88. 7-Substituted 7-Deaza-2′-deoxyguanosines: Regioselective Halogenation of Pyrrolo[2,3-*d*]pyrimidine Nucleosides

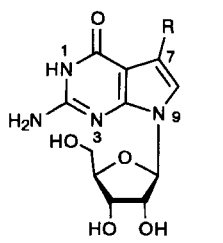
by **Natalya Ramzaeva** and **Frank Seela***

Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastr. 7, D-49076 Osnabrück

(7.IV.95)

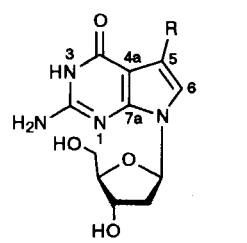
The synthesis of 7-chloro-, 7-bromo-, and 7-iodo-substituted 7-deaza-2′-deoxyguanosine derivatives **2b–d** is described. The regioselective 7-halogenation with *N*-halogenosuccinimides was accomplished using 7-[2-deoxy-3,5-*O*-di(2-methylpropanoyl)-β-D-*erythro*-pentofuranosyl]-2-(formylamino)-4-methoxy-7*H*-pyrrolo[2,3-*d*]-pyrimidine (**4**) as the common precursor. A one-pot reaction (2N aq. NaOH) of the halogenated intermediates **5a–c** furnished the desired compounds. Also the 7-hexynyl derivative **2e** of 7-deaza-2′-deoxyguanosine is described.

The 7-deazaguanine nucleosides bearing different substituents in position 7 (see **1**) have gained attention since some of them, *e.g.* queuosine [1–4], nucleoside pre Q [5] [6], cadeguomycin [7–11], kanagawamycin [12], and archaeosine [13] were isolated from natural sources. The present investigation is part of a study involving pyrrolo[2,3-*d*]-pyrimidine 2′-deoxynucleosides as substitutes of regular purine 2′-deoxynucleosides in DNA fragments [14–16].



1a R = H
b R = –CH_2NH– (cyclopentenediol)
c R = –C(=NH)–NH_2

purine numbering



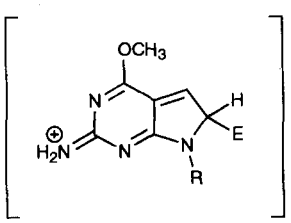
2a R = H
b R = Cl
c R = Br
d R = I
e R = $Me(CH_2)_3C{\equiv}C$

systematic numbering

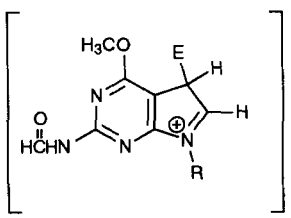
Recently, we introduced different substituents such as 7-halogeno, 7-alkyl, 7-alkynyl [16] [17], and 7-alkenyl groups into 7-deaza-2′-deoxyadenosine (2′-deoxytubercidin, c^7A_d) [17]. The incorporation of such 7-halogeno- or 7-methyl-substituted 7-deaza-2′-deoxy-adenosines into oligodeoxynucleotides leads to significantly enhanced duplex stabilities compared to the corresponding dA- or c^7A_d-containing oligomers [18].

In 1983, the first synthesis of 7-deaza-2′-deoxyguanosine (**2a**) was reported from our laboratory [19]. Later, a number of related 7-deazaguanine nucleosides were synthesized including 7-deaza-2′-deoxy-7-methylguanosine [20]. We now describe the synthesis of 7-chloro-, 7-bromo-, and 7-iodo-7-deaza-2′-deoxyguanosine derivatives as well as of some 7,8-disubstituted congeners. These compounds are of high importance, as they allow not only stabilization of DNA-duplex structures but can be further transformed to derivatives by side chains carrying reporter groups at this sterically favorable position.

Results and Discussion. – It was reported for 7-deazaguanines that the position of substitution strongly depends on the particular substituent pattern of the base as well as the reaction conditions [21] [22]. Of decisive importance is the observation that the 2-amino group directs the electrophilic attack into the undesired 8-position of a 7-deazaguanine moiety – a fact which was first recognized during *Mannich* reactions of 7-deazaguanine [23] [24]. This is the result of mesomeric stabilization of the σ-complex formed during electrophilic attack at the 8-position which is stabilized by the structure shown in formula **A**. Thus, an unprotected 2-amino derivative cannot be chosen as intermediate for halogenation at position 7. On the other hand, 7-deazaguanine derivatives without a free 2-amino group (see **B**) form the desired 7-substituted derivatives [24]. Moreover, it



A

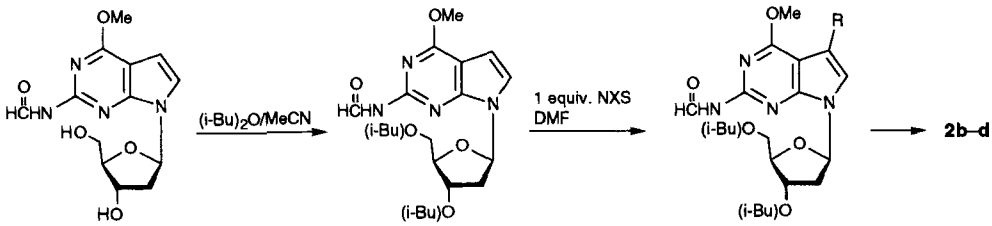


B

was shown in the case of 2′,3′-dideoxynucleosides, *e.g.* 7-deaza-6-methoxy-2-(methylthio)-9-[5-*O*-(triphenylmethyl)-2,3-dideoxy-β-D-ribofuranosyl]purine, that *N*-iodosuccinimide treatment in DMF at room temperature gave 7-deaza-7-iodo-6-methoxy-2-(methylthio)-9-[5-*O*-(triphenylmethyl)-2,3-dideoxy-β-D-ribofuranosyl]purine in almost quantitative yield as the sole regioisomer [21]. The 6-oxo and the 2-amino groups were generated thereafter [21]. An analogous regioselectivity of electrophilic halogenation was observed when 4-chloro-7-deaza-2-(methylthio)purine was reacted with *N*-halogenosuccinimides in DMF [25]. However, this route is inconvenient, as it requires several steps and problematic due to the fact that the 2-(methylthio) group of pyrrolo[2,3-*d*]pyrimidines is difficult to displace by nucleophiles compared to corresponding purine nucleosides [26].

Our research in this area was first focussed on a readily available synthetic nucleoside **3** [27] which was converted into the key intermediate **4** in which both of the carbohydrate OH groups as well as the base moiety were protected (*Scheme*). When compound **4** was treated with *N*-iodosuccinimide (NIS) in DMF according to [21], a clean reaction was observed affording the 7-substituted **5c** in 92% yield. No formation of a 7,8-diiodo compound was detected by TLC or NMR spectroscopy of the crude reaction mixture.

Scheme



3 **4** **5a** R = Cl, **b** R = Br, **c** R = I

NXS = *N*-chloro-, *N*-bromo-, or *N*-iodosuccinimide

The protecting groups were removed in a one-pot reaction using 2N aqueous NaOH (reflux, 3 h) to give compound **2d** in almost quantitative yield. Under these conditions, deacylation and nucleophilic displacement of the MeO group occurred without affecting the 7-iodo substituent (*Scheme*).

The chloro and bromo analogues **5a** and **5b** were prepared by reaction of **4** with 1 equiv. *N*-chloro- or *N*-bromosuccinimide (NClS or NBS), respectively, using the same experimental reaction conditions as for **5c** (*Scheme*, *Table 1*).

Table 1. *Halogenation of Compound* **4**: *Yields under Various Reaction Conditions*

Entry	Reagent	Solvent	Time	Product	Yield [%]
1	NIS	MeCN	23 h	**5c**	78
2	NIS	DMF	23 h	**5c**	92
3	NBS	MeCN	5 min	**5b**	65
4	NBS	DMF	1.5 h	**5b**	78
5	NCS	MeCN	1.5 h	[a]	–
6	NCS	DMF	20 h	**5a**	71
7	NCS	DCE[b]	18 h	[a]	–

[a]) Mixture of unidentified product. [b]) Dichloroethane.

The bromination and iodination could be carried out also in MeCN (*Table 1*). The fastest conversion within a series of experiments was observed, when compound **4** was treated with NBS in MeCN (5 min, *Entry 3*). Chlorination of the intermediate **4** with *N*-chlorosuccinimide (*Entry 5*) in MeCN was not accomplished and led to the formation of a complicated mixture with a relatively low yield. The same phenomenon was observed when 1,2-dichloroethane was used as solvent (*Entry 7*).

All compounds were characterized by ^{1}H, ^{13}C, and ^{1}H,^{13}C-correlation spectroscopy as well as by elemental analyses (*Tables 2* and *3* and *Exper. Part*). Inspection of the gated-decoupled ^{13}C-NMR spectra of compounds **4** and **5a–c** displays an interesting finding with respect to the ^3J(C(4a),H–C(6)) coupling: the introduction of a Cl substituent into position 5 (see **5a**, pyrrolo[2,3-*d*]pyrimidine numbering) decreases the ^3J coupling constant compared to **4** by 1.1 Hz, a Br or a I substituent enhances the coupling

by 2.8 or 3.4 Hz. This reflects the different electron-withdrawing or electron-donating effects of the halogeno substituents; however, no linear correlations could be observed between the C,H-coupling constants (or ^{13}C-NMR chemical shifts) and *Hammett* constants of the corresponding substituents.

Table 2. *^{13}C-NMR Data of 7-Deaza-2′-deoxyguanosines*[a])

	C(2)[b]) C(2)[c])	C(4)[b]) C(6)[c])	C(4a)[b]) C(5)[c])	C(5)[b]) C(7)[c])	C(6)[b]) C(8)[c])	C(7a)[b]) C(4)[c])	Me
4	152.2	162.9	101.8	99.9	122.8	152.5	53.8
5a	151.2	163.5	103.8	99.4	119.7	152.7	54.2
b	152.7	162.9	100.9	87.9	122.3	151.8	54.2
c	152.3	162.8	103.3	52.5	127.3	152.2	53.9
6a	152.5	163.8	101.9	99.1	119.2	149.8	54.2
b	152.1	163.4	101.8	91.6	112.0	151.2	54.2
2b	153.0	157.4	97.0	106.2	113.9	149.7	–
c	153.0	157.7	90.4	98.2	116.5	150.2	–
d	152.7	157.7	99.8	102.2	121.5	150.5	–
e	153.0	157.8	99.4	89.7	120.6	150.0	–
	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)		
4	83.3	35.8	74.3	81.2	63.7		
5a	83.9	35.6	74.0	81.2	63.5		
b	83.1	35.8	74.1	81.4	63.6		
c	82.9	37.8	74.0	81.2	63.5		
6a	83.9	34.2	73.6	81.1	63.2		
b	85.9	34.5	73.8	81.1	63.3		
2b	82.1	38.7	70.8	87.1	61.8		
c	82.3	38.5	71.0	87.2	61.9		
d	82.2	38.5	70.9	87.0	61.9		
e	81.9	39.5	70.6	86.8	61.6		

[a]) Measured in (D_6)DMSO. [b]) Systematic numbering. [c]) Purine numbering.

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

	4	**5a**	**5b**	**5c**
^1J(C=O,H–C=O)	201.7	197.7	197.1	192.4
^2J(C(7a),H–C(6))	6.9	8.0	8.0	7.7
^3J(C(7a),H–C(1′))	2.6	2.3	2.5	2.9
^1J(C(6),H–C(6))	189.5	194.6	194.9	194.7
^3J(C(6),H–C(1′))	4.4	4.5	4.5	4.7
^2J(C(6),H–C(5))	7.8	–	–	–
^3J(C(4a),H–C(6))	4.0	2.9	6.8	7.4
^2J(C(4a),H–C(5))	8.3	–	–	–
^2J(C(5),H–C(6))	6.9	6.3	3.3	4.8
^1J(C(5),H–C(5))	179.0	–	–	–
^1J(C(1′),H–C(1′))	164.9	166.5	164.9	166.0
^1J(C(4′),H–C(4′))	152.7	152.9	152.3	151.9
^1J(C(3′),H–C(3′))	158.1	158.6	158.8	157.2
^1J(C(5′),CH_2(5′))	149.1	149.3	149.3	149.2
^1J(CH_3O,CH_3O)	147.6	148.0	147.9	148.0

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

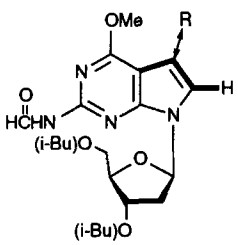
To confirm the position of halogenation, ^{1}H-NOE difference spectra of compounds **2a–d** were measured. As can be seen from *Table 4*, irradiation of the corresponding H–C(8) signals resulted in NOE effects at H–C(1′) of 2.5–3%. This proves both halogenation at C(7) as well as a preferred '*anti*'-conformation at the *N*-glycosylic bond for all cases. Application of a calibration graph for the estimation of '*syn*'- and '*anti*'-conformer populations of nucleosides according to [28] gave '*anti*'-rotamer populations of 75–80% for all compounds (*Table 4*). This is in line with results obtained for dG (70% '*anti*').

Table 4. *NOE Data of 7-Halogenated 7-Deaza-2′-deoxyguanosines*[a])

	Proton irradiated	NOE observed ([%])
2b	H–C(4′)	H–C(1′) + NH_2 (4.0), OH–C(3′) (4.0), OH–C(5′) (2.5), H–C(3′) (3.6), CH_2(5′) (3.9), H_α–C(2′) (2.7)
	H–C(8)	H–C(1′) (2.6), OH–C(5′) (1.4), H–C(3′) (1.6), CH_2(5′) (1.2), H_α–C(2′) (6.0)
2c	H–C(4′)	H–C(1′) (1.5), OH–C(3′) (2.7), OH–C(5′) (2.4), H–C(3′) (3.2), CH_2(5′) (4.5), H_α–C(2′) (2.2)
	H–C(8)	H–C(1′) (2.6), OH–C(5′) (1.0), H–C(3′) (1.9), CH_2(5′) (3.1), H_α–C(2′) (4.3)
2d	H–C(4′)	H–C(1′) (1.7), OH–C(3′) (5.4), OH–C(5′) (2.7), H–C(3′) (3.9), CH_2(5′) (7.8), H_α–C(2′) (2.0)
	H–C(8)	H–C(1′) (2.3), OH–C(5′) (1.7), H–C(3′) (0.9), H_α–C(2′) (5.1)
2a	H–C(4′)	H–C(1′) (2.9), OH–C(3′) (1.9), OH–C(5′) (1.7), H–C(3′) (1.1), CH_2(5′) (5.1), H_α–C(2′) (1.8)
	H–C(8)	H–C(1′) + H–C(7) + NH_2 (11.3), H–C(3′) (1.1), CH_2(5′) (1.9), H_α–C(2′) (4.3)

[a]) Taken from spectra measured in (D_6)DMSO at 23°.

The 7-position of 7-substituted 7-deazapurines is ideal for the labelling of DNA with reporter groups not showing the drawback of the destabilizing effects of purines with substituents located at C(8), at least from the stereochemical behavior of B-DNA. The iodonucleoside **2d** was, therefore, converted into several 7-substituted derivatives carrying various reporter groups by the Pd-catalyzed C–C cross-coupling reaction [29]. Reaction of **2d** with hex-1-yne in the presence of tetrakis(triphenylphosphine)-



	R	^3J(C(4a),H–C(6))
4	H	4.0
5a	Cl	2.9
b	Br	6.8
c	I	7.4

palladium(0), CuI, and Et_3N in DMF as a solvent gave the desired alkynyl derivative **2e** which was characterized by ^{1}H- and ^{13}C-NMR and mass spectra.

In conclusion, it was shown that Cl, Br, or I substituents can be introduced at the 7-position, regioselectively, when the amino-protected compound **4** is used for halogena-

tion of 7-deazapurines. Investigations regarding the incorporation of 7-substituted 7-deazaguanine nucleosides into oligonucleotides including their duplex stability will be the subject of another publication.

Experimental Part

General. See [16]. Solvent systems: CH_2Cl_2/acetone 95:5 (*A*), CH_2Cl_2/MeOH 85:15 (*B*), CH_2Cl_2/MeOH 80:20 (*C*). Column flash chromatography (FC): silica gel *60H* at 0.3 bar. M.p.: *Büchi-SMP-20* apparatus (*Büchi*, Switzerland); uncorrected. NMR Spectra: *AC-250* and *AMX-500* spectrometers (*Bruker*, Germany). Mass spectrum: *Fisons-TRI-1000*; EI, 70 eV (*VG-Instruments*, Mainz, Germany). Microanalyses were performed by *Mikroanalytisches Labor Beller* (Göttingen, Germany).

*7-[2-Deoxy-3,5-bis-*O*-(2-methylpropanoyl)-β-*D*-*erythro*-pentofuranosyl]-2-(formylamino)-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**4**). A suspension of **3** [27] (1 g, 3.3 mmol) in MeCN (20 ml) was treated with isobutyric anhydride (5 ml) in the presence of Et_3N (2.3 ml) at r.t. overnight. The clear soln. was evaporated and the residue chromatographed (silica gel, column 5 × 15 cm, *A*). The main zone was separated and evaporated. Crystallization from cyclohexane gave a colorless solid (1.2 g, 81%). M.p. 136–137°. TLC (silica gel, *A*): R_f 0.4. ^{1}H-NMR ((D$_6$)DMSO): 1.09 (*d*, *J* = 7.0, Me); 1.15 (*d*, *J* = 7.0, Me); 2.47, 2.57, 2.62, 2.92 (4*m*, CH, 2 H–C(2′)); 4.04 (*s*, MeO); 4.18 (*m*, CH_2(5′)); 4.27 (*m*, H–C(4′)); 5.37 (*m*, H–C(3′)); 6.49 (*m*, H–C(1′)); 6.55 (*d*, *J* = 3.7, H–C(5)); 7.42 (*d*, *J* = 3.7, H–C(6)); 9.46 (*d*, *J* = 9.5, NH); 10.75 (*d*, *J* = 9.9, HCO). Anal. calc. for $C_{21}H_{28}N_4O_7$ (448.5): C 56.24, H 6.29, N 12.49; found: C 56.44, H 6.26, N 12.44.

*5-Chloro-7-[2-deoxy-3,5-bis-*O*-(2-methylpropanoyl)-β-*D*-*erythro*-pentofuranosyl]-2-(formylamino)-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**5a**). To a soln. of **4** (300 mg, 0.67 mmol) in DMF (5 ml), *N*-chlorosuccinimide (87 mg, 0.67 mmol) was added. After stirring for 20 h at r.t., the soln. was poured into CH_2Cl_2/5% aq. $NaHCO_3$ soln. 9:1 (50 ml). The org. layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was redissolved in CH_2Cl_2 and chromatographed (silica gel, column 5 × 20 cm, *A*). The main zone was concentrated and poured into hexane giving colorless crystals (230 mg, 71%). TLC (silica gel, *A*): R_f 0.4. M.p. 119–120°. ^{1}H-NMR ((D$_6$)DMSO): 1.09 (*d*, *J* = 7.0, Me); 1.15 (*d*, *J* = 6.9, Me); 2.45, 2.60, 2.63, 2.89 (4*m*, CH, 2 H–C(2′)); 4.06 (*s*, MeO); 4.18 (*m*, H–C(5′)); 4.28 (*m*, H–C(4′)); 5.35 (*m*, H–C(3′)); 6.47 (*m*, H–C(1′)); 7.58 (*s*, H–C(6)); 9.45 (*d*, *J* = 8.9, NH); 10.84 (*d*, *J* = 9.6, HCO). Anal. calc. for $C_{21}H_{27}ClN_4O_7$ (482.9): C 52.23, H 5.64, N 11.60; found: C 52.51, H 5.69, N 11.65.

*5-Bromo-7-[2-deoxy-3,5-bis-*O*-(2-methylpropanoyl)-β-*D*-*erythro*-pentofuranosyl]-2-(formylamino)-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**5b**). As described for **5a**, with **4** (200 mg, 0.45 mmol) and *N*-bromosuccinimide (80 mg, 0.45 mmol; 1.5 h). The product was purified by FC (silica gel, column 5 × 20 cm, *A*). From the main zone, after crystallization from cyclohexane, colorless crystals (185 mg, 78%) were obtained. TLC (silica gel, *A*): R_f 0.4. M.p. 125–126°. ^{1}H-NMR ((D$_6$)DMSO): 1.09 (*d*, *J* = 7.0, Me); 1.15 (*d*, *J* = 7.0, Me); 2.45, 2.60, 2.63, 2.89 (4*m*, CH, 2 H–C(2′)); 4.06 (*s*, MeO); 4.17 (*m*, H–C(5′)); 4.28 (*m*, H–C(4′)); 5.35 (*m*, H–C(3′)); 6.48 (*m*, H–C(1′)); 7.63 (*s*, H–C(6)); 9.45 (*d*, *J* = 7.2, NH); 10.84 (*d*, *J* = 8.7, HCO). Anal. calc. for $C_{21}H_{27}BrN_4O_7$ (527.4): C 47.83, H 5.16, N 10.62; found: C 47.77, H 5.15, N 10.57.

*7-[2-Deoxy-3,5-bis-*O*-(2-methylpropanoyl)-β-*D*-*erythro*-pentofuranosyl]-2-(formylamino)-5-iodo-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine* (**5c**). As described for **5a**, with **4** (500 mg, 1.11 mmol) and *N*-iodosuccinimide (264 mg, 1.16 mmol; 23 h). Colorless crystals (590 mg, 92%) from cyclohexane. TLC (silica gel, *A*): R_f 0.4. M.p. 129–130°. ^{1}H-NMR ((D$_6$)DMSO): 1.09 (*d*, *J* = 7.0, Me); 1.15 (*d*, *J* = 7.0, Me); 2.46, 2.60, 2.89 (3*m*, CH, 2 H–C(2′)); 4.06 (*s*, MeO); 4.17 (*m*, H–C(5′)); 4.27 (*m*, H–C(4′)); 5.35 (*m*, H–C(3′)); 6.46 (*m*, H–C(1′)); 7.62 (*s*, H–C(6)); 9.55 (*d*, *J* = 9.7, NH); 10.81 (*d*, *J* = 9.9, HCO). Anal. calc. for $C_{21}H_{27}IN_4O_7$ (574.4): C 43.91, H 4.74, N 9.75; found: C 43.98, H 4.75, N 9.82.

*2-Amino-5-chloro-7-[2-deoxy-β-*D*-*erythro*-pentofuranosyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one* (**2b**). A suspension of **5a** (200 mg, 0.4 mmol) in 2N aq. NaOH (8 ml) was refluxed for 3 h. The soln. was neutralized with AcOH and the product collected by filtration, washed with H_2O, and dried. FC (column 5 × 20 cm, *B*) and crystallization from MeCN gave colorless crystals (115 mg, 96%). TLC (silica gel, *C*): R_f 0.7. M.p. 212–214°. UV (MeOH): 264 (12 500), 285 (sh, 7600). ^{1}H-NMR ((D$_6$)DMSO): 2.09 (*m*, H_α–C(2′)); 2.32 (*m*, H_β–C(2′)); 3.51 (*m*, H–C(5′)); 3.76 (*m*, H–C(4′)); 4.34 (*m*, H–C(3′)); 4.88 (*t*, OH–C(5′)); 5.19 (*d*, OH–C(3′)); 6.28 (*dd*, H–C(1′)); 6.36

(br., NH_2); 7.05 (*s*, H–C(6)); 10.49 (*s*, NH). Anal. calc. for $C_{11}H_{13}ClN_4O_4$ (300.7): C 43.94, H 4.36, N 18.63; found: C 43.91, H 4.44, N 18.51.

*2-Amino-5-bromo-7-[2-deoxy-β-*D-erythro-*pentofuranosyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one* (**2c**). As described for **2b**, from **5b** (500 mg, 0.95 mmol). FC (column 5 × 20 cm, *B*) and crystallization from MeCN gave colorless crystals (300 mg, 91%). M.p. 231–232°. TLC (silica gel, *C*): R_f 0.7. UV (MeOH): 265 (10900), 285 (sh, 7100). ^{1}H-NMR ((D$_6$)DMSO): 2.09 (*m*, H_α–C(2′)); 2.32 (*m*, H_β–C(2′)); 3.49 (*m*, 2 H–C(5′)); 3.74 (*m*, H–C(4′)); 4.26 (*m*, H–C(3′)); 4.86 (*t*, OH–C(5′)); 5.16 (*d*, OH–C(3′)); 6.28 (*dd*, H–C(1′)); 6.33 (br., NH_2); 7.07 (*s*, H–C(6)); 10.48 (br., NH). Anal. calc. for $C_{11}H_{13}BrN_4O_4$ (345.2): C 38.27, H 3.80, N 16.23; found: C 38.38, H 3.86, N 16.17.

*2-Amino-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-3,7-dihydro-5-iodo-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one* (**2d**). As described for **2b**, from **5c** (200 mg, 0.35 mmol). Colorless crystals (126 mg, 92%) from MeCN. M.p. 218–220°. TLC (silica gel, *C*): R_f 0.7. UV (MeOH): 266 (12000), 285 (sh, 8400). ^{1}H-NMR ((D$_6$)DMSO): 2.08 (*m*, H_α–C(2′)); 2.30 (*m*, H_β–C(2′)); 3.48 (*m*, H–C(5′)); 3.74 (*m*, H–C(4′)); 4.26 (*m*, H–C(3′)); 4.89 (*t*, OH–C(5′)); 5.18 (*d*, OH–C(3′)); 6.25 (*dd*, H–C(1′)); 6.34 (br., NH_2); 7.09 (*s*, H–C(6)); 10.51 (br., NH). Anal. calc. for $C_{11}H_{13}IN_4O_4$ (392.2): C 33.69, H 3.34, N 14.29; found: C 33.78, H 3.42, N 14.29.

*2-Amino-7-(2-deoxy-β-*D-erythro-*pentofuranosyl)-5-(hex-1-ynyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one* (**2e**). A soln. of **2d** (390 mg, 1 mmol) in dry DMF (5 ml) was flushed with Ar. CuI (38.1 mg, 0.2 mmol), Et_3N (2.8 ml, 2 mmol), tetrakis(triphenylphosphine)palladium(0) (40.5 mg, 0.1 mmol), and hex-1-yne (492 mg, 6 mmol) were added, and the mixture was stirred at r.t. for 24 h. The soln. was evaporated onto silica gel and the residue placed on the top of a silica-gel column (5 × 25 cm). Stepwise elution with 5, 10, and 20% of MeOH in CH_2Cl_2 afforded **2e**. Crystallization from MeCN gave a colorless solid (120 mg, 35%). ^{1}H-NMR ((D$_6$)DMSO): 0.94 (*m*, Me); 1.49, 2.38 (*m*, CH_2); 2.08 (*m*, H_α–C(2′)); 2.35 (*m*, H_β–C(2′)); 3.50 (*m*, 2 H–C(5′)); 3.76 (*m*, H–C(4′)); 4.28 (*m*, H–C(3′)); 4.88 (*t*, OH–C(5′)); 5.18 (*d*, *J* = 3.5, OH–C(3′)); 6.27 (*m*, H–C(1′), NH_2); 7.13 (*s*, H–C(6)); 10.34 (br., NH). MS: 346 (M^+).

We thank Dr. *H. Rosemeyer* for discussion. Financial support by the *Bundesminsterium für Bildung und Wissenschaft* is gratefully acknowledged.

REFERENCES

[1] H. M. Goodman, J. Abelson, A. Landy, S. Brenner, J. D. Smith, *Nature (London)* **1968,** *217,* 1019.
[2] B. P. Doctor, J. E. Loebel, M. A. Sodd, D. B. Winter, *Science* **1969,** *163,* 693.
[3] U. L. RajBhandary, S. H. Chang, H. J. Gross, F. Harada, F. Kimura, S. Nishimura, *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1969,** *28,* 409.
[4] H. Kasai, Z. Ohashi, F. Harada, S. Nishimura, N. J. Oppenheimer, P. F. Crain, J. G. Liehr, D. L. von Minden, J. A. McCloskey, *Biochemistry* **1975,** *14,* 4198.
[5] S. Noguchi, Z. Yamaizumi, T. Ohgi, T. Goto, Y. Nishimura, Y. Horita, S. Nishimura, *Nucleic Acids Res.* **1978,** *5,* 4215.
[6] T. Kondo, K. Okamoto, T. Ohgi, *Tetrahedron* **1986,** *42,* 207.
[7] N. Tanaka, R. T. Wu, T. Okabe, H. Yamashita, A. Shimazu, T. Nishimura, *J. Antibiot.* **1982,** *35,* 272.
[8] R. T. Wu, T. Okabe, M. Namikoshi, S. Okuda, T. Nishimura, N. Tanaka, *J. Antibiot.* **1982,** *35,* 279.
[9] T. Kondo, T. Goto, T. Okabe, N. Tanaka, *Tetrahedron Lett.* **1983,** *24,* 3647.
[10] V. G. Beylin, A. M. Kawasaki, C. S. Cheng, L. B. Townsend, *Tetrahedron Lett.* **1983,** *24,* 4793.
[11] T. Kondo, K. Okamoto, M. Yamamoto, T. Goto, *Tetrahedron* **1986,** *42,* 199.
[12] S. Naruto, H. Uno, A. Tanaka, H. Kotani, Y. Takase, *Heterocycles* **1983,** *20,* 27.
[13] J. M. Gregson, P. F. Crain, C. G. Edmonds, R. Gupta, T. Hashizume, D. W. Phillipson, J. A. McCloskey, *J. Biol. Chem.* **1993,** *268,* 10076.
[14] F. Seela, A. Kehne, *Biochemistry* **1987,** *26,* 2232.
[15] F. Seela, H. Driller, *Nucleic Acids Res.* **1985,** *13,* 911.
[16] F. Seela, H. Thomas, *Helv. Chim. Acta* **1994,** *77,* 897.
[17] M. Zulauf, Diploma Work, Osnabrück, 1995.
[18] F. Seela, H. Thomas, *Helv. Chim. Acta* **1995,** *78,* 94.
[19] H.-D. Winkeler, F. Seela, *J. Org. Chem.* **1983,** *48,* 3119.

[20] H.-D. Winkeler, F. Seela, *Liebigs Ann. Chem.* **1984,** 708.
[21] A.J. Cocuzza, *Tetrahedron Lett.* **1988,** *29,* 4061.
[22] E.C. Taylor, D.G. Kuhnt, C. Shih, S.M. Rinzel, G.B. Grindey, J. Barredo, M. Jonnatipour, R.G. Moran, *J. Med. Chem.* **1992,** *35,* 4450.
[23] F. Seela, U. Lüpke, *Chem. Ber.* **1977,** *110,* 1462.
[24] F. Seela, R. Richter, *Chem. Ber.* **1978,** *111,* 2925.
[25] N. Ramzaeva, F. Seela, unpublished.
[26] F. Seela, D. Hasselmann, *Chem. Ber.* **1981,** *114,* 3395.
[27] F. Seela, H. Driller, *Nucleosides Nucleotides* **1989,** *8,* 1.
[28] H. Rosemeyer, G. Toth, B. Golankiewicz, Z. Kazimierczuk, W. Bourgeois, U. Kretschmer, H.-P. Muth, F. Seela, *J. Org. Chem.* **1990,** *55,* 5784.
[29] F.W. Hobbs, *J. Org. Chem.* **1989,** *54,* 3420.