The solid residue is crystallized from H_2O; yield of **2**: 51 mg (58%); mp 147–148 °C; TLC (solvent H): R_f = 0.3.

$C_{12}H_{14}N_2O_4$	calc.	C 57.59	H 5.64	N 11.19	
(250.25)	found	57.64	5.74	11.06	

UV (MeOH): λ_{max} (log ε) = 264 (4.07); 282 (sh) (3.90), 295 (sh) nm (3.71).

^{1}H-NMR (DMSO-d_6): δ = 2.22 (m, 1 H, H-2'$_b$); 2.40 (m, 1 H, H-2'$_a$); 3.52 (m, 2 H, H-5'); 3.81 (m, 1 H, H-4'); 4.32 (m, 1 H, H-3'); 4.93 (t, 1 H, J = 5.4 Hz, 5'-OH); 5.32 (d, 1 H, J = 4.3 Hz, 3'-OH); 6.21 (pt, 1 H, H-1'); 6.54 (d, 1 H, J = 3 Hz, H-3); 6.62 (d, 1 H, J = 7 Hz, H-7); 7.03 (d, 1 H, J = 7 Hz, H-6); 7.34 (d, 1 H, J = 3 Hz, H-2); 10.87 (br, NH).

6-Chloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-4-methoxy-1*H*-pyrrolo-[3,2-*c*]pyridine (13a):

Compound **10** (500 mg, 1.65 mmol) is dissolved in a 1 M solution of MeONa in MeOH (40 mL) and this solution is heated to reflux for 40 h. The solution is then neutralized with pure AcOH and evaporated to dryness. The residue is extracted with CH_2Cl_2 (2 × 100 mL). Unsoluble material is filtered off and the filtrate is dried (Na_2SO_4) and evaporated to give product **13a** as a colorless oil. Product **13a** crystallizes from MeOH/H_2O as colorless needles; yield: 255 mg (52%); TLC (solvent G): R_f = 0.4.

$C_{13}H_{15}ClN_2O_4$	calc.	C 52.27	H 5.06	Cl 11.87	N 9.38	
(298.7)	found	52.24	5.14	12.05	9.46	

UV (MeOH): λ_{max} (log ε) = 271 (4.08); 280 nm (4.04).

^{1}H-NMR (DMSO-d_6): δ = 2.25 (m, 1 H, H-2'$_b$); 2.42 (m, 1 H, H-2'$_a$); 3.54 (m, 2 H, H-5'); 3.82 (m, 1 H, H-4'); 3.96 (s, 3 H, OCH_3); 4.35 (m, 1 H, H-3'); 4.96 (t, 1 H, J = 5.3 Hz, 5'-OH); 5.30 (d, 1 H, J = 4.2 Hz, 3'-OH); 6.34 (pt, 1 H, H-1'); 6.57 (d, 1 H, J = 3.4 Hz, H-3); 7.45 (s, 1 H, H-7); 7.60 (d, 1 H, J = 3.4 Hz, H-2).

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-4-methoxy-1*H*-pyrrolo[3,2-*c*]-pyridine (13b):

A solution of compound **13a** (200 mg, 0.67 mmol) in MeOH (20 mL) containing conc. aq. NH_3 (0.5 mL, 6.6 mmol) is hydrogenated in the presence of Pd/charcoal (40 mg, 10% Pd) for 1 h under normal pressure at room temperature. The catalyst is then filtered off and the solvent is evaporated. The solid residue is recrystallized from a small volume of H_2O to give product **13b** as colorless crystals; yield: 85 mg (48%); mp 147–148 °C; TLC (solvent H): R_f = 0.6.

$C_{13}H_{16}N_2O_4$	calc.	C 59.08	H 6.10	N 10.60
(264.3)	found	59.09	6.07	10.65

UV (MeOH): λ_{max} (log ε) = 262 (4.02), 275 (sh) nm (3.93).

^{1}H-NMR (DMSO-d_6): δ = 2.23 (m, 1 H, H-2'$_b$); 2.47 (m, 1 H, H-2'$_a$); 3.53 (m, 2 H, H-5'); 3.83 (m, 1 H, H-4'); 3.95 (s, 3 H, OCH_3); 4.35 (m, 1 H, H-3'); 4.95 (t, 1 H, J = 5.4 Hz, 5'-OH); 5.33 (d, 1 H, J = 4.2 Hz, 3'-OH); 6.35 (pt, 1 H, H-1'); 6.55 (d, 1 H, J = 3.4 Hz, H-3); 7.27 (d, 1 H, J = 6.0 Hz, H-7); 7.56 (d, 1 H, J = 3.4 Hz, H-3); 7.76 (d, 1 H, J = 6.0 Hz, H-6).

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrrolo[3,2-*c*]pyridine (3,7-Dideaza-2'-deoxynebularin, 3):

A solution of compound **10** (300 mg, 0.99 mmol) in MeOH (25 mL) containing conc. aq. NH_3 (0.5 mL, 6.6 mmol) is hydrogenated as described above (60 mg Pd/C, 10% Pd). The crude product obtained upon evaporation is dissolved in H_2O (100 mL) (pH 12, NH_3) and adsorbed on a Amberlite XAD-4-column (20 × 2 cm; 20–50 mesh). The inorganic salt is washed out with water (pH 12, NH_3). Product **3** is eluted with MeOH and crystallized from a small volume of water (traces NH_3) to give colorless crystals; yield: 95 mg (41%); mp 175–176 °C; TLC (solvent H): R_f = 0.3.

$C_{12}H_{14}N_2O_3$	calc.	C 61.53	H 6.02	N 11.96
(234.25)	found	61.55	6.12	12.02

UV (MeOH): λ_{max} (log ε) = 268 nm (3.69).

^{1}H-NMR (DMSO-d_6): δ = 2.23 (m, 1 H, H-2'$_b$); 2.29 (m, 1 H, H-2'$_a$); 3.55 (m, 2 H, H-5'); 3.85 (m, 1 H, H-4'); 4.38 (m, 1 H, H-3'); 4.99 (m, 1 H, 5'-OH); 5.37 (m, 1 H, 3'-OH); 6.42 (pt, 1 H, H-1'); 6.66 (d, 1 H, J = 3.3 Hz, H-3); 7.62 (d, 1 H, J = 5.7 Hz, H-7); 7.71 (d, 1 H, J = 3.3 Hz, H-2); 8.21 (d, 1 H, J = 5.7 Hz, H-6); 8.82 (s, 1 H, H-4).

4,6-Dichloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5'-*O*-(4,4'-dimethoxytrityl)-1*H*-pyrrolo[3,2-*c*]pyridine (15):

Compound **10** (500 mg, 1.65 mmol) is dried by coevaporation with absolute pyridine (10 mL), then dissolved in absolute pyridine (10 mL). To this are added ethyldiisopropylamine (Hünig's base; 0.7 mL, 4.1 mmol) and 4,4'-dimethoxytritylchloride (690 mg 2.0 mmol) and the mixture is stirred for 1 h at room temperature. Then, 5% aq. $NaHCO_3$ (75 mL) is added and this mixture is extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers are dried (Na_2SO_4) and filtered and the solvent is evaporated. The residue is chromatographed on a silica gel column (30 × 3 cm, solvent A followed by D). From the main zone, yellowish amorphous **15** is obtained; it is dissolved in Et_2O (5 mL) and precipitated in hexane; yield of **15** as a colorless powder: 740 mg (74%); TLC (solvent E): R_f = 0.5.

$C_{33}H_{30}Cl_2N_2O_5$	calc.	C 65.46	H 4.99	Cl 11.71	N 4.63	
(605.5)	found	65.47	5.09	11.78	4.56	

UV (MeOH): λ_{max} (log ε) = 226 (4.76); 276 (3.99), 288 (sh) nm (3.79).

^{1}H-NMR (DMSO-d_6): δ = 2.39 (m, 1 H, H-2'$_b$); 2.64 (m, 1 H, H-2'$_a$); 3.09 (m, 2 H, H-5'); 3.72 (s, 6 H, 2 OCH_3); 3.96 (m, 1 H, H-4'); 4.42 (m, 1 H, H-3'); 3.72 (s, 6 H, 2 OCH_3); 3.96 (m, 1 H, H-4'); 4.42 (m, 1 H, H-3'); 5.41 (d, 1 H, J = 4.8 Hz, 3'-OH); 6.47 (pt, 1 H, H-1'); 6.65 (d, 1 H, J = 3.5 Hz, H-3); 6.76–7.27 (m, 13 H_{arom}); 7.76 (d, 1 H, J = 3.5 Hz, H-2); 7.89 (s, 1 H, H-7).

4,6-Dichloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5'-*O*-(4,4'-dimethoxytrityl)-3'-*O*-phenoxythiocarbonyl-1*H*-pyrrolo[3,2-*c*]pyridine (16):

A solution of compound **15** (300 mg, 0.5 mmol) in anhydrous CH_3CN (11 mL) is stirred with 4-dimethylaminopyridine (350 mg, 2.9 mmol) and *O*-phenyl carbonochloridothioate (ClCSOPh; 150 µL, 1.1 mmol) for 16 h at room temperature. The mixture is then evaporated to dryness and the residue is chromatographed on a silica gel column (8 × 4 cm; solvent A). From the main zone, product **16** is isolated as a colorless foam; yield: 310 mg (84%); TLC (solvent B): R_f = 0.6, (solvent D): R_f = 0.4.

$C_{40}H_{34}Cl_2N_2O_6S$	calc.	C 64.78	H 4.62	Cl 9.56	N 3.78	S 4.32	
(741.7)	found	64.66	4.59	9.65	3.74	4.40	

UV (MeOH): λ_{max} (log ε) = 225 (4.80); 275 (4.03), 291 (sh) nm (3.74).

^{1}H-NMR (DMSO-d_6): δ = 2.92 (m, 2 H, H-2'$_{a,b}$); 3.35 (m, 2 H, H-5'); 3.72 (s, 6 H, 2 OCH_3); 4.43 (m, 1 H, H-4'); 5.89 (m, 1 H, H-3'); 6.61 (pt, 1 H, H-1'); 6.71 (d, 1 H, J = 3.5 Hz, H-3); 6.81–7.52 (m, 18 H_{arom}); 7.76 (d, 1 H, J = 3.5 Hz, H-2); 8.01 (s, 1 H, H-7).

4,6-Dichloro-1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-5'-*O*-(4,4'-dimethoxytrityl)-1*H*-pyrrolo[3,2-*c*]pyridine (17):

Compound **16** (170 mg, 0.23 mmol) and bis(1-cyano-1-methylethyl)diazene (azoisobutyronitrile, AIBN; 15 mg, 0.1 mmol) are dissolved in anhydrous toluene (10 mL, argon atmosphere) with stirring. Tributylstannane (140 µL, 0.51 mmol) is added and stirring is continued at 80 °C for 3 h. The solvent is then evaporated and the residue is chromatographed on a silica gel column (10 × 4 cm, solvent A). From the main zone, product **17** is isolated as a colorless foam; yield: 115 mg (85%); TLC (solvent B): R_f = 0.4.

$C_{33}H_{30}Cl_2N_2O_4$	calc.	C 67.24	H 5.13	N 4.75	Cl 12.03
(589.5)	found	67.37	5.26	4.73	11.89

UV (MeOH): λ_{max} (log ε) = 226 (4.72), 275 (3.98); 291 (sh) nm (3.70).

^{1}H-NMR (DMSO-d_6): δ = 2.05 (m, 1 H, H-3'); 2.50 (H-2', superimposed by solvent signals); 2.90–3.15 (m, 2 H, H-5'); 4.25 (m, 1 H, H-4'); 6.38 (m, 1 H, H-1'); 6.63 (d, 1 H, J = 3.4 Hz, H-3); 6.69–7.30 (m, 13 H_{arom}); 7.79 (d, 1 H, J = 3.4 Hz, H-2); 7.89 (s, 1 H, H-7).

4,6-Dichloro-1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-1*H*-pyrrolo-[3,2-*c*]pyridine (14):

A solution of compound **17** (300 mg, 0.51 mmol) in 80% aq. AcOH acid (12 mL) is stirred at room temperature for 30 min. The solvent is then evaporated and AcOH is removed by coevaporation with H_2O. The residue is chromatographed on a silica gel column (10 × 3 cm, solvent A followed by F). Product **14** is isolated from the main zone, and crystallized from MeOH/H_2O to give colorless needles; yield: 76 mg (52%); mp 128–129 °C; TLC (solvent F): R_f = 0.5.

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$C_{12}H_{12}N_2Cl_2O_2$	calc.	C 50.19	H 4.21	N 9.76	Cl 24.69
(287.1)	found	50.44	4.12	9.83	24.52

UV (MeOH): λ_{max} (log ε) = 278 (3.80), 291 (sh) nm (3.67).

^{1}H-NMR (DMSO-d_6): δ = 2.02 (m, 2H, H-3'); 2.22 (m, 1H, H-2'$_b$); 2.40 (m, 1H, H-2'$_a$); 3.53 (m, 2H, H-5'); 4.10 (m, 1H, H-4'); 4.95 (t, 1H, J = 5.1 HZ, 5'-OH); 6.32 (dd, 1H, J = 3.9, 6.5 Hz, H-1'); 6.65 (d, 1H, J = 3.4 Hz, H-3); 7.88 (s, 1H, H-7); 7.91 (d, 1H, J = 3.4 Hz, H-2).

4-Amino-6-chloro-1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-1*H*-pyrrolo[3,2-*c*]pyridine (18):

In an analogous manner as described for compound **11**, compound **18** is obtained from 4,6-dichloro-1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-1*H*-pyrrolo[3,2-*c*]pyridine (**14**; 480 mg, 1.67 mmol) and anhydrous N_2H_4 (5.5 mL). Heating with Raney Ni (1.5 g) and purification by flash chromatography (column 15 × 4 cm, solvent F) affords product **18** as colorless needles; yield: 251 mg (56%); mp 210–211 °C (MeOH); TLC (solvent F): R_f = 0.3.

$C_{12}H_{14}ClN_3O_2$	calc.	C 53.84	H 5.27	N 15.70	Cl 13.24
(267.7)	found	53.73	5.28	15.68	13.32

UV (MeOH): λ_{max} (log ε) = 278 (4.15), 285 (sh) nm (4.12).

^{1}H-NMR (DMSO-d_6): δ = 1.96 (m, 2H, H-3'); 2.15 (m, 1H, H-2'$_b$); 2.33 (m, 1H, H-2'$_a$); 3.48 (m, 2H, H-5'); 4.03 (m, 1H, H-4'); 4.85 (t, 1H, J = 5.5 Hz, 5'-OH); 6.10 (dd, 1H, J = 4.2, 6.7 Hz, H-1'); 6.54 (s, 2H, NH_2); 6.63 (d, 1H, J = 3.4 Hz, H-3); 6.81 (s, 1H, H-7); 7.36 (d, 1H, J = 3.4 Hz, H-2).

4-Amino-1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-1*H*-pyrrolo[3,2-*c*]-pyridine (3,7-Dideaza-2',3'-dideoxyadenosine, 4):

Hydrogenation of **18** (120 mg, 0.49 mmol) as described for the preparation of compound **1** affords product **4** as colorless needles; yield: 55 mg (53%); mp 176.5 °C (H_2O).

$C_{12}H_{15}N_3O_2$	calc.	C 61.79	H 6.48	N 18.01
(233.3)	found	61.62	6.49	17.93

UV (MeOH): λ_{max} (log ε) = 272 nm (4.07).

^{1}H-NMR (DMSO-d_6): δ = 1.98 (m, 2H, H-3'); 2.16 (m, 1H, H-2'$_b$); 2.34 (m, 1H, H-2'$_a$); 3.49 (m, 2H, H-5'); 4.03 (m, 1H, H-4'); 4.85 (m, 1H, 5'-OH); 6.06 (s, 2H, NH_2); 6.12 (dd, 1H, J = 4.7, 6.5 Hz, H-1'); 6.63 (d, 1H, J = 3.3 Hz, H-3); 6.74 (d, 1H, J = 6.0 Hz, H-7); 7.34 (d, 1H, J = 3.3 Hz, H-2); 7.55 (d, 1H, J = 6.0 Hz, H-6).

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