84. Synthesis of Certain 5-Substituted 2′-Deoxytubercidin Derivatives

by **Frank Seela*** and **Horst Thomas**

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

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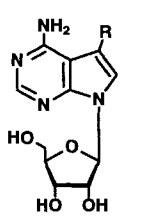
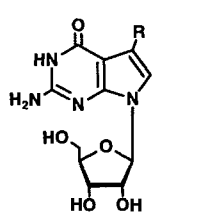
The synthesis of the 7-deaza-2′-deoxy-adenine derivatives **7b–d** with chloro, bromo, or methyl substituents at C(5) is described. Glycosylation of the 5-substituted 4-chloropyrrolo[2,3-*d*]pyrimidines **4b–d** with 2-deoxy-3,5-di-*O*-(4-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**3**) gave the β-D-nucleosides **5b–d**, exclusively. They were deblocked (→**6b–d**) and converted into the tubercidin derivatives **7b–d**.

The 5-methyl group of 2′-deoxyribosylthymine (= 2′-deoxythymidine; T_d) has a major impact on the DNA duplex structure. Oligonucleotides containing 2′-deoxyuridine (U_d) in place of T_d form less stable duplexes [1]. On the other hand, the isosteric replacement of T_d by Br^5U_d containing a 5-substituent of the same size but different electronegativity influences base-pairing pattern and causes mutagenesis. The inspection of the DNA duplex structure suggests that a Me group introduced at the 7-position of purines has considerable steric freedom but hydrophobizes the major groove in a similar manner as observed for the Me group of T_d. However, the introduction of a 7-Me group into purines generates a positive charge which can be compensated by deprotonation of the six-membered ring yielding a zwitterionic structure. Ionic structures can be circumvented if a pyrrolo[2,3-*d*]pyrimidine is replacing the purine moiety, as in 2′-deoxytubercidin (**7a**). The latter was obtained from the naturally occurring ribonucleosides by deoxygenation [2] [3], by convergent syntheses [6], and in the form of the 5′-triphosphate by ribonucleotide reductase [4] [5]. It was already incorporated into oligonucleotides [7–10].

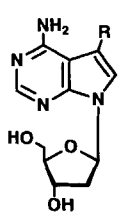
Tubercidin (**1a**) and some 5-substituted pyrrolo[2,3-*d*]pyrimidine ribonucleosides such as toyocamycin (**1b**), sangivamycin (**1c**), queuosine (**2a**), or archaeosine (**2b**) have been already described [11–18]. In particular, the 5-halogeno-substituted derivatives



1a R = H
b R = CN
c R = COOH



2a R = CH_2NH-(cyclopentenediol)
b R = 2-aminoimidazole-4-carboxamide

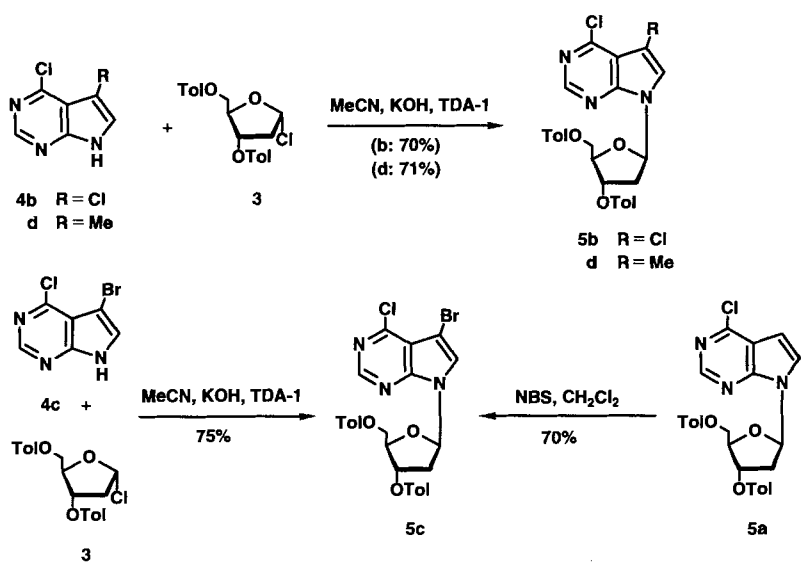


7a R = H
b R = Cl
c R = Br
d R = Me

exhibited a broad spectrum of biological activity. Thus, 5-iodotubercidin is a potent inhibitor of adenosine kinase [19] [20]. Apart from the naturally occurring compounds, a few 5-substituted pyrrolo[2,3-*d*]pyrimidine 2′-deoxyribonucleosides were synthesized [16]. In the following, we report on the synthesis of the pyrrolo[2,3-*d*]pyrimidine deoxynucleosides **7b–d** which are related to purine nucleosides but carry a substituent at position 5. Compounds **7b–d** are key intermediates for later studies on oligonucleotides.

Results and Discussion. – Two routes were employed for the synthesis of 5-substituted tubercidin derivatives: *i*) introduction of the 5-substituent in the nucleobase followed by glycosylation and *ii*) conversion of a preformed nucleoside precursor into a 5-substituted nucleoside. Derivatives of 4-chloropyrrolo[2,3-*d*]pyrimidine (**4a**) with a 5-halogeno substituent were already prepared by the action of *N*-chloro-, *N*-bromo-, or *N*-iodosuccinimide [21–23]. In our hands, 5-Cl compound **4b** was difficult to obtain. However, the reaction went on smoothly using *N*-chlorosuccinimide in THF in the presence of AIBN (= 2,2′-dimethyl-2,2′-azobis[propanenitrile]), with a yield of 85%. Bromo compound **4c** was converted into 4-chloro-5-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4d**) by lithiation with BuLi in THF [23] and subsequent treatment with MeI [23].

Scheme 1



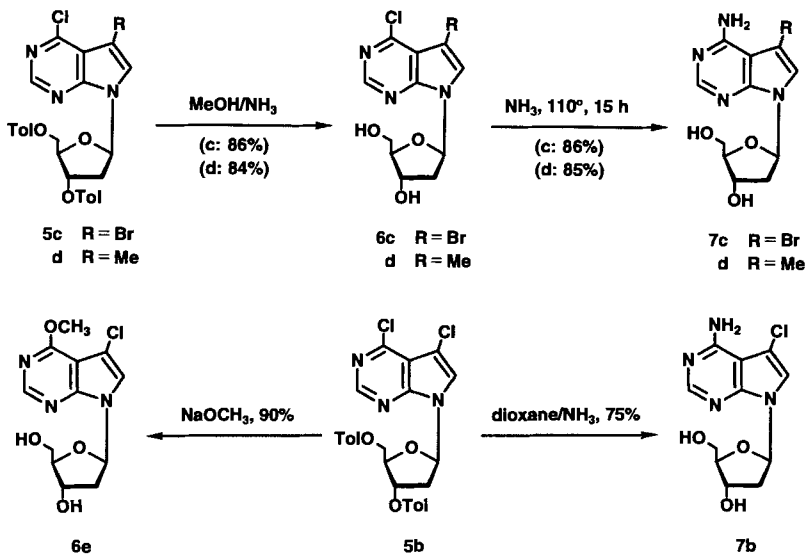
Nucleobase-anion glycosylation [24] [25] of **4b–d** with 2-deoxy-3,5-di-*O*-(4-toluoyl)-α-D-*erythro*-pentofuranosyl chloride [26] (**3**) afforded the toluoyl-protected nucleosides **5b–d** in 70–75% yield (*Scheme 1*). In all cases, the reaction was stereoselective and gave only one regioisomer. All compounds were isolated in crystalline form. Compound **5c** was also prepared by bromination of the protected 4-chloronucleoside **5a** with *N*-bromosuccinimide (NBS) in CH_2Cl_2. The 5-Br and 5-Me compounds **5c, d** were deblocked with methanolic ammonia affording **6c** and **6d** (85% yield, each), respectively (*Scheme 2*). The

4-Cl substituent of **6c** and **6d** could be selectively replaced by NH_2 by treatment with 25% aqueous ammonia in a steel bomb without affecting the 5-Br group (→**7c, d**). Compound **7c** was prepared earlier by direct bromination of 2′-deoxytubercidin (**7a**) with NBS in low yield (11%); as by-product, the internal ether of 4-amino-5-bromo-7-(2-deoxy-β-D-*ery-thro*-pentofuranosyl)-6-hydroxy-7*H*-pyrrolo[2,3-*d*]pyrimidine [27] was formed from the intermediate 5,6-dibromo compound by intramolecular cyclization under the reaction conditions chosen.

In comparison to the 5-Br compound **5c**, the deprotection of the dichloro compound **5b** was difficult, since treatment with methanolic ammonia resulted in a mixture of **6b** (NMR data given below in *Table 2*), **6e**, and **7b**. As the separation of this mixture was difficult, it was treated with methanolic ammonia at elevated temperature (50°) to give the mixture **7b**/**6e** which was easily separated.

The formation of the NH_2 derivative **7b** from **5b** was avoided when the reaction was carried out in 25% aqueous ammonia/dioxane at 60° for 3 days: as the only product, **7b** was isolated in 75% yield (*Scheme 2*). On the other hand, deprotection of **5b** in 1M NaOMe yielded pure **6e** (90%).

Scheme 2



It was reported in the case of pyrrolo[2,3-*d*]pyrimidine ribonucleosides that the position of the halogenation depends on the particular base and the reaction conditions. Therefore, it was necessary to assign the structures of the 5-substituted compounds unequivocally. This was achieved by spectroscopic means.

In case of the aglycons **4b–d**, irradiation of *H*–N(7) resulted in NOE's at *H*–C(6) (*Table 1*). From the 2D $^1H,^{13}C$-NMR correlation spectra, C(6) as well as C(2) were identified. The assignments of C(5) and the bridge-head C-atoms resulted from splitting patterns of the gated-decoupled ^{13}C-NMR spectra (*Table 3*). Therefore, C(5) was established as the position of substitution.

Table 1. *NOE Data of the Pyrrolo[2,3-d]pyrimidines* **4b–d** *and the 2'-Deoxyribonucleosides* **7a, c, d** *upon Irradiation of H–N(7) and H–C(6), Respectively*[a])

	Irradiated proton	Observed NOE [%]
4b	H–N(7)	H–C(6) (9.1)
c	H–N(7)	H–C(6) (10.2)
d	H–N(7)	H–C(6) (7.5)
7a	H–C(6)	H–C(1') (4.1), H–C(3') (0.8)
c	H–C(6)	H–C(1') (3.1), H–C(3') (1.3)
d	H–C(6)	H–C(1') (3.7), H–C(3') (1.4)

[a]) Measured in (D_6)DMSO at 25°.

Table 2. ^{13}*C-NMR Chemical Shifts of Pyrrolo[2,3-d]pyrimidines*[a])

	C(2)	C(4)	C(4a)	C(5)	C(6)	C(7a)	Me	C(1')	C(2')	C(3')	C(4')	C(5')
4a [29]	150.2	150.4	116.5	98.7	128.3	151.7						
b	151.1	149.9	112.6	101.6	126.1	150.5						
c	150.9	150.2	113.6	85.8	128.6	151.0						
d	150.0	150.5	115.3	108.9	125.6	152.0	11.2					
5a [29]	150.7	151.0	117.7	100.2	128.7	151.1		84.0	36.1	75.0	81.5	64.2
b	151.4	150.3	113.4	103.3	126.5	149.7		83.7	36.1	74.6	81.6	63.9
c	151.3	150.8	114.7	87.9	128.3	150.2		83.7	36.1	74.6	81.6	63.9
d	151.3	151.1	116.5	110.6	125.3	150.5	11.2	83.2	36.2	74.9	81.4	64.1
6a [29]	150.5	150.8	117.4	99.7	128.5	150.6		83.4	39.9	70.9	87.7	61.8
b[b])	151.4	149.6	113.3	102.8	125.8	150.3		83.4	39.8	70.7	87.8	61.6
c	151.1	150.5	114.3	87.1	128.2	149.9		83.4	39.8	70.6	87.9	61.5
d	151.0	150.9	116.0	109.9	125.4	150.1	11.1	82.7	40.1	70.9	87.4	61.8
e	151.6	162.3	121.6	102.7	121.6	150.1		83.1	40.6	70.9	87.7	61.8
7a [29]	151.3	157.3	102.8	99.4	121.4	149.5		85.8	40.2	70.8	87.8	61.7
b	152.7	156.8	102.8	99.9	119.0	148.8		83.0	39.8	71.0	87.5	62.0
c [27]	152.5	157.0	101.0	86.8	121.5	149.3		83.0	39.9	71.0	87.5	62.0
d	151.4	157.9	102.7	109.8	119.0	150.3	11.9	82.6	39.4	71.1	87.1	62.2

[a]) Measured in (D_6)DMSO at 25°. [b]) Data taken from the mixture **6b**/**6e**.

Table 3. *J(C,H) Values* [Hz] *of Pyrrolo[2,3-d]pyrimidines*[a])

	4a	**4b**	**4c**	**4d**	**5b**	**5c**	**5d**
J(C(2), H–C(2))	207.6	208.8	196.8	207.0	210.0	210.5	208.8
J(C(2), H–C(4))	14.7	13.8	13.1	13.3	13.8	13.0	13.1
J(C(6), H–C(4a))	4.2	6.3	4.3	3.1	6.3	6.9	*m*
J(C(6), H–C(5))	7.7	10.0	6.7	6.7	2.5	3.1	6.7
J(C(6), H–C(6))	188.5	193.7	194.3	180.6	196.2	196.0	188.3
J(C(1'), H–C(6))					5.0	4.5	5.1

[a]) Data taken from measurements in (D_6)DMSO at 25°.

According to *Table 2*, the C(5) signal of the 5-unsubstituted pyrrolo[2,3-*d*]pyrimidine is shifted upfield upon bromination and downfield upon methylation. The chemical shift of C(5) of the 5-Cl derivatives (**4b–7b**) is more similar to that of the unsubstituted compounds (**4a–7a**). From measurement of NOE spectra, the ratio of '*syn*' to '*anti*' conformation was calculated for the 2'-deoxy-tubercidin derivatives **7a–d** (*Table 1*) [28]. Irradiation of *H*–C(6) resulted in NOE effects at *H*–C(1') and *H*–C(3'). By use of the graph published recently (% '*anti*' = (11.3-f_1(8))/0.1125) [27], the '*syn*'/'*anti*' ratio was calculated: 64% '*anti*' for **7a** [28], 73% '*anti*' for **7c**, and 68% '*anti*' for **7d**.

Oligonucleotide duplex stability is controlled by the number and strength of the H-bonds between the bases, the stacking of the bases, as well as the solvation of the molecule. It is found that the ease of protonation increases from 2′-deoxyadenosine ($pK_a = 3.8$ [7]) *via* the 5-Br derivative **7c** ($pK_a = 4.5$) to the 5-Me compound **7d** ($pK_a = 5.4$). The pK_a of **7d** is similar to that of 2′-deoxytubercidin (**7a**; $pK_a = 5.3$ [7]). As can be expected from earlier investigations N(3) is the site of protonation in all cases. As a result, N(3) of the 5-Me compound **7d** should be the best proton acceptor in the *Watson-Crick* base pair and, therefore, show the highest duplex stability with T_d. On the other hand, it was reported that Me as well as Br substituents introduced at C(8) (purine numbering) of purines destabilize DNA structures. It stays to proof if this is also the case for substituents at C(5) of pyrrolo[2,3-*d*]pyrimidines. Investigations on this subject are in progress.

Experimental Part

General. See [30]. TLC: glass plates coated with a 0.25-mm layer of silica gel *Sil G-25* with fluorescent indicator UV_{254} (*Merck*, Germany). TLC Scanning: *CS-930* TLC scanner (*Shimadzu*, Japan). Column flash chromatography (FC): silica gel *60 H* at 0.5 bar. HPLC: *Merck-Hitachi*, model *655-12* with proportioning valve, model *655A* variable-wavelength monitor, model *L-5000* controller, and *D-2000* integrator; 4 × 25 cm *RP-18-LiChrosorb* column (*Merck*, Germany). Solvent systems: petroleum ether/AcOEt 4:1 (*A*), CH_2Cl_2/MeOH 9:1 (*B*), CH_2Cl_2/MeOH/Et_3N 88:10:2 (*C*), CH_2Cl_2/Et_3N 98:2 (*D*). M.p.: *Büchi SMP-20* apparatus (*Büchi*, Switzerland); uncorrected. NMR Spectra: *AC-250-Bruker* and *500-Bruker* spectrometer, coupling constants of **4a–d** and **5b–d** in *Table 3*. Microanalyses were performed by *Mikroanalytisches Labor Beller*, Göttingen, Germany.

*4,5-Dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**4b**). To a soln. of **4a** [29] (1.0 g, 6.5 mmol) in THF (30 ml), *N*-chlorosuccinimide (950 mg, 7.33 mmol) and AIBN (50 mg) were added. After heating under reflux for 2 h, the solvent was evaporated to yield a yellow solid which was washed with H_2O (2 × 50 ml), filtrated, and recrystallized from AcOEt: colourless crystals (1.0 g, 82%). M.p. 220° ([29]: 222–224°). TLC (silica gel, *B*): R_f 0.4. ^{1}H-NMR ((D_6)DMSO): 7.86 (*s*, H–C(6)); 8.59 (*s*, H–C(2)); 12.86 (br., NH).

*5-Bromo-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**4c**) was prepared as described [22] from **4a** (1.0 g, 6.5 mmol) and *N*-bromosuccinimide (1.2 g, 6.8 mmol) in dry CH_2Cl_2 (50 ml) and crystallized from AcOEt: colourless crystals (1.2 g, 79.4%). M.p. 228° ([22]: 229°). TLC (silica gel, *B*): R_f 0.4. ^{1}H-NMR ((D_6)DMSO): 7.96 (*s*, H–C(6)); 8.64 (*s*, H–C(2)); 12.99 (br., NH).

*4-Chloro-5-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**4d**) was prepared as described [23] by reaction of **4c** (3.0 g, 12.8 mmol) with 1.6M BuLi in hexane (18 ml, 28.8 mmol) and MeI (1.3 ml, 21 mmol) in dry THF at –78°. Crystallization from AcOEt yielded colourless needles (1.2 g, 55.9%). M.p. 221° ([23]: 221–222°). TLC (silica gel, *B*): R_f 0.4. ^{1}H-NMR ((D_6)DMSO): 2.36 (*s*, Me–C(5)); 7.43 (*s*, H–C(6)); 8.51 (*s*, H–C(2)); 12.23 (br., NH).

*4,5-Dichloro-7-[2-deoxy-3,5-di-*O*-(4-toluoyl)-β-*D*-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**5b**). To a soln. of **4b** (1.0 g, 5.3 mmol) in MeCN (60 ml), KOH (0.75 g, 13.4 mmol) and TDA-1 (= tris[2-(2-methoxyethoxy)ethyl]amine; 125 µl, 0.40 mmol) was added. After stirring at r.t. for 10 min, 2-deoxy-3,5-di-*O*-(4-toluoyl)-α-*D*-*erythro*-pentofuranosyl chloride [26] (**3**; 3.0 g, 7.7 mmol) was added and stirring continued for another 10 min. Insoluble material was filtered off and the filtrate cooled to 10° whereby **5b** crystallized. Recrystallization from MeCN yielded colourless needles (2.0 g, 70%). M.p. 142°. TLC (silica gel, *A*): R_f 0.36. UV (MeOH): 232 (50500), 242 (sh, 37700). ^{1}H-NMR ((D_6)DMSO): 2.35, 2.38 (2*s*, 2 arom. Me); 2.77 (*m*, H_α–C(2′)); 3.09 (*m*, H_β–C(2′)); 4.55 (*m*, 2 H–C(5′)); 4.58 (*m*, H–C(4′)); 5.74 (*m*, H–C(3′)); 6.76 (*dd*, *J* = 6.7, H–C(1′)); 7.31, 7.90 (2*dd*, 8 arom. H); 8.17 (*s*, H–C(6)); 8.67 (*s*, H–C(2)). Anal. calc. for $C_{27}H_{23}Cl_2N_3O_5$ (540.41): C 60.01, H 4.29, N 7.78; found: C 60.17, H 4.46, N 7.82.

*5-Bromo-4-chloro-7-[2-deoxy-3,5-di-*O*-(4-toluoyl)-β-*D*-erythro-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**5c**). *Method A:* As described for **5b**, with **4c** (1.4 g, 6.0 mmol), MeCN (80 ml), KOH (0.95 g, 17.0 mmol), TDA-1 (200 µl, 0.60 mmol), and **3** (2.5 g, 6.4 mmol). The filtrate was evaporated and the residue purified by FC (column 20 × 5 cm, *A*) and recrystallized from i-PrOH: colourless needles (2.6 g, 74.1%). M.p. 134°. TLC (silica gel, *A*): R_f 0.35. UV (MeOH): 232 (44700), 242 (32400). ^{1}H-NMR ((D_6)DMSO): 2.36, 2.39 (2*s*, 2 arom. Me); 2.78 (*m*, H_α–C(2′)); 3.11 (*m*, H_β–C(2′)); 4.56 (*m*, 2 H–C(5′)); 4.65 (*m*, H–C(4′)); 5.76 (*m*, H–C(3′)); 6.78 (*dd*, *J* = 6.7, H–C(1′)); 7.32, 7.88 (2 *dd*, 8 arom. H); 8.21 (*s*, H–C(6)); 8.67 (*s*, H–C(2)). Anal. calc. for $C_{27}H_{23}BrClN_3O_5$ (584.86): C 55.49, H 3.96, N 7.18; found: C 55.61, H 4.00, N 7.11.

Method B: To a soln. of **5a** (2.0 g, 4.0 mmol) in CH_2Cl_2 (50 ml), *N*-bromosuccinimide (0.73 g, 4.1 mmol) was added. After heating for 1 h under reflux, the solvent was evaporated and the foam purified by FC (column 20 × 5 cm, *A*) and recrystallization from i-PrOH: colourless needles (1.65 g, 71%).

*4-Chloro-7-[2-deoxy-3,5-di-*O*-(4-toluoyl)-β*-D-erythro-*pentofuranosyl]-5-methyl-7*H*-pyrrolo[2,3-d]pyrimidine* (**5d**). Compound **4d** (1.0 g, 6.0 mmol) was glycosylated as described for **5c** (*Method A*). FC (column 20 × 5 cm, *A*) yielded **5d** (2.2 g, 71%). Colourless needles from MeCN. M.p. 110°. TLC (silica gel, *A*): R_f 0.28. UV (MeOH): 232 (19900), 242 (sh, 13700). ^{1}H-NMR ((D$_6$)DMSO): 2.36, 2.38 (2*s*, 2 arom. Me); 2.27 (*s*, Me–C(5)); 2.74 (*m*, H$_\alpha$–C(2′)); 3.04 (*m*, H$_\beta$–C(2′)); 4.53 (*m*, 2 H–C(5′)); 4.63 (*m*, H–C(4′)); 5.74 (*m*, H–C(3′)); 6.74 (*dd*, *J* = 6.7, H–C(1′)); 7.32, 7.88 (2 *dd*, 8 arom. H); 7.62 (*s*, H–C(6)); 8.56 (*s*, H–C(2)). Anal. calc. for $C_{28}H_{26}ClN_3O_5$ (519.99): C 64.68, H 5.04, N 8.08; found: C 64.84, H 4.95, N 8.07.

*5-Bromo-4-chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-7*H*-pyrrolo[2,3-d]pyrimidine* (**6c**). Compound **5c** (2.3 g, 4.0 mmol) was stirred for 20 h at r.t. in MeOH (80 ml, sat. with NH_3 at 0°). The soln. was evaporated. FC (column 20 × 5 cm, *B*) and crystallization from i-PrOH gave colourless crystals (1.2 g, 86%). M.p. 163°. TLC (silica gel, *B*): R_f 0.24. UV (MeOH): 230 (21400), 270 (3000), 295 (2850). ^{1}H-NMR ((D$_6$)DMSO): 2.31 (*m*, H$_\alpha$–C(2′)); 2.54 (*m*, H$_\beta$–C(2′)); 3.58 (*m*, 2 H–C(5′)); 3.88 (*m*, H–C(4′)); 4.39 (*m*, H–C(3′)); 5.02 (*t*, OH–C(5′)); 5,36 (*d*, OH–C(3′)); 6.67 (*dd*, *J* = 6.7, H–C(1′)); 8.24 (*s*, H–C(6)); 8.71 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{11}BrClN_3O_3$ (348.59): C 37.90, H 3.18, N 12.05; found: C 38.12, H 3.13, N 12.13.

*4-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-5-methyl-7*H*-pyrrolo[2,3-d]pyrimidine* (**6d**). As described for **6c**, **5d** (3.0 g, 5.8 mmol) was deprotected. FC (column 20 × 5 cm, *B*): colourless crystals (1.39 g, 84.4%). M.p. 144°. TLC (silica gel, *B*): R_f 0.37. UV (MeOH): 230 (10300), 272 (sh, 1300), 297 (sh, 2850). ^{1}H-NMR ((D$_6$)DMSO): 2.27 (*m*, H$_\alpha$–C(2′)); 2.37 (*s*, Me–C(5)); 2.49 (*m*, H$_\beta$–C(2′)); 3.58 (*m*, 2 H–C(5′)); 3.88 (*m*, H–C(4′)); 4.40 (*m*, H–C(3′)); 4.98 (*t*, OH–C(5′)); 5.35 (*d*, OH–C(3′)); 6.63 (*dd*, *J* = 6.7, H–C(1′)); 7.68 (*s*, H–C(6)); 8.53 (*s*, H–C(2)). Anal. calc. for $C_{12}H_{14}ClN_3O_3$ (283.72): C 50.80, H 4.97, N 14.81; found: C 50.97, H 4.85, N 14.95.

*5-Chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-7*H*-pyrrolo[2,3-d]pyrimidine* (**6e**) *and 4-Amino-5-chloro-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-7*H*-pyrrolo[2,3-d]pyrimidine* (**7b**). Compound **5b** (3.24 g, 6.0 mmol) in MeOH (80 ml, sat. with NH_3 at 0°) was stirred for 48 h at 50°. The soln. was evaporated and applied to FC (column 20 × 5 cm, *B*). The faster migrating zone yielded after crystallization from i-PrOH, **6e** (360 mg, 20%). Colourless crystals. M.p. 184°. TLC (silica gel, *B*): R_f 0.49. UV (MeOH): 266 (9200), 273 (sh, 7000). ^{1}H-NMR ((D$_6$)DMSO): 2.22 (*m*, H$_\alpha$–C(2′)); 2.45 (*m*, H$_\beta$–C(2′)); 3.53 (*m*, 2 H–C(5′)); 3.82 (*m*, H–C(4′)); 4.04 (*s*, MeO–C(4)); 4.33 (*m*, H–C(3′)); 4.98 (*t*, OH–C(5′)); 5.30 (*d*, OH–C(3′)); 6.59 (*dd*, *J* = 8.7, H–C(1′)); 7.81 (*s*, H–C(6′)); 8.44 (*s*, H–C(2)). Anal. calc. for $C_{12}H_{14}ClN_3O_4$ (299.72): C 48.09, H 4.71, N 14.02; found: C 48.09, H 4.71, N 14.02.

From the slower migrating zone, **7b** was isolated and crystallized from i-PrOH: colourless needles (1.1 g, 64.4%). M.p. 179°. TLC (silica gel, *B*): R_f 0.31. UV (MeOH): 280 (9050). ^{1}H-NMR ((D$_6$)DMSO): 2.18 (*m*, H$_\alpha$–C(2′)); 2.43 (*m*, H$_\beta$–C(2′)); 3.51 (*m*, 2 H–C(5′)); 3.79 (*m*, H–C(4′)); 4.31 (*m*, H–C(3′)); 5.02 (*t*, OH–C(5′)); 5.26 (*d*, OH–C(3′)); 6.49 (*dd*, *J* = 6.9, H–C(1′)); 6.84 (br., NH_2–C(3′)); 7.56 (*s*, H–C(6)); 8.08 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{13}ClN_4O_3$ (284.7): C 46.41, H 4.60, N 19.76; found: C 46.55, H 4.64, N 19.74.

6e *from* **5b** *and NaOMe*. Treatment of **5b** (540 mg, 1.0 mmol) with 1M NaOMe (10 ml) at 50° for 10 h, evaporation, FC (column 20 × 5 cm, *B*), and crystallization from i-PrOH yielded **6e** (270 mg, 90%). M.p. 184°.

7b *from* **5b** *and NH$_3$/Dioxane*. Treatment of **5b** (540 mg, 1.0 mmol) with dioxane/25% aq. NH_3 soln. (10 ml each) at 60° for 72 h, evaporation, FC (column 20 × 5 cm, *B*), and crystallization from i-PrOH gave **7b** as colourless needles (210 mg, 75%). M.p. 179°.

*4-Amino-5-bromo-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-7*H*-pyrrolo[2,3-d]pyrimidine* (**7c**). A suspension of **6c** (1.0 g, 2.9 mmol) in 25% aq. NH_3 soln. (80 ml) was stirred for 15 h at 110° under pressure in a steel bomb. After evaporation the residue was submitted to FC (column 20 × 5 cm, *B*): colourless needles from i-PrOH (0.82 g, 86%). M.p. 172°. TLC (silica gel, *B*): R_f 0.32. UV (MeOH): 280 (9500). ^{1}H-NMR ((D$_6$)DMSO): 2.13 (*m*, H$_\alpha$–C(2′)); 2.43 (*m*, H$_\beta$–C(2′)); 3.54 (*m*, 2 H–C(5′)); 3.81 (*m*, H–C(4′)); 4.33 (*m*, H–C(3′)); 5.04 (*t*, OH–C(5′)); 5.27 (*d*, OH–C(3′)); 6.51 (*dd*, *J* = 6.7, H–C(1′)); 6.81 (br., NH_2–C(4)); 7.64 (*s*, H–C(6)); 8.11 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{13}BrN_4O_3$ (329.2): C 40.13, H 3.98, N 17.02; found: C 40.29, H 3.97, N 17.13.

*4-Amino-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-5-methyl-7*H*-pyrrolo[2,3-d]pyrimidine* (**7d**) was prepared analogously to **7c**: 1.13 g. FC (column 20 × 5 cm, *B*) and crystallization of the product (0.90 g, 85%) gave colourless needles. M.p. 203°. TLC (silica gel, *B*): R_f 0.185. UV (MeOH): 281 (7250). ^{1}H-NMR ((D$_6$)DMSO): 2.11 (*m*, H$_\alpha$–C(2′)); 2.35 (*s*, Me–C(5)); 2.41 (*m*, H$_\beta$–C(2′)); 3.52 (*m*, 2 H–C(5′)); 3.80 (*m*, H–C(4′)); 4.33 (*m*, H–C(3′)); 5.08 (*t*, OH–C(5′)); 5.24 (*d*, OH–C(3′)); 6.02 (*s*, NH_2–C(4)); 6.47 (*dd*, *J* = 6.7, H–C(1′)); 7.10 (*s*, H–C(6)); 8.02 (*s*, H–C(2)). Anal. calc. for $C_{12}H_{16}N_4O_3$ (264.29): C 54.54, H 6.10, N 21.20; found: C 54.28, H 6.12, N 21.11.

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