Regioselective Preparation of N^7- and N^9-Alkyl Derivatives of N^6-[(Dimethylamino)methylene]adenine Bearing an Active Methylene Group and Their Further Derivatization Leading to α-Branched Acyclic Nucleoside Analogues

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Keywords: Nucleosides / Acyclic analogues / Purines / Alkylations / ^{15}N NMR

N^7- and N^9-regioisomers of cyanomethyl and trifluoroethyl-N^6-[(dimethylamino)methylene]adenine (**1**, **2**, **6**, **7**) were prepared regioselectively, the former by the direct alkylation of N^6-[(dimethylamino)methylene]adenine, the latter by the alkylation of adenine followed by protection of the amino group. These derivatives, which bear an active methylene group, were submitted to reactions with allyl bromide, aldehydes or *tert*-butoxybis(dimethylamino)methane in order to modify their side chain. In this way, several new α-branched acyclic adenosine analogues (**8**, **10**–**16**) were prepared; the regioselectivity of the alkylation and the product structures were determined by ^{1}H- and ^{13}C-NMR spectroscopy. ^{15}N-NMR parameters for selected compounds were studied by gradient-enhanced inverse-detected techniques. In addition, X-ray data of derivatives **1**, **2** and **7** are reported.

Introduction

Analogues of nucleosides are intensively studied in the context of cancer therapy and viral diseases. In addition to their biological effects, new synthetic antimetabolites should exhibit high biological stability in target systems.[1] Acyclic analogues of nucleosides are characterized by significant resistance against chemical and biological degradation.[2] This is caused mainly by the absence of a glycosidic bond. A further advantage of this type of nucleoside analogues is the flexibility of the acyclic chain, which enables the compounds to adopt, on interaction with an enzyme, a conformation suitable for interaction with an active site of the enzyme or with a receptor.

Although a broad spectrum of acyclic analogues has already been studied,[3] very few analogues with α-branched side chains have been prepared.[4] The only exceptions are acyclic compounds with a C−O or C−S bond in the α-position, since they can be easily obtained from sugar derivatives.[5] Another synthetically advantageous route to such compounds is ring cleavage of carbocyclic analogues prepared by allylic substitution.[6] Other types of α-branched acyclic analogues of nucleosides are difficult to prepare by direct alkylation of a heterocyclic base[7] on account of competing elimination or low reactivity of the alkylation agent. The method of choice for their synthesis is usually either the Mitsunobu reaction[8] or building up of a purine base with a suitable amino derivative of the future side chain. The latter method was successfully used for the synthesis of the well-known α-branched biologically active compound *erythro*-9-(2-hydroxy-3-nonyl)adenine (EHNA) and its analogues.[9]

Preparation of α-branched analogues with various electron-withdrawing functional groups in the α-position is particularly difficult, since the elimination process during alkylation of the heterocyclic base is strongly preferred. In order to improve the methodology for the preparation of this type of acyclic nucleoside analogues, we investigated a complementary synthetic method based on further derivatization of *N*-substituted intermediary compounds bearing an active methylene group.

Results and Discussion

N^6-[(Dimethylamino)methylene]adenine[10] was used as a suitable purine derivative with a fully protected amino group. In order to introduce the active methylene group into the molecule, the heterocyclic base was alkylated under standard conditions by chloroacetonitrile, 2-iodo-1,1,1-trifluoroethane and ethyl bromoacetate in THF using NaH or DBU as a base (Scheme 1). Surprisingly, and in contrast with the literature (where formation of either 9-alkyl- or mixture of 7- and 9-alkyl derivatives of N^6-[(dimethylamino)methylene]adenine was reported),[11] only 7-alkyl isomers **1**, **2** and **3** were isolated and no alkylation at position 9 was observed.

The required *N*-protected 9-substituted derivatives had to be prepared by a different route: alkylation of unprotected

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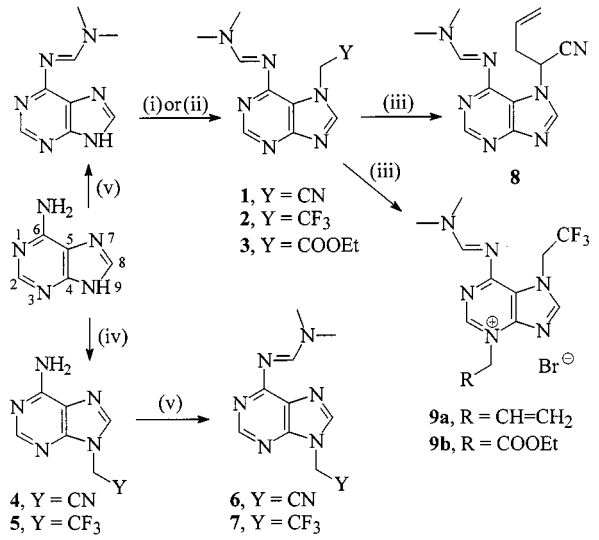
adenine with chloroacetonitrile or 2-iodo-1,1,1-trifluoroethane in DMF using NaH as a base led preferentially to 9-cyanomethyl (**4**) and 9-trifluoroethyl adenine (**5**), respectively. The amino group of both compounds was then protected by a standard procedure[10] with dimethylformamide dineopentyl acetal[12] to form the desired 9-substituted derivatives **6** and **7**.



Scheme 1. (i) 1. NaH/THF, 2. $ClCH_2CN$ or $BrCH_2COOEt$; (ii) 1. DBU/THF, 2. ICH_2CF_3; (iii) 1. NaH/THF, 2. allyl bromide (or $BrCH_2COOEt$ for **9b**); (iv) 1. NaH/DMF, 2. $ClCH_2CN$ or ICH_2CF_3; (v) DMF dineopentyl acetal/DMF

In order to determine the position of alkylation in N^6-[(dimethylamino)methylene]adenine, we applied an NMR method based on vicinal coupling constants J(C,H) of α-methylene protons of substituents to certain carbon atoms of the purine ring; such coupling can be observed in proton-coupled ^{13}C-NMR spectra.[13] Selective heteronuclear decoupling was then used to assign the observed couplings. The unequivocal structural assignment of the adenine quaternary carbon atoms follows from characteristic vicinal J(C,H) coupling to protons H-2 and H-8. The additional vicinal couplings (2.5 to 5 Hz) of α-methylene protons to carbon atoms [C-5 and C-8], [C-4 and C-8] or [C-2 and C-4] indicate N^7-, N^9- or N^3-alkylation, respectively. The N^7- and N^9-alkylated compounds can also be distinguished by the size of vicinal couplings of H-8 to C-4 and C-5, as a result of the different N=CH double bond position. Characteristic values of J(H-8,C-4) and J(H-8,C-5) are 12.5 and 4.0 Hz for N^7-regioisomers and 4.5 and 11.5 Hz for N^9-substituted compounds.[14]

Comparison of ^{13}C chemical shifts (Table 1) in pairs of N^7- and N^9-substituted N^6-[(dimethylamino)methylene]-adenines shows systematic differences with the largest values for carbon atoms C-4 (downfield shifts of 6.6 to 9.7 ppm) and C-5 (upfield shifts of −5.4 to −8.5 ppm) and moderate shifts of opposite signs at C-6 (*ca.* −4.5 ppm) and C-8 (*ca.* +4.5 ppm).

Regioselectivity of the alkylation at the N^7-position motivated our interest in the tautomeric equilibrium of N^6-[(dimethylamino)methylene]adenine. The ^{13}C-NMR spectrum of this compound measured at 0°C in CD_3OD showed coupling constants J(H-8,C-4) = 9.5 Hz and J(H-8,C-5) = 7.4 Hz, corresponding to a time-averaged contribution of both N^7−H and N^9−H tautomers. Using data from N^7- and N^9-isomers we can estimate *ca.* 60% population of the N^7−H tautomer. This value is significantly higher compared to the value of about 15% of the N^7−H tautomer determined for adenine.[15]

Various conditions were examined for further alkylation of compounds **1**, **2**, **3**, **6** and **7**. Allyl bromide was used as a model alkylating agent. NaH, DBU and LDA were tested for the deprotonation of the active methylene group. Reaction conditions LDA/THF/−70°C and NaH/DMF/80°C led to very complex mixtures. The best results were obtained when the 7-substituted derivative and one equivalent of NaH were suspended in THF, sonicated for 10 min, heated, and then allyl bromide added. Under these conditions, the cyano derivative **1** afforded the desired compound **8** in a yield of 66%. This product is a suitable starting material for the preparation of various acyclic analogues of N^7-regioisomers of nucleosides[16] by further reactions on allyl and/or cyano groups that are now under study.

Surprisingly, the course of the allylation of the trifluoroethyl derivative **2** under the aforementioned conditions was completely different and led to quaternization of N-3 to form the 7,3-disubstituted compound **9a**. The same results were obtained when ethyl bromoacetate was used instead of allyl bromide (compound **9b**, Scheme 1).

In further reactions 7-[(ethoxycarbonyl)methyl]-N^6-[(dimethylamino)methylene]adenine (**3**) afforded only inseparable mixtures. Thus, a transformation of the cyano derivative would be a better choice for the preparation of carboxylic acid derivatives.

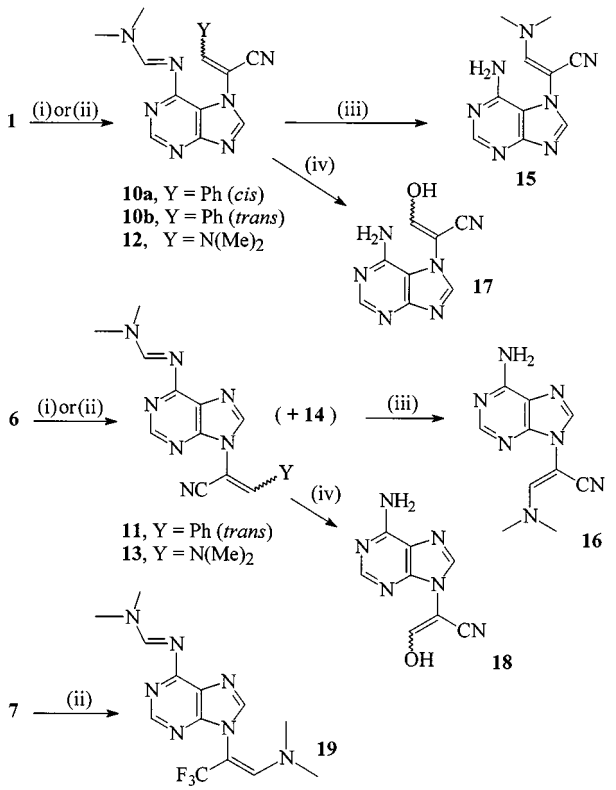
All attempts to carry out an allylation reaction on 9-substituted derivatives fell short of our expectations; only traces of desired products were detected in complex reaction mixtures. The limited applicability of this method seems to be caused by the lower stability of the dimethylaminomethylene protecting group in compounds **6** and **7**. Formation of easily cleavable N^6-formyl derivatives was observed during their preparation.

In order to prepare highly functionalised 7- and 9-vinyladenine derivatives, introduction of a double bond into the α-position can be achieved by condensation with an aldehyde. Compounds **1** and **6**, which bear an active methylene group, were treated with sodium hydride. The reaction with benzaldehyde afforded the expected 1-cyano-2-phenylvinyl derivatives **10** and **11** of adenine in moderate yields (Scheme 2). In the case of 7-substituted derivative **10**, *cis*-**10a** and *trans*-**10b** isomers were separable by preparative TLC. In contrast, only the *trans* form of 9-substituted derivative **11** was isolated. While no reaction of cyano derivatives **1** and **6** with crotonaldehyde was detected (probably due to self-condensation of this particular aldehyde), their condensation with methacrolein afforded a complex mixture of products.

Table 1. ^{13}C-NMR data of compounds **1**−**19** in [D_6]DMSO

Comp.	C-2	C-4	C-5	C-6	C-8	N=CH	N−CH_3	CN (CF_3)	C-1′	C-2′
N-7 regioisomers										
1	152.96	160.80	116.45	155.03	146.57	156.76	40.92; 35.04	116.68	35.34	–
2	152.70	160.48	116.71	154.90	147.16	156.65	40.91; 34.83	(123.80)	46.56	–
8 [a]	152.85	161.08	116.10	154.71	145.86	157.00	41.07; 35.38	117.70	47.28	37.50
9a [b]	147.81	149.56	116.58	157.24	149.14	156.91	42.33; 36.30	(123.26)	46.81	–
10a (*cis*)[c]	153.65	160.92	116.11	155.18	145.91	156.81	40.81; 34.89	117.07	107.45	143.95
10b (*trans*)[d]	153.31	160.95	117.04	154.87	146.96	156.71	40.85; 34.82	115.93	106.56	144.51
12 (*cis*)	153.01	160.66	119.18	155.35	149.42	156.55	40.67; 34.68; 41.4 (2C)*	121.38	75.53	148.48
12 (*trans*)	152.55	160.63	118.24	155.00	148.74	156.38	40.67; 34.52; 41.4 (2C)*	119.65	75.36	152.88
15	152.96	159.18	111.89	151.68	148.20	–	41.5 (2C)*	119.33	72.18	153.46
17	152.25	158.87	113.00	152.22	147.74	–	–	125.00	76.44	171.97
N-9 regioisomers										
5	153.35	149.96	118.31	156.33	141.04	–	–	(123.82)	43.46	–
6	152.57	151.25	125.00	159.50	142.11	158.32	40.86; 34.75	115.83	31.23	–
7	152.64	151.87	124.82	159.58	142.80	158.29	40.82; 34.71	(123.85)	43.51	–
11 [e]	152.94	151.28	125.25	159.75	142.47	158.29	40.93; 34.84	114.51	104.18	141.46
13 (*cis*)	153.14	154.02	124.67	159.68	145.15	158.29	40.86; 34.74; 41.5 (2C)*	120.78	70.99	149.80
13 (*trans*)	152.58	152.88	124.88	159.47	144.73	158.22	40.82; 34.71; 41.5 (2C)*	119.03	70.72	153.27
14	152.68	153.22	120.49	149.82	146.84	–	41.5 (2C)*	118.70	70.18	153.49
16	153.22	150.89	118.34	156.26	142.87	–	41.5 (2C)*	119.04	70.78	153.20
18	152.44	150.54	118.44	155.98	143.96	–	–	124.37	75.83	170.00
19	153.12	155.19	124.55	159.64	146.00	158.25	40.80; 34.69; 41.5 (2C)*	(124.98)	86.06	142.15

Additional signals: [a] 120.58 (C-3′), 131.43 (C-4′). − [b] N^3 substituent: 51.68 (NCH_2), 131.56 (CH), 120.06 (CH_2). − [c] 131.51, 131.33, 129.59 (2C), 129.34 (2C) (C_6H_5). − [d] 131.80, 130.94, 129.46 (2C), 129.25 (2C) (C_6H_5). − [e] 131.67, 131.06, 129.43 (2C), 129.33 (2C) (C_6H_5). − * The −$N(CH_3)_2$ carbon atom signals (C in the side chain) were detected as very broad signals at higher temperature (50°C).



Scheme 2. (i) 1. NaH/THF, 2. PhCHO; (ii) *tert*-butoxybis(dimethylamino)methane/DMF; (iii) NH_3/MeOH; (iv) 1. CF_3COOH/H_2O, 2. NH_3/MeOH

Introduction of a double bond into the α-position was accomplished by a smooth reaction of cyanomethyl derivatives **1** and **6** with *tert*-butoxybis(dimethylamino)methane,[17] and mixtures of *cis* and *trans* isomers were isolated in both cases. An N^6-protecting group of each of the obtained [1-cyano-2-(dimethylamino)vinyl]adenines **12** and **13** was quantitatively cleaved by methanolic ammonia at room temperature to form free nucleoside analogues **15** and **16**. Complete deprotection of compounds **12** and **13** by trifluoroacetic acid and methanolic ammonia led to the enol forms of aldehydes **17** and **18** in moderate yields. The NMR and IR spectra demonstrated the enol character of these derivatives.

Trifluoroethyl derivatives **2** and **7** were also submitted to the reaction with *tert*-butoxybis(dimethylamino)methane. In the case of 7-substituted derivative **2** no reaction was observed, but the 9-regioisomer **7** afforded the *cis* product **19** in low yield.

Since the preparation of the derivatives **10**−**19** may lead to both the *cis* and *trans*-configuration at the trisubstituted double bond, the NMR assignment was derived on the basis of the value of vicinal coupling constant between the olefinic proton and the carbon atom of the cyano group. The values of *J*(**H**−C=C−**C**N) in the range 9.2−12.7 Hz were assigned to *trans* isomers while values of 3.4−5.9 Hz were taken as indicative of *cis* isomers.[14]

This method failed in the cases of compounds **17** and **18** due to extreme broadening of the carbon signals (probably the result of medium rate *cis*/*trans* isomerism *via* the keto form). Dynamic effects also exert a strong influence on the

appearance of the $N-CH_3$ signals of the fragment $-C(-CX)=CH-N(CH_3)_2$ in both *cis* and *trans isomer*s of compounds **12**−**16** and **19**: a very broad signal due to the $N(CH_3)_2$ methyl protons at δ 3.15 in the ^{1}H-NMR spectra (at room temp.) and a carbon signal as a broad peak at δ 41.5 only at elevated temperature (50°C) was observed. On the other hand, *N*-methyl groups of the $-N=CH-N(CH_3)_2$ substituent at position 6 give two sharp signals in both ^{1}H- and ^{13}C-NMR spectra, indicating slow exchange of methyl groups due to hindered rotation around C−N bond.

In order to further study the electron distribution, its influence on physicochemical parameters and structural arrangement for different substitution patterns, ^{15}N-NMR and X-ray analyses were carried out for selected compounds. Although gradient-enhanced ^{1}H-^{15}N-NMR experiments have recently become a routine tool for structure elucidation of nitrogen-containing organic compounds, there is a lack of data in nucleoside chemistry. Here we present the first application of the phase-sensitive ^{1}H-^{15}N-GSQMBC[18][19] technique in the chemistry of purine derivatives, a technique that offers an advantage over standard ^{1}H-^{15}N HMBC experiments for the study of such a class of compounds.

The assignment of the observed ^{15}N chemical shifts and selected ^{1}H-^{15}N long-range coupling constants are summarized in Table 2 (for numbering of atoms see the ORTEP drawing in Figure 1). The nitrogen atoms in the purine moiety gave significant correlation signals with the H-2 and H-8 hydrogen atoms. Unequivocal assignment of N-1 *vs.* N-3 was based on the observation of an interaction between the H-11 and N-1 atoms and the assignment of nitrogen atoms N-7 and N-9 was based on the observation of correlation signals with hydrogen atoms of the $N-CH_2$ group.

The nitrogen atom N-3 in compounds **1** and **2** is significantly deshielded (Δ 22 ppm) in comparison with N-3 for structures **6** and **7**. On the other hand, nitrogen atom N-10 is deshielded in compounds **6** and **7** in comparison with compounds **1** and **2**. This seems to be one of the typical characteristics for the resolution of N-7 *vs.* N-9 regioisomers of the compounds investigated. These findings are in good agreement with previously published data concerning purines.[20]

The chemical shift of positively charged nitrogen atom N-3 (δ = 166.4) in compound **9a** is in accordance with such a structural and electronic arrangement. Although the signal for nitrogen atom N-10 is situated in the resonance frequency range similar to those observed for compounds **1**, **2** and **6**, **7**, the presence of a positively charged nitrogen atom N-3 clearly manifests itself by significant deshielding (Δ 27 ppm for **9a** vs. **1**, **2**) of the N-12 nitrogen atom at the end of the conjugated system (Table 2).

Results of X-ray structure analyses[21][22] for compounds **1**, **2** and **7** (Figure 1) indicate that in the N^9-substituted compound **7** both purine rings are planar (in agreement with the reference[23]), while in the N^7-substituted derivatives the $N^7-C^8-N^9$ moiety is substantially displaced from the plane of the six-membered ring. The substituent in position 6 is, in all cases, in plane with the six-membered ring, while the substituent in position 7 or 9 tends to be out of the approximate plane of purine: torsion angle defined by atoms C8, N7 (or N9), C15, C16 is −109° in **1**, −90° in **2**, and −74° in **7**.

Conclusion

In conclusion, the dramatic effect of N^6-(dimethylamino)-methylene protection of the amino group on regioselectivity of alkylation was confirmed. The protected adenine derivative selectively gives, under the conditions used, 7-substituted isomers, while alkylation of adenine affords 9-substituted derivatives. Further alkylation of the active methylene group of these compounds led in most cases to complex mixtures. Synthetically applicable reactions are the introduction of an allyl moiety into the α-position of 7-cyanomethyl-N^6-[(dimethylamino)methylene]adenine (**1**) and condensation of 7- and 9-cyanomethyl derivatives **1** and **6** with *tert*-butoxybis(dimethylamino)methane. The resulting compounds can be used as starting materials for acyclic adenosine analogues or PNA synthesis.

Table 2. ^{15}N-NMR chemical shifts (ppm) and selected ^{1}H-^{15}N coupling constants (Hz) for compounds **1**, **2**, **6**, **7** and **9a** in [D$_6$]DMSO at 303 K

Chemical shifts [δ] Comp.	N-1	N-3	N-7	N-9	N-10	N-12	N-17
1	248.3	256.4	141.1	248.7	202.1	107.2	253.1
2	249.1	256.5	138.9	249.8	202.1	106.6	-
6	252.2	234.3	246.6	146.2	211.2	105.2	253.2
7	252.8	234.6	247.4	145.2	211.4	105.0	-
9a	245.3	166.4	149.5	236.1	205.1	134.1	−

Coupling constants [Hz]	H2,N1	H2,N3	H8,N7	N8,N9	H11,N10	H11,N12	H13,N12	H14,N12	H15,N17
1	15.7	15.0	7.9	12.1	2.6	6.6	2.3	2.3	2.3
2	15.5	14.9	8.1	12.0	3.6	6.5	3.4	3.3	−
6	15.4	15.4	12.3	8.5	2.8	6.8	2.8	2.7	2.9
7	15.5	15.5	12.0	8.5	3.6	6.6	3.8	3.8	−
9a	13.4	6.8	7.8	12.2	3.3	5.6	3.0	2.8	−

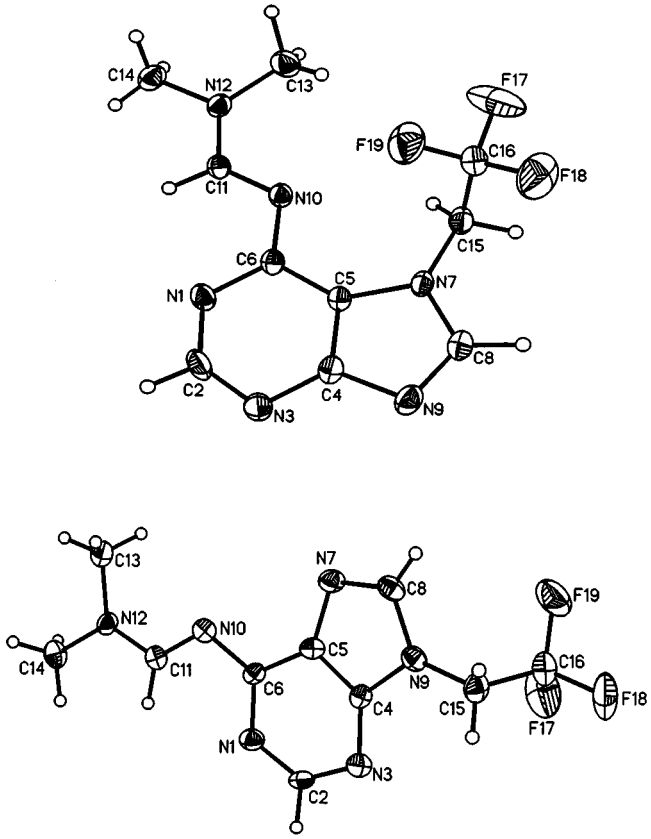


Figure 1. ORTEP view of 7- and 9-regioisomers **2** and **7**

The target compounds were prepared within the framework of our studies into structure/activity relationships in the series of acyclic adenine nucleoside analogues. The cytostatic assays were performed by Dr. I. Votruba at the Institute of Organic Chemistry and Biochemistry, Prague. Neither of the compounds exhibited significant cytostatic activity or cytotoxicity in L-1210 mouse leukemia cells. *In vitro* effects against the DNA viruses and retroviruses were examined at the Rega Institute for Medical Research (Head, Professor E. De Clercq), Catholic University Leuven (Belgium), and only compound **10** had a weak effect (IC_{50} 4 μg/mL) on TK^+ VZV.[24]

Experimental Section

General Remarks: Melting points were determined on a Kofler block and are uncorrected. − Chromatography was performed on silica gel (230−400 mesh). Analytical TLC was performed on Silufol UV_{254} plates (Kavalier Votice, Czech Republic). Preparative TLC was carried out on 40 × 17 × 0.4 cm loose-layer plates of silica gel containing UV indicator. − IR spectra were obtained on Bruker IFS 88. − Mass spectra were obtained with a ZAB-EQ (VG Analytical) spectrometer using the FAB technique (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). − Paper electrophoresis was performed on Whatman No.3 MM paper at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogen carbonate (TEAB) at pH 7.5; the electrophoretical mobilities are referenced to uridine 3′-phosphate. − ^{1}H- and ^{13}C-NMR spectra were measured on a Varian UNITY 500 spectrometer (^{1}H at 499.88; ^{13}C at 125.71 MHz) at room temperature (293 K) in [D_6]DMSO referenced to the solvent signal (δ = 2.5 for ^{1}H and δ = 39.7 for ^{13}C NMR). − ^{15}N-NMR spectra were recorded in [D_6]DMSO using a Bruker Avance DRX 500 spectrometer operating at frequencies of 500.13 MHz (^{1}H) and 50.68 MHz (^{15}N). The temperature of measurement was 303 K. Sample concentrations ranged between 20−50 mg/500 μL. The ^{15}N chemical shifts were referenced to the signal of 1 M urea[25] in [D_6]DMSO (δ = 77.0). The final digital resolution was better than 1 Hz and 10 Hz in the ^{1}H and ^{15}N dimensions, respectively. For a detailed description of parameters see ref.[26] − X-ray crystallographic studies: for a detailed description of parameters see refs.[21][22]

7-(Cyanomethyl)-N^6-[(dimethylamino)methylene]adenine (1) and 7-[(Ethoxycarbonyl)methyl]-N^6-[(dimethylamino)methylene]adenine (3). − General Procedure: A mixture of N^6-[(dimethylamino)methylene]adenine[10] (7.1 g, 37.4 mmol), sodium hydride (1.45 g, 37.8 mmol, 60% dispersion in mineral oil) and tetrahydrofuran (100 mL) was sonicated for 10 min and then refluxed for 3.5 h. After cooling the mixture to room temperature, chloroacetonitrile (for **1**, 6 mL, 94.8 mmol) or ethyl bromoacetate (for **3**, 4.8 mL, 43.6 mmol) was added and the stirring at room temperature was continued for 24 h. The solvent was evaporated.

Compound 1: The residue was dissolved in hot methanol, decolorized with charcoal, filtered through a pad of Celite and the solvent removed. The residue was crystallized from ethanol. Yield: 4.35 g (51%), m.p. 203−204°C. − ^{1}H NMR: δ = 8.95 (s, 1 H, NCH), 8.47 (s, 1 H, H-2), 8.46 (s, 1 H, H-8), 5.70 (s, 2 H, H-1′), 3.23 and 3.19 (2 × s, 2 × 3 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − ^{15}N NMR: see Table 2. − $C_{10}H_{11}N_7$ (229.2): calcd. C 52.39, H 4.84, N 42.77; found C 52.67, H 4.89, N 42.54. − FAB MS; *m/z* (rel.%): 230 (80) $[M + H]^+$. − X-ray Crystallographic Study:[21] for selected data see ref.[22]

Compound 3: Chromatography (1% methanol in chloroform) afforded the crude product, which was crystallized from ethanol/diethyl ether. Yield: 3.74 g (36%), m.p. 176−179°C. − ^{1}H NMR: δ = 8.87 (s, 1 H, NCH), 8.43 and 8.33 (2 × s, 2 × 1 H, H-2 and H-8), 5.37 (s, 2 H, H-1′), 4.14 [q, 2 H, $J(CH_2,CH_3)$ = 7.0 Hz, OCH_2], 3.19 and 3.06 (2 × s, 2 × 3 H, 2 × NCH_3), 1.17 [t, 3 H, $J(CH_3,CH_2)$ = 7.0 Hz, CH_3]. − $C_{12}H_{16}N_6O_2$ (276.3): calcd. C 52.17, H 5.84, N 30.427; found C 51.99, H 5.87, N 30.21. − FAB MS; *m/z* (rel.%): 277 (100) $[M + H]^+$.

7-(2,2,2-Trifluoroethyl)-N^6-[(dimethylamino)methylene]adenine (2): A mixture of N^6-[(dimethylamino)methylene]adenine[10] (3.67 g, 19.3 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.9 mL, 19.4 mmol) and tetrahydrofuran (30 mL) was sonicated for 10 min and then refluxed for 45 min. 2-Iodo-1,1,1-trifluoroethane (2.85 mL, 28.9 mmol, 1.5 equiv.) was added and stirring at 70°C was continued for 18 h. The solvent was evaporated and chromatography of the residue (2% of methanol in chloroform) afforded the pure product, which was crystallized from ethanol/light petroleum. Yield: 1.68 g (32%), m.p. 158−160°C. − ^{1}H NMR: δ = 8.95 (s, 1 H, NCH), 8.49 and 8.48 (2 × s, 2 × 1 H, H-2 and H-8), 5.59 [q, 2 H, $J(1',F)$ = 9.1 Hz, H-1′], 3.22 and 3.11 (2 × s, 2 × 3 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − ^{15}N NMR: see Table 2. − $C_{10}H_{11}N_6F_3$ (272.2): calcd. C 44.12, H 4.07, N 30.87; found C 44.26, H 4.10, N 31.12. − FAB MS; *m/z* (rel.%): 273 (100) $[M + H]^+$. − X-ray crystallographic study:[21] for selected data see ref.[22]

9-(Cyanomethyl)adenine (4): A mixture of adenine (9.8 g, 72.6 mmol), sodium hydride (2.8 g, 73.0 mmol, 60% dispersion in mineral oil) and dimethylformamide (200 mL) was sonicated for 10 min and then heated at 100°C for 2 h. After cooling the mixture to room temperature, chloroacetonitrile (6 mL, 94.8 mmol) in di-

methylformamide (20 mL) was added and the stirring at room temperature was continued for 3 d (some starting material could still be observed by TLC). The solvent was evaporated and the residue was codistilled with toluene. Chromatography (methanol/chloroform, 10.90) afforded the crude product, which was crystallized from ethanol. Yield: 5.43 g (43%), m.p. decomp. − ^{1}H NMR: δ = 8.21 (s, 2 H, H-2 and H-8), 7.40 (br. s, 2 H, NH_2), 5.44 (s, 2 H, H-1′). − $C_7H_6N_6$ (174.2): calcd. C 48.27, H 3.47, N 48.25; found C 48.52, H 3.55, N 47.92. − EI MS; *m*/*z* (rel.%):174 (100) [M].

9-(2,2,2-Trifluoroethyl)adenine (5): A mixture of adenine (3.0 g, 22.2 mmol), sodium hydride (0.85 g, 22.2 mmol, 60% dispersion in mineral oil) and dimethylformamide (50 mL) was sonicated for 10 min and then heated at 100°C for 1.5 h. After cooling the mixture to 70°C, 2-iodo-1,1,1-trifluoroethane (3.4 mL, 37.2 mmol) was added and stirring at 70°C was continued for 2 d (some starting material could still be observed by TLC). The solvent was evaporated and the residue was codistilled with toluene. Chromatography (methanol/chloroform, 5:95) afforded the crude product, which was crystallized from ethanol. Yield: 1.77 g (37%), m.p. 204−206°C. − ^{1}H NMR: δ = 8.21 and 8.19 (2 × s, 2 × 1 H, H-2 and H-8), 7.39 (br. s, 2 H, NH_2) 5.13 [q, 2 H, *J*(1′,F) = 9.4 Hz, H-1′). − ^{13}C NMR: see Table 1. − $C_7H_6N_5F_3$ (217.2): calcd. C 38.72, H 2.78, N 32.25, F 26.25; found C 39.20, H 2.84, N 32.08, F 26.37. − FAB MS; *m*/*z* (rel.%): 218 (100) $[M + H]^+$.

9-(Cyanomethyl)-*N*^{6}-[(dimethylamino)methylene]adenine (6) and 9-(2,2,2-Trifluoroethyl)-*N*^{6}-[(dimethylamino)methylene]adenine (7). − General Procedure: A stirred mixture of 9-(cyanomethyl)adenine (**4**, 0.97 g, 5.58 mmol) or 9-(2,2,2-trifluoroethyl)adenine (**5**, 1.21 g, 5.58 mmol) in dimethylformamide (15 mL) was heated up to 80°C. Dimethylformamide dineopentyl acetal[12] (2.5 mL, 10.8 mmol) was added and heating was continued for 3.5 h. After stirring at room temperature overnight, the reaction mixture was concentrated and codistilled with toluene. Solid CO_2 and ethanol were added to the residue and, after standing for 20 min, the solvent was evaporated. Chromatography (5% methanol in chloroform) afforded the crude product.

Compound 6: Yield: (crystallized from ethanol) 5.25 g (78%), m.p. 185−188°C. − ^{1}H NMR: δ = 8.94 (s, 1 H, NCH), 8.49 (s, 1 H, H-2), 8.32 (s, 1 H, H-8), 5.49 (s, 2 H, H-1′), 3.20 and 3.13 (2 × s, 2 × 3 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − ^{15}N NMR: see Table 2. − $C_{10}H_{11}N_7$ (229.2): calcd. C 52.39, H 4.84, N 42.77; found C 52.41, H 5.08, N 42.49. − FAB MS; *m*/*z* (rel.%): 230 (100) $[M + H]^+$.

Compound 7: Yield: 1.22 g (66%), m.p. 178−179°C. − ^{1}H NMR: δ = 8.92 (s, 1 H, NCH), 8.47 (s, 1 H, H-2), 8.32 (s, 1 H, H-8), 5.20 [q, 2 H, *J*(1′,F) = 9.3 Hz, H-1′], 3.20 and 3.13 (2 × s, 2 × 3 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − ^{15}N NMR: see Table 2. − $C_{10}H_{11}N_6F_3$ (272.2): calcd. C 44.12, H 4.07, N 30.87; found C 44.35, H 4.01, N 30.73. − FAB MS; *m*/*z* (rel.%): 273 (100) $[M + H]^+$. − X-ray Crystallographic Study:[21] for selected data see ref.[22]

7-(1-Cyano-3-butenyl)-*N*^{6}-[(dimethylamino)methylene]adenine (8): A mixture of **1** (4.28 g, 18.7 mmol), sodium hydride (0.72 g, 18.7 mmol, 60% dispersion in mineral oil) and tetrahydrofuran (70 mL) was sonicated for 10 min and then refluxed for 1.5 h. Allyl bromide (1.9 mL, 22.4 mmol) was added and the heating was continued for 3.5 h. The reaction mixture was concentrated and extracted with hot chloroform. Chromatography afforded the pure product, which was crystallized from ethanol. Yield: 3.32 g (66%), m.p. 192−194°C. − ^{1}H NMR: δ = 8.98 (s, 1 H, NCH), 8.56 and 8.49 (2 × s, 2 × 1 H, H-2 and H-8), 6.41 [t, 1 H, *J*(1′,2′) = 7.6 Hz, H-1′], 5.74 [ddt, 1 H, *J*(3′,2′) = 7.0 Hz, *J*(3′,4′*cis*) = 11.0 Hz, *J*(3′,4′*trans*) = 16.4 Hz, H-3′], 5.12 [brdq, 1 H, *J*(4′,2′) = *J*(gem) = 1.7 Hz, *J*(4′,3′) = 11.0 Hz, H-4′*cis*], 5.11 [brdq, 1 H, *J*(4′,2′) = *J*(gem) = 1.7 Hz, *J*(4′,3′) = 16.4 Hz, H-4′*trans*], 3.25 (s, 3 H, NCH_3), 3.23 [brdt, 1 H, *J*(2′a,1′) = 7.6 Hz, *J*(2′a, 3′) = 7.0 Hz, *J*(gem) = 13.9 Hz, H-2′a], 3.19 (s, 3 H, NCH_3), 3.14 [brdt, 1 H, *J*(2′b,1′) = 7.6 Hz, *J*(2′b,3′) = 7.0 Hz, *J*(gem) = 13.9 Hz, H-2′b]. − ^{13}C NMR: see Table 1. − $C_{13}H_{15}N_7$ (269.3): calcd. C 57.98, H 5.61, N 36.41; found C 57.83, H 5.62, N 36.56. − FAB MS; *m*/*z* (rel.%): 270 (100) $[M + H]^+$.

3-Allyl-7-(2,2,2-trifluoroethyl)-*N*^{6}-[(dimethylamino)methylene]-adeninium Bromide (9a) and 3-[(Ethoxycarbonyl)methyl]-7-(2,2,2-trifluoroethyl)-*N*^{6}-[(dimethylamino)methylene]adeninium Bromide (9b). − General Procedure: A mixture of **2** (0.7 g, 2.57 mmol), sodium hydride (0.1 g, 2.61 mmol, 60% dispersion in mineral oil) and tetrahydrofuran (15 mL) was sonicated for 10 min and heated at 60°C for 15 min. Allyl bromide (for **9a**, 0.3 mL, 3.47 mmol, 1.35 equiv.) or ethyl bromoacetate (for **9b**, 0.34 mL, 3.08 mmol, 1.2 equiv.) was added and the heating was continued for 5 h. The solvent was evaporated and the residue purified by preparative TLC (15% methanol in chloroform for **9a**, 20% methanol in chloroform for **9b**) to afford the pure product, which was triturated with acetone.

Compound 9a: Yield: 0.38 g, (38%). − ^{1}H NMR: δ = 9.22 (s, 1 H, NCH), 9.05 (s, 1 H, H-2), 8.93 (s, 1 H, H-8), 6.15 [ddt, 1 H, *J*(2″,3″*cis*) = 10.4 Hz, *J*(2″,3″*trans*) = 16.2 Hz, *J*(2″,1″) = 5.8 Hz, H-2″], 5.70 [q, 2 H, *J*(1′,F) = 8.8 Hz, H-1′], 5.33 [dq, 1 H, *J*(3″,1″) = *J*(gem) = 1.5 Hz, *J*(3″,2″) = 10.4 Hz, H-3″*cis*], 5.31 (dq, 1 H, *J*(3″,1″) = *J*(gem) = 1.5 Hz, *J*(3″,2″) = 16.2 Hz, H-3″*trans*], 5.15 [dt, 2 H, *J*(1″,2″) = 5.8 Hz, *J*(1″,3″*cis*) = *J*(1″,3″*trans*) = 1.5 Hz, H-1″], 3.42 and 3.29 (2 × s, 2 × 3 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − ^{15}N NMR: see Table 2. − FAB MS; *m*/*z* (rel.%): 313 (100) $[M - Br^-]^+$.

Compound 9b: Yield: 0.32 g, (35%). − ^{1}H NMR: δ = 9.28 (s, 1 H, NCH), 9.01 (s, 1 H, H-2), 8.92 (s, 1 H, H-8), 5.69 [q, 2 H, *J*(1′,F) = 8.9 Hz, H-1′], 5.47 (s, 2 H, H-1″), 4.23 [q, 2 H, *J*(CH_2,CH_3) = 7.3 Hz, OCH_2], 3.44 and 3.32 (2 × s, 2 × 3 H, 2 × NCH_3), 1.24 [t, 3 H, *J*(CH_3,CH_2) = 7.3 Hz, CH_3]. − FAB MS; *m*/*z* (rel.%): 359 (100) $[M - Br^-]^+$. − HR MS (FAB) $C_{14}H_{18}F_3N_6O_2$: calcd. 359.1443, found 359.1368.

7-(1-Cyano-2-phenylvinyl)-*N*^{6}-[(dimethylamino)methylene]adenine (10) and 9-(1-Cyano-2-phenylvinyl)-*N*^{6}-[(dimethylamino)methylene]-adenine (11). − General Procedure: A mixture of the cyanomethyl derivative (**1** or **6**, 0.34 g, 1.48 mmol), sodium hydride (60 mg, 1.56 mmol, 60% dispersion in mineral oil) and tetrahydrofuran (5 mL) was sonicated for 10 min and then heated at 70°C for 2 h. After cooling the mixture to room temperature, benzaldehyde (0.25 mL, 2.45 mmol) was added and the stirring at 70°C was continued for 3 h (in the case of the 7-isomer) or 20 h (in the case of the 9-isomer; some starting material could still be observed by TLC). The reaction mixture was concentrated and purified by chromatography (3% methanol in chloroform).

Compound 10: Yield: 0.22 g (47%, yellow foam) mixture of *cis* and *trans* isomer in the ratio 3:4. The isomers were separated by preparative TLC. − *cis* Isomer **10a**: ^{1}H NMR: δ = 8.91 (s, 1 H, NCH), 8.56 and 8.50 (2 × s, 2 × 1 H, H-2 and H-8), 8.06 (s, 1 H, H-2′), 7.38 (t, 1 H, arom. H), 7.29 (t, 2 H, arom. H), 6.85 (d, 2 H, arom. H), 3.19 and 3.13 (2 × s, 2 × 3 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − FAB MS; *m*/*z* (rel.%): 318 (100) $[M + H]^+$. − *trans* Isomer **10b**: ^{1}H NMR: δ = 8.91 (s, 1 H, NCH), 8.67 and 8.40 (2 × s, 2 × 1 H, H-2 and H-8), 7.96 (s, 1 H, H-2′), 7.91 (m, 2 H, arom. H), 7.59 (m, 3 H, arom. H), 3.18 and 3.03 (2 × s, 2 × 3 H,

2 × NCH_3). − ^{13}C NMR: see Table 1. − FAB MS; *m/z* (rel.%): 318 (100) $[M + H]^+$.

Compound 11: Yield: 0.14 g (30%, yellow solid), *trans* isomer, crystallization from wet ethanol afforded a white product (70 mg), m.p. 192−197°C. − ^1H NMR: δ = 8.96 (s, 1 H, NCH), 8.56 and 8.53 (2 × s, 2 × 1 H, H-2 and H-8), 8.18 (s, 1 H, H-2′), 7.91 (m, 2 H, arom. H), 7.61 (m, 3 H, arom. H), 3.23 and 3.16 (2 × s, 2 × 3 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − $C_{17}H_{15}N_7.1/2\ H_2O$ (326.4): calcd. C 62.56, H 4.94, N 30.04; found C 62.24, H 4.81, N 29.85. − FAB MS; *m/z* (rel.%): 318 (100) $[M + H]^+$.

7-[1-Cyano-2-(dimethylamino)vinyl]-N^6-[(dimethylamino)-methylene]adenine (12): A mixture of **1** (2.12 g, 9.26 mmol), *tert*-butoxybis(dimethylamino)methane (5 mL, 24.21 mmol, 2.6 equiv.) and dimethylformamide (10 mL) was stirred for 3 h at 80°C under argon and then at room temp. overnight. The mixture was concentrated and codistilled with toluene. Crystallization from ethanol/ether afforded the product as a mixture of *cis* and *trans* isomers in the ratio 1:2. Yield: 1.83 g (70%). − *cis* isomer: ^1H NMR: δ = 8.90 (s, 1 H, NCH), 8.47 and 8.43 (2 × s, 2 × 1 H, H-2 and H-8), 7.35 (s, 1 H, H-2′), 3.21 and 3.13 (2 × s, 2 × 3 H, 2 × NCH_3), 2.65 (br. s, 6 H, 2 × NCH_3); *trans* isomer: ^1H NMR: δ = 8.87 (s, 1 H, NCH), 8.44 and 8.32 (2 × s, 2 × 1 H, H-2 and H-8), 7.38 (s, 1 H, H-2′), 3.20 and 3.16 (2 × s, 2 × 3 H, 2 × NCH_3), 2.13 (br. s, 6 H, 2 × NCH_3). −^{13}C NMR: see Table 1. − $C_{13}H_{16}N_8$ (284.2): calcd. C 54.92, H 5.67, N 39.41; found C 54.60, H 5.59, N 39.58. − FAB MS; *m/z* (rel.%): 285 (100) $[M + H]^+$.

9-[1-Cyano-2-(dimethylamino)vinyl]-N^6-[(dimethylamino)-methylene]adenine (13), 9-[1-Cyano-2-(dimethylamino)vinyl]-N^6-formyladenine (14) and 9-[1-Trifluoromethyl-2-(dimethylamino)vinyl]-N^6-[(dimethylamino)methylene]adenine (19). − General Procedure: A mixture of **6** (1.0 g, 4.37 mmol) or **7** (0.45 g, 1.65 mmol), *tert*-butoxybis(dimethylamino)methane (1.5 mL, 7.26 mmol, 1.7 equiv. or 4.4 equiv., respectively) and dimethylformamide (15 mL or 2 mL, respectively) was stirred for 3 h at 80°C under argon and then at room temp. overnight. The mixture was concentrated and codistilled with toluene. − Compounds **13** and **14**: Chromatography (5% methanol in chloroform) afforded the product as a mixture of *cis* and *trans* isomers in the ratio 1:3. Formyl derivative **14** (*trans* isomer) was isolated as a side product.

Compound 13: Yield: 1.06 g (85%). − *cis* Isomer: ^1H NMR: δ = 8.91 (s, 1 H, NCH), 8.47 and 8.33 (2 × s, 2 × 1 H, H-2 and H-8), 7.48 (s, 1 H, H-2′), 3.20 and 3.13 (2 × s, 2 × 3 H, 2 × NCH_3), 3.16 (br. s, 6 H, 2 × NCH_3). − *trans* Isomer: ^1H NMR: δ = 8.91 (s, 1 H, NCH), 8.44 and 8.22 (2 × s, 2 × 1 H, H-2 and H-8), 7.40 (s, 1 H, H-2′), 3.19 and 3.13 (2 × s, 2 × 3 H, 2 × NCH_3), 3.16 (br. s, 6 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − $C_{13}H_{16}N_8$ (284.2): calcd. C 54.92, H 5.67, N 39.41; found C 54.77, H 5.47, N 39.30. − FAB MS; *m/z* (rel.%): 285 (100) $[M + H]^+$.

Compound 14: Yield: 0.15 g (13%), m.p. 258−260°C. − ^1H NMR: δ = 11.39 (br. s, 1 H, NH), 9.95 (s, 1 H, CH=O), 8.63 and 8.52 (2 × s, 2 × 1 H, H-2 and H-8), 7.47 (s, 1 H, H-2′), 3.14 (br. s, 6 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − $C_{11}H_{11}N_7O$ (257.25): calcd. C 51.36, H 4.31, N 38.11; found C 50.96, H 4.09, N 37.84. − FAB MS; *m/z* (rel.%): 258 (30) $[M + H]^+$.

Compound 19: Preparative TLC (20% methanol in chloroform) afforded a product determined to be the *cis* isomer. Yield: 0.15 g (28%). − ^1H NMR: δ = 8.91 (s, 1 H, NCH), 8.45 (s, 1 H, H-2), 8.22 (s, 1 H, H-8), 7.26 (s, 1 H, H-2′), 3.20 and 3.13 (2 × s, 2 × 3 H, 2 × NCH_3), 2.52 (br. s, 6 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − $C_{13}H_{16}F_3N_7$ (327.3): calcd. C 47.70, H 4.93, N 29.96; found C 47.53, H 4.85, N 29.68. − FAB MS; *m/z* (rel.%): 328 (100) $[M + H]^+$.

7-[1-Cyano-2-(dimethylamino)vinyl]adenine (15) and 9-[1-Cyano-2-(dimethylamino)vinyl]adenine (16). − General Procedure: Compound **12** or **13** (0.3 g, 1.06 mmol) in methanolic ammonia (20 mL) was stirred for 24 h at room temperature. The solvent was evaporated, ethanol (20 mL) was added and the solid product was filtered off. − Compound **15**: Yield: 0.23 g (95%), m.p. 260−265°C, *trans* isomer. − ^1H NMR: δ = 8.21 and 8.20 (2 × s, 2 × 1 H, H-2 and H-8), 7.51 (s, 1 H, H-2′), 6.93 (br. s, 2 H, NH_2), 3.15 (br. s, 6 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − $C_{10}H_{17}N_7{\cdot}H_2O$ (247.3): calcd. C 48.58, H 5.30, N 39.65; found: C 48.24, H 5.46, N 39.33. − FAB MS; *m/z* (rel.%): 230 (100) $[M + H]^+$.

Compound 16: Yield: 0.20 g (82%), m.p. 268−270°C, *trans* isomer. − ^1H NMR: δ = 8.16 and 8.11 (2 × s, 2 × 1 H, H-2 and H-8), 7.37 (s, 1 H, H-2′), 7.29 (br. s, 2 H, NH_2), 3.15 (br. s, 6 H, 2 × NCH_3). − ^{13}C NMR: see Table 1. − $C_{10}H_{17}N_7$ (229.2) calcd. C 52.39, H 4.84, N 42.77; found C 52.12, H 4.89, N 42.51. − FAB MS; *m/z* (rel.%): 230 (100) $[M + H]^+$.

7-(1-Cyano-2-hydroxyvinyl)adenine (17) and 9-(1-Cyano-2-hydroxyvinyl)adenine (18). − General Procedure: Compound **12** or **13** (0.4 g, 1.41 mmol) was suspended in a mixture of water (20 mL) and trifluoroacetic acid (0.35 mL, 4.5 mmol) and stirred for 24 h at room temperature. The solvent was evaporated and the residue was codistilled with ethanol and dried under reduced pressure. Methanolic ammonia (20 mL) was added and the reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated, the residue was mixed with ethanol, filtered and the solvent was removed from the filtrate. Preparative TLC (acetone/water/ethanol/ethyl acetate, 1:1:1:4) afforded the pure product. − Compound **17**: Yield: 120 mg (42%), E_{Up} = 0.62, m.p. 186−190°C. − IR (KBr): HO−C=C−CN: $\tilde{\nu}$ = 2182 cm^{-1} (CN). − ^1H NMR: δ = 8.41 and 8.15 (2 × s, 2 × 1 H, H-2 and H-8), 7.97 (s, 1 H, H-2′), 6.52 (br. s, 2 H, NH_2). − ^{13}C NMR: see Table 1. − FAB MS; *m/z* (rel.%): 203 (100) $[M + H]^+$. − HR MS (FAB) $C_8H_6N_6O$: calcd. 203.0681, found 203.0675.

Compound 18: Yield: 90 mg (32%), E_{Up} = 0.63. − ^1H NMR: δ = 8.34 and 8.08 (2 × s, 2 × 1 H, H-2 and H-8), 7.83 (s, 1 H, H-2′), 7.06 (br. s, 2 H, NH_2). − ^{13}C NMR: see Table 1. − FAB MS; *m/z* (rel.%): 203 (100) $[M + H]^+$. − HR MS (EI) $C_8H_6N_6O$: calcd. 202.0603, found 202.0612.

Acknowledgments

This study was supported by the grants of the State Grant Agency of the Czech Republic No. 203/96/K001, No. 203/98/P026, grant of Ministry of Education VS 96 095 and by Gilead Sciences (Foster City, CA, U.S.A.).

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Received February 24, 1999
[O99113]