171. Stereoselective Synthesis of Pyrrolo[2,3-*d*]pyrimidine α- and β-D-Ribonucleosides from Anomerically Pure D-Ribofuranosyl Chlorides: Solid-Liquid Phase-Transfer Glycosylation and ^{15}N-NMR Spectra

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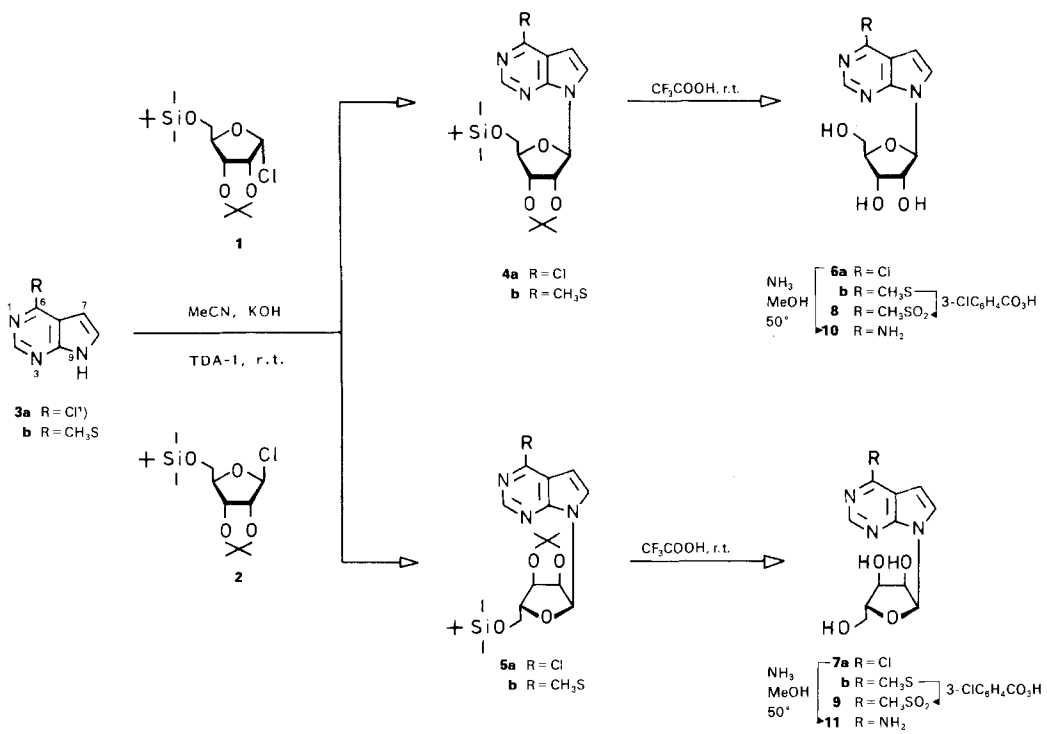
Solid-liquid phase-transfer glycosylation (KOH, tris[2-(2-methoxyethoxy)ethyl]amine (= TDA-1), MeCN) of pyrrolo[2,3-*d*]pyrimidines such as **3a** and **3b** with an equimolar amount of 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-α-D-ribofuranosyl chloride (**1**) [6] gave the protected β-D-nucleosides **4a** and **4b**, respectively, stereoselectively *(Scheme)*. The β-D-anomer **2** [6] yielded the corresponding α-D-nucleosides **5a** and **5b** with traces of the β-D-compounds. The 6-substituted 7-deazapurine nucleosides **6a**, **7a**, and **8** were converted into tubercidin (**10**) or its α-D-anomer (**11**). Spin-lattice relaxation measurements of anomeric ribonucleosides revealed that T_1 values of H–C(8) in the α-D-series are significantly increased compared to H–C(8) in the β-D-series while the opposite is true for T_1 of H–C(1'). ^{15}N-NMR data of 6-substituted 7-deazapurine D-ribofuranosides were assigned and compared with those of 2'-deoxy compounds. Furthermore, it was shown that 7-deaza-2'-deoxyadenosine (= 2'-deoxytubercidin; **12**) is protonated at N(1), whereas the protonation site of 7-deaza-2'-deoxyguanosine (**20**) is N(3).

Introduction. – Pyrrolyl anions have been proved to be effective in regioselective glycosylation of pyrrolo[2,3-*d*]pyrimidines. They were employed first by *Goto* during the synthesis of queosine and were generated with NaH [1].

In 1983, the synthesis of 7-deazaguanosine and -inosine has been reported by our laboratory using liquid-liquid phase-transfer conditions for anion generation and employing benzyl-protected D-ribofuranosyl bromide during glycosylations [2–4]. According to the configuration of the bromo sugar, predominant formation of α-D-configurated glycosylation products was observed (α/β 5:2). Nevertheless, it was recognized that glycosylation proceeded stereoselectively and was controlled by the anomeric ratio of halogenoses present in the reaction mixture. Unfortunately, it was not possible to generate the anomerically pure bromo sugar separately. Moreover, all attempts to use acyl-protected halogenoses failed. While acyloxonium ions are formed as intermediates, nucleophilic attack of the nucleobase resulted in orthoamides which were not rearranged to nucleosides [5]. As a consequence, neighbouring-group participation which directs the incoming nucleobase into the β-face cannot be exploited.

Recently, *Wilcox* and coworkers have described the preparation of α- and β-D-configurated 2,3-*O*-isopropylidene-5-*O*-[(*tert*-butyl)dimethylsilyl]-D-ribofuranosyl chlorides **1** and **2**, respectively [6]. As these halogenoses can be prepared as pure anomers and do not contain a participating substituent at C(2), we have employed them for the synthesis of pyrrolo[2,3-*d*]pyrimidine D-ribofuranosides. In the following, we describe the stereoselective synthesis of either β- or α-D-configurated tubercidin (**10** and **11**, resp.) employing the halogenose **1** or **2** upon solid-liquid phase-transfer glycosylation.

Scheme



As now pyrrolo[2,3-*d*]pyrimidine D-ribonucleosides as well as 2'-deoxy-D-ribonucleosides are available in sufficient quantities, we report also for the first time on their ^{15}N-NMR spectra. They enabled us to assign the protonation sites of purine-isosteric molecules.

Results and Discussion. – *Syntheses.* Preparation of the α-D-halogenose **1** (see *Scheme*), is accomplished by chlorination of 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-β-D-ribofuranose [7] with CCl_4 and tris(dimethylamino)-phosphane according to *Wilcox* [6]. The application of this *Appel* chlorination [8] [9] to sugar chemistry goes back to *Ireland* [10]. The purity of the sugar can be checked by ^{1}H-NMR spectroscopy directly from the reaction mixture (α-D-anomer **1**: *d* for H–C(1) with J = 3.7 Hz; β-D-anomer **2**: *s* for H–C(1) [6]). *In situ* aging of the α-D-halogenose **1** *(Fig. 1)* leads to anomerisation under formation of the thermodynamically more stable β-D-halogenose **2**. As **1** is also unstable during chromatographic workup, it is immediately used after its generation.

It has been reported earlier that 6-chloro-7-deazapurine[1]) (**3a**) [11] as well as 7-deaza-6-(methylthio)purine[1]) (**3b**) [12] are versatile candidates for glycosylations employing nucleobase anions [13] [14]. Therefore, we have set up a solid-liquid phase-transfer system

[1]) Purine numbering as indicated in *Formulae* **3a** and **13** is used throughout the manuscript, except within the *Exper. Part*; *Tables 1–4* provide purine as well as pyrrolo[2,3-*d*]pyrimidine (see *Formula* **10**) numberings.

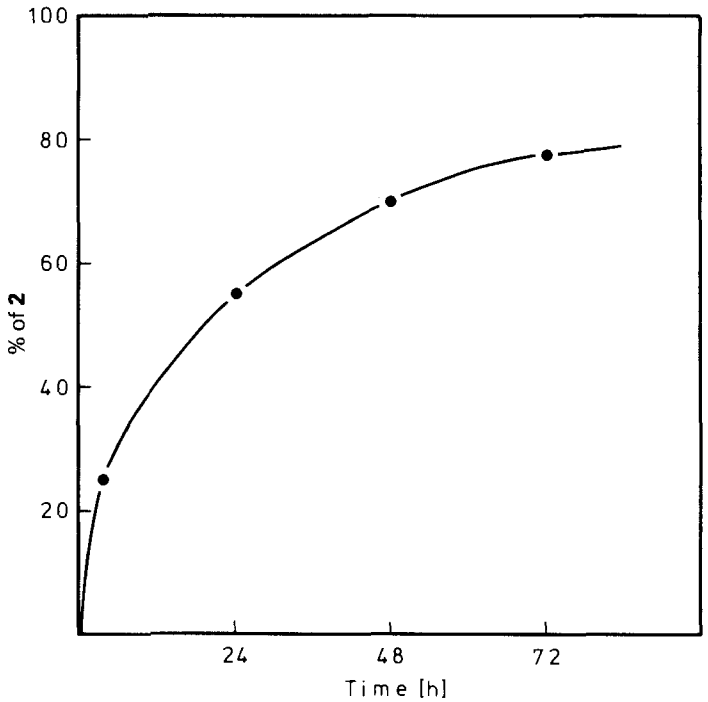


Fig. 1. *Anomerisation of the* α-D-*halogenose* **1** *as a function of time.* Aliquots of the *in-situ* reaction mixture (see *Exper. Part*) were evaporated, the residues dissolved in $CDCl_3$, and ^{1}H-NMR spectra immediately run; the β/α ratio **2**/**1** was taken from the integrals of the H–C(1) signals.

[15] [16] containing **3a** or **3b**, solid KOH, the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (= TDA-1) [17], and MeCN as aprotic solvent under N_2 [18] (see *Scheme*). To this suspension, a fresh THF solution of 1 equiv. of the anomerically pure α-D-halogenose **1** (see *Exper. Part*) is added. After 20 h at r.t., inorganic salt is removed by filtration and anomerically pure **4a** or **4b**, respectively, is isolated upon chromatographic workup, both in 65% yield based on the corresponding aglycone **3** (structural proof by ^{1}H- and ^{13}C-NMR spectra, see *Table 1* and *Exper. Part*).

In addition, we have tested the glycosylation of **3a** by the halogenose **1** in the absence of the catalyst TDA-1. In that case, a 2-fold excess of **3a** is necessary to drive the reaction, and the β-D-nucleoside **4a** is obtained in only 34% yield (68%, based on **1**). Similar yields have been reported by *Robins* and coworkers [19] employing NaH as condensation reagent, 1 equiv. of **1**, and 2 equiv. of the aglycone **3a**. This shows that the presence of the cryptand TDA-1 strongly increases the nucleophilicity of the nucleobase anion by complexation of the alkali cation thus allowing the use of equimolar quantities of educts. As the nucleobase is generally more difficult to obtain, the TDA-1-catalyzed reaction is superior over the non-catalyzed glycosylation.

The configurationally pure β-D-halogenose **2** which can be prepared under thermodynamically controlled conditions (67°) [6] should lead to anomerically pure α-D-nucleosides upon solid-liquid phase-transfer glycosylation. Setting up analogous glycosylation

Table 1. *^{13}C-NMR Shifts of Anomeric Pyrrolo[2,3-d]pyrimidine* D-*Ribofuranosides*[a])[b])

Compd.	C(2)(C(2))	C(4)(C(6))	C(4a)(C(5))	C(5)(C(7))	C(6)(C(8))	C(7a)(C(4))
4a (β)	150.6	150.7	117.6	99.9	129.2	151.0
5a (α)	150.7	150.6	117.1	98.7	129.8	150.7
6a (β)	150.6	150.8	117.5	99.8	128.7	151.3
7a (α)	150.3	150.4	117.0	98.3	131.7	151.1
4b (β)	150.5	160.8	115.9	99.3	126.4	147.6
5b (α)	150.6	160.3	115.5	98.3	127.3	147.6
6b (β)	150.6	160.6	116.0	99.2	126.2	148.3
7b (α)	150.2	159.9	115.4	97.8	129.1	148.2
8 (β)	153.6	155.4	114.0	100.3	131.4	150.3
9 (α)	153.4	154.8	113.6	98.8	134.4	149.8
10 (β)	151.5	157.5	103.1	99.5	122.3	149.9
11 (α)	151.1	157.2	102.3	98.2	124.5	150.0
	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	MeS/$MeSO_2$
4a (β)	89.7	80.9	83.9	86.1	63.3	
5a (α)	85.3	79.6	82.0	82.6	64.9	
6a (β)	87.3	74.4	70.7	85.5	61.5	
7a (α)	84.0	71.0	70.7	85.0	61.6	
4b (β)	89.1	80.8	83.7	85.6	63.1	11.2
5b (α)	84.9	79.6	82.0	82.4	64.8	11.4
6b (β)	87.0	74.2	70.6	85.3	61.6	11.4
7b (α)	83.5	71.0	70.7	84.6	61.6	11.4
8 (β)	87.1	74.5	70.6	85.6	61.5	39.9
9 (α)	85.2	71.0	70.7	84.0	61.6	39.9
10 (β)	87.6	73.7	70.8	85.1	61.9	
11 (α)	83.9	70.9	70.7	83.4	61.6	
	$Me_2C<$	Me_2Si	Me_3C	Me_3C	$Me_2C<$	
4a (β)	113.4	−5.4, −5.6	25.8	18.0	27.1, 25.3	
5a (α)	112.5	−5.5, −5.6	25.8	17.9	25.7, 24.0	
4b (β)	113.2	−5.6, −5.7	25.6	17.9	27.0, 25.2	
5b (α)	112.5	−5.5, −5.4	25.9	18.0	25.7, 24.1	

[a]) In (D_6)DMSO. [b]) Purine numbering in parentheses[1]).

reactions as described above but using **2** gives the protected α-D-nucleosides **5a** and **5b**, respectively, in 46% yield (structural proof by ^{1}H- and ^{13}C-NMR spectra, see *Table 1* and *Exper. Part*), accompanied by *ca.* 10% (^{1}H-NMR) of the corresponding β-D-nucleosides **4a** and **4b**, respectively (see *Scheme*). It is not clear, whether the presence of **4a** and **4b** is due to a non-stereospecific reaction starting with **2** or to a small pre-equilibration **2**⇄**1** in the glycosylation mixture.

Table 2. *^{1}H-NMR Shift Differences (Δδ) of* 'exo'- *and* 'endo'-*Methyl Groups of Isopropylidene-Protected Compounds*

Compd.	Solvent	Δδ [ppm]	Compd.	Solvent	Δδ [ppm]
1 (α)	$CDCl_3$	0.27	**5a** (α)	(D_6)DMSO	0.15
2 (β)	$CDCl_3$	0.12	**4b** (β)	(D_6)DMSO	0.23
4a (β)	(D_6)DMSO	0.22	**5b** (α)	(D_6)DMSO	0.16
4a (β)	$CDCl_3$	0.27			

The ^{1}H-NMR shift differences ($\Delta\delta$) of the isopropylidene methyl groups may be used to determine the anomeric configuration of the protected D-ribonucleosides **4** and **5** [20] [21]. As the $\Delta\delta$ of compound **4** is significantly larger (0.22–0.23 ppm) than that of the corresponding anomers **5** (0.15–0.16 ppm; *Table 2*) the anomeric configuration (β-D) of compounds **4** is in accordance with *Imbach*'s rule [20] [21]. In contrast to this, the anomeric halogenoses **1** and **2** show a reversed behavior *(Table 2)*.

Treatment of the protected β- and α-D-ribonucleosides **4** and **5** with 10% aqueous CF_3COOH gives the deprotected compounds **6** [22] and **7**, respectively (structural proof by ^{1}H- and ^{13}C-NMR spectra, see *Table 1* and *Exper. Part*).

An unequivocal assignment of the almost identical chemical shifts of C(2), C(6), and C(4) for the 6-chloro nucleosides **6a** and **7a** is made on the basis of their gated-decoupled ^{13}C-NMR spectra *(Table 3)*. In addition, these spectra allow the specification of the sequence order of the glyconic ^{13}C-NMR signals (**6a**: C(1′)–C(4′); **7a**: C(4′)–C(1′), increasing field) [23]. Moreover, the coupling constants of C(8) with the corresponding anomeric proton *(Table 3)* give torsion angles $\theta = 145°$ for **6a** and 155° for **7a**. This corresponds to glycosylic torsion angles $\chi = 25$ and $-95°$ in the case of the β-D-anomer **6a** and 35 and $-85°$ for the α-D-anomer **7a** [24] [25]. Therefore, both anomers exhibit *anti*-orientation of the nucleobase.

The 6-(methylthio) nucleosides **6b** and **7b** are oxidised with 3-chloroperbenzoic acid under formation of the sulfones **8** and **9**, respectively (structural proof by ^{1}H- and ^{13}C-NMR spectra, see *Table 1* and *Exper. Part*). No elemental analyses have been obtained as both compounds decompose at slightly elevated temperatures on drying. Surprisingly, the 6-(methylsulfonyl) nucleosides **8** and **9** exhibit strong fluorescence – a phenomenon which is usually encountered only with 2-substituted 7-deazapurine nucleosides [26].

Both, the 6-chloro nucleosides **6a** and **7a** as well as the 6-(methylsulfonyl) nucleosides **8** and **9** are valuable candidates for nucleophilic displacement reactions. Treatment of the β-D-anomer **6a** or the α-D-anomer **7a** with NH_3/MeOH at 50° (24 h) affords tubercidin (**10**) or α-tubercidin (**11**), respectively [27] [28]. Nucleophilic displacement of the 6-(methylsulfonyl) residue of **8** by NH_3/MeOH (50°) is complete already within 12 h but requires chromatographic workup to give **10** in 75% yield.

In order to find generally applicable criteria for the assignment of anomeric nucleosides, we have measured the spin-lattice relaxation times (T_1) of all protons of the deprotected nucleosides **6a, b** and **7a, b**. As can be seen from *Table 4*, nearly all T_1 values are identical in both anomers within experimental error but with two exeptions: T_1 of H–C(8) of the α-D-anomers **7a, b** as well as T_1 of H–C(1′) of the β-D-anomers **6a, b** are

Table 3. *^{13}C,^{1}H Coupling Constants* [Hz] *of Compounds* **6a** *and* **7a** [a][b])

C[c])	H[c])	**6a**	**7a**	C	H	**6a**	**7a**
C(2)(C(2))	H–C(2)(H–C(2))	209.2	208.8	C(1′)	H–C(1′)	164.7	165.0
C(4)(C(6))	H–C(2)(H–C(2))	13.2	13.3	C(2′)	H–C(2′)	146.5	149.4
C(4a)(C(5))	H–C(5)(H–C(7))	8.0	8.5	C(3′)	H–C(3′)	148.1	149.6
C(4a)(C(5))	H–C(6)(H–C(8))	3.4	4.1	C(4′)	H–C(4′)	148.1	145.8
C(5)(C(7))	H–C(5)(H–C(7))	181.7	181.2	C(5′)	H–C(5′)	139.4	140.2
C(5)(C(7))	H–C(6)(H–C(8))	7.2	7.6				
C(6)(C(8))	H–C(6)(H–C(8))	191.7	192.9				
C(6)(C(8))	H–C(5)(H–C(7))	8.0	8.1				
C(6)(C(8))	H–C(1′)	4.6	5.2				

[a]) In (D_6)DMSO. [b]) Digital resolution ±0.5 Hz. [c]) Purine numbering in parentheses[1]).

Table 4. *Spin-Lattice Relaxation Times of Protons of* **6a, b** and **7a, b**[a])

Proton[b])	$T_1 \pm 0.1$ [s]			
	6a (β)	**7a** (α)	**6b** (β)	**7b** (α)
H–C(2)(H–C(2))	4.9	4.9	4.2	4.2
H–C(6)(H–C(8))	0.75	1.2	0.75	1.1
H–C(5)(H–C(7))	2.1	2.1	2.0	2.0
H–C(1′)	1.3	1.0	1.2	0.9
OH	1.0	0.9	1.0	1.0
OH	1.0	0.9	1.0	1.0
OH	1.0	0.9	1.0	1.0
H–C(2′)	0.5	0.4	0.5	0.5
H–C(3′)	0.5	0.5	0.5	0.5
H–C(4′)	0.7	0.7	0.7	0.7
H–C(5′)	0.3	0.3	0.2	0.2
CH_3S			0.7	0.7

[a]) In (D_6)DMSO. [b]) Purine numbering in parentheses[1]).

significantly longer (0.3–0.4 s) than those of their anomeric counterparts. This result is in line with findings reported for anomeric 5-aza-7-deaza-2′-deoxyguanosine [29]. Notwithstanding the fact that the reason for this effect remains unclear, it seems to be an additional criterion for the assignment of anomeric configuration.

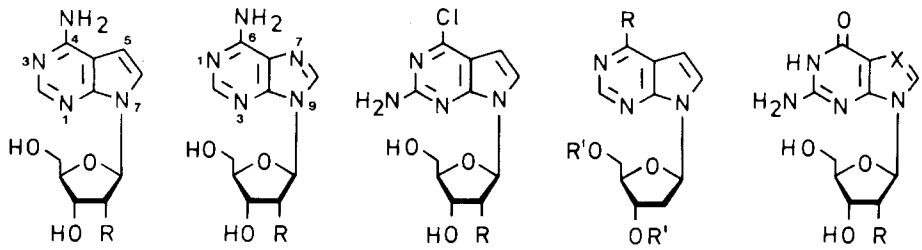
^{15}N-NMR Spectra. As ^{15}N-NMR spectroscopy offers more precise insight into the electronic grounds and chemical behavior than ^{1}H- and ^{13}C-NMR spectra [30], we have measured the ^{15}N-NMR spectra of tubercidin (**10**), 2′-deoxytubercidin (**12**), as well as of their precursors and related nucleosides *(Table 5)*. For this purpose, we have applied the INEPT pulse sequence [31].

As can be seen from *Table 5*, the ^{15}N-NMR spectrum of **10** shows an upfield shift of the signal of the glycosylic N-atom ($\Delta\delta = 15.6$ ppm) as compared to adenosine (**13**) [32]. This reflects the increased electron density of the pyrrole system which causes a shorter glycosylic bond length for **10** [33] in comparison with **13**. The signals of the pyrimidine

Table 5. *^{15}N-NMR Shifts and Coupling Constants of Purine and Pyrrolo[2,3-d]pyrimidine Nucleosides*[a])[b])

Compd.	N(3)(N(1))	N(1)(N(3))	(N(7))	N(7)(N(9))	NH_2
10	−150.5 (J = 15,2.5)	−157.9 (J = 15)		−227.0 (J = 8)	−298.3 (J = 89)
12	−150.3 (J = 18.2)	−157.8 (J = 15)		−223.8 (J = 10)	−298.4 (J = 89)
13	−145.0 (J = 17)	−158.3 (J = 16)	−140.0 (J = 12)	−211.4 (J = 9)	−299.3 (J = 89)
14	−145.1 (J = 19,2.3)	−157.8 (J = 15)	−140.4 (J = 12)	−207.6 (J = 10)	−299.1 (J = 88)
15	−147.5 (J = 3)	−184.0 (J = 3)		−229.1 (J = 9)	−299.5 (J = 89)
16	−147.3 (J = 4)	−184.1 (J = 3)		−225.7 (J = 8)	−299.7 (J = 88)
17	−112.3 (J = 15)	−134.4 (J = 16)		−219.3 (J = 8)	
18	−111.3 (J = 16)	−133.7 (J = 15)		−222.9 (J = 8)	
19	−119.2 (J = 16)	−143.3 (J = 15)		−225.3 (J = 8)	
6a	−112.1 (J = 16)	−134.2 (J = 15)		−222.8 (J = 9)	
7a	−113.1 (J = 16)	−134.7 (J = 15)		−222.7 (J = 9)	
20	−218.1 (J = 90)	−212.6 (J = 3)		−222.6 (J = 8)	−309.7 (J = 89)
21	−233.4 (J = 90)	−214.9 (J = 4)	−132.8 (J = 12)	−210.7 (J = 9)	−307.3 (J = 90)

[a]) In (D_6)DMSO. [b]) Purine numbering in parentheses[1]).



10 R = OH') **13** R = OH') **15** R = OH **20** X = CH, R = H
12 R = H **14** R = H **16** R = H **21** X = N, R = OH

	R	R'
18	Cl	Tol
19	CH_3S	Tol
17	Cl	H

N-atoms of **10** are assigned unequivocally as only N(1) shows a ^2J(N(1), H–C(2)) and a ^3J(N(1), NH_2). Interestingly, only N(1) of **10** is shifted upfield as compared to adenosine (**13**; $\Delta\delta$ = 5.5 ppm), while N(3) remains unaffected. This reflects the higher basicity of N(1) of **10** which is in line with the pK values of protonation (**10**: pK_a 5.5; **13**: pK_a 3.5) [34].

Changing to 2'-deoxytubercidin (**12**) [35], only N(9) undergoes a slight downfield shift ($\Delta\delta$ = 3.2 ppm) demonstrating the γ-substituent effect of the 2'-hydroxy group of the

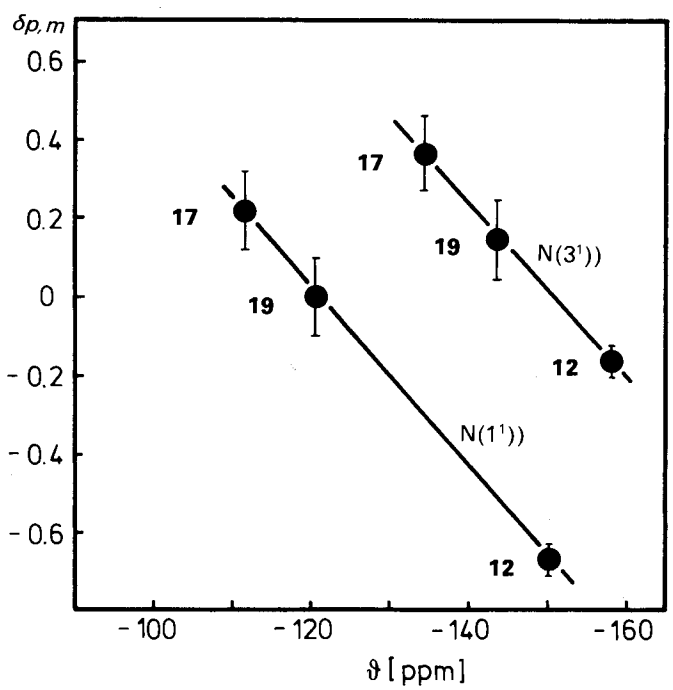


Fig. 2. *Correlation of* Hammett *constants* σ_p (N(3)) *and* σ_m (N(1)) *with* ^{15}*N-NMR chemical shifts for the compounds* **12**, **17** *and* **19**[1])

glyconic moiety [36]. This shift difference is of the same order as that between adenosine (**13**) and 2′-deoxyadenosine (**14**) ($\Delta\delta$ = 3.8 ppm) as well as that for the nucleoside pairs **15**/**16** ($\Delta\delta$ = 3.4 ppm) and **6**/**17** ($\Delta\delta$ = 3.5 ppm). This correlates with the decreased stability of the N-glycosylic bonds of 2′-deoxynucleosides towards proton-catalysed hydrolysis as compared to D-ribonucleosides.

Introduction of toluoyl protecting groups into the glyconic moiety of the 2′-deoxynucleoside **17** causes an upfield shift of N(9) (see **18** in *Table 5*, $\Delta\delta$ = 3.6 ppm), while the pyrimidine N-atoms remain almost unaffected ($\Delta\delta$ < 1 ppm). This points to an altered conformational equilibrium around the N-glycosylic bond in **18**.

The assignment of N(1) and N(3) of the 2′-deoxynucleosides **17**–**19** [13] [37] as well as of the ribonucleosides **6a** and **7a** is tentative as there is no additional coupling of N(1) like in the case of tubercidin (**10**). Nevertheless, it is likely that different 6-substituents affect mainly the chemical shift of N(1) being in α-position to the substitution site. Therefore, the signal which shows the largest shift by changing the 6-substituent is assigned to N(1). This assumption is corroborated by linear correlations of the δ-values of the N(1) and N(3) signals of compounds **12**, **17**, and **19** with the corresponding *Hammett* constants (σ_p, σ_m) of the 6-substituents *(Fig. 2)* [38].

Comparison of the ^{15}N-NMR spectra of the anomeric nucleosides **6a** and **7a** show that all δ-values are identical within experimental error. This demonstrates that different configuration at the anomeric center does not affect the electronic state of the glycosylic N-atom.

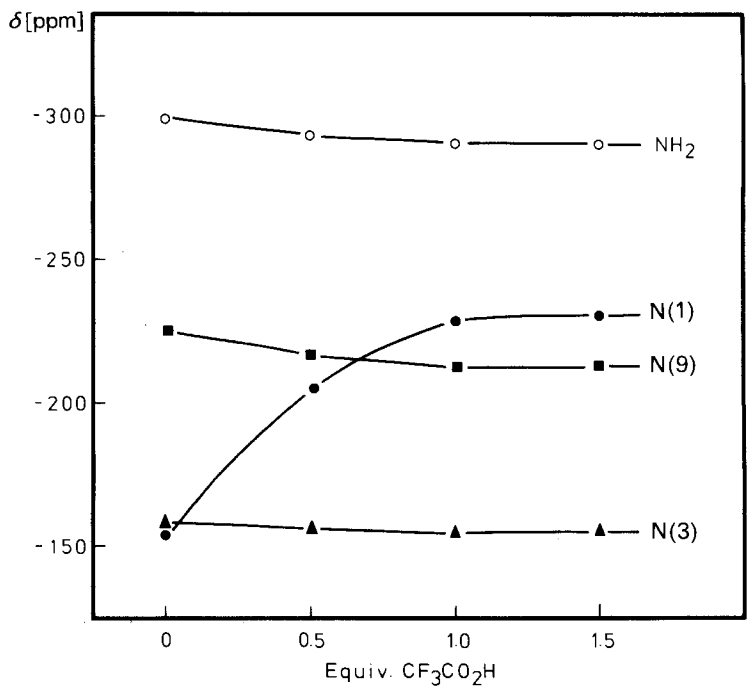


Fig. 3. *^{15}N-NMR Chemical shifts of 2′-deoxytubercidin* (**12**; 0.67M in (D_6)DMSO) *as a function of CF_3COOH concentration*[1])

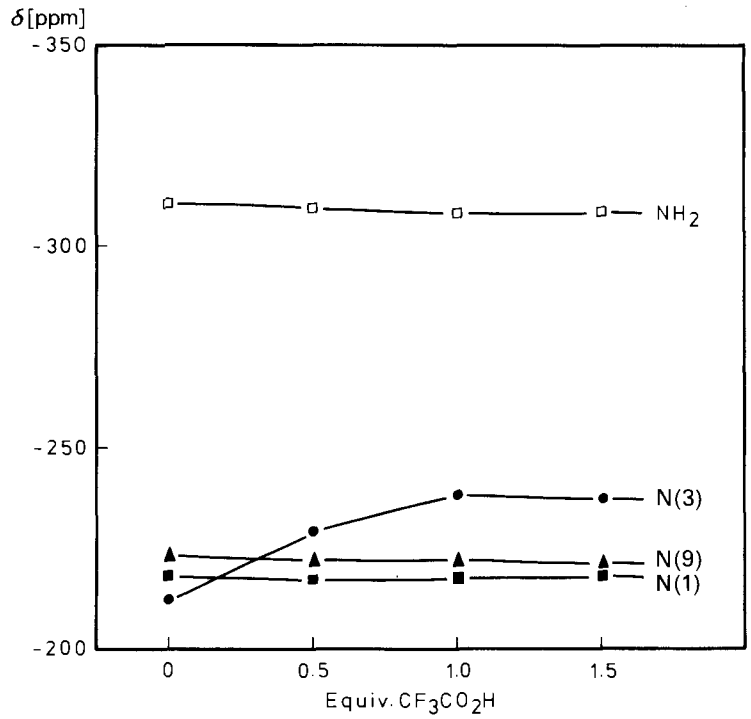


Fig. 4. *^{15}N-NMR Chemical shifts of 7-deaza-2′-deoxyguanosine* (**20**; 0.6M in (D_6)DMSO) *as a function of CF_3COOH concentration*[1])

As ^{15}N-NMR spectroscopy is a valuable tool for determination of protonation sites of N-heterocycles, we have measured the ^{15}N-NMR spectra of 2′-deoxytubercidin (**12**) as a function of CF_3COOH concentration *(Fig. 3)*. As can be seen from *Fig. 3*, N(1) of **12** shows the strongest shift upon addition of CF_3CO_2H, while the other N-atoms are only slightly shifted in the opposite direction. This shows that protonation of 2′-deoxytubercidin (**12**) occurs at N(1) as observed for adenosine [32].

Similar ^{15}N-NMR experiments have been undertaken with 7-deaza-2′-deoxyguanosine (**20**) [39]. Assignment is unproblematic because of the ^1J(N,H) coupling constant of N(1) to H–N(1). As *Table 5* shows, compound **20** has almost identical chemical shifts for N(1) and for the exocyclic NH_2 group as compared to its purine congener **21**. The upfield shift of the glycosylic N-atom is similar to that found for **10** *vs.* **13**. Strong differences, however, are observed for the N(3) signals of **20** *vs.* **21** (downfield shift $\Delta\delta$ = 15.3 ppm). From these data it can be concluded that the N(1) of tubercidin (**10**) is a better proton acceptor than that of adenosine (**13**), while 7-deaza-2′-deoxyguanosine (**20**) is a better proton donator at N(1) than the corresponding purine nucleoside **21**. Moreover, protonation experiments of **20** with CF_3COOH show that N(3) is protonated which is different to guanosine being protonated at N(7) [40] (see *Fig. 4*).

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Experimental Part

General. MeCN was freshly distilled from CaH_2 before use. Anh. THF (99.9%, under N_2, H_2O 0.005%) was purchased from *Aldrich Chemicals* (Milwaukee, USA). TLC: silica gel *SIL G-25 UV$_{254}$* plates (*Macherey-Nagel & Co.*, Düren, FRG). Column flash chromatography (FC): 0.5 bar; silica gel *60H* (*Merck*, FRG); connection to *Uvicord S* detector and *Multirac* fractions collector (*LKB Instruments*, Bromma, Sweden). Solvent systems; *A* = $CHCl_3$/MeOH 95:5, *B* = $CHCl_3$/MeOH 9:1, *C* = AcOEt/light petroleum 2:8, *D* = AcOEt/light petroleum 4:6, *E* = MeOH/H_2O 2:8. M.p.: *Büchi-SMP-20* apparatus (*Büchi*, Switzerland); not corrected. UV spectra (λ_{max} (ε) in nm): *Hitachi-150-20* spectrophotometer (*Hitachi*, Japan). NMR spectra: at 25°; *AC-250* spectrometer equipped with an *Aspect 3000* data system, an array processor, and a variable temp. control unit *B-VT 1000* (*Bruker*, FRG); operational frequencies 250.133 (^{1}H), 62.898 (^{13}C), and 25.346 MHz (^{15}N); δ's rel. to Me_4Si as internal standard for ^{1}H and ^{13}C and rel. to CH_3NO_2 (containing 5% of (D_6)DMSO for frequence stabilisation) for ^{15}N (0 ppm); digital resolutions 0.275 Hz/pt (^{1}H), 0.526 Hz/pt (^{13}C), 1.220 Hz/pt (^{15}N). Spin-lattice relaxation times (T_1): inversion recovery technique; pulse sequence D_1-180°-*VD*-90°-FID with 18 variable delays (*VD*) of 0.1–1.5, 2.0, 3.0, and 4.0 s (D_1 = 10 s; ^{1}H-90° pulse width, 10.8 µs). ^{15}N-NMR spectra: 10-mm probehead, either application of the basic INEPT pulse sequence D_1-90°-D_2-180°-D_2-90°; (^{1}H) and 180°-90°-FID (^{15}N; D_1 = 1 s; ^{1}H-90°, 28.8 µs; ^{15}N-90°, 11.2 µs; D_2 = 0.25/J(N, H) = 50, 25, or 2.8 ms) or from inverse-gated decoupled spectra without NOE (pulse sequence delay, 10 s; pulse delay, 5 ms). In all cases, the FID was line-broadened before *Fourier* transformation by a factor which was identical to the corresponding digital resolution. Elemental analyses were performed by Mikroanalytisches Labor Beller (Göttingen FRG).

*4-Chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**3a**) was synthesised according to *Davoll* [11] and *4-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**3b**) according to *Mizuno et al.* [12].

*5-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-β-*D*-ribofuranose* was prepared according to *Kane et al.* [7]. M.p. 50° ([7]: 47°). ^{1}H-NMR ((D_6)DMSO): 0.06 (*s*, $(CH_3)_2Si$); 0.88 (*s*, *t*-Bu); 1.25, 1.37 (2*s*, 2 CH_3); 3.59 (*d*, *J* = 7.0, H–C(5)); 3.95 (*t*, *J* = 7.0, H–C(4)); 4.46 (*d*, *J* = 5.8, H–C(2)); 4.63 (*d*, *J* = 5.8, H–C(3)); 5.18 (*d*, *J* = 4.4, H–C(1)); 6.44 (*d*, *J* = 4.4, HO–C(1)). ^{13}C-NMR ((D_6)DMSO): –5.3, –5.4 ($(CH_3)_2Si$); 18.0 ($(CH_3)_3C$); 25.8 ($(CH_3)_3C$); 24.8, 26.5 (2 CH_3); 64.4 (C(5)); 81.9 (C(3)); 85.7 (C(4)); 86.0 (C(2)); 101.9 (C(1)); 111.2 ($(CH_3)_2C$).

*5-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-α-*D*-ribofuranosyl Chloride* (**1**), [6] *in THF Solution.* To a stirred soln. of 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-β-D-ribofuranose (1.54 g, 4 mmol) in anh. THF (15.8 ml), CCl_4 (0.6 ml, 6.2 mmol) was added with a syringe under N_2. The soln. was cooled to –78°, and tris(dimethylamino)phosphane (0.96 ml, 5.2 mmol) added dropwise within 15 min. Stirring was continued for 2 h at –78°. Occasional gel formation was reduced by temporary increase of the temp. to –50°. Then the soln. was allowed to warm up slowly to r.t., evaporated to ½ of its volume without heating, and directly used for the glycosylations. Anal. data of **1** were obtained from a small portion of the evaporated mixture: TLC (*D*): R_f 0.9. ^{1}H-NMR ($CDCl_3$): –0.03, –0.01 (2*s*, 2 $(CH_3)_2Si$); 0.81 (*s*, *t*-Bu); 1.31, 1.58 (2*s*, 2 CH_3); 3.73 (*d*, *J*(5,4) = 2.9, H–C(5)); 4.31 (*dd*, *J*(4,5) = 2.8, H–C(4)); 4.70 (*m*, H–C(2), H–C(3)); 6.08 (*d*, *J*(1,2) = 3.7, H–C(1)).

*5-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-β-*D*-ribofuranosyl Chloride* (**2**) [6] *in THF Solution.* The THF soln. of **2** was prepared as described for **1**, exept that the reaction temp. was 67° and the reaction time 30 min. Anal. data of **2** were obtained from a small portion of the evaporated soln. TLC (*D*): R_f 0.9. ^{1}H-NMR ($CDCl_3$): –0.3 (*s*, $(CH_3)_2Si$); 0.52 (*s*, *t*-Bu); 0.95, 1.07 (2*s*, 2 CH_3); 3.4 (*m*, H–C(5); superimposed by THF); 3.94 (*t*, *J* = 7.4, H–C(4)); 4.44 (*d*, *J*(3,2) = 5.8, H–C(3)); 4.59 (*d*, *J*(2,3) = 5.8, H–C(2)); 5.72 (*s*, H–C(1)).

*4-Chloro-7-{5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-β-*D*-ribofuranosyl}-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**4a**). a) *In the Presence of TDA-1.* To a stirred suspension of powdered KOH (500 mg, 8.9 mmol) in anh. MeCN (25 ml; r.t., N_2), tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1; 26 µl, 0.08 mmol) was added. After 10 min, **3a** (615 mg, 4 mmol) was dissolved in the mixture and stirring continued for another 10 min. Upon addition of the freshly prepared THF soln. of **1** [6] (4.9 mmol, calculated on the basis of 100% yield of **1**), the mixture turned dark-brown. Insoluble material was filtered off after 20 h. The filtrate was evaporated, and FC (20 × 6 cm, *C*) of the residue gave, from the main zone, **4a** as a colorless gum (1.06 g, 65%). TLC (*D*): R_f 0.8. UV (MeOH): 273 (4800). ^{1}H-NMR ($CDCl_3$): 0.05 (*s*, $(CH_3)_2Si$); 0.88 (*s*, *t*-Bu); 1.37, 1.64 (2*s*, 2 CH_3); 3.83 (*m*, *J* = 3.7, H–C(5')); 4.34 (*m*, *J* = 3.2, H–C(4')); 4.94 (*m*, *J* = 2.9, H–C(3')); 5.05 (*m*, *J* = 2.9, H–C(2')); 6.39 (*d*, *J* = 3.0, H–C(1')); 6.61 (*d*, *J* = 3.8, H–C(5)); 7.56 (*d*, *J* = 3.8, H–C(6)); 8.65 (*s*, H–C(2)). ^{1}H-NMR ((D_6)DMSO): 0.03 (*s*, $(CH_3)_2Si$); 0.80 (*s*, *t*-Bu); 1.33, 1.55 (2*s*, 2 CH_3); 3.77 (*m*, H–C(5')); 4.21 (*m*, *J* = 3.3, H–C(4')); 4.94 (*m*, *J* = 3.1, H–C(3')); 5.28 (*m*, *J* = 3.6, H–C(2')); 6.35 (*d*, *J* = 2.6, H–C(1')); 6.75 (*d*, *J* = 3.7, H–C(5)); 7.90 (*d*, *J* = 3.7, H–C(6)); 8.68 (*s*, H–C(2)). Anal. calc. for $C_{20}H_{30}ClN_3O_4Si$: C 54.59, H 6.87, N 9.55; found: C 54.50, H 6.82, N 9.43.

b) *Without Catalyst.* The reaction was carried out as described above but without TDA-1 and a two-fold excess of **3a** (1.23 g, 8 mmol). Yellowish gum (555 mg, 68% based on **1**), identical with **4a** obtained by *Method a.*

*7-{5-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-β-*D*-ribofuranosyl}-4-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine* (**4b**). As described for **4a**, **3b** (661 mg, 4 mmol) was reacted with a THF soln. of **1** (4 mmol): **4b** as a yellowish gum (1.17 g, 65%). TLC (*D*): R_f 0.9. UV (MeOH): 292 (15800), 249 (8400), 221 (26300). ^{1}H-NMR ((D$_6$)DMSO): 0.03 (*s*, $(CH_3)_2Si$); 0.81 (*s*, *t*-Bu); 1.32, 1.55 (2*s*, 2 CH_3); 2.65 (*s*, CH_3S); 3.71 (*m*, H–C(5′)); 4.17 (*m*, *J* = 5.0, 8.1, H–C(4′)); 4.94 (*m*, *J* = 2.9, 6.3, H–C(3′)); 5.25 (*m*, *J* = 2.8, 6.3, H–C(3′)); 6.33 (*d*, *J* = 2.8, H–C(1′)); 6.59 (*d*, *J* = 3.7, H–C(5)); 7.67 (*d*, *J* = 3.7, H–C(6)); 8.65 (*s*, H–C(2)). Anal. calc. for $C_{21}H_{33}N_3O_4SSi$: C 55.85, H 7.36, N 9.30; found: C 55.95, H 7.36, N 9.30.

*4-Chloro-7-{5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-α-*D*-ribofuranosyl}-7H-pyrrolo[2,3-d]pyrimidine* (**5a**). As described for **4a**, **3a** (615 mg, 4 mmol) was reacted (26 h) with the freshly prepared THF soln. of **2** (4 mmol). From the main zone, **5a** was obtained a colorless gum (750 mg, 46%). TLC (*D*): R_f 0.8. UV (MeOH): 273 (4950). ^{1}H-NMR ((D$_6$)DMSO): 0.09, 0.10 (2*s*, $(CH_3)_2Si$); 0.91 (*s*, *t*-Bu); 1.23, 1.38 (2*s*, 2 CH_3); 3.81 (*m*, *J* = 2.9, H–C(5′)); 4.39 (*m*, H–C(4′)); 4.9 (*m*, H–C(2′), H–C(3′)); 6.67 (*d*, *J* = 3.7, H–C(5)); 6.76 (*d*, *J* = 3.9, H–C(1′)); 7.72 (*d*, *J* = 3.7, H–C(6)); 8.63 (*s*, H–C(2)). Anal. calc. for $C_{20}H_{30}ClN_3O_4Si$: C 54.59, H 6.87, N 9.55; found: C 54.61, H 6.91, N 9.63.

*7-{5-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-O-(methylethylidene)-α-*D*-ribofuranosyl}-4-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine* (**5b**). As described for **4a**, **3b** (661 mg, 4 mmol) was reacted with a THF soln. of **2** (4 mmol): **5b** as a yellowish gum (810 mg, 45%). TLC (*D*): R_f 0.8. UV (MeOH): 292 (15200), 249 (7800), 221 (26000). ^{1}H-NMR ((D$_6$)DMSO): 0.11, 0.12 (2*s*, $(CH_3)_2Si$); 0.94 (*s*, *t*-Bu); 1.24, 1.40 (2*s*, 2 CH_3); 2.66 (*s*, CH_3S); 3.81 (*m*, *J* = 3.0, H–C(5′)); 4.35 (*m*, H–C(4′)); 4.86 (*m*, H–C(2′), H–C(3′)); 6.55 (*d*, *J* = 3.7, H–C(5)); 6.73 (*d*, *J* = 4.0, H–C(1′)); 7.53 (*d*, *J* = 3.7, H–C(6)); 8.61 (*s*, H–C(2)). Anal. calc. for $C_{21}H_{33}N_3O_4SSi$: C 55.85, H 7.36, N 9.30; found: C 55.99, H 7.57, N 9.21.

*4-Chloro-7-(β-*D*-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine* (**6a**). A soln. of **4a** (1.06 g, 2.41 mmol) in 90% aq. CF_3COOH (3 ml) was stirred for 1 h at r.t. The mixture was evaporated, and traces of CF_3COOH were removed by repeated coevaporation with MeOH. FC (10 × 6 cm, *A*) of the residue gave, from the main zone, **6a** as colorless needles (612 mg, 89%), after crystallization from H_2O. M.p. 160–162° ([22]: 160°). TLC (*B*): R_f 0.78. UV (MeOH): 273 (4800). ^{1}H-NMR ((D$_6$)DMSO): 3.61 (*m*, H–C(5′)); 3.94 (*m*, *J* = 3.4, H–C(4′)); 4.12 (*m*, *J* = 3.4, H–C(3′)); 4.32 (*m*, *J* = 5.3, H–C(2′)); 5.08 (*t*, *J* = 5.1, OH–C(5′)); 5.21, 5.42 (2*d*, 2 OH); 6.21 (*d*, *J* = 6.0, H–C(1′)); 6.76 (*d*, *J* = 3.7, H–C(5)); 8.01 (*d*, *J* = 3.7, H–C(6)); 8.67 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{12}ClN_3O_4$: C 46.25, H 4.23, N 14.71; found: C 46.41, H 4.33, N 14.73.

*4-(Methylthio)-7-(β-*D*-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine* (**6b**). As described for **6a**, 500 mg (1.11 mmol) of **4b** was treated with 10% aq. CF_3COOH (3 ml). Crystalline **6b** (225 mg, 68%) was obtained by crystallization from MeOH. M.p. 190–192° ([22]: 193–194°). TLC (*B*): R_f 0.4. UV (MeOH): 292 (16000), 250 (8500), 222 (26800). ^{1}H-NMR ((D$_6$)DMSO): 2.66 (*s*, CH_3S); 3.59 (*m*, H–C(5′)); 3.93 (*m*, H–C(4′)); 4.12 (*m*, H–C(3′)); 4.42 (*m*, H–C(2′)); 5.2, 5.4 (br., 3 OH); 6.17 (*d*, *J* = 6.1, H–C(1′)); 6.61 (*d*, *J* = 3.7, H–C(5)); 7.78 (*d*, *J* = 3.7, H–C(6)); 8.64 (*s*, H–C(2)). Anal. calc. for $C_{12}H_{15}N_3O_4S$: C 48.48, H 5.09, N 14.13; found: C 48.54, H 5.19, N 14.08.

*4-Chloro-7-(α-*D*-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine* (**7a**). As described for **6a**; **5a** (550 mg, 1.25 mmol) was deprotected to give, after crystallization from H_2O, 258 mg (72%) of **7a** as colorless needles. M.p. 182–184°. TLC (*B*): R_f 0.7. UV (MeOH): 274 (4500). ^{1}H-NMR ((D$_6$)DMSO): 3.56 (*m*, H–C(5′)); 4.16 (*m*, H–C(4′), H–C(3′)); 4.38 (*m*, *J* = 5.2, H–C(2′)); 4.89 (*t*, *J* = 6.0, OH–C(5′)); 5.32, 5.35 (2*d*, *J* = 5.6, 2 OH); 6.60 (*d*, *J* = 5.3, H–C(1′)); 6.65 (*d*, *J* = 3.8, H–C(5′)); 8.00 (*d*, *J* = 3.8, H–C(6)); 8.64 (*s*, H–C(2)). Anal. calc. for $C_{11}H_{12}ClN_3O_4$: C 46.25, H 4.23, N 14.71; found: C 46.33, H 4.39, N 14.72.

*4-(Methylthio)-7-(α-*D*-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine* (**7b**). As described for **6a**, 530 mg (1.18 mmol) of **5b** gave **7b** as a colorless foam (240 mg, 69%). TLC (*B*): R_f 0.26. UV (MeOH): 292, (15600), 249 (8000), 222 (26600). ^{1}H-NMR ((D$_6$)DMSO): 2.66 (*s*, CH_3S); 3.53 (*m*, H–C(5′)); 4.08 (*m*, H–C(4′)); 4.15 (*m*, H–C(3′)); 4.33 (*m*, H–C(2′)); 4.9, 5.3 (br., 3 OH); 6.51 (*d*, *J* = 3.7, H–C(5)); 6.57 (*d*, *J* = 5.2, H–C(1′)); 7.79 (*d*, *J* = 3.7, H–C(6)); 8.62 (*s*, H–C(2)). Anal. calc. for $C_{12}H_{15}N_3O_4S$: C 48.48, H 5.09, N 14.13; found: C 48.35, H 5.12, N 13.96.

*4-(Methylsulfonyl)-7-(β-*D*-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine* (**8**). Compd. **6b** (100 mg, 0.34 mmol) was dissolved in MeOH (5 ml) under warming and 3-chloroperbenzoic acid (200 mg; technical grade, 80%) added. The soln. was stirred at r.t. for 2 h and evaporated, FC (10 × 6 cm, *A*) of the residue gave from the main zone, **8** as a colorless foam (90 mg, 81%). TLC (*B*): R_f 0.5. UV (MeOH): 230 (15700), 285 (3600). ^{1}H-NMR ((D$_6$)DMSO): 3.43 (*s*, CH_3SO_2); 3.63 (*m*, H–C(5′)); 3.97 (*m*, H–C(4′)); 4.15 (*m*, H–C(3′)); 4.44 (*m*, H–C(2′)); 5.1–5.5 (br., 3 OH); 6.31 (*d*, *J* = 6.0, H–C(1′)); 7.02 (*d*, *J* = 3.8, H–C(5)); 8.22 (*d*, *J* = 3.8, H–C(6)); 9.04 (*s*, H–C(2)).

4-(Methylsulfonyl)-7-(α-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine (**9**). As described for **8**, **7b** (90 mg, 0.3 mmol) was oxidized to give **9** as a colorless foam (74 mg, 74%). TLC (*B*): R_f 0.3. UV (MeOH): 230 (16000), 285 (3900). ^{1}H-NMR ((D_6)DMSO): 3.42 (*s*, CH_3SO_2); 3.58 (*m*, H–C(5')); 4.16 (*m*, H–C(3'), H–C(4')); 4.42 (*m*, H–C(2')); 4.9, 5.4 (br., 3 OH); 6.69 (*d*, *J* = 5.4, H–C(1')); 6.94 (*d*, *J* = 3.7, H–C(5)); 8.19 (*d*, *J* = 3.7, H–C(6)); 9.00 (*s*, H–C(2)).

7-(β-D-Ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (= *Tubercidin*; **10**). *From* **6a**. A soln. of **6a** (50 mg, 0.175 mmol) in NH_3/MeOH (sat. at 0°) was stirred in a sealed vessel at 50° for 24 h. The solvent was evaporated and the residue crystallized from MeOH to give **10** as colorless needles (38 mg, 82%). M.p. 145–148° ([27]: 148–150°).

From **8**. Compound. **8** (200 mg, 0.61 mmol) was treated as described above, exept that the reaction time was only 12 h and the crude product desalted on *Amberlite XAD-4* (1.5 × 30 cm, *E*): **10** as colorless needles (120 mg, 75%) upon crystallization from MeOH, identical with those obtained from **6a**.

7-(α-D-Ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (= *α-Tubercidin*; **11**). As described for **10**; **7a** (60 mg, 0.21 mmol) gave colorless needles (49 mg, 87%), after recrystallization from MeOH. M.p. 189–192° ([27]: 192°).

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