Purines. XXXIX.[1] The Crystal Structure of 9-Benzyl-N^6-methoxyadenine

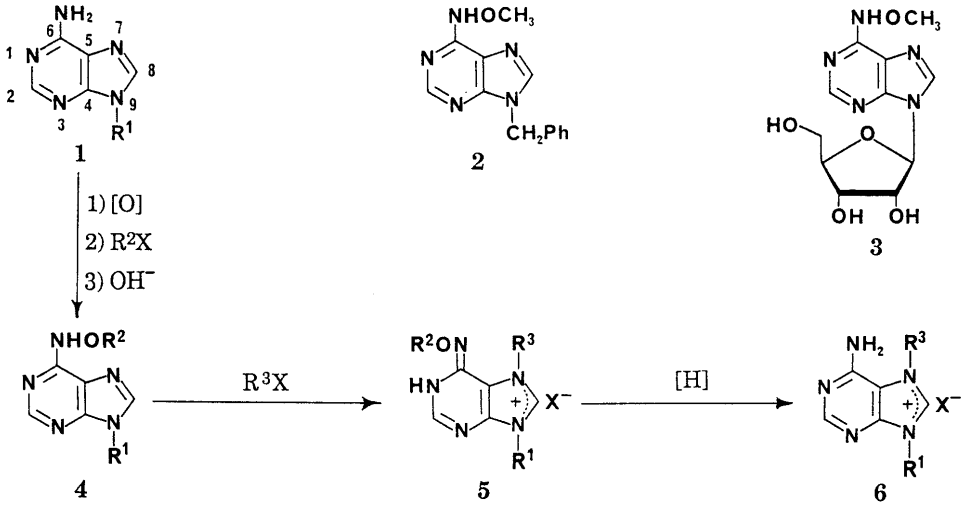
Tozo FUJII,*[,a] Tohru SAITO,[a] Tadamasa DATE,[b] and Yoshihiko NISHIBATA[b]

Faculty of Pharmaceutical Sciences, Kanazawa University,[a] Takara-machi, Kanazawa 920, Japan and Organic Chemistry Research Laboratory, Tanabe Seiyaku, Co., Ltd.,[b] Kawagishi-2-chome, Toda 335, Japan. *Received September 18, 1989*

The X-ray crystal structure of 9-benzyl-N^6-methoxyadenine (2) has been determined. In the crystal, this compound exists in two different conformations with respect to the N(9)-benzyl group. Each conformer has been found to possess the *syn*-6-imino-1*H*-purine structure (13).

Keywords 9-benzyl-N^6-methoxyadenine; X-ray crystal structure; *syn*-imino form; benzyl conformation; hydrogen bonding; MNDO calculation; amino–imino tautomerism

9-Substituted N^6-alkoxyadenines (type **4**) are a unique group of disubstituted adenines[2] to which belong the title compound, 9-benzyl-N^6-methoxyadenine (**2**), and promutagenic N^6-methoxyadenosine (**3**),[3] which is formed by interaction between the mutagen methoxyamine and adenosine. They are readily obtainable from 9-substituted adenines (type **1**) in three steps involving N(1)-oxidation,[4] *O*-alkylation,[4c,h,5] and Dimroth rearrangement,[1,5a,b,d,6] as shown in Chart 1, and represent the starting point for our two-step synthesis of 7,9-disubstituted adenines (type **6**), by regioselective N(7)-alkylation of **4** to give **5** and subsequent reductive dealkoxylation.[1,5c,7] A number of 7,9-dialkyladenines (**6a**),[1,5c,7a,b] 7-methyladenosine (**6b**),[7a,c] 7-ethyladenosine (**6c**),[7c] and agelasine B (**6d**: X=Cl),[8] a sea sponge bicyclic diterpene with the 9-methyl-7-adeninylium moiety,[9] have been synthesized through this route. For a better understanding of the above unique regioselectivity in alkylation of **4**, it is of prime importance to know the exact molecular structures of **4**. It is necessary to determine whether they exist in the 6-amino (type **7** and/or **8**) or 6-imino form (type **9** and/or **10**) or in equilibrium between the two forms, and also to determine the conformation or configuration of the exocyclic N^6-alkoxy group [*e.g.*, *syn* or *anti* with respect to the ring N(1) atom, as represented by formulas **7**—**10**]. Our recent proton nuclear magnetic resonance, ultraviolet, and infrared spectroscopic approaches to these problems have shown that amino–imino tautomerism is common to 9-substituted N^6-alkoxyadenines (type **4**) in solution.[6e] However, no conclusive evidence has been obtained in regard to the conformation and configuration of the exocyclic N^6-alkoxy groups in the two tautomeric forms.[6e] In this paper, we report the crystal structure of 9-



a: R^1 and R^3 = alkyl

b: R^1 = β-D-ribofuranosyl; R^3 = Me

c: R^1 = β-D-ribofuranosyl; R^3 = Et

d: R^1 = Me; R^3 =

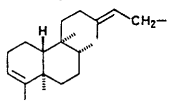
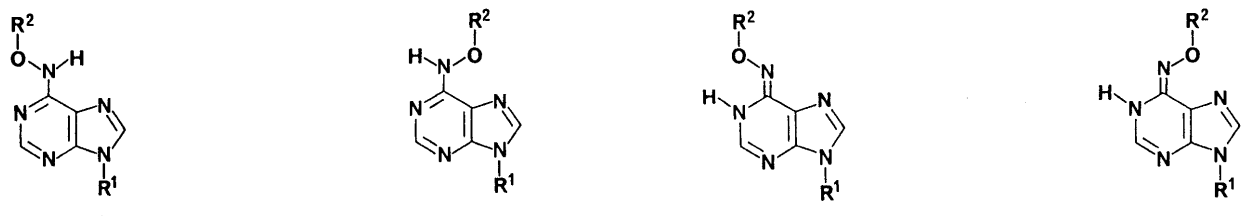


Chart 1



7 (*syn*-amino) **8** (*anti*-amino) **9** (*syn*-imino) **10** (*anti*-imino)

benzyl-N^6-methoxyadenine (**2**), which was the only one among the 9-substituted N^6-alkoxyadenines (type **4**) in hand [6e] that afforded an adequate single crystal for X-ray diffraction after extensive efforts.

Experimental

X-Ray Analysis 9-Benzyl-N^6-methoxyadenine (**2**) was prepared as described previously,[6e] and colorless transparent plates [mp 224—225 °C (dec.)] of **2** were grown from MeOH. A crystal measuring 0.3 × 0.3 × 0.2 mm was selected from among them and used for all data collection. Unit cell constants and intensity data were obtained with a Rigaku AFC/5 automatic diffractometer using graphite-monochromated Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å). The unit cell dimensions were determined from angular settings of 20 2θ-values in the range of 40—60°, affording the following crystal data: crystal system, triclinic; $a = 11.026\ (2)$ Å; $b = 11.415\ (1)$ Å; $c = 10.776\ (2)$ Å; $\alpha = 89.17\ (1)°$; $\beta = 104.89\ (1)°$; $\gamma = 90.49\ (1)°$; $U = 1310.9$ Å^3; space group $P\bar{1}$; $Z = 4$; $D_x = 1.293$ g/cm^3; $F(000) = 536$; μ(Cu $K\alpha$) = 7.269 cm^{-1}. Out of 4478 unique reflections ($2\theta \leqq 130°$) measured by using the $\omega/2\theta$ scan technique at a rate of 4°/min, 3838 with $|F_{obs}| \geqq 2.67\sigma(F)$ were considered unique and observed. No absorption corrections were applied.

Structure Determination and Refinement The structure was solved by direct methods using the program SIR-85[10] and the difference Fourier method. Refinement of atomic parameters was carried out using the block-diagonal least-squares method with anisotropic temperature factors. All hydrogen atoms were clearly located on difference Fourier maps and refined with isotropic temperature factors. Throughout the refinement, the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized, and the weight used during the final refinement stage was $\sqrt{w} = 1/\sigma(F_o)$; the final R value, 0.055 (R_w = 0.048). No residual density over 0.17 e/Å^3 was observed on the final difference Fourier maps. The atomic scattering factors were taken from the literature.[11]

Results

Figure 1 shows the atomic numbering scheme employed. There are two kinds of crystallographically independent molecules in a unit cell, and they are designated as molecule A and molecule B in this paper. The final atomic positions and equivalent isotropic thermal parameters of the non-hydrogen atoms are listed in Table I. The positional parameters and isotropic temperature factors for the hydrogen atoms are given in Table II. The bond lengths and

TABLE I. Final Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters for Non-hydrogen Atoms of Molecules A and B

Atom	Molecule A[a]				Molecule B[a]			
	x	y	z	B_{eq} (Å^2)	x	y	z	B_{eq} (Å^2)
N(1)	0.9672 (1)	0.9424 (1)	0.7330 (2)	4.28 (6)	0.9580 (1)	0.5558 (1)	0.2216 (2)	4.34 (7)
C(2)	0.8868 (2)	0.8996 (2)	0.6254 (2)	4.72 (8)	0.8765 (2)	0.5994 (2)	0.1150 (2)	4.76 (8)
N(3)	0.8350 (1)	0.9585 (1)	0.5214 (2)	4.73 (7)	0.8242 (2)	0.5429 (1)	0.0108 (2)	4.72 (7)
C(4)	0.8711 (2)	1.0742 (2)	0.5328 (2)	4.07 (8)	0.8629 (2)	0.4287 (2)	0.0212 (2)	4.08 (7)
C(5)	0.9491 (2)	1.1278 (1)	0.6347 (2)	3.92 (7)	0.9425 (2)	0.3736 (1)	0.1224 (2)	3.99 (7)
C(6)	1.0092 (2)	1.0589 (1)	0.7459 (2)	3.85 (7)	1.0010 (2)	0.4402 (1)	0.2336 (2)	4.02 (7)
N(7)	0.9640 (2)	1.2447 (1)	0.6075 (2)	4.68 (7)	0.9588 (2)	0.2578 (1)	0.0939 (2)	4.80 (7)
C(8)	0.8957 (2)	1.2581 (2)	0.4895 (2)	4.97 (9)	0.8899 (2)	0.2470 (2)	−0.0240 (2)	4.96 (9)
N(9)	0.8371 (1)	1.1579 (1)	0.4379 (2)	4.53 (7)	0.8294 (2)	0.3469 (1)	−0.0745 (2)	4.40 (7)
N(10)	1.0922 (2)	1.1002 (1)	0.8414 (2)	4.68 (7)	1.0846 (2)	0.3971 (1)	0.3291 (2)	4.75 (7)
O(11)	1.1357 (1)	1.0086 (1)	0.9335 (1)	5.57 (6)	1.1267 (1)	0.4860 (1)	0.4232 (1)	5.57 (6)
C(12)	1.2325 (3)	1.0552 (3)	1.0325 (3)	7.84 (14)	1.2238 (3)	0.4360 (2)	0.5215 (3)	7.35 (13)
C(13)	0.7558 (2)	1.1427 (2)	0.3078 (2)	5.51 (10)	0.7449 (2)	0.3627 (2)	−0.2020 (2)	5.19 (9)
C(14)	0.6271 (2)	1.1927 (2)	0.2927 (2)	4.80 (9)	0.6169 (2)	0.3106 (2)	−0.2136 (2)	4.88 (9)
C(15)	0.5979 (3)	1.3021 (3)	0.2413 (3)	7.50 (14)	0.5543 (2)	0.2546 (2)	−0.3233 (2)	6.35 (11)
C(16)	0.4771 (3)	1.3460 (3)	0.2255 (3)	10.03 (19)	0.4341 (3)	0.2097 (2)	−0.3346 (3)	7.49 (13)
C(17)	0.3888 (3)	1.2803 (3)	0.2645 (3)	9.55 (18)	0.3775 (2)	0.2193 (3)	−0.2389 (3)	7.82 (14)
C(18)	0.4180 (3)	1.1733 (3)	0.3155 (3)	9.17 (18)	0.4378 (3)	0.2755 (3)	−0.1302 (3)	8.69 (17)
C(19)	0.5368 (2)	1.1287 (3)	0.3297 (3)	7.04 (13)	0.5569 (3)	0.3221 (3)	−0.1177 (3)	7.51 (14)

a) Estimated standard deviations are given in parentheses and denote the least significant digits.

TABLE II. Final Fractional Atomic Coordinates and Isotropic Temperature Factors for Hydrogen Atoms of Molecules A and B

Atom	Molecule A[a]				Molecule B[a]			
	x	y	z	B_{iso} (Å^2)	x	y	z	B_{iso} (Å^2)
H(1)	0.999	0.889	0.803	3.81	0.990	0.605	0.289	2.39
H(2)	0.872	0.813	0.636	2.71	0.857	0.681	0.120	3.07
H(8)	0.885	1.333	0.441	3.80	0.882	0.175	−0.072	3.11
H(12a)	1.259	0.998	1.100	7.23	1.257	0.494	0.582	6.58
H(12b)	1.305	1.075	0.994	7.33	1.291	0.407	0.490	7.33
H(12c)	1.202	1.130	1.070	11.84	1.184	0.358	0.561	7.95
H(13a)	0.755	1.061	0.288	3.81	0.740	0.451	−0.216	4.45
H(13b)	0.801	1.185	0.245	5.08	0.784	0.321	−0.264	5.05
H(15)	0.662	1.343	0.209	6.78	0.603	0.252	−0.400	5.70
H(16)	0.449	1.415	0.190	11.10	0.391	0.169	−0.423	6.34
H(17)	0.305	1.313	0.259	8.39	0.296	0.188	−0.243	6.09
H(18)	0.352	1.118	0.339	10.03	0.402	0.280	−0.056	9.82
H(19)	0.559	1.051	0.375	8.18	0.601	0.356	−0.036	6.78

a) The estimated standard deviations for x, y, and z lie within 0.002—0.003; those for B_{iso}, within 0.4—1.0.

angles are shown in Tables III and IV, respectively. Stereoscopic views of the structures of molecules A and B are presented in Figs. 2 and 3, respectively.

Discussion

It may be seen from Tables III and IV that the bond lengths and angles of the pyrimidine moiety in both molecule A and molecule B are not always in agreement with

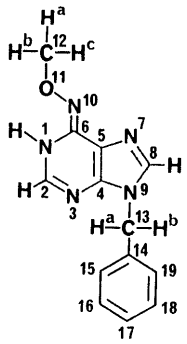


Fig. 1. Numbering Scheme Used for the *syn*-Imino Form (**13**) of 9-Benzyl-N^6-methoxyadenine (**2**)

TABLE III. Bond Lengths in Molecules A and B

Bond	Length[a] (Å)		Bond	Length[a] (Å)	
	Mol. A	Mol. B		Mol. A	Mol. B
N(1)–C(2)	1.360(2)	1.354(2)	C(15)–C(16)	1.396(5)	1.393(4)
N(1)–C(6)	1.401(2)	1.399(2)	C(16)–C(17)	1.370(5)	1.342(5)
C(2)–N(3)	1.300(3)	1.301(3)	C(17)–C(18)	1.340(5)	1.356(4)
N(3)–C(4)	1.374(2)	1.369(2)	C(18)–C(19)	1.380(4)	1.387(4)
C(4)–C(5)	1.359(2)	1.361(2)	N(1)–H(1)	0.960(19)	0.917(26)
C(4)–N(9)	1.371(2)	1.378(2)	C(2)–H(2)	1.015(19)	0.969(29)
C(5)–C(6)	1.438(2)	1.432(3)	C(8)–H(8)	0.983(19)	0.963(30)
C(5)–N(7)	1.380(2)	1.384(2)	C(12)–H(12a)	0.962(21)	0.940(24)
C(6)–N(10)	1.282(2)	1.287(2)	C(12)–H(12b)	1.015(26)	0.959(29)
N(7)–C(8)	1.308(3)	1.309(3)	C(12)–H(12c)	1.036(21)	1.118(31)
C(8)–N(9)	1.362(3)	1.361(2)	C(13)–H(13a)	0.959(22)	1.019(30)
N(9)–C(13)	1.469(3)	1.458(2)	C(13)–H(13b)	1.045(27)	1.014(41)
N(10)–O(11)	1.428(2)	1.433(2)	C(15)–H(15)	0.980(23)	1.101(32)
O(11)–C(12)	1.407(3)	1.416(3)	C(16)–H(16)	0.895(28)	1.061(33)
C(13)–C(14)	1.502(3)	1.503(3)	C(17)–H(17)	0.984(25)	0.950(34)
C(14)–C(15)	1.366(4)	1.370(3)	C(18)–H(18)	1.033(29)	0.984(30)
C(14)–C(19)	1.366(4)	1.371(4)	C(19)–H(19)	1.006(27)	0.969(31)

a) Estimated standard deviations are given in parentheses and denote the least significant digits.

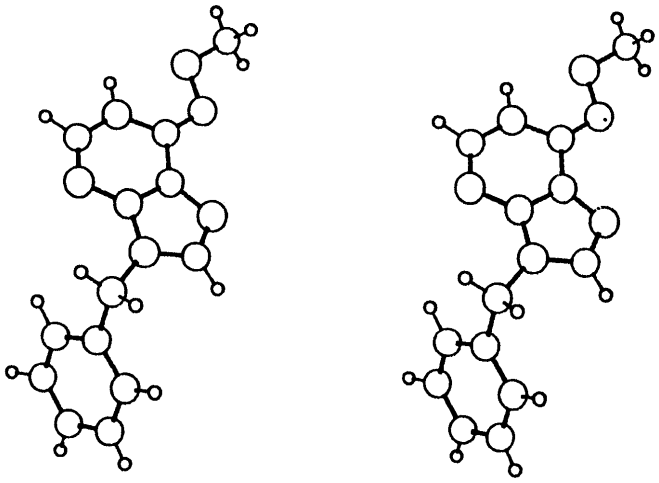


Fig. 2. Stereoview of the Structure of Molecule A

TABLE IV. Bond Angles in Molecules A and B

Bond	Angle[a] (°)		Bond	Angle[a] (°)	
	Mol. A	Mol. B		Mol. A	Mol. B
C(2)–N(1)–C(6)	123.9 (2)	123.7 (2)	C(2)–N(1)–H(1)	117.9 (11)	119.0 (17)
N(1)–C(2)–N(3)	126.5 (2)	126.8 (2)	C(6)–N(1)–H(1)	118.2 (11)	117.2 (17)
C(2)–N(3)–C(4)	111.0 (2)	110.6 (2)	N(1)–C(2)–H(2)	110.6 (10)	114.5 (15)
N(3)–C(4)–C(5)	128.3 (2)	128.6 (2)	N(3)–C(2)–H(2)	122.9 (10)	118.7 (15)
N(3)–C(4)–N(9)	125.2 (2)	125.1 (2)	N(7)–C(8)–H(8)	124.7 (10)	123.8 (16)
C(5)–C(4)–N(9)	106.4 (2)	106.3 (2)	N(9)–C(8)–H(8)	121.6 (10)	122.4 (16)
C(4)–C(5)–C(6)	119.2 (2)	118.9 (2)	O(11)–C(12)–H(12a)	110.0 (12)	108.5 (14)
C(4)–C(5)–N(7)	110.7 (2)	110.7 (2)	O(11)–C(12)–H(12b)	107.4 (12)	112.4 (14)
C(6)–C(5)–N(7)	129.9 (2)	130.2 (2)	O(11)–C(12)–H(12c)	110.6 (10)	107.9 (14)
N(1)–C(6)–C(5)	111.0 (1)	111.2 (1)	H(12a)–C(12)–H(12b)	109.5 (19)	107.9 (22)
N(1)–C(6)–N(10)	125.7 (2)	125.9 (2)	H(12a)–C(12)–H(12c)	109.0 (18)	114.6 (22)
C(5)–C(6)–N(10)	123.3 (2)	122.8 (2)	H(12b)–C(12)–H(12c)	110.3 (18)	105.6 (23)
C(5)–N(7)–C(8)	103.8 (2)	103.8 (2)	N(9)–C(13)–H(13a)	107.8 (12)	104.4 (16)
N(7)–C(8)–N(9)	113.6 (2)	113.8 (2)	N(9)–C(13)–H(13b)	106.7 (12)	106.8 (18)
C(4)–N(9)–C(8)	105.4 (2)	105.4 (2)	C(14)–C(13)–H(13a)	113.3 (13)	111.3 (17)
C(4)–N(9)–C(13)	127.4 (2)	127.6 (2)	C(14)–C(13)–H(13b)	110.4 (13)	108.0 (20)
C(8)–N(9)–C(13)	127.3 (2)	127.0 (2)	H(13a)–C(13)–H(13b)	105.8 (20)	113.2 (29)
C(6)–N(10)–O(11)	109.3 (1)	109.3 (1)	C(14)–C(15)–H(15)	116.7 (12)	115.8 (14)
N(10)–O(11)–C(12)	107.6 (2)	106.8 (2)	C(16)–C(15)–H(15)	122.9 (12)	123.9 (13)
N(9)–C(13)–C(14)	112.5 (2)	113.2 (2)	C(15)–C(16)–H(16)	125.9 (20)	115.9 (21)
C(13)–C(14)–C(15)	120.9 (2)	120.7 (2)	C(17)–C(16)–H(16)	114.3 (20)	122.9 (21)
C(13)–C(14)–C(19)	120.3 (2)	121.2 (2)	C(16)–C(17)–H(17)	120.1 (15)	123.5 (21)
C(15)–C(14)–C(19)	118.8 (2)	118.0 (2)	C(18)–C(17)–H(17)	119.9 (15)	117.3 (21)
C(14)–C(15)–C(16)	120.0 (3)	120.2 (3)	C(17)–C(18)–H(18)	122.1 (15)	121.6 (15)
C(15)–C(16)–C(17)	119.8 (3)	121.2 (2)	C(19)–C(18)–H(18)	117.2 (15)	117.7 (15)
C(16)–C(17)–C(18)	119.9 (3)	119.2 (3)	C(14)–C(19)–H(19)	119.6 (17)	120.1 (23)
C(17)–C(18)–C(19)	120.5 (3)	120.5 (3)	C(18)–C(19)–H(19)	119.3 (17)	118.8 (23)
C(14)–C(19)–C(18)	120.9 (3)	120.8 (3)			

a) Estimated standard deviations are given in parentheses and denote the least significant digits.

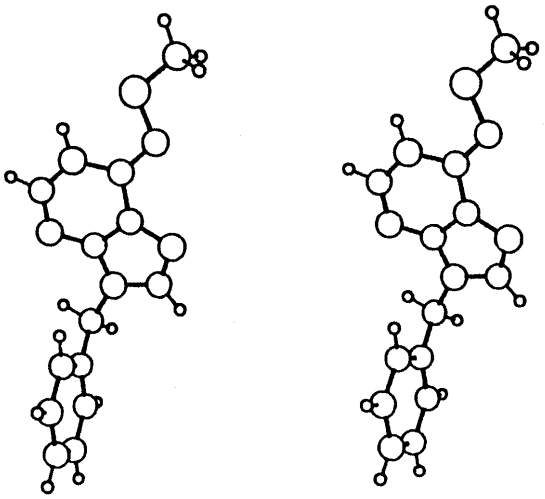
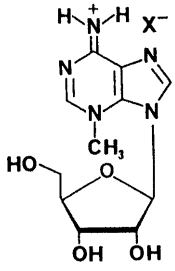
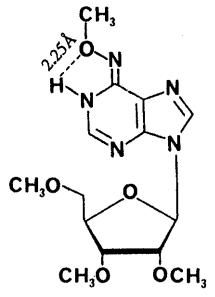


Fig. 3. Stereoview of the Structure of Molecule B

the average values reported for the usual adenine system,[12] indicating the localization of double bonds at C(2)=N(3), C(4)=C(5), and C(6)=N(10) (Fig. 1). The C(6)=N(10) bond length of 1.282 Å for molecule A or 1.287 Å for molecule B is shorter than that (1.305 Å)[13] in 3-methyladenosine *p*-toluenesulfonate (**11**: X=*p*-$MeC_6H_4SO_3$) and is similar to that (1.287 Å)[14] in the *syn*-imino form (**12**) of N^6-methoxy-2′,3′,5′-tri-*O*-methyladenosine. In both molecule A and molecule B, a hydrogen atom peak was found around the N(1) atom at a chemically significant position in the difference Fourier maps, as shown in Table II, but could not be found around the N(10) atom, pointing to a 6-imino-1*H*-purine structure. The configuration of the exocyclic N^6-OMe group is *syn* with respect to the ring N(1) atom, as represented in Figs. 2 and 3. The methoxy group is almost coplanar with the adenine ring, the torsion angle C(6)–N(10)–O(11)–C(12) being 176.11° in molecule A or −176.30° in molecule B.



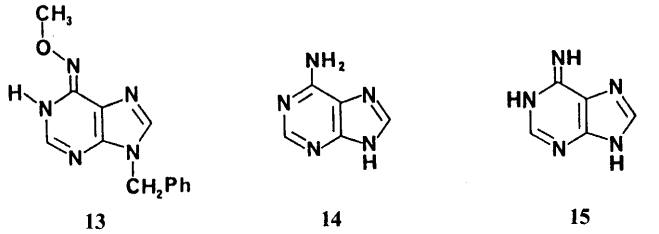
11



12

The most significant difference between molecules A and B lies in the conformation of the N(9)-benzyl group. The angle between the two best-planes of the adenine and phenyl rings is 111.6° in molecule A; 84.8° in molecule B. Apart from the conformations of the N(9)-substituents, the geometries of the two molecules in the adenine moieties including the exocyclic N^6-OMe groups are alike and very similar to that[14] of **12**. These findings allow formula **13** to be a general expression for the two conformers.

In the crystal, the N(1)-H atom of a molecule of conformer A is hydrogen-bonded to the N(7) atom of a molecule of conformer B′ [with a distance of 2.91 Å between the N(1) and N(7) atoms]; the N(1)-H atom of this B′ molecule, to the N(7) atom [N(1)···N(7) 2.93 Å] of another A molecule



13 **14** **15**

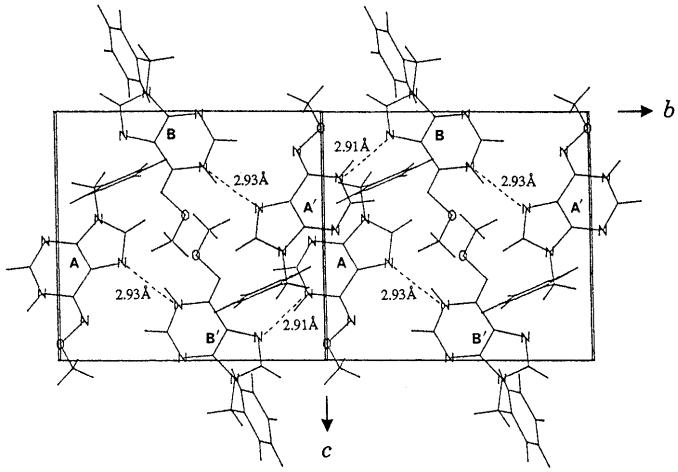


Fig. 4. Crystal Packing of the *syn*-Imino Form (**13**) of 9-Benzyl-N^6-methoxyadenine Viewed down the *a* Axis

which is the translational equivalent along the *b* axis so that an infinite chain of the hydrogen-bonded molecules (···A···B′···A···B′···) may be formed (Fig. 4).

On the basis of their MNDO (modified neglect of diatomic overlap[15]) calculations, Sygula and Buda[16] have reported that the 6-amino form (**14**) of adenine is more stable than the 6-imino-1*H*-purine form (**15**) by *ca.* 11 kcal/mol. We performed MNDO calculations[17] for the 6-amino form **2** and *syn*-6-imino-1*H*-purine form **13**, and the geometries were optimized by the DFP (Davidon–Fletcher–Powell) optimization procedure.[18] The heats of formation thus estimated for **2** and **13** were 77.51 and 76.36 kcal/mol, respectively, indicating that the *syn*-6-imino-1*H*-purine form **13** is more stable than the 6-amino form **2** only by *ca.* 1 kcal/mol. These calculation results are consistent with our previous finding[6e] of the existence of amino–imino equilibrium [**2**⇌**13** (and/or the *anti*-imino form (type **10**))] of 9-benzyl-N^6-methoxyadenine in $CHCl_3$ or Me_2SO-d_6 solution. The imino form in such a solution may be considered the *syn*-imino type (**13**) in the light of the above X-ray crystal structure. In Me_2SO-d_6 solution at 0.05 M concentration and 25 °C, **2** and **13** have been found to coexist in a ratio of 1 : 3.5.[6e] The preference for the *syn*-imino form **13** in this case may be a result of the effect of solvent polarity as well as the stabilization of **13** by forming an intramolecular N(1)-H···O(11) hydrogen bond, similar to that suggested by Shugar's group[14] for **12** in the absence of intermolecular hydrogen bonds. In the crystal, however, stabilization of **13** by the formation of the above intermolecular N(1)-H···N(7) hydrogen bonds appears to be an effectual determinant of the exclusive occurrence of the imino form.

Conclusion

The above X-ray crystallographic structure analysis has

revealed that 9-benzyl-N^6-methoxyadenine exists in the crystal in two different conformations with respect to the N(9)-benzyl group, and each conformer has the *syn*-6-imino-1*H*-purine structure **13**. By analogy with this geometry as well as the result of the X-ray analysis of **12** by Shugar's group,[14] similar *syn*-imino structures (type **9**) are inferred for the 6-imino tautomers previously detected[6e] in amino–imino equilibria of many 9-substituted N^6-alkoxyadenines (type **4**). These N^6-alkoxyadenine derivatives include promutagenic N^6-methoxyadenosine (**3**),[3] which is formed by interaction between the mutagen methoxyamine and adenosine. If alkylation of **4** proceeds through the *syn*-imino form **9** as inferred, the N(7) atom should be a sterically favored site of alkylation. The previously reported,[1,5c,7,8] preferential N(7)-alkylation of **4** is of particular interest in this connection.

Acknowledgment We are grateful to Emeritus Professor Dr. Shigehiko Sugasawa (University of Tokyo) and Drs. Seiichi Saito, Keishi Kotera, and Mikio Takeda (Tanabe Seiyaku, Co.) for their interest and encouragement.

References and Notes

1) Paper XXXVIII in this series, T. Fujii, T. Saito, T. Sakuma, M. Minami, and I. Inoue, *Chem. Pharm. Bull.*, **38**, 652 (1990).
2) For a review on the syntheses and reactions of this group of compounds, see T. Fujii, T. Itaya, and T. Saito, *Yuki Gosei Kagaku Kyokai Shi*, **41**, 1193 (1983).
3) *a*) For a review, see E. I. Budowsky, *Prog. Nucleic Acid Res. Mol. Biol.*, **16**, 125 (1976); *b*) B. Singer and S. Spengler, *FEBS Lett.*, **139**, 69 (1982).
4) *a*) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958); *b*) H. Klenow and S. Frederiksen, *Biochim. Biophys. Acta*, **52**, 384 (1961); *c*) T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.*, **19**, 1368 (1971); *d*) J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, **15**, 182 (1972); *e*) T. Fujii, T. Saito, T. Itaya, and K. Yokoyama, *Chem. Pharm. Bull.*, **21**, 209 (1973); *f*) K. Kikugawa, H. Suehiro, R. Yanase, and A. Aoki, *ibid.*, **25**, 1959 (1977); *g*) T. Ueda, K. Miura, and T. Kasai, *ibid.*, **26**, 2122 (1978); *h*) T. Fujii, T. Saito, and T. Fujisawa, *Heterocycles*, **27**, 1163 (1988).
5) *a*) T. Fujii, C. C. Wu, T. Itaya, S. Moro, and T. Saito, *Chem. Pharm. Bull.*, **21**, 1676 (1973); *b*) T. Itaya, T. Saito, S. Kawakatsu, and T. Fujii, *ibid.*, **23**, 2643 (1975); *c*) T. Fujii, T. Itaya, F. Tanaka, T. Saito, K. Mohri, and K. Yamamoto, *ibid.*, **31**, 3149 (1983); *d*) T. Fujii, T. Itaya, T. Saito, and S. Kawakatsu, *ibid.*, **32**, 4842 (1984); *e*) T. Fujii, T. Saito, and T. Nakasaka, *ibid.*, **37**, 2601 (1989).
6) *a*) T. Fujii, T. Itaya, C. C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971); *b*) T. Itaya, F. Tanaka, and T. Fujii, *ibid.*, **28**, 535 (1972); *c*) T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.*, **20**, 1818 (1972); *d*) T. Fujii, T. Itaya, T. Saito, and M. Kawanishi, *ibid.*, **26**, 1929 (1978); *e*) T. Fujii, T. Saito, T. Itaya, K. Kizu, Y. Kumazawa, and S. Nakajima, *ibid.*, **35**, 4482 (1987); *f*) T. Fujii, T. Itaya, T. Saito, K. Mohri, M. Kawanishi, and T. Nakasaka, *ibid.*, **37**, 1504 (1989).
7) *a*) T. Fujii, F. Tanaka, K. Mohri, T. Itaya, and T. Saito, *Tetrahedron Lett.*, **1973**, 4873; *b*) T. Fujii, T. Saito, T. Sakuma, M. Minami, and I. Inoue, *Heterocycles*, **16**, 215 (1981); *c*) T. Fujii and T. Saito, *ibid.*, **17**, 117 (1982).
8) H. Iio, K. Asao, and T. Tokoroyama, *J. Chem. Soc., Chem. Commun.*, **1985**, 774.
9) *a*) H. Nakamura, H. Wu, Y. Ohizumi, and Y. Hirata, *Tetrahedron Lett.*, **25**, 2989 (1984); *b*) H. Wu, H. Nakamura, J. Kobayashi, M. Kobayashi, Y. Ohizumi, and Y. Hirata, *Bull. Chem. Soc. Jpn.*, **59**, 2495 (1986).
10) *a*) G. L. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna, and D. Viterbo, *Acta Crystallogr., Sect. A*, **38**, 663 (1982); *b*) G. Cascarano, C. Giacovazzo, M. Camalli, R. Spagna, M. C. Burla, A. Nunzi, and G. Polidori, *ibid.*, **40**, 278 (1984); *c*) G. Cascarano, C. Giacovazzo, and D. Viterbo, *ibid.*, **43**, 22 (1987).
11) J. A. Ibers and W. C. Hamilton (eds.), "International Tables for X-ray Crystallography," Vol. IV, Kynoch Press, Birmingham, 1974.
12) *a*) R. Taylor and O. Kennard, *J. Mol. Struct.*, **78**, 1 (1982); *b*) T. F. Lai and R. E. Marsh, *Acta Crystallogr., Sect. B*, **28**, 1982 (1972).
13) T. Fujii, T. Saito, and T. Date, *Chem. Pharm. Bull.*, **37**, 1208 (1989).
14) G. I. Birnbaum, B. Kierdaszuk, and D. Shugar, *Nucleic Acids Res.*, **12**, 2447 (1984).
15) *a*) M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899 (1977); *b*) *Idem*, *ibid.*, **99**, 4907 (1977).
16) A. Sygula and A. Buda, *J. Mol. Struct.* (*THEOCHEM*), **92**, 267 (1983).
17) Program No. 464, Quantum Chemistry Program Exchange (MOPAC), Indiana University, Bloomington, IN.
18) *a*) R. Fletcher and M. J. D. Powell, *Comput. J.*, **6**, 163 (1963); *b*) W. C. Davidon, *ibid.*, **10**, 406 (1968).