115. Nucleosides

Part LVI[1])

Aminolysis of Carbamates of Adenosine and Cytidine

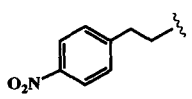
by **Harald Sigmund** and **Wolfgang Pfleiderer***

Fakultät für Chemie, Universität Konstanz, Postfach 5560, D–78434 Konstanz

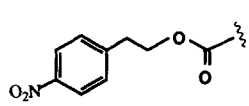
(26.V.94)

The 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) group, introduced 1984 as protecting group for exocyclic amino functions of nucleic-acid bases, reacts with amines under mild conditions to urea derivatives. Treatment of 2′,5′-di-*O*-acetyl-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]cordycepin (**3**) with NH_3/MeOH overnight at room temperature affords cordycepin (**4**) and N^6-carbamoylcordycepin (**5**). Preliminary investigations towards the elucidation of the reaction mechanism indicate that the aminolysis proceeds *via* an addition-elimination or an isocyanate mechanism, depending on the reaction conditions. The phenoxycarbonyl (phoc) group at N^6 or N^4 was chosen to study the mild conversion of carbamates with aromatic amines into ureas of adenosine and cytidine, respectively.

1. Introduction. – The chemistry of nucleosides and nucleotides deals to a large extent with protecting strategies to avoid side reactions of these multifunctional components during modifications or oligonucleotide syntheses; it is resumed in various reviews [2]. The principle of β-eliminating protecting groups dates back to *Tener* [3] and was extended by *Köster* and coworkers [4] to phosphoramidite chemistry which allows the protection of the internucleotide linkage during oligonucleotide synthesis [5]. In the last decade, we introduced the β-elimination as a versatile deprotection principle by using the 2-(4-nitrophenyl)ethyl (npe; **1**) and the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc; **2**) function as



1 2-(4-nitrophenyl)ethyl (npe)



2 2-(4-nitrophenyl)ethoxycarbonyl (npeoc)

blocking groups for the phosphate [6] and the OH and NH_2 functions [7], in the synthesis of oligonucleotides [8], antivirally active oligoadenylates [9], peptides and oligopeptides [10], nucleoside-lipid conjugates [11], and fluorescence-labeled nucleic-acid components [12].

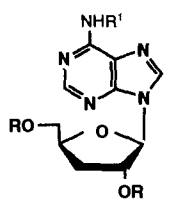
The deprotection of the β-eliminating npe and npeoc groups is basically performed with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in MeCN or pyridine under aprotic con-

[1]) Part LV: [1].

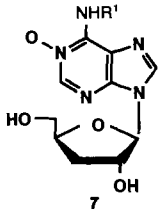
ditions. It was generally accepted for a long time that the npeoc function, as a protecting group for the exocyclic NH_2 function in nucleobases, is quite stable under aqueous basic conditions, a fact that was used to deprotect the acylated sugar moiety selectively in the presence of the npeoc group [7].

We now describe an unexpected lability of the npeoc protecting group during long-time treatment with NH_3/MeOH and preliminary studies of the mechanistic aspects of the ensuing transformations. The latter allowed us to prepare urea derivatives of the DNA bases adenosine and cytidine by applying the aminolysis to model *O*-phenyl carbamates.

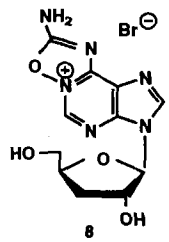
2. Results and Discussion. – During our attempts to prepare lipid conjugates [11] of the antivirally active nucleoside cordycepin (**4**), we observed incidentally a so far unexpected lability of the npeoc group in 2′,5′-di-*O*-acetyl-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]cordycepin (**3**) on treatment with NH_3/MeOH. Reaction of **3** with 150 equiv. of NH_3 overnight at room temperature resulted in the formation of *ca.* 1:1 mixture of cordycepin (**4**) and N^6-carbamoylcordycepin (**5**), indicating that the desired deacetylated N^6-[2-(4-nitrophenyl)ethoxycarbonyl]cordycepin (**6**), which was isolated in 78% yield under the same conditions after 2 h, was furthermore transformed to **4** and **5** on prolonged reaction.



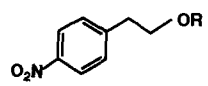
	R	R′
3	Ac	npeoc
4	H	H
5	H	$CONH_2$
6	H	npeoc



7



8



	R
9	H
10	$CONH_2$
11	CONHMe
12	CONHEt
13	$CONMe_2$
14	CO(morpholin-4-yl)
15	CONHPh
16	$CONH(4\text{-}NO_2C_6H_4)$
17	$CONH[2,4\text{-}(MeO)_2C_6H_3]$
18	COCl
19	COO(npe)

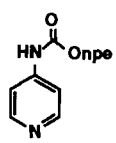
The structure of **5** was proven by an independent synthetic route, originally developed by *Ueda et al.* for the synthesis of N^6-carbamoyladenosine [13]. Oxidation of cordycepin (**4**) with H_2O_2, as described for the preparation of adenosine N^1-oxide [13], afforded only a moderate yield of the desired cordycepin N^1-oxide [14] (**7**), but treatment with 3-chloroperbenzoic acid worked well (65% yield of **7**). Subsequent reaction with bromocyan (→ **8**; 88% yield) and hydrogenation gave **5** in 88% yield which was identical with the substance isolated from the aminolysis of **3**.

The examination of the by-products of the aminolysis of **3**, *i.e.* 2-(4-nitrophenyl)-ethanol (**9**) and 2-(4-nitrophenyl)ethyl carbamate (**10**), indicated that no β-elimination took place, but that the reaction proceeded most likely *via* an addition-elimination

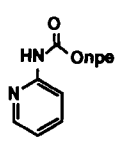
mechanism [15], which is supported by the formation of urethane **10**, or/and *via* an elimination-addition mechanism with the intermediary formation of an isocyanate. This latter possibility was first described by *Lyon* and *Reese* during their studies converting 2′,3′,5′-tri-*O*-acetyladenosine with phenyl chloroformate [16] and subsequent ammonolysis to N^6-carbamoyladenosine.

The aminolysis mechanism was further examined by the reaction of N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine [7] **37**; see below with $MeNH_2$ instead of NH_3. This aminolysis proceeded much faster than with NH_3, yielding, with 300 equiv. of $MeNH_2$ in dioxane at room temperature within 30 min, 87% of adenosine (**39**) and 88% of 2-(4-nitrophenyl)ethyl *N*-methylcarbamate (**11**). The reaction of **37** with 50 equiv. of NH_3 in dioxane for 24 h at room temperature or with 45 equiv. of morpholine in dioxane for 60 h at room temperature showed no aminolysis. Thus the nature of the amine as well as of the solvent obviously plays an important role in these interconversions.

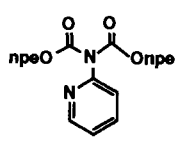
A series of carbamates **10**–**17** were prepared from 2-(4-nitrophenyl)ethyl chloroformate (**18**) [7] and some of them were used as appropriate model substances for detailed aminolysis studies. Heteroaromatic model carbamates turned out to be much more difficult to prepare. Only 4-aminopyridine reacted well with chloroformate **18** to give 2-(4-nitrophenyl)ethyl *N*-(pyridin-4-yl)carbamate (**20**) in 88% yield. In the case of amines with the NH_2 function in *ortho*-position to a ring N-atom, **18**, was too reactive. Thus, 2-aminopyridine afforded bis[2-(4-nitrophenyl)ethyl] carbonate (**19**), the desired *N*-(pyridin-2-yl)carbamate (**21**), and the by-products **22** and **23**. Carbamate **21** could, however, be synthesized in 80% yield using the more selective and less reactive 3-methyl-1-[2-(4-nitrophenyl)ethoxy-carbonyl]-1*H*-imidazolium chloride [7] (no carbonate **19** formed). With the same reagent 2-aminopyrimidine gave **24** in 60% yield besides carbonate **19**.



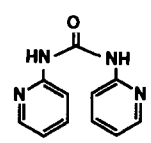
20



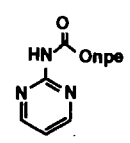
21



22



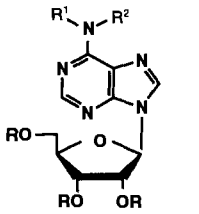
23



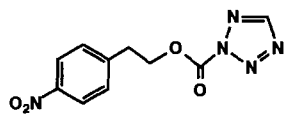
24

Aminolysis experiments with carbamates **15**, **16**, **20**, **21**, and **24**, using NH_3 or $MeNH_2$, did not give rise to homogeneous reactions, indicating that the aryl and heteroaryl substituent at the N-atom of the carbamates influences to some extent the cleavage mechanism of the *N*-npeoc group.

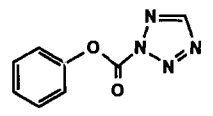
The second class of model substances were adenosine-derived carbamates having the N^6-position blocked by an alkyl group to avoid deprotonation, the initial step of the isocyanate mechanism. Thus N^6-methyladenosine [17] (**25**) was acetylated and the resulting 2′,3′,5′-tri-*O*-acetyl-N^6-methyladenosine (**26**) treated with 2-(4-nitrophenyl)ethyl chloroformate [7] (**18**) or 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride [7]. However, in both cases, 2′,3′,5′-tri-*O*-acetyl-N^6-methyl-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine (**27**) was obtained in only moderate yields, besides large amounts of educt **26** and carbonate **19**, due to some steric hindrance by the Me group. But using 2-(4-nitrophenyl)ethyl 2*H*-tetrazole-2-carboxylate (**28**) as acylating



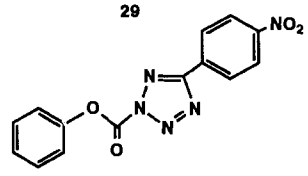
R	R^1	R^2	
25	H	H	Me
26	Ac	H	Me
27	Ac	npeoc	Me
31	Ac	phoc	H
32	Ac	phoc	Me
33	H	npeoc	Me
34	H	phoc	Me
35	H	COOMe	H
36	H	$CONH_2$	H



28



29



30

reagent, **27** was formed in a clean reaction in > 90% yield. This is in agreement with observations of *Adamiak et al.* [18] who introduced the phenyloxycarbonyl (phoc) group using phenyl 2*H*-tetrazole-2-carboxylate (**29**) to prepare 2′,3′,5′-tri-*O*-acetyl-N^6-(phenyloxycarbonyl)adenosine (**31**) from 2′,3′,5′-tri-*O*-acetyladenosine in better yields. Similarly, the newly synthesized 2*H*-tetrazole-2-carboxylate **30** afforded also a very high yield of **31**, and of 2′,3′,5′-tri-*O*-acetyl-N^6-methyl-N^6-(phenyloxycarbonyl)adenosine (**32**) from **26**. The deprotection of the triacetates **27** and **32** to **33** and **34**, respectively, was achieved by treatment with K_2CO_3 in MeOH in excellent yields. It is noteworthy that **31** could not be deprotected analogously under these conditions due to its high reactivity, which led to the methyl carbamate **35**. *Lyon* and *Reese* [16] also described the aminolysis of **31** with NH_3 to N^6-carbamoyladenosine (**36**) in 92% yield.

With the model carbamates **31**, **33**, **34**, and N^6-[2-(4-nitrophenyl)ethoxycarbonyl]-adenosine [7] (**37**), further investigations of the aminolysis mechanism were performed. The dependency of the aminolysis of the aliphatic carbamate **37** on the temperature as a determining factor regarding product formation (**38**/**9** *vs.* **39**/**11**) was clearly established (see *Table 1* and *Scheme*). We thus assume that, at elevated temperatures, the isocyanate mechanism, and at room temperature, the addition-elimination mechanism takes place

Table 1. *Aminolysis of* **37**

Equiv. of $MeNH_2$	Temp.	Time	Solvent	Products [%]			
				38	**9**	**39**	**11**
2	120°	6 h	pyridine	92	81	–	–
1	120°	6 h	pyridine	89	83	–	–
2	r.t.	11 d	pyridine	–	–	88	80
100	r.t.	1 h	pyridine	–	–	94	92
2	120°	2.5 h	dioxane	90	83	–	–
3	r.t.	10 d	dioxane	–	–	10	10
300	r.t.	1.5 h	dioxane	–	–	93	99

Scheme

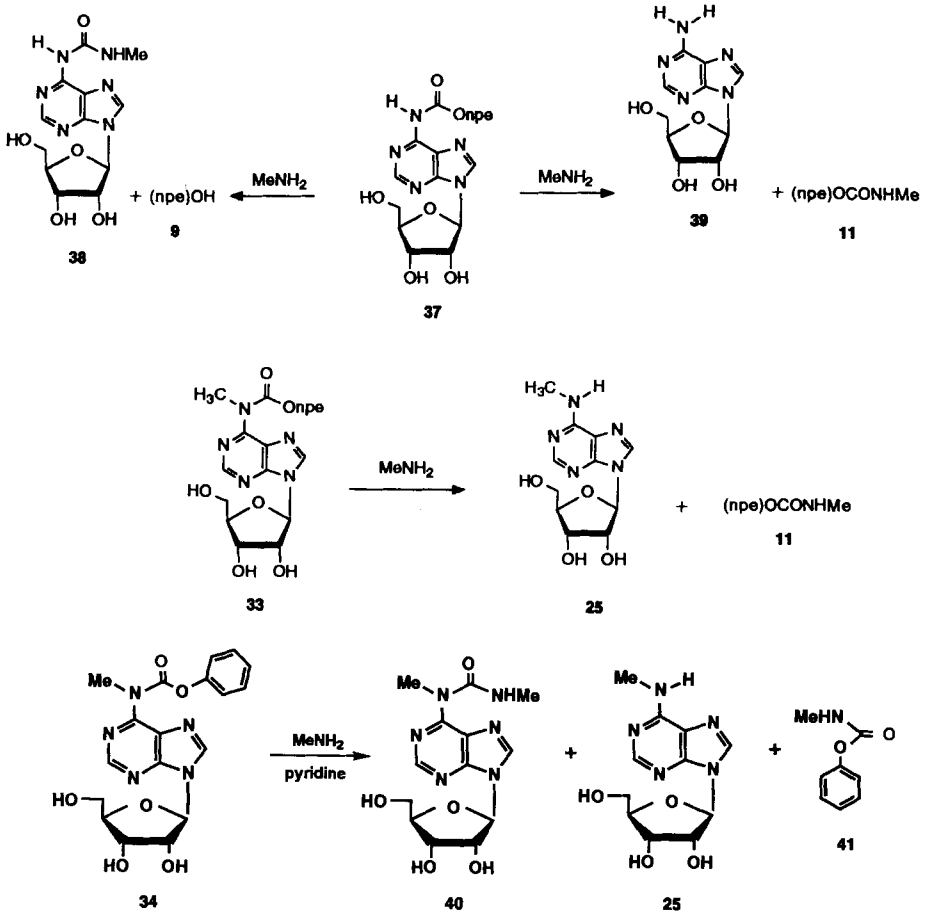


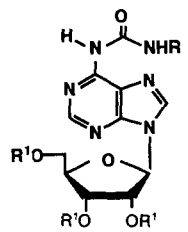
Table 2. *Aminolysis of* **33**

Equiv. of $MeNH_2$	Temp.	Time	Solvent	Products [%]	
				25	**11**
2	120°	3.5 h	pyridine	86	83
2	r.t.	7 d	pyridine	92	89
2	120°	2.5 h	dioxane	91	*ca.* 71
2	r.t.	12 d	dioxane	94	91
300	r.t.	30 min	dioxane	87	88

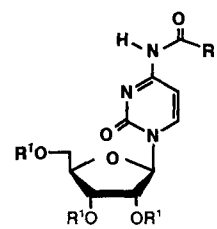
preferentially. This was confirmed by the aminolysis of **33** which has its N^6-position blocked by a Me group (results in *Table 2*).

For the aromatic carbamate **31**, the situation changed dramatically because of the excellent leaving characteristics of phenol, an aliphatic amine like $MeNH_2$ forming with **31** the corresponding *N*-substituted carbamoyl derivatives, most likely *via* the isocyanate

mechanism as proposed by *Lyon* and *Reese* [16] in 1978 and generally accepted for basic hydrolysis of this type of carbamates [19]. The N^6-methyl-N^6-(phenyloxycarbonyl)-adenosine (**34**), however, did not react with $MeNH_2$ *via* this mechanism but *via* the addition-elimination pathway as seen from the reaction products **40**/phenol and **25**/**41** obtained at room temperature (*Scheme*): after addition of $MeNH_2$ to **34** forming an orthoester-type intermediate two different bond-scissions can take place eliminating either phenol or phenyl *N*-methylcarbamate (**41**). The N^6-(phenoxycarbonyl) group of **31** reacted even with heteroaromatic amines, since N^6,$N^{6'}$-carbonylbis(adenine) was isolated on treatment of 2′,3′,5′-tri-*O*-acetyladenosine with phenyl chloroformate [16]. Interestingly N^6-(arylcarbamoyl)adenosines have so far only been synthesized of protected adenosines with aromatic isocyanates [20]. Treatment of **31**, however, with various aromatic amines in pyridine or dioxane at elevated temperature proceeded nicely to the corresponding urea derivatives **42**, **44**, and **46**, which were deprotected to **43**, **45**, and **47**, respectively, with K_2CO_3/MeOH in high yields. The ureas **44** and **46** could also be obtained from **31** with 1 equiv. of the corresponding amine at room temperature in yields of 58 and 79%. To the contrary, analogous treatment of the N^6-methyladenosine derivative **34** with aromatic amines at 70° for 17 h did not give any urea derivatives, because the isocyanate mechanism cannot proceed, and the addition-elimination mechanism is probably unattractive for steric reasons.



	R	R¹
42	Ph	Ac
43	Ph	H
44	4-EtOOC–C_6H_4	Ac
45	4-EtOOC–C_6H_4	H
46	4-O_2N–C_6H_4	Ac
47	4-O_2N–C_6H_4	H



	R	R¹
48	PhO	Ac
49	PhNH	Ac
50	PhNH	H
51	4-EtOOC–C_6H_4–NH	Ac
52	4-EtOOC–C_6H_4–NH	H
53	4-O_2N–C_6H_4–NH	Ac
54	4-O_2N–C_6H_4–NH	H

The general applicability of this urea-yielding aminolysis was demonstrated by the analogous treatment of 2′,3′,5′-tri-*O*-acetyl-N^4-(phenoxycarbonyl)cytidine (**48**) with aromatic amines to give the corresponding N^4-carbamoylcytidines **49**, **51**, and **53** and, after deacetylation, the urea derivatives **50**, **52**, and **54**, respectively.

3. Physical Data. – All newly synthesized compounds were characterized in the usual manner by elemental analysis, and UV and ^{1}H-NMR spectra (see *Exper. Part*).

Experimental Part

General. Pyridine was used at *p.a.* degree (*Merck*), all other solvents were purified by known methods [22]. TLC: precoated SiO_2 thin-layer sheets (*Merck DC-SiO$_2$60 F254*); SSE = org. phase of AcOEt/H_2O/PrOH 4:2:1. Prep. TLC: silica gel *60 PF$_{254}$* (*Merck*). Prep. column chromatography (CC): silica gel (*Merck 60*, 0.063–0.2 mesh). Flash column chromatography (FC): silica gel (*Baker*). M.p.: *Büchi* apparatus, model Dr. *Tottoli*, no corrections. UV/VIS: *Perkin-Elmer Lambda 5*; λ_{max} (log ε). p*K* Measurements: spectrophotometric method [21]. ^{1}H-NMR: *Bruker-WM 250, AC 250*, δ in pm rel. to TMS or $CDCl_3$ ((D_6)DMSO). ^{31}P-NMR: *Jeol JNM-GX400*; δ in ppm rel. to H_3PO_4. FAB-MS: *Finnigan* model *MAT 312*.

1. *3′-Deoxyadenosine* [16] (**4**) *and* N^6*-Carbamoyl-3′-deoxyadenosine* (**5**). 1.1. A suspension of 2′,5′-di-*O*-acetyl-3′-deoxy-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine [11] (**3**; 500 mg, 0.94 mmol) in 7.5M NH_3/MeOH (20 ml, cold saturated) was stirred for 18 h at r.t. The clear mixture was evaporated with silica gel (5 g) and purified by FC (silica gel (15 g), $CHCl_3$ (400 ml) and $CHCl_3$/MeOH 2:1 (200 ml), 100-ml fractions). The residue of *Fr. 5* and *6* was dissolved in $CHCl_3$/MeOH 2:1 (20 ml) and crystallization initiated with a few crystals of **5**. After two days, **5** was isolated (90 mg, 41%) as colorless crystals of m.p. 188–189°. The mother liquor was evaporated and the residue recrystallized from MeOH to give **4** (60 mg, 25%), m.p. 208–209° ([16]: 212°).

1.2. A soln. of **8** (see *Exper. 3*; 1.5 g, 4.02 mmol) in 50% EtOH (60 ml) was stirred under H_2 with Pd/C (150 mg) at r.t. (H_2 consumption: 90 ml after 1 h). After 3 h, the hydrogenation was stopped and the mixture neutralized with ion-exchange resin (*Dowex AG* type *44*, 20–50 mesh OH form). The filtrate was concentrated to 30 ml and crystallization initiated with a few crystals of **5**. The precipitate was collected after 3 days, washed with Et_2O/EtOH and dried: 0.67 g (56%). Workup of the mother liquor gave a second crop (0.37 g, 32%) from H_2O of m.p. 188–189°. TLC (SSE): R_f 0.33. UV (MeOH): 267 (4.31), 272 (sh, 4.23). ^{1}H-NMR ((D_6)DMSO): 9.43 (*s*, NH); 8.81 (br., NH); 8.68 (*s*, H–C(2)); 8.54 (*s*, H–C(8)); 7.31 (br., NH); 5.97 (*d*, *J* = 1.5, H–C(1′)); 5.73 (*d*, *J* = 4.0, OH–C(2′)); 5.08 (*t*, *J* = 5.2, OH–C(5′)); 4.58 (br., H–C(2′)); 4.38 (*m*, H–C(4′)); 3.75–3.67 (*m*, H–C(5′)); 3.57–3.49 (*m*, H′–C(5)); 2.30–2.19 (*m*, H–C(3′)); 1.95–1.86 (*m*, H–C(3′)). Anal. calc. for $C_{11}H_{14}N_6O_4$ (294.3): C 44.90, H 4.79, N 28.56; found: C 44.69, H 4.90, N 28.31.

2. *Cordycepin* N^1*-Oxide* [14] (= *3′-Deoxyadenosine* N^1*-Oxide*; **7**). A soln. of cordycepin [16] (**4**; 1.0 g, 4 mmol) and 3-chloroperbenzoic acid (1.4 g, 8 mmol) in 30% dioxane (100 ml) was stirred for 3 h at r.t. in the dark. The soln. was treated with activated carbon (200 mg), stirred for 1 h to destroy excess peroxide, and then filtered. The filtrate was concentrated, filtered again, if necessary, from the precipitating 3-chlorobenzoic acid, and then evaporated. To remove 3-chlorobenzoic acid, the residue was treated with Et_2O (50 ml) and the insoluble nucleoside collected to give crude product (1.15 g). After recrystallization from EtOH/H_2O 4:1 (50 ml) and drying (r.t./high vacuum) **7** was isolated as slightly brownish needles (500 mg). From the mother liquor, a second crop of **7** (180 mg) was obtained: 680 mg (64%) of **7**. M.p. 252–254° (dec.). TLC (SSE/i-PrOH/H_2O 5:4:1): R_f 0.4. UV (MeOH): 233 (4.61), 262 (3.89), 297 (3.33). ^{1}H-NMR ((D_6)DMSO): 8.62 (*s*, H–C(2)); 8.53 (*s*, H–C(8)); 8.80–7.40 (br., NH_2); 5.87 (*d*, *J* = 1.5, H–C(1′)); 5.77 (*d*, OH–C(2′)); 5.06 (*t*, OH–C(5′)); 4.53 (*m*, H–C(2′)); 4.37 (*m*, H–C(4′)); 3.67 (*dd*, H–C(5′)); 3.49 (*dd*, H′–C(5)); 2.17 (*m*, H–C(3′)); 1.89 (*m*, H′–C(3)). Anal. calc. for $C_{10}H_{13}N_5O_4$ (267.3): C 44.94, H 4.90, N 26.21; found: C 44.94, H 4.97, N 26.29.

3. *2-Amino-7-(3′-deoxy-β-*D*-ribofuranosyl)-7*H*-[1,2,4]oxadiazolo[3,2-i]purin-4-ium Bromide* (**8**). A suspension of **7** (1.1 g, 4.1 mmol) in MeOH (50 ml) was treated with bromocyan (0.53 g, 5.05 mmol) and the mixture stirred for 3 h at r.t. (→clear soln.). The mixture was evaporated for 2 h to remove bromocyan, the residue then dissolved in warm MeOH (200 ml), and the soln. filtered, evaporated to 50 ml, and treated with AcOEt until turbidness appeared (*ca.* 100 ml). The colorless product crystallized at 4° and was dried *in vacuo*: 1.36 g (88%). M.p. 183–185° (dec.). TLC (SSE/i-PrOH/H_2O 5:4:1): R_f 0.71. UV (MeOH): 226 (4.32), 284 (4.30). ^{1}H-NMR ((D_6)DMSO): 10.6 (br., NH); 10.1 (*s*, H–C(2)); 9.07 (*s*, H–C(8)); 6.09 (*s*, H–C(1′)); 5.90–4.70 (br., OH–C(2′), OH–C(5′)); 4.58 (*m*, H–C(2′)); 4.45 (*m*, H–C(4′)); 3.78–3.57 (*dd*, H–C(5′)); 3.54–3.39 (*m*, H′–C(5)); 2.24 (*m*, H–C(3′)); 1.92 (*m*, H′–C(3)). Anal. calc. for $C_{11}H_{13}BrN_6O_4$ (373.2): C 35.41, H 3.51, N 22.52; found: C 35.78, H 3.60, N 22.56.

4. *2-(4-Nitrophenyl)ethyl Carbamates* **10–17**. *General Procedure.* To a soln. of 2-(4-nitrophenyl)ethyl chloroformate [7] (**18**), the appropriate amine was added dropwise under cooling. The mixture was stirred at r.t. and the precipitating salt removed by filtration. If necessary, the filtrate was evaporated and the residue crystallized.

4.1. *2-(4-Nitrophenyl)ethyl Carbamate* (**10**). From **18** (1 g, 4.4 mmol) in CH_2Cl_2 (20 ml) and 7.5M NH_3/MeOH (20 ml; at −25°; 10 min at r.t.). Crystallization from MeOH/H_2O 1:1 (40 ml) afforded 0.71 g (78%) of **10**. M.p. 141–142°. TLC (toluene/AcOEt 4:1): R_f 0.17. UV (MeOH): 271 (3.99). ^{1}H-NMR ($CDCl_3$): 8.16 (*d*, 2 H_m); 7.39 (*d*, 2 H_o); 4.72 (br., NH_2); 4.32 (*t*, CH_2(1)); 3.04 (*t*, CH_2(2)). Anal. calc. for $C_{10}H_{12}N_2O_4$ (224.2): C 51.43, H 4.80, N 13.33; found: C 51.37, H 4.86, N 13.20.

4.2. *2-(4-Nitrophenyl)ethyl* N-*Methylcarbamate* (**11**). From **18** (1 g, 4.4 mmol) in CH_2Cl_2 (20 ml) and $MeNH_2$ (2 ml in MeOH (20 ml), at −25° within 5 min; 10 min at r.t.). Crystallization from MeOH/H_2O 1:1 (40 ml) gave 0.78 g (80%) of **11**. M.p. 108–109°. TLC (toluene/AcOEt 4:1): R_f 0.22. UV (MeOH): 213 (sh, 3.90), 270 (4.00). ^{1}H-NMR ($CDCl_3$): 8.16 (*d*, 2 H_m); 7.39 (*d*, 2 H_o); 4.64 (br., NH); 4.32 (*t*, CH_2(1)); 3.04 (*t*, CH_2(2)); 2.78 (*d*, Me). Anal. calc. for $C_{10}H_{12}N_2O_4$ (224.2): C 53.57, H 5.40, N 12.49; found: C 53.55, H 5.41, N 12.41.

4.3. *2-(4-Nitrophenyl)ethyl* N-*Ethylcarbamate* (**12**). From **18** (1 g, 4.4 mmol) in dioxane (10 ml) and H_2O/$EtNH_2$ 1:1 (2 ml, at 10° within 10 min; 10 min at r.t.). Crystallization from MeOH/H_2O 1:1 (30 ml) afforded 0.825 g (79%) of **12**. M.p. 108–109°. TLC (toluene/AcOEt 4:1): R_f 0.27. UV (MeOH): 213 (sh, 3.84), 270 (4.00). ^{1}H-NMR ((D$_6$)DMSO): 8.14 (*d*, 2 H_m); 7.52 (*d*, 2 H_o); 7.09 (br., NH); 4.17 (*t*, CH_2(1)); 3.04 (*t*, CH_2(2), MeCH_2); 0.96 (*t*, *Me*CH_2). Anal. calc. for $C_{11}H_{14}N_2O_4$ (238.3): C 55.46, H 5.92, N 11.76; found: C 55.52, H 5.94, N 11.65.

4.4. *2-(4-Nitrophenyl)ethyl* N,N-*Dimethylcarbamate* (**13**). From **18** (1 g, 4.4 mmol) in dioxane (10 ml) with 40% Me_2NH/H_2O (5 ml in dioxane (10 ml), at 10° within 10 min; 1 h at r.t.). Crystallization from MeOH/H_2O 1:4 (25 ml) gave 0.91 g (86%) of **13**. M.p. 84–85°. TLC (toluene/AcOEt 4:1): R_f 0.26. UV (MeOH): 214 (3.89), 270 (3.99). ^{1}H-NMR ((D$_6$)DMSO): 8.14 (*d*, 2 H_m); 7.52 (*d*, 2 H_o); 4.22 (*t*, CH_2(1)); 3.04 (*t*, CH_2(2)); 2.75 (*s*, 2 Me). Anal. calc. for $C_{11}H_{14}N_2O_4$ (238.3): C 55.46, H 5.92, N 11.76; found: C 55.24, H 5.93, N 11.52.

4.5. *2-(4-Nitrophenyl)ethyl Morpholine-4-carboxylate* (**14**). From **18** (1 g, 4.4 mmol) in CH_2Cl_2 (10 ml) and morpholine (5 ml, at −20° within 5 min; 30 min at r.t.). Crystallization from MeOH (20 ml) gave 0.97 g (80%) of **14**. M.p. 114–115°. TLC (toluene/AcOEt 4:1): R_f 0.22. UV (MeOH): 216 (sh, 3.86), 237 (sh, 3.45), 269 (4.00). ^{1}H-NMR ((D$_6$)DMSO): 8.15 (*d*, 2 H_m); 7.52 (*d*, 2 H_o); 4.25 (*t*, CH_2(1)); 3.48 (*m*, 4 H, CH_2(morpholine)); 3.26 (*m*, 4 H, CH_2(morpholine)); 3.02 (*t*, 4 H, CH_2(2)). Anal. calc. for $C_{13}H_{16}N_2O_5$ (280.3): C 55.71, H 5.75, N 10.00; found: C 55.87, H 5.76, N 9.95.

4.6. *2-(4-Nitrophenyl)ethyl* N-*Phenylcarbamate* (**15**). From **18** (2 g, 8.8 mmol) in dioxane (20 ml) and aniline (5 ml in dioxane (10 ml), at 10° within 10 min (→yellow); 1 h at r.t.). Precipitation from H_2O/MeOH 1:1 (30 ml) and recrystallization from MeOH (40 ml) gave 1.9 g (76%) of **15**. M.p. 132–133°. TLC (toluene/AcOEt 4:1): R_f 0.60. UV (MeOH): 218 (sh, 4.09), 234 (4.29), 271 (4.05), 280 (sh, 3.98). ^{1}H-NMR ((D$_6$)DMSO): 9.91 (*s*, NH); 8.17 (*d*, 2 H_m of $NO_2C_6H_4$); 7.57 (*d*, 2 H_o of $NO_2C_6H_4$); 7.43 (*d*, 2 H_m of Ph); 7.24 (*d*, 2 H_o of Ph); 6.96 (*d*, H_p of Ph); 4.36 (*t*, CH_2(1)); 3.15 (*t*, CH_2(2)). Anal. calc. for $C_{15}H_{14}N_2O_4$ (286.3): C 62.93, H 4.93, N 9.79; found: C 62.85, H 4.94, N 9.61.

4.7. *2-(4-Nitrophenyl)ethyl* N-*(4-Nitrophenyl)carbamate* (**16**). From **18** (1 g, 4.4 mmol) in CH_2Cl_2 (20 ml) and 4-nitroaniline (600 mg in pyridine (10 ml), at 0°; 30 min at r.t.). After treatment with CH_2Cl_2/Et_2O 2:5 (→precipitate of pyridine·HCl), filtration, evaporation, and co-evaporation with toluene, the residue was recrystallized from MeOH/EtOH/H_2O 3:4:1 (80 ml): 1.18 g (81%) of **16**. M.p. 160–161°. TLC (toluene/AcOEt 4:1): R_f 0.46. UV (MeOH): 215 (4.23), 286 (sh, 4.15), 312 (4.19). ^{1}H-NMR ((D$_6$)DMSO): 10.3 (*s*, NH); 8.15 (2*d*, 4 H_m); 7.60 (2*d*, 4 H_o); 4.45 (*t*, CH_2(1)); 3.10 (*t*, CH_2(2)). Anal. calc. for $C_{15}H_{13}N_3O_6$ (331.3): C 54.38, H 3.96, N 12.68; found: C 54.50, H 4.06, N 12.44.

4.8. *2-(4-Nitrophenyl)ethyl* N-*(2,4-Dimethoxyphenyl)carbamate* (**17**). From **18** (2 g, 8.8 mmol) in CH_2Cl_2 (20 ml) and 2,4-dimethoxyaniline (1.4 g in pyridine (20 ml), at −20° within 10 min; 30 min at r.t.). Et_2O (80 ml) was added, the resulting precipitate filtered off, the filtrate evaporated and co-evaporated with toluene, and the residue treated with MeOH/H_2O 1:1 (30 ml). Cooling, filtration, and recrystallization from MeOH/H_2O 2:1 (80 ml) gave **17** (2.62 g, 86%). M.p. 59–60°. TLC (toluene/AcOEt 4:1): R_f 0.63. UV (MeOH): 238 (4.17), 282 (4.08). ^{1}H-NMR ((D$_6$)DMSO): 8.36 (*s*, NH); 8.14 (*d*, 2 H_m of $NO_2C_6H_4$); 7.57 (*d*, 2 H_o of $NO_2C_6H_4$); 7.28 (br., H–C(3) of $(MeO)_2C_6H_3$); 6.89 (*d*, H–C(6) of $(MeO)_2C_6H_3$); 6.58 (*dd*, H–C(5) of $(MeO)_2C_6H_3$); 4.33 (*t*, CH_2(1)); 3.71, 3.65 (2*s*, 2 MeO); 3.07 (*t*, CH_2(2)). Anal. calc. for $C_{17}H_{18}N_2O_6$ (346.3): C 58.96, H 5.24, N 8.09; found: C 59.04, H 5.26, N 7.99.

5. *2-(4-Nitrophenyl)ethyl* N-*(Pyridin-4-yl)carbamate* (**20**). A suspension of 4-aminopyridine (500 mg, 5.3 mmol) in Et_3N (2 ml) was treated with a soln. of **18** (1.25 g, 5.4 mmol) in abs. CH_2Cl_2 (10 ml). The mixture was warmed up to 40° and stirred for 6 h at r.t. The precipate (1.35 g, 88%) was filtered and recrystallized from MeOH/H_2O 2:1 (30 ml): 1.02 g (66%) of **20**. M.p. 177–178° (dec.). TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.25. UV (MeOH): 218 (4.06), 239 (4.33), 259 (sh, 4.07), 268 (sh, 4.03). ^{1}H-NMR ((D$_6$)DMSO): 10.1 (br., NH); 8.34 (*m*, H–C(2), H–C(6) of Py); 8.17 (*d*, 2 H_m); 7.59 (*d*, 2 H_o); 7.40 (*m*, H–C(3), H–C(5) of Py); 4.40 (*t*, CH_2(1)); 3.10 (*t*, CH_2(2)). Anal. calc. for $C_{14}H_{13}N_3O_4$ (287.3): C 58.53, H 4.56, N 14.63; found: C 58.41, H 4.62, N 14.40.

6. *Bis[2-(4-nitrophenyl)ethyl] Carbonate* (**19**), *2-(4-Nitrophenyl)ethyl* N-*(Pyridin-2-yl)carbamate* (**21**), *Bis[2-(4-nitrophenyl)ethyl]* N-*(Pyridin-2-yl)imidodicarbonate* (**22**), *and* N,N′-*Bis(pyridin-2-yl)urea* (**23**). 6.1. A suspension of 2-aminopyridine (1.75 g, 18.7 mmol) in Et_3N (3 ml) was treated with a soln. of **18** (3.95 g, 17.2 mmol) in abs.

CH_2Cl_2 (20 ml) and stirred for 16 h at r.t. The mixture was evaporated with silica gel (50 g) and separated by FC (toluene→toluene/AcOEt 4:1). The isolated products were recrystallized: **19** (1.05 g, 33%; from MeOH), **21** (1.22 g, 25%; from MeCN), **22** (610 mg, 17%; from EtOH), and **23** (156 mg, 4%; from EtOH).

6.2. A soln. of 2-aminopyridine (750 mg, 7.9 mmol) in abs. CH_2Cl_2 (10 ml) was stirred with 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride [7] (3 g, 9.6 mmol) for 48 h at r.t. The excess of the reagent was removed by filtration and the mother liquor evaporated. Recrystallization from MeCN (80 ml) afforded **21** (1.83 g, 80%).

19: M.p. 138–139°. TLC (toluene/AcOEt 1:1): R_f 0.29. ^{1}H-NMR ((D$_6$)DMSO): 8.17 (*d*, 2 H$_m$); 7.35 (*d*, 2 H$_o$); 4.40 (*t*, CH_2(1)); 3.05 (*t*, CH_2(2)).

21: M.p. 185–186°. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.83. TLC (toluene/AcOEt 1:1): R_f 0.29. UV (MeOH): 227 (4.20), 273 (4.14). ^{1}H-NMR ((D$_6$)DMSO): 10.2 (*s*, NH); 8.22 (*m*, H–C(6) of Py); 8.15 (*d*, 2 H$_m$); 7.79–7.69 (*m*, H–C(3), H–C(4) of Py); 7.59 (*d*, 2 H$_o$); 7.00 (*m*, H–C(5) of Py); 4.34 (*t*, CH_2(1)); 3.08 (*t*, CH_2(2)). Anal. calc. for $C_{14}H_{13}N_3O_4$ (287.3): C 58.53, H 4.56, N 14.63; found: C 58.51, H 4.67, N 14.46.

22: M.p. 113°. TLC (toluene/AcOEt 1:1): R_f 0.32. UV (MeOH): 215 (sh, 4.24), 262 (sh, 4.28), 256 (4.30). ^{1}H-NMR ((D$_6$)DMSO): 8.36 (*m*, H–C(6) of Py); 8.04 (*m*, 4 H$_m$); 7.80 (*m*, H–C(3) of Py); 7.40 (*m*, H–C(4) of Py); 7.38–7.22 (*m*, 4 H$_o$, H–C(5) of Py); 4.31 (*t*, 2 CH_2(1)); 2.89 (*t*, 2 CH_2(2)). Anal. calc. for $C_{23}H_{20}N_4O_8$ (480.4): C 57.50, H 4.20, N 11.66; found: C 57.54, H 4.23, N 11.53.

23: M.p. 177–178°. TLC (toluene/AcOEt 1:1): R_f 0.29. UV (MeOH): 246 (4.46), 278 (4.15), 282 (sh, 4.14). ^{1}H-NMR ((D$_6$)DMSO): 10.6 (br. *s*, 2 NH); 8.27 (*m*, 2 H, H–C(6) of Py); 7.79–7.68 (*m*, 4 H, H–C(3), H–C(4) of Py); 7.03 (*m*, 2 H, H–C(5) of Py). Anal. calc. for $C_{11}H_{10}N_4O$ (214.2): C 61.67, H 4.71, N 26.15; found: C 61.47, H 4.70, N 25.76.

7. *2-(4-Nitrophenyl)ethyl* N-*(Pyrimidin-2-yl)carbamate* (**24**). A soln. of 2-aminopyrimidine (0.5 g, 5.2 mmol) and 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride [7] (2.5 g, 8 mmol) in abs. CH_2Cl_2 (10 ml) was stirred for 96 g at r.t. The colorless precipitate was filtered with suction and the residue recrystallized from MeCN (40 ml): 0.72 g (48%) of **24**. The mother liquors were evaporated with silica gel (30 g) and purified by FC (silica gel (50 g), toluene→toluene/AcOEt 1:1), giving, after crystallization 0.31 g (60%) of **19** (from MeOH) and a second crop of 0.18 g (12%) of **24** (from MeCN). Total yield of **24**: 0.9 g (60%). M.p. 201–202°. TLC (toluene/AcOEt): R_f 0.21. UV (MeOH): 224 (4.39), 269 (4.13). ^{1}H-NMR ((D$_6$)DMSO): 10.4 (*s*, NH); 8.59 (*d*, H–C(4), H–C(6) of pyrim.); 8.15 (*d*, 2 H$_m$); 7.60 (*d*, 2 H$_o$); 7.10 (*m*, H–C(5) of pyrim.); 4.33 (*t*, CH_2(1)); 3.07 (*t*, CH_2(2)). Anal. calc. for $C_{13}H_{12}N_4O_4$ (288.3): C 54.16, H 4.20, N 10.44; found: C 54.13, H 4.26, N 19.28.

8. *2′,3′,5′-Tri-*O*-acetyl-*N^6*-methyladenosine* [20] (**26**). To a soln. of N^6-methyladenosine [17] (**25**, 2 g, 7.1 mmol) in abs. pyridine (30 ml), a mixture of Ac_2O (5 ml) in pyridine (10 ml) was added dropwise within 10 min. After 2 h, the mixture was concentrated to 10 ml, poured on ice, and extracted with CH_2Cl_2/$NaHCO_3$ soln. After thorough washing, the org. phase was dried ($MgSO_4$), evaporated, co-evaporated with toluene, and evaporated from CH_2Cl_2: 2.6 g (90%) of a colorless foam. ^{1}H-NMR ($CDCl_3$): 8.40 (*s*, H–C(2)); 7.95 (*s*, H–C(8)); 6.65 (br., NH); 6.20 (*d*, H–C(1′)); 5.95 (*t*, H–C(2′)); 5.71 (*t*, H–C(3′)); 4.50–4.35 (*m*, H–C(4′), 2 H–C(5′)); 2.17–2.13 (3*s*, 3 Me).

9. *2′,3′,5′-Tri-*O*-acetyl-*N^6*-methyl-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**27**). 9.1. A soln. of **26** (500 mg, 1.23 mmol) in abs. pyridine (4 ml) was cooled to −60° and treated with **18** (800 mg, 3.5 mmol, syringe) in CH_2Cl_2 (1 ml) and stirred for 4 h (TLC: **26**/**27** *ca.* 1:1). Neither addition of 4-(dimethylamino)pyridine (30 mg) nor prolongation of the reaction time (24 h) could the ratio **26**/**27**. The mixture was evaporated with silica gel (5 g) and purified by FC (silica gel (35 g), 3.5 × 8 cm toluene, toluene/AcOEt 4:1→2:3 + 2% MeOH): 0.325 g (65%) of **26** and 0.265 g (35%) of **27**.

9.2. A soln. of **26** (6.6 g, 16.2 mmol) and **28** (see *Exper. 10*; 5 g, 19 mmol) in abs. dioxane (25 ml) was stirred for 18 h at 50°. The mixture was evaporated, the residue dissolved in abs. CH_2Cl_2 (30 ml), the precipitating 1*H*-tetrazole (1.2 g) filtered off, and the filtrate evaporated. The residue in toluene was applied to FC (silica gel (60 g), 5.5 × 8 cm, toluene, toluene/AcOEt 1:1→1:1 + 4% MeOH): 9.1 g (93%) of **27**. Colorless foam. TLC (toluene/AcOEt/MeOH 5:4.1): R_f 0.53. UV (MeOH): 272 (4.36). ^{1}H-NMR ($CDCl_3$): 8.77 (*s*, H–C(2)); 8.10 (*s*, H–C(8)); 8.10 (*d*, 2 H$_m$); 7.29 (*d*, 2 H$_o$); 6.21 (*d*, J = 5.3, H–C(1)); 5.94 (*t*, J = 5.4, H–C(2′)); 5.67 (*t*, J = 5.2, H–C(3′)); 4.54–4.40 (*m*, H–C(4′), 2 H–C(5′), CH_2(1) (npeoc)); 3.51 (*s*, MeN); 3.08 (*t*, CH_2(2) (npeoc)); 2.17, 2.15, 2.13 (3*s*, 3 Me). Anal. calc. for $C_{26}H_{28}N_6O_{11}$ (600.6): C 52.00, H 4.70, N 13.99; found: C 51.77, H 4.73, N 13.78.

10. *2-(4-Nitrophenyl)ethyl* 2H-*Tetrazole-2-carboxylate* (**28**). A soln. of 1*H*-tetrazole (3.78 g, 54 mmol) in abs. Et_3N (4.2 ml, 60 mmol) and abs. dioxane (50 ml) was cooled to 10°, treated under cooling with **18** (13.8 g, 60 mmol),

and stirred under cooling for 3 min and without cooling for 5 min. The solid Et_3NHCl was filtered, the filtrate evaporated, the residue dissolved in abs. CH_2Cl_2 (70 ml), then Et_2O (200 ml) added, and crystallization stimulated by scratching: 5.2 g. From the mother liquor, a second crop was isolated by dilution with petroleum (30 ml). Total of **28** yield: 8.7 g (55%). M.p. 100° (dec.). ^{1}H-NMR ($CDCl_3$): 9.15 (*s*, H–C(5) of tetrazole); 8.20 (*d*, 2 H_m); 7.50 (*d*, 2 H_o); 4.85 (*t*, CH_2(1)); 3.37 (*t*, CH_2(2)). Anal. calc. for $C_{10}H_9N_5O_4$ (263.2): C 45.63, H 3.45, N 26.61; found: C 45.88, H 3.77, N 25.72.

11. *Phenyl 5-(4-Nitrophenyl)-2*H*-tetrazole-2-carboxylate* (**30**). A suspension of 5-(4-nitrophenyl)-1*H*-tetrazole [23] (2.5 g, 13 mmol) in abs. dioxane (50 ml) was treated with Et_3N (1.8 ml) and cooled until crystallization of the solvent occurred (10°). The mixture was then treated with phenyl chloroformate (1.6 ml, 13 mmol) by dropwise addition within 2 min and stirred for another 5 min at 10°. The precipitate was filtered and washed with abs. dioxane, the colorless filtrate evaporated (< 25%), the residue treated with CH_2Cl_2 (30 ml), and the precipitate filtered with suction (1.6 g). The filtrate was heated to boiling and treated with petroleum ether (50 ml). On cooling, 1.0 g of colorless crystals separated. From the filtrate, a second crop was obtained after recrystallization with CH_2Cl_2/petroleum ether 1:1 (50 ml). Total yield of **30**: 2.35 g (50%). M.p. 139° (dec.). ^{1}H-NMR ($CDCl_3$): 8.54–8.40 (*m*, $NO_2C_6H_4$); 7.57–7.40 (*m*, Ph). Anal. calc. for $C_{14}H_9N_5O_4$ (311.3): C 54.03, H 2.92, N 22.50; found: C 54.14, H 2.95, N 22.55.

12. *2′,3′,5′-Tri-*O*-acetyl-*N^6*-(phenyloxycarbonyl)adenosine* [18] (**31**). A soln. of 2′,3′,5′-tri-*O*-acetyladenosine [24] (3.93 g, 10 mmol) and phenyl 5-(4-nitrophenyl)-2*H*-tetrazole-2-carboxylate (**30**; 9.3 g, 30 mmol) in dioxane (100 ml) was stirred for 24 h at 40°. The mixture was evaporated, the residue dissolved in toluene (100 ml), and the precipitating 5-(4-nitrophenyl)-1*H*-tetrazole filtered off, and the filtrate evaporated. The residue in AcOEt was applied to FC (silica gel (50 g), 3.5 × 12 cm, toluene, toluene/AcOEt 4:1→1:1 + 6% MeOH): 5.0 g (97%) of colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.54. ^{1}H-NMR ($CDCl_3$): 9.90 (br. *s*, NH); 8.75 (*s*, H–C(2)); 8.30 (*s*, H–C(8)); 7.40–7.15 (*m*, 5 arom. H); 6.27 (*d*, H–C(1′)); 5.95 (*t*, H–C(2′)); 5.67 (*t*, H–C(3′)); 4.54–4.40 (*m*, H–C(4′), 2 H–C(5′)); 2.17–2.13 (3*s*, 3 Me).

13. *2′,3′,5′-Tri-*O*-acetyl-*N^6*-methyl-*N^6*-(phenyloxycarbonyl)adenosine* (**32**). As described for **31**, with 2′,3′,5′-tri-*O*-acetyl-N^6-methyladenosine (**26**, 8.2 g, 20 mmol), dioxane (200 ml), and **30** (18.7 g, 60 mmol; 16 h at 40°). Workup with toluene (200 ml). FC (silica gel (90 g), 5.5 × 12 cm, toluene, toluene/AcOEt 3:2) of the residue gave 10.3 g (97%) of a colorless foam. TLC (toluene/AcOEt 1:1): R_f 0.22. UV (MeOH): 272 (4.13), 258 (sh, 3.97). ^{1}H-NMR ($CDCl_3$): 8.84 (*s*, H–C(2)); 8.19 (*s*, H–C(8)); 7.40–7.16 (*m*, 5 arom H); 6.23 (*d*, J = 5.1, H–C(1′)); 5.98 (*t*, J = 5.4, H–C(2′)); 5.68 (*t*, J = 4.8, 5.2, H–C(3′)); 4.47–4.33 (*m*, H–C(4′), 2 H–C(5′)); 3.69 (*s*, MeN); 2.15, 2.10, 2.09 (3*s*, 3 Me). Anal. calc. for $C_{24}H_{25}N_5O_9$ (527.5)·0.1 toluene: C 55.27, H 4.85, N 13.05; found: C 55.65, H 4.93, N 10.07.

14. *N^6-Methyl-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**33**). 14.1. A suspension of N^6-methyladenosine [17] (**25**, 2 g, 7.11 mmol) in hexamethyldisilizane (HMDS, 20 ml) and dioxane (30 ml) and a few crystals of $(NH_4)_2SO_4$ were refluxed for 2.5 h. The clear soln. was evaporated, the residue dissolved in abs. toluene (30 ml), and the soln. filtered and again evaporated. The resulting colorless oil was dissolved in CH_2Cl_2 (30 ml), then 4-(dimethylamino)pyridine (200 mg, 1.6 mmol), and 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride [7] (4.4 g, 14.2 mmol) were added and stirred for 72 h at r.t. The precipitate was filtered, the filtrate evaporated, and the residue treated with H_2O (10 ml), MeOH (30 ml), and Et_3N (10 ml) by stirring overnight. The mixture containing **25**/**33**/**9**/**19** was evaporated with silica gel (10 g) and separated by FC (silica gel (50 g), 3.5 × 14 cm, toluene→toluene/AcOEt 1:1 + 1% MeOH): 1.15 g (35%) of **33**. Colorless foam.

14.2. A soln. of **27** (8 g, 13 mmol) in abs. MeOH (50 ml) was stirred with K_2CO_3 (0.7 g) for 60 min at r.t. AcOH (0.6 g in 10 ml MeOH) was added and the mixture evaporated with silica gel (20 g). FC (silica gel (50 g), toluene, toluene/AcOEt 1:1→1:1 + 12% MeOH) gave 5.5 g (89%) of **33** (from toluene). TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.31. UV (H_0 = −1): 280 (4.38). UV (pH 3): 274 (4.30), 309 (sh, 3.55). pK_a = 0.59. ^{1}H-NMR ((D$_6$)DMSO): 8.74 (*s*, H–C(2)); 8.71 (*s*, H–C(8)); 8.04 (*d*, 2 H_m); 7.32 (*d*, 2 H_o); 6.00 (*d*, J = 5.8, H–C(1′)); 5.53 (*d*, J = 6.1, OH–C(2′)); 5.27 (*d*, J = 4.9, OH–C(3′)); 5.11 (*t*, J = 5.4, OH–C(5′)); 4.61 (*q*, J = 5.6, 5.5, 6.0, H–C(2′)); 4.37 (*m*, CH_2(1) (npeoc)): 4.15 (*q*, J = 4.4, H–C(3′)); 3.97 (*m*, H–C(4′)); 3.71–3.40 (*m*, 2 H–C(5′)); 3.60 (*s*, MeN): 2.98 (*t*, CH_2(2)(npeoc)). Anal. calc. for $C_{20}H_{22}N_6O_8$ (474.4): C 50.63, H 4.67, N 17.71; found: C 49.96, H 4.85, N 17.35.

15. *N^6-Methyl-N^6-(phenyloxycarbonyl)adenosine* (**34**). A soln. of **32** (2.1 g, 4 mmol) in abs. MeOH (50 ml) was stirred with K_2CO_3 (100 mg). After 30 min, the mixture was treated with AcOH (6 drops) and evaporated. The residue in CH_2Cl_2 (10 ml) was applied to FC (silica gel (40 g), toluene, toluene/AcOEt 1:1→1:1 + 8% MeOH): 1.48 g (93% of **34**). TLC (CH_2Cl_2/MeOH 9:1): R_f 0.35. UV (H_0 = −2): 250 (sh, 3.81), 280 (4.22). UV (pH 2): 251 (sh,

3.87), 273 (4.12). pK_a = 0.16. ^{1}H-NMR ((D$_6$)DMSO): 8.86 (*s*, H–C(2)); 8.84 (*s*, H–C(8)); 7.43–7.37 (*m*, 2 H$_m$); 7.27–7.09 (*m*, 2 H$_o$, H$_p$); 6.04 (*d*, H–C(1′)); 5.55 (*d*, OH–C(2′)); 5.25 (*d*, OH–C(3′)); 5.10 (*t*, OH–C(5′)); 4.65 (*q*, H–C(2′)); 4.17 (*q*, H–C(3′)); 3.98 (*m*, H–C(4′)); 3.67–3.55 (*m*, H–C(5′)); 3.53 (*s*, MeN). Anal. calc. for $C_{18}H_{19}N_5O_6$ (401.4): C 53.86, H 4.77, N 17.45; found: C 53.95, H 4.98, N 17.03.

16. N^6-*(Methoxycarbonyl)adenosine* (**35**). 16.1. A suspension of adenosine (5 g, 18.5 mmol) in HMDS (22.5 ml) and abs. dioxane (22.5 ml) was refluxed with a few crystals of $(NH_4)_2SO_4$ for 2.5 h. After evaporation, the colorless oil was dissolved in abs. toluene (50 ml), the soln. filtered, the filtrate evaporated, and the residue dissolved in abs. CH_2Cl_2 (100 ml). Another soln. of methyl chloroformate (8 ml, 104 mmol) in abs. CH_2Cl_2 (50 ml) was treated with 1-methyl-1*H*-imidazole (8 ml in 10 ml of CH_2Cl_2) at 0°, the mixture stirred for 30 min, the precipitate filtered, the filtrate added to the silylated adenosine in CH_2Cl_2, and the mixture stirred for 96 h at r.t. (→clear soln.). The mixture was treated with petroleum ether (150 ml) and the upper phase collected and treated with MeOH/Et_3N 2:1 (150 ml) and H_2O (10 ml) with stirring for 24 h. The precipitate was collected (4.5 g), recrystallized from MeOH (50 ml), and dried (50°/high vacuum): 3.76 g (63%) of **35**.

16.2. A soln. of **31** (513 mg, 1 mmol) in abs. MeOH (10 ml) and K_2CO_3 (125 mg) was stirred at r.t. for 18 h. The mixture was filtered and then treated with a few crystals of **35**. After 6 h, the precipitate was filtered: 0.2 g (61%) of **35**. M.p. 138° (dec.). TLC ($CHCl_3$/MeOH 9:1): R_f 0.29. UV (MeOH): 266 (4.24), 271 (sh, 4.17). ^{1}H-NMR ((D$_6$)DMSO): 10.6 (*s*, NH); 8.67 (*s*, H–C(2)); 8.63 (*s*, H–C(2)); 6.00 (*d*, *J* = 5.5, H–C(1′)); 5.55 (*d*, *J* = 5.8, OH–C(2′)); 5.25 (*d*, *J* = 4.8, OH–C(3′)); 5.15 (*t*, *J* = 5.5, OH–C(5′)); 4.62 (*q*, H–C(2′)); 4.15 (br., H–C(3′)); 3.99 (br., H–C(4′)); 3.77 (*s*, MeO). Anal. calc. for $C_{12}H_{15}N_5O_6 \cdot H_2O$ (343.3): C 42.00, H 4.99, N 20.40; found: C 42.19, H 4.96, N 20.26.

17. N^6-*(Methylcarbamoyl)adenosine* [20] (**38**). A soln. of *N*^{6}-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine [7] (**37**; 200 mg, 0.43 mmol) in abs. pyridine (10 ml) was treated with 1M $MeNH_2$/pyridine (1 ml, 1 mmol) and stirred for 6 h at 120° (autoclave). The mixture was evaporated and co-evaporated with toluene, and the residue solidified with EtOH; 0.13 g (82%) of **38**. From the mother liquor, **9** was isolated by prep. TLC (59 mg, 81%). **38**: ^{1}H-NMR ((D$_6$)DMSO): 9.50 (br. *s*, NH); 9.20 (*q*, NH); 8.60 (*s*, H–C(2)); 8.55 (*s*, H–C(8)); 5.97 (*d*, *J* = 5,5, H–C(1′)); 5.53 (*d*, *J* = 6.1, OH–C(2′)); 5.25 (*d*, *J* = 4.9, OH–C(3′)); 5.15 (*t*, *J* = 5.4, OH–C(5′)); 4.61 (*q*, H–C(2′)); 4.17 (*q*, H–C(3′)); 3.96 (*m*, H–C(4′)); 3.72–3.41 (*m*, 2 H–C(5′)); 2.81 (*d*, MeN).

Similarly, **37**, was transformed to **39**/**11** and **33** to **25**/**11**; for conditions, see *Tables 1* and *2*, resp.

18. N^6-*Methyl*-N^6-*(methylcarbamoyl)adenosine* (**40**). A soln. of **34** (200 mg, 0.5 mmol) in 1M $MeNH_2$/pyridine (1 ml, 1 mmol) was stirred for 30 min at r.t. The mixture was evaporated and co-evaporated with toluene and the residue treated with little EtOH and filtered. The crude product (55 mg, 32%) was recrystallized from EtOH (2 ml); anal. pure **40** (47 mg). The filtrate was separated by FC (CH_2Cl_2/MeOH). The two main fractions were analyzed by ^{1}H-NMR: phenol (69%)/*N*^{6}-methyl-*N*^{6}-(methylcarbamoyl)adenosine (**40**, 24%) and *N*^{6}-methyladenosine (**25**, 26%)/phenyl *N*-methylcarbamate (**41**; 16%). Total yield of **40**: 56%. M.p. 167–169°. TLC (toluene/AcOEt 1:1): R_f 0.21. UV (MeOH): 276 (4.32), 282 (sh, 4.29). ^{1}H-NMR ((D$_6$)DMSO): 9.70 (br. *q*, NH); 8.70 (*s*, H–C(2)); 8.52 (*s*, H–C(8)); 6.00 (*d*, *J* = 5.6, H–C(1′)); 5.52 (*d*, *J* = 6.1, OH–C(2′)); 5.23 (*d*, *J* = 4.9, OH–C(3′)); 5.13 (*t*, *J* = 5.4, OH–C(5′)); 4.55 (*q*, H–C(2′)); 4.17 (*q*, H–C(3′)); 3.96 (*m*, H–C(4′)); 3.76 (*s*, MeN^6); 3.72–3.51 (*m*, 2 H–C(5′)); 2.80 (*d*, MeN). Anal. calc. for $C_{13}H_{18}N_6O_5$ (338.3): C 46.15, H 5.36, N 24.84; found: C 45.71, H 5.76, N 24.75.

19. *2′,3′,5′-Tri*-O-*acetyl*-N^6-*(phenylcarbamoyl)adenosine* (**42**). A soln. of **31** (2.56 g, 5 mmol) in aniline (560 mg, 6 mmol) and abs. pyridine (20 ml) was stirred for 90 min at 70°. The mixture was evaporated and co-evaporated with toluene, the residue dissolved in a small volume of AcOEt and applied to FC (silica gel (40 g), 3.5 × 10 cm, toluene, toluene/acetone 95:5→7:3): **42** (2.1 g, 82%). Colorless foam. A sample crystallized in 3 weeks from EtOH/H_2O. M.p. 137–139°. TLC (toluene/AcOEt/MeOH 5:4.5:0.5): R_f 0.38. UV (MeOH): 235 (sh, 3.99), 277 (4.46). ^{1}H-NMR ((D$_6$)DMSO): 11.7 (*s*, NH); 10.2 (*s*, N^{6}H); 8.71, 8.68 (2*s*, H–C(8), H–C(2)); 7.63 (*d*, 2 H$_o$); 7.34 (*t*, 2 H$_m$); 7.06 (*t*, H$_p$); 6.32 (*d*, H–C(1′)); 6.04 (*t*, H–C(2′)); 5.64 (*t*, H–C(3′)); 4.45–4.22 (*m*, H–C(4′), 2 H–C(5′)); 2.12, 2.03, 2.01 (3*s*, 3 Me). Anal. calc. for $C_{23}H_{24}N_6O_8$ (512.5): C 53.91, H 4.72, N 16.40; found: C 53.84, H 4.76, N 16.40.

20. N^6-*(Phenylcarbamoyl)adenosine* [20] (**43**). 20.1. A soln. of **42** (200 mg, 0.4 mmol) in EtOH (5 ml) and 25% NH_3/H_2O (10 ml) was stirred for 20 h at r.t. The resulting precipitate was filtered: 0.14 g (90%) of **43**.

20.2. A soln. of **37** (460 mg, 1 mmol) in aniline (930 mg, 10 mml) and pyridine (10 ml) was stirred for 30 h at 80°, then evaporated and co-evaporated with toluene. The residue was dissolved in hot H_2O/MeOH 1:3 (50 ml) and crystallization induced by a few crystals of **43**: 0.25 g (67%) of colorless needles. M.p.194–196° ([20]: 189–190°). TLC (CH_2Cl_2/MeOH): R_f 0.3. UV (MeOH): 233 (sh, 3.98), 278 (4.45). pK_a = 1.45, 12.21. ^{1}H-NMR ((D$_6$)DMSO):

11.8 (*s*, NH); 10.2 (*s*, N^6H); 8.71 (*s*, H–C(2)); 8.68 (*s*, H–C(8)); 7.62 (*m*, 2 H_m); 7.35 (*m*, 2 H_o); 7.07 (*m*, H_p); 6.00 (*d*, H–C(1′)); 5.55 (*d*, OH–C(2′)); 5.25 (*d*, OH–C(3′)); 5.14 (*t*, OH–C(5′)); 4.60 (*q*, H–C(2′)); 4.17 (*q*, H–C(3′)); 3.97 (*m*, H–C(4′)); 3.68 (*m*, H–C(5′)); 3.57 ppm (*m*, H′–C(5′)). Anal. calc. for $C_{17}H_{18}N_6O_5$ (386.4): C 52.85, H 4.69, N 21.75; found: C 52.71, H 4.59, N 22.05.

21. *2′,3′,5′-Tri-*O*-acetyl-*N^6*-{[4-(ethoxycarbonyl)phenyl]carbamoyl}adenosine* (**44**). A soln. of ethyl 4-aminobenzoate (825 mg, 5 mmol) and **31** (3.1 g, 6 mmol) in pyridine (20 ml) was heated for 30 min at 70°. The mixture was evaporated and co-evaporated with toluene, the residue dissolved in AcOEt and purified by FC (silica gel (50 g), 3.5 × 11 cm, toluene, toluene/AcOEt 8:2→1:1 + 10% MeOH). The main fraction was evaporated and the residue crystallized from MeOH (50 ml) for 2 days: 2.2 g (75%). M.p. 155–156°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.87. UV (MeOH): 261 (sh, 4.23), 288 (4.66). ^{1}H-NMR ($CDCl_3$): 12.1 (*s*, NH); 9.15 (*s*, NH); 8.66 (*s*, H–C(2)); 8.49 (*s*, H–C(8)); 8.05 (*d*, 2 H_m); 7.73 (*d*, 2 H_o); 6.26 (*d*, H–C(1′)); 6.02 (*t*, H–C(2′)); 5.70 (*t*, H–C(3′)); 4.49–4.33 (*m*, 5 H, H–C(4′), 2 H–C(5′), CH_2); 2.17–2.10 (3*s*, 3 Me); 1.40 (*t*, Me). Anal. calc. for $C_{26}H_{28}N_6O_{10}$ (584.5): C 53.42, H 4.83, N 14.38; found: C 53.30, H 4.82, N 14.42.

22. *N^6-{[4-(Ethoxycarbonyl)phenyl]carbamoyl}adenosine* (**45**). A suspension of **44** (1.8 g, 3.1 mmol) in MeOH (100 ml) was cooled to −40°, treated with liq. NH_3 (10 ml), and stirred for 26 h at r.t. The colorless precipitate was filtered (1.3 g, 88%) and recrystallized from EtOH/H_2O 1:1 (300 ml): 1.2 g (82%). M.p. 197–198°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.5. UV (MeOH): 261 (sh, 4.17), 288 (4.60). ^{1}H-NMR ((D_6)DMSO): 12.1 (*s*, NH); 10.4 (*s*, NH); 8.72 (*s*, H–C(2)); 8.70 (*s*, H–C(8)); 7.94 (*d*, 2 H_m); 7.77 (*d*, 2 H_o); 6.00 (*d*, H–C(1′)); 5.55 (*d*, OH–C(2′)); 5.24 (*d*, OH–C(3′)); 5.13 (*t*, OH–C(5′)); 4.60 (*q*, H–C(2′)); 4.29 (*q*, CH_2); 4.18 (*q*, H–C(3′)); 3.97 (*q*, H–C(4′)); 3.66–3.57 (*m*, 2 H–C(5′)); 1.31 (*t*, Me). Anal. calc. for $C_{20}H_{22}N_6O_7 \cdot H_2O$ (476.4): C 50.42, H 5.01, N 17.64; found: C 50.58, H 5.07, N 17.88.

23. *2′,3′,5′-Tri-*O*-acetyl-*N^6*-[(4-nitrophenyl)carbamoyl]adenosine* (**46**). A soln. of 4-nitroaniline (690 mg, 5 mmol) and **31** (3.1 g, 6 mmol) in pyridine (20 ml) was heated for 30 min to 75°. The yellow mixture was treated with MeOH (50 ml) and cooled. The creme-colored precipitate was filtered and stirred in MeOH/AcOEt 1:1 (100 ml). After 10 min, **46** was collected, washed with Et_2O, and dried in a desiccator: 2.3 g (82%). M.p. 220–239° (dec.). TLC (soln. of **46** in pyridine, first Et_2O, then CH_2Cl_2/MeOH 9:1): R_f 0.75. UV (MeOH): 268 (sh, 4.14), 276 (4.18), 315 (4.32). ^{1}H-NMR ((D_6)DMSO): 12.1 (*s*, NH); 10.6 (*s*, NH); 8.74 (*s*, H–C(2)); 8.68 (*s*, H–C(8)); 8.25 (*d*, 2 H_m); 7.87 (*d*, 2 H_o); 6.32 (*d*, H–C(1′)); 6.05 (*t*, H–C(2′)); 5.66 (*t*, H–C(3′)); 4.41–4.28 (*m*, 2 H–C(5′), H–C(4′)); 2.25–1.97 (3*s*, 3 Me). Anal. calc. for $C_{23}H_{23}N_7O_{10}$ (557.5): C 49.55, H 4.16, N 17.59; found: C 49.49, H 4.16, N 17.79.

24. *N^6-[(4-Nitrophenyl)carbamoyl]adenosine* (**47**). As described in *Exper. 22*, with **46** (350 mg, 0.63 mmol), MeOH (50 ml), and liq. NH_3 (8 ml; 18 h). The creme-colored **47** was collected and dried in a desiccator: 0.27 g (98%) of **47**. M.p. 209–210°. TLC (soln. of **47** in pyridine, first Et_2O, then CH_2Cl_2/MeOH 9:1): R_f 0.25. UV (H_o = −0.54): 288 (sh, 4.31), 315 (4.43). UV (pH 4): 278 (4.24), 321 (4.30). UV (pH 9): 277 (4.23), 3.21 (4.30). UV (pH 14): 297 (4.27), 365 (4.40). pK_a: 1.47, 11.4. ^{1}H-NMR ((D_6)DMSO): 12.2 (*s*, NH); 10.5 (*s*, NH); 8.72 (*s*, H–C(2)); 8.69 (*s*, H–C(8)); 8.23 (*d*, 2 H_m); 7.87 (*d*, 2 H_o); 6.01 (*d*, H–C(1′)); 5.56 (br., OH–C(2′)); 5.26 (br., OH–C(3′)); 5.16 (br., OH–C(5′)); 4.60 (br., H–C(2′)); 4.18 (br., H–C(3′)); 3.97 (br., H–C(4′)); 3.72–3.60 (br., 2 H–C(5′)). Anal. calc. for $C_{17}H_{17}N_7O_7$ (431.4): C 47.33, H 3.97, N 22.73; found: C 47.11, H 4.01, N 22.72.

25. *2′,3′,5′-Tri-*O*-acetyl-*N^4*-(phenyloxycarbonyl)cytidine* (**48**). A soln. of 2′,3′,5′-tri-*O*-acetylcytidine [20] (3.7 g, 10 mmol) and **29** (2.5 g, 13 mmol) in dioxane (50 ml) was stirred for 30 min at 40°. The mixture was evaporated and the residue treated with abs. CH_2Cl_2 (30 ml) to precipitate the 1*H*-tetrazole. After 1 h at −10° the latter was filtered off and the filtrate applied to FC (silica gel (50 g), 3.5 × 12 cm, toluene, toluene/acetone 9:1→7:3). The main fraction gave, on evaporation, a colorless foam (4.9 g, 100%) containing *ca.* 5% of 1*H*-tetrazole. An anal. pure sample of **48** was obtained by prep. TLC. TLC (toluene/acetone 1:1): R_f 0.5. UV (MeOH): 243 (4.28), 264 (3.89). ^{1}H-NMR ((D_6)DMSO): 11.4 (br. *s*, NH); 8.14 (*d*, H–C(6)); 7.46–7.17 (*m*, 5 arom. H); 7.06 (*d*, H–C(5)); 5.90 (*d*, H–C(1′)); 5.49 (*dd*, H–C(2′)); 5.36 (*t*, H–C(3′)); 4.38–4.17 (*m*, 3 H, H–C(4′), 2 H–C(5′)); 2.07, 2.06, 2.03 (3*s*, 3 Me). Anal. calc. for $C_{22}H_{23}N_3O_{10}$ (489.4): C 53.99, H 4.74, N 8.59; found: C 54.08, H 4.71, N 9.02.

26. *2′,3′,5′-Tri-*O*-acetyl-*N^4*-(phenylcarbamoyl)cytidine* (**49**). A soln. of aniline (290 mg, 3 mmol) and **48** (1.0 g, 2 mmol) in pyridine (10 ml) was stirred for 2.5 h at 70°. The mixture was evaporated and co-evaporated with toluene and with H_2O/EtOH. The solid residue was crystallized from EtOH (20 ml) overnight: 0.8 g (81%) of **49**. M.p. 111–112°. TLC (toluene/AcOEt/MeO 5:4:1): R_f 0.67. UV (MeOH): 227 (sh, 4.21), 292 (4.24). ^{1}H-NMR ((D_6)DMSO): 11.2 (br. *s*, NH); 10.3 (br. *s*, NH); 8.03 (*d*, H–C(6)); 7.48 (*d*, 2 H_m); 7.33 (*t*, 2 H_o); 7.07 (*t*, H_p); 6.43 (*d*, H–C(5)); 5.90 (*d*, J = 4, H–C(1′)); 5.48 (*dd*, H–C(2′)); 5.36 (*t*, H–C(3′)); 4.37–4.19 (*m*, H–C(4′), 2 H–C(5′)); 2.05 (2*s*, 3 Me). Anal. calc. for $C_{22}H_{24}N_4O_9$ (488.5): C 54.10, H 4.95, N 11.47; found: C 53.83, H 4.97, N 11.45.

27. N^4-*(Phenylcarbamoyl)cytidine* (**50**). As described in *Exper. 22*, with **49** (500 mg, 1.1 mmol), MeOH (30 ml), and liq. NH_3 (5 h). The soln. was evaporated and the solid residue recrystallized from EtOH: 0.3 g (75%) of **50**. M.p. 180–181° (dec.). TLC (CH_2Cl_2/MeOH 8:2): R_f 0.54. UV ($H_0 = -1$): 226 (4.18), 310 (4.41). UV (pH 3 or 10): 212 (sh, 4.30), 228 (4.15), 292 (4.24). UV (pH 14): 234 (sh, 4.09), 304 (4.44). pK_a = 0.99, 11.99. ^{1}H-NMR ((D$_6$)DMSO): 11.4 (br. *s*, NH); 10.2 (br. *s*, NH); 8.42 (*d*, H–C(6)); 7.46 (*d*, 2 H$_m$); 7.33 (*t*, 2 H$_o$); 7.07 (*t*, H$_p$); 6.37 (*d*, H–C(5)); 5.78 (*d*, J = 4.2, H–C(1′)); 5.48 (*d*, OH–C(2′)); 5.16 (*t*, OH–C(5′)); 5.07 (*d*, OH–C(3′)); 4.02–3.88 (*m*, H–C(2′), H–C(3′), H–C(4′)); 3.74–3.54 (*m*, H–C(5′)). Anal. calc. for $C_{16}H_{18}N_4O_6$ (362.3): C 53.04, H 5.01, N 15.46; found: C 52.86, H 5.02, N 15.60.

28. *2′,3′,5′-Tri-*O*-acetyl-*N^4-{*[4-(ethoxycarbonyl)phenyl]carbamoyl*}*cytidine* (**51**). A soln. of ethyl 4-aminobenzoate (320 mg, 2 mmol) and **48** (1.0 g, 2 mmol) in pyridine (20 ml) was stirred for 1 h at 70°. The mixture was evaporated and co-evaporated with toluene and with H_2O/EtOH until **51** became solid. After addition of EtOH (20 ml), the precipitate was collected after 20 h, washed with Et_2O, and dried: 0.8 g (71%). M.p. 203–205°. TLC (CH_2Cl_2/MeOH 95:5): R_f 0.54. UV (MeOH): 245 (4.16), 296 (4.47). ^{1}H-NMR ($CDCl_3$): 11.3 (br. *s*, NH); 11.1 (br. *s*, NH); 7.99–7.93 (*m*, 2 H$_m$, H–C(6)); 7.75–7.71 (*m*, 2 H$_o$, H–C(5)); 6.05 (*d*, J = 3, H–C(1′)); 5.54 (*dd*, H–C(2′)); 5.31 (*t*, H–C(3′)); 4.45–4.31 (*m*, H–C(4′), 2 H–C(5′), CH_2); 2.15–2.11 (2*s*, 3 Me); 1.39 (*t*, Me). Anal. calc. for $C_{25}H_{28}N_4O_{11}$ (560.5): C 53.57, H 5.04, N 9.99; found: C 53.48, H 5.07, N 9.95.

29. N^4-{*[4-(Ethoxycarbonyl)phenyl]carbamoyl*}*cytidine* (**52**). A suspension of **51** (600 mg, 1.06 mmol) in 7.5M NH_3/MeOH (30 ml) was stirred for 20 h at r.t. The slurry was evaporated, co-evaporated with H_2O/EtOH, and stirred with H_2O (20 ml) overnight. The suspension was filtered and the solid dried (50°/high vacuum): 0.39 g (82%) of **52**. M.p. 180–181° (dec.). TLC (CH_2Cl_2/MeOH 9:1): R_f 0.20. UV ($H_0 = -2$): 256 (4.08), 315 (4.55). UV (pH 3 or 9): 242 (4.10), 297 (4.50). UV (pH 13): 226 (sh, 4.00), 262 (sh, 409), 317 (4.62). pK_a 0.62, 11.44. ^{1}H-NMR ((D$_6$)DMSO): 11.7 (br. *s*, NH); 10.3 (br. *s*, NH); 8.35 (*d*, H–C(6)); 7.92 (*d*, 2 H$_m$); 7.60 (*d*, 2 H$_o$); 6.41 (*d*, H–C(5)); 5.79 (*d*, H–C(1′)); 5.48 (*d*, OH–C(2′)); 5.16 (*t*, OH–C(5′)); 5.08 (*d*, OH–C(3′)); 4.27 (*q*, CH_2); 3.99–3.90 (*m*, H–C(2′), H–C(3′), H–C(4′)); 3.75–3.56 (*m*, 2 H–C(5′)); 1.30 (*t*, Me). Anal. calc. for $C_{19}H_{22}N_4O_8 \cdot 0.5\ H_2O$ (443.4): C 51.46, H 5.22, N 12.64; found: C 51.56, H 5.19, N 12.90.

30. *2′,3′,5′-Tri-*O*-acetyl-*N^4-*[(4-nitrophenyl)carbamoyl]cytidine* (**53**). A soln. of 4-nitroaniline (220 mg, 1.6 mmol) and **48** (1 g, 2 mmol) in pyridine (10 ml) was stirred for 60 min at 70°. The mixture was evaporated and co-evaporated with toluene and with H_2O/EtOH until **53** became solid. After addition of EtOH (20 ml), **53** was stirred for 1 h at r.t., filtered, and dried: 0.5 (60%). M.p. 209–210° (dec.). TLC (CH_2Cl_2/MeOH 9:1): R_f 0.42. UV (MeOH): 212 (sh, 4.29), 238 (sh, 4.08), 314 (4.37). ^{1}H-NMR ((D$_6$)DMSO): 11.7 (br. *s*, NH); 10.5 (br. *s*, NH); 8.23 (*d*, 2 H$_m$); 8.06 (*d*, H–C(6)); 7.71 (*d*, 2 H$_o$); 6.50 (*d*, H–C(5)); 5.90 (*d*, J = 3.8, H–C(1′)); 5.50 (*m*, H–C(2′)); 5.36 (*t*, H–C(3′)); 4.37–4.19 (*m*, H–C(4′), 2 H–C(5′)); 2.06–2.04 (2*s*, 3 Me). Anal. calc. for $C_{22}H_{23}N_5O_{11}$ (533.4): C 49.54, H 4.35, N 13.13; found: C 49.33, H 4.35, N 13.07.

31. N^4-*[(4-Nitrophenyl)carbamoyl]cytidine* (**54**). A suspension of **53** (600 mg, 1.12 mmol) in 7.5M NH_3/MeOH (30 ml) was stirred for 20 h at r.t. The precipitate was filtered, washed with MeOH and Et_2O, and dried (50°/high vacuum): 0.39 g (85%) of **54**. M.p. 175° (dec.). TLC (CH_2Cl_2/MeOH 8:2): R_f 0.69. UV ($H_0 = -1$): 220 (sh, 4.21), 232 (4.54). UV (pH 3 or 10): 236 (sh, 4.06), 314 (4.33). UV (pH 13): 232 (4.09), 306 (4.17), 352 (4.38). pK_a 0.7, 11.4. ^{1}H-NMR ((D$_6$)DMSO): 11.9 (br. *s*, NH); 10.4 (br. *s*, NH); 8.38 (*d*, H–C(6)); 8.24 (*d*, 2 H$_m$); 7.31 (*d*, 2 H$_o$); 6.42 (*d*, H–C(5)); 5.79 (*d*, J = 3, H–C(1′)); 5.49 (*d*, OH–C(2′)); 5.17 (*t*, OH–C(5′)); 5.10 (*d*, OH–C(3′)); 4.00–3.88 (*m*, H–C(2′), H–C(3′), H–C(4′)); 3.74–3.55 (*m*, 2 H–C(5′)). Anal. calc. for $C_{16}H_{17}N_5O_8$ (407.3): C 47.18, H 4.21, N 17.19; found: C 46.77, H 4.48, N 17.11.

REFERENCES

[1] M. Resmini, W. Pfleiderer, *Helv. Chim. Acta* **1994,** *77,* 429.

[2] H. G. Khorana, *Pure Appl. Chem.* **1968,** *17,* 349; M. J. Gait, H. W. D. Matthes, M. Singh, B. S. Sproat, R. C. Titmas, in 'Chemical and Enzymatic Synthesis of Gene Fragments', Springer, New York, 1982; K. L. Agarwal, A. Yamazaki, P. J. Cashion, H. G. Khorana, *Angew. Chem.* **1972,** *84,* 489; E. Sonveaux, *Bioorg. Chem.* **1986,** *14,* 274; V. Amarnath, A. D. Broom, *Chem. Rev.* **1977,** *77,* 183; H. Kössel, H. Seliger, *Fortschr. Chem. Org. Naturst.* **1975,** *32,* 298; J. Engels, E. Uhlmann, *Adv. Biochem. Engin. Biotech.* **1988,** *37,* 73; S. Beaucage, R. P. Iyer, *Tetrahedron* **1992,** *48,* 2223; **1993,** *49,* 6123.

[3] G. M. Tener, *J. Am. Chem. Soc.* **1961,** *83,* 159.

[4] N. D. Sinha, J. Biernat, J. McManus, H. Köster, *Nucleic Acids Res.* **1984,** *12,* 4539; N. D. Sinha, J. Biernat, H. Köster, *Tetrahedron Lett.* **1983,** *24,* 5843.
[5] S. L. Beaucage, R. P. Iyer, *Tetrahedron* **1992,** *48,* 2223.
[6] E. Uhlmann, W. Pfleiderer, *Helv. Chim. Acta* **1981,** *64,* 1688; A. H. Beiter, W. Pfleiderer, *Tetrahedron Lett.* **1984,** *25,* 1975; M. W. Schwarz, W. Pfleiderer, *Nucleos. Nucleot.* **1985,** *4,* 291.
[7] F. Himmelsbach, B. S. Schulz, T. Trichtinger, R. Charubala, W. Pfleiderer, *Tetrahedron* **1984,** *40,* 59; W. Pfleiderer, F. Himmelsbach, R. Charubala, H. Schirmeister, A. Beiter, B. Schulz, T. Trichtinger, *Nucleos. Nucleot.* **1985,** *4,* 81; H. Schirmeister, F. Himmelsbach, W. Pfleiderer, *Helv. Chim. Acta* **1993,** *76,* 385.
[8] K. P. Stengele, W. Pfleiderer, *Tetrahedron Lett.* **1990,** *31,* 2549.
[9] W. Pfleiderer, R. Charubala, *Konstanzer Bibliothek Band* **1985,** *1,* 9; W. E. G. Müller, B. E. Weiler, R. Charubala, W. Pfleiderer, L. Leserman, R. W. Sobol, R. J. Suhadolnik, H. C. Schröder, *Biochemistry* **1991,** *30,* 2027.
[10] C. Buschhaus, Ph. D. Thesis, University of Konstanz, 1988.
[11] H. Sigmund, W. Pfleiderer, *Helv. Chim. Acta* **1994,** *77,* in press.
[12] H. Sigmund, Ph. D. Thesis, University of Konstanz, 1993.
[13] T. Ueda, K. Mirua, T. Kasai, *Chem. Pharm. Bull.* **1978,** *26,* 2122; K. Miura, T. Kasai, T. Ueda, *ibid.* **1975,** *23,* 464; K. Kikugawa, H. Suehiru, R. Yanase, A. Akoi, *ibid.* **1977,** *25,* 1959.
[14] S. Fredriksen, A. H. Rasmussen, *Cancer Res.* **1967,** *27,* 385; K. R. Svendsen, K. Overgaard-Hansen, S. Fredriksen, *Chem. Abstr.* **1988,** *108,* 197944p; S. Fredriksen, *Biochim. Biophys. Acta* **1963,** *76,* 366.
[15] A. S. Shawali, A. Harhash, M. M. Sidky, H. M. Hassaneen, S. S. Elkaabi, *J. Org. Chem.* **1986,** *51,* 3498; F. M. Menger, L. E. Glass, *ibid.* **1974,** *39,* 2469; V. Löscei, O. Facsko, T. Chirila, *J. Prakt. Chem.* **1983,** *325,* 49; *ibid.* **1982,** *324,* 816; Y. Furuya, S. Goto, K. Itoho, I. Urasaki, A. Morita, *Tetrahedron* **1968,** *24,* 2367.
[16] P. A. Lyon, C. B. Reese, *J. Chem. Soc., Perkin Trans. 1* **1978,** 131.
[17] J. W. Jones, R. K. Robins, *J. Am. Chem. Soc.* **1963,** *85,* 193.
[18] R. W. Adamiak, J. Stawinski, *Tetrahedron Lett.* **1977,** 1935; R. W. Adamiak, M. Wiewiorowski, *Bull. Acad. Pol. Sci. Ser. Sci. Chim.* **1975,** *23,* 241.
[19] T. Vontor, M. Vecera, *Collect. Czech. Chem. Commun.* **1973,** *38,* 3139.
[20] C. I. Hong, G. B. Chheda, S. P. Dutta, A. O'Grady-Curtis, G. L. Tritsch, *J. Med. Chem.* **1973,** *16,* 139; S. P. Dutta, C. I. Hong, G. L. Tritsch, C. Cox, R. Parthasarthy, G. B. Chheda, *ibid.* **1977,** *20,* 1598; S. P. Dutta, G. B. Chheda, *Nucleic Acid Chem.* **1978,** *2,* 655; S. P. Dutta, C. I. Hong, G. P. Murphy, A. Mittelman, G. B. Chheda, *Biochemistry* **1975,** *14,* 3411.
[21] A. Albert, E. P. Serjant, in 'The Determination of Ionisation Constants', Chapman and Hall Ltd., London, 1977, p. 44.
[22] 'Organikum – Organisch chemisches Grundpraktikum', VEB Deutscher Verlag der Wissenschaften, Berlin, 1964; D. D. Perrin, W. L. F. Armarego, D. R. Perrin, in 'Purification of Laboratory Chemicals', 2nd edn., Pergamon Press, New York, 1988.
[23] W. G. Finnigan, R. A. Henry, R. Lofquist, *J. Am. Chem. Soc.* **1958,** *80,* 3908.
[24] H. Bredereck, *Chem. Ber.* **1947,** *80,* 401.