16. Synthesis of 6-Substituted 1-Deazapurine 2′-Deoxyribonucleosides

by **Thomas Wenzel** and **Frank Seela***

Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastr. 7, D-49069 Osnabrück

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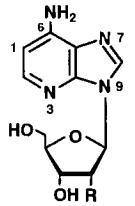
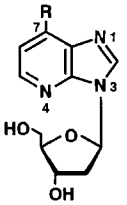
The synthesis of 6-substituted 1-deazapurine 2′-deoxyribonucleosides is described. Glycosylation of the 1-deazapurine (imidazo[4,5-*b*]pyridine) anions with the α-D-halogenose **5** gives stereoselectively N^7- and N^9-regioisomers. ^{1}H-NMR NOE and ^{13}C-NMR spectroscopy are used for unambiguous assignment of isomers, and ^{15}N-NMR chemical shifts are correlated with σ_{para} *Hammett* constants and point charges.

Introduction. – The 1-deazapurine nucleosides, such as 1-deaza-2′-deoxyadenosine (**1a**) [1] [2] (purine numbering is used throughout the *General Part*) or the ribonucleoside **1b** [3] [4] can form *Hoogsteen* base pairs within oligonucleotide duplexes [2] [5]. The synthesis of 1-deazapurine deoxyribonucleosides can be performed by *i*) deoxygenation of ribonucleosides [1], *ii*) the microbial transglycosylation of imidazo[4,5-*b*]pyridine bases [6] [7], and *iii*) the stereoselective glycosylation of the nucleobases with sugar halides [8] [9]. In the following, we report on the nucleobase-anion glycosylation of 6-substituted 1-deazapurines and their conversion into the nucleosides **2a–d** or **3a–d**. These reactions should give information on steric and electronic effects of 6-substituents on the distribution of regioisomers. The formation of compounds **2a** and **2c** leads to immediate precursors for the synthesis of 1-deaza-2′-deoxyadenosine (**1a**). The assignment of regioisomeric 1-deazapurine nucleosides by UV or usual ^{1}H-NMR spectroscopy was shown to be problematic and led to the revision of structures [10] [11]. We now present the unambiguous assignment of regioisomers on the basis of ^{1}H-NOE and ^{13}C-NMR spectroscopy. Also the glycosylic-bond stability of regioisomers will be investigated, and a correlation of ^{15}N-NMR chemical shifts with point charges and *Hammett* constants will be undertaken.



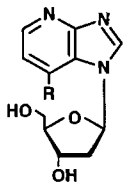
(purine numbering)

1a R = H
b R = OH



(systematic numbering)

2a R = NO_2
b R = H
c R = Cl
d R = MeO



3a R = NO_2
b R = H
c R = Cl
d R = MeO

Results and Discussion. – *Synthesis.* The glycosylation of the nucleobases **4a–c** was performed under conditions developed in our laboratory for the stereoselective synthesis of 2′-deoxyribonucleosides [12] [13] (*Scheme 1*). For this purpose, the bases were dissolved in MeCN and treated with 2-deoxy-3,5-di-*O*-(4-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**5**) in the presence of powdered KOH (5 equiv.) and *TDA-1* as catalyst.

Scheme 1

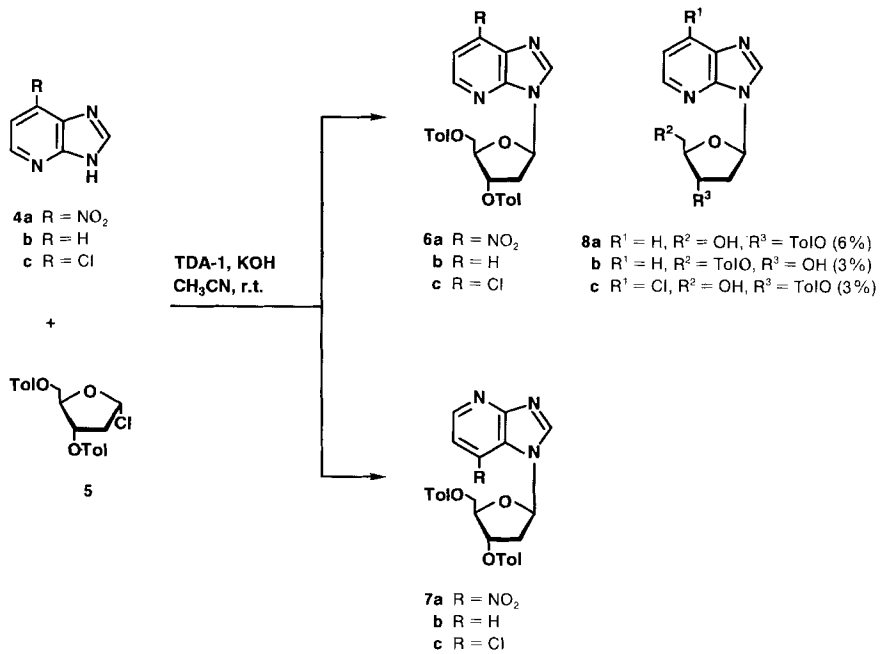


Table 1. *Yields*[a]) *of Regioisomeric 1-Deazapurine* N^9- *and* N^7-*Nucleosides during Nucleobase-Anion Glycosylation of* **4a–c** *with the Halogenose* **5**

	Products		Total yield [%]
	N^9-Isomer [%]	N^7-Isomer [%]	
4a[b])	48 (**6a**)	6 (**7a**)	54
a[c])	57 (**6a**)	16 (**7a**)	73
b[c])	48 (**6b**)	29 (**7b**)	77
c[c])	67 (**6c**)	–	67

[a]) Determined after FC purification. [b]) At 0°; 3 h. [c]) At r.t., 20 min.

Table 1 shows the distribution of regioisomers of the various glycosylation experiments and their yields. At room temperature, two glycosylation products, **6a**/**7a** and **6b**/**7b**, were formed, in the case of the bases **4a** and **4b**, respectively, and only one, **6c**, in the case of **4c** (*Scheme 1*). The faster-migrating zones on TLC were identified as the N^9-regioisomers **6a–c** (see below) and separated by flash chromatography (FC). Small quantities (3–6%) of the partially deprotected nucleosides **8a–c** were obtained from the glycosylation of

4b and **4c**. As the m.p. of compound **6a** did not agree with literature data (see *Exper. Part*), a full set of analytical data was collected which confirmed the structure already reported [8].

When the glycosylation of **4a** was carried out at 0° – conditions which had already been used by *Cristalli et al.* [8], also the two regioisomers **6a** and **7a** were formed, a finding which is different from studies described earlier [8] [9]. The total yield decreased from 73% (25°) to 54%. The N^9/N^7-isomer ratio was 8:1 at low temperature compared to 3.6:1 at 25°. However, the highest yield of isomer **6a** was observed at 25°. In the presence of KOH instead of NaH (*cf.* [8] [9]), only marginal changes in the glycosylation products were observed.

Thus, the 6-unsubstituted base **4b** [14] yielded significantly higher amounts of N^7-isomer than **4a** (R = NO_2) and **4c** (R = Cl; see *Table 1*). Apparently, the bulky 6-NO_2 or 6-Cl substituents hinder the glycosylation at N(7) and direct the reaction towards N(9). The more favorable N^9/N^7-isomer ratio obtained on glycosylation of **4a** at lower temperature can be explained by the kinetic control of the glycosylation with N(9) as the most reactive site.

Regarding the synthesis of nucleoside **1a**, the 6-chloro glycosylation product **6c** seems to be superior to the 6-nitro derivative **6a**. However, the nucleophilic displacement of the Cl-atom requires hydrazine for displacement, and a second step is necessary to convert the hydrazino into the amino group which makes this route more laborious. Indeed, hydrogenation of nitro compound **2a** (NH_2NH_2/*Raney*-Ni catalyst, room temperature) proceeded smoothly to 1-deaza-2′-deoxyadenosine (**1a**) in high yield [15].

Detoluoylation of the compounds **6a–c** and **7a–c** was performed in NH_3/MeOH. In the case of **6a**, the NO_2 group was partially displaced by a MeO group [8] yielding 19% of the methoxy derivative **2d** and 68% of nitro derivative **2a**. On deblocking of the N^7-isomer **7a**, the 6-methoxy nucleoside **3d** was the main product (36%), and the 6-nitro compound **3a** was isolated in only 16% yield. Apparently, the *ipso*-substitution is favored when a bulky residue is attached at N(7). The *ipso*-substitution of the NO_2 group was circumvented when 1,4-dioxane/conc. aqueous NH_3 2:1 was used instead of NH_3/MeOH. The low yield (37%) of compound **3a** can be attributed to hydrolytic decomposition due to its very labile *N*-glycosylic bond.

It was of interest to compare the half-life values of the 1-deazapurine N^7- and N^9-(2′-deoxyribofuranosides) **1a** and **2a–d**, and **3a–d**, respectively, in aqueous 0.1N or 0.01N HCl at 20°. Data are shown in *Table 2*. The half-life values were determined

Table 2. *Half-Life Values ($t_{1/2}$) of Proton-Catalyzed Hydrolysis of the Glycosylic Bond of 1-Deazapurine 2′-Deoxyribofuranosides*[a])

	$t_{1/2}$ [min] 0.1N HCl	$t_{1/2}$ [min] 0.01N HCl	λ [nm]
1a	4	63	287
dA	160	> 1000	258
2a	1	12	302
b	27	317	275
c	45	638	281
d	3	39	271
3a	[b])	1	290
b	3	35	270
d	[b])	4	270

[a]) Determined UV-spectrophotometrically at 20°. [b]) Too labile for determination.

UV-spectrophotometrically [16]. Similarly to purine nucleosides, the N^7-regioisomers are always more labile than the N^9-compounds. Compared to 2′-deoxyadenosine (dA), the 1-deaza-2′-deoxyadenosine (**1a**) is very labile at the *N*-glycosylic bond, a factor which plays a role in oligonucleotide synthesis [2].

Structural Assignment and NMR Spectra. Modifications in previous assignments of regioisomeric 1-deazapurine nucleosides were necessary [8–11], due to the methods used for identification. Neither UV spectroscopy nor ^{1}H-NMR spectra give sufficient information for the assignment of regioisomeric 1-deazapurine nucleosides. Unequivocal identification of the glycosylation site as well as of the anomeric configuration of all nucleosides described herein was made by ^{1}H-NOE difference spectroscopy (*Table 3*).

Table 3. *^{1}H-NMR 1D-NOE Data of 1-Deazapurine 2′-Deoxyribofuranosides*[a])[b])

	Irradiated proton	Observed NOE's [%]
1a	H–C(1′)	H–C(8) (7.8), H_α–C(2′) (6.7), H–C(4′) (2.2), OH–C(3′) (1.5)
	H–C(8)	H_β–C(2′) (2.4), H–C(3′) (0.9), OH–C(5′) (1.0)
2a	H–C(1′)	H–C(8) (4.6), H_α–C(2′) (6.9), H–C(4′) (1.8), OH–C(3′) (1.2)
	H–C(8)	H–C(1′) (4.4), H_β–C(2′) (3.4), H–C(3′) (1.4), OH–C(5′) (1.3)
2b	H–C(1′)	H–C(8) (6.1), H_α–C(2′) (6.4), H–C(4′) (2.5), OH–C(3′) (1.6)
	H–C(8)	H–C(1′) (5.5), H_β–C(2′) (3.5), H–C(3′) (1.0), OH–C(5′) (1.2)
2c	H–C(1′)	H–C(8) (5.9), H_α–C(2′) (7.0), H–C(4′) (2.4), OH–C(3′) (1.6)
	H–C(8)	H–C(1′) (5.6), H_β–C(2′) (4.0), H–C(3′) (1.7), OH–C(5′) (1.2)
2d	H–C(1′)	H–C(8) (6.5), H_α–(2′) (6.6), H–C(4′) (2.6), OH–C(3′) (1.4)
	H–C(8)	H–C(1′) (6.9), H_β–C(2′) (3.9), H–C(3′) (1.3), OH–C(5′) (1.1)
3a	H–C(1′)	H–C(8) (1.1), H_α–(2′) (5.3), H–C(4′) (2.2), OH–C(3′) (1.7)
	H–C(8)	H–C(1′) (1.5), H_β–C(2′) (6.0), H–C(3′) (2.5), OH–C(5′) (1.5)
3b	H–C(1′)	H–C(8) (6.8), H–C(6) (5.2), H_α–C(2′) (7.2), H–C(4′) (2.5), OH–C(3′) (1.2)
	H–C(8)	H–C(1′) (6.0), H_β–C(2′) (3.3), H–C(3′) (1.2), OH–C(5′) (1.0)
3d	H–C(1′)	H–C(8) (2.2), H_α–C(2′) (6.4), H–C(4′) (2.0), OH–C(3′) (0.8), MeO (1.5)
	H–C(8)	H–C(1′) (2.5), H_β–C(2′) (4.1), H–C(3′) (1.6), OH–C(5′) (1.3)

[a]) Spectra are measured in (D_6)DMSO at 23°. [b]) Purine numbering.

All N^7- and N^9-isomers give NOE's on H–C(8) upon irradiation of H–C(1′). As no NOE's are observed on H–C(2), the presence of N^3-regioisomers can be excluded. They were observed in the case of ribonucleosides prepared by the *Vorbrüggen* glycosylation of **4a** [9]. The NOE's on the 6-substituents – the MeO group of **3d** and H–C(6) of **3b** – confirm N^7-glycosylation in these cases. As the methoxy compounds were formed by *ipso*-substitution of nitro compounds, the assignment is also unequivocal for the nitro compounds **2a** and **3a**. The NOE's on H_α–C(2′) and H–C(4′) upon irradiation of H–C(1′) confirm β-D-configuration in all cases [17].

As only a few ^{13}C-NMR data exist of 1-deazapurine nucleosides [7] [15] [18], the ^{13}C-NMR spectra were measured (*Table 4*). The assignment was performed on the basis of [^{1}H,^{13}C] gated-decoupled NMR spectra (*Table 5*) as well as 2D ^{1}H,^{13}C-correlation spectra.

The most straightforward assignment is made for C(1) and the bridgehead atoms C(4) and C(5) which show couplings to H–C(1) and H–C(8) for C(5) (*dd*) and couplings to H–C(2), H–C(8), and H–C(1′) for C(4) (*ptd*), respectively. The change of the glycosylation position from N(9) to N(7) results in a significant downfield shift of C(4) (10–15 ppm) and a similar upfield shift of C(5) which is in line with observations on regioisomeric purine N^9- *vs.* N^7-nucleosides [19]. The chemical shifts of C(2) shows minor changes compared to C(1) within the series of 6-substituted 1-deazapurine derivatives (**1a**, **2a–d**, and **3a–d**).

Table 4. *^{13}C-NMR Chemical Shifts δ* [ppm] *of 1-Deazapurine 2′-Deoxyribonucleosides*[a])

Comp.	C(2)[b]) C(8)[c])	C(3a)[b]) C(4)[c])	C(5)[b]) C(2)[c])	C(6)[b]) C(1)[c])	C(7)[b]) C(6)[c])	C(7a)[b]) C(5)[c])	CO
1a	139.4	146.4	144.2	102.3	147.2	123.6	
2a	147.8	143.7	144.8	112.1	150.0	127.2	
b	143.9	146.3	143.7	118.9	127.9	135.6	
c	144.6	147.1	144.6	118.7	133.3	133.0	
d	141.5	148.1	144.6	102.3	157.5	125.4	
3a	147.2	160.4	144.5	112.3	141.8	115.6	
b	144.5	156.3	144.4	118.1	120.0	125.2	
d	142.4	157.6	145.8	101.4	153.1	115.0	
4a	148.0	156.9	144.9	111.5	140.0	118.7	
b	143.8	150.9	143.6	117.6	123.9	130.6	
6a	148.4	144.2	144.9	112.4	149.9	127.4	165.4, 165.5
b	144.3	146.3	144.0	118.8	127.8	135.7	165.3, 165.5
c	145.1	147.1	144.8	119.1	133.5	133.3	165.4, 165.6
7a	146.6	160.0	145.0	112.6	142.1	115.6	165.3, 165.5
b	144.7	156.4	144.5	118.2	120.0	125.0	165.4, 165.6
8a	144.1	146.3	143.9	118.8	128.1	135.8	165.4
b	144.0	146.4	143.8	118.7	127.8	135.6	165.6
c	144.6	147.0	143.9	118.8	133.4	133.0	165.2

	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	Me
1a	84.5	[d])	71.4	88.1	62.1	–
2a	84.1	[d])	70.5	88.1	61.5	–
b	83.6	[d])	71.0	88.1	61.9	–
c	84.0	[d])	70.7	88.0	61.6	–
d	83.9	[d])	71.0	88.0	62.0	–
3a	87.4	40.9	69.4	87.8	60.6	–
b	85.2	40.3	70.6	87.8	61.5	–
d	86.0	41.1	70.2	87.7	61.3	–
6a	84.6	35.7	74.9	82.0	64.0	21.2, 21.3
b	84.0	35.3	75.0	81.6	64.1	21.2, 21.3
c	84.4	35.5	75.0	81.8	64.1	21.2, 21.3
7a	87.3	37.2	74.2	82.0	63.7	21.2, 21.3
b	85.4	36.3	69.6	81.7	64.1	21.2, 21.3
8a	84.1	36.6	76.0	85.3	61.9	21.3
b	83.5	38.6	70.7	84.1	64.4	21.2
c	84.1	36.1	75.6	85.3	61.5	21.1

[a]) In (D_6)DMSO relative to $SiMe_4$. [b]) Systematic numbering. [c]) Purine numbering. [d]) Superimposed by (D_6)DMSO.

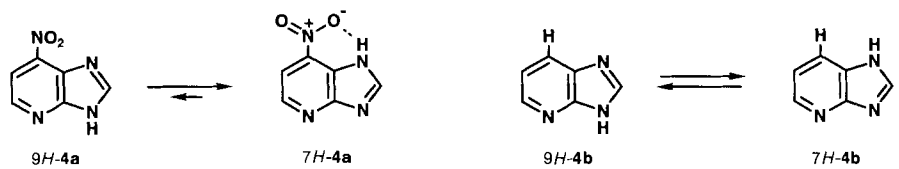
The chemical shifts of the bridgehead C-atoms of the N^7- and N^9-nucleosides allow the assignment of the tautomeric forms of the bases. For this purpose, the ^{13}C-NMR chemical-shift differences of these C-atoms of **2a**, **b** and **3a**, **b** were compared to those of the nucleobases **4a**, **b** in (D_6)DMSO. Good agreement was found using either C(4) or C(5) for the calculation. According to that, the preferred tautomeric form of nitroimidazo-[4,5-*b*]pyridine **4a** is the 7*H*-tautomer 7*H*-**4a** (75%; see *Scheme 2*). Almost equal quantities of the 7*H*- and 9*H*-tautomers are determined for the imidazo[4,5-*b*]pyridine **4b**. The contribution of a 3*H*-tautomer is neglected, as its formation is very unlikely. The higher

Table 5. *^1H,^{13}C-Coupling Constants* [Hz] *of 1-Deazapurine 2′-Deoxyribonucleosides*[a])[b])

Coupling atoms	J(C,H)				
	1a	**2a**	**2b**	**2c**	**2d**
C(2)/*H*–C(2)	210.0	214.6	212.2	213.8	212.6
H–C(1′)	3.8	4.2	3.8	3.8	3.8
C(3a)/*H*–C(2), H–C(5)	*m*[c])	*m*	*m*	*m*	*m*
C(5)/*H*–C(5)	184.5	186.8	183.1	186.1	178.6
C(6)/*H*–C(6)	174.9	171.7	164.0	169.3	163.5
H–C(5)	10.4	10.1	8.9	9.5	8.8
C(7)/*H*–C(7)	–	–	164.9	–	–
H–C(5)	3.5	3.7	3.8	3.6	3.8
H–C(6)	8.8	9.4	11.3	9.9	8.8
C(7)/*H*–C(2)	5.7	5.9	6.0	6.2	6.2
H–C(6)	10.7	12.1	10.1	11.3	11.3
C(1′)/*H*–C(1′)	167.9	168.0	168.2	166.4	167.3
C(2′)/*H*–C(2′)	[d])	[d])	[d])	[d])	[d])
C(3′)/*H*–C(3′)	149.7	148.3	159.7	149.6	149.7
C(4′)/*H*–C(4′)	149.1	148.2	149.8	147.2	147.2
C(5′)/*H*–C(5′)	140.9	140.1	141.6	139.0	139.6

[a]) Data taken from measurements in (D_6)DMSO at 23°. [b]) Systematic numbering. [c]) *m* = Multiplett. [d]) Superimposed by (D_6)DMSO.

Scheme 2



percentage of the 7*H*-tautomer in the case of **4a** can be attributed to a H-bond to the NO_2 group which was already suggested for 7-nitro-1*H*-benzimidazole [20].

As 6-substituted 1-deazapurine 2′-deoxyribonucleosides (see **1a** and **2a–d**) were available in sufficient quantities, the ^{15}N-NMR spectra were measured in (D_6)DMSO (*Table 6*). The assignment of the ^{15}N signals was made on the basis of [^{1}H,^{15}N]-coupled spectra (*Table 7*).

Table 6. *^{15}N-NMR Chemical Shifts* δ [ppm] *of 1-Deazapurine 2′-Deoxyribofuranosides*[a])[b])

	N(1)[c]) N(6)[d])	N(3)[c]) N(4)[d])	N(7)[c]) N(1)[d])	N(9)[c]) N(3)[d])	NH_2	NO_2
1a	–	−150.1	−142.4	−210.5	−313.7	–
dA	−145.1	−157.8	−140.4	−207.6	−299.1	–
2a	–	− 95.2	−142.5	−204.5	–	−13.2
b	–	−112.4	−137.6	−209.5	–	–
c	–	−114.7	−140.7	−205.9	–	–
d	–	−131.9	−142.9	−209.2	–	–

[a]) Measured in (D_6)DMSO relative to nitromethane at 23°. [b]) Assignment from ^{1}H, ^{15}N-coupled spectra. [c]) Purine numbering. [d]) Systematic numbering.

Table 7. *Multiplicities and Coupling Constants* J [Hz] *of Several 1-Deazapurine 2′-Deoxyribofuranosides*[a])[b])

	N(1) H–C(2)	N(3) H–C(2)	N(7) H–C(8)	N(9) H–C(1′),H–C(8)	NH_2 H
1a		*d* (*J* = 10.1)	*d* (*J* = 15.2)	*dd* (*J* = 4.0, 9.0)	*t* (*J* = 90.0)
dA	*d* (*J* = 17.0)	*d* (*J* = 15.0)	*d* (*J* = 12.0)	*d* (*J* = 10.0)	*t* (*J* = 88.0)
2b		*d* (*J* = 10.9)	*d* (*J* = 13.2)	*d* (*J* = 6.5)	–
c		*d* (*J* = 11.0)	*d* (*J* = 13.7)	*d* (*J* = 7.0)	–

[a]) Measured in (D_6)DMSO relative to nitromethane at 23°. [b]) Purine numbering.

The imidazole N-atoms of **1a** show chemical shifts very similar to those of 2′-deoxyadenosine (dA) [21]. N(3) can be assigned according to the coupling with H–C(2), whereas N(7) shows a coupling with H–C(8). The exocyclic NH_2 group of **1a** and dA exhibits a *t*. It can be seen from *Table 6* that the exocyclic NH_2 group of **1a** is shifted upfield compared to the parent dA. This is in line with an increase of the electron density within the π-system of the 1-deazapurine system over that of purines. A strong shift is observed on the δ of N(3) when the 6-substituent changes (*Table 6*).

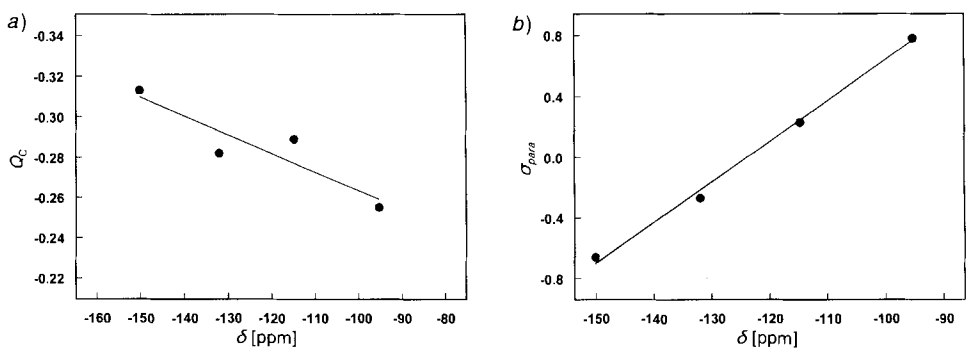


Fig. a) *Correlation of electron charges* Q_C (N(3)) *with* ^{15}*N-NMR chemical shifts at N(3) for* **1a**, **2a**, **2b**, *and* **2d**; b) *correlation of* Hammett *constants* σ_{para} (N(3)) *with N(3)* ^{15}*N-NMR chemical shifts for* **1a**, **2a**, **2b**, *and* **2d**

The ^{15}N-NMR chemical shifts of the nucleosides **1b**, **2a**, **2c**, and **2d** revealed an almost linear dependence on the point-charges at position N(3) which were calculated using Alchemy III [22–24] (*Fig. a*). A linear correlation ($r^2 = 0.99$) was also found in the graph of the ^{15}N-NMR chemical shifts of N(3) *vs.* the σ_{para} *Hammett* constants (*Fig. b*). These results support the assignment of ^{15}N-NMR chemical shifts of the 6-substituted 1-deazapurine 2′-deoxyribonucleosides **1a** and **2a–d**.

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Experimental Part

General. See [2]. Flash chromatography (FC): at 0.5 bar on silica gel *60H* (*Merck*, Darmstadt, Germany). Thin-layer chromatography (TLC): glass plates coated with a 0.25-mm layer of silica gel *G-25* with fluorescent indicator *UV 254* (*Macherey-Nagel*, Germany). Solvent systems for flash chromatography and TLC: light petroleum ether/AcOEt 3:7 (*A*), light petroleum ether/AcOEt 1:1 (*B*), light petroleum ether/AcOEt 7:3 (*C*), $CHCl_3$/MeOH/NH_3 88:10:2 (*D*), and $CHCl_3$/MeOH/NH_3 78:20:2 (*E*).

*7-Nitro-1*H*-imidazo[4,5-*b*]pyridine* (**4a**) was prepared as described [25]. ^{1}H-NMR ((D$_6$)DMSO): 8.05 (*d*, *J* = 5.3, H–C(6)); 8.73 (*d*, *J* = 5.4, H–C(5)); 9.00 (*s*, H–C(2)); 13.50 (*s*, NH).

Glycosylation of **4a** *with 2-Deoxy-3,5-di-*O*-(4-toluoyl)-α-*D*-*erythro*-pentofuranosyl Chloride* (**5**). *Method A*: Powdered KOH (1.4 g, 25.0 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1; 100 µl, 0.24 mmol) were added to a soln. of **4a** (800 mg, 4.9 mmol) in dry MeCN (100 ml) at r.t. with stirring. After 15 min, **5** [26] (2.1 g, 5.4 mmol) was added in portions, and stirring was continued for another 20 min at r.t. Insoluble material was filtered off and the solvent evaporated. The oily residue was chromatographed (silica gel *60H*, column 30 × 3 cm, *B*).

Method B: As described for *Method A*, except that the reaction temp. was 0° and the reaction time 3 h.

*3-[2-Deoxy-3,5-di-*O*-(4-toluoyl)-β-*D*-erythro-pentofuranosyl]-7-nitro-3*H*-imidazo[4,5-*b*]pyridine* (**6a**): From the faster migrating zone (solvent *B*), **6a** was obtained as a colourless foam (*Method A:* 1.43 g, 57%; *Method B:* 1.21 g, 48%). Colorless needles. M.p. 123° (MeOH); [8]: 69–71°. TLC (*B*): R_f 0.5. ^{1}H-NMR ((D$_6$)DMSO): 2.35, 2.39 (2*s*, 2 Me); 2.87 (*m*, H$_\alpha$–C(2′)); 3.45 (*m*, H$_\beta$–C(2′)); 4.55–4.68 (*m*, H–C(4′), 2 H–C(5′)); 5.85 (*m*, H–C(3′)); 6.74 (*t*, *J* = 6.7, H–C(1′)); 7.25–7.37 (2*d*, *J* = 7.9, arom. H); 7.79–7.96 (2*d*, *J* = 7.7, arom. H); 8.01 (*d*, *J* = 5.3, H–C(6)); 8.61 (*d*, *J* = 5.2, H–C(5)); 9.02 (s, H–C(2)). Anal. calc. for $C_{27}H_{24}N_4O_7$ (516.5): C 62.79, H 4.68, N 10.85; found: C 62.91, H 4.65, N 10.79.

*1-[2-Deoxy-3,5-di-*O*-(4-toluoyl)-β-*D*-erythro-pentofuranosyl]-7-nitro-1*H*-imidazo[4,5-*b*]pyridine* (**7a**): The slower migrating zone (solvent *A*) yielded **7a** as a light yellow foam (*Method A:* 400 mg, 16%; *Method B:* 150 mg, 6%). TLC (*A*): R_f 0.3. ^{1}H-NMR ((D$_6$)DMSO): 2.35, 2.39 (2*s*, 2 Me); 2.95 (*m*, H$_\alpha$–C(2′)); 3.24 (*m*, H$_\beta$–C(2′)); 4.43–4.67 (*m*, H–C(4′), 2 H–C(5′)); 5.62 (*m*, H–C(3′)); 6.60 (*t*, *J* = 5.8, H–C(1′)); 7.23–7.37 (2*d*, *J* = 8.0, arom. H); 7.62 (*d*, *J* = 8.0, arom. H); 7.84 (*d*, *J* = 5.2, H–C(6)); 7.91 (*d*, *J* = 8.0, arom. H); 8.65 (*d*, *J* = 5.4, H–C(5)); 9.07 (*s*, H–C(2)). Anal. calc. for $C_{27}H_{24}N_4O_7$ (516.5): C 62.79, H 4.68, N 10.85; found: C 62.73, H 4.74, N 10.87.

*3-(2-Deoxy-β-*D*-erythro-pentofuranosyl)-7-nitro-3*H*-imidazo[4,5-*b*]pyridine* (**2a**) *and 3-(2-Deoxy-β-*D*-erythro-pentofuranosyl)-7-methoxy-3*H*-imidazo[4,5-*b*]pyridine* (**2d**) were prepared as described [8].

2a: Pale yellow crystals. M.p. 132–133° (acetone). UV (MeOH): 309 (5800). ^{1}H-NMR ((D$_6$)DMSO): 2.43 (*m*, H$_\alpha$–C(2′)); 2.79 (*m*, H$_\beta$–C(2′)); 3.52–3.70 (*m*, 2 H–C(5′)); 3.93 (*d*, *J* = 3.6, H–C(4′)); 4.48 (*m*, H–C(3′)); 5.02 (*t*, *J* = 5.4, OH–C(5′)); 5.40 (*d*, *J* = 4.1, OH–C(3′)); 6.59 (*t*, *J* = 6.5, H–C(1′)); 8.02 (*d*, *J* = 5.3, H–C(6)); 8.68 (*d*, *J* = 5.3, H–C(5)); 9.04 (*s*, H–C(2)).

2d: UV (MeOH): 253 (10300). ^{1}H-NMR ((D$_6$)DMSO): 2.30 (*m*, H$_\alpha$–C(2′)); 2.75 (*m*, H$_\beta$–C(2′)); 3.55 (*m*, 1 H–C(5′)); 3.63 (*m*, 1 H–C(5′)); 3.90 (*m*, H–C(4′)); 4.07 (*s*, MeO); 4.44 (*m*, H–C(3′)); 5.18 (*t*, *J* = 5.8, OH–C(5′)); 5.30 (*d*, *J* = 4.0, OH–C(3′)); 6.48 (*t*, *J* = 7.0, H–C(1′)); 6.88 (*d*, *J* = 5.5, H–C(6)); 8.21 (*d*, *J* = 5.5, H–C(5)); 8.49 (*s*, H–C(2)).

*1-(2-Deoxy-β-*D*-erythro-pentofuranosyl)-7-nitro-1*H*-imidazo[4,5-*b*]pyridine* (**3a**). *Method A:* A soln. of **7a** (800 mg, 1.55 mmol) in 1,4-dioxane (50 ml) was treated with 25% aq. ammonia (25 ml) and stirred for 72 h at 50°. The soln. was evaporated and the residue adsorbed on silica gel and submitted to FC (silica gel, column 15 × 3 cm, *E*). The main zone was evaporated and crystallized from acetone: yellow crystals of **3a** (160 mg, 37%).

Method B: A soln. of **7a** (800 mg, 1.55 mmol) in MeOH (60 ml; sat. with ammonia at 0°) was stirred for 48 h at r.t. After evaporation, the product was purified by FC (silica gel, column 20 × 3 cm, *E*). The faster migrating zone yielded **3a** as yellow solid, which was crystallized from acetone (70 mg, 16%). M.p. 166°. TLC (*E*): R_f 0.4. UV (MeOH): 287 (3300), 319 (3400). ^{1}H-NMR ((D$_6$)DMSO): 2.45 (*m*, H$_\alpha$–C(2′)); 2.68 (*m*, H$_\beta$–C(2′)); 3.48 (*m*, 2 H–C(5′)); 3.84 (*d*, *J* = 3.0, H–C(4′)); 4.35 (*m*, H–C(3′)); 4.87 (*s*, OH–C(5′)); 5.30 (*d*, *J* = 3.8, OH–C(3′)); 6.42 (*t*, *J* = 4.9, H–C(1′)); 7.89 (*d*, *J* = 4.8, H–C(6)); 8.68 (*d*, *J* = 4.9, H–C(5)); 9.12 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{12}N_4O_5$ (280.24): C 47.15, H 4.32, N 19.99; found: C 47.19, H 4.56, N 19.98.

*1-(2-Deoxy-β-*D*-erythro-pentofuranosyl)-7-methoxy-1*H*-imidazo[4,5-*b*]pyridine* (**3d**): The slower migrating zone (see **3a**, *Method B*) yielded **3d** as a colorless solid which was crystallized from acetone (150 mg, 36%). M.p. 148–149°. TLC (*E*): R_f 0.35. UV (MeOH): 258 (sh, 8300), 266 (8500). ^{1}H-NMR ((D$_6$)DMSO): 2.37 (*m*, H$_\alpha$–C(2′)); 2.62 (*m*, H$_\beta$–C(2′)); 3.59 (*m*, 2 H–C(5′)); 3.89 (*m*, H–C(4′)); 4.01 (*s*, MeO); 4.37 (*m*, H–C(3′)); 5.03 (*s*, OH–C(5′)); 5.36 (*d*, *J* = 3.6, OH–C(3′)); 6.62 (*t*, *J* = 6.5, H–C(1′)); 6.96 (*d*, *J* = 5.5, H–C(6)); 8.31 (*d*, *J* = 5.2, H–C(5)); 8.69 (*s*, H–C(2)). Anal. calc. for $C_{12}H_{15}N_3O_4$ (265.3): C 54.33, H 5.70, N 15.84; found: C 54.34, H 5.70, N 15.89.

1H-Imidazo[4,5-b]pyridine (**4b**) was prepared as described [14]. ^{1}H-NMR ((D$_6$)DMSO): 7.22 (*dd*, J = 4.8, 7.7, H–C(6)); 8.02 (*d*, J = 5.2, H–C(7)); 8.35 (*d*, J = 5.0, H–C(5)); 8.45 (*s*, H–C(2)); 12.99 (*s*, NH).

Glycosylation of **4b** *with* **5**. A soln. of **4b** (800 mg, 6.7 mmol) in anh. MeCN (150 ml) containing powdered KOH (1.9 g, 33.9 mmol) and TDA-1 (100 µl, 0.3 mmol) was stirred for 10 min at r.t. Then **5** (2.9 g, 7.5 mmol) was added, and stirring was continued for 20 min. Insoluble material was filtered off and the filtrate evaporated. The resulting oil was chromatographed (silica gel *60H*, column 20 × 3 cm, *A*).

*3-[2-Deoxy-3,5-di-O-(4-toluoyl)-β-*D-erythro-*pentofuranosyl]-3H-imidazo[4,5-b]pyridine* (**6b**): From the fast migrating zone, **6b** was obtained as a colorless foam (1.52 g, 48%). TLC (*A*): R_f 0.4. ^{1}H-NMR ((D$_6$)DMSO): 2.36, 2.39 (2*s*, 2 Me); 2.78 (*m*, H$_\alpha$–C(2′)); 3.47 (*m*, H$_\beta$–C(2′)); 4.55–4.70 (*m*, H–C(4′), 2 H–C(5′)); 5.84 (*m*, H–C(3′)); 6.69 (*'t'*, J = 7.0, H–C(1′)); 7.27–7.38 (*m*, H–C(6), arom. H); 7.85–7.97 (*m*, arom. H); 8.13 (*d*, J = 8.0, H–C(7)); 8.35 (*d*, J = 3.8, H–C(5)); 8.69 (*s*, H–C(2)). Anal. calc. for $C_{27}H_{25}N_3O_5$ (471.5): C 68.78, H 5.34, N 8.91; found: C 68.84, H 5.37, N 8.92.

*3-[2-Deoxy-3-O-(4-toluoyl)-β-*D-erythro-*pentofuranosyl]-3H-imidazo[4,5-b]pyridine* (**8a**): Zone II yielded **8a** (140 mg, 6%) as colorless foam. M.p. 163° (colorless crystals, acetone). TLC (*A*): R_f 0.2. ^{1}H-NMR ((D$_6$)DMSO): 2.40 (*s*, Me); 2.66 (*ddd*, J = 3.2, 5.7, 13.8, H$_\alpha$–C(2′)); 3.15 (*m*, H$_\beta$–C(2′)); 3.71 (*d*, J = 4.0, 2 H–C(5′)); 4.26 (*m*, H–C(4′)); 5.37 (*t*, J = 5.5, OH–C(5′)); 5.64 (*m*, H–C(3′)); 6.64 (*dd*, J = 5.9, 8.6, H–C(1′)); 7.32–7.39 (*m*, H–C(6), arom. H); 7.95 (*m*, arom. H); 8.15 (*d*, J = 7.8, H–C(7)); 8.38 (*d*, J = 4.4, H–C(5)); 8.73 (*s*, H–C(2)). Anal. calc. for $C_{19}H_{19}N_3O_4$ (353.4): C 64.58, H 5.42, N 11.89; found: C 64.71, H 5.48, N 11.90.

*1-[2-Deoxy-3,5-di-O-(4-toluoyl)-β-*D-erythro-*pentofuranosyl]-1H-imidazo[4,5-b]pyridine* (**7b**): Elution with AcOEt gave **7b**/**8b** which were separated by FC (column 20 × 3 cm, *D*). The faster migrating zone yielded **7b** (920 mg, 29%) as colorless foam. TLC (*D*): R_f 0.7. ^{1}H-NMR ((D$_6$)DMSO): 2.36, 2.39 (2*s*, 2 Me); 2.81 (*m*, H$_\alpha$–C(2′)); 3.08 (*m*, H$_\beta$–C(2′)); 4.59 (*m*, H–C(4′), 2 H–C(5′)); 5.73 (*m*, H–C(3′)); 6.61 (*'t'*, J = 6.9, H–C(1′)); 7.17 (*dd*, J = 4.7, 7.9, H–C(6)); 7.28–7.38 (*m*, arom. H); 7.81–7.99 (2*d*, J = 7.9, arom. H); 8.17 (*d*, J = 8.0, H–C(7)); 8.43 (*d*, J = 4.3, H–C(5)); 8.74 (*s*, H–C(2)). Anal. calc. for $C_{27}H_{25}N_3O_5$ (471.5): C 68.78, H 5.34, N 8.91; found: C 68.62, H 5.39, N 8.98.

*3-[2-Deoxy-5-O-(4-toluoyl)-β-*D-erythro-*pentofuranosyl]-3H-imidazo[4,5-b]pyridine* (**8b**): From the slower migrating zone (see **7b**), **8b** (70 mg, 3%) was isolated as a colorless foam. TLC (*D*): R_f 0.6. ^{1}H-NMR ((D$_6$)DMSO): 2.36 (*s*, Me); 2.39 (*m*, H$_\alpha$–C(2′)); 3.01 (*m*, H$_\beta$–C(2′)); 4.16 (*m*, H–C(4′)); 4.41 (*dd*, J = 5.8, 11.7, 1 H–C(5′)); 4.53 (*dd*, J = 4.2, 11.7, 1 H–C(5′)); 4.66 (*m*, H–C(3′)); 5.57 (*d*, J = 4.0, OH–C(3′)); 6.55 (*'t'*, J = 6.6, H–C(1′)); 7.26–7.33 (*m*, H–C(6), arom. H); 7.80 (*d*, J = 8.0, arom. H); 8.10 (*d*, J = 8.0, H–C(7)); 8.35 (*d*, J = 4.5, H–C(5)); 8.63 (*s*, H–C(2)). Anal. calc. for $C_{19}H_{19}N_3O_4$ (353.4): C 64.58, H 5.42, N 11.89; found: C 64.67, H 5.43, N 11.82.

*3-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-3H-imidazo[4,5-b]pyridine* (**2b**). A soln. of **6b** (800 mg, 1.7 mmol) in MeOH (60 ml), saturated with ammonia at 0°, was stirred at r.t. for 36 h. The mixture was evaporated and the residue chromatographed (silica gel *60H*, column 15 × 3 cm, *D*): **2b** (360 mg, 90%) as colorless foam. Crystallization from acetone afforded colorless needles. M.p. 144°. TLC (*D*): R_f 0.4. UV (MeOH): 246 (4900), 282 (8200), 287 (sh, 6400). ^{1}H-NMR ((D$_6$)DMSO): 2.33 (*m*, H$_\alpha$–C(2′)); 2.80 (*m*, H$_\beta$–C(2′)); 3.56 (*m*, 1 H–C(5′)); 3.65 (*m*, 1 H–C(5′)); 3.92 (*m*, H–C(4′)); 4.46 (*m*, H–C(3′)); 5.10 (*t*, J = 5.8, OH–C(5′)); 5.33 (*d*, J = 4.5, OH–C(3′)); 6.53 (*'t'*, J = 6.8, H–C(1′)); 7.31 (*dd*, J = 3.5, 8.0, H–C(6)); 8.11 (*d*, J = 8.0, H–C(7)); 8.36 (*d*, J = 5.0, H–C(5)); 8.68 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{13}N_3O_3$ (235.2): C 56.16, H 5.57, N 17.86; found: C 56.09, H 5.58, N 17.87.

*1-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-1H-imidazo[4,5-b]pyridine* (**3b**). As described for **3a** (see *Method B*), with **7b** (600 mg, 1.3 mmol) in MeOH (50 ml; sat. with NH_3; 16 h). Crystallization from acetone, gave **3b** (220 mg, 72%). Colorless crystals. M.p. 142°. TLC (*D*): R_f 0.2. UV (MeOH): 250 (4100), 282 (10000), 287 (sh, 8200). ^{1}H-NMR ((D$_6$)DMSO): 2.30 (*m*, H$_\alpha$–C(2′)); 2.60 (*m*, H$_\beta$–C(2′)); 3.57 (*m*, 2 H–C(5′)); 3.88 (*m*, H–C(4′)); 4.40 (*m*, H–C(3′)); 5.01 (*t*, J = 5.1, OH–C(5′)); 5.37 (*d*, J = 3.9, OH–C(3′)); 6.38 (*'t'*, J = 6.8, H–C(1′)); 7.31 (*dd*, J = 4.7, 8.1, H–C(6)); 8.20 (*d*, J = 7.2, H–C(7)); 8.42 (*d*, J = 3.8, H–C(5)); 8.72 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{13}N_3O_3$ (235.2): C 56.16, H 5.57, N 17.86; found: C 56.22, H 5.59, N 17.97.

Glycosylation of 7-Chloro-3H-imidazo[4,5-b]pyridine (**4c**) *with* **5**. As described for **4b**, with **4c** (400 mg, 2.6 mmol), MeCN (50 ml), KOH (730 mg, 13.0 mmol), TDA-1 (40 µl, 0.15 mmol; 15 min), and **5** (1.1 g, 2.83 mmol; 20 min). Chromatography on silica gel *60H* (column 10 × 3 cm, *C*).

*7-Chloro-3-[2-deoxy-3,5-di-O-(4-toluoyl)-β-*D-erythro-*pentofuranosyl]-3H-imidazo[4,5-b]pyridine* (**6c**): The main zone yielded **6c** as colorless foam (880 mg, 67%). Crystallization from MeOH afforded colorless plates. M.p. 67–68°. TLC (*C*): R_f 0.3. ^{1}H-NMR ((D$_6$)DMSO): 2.36, 2.40 (*s*, 2 Me); 2.80 (*m*, H$_\alpha$–C(2′)); 3.47 (*m*, H$_\beta$–C(2′)); 4.54–4.67 (*m*, H–C(4′), 2 H–C(5′)); 5.85 (*m*, H–C(3′)); 6.67 (*'t'*, J = 7.0, H–C(1′)); 7.27–7.38 (2*d*,

J = 8.0, arom. H); 7.49 (*d*, J = 5.3, H–C(6)); 7.82–7.97 (2*d*, J = 7.9, arom. H); 8.29 (*d*, J = 5.3, H–C(5)); 8.78 (*s*, H–C(2)). Anal. calc. for $C_{27}H_{24}ClN_3O_5$ (506.0): C 64.10, H 4.78, N 8.30; found: C 64.25, H 4.90, N 8.31.

*7-Chloro-3-[2-deoxy-3-*O*-(4-toluoyl)-β-*D*-*erythro*-pentofuranosyl]-3*H*-imidazo[4,5-*b*]pyridine* (**8c**): The slower migrating zone yielded 30 mg (3%) of **8c**. Colorless foam. TLC (*A*): R_f 0.3. ^{1}H-NMR ((D$_6$)DMSO): 2.40 (*s*, Me); 2.71 (*m*, H$_\alpha$–C(2′)); 3.13 (*m*, H$_\beta$–C(2′)); 3.70 (*m*, 2 H–C(5′)); 4.27 (*m*, H–C(4′)); 5.26 (*t*, J = 5.4, OH–C(5′)); 5.62 (*m*, H–C(3′)); 6.62 (*t*′, J = 7.0, H–C(1′)); 7.37 (*d*, J = 8.0, arom. H); 7.51 (*d*, J = 5.2, H–C(6)); 7.95 (*d*, J = 8.0, arom. H); 8.35 (*d*, J = 5.2, H–C(5)); 8.83 (*s*, H–C(2)). Anal. calc. for $C_{19}H_{18}ClN_3O_4$ (387.8): C 58.84, H 4.68, N 10.83; found: C 58.92, H 4.59, N 10.79.

*7-Chloro-3-(2-deoxy-β-*D*-erythro-pentofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine* (**2c**). As described for **2b**, with **6c** (600 mg, 1.19 mmol) in MeOH (50 ml; sat. with NH_3; 24 h). Crystallization from acetone gave **2c** (280 mg, 88%). Colorless plates. M.p. 149°. TLC (*D*): R_f 0.2. UV (MeOH): 253 (7600), 278 (8100), 284 (sh, 7200). ^{1}H-NMR ((D$_6$)DMSO): 2.34 (*ddd*, J = 3.4, 6.2, 13.2, H$_\alpha$–C(2′)); 2.76 (*m*, H$_\beta$–C(2′)); 3.47–3.67 (*m*, 2 H–C(5′)); 3.89 (*dd*, J = 4.3, 7.4, H–C(4′)); 4.44 (*m*, H–C(3′)); 5.03 (*t*, J = 5.6, OH–C(5′)); 5.35 (*d*, J = 4.1, OH–C(3′)); 6.50 (*t*′, J = 6.7, H–C(1′)); 7.46 (*d*, J = 4.8, H–C(6)); 8.31 (*d*, J = 4.9, H–C(5)); 8.77 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{12}ClN_3O_3$ (269.7): C 48.99, H 4.49, N 15.58; found: C 49.04, H 4.48, N 15.58.

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