7-Iodo-5-aza-7-deazaguanine: Syntheses of Anomeric D- and L-Configured 2-Deoxyribonucleosides

by **Wenqing Lin**, **Xiaomei Zhang**, and **Frank Seela***

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

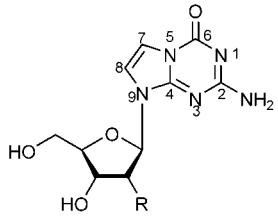
and

Center for Nanotechnology (CeNTech), Gievenbecker Weg 11, D-48149 Münster

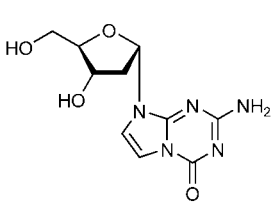
Iodination of N^2-isobutyryl-5-aza-7-deazaguanine (**7**) with *N*-iodosuccinimide (NIS) gave 7-iodo-N^2-isobutyryl-5-aza-7-deazaguanine (**8**) in a regioselective reaction (*Scheme 1*). Nucleobase-anion glycosylation of **8** with 2-deoxy-3,5-di-*O*-toluoyl-α-D- or α-L-*erythro*-pentofuranosyl chloride furnished anomeric mixtures of D- and L-nucleosides. The anomeric D-nucleosides were separated by crystallization to give the α-D-anomer and β-D-anomer with excellent optical purity. Deprotection gave the 7-iodo-5-aza-7-deazaguanine 2′-deoxyribonucleosides **3** (β-D; $\geq$99% de) and **4** (α-D; $\geq$99% de). The reaction sequence performed with the D-series was also applied to L-nucleosides to furnish compounds **5** (β-L; $\geq$99% de) and **6** (α-L; $\geq$95% de).

Introduction. – The 5-aza-7-deazapurines (imidazo[1,2-*a*]-1,3,5-triazines) display a shape similar to that of the parent purines. In the series of guanine nucleoside analogs, *e.g.*, in nucleoside **1** with the imidazole N-atom in the bridgehead position 5, the donor–acceptor pattern of the 'pyrimidine' as well as the imidazole moiety changes [1] (purine numbering is used throughout the discussion). The absence of N(7) in **1** prevents *Hoogsteen* base-pair formation, and N(1) is no longer a proton donor but acts as proton acceptor. As a consequence, 5-aza-7-deazaguanine shows the base-pair-recognition properties of isocytidine. Thus, stable base pairs can be formed with guanine or isoguanine resulting in duplexes with parallel or antiparallel chain orientation [2][3]. As the chain orientation can be changed not only by alteration of the nucleobase donor–acceptor pattern but also by the configuration at the anomeric center of the nucleoside, compounds **1** and **2** form duplexes with opposite chain orientations [4]. Meanwhile, 5-aza-7-deazaguanine and its nucleosides and nucleotides have been shown to develop antiviral activity, especially against rhino viruses, herpes-simplex virus type I and herpes simplex virus type II [5]. The 5-aza-7-deazaguanine can also act as inhibitor of xanthine oxidase [6] and its 2′,3′-dideoxyribonucleoside triphosphate has the potential to inhibit HIV reverse transcriptase [7].

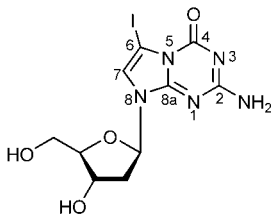
Earlier, 7-halogenated 7-deazapurine and 8-aza-7-deazapurine (= pyrrolo[2,3-*d*]-pyrimidine and pyrazolo[3,4-*d*]pyrimidine, resp.) nucleosides have been incorporated into DNA either chemically or enzymatically [8–16]. By this means, oligonucleotide duplexes became stabilized. Moreover, the iodinated compounds have been subjected to the *Sonogashira* cross-coupling reaction, which allowed the introduction of side chains into the molecules [17]. As we want to extend our studies on 5-aza-7-deazapurine nucleosides and oligonucleotides with various substituents at position 7



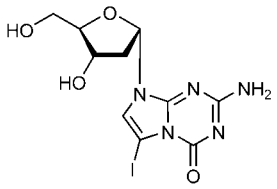
1a R = H
b R = OH
purine numbering



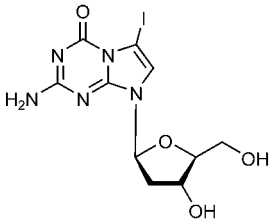
2



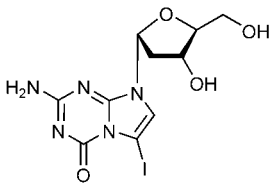
3
systematic numbering



4



5

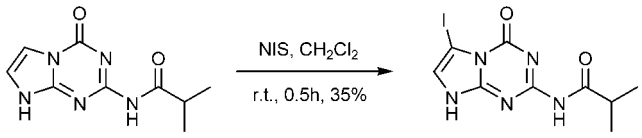


6

from the D-series to those with L-configuration [18–21], this communication reports the synthesis of the iodinated D-nucleosides **3** and **4** as well as of the corresponding L-enantiomers **5** and **6**. According to earlier work, the glycosylation of 5-aza-7-deazaguanine always results in the formation of anomeric mixtures [5]. Thus, an effective separation had to be developed to allow large-scale preparation and avoid chromatography, which is unsuccessful in this series of nucleosides.

Results and Discussion. – First, 5-aza-7-deazaguanine was isobutyrylated in the presence of isobutyric anhydride/phosphoric acid to give N^2-isobutyryl-5-aza-7-deazaguanine (**7**) as previously described [5]. Compound **7**, which is much better soluble than its nonprotected precursor, was anticipated to undergo regioselective halogenation as was observed with pyrrolo[2,3-*d*]pyrimidines [22–25]. Treatment of **7** with *N*-iodosuccinimide (NIS) in anhydrous CH_2Cl_2 (room temperature) furnished 7-iodo-N^2-isobutyryl-5-aza-7-deazaguanine (**8**) as a single isomer in 35% yield (*Scheme 1*). No desired product was obtained with NIS in anhydrous DMF or with iodomonochloride (ICl) in aqueous AcONa solution. We failed to improve the yield,

Scheme 1

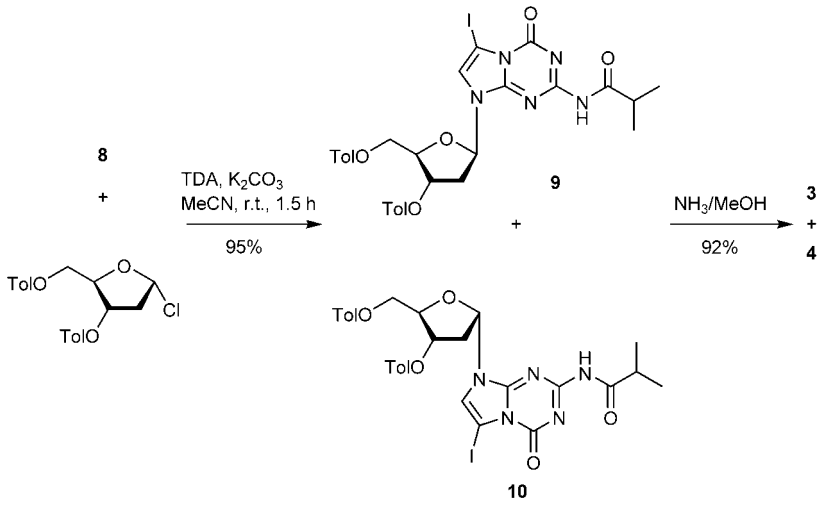


7 **8**

probably due to an oxidative destruction of **7** or of its reaction product **8**. The site of iodination was determined by NOE difference spectra and gated-decoupled ^{13}C-NMR spectra of compound **3** (see below).

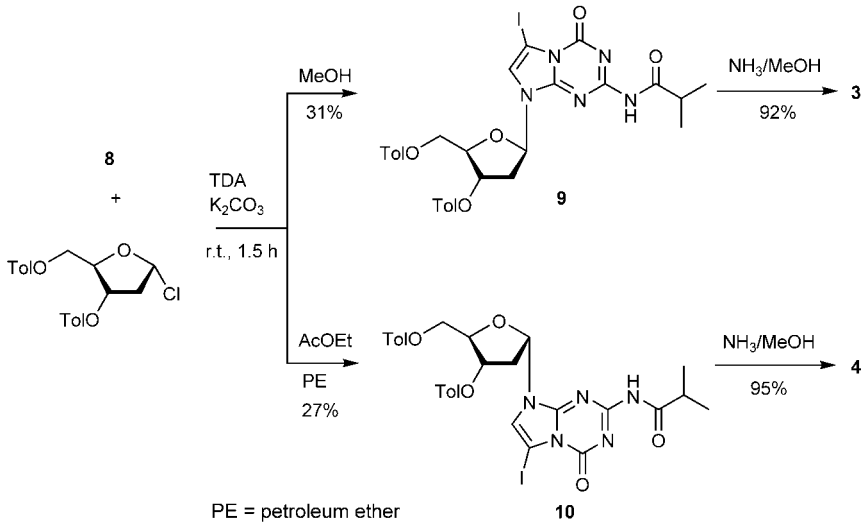
Compound **8** was glycosylated according to our previously described procedure [5]. Thus, 2-deoxy-3,5-di-*O*-toluoyl-α-D-*erythro*-pentofuranosyl chloride was prepared according to *Hoffer* [26] and *Kotera* and co-workers [27] and was employed in the glycosylation of **8** in the presence of potassium carbonate and tris[2-(2-methoxyethoxy)ethyl]amine (TDA) to give a colorless foam in 95% yield (*Scheme 2*). This foam was a mixture of the β-D and α-D-anomers **9** and **10** as shown by ^{1}H-NMR and reversed-phase HPLC. As expected, attempts to separate the anomers **9**/**10** by column chromatography failed. Therefore, the mixture **9**/**10** was deprotected with NH_3/MeOH to furnish the anomer mixture **3**/**4**. Nevertheless, this mixture could not be separated by column chromatography either. Later, the anomer mixture of **3**/**4** was silylated, and the reaction products were separated by column chromatography according to a protocol described for the separation of 2′,3′-dideoxy-5-aza-7-deazaguanosine [1]. Unfortunately, the purification of **3** and **4** was laborious, and pure **3** and **4** could not be obtained even by repeated column chromatography.

Scheme 2

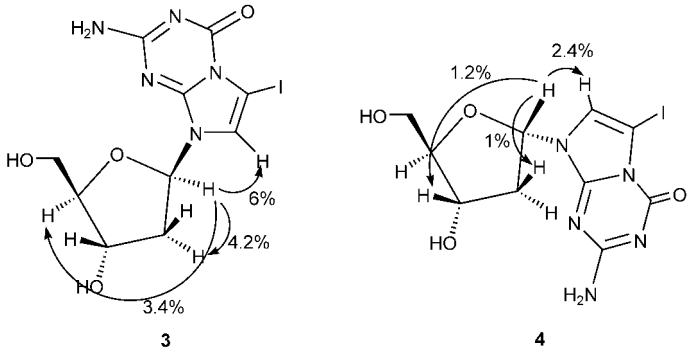


Since the anomer mixtures **9**/**10** and **3**/**4** could not be separated chromatographically, we had to search for another method of separation. When the anomer mixture **9**/**10** was dissolved in hot MeOH, only the β-D-anomer **9** crystallized upon cooling. The solvent of the mother liquid was then removed and the α-D-anomer **10** was recrystallized from AcOEt/petroleum ether (60–80°). Then, **9** and **10** were deprotected separately in saturated NH_3/MeOH solution to furnish the nucleosides **3** and **4** in 92 and 95% yield, respectively (*Scheme 3*). Both nucleosides were of excellent optical purity (≥ 99% de), as determined by reversed-phase HPLC (*RP-18* column, phosphate buffer (pH 7.2)/MeCN 95:5, 0.7 ml/min; t_R 27 (β-D-anomer) and 29 min (α-D-anomer)).

Scheme 3



The anomer configurations of **3** and **4** were confirmed by NOE difference spectra (*Table 1*). Irradiation of H–C(1′) of nucleoside **3** resulted in an NOE at H_α–C(2′) of 4.2% and at H–C(4′) of 3.4%, which demonstrates that H–C(1′), H_α–C(2′), and H–C(4′) are on the same side of the sugar ring; thus, **3** was assigned to be the β-D-anomer. Irradiation of H–C(1′) of **4** resulted in an NOE at H_β–C(2′) of 1.0% and at H–C(3′) of 1.2%; thus, **4** was assigned to be the α-D-anomer. According to the configurational assignments of **3** and **4**, compounds **9** and **10** were assigned accordingly.



When H–C(1′) of **3** was irradiated, an NOE of 6.0% was observed at H–C(8) (*Table 1*). Thus, the I-atom was selectively introduced at C(7) of **8** (see above). The ^{13}C-NMR spectrum of nucleoside **3** (*Table 2*) shows a resonance of the nucleobase at δ(C) 120.9 splitting into four signals (*dd*s with $^1J = 203.80$ Hz and $^3J = 3.96$ Hz). This reveals that this C-atom is bonded to a proton and that there is another proximal proton, *i.e.*, C(8) shows couplings with H–C(8) ($^1J = 203.80$ Hz) and H–C(1′) ($^3J = 3.96$ Hz).

Table 1. *NOE Data and Conformation of Nucleosides* **3–6** [a])

	Proton irradiated	NOE observed [%]						*anti* [%]
		H–C(1′)	H_β–C(2′)	H_α–C(2′)	H–C(3′)	H–C(4′)	H–C(8)	
3	H–C(8)	1.1	3.7		1.1			52
	H–C(1′)			4.2		3.4	6	
4	H–C(8)	1.2		3.1		1.5		47
	H–C(1′)		1		1.2		2.4	
5	H–C(8)	1.3	4.6		1.0			60
6	H–C(8)	0.7		3.3		1.7		53
	H–C(1′)		4.5		1.7		4.8	

[a]) Measured in (D_6) DMSO at 303 K.

Encouraged by the success in separating the anomer mixture **9/10**, compound **8** was glycosylated with 2-deoxy-3,5-di-*O*-toluoyl-α-L-*erythro*-pentofuranosyl chloride, which was prepared according to the procedure for the D-sugar [26–28]. The obtained mixture **11/12** of β-L- and α-L-anomers was crystallized from MeOH to afford the β-L-anomer **11** (*Scheme 4*). From the mother liquor, the α-L-anomer **12** was obtained by crystallization from AcOEt/petroleum ether. Removal of the toluoyl and isobutyryl groups from **11** and **12** resulted in **5** and **6**, respectively, which was accomplished in NH_3/MeOH at room temperature. The nucleosides **5** and **6** were of excellent optical purity (≥ 99 and ≥ 95% de, resp.), as determined by reversed-phase HPLC (*RP-18* column, phosphate buffer (pH 7.2)/MeCN 95 : 5, 0.7 ml/min; t_R 27 (L-β-anomer and 29 min (α-L-anomer). The configurations of **11**, **12**, **5**, and **6** were assigned as described for the D-compounds and were in full agreement with the data expected (*Table 1*).

Scheme 4

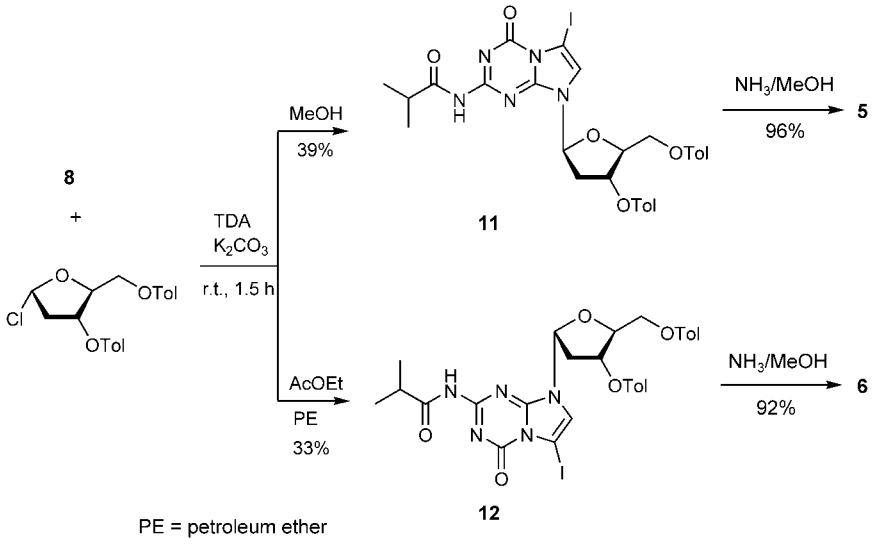


Table 2. *^{13}C-NMR Chemical Shifts* [ppm] *of 7-Iodo-5-aza-7-deazaguanine Derivative* **8** *and of 2′-Deoxyribonucleoside Derivatives* **3**–**6** *and* **9**–**12** [a])

	C(2) [b] [d]) C(2) [c])	C(4) [b] [d]) C(8a) [c])	C(6) [b]) C(4) [c])	C(7) [b]) C(6) [c])	C(8) [b]) C(7) [c])	CH	Me	C=O	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	Ar
3 [f])	150.5	150.1	164.2	57.4	120.9				82.7	38.4	70.3	87.6	61.3	
4	150.3	150.2	164.2	56.8	122.1				83.7	38.4	70.5	88.9	61.6	
5	150.3	150.1	164.0	57.2	120.8				81.6	38.3	70.1	87.4	61.2	
6	150.3	150.1	164.2	56.7	122.1				83.7	39.0	70.5	88.9	61.6	
8	[e])	150.1	[e])	57.5	[e])	34.8	18.8	179.4						
9	150.2	150.0	159.8	58.9	123.1	34.7	19.0, 21.2	175.6, 165.4, 165.1	81.9	35.6	74.6	84.2	63.9	144.1, 143.8, 129.4, 129.3, 129.2, 126.5, 126.4
10	150.7	149.7	160.1	54.6	123.2	36.4	19.4, 22.1	176.8, 166.4, 165.8	86.0	38.7	74.9	87.4	64.2	145.2, 144.7, 130.1, 130.0, 129.8, 129.7, 126.8, 126.2
11	150.2	149.9	159.8	58.9	123.1	34.6	18.9, 21.1	175.5, 165.3, 165.1	81.8	35.6	74.6	84.1	63.9	144.0, 143.7, 129.4, 129.3, 129.2, 126.5, 126.4
12	151.2	149.9	160.5	58.6	124.1	35.4	19.9, 22.1	176.5, 166.3, 165.8	84.8	38.1	75.4	87.0	64.9	144.7, 130.2, 127.4, 127.3

[a]) Measured in (D_6) DMSO at 303 K. [b]) Purine numbering. [c]) Systematic numbering. [d]) Tentative. [e]) Not detectable. [f]) Data of gated-decoupled: C(4), $^3J(C(4),H-C(8)) = 5.54$ Hz; C(8), $^1J(C(8),H-C(8)) = 203.8$ Hz, $^3J(C(8),H-C(1')) = 3.96$ Hz; C(7), $^3J(C(7),H-C(8)) = 8.76$ Hz.

No significant difference of the p*K* values of protonation between compound **3** ($pK_a = 3.6$) and the nonhalogenated **1a** ($pK_a = 3.7$) [5] was observed by pH-dependent UV spectra [29]. The UV maximum of the compounds **3**–**6** (λ_{max} 265 nm, pH 7) show a small red shift compared to the noniodinated **1a** (λ_{max} 257 nm, pH 7).

The conformation of the 5-aza-7-deazaguanine relative to the sugar moiety can be calculated from a calibration graph according to the NOE data of *Table 1* [30]. No significant difference was observed among the conformation of **3**–**6**. The *anti*-conformation populations of **3**–**6** are 52, 47, 60, and 53%, respectively. Next, the $N \leftrightarrow S$ pseudorotational equilibrium of the sugar moiety was determined. The ^{1}H-NMR spectra of compound **3**–**6** were measured in D_2O, ^3J(H,H) coupling constants were determined (*Table 3*). The conformational analysis was performed with the program PSEUROT [31]. As can be seen from *Table 3*, compounds **3**, **5**, and **1a** (β-anomers) show the same population of *S*-conformers (62–63%); compounds **4**, **6**, and **2** (α-anomers) show significantly higher populations of the *S*-conformers (76–79%). The conformational differences between the β- and α-anomers result from differences of the anomeric effect caused by the base, which is favorable to *N*-conformation in β-anomers and favorable to *S*-conformation in series of α-anomers. The conformation of the exocyclic C(4′)–C(5′) bond of **3**–**6** were calculated based on *J*(4′,5′a) and *J*(4′,5′b) according to *Westhof et al.* [32]. Compounds **1a**, **2**, and **3**–**6** show similar population of the *gauche*,*gauche*-conformation. Thus, it can be concluded that the iodo substituent does not have a significant influence on the conformation of the sugar puckering as well as of the C(4′)–C(5′) bond.

Table 3. *^{1}H-NMR Coupling Constants ^{3}J(H,H)* [Hz] *and Conformation of the Nucleosides* **1**–**6** [a])

	Conformation											
	J(1′,2′a)	*J*(1′,2′b)	*J*(2′,3′)	*J*(2′b,3′)	*J*(3′,4′)	*J*(4′,5′a)	*J*(4′,5′b)	%*N*	%*S*	γ^{g+}	γ^{t}	γ^{g-}
1a[2]								37	63	48	33	19
2[5]								22	78			
3	6.55	6.55	6.38	4.22	3.88	3.71	5.07	38	62	47	34	19
4	7.41	2.56	6.86	2.71	3.22	3.71	5.17	21	79	46	35	19
5	6.51	6.51	6.33	4.14	3.89	3.69	5.07	38	62	48	34	18
6	7.42	2.61	6.88	2.61	3.21	3.73	5.20	24	76	46	35	19

[a]) Measured in D_2O at 303 K.

Finally, the CD spectra of compounds **3**–**6** were measured; they show mirror-like curves for the D- and L-series. Compound **3** (β-D) exhibits negative *Cotton* effects around 275 and 228 nm and **5** (β-L) positive ones at the same wavelengths. Similarly, **4** (α-D) gives rise to a positive *Cotton* effect around 275 nm and to a negative one around 235 nm; compound **6** (α-L) exhibits the opposite behavior.

In conclusion, we successfully accomplished the regioselective introduction of a iodo substituent in a 5-aza-7-deazaguanine nucleoside and developed a simple and convenient practical procedure to separate the α- and β-anomer mixtures both in the D- and the L-series of the nucleosides. The separated anomeric 2-deoxy-D-ribonucleosides of 7-iodo-5-aza-7-deazaguanine were obtained in $\geq$99% de, and the β- and α-anomers of the 2-deoxy-L-ribonucleosides in $\geq$99 and $\geq$95% de, respectively. Studies on the

biological activities and base-pairing properties in duplex DNA are under investigation.

We are grateful to Dr. *Helmut Rosemeyer* for helpful discussions and for measuring the NMR spectra. We also acknowledge the support by Mrs. *M. Dubiel*, Mrs. *Eva-Maria Becker*, Mrs. *Elisabeth Michalek*, and Dr. *Peter Leonard*. The work was financially supported by the *European Community* (Grant No.: QLRT-2001-00506, 'Flavitherapeutics').

Experimental Part

General. Solvents: technical grade, distilled before use. Flash chromatography (FC): 0.4 bar, silica gel *60 H* (*VWR*, Darmstadt, Germany). TLC: aluminium sheet, silica gel *60* F_{254} (0.2 mm; *VWR*, Germany). UV Spectra: *U3200* spectrophotometer (*Hitachi*, Japan). NMR Spectra: *Avance-DPX-250* spectrometer or *AMX-500* spectrometer (*Bruker*, Rheinstetten, Germany), at 250.13 and 500 MHz for ^{1}H and 62.90 and 125.13 MHz for ^{13}C; δ values in ppm rel. to internal $SiMe_4$ (^{1}H,^{13}C). CD Spectra: *Jasco-600* instrument (*Jasco*, Japan); at r.t. Microanalyses were performed by *Mikroanalytisches Labor Beller* (Göttingen, Germany). Chemicals were purchased from *Acros*, *Fluka*, or *Sigma-Aldrich*.

N-*(4,8-Dihydro-6-iodo-4-oxoimidazo[1,2-*a*]-1,3,5-triazin-2-yl)-2-methylpropanamide* (**8**). To the stirred suspension of *N*-(4,8-dihydro-4-oxoimidazo[1,2-*a*]-1,3,5-triazin-2-yl)-2-methylpropanamide (**7**; 4.0 g, 18.08 mmol) [6] in anh. CH_2Cl_2 (400 ml) was added *N*-iodosuccinimide (4.5 g, 20.00 mmol) in one portion at r.t. Stirring was continued for 30 min and the solvent evaporated. The residue was applied to FC (silica gel, CH_2Cl_2/MeOH 100:2): **8** (2.2 g, 35%). Yellowish powder. TLC (silica gel, CH_2Cl_2/MeOH 20:1): R_f 0.24. UV (MeOH): 295 (10200). ^{1}H-NMR ((D$_6$)DMSO): 1.10 (*s*, 2 Me); 2.75 (*m*, CH); 7.31 (*s*, H–C(7)); 11.47, 12.00 (2*s*, 2 NH). Anal. calc. for $C_9H_{10}IN_5O_2$ (347.11): C 31.14, H 2.90, I 36.56; N 20.18; found: C 31.28, H 3.03, I 36.50, N 20.25.

N-*{8-[2-Deoxy-3,5-di*-O-*(p-toluoyl)*-D-erythro-*pentofuranosyl]-4,8-dihydro-6-iodo-4-oxoimidazo[1,2-*a*]-1,3,5-triazin-2-yl}-2-methylpropanamides* (**9/10**). Compound **8** (2.36 g, 6.80 mmol) was dissolved in hot MeCN (200 ml), then K_2CO_3 (3.0 g, 21.7 mmol) and TDA (0.3 ml, 0.94 mmol) were added under stirring. Stirring was continued at r.t. for 15 min. Then 2-deoxy-3,5-di-*O*-toluoyl-α-D-*erythro*-pentofuranosyl chloride (4.2 g, 10.80 mmol) was added, and stirring was continued for 1.5 h. The mixture was filtered, the filtrate evaporated, and the residue subjected to FC (silica gel, CH_2Cl_2/MeOH 500:1): **9/10** (4.5 g, 95%). Yellowish foam. TLC (silica gel, CH_2Cl_2/MeOH 200:1): R_f 0.23 (one spot).

2-Amino-8-(2-deoxy-D-erythro-*pentofuranosyl)-6-iodoimidazo[1,2-*a*]-1,3,5-triazin-4-(8*H*)-ones* (**3/4**). A mixture **9/10** (0.33 g, 0.47 mmol) in NH_3/MeOH (50 ml) was stirred at r.t. for 2 days. The mixture was evaporated and the residue applied to FC (silica gel, CH_2Cl_2/MeOH 20:1 → 2:1): **3/4** (0.17 g, 92%). Colorless powder. TLC (silica gel, CH_2Cl_2/MeOH 4:1): R_f 0.36 (one spot). UV (MeOH): 265 (13400).

N-*{8-[2-Deoxy-3,5-di*-O-*(p-toluoyl)*-β-D-erythro-*pentofuranosyl]-4,8-dihydro-6-iodo-4-oxoimidazo[1,2-*a*]-1,3,5-triazin-2-yl}-2-methylpropanamide* (**9**) *and* N-*{8-[2-Deoxy-3,5-di*-O-*(*p*-toluoyl)*-α-D-erythro-*pentofuranosyl]-4,8-dihydro-6-iodo-4-oxoimidazo[1,2-*a*]-1,3,5-triazin-2-yl}-2-methylpropanamide* (**10**). The mixture **9/10** (2.1 g, 3.00 mmol) was dissolved in hot MeOH (15 ml). Cooling in the refrigerator (8°) for 2 h and filtration gave the β-D-anomer **9** (0.65 g, 31%) as colorless crystals. The mother liquid was evaporated and redissolved in hot AcOEt (7 ml); petroleum ether (14 ml) was added. The soln. was put in the refrigerator for 2 days. Then the precipitate was filtered to furnish the α-D-anomer **10** (0.57 g, 27%) as a yellowish solid.

Data of **9**: M.p. 160–161°. TLC (silica gel, CH_2Cl_2/MeOH 200:1): R_f 0.23. UV (MeOH): 242 (38800). ^{1}H-NMR ((D$_6$)DMSO): 1.01, 1.04 (2*s*, 2Me); 2.36, 2.39 (2*s*, 2Me); 2.63 (*m*, CH), 2.96, 2.99 (2*m*, 2 H–C(2′)); 4.47 (*m*, H–C(4′), 2 H–C(5′)); 5.65 (*t*, *J* = 2.93, H–C(3′)); 6.25 (*t*, *J* = 6.80 Hz, H–C(1′)); 7.22, 7.76 (2*m*, H–C(7), 8 arom. H); 10.28 (*s*, NH). Anal. calc. for $C_{30}H_{30}IN_5O_7$ (699.49): C 51.51, H 4.32, I 18.14, N 10.01; found: C 51.65, H 4.28, I 18.30, N 10.08.

Data of **10**: M.p. 144–146°. TLC (silica gel, CH_2Cl_2/MeOH 200:1): R_f 0.23. UV (MeOH): 240 (37700). ^{1}H-NMR ((D$_6$)DMSO): 1.01, 1.04 (2*s*, 2 Me); 2.32, 2.34 (2*s*, 2 Me); 2.91 (*m*, CH, 2 H–C(2′)); 4.47 (*d*, *J* = 4.13, 2 H–C(5′)); 4.78 (*t*, *J* = 4.13 Hz, H–C(4′)); 5.60 (*d*, *J* = 5.02, H–C(3′)); 6.41 (*dd*, *J* = 5.73, 1.97, H–C(1′)); 7.17, 7.61, 7.86 (3*m*, H–C(7), 8 arom. H); 8.04 (*s*, NH). Anal. calc. for $C_{30}H_{30}IN_5O_7$ (699.49): C 51.51, H 4.32, I 18.14, N 10.01; found: C 51.55, H 4.41, I 18.20, N 10.10.

2-Amino-8-(2-deoxy-β-D-erythro-*pentofuranosyl)-6-iodoimidazo[1,2-*a*]-1,3,5-triazin-4-(8*H*)-one* (**3**). Compound **9** (236 mg, 0.34 mmol) suspended in NH_3/MeOH (30 ml) was stirred at r.t. overnight. After

evaporation, the residue was purified by FC (silica gel, CH_2Cl_2/MeOH 15:1 → 4:1): **3** (122 mg, 92%). Colorless powder. TLC (silica gel, CH_2Cl_2/MeOH 4:1): R_f 0.36. UV (MeOH): 265 (13200). ^{1}H-NMR ((D$_6$)DMSO): 2.13 (*d*, *J* = 14.42, 1 H–C(2′)); 2.36 (*m*, 1 H–C(2′)); 3.51 (*m*, 2 H–C(5′)); 3.79 (*d*, *J* = 2.68, H–C(4′)); 4.29 (*s*, H–C(3′)); 4.97 (*t*, *J* = 4.86, OH–C(5′)); 5.27 (*d*, *J* = 3.33, OH–C(3′)); 6.13 (*t*, *J* = 6.71, H–C(1′)); 6.94 (*s*, NH_2); 7.57 (*s*, H–C(7)). Anal. calc. for $C_{10}H_{12}IN_5O_4$ (393.14): C 30.55, H 3.08, I 32.28, N 17.81; found: C 30.65, H 3.15, I 32.40, N 17.74.

*2-Amino-8-(2-deoxy-α-*D-erythro-*pentofuranosyl)-6-iodoimidazo[1,2-*a*]-1,3,5-triazin-4-(8*H*)-one* (**4**). As described for **3**, with **10** (200 mg, 0.29 mmol): **4** (103 mg, 95%). Colorless powder. TLC (silica gel, CH_2Cl_2/MeOH 4:1): R_f 0.36. UV (MeOH): 265 (12700). ^{1}H-NMR ((D$_6$)DMSO): 2.09 (*d*, *J* = 14.42, 1 H–C(2′)); 2.64 (*m*, 1 H–C(2′)); 3.39 (*m*, 2 H–C(5′)); 4.10 (*s*, H–C(4′)); 4.27 (*s*, H–C(3′)); 4.83 (*t*, *J* = 5.11, OH–C(5′)); 5.49 (*d*, *J* = 2.65, OH–C(3′)); 6.14 (*dd*, *J* = 7.71, 1.92, H–C(1′)); 6.92 (*s*, NH_2); 7.60 (*s*, H–C(7)). Anal. calc. for $C_{10}H_{12}IN_5O_4$ (393.14): C 30.55, H 3.08, I 32.28, N 17.81; found: C 30.42, H 3.20, I 32.40, N 17.68.

N-*{8-[2-Deoxy-3,5-di-*O-(p-*toluoyl)-β-*L-erythro-*pentofuranosyl]-4,8-dihydro-6-iodo-4-oxoimidazo[1,2-*a*]-1,3,5-triazin-2-yl}-2-methylpropanamide* (**11**) *and* N-*{8-[2-Deoxy-3,5-di-*O-(p-*toluoyl)-α-*L-erythro-*pentofuranosyl]-4,8-dihydro-6-iodo-4-oxoimidazo[1,2-*a*]-1,3,5-triazin-2-yl}-2-methylporpanamide* (**12**). As described for **9** and **10**, with **8** (0.41 g, 1.18 mmol) and 2-deoxy-3,5-di-*O*-toluoyl-α-L-*erythro*-pentofuranosyl chloride (0.7 g, 1.80 mmol): **11** (0.32 g, 39%) and **12** (0.27 g, 33%).

Data of **11**: Colorless solid. M.p. 163–164°. TLC (silica gel, CH_2Cl_2/MeOH 200:1): R_f 0.23. UV (MeOH): 242 (38600). ^{1}H-NMR ((D$_6$)DMSO): 1.01, 1.04 (2*s*, 2 Me); 2.37, 2.39 (2*s*, 2 Me); 2.70 (*m*, CH); 2.86, 3.08 (2*m*, 2 H–C(2′)); 4.55 (*m*, H–C(4′), 2 H–C(5′)); 5.75 (*s*, H–C(3′)); 6.34 (*t*, *J* = 6.69, H–C(1′)); 7.33, 7.86 (2*m*, H–C(7), 8 arom. H); 10.38 (*s*, NH). Anal. calc. for $C_{30}H_{30}IN_5O_7$ (699.49): C 51.51, H 4.32, I 18.14, N 10.01; found: C 51.57, H 4.10, I 18.30, N 10.10.

Data of **12**: Colorless solid. M.p. 139–140°. TLC (silica gel, CH_2Cl_2/MeOH 200:1): R_f 0.23. UV (MeOH): 241 (37800). ^{1}H-NMR ((D$_6$)DMSO): 1.01, 1.04 (2*s*, 2 Me); 2.38 (*s*, 2 Me); 2.86 (*m*, CH, 2 H–C(2′)); 4.48 (*s*, 2 H–C(5′)); 5.10 (*s*, H–C(4′)); 5.61 (*s*, H–C(3′)); 6.38 (*s*, H–C(1′)); 7.33, 7.75, 7.88 (3*m*, H–C(7), 8 arom. H); 10.29 (*s*, NH). Anal. calc. for $C_{30}H_{30}IN_5O_7$ (699.49): C 51.51, H 4.32, I 18.14, N 10.01; found: C 51.80, H 4.13, I 18.29, N 9.95.

*2-Amino-8-(2-deoxy-β-*L-erythro-*pentofuranosyl)-6-iodoimidazo[1,2-*a*]-1,3,5-triazin-4-(8*H*)-one* (**5**). As described for **3**, with **11** (210 mg, 0.30 mmol): **5** (113 mg, 96%). Colorless powder. TLC (silica gel, CH_2Cl_2/MeOH 4:1): R_f 0.36. UV (MeOH): 265 (12900). ^{1}H-NMR ((D$_6$)DMSO): 2.13 (*m*, 1 H–C(2′)); 2.36 (*m*, 1 H–C(2′)); 3.52 (*m*, 2 H–C(5′)); 4.09 (*d*, *J* = 2.60, H–C(4′)); 4.28 (*s*, H–C(3′)); 4.96 (*t*, *J* = 5.12, OH–C(5′)); 5.27 (*d*, *J* = 3.71, OH–C(3′)); 6.13 (*t*, *J* = 6.65, H–C(1′)); 6.94 (*s*, NH_2); 7.57 (*s*, H–C(7)). Anal. calc. for $C_{10}H_{12}IN_5O_4$ (393.14): C 30.55, H 3.08, I 32.28, N 17.81; found: C 30.64, H 3.16, I 32.25, N 17.76.

*2-Amino-8-(2-deoxy-α-*L-erythro-*pentofuranosyl)-6-iodoimidazo[1,2-*a*]-1,3,5-triazin-4-(8*H*)-one* (**6**). As described for **3**, with **12** (200 mg, 0.29 mmol): **6** (103 mg, 92%). Colorless powder. TLC (silica gel, CH_2Cl_2/MeOH 4:1): R_f 0.36. UV (MeOH): 265 (12700). ^{1}H-NMR ((D$_6$)DMSO): 2.10 (*d*, *J* = 7.20, 1 H–C(2′)); 2.64 (*m*, 1 H–C(2′)); 3.39 (*m*, 2 H–C(5′)); 4.10 (*s*, H–C(4′)); 4.28 (*s*, H–C(3′)); 4.85 (*t*, *J* = 5.38, OH–C(5′)); 5.50 (*d*, *J* = 1.38, OH–C(3′)); 6.15 (*d*, *J* = 6.88, H–C(1′)); 6.91, 6.95 (2*s*, NH_2); 7.60 (*s*, H–C(7)). Anal. calc. for $C_{10}H_{12}IN_5O_4$ (393.14): C 30.55, H 3.08, I 32.38, N 17.81; found: C 30.52, H 3.15, I 32.50, N 17.45.

REFERENCES

[1] F. Seela, H. Rosemeyer, in 'Recent Advances in Nucleosides: Chemistry and Chemotherapy', Ed. C. K. Chu, Elsevier Science B.V., 2002, p. 505.
[2] F. Seela, A. Melenewski, *Eur. J. Org. Chem.* **1999**, 485.
[3] F. Seela, A. Melenewski, C. Wei, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2173.
[4] F. Seela, S. Amberg, A. Melenewski, H. Rosemeyer, *Helv. Chim. Acta* **2001**, *84*, 1996.
[5] H. Rosemeyer, F. Seela, *J. Org. Chem.* **1987**, *52*, 5136.
[6] S.-H. Kim, D. G. Bartholomew, L. B. Allen, R. K. Robins, G. R. Revankar, P. Dea, *J. Med. Chem.* **1978**, *21*, 883.
[7] F. Seela, W. Bourgeois, R. Gumbiowski, A. Röling, H. Rosemeyer, A. Mertens, H. Zilch, B. König, E. Koch, US Pat. 5,446,139, 1995.
[8] F. Seela, R. Kröschel, *Nucleic Acids Res.* **2003**, *31*, 7150.
[9] F. Seela, M. Zulauf, *Chem.–Eur. J.* **1998**, *4*, 1781.

[10] G. Balow, V. Mohan, E. A. Lesnik, J. F. Johnston, B. P. Monia, O. L. Acevedo, *Nucleic Acids Res.* **1998**, *26*, 3350.
[11] A. Okamoto, K. Tanaka, I. Saito, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 97.
[12] F. Seela, H. Thomas, *Helv. Chim. Acta* **1995**, *78*, 94.
[13] F. Seela, N. Ramzaeva, Y. Chen, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3049.
[14] N. Ramzaeva, F. Seela, *Helv. Chim. Acta* **1996**, *79*, 1549.
[15] N. Ramzaeva, C. Mittelbach, F. Seela, *Helv. Chim. Acta* **1997**, *80*, 1809.
[16] F. Seela, N. Ramzaeva, M. Zulauf, *Nucleosides Nucleotides* **1997**, *16*, 963.
[17] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467.
[18] P. Wang, J. H. Hong, J. S. Cooperwood, C. K. Chu, *Antiviral Res.* **1998**, *40*, 19.
[19] A. Verri, A. Montecucco, G. Gosselin, V. Boudou, J.-L. Imbach, S. Spadari, F. Focher, *Biochem. J.* **1999**, *337*, 585.
[20] E. De Clercq, *Nat. Rev. Drug Discov.* **2002**, *1*, 13.
[21] H. Urata, H. Miyagoshi, T. Kumashiro, T. Yumoto, K. Mori, K. Shoji, K. Gohda, M. Akagi, *Org. Biomol. Chem.* **2004**, *2*, 183.
[22] N. Ramzaeva, F. Seela, *Helv. Chim. Acta* **1995**, *78*, 1083.
[23] F. Seela, U. Lüpke, *Chem. Ber.* **1977**, *110*, 1462.
[24] F. Seela, R. Richter, *Chem. Ber.* **1978**, *111*, 2925.
[25] F. Seela, X. Peng, *Synthesis* **2004**, 1203.
[26] M. Hoffer, *Chem. Ber.* **1960**, *93*, 2777.
[27] V. Rolland, M. Kotera, J. Lhomme, *Synth. Commun.* **1997**, *27*, 3505.
[28] J. Šmekal, F. Šorm, *Collect. Czech. Chem. Commun.* **1964**, *29*, 2809.
[29] A. Albert, E. P. Serjeant, 'The Determination of Ionization Constants', Chapman and Hall, Ltd., London, 1971, p. 44.
[30] H. Rosemeyer, G. Tóth, B. Golankiewicz, Z. Kazimierczuk, W. Bourgeois, U. Kretschmer, H.-P. Muth, F. Seela, *J. Org. Chem.* **1990**, *55*, 5784.
[31] J. van Wijk, C. Altona, 'PSEUROT 6.2 – A Program for the Conformational Analysis of the Five-Membered Rings', University of Leiden, July, 1993.
[32] E. Westhof, O. Röder, I. Croneiss, H.-D. Lüdemann, *Z. Naturforsch., C* **1975**, *30*, 131.

Received May 4, 2004