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Synthesis of 4,6-diamino-5-(polyhydroxyalkylamido)pyrimidines: conformation of the sugar chain

Derek Horton *, Oscar Varela [1]

Department of Chemistry, The Ohio State University, Columbus, OH 43210, USA

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Abstract

Condensation of 4,5,6-triaminopyrimidine with ethyl glycolate, D-ribono-1,4-lactone, D-allono-1,4-lactone, D-glucono-1,5-lactone, and L-gulono-1,4-lactone led to the corresponding 4,6-diamino-5-(hydroxyalkylamido)pyrimidines (**1a**–**e**). The conformations in acidic aqueous solution of these acyclic carbohydrate derivatives were determined from the proton–proton NMR coupling constants at 300 MHz. The polyhydroxyalkyl chain of compounds **1b**–**e** adopt sickle conformations in order to avoid the 1,3-parallel interactions between hydroxyl groups present in the planar zigzag conformer. Cyclization of 4,6-diamino-5-(hydroxyacetamido)pyrimidine (**1a**) afforded 8-(hydroxymethyl)adenine (**2a**), which was acetylated to give **2f**. The ^{13}C NMR spectra of compounds **1a**–**e** and **2a** and **f** are also reported.

Keywords: C-Nucleosides; Pyrimidine; Adenine; Open-chain sugar derivatives; Conformation

1. Introduction

The antiviral and/or antitumor activities of many naturally occurring C-nucleosides has prompted the synthesis of these compounds and related analogues having structural modifications in the heterocycle and carbohydrate portions [1]. El Khadem and Sindric have synthesized C-nucleoside analogues containing acyclic sugars by condensing aldonic acids with 4,5,6-triaminopyrimidine and pyrolysis of the resulting amides [2]. Such compounds have been also employed as precursors of ribofuranosyl heterocycles, formed by acid-catalyzed cyclization of the sugar chain [1].

We report here the preparation of a range of 4,6-diamino-5-(polyhydroxyalkylamido)pyrimidines, which constitute useful intermediates in the synthesis of 8-(polyhydroxyalkyl)adenines [2]. The latter are C-linked analogues of nucleosides containing acyclic sugars, a class of compounds that has been studied in detail in our laboratory [3]. The free hydroxyl groups of the carbohydrate portion can undergo further modifications or substitutions, leading to a wide variety of pyrimidine or adenine analogues.

* Corresponding author. Present address: Department of Chemistry, American University, Washington, DC 20016, USA.

[1] Present address: Departamento de Química Orgánica, Facultad Ciencias Exactas y Naturales, Pabellón 2, Ciudad Universitaria, 1428-Buenos Aires, Argentina.

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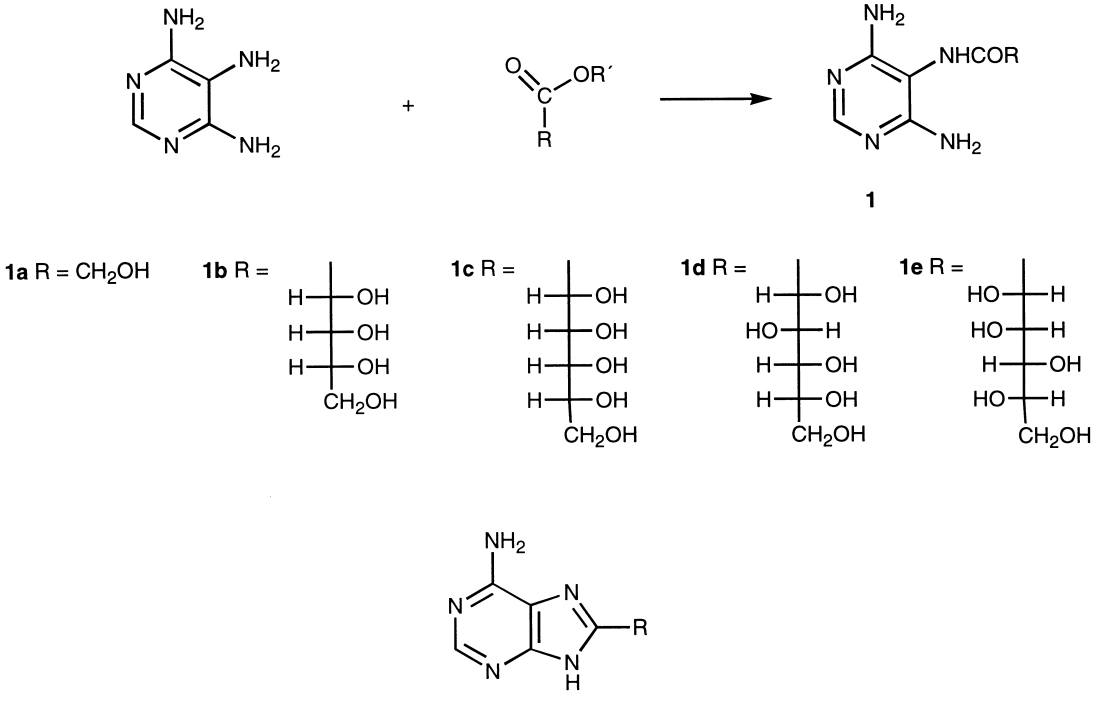
In order to provide conformational data of potential value in understanding the behavior of these compounds in biological systems, a study of the conformation of these pyrimidine derivatives in solution was undertaken. The favored conformations in solution for various unsubstituted derivatives of acyclic sugars, such as phenylosotriazoles [4], quinoxalines [5], benzylphenylhydrazones [6], diethyl and diphenyl dithioacetals [7], and 1-amino-1-deoxypentitols [8] have been reported. There has been much interest in the solution conformations of alditols, both free and partially or fully acetylated. Angyal [9,10] and Lewis [11] and their co-workers have performed extensive studies on such compounds, based on ^{1}H and ^{13}C NMR data. Also, the conformations of acetylated aldononitriles have been established by means of $J_{H,H}$ values and with the aid of molecular-mechanics calculations [12].

The aforementioned studies have shown that, in solution, the polyhydroxyalkyl chains follow the general principle [7] that the extended conformation is favored except when a parallel 1,3-interaction of substituent groups would thereby result. In such a case, in order to avoid this unfavorable interaction, 'sickle' conformations are adopted. Related work on the conformations of D-glucaric acid [13] and D-aldonic acids [14] in solution likewise indicated that rotation along a C–C bond of the hydroxyalkyl chain to eliminate 1,3-parallel interactions takes place, unless additional factors, such as hydrogen bonding, provide additional stabilization of the planar, extended form.

2. Results and discussion

Synthesis.—The amido derivatives were synthesized by condensing 4,5,6-triaminopyrimidine with aldonolactones, except for compound **1a** which was obtained from ethyl glycolate (see Scheme 1). The condensation took place by direct melting of the sugar lactone with 4,5,6-triaminopyrimidine or, alternatively, by boiling an acidic, aqueous solution of the two compounds. The pyrimidine derivatives crystallized from the neutral reaction mixture or were purified by column chromatography on H^+ form resin. The optimized results for each individual lactone are described in the experimental section. The yields obtained were higher than those reported in the literature for analogous reactions [2]. Only one of the two possible isomeric amides was obtained, because the 4- and 6-amino groups of 4,5,6-triaminopyrimidine are less



Scheme 1.

nucleophilic than N-5, owing to the inductive effect of the two ring-nitrogen atoms, and consequently substitution takes place on N-5 [2,15]. Similarly, under acidic conditions, the protonated N-5 contributes less to the resonance hybrids than the protonated N-4 or N-6, and again the 5-amido derivative is formed.

Pyrolysis of compound **1a** afforded 8-(hydroxymethyl)adenine (**2a**), which could also be readily prepared by a modification of the procedure of Giner-Sorolla and Brown [16]. Acetylation of **2a** with 1.2 molar equivalents of acetic anhydride in pyridine led to the *O*-acylated product **2f** in 62% yield. Attempted cyclization by pyrolysis of compounds **1b**–**e** to the adenine derivatives was unsuccessful, as extensive decomposition was observed. El Khadem and Sindric [2] reported a low yield (10%) of an 8-(tetritol-1-yl)adenine produced upon pyrolysis of the corresponding amide.

The structures of compounds **1a**–**e** and **2a**,**f** were confirmed on the basis of their ^{13}C and ^{1}H NMR spectra. The lowest-field signal in the ^{13}C NMR spectra of **1a**–**e** (Table 1) corresponded to the carbonyl group of the amide (177–179 ppm), and C-4 and C-6, being equivalent, gave a single signal downfield of the C-2 peak. The C-5 signal appeared upfield (94–98.5 ppm) because of shielding exerted by two ring-nitrogen atoms. The carbon atoms of the sugar chain (C-2′–C-4′ in **1b** and C-2′–C-5′ in **1c**–**e**) showed their signals in a rather narrow range (73–76 ppm), downfield from the hydroxymethyl group resonance (ca. 65 ppm). When compound **1a** was cyclized to **2a**, the carbon signal of the amide function, now incorporated into the aromatic system, was shifted upfield (150.5 ppm). Acetylation of **2a** gave the *O*-acylated derivative, with an accompanying large downfield shift of the methylene singlet from 4.22 to 5.25 ppm.

Conformational analysis.—The ^{1}H NMR spectra at 300 MHz of compounds **1a**–**e** were recorded for very dilute solutions of DCl in D_2O at 29 °C, and they were considered to be essentially first order, although in the case of the *ribo* (**1b**) and *allo* (**1c**) derivatives the H-4 and H-5 signals were partially overlapped. The proton assignments were verified by decoupling experiments. The values of the coupling constants (Table 2) provided information about the conformation of the sugar chain in solution.

The D-*ribo* derivative (**1b**) in the planar zigzag conformation (**P**) would have a parallel interaction between the hydroxyl groups attached at C-2 and C-4. Such a planar conformation should show a large coupling constant value for $J_{2',3'}$. However, the observed value ($J_{2',3'}$ 3.2 Hz) indicates gauche-disposed protons at C-2 and C-3, which suggests rotation along the C-2–C-3 bond to a sickle conformer. The resulting $_2G^-$ conformer is free of any parallel interaction of hydroxyl substituents. Taking into account that the observed $J_{2',3'}$ value should be the weighted average of the anti coupling (9.5 Hz) and the gauche coupling (2 Hz) [9], it is evident that the $_2G^-$ conformer of **1b** preponderates (> 80%) in solution. This observation is in accord with the favored conformational state found for

Table 1
^{13}C NMR chemical shifts (300 MHz) for pyrimidine derivatives **1a**–**e**

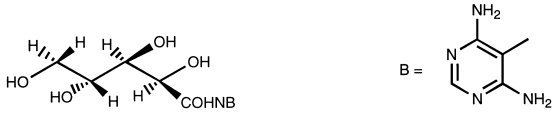
Compound	Configuration of the chain	*C*O	C-2	C-4	C-5	C-6	C-2′–6′
1a	Hydroxymethyl	178.6	151.4	158.9	98.3	158.9	64.2
1b	*ribo*	177.8	151.4	159.5	94.7	159.5	76.2; 75.5; 74.1; 65.4
1c	*allo*	178.5	152.1	159.6	95.5	159.6	75.6; 74.8; 74.6; 73.6; 65.6
1d	*gluco*	178.3	151.1	158.5	94.4	158.5	75.8; 74.0; 73.7; 73.5; 65.1
1e	*gulo*	177.9	151.1	158.5	94.2	158.5	75.9; 74.5; 74.4; 72.8; 65.1

Table 2
^{1}H NMR spectral data (300 MHz) for pyrimidine derivatives **1a**–**e**

Compound	Configuration of the chain	Coupling constant (Hz)						Chemical shift, δ (ppm)						
		$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'}$	$J_{5',6''}$	$J_{6',6''}$	H-aryl	H-2′	H-3′	H-4′	H-5′	H-6′	H-6″
1a	Hydroxymethyl							7.83	4.22					
1b	*ribo*	3.1	8.2	2.8	6.1 [a]		11.9 [b]	7.90	4.15	3.73	3.64	3.62	3.44 [c]	
1c	*allo*	2.7	8.5	4.2	2.8	7.1	11.8	7.89	4.31	3.90	3.68	3.66	3.53	3.41
1d	*gluco*	3.5	3.4	7.3	2.8	5.8	11.2	7.93	4.36	3.96	3.65	3.59	3.53	3.44
1e	*gulo*	5.6	4.2	4.2	4.3	6.8	11.7	7.94	4.27	3.77	3.69	3.63	3.50	3.42

[a] $J_{4',5'}$. [b] $J_{5',5''}$. [c] H-5″.

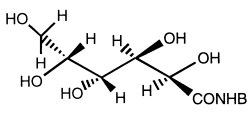
the diethyl dithioacetal [7], the 1-amino-1-deoxyalditol [8] and the alditol [9–11] of the *ribo* configuration, all of which are also $_2G^-$.



1b ($_2G^-$)

Regarding the terminal hydroxymethyl group, the observed value for $J_{4',5'}$ (6.1 Hz) is somewhat small for an exclusively antiperiplanar disposition of these protons, the arrangement encountered in the *gt* rotamer. Therefore, a conformer (*gg*) having H-4 bisecting the dihedral angle of the methylene group is to be expected, and the $J_{4',5''}$ value reflects the average of the rotamers present in the equilibrium mixture. In both rotamers H-4 and H-5 have the gauche disposition, and $J_{4',5''}$ (2.8 Hz) shows the expected small value. Crystallographic studies [17] support the idea that the terminal oxygen atom of an acyclic sugar derivative may readily adopt a disposition gauche to O-4 as well as an antiperiplanar arrangement. The average of coupling constants procedure allows the conclusion that the *gt* and *gg* rotamers are preponderant in the conformational equilibrium. The hydroxymethyl group of ribitol shows a similar behavior [11].

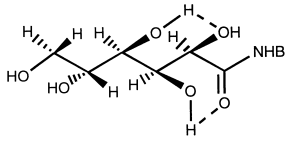
The *allo* derivative (**1c**) presents two sets of parallel interactions (OH-2–OH-4 and OH-3–H-5) in the **P** conformation. The C-2–C-4 segment of allose has the *ribo* relative stereochemistry, which would lead to prediction of a $_2G^-$ sickle conformation in this region, which is supported by the small $J_{2',3'}$ coupling constant (2.7 Hz). Also the magnitude of $J_{4',5'}$ (4.2 Hz) indicates another rotameric state along the C-4–C-5 bond, the $_4G^+$ sickle, in which the OH-3–OH-5 interaction is avoided. Therefore, the conformation of the allose pyrimidine derivative (**1c**) may be expressed as a double sickle arrangement ($_2G^-$,$_4G^+$). The same conformational preference was found for allitol [9,11] and fully acetylated derivatives of allose [18].



1c ($_4G^+$, $_2G^-$)

Similar considerations to those for the ribose derivative would indicate a significant proportion of other rotameric states along the C-5–C-6 bond. This type of chain-end flexibility is encountered in other acyclic hexose derivatives [18], and comparable arrangements have been found by crystallographic studies [19]. The other isomeric amidopyrimidines studied here [D-*gluco* (**1d**) and L-*gulo* (**1e**)] show the same behavior.

The pyrimidine derivative of D-*gluco* configuration (**1d**) shows an eclipsing interaction between OH-2 and OH-4 in the **P** conformation. Rotameric states having H-2 and H-3 antiparallel ($_2G^-$) or H-3 and H-4 antiparallel ($_3G^+$) would allow about the same steric relief as compared to the extended form. However, the observed values of $J_{2',3'}$ (3.3 Hz) and $J_{3',4'}$ (3.4 Hz) show very good concordance with those expected for the extended conformation (**P**). Crystallographic studies have shown that, despite the presence of an OH-2–OH-4 interaction, the gluconate ion adopts the planar, extended conformation in salts of gluconic acid [20], and it was established that intramolecular 4-OH–O-2 hydrogen bonding takes place in the crystalline state [21]. Work from this laboratory [14] has indicated a conformational equilibrium between the **P** and the $_3G^+$ sickle forms for D-gluconic acid in aqueous solution, and it was suggested that the extended conformer would be stabilized, as in the crystal, by a hydrogen bond between the hydroxyl groups involved in the parallel interaction. This idea is supported by the fact that intramolecular bonding has been observed with free sugars, even in dilute aqueous solution [22].



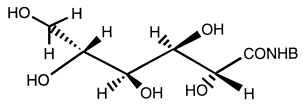
1d (P)

Compound **1d** evidently behaves similarly to D-gluconic acid, and adopts the planar (**P**) form as the most populated conformational state. Stabilization would be provided by a well defined 4-OH–O-2 intramolecular bond and a weaker 3-OH–O-1 interaction. When the possibility of hydrogen bonding is eliminated as is the case in fully acetylated derivatives of D-gluconic acid [14], D-glucononitrile [16,23], and the dimethyl and diethyl dithioacetals of D-glucose [18], rotameric states, other than the extended form, have been found.

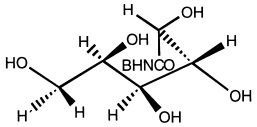
The proton–proton coupling data for the gulose derivative **1e** are all of 'intermediate' magnitude, corresponding to mixtures of conformational

states. Rotations along the C-3–C-4 or C-4–C-5 bonds might occur to alleviate the 1,3-interaction between OH-3 and OH-5 present in the **P** conformation. Those rotations would produce two sickle forms, ${}_3G^-$ and ${}_4G^+$, respectively. However, the ${}_3G^-$ form would generate an interaction between O-2 and C-5. Under these circumstances, a simultaneous rotation of the C-2–C-3 bond could take place, and the resulting rotamer (${}_2G^-,{}_3G^-$) would be free of interactions. The presence of this conformer in the equilibrium would justify the value of $J_{2',3'}$ (5.6 Hz) being smaller than that expected for an exclusive antiperiplanar disposition of H-2 and H-3. The conformation of the gulose pyrimidine derivative (**1d**) may thus be expressed as a mixture of ${}_4G^+$ and (${}_2G^-,{}_3G^-$) rotamers. Furthermore, if some stabilization by hydrogen bonding between OH-3 and OH-4 does occur, then the presence of an appreciable proportion of the planar, extended conformer cannot be discounted.

For the sake of uniformity in the representation, the *gulo* derivative is depicted as being of the D-series, even though the actual compound belongs to the L-series.



1e (${}_4G^+$)



1e (${}_2G^-,{}_3G^-$)

3. Experimental

General methods.—Melting points were determined in open glass capillaries and by using a Thomas–Hoover apparatus, and are uncorrected. Optical rotations were recorded for solutions in 0.1 M hydrochloric acid. IR spectra were recorded with a Perkin–Elmer 457 grating spectrophotometer. ^{1}H NMR spectra were determined by Dr O. Mols at 200 MHz with a Bruker WP 200 spectrometer or with a Bruker WP 300 instrument at 300 MHz. Samples were dissolved in D_2O and a small drop of DCl in D_2O was added. The HOD signal was used as the reference. ^{13}C NMR spectra were recorded by Dr O. Mols at 50 MHz with a Bruker WP 200 spectrometer; for solutions of DCl–D_2O with 1,4-dioxane as internal reference. TLC was performed on precoated sheets (0.2 mm) and glass plates (0.25 mm) using 3:3:1 $CHCl_3$–MeOH–NH_4OH (28%) as eluent; spots were detected by UV light. Elemental analyses were performed by Dr O. Mols.

Materials.—Ethyl glycolate was provided by Eastman Kodak, and D-ribono-1,4-lactone by Aldrich Chemicals. L-Gulono-1,4-lactone and D-glucono-1,5-lactone were obtained from Pfanstiehl Laboratories Inc. D-Allono-1,4-lactone was prepared by cyanohydrin synthesis from D-ribose [24]. 4,5,6-Triaminopyrimidine was obtained by dissolving the sulfate hydrate (Aldrich) in hot 2 M NaOH. The free amine, which precipitated upon cooling, was recrystallized from water; mp 248 °C.

4,6-Diamino-5-(2-hydroxyacetamido)pyrimidine (**1a**).—Ethyl glycolate (0.94 g, 9 mmol) was heated for 5 min at *ca*. 90°C with 3 M NaOH (3 mL) to afford a neutral solution to which 4,5,6-triaminopyrimidine (1.25 g, 10 mmol) was added. Concentrated aq HCl (1.6 mL) was added, and the mixture was boiled, with magnetic stirring, for 2.5 h. The mixture became pasty, and 1 mL portions of water were added to maintain the stirring. The paste was then dissolved in hot water (10 mL), decolorized with activated charcoal, and the mixture filtered. The filtrate was made neutral with 28% NH_4OH and the solution allowed to cool, whereupon a white solid precipitated. It was filtered off and washed successively with cold water, MeOH, and ether; yield 0.74 g. Evaporation of the mother liquors gave a further 0.30 g; total yield of **1a** 63%; mp 238–241 °C (lit. [2] 240 °C). Anal. Calcd. for $C_6H_9N_5O_2$ (183.17): C, 39.34; H, 4.95; N, 38.23. Found: C, 39.21; H, 5.06; N, 38.22.

*4,6-Diamino-5-(*D*-ribo-2,3,4,5-tetrahydroxypentanamido)pyrimidine* (**1b**).—D-Ribono-1,4-lactone (0.74 g, 5 mmol) and 4,5,6-triaminopyrimidine (0.63 g, 5 mmol) were dissolved in 2.5 M HCl (4 mL) and treated as described for **1a**. The resulting paste was dissolved in water (10 mL), decolorized with activated charcoal, and the clear, yellow solution passed through a column (30×2.5 cm) of Dowex 50 (H^+) resin, which was eluted with water until the effluent was chloride free ($AgNO_3$). The column was then eluted with 2% aq NH_4OH and fractions were monitored by TLC. Those containing a component having R_f 0.23 were pooled and concentrated. Initial solid material that separated was 4,5,6-triaminopyrimidine. Refrigeration of the mother liquors gave compound **1b** as a precipitate; yield 0.30 g (22%). The product was recrystallized from water: mp 185–187 °C, $[\alpha]_D$ +31° (*c* 1.5). Anal. Calcd for $C_9H_{15}N_5O_5$ (273.25): C, 39.56; H, 5.53; N, 25.63. Found: C, 39.17; H, 5.50; N, 25.57.

*4,6-Diamino-5-(*D-allo-*2,3,4,5,6-pentahydroxyhexanamido)pyrimidine* (**1c**).—The procedure used for **1b** was repeated with D-allono-1,4-lactone (0.90 g, 5 mmol) and 4,5,6-triaminopyrimidine (0.63 g, 5 mmol) in 2.5 M HCl (15 mL). The yield of **1c** was 0.47 g (30%); mp 190–192 °C (lit. [2] 184 °C); $[\alpha]_D$ +32° (*c* 0.8); R_f 0.18. Anal. Calcd for $C_{10}H_{17}N_5O_6 \cdot 0.5H_2O$ (312.28): C, 38.46; H, 5.81; N, 22.43. Found: C, 38.25; H, 5.58; N, 22.37.

*4,6-Diamino-5-(*D-gluco-*2,3,4,5,6-pentahydroxyhexanamido)pyrimidine* (**1d**).—A mixture of D-glucono-1,5-lactone (0.9 g, 5 mmol) and 4,5,6-triaminopyrimidine (0.63 g, 5 mmol) was slowly heated until melting occurred (165 °C), and the mixture was kept for 2.5 h at this temperature. The resultant solid was dissolved in boiling water (20 mL), and the solution was decolorized and concentrated to 5 mL. After 4 days, crystals of **1d** were obtained: yield 0.92 g (57%). Recrystallized from water, the product had mp 215–217 °C, $[\alpha]_D$ +58.5° (*c* 1.0); R_f 0.17. Anal. Calcd for $C_{10}H_{17}N_5O_6$ (303.28): C, 39.60; H, 5.65; N, 23.09. Found: C, 39.47; H, 5.57; N, 23.04.

*4,6-Diamino-5-(*L-gulo-*2,3,4,5,6-pentahydroxyhexanamido)pyrimidine* (**1e**).—L-Gulono-1,4-lactone (0.9 g, 5 mmol) was allowed to react with 4,5,6-triaminopyrimidine (0.63 g, 5 mmol) using the procedure employed for **1d.** As crystallization could not be induced from the decolorized solution, the product was purified, as for **1b**, by ion-exchange chromatography. Fractions containing the product having R_f 0.15 were pooled, concentrated, and refrigerated. Crystals of **1e** formed after three days: yield 0.53 g (34%); mp 224–225 °C (after recrystallization from water), $[\alpha]_D$ −2° (*c* 0.8). Anal. Calcd for $C_{10}H_{17}N_5O_6 \cdot 0.5H_2O$ (312.28): C, 38.46; H, 5.81; N, 22.43. Found: C, 38.35; H, 5.85; N, 22.39.

8-(Hydroxymethy1)adenine (**2a**).—*Method A.* The amide **1a** (1 g) was heated in a boiling tube to its melting temperature. The dense paste was vigorously stirred, and it began to solidify within a few minutes. The brown solid was cooled and extracted 5 times with 20 mL portions of boiling water. The resulting extract was decolorized with charcoal and evaporated to a few mL under diminished pressure, whereupon compound **2a** crystallized: yield 0.36 g (40%).

Method B. 4,5,6-Triaminopyrimidine (1.25 g, 10 mmol) was dissolved in ethyl glycolate (4 mL) and boiled under reflux with magnetic stirring. After 1 h the mixture began to solidify and 2 mL of ethyl glycolate was added (this step avoided carbonization of the solid product). The suspension was heated for 2 h and cooled to give a thick paste that was suspended in water. The mixture was filtered and the residue washed with water at 50 °C and then with EtOH and ether, and the product was dried in vacuum: yield 0.62 g (38%); mp >290 °C (lit. [16] 320 °C); R_f 0.61; ^{1}H NMR (300 MHz): δ 8.26 (1 H, aryl), 4.76 (2 H, CH_2); ^{13}C NMR (50 MHz): 57.8 (CH_2), 115.7 (C-5), 145.3 (C-2), 150.5 (C-4, 8), and 157.8 (C-6). Anal. Calcd for $C_6H_7N_5O$ (165.15): C, 43.64; H, 4.27; N, 42.41. Found: C, 43.47; H, 4.33; N, 42.13.

8-(Acetoxymethyl)adenine (**2f**).—To a suspension of 8-(hydroxymethyl)adenine (**2a,** 1.32 g, 8 mmol) in dry pyridine (50 mL) was added Ac_2O (0.91 mL, 9.6 mmol), and the mixture was stirred for 20 h at room temperature. A small amount of solid remained. The suspension was concentrated with additions of MeOH (30 mL, twice) to remove the excess of Ac_2O, and then with toluene to remove pyridine. The residue was extracted three times with hot EtOH, and the solution decolorized with charcoal. Compound **2f** precipitated from the cooled solution: yield 1.02 g (61%). Recrystallized from EtOH it had mp 246–248 °C; R_f 0.84. ^{1}H NMR ($CDCl_3$): δ 8.28 (1 H, aromatic), 5.25 (CH_2), and 2.06 (CH_3); ^{13}C NMR: δ 21.1 (CH_3), 58.0 (CH_2), 115.7 (C-5), 145.7 (C-2), 150.7 (C-4, C-8), 158.0 (C-6), 177.2 (*C*O). Anal. Calcd for $C_8H_9N_5O_2$ (207.2): C, 46.38; H, 4.38; N, 33.80. Found: C, 46.26; H, 4.20; N, 33.72.

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