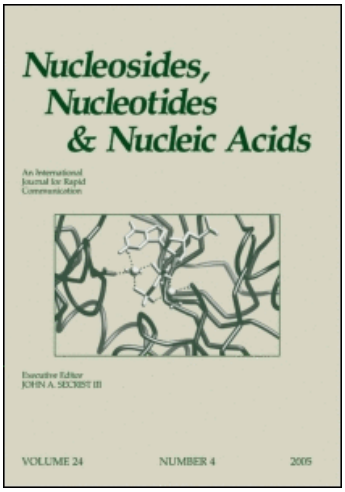

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Crystal and Molecular Structure of a Cytosine Analog; 5-Bromo-6-Benzylamino Isocytosine

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CRYSTAL AND MOLECULAR STRUCTURE OF A CYTOSINE ANALOG; 5-BROMO-6-BENZYLAMINO ISOCYTOSINE

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Abstract: Isocytosines are formal analogue of isoguanines for pairing with hydrogen bonds and are substrates for target enzymes for chemotherapy of infections diseases. The compound 5-bromo-6-benzylamino isocytosine crystallized in space group $P2_1/c$ with a =11.393(1)Å, b = 7.341(2)Å, c = 14.425(1) Å, β = 92.06(2)°. The structure was determined by heavy atom methods and refined by full matrix least squares to R = 6.8% based on 1935 X-ray structure amplitudes. The isocytosine ring in the molecule is protonated at N(3) with internal bond angle of 122° compared to 117° at N(1). The structure is stabilized by intermolecular hydrogen bonding pattern based on N-H..N and N-H....O hydrogen bonds.

The crystal and molecular structure of 5-bromo-6-benzylamino isocytosine was undertaken as a part of a major programme of research on the structure of components related to nucleic acids. This class of compounds under investigation are natural substrates to target enzymes for chemotherapy of infectious diseases and cancer, and the present compound is a potential inhibitor of the bacterial polymerase III[1].

EXPERIMENTAL

The title compound crystallizes from ethanol in the form of transparent needles by slow evaporation. One of them measuring 0.10 x 0.17 x 0.26 mm, was used for photography and data collection. Precession photographs showed systematic absences corresponding to the space group $P2_1/c$. The crystal was mounted on a CAD-4 diffractometer, and cell dimensions were calculated from least-squares refinement of 25 reflections.

Crystal data are: $C_{11}N_4OBrH_{11}$, Mr = 295, monoclinic, a = 11.393(1), b = 7.341(2), c = 14.425(1)Å, β = 92.06(2)°, V = 1205.7 Å^3, Z = 4, Dx = 1.626 gm/cm^{-3}, μ= 46.02 cm^{-1}, F(OOO) = 592.

Intensities were measured with Ni-filtered CuKα radiation, using ω-2θ scan mode. There were 2048 unique reflections with $2\theta < 110°$, of

TABLE 1. Final atomic co-ordinates with e.s.d's in parentheses and equivalent isotropic values of the anisotropic thermal parameters for non-H atoms.

$$Beq = \frac{4}{3} \Sigma_i \Sigma_j \beta_{ij} \cdot a_i \cdot a_j$$

Atoms	X	Y	Z	Beq (Å)
Br	Ø.2780(Ø)	Ø.4948(1)	Ø.3782(Ø)	3.77
O(4)	Ø.4373(3)	Ø.1538(4)	Ø.4160(2)	3.51
N(2)	Ø.4841(4)	Ø.2067(6)	Ø.7306(3)	2.99
N(1)	Ø.3720(3)	Ø.4245(5)	Ø.6560(3)	2.67
C(4)	Ø.4143(4)	Ø.2462(6)	Ø.4865(3)	2.59
N(6)	Ø.2548(4)	Ø.6343(6)	Ø.5800(3)	3.65
C(2)	Ø.4377(3)	Ø.2745(6)	Ø.6522(3)	2.34
C(6)	Ø.3254(4)	Ø.4871(5)	Ø.5745(4)	2.65
N(3)	Ø.4594(3)	Ø.1873(5)	Ø.5720(2)	2.74
C(5)	Ø.3458(4)	Ø.4043(6)	Ø.4903(3)	2.60
C(8)	Ø.1292(4)	Ø.8583(7)	Ø.6494(3)	3.39
C(7)	Ø.2272(6)	Ø.7234(11)	Ø.6659(4)	5.33
C(9)	Ø.1556(6)	1.Ø393(9)	Ø.6345(6)	5.11
C(1Ø)	Ø.Ø143(6)	Ø.8Ø57(9)	Ø.6485(5)	5.13
C(11)	-Ø.Ø485(8)	1.1Ø75(13)	Ø.6154(5)	6.75
C(12)	-Ø.Ø765(6)	Ø.9271(14)	Ø.6313(7)	6.74
C(13)	Ø.Ø634(1Ø)	1.16Ø1(1Ø)	Ø.6175(7)	7.Ø5

those 1935 reflections had $I > 3\sigma(I)$ and were considered observed. The intensities were corrected for Lorentz Polarization factors but not for absorption correction. The structure was determined by heavy atom methods and refined by full matrix least squares on F. All the H-atoms have been located from ΔF synthesis and refined isotropically. Final R value is 0.068 and wR = 0.077; with $(\Delta/\sigma)_{max}$ = 0.99. Final difference fourier map showed no significant features. Atomic scattering factors were taken from International Tables for X-ray crystallography[2]. All calculations were performed on B6700 computer using XRAY ARC programme[3].

RESULTS AND DISCUSSIONS

Atomic co-ordinates are given in TABLE 1. Bond lengths and bond angles for the molecule are shown in FIG 1. Packing of the title compound is shown in FIG 2. Isocytosines are formal analogue of isoguanines, structural data and comprehensive study on tautomerism for these are reported[4]. To

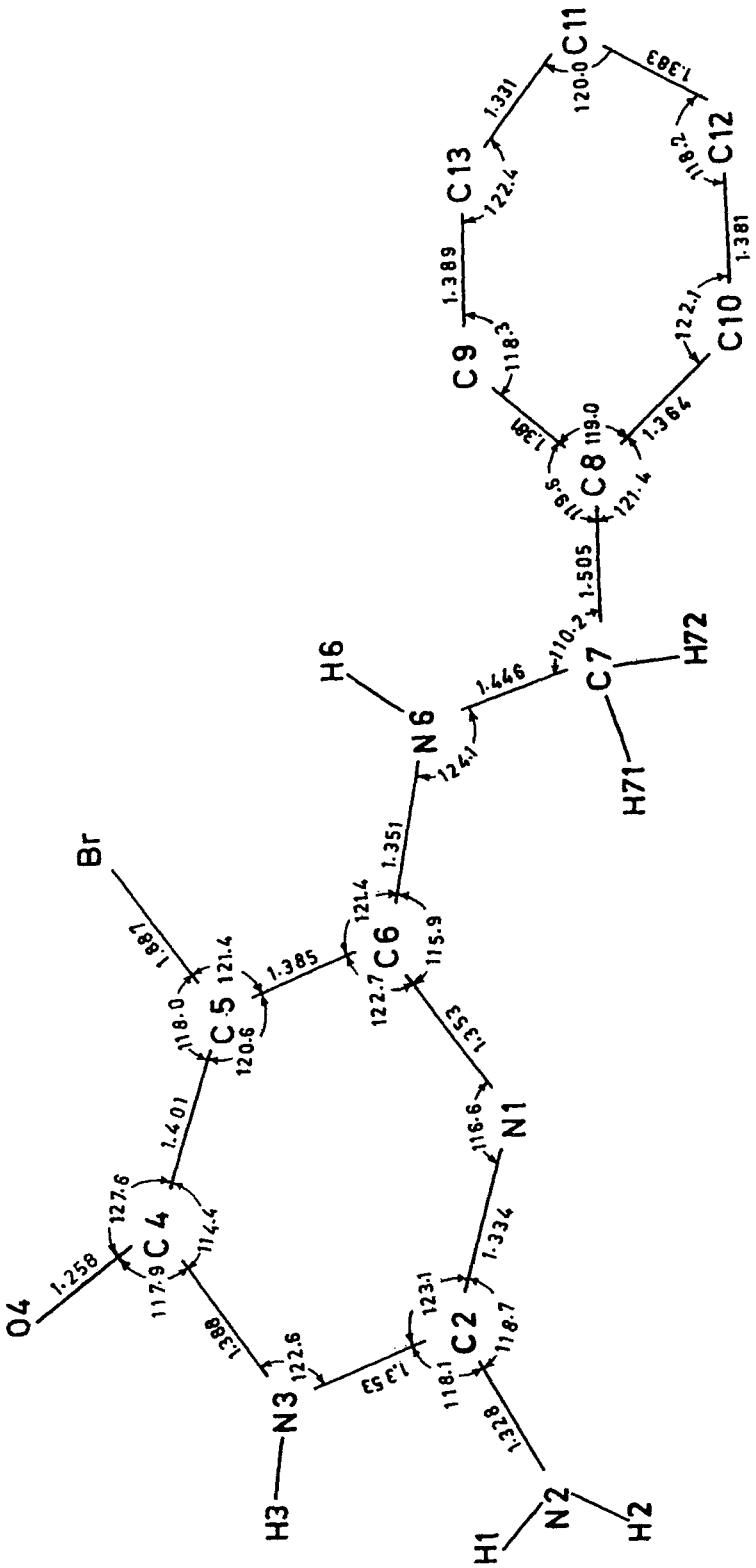

Fig. 1 A schematic diagram of the molecule with bond lengths and bond angles.

TABLE 2. Some selected dihedral angles (°).

C(6) - N(1) - C(2) - N(2)	-179.2	(4)
C(2) - N(1) - C(6) - C(5)	-1.4	(6)
C(2) - N(1) - C(6) - N(6)	177.1	(4)
C(6) - N(1) - C(2) - N(3)	Ø.7	(6)
N(3) - C(4) - C(5) - Br	-179.1	(3)
O(4) - C(4) - C(5) - C(6)	177.7	(5)
O(4) - C(4) - N(3) - C(2)	-178.5	(4)
N(3) - C(4) - C(5) - C(6)	-1.4	(6)
C(5) - C(4) - N(3) - C(2)	Ø.7	(6)
C(7) - N(6) - C(6) - N(1)	-Ø.5	(7)
C(6) - N(6) - C(7) - C(8)	-169.2	(5)
C(7) - N(6) - C(6) - C(5)	178.1	(5)
N(2) - C(2) - N(3) - C(4)	179.5	(4)
N(6) - C(6) - C(5) - C(4)	-176.6	(4)
C(9) - C(8) - C(7) - N(6)	-95.4	(6)
C(1Ø) - C(8) - C(1Ø) - C(12)	1.3	(1Ø)
C(7) - C(8) - C(1Ø) - C(12)	-178.5	(7)
C(7) - C(8) - C(9) - C(13)	178.7	(7)
C(1Ø) - C(8) - C(9) - C(13)	-1.1	(9)
C(8) - C(9) - C(13) - C(11)	Ø.2	(13)
C(8) - C(1Ø) - C(12) - C(11)	-Ø.6	(12)
C(12) - C(11) - C(13) - C(9)	Ø.6	(14)
C(13) - C(11) - C(12) - C(1Ø)	-Ø.4	(13)

a chemist, 5-bromo-6-benzylamino isocytosine can have two tautomer forms (Fig 3). Of the two tautomeric forms, 3(a) is theoritically more populated due to more mesomeric forms. The difference fourier map also confirmed the protonation sites as N(3) as predicated above.

The N(6)-C(7) and N(6)-C(6) bonds are significantly different: 1.446(8) and 1.351(6) Å respectively. This N(6) - C(6) bond is the intermediate between a single and a double bond character, while the former N(6) - C(7) is a single bond. This difference is probably due to the delocalization of the loan pair electron on N(6) which remains in conjugation with C(5) - C(6) bond whereas C(7) - C(8) has no π electrons, and does not take part in the delocalization over N(6) - C(7) bond. It is observed that the isocytosine ring and phenyl ring are not coplanar. Free rotation of isocytosine ring about single bond N(6) - C(7) and phenyl ring about C(7) - C(8) are possible. The final molecular conformation is determined by the hybridization of N(6) and C(7) atoms and steric factors. The dihedral angle between the mean planes of the two rings is 93.7°. The atoms C(7), N(6) are coplanar with the isocytosine ring whereas the N(6) - C(7) bond is perpendicular to the phenyl

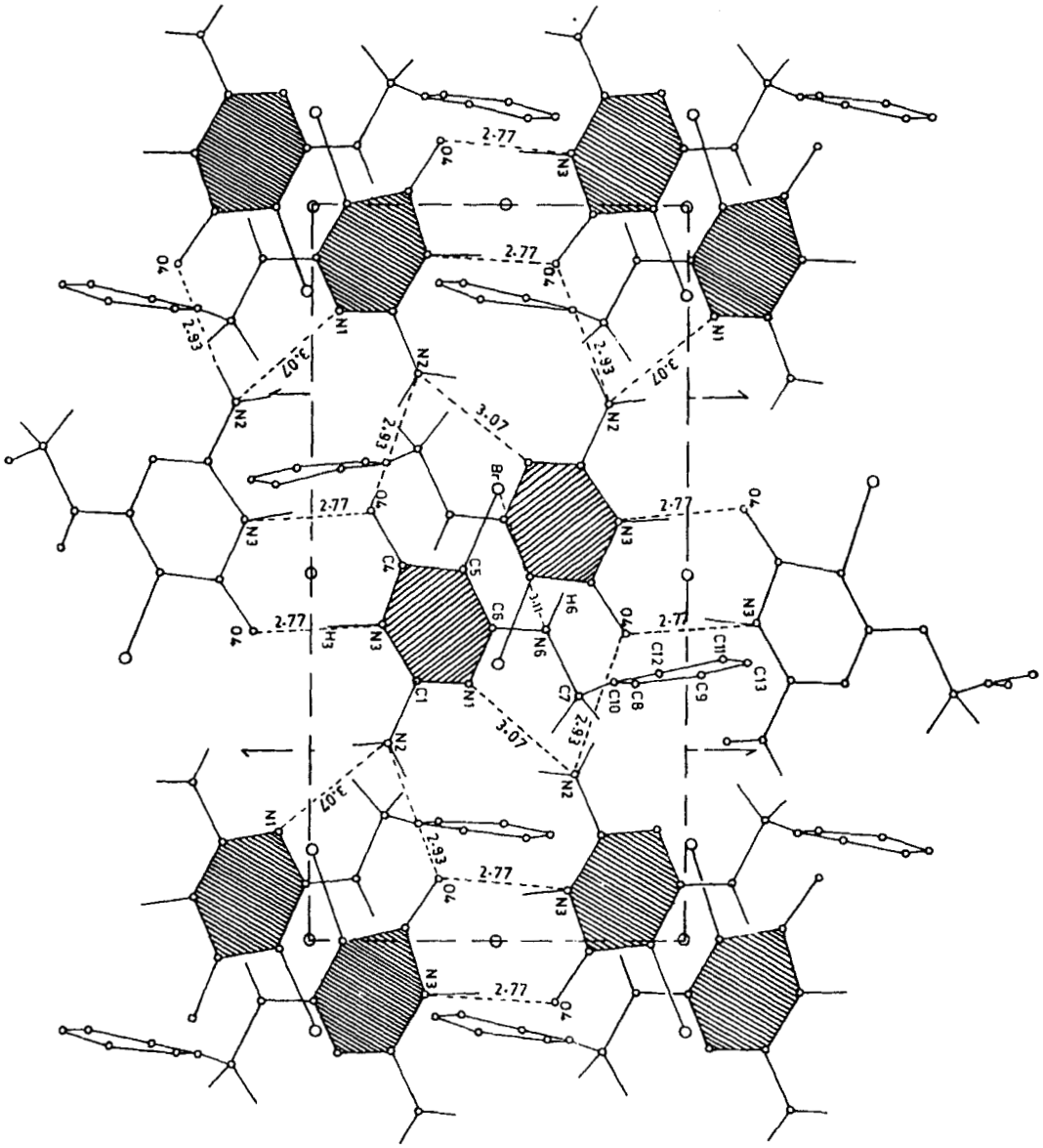

Fig. 2 A detailed packing of 5-bromo-6-benzylamino isocytosine molecules down a -axis.

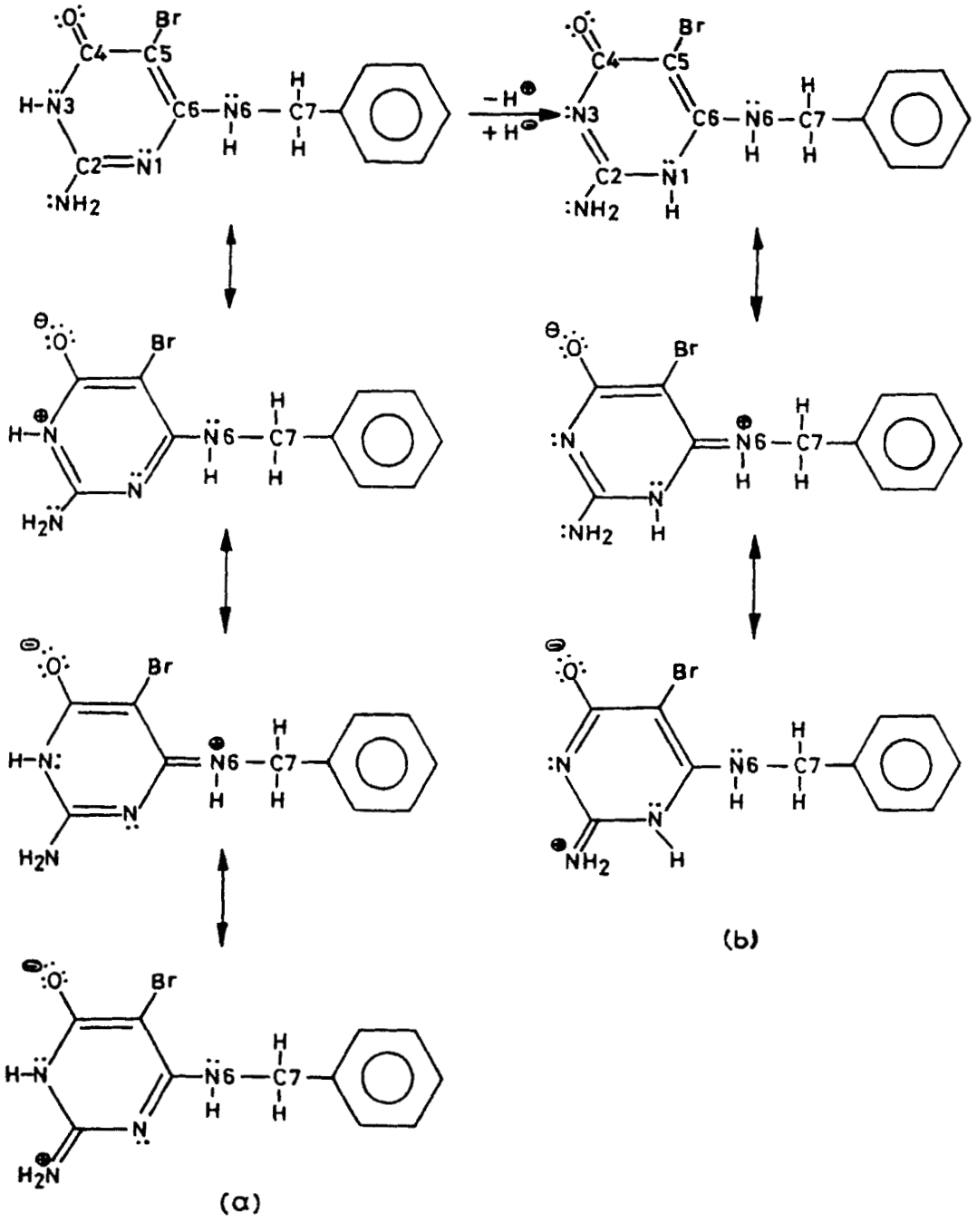

Fig.3 The two possible tautomeric forms of 5-bromo-6-benzyl-amino isocytosine and their mesomeric structure.

TABLE 3. Hydrogen contact distances and angles of 5-bromo-6-benzylamino isocytosine, 6-methyl isocytosine and isocytosine molecules.

D	A	A at	distance, Å		angle, deg
			D-A	H-A	D-H...A
5-bromo-6-benzylamino isocytosine					
N(6)-H(6)...Br		X, Y, Z	3.1Ø6(4)	2.62(6)	122.1(5.Ø)
N(3)-H(3)...O(4)		-X+1,-Y,-Z+1	2.77Ø(5)	1.65(6)	176.5(5.3)
N(2)-H(1)...O(4)		X,-Y+1/2,Z+1/2	2.93Ø(5)	2.17(6)	169.8(5.7)
N(2)-H(2)...N(1)		-X+1,Y-1/2,-Z+3/2	3.Ø76(6)	2.36(6)	143.5(5.3)
6-methyl isocytosine					
N(1)-H(1)...O(8)		X,1+Y,Z	2.716		15Ø.Ø
N(7)-H(2)...O(8)		2-X,-Y,-Z	2.973		171.Ø
N(7)-H(3)...O(8)		X,1+Y,Z	2.855		152.Ø
Isocytosine					
N(7B)-H....O(8A)		X,Y,Z	2.861	1.967	177.8
N(3B)-H....N(3A)		X,Y,Z	2.9Ø8	1.955	177.2
N(7A)-H....O(8B)		X,Y,Z	2.9Ø4	1.954	174.6

ring. In numerous pyrimidine structures[5], the interior bond angle is usually smaller at the ring N with a lone pair of electrons than at the protonated N as in 6-methyl isocytosine[6]; and in our case the angle C(6) - N(1) - C(2) [116.6°(4)] is 6° less than C(2) - N(3) - C(4) [122.6°(4)] in good agreement with convensional cases. The bonds about the atoms N(1) & N(3) in our

structure are N(1) - C(2) 1.334(5)Å and C(2) - N(3) 1.353(5)Å; C(6) - N(1) 1.353(7)Å and N(3) - C(4) 1.388(5)Å. The nature of bonds is comparable to those of 6-methyl isocytosine but the bonding about N(1) are weaker and longer than those to N(3). The C=0 and N(2) - C(2) bond distances of 1.258(5)Å & 1.328(5)Å respectively are expected for this class of compounds[7,8].

Hydrogen bond is important in biosystems & biomolecular interactions. The structure is stabilized by intermolecular hydrogen bonding N(3)-H....0(4) [2.77(5)Å] ; N(2)-H...0(4)[2.93(5)Å] ; N(2)-H...N(1) [3.07(6)Å] Fig 2, but no significant base stacking is observed. The protonated N(3) is hydrogen bonded to 0(4) in a symmetrical fashion about a center of inversion forming a plate like base-pair. A network of hydrogen bonds as observed in our compound, 6-methyl isocytosine and isocytosine are given in TABLE 3 for comparison. The N....N contact distance [3.076(6)Å] found here is rather longer than N.... N distance of 6-methyl isocytosine [2.973(3)Å] . Oxygen 0(4) acts as proton acceptor in two hydrogen bonds one from the amino group N(2) (at X,-Y+1/2,Z-1/2) of distance 2.93(5)Å and the other from the protonated N(3) (-X+1,-Y,-Z+1) of 2.77(5)A, in the 6-methyl isocytosine 0(8) acts as proton acceptor in two hydrogen bonds from the same adjacent molecule, one with the protonated N(1) (2.72Å) and the other with the amino group (2.85Å); while in N-methyl cytosine[9] the interactions N-H....N (3.04Å) occured with one partner molecule and the N-H...0 (2.90Å) with another.

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