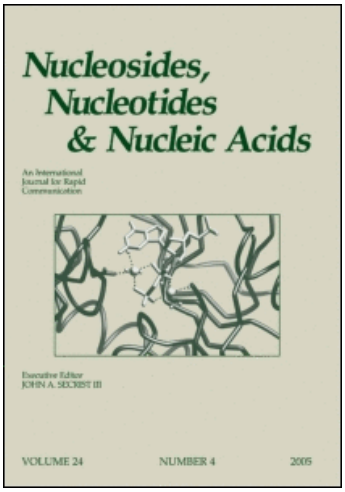

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Crystal Structure and Conformation of 8-(2-Hydroxyethylamino) and 8-(Pyrrolidin-1-yl) Adenosines

S. Belyakov[a]; E. Alksnis[a]; V. Muravenko[a]; I. Turovskis[a]; J. Popelis[a]; E. Lukevics[a]
[a] Latvian Institute of Organic Synthesis, Riga, Latvia

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CRYSTAL STRUCTURE AND CONFORMATION OF 8-(2-HYDROXYETHYLAMINO) AND 8-(PYRROLIDIN-1-YL) ADENOSINES

S. Belyakov, E. Alksnis, V. Muravenko, I. Turovskis, J. Popelis, and E. Lukevics
▫ *Latvian Institute of Organic Synthesis, Riga, Latvia*

▫ *In the course of investigation of 8-alkylamino substituted adenosines, the title compounds were synthesized as potential partial agonists for adenosine receptors. The structure determination of these compounds was carried out with the X-ray crystallography study. Crystals of 8-(2-hydroxyethylamino)adenosine are monoclinic, space group P 2_1; a = 7.0422(2), b = 11.2635(3), c = 8.9215(2) Å, β = 92.261(1)°, V = 707.10(3) Å^3, Z = 2; R-factor is 0.0339. The nucleoside is characterized by the anti conformation; the ribose ring has the C(2′)-endo conformation and gauche – gauche form across C(4′) – C(5′) bond. The molecular structure is stabilized by intramolecular hydrogen bond of N – H···O type. Crystals of 8-(pyrrolidin-1-yl)adenosine are monoclinic, space group C 2; a = 19.271(1), b = 7.3572(4), c = 11.0465(7) Å, β = 103.254(2)°, V = 1524.4(2) Å^3, Z = 4; R-factor is 0.0498. In this compound, there is syn conformation of the nucleoside; the ribose has the C(2′)-endo conformation and gauche – gauche form across C(4′) – C(5′) bond. The molecular structure is stabilized by intramolecular hydrogen bond of O – H···N type. For both compounds, the branching net of intermolecular hydrogen bonds occur in the crystal structures.*

Keywords Adenosines, X-ray diffraction

INTRODUCTION

The main problem restricting the therapeutic use of adenosine agonists is connected with their side effects, e.g., strong hypotensive and cardiac depressant action. Partial agonists could have several advantages compared to full agonists: higer receptor subtype selectivity, less side effects, induction of less receptor downregulation and desensitization.[1,2]

One of the posibilities for generation of a partial agonist for adenosine $\mathbf{A}_1$ receptors is the C8-substitution of purine moiety of adenosine, particularly, with an 9-alkylamino group.[1] Therefore, the new 8-aminosubstitutes adenosine derivatives

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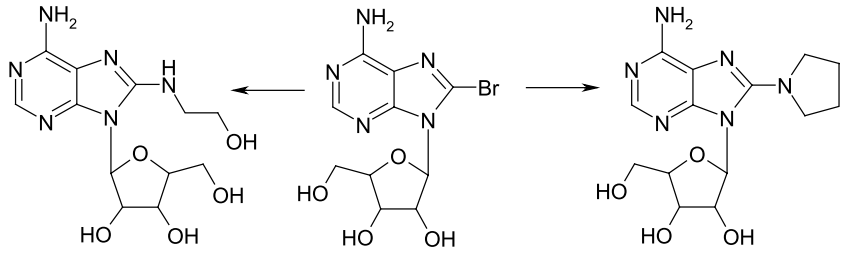
Address correspondence to S. Belyakov, Latvian Institute of Organic Synthesis, Aizkraukles 21, Riga LV-1006, Latvia.

have been synthesized—8-(hydroxy-ethylamino) (**1**) and 8-(pyrrolidin-1-yl)adenosine (**2**)—by heating of 8-bromadenosine with the excess of the corresponding amine.



1 **2**

As *anti* conformation of the ribose moiety in such type of compounds is thought to be essential for receptor binding,[3] the X-ray crystal structure study of the synthesized compounds has been performed to establish their conformation and thus to determine their suitability for further pharmacological and biochemical studies as new potential partial agonists of adenosine receptors.

EXPERIMENTAL METHODS

8-(2-Hydroxyethylamino)adenosine (1). 8-Bromoadenosine (3.46 g, 10 mmol) and 2-aminoethanol (6 mL, ca. 100 mmol) was stirred at 120°C overnight. Ten milliliters of water was added and the mixture neutralized (pH = 7) with acetic acid and cooled. Obtained crystals were recrystallized from water. Yield 1.55 g (45%). M.p. >210°C (decomp.). Anal. calcd. for $C_{12}H_{18}N_6O_5 \times {}^1\!/_2H_2O$ C, 42.98; H, 5.71; N, 25.06. Found C, 43.15; H, 5.76; N, 24.85.

^{1}H NMR spectrum of **1** was recorded on Varian Mercury 200MHz spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. ^{1}H NMR spectrum of **1** (δ, ppm, J, Hz): 3.29-3.50 (m, 2H, NCH_2), 3.50-3.68 (m, 4H, CH_2O, 5′-H), 3.96 (br.s, 1H, 4′-H), 4.12 (br.s, 1H, 3′-H), 4.63-4.82 (m, 2H, OH), 5.15-5.30 (m, 2H, 2′-H, OH), 5.82-5.93 (m, 2H,1′-H, OH), 6.54 (br.s, 2H, NH_2), 6.89 (t, 1H, NH, J = 10.5), 7.91 (s, 1H, purine-2H).

8-(Pyrrolidin-1-yl)adenosine (2). 8-Bromoadenosine (3.46 g, 10 mmol) and pyrrolidine (8.2 mL, 100 mmol) was refluxed overnight. 10 ml of water was added and the mixture neutralized (pH = 7) with acetic acid and cooled. Obtained crystals were recrystallized from water. Yield 1.12 g (33%). M.p. >185°C (decomp.). Anal. Calcd. for $C_{14}H_{20}N_6O_4$ C, 49.99; H, 5.99; N, 24.99. Found C, 49.87; H, 5.93; N, 25.14. ^{1}H NMR spectrum of **2** (δ, ppm, J, Hz) 1.89 (m, 4H, pyrrolidine-3,4), 3.51 (m, 4H, pyrrolidine-2,5), 3.64 (t, 2H, 5′-H), 3.94 (br.s, 1H, 4′-H), 4.17 (br.s, 1H, 3′-H), 5.08-5.20 (m, 2H, OH), 5.37 (d, 1H, 2′-H, J = 6.0), 5.71-5.92 (m, 2H,1′-H, OH), 6.84 (br.s, 2H, NH_2), 7.95 (s, 1H, purine-2H).

X-RAY STRUCTURE ANALYSIS

The monocrystals of **1** and **2** were grown from water. The crystal data, diffraction data collection parameters, and refinement information are summarized in Table 1. The data were collected on a Nonius KappaCCD diffractometer at room temperature (20 ± 2°C) using MoK$_\alpha$ radiation (λ = 0.71073 Å) by the φ and ω scan method. Accurate lattice parameters were determined from 1669 (for **1**) and 2402 (for **2**) reflections. Crystallographic computations were carried out with the Denzo-SMN program[4] of Bruker-Nonius. The structures were solved by an application of the multi solution methods using the programs SIR97[5] (for **1**) and SIR92[6] (for **2**). Absolute structures were determined using known chiral centers. The crystal structures were refined by full-matrix least-squares method using the SHELXL97[7] (for **1**) and maXus[8] (for **2**) programs. Minimized functional was $\Sigma w[|F_o|^2 - (1/k)|F_c|^2]$. Then, for the structure of **1**, a difference Fourier synthesis computed at this stage revealed all the hydrogen atoms in the molecule. The final round of refinement for **1** was performed with anisotropic thermal parameters for

TABLE 1 Crystal Data, Data Collection Parameters, and Refinement Details for **1** and **2**

	1	**2**
Empirical formula	$C_{12}H_{18}N_6O_5$	$C_{14}H_{20}N_6O_4$
Formula weight	326.313	336.352
Crystal shape, color	Plate, colorless	Prism, colorless
Crystal size (mm)	0.09 × 0.33 × 0.38	0.21 × 0.27 × 0.32
Crystal system	Monoclinic	Monoclinic
Space group	$P\,2_1$	$C\,2$
Unit cell parameters:		
a (Å)	7.0422(2)	19.271(1)
b (Å)	11.2635(3)	7.3572(4)
c (Å)	8.9215(2)	11.0465(7)
β (°)	92.261(1)	103.254(2)
V (Å^3)	707.10(3)	1524.4(2)
F (000)	344	712
Z	2	4
D_{calc} (g · cm^{-3})	1.533	1.466
μ (mm^{-1})	0.121	0.111
2θ range (°)	0-55	0-50
No. of measured reflections	3166	2402
No. of independent reflections	1701	1450
R_{int}	0.024	0.032
No. of observed reflections	1538	1291
Observed criterion expression	$I > 2\sigma(I)$	$I > 3\sigma(I)$
No. of variables refined	280	217
R-factor	0.0339	0.0498
R-index for all data	0.0392	0.0560
Weighted R-index on F^2	0.0853	0.1011
Weighting scheme	$w = 1/[\sigma^2(I) + 0.0546P + (0.0547P)^2]$, where $P = (\lvert F_o\rvert^2 + 2\lvert F_c\rvert^2)/3$	$w = 1/[\sigma^2(I) + 0.1\lvert F_o\rvert^2]$
$\Delta\rho_{max}$ (e · Å^{-3})	0.280	0.301
$\Delta\rho_{min}$ (e · Å^{-3})	−0.300	−0.243

the non-hydrogen atoms and isotropic thermal parameters for the hydrogen atoms. For the structure **2**, the positions of hydrogen atoms in the pyrrolidine cycle were calculated geometrically; all the other hydrogen atoms were located from difference synthesis. The hydrogen atoms in **2** were refined using a riding model. The molecular graphics were performed with the help of the program ORTEP.[9] The CCDC deposition numbers for the structures **1** and **2** are 265115 and 265116, respectively.

RESULTS AND DISCUSSION

There are only few examples of crystal structures of 8-substituted adenosines in literature. A search of the Cambridge Structural Database (CSD, Version 5.25) indicated that there are only 7 entries of 8-substituted derivatives from 48 crystal structures of adenosines and arabinofuranosyladenines. Figures 1 and 2 illustrate diagrams of the molecules **1** and **2** giving the atomic numbering scheme followed in the text. Table 2 lists the principal bond lengths and valence angles in **1** and **2**.

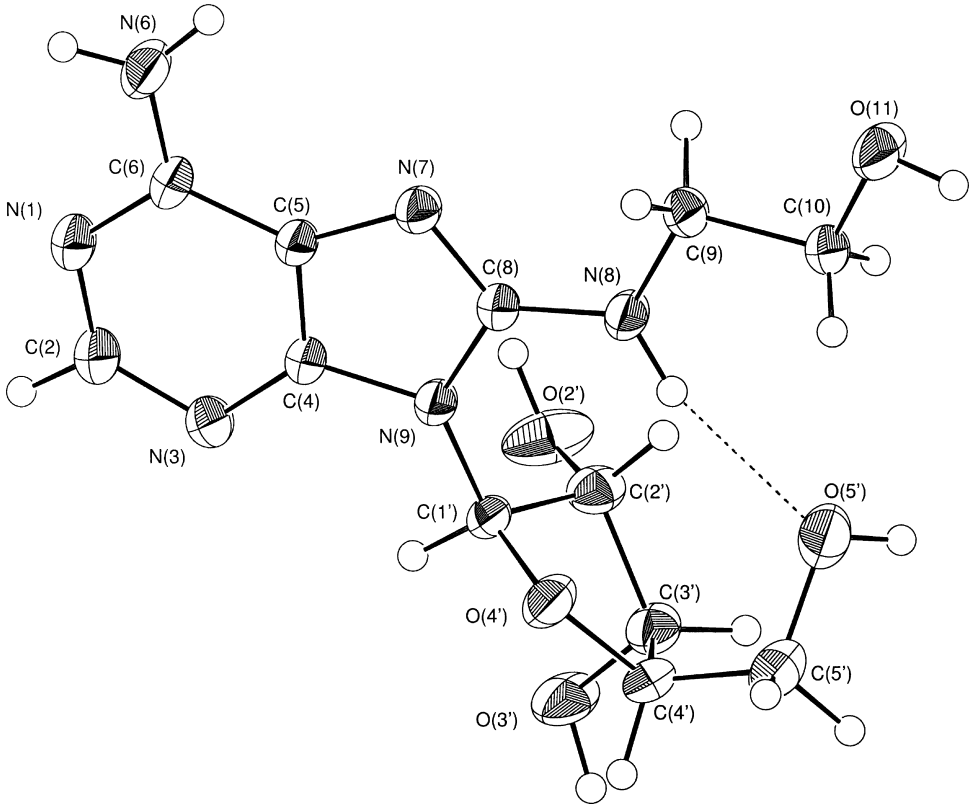


FIGURE 1 Molecular structure of **1**.

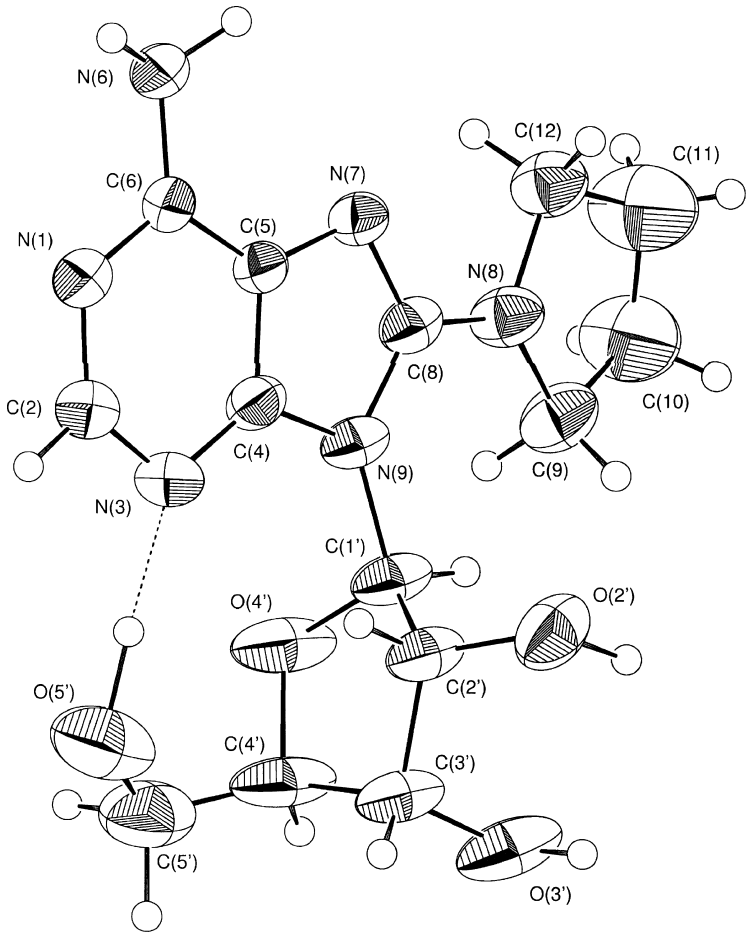


FIGURE 2 Molecular structure of **2**.

The molecular structures are stabilized by intramolecular hydrogen bonds (see Figures 1 and 2).

In molecule **1**, the hydrogen bond bridge joins the N(8) and O(5′) atoms. The length of the NH···O type hydrogen bond is 3.069(3) Å [N(8)-H = 0.91(4) Å, H···O(5′) = 2.18(4) Å, angle N(8)-H···O(5′) = 164(3)°]. It is a moderate bond; usually the length is less than 3 Å, especially for intramolecular bonds.[10]

In compound **2**, the intramolecular hydrogen bond of OH···N type occurs between the O(5′)-H group and the nitrogen N(3) in the heterocycle system. This bond is quite strong [O(5′)···N(3) = 2.776(7) Å, O(5′)–H = 1.17 Å, H···N(3) = 1.62 Å, angle O(5′)-H···N(3) = 167°]. This bond is present also in solutions; it explains the difference in NMR signal of the amino group for compounds **1** and **2** (6.54 ppm and 6.84 ppm, respectively). In adenosines, the hydrogen bond of O(5′)-H···N(3) is a relatively uncommon phenomenon. The similar bonds are found in 8-bromoadenosine [O(5′)···N(3) = 2.731 Å],[11]

TABLE 2 Bond Lengths (in Å) and Valence Angles (in deg.) in Molecules **1** and **2**

Bond	**1**	**2**	Bond	**1**	**2**
N(1)-C(2)	1.348(3)	1.343(6)	C(9)-C(10)	1.507(3)	1.533(8)
N(1)-C(6)	1.353(3)	1.342(5)	C(10)-C(11)	—	1.416(11)
C(2)-N(3)	1.328(3)	1.326(6)	C(10)-O(11)	1.417(3)	—
N(3)-C(4)	1.334(3)	1.341(6)	C(11)-C(12)	—	1.476(8)
C(4)-C(5)	1.388(3)	1.385(5)	C(1′)-N(9)	1.441(3)	1.453(5)
C(4)-N(9)	1.384(3)	1.391(6)	C(1′)-C(2′)	1.521(4)	1.516(6)
C(5)-C(6)	1.401(3)	1.394(5)	C(1′)-O(4′)	1.415(3)	1.424(6)
C(5)-N(7)	1.395(3)	1.385(5)	C(2′)-O(2′)	1.409(3)	1.399(6)
C(6)-N(6)	1.352(3)	1.366(5)	C(2′)-C(3′)	1.523(3)	1.540(6)
N(7)-C(8)	1.326(3)	1.328(5)	C(3′)-O(3′)	1.423(3)	1.408(7)
C(8)-N(8)	1.341(3)	1.339(5)	C(3′)-C(4′)	1.537(4)	1.548(7)
C(8)-N(9)	1.391(3)	1.408(6)	C(4′)-O(4′)	1.459(3)	1.456(6)
N(8)-C(9)	1.458(3)	1.449(5)	C(4′)-C(5′)	1.510(4)	1.505(11)
N(8)-C(12)	—	1.473(6)	C(5′)-O(5′)	1.427(4)	1.420(9)

Angle	**1**	**2**	Angle	**1**	**2**
C(2)-N(1)-C(6)	119.2(2)	118.3(4)	C(9)-N(8)-C(12)	—	112.2(4)
N(1)-C(2)-N(3)	127.8(2)	128.4(4)	C(4)-N(9)-C(8)	106.2(2)	105.7(3)
C(2)-N(3)-C(4)	111.4(2)	111.5(3)	C(4)-N(9)-C(1′)	123.5(2)	123.0(4)
N(3)-C(4)-C(5)	127.6(2)	126.6(4)	C(8)-N(9)-C(1′)	130.1(2)	130.9(4)
N(3)-C(4)-N(9)	126.7(2)	127.6(3)	N(9)-C(1′)-C(2′)	115.5(2)	115.2(3)
C(5)-C(4)-N(9)	105.7(2)	105.8(3)	N(9)-C(1′)-O(4′)	109.4(2)	108.1(3)
C(4)-C(5)-C(6)	116.0(2)	116.2(3)	C(2′)-C(1′)-O(4′)	104.7(2)	106.2(4)
C(4)-C(5)-N(7)	111.0(2)	111.5(3)	C(1′)-C(2′)-O(2′)	113.6(2)	114.5(4)
C(6)-C(5)-N(7)	133.0(2)	132.3(3)	C(1′)-C(2′)-C(3′)	100.1(2)	101.3(3)
N(1)-C(6)-C(5)	118.0(2)	119.0(3)	O(2′)-C(2′)-C(3′)	112.8(2)	114.1(4)
N(1)-C(6)-N(6)	118.7(2)	117.8(3)	C(2′)-C(3′)-O(3′)	106.4(2)	110.9(5)
C(5)-C(6)-N(6)	123.3(2)	123.1(4)	C(2′)-C(3′)-C(4′)	101.6(2)	102.8(3)
C(5)-N(7)-C(8)	104.3(2)	104.7(3)	O(3′)-C(3′)-C(4′)	112.4(2)	109.8(4)
N(7)-C(8)-N(8)	125.0(2)	121.9(4)	C(3′)-C(4′)-O(4′)	106.4(2)	105.8(4)
N(7)-C(8)-N(9)	112.7(2)	112.2(3)	C(3′)-C(4′)-C(5′)	115.9(2)	117.7(5)
N(8)-C(8)-N(9)	122.3(2)	125.8(3)	O(4′)-C(4′)-C(5′)	107.8(2)	109.3(5)
C(8)-N(8)-C(9)	119.1(2)	128.9(4)	C(1′)-O(4′)-C(4′)	107.8(2)	109.7(3)
C(8)-N(8)-C(12)	—	117.1(3)	C(4′)-C(5′)-O(5′)	110.7(2)	117.2(5)

8-(α-hydroxyisopropyl)-adenosine [O(5′)···N(3) = 2.782 Å],[12] N-[1-phenyl-2(R)-propyl]-2-chloroadenosine [O(5′)···N(3) = 2.796 Å].[13]

In compounds **1** and **2**, the conformations of the molecules are defined to a marked degree by the intramolecular hydrogen bonds. Due to the N(8)-H···O(5′) bond, the adenine system in **1** exhibits the *anti* conformation [C(8)-N(9)-C(1′)-O(4′) torsion angle is equal 58.6(3)°] across the glycosidic bond. In molecule **2**, the O(5′)-H group is bonded with N(3) of the adenine moiety. Therefore, the *syn* conformation [C(8)-N(9)-C(1′)-O(4′) = −123.5(5)°] occurs in **2**.

For both molecules **1** and **2**, the ribose ring is characterized by envelope conformation. The sugar puckerings of both molecules are the C(2′)-*endo* type. The displacements of the atom C(2′) from the plane defined by the atoms C(1′), C(3′),

TABLE 3 The Values of Ribose Torsion Angles (in deg.) in Molecules **1** and **2**

Torsion angle	**1**	**2**
N(9)-C(1′)-C(2′)-C(3′)	164.1(2)	156.3(5)
C(1′)-C(2′)-C(3′)-C(4′)	−38.8(2)	−34.6(4)
C(2′)-C(3′)-C(4′)-O(4′)	22.3(2)	21.5(4)
C(2′)-C(3′)-C(4′)-C(5′)	−97.5(2)	−100.8(6)
C(3′)-C(4′)-O(4′)-C(1′)	4.9(2)	1.2(4)
C(3′)-C(4′)-C(5′)-O(5′)	54.8(3)	58.1(6)
C(4′)-O(4′)-C(1′)-N(9)	−154.9(2)	−148.4(5)
C(4′)-O(4′)-C(1′)-C(2′)	−30.5(2)	−24.2(4)
O(4′)-C(4′)-C(5′)-O(5′)	−64.2(2)	−62.5(6)
O(4′)-C(1′)-C(2′)-C(3′)	47.7(2)	36.7(4)

C(4′), and O(4′) are 0.659(2) and 0.576(5) Å for molecules **1** and **2**, respectively. The dihedral angles between the plane of C(1′), C(3′), C(4′), O(4′), and the triangle C(1′), C(2′), C(3′) are 137.6(2) (for **1**) and 143.5(2)° (for **2**). The conformation of the exocyclic C(4′)-C(5′) bond is *gauche-gauche* in both molecules. The torsion angles, which characterize the conformation of sugar fragments are given in Table 3.

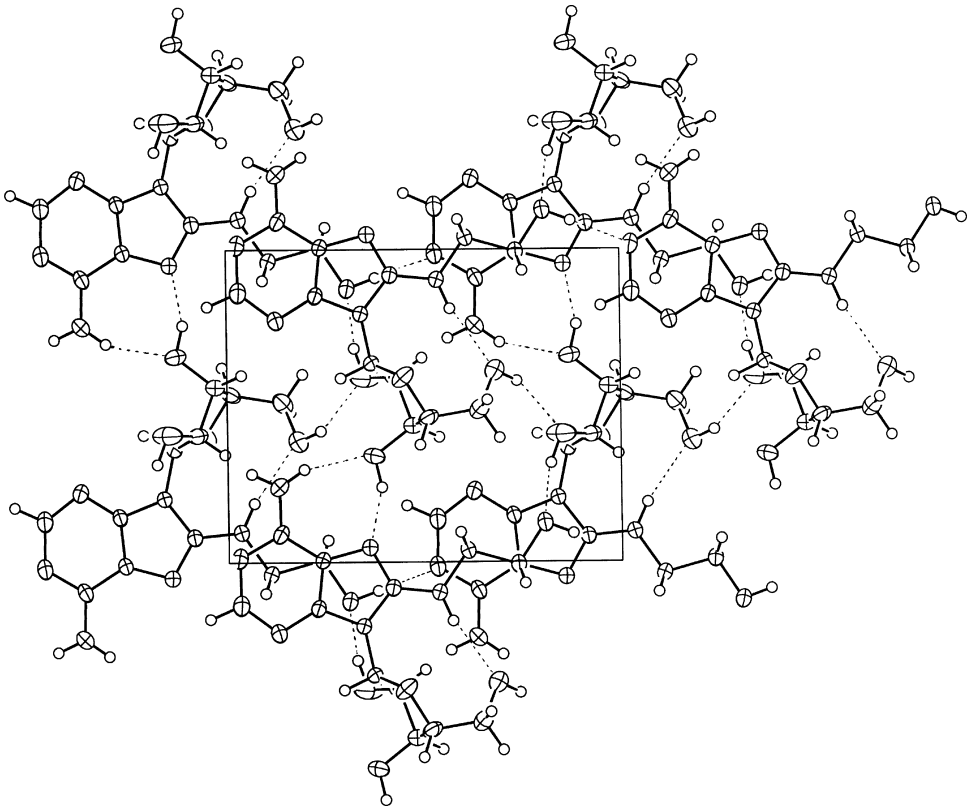


FIGURE 3 The molecular packing of **1**, viewed down the *x* axis.

Generally, the purine system in nucleosides does not assume a planar conformation.[14] However, in molecule **1**, the pyrimidine and imidazole planes are coplanar in the error limits. The displacements of N(6), N(8), and C(1′) from the heterocycle plane are 0.028(3), −0.012(2), and −0.068(2) Å, respectively. The chain of N(8), C(9), C(10), O(11) is nearly planar (N(8)-C(9)-C(10)-O(11) torsion angle is −177.2(2)°). The dihedral angle between the chain plane and the purine system is equal 4.6(1)°.

In the molecule **2**, atoms C(2) and N(9) have the maximum deviations from the heterocycle plane of 0.022(5) and −0.018(3) Å, respectively, and the displacements of N(6), N(8), and C(1′) are 0.049(4), 0.079(3), and − 0.195(4) Å, respectively. The semi-chair conformation is observed for the pyrrolidine cycle. The least-squares plane defined by the atoms of the pyrrolidine and the plane of the purine system form the dihedral angle of 14.9(2)°. Unlike **1**, in molecule **2**, the substituent in 8th position does not participated in hydrogen bonds. That is why the thermal motions of the atoms in the pyrrolidine substituent are considerable (the values of U_{eq} are 0.098(4) and 0.106(5) Å^2 for atoms C(10) and C(11), respectively), therefore, the melting point of **2** is dropped.

Figures 3 and 4 give packing diagrams for **1** and **2**. In the crystal structures, besides the intramolecular hydrogen bonds, the branching net of intermolecular hydrogen bonds are also observed. It should be noted that the typical base-base hydrogen bonding interactions are present only in the crystal structure of **2**. The

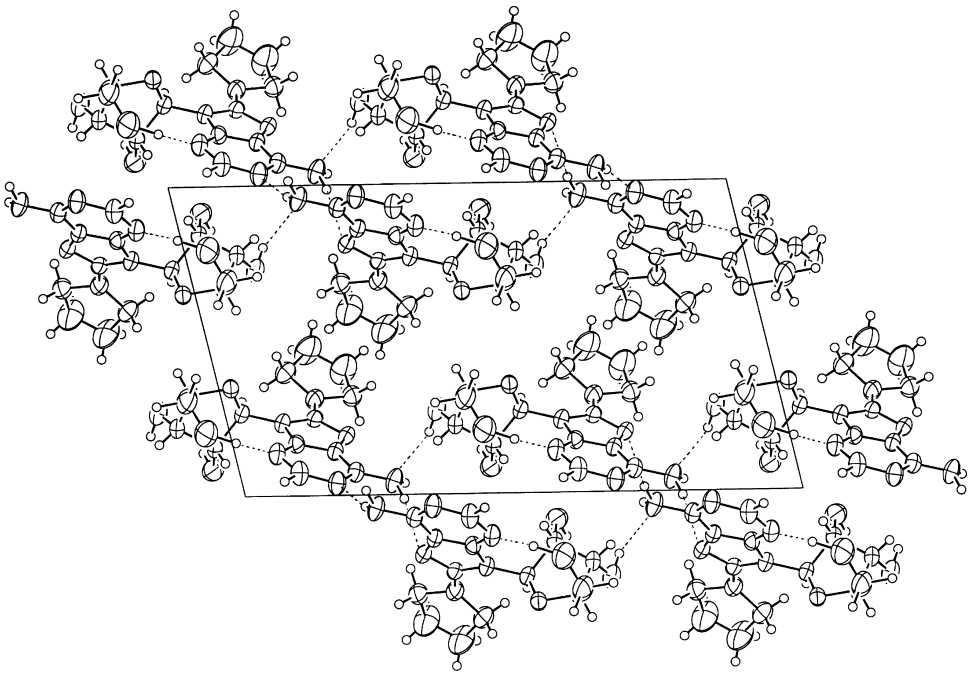


FIGURE 4 The molecular packing of **2**, viewed down the *y* axis.

TABLE 4 Distances and Angles of the Intermolecular Hydrogen Bonds in Crystals **1** and **2**

Hydrogen bridge D-H···A	Distances in Å			Angle D-H···A in deg.	Position of atom A
	D···A	H···A	D-H		
Compound **1**					
O(11)-H···N(1)	2.714(3)	1.84(6)	0.88(6)	173(4)	$-x$, $-\frac{1}{2}+y$, $-z$
O(2′)-H···O(11)	2.743(3)	1.84(5)	0.92(5)	165(3)	$1-x$, $\frac{1}{2}+y$, $2-z$
O(3′)-H···N(7)	2.745(3)	1.86(5)	0.95(5)	156(3)	$-x$, $\frac{1}{2}+y$, $1-z$
O(5′)-H···O(2′)	2.848(3)	2.08(5)	0.84(5)	152(3)	$-1-x$, $-\frac{1}{2}+y$, $-1-z$
N(6)-H_A···O(3′)	3.055(3)	2.24(4)	0.88(4)	153(3)	$-x$, $\frac{1}{2}+y$, $-1-z$
Compound **2**					
N(6)-H_A···N(1)	2.936(5)	2.06	0.90	163	$\frac{1}{2}-x$, $+y$, $1-z$
O(3′)-H···N(6)	3.089(6)	2.07	1.12	149	$+x$, $+y$, z
O(2′)-H···O(5′)	3.094(7)	2.24	1.01	141	$-x$, $1+y$, $-z$
N(6)-H_B···N(7)	3.147(5)	2.34	0.87	156	$\frac{1}{2}-x$, $-\frac{1}{2}+y$, $1-z$

amino group in **2** takes part in hydrogen bonds both as a donor and as an acceptor. That is why, in crystals **2**, the nitrogen atom of N(6) has a pyramidal configuration. The parameters of the intermolecular hydrogen bonds are listed in Table 4.

In conclusion, it has found that the adenosine derivative **1** containing a secondary amino group (2-hydroxyethylamino) in the 8-position due to intramolecular hydrogen bonding has ribose moiety in an *anti* conformation necessary for binding with adenosine receptors, while in compound **2** the tertiary amino group (pyrrolidino) in the 8-position forces the ribose ring into the *syn* conformation stabilyzed by the hydrogen bond O(5′)-H···N(3).

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