61. Facile Synthesis of 2′-Deoxyisoguanosine and Related 2′,3′-Dideoxyribonucleosides

by **Frank Seela*** and **Bert Gabler**

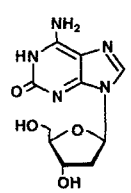
Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastrasse 7, D–49069 Osnabrück

(17.XII.93)

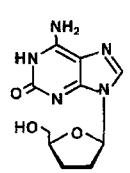
The 2′-deoxyisoguanosine (**1**) was synthesized by a two-step procedure from 2′-deoxyguanosine (**5**). Amination of silylated 2′-deoxyguanosine yielded 2-amino-2′-deoxyadenosine (**6**) which was subjected to selective deamination of the 2-NH_2 group resulting in compound **1**. Also 2′,3′-dideoxyisoguanosine (**2**) was prepared employing the photo-substitution of the 2-substituent of 2-chloro-2′,3′-dideoxyadenosine (**4**). The latter was synthesized by *Barton* deoxygenation from 2-chloro-2′-deoxyadenosine (**3**) or *via* glycosylation of 2,6-dichloropurine (**12**) with the lactol **13**. Compound **1** was less stable at the N-glycosylic bond than 2′-deoxyguanosine (**5**). The dideoxynucleoside **2** was deaminated by adenosine deaminase affording 2′,3′-dideoxyxanthosine (**17**).

Although isoguanine was already synthesized in 1897 by *E. Fischer* [1], corresponding nucleosides were unknown for many years. In 1951, *Davoll* reported on the synthesis of the isoguanine ribonucleoside [2]. The base as well as the ribonucleoside were discovered in nature [3–5]. The corresponding 2′-deoxyisoguanosine (**1**) was not found, neither as a constituent of DNA nor as the monomeric nucleoside. However, its synthesis was recently reported [6] [7]. Isoguanine nucleosides show an extraordinary behaviour. The 2′-deoxyisoguanosine (**1**) [8] forms base pairs with 2′-deoxycytidine as well as with 2′-deoxythymidine [9]; but contrary to 2′-deoxyguanosine, the duplex with dC shows parallel strand orientation [8]. Aggregates are formed in solution similar to 2′-deoxyguanosine (**5**) but the aggregates have an altered structure [10].

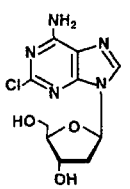
Compound **1** was synthesized by two different methods: *i*) by glycosylation of an imidazole precursor which was then converted into **1** [6], and *ii*) by photo-substitution of 2-chloro-2′-deoxyadenosine (**3**) [6]. Both methods are laborious. In the following, a short and efficient synthesis of **1** is described. Moreover, the preparation of 2′,3′-dideoxyisoguanosine (**2**) is reported by photo-substitution on 2-chloro-2′,3′-dideoxyadenosine (**4**) obtained from 2-chloro-2′-deoxyadenosine (**3**) by deoxygenation or by convergent synthesis using *Mitsunobu* conditions.



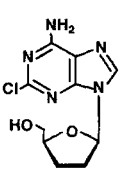
1



2



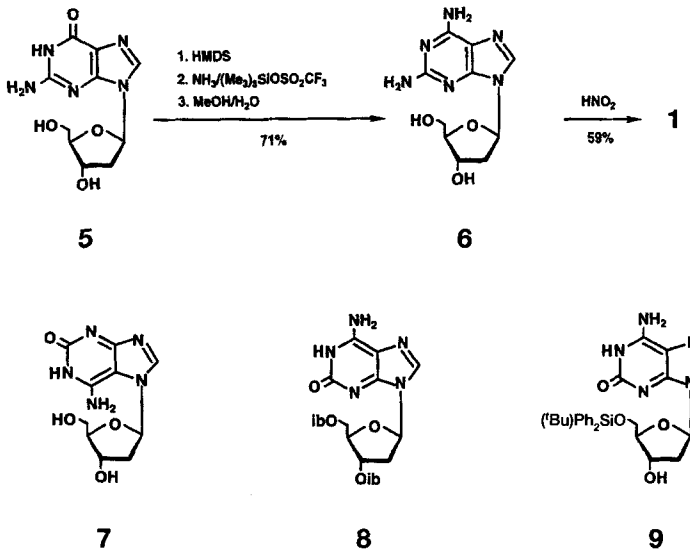
3



4

Results and Discussion. – An efficient synthesis of 2′-deoxyisoguanosine (**1**) should make use of 2′-deoxyguanosine (**5**) as starting material. The 2-amino-2′-deoxyadenosine (**6**) was considered as intermediate, because the corresponding ribonucleosides can be deaminated selectively at the 2-position [2]. Various syntheses of compound **6** were reported [11] [12]. However, most of them resulted in low yield. We applied the effective amination method of guanosine [13] [14] to **5**. Thus, the latter was silylated with an excess of 1,1,1,3,3,3-hexamethyldisilazane in the presence of (chloro)trimethylsilane (*Scheme 1*). The silylated intermediate was treated with NH_3 in an autoclave under the catalytic action of trimethylsilyl trifluoromethanesulfonate. Upon transsilylation (MeOH), crystalline **6** was isolated in 71% yield. Compound **6** was deaminated selectively by diazotization of the 2-NH_2 group affording 2′-deoxyisoguanosine (**1**) in 59% yield (42% rel. to **5**), after removal of the inorganic salt by chromatography on a hydrophobic resin.

Scheme 1



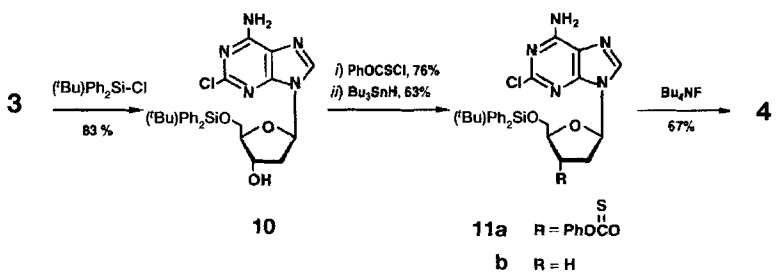
Compound **1** was identical with an authentic sample prepared earlier by photo-substitution [6]. However, contrary to earlier observations [6], the N-glycosylic bond of 2′-deoxyisoguanosine (**1**) is less stable than that of 2′-deoxyguanosine (**5**). The hydrolysis of **1** was followed UV-spectrophotometrically in 0.1N HCl at 236 nm, and a half-live value of 8 min was observed. Under identical conditions, the corresponding N^7-isomer **7** was slightly more stable ($t_{1/2}$ 18 min; 284 nm). The higher glycosylic-bond stability of the N^7-nucleoside is also found in case of the regioisomeric guanine 2′-deoxyribofuranosides [15]. However, the stability of both guanine 2′-deoxynucleosides is much higher than that of compounds **1** or **7**.

It is interesting to note that the UV spectrum of the N^7-nucleoside **7** (λ_{max} 282 nm) is hypsochromically shifted compared to compound **1** (λ_{max} 292 nm) [6], while in most other cases, purine N^7-nucleosides, including 2′-deoxyguanosine, show maxima at longer wave-

lengths than their N^9-counterparts. The UV spectra of protonated compounds **1** and **7** (0.1N HCl) look similar to each other and also to that of isoguanine measured under the same conditions. This implies that the protonation of all three compounds occurs at the imidazole moiety. It should also be mentioned that acylation of the NH_2 group of **1** is difficult to perform. Isobutyrylation under standard conditions gave only the 3′,5′-di-*O*-acyl derivative **8**, while in case of **5** the tri-isobutyryl derivate was formed [16]. This demonstrates the weak nucleophilicity of the NH_2 group of **1**.

As 2′,3′-dideoxyadenosine and 2′,3′-dideoxyguanosine are active compounds against HIV and show chain-terminating properties in the form of their 5′-triphosphates, the unknown 2′,3′-dideoxyisoguanosine (**2**) was synthesized. It was reported that the 2-substituent of 2-chloro-2′-deoxyadenosine (**3**) can be displaced photochemically to give **1** [6]. The same was expected for 2-chloro-2′,3′-dideoxyadenosine (**4**). Thus, compound **3** was first subjected to 3′-deoxygenation. The deoxygenation sequence was carried out on compound **3** as 2-chloroadenine nucleosides do not show the unfavourable aggregation properties of isoguanine nucleosides. Compound **4** was already prepared from the ribonucleoside (2-chloroadenosine) [17]; however, several reaction products were formed in this case. As a consequence, 2-chloro-2′-deoxyadenosine (**3**) [18] was reacted with (*t*-Bu)Ph_2SiCl in pyridine affording **10** (*Scheme 2*). Under similar conditions, compound **9** was obtained from **1**. Then compound **10** was converted into the 3′-*O*-phenoxythiocarbonyl derivative **11a**, which was reacted with tributylstannane in toluene yielding **11b**. After desilylation, crystalline 2-chloro-2′,3′-dideoxyadenosine (**4**) was obtained.

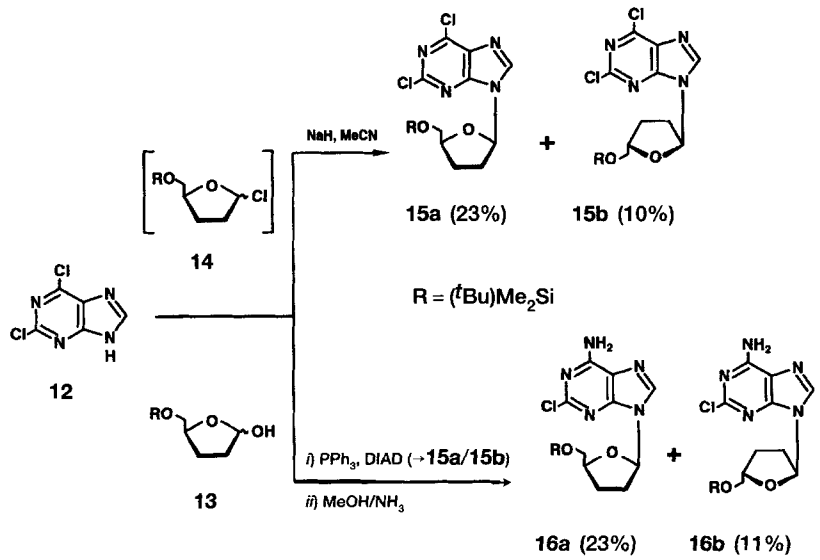
Scheme 2



As an alternative route for the synthesis of compound **4**, the direct glycosylation of 2,6-dichloropurine (**12**) with anomeric halide **14** was investigated (*Scheme 3*). For this purpose, lactol **13** [19] was prepared and converted into **14** [20]. Compound **12** was then reacted with **14** under the conditions of nucleobase-anion glycosylation yielding the 2,6-dichloronucleosides **15a**/**15b**. The anomers were separated very efficiently affording the β-D-compound **15a** in 23% and the corresponding α-D-nucleoside **15b** in 10% yield. Efficient separation of anomers on the stage of the silylated nucleosides was already reported for other deoxy- and dideoxynucleosides [21]. The N^7-isomers were not detected. Either they were not formed or its N-glycosyl bond is too labile to survive the workup conditions.

The 2,6-dichloropurine (**12**) could also be glycosylated directly with the 2,3-dideoxy sugar **13** under *Mitsunobu* conditions [22] (*Scheme 3*). This method was already used for the synthesis of carbocyclic [23] and hexose nucleosides [24]. The route circumvents the

Scheme 3



formation of the labile sugar halide **14**. In this case the intermediates **15a**/**15b** were not isolated. They were treated with NH_3/MeOH yielding the silylated 6-amino-2-chloro-nucleosides **16a**/**16b**, which were also separated to give **16a** in 23% and anomer **16b** in 11% yield. The β-D-compound **16a** was deprotected with Bu_4NF affording 2-chloro-2′,3′-dideoxyadenosine (**4**) which was identical to that obtained by deoxygenation.

The assignment of the anomeric 2′,3′-dideoxynucleosides based on chemical-shift differences of H–C(4′) and 2 H–C(5′) of the 5′-*O*-silylated compounds. *Table 1* shows that these differences are always smaller for the β-D-anomers than that of the α-D-compounds. This empirical finding was earlier proved by an unambiguous method [21]. The assignment of N^9 as glycosylation position was derived from the ^{13}C-NMR data (*Table 2*). Regioisomeric N^7- and N^9-nucleosides show very characteristic shifts of their bridgehead C-atoms (C(4) and C(5)) [25] which are also found for the anomers **15a, b** and **16a, b**.

Finally, compound **4** was subjected to photo-substitution under the same conditions as described for 2′-deoxynucleoside **3**. The reaction proceeded smoothly affording 2′,3′-dideoxyisoguanosine (**2**; *Scheme 4*) as the only reaction product (see *Fig. a*). This compound proved to be very labile against acid ($t_{1/2}$ 2 min, 0.01N HCl). Adenosine deaminase

Table 1. *^{1}H-NMR Chemical Shifts of H–C(4′) and 2 H–C(5′) of the Anomeric 2′,3′-Dideoxyribonucleosides* **15a, b** *and* **16a, b** *in (D$_6$)DMSO*

	15a (β-D)	**15b** (α-D)	**16a** (β-D)	**16b** (α-D)
δ(H–C(4′))	4.19	4.50	4.13	4.41
δ(CH_2(5′))	3.77	3.63	3.74	3.62
$\Delta\delta$	0.42	0.87	0.39	0.79

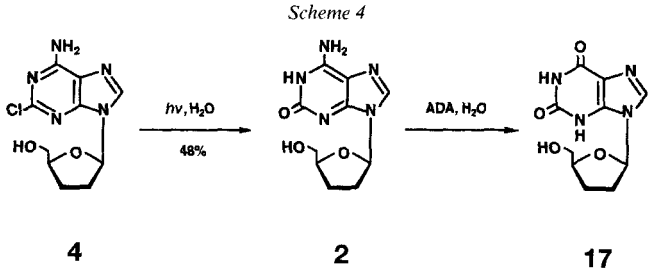
Table 2. *^{13}C-NMR Chemical Shifts of 2,6-Disubstituted Purine 2′-Deoxynucleosides and 2′,3′-Dideoxynucleosides in (D_6)DMSO at 23°*

	C(6)[a])	C(2)[a])	C(4)[a])	C(8)	C(5)
1	152.6	156.5	[c])	137.5	109.8
2	152.5	156.6	[c])	139.7	109.4
3 [6]	156.8	153.0	150.0	139.8	118.1
4	156.8	153.0	149.9	139.5	118.2
6[b])	159.9	156.1	151.3	135.9	113.5
8	152.4	157.1	154.6	136.8	109.4
9 [8]	152.1	155.7	153.6	137.7	109.2
10	156.9	153.1	150.1	139.8	118.4
11a	156.9	153.1	150.1	139.8	118.4
b	156.9	153.1	150.0	139.3	118.3
15a[d])	149.0	152.7	151.0	146.3	131.1
b[d])	148.8	152.7	151.3	146.6	131.1
16a[e])	156.8	153.0	149.1	139.8	154.2
b[e])	156.9	152.9	150.0	134.2	152.8

	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	Me_3C	Me_3C	Me
1	83.5	DMSO	71.0	87.6	61.6			
2[f])	84.0	31.8	25.7	81.4	63.0			
3	83.5	DMSO	70.7	88.2	63.3			
4[f])	84.5	31.9	25.6	82.0	62.8			
6	83.5	DMSO	70.7	88.2	63.3			
8	82.6	35.6	74.3	81.5	63.6			18.6
9	82.1	DMSO	70.1	86.8	64.2	26.7	18.9	
10	83.5	DMSO	70.2	87.1	64.1	26.7	18.9	
11a	84.3[a])	35.6	84.0[a])	83.9[a])	64.0	26.7	18.9	
b	84.4	31.3	25.7	81.5	65.4	26.7	18.8	
15a	85.6	31.7	24.9	82.3	64.0	25.9	18.1	
b	86.1	31.3	25.8	81.1	65.0	25.9	18.1	
16a	84.4	31.7	25.3	81.6	64.3	25.9	18.2	
b	84.8	31.1	26.1	80.7	65.1	25.9	18.0	

[a]) Tentative.
[b]) According to the ribonucleoside [14].
[c]) Not detectable.
[d]) According to 2,6-dichloro-9-methylpurine [25].
[e]) According to [6].
[f]) According to [26].

Scheme 4



4 **2** **17**

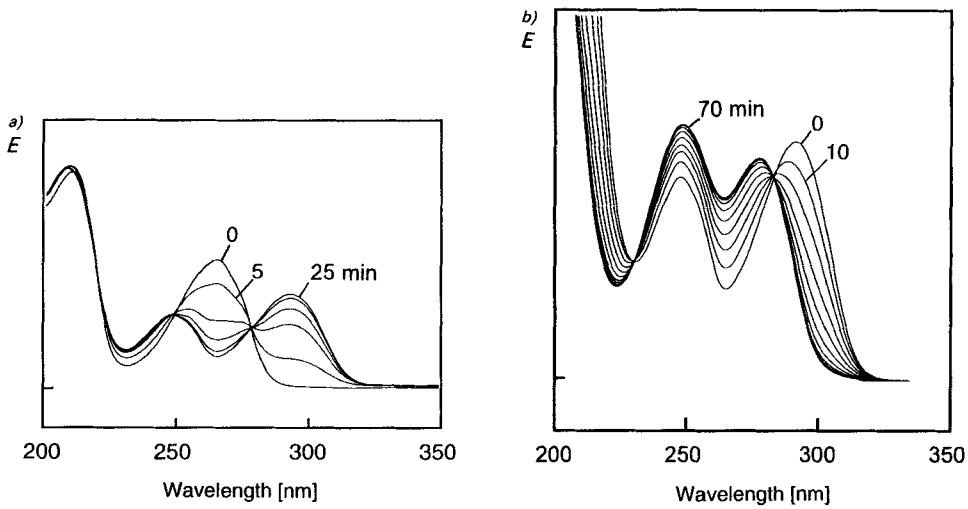


Figure. a) *Time-dependent UV spectra of the conversion of 2-chloro-2′,3′-dideoxyadenosine* (**4**) *in 2′,3′-dideoxyisoguanosine* (**2**) *by irradiation in water* (conditions, see [6]) *and* b) *enzymatic conversion of* **2** *into 2′,3′-dideoxyxanthosine* (**17**) *by adenosine deaminase in water*

(ADA) converted **2** into 2′,3′-dideoxyxanthosine (**17**; *Fig. b*) [27]. The latter was also obtained enzymatically by transdideoxyribosylation with live *E. coli* cells [28]. The evaluation of the antiviral activity of dideoxynucleoside **2** is under investigation.

We thank Prof. Dr. *H. Vorbrüggen* and Dr. *Z. Kazimierczuk* for helpful discussions and Dr. *H. Winter* for a sample of compound **7**. Financial support by the *Deutsche Forschungsgemeinschaft* is gratefully acknowledged.

Experimental Part

General. See [29]. Photoreactions were carried out as described [6]. The 2,6-dichloropurine (**12**) was a generous gift of *Boehringer Mannheim GmbH*.

*9-(2-Deoxy-β-*D-erythro-*pentofuranosyl)-9*H-*purine-2,6-diamine* (= *2-Amino-2′-deoxyadenosine*; **6**). A soln. of 2′-deoxyguanosine (**5**; 5.0 g, 18.6 mmol) in hexamethyldisilazane (HMDS; 150 ml, 0.71 mol) containing chlorotrimethylsilane (0.5 ml, 5 mmol) was refluxed for 10 h at 145°. The excess of HMDS was evaporated and the silylation procedure repeated on the residual sirup with the same amount of reagents. This soln. was evaporated again, the yellow oil dissolved in anh. toluene/HMDS 15:1 (30 ml), and 0.5M $CF_3SO_3SiMe_3$ in anh. toluene (4 ml, 2.0 mmol) added. The mixture was transferred into a steel vessel, which was maintained for 0.5 h under NH_3 (10 bar) at 0°. Then it was heated for 48 h at 145°. After cooling, the NH_3 was carefully vented, the mixture suspended in MeOH/H_2O 1:1 (300 ml), heated under reflux for 4 h, and the MeOH removed by evaporation. H_2O (250 ml) and charcoal were added, and the hot mixture was filtered. The yellow filtrate was concentrated to 200 ml to induce crystallization: colourless crystals (3.1 g). M.p. 146° ([12]: 148°). The mother liquor was applied to a *Dekker* [30] *Dowex 1-X2* column (OH^- form, 2.5 × 30 cm) and the resin washed with H_2O (500 ml). Elution with MeOH/H_2O 3:7 (300 ml) afforded additional 400 mg. Total yield 71%.

*6-Amino-9-(2-deoxy-β-*D-erythro-*pentofuranosyl)-1,9-dihydro-2*H-*purin-2-one* (= *2′-Deoxyisoguanosine*, $isoG_d$; **1**). To a stirred soln. of $NaNO_2$ (1.2 g, 17.4 mmol) in H_2O (50 ml), **6** (1.2 g, 4.5 mmol) was added at 50°. AcOH (1.8 ml, 31.2 mmol) was introduced dropwise and stirring continued for 5 min. Upon dilution with H_2O (40 ml), conc. NH_3 soln. was added until pH 8 was reached. The soln. was applied to a column (4 × 20 cm; *Serdolit AD-4* resin, 0.1–0.2 mm, *Serva*, Germany). The resin was washed with H_2O (500 ml) and **1** eluted with H_2O/i-PrOH 95:5 (500 ml). After evaporation, a yellow powder (710 mg, 59%) was isolated. ^{13}C-NMR: identical with the published data [6].

*6-Amino-9-[2-deoxy-3,5-bis-*O*-(2-methylpropanoyl)-β-*D*-erythro-pentofuranosyl]-1,9-dihydro-2*H*-purin-2-one* (**8**). Compound **1** (500 mg, 1.9 mmol) was dried by co-evaporation with anh. pyridine and dissolved in pyridine (20 ml). Isobutyryl chloride (ibCl; 1.95 ml, 18.5 mmol) was added at 0° and stirred for 1 h at r.t. The mixture was poured into 5% aq. $NaHCO_3$ soln. (50 ml) and concentrated to 20 ml to induce crystallization. The solid material was collected to give **8** (335 mg, 44%). White powder. TLC (CH_2Cl_2/MeOH 4:1): R_f 0.3. UV (MeOH): 298 (9700), 250 (8400). ^{1}H-NMR ((D_6)DMSO): 7.92 (*s*, H–C(8)); 7.86 (br. *s*, NH_2); 6.12 ('*t*', *J* = 6.5, H–C(1')); 5.30 (*m*, H–C(3')); 4.16 (*m*, H–C(4')); 4.23 (*m*, H–C(5')); 2.92, 2.59 (*m*, 2 H–C(2')); 1.05 (*m*, 4 Me). Anal. calc. for $C_{18}H_{25}N_5O_6$ (407.4): C 53.06, H 6.18, N 17.19; found: C 52.97, H 6.18, N 17.30.

*6-Amino-9-{2-deoxy-5-*O*-[(1,1-dimethylethyl)diphenylsilyl]-β-*D*-erythro-pentofuranosyl}-1,9-dihydro-2*H*-purin-2-one* (**9**). To a stirred soln. of **1** (530 mg, 2.0 mmol) in anh. DMF (20 ml), 1*H*-imidazole (340 mg, 5 mmol) and (*t*-Bu)Ph_2SiCl (1.5 ml, 6 mmol) were added. Stirring was continued for 12 h. The mixture was evaporated and dried by repeated co-evaporation with toluene. The residue was dissolved in MeOH and adsorbed on silica gel (5 g). This was loaded onto a column (20 × 4 cm; silica gel). Non-nucleoside material was eluted with CH_2Cl_2/MeOH 9:1. Further elution with CH_2Cl_2/MeOH 4:1 afforded a main zone. Upon concentration, **9** precipitated as a white powder (580 mg, 57%). TLC (CH_2Cl_2/MeOH 4:1): R_f 0.3. UV (MeOH): 298 (9100), 250 (8400). ^{1}H-NMR ((D_6)DMSO): 7.88 (*s*, H–C(8)); 7.86 (br. *s*, NH_2); 7.61–7.33 (*m*, 2 Ph); 6.13 ('*t*', *J* = 6.4, H–C(1')); 5.39 (br. *s*, OH–C(3')); 4.43 (*m*, H–C(3')); 3.87 (*m*, H–C(4')); 3.76 (*m*, H–C(5')); 2.56, 2.25 (*m*, 2 H–C(2')); 0.97 (*s*, *t*-Bu). Anal. calc. for $C_{26}H_{31}N_5O_4Si$ (505.7): C 61.76, H 6.18, N 13.85; found: C 61.23, H 6.29, N 13.82.

*2-Chloro-9-{2-deoxy-5-*O*-[(1,1-dimethylethyl)diphenylsilyl]-β-*D*-erythro-pentofuranosyl}-9H-purin-6-amine* (**10**). Compound **3** (860 mg, 3 mmol) was co-evaporated with anh. pyridine (2 × 20 ml) and dissolved in anh. pyridine (20 ml) while stirring. Then (*t*-Bu)Ph_2SiCl (0.85 ml, 3.3 mmol) was added and the soln. stirred for 14 h under Ar. The mixture was poured into 5% aq. $NaHCO_3$ soln. (100 ml) and extracted with CH_2Cl_2 (3 × 100 ml), the combined org. phase dried (Na_2SO_4), evaporated, and co-evaporated with anh. toluene, and the residue separated by FC (silica gel, column 30 × 3 cm, CH_2Cl_2/MeOH 95:5): colourless foam (1.3 g, 83%). TLC (CH_2Cl_2/MeOH 95:5): R_f 0.4. UV (MeOH): 264 (17300). ^{1}H-NMR ((D_6)DMSO): 8.25 (*s*, H–C(8)); 7.80 (*s*, NH_2); 7.57–7.30 (*m*, 2 Ph); 6.28 ('*t*', *J* = 6.5, H–C(1')); 5.39 (*d*, *J* = 4.4, OH–C(3')); 4.50 (*m*, H–C(3')); 3.92 (*m*, H–C(4')); 3.80 (*m*, 2 H–C(5')); 2.74, 2.34 (*m*, 2 H–C(2')); 0.95 (*s*, *t*-Bu). Anal. calc. for $C_{26}H_{31}ClN_5O_3Si$ (525.1): C 59.47, H 5.95, N 13.34; found: C 59.79, H 5.79, N 13.37.

*2-Chloro-9-{2-deoxy-5-*O*-[(1,1-dimethylethyl)diphenylsilyl]-3-*O*-(phenoxythiocarbonyl)-β-*D*-erythro-pentofuranosyl}-9H-purin-6-amine* (**11a**). To a stirred soln. of **10** (1.05 g, 2 mmol) in abs. CH_2Cl_2 (20 ml), 4-(dimethylamino)pyridine (610 mg, 5 mmol) and *O*-phenyl carbonochloridothioate (0.54 ml, 690 mg, 4 mmol) were added. Stirring was continued for 15 h and the mixture adsorbed on silica gel (5 g). This was applied to FC (silica gel, column 30 × 3 cm, CH_2Cl_2/MeOH 95:5): colourless powder (1.0 g, 76%). TLC (CH_2Cl_2/MeOH 95:5): R_f 0.5. UV (MeOH): 264 (15100). ^{1}H-NMR ((D_6)DMSO): 8.29 (*s*, H–C(8)); 7.86 (*s*, NH_2); 7.61–7.21 (*m*, 3 Ph); 6.37 ('*t*', *J* = 5, H–C(1')); 5.97 (*m*, H–C(3')); 4.44 (*m*, H–C(4')); 3.95 (*m*, 2 H–C(5')); 3.20, 2.82 (*m*, 2 H–C(2')); 0.98 (*s*, *t*-Bu). Anal. calc. for $C_{33}H_{34}ClN_5O_4SSi$ (660.3): C 60.03, H 5.19, N 10.61; found: C 60.18, H 5.39, N 10.67.

*2-Chloro-9-{2,3-dideoxy-5-*O*-[(1,1-dimethylethyl)diphenylsilyl]-β-*D*-glycero-pentofuranosyl}-9H-purin-6-amine* (**11b**). A soln. of **11a** (330 mg, 0.5 mmol) in abs. toluene (20 ml) was stirred with 2,2'-azobis(isobutyronitrile) (AIBN; 24 mg, 0.15 mmol) and Bu_3SnH (0.27 ml, 291 mg, 1 mmol) under Ar for 4 h at 80°. The solvent was evaporated, the residue co-evaporated with toluene (2 × 10 ml), and the residue applied to FC (silica gel, column 20 × 3 cm, CH_2Cl_2/MeOH 95:5): colourless foam (160 mg, 63%). TLC (CH_2Cl_2/MeOH 95:5): R_f 0.4. UV (MeOH): 265 (14200). ^{1}H-NMR ((D_6)DMSO): 8.25 (*s*, H–C(8)); 7.76 (*s*, NH_2); 7.56–7.29 (*m*, 2 Ph); 6.19 ('*t*', *J* = 4.7, H–C(1')); 4.21 (*m*, H–C(4')); 3.77 (*m*, 2 H–C(5')); 2.45 (*m*, 2 H–C(2')); 2.10 (*m*, 2 H–C(3')); 0.94 (*s*, *t*-Bu). Anal. calc. for $C_{26}H_{30}ClN_5O_2Si$ (508.1): C 61.46, H 5.95, N 13.78; found: C 61.32, H 5.98, N 13.72.

*2-Chloro-9-(2,3-dideoxy-β-*D*-glycero-pentofuranosyl)-9H-purin-6-amine* (= *2-Chloro-2',3'-dideoxyadenosine*; **4**). From **11b**: A soln. of **11b** (510 mg, 1 mmol) in abs. THF (10 ml) containing Bu_4NF (1.1 mmol) was stirred at r.t. for 12 h. After evaporation, the residue was applied to FC (silica gel, column 40 × 3 cm, CH_2Cl_2/MeOH 98:2): colourless crystals (180 mg, 67%) after recrystallization from EtOH. M.p. 185° ([17]: 238–240°).

From **16a**: Analogously, **16a** (580 mg, 1.5 mmol) was treated with Bu_4NF (1.1 mmol) in THF (10 ml). FC as described above and evaporation yielded a colourless powder (230 mg, 57%). TLC (CH_2Cl_2/MeOH 9:1): R_f 0.5. UV (MeOH): 265 (14700). ^{1}H-NMR ((D_6)DMSO): 8.37 (*s*, H–C(8)); 7.77 (*s*, NH_2); 6.14 (*dd*, *J* = 3.8, 6.0, H–C(1')); 4.93 (*t*, *J* = 5.4, OH–C(5')); 4.09 (*m*, H–C(4')); 3.51 (*m*, 2 H–C(5')); 2.38 (*m*, 2 H–C(2')); 2.02 (*m*, 2 H–C(3')). Anal. calc. for $C_{10}H_{12}ClN_5O_2$ (269.7): C 44.54, H 4.48, N 25.97; found: C 44.54, H 4.67, N 25.83.

*2,6-Dichloro-9-{2,3-dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-β-*D*- and -α-*D*-glycero-pentofuranosyl}-9H-purine* (**15a** and **15b**, resp.). To a soln. of 2,6-dichloropurine [31] (**12**; 756 mg, 4.0 mmol) in MeCN (20 ml), NaH (128 mg, 80% in oil, 4.25 mmol) was added. After stirring for 20 min at r.t., a freshly prepared cold (–80°) THF

soln. (20 ml) of 2,3-dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-D-*glycero*-pentofuranosyl chloride (**14**) [20], obtained from lactol **13** [19] (1.9 g, 8 mmol), was added during 30 min. Stirring was continued for another 30 min, insoluble material filtered off, and the filtrate poured into 20% aq. $NaHCO_3$ soln. (100 ml). The aq. layer was extracted twice with CH_2Cl_2 and the combined extract dried and evaporated. FC (column 40 × 3 cm, light petroleum ether/AcOEt 9:1) gave from the faster migrating zone **15a** (365 mg, 23%). Pale yellow oil. TLC (CH_2Cl_2/MeOH 98:2): R_f 0.7. UV (MeOH): 275 (8800). ^{1}H-NMR ((D$_6$)DMSO): 8.85 (*s*, H–C(8)); 6.31 ('*t*', *J* = 6.0, H–C(1')); 4.19 (*m*, H–C(4')); 3.77 (*m*, 2 H–C(5')); 2.38 (*m*, 2 H–C(2')); 2.07 (*m*, 2 H–C(3')); 0.80 (*s*, *t*-Bu); 0.04 (*s*, 2 Me). Anal. calc. for $C_{16}H_{24}Cl_2N_4O_2Si$ (403.4): C 47.64, H 6.00, N 13.89; found: C 47.86, H 6.29, N 13.89.

The slower migrating zone gave **15b** (165 mg, 10%). Pale yellow oil. TLC (CH_2Cl_2/MeOH 98:2): R_f 0.6. UV (MeOH): 274 (9000). ^{1}H-NMR ((D$_6$)DMSO): 8.84 (*s*, H–C(8)); 6.36 ('*t*', *J* = 4.6, H–C(1')); 4.5 (*m*, H–C(4')); 3.63 (*m*, 2 H–C(5')); 2.45 (*m*, 2 H–C(2')); 1.92 (*m*, 2 H–C(3')); 0.86 (*s*, *t*-Bu); 0.05 (*s*, 2 Me).

*2-Chloro-9-{2,3-dideoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-β-*D*- and -α-*D*-glycero-pentofuranosyl}-9*H*-purin-6-amine* (**16a** and **16b**, resp.). To a soln. of lactol **13** (2.2 g, 9.5 mmol) [19] and triphenylphosphine (2.7 g, 10 mmol) in abs. THF (20 ml), 2,6-dichloropurine (**12**; 1.9 g, 10 mmol) was added. A soln. of diisopropyl azodicarboxylate (DIAD; 2.4 ml, 11.5 mmol) in THF (10 ml) was added dropwise at 0° within 30 min. Stirring was continued at r.t. for 12 h, the soln. evaporated, the residue dissolved in MeOH (100 ml, sat. with NH_3), and the soln. stirred at 60° for 5 h and then at r.t. for 12 h. After evaporation, the residue was applied to FC (column 40 × 5 cm, CH_2Cl_2/MeOH 95:5). The faster migrating zone was evaporated and leached with Et_2O: **16a** (840 mg, 23%). Colourless powder. TLC (CH_2Cl_2/MeOH 95:5): R_f 0.5. UV (MeOH): 265 (15100). ^{1}H-NMR ((D$_6$)DMSO): 8.29 (*s*, H–C(8)); 7.77 (*s*, NH_2); 6.14 (*dd*, *J* = 3.2, 6.2, H–C(1')); 4.13 (*m*, H–C(4')); 3.74 (*m*, 2 H–C(5')); 2.38 (*m*, 2 H–C(2')); 2.07 (*m*, 2 H–C(3')); 0.82 (*s*, *t*-Bu); 0.04 (*s*, 2 Me). Anal. calc. for $C_{16}H_{26}ClN_5O_2Si$ (384.0): C 50.05, H 6.83, N 18.24; found: C 49.85, H 6.84, N 18.10.

Analogously, **16b** (400 mg, 11%) was obtained from the slower migrating zone. Colourless powder. TLC (CH_2Cl_2/MeOH 95:5): R_f 0.4. UV (MeOH): 265 (15000). ^{1}H-NMR ((D$_6$)DMSO): 8.29 (*s*, H–C(8)); 7.79 (*s*, NH_2); 6.20 ('*t*', *J* = 4, H–C(1')); 4.41 (*m*, H–C(4')); 3.62 (*m*, 2 H–C(5')); 2.33 (*m*, 2 H–C(2')); 1.67 (*m*, 2 H–C(3')); 0.87 (*s*, *t*-Bu); 0.05 (*s*, 2 Me).

*6-Amino-9-(2,3-dideoxy-β-*D*-glycero-pentofuranosyl)-1,9-dihydro-2*H*-purin-2-one* (= *2',3'-Dideoxyisoguanosine*; **2**). A soln. of **4** (135 mg, 0.5 mmol) in H_2O (250 ml) containing 25% aq. NH_3 soln. (1 ml) was irradiated in a quartz reactor for 30 min at r.t. Then, the soln. was concentrated to 100 ml and applied to a *Serdolit AD-4* column (20 × 2 cm). The resin was washed with H_2O. Elution with H_2O/i-PrOH 9:1 (300 ml) and evaporation afforded a pale yellow powder (60 mg, 48%). TLC (i-PrOH/H_2O/aq. NH_3 soln. 3:1:1): R_f 0.7. UV (H_2O): 292 (10300), 247 (7900). ^{1}H-NMR ((D$_6$)DMSO): 7.95 (*s*, H–C(8)); 7.67 (br. *s*, NH_2); 5.96 ('*t*', *J* = 6.3, H–C(1')); 5.20 (br. *s*, OH–C(5')); 4.06 (*m*, H–C(4')); 3.53 (*m*, 2 H–C(5')); 2.28 (*m*, 2 H–C(2')); 1.98 (*m*, 2 H–C(3')). Anal. calc. for $C_{10}H_{13}N_5O_3$ (251.2): C 47.81, H 5.22, N 27.87; found: C 47.61, H 5.33, N 27.74.

REFERENCES

[1] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1897,** *30,* 2226.
[2] J. Davoll, *J. Am. Chem. Soc.* **1951,** *73,* 3174.
[3] F. A. Fuhrman, G. J. Fuhrman, R. J. Nachman, H. S. Mosher, *Science* **1981,** *212,* 557.
[4] E. Cherbuliez, K. Bernhard, *Helv. Chim. Acta* **1932,** *15,* 464, 978.
[5] G. R. Pettit, R. H. Ode, M. R. Coomes, S. L. Ode, *Lloydia* **1976,** *39,* 363.
[6] Z. Kazimierczuk, R. Mertens, W. Kawczynski, F. Seela, *Helv. Chim. Acta* **1991,** *74,* 1742.
[7] Z. Kazimierczuk, D. Shugar, *Acta Biochim. Pol.* **1973,** *20,* 395.
[8] F. Seela, B. Gabler, Z. Kazimierczuk, *Collect. Czech. Chem. Commun.* **1993,** *58,* 170.
[9] F. Seela, R. Mertens, Z. Kazimierczuk, *Helv. Chim. Acta* **1992,** *75,* 2298.
[10] T. Golas, M. Fikus, Z. Kazimierczuk, D. Shugar, *Eur. J. Biochem.* **1976,** *65,* 183.
[11] R. H. Iwamoto, E. M. Acton, L. Goodman, *J. Med. Chem.* **1963,** *6,* 684.
[12] R. Fathi, B. Goswami, P.-P. Kung, B. L. Gaffney, R. A. Jones, *Tetrahedron Lett.* **1990,** *31,* 319.
[13] H. Vorbrüggen, K. Krolikiewicz, *Liebigs Ann. Chem.* **1976,** 745.
[14] M. J. Robins, F. Hansske, S. E. Bernier, *Can. J. Chem.* **1981,** *59,* 3360.
[15] F. Seela, P. Leonard, unpublished results.
[16] B. L. Gaffney, L. A. Marky, R. A. Jones, *Tetrahedron* **1984,** *40,* 3.
[17] A. Rosowsky, V. C. Solan, J. G. Sodroski, R. M. Ruprecht, *J. Med. Chem.* **1989,** *32,* 1135.

[18] Z. Kazimierczuk, H. B. Cottam, G. R. Revankar, R. K. Robins, *J. Am. Chem. Soc.* **1984,** *106,* 6379.
[19] M. Okabe, R. C. Sun, S. Y.-K. Tam, L. J. Todaro, D. L. Coffen, *J. Org. Chem.* **1988,** *53,* 4780.
[20] F. Seela, W. Bougeois, H.-P. Muth, H. Rosemeyer, *Heterocycles* **1989,** *29,* 2193.
[21] F. Seela, H. P. Muth, A. Röling, *Helv. Chim. Acta* **1991,** *74,* 554.
[22] O. Mitsunobu, *Synthesis* **1981,** 1.
[23] T. F. Jenny, J. Horlacher, N. Previsani, S. A. Benner, *Helv. Chim. Acta* **1992,** *75,* 1944.
[24] W. A. Szarek, C. Depew, H. C. Jarell, J. K. N. Jones, *J. Chem. Soc., Chem. Commun.* **1975,** 648.
[25] P. Fischer, G. Lösch, R. R. Schmidt, *Tetrahedron Lett.* **1978,** 1505.
[26] F. Seela, H.-P. Muth, *Liebigs Ann. Chem.* **1988,** 215.
[27] D. B. Dunn, R. H. Hall, in 'Handbook of Biochemistry and Molecular Biology', Ed. G. D. Fasman, CRC Press, Cleveland, 1975, Vol. I, 'Nucleic Acids', p. 140.
[28] K. Murakami, T. Shirasaka, H. Yoshioka, E. Kojima, S. Aoki, H. Ford, Jr., J. S. Driscoll, J. A. Kelley, H. Mitsuya, *J. Med. Chem.* **1991,** *34,* 1606.
[29] Z. Kazimierczuk, U. Binding, F. Seela, *Helv. Chim. Acta* **1989,** *72,* 1527.
[30] C. A. Dekker, *J. Am. Chem. Soc.* **1965,** *87,* 4027.
[31] G. B. Elion, G. H. Hitchings, *J. Am. Chem. Soc.* **1956,** *78,* 3508.