143. Synthesis of 3-Deaza-2′-deoxyadenosine and 3-Deaza-2′,3′-dideoxyadenosine: Glycosylation of the 4-Chloroimidazo[4,5-*c*]pyridinyl Anion

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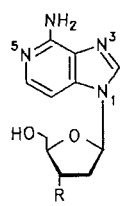
(2.V.90)

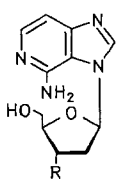
The convergent syntheses of 3-deazapurine 2′-deoxy-β-D-ribonucleosides and 2′,3′-dideoxy-D-ribonucleosides, including 3-deaza-2′-deoxyadenosine (**1a**) and 3-deaza-2′,3′-dideoxyadenosine (**1b**) is described. The 4-chloro-1*H*-imidazo[4,5-*c*]pyridinyl anion derived from **5** was reacted with either 2′-deoxyhalogenose **6** or 2′,3′-dideoxyhalogenose **10** yielding two regioisomeric (N^1 and N^3) glycosylation products. They were deprotected and converted into 4-substituted imidazo[4,5-*c*]pyridine 2′-deoxy-β-D-ribonucleosides and 2′,3′-dideoxy-D-ribonucleosides. Compounds **1a** and **1b** proved to be more stable against proton-catalyzed *N*-glycosylic bond hydrolysis than the parent purine nucleosides and were not deaminated by adenosine deaminase.

Introduction. – The 3-deazapurines (imidazo[4,5-*c*]pyridines) have been isolated from the green leaves of spinach and the cutaneous glands and liver of sharks and amphibians. Furthermore, they have been identified as integral part of streptothricin antibiotics [1–3]. Nucleosides have already been prepared [4–8]. According to the widespread biological activity of 3-deazapurines, we have developed a stereoselective synthesis of 2′-deoxy-β-D-ribofuranosides. Furthermore, we describe the synthesis of the 2′,3′-dideoxy-

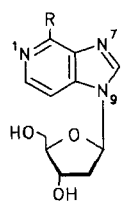


1a R = OH
b R = H

systematic numbering

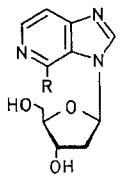


2a R = OH
b R = H



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

purine numbering

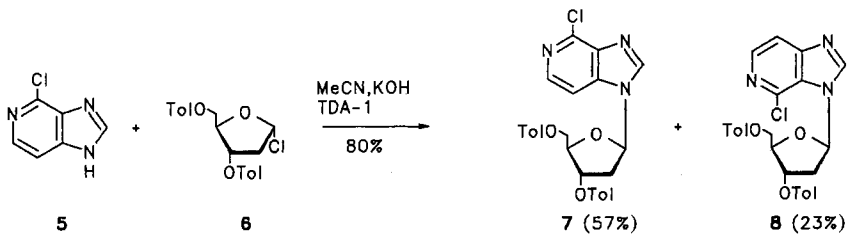


4a R = Cl
b R = MeO

ribonucleosides **1b** and **2b** by direct glycosylation of the 4-chloroimidazo[4,5-*c*]pyridinyl anion with 2′,3′-dideoxyhalogenose **10** [9]. As compound **1b** has similar spatial requirements as 2′,3′-dideoxyadenosine, its triphosphate may act as active site directed inhibitor of HIV reverse transcriptase, the ethiological agent of AIDS [10] [11].

Results and Discussion. – Compound **5** was chosen as versatile starting material as it can be prepared from commercially available 3,4-diaminopyridine [12] or 2-chloropy-

Scheme 1



5 6 7 (57%) 8 (23%)

ridine [13]. It was reacted at 40° with the anomerically pure halogenose **6** [14] in MeCN in the presence of powdered KOH and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) [15–17]. The reaction was stereoselective similar to that reported for the 4,6-dichloro derivative [18]. Two regioisomers (**7** and **8**) were formed in 80% yield in a ratio of 2.5:1 (N^1/N^3-glycosides) [19]. They were separated by fractionated crystallization and flash chromatography and were characterized by NMR spectroscopy (see *Exper. Part* and *Tables 1* and *2*). Compound **7** has been already obtained in a non-stereoselective reaction together with its α-D-anomer as non-separable anomeric mixture [8]. The regioisomers **7** and **8** were deprotected (NH_3/MeOH) affording the nucleosides **3a** and **4a**, respectively. The anomeric configuration of **3a** and **4a** (β-D) was assigned by ^{1}H-NMR NOE difference spectroscopy [20] *(Table 1)* confirming a stereoselective glycosylation. The glycosylation position was unequivocally deduced from the same experiment: a NOE at H–C(7) upon saturation of H–C(1′) of regioisomer **3a** proves N(1) as glycosylation site (systematic numbering). Compound **4a** shows only a NOE at H–C(2) upon irradiation of H–C(1′).

Table 1. *NOE Data of 3-Deazapurine Nucleosides in (D_6)DMSO at 23°*. Systematic numbering.

	Irradiated proton	Observed NOE (%)
1a	H–C(2)	H–C(1′) (4.2), H_β–C(2′) (3.5), H–C(3′) (0.7)
1b	H–C(4′)	H–C(1′) (1.2), H–C(3′) (4.3)
	H–C(2)	H–C(1′) (3.9), H–C(2′) (2.6)
2a	H–C(2)	H–C(1′) (4.5), H_β–C(2′) (4.2)
	H–C(1′)	H–C(2) (5.2), H–C(4′) (2.9), H_α–C(2′) (6.3)
4a	H–C(2)	H–C(1′) (1), H–C(3′) (1.2), H_β–C(2′) (3.7)
	H–C(1′)	H–C(2) (1), H–C(4′) (1.7), H_α–C(2′) (5.0)
3a	H–C(1′)	H–C(7) (5.1), H–C(2) (5.6), H–C(4′) (2.0), H_α–C(2′) (6.6)
	H–C(2)	H–C(1′) (5.1), H–C(3′) (0.8), H_β–C(2′) (3.0)
12	H–C(1′)	H–C(2) (1.2), H–C(4′) (2.5), H–C(2′) (4.4)
	H–C(2)	H–C(1′) (0.9), H–C(2′) (2.6), H–C(3′) (2.1)
14	H–C(1′)	H–C(2) (1.1), H–C(3′) (0.7), H–C(2′) (5.4)
	H–C(2)	H–C(1′) (0.8), H_α–C(2′) (3.0), H–C(4′) (3.4)
13	H–C(2)	H–C(1′) (3.6), H–C(4′) (1.9), H_α–C(2′) (3.0), H–C(3′) (1.2)
	H–C(1′)	H–C(2) (3.2), H–C(7) (4.3), H_β–C(2′) (4.3)
	H–C(4′)	H–C(2) (2.1), H–C(7) (1.8), H–C(5′) (9.3), H_α–C(3′) (4.9)
11	H–C(1′)	H–C(2) (2.2), H–C(7) (4.2), H–C(4′) (1.4), H–C(2′) (4.2)
16	H–C(1′)	H–C(2) (1.0), H–C(4′) (2.1), H–C(2′) (7.6)
	H–C(2)	H–C(1′) (1.2), 5′–OH (2.4), H–C(2′) (1.6), H–C(3′) (2.2)

Table 2. *^{13}C-NMR Chemical Shifts of 3-Deazapurine Derivatives*[a])

	C(2) [C(8)]	C(3a) [C(5)]	C(4) [C(6)]	C(6) [C(2)]	C(7) [C(3)]	C(7a) [C(4)]	CH_3
1a	139.7	126.8	152.4	140.6	97.2	137.5	
b	139.4	126.7	152.4	140.3	97.2	137.5	
2a	143.1	118.2	150.2	139.5	105.7	147.1	
b	142.7	118.0	150.3	139.7	105.6	147.4	
3a	144.3	137.4	[b])	141.0	107.7	139.2	
b	141.5	139.5	155.6	138.7	102.3	128.1	52.9
c	143.9	141.0	142.2	141.8	107.8	137.7	
4a	145.7	127.3	132.6	140.7	114.7	152.2	
b	143.4	151.1	150.5	137.8	109.6	118.1	53.3
5	144.6	[b])	[b])	140.5	108.7	[b])	
7	144.1	137.4	141.1	139.2	107.5	141.1	21.1
8	145.5	126.5	132.9	141.2	115.0	151.4	21.1
11	143.6	137.5	141.0	140.9	107.6	139.4	–5.5
12	145.3	127.2	132.9	140.7	114.7	151.6	–5.6
13	144.0	137.5	141.1	141.1	107.5	139.2	–5.3
14	145.6	127.3	132.9	140.8	114.8	151.5	–5.3
15	144.0	137.5	141.0	141.0	107.5	139.2	
16	145.7	127.2	132.9	140.7	114.7	151.6	
17	144.1	137.5	141.1	141.1	107.5	139.2	
18	145.7	127.3	133.0	140.8	114.8	151.6	

	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	$(CH_3)_3C$	$(CH_3)_3C$
1a	84.6	39.7	70.5	87.6	61.5		
b	85.4	31.6	25.7	81.5	62.9		
2a	84.9	40.2	69.6	87.7	60.7		
b	86.0	31.6	25.2	81.6	62.7		
3a	85.3	39.8	70.3	87.9	61.2		
b	84.8	39.8	70.4	87.7	61.4		
c	84.9	39.8	70.6	87.9	61.5		
4a	85.5	41.5	69.6	87.9	60.8		
b	85.9	41.4	70.2	87.8	61.3		
7	85.4	39.8	74.5	81.9	63.9		
8	85.2	39.2	74.5	82.1	64.0		
11	86.0	31.6	24.9	81.6	64.2	25.8	18.1
12	86.8	33.9	24.1	82.5	63.5	25.8	18.1
13	86.6	31.2	25.9	80.6	65.0	25.9	18.1
14	87.3	32.8	25.0	80.9	65.1	25.9	18.1
15	86.0	31.9	25.3	82.0	62.5		
16	86.7	34.2	24.3	83.0	61.7		
17	86.4	31.2	25.9	81.1	63.3		
18	87.4	32.9	25.1	81.5	63.3		

[a]) Measured in (D_6)DMSO and assigned by ^{13}C-INAPT spectroscopy; purine numbering in brackets.
[b]) Not detectable due to long relaxation times.

The 4-chloro substituents of **3a** and **4a** proved to be less reactive than those of the corresponding 6-chloropurine nucleosides. However, 18 h of heating of **3a** and **4a** (NaOMe/MeOH) furnished compounds **3b** and **4b**, respectively. Conversion into the aminonucleosides **1a** and **2a** was accomplished with hydrazine. *Raney*-Nickel reduction of the *in situ* formed hydrazino intermediates gave **1a** [8] [21] and **2a**. Catalytic hydro-

genation of **3a** afforded 3-deaza-2′-deoxynebularine (**3c**). The structures of the N^3-nucleosides **2a** and **4a** imply significant *'anti'*-conformer population. This can be determined from NOE difference spectra based on a calibration graph using conformationally rigid molecules [22] [23]. Application of this matter to **4a** resulted in an *'anti'*-conformer population of 90%. To the contrary, compound **2a** exhibits a *'syn'*-conformer population of 40%. This suggests H-bonding between O–C(4′) and the 4-NH_2 group. Increase of the temperature reduces the NOE values. Assuming temperature independence of all dipolar relaxation terms, the activation energy (−11 kJ/mol) was estimated from an *Arrhenius* plot *(Fig.)*.

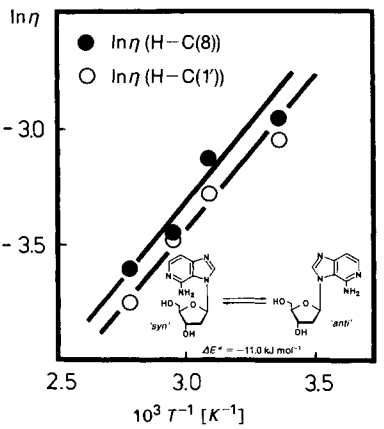


Figure. Arrhenius *plot of the NOE values* (η) *at* H–C(1′) (irradiation of H–C(8)) *and* H–C(8) (irradiation of H–C(1′)) vs. T^{-1} *for compound* **2a**

Regarding oligonucleotide synthesis (depurination) and duplex stability (*Watson-Crick* base pairing), it was of interest [24] [25] to determine pK_{BH^+} values and *N*-glycosylic bond stability of compound **1a** and related imidazo[4,5-*c*]pyridine nucleosides (**3a**, **b**). *Table 3* shows that 3-deaza-2′-deoxyadenosine (**1a**) is much more easily protonated (*Teorell-Stenhagen* buffer [26]) than the parent 2′-deoxyadenosine (A_d). Half of the molecules **1a** are already cations at pH 7.3; 3,7-dideaza-2′-deoxyadenosine is almost fully protonated under these conditions, whereas 2′-deoxy-1,7-dideazaadenosine is much more difficult to protonate. Although it is not known whether N(3) or N(5) (systematic numbering) is the protonation position of **1a**, this behaviour will affect DNA structure. Kinetic data were determined UV-spectrophotometrically at a wavelength of maximal difference of UV absorbance. Compound **1a** is less sensitive to N-glycosylic bond hydrolysis as compared to the parent A_d by one order of magnitude, while **3a**, **b** are hydrolyzed at a significantly higher rate than **1a** *(Table 3)*. Comparison of the data of the N^3-regioisomers **4a**, **b** and **2a** show that the latter is 10-fold more labile than its regioisomer **1a**. This is similar to regioisomeric adenine N^7- and N^9-(2′-deoxyribofuranosides) [27]. A plot of the kinetic pseudo-first-order constants of the N^1-glycosylated compounds **1a** and **3a**, **b** *vs.* the σ_p^+ constants [28] of the corresponding 4-substituents (data not shown)

Table 3. *p*K$_{BH+}$ *Values and Kinetic Data of N-Glycosyl Bond Hydrolyses of Nucleosides Measured at 25°*[a])

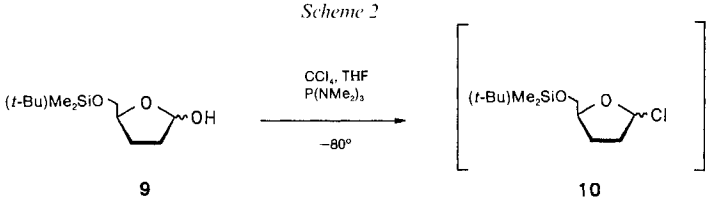
	pK_{BH+}	$\tau/2$ [min] in aq. HCl solution			
		1N	0.1N	0.01N	0.001N
1a	7.3	17.0	–	–	–
1b	–	0.95	10.3	–	–
2a	6.3	–	–	1.9	–
2b	–	–	–	0.07	0.69
3a	–	4.0	–	–	–
4a	–	3.1	–	–	–
3b	–	13.2	–	–	–
4b	–	16.0	–	–	–
A_d	3.8	1.6	–	–	–
$c^3c^7A_d$	8.6	st.	st.	st.	st.
$c^1c^7A_d$	3.6	st.	st.	st.	st.
c^7A_d	5.3	st.	st.	st.	st.
$A_{d\,2'3'}$	–	–	1.6	14.3	–

[a]) $c^3c^7A_d$ = 3,7-Dideaza-2′-deoxyadenosine; $c^1c^7A_d$ = 1,7-dideaza-2′-deoxyadenosine; c^7A_d = 7-deaza-2′-deoxyadenosine; st. = stable.

gives a roughly linear correlation ($r^2 = 0.902$), while there is non for the N^3-regioisomers **2a** and **4a, b**. This points to a change of the protonation pattern within the N^3-series causing the hydrolytic instability of compound **2a**.

Similarly to the 2′-deoxyribonucleosides, corresponding 2′,3′-dideoxyribonucleosides have been prepared. Earlier, we have reported on multi-step syntheses of base-modified 2′,3′-dideoxyribonucleosides from corresponding 2′-deoxyribonucleosides as starting materials and *Barton* deoxygenation or an elimination/hydrogenation procedure [29] [30].

Scheme 2

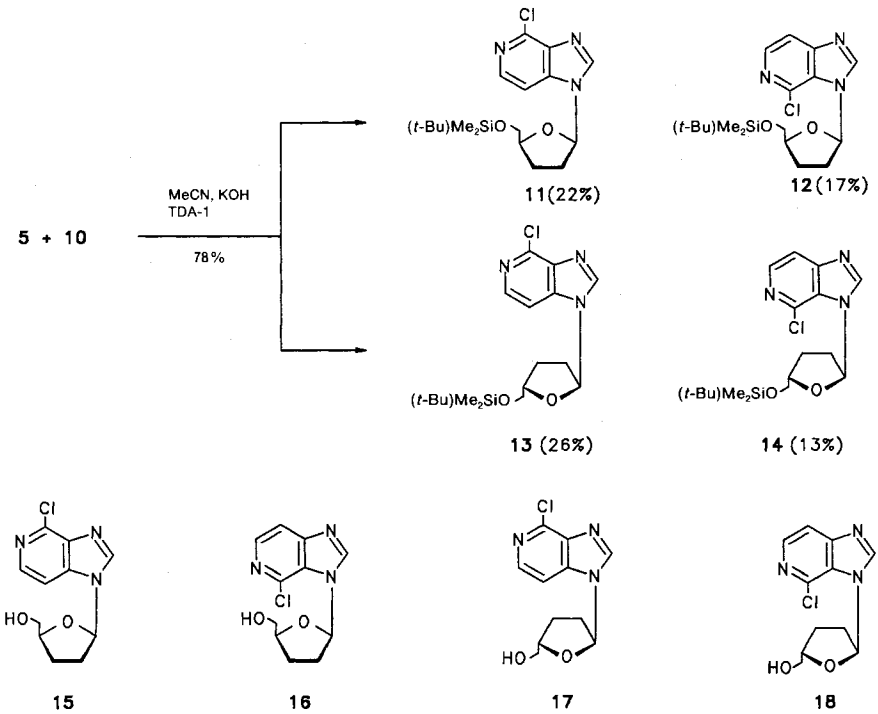


9 **10**

As this reaction route is laborious in case of base-modified 2′,3′-dideoxyribonucleosides, we have prepared halogenose **10** from an anomeric mixture of the corresponding lactol [31] by stereoselective *Appel* chlorination *(Scheme 2)*. Halogenose **10** was used for direct glycosylation of the anion of compound **5**. As shown for nucleobase-anion glycosylations in case of D-ribonucleosides [32] and 2′-deoxy-D-ribonucleosides, β-D-anomers are formed exclusively from α-D-halogenoses. We assume that this is also true for the above-mentioned glycosylation with halogenose **10**. Unfortunately, we were not able to isolate the α-D-anomer of **10** in pure state.

Condensation of the *in situ* prepared 2′,3′-dideoxyhalogenose **10** [9] with **5** yielded the four glycosylation products **11–14** in a total yield of 78% which could be separated by

Scheme 3



flash chromatography (*Scheme 3*; order of chromatographic mobilities: N^3-β > N^3-α > N^1-α > N^1-β; see *Exper. Part*). The anomeric ratio for both regioisomers was approximately 1:1, as expected from the anomeric mixture of halogenose **10** employed in the glycosylation. The ratio of regioisomers was different in case of the reaction of **5** with halogenose **6** ($N^1/N^3 = 2.5:1$) from that obtained with the more reactive halogenose **10** (1.6:1). Assignment of the glycosylation positions of **11**–**14** as well as the anomeric configuration was accomplished as described for the 2′-deoxynucleosides (*Tables 1* and *2*).

Compounds **11**–**14** were desilylated with Bu_4NF yielding **15**–**18**. The chloro nucleosides **15** and **16** were converted into 3-deaza-2′,3′-dideoxyadenosine (**1b**) and its regioisomer **2b**, respectively, as described for the 2′-deoxynucleosides. Both 2′,3′-dideoxynucleosides **1b** and **2b** proved 20–30 fold more labile towards acidic *N*-glycosylic bond hydrolysis as compared with the corresponding 2′-deoxy-β-D-ribonucleosides, but only **1b** is more stable as 2′,3′-dideoxyadenosine ($A_{d2}^{2',3'}$; *Table 3*). Compound **1b** – as the 2′-deoxynucleoside **1a** – is not deaminated by adenosine deaminase.

The structures of all compounds described above have been verified by ^{1}H- and ^{13}C-NMR as well as ^{1}H-NOE difference spectroscopy (*Tables 1* and *2*). The assignment of ^{13}C-NMR chemical shifts is based on ^{13}C-INAPT spectroscopy [33].

The authors gratefully acknowledge financial support by the *Bundesministerium für Forschung und Technologie*.

Experimental Part

General. See [32]. The 2,3-dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-D-*glycero*-pentofuranose (**9**) was prepared according to [31]. CC: column chromatography; FC: flash chromatography.

*Glycosylation of 4-Chloro-1*H*-imidazo[4,5-c]pyridine* (**5**) *with 2-Deoxy-3,5-di-*O*-(4-toluoyl)-β-*D-erythro-*pentofuranosyl Chloride* (**6**). A suspension of KOH (800 mg, 14.3 mmol) and TDA-1 (100 µl, 0.3 mmol) in MeCN (200 ml) was stirred for 5 min at r.t. Then, **5** [12] [13] (962 mg, 6 mmol) was dissolved therein under warming (80°). The soln. was brought to 40°, and **6** [14] (2.6 g, 6.6 mmol) was added portionwise under stirring. The mixture was held at 40° for 15 min, then filtered over *Celite*, and evaporated. FC (silica gel, *60H*, column 15 × 3 cm, 0.5 bar, CH_2Cl_2/MeOH 99:1) gave **7**/**8** (2.42 g, 80%) as a colourless foam. The main amount of **7** crystallized from a small volume of AcOEt/cyclohexane 1:1 upon cooling (5°). The filtrate was separated by FC (silica gel *60H*, column 40 × 3 cm, 0.5 bar, AcOEt/cyclohexane 7:3), giving the less polar **8** (690 mg, 23%) as colourless needles and, the more polar **7** which was pooled with the material of the crystallization to yield a total of 1.71 (57%) of colourless crystals.

*4-Chloro-3-[2′-deoxy-3′,5′-di-*O*-(4-toluoyl)-α-*D-erythro-*pentofuranosyl]-3*H*-imidazo[4,5-c]pyridine* (**8**). M.p. 143–144° (MeOH). TLC (silica gel, AcOEt/cyclohexane 1:1): R_f 0.4. UV (MeOH): 241 (37000), 272 (8300). ^{1}H-NMR ((D$_6$)DMSO): 8.90 (*s*, H–C(2)); 8.20 (*d*, *J* = 5,6, H–C(6)); 7.76 (*d*, *J* = 5.6, H–C(7)); 7.02 ('*t*', H–C(1′)); 5.73 (*m*, H–C(3′)); 4.65 (*m*, H–C(4′)); 4.58 (*m*, CH_2(5′)); 3.07 (*m*, CH_2(2′)); 7.94, 7.78, 7.36, 7.28 (4*m*, arom. H); 2.38 (*s*, Me). Anal. calc. for $C_{27}H_{24}ClN_3O_5$: C 64.10, H 4.78, N 8.31; found: C 64.30, H 4.88, N 8.26.

*4-Chloro-1-[2′-deoxy-3′,5′-di-*O*-(4-toluoyl)-β-*D-erythro-*pentofuranosyl]-1*H*-imidazo[4,5-c]pyridine* (**7**). M.p. 160–161° (MeOH): TLC (silica gel, AcOEt/cyclohexane 1:1): R_f 0.36. UV (MeOH): 272 (sh, 6200), 277 (sh, 5500). ^{1}H-NMR ((D$_6$)DMSO): 8.75 (*s*, H–C(2)); 8.08 (*d*, *J* = 5.6, H–C(6)); 7.84 (*d*, *J* = 5.6, H–C(7)); 6.66 ('*t*', H–C(1′)); 5.77 (*m*, H–C(3′)); 4.55–4.70 (*m*, H–C(4′), CH_2(5′)); 3.03 (*m*, CH_2(2′)); 7.99, 7.79, 7.38, 7.29 (4*m*, arom. H); 2.39 (*s*, Me). Anal. calc. for $C_{27}H_{24}ClN_3O_5$: C 64.10, H 4.78, N 8.31; found: C 64.23, H 4.86, N 8.28.

*4-Chloro-3-(2′-deoxy-β-*D-erythro-*pentofuranosyl)-3*H*-imidazo[4,5-c]pyridine* (**4a**). At r.t. **8** (690 mg, 1.36 mmol) was stirred in NH_3/MeOH (saturated at 0°) for 48 h. CC (silica gel, column 20 × 3 cm, CH_2Cl_2/MeOH 9:1) gave **4a** (230 mg, 63%). Colourless crystals. M.p. 132–133° (i-PrOH). TLC (silica gel, CH_2Cl_2/MeOH 9:1): R_f 0.43. UV (MeOH): 242 (4800), 279 (6500), 287 (sh, 4700). ^{1}H-NMR ((D$_6$)DMSO): 8.93 (*s*, H–C(2)); 8.18 (*d*, *J* = 5.5, H–C(6)); 7.75 (*d*, *J* = 5.5, H–C(7)); 6.86 ('*t*', H–C(1′)); 5.40 (*m*, OH–C(3′)); 5.07 (*m*, OH–C(5′)); 4.41 (*m*, H–C(3′)); 3.94 (*m*, H–C(4′)); 3.62 (*m*, CH_2(5′)); 2.58 (*m*, CH_2(2′)). Anal. calc. for $C_{11}H_{12}ClN_3O_3$: C 48.99, H 4.48, N 15.58; found: C 48.93, H 4.59, N 15.64.

*4-Chloro-1-(2′-deoxy-β-*D-erythro-*pentofuranosyl)-1*H*-imidazo[4,5-c]pyridine* (**3a**). Compound **7** (680 mg, 1.34 mmol) was deprotected as described for **8**. CC (silica gel, column 15 × 3 cm, CH_2Cl_2/MeOH 9:1) furnished **3a** (310 mg, 86%). Colourless crystals. M.p. 169–170° (i-PrOH; [8]: 173–174°). TLC (silica gel, CH_2Cl_2/MeOH 9:1): R_f 0.35. UV (MeOH): 255 (7100), 265 (sh, 6200), 273 (4700). ^{1}H-NMR ((D$_6$)DMSO): 8.72 (*s*, H–C(2)); 8.18 (*d*, *J* = 5.6, H–C(6)); 7.88 (*d*, *J* = 5.6, H–C(7)); 6.43 (*m*, H–C(1′)); 5.40 (*m*, OH–C(3′)); 5.04 (*m*, OH–C(5′)); 4.44 (*m*, H–C(3′)); 3.92 (*m*, H–C(4′)); 3.60 (*m*, CH_2(5′)); 2.60 (*m*, CH_2(2′)). Anal. calc. for $C_{11}H_{12}ClN_3O_3$: C 48.99, H 4.48, N 15.58; found: C 48.95, H 4.45, N 15.50.

*4-Amino-1-(2′-deoxy-β-*D-erythro-*pentofuranosyl)-1*H*-imidazo[4,5-c]pyridine* (**1a**). At 90°, **3a** (500 mg, 1.85 mmol) was stirred in anh. hydrazine (7 ml) for 1 h. Repeated coevaporation with EtOH removed hydrazine. The residue was dissolved in EtOH (50 ml) and heated in the presence of *Raney*-Ni for 1 h under reflux. The catalyst was filtered off and washed with hot EtOH, and the filtrate was evaporated. CC (*Dowex 1 × 2*, 100–200 mesh, column 12 × 3 cm, H_2O/MeOH 8:2) furnished **1a** (270 mg, 58%). Colourless crystals. M.p. 209–211° (H_2O; [8]: 209–211°). TLC (silica gel, CH_2Cl_2/MeOH 8:2): R_f 0.14. UV (MeOH): 266 (11100). ^{1}H-NMR ((D$_6$)DMSO): 8.33 (*s*, H–C(2)); 7.70 (*d*, *J* = 5.8, H–C(6)); 6.91 (*d*, *J* = 5.8, H–C(7)); 6.28 (*m*, H–C(1′)); 6.24 (br. *s*, NH_2); 5.40 (*m*, OH–C(3′)); 5.01 (*m*, OH–C(5′)); 4.41 (*m*, H–C(3′)); 3.89 (*m*, H–C(4′)); 3.59 (*m*, CH_2(5′)); 2.44 (*m*, CH_2(2′)).

*4-Amino-3-(2′-deoxy-β-*D-erythro-*pentofuranosyl)-3*H*-imidazo[4,5-c]pyridine* (**2a**). Compound **4a** (500 mg, 1.85 mmol) was reacted with anh. hydrazine and treated with *Raney*-Ni as described for **3a**. Ion-exchange chromatography, as described for **1a**, followed by CC (silica gel, column 30 × 3 cm, CH_2Cl_2/MeOH 85:15) afforded **2a** (170 mg, 37%). Colourless crystals. M.p. 195–196° (H_2O). TLC (silica gel, CH_2Cl_2/MeOH 8:2): R_f 0.2. UV (MeOH): 249 (4300), 288 (5400). ^{1}H-NMR ((D$_6$)DMSO): 8.43 (*s*, H–C(2)); 7.71 (*d*, *J* = 5.7, H–C(6)); 6.92 (*d*, *J* = 5.7, H–C(7)); 6.40 (*m*, H–C(1′)); 6.04 (br. *s*, NH_2); 5.42 (*m*, OH–C(3′)); 5.04 (*m*, OH–C(5′)); 4.41 (*m*, H–C(3′)); 3.93 (*m*, H–C(4′)); 3.54 (*m*, CH_2(5′)); 2.50 (*m*, CH_2(2′)). Anal. calc. for $C_{11}H_{14}N_4O_3$: C 52.79, H 5.64, N 22.39; found: C 52.83, H 5.84, N 22.20.

*1-(2′-Deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-1*H*-imidazo[4,5-c]pyridine* (**3b**). Compound **3a** (500 mg, 1.85 mmol) was dissolved in 1M NaOMe/MeOH (50 ml) and refluxed for 18 h. After neutralisation with AcOH

and evaporation, the residue was extracted with CH_2Cl_2. CC (silica gel, column 24 × 3 cm, CH_2Cl_2/MeOH 9:1) furnished **3b** (300 mg, 61%). Colourless foam. TLC (silica gel, CH_2Cl_2/MeOH 8:2): R_f 0.7. UV (MeOH): 251 (8800). ^{1}H-NMR ((D$_6$)DMSO): 8.46 (*s*, H–C(2)); 7.88 (*d*, *J* = 5.8, H–C(6)); 7.39 (*d*, *J* = 5.8, H–C(7)); 6.34 (*m*, H–C(1′)); 5.38 (*m*, OH–C(3′)); 5.01 (*m*, OH–C(5′)); 4.40 (*m*, H–C(3′)); 4.00 (*s*, MeO); 3.88 (*m*, H–C(4′)); 3.57 (*m*, CH_2(5′)); 2.45 (*m*, CH_2(2′)). Anal. calc. for $C_{12}H_{15}N_3O_4$: C 54.33, H 5.70, N 15.84; found: C 54.29, H 5.71, N 15.62.

*3-(2′-Deoxy-β-*D-erythro-*pentofuranosyl)-4-methoxy-3*H-*imidazo[4,5-*c*]pyridine* (**4b**). Compound **4a** (480 mg, 1.78 mmol) was treated with 1M NaOMe/MeOH as described for **3a**. CC (*Amberlite XAD-4*, column 10 × 6 cm, H_2O/i-PrOH 9:1) yielded **4b** (158 mg, 34%). Colourless needles. M.p. 162–165° (H_2O). TLC (silica gel, CH_2Cl_2/MeOH 8:2): R_f 0.8. UV (MeOH): 238 (4700), 274 (5600). ^{1}H-NMR ((D$_6$)DMSO): 8.67 (*s*, H–C(2)); 7.88 (*d*, *J* = 5.7, H–C(6)); 7.30 (*d*, *J* = 5.7, H–C(7)); 6.66 ('*t*', H–C(1′)); 5.35 (*m*, OH–C(3′)); 5.02 (*m*, OH–C(5′)); 4.39 (*m*, H–C(3′)); 4.05 (*s*, MeO); 3.90 (*m*, H–C(4′)); 3.60 (*m*, CH_2(5′)); 2.46 (*m*, CH_2(2′)). Anal. calc. for $C_{12}H_{15}N_3O_4$: C 54.33, H 5.70, N 15.84; found: C 54.18, H 5.88, N 15.90.

*1-(2′-Deoxy-β-*D-erythro-*pentofuranosyl)-1*H-*imidazo[4,5-*c*]pyridine* (**3c**). At r.t., **3a** (170 mg, 0.63 mmol), dissolved in MeOH (20 ml), was hydrogenated in the presence of MgO (150 mg, 3.72 mmol) and Pd/C (10% Pd, 100 mg) for 5 h. The catalyst was filtered off, the filtrate evaporated, and the residue applied to FC (silica gel *60*, column 15 × 3 cm, CH_2Cl_2/MeOH 85:15): **3c** (90 mg, 61%) as amorphous solid. TLC (silica gel, CH_2Cl_2/MeOH 8:2): R_f 0.45. ^{1}H-NMR ((D$_6$)DMSO): 8.98 (*s*, H–C(4)); 8.63 (*s*, H–C(2)); 8.36 (*d*, *J* = 5.6, H–C(6)); 7.81 (*d*, *J* = 5.6, H–C(7)); 6.42 ('*t*', H–C(1′)); 5.40 (*m*, OH–C(3′)); 5.02 (*m*, OH–C(5′)); 4.43 (*m*, H–C(3′)); 3.90 (*m*, H–C(4′)); 3.59 (*m*, CH_2(5′)); 2.48 (*m*, CH_2(2′)).

*2,3-Dideoxy-5-*O-*[(1,1-dimethylethyl)dimethylsilyl]-*D-glycero-*pentofuranosyl Chloride* (**10**) *in THF Solution.* To a stirred soln. of **9** [31] (3.5 g, 15.1 mmol) in anh. THF (60 ml), CCl_4 (2.25 ml, 23.3 mmol) was added with a syringe under N_2. The soln. was cooled to –80°, and tris(dimethylamino)phosphane (3.6 ml, 19.8 mmol) was added dropwise within 20 min. Stirring was continued for 4 h at –80°. The cold soln. was immediately used for the glycosylation.

Glycosylation of **5** *with* **10**. Powdered KOH (1.5 g, 26.7 mmol) and TDA-1 (100 µl, 0.31 mmol) were stirred in anh. MeCN (200 ml) for 5 min at r.t. Compound **5** [12] [13] (1.15 g, 7.5 mmol) was added and dissolved by gentle heating. The soln. was cooled to r.t. and the cold (–80°) THF soln. of **10** (15 mmol, calculated on the basis of 100% yield of **10**) was added in 10 portions within 20 min. Stirring was continued for 10 min and the mixture poured into 10% aq. $NaHCO_3$ soln. (500 ml). This was extracted twice with AcOEt (500 ml, each). The combined org. layers were washed with H_2O and brine, dried ($MgSO_4$), evaporated to a small volume, and filtered over a 4-cm layer of silica gel. Elution with AcOEt furnished a colourless oil upon evaporation. This was separated by FC (silica gel *60H*, column 35 × 6 cm, AcOEt/cyclohexane 3:7) into zones *I–IV*. Zone *I* yielded **12** (480 mg, 17%) as colourless oil. Zone *II* gave **14** (220 mg, 8%) as colourless oil. Additional 140 mg (5%) were isolated from the overlapping zones *II* and *III* by rechromatography (13%). Zone *III* yielded **13** (440 mg, 16%) as colourless crystals. Additional 280 mg (10%) were obtained from the overlapping zones *II* and *III* by rechromatography (26%). Zone *IV* gave **11** (600 mg, 22%) as colourless foam.

*4-Chloro-3-{2′,3′-dideoxy-5′-*O-*[(1″,1″-dimethylethyl) dimethylsilyl]-β-*D-glycero-*pentofuranosyl}-3*H-*imidazo[4,5-*c*]pyridine* (**12**). TLC (silica gel, AcOEt/cyclohexane 3:7; 3 developments of 7 cm, each): R_f 0.8. UV (MeOH): 244 (4300), 279 (7100). ^{1}H-NMR ((D$_6$)DMSO): 8.85 (*s*, H–C(2)); 8.12 (*d*, *J* = 5.4, H–C(6)); 7.68 (*d*, *J* = 5.4, H–C(7)); 6.70 (*d*, *J* = 6.1, H–C(1′)); 4.21 (*m*, H–C(4′)); 3.80 (*m*, CH_2(5′)); 2.50 (*m*, CH_2(2′)); 1.97 (*m*, CH_2(3′)); 0.82 (*s*, *t*-Bu); –0.02 (*s*, Me_2Si).

*4-Chloro-3-{2′,3′-dideoxy-5′-*O-*[(1″,1″-dimethylethyl) dimethylsilyl]-α-*D-glycero-*pentofuranosyl}-3*H-*imidazo[4,5-*c*]pyridine* (**14**). TLC (silica gel, AcOEt/cyclohexane 3:7; 3 developments of 7 cm, each): R_f 0.63. UV (MeOH): 245 (4500), 278 (7300). ^{1}H-NMR ((D$_6$)DMSO): 8.70 (*s*, H–C(2)); 8.16 (*d*, *J* = 5.5, H–C(6)); 7.72 (*d*, *J* = 5.5, H–C(7)); 6.80 (*dd*, *J* = 6.4, 2.4, H–C(1′)); 4.50 (*m*, H–C(4′)); 3.64 (*m*, CH_2(5′)); 2.5 (*m*, CH_2(2′)); 2.11, 1.93 (2*m*, CH_2(3′)); 0.88 (*s*, *t*-Bu); 0.07 (Me_2Si).

*4-Chloro-1-{2′,3′-dideoxy-5′-*O-*[(1″,1″-dimethylethyl) dimethylsilyl]-α-*D-glycero-*pentofuranosyl}-1*H-*imidazo[4,5-*c*]pyridine* (**13**). M.p. 65–68° (AcOEt). TLC (silica gel, AcOEt/cyclohexane 3:7; 3 developments of 7 cm, each): R_f 0.57. UV (MeOH): 256 (7100), 265 (6500), 273 (5000). ^{1}H-NMR ((D$_6$)DMSO): 8.63 (*s*, H–C(2)); 8.16 (*d*, *J* = 5.6, H–C(6)); 7.73 (*d*, *J* = 5.6, H–C(7)); 6.39 (*dd*, *J* = 6.4, 4.0, H–C(1′)); 4.39 (*m*, H–C(4′)); 3.65 (*m*, CH_2(5′)); 2.5 (*m*, CH_2(2′)); 2.20 (*m*, H_α–C(3′)); 1.94 (*m*, H_β–C(3′)); 0.87 (*s*, *t*-Bu); 0.06 (Me_2Si). Anal. calc. for $C_{17}H_{26}ClN_3O_2Si$: C 55.49, H 7.12, N 11.42; found: C 55.65, H 7.13, N 11.38.

*4-Chloro-1-{2′,3′-dideoxy-5′-*O-*[(1″,1″-dimethylethyl) dimethylsilyl]-β-*D-glycero-*pentofuranosyl}-1*H-*imidazo[4,5-*c*]pyridine* (**11**). TLC (silica gel, AcOEt/cyclohexane 3:7; 3 developments of 7 cm, each): R_f 0.43. UV (MeOH): 256 (7100), 265 (sh, 6400), 273 (5100). ^{1}H-NMR ((D$_6$)DMSO): 8.65 (*s*, H–C(2)); 8.14 (*d*, *J* = 5.6, H–C(6)); 7.75 (*d*, *J* = 5.6, H–C(7)); 6.31 ('*t*', *J* = 4.3, H–C(1′)); 4.20 (*m*, H–C(4′)); 3.69 (*m*, CH_2(5′)); 2.5 (*m*,

$CH_2(2')$); 2.04 (*m*, $CH_2(3')$); 0.78 (*s*, *t*-Bu); −0.05, −0.07 (2*s*, Me_2Si). Anal. calc. for $C_{17}H_{26}ClN_3O_2Si$: C 55.49, H 7.12, N 11.42; found: C 55.60, H 7.21, N 11.50.

*4-Chloro-1-(2′,3′-dideoxy-β-*D*-glycero-pentofuranosyl)-1*H*-imidazo[4,5-c]pyridine* (**15**). To a soln. of **11** (1.14 g, 3.1 mmol) in THF (10 ml) was added Bu_4NF (1M in THF, 10 ml), and the mixture was stirred for 15 min at r.t. FC (silica gel, 60 *H*, column 10 × 6 cm, 0.5 bar, CH_2Cl_2/MeOH 9:1) gave **15** (730 mg, 93%). Colourless needles. M.p. 74–76° (EtOH/H_2O). TLC (silica gel, CH_2Cl_2/MeOH 9:1): R_f 0.45. UV (MeOH): 256 (7100), 264 (6100), 272 (4600). ^{1}H-NMR ((D$_6$)DMSO): 8.73 (*s*, H–C(2)); 8.15 (*d*, *J* = 5.6, H–C(6)); 7.78 (*d*, *J* = 5.6, H–C(7)); 6.32 (*dd*, *J* = 6.4, 3.4, H–C(1′)); 4.98 (*t*, *J* = 5.3, OH–C(5′)); 4.13 (*m*, H–C(4′)); 3.53 (*m*, $CH_2(5')$); 2.40 (*m*, $CH_2(2')$); 2.05 (*m*, $CH_2(3')$).

*4-Chloro-1-(2′,3′-dideoxy-α-*D*-glycero-pentofuranosyl)-1*H*-imidazo[4,5-c]pyridine* (**17**). Compound **13** (300 mg, 0.82 mmol) was deprotected and worked up as described for **11**. Colourless crystals (160 mg, 77%) from MeOH. M.p. 153–155°. TLC (silica gel, CH_2Cl_2/MeOH 9:1): R_f 0.42. UV (MeOH): 256 (7000), 265 (6300), 273 (4800). ^{1}H-NMR ((D$_6$)DMSO): 8.64 (*s*, H–C(2)); 8.17 (*d*, *J* = 5.6, H–C(6)); 7.74 (*d*, *J* = 5.6, H–C(7)); 6.39 (*dd*, *J* = 6.2, 4.1, H–C(1′)); 4.86 (*t*, *J* = 5.3, OH–C(5′)); 4.34 (*m*, H–C(4′)); 3.46 (*m*, $CH_2(5')$); 2.40 (*m*, $CH_2(2')$); 2.19, 1.93 (2*m*, $CH_2(3')$).

*4-Chloro-3-(2′,3′-dideoxy-β-*D*-glycero-pentofuranosyl)-3*H*-imidazo[4,5-c]pyridine* (**16**). Compound **12** (480 mg, 1.30 mmol) was deprotected and worked up as described for **11**. Colourless crystals (290 mg, 88%). M.p. 122–124° (MeOH). UV (MeOH): 244 (4500), 279 (7300), 287 (sh, 5200). ^{1}H-NMR ((D$_6$)DMSO): 8.98 (*s*, H–C(2)); 8.14 (*d*, *J* = 5.5, H–C(6)); 7.70 (*d*, *J* = 5.5, H–C(7)); 6.72 (*dd*, *J* = 6.5, 1.8, H–C(1′)); 5.13 (*t*, *J* = 5.3, OH–C(5′)); 4.18 (*m*, H–C(4′)); 3.64 (*m*, $CH_2(5')$); 2.50, 2.39 (2*m*, $CH_2(2')$); 1.97 (*m*, $CH_2(3')$). Anal. calc. for $C_{11}H_{12}ClN_3O_2$: C 52.08, H 4.77, N 16.56; found: C 52.17, H 4.83, N 16.46.

*4-Chloro-3-(2′,3′-dideoxy-α-*D*-glycero-pentofuranosyl)-3*H*-imidazo[4,5-c]pyridine* (**18**). Compound **14** (220 mg, 0.60 mmol) was deprotected and worked up as described for **11**. Colourless oil (110 mg, 73%). TLC (silica gel, CH_2Cl_2/MeOH 9:1): R_f 0.45. UV (MeOH): 245 (4300), 277 (7000), 287 (sh, 5000). ^{1}H-NMR ((D$_6$)DMSO): 8.69 (*s*, H–C(2)); 8.16 (*d*, *J* = 5.5, H–C(6)); 7.73 (*d*, *J* = 5.5, H–C(7)); 6.81 (*dd*, *J* = 6.3, 2.4, H–C(1′)); 4.86 (*t*, *J* = 5.4, OH–C(5′)); 4.46 (*m*, H–C(4′)); 3.4 (*m*, $CH_2(5')$); 2.5 (*m*, $CH_2(2')$); 2.10, 1.95 (2*m*, $CH_2(3')$). Anal. calc. for $C_{11}H_{12}ClN_3O_2$: C 52.08, H 4,77, N 16.56; found: C 52.26, H 4.88, N 16.54.

*4-Amino-1-(2′,3′-dideoxy-β-*D*-glycero-pentofuranosyl)-1*H*-imidazo[4,5-c]pyridine (= 3-Deaza-2′,3′-dideoxyadenosine;* **1b**). Compound **15** (300 mg, 1.19 mmol) was stirred in hydrazine hydrate (100%; 25 ml) under N_2 and under heating (120–130°) for 90 min. Hydrazine was removed by repeated coevaporation with EtOH. The residue in EtOH (25 ml) and *Raney*-Ni (2.0 g) were heated for 2 h. After filtration and washing with hot EtOH, the combined filtrates were evaporated. FC (silica gel, column 6 × 6 cm, 0.5 bar, CH_2Cl_2/MeOH 9:1) furnished **1b** (240 mg, 87%). Colourless foam. TLC (silica gel, CH_2Cl_2/MeOH 9:1): R_f 0.1. UV (MeOH): 267 (9800). ^{1}H-NMR ((D$_6$)DMSO): 8.33 (*s*, H–C(2)); 7.67 (*d*, *J* = 5.8, H–C(6)); 6.65 (*d*, *J* = 5.8, H–C(7)); 6.25 (br. *s*, NH_2); 6.14 (*dd*, *J* = 6.5, 3.9, H–C(1′)); 4.12 (*m*, H–C(4′)); 3.53 (*m*, $CH_2(5')$); 2.33 (*m*, $CH_2(2')$); 2.01 (*m*, $CH_2(3')$). Anal. calc. for $C_{11}H_{14}N_4O_2$: C 56.40, H 6.02, N 23.92; found: C 56.57, H 6.16, N 23.71.

*4-Amino-3-(2′,3′-dideoxy-β-*D*-glycero-pentofuranosyl)-3*H*-imidazo[4,5-c]pyridine* (**2b**). Compound **16** (100 mg, 0.4 mmol) was treated with hydrazine and worked up as described for **15**: 43 mg (47%) of colourless foam. TLC (silica gel, CH_2Cl_2/MeOH 9:1): R_f 0.2. UV (MeOH): 248 (4000), 289 (5200). ^{1}H-NMR ((D$_6$)DMSO): 8.45 (*s*, H–C(2)); 7.69 (*d*, *J* = 5.6, H–C(6)); 6.90 (*d*, *J* = 5.6, H–C(7)); 6.34 ('*t*', *J* = 5.0, H–C(1′)); 5.99 (br. *s*, NH_2); 4.99 (br. *s*, OH–C(5′)); 4.19 (*m*, H–C(4′)); 3.4 (*m*, $CH_2(5')$); 2.4 (*m*, $CH_2(2')$); 2.02 (*m*, $CH_2(3')$).

REFERENCES

[1] A. Chibnall, *J. Biol. Chem.* **1924**, *61*, 303.
[2] D. Ackermann, M. Mohr, *Z. Biol. Chem.* **1936**, *98*, 73.
[3] S.A. Waksman, H.B. Woodruff, *Proc. Soc. Exp. Biol. Med.* **1942**, *49*, 207.
[4] R.J. Rousseau, L.B. Townsend, R.K. Robins, *Biochemistry* **1966**, *5*, 756.
[5] J.A. May, Jr., L.B. Townsend, *J. Chem. Soc., Perkin Trans.1* **1975**, 125.
[6] J.A. Montgomery, A.T. Shortnacy, S.D. Clayton, *J. Heterocycl. Chem.* **1977**, *14*, 195.
[7] T. Itoh, T. Ishikura, Y. Mizuno, *Chem. Pharm. Bull.* **1983**, *31*, 4130.
[8] T. Itoh, T. Yamaguchi, Y. Mizuno, *J. Carbohydr. Nucleos. Nucleot.* **1981**, *8*, 119.
[9] F. Seela, W. Bourgeois, H.-P. Muth, H. Rosemeyer, *Heterocycles* **1989**, *29*, 2193.
[10] E. De Clercq, A. van Aerschot, P. Herdewijn, H. Baba, R. Pauwels, J. Balzarini, *Nucleos. Nucleot.* **1989**, *8*, 659.

[11] K. L. Prus, G. Wolberg, P. M. Keller, J. A. Fyte, C. R. Stopford, T. P. Zimmerman, *Biochem. Pharmacol.* **1989,** *38,* 509.
[12] Y. Mizuno, T. Itoh, K. Saito, *Chem. Pharm. Bull.* **1964,** *12,* 866.
[13] R. J. Rousseau, R. K. Robins, *J. Heterocycl. Chem.* **1965,** *2,* 196.
[14] M. Hoffer, *Chem. Ber.* **1960,** *93,* 2777.
[15] H.-D. Winkeler, F. Seela, *J. Org. Chem.* **1983,** *48,* 3119.
[16] F. Seela, B. Westermann, U. Bindig, *J. Chem. Soc., Perkin Trans. 1* **1988,** 697.
[17] G. J. Soula, *J. Org. Chem.* **1985,** *50,* 3717.
[18] Z. Kazimierczuk, H. B. Cottam, G. R. Revankar, R. K. Robins, *J. Am. Chem. Soc.* **1984,** *106,* 6379.
[19] S. Fischer, Diplomarbeit, Universität Osnabrück, 1989.
[20] H. Rosemeyer, G. Toth, F. Seela, *Nucleos. Nucleot.* **1989,** *8,* 587.
[21] T. A. Krenitsky, J. L. Rideout, E. Y. Chao, G. W. Koszalka, F. Gurney, R. C. Crouch, N. K. Cohn, G. Wolberg, R. Vinegar, *J. Med. Chem.* **1986,** *29,* 138.
[22] H. Rosemeyer, F. Seela, *Nucleos. Nucleot.* **1990,** in press.
[23] H. Rosemeyer, G. Toth, B. Golankiewicz, Z. Kazimierczuk, W. Bourgeois, H. P. Muth, U. Kretschmer, F. Seela, *J. Org. Chem.* **1990,** in press.
[24] A. Ono, T. Ueda, *Nucleic Acids Res.* **1987,** *15,* 3059.
[25] F. Seela, H. Rosemeyer, T. Grein, *Collect. Czech. Chem. Commun.* **1990,** in press.
[26] T. Teorell, E. Stenhagen, *Biochem. Z.* **1938,** *229,* 416.
[27] R. P. Panzika, R. J. Rousseau, R. K. Robins, L. B. Townsend, *J. Am. Chem. Soc.* **1972,** *94,* 4708.
[28] J. Swain, R. Lupton, *J. Am. Chem. Soc.* **1968,** *90,* 4328.
[29] F. Seela, H.-P. Muth, *Liebigs Ann. Chem.* **1988,** 215.
[30] H. Rosemeyer, F. Seela, *Helv. Chim. Acta* **1989,** *72,* 1084.
[31] M. Okabe, R.-C. Sun, S. Y.-K. Tam, L. J. Todaro, D. L. Coffen, *J. Org. Chem.* **1988,** *53,* 4780.
[32] H. Rosemeyer, F. Seela, *Helv. Chim. Acta* **1988,** *71,* 1573.
[33] A. Bax, *J. Magn. Reson.* **1984,** *57,* 314.