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Molecular and crystal structures of dialkylated adenines (N^6,N^9-Me_2Ade, N^3,N^6-MeBnAde) and cytosines (N^1,N^4-Me_2Cyt)

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ABSTRACT

N^6,N^9-Dimethyladenine (N^6,N^9-Me_2Ade, **1**) and N^1,N^4-dimethylcytosine (N^1,N^4-Me_2Cyt, **3**) were obtained by conventional methods, whereas the reaction of N^6-benzyladenine with MeI/NaOH resulted in the formation of N^3,N^6-MeBnAde (**2a**) and N^6,N^9-BnMeAde (**2b**). All compounds were fully characterized by microanalysis, NMR spectroscopy (^{1}H, ^{13}C) and **1**, **2a**·2MeOH and **3** also by single-crystal X-ray diffraction analyses. In single-crystals of **1**, obtained from THF solutions, twofold N6–H···N7′ hydrogen-bonded dimeric units (N^6,N^9-Me_2Ade)$_2$ (AA1^2 type according to Jeffrey and Saenger, 1991) were found. This proved to be another modification than that obtained by crystallization N^6,N^9-Me_2Ade from MeOH/PhCl (Sternglanz, 1978). Crystals of **2a**·2MeOH exhibited an analogous hydrogen bond pattern as found in **1**. The shorter N6···N7′ distance in **2a**·2MeOH (2.932(2) Å) indicates slightly stronger hydrogen bonds than in **1** (3.078(3) Å). Crystals of **3** are built up from centrosymmetric dimers (N^1,N^4-Me_2Cyt)$_2$ having a twofold N4–H···N3′ hydrogen bond, thus exhibiting the CC3^2 hydrogen bond pattern. The hydrogen bonding patterns in the dialkylated nucleobase derivatives are discussed in terms of those found in crystals of the less substituted nucleobases N^9-MeAde and Cyt/N^1-MeCyt, respectively.

1. Introduction

Although hydrogen bonds belong to the weaker forces in chemistry, they play a major role for understanding the chemistry of life. Thus hydrogen bonds between nucleobases are fundamental to understanding their structures, reactivities and intermolecular associations, both between different (hetero-base pairing) and identical nucleobases (homo-base pairing) [1,2]. Due to the manifold hydrogen donor and acceptor sites and the existence in different tautomeric forms, a large number of hydrogen bond patterns exists between nucleobases, even in homo-base pairs. Overall six homo-base pairs of adenine and three of cytosine were described. All these types were denoted in a four-character code (e.g., AA1^2) whereas the first two letters stand for the involved bases (A, Ade; C, Cyt; G, Gua; U, Ura) followed by a sequential number and an exponent describing twofold (2) and threefold (3) hydrogen bonds, respectively, see Scheme 2 for examples [1]. Besides the "parent" nucleobases, a multitude of *N*-alkylated nucleobases are known. These derivatives, found in mutant organisms [3], may give rise to base mispairing under biological conditions [4]. This may be caused, at least in part, by different hydrogen bond patterns that proved to be highly sensitive even against small variations in substituents and environmental conditions. Blocking the N^9 and N^1 position in adenines and cytosines, respectively, by an alkyl group leads to model compounds for nucleosides that are frequently used in coordination chemistry [5]. Here we report the crystal structures of the dialkylated nucleobases N^6,N^9-dimethyladenine (**1**), N^3-methyl-N^6-benzyladenine (**2a**·2MeOH) and N^1,N^4-dimethylcytosine (**3**) and discuss their hydrogen bonding patterns in crystals.

2. Results and discussion

2.1. Synthesis and characterization

As described in Ref. [6] N^6,N^9-dimethyladenine (**1**, Scheme 1) was synthesised by the reaction of N^9-methyladenine and methyl iodide resulting in the N^1 methylated product that underwent in alkaline medium a Dimroth rearrangement yielding **1** [7]. The cytosine derivative N^1,N^4-dimethylcytosine (**3**, Scheme 1) was obtained by the reaction of 1-methyl-4-methoxypyrimidin-2-one with methyl amine according to Ref. [8]. Own experiments exhibited that the reaction of the commercially available N^6-benzyladenine with methyl iodide and sodium hydroxide resulted in a mixture of N^3-methyl-N^6-benzyladenine (**2a**) and N^6-benzyl-N^9-methyladenine (**2b**). The isomers were separated by preparative centrifugal thin-layer chromatography and obtained as white microcrystalline products in 25% and 30% yield, respectively

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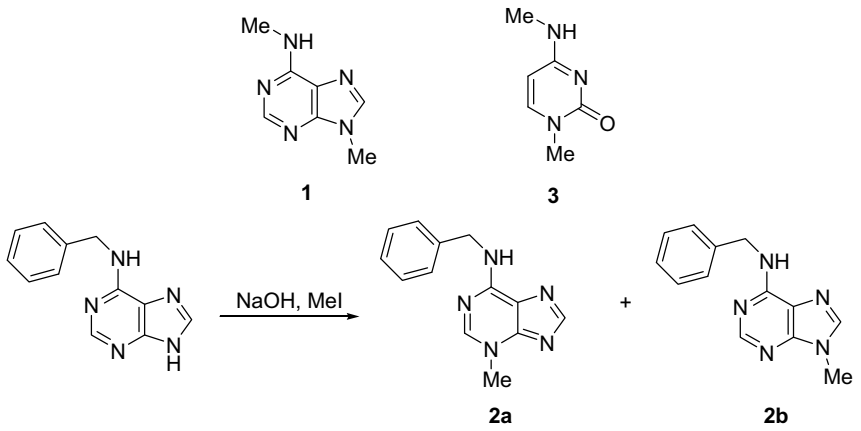


Scheme 1. Formulae and synthesis of nucleobase derivatives **1–3**.

(Scheme 1). The identities of all substances were characterized by microanalysis and by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR data of **1** [6], **2b** [9] and **3** [10] proved to be identical with those given in the literature. Furthermore, the crystal structures of **1**, **2a**·2MeOH and **3** could be obtained by single-crystal X-ray diffraction analyses.

2.2. Crystal structure of N^6,N^9-dimethyladenine (*1*)

Crystals of **1** for X-ray diffraction measurements were obtained from THF solution. **1** crystallized in the monoclinic space group $P2_1/c$ in dimeric (N^6,N^9-Me$_2$Ade)$_2$ units between them no unusual contacts were found (shortest contact between non-hydrogen atoms: 3.355(7) Å for N1···C8″). The structure of the dimers is shown in Fig. 1, selected bond lengths and angles are listed in the Figure caption. The monomers are planar in good approximation (greatest deviation from the mean plane: 0.075(3) Å for C9). The centrosymmetric dimers represent a twofold hydrogen-bonded homo-base pair of the type AA1[2] [1], the geometric parameters of the N6–H···N7′ hydrogen bonds are given in Table 1. By recrystallization from MeOH/PhCl Sternglanz [11] obtained another modification of N^6,N^9-dimethyladenine (**1′**; monoclinic, space group $P2_1/c$). Although the two modifications crystallize in the same space group, the hydrogen bond patterns in crystals of **1** and **1′** are different. As for **1**, the central units in **1′** are dimers of the AA1[2] type. Additionally, the N1 atoms act as H acceptors yielding N6–H···N1 hydrogen bonds. Thus, the crystals of **1′** consist of tetrameric units (Scheme 2).

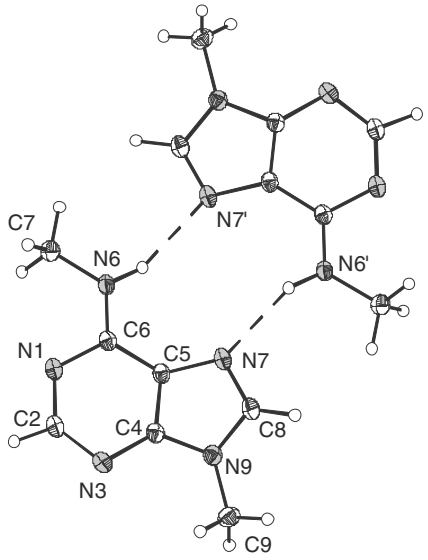


Fig. 1. The dimeric unit (N^6,N^9-Me$_2$Ade)$_2$ in crystals of **1**. The displacement ellipsoids are drawn at the 30% probability level. Selected bond lengths (in Å) and angles (in °): N1–C6 1.361(3), N6–C6 1.334(3), N6–C7 1.449(3), N9–C8 1.368(3), N9–C9 1.449(3), C2–N1–C6 118.2(2), C2–N3–C4 110.7(2), C5–N7–C8 103.9(2).

Table 1
Geometrical parameters of hydrogen bonds of AA1[2] type [1] in adenine derivatives and of CC3[2] type [1] in cytosine derivatives

	1[a]	**1′**[b]	**2a** 2MeOH[a]	(AdeH)Cl·$^{1/2}$H$_2$O[c]
N6···N7′	3.078(3)	3.020	2.932(2)	2.901(1)
N6–H	0.90	0.89	0.98	0.95
H···N7′	2.33	2.17	2.01	2.00
N6–H···N7′	159	159	157	159
	3[a]	N^1-MeCyt[d]	5-MeCyt·$^{1/2}$H$_2$O[e]	
N4···N3′	3.024(3)	3.038(2)	3.064(3)	
N4–H	0.90	0.91	0.89	
H···N3′	2.13	2.14	2.18	
N4–H···N3′	176	167	177	

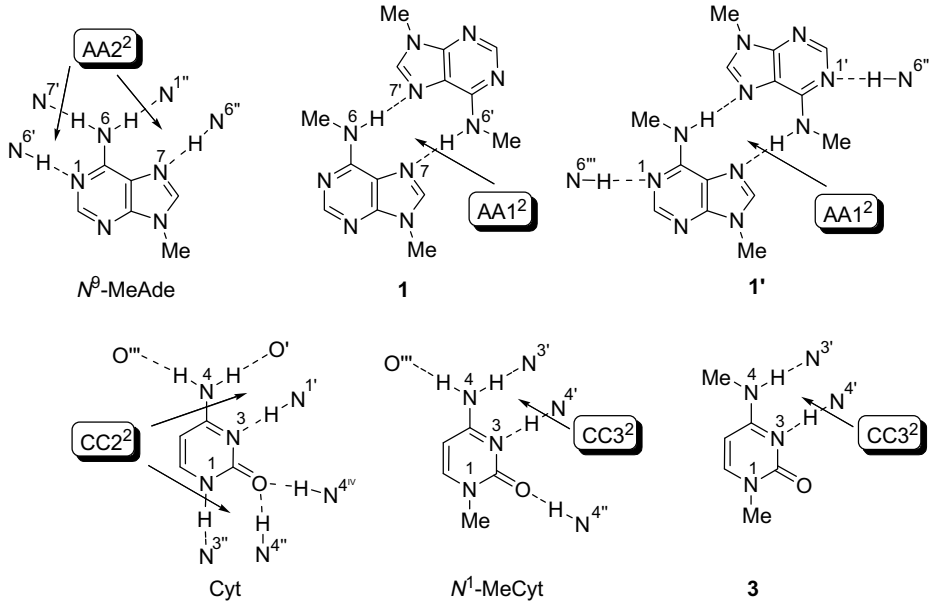
[a] This work.
[b] Taken from Refs. [11,24].
[c] Taken from Refs. [16,24].
[d] Taken from Refs. [15,24].
[e] Taken from Refs. [18,24].

2.3. Crystal structure of N^3-methyl-N^6-benzyladenine (*2a*·2MeOH)

Well shaped crystals of **2a**·2MeOH suitable for single-crystal X-ray diffraction measurements were obtained from methanol solution at 6 °C. **2a**·2MeOH crystallized in the monoclinic space group $C2/c$ in isolated centrosymmetric dimeric (N^3,N^6-MeBnAde·2MeOH)$_2$ units that are shown in Fig. 2 along with selected bond lengths and angles in the Figure caption. Between these units no unusual contacts were found (shortest distance between non-hydrogen atoms: 3.311(8) Å for N9···C2″). Analogous to **1**, the planar nucleobases (greatest deviation from the mean plane is 0.031(2) Å for C5) are twofold N6–H···N7′ hydrogen-bonded (Table 1; type: AA1[2]). Furthermore, the N9 atoms act as hydrogen acceptor for solvate MeOH molecules (N9···O1 2.748(2) Å, O1–H 0.93 Å, H···N9 1.82 Å, N9–H–O1 176°). Additionally, the O1 atoms act as hydrogen acceptors for another solvate molecules forming O2–H···O1 hydrogen bonds (O2···O1 2.748(3) Å, O2–H 0.96 Å, H···O1 1.80 Å, O2–H–O1 169°).

2.4. Crystal structure of N^1,N^4-dimethylcytosine (*3*)

Recrystallization from boiling ethanol resulted in monoclinic single-crystals of **3** (space group $P2_1/c$). The crystals are built up from centrosymmetric (N^1,N^4-Me$_2$Cyt)$_2$ dimers shown in Fig. 3.



Scheme 2. Hydrogen bond patterns in crystals of cytosine and in mono- and dimethylated adenines and cytosines.

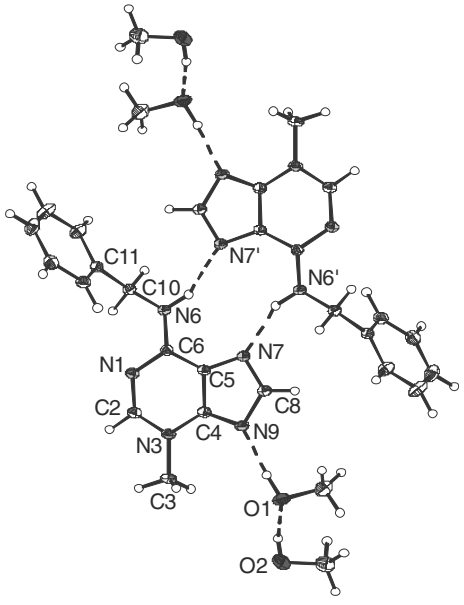


Fig. 2. The dimeric unit (N^3,N^6-MeBnAde·2MeOH)$_2$ in crystals of **2a**·2MeOH. The displacement ellipsoids are drawn at the 30% probability level. Selected bond lengths (in Å) and angles (in °): N1–C6 1.376(2), N6–C6 1.334(2), N3–C3 1.471(2), N6–C10 1.455(2), N9–C8 1.363(2), C2–N1–C6 119.5(2), C2–N3–C4 116.4(2), C5–N7–C8 102.2(1).

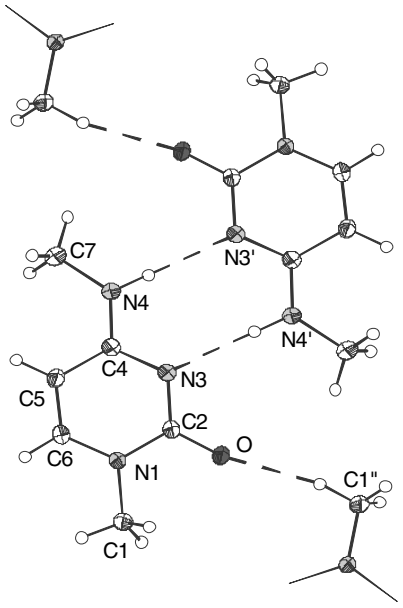


Fig. 3. The dimeric unit (N^1,N^4-Me$_2$Cyt)$_2$ in crystals of **3**. The displacement ellipsoids are drawn at the 30% probability level. Selected bond lengths (in Å) and angles (in °): N1–C1 1.468(3), N1–C2 1.401(3), N4–C4 1.341(3), N4–C7 1.456(3), C2–O 1.237(3), C2–N1–C6 120.5(2), N1–C2–N3 119.1(2), C2–N3–C4 120.0(2).

Selected bond lengths and angles are given in the Figure caption. The molecules are planar in good approximation (greatest deviation from the mean plane: 0.036(3) Å for N4). Two cytosine molecules were found to be twofold hydrogen-bonded (N4–H···N3′, Table 1), thus exhibiting a hydrogen bond pattern of the CC3^2 type [1]. Furthermore, these dimers are connected by additional C1″–H···O hydrogen bonds resulting in a two dimensional structure. The C1″···O distance (3.197(3) Å) is in the typical range for C–H···O hydrogen bonds of this type [12].

2.5. Discussion

In general, stepwise alkylation of the "parent" nucleobases (adenine, cytosine) limits the number of possible tautomers and, as a consequence, also the variety of hydrogen bond patterns. To verify this, only nucleobases crystallizing without additional solvent molecules should be considered. Because the crystal structure of solvate-free non-methylated adenine is not described yet, in Scheme 2 the hydrogen bonding patterns in crystals of the monomethylated adenine N^9-MeAde [13] and dimethylated adenine N^6,N^9-Me$_2$Ade **1**/**1**′ are shown. In crystals of N^9-MeAde the molecules are linked via hydrogen bonds of AA2^2 type (N6–H···N7′, N1···H–N6′) in ribbons. For N^6,N^9-Me$_2$Ade dimeric (**1**) and tetrameric units (**1**′), respectively, resulting from the hydrogen bonds of AA1^2 type were found.

In crystals of solvate-free cytosine (Cyt) [14] homo-base pairs of the CC2^2 types (N4–H···O′, N3···H–N1′) were found as shown in Scheme 2. Further N–H···O hydrogen bonds give rise to a three

Table 2
Crystal data, data collection and refinement parameters of **1** and **2a**·2MeOH and **3**

	1	**2a**·2MeOH	**3**
Empirical formula	$C_7H_9N_5$	$C_{15}H_{21}N_5O_2$	$C_6H_9N_3O$
Formula weight	163.19	303.37	139.16
T/K	220(2)	100(2)	153(2)
Crystal system/space group	Monoclinic/$P2_1/c$	Monoclinic/$C2/c$	Monoclinic/$P2_1/c$
a/Å	6.448(2)	30.951(4)	9.581(2)
b/Å	8.007(2)	4.963(2)	10.209(1)
c/Å	15.300(5)	21.335(3)	6.846(1)
β/°	100.14(4)	103.34(3)	96.04(2)
V/Å^3	777.6(4)	3189(2)	665.9(2)
Z	4	8	4
ρ/g cm^{-3}	1.394	1.264	1.388
μ/mm^{-1}	0.095	0.711	0.100
F(000)	344	1296	296
Scan range/°	$2.70 < \theta < 25.97$	$4.26 < \theta < 69.99$	$2.14 < \theta < 25.00$
Reciprocal lattice segments h,k,l	$-7 \rightarrow 7, -9 \rightarrow 9, -18 \rightarrow 18$	$-18 \rightarrow 37, -5 \rightarrow 6, -26 \rightarrow 25$	$-11 \rightarrow 11, -12 \rightarrow 10, -8 \rightarrow 8$
Reflections collected	5533	13358	4177
Reflections independent	1428 (R_{int} = 0.1390)	2903 (R_{int} = 0.0886)	1173 (R_{int} = 0.0754)
Data/restraints/parameters	1428/0/145	2903/0/284	1173/0/97
Goodness-of-fit on F^2	0.958	1.082	0.981
R_1, wR_2 [$I > 2\sigma(I)$]	0.0547, 0.1292	0.0702, 0.1989	0.0441, 0.1109
R_1, wR_2 (all data)	0.0811, 0.1446	0.0752, 0.2087	0.0738, 0.1178
Largest diff. peak and hole/e Å^{-3}	0.247/−0.279	0.452/−0.353	0.164/−0.197

dimensional cross linking of the cytosine molecules. In N^1-methylcytosine (N^1-MeCyt) [15] and N^1,N^4-dimethylcytosine (**3**) homobase pairs of the CC3^2 type are the central building blocks. Only in the monomethylated cytosine N^1-MeCyt these units are connected further via N4–H···O′ hydrogen bonds (Scheme 2).

In Table 1 geometrical parameters of the N6–H···N7′ hydrogen bonds in adenine derivatives of the AA1^2 type (N^6,N^9-Me$_2$Ade, **1**/**1**′; N^3,N^6-MeBnAde·2MeOH, **2a**·2MeOH; (AdeH)Cl·$^1/_2$H$_2$O) [16]) are given. The N6···N7′ distances indicate a much stronger hydrogen bond in the latter one, most likely, due to the positive charge in (AdeH)$_2^{2+}$. Furthermore, the quite strong hydrogen bond in the benzylated derivative **2a**·2MeOH can be interpreted in terms of the electron withdraw of the benzyl group [17]. The geometrical data of the N4–H···N3′ hydrogen bonds in CC3^2 type derivatives (N^1,N^4-Me$_2$Cyt, **3**; N^1-MeCyt [15], 5-MeCyt·$^1/_2$H$_2$O [18]) given in Table 1 are very similar in all three derivatives. The slightly longer N4···N3′ distance in 5-MeCyt·$^1/_2$H$_2$O might indicate a slightly weaker hydrogen bond.

3. Experimental part

3.1. General information

NMR spectra were recorded on Varian Gemini 2000 and Unity 500 spectrometers operating at 400 and 500 MHz for ^{1}H, respectively. Solvent signals (^{1}H, ^{13}C) were used as internal references. When necessary assignments were verified by gHMQC experiments and by running ^{13}C NMR spectra in APT mode, respectively. Microanalyses (C, H, N) were performed by the microanalytical laboratory of the University of Halle using CHNS-932 (LECO) elemental analyzer. Starting materials were commercially available. N^9-Methyladenine [19] and 1-methyl-4-methoxypyrimidin-2-one [20] were prepared according to the literature. The preparative thin layer chromatography was made by using a Chromatotron (Harrison Research).

3.2. Synthesis of N^6,N^9-dimethyladenine (*1*)

Compound **1** was synthesized from N^9-methyladenine (3.0 g, 20.1 mmol) and methyl iodide (4.3 g, 30.0 mmol) in dimethylacetamide (100 ml) according to Ref. [6]. The product was recrystallized from acetonitrile (30 ml) and finally dried in vacuo. Yield: 1.0 g (30%). Fp: 182–184 °C (Ref. [21] 181.5–182.5 °C). Anal. Calc. for $C_7H_9N_5$: C, 51.52; H, 5.56; N, 42.92. Found: C, 51.47; H, 5.60; N, 42.82%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.95 (s, br, 3H, N^6–C*H*$_3$); 3.71 (s, 3H, N^9–C*H*$_3$); 7.59 (s, br, 1H, N*H*); 8.05 (s, 1H, *H*^{8}); 8.21 (s, 1H, *H*^{2}). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 27.3 (s, N^6–*C*H$_3$); 29.3 (s, N^9–*C*H$_3$); 120.8 (s, *C*^{5}); 140.9 (s, *C*^{8}); 150.4 (s, *C*^{2}); 153.6 (s, *C*^{4}); 156.5 (s, *C*^{6}).

3.3. Synthesis of N^3-methyl-N^6-benzyladenine (*2a*) and N^6-benzyl-N^9-methyladenine (*2b*)

To a solution of N^6-benzyladenine (3.0 g, 13.3 mmol) and sodium hydroxide (560 mg, 14.0 mmol) in ethanol (100 ml) methyl iodide (1.99 g, 14.0 mmol) was added dropwise with stirring at −5 °C. After 2 h the solution was refluxed for 1 h. Then the solvent was removed in vacuo and the residue was extracted with methylene chloride (2 × 25 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The both formed isomers were separated by preparative centrifugal thin layer chromatography using at first diethyl ether/methanol (8/1) and then chloroform/methanol (4/1) as eluent to elute at first **2b** and then **2a**. The solvents of both fractions were removed in vacuo and the obtained products were dried under reduced pressure.

2a: Yield: 800 mg (25%). Fp.: 194–195 °C (Ref. [22] 203–204 °C). Anal. Calc. for $C_{13}H_{13}N_5$: C, 65.25; H, 5.48; N, 29.27. Found: C, 65.69; H, 5.67; N, 29.16%. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.87 (s, N^3–C*H*$_3$); 4.70 (s, br, 2H, N–C*H*$_2$); 7.18–7.33 (m, 5H, Phenyl); 7.74 (s, 1H, *H*^{8}); 8.33 (s, 1H, *H*^{2}), 8.85 (s, br, N*H*). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 35.8 (s, N^3–*C*H$_3$), 43.3 (s, N–*C*H$_2$); 109.5 (s, *C*^{5}); 126.7 (s, *p*-*C*H); 127.1 (s, *m*-*C*H); 128.2 (s, *o*-*C*H); 139.6 (s, *C*^{2}); 139.9 (s, *i*-*C*); 149.7 (s, *C*^{4}); 153.1 (s, *C*^{8}); 154.0 (s, C*6*).

2b: Yield: 950 mg (30%). Fp.: 124 °C (Ref. [9] 127–128 °C). Anal. Calc. for $C_{13}H_{13}N_5$: C, 65.25; H, 5.48; N, 29.27. Found: C, 65.22; H, 5.53; N, 28.92%. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.71 (s, N^9–C*H*$_3$); 4.71 (s, 2H, N–C*H*$_2$); 7.17–7.33 (m, 5H, Phenyl); 8.09 (s, 1H, *H*^{8}); 8.24 (s, 1H, *H*^{2}), 8.30 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 29.5 (s, N^3–*C*H$_3$), 43.0 (s, N–*C*H$_2$); 119.1 (s, *C*^{5}); 126.7 (s, *p*-*C*H); 127.2 (s, *m*-*C*H); 128.3 (s, *o*-*C*H), 139.8 (s, *i*-*C*); 140.4 (s, *C*^{8}); 148.7 (s, *C*^{4}); 152.5 (s, *C*^{2}); 154.5 (s, C*6*).

3.4. Synthesis of N^1,N^4-dimethylcytosine (**3**)

Compound **3** was synthesized according to Ref. [8] from 1-methyl-4-methoxypyrimidin-2-one (1.00 g, 7.1 mmol) and methyl amine (4 ml) in methanol whereas in Ref. [8] methyl amine in water was used. The product was recrystallized from boiling ethanol and finally dried in vacuo. Yield: 420 mg (43%). Fp.: 177 °C (Ref. [8] 179 °C). Anal. Calc. for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.20. Found: C, 52.10; H, 6.52; N, 29.81%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.73 (d, $^3J_{H,H}$ = 4.7 Hz, 3H, N^4–CH_3); 3.19 (s, 3H, N^1–CH_3); 5.61 (d, $^3J_{H,H}$ = 7.2 Hz, 1H, H^5); 7.44 (1H, br, NH); 7.48 (d, $^3J_{H,H}$ = 7.2 Hz, 1H, H^6). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 26.7 (s, N^4–CH_3); 36.4 (s, N^1–CH_3); 93.5 (s, C^5); 145.2 (s, C^6); 156.3 (s, C^2); 164.3 (s, C^4).

3.5. X-ray crystallography

Single-crystals of **1**, **2a** 2MeOH and **3** suitable X-ray diffraction analyses were obtained from THF, MeOH (at 6 °C) and EtOH solutions, respectively. The X-ray measurements were performed on a STOE IPDS diffractometer (**1**, **3**) and a Xcalibur PX diffractometer with Onyx CCD camera (**2a**·2MeOH), respectively, using Mo-$K\alpha$ (**1**, **3**; λ = 0.71073 Å) and Cu-$K\alpha$ radiation (**2a**·2MeOH; λ = 1.54180 Å). The crystallographic data and structure refinement parameters are listed in Table 2. The structures were solved by direct methods with SHELXS-97 [23] and refined using full-matrix least-squares routines against F^2 with SHELXL-97 [23]. Non-hydrogen atoms were refined with anisotropic and hydrogen atoms with isotropic displacement parameters. Hydrogen atoms were found in the difference Fourier maps and refined freely except the carbon bound H atoms of **3** which were included in calculated positions according to the riding model.

4. Supplemental materials

Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publication Nos. CCDC 676792 (**1**), CCDC 676793 (**2a** ·2MeOH) and CCDC 676794 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2, IEZ, UK [Fax: +44(0)1223/336 033; E-mail: deposit@ccdc.cam.ac.uk].

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