26. Ring-Open Analogues of Adenine Nucleoside. Aminoacyl Derivatives of Cyclo- and Acyclo-nucleosides

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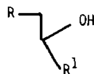
The synthesis of acyclic analogues of ribo- and deoxyribonucleosides is described. These compounds (*Table 3*) are both poor substrates and poor inhibitors of adenosine deaminase. The synthesis of dinucleotides from these analogues is also described, and the activity along with the inhibitory properties of some of them are studied against deaminase enzyme. These nucleotides are resistant to degradation by phosphodiesterases. HCl impregnated on silica gel is an excellent reagent for the preparation of the chloromethyl ether precursors of acyclo-nucleosides. A general and rapid procedure is developed for the preparation and isolation of the 5'-aminoacyl derivatives of ribo- and arabinonucleosides. Quinoline has a marked effect on aminoacylations without racemization. Compounds **35a, b** possess remarkable antiviral effects *in vitro*. A procedure is also developed for the conversion of acyclo-ribonucleosides **13e, f** to acyclo-deoxyribonucleosides **11e, f**.

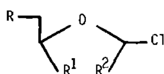
1. Introduction. – Many nucleoside analogues possess remarkable biological activity, particularly as antiviral and anticancer [1] [2]. Among them, the potent antiviral nucleoside 9-(β-D-arabinofuranosyl)adenine (*ara*-A) has shown activity against certain DNA viruses [3] [4]. Despite its proven efficacy, the practical value of *ara*-A is often reduced by its deamination *in vivo* by adenosine deaminase to give 9-(β-D-arabinofuranosyl)-hypoxanthine (*ara*-Hx), the main metabolite which possesses a low level of antiviral activity [5]. It was suggested that adenosine deaminase would recognize as substrate only those analogues capable of existing in the *anti*-conformation [6]. Consequently, many investigations have been carried out on flexible analogues of enzyme substrates, which have all the chemical features of deoxyadenosine, but which lack a rigid carbohydrate ring structure [7–15]. Furthermore, a low lipophilicity of *ara*-A precludes its use as a topical agent for treating genital, oral, and other cutaneous herpes infections [16]. In addition, the parental administration of *ara*-A does suffer from a low aqueous solubility of the drug [16].

In an attempt to overcome these problems which manifest themselves as difficulties in formulation, delivery, and topical application as well as in a lack of resistance to enzymic deactivation *in vivo*, a series of acyclo-nucleosides including adenine analogues of acyclovir [17] possessing aminoacyl side-chains with D- or L-configuration was synthesized. These analogues exhibit complete resistance to deamination.

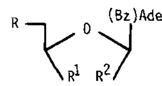
2. Synthesis of Acyclo-nucleosides. – The general scheme for the synthesis of acyclo-nucleosides consists in the transformation **1**→**2**→**3**→**9**. In a model reaction, the chloromethyl ether **2a** is prepared from 2-chloroethanol (**1a**) and 1,3,5-trioxane in the presence of HCl adsorbed on silica gel. The concept of utilizing reagents adsorbed on inert inorganic supports for organic synthesis has been frequently employed [18–23]. In the



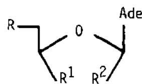
1a R = Cl, R' = H
b R = Cl, R' = CH_2Cl
c R = OBz, R' = H
d R = OBz, R' = $CH(OBz)CH_2OBz$(*2RS,3SR*)
e R = OBz, R' = $CH(OBzl)CH_2OBz$(*2R,3R*)
f R = OBz, R' = $CH(OBzl)CH_2OBz$(*2S,3S*)



2a R = Cl, R' = H, R² = H
b R = Cl, R' = CH_2Cl, R² = H
c R = OBz, R' = H, R² = H
d R = OBz, R' = $CH(OBz)CH_2OBz$, R² = H(*2RS,3SR*)
e R = OBz, R' = $CH(OBzl)CH_2OBz$, R² = H(*2R,3R*)
f R = OBz, R' = $CH(OBzl)CH_2OBz$, R² = H(*2S,3S*)
c' R = OBz, R' = H, R² = COOMe



3a R = Cl, R' = H, R² = H
b R = Cl, R' = Ch_2Cl, R² = H
c R = OBz, R' = H, R² = H
d R = OBz, R' = $CH(OBz)CH_2OBz$, R² = H(*2RS,3SR*)
e R = OBz, R' = $CH(OBzl)CH_2OBz$, R² = H(*2R,3R*)
f R = OBz, R' = $CH(OBzl)CH_2OBz$, R² = H(*2S,3S*)
c' R = OBz, R' = H, R² = COOMe



9b R = Cl, R' = CH_2Cl, R² = H
c R = OH, R' = H, R² = H
d R = OH, R' = $CH(OH)CH_2OH$, R² = H(*2RS,3SR*)
e R = OH, R' = $CH(OBzl)CH_2OH$, R² = H(*2R,3R*)
f R = OH, R' = $CH(OBzl)CH_2OH$, R² = H(*2S,3S*)
c' R = OH, R' = H, R² = CH_2OH

Bz = PhCO, Bzl = $PhCH_2$, Ade = Adenin-9-yl

same perspective, HCl in aq. solution can be adsorbed on silica gel and then converts alcohols in aprotic solvents to the corresponding chloromethyl ethers in the presence of aldehydes.

Addition of silica gel (*Merck*, act. 1) to conc. aq. HCl (37%) and refluxing the mixture for a few hours affords a white granular material (see *Exper. Part*). Titration of the HCl impregnated on silica gel reveals, even after two months, that the reagent activity does not vary appreciably with time. The reaction rate of **1**→**2** is, apparently, dependent both on the structure of the alcohol and on the ratio substrates/HCl. However, with 2 g of HCl/silica gel per 1 mmol of each substrate, the reaction is complete within 24 h at 25°. It may be carried out in solvents such as Et_2O or $CHCl_3$ without any considerable effect in yield.

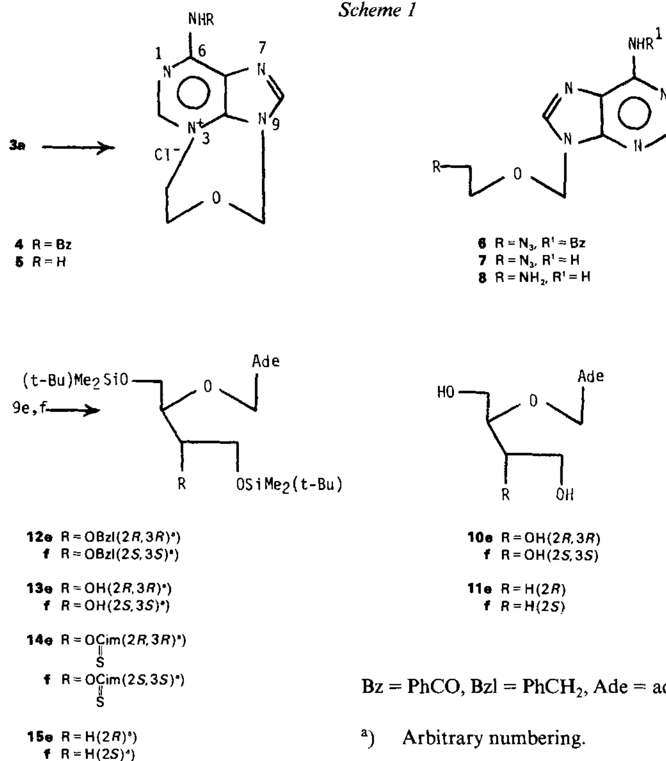
Thus, treatment of 1,3-dichloropropan-2-ol (**1b**), 2-(benzoyloxy)ethanol[1]) (**1c**), (*2RS,3SR*)-1,3,4-tris(benzoyloxy)-2-butanol[1]) (**1d**), and (*2R,3R*)- (**1e**), and (*2S,3S*)-2-benzyloxy-1,4-bis(benzoyloxy)-3-butanol[1]) (**1f**) with 1,3,5-trioxane or methyl glyoxylate in the case of **1c** gave the corresponding chloromethyl ethers **2a–f** and **2c'** by means of HCl/silica gel in $CHCl_3$.

In principle, compounds **2a–f** and **2c'** can be coupled directly to purines. Bu_4NI has been proposed as a mild catalyst in coupling reactions of this type [24]. Thus, when **2a** and *N*-benzoyladenine were condensed in toluene using Bu_4NI, a fairly rapid reaction to the desired product **3a** occurred (80% yield).

Reaction of **3a** with NaN_3 in DMF [14] gave a very low yield of compound **6** *(Scheme 1)*. Therefore, it was decided to carry out the reaction in refluxing MeOH; to our surprise, a quantitative yield of salt **5** was obtained. To establish the feature of reaction **3a**→**5**, the following experiments were carried out *(Scheme 1)*. Treatment of **3a** in refluxing MeOH in the absence of NaN_3 afforded, after 12 h, **5** (98%) as evidenced by IR, NMR, UV, and microanalysis. The same reaction at 25° gave compound **4** after 72 h. The structure of **4** is based on the fact that in the IR the amide group absorbs at 1715 cm^{-1} and its NH as doublets at 3350 and 3480 cm^{-1}, with a concomitant lowering of the ^{1}H-NMR chemical shift of H–C(2) and H–C(8) of the purine base to 8.68 and 8.85 ppm (*cf.* data of **3a**: 1680, 3115 cm^{-1} and 8.20, 8.51 ppm, resp.). Separate treatment of **4** in refluxing MeOH resulted in the formation of **5**. Crystallization of **3a** with H_2O also afforded **4**, which in turn was

[1]) The systematic names of **1c–f** are; 2-hydroxyethyl benzoate (**1c**), 3-hydroxybutane-1,2,4-triyl tribenzoate (**1d**), and 2-benzyloxy-3-hydroxybutane-1,4-diyl dibenzoate (**1e**, **1f**).

Scheme 1



Bz = PhCO, Bzl = $PhCH_2$, Ade = adenine, im = imidazole

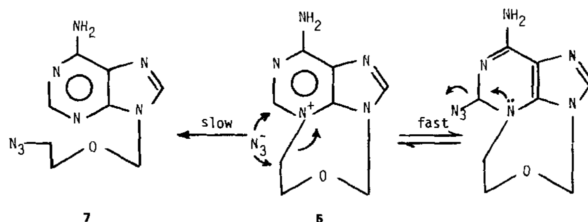
[a]) Arbitrary numbering.

converted to **5** by NaOMe/MeOH at 25° after 1 h. Reaction of **5** with NaN_3 in refluxing DMF gave **7** (λ_{max} 260 nm) in 70% yield.

As the electrophilic substitution at C(2) of **5** is a favorable reaction, the formation of **7** could be due to the leaving-group capacity of the N_3 function and the tendency of the purine system to stay in its aromatic form (see *Scheme 2*). Hydrogenolysis of **7** with Pd/C in EtOH at 30 psi gave acyclo-nucleoside **8** (60%).

As described above for **2a**, *N*-benzoyladenine was reacted with **2b–f** and **2c'** in toluene to give the 9-alkylated products **3b–f** and **3c'** in *ca.* 65–80% yield. It should be noted that in benzene or CH_3CN, isomeric mixtures (N(7) and N(9)-substituted isomers) were formed. However, complete conversion to the desired N(9)-alkylated products took place upon heating the isomeric mixtures in toluene.

Scheme 2

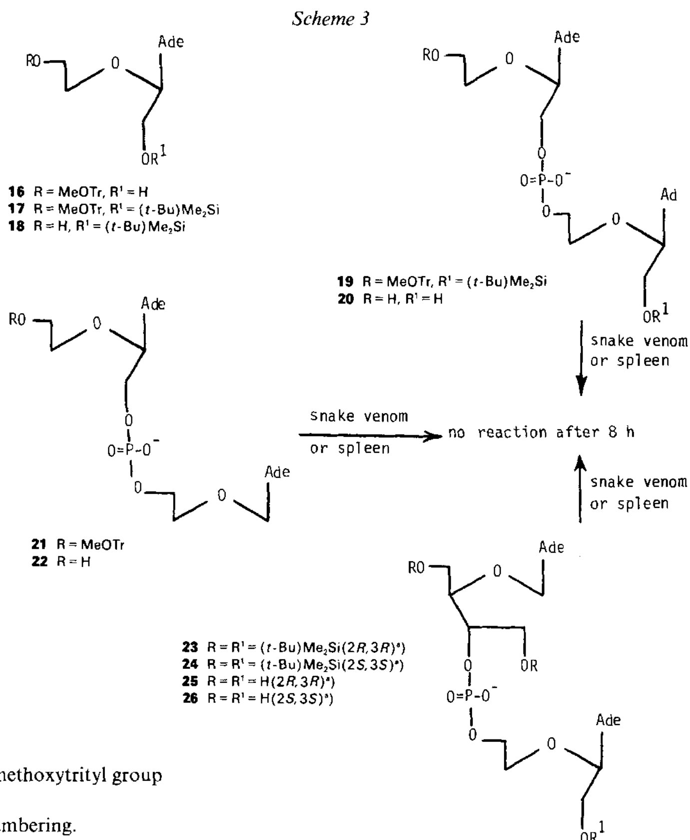


Treatment of **3b–f** with NH_3/MeOH resulted in the adenine compounds **9b–f**. The ester groups in **3c'** were readily reduced with $NaBH_4$ in dry MeOH to give **9c'** in high yield. The benzyl group can easily be removed from **9e, f** by catalytic hydrogenation to afford **10e,f** in good yields.

At this point, we turned our attention to the preparation of acyclo-nucleosides **11**. In principle, reaction of compounds of type **13** with 1,1'-(thiocarbonyl)diimidazole should give products **14** that can be readily reduced to the deoxy-acyclo-nucleosides **15** [25]. Indeed, **9e,f** were silylated with (*t*-Bu)Me_2SiCl and the resulting products **12e,f** hydrogenated to **13e,f,** from which **14e,f** were obtained (*ca.* 70%) on reaction with 1,1'-(thiocarbonyl)diimidazole. Subsequent reaction with Bu_3SnH and 2,2'-azobis(2-methylpropionitrile) in toluene gave the protected acyclo-nucleosides **15e,f** (55%), and removal of the silyl group with Bu_4NF [26] generated **11e,f** (80%).

3. Synthesis of Dinucleotides from Acyclo-nucleosides. – We next attempted to prepare dinucleotide-monophosphate analogues from acyclo-nucleosides and to study their behavior toward phosphodiesterase enzymes. The nucleotide analogue **20** was readily obtained from **9c'** by preparing its monomethoxytrityl derivative **16** *(Scheme 3)*. Silylation (→**17**) and deprotection gave **18** (see *Exper. Part*). Coupling of 1 equiv. each of **16** and **18** with 1 equiv. of 2,2,2-trichloroethylphosphorodichloridite followed by I_2 oxida-

Scheme 3



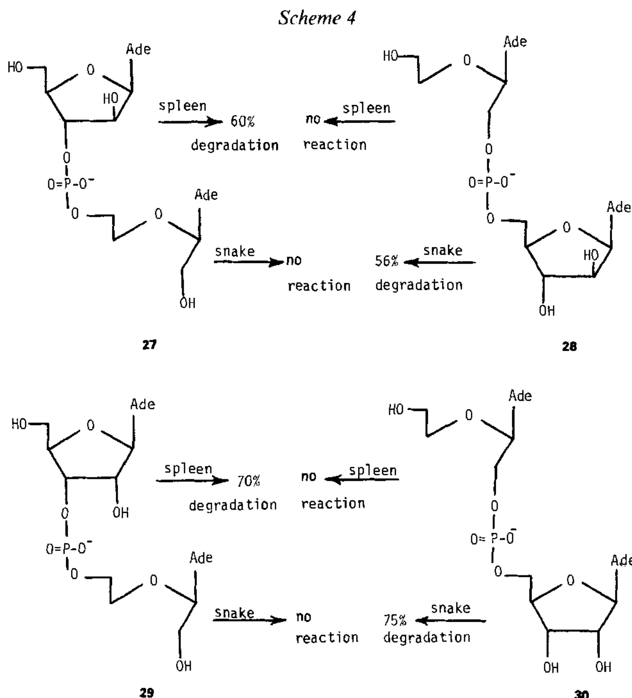
MeOTr = monomethoxytrityl group

a) Arbitrary numbering.

tion of the phosphite group [27] (→**19**) and complete deprotection afforded **20** in good yield (see *Exper. Part*). The dinucleotides **21–30** (*Schemes 3* and *4*) were prepared in a similar manner.

Compounds **20, 22, 25,** and **26** were completely resistant to both snake-venom and spleen phosphodiesterases for 8 h under standard conditions *(Scheme 3)*. However, the mixed nucleotides **27–30** possessing a unit of *ara*-A or adenosine and **9c′**, showed some degradation after 8 h *(Scheme 4)*. These results were consistent with those reported [14] on another series of dinucleotides containing acyclo-nucleosides and indicate that the acyclo-nucleosides are not recognized as a normal substrate by phosphodiesterases.

Scheme 4



4. Adenosine-Deaminase Studies on Acyclo-nucleosides and Dinucleotide Analogues. – The rate of deamination of **9c′**, **10e,f**, **11e,f**, **27–30**, and adenosine in the presence of calf mucosal adenosine deaminase in buffered solutions of varying substrate concentration were determined according to the procedures described in [14]. The inhibition studies on the above substrates were also carried out following the procedure in [14]. The results are shown in *Table 1*.

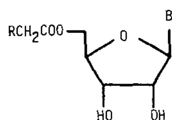
Clearly, compared with adenosine, the conformational flexibility of the acyclo-nucleosides **9c′**, **10e,f**, and **11e,f** prevent their efficient binding to the enzyme. The substrates **9c′**, **10e,f**, and **11e,f** were also found to be weak competitive inhibitors of adenosine deaminase. Dinucleotides **27** and **29** are both good substrates and good inhibitors of adenosine deaminase, while **28** and **30** are both poor substrates and poor inhibitors. These findings are in accord with the structure-activity relationships [28] of various

Table 1. *Substrate Activities and Inhibitory Properties against Adenosine-Deaminase Enzyme*

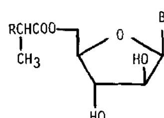
Substrate	K_m (M · 10^5)	Rel. V_{max}	K_i
Adenosine	4.68	1	–
9c′	210	$1.22 \cdot 10^{-2}$	$1.73 \cdot 10^{-4}$
10e	155	$3.02 \cdot 10^{-2}$	$2.55 \cdot 10^{-4}$
f	190	$2.47 \cdot 10^{-2}$	$2.08 \cdot 10^{-3}$
11e	165	$2.80 \cdot 10^{-2}$	$3.00 \cdot 10^{-4}$
f	220	$2.12 \cdot 10^{-2}$	$1.54 \cdot 10^{-3}$
27	30	$15.60 \cdot 10^{-2}$	$6.01 \cdot 10^{-1}$
28	255	$1.83 \cdot 10^{-2}$	$2.21 \cdot 10^{-4}$
29	22	$21.27 \cdot 10^{-2}$	$8.25 \cdot 10^{-1}$
30	242	$1.93 \cdot 10^{-2}$	$2.87 \cdot 10^{-4}$

adenine nucleosides showing a profound dependence of the binding to the enzyme on an available 5′-OH group. Compounds **27** and **29** have an available 5′-OH function on the rigid furanosyl ring of their adenosine moiety, whereas the 5′-position of the furanosyl ring in **28** and **30** is protected by the phosphate linkage. Since **27** and **29** possess good inhibitory properties and exhibit some degradation characteristics *(Scheme 4)*, one might expect that the adenosine residue of **27** and **29** behave as a carrier having inhibitory properties to inactivate the deaminases, and then, by the aid of some phosphodiesterases, the acyclo-nucleoside moiety is liberated as a potential drug which hopefully is toxic to the infecting cells.

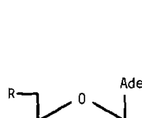
5. Aminoacylation Reactions of Cyclo- and Acyclo-nucleosides. – Direct acylation of the four common ribonucleosides uridine, cytidine, adenosine, and guanosine by adding (phthalimido)acetyl chloride to the nucleosides in DMF/THF in the presence of quinoline at 10° (at 60° for guanosine) afforded the corresponding compounds **31a, b** and **d** in *ca.* 70–90% and **31c** in 20% yield. Other bases such at Et_3N or pyridine did not facilitate the selectivity of the acylation of the primary OH function over the secondary OH functions or the NH_2 group of cytidine or adenosine. When cytidine or adenosine were acylated with phthalimidoacetic acid in the presence of dicyclohexylcarbodiimide or *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, a 1:1 mixture of *N*-protected and 5′-*O*-protected ribonucleoside was obtained. Reaction of **31a, b** with phenylhydrazine [29] afforded aminoacyl derivatives **32a, b** in good yields.



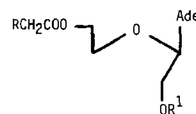
31a R = NPht, B = adenine
b R = NPht, B = cytosine
c R = NPht, B = guanine
d R = NPht, B = uracil
32a R = NH_2, B = adenine
b R = NH_2, B = cytosine



33a R = NPht, B = adenine (D)
b R = NPht, B = adenine (L)
34a R = NPht, B = cytosine (D)
b R = NPht, B = cytosine (L)
35a R = NH_2, B = adenine (D)
b R = NH_2, B = adenine (L)
36a R = NH_2, B = cytosine (D)
b R = NH_2, B = cytosine (L)

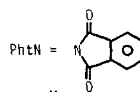


37a R = $OCOCH(CH_3)NPht$ (D)
b R = $OCOCH(CH_3)NPht$ (L)
38a R = $OCOCH(CH_3)NH_2$ (D)
b R = $OCOCH(CH_3)NH_2$ (L)
42a R = $OCOCH(CH_3)NHRet.$ (D)
b R = $OCOCH(CH_3)NHRet.$ (L)
43 R = NHRet.
44 R = $NHCOCH_2NPht$
45 R = $NHCOCH_2NH_2$
46 R = $NHCOCH_2NHRet.$

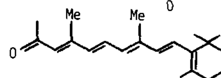


39 R = NPht, R′ = Si
40 R = NH_2, R′ = Si
41 R = NH_2, R′ = H

PhtN =



Ret. =



Having established a method for the selective 5'-aminoacylation of ribonucleosides, we prepared the aminoacyl derivatives **35** and **36** of 9-(β-D-arabinofuranosyl)adenine and 9-(β-D-arabinofuranosyl)cytosine, respectively. Thus, D- or L-2-methyl-2-(phthalimido)-acetyl chloride were reacted with *ara*-A and *ara*-C in the presence of quinoline to afford **33** and **34**, respectively, in high yields. Cleavage of the phthalimido group in **33** and **34** using pyridine/AcOH/phenylhydrazine gave **35** and **36**, respectively, in less than 1 h. The cleavage conditions did neither affect ester groups nor caused racemization of the amino-acid side-chain. This was evidenced by mild hydrolysis of **35** and **36** to the corresponding D- or L-alanine.

As compound **9c** was previously reported to have a remarkable antiviral activity [17], we prepared its aminoacyl derivatives **38** by reacting **9c** with D- or L-2-methyl-2-(phthalimido)acetyl chloride as above (→**37**) followed by treatment with phenylhydrazine. That the NH_2 group on the adenine ring remained unacylated was demonstrated by the UV (λ_{max}(EtOH) 258–260 nm) and ^{1}H-NMR spectrum of **37** (br. *s* at 7.31 ppm, 2 H, NH_2). By the same method, the silyl derivative **18** was transformed to **39** and **40**. The latter was deprotected by treatment with Bu_4NF to afford **41** in 50% overall yield [26].

We recently have described [30] the pronounced *antileukemic* effect of some azetidinone derivatives containing a retinoic-acid chain (ED_{50} $1.98 \cdot 10^{-10}$ M). Unfortunately, the unstability of the retinoids make their synthesis difficult and their use limited. Therefore, we decided to study the synthesis of acyclo-nucleosides having a retinoic-acid side-chain and examine their stability at different conditions. Thus, treatment of the aminoacyl derivatives **38** with retinoic acid in the presence of ClCOOEt led to an 80% isolated yield of **42**. The same conditions were applied to **8** yielding **43**. To bind retinoic acid on **8** *via* an amino-acid adaptor, **8** was transformed to the phthalimido derivative **44** by our standard procedure. Deprotection of **44** afforded **45** and reaction with retinoic acid/ClOOEt **46** in 55% overall yield. The prepared retinoids were stable under neutral conditions at 25–37° for 1 to 2 weeks as evidenced by TLC.

All the aminoacyl derivatives of cyclo- and acyclo-nucleosides **31**–**41** were found to exhibit complete resistance to deamination when assayed against calf mucosal adenosine deaminase *in vitro* [14] [31].

Table 2. *Solubility in H_2O and Lipophilicity of Nucleoside Analogues*

Substrate	Solubility in H_2O [mg/ml]	log *P* (1-pentanol/H_2O)[a])
ara-A	0.40	– 0.47
35a	9.71	0.58
b	8.17	0.61
10e	2.60	0.11
f	2.21	0.12
11e	1.70	0.20
f	1.45	0.27
9c'	3.11	0.18
41	16.90	1.39
9c	1.95	0.98
38a	12.59	1.99
b	11.70	2.15
8	1.12	0.66
45	10.16	1.59

[a]) Partition coefficients were calculated as $P = [\text{substrate}]_{\text{pentanol}}/[\text{substrate}]_{H_2O}$.

6. Solubility in Water and Lipophilicity of Adenine Derivatives. – The aminoacyl compounds showed fair increases of solubility in H_2O compared with the corresponding cyclo- and acyclo-nucleosides *(Table 2)*. The lipophilicities were also determined *via* a pentanol/H_2O distribution according to the methods described in [16] *(Table 2)*.

7. Biological Activity. – The compounds **33–36** were tested for activity against *herpes-simplex*-type-1 virus (HSV-1). The two active compounds were adenine derivatives **35a** and **b** with ED_{50} values *vs.* HSV-1 of 0.5 µg/ml and 0.12 µg/ml, respectively. The control experiment showed *ara*-A to be active against HSV-1 with an ED_{50} value of *ca.* 7 µg/ml. The increased activity of **35a, b** over *ara*-A might be due to a combination of increased H_2O solubility and favorable lipophilicity along with their resistance to deamination toward adenosine deaminase (see above). Since the 5′-triphosphate of *ara*-A is the presumed bioactive component, it might be speculated that **35a, b** do act as prodrugs and must liberate *ara*-A which is the active agent. Supporting evidence for this comes from the fact that the much more stable esters **33a, b** were inactive against HSV-1 up to 100 µg/ml.

It should be noted that the NH_2 group of esters **35a, b** can assist hydrolysis of their corresponding ester functions as evidenced by gradual auto-hydrolysis of these compounds at 37°. This could be a reason for biological activity of *ara*-A carrying amino acid with D- and L-configuration.

The dinucleotide analogues **27–30** were also tested against HSV-1. The only active compound was **27** with an ED_{50} value of 24 µg/ml.

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Experimental Part

General. Reagent-grade solvents were distilled first and then stored over molecular sieves (type 4 Å). Adenine and calf mucosal adenosine deaminase were purchased from *Sigma Chemical Comp.* Column chromatography: short columns of silica gel *60 Merck* (230–400 mesh) were packed in glass columns (∅ 2 or 3 cm) using 15–30 g of silica gel per g of crude mixture. TLC: *Merck* silica gel *60 F 254* anal. sheets. Paper chromatography: *Whatman* 3 mm. i-PrOH/conc. NH_4OH/H_2O 7:1:2 (*v/v*). Paper electrophoresis: *Whatman* 3 mm; *Savant Flat* plate electrophoretic chamber with a *Savant Flat* plate model *HV* power supply; 2000 V for 1 h; the soln. was buffered at pH 8.0 with $3.3 \cdot 10^{-3}$ M KH_2PO_4 and $6.3 \cdot 10^{-2}$ M K_2HPO_4. M.p. *Büchi 510*; uncorrected. UV spectra: *Cary 118* spectrophotometer. IR spectra: *Beckman IR 8* spectrophotometer. ^{1}H-NMR spectra: *Hitachi R-248* spectrometer.

Preparation of HCl/Silica Gel. A soln. of silica gel (*Merck*, act. 1, 230–400 mesh; 100 g) in conc. HCl (700 ml, 37% in H_2O) was refluxed with stirring for 5 h. The solid product was filtered and dried in a desiccator. The material was then kept in a tapped jar at ambient pressure and r.t. without any particular precaution.

Preparation of Chloromethyl Ethers **2a–f**. Representative procedure: To HCl/silica gel (10 g), a soln. of 2-chloroethanol (**1a**, 0.8 g, 10 mmol) and 1,3,5-trioxane (0.9 g, 10 mmol) in $CHCl_3$ (30 ml) was added with stirring. After 24 h at 25°, the solid material was filtered and washed with $CHCl_3$ (3 × 15 ml). The combined filtrate and washings were evaporated to afford *1-chloro-2-(chloromethoxy)ethane* (**2a**) in 95% yield as an oil. IR (film): 1110 (ether). ^{1}H-NMR (CCl_4): 3.88–4.18 (*m*, $ClCH_2CH_2O$); 5.78 (*s*, OCH_2Cl). Methyl glyoxylate was used instead of 1,3,5-trioxane in the case of **2c′**.

Condensation of N-*Benzoyladenine with Chloromethyl Ethers* **2**: *Compounds* **3a–f** *and* **3c′**. Representative procedure (yields 65–80%): *N*-Benzoyladenine (2.39 g, 0.01 mol) was suspended in toluene (600 ml) and **2a** (2.58 g, 0.02 mol) and Bu_4NI (0.5 g) were added. The mixture was refluxed for 4 h (TLC: presence of **3a** and its N(7)-alkylated isomer). Heating for 24 h resulted in entire conversion to **3a**. After cooling, H_2O (200 ml) was added, and the org. layer dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel. Elution

Table 3. *Properties of Nucleoside Analogues*

Compound	M.p. [°C]	λ_{max}(EtOH) [nm] (ε)	R_f (TLC)	Compound	M.p. [°C]	λ_{max}(EtOH) [nm] (ε)	R_f (TLC)
3a	112–113	282 (19800)	0.31[a])	**18**	138–140	259 (15103)	0.68[a])
b	138–140	282 (17426)	0.36[a])	**31a**	145–146	259 (13150)	0.23[b])
c	foam	282 (18965)	0.32[a])	**b**	169–172	275 (12650)	0.16[b])
d	foam	282 (16843)	0.35[a])	**c**	259 (dec).	253, 270 (sh, 14125)	0.10[b])
e	foam	281 (17125)	0.44[a])	**d**	foam	264 (11202)	0.32[b])
f	foam	281 (16949)	0.44[a])	**32a**	192–194	258 (13251)	0.12[b])
c'	foam	282 (22122)	0.36[a])	**b**	215–216	275 (12345)	0.09[b])
6	120–123	281 (21720)	0.29[a])	**33a**	143–145	260 (14120)	0.25[b])
9b	189–192	260 (14195)	0.44[b])	**b**	150–152	260 (14220)	0.25[b])
c	197.4	260 (13720)	0.62[b])	**34a**	165–166	275 (12710)	0.18[b])
d	185	260 (13970)	0.29[c])	**b**	160–163	275 (12685)	0.18[b])
e	180–182	260 (13889)	0.41[c])	**35a**	218	259 (13975)	0.15[b])
f	183–186	260 (14023)	0.41[c])	**b**	222	259 (14110)	0.15[b])
c'	188–190	260 (13763)	0.25[c])	**36a**	220–222	275 (12750)	0.11[b])
10e	205	260 (14489)	0.28[c])	**b**	225–227	275 (12721)	0.11[b])
f	215	261 (14430)	0.28[c])	**37a**	140–142	259 (14410)	0.31[b])
11e	186–188	260 (13320)	0.32[c])	**b**	140–143	259 (14413)	0.31[b])
f	189–191	260 (13315)	0.32[c])	**38a**	209–212	259 (13550)	0.19[b])
12e	foam	259 (14832)	0.85[a])	**b**	207–208	259 (13525)	0.19[b])
f	foam	259 (14850)	0.85[a])	**39**	foam	260 (14925)	0.70[b])
13e	foam	260 (13712)	0.69[a])	**40**	120–121	260 (14765)	0.36[b])
f	foam	260 (13720)	0.69[a])	**41**	180–182	260 (14730)	0.19[b])
14e	foam	260 (13950)	0.75[a])	**42a**	103–106	259, 350	0.79[b])
f	foam	260 (13938)	0.75[a])	**b**	99–101	259, 350	0.79[b])
15e	foam	259 (14589)	0.90[a])	**43**	foam	259, 350	0.85[b])
f	foam	260 (14603)	0.90[a])	**44**	135–138	260 (13452)	0.28[b])
16	foam	260 (14952)	0.70[a])	**45**	197–199	260 (13110)	0.18[b])
17	oil	260 (14853)	0.92[a])	**46**	foam	259, 350	0.71[b])

[a]) AcOEt. [b]) AcOEt/MeOH 9.5:0.5. [c]) AcOEt/MeOH 1:1.

with CH_2Cl_2/CCl_4 1:1 removed impurities, and N-*benzoyl-9-[(2-chloroethoxy)methyl]adenine* (**3a**; 80%) was eluted with $CHCl_3$/AcOEt 1:1. Data: *Table 3*. IR (nujol): 3115 (NH), 1680 (C=O), 1113 (ether). ^1H-NMR ($CDCl_3$): 3.77–4.01 (*m*, $ClCH_2CH_2O$); 5.80 (*s*, OCH_2N); 7.39–8.21 (*m*, Ph, NH); 8.20 (*s*, H–C(2)); 8.51 (*s*, H–C(8)). Anal. calc. for $C_{15}H_{14}ClN_5O_2$ (331.58): C 54.29, H 4.22, N 21.12, Cl 10.71; found: C 54.01, H 4.11, N 21.30, Cl 10.83.

N-*Benzoyl-3,9-(ethanoxymethano)adenin-3-ium and 3,9-(Ethanoxymethano)adenin-3-ium Chloride* (**4** and **5**, resp.). A suspension of **3a** (3.31 g, 0.01 mol) in H_2O (200 ml) was refluxed to give a clear soln. After cooling, **4** (98%) was precipitated, m.p. 118–120°, R_f (AcOEt) 0.14. UV (EtOH): 280. IR (nujol): 3350, 3480 (NH), 1715 (C=O), 1120 (ether). ^1H-NMR ((D_6)DMSO): 3.61–3.99 (br. *s*, NCH_2CH_2O); 5.75 (*s*, OCH_2N); 7.50–8.31 (*m*, Ph); 8.68 (*s*, H–C(2)); 8.85 (*s*, H–C(8)); 9.51 (br. *s*, NH).

Compound **5** (99%) was obtained by treatment of **4** with 1 equiv. of NaOMe in MeOH for 1 h at 25°, m.p. 225°. R_f (AcOEt) 0.04. UV (EtOH): 257. IR (nujol): 3290 (NH_2), 1105 (ether). ^1H-NMR ((D_6)DMSO): 3.75 (*s*, NCH_2CH_2O); 5.61 (*s*, OCH_2N); 7.81 (br. *s*, NH_2); 8.32 (*s*, H–C(2)); 8.42 (*s*, H–C(8)). Anal. calc. for $C_8H_{10}ClN_5O$ (227.53): C 42.19, H 4.39, N 30.77, Cl 15.60; found: C 42.01, H 4.22, N 30.56, Cl 15.21.

9-[(2-Azidoethoxy)methyl]adenine (**7**) *and 9-[(2-Aminoethoxy)methyl)]adenine* (**8**). To a soln. of **5** (2.27 g, 0.01 mol) in DMF (50 ml), NaN_3 (3.25 g, 0.05 mol) was added. The soln. was refluxed for 24 h and then poured into H_2O (200 ml). Filtration of the precipitate and crystallization from H_2O afforded **7** (70%), m.p. 190–192°, R_f (AcOEt) 0.02. UV (EtOH): 260. IR (nujol): 3100–3260 (NH_2), 2100 (N_3), 1110 (ether). ^1H-NMR ((D_6)DMSO): 3.59 (*m*, CH_2N_3); 3.88 (*m*, CH_2O); 5.79 (*s*, OCH_2N); 6.81 (br. *s*, NH_2); 7.88 (*s*, H–C(2)); 8.16 (*s*, H–C(8)).

Compound **7** was hydrogenated in EtOH with Pd/C at 25° and 30 psi for 1 h to give **8** (60%) which was crystallized from H_2O, m.p. 221–224°, R_f (AcOEt/MeOH 9:1) 0.13. UV (EtOH): 260. IR (nujol): 3100–3300 ($2NH_2$), 1100 (ether). ^{1}H-NMR ((D_6)DMSO/D_2O): 2.98 (*m*, CH_2ND_2); 3.79 (*m*, CH_2O); 5.78 (*s*, OCH_2N); 7.85 (*s*, H–C(2)); 8.00 (*s*, H–C(8)). Anal. calc. for $C_8H_{12}N_6O$ (208.13): C 46.15, H 5.77, N 40.38; found: C 46.01, H 5.81, N 40.41.

Debenzoylation of Acyclic Adenine Nucleosides: Compounds **9b–f.** Representative procedure: To a soln. of **3d** (2.69 g, 0.01 mol) in MeOH (20 ml), 80 ml of sat. NH_3/MeOH was added. The soln. was sealed and maintained at 25° for 24 h. The mixture was concentrated to 30 ml and left overnight to afford *3-[(adenin-9-yl)methoxy]butane-1,2,4-triol* (**9d**; 90%) as a white solid. Data: *Table 3.* ^{1}H-NMR ((D_6)DMSO/D_2O): 3.32–3.78 (*m*, $2CH_2OD$, CHOD); 3.87–4.22 (*m*, CHO); 5.61 (*s*, OCH_2N); 8.07 (*s*, H–C(2)); 8.13 (*s*, H–C(8)). Anal. calc. for $C_{10}H_{15}N_5O_4$ (269.33): C 44.61, H 5.57, N 26.02; found: C 44.39, H 5.56, N 26.10.

2-(Adenin-9-yl)-2-(2-hydroxymethoxy)ethanol (**9c'**). To a soln. of **3c'** (4.75 g, 0.01 mol) in dry MeOH (30 ml) at 0°, $NaBH_4$ (2.8 g, 0.07 mol) was added in portions with stirring within 2 h. Then, the solvent was evaporated and the residue washed with Et_2O. Crystallization from H_2O gave **9c'** (80%). Data: *Table 3.* Anal. calc. for $C_{24}H_{21}N_5O_6$ (475.31): C 60.63, H 4.42, N 14.74; found: C 60.35, H 4.32, N 14.81.

(2R,3R)- and (2S,3S)-3-[(Adenin-9-yl)methoxy]butane-1,2,4-triol (**10e** and **10f**, resp.). Representative procedure: Compound **9e** (5 g) was dissolved in hot EtOH (100 ml), and PdO_2 (2 g) and cyclohexene (50 ml) were added. The mixture was stirred for 20 h at 25° followed by heating at reflux for 3 h. The mixture was cooled and filtered. The residue was washed with 280 ml of hot EtOH. The filtrate and washings were combined and evaporated to yield 2 g of crude product. Crystallization from H_2O gave 1.5 g of **10e** (40%). Data: *Table 3.* ^{1}H-NMR ((D_6)DMSO/D_2O): 3.30–3.78 (*m*, $2CH_2OD$, CHOD); 3.91–4.35 (*m*, CHO); 5.69 (*s*, OCH_2N); 8.06 (*s*, H–C(2)); 8.13 (*s*, H–C(8)).

10f: Spectral data are the same as for **10e**.

*9-{(1R,2R)- and (1S,2S)-2-Benzyloxy-3-{[(*tert*-butyl)dimethylsilyl]oxy}-1-{[(*tert*-butyl)dimethylsilyl]-oxymethyl}propoxy}adenine* (**12e** and **12f**, resp.). Procedure: To a suspension of **9e** (3.59 g, 0.01 mol) in THF (60 ml), pyridine (4 g, 0.05 mol), (*t*-Bu)Me_2SiCl (3.20 g, 0.02 mol), and $AgNO_3$ (3.40 g, 0.02 mol) were added, the mixture was stirred for 10 h at 25° and then filtered into H_2O (100 ml). The aq. soln. was extracted with AcOEt and the extract dried (Na_2SO_4), filtered, and evaporated. The residue was applied to a column of silica gel and **12e** (96%) was eluted with $CHCl_3$ as a foam. Data: *Table 3.* ^{1}H-NMR ($CDCl_3$): 0.17, 0.19 (2 *s*, $2(CH_3)_2Si$); 1.01 (*s*, $2(CH_3)_3C$); 3.52–4.29 (*m*, $CH_2CHCHCH_2$); 4.55 (*s*, $PhCH_2$); 5.88 (*s*, OCH_2N); 4.75 (*s*, Ph); 7.15 (*s*, NH_2); 8.00 (*s*, H–C(2)); 8.12 (*s*, H–C(8)). Similar spectral data for **12f**.

*(2R,3R)- and (2S,3S)-3-[(Adenin-9-yl)methoxy]-1,4-bis{[(*tert*-butyl)dimethylsilyl]oxy}butan-2-ol* (**13e** and **13f**, resp.) were prepared from **12e,f** like **8** from **7** (AcOEt instead of EtOH). Data: *Table 3.*

*O-(1R,2R)- and (1S,2S)-2-[(Adenin-9-yl)methoxy]-3-{[(*tert*-butyl)dimethylsilyl]oxy}-1-[(*tert*-butyl)dimethylsilyl]oxymethyl}propyl Imidazol-1-carbothioate* (**14e** and **14f**, resp.). Procedure: To a soln. of **13e** (2 mmol) in DMF (20 ml) was added 1,1'-(thiocarbonyl)diimidazole (6 mmol). After stirring at 25° for 5 h, the soln. was diluted with AcOEt (100 ml) and H_2O (100 ml). The org. layer was separated and washed with H_2O (3 × 70 ml), dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on silica gel and eluted with $CHCl_3$ to afford **14e** (70%) as a foam. Data: *Table 3.* ^{1}H-NMR of **14e,f**: similar to the one of **12e**.

*9-{(1R,2R)- and (1S,2S)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-1-{[(*tert*-butyl)dimethylsilyl]oxymethyl}-propoxy}adenine* (**15e** and **15f**, resp.). Procedure: A mixture of **14e** (6 mmol), 2,2'-azobis(2-methylpropionitrile) (1 g), and Bu_3SnH (27 mmol) was heated at reflux in toluene for 3–4 h. Solvent was removed and **15e** (55%) isolated as a foam after silica-gel chromatography using $CHCl_3$/AcOEt 8:2. ^{1}H-NMR ($CDCl_3$): 0.18, 0.19 (2 *s*, $2(CH_3)_2Si$); 1.02 (*s*, $2(CH_3)_3C$); 1.31–1.58 (*m*, CH_2); 3.52–4.02 (*m*, $2CH_2OSi$, CHO); 5.71 (*s*, OCH_2N); 7.21 (*s*, NH_2); 7.99 (*s*, H–C(2)); 8.15 (*s*, H–C(8)). Data: *Table 3.* Anal. calc. for $C_{22}H_{43}N_5O_3Si_2$ (461.53): C 52.27, H 9.33, N 15.18; found: C 57.21, H 9.23, N 15.17.

Spectral data of **15f**: similar to that of **15e**.

(2R)- and (2S)-2-[(Adenin-9-yl)methoxy]butane-1,4-diol (**11e** and **11f**, resp.). Procedure: to a soln. of **15e** (0.461 g, 1 mmol) in THF (20 ml), Bu_4NF (2.5 mmol) was added and stirred for 2 h (TLC: no **15e** left). The solvent was evaporated and the residue treated with H_2O (5 ml). The solid material was collected and crystallized from EtOH to afford **11e** (80%). Data: *Table 3.* ^{1}H-NMR ((D_6)DMSO/D_2O): 1.45 (*m*, CH_2); 3.56 (*m*, $2CH_2OD$); 3.81 (*m*, CHO); 5.61 (*s*, OCH_2N); 8.01 (*s*, H–C(2)); 8.15 (*s*, H–C(8)). Anal. calc. for $C_{10}H_{15}N_5O_3$ (253.33): C 47.43, H 5.93, N 27.66; found: C 47.33, H 5.82, N 27.45.

Spectral data of **11f**: similar to that of **11e**.

2-(Adenin-9-yl)-2-{[2-(monomethoxytrityl)oxy]ethoxy}ethanol (**16**), *9-{2-{[(*tert*-Butyl)dimethylsilyl]-oxy}-1-{2-[(monomethoxytrityl)oxy]ethoxy}ethyl}adenine* (**17**), *and 2-{1-(Adenin-9-yl)-2-{[(*tert*-butyl)di-methylsilyl]oxy}ethoxy}ethanol* (**18**). To a soln. of **9c'** (4.75 g, 0.01 mol) in dry pyridine (150 ml), monomethoxytrityl chloride (3.24 g, 0.01 mol) was added and stirred at 25° for 24 h. Pyridine was removed under reduced pressure by co-distillation with toluene to afford a residue which was applied to a silica-gel column. Impurities were eluted with CH_2Cl_2 and pure **16** (80%) was eluted with $CHCl_3$ as a foam. Data: *Table 3*. ^{1}H-NMR ($CDCl_3$): 3.35–3.78 (*m*, CH_3O, OCH_2CH_2O, CH_2OH); 5.59 (*s*, OCH_2N); 6.31 (*s*, NH_2); 6.71–7.43 (*m*, 2Ph, $CH_3OC_6H_4$); 7.91 (*s*, H–C(2)); 8.25 (*s*, H–C(8)).

As described for **12e**, **16** was silylated to **17** (90%). Data: *Table 3*. Spectral data: similar to that of **16**.

Hydrolysis of **17** by benzenesulfonic acid (1% in CH_3CN) at 25° gave **18**. (95%) after 20 min. Data: *Table 3*. Anal. calc. for $C_{15}H_{27}N_5O_3Si$ (353.53): C 50.99, H 7.65, N 19.83; found: C 60.11, H 7.65, N 19.79.

Nucleotides **19**–**26**. Representative procedure (40–50% yield for condensation, 30–50% for deprotection): Collidine (5 equiv.) was added to THF (1 ml) at – 78° in a vial (rubber septum, magnetic stirrer), followed by 2,2,2-trichloroethyl phosphodichloridite (0.6 equiv.). A soln. of **16** (0.5 mmol) in THF (0.5 ml) was added dropwise within 15 min. Then, **18** (0.5 mmol) in THF (0.5 ml) was added and the mixture stirred at – 78° and allowed to warm up to 20° during 1 h. I_2 (1.2 equiv.) in 3 ml of THF/H_2O 2:1 was added and the soln. stirred for 25 min. The solvents were removed, the residue was taken up in CH_2Cl_2 (50 ml), washed with 5% $NaHSO_3$ (30 ml) and H_2O (30 ml), the org. layer concentrated and the residue chromatographed on 10 prep. TLC plates with $CHCl_3$/EtOH 6:1. The band at R_f *ca.* 0.67 was eluted with AcOEt and *2-{1-(adenin-9-yl)-2-{[(*tert*-butyl)dimethylsilyl]oxy}-ethoxy}ethyl 2-(adenin-9-yl)-2-{2-[(monomethoxytrityl)oxy]ethoxy}ethyl phosphate* (**19**; 40%) obtained after evaporation and washing with hexane. Data: *Table 4*.

Table 4. *Properties of Nucleotide Analogues*

Nucleotide	M.p. [°C]	λ_{max}(EtOH) [nm]	R_f	E_m^{Tp}(pH 8)
19	85– 88	258	0.52[a])	–
21	130–132	258	0.32[a])	–
23	90– 93	259	0.67[a])	–
24	105–107	258	0.67[a])	–
20	–	258	0.40[b])	0.25
22	–	258	0.49[b])	0.25
25	–	259	0.37[b])	0.24
26	–	259	0.37[b])	0.24
27	–	260	0.45[b])	0.23
28	–	259	0.48[b])	0.22
29	–	260	0.46[b])	0.21
30	–	260	0.41[b])	0.23

[a]) Solvent for TLC: $CHCl_3$/EtOH 6:1.
[b]) Solvent for paper chromatography: i-PrOH/NH_4OH/H_2O 7:1:2.

Compound **19** was deprotected *a*) with 1% benzenesulfonic acid in CH_3CN (MeOTr group), *b*) by Zn-Cu couple in DMF at 55° for 10 h [27] (CCl_3CH_2 group), and *c*) with Bu_4NF at 25° for 2 h ((*t*-Bu)Me_2Si group) to afford *2-[1-(adenin-9-yl)-2-hydroxyethoxy]ethyl 2-(adenin-9-yl)-2-(2-hydroxyethoxy)ethyl phosphate* (**20**; 35%), m.p. > 300°. Data: *Table 4*.

Mixed Nucleotides **27**–**30**. Using the methods for the protection of adenosine and *ara*-A [32] [33] 5'-*O*-(monomethoxytrityl)-2'-*O*-[(*tert*-butyl)dimethylsilyl]adenosine, 5'-*O*-(monomethoxytrityl)-2'-*O*-[(*tert*-butyl)dimethylsilyl]-arabinoadenosine, and 2',3'-disilylated derivatives of ribo- and arabinoadenosine were prepared. These compounds were condensed with acyclo-nucleosides **16** or **18** to afford the corresponding dinucleotides **27**–**30** after complete deprotection by the same method as described above. Data: *Table 4*.

Enzyme Assays. The procedures used for adenosine deaminase, snake venom and spleen phosphodiesterases have been described previously [14]. The results are collected in *Table 1* and *Scheme 4*.

Aminoacylation of Cyclo- and Acyclo-nucleosides: Compounds **31**–**41**. Representative procedure: Adenosine (0.27 g, 1 mmol) was dissolved with gentle heating in dry DMF (10 ml). Then, THF (10 ml) and quinoline (0.129 g,

1 mmol) were added, and the mixture was cooled to 10°. A soln. of phthalimidoacetyl chloride (0.223 g, 1 mmol) in dry THF (1 ml) was added dropwise during 10 min and the mixture stirred at 25° for 3 h. The solvent was then evaporated at 50°. The residue was dissolved in a minimum of $CHCl_3$ and applied to a short silica-gel column (12 × 2 cm). Elution with $CHCl_3$ removed impurities, and *5'-O-(2-phthalimidoacetyl)-adenosine* (**31a**; 80%) was eluted with AcOEt/acetone 1:1. Data: *Table 3.* IR (nujol): 1750 (ester), 1720 (amide).

Compound **31a** (0.454 g, 1 mmol) was then dissolved in pyridine (1 ml), and 10 equiv. of 0.5 M phenylhydrazine in pyridine/AcOH 3:2 were added. After 1 h, pentane-2,4-dione (10 equiv.) was added with cooling. Solvents were removed, and the residue was suspended in $CHCl_3$ to dissolve impurities. The precipitate was filtered and washed with $CHCl_3$ to afford *5'-O-glycyladenosine* (**32a**; 60%). Data: *Table 3.* IR (nujol): 1740 (ester). Anal. calc. for $C_{12}H_{16}N_6O_5$ (324.62): C 44.44, H 4.94, N 25.93; found: C 44.23, H 4.87, N 25.89.

Compound **40** was prepared from **18** *via* **39** by the same method. After treatment with Bu_4NF, **41** was obtained. Data: *Table 3.*

Retinoic-Acid Derivatives **42** *and* **43**. Representative procedure (yields *ca.* 80%): Retinoic acid (0.3 g, 1 mmol) was dissolved in dry CH_2Cl_2 (20 ml) under a stream of N_2. Pyridine (0.2 g, 2.5 mmol) was added. A soln. of ClOOEt (0.11 g, 1.1 mmol) in 5 ml CH_2Cl_2 was added dropwise. The mixture was stirred for 15 min at 0°. Then, **38a** (0.28 g, 1 mmol) was added. After 1 h, the soln. was evaporated and the residue crystallized from Et_2O to afford *2-[(adenin-9-yl)methoxy]ethyl* N*-retinoylalaninate* (**42a**; 80%). Data: *Table 3.* IR (CH_2Cl_2): 3200–3400 (NH, NH_2), 1750 (ester), 1620 (amide).

N^1*-[(Adenin-9-yl)methoxy]ethyl-*N^2*-retinoylglycinamide* (**46**). Compound **8** was treated with phthalimidoacetyl chloride by the same method as described for the synthesis of **31a** to afford N*-2-[(adenin-9-yl)methoxy]ethyl-2-(phthalimido)acetamide* (**44**; 90%). Reaction of **44** with phenylhydrazine, (see preparation of **32a**) gave N^1*-{2-[(adenin-9-yl)methoxy]ethyl}glycinamide* (**45**; 80%). Then **45** was converted to **46** (78%) by the same procedure as described for the synthesis of **42a**. Data: *Table 3.*

Determination of Solubility. An excess of each compound (see *Table 2,* 10 mg) was agitated for 20 h in a 25-ml volumetric flask with 5 ml of 0.1 M phosphate buffer. The soln. was filtered from undissolved solids through a 4–5.5 mesh (ASTM) sintered glass funnel and the concentration of the solute determined by UV absorbance *(Table 2).*

Determination of Partition Coefficients (Lipophilicities). A soln. of each compound (see *Table 2,* 10 ml) in 0.1 M phosphate buffer possessing an absorbance of 2–2.8 at 260 nm was shaken with pentanol (10 ml) in a 50-ml separatory funnel for 1 h. The layers were separated and their concentrations determined by UV. The partition coefficient was calculated as $P = [S]_{pentanol}/[S]_{H_2O}$ *(Table 2).*

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