Purines. LXXV.¹⁾ Dimroth Rearrangement, Hydrolytic Deamination, and Pyrimidine-Ring Breakdown of 7-Alkylated 1-Alkoxyadenines: N(1)–C(2) versus N(1)–C(6) Bond Fission

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On treatment with boiling H₂O for 5–6 h, 1-alkoxy-7-alkyladenines (**13**) underwent hydrolytic cleavage at the N(1)–C(2) and the N(1)–C(6) bonds to produce the imidazole-5-carboxamidines (**14**) in 53–60% yields and the imidazole-5-carboxamides (**18**) in 5–7% yields, respectively. The Dimroth rearrangement of **13** to *N*⁶-alkoxy-7-alkyladenine (**15**) was found to proceed through **14** more slowly than that of the 9-alkyl analogues **1** at pH 7 and above, being accompanied by hydrolysis to give the deformed product (**16**) and by deamination through **18** leading to 7-alkylhypoxanthine (**12**), 1-alkoxy-7-alkylhypoxanthine (**19**), and 1-alkyl-4-aminoimidazole-5-carboxamide (**20**). Interestingly, the N(1)–C(6) bond fission product **17a** was obtained from **13a** by treatment with 0.01 *N* aqueous NaOH at 4°C for 35 d, but in only 2% yield, or more efficiently (in 56% yield) by pyrolysis at 150°C for 1 h. On the other hand, **13** underwent acid hydrolysis faster than **1**, providing the deformed product **16** in 85–96% yields on treatment with 1–2 *N* aqueous HCl at room temperature for 2–5 h. 4-Amino-*N*⁶-methoxy-1-methyl-5-carboximidine (**16a**) was alternatively obtained in 59% yield by treatment of 1-methoxy-7-methyladenine (**13a**) with boiling 2 *N* aqueous NaOH for 10 min. Efficient preparations of the rearranged products **15** (80–86%) were accomplished by treating **13** with boiling 0.1 *N* aqueous NaOH for 20–30 min.

Key words 1-alkoxy-7-alkyladenine; Dimroth rearrangement; adenine deamination; imidazolecarbonitrile [(alkoxy-amino)methylene]amino derivative ring-chain tautomer; hydrolytic deamination mechanism; 1-alkoxyadenine acidic hydrolysis

The chemistry of the 9-substituted 1-alkoxyadenines **1** has been extensively investigated in our laboratory for many years.²⁾ These compounds undergo Dimroth rearrangement to provide the *N*⁶-alkoxyadenines **3** on treatment with boiling H₂O, whereas at lower temperature they afford the monocyclic intermediates **2** in good yields, and the deformed products **4** are produced by treatment of **1** or **2** with hot aqueous alkali (Chart 1).^{2c,g,h,j–m,p} On the other hand, 1,9-dialkyladenines (**5**) usually undergo Dimroth rearrangement leading to *N*⁶,9-dialkyladenines (**7**)^{2d,3)} under basic conditions, but no ring-opened intermediates **6** are detectable (Chart 2).⁴⁾ 1,7-Dialkyladenines (**8**) also undergo Dimroth rearrangement to form isomeric *N*⁶,7-dialkyladenines (**10**) under basic conditions or in the absence of added base.⁵⁾ In some cases, the rearrangement reactions of **8** are accompanied with hydrolytic deaminations to give 1,7-dialkylhypoxanthines (**11**)^{5a)} and/or 7-alkylhypoxanthines (**12**),^{5a,6)} when effected in boiling H₂O (Chart 3). Interestingly, however, no deaminated products are detectable in the Dimroth rearrangement of 1,9-dialkyladenines (**5**), with the exception of the 1-(*ω*-hydroxyalkyl) analogues.^{3d)} Such a difference in reactivity between 1,7-dialkyladenines (**8**) and 1,9-dialkyladenines (**5**) led us to investigate the Dimroth rearrangement of 1-alkoxy-7-alkyladenines (**13**)⁷⁾ in the present study in order to compare the results with those for 1-alkoxy-9-alkyladenines (**1**).

Unlike **1**, 1-methoxy-7-methyladenine (**13a**)⁷⁾ was stable on storage of its concentrated aqueous solution at room temperature for 6 d. When **13a** was treated with boiling H₂O for 5 h, a mixture of many products was obtained

Chart 1

Chart 2

Chart 3

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(Chart 4). From the mixture, we isolated the ring-opened formamide **14a** (53% yield), the rearranged product **15a**⁸⁾ (17%), the ring-opened formamidine **18a** (7%), and a trace of the deaminated product **19a** by means of repeated chromatography and fractional recrystallization (Table 1, entry 7). The reaction was repeated on a larger scale with the intention of obtaining other minor products, providing the deformylated product **16a** (4%), the deaminated product **19a** (0.4%), and the imidazolecarboxamide **20** ($R^1 = \text{Me}$)⁹⁾ (0.9%), besides **14a** (38%), **15a** (13%), and **18a** (7%) (Table 1, entry 8). The structures of **14a** and **16a** were elucidated as in the cases^{2c)} of **2** and **4**. The structure determination of **19a** rested on the following spectral data: the high resolution MS showed that the reaction caused the replacement of NH by O; no signal

other than two three-proton and two one-proton singlets was detectable in the ¹H-NMR spectrum measured in Me₂SO-*d*₆; and the absorption band at 1707 cm⁻¹ in the IR spectrum (Nujol) supported the existence of a carbonyl group. The structure of **18a** was determined on the basis of the following data: the MS and elemental analyses were indicative of a structure isomeric with that of **14a**; a set of doublets at δ 7.50 ($J=11$ Hz) and 8.91 ($J=11$ Hz) in the ¹H-NMR spectrum measured in Me₂SO-*d*₆ showed the existence of a fragment -N=CH-NH-, and the former signal changed into a singlet with disappearance of the latter on addition of D₂O; and the IR spectrum (Nujol) exhibited the absorption band at 1634 cm⁻¹ assignable to the amide carbonyl group. Corroboration of the assigned structure **18a** was obtained by its simultaneous conver-

a: $R^1 = R^2 = \text{Me}$ b: $R^1 = R^2 = \text{Et}$ c: $R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$ d: $R^1 = \text{PhCH}_2$; $R^2 = \text{Et}$

Chart 4

Table 1. Reaction of **13a** in Aqueous Solutions^{a)}

Entry	Reaction conditions			Isolated yield (%)				Recovery (%)
	Medium	Temperature	Time	14a	15a	16a	Others	
1 ^{b)}	2 N aq. HCl	r.t.	2 h	—	3	88	—	—
2 ^{b)}	1 N aq. HClO ₄	r.t.	6 h	—	8	82	—	—
3 ^{b,c)}	1 N aq. HCl (10 ml)	r.t.	4 h	—	—	85	—	—
4	0.2 N aq. HCl	4 °C ^{d)}	3 d	38	3	40	—	7
5 ^{b)}	0.01 N aq. HCl	40 °C	8 h	36	—	12	—	27
6 ^{b)}	0.01 N aq. HCl	4 °C ^{d)}	20 d	40	6	26	—	18
7	H ₂ O (5 ml)	Reflux	5 h	53	17	—	18a (7%) 19a (trace) 18a (7%) 19a (0.4%) 20 ($R^1 = \text{Me}$) (0.9%)	2
8 ^{e)}	H ₂ O (50 ml)	Reflux	5 h	38	13	4	18a (2%) 19a (3%) 17a (2%)	—
9	0.1 M carbonate buffer (pH 9.0 at 22 °C)	40 °C	20 d	10	15	31	18a (2%) 19a (3%) 17a (2%)	—
10	0.01 N aq. NaOH	4 °C ^{d)}	35 d	12	9	—	—	55
11	0.1 N aq. NaOH	4 °C ^{d)}	4 d	41	19	7	—	12
12 ^{f)}	0.1 N aq. NaOH (30 ml)	45 °C	5 h	—	74	2	—	—
13	0.1 N aq. NaOH (10 ml)	45 °C	20 h	—	56	4	12 ($R^1 = \text{Me}$) (12%)	—
14	0.1 N aq. NaOH	Reflux	30 min	—	82	—	—	—
15	2 N aq. NaOH	Reflux	10 min	—	21	59	—	—

a) Unless otherwise stated, the reaction was carried out by use of the free base **13a**, which was prepared from **13a**·HClO₄ (140 mg, 0.5 mmol), in 5 ml of the medium. b) The perchlorate **13a**·HClO₄ was used as the substrate. c) One mmol of **13a** was used. d) Carried out in a refrigerator. e) Five mmol of **13a** was used. f) Two mmol of **13a** was used.

sions into **19a** (10%), 7-methylhypoxanthine (**12**: $R^1 = \text{Me}$)¹⁰ (23%), and a trace of **20** ($R^1 = \text{Me}$) by treatment with boiling 0.1 M acetate buffer (pH 5.2)¹¹ for 5 h. Furthermore, treatment of **18a** with 0.1 N aqueous HCl at 50 °C for 4 h yielded **19a** (7%) and **20** ($R^1 = \text{Me}$) (27%). We prefer structure **18a**, in which more stabilization would be expected through extended conjugation and an extra hydrogen bonding, to the alternative tautomer **21**. The large vicinal coupling constant ($J = 11 \text{ Hz}$) observed for the formamidine fragment in **18a**, together with bathochromic shifts in the UV spectrum of **18a** when compared with **20** ($R^1 = \text{Me}$),⁹ are considered to support this preference.

Table 1 assembles the results of the reactions of **13a** in H_2O under various conditions. It may be seen that **14a** was obtainable over a wide pH range. However, it was difficult to find better conditions for selective production of **14a** than those specified under entry 7. The major product from the reaction of the 1-ethoxy compound **13b**⁷ with boiling H_2O was also suggested by TLC to be the ring-opened formamide **14b**, but we failed to isolate it in a pure state. From the 7-benzyl analogue **13d**, derived from the corresponding perchlorate salt (**13d**· HClO_4),⁷ we were able to obtain the ethoxy compounds, **14d** (56%), **15d** (4%), **16d** (2%), and **18d** (6%), together with 7-benzylhypoxanthine (**12**: $R^1 = \text{PhCH}_2$)^{5a} (2%). More efficient preparation of **14** might be attained by the use of a 1-benzyloxy analogue because our previous kinetic studies on the Dimroth rearrangement of **1** revealed that the 1-benzyloxy group is superior for the preferential formation of the ring-opened intermediate **2**.^{2b} However, on treatment with boiling H_2O for 6 h, 1-benzyloxy-7-ethyladenine (**13c**)⁷ afforded **14c** in only a slightly increased yield (60%), together with **15c** (9%), **18c** (5%), and 7-ethyladenine 1-oxide⁷ (7%). The formation of the 1-oxide may be interpreted in terms of nucleophilic attack of H_2O at the benzylic carbon^{2e,12} of **13c**. Similar debenzilation has been observed in the rearrangement of 1-benzyloxyadenine (**1**: $R^1 = \text{H}$; $R^2 = \text{PhCH}_2$)¹³ which undergoes ring opening more slowly than do the 9-substituted derivatives (type **1**).

Now that it had become clear that **13** undergoes Dimroth rearrangement much more slowly than **1**, we treated **13a** with 0.1 N aqueous NaOH at 45 °C for 20 h and obtained the rearranged product **15a** in 56% yield, along with **16a** (4%) and **12** ($R^1 = \text{Me}$)¹⁰ (12%) (Table 1, entry 13). When the reaction time was shortened to 5 h, the yield of **15a** increased to 74% (Table 1, entry 12), suggesting that a considerable amount of **12** ($R^1 = \text{Me}$) was formed from **15a** in the above hydrolysis for 20 h. Compound **12** ($R^1 = \text{Me}$) was indeed obtained from **15a** in 14% yield, along with a compound inferred to be 7-methyladenine (12%) and 47% recovery of **15a**, by hydrolysis with 0.1 N aqueous NaOH at 45 °C for 78 h. A higher yield (82%) of **15a** was achieved when **13a** was treated with boiling 0.1 N aqueous NaOH for 30 min (Table 1, entry 14). Similar treatment of **13b—d** afforded **15b—d** in 80–86% yields. The ring-opened formamides **14a, c** also produced **15a, c** in 87–90% yields under similar conditions. The ¹H-NMR spectral data [$J = 3$ –4 Hz for C(2)-H] for **15** reveal that these compounds exist

in the single 6-imino form in $\text{Me}_2\text{SO}-d_6$, in contrast to the 9-alkyl analogues **3** that exist as equilibrated mixtures of the 6-imino and 6-amino tautomers in $\text{Me}_2\text{SO}-d_6$.¹⁴ We prefer the *syn*-1*H*-purine form **15** to the *anti*-form **23** or the 3*H*-purine form **24** by analogy with the X-ray crystal structure (in the *syn*-6-imino-1*H*-purine form)¹⁵ of 9-benzyl-*N*⁶-methoxyadenine (**3**: $R^1 = \text{PhCH}_2$; $R^2 = \text{Me}$). However, it remains uncertain whether possible stabilization of **15** through intramolecular hydrogen bonding between N(1)-H and *N*⁶-O is operative, since no data are available in the present study to support this idea.

Having established the preferential preparation of **15** under more strongly alkaline conditions than those employed for the synthesis of the 9-alkyl analogues **3**, we next treated **13a** with a more concentrated solution of NaOH in order to obtain the deformylated product **16** selectively, based on the analogy with the synthesis of **4**.^{2c} Thus, **16a** was obtained in 59% yield, along with **15a** (21%), by heating **13a** in boiling 2 N aqueous NaOH for 10 min (Table 1, entry 15). Under similar conditions, **14a** also yielded **16a** (73%) and **15a** (24%).

However, one of the most striking characteristics of **13a** was its sensitivity to acid: it underwent hydrolysis under mild conditions to afford **14a** (Table 1, entries 4–6). On treatment with 1 N aqueous HCl at room temperature for 4 h, **14a** produced **16a** and **15a** in 79% and 6% yields, respectively. When this reaction of **14a** was interrupted after 30 min, **13a** was obtained in 8% yield, together with **16a** (18%), **15a** (4%), and **14a** (48% recovery). Compound **16a** was alternatively produced in 85% yield directly from **13a**· HClO_4 by keeping a solution of the latter in 1 N aqueous HCl at room temperature for 4 h (Table 1, entry 3). Similar treatment of **13b—d** afforded **16b—d** in 88–96% yields, establishing a highly selective synthesis of **16**. Compounds **16** have potential utility as synthetic intermediates by analogy with **4**,^{2m,14,16} provided that their alkoxy groups are removable. Catalytic hydrolysis of **16c** according to the procedure reported for **4**^{16b} afforded 4-amino-1-ethyl-1*H*-imidazole-5-carboxamide (**22**), which was isolated as the dipicrate in 67% yield.

The instability observed for **13** under acidic conditions reminded us that we had not checked the behavior of the 9-alkyl analogues **1** under similar conditions. We thus

investigated the reaction of 1-benzyloxy-9-ethyladenine hydrochloride [$1 \cdot \text{HCl}$ ($R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$)] in 1N aqueous HCl at room temperature and found that the reaction proceeded much more slowly than that of **13c**, producing after 50 h **3** ($R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$) and **4** ($R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$) in 8% and 73% yields, respectively. From a qualitative viewpoint, therefore, the formation of **15** and **16** from **13** through **14** is parallel to that of **3** and **4** from **1** through **2**. From a quantitative viewpoint, however, there are considerable differences in chemical behavior between **1** and **13**. Table 2 lists the pK_a values of **13a–c** and 1,7-dimethyladenine (**8**: $R^1 = R^2 = \text{Me}$) determined spectrophotometrically for comparison with those^{2d)} of **1** ($R^1 = R^2 = \text{Me}$ and $R^1 = \text{Me}$; $R^2 = \text{PhCH}_2$) and 1,9-dimethyladenine (**5**: $R^1 = R^2 = \text{Me}$). It may be seen that the pK_a of 1-methoxy-7-methyladenine (**13a**) is lower than that of the 1-methyl compound **8** ($R^1 = R^2 = \text{Me}$) by 0.85 pK_a unit, analogously with the observed relationship between the two parallel 9-alkyl series.^{2h)} The larger difference (1.30–1.43 unit) in pK_a observed between the 1-alkoxy compounds **13a** and **1** offers an analogy with that (1.08 unit) existing between the 1-alkyl compounds **8** ($R^1 = R^2 = \text{Me}$) and **5** ($R^1 = R^2 = \text{Me}$). Such differences may be explained in terms of the stabilization of their conjugate acids, in which protonation occurs at the N^6 -position to give possible resonance hybrids including the important contributors B and E, as shown in Chart 5. The lower pK_a 's of the 7-substituted compounds **8** and **13** might be ascribed to the sterically destabilized resonance structure A, which seems less important than the resonance structure D in

the 9-substituted series. Table 3 assembles the rate constants for the decay of **13c** and ring-opening^{2j)} of **1** ($R^1 = \text{Me}$; $R^2 = \text{PhCH}_2$) in H_2O at various pH's and 40 °C, showing that the reaction of **13c** is slower than that of **1** ($R^1 = \text{Me}$; $R^2 = \text{PhCH}_2$) at pH 7 and above. The difference in reaction rate at near neutrality is probably a reflection of the difference in pK_a and hence in the populations of the protonated species. However, further discussion must await the availability of more detailed kinetic data.

The most prominent feature of the chemical behavior of **13** was the formation of **12** and **17–20** (Chart 4). Treatment of **14a** with boiling H_2O or acetate buffer (pH 5.2) yielded no product other than **15a** and **16a**, and these two products proved stable enough to be recovered almost quantitatively after treatment with boiling H_2O for 5 h. On the other hand, similar treatment of **18a**, obtainable from **13a**, produced **19a** and **20** ($R^1 = \text{Me}$) (*vide supra*),

Table 2. Acid Dissociation Constants of **13** and Related Compounds at 40 °C and Ionic Strength 0.5

Compound	pK_a	Analytic wavelength (nm)
13a · HClO_4	7.01 ± 0.04	263
13b	6.99 ± 0.04	263
13c	6.66 ± 0.05	261
1 · HClO_4 ($R^1 = R^2 = \text{Me}$)	$8.44 \pm 0.04^a)$	—
1 · HClO_4 ($R^1 = \text{Me}$; $R^2 = \text{PhCH}_2$)	$8.31 \pm 0.01^{b,c)}$	—
8 · HClO_4 ($R^1 = R^2 = \text{Me}$) ¹⁰⁾	7.86 ± 0.03	265
5 · HClO_4 ($R^1 = R^2 = \text{Me}$)	$8.94 \pm 0.05^a)$	—

a) Taken from ref. 2d. b) At ionic strength 1.0. c) Taken from ref. 2j.

Chart 5

Table 3. Rate of Decay of **13c** and **1** in H_2O at 40 °C and Ionic Strength 1.0

Substrate	Pseudo-first-order rate constant, $k_{\text{obsd}} \times 10^4 \text{ (min}^{-1}\text{)}$												
	pH value												
	2.00	3.00	4.00	5.00	6.14	7.00	7.76	7.80	9.00	10.00	11.00	11.20	11.40
13c · HClO_4	39	6.0	2.2	1.7	1.6	1.5	1.3	—	1.4	2.4	13	—	32
1 · HClO_4 ($R^1 = \text{Me}$; $R^2 = \text{PhCH}_2$) ^{a)}	—	—	—	—	—	7.3	—	34	120	150	190	240	—

a) Taken from ref. 2j.

and the formation of **13a** was not detectable in the course of the reaction. Consequently, the Dimroth rearrangement of **13** to **15** through **14** may be considered to occur in competition with the hydrolysis of **13** leading to **18**, which then produces the deaminated products **12**, **19**, and **20** as shown in Chart 4. In addition, the pathway from **15** to **12** is also possible since treatment of **15a** with 0.1 N aqueous NaOH at 45 °C has been shown to give **12a** (*vide supra*). It is of interest to note that treatment of **13a** with 0.01 N aqueous NaOH at 4 °C for 35 d gave **17a**, but in only 2% yield (Table 1, entry 10). Alternatively, **17a** was obtained in 56% yield by pyrolysis of **13a** at 150 °C for 1 h. The structure **17a** was assignable on the basis of the IR absorption band at 2207 cm⁻¹ characteristic of a nitrile group and a comparison of its ¹H-NMR spectrum with that of **18a**. This type of ring fission at the N(1)–C(6) bond has already been reported by us for 1-methoxy-9-methyl-2-azaadenine, together with a postulated mechanism.¹⁷⁾ On treatment with boiling H₂O for 5 min, **17a** provided a mixture of **13a**, **14a**, **18a**, and **17a** in a molar ratio of 101:13:3:1. Similar treatment of **13a** also afforded a mixture of almost the same composition. These results indicate that **17a** rapidly comes into equilibrium with an overwhelming amount of **13a** under these conditions. At present, however, it is difficult to judge whether **18a** was formed through **17a** and/or directly from **13a**.

In conclusion, we have revealed that the Dimroth rearrangement of **13** is sufficiently slow to allow the concomitant hydrolytic deamination that is unusual in the case of the 9-alkyl analogues **1**.²⁾ It has already been reported by us that 1-ethyladenine undergoes Dimroth rearrangement more slowly than 1-ethyl-9-methyladenine (type **5**), and this reaction is accompanied with hydrolytic deamination.¹⁸⁾ The difference in reactivity between **13** and **1** resembles that^{5a)} between 1-methyl-7-alkyladenines (**8**) and their 9-alkyl analogues **5**. For the concomitant deamination in the Dimroth rearrangement of **8**, we have proposed possible mechanisms involving hydrolysis of the amidine moiety of the putative intermediate **9** [resulting from hydrolytic fission at the N(1)–C(2) bond] and/or a direct hydrolytic deamination *via* an addition–elimination at C(6).^{5a,19)} However, the present results suggest that a third mechanism, which proceeds through N(1)–C(6) bond fission to form intermediates analogous to **17** and/or **18**, may operate in these deamination reactions. Interestingly, this type of N(1)–C(6) bond fission has also been postulated for a 1-substituted adenosine nucleotide in the biosynthesis of histidine.²⁰⁾

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus and values are corrected. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Hitachi model 320 UV spectrophotometer [for solutions in 95% aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13)], a Shimadzu FTIR-8100 IR spectrophotometer, or a JEOL JNM-EX-270 NMR spectrometer (measured at 25 °C in Me₂SO-*d*₆ with tetramethylsilane as an internal standard). For the measurements of pH values, a Toa HM-18ET pH meter equipped with a Toa type GST-5211C glass electrode was employed. Acid dissociation constants were determined spectrophotometrically in a manner similar to that described previously.^{3b)} Elemental analyses and MS measurements were performed by Mr. Y. Itatani, Dr. M. Takani, and their associates at Kanazawa University.

Flash chromatography was performed according to the reported procedure.²¹⁾ The following abbreviations are used: br=broad, d=doublet, m=multiplet, q=quartet, s=singlet, sh=shoulder, t=triplet.

7-Benzyl-1-ethoxyadenine (13d) A solution of **13d**·HClO₄⁷⁾ (1.98 g, 5.35 mmol) in H₂O (500 ml) was neutralized with saturated aqueous NaHCO₃ and extracted with CHCl₃ (5 × 100 ml). The organic layers were combined, washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The oily residue was triturated with a mixture of hexane–AcOEt (1:1, v/v) (3 ml). The precipitate that resulted was collected by filtration, washed with a little hexane–AcOEt (1:1, v/v), and dried to provide **13d** (1.32 g, 92%), mp 95.5–97 °C. Recrystallization of **13d** from hexane–AcOEt (1:1, v/v) afforded an analytical sample as colorless prisms, mp 97–97.5 °C; MS *m/z*: 269 (M⁺); UV λ_{max}^{95% EtOH} 264 nm (ε 9800), 270 (sh) (9200); λ_{max}^{H₂O} (pH 1) (unstable) 220 (ca. 27000), 270 (ca. 9000); λ_{max}^{H₂O} (pH 7) 265 (10000); λ_{max}^{H₂O} (pH 13) (unstable) 264 (ca. 11000); IR ν_{max}^{Nujol} cm⁻¹: 3312 (NH), 1668 (C=N); ¹H-NMR δ: 1.34 (3H, t, *J* = 7 Hz, MeCH₂), 4.15 (2H, q, *J* = 7 Hz, MeCH₂), 5.70 (2H, s, PhCH₂), 6.95 (1H, br, NH), 7.24–7.41 (5H, m, PhCH₂), 8.17 [1H, s, C(8)-H],²²⁾ 8.26 [1H, s, C(2)-H],²²⁾ *Anal.* Calcd for C₁₄H₁₅N₅O: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.62; H, 5.60; N, 25.87.

4-Formamido-*N'*-methoxy-1-methyl-1*H*-imidazole-5-carboxamide (14a) A solution of **13a**, which was prepared from **13a**·HClO₄ (1.40 g, 5 mmol) according to the reported procedure,⁷⁾ in H₂O (50 ml) was heated under reflux for 5 h and then concentrated *in vacuo*, leaving a heavy oil (987 mg) after drying. This was subjected to column chromatography on alumina (90 g) [CHCl₃–MeOH (20:1, v/v)]. Purification of the product obtained from earlier fractions by preparative TLC on silica gel [CHCl₃–AcOEt–MeOH (3:1:1, v/v)], followed by recrystallization from EtOH, afforded 1-methoxy-7-methylhypoxanthine (**19a**) (4 mg, 0.4%) as slightly brown prisms, mp 192.5–193.5 °C; MS *m/z*: 180 (M⁺); IR ν_{max}^{Nujol} cm⁻¹: 1707 (C=O); ¹H-NMR δ: 3.97 [3H, s, N(7)-Me],²³⁾ 4.04 (3H, s, OMe),²³⁾ 8.21 [1H, s, C(8)-H],²²⁾ 8.56 [1H, s, C(2)-H].²²⁾

The crude product obtained from the middle fractions was recrystallized from AcOEt to afford a first crop of crude **18a** (68 mg), mp 198.5–200 °C. The mother liquor of this recrystallization was concentrated *in vacuo*, and the solid residue was recrystallized from benzene–AcOEt (5:1, v/v) to afford 4-amino-*N'*-methoxy-1-methyl-1*H*-imidazole-5-carboxamide (**16a**) (14 mg), mp 108.5–110 °C, which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic sample (*vide infra*). The crude product obtained from later fractions of the above chromatography was recrystallized from AcOEt to afford *N*⁶-methoxy-7-methyladenine (**15a**) (106 mg), mp 234–235 °C; ¹H-NMR δ: 3.76 (3H, s, OMe), 3.85 [3H, s, N(7)-Me], 7.47 [1H, d, *J* = 3.3 Hz, C(2)-H], 7.83 [1H, s, C(8)-H], 11.09 [1H, br, N(1)-H]. This sample was identical (by comparison of the IR and ¹H-NMR spectra and TLC mobility) with authentic **15a**.⁸⁾ The mother liquor from this recrystallization was concentrated *in vacuo*, and the residue was again recrystallized from AcOEt to afford a first crop of crude **14a** (306 mg). The mother liquor, obtained after collection of the crude **14a** by filtration, was concentrated *in vacuo*, and the residue was purified by flash chromatography [CHCl₃–AcOEt–MeOH (3:1:1, v/v)] to afford a second crop of **15a** (5 mg), a mixture of **14a**, **18a**, and **16a**, and a mixture of **14a** and **20** (R¹ = Me). The latter mixture of **14a** and **20** (R¹ = Me) was purified by preparative TLC on silica gel [CHCl₃–AcOEt–MeOH (3:1:1, v/v)] to afford a second crop of crude **14a** (16 mg) and 4-amino-1-methyl-1*H*-imidazole-5-carboxamide (**20**: R¹ = Me) (6 mg, 0.9%), mp 183–186 °C. This sample of **20** (R¹ = Me) was identical (by comparison of the IR and ¹H-NMR spectra and TLC mobility) with authentic **20** (R¹ = Me).⁹⁾ The mixture of **14a**, **16a**, and **18a** described above was recrystallized from AcOEt to afford a third crop of crude **14a** (113 mg). The mother liquor of this recrystallization was concentrated, and the residue was purified by column chromatography on alumina [CHCl₃–MeOH (20:1, v/v)] to afford a fourth crop of **14a** (58 mg) and a mixture of **18a** and **16a**. The mixture of **18a** and **16a** was recrystallized from AcOEt to afford a second crop of **18a** (6 mg; the total yield was 74 mg, 7%). The mother liquor obtained by this recrystallization was concentrated *in vacuo*, and the residue was purified by repeated recrystallization from benzene–AcOEt (3:1, v/v) to afford a second crop of **16a** (20 mg; the total yield was 34 mg, 4%), mp 106.5–108 °C. All four crops of crude **14a** were combined and purified by flash chromatography [CHCl₃–AcOEt–MeOH (3:1:1, v/v)] to afford a third crop of **15a** (8 mg; the total yield was 119 mg, 13%) and 4-formamido-*N'*-methoxy-1-methyl-1*H*-imidazole-5-carboxamide (**14a**) (377 mg, 38%),

mp 107—109 °C. Recrystallization of the latter sample from AcOEt afforded an analytical sample of **14a** as colorless prisms, mp 113.5—116 °C; MS m/z : 197 (M^+); UV $\lambda_{\max}^{95\% \text{ EtOH}}$ 227 nm (ϵ 10900); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) (unstable) 222 (ϵ 13000); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 223 (11700); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) (unstable) 265 (ϵ 10000); IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3482, 3364, 3173, 3115 (NH), 1682 (C=O), 1628 (C=N); $^1\text{H-NMR}$ δ : 3.63 (8/11 $\times$ 3H), 3.65 (3/11 $\times$ 3H), 3.69 (3/11 $\times$ 3H), and 3.70 (8/11 $\times$ 3H) (s each, two Me's), 5.90 (3/11 $\times$ 2H) and 6.09 (8/11 $\times$ 2H) (br each, *cis*- and *trans*-NH₂), 7.55 (8/11H) and 7.57 (3/11H) [s each, *trans*- and *cis*-C(2)-H], 8.12 (3/11H, d, J = 2 Hz) and 8.42 (8/11H, d, J = 11 Hz) (*cis*- and *trans*-NHCHO), 9.46 (8/11H, br d, J = 11 Hz) and 9.71 (3/11H, br) (*trans*- and *cis*-NHCHO). *Anal.* Calcd for C₇H₁₁N₅O₂: C, 42.64; H, 5.62; N, 35.51. Found: C, 42.53; H, 5.67; N, 35.45. Sometimes, **14a** crystallized from an AcOEt solution in colorless prisms of mp 122—122.5 °C [IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3410, 3300, 3182 (NH), 1693 (C=O), 1636 (C=N)], probably another dimorphic form. Analytical data obtained for this sample were consistent with the proposed structure.

The above crude **18a** was recrystallized from AcOEt to afford an analytical sample of 4-[(methoxyamino)methylene]amino-1-methyl-1*H*-imidazole-5-carboxamide (**18a**) as colorless prisms, mp 201—201.5 °C; MS m/z : 197 (M^+); UV $\lambda_{\max}^{95\% \text{ EtOH}}$ 221 nm (ϵ 17800), 255 (sh) (8900), 285 (15100); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) (unstable) 258 (ϵ 10000); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 221 (17300), 282 (12300); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) (unstable) 282 (ϵ 8500), 323 (ϵ 13000); IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3449, 3291, 3177, 3108, 3067 (NH), 1634 (C=O and C=N); $^1\text{H-NMR}$ δ : 3.74 and 3.77 (3H each, s, two Me's), 7.18 (2H, br, NH₂), 7.50 (1H, d, J = 11 Hz, N=CHNH), 7.52 [1H, s, C(2)-H], 8.91 (1H, d, J = 11 Hz, N=CHNH). *Anal.* Calcd for C₇H₁₁N₅O₂: C, 42.64; H, 5.62; N, 35.51. Found: C, 42.54; H, 5.58; N, 35.40. This sample frequently crystallized from a solution in AcOEt in colorless prisms of mp 203—203.5 °C [IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3455, 3300, 3250, 3197, 3131, 3069 (NH), 1644, 1634 (C=O and C=N)], probably another dimorphic form. Analytical data obtained for this sample were consistent with the proposed structure.

These results are summarized in Table 1 (entry 8).

***N'*-Benzyloxy-1-ethyl-4-formamido-1*H*-imidazole-5-carboxamidine (14c)** A suspension of **13c**⁷⁾ (1.35 g, 5 mmol) in H₂O (100 ml) was heated under reflux for 6 h, cooled to room temperature, and extracted with CHCl₃ (4 $\times$ 100 ml). The aqueous layer was concentrated *in vacuo* and dried to afford a solid residue (124 mg). This was purified by preparative TLC on silica gel [CHCl₃–MeOH (4:1, v/v)] to afford 7-ethyladenine 1-oxide dihydrate (75 mg, 7%), mp 240—241 °C (dec.). Recrystallization from EtOH, followed by exposure to air at room temperature until a constant weight was reached, afforded a pure sample of 7-ethyladenine 1-oxide dihydrate, mp 245—246 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.⁷⁾

The above CHCl₃ extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to leave an oily residue (1.43 g). This was subjected to flash chromatography [CHCl₃–MeOH (10:1, v/v)] to afford a mixture (663 mg) of **14c**, **15c**, and **18c** from earlier fractions and a first crop of crude **14c** (616 mg) from later fractions. The mixture of the three components was further purified by flash chromatography [CHCl₃–AcOEt–MeOH (4:4:1, v/v)] to afford a second crop of crude **14c** (223 mg) and a mixture of **15c** and **18c** (209 mg). The mixture of **15c** and **18c** was purified by column chromatography on alumina (42 g) [CHCl₃–MeOH (30:1, v/v)] to afford crude **18c** (73 mg, 5%) (mp 143—144 °C) and *N*⁶-benzyloxy-7-ethyladenine (**15c**) (117 mg, 9%) (mp 165.5—166 °C). The latter sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **15c**.⁸⁾ The first and second crops of crude **14c** were combined and triturated with hexane–AcOEt (1:1, v/v) (5 ml). The resulting precipitate was collected by filtration and dried to afford *N'*-benzyloxy-1-ethyl-4-formamido-1*H*-imidazole-5-carboxamidine (**14c**) (858 mg, 60%), mp 128—129 °C. Recrystallization of this sample from AcOEt afforded an analytical sample of **14c** as colorless prisms, mp 130—130.5 °C; MS m/z : 287 (M^+); UV $\lambda_{\max}^{95\% \text{ EtOH}}$ 242 nm (sh) (ϵ 11000); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) (unstable) 224 (sh) (ϵ 14500); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 226 (sh) (12300); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) (unstable) 261 (ϵ 10500); IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3437, 3310, 3279, 3113 (NH), 1663 (C=O), 1626 (C=N); $^1\text{H-NMR}$ δ : 1.09 (1/3H) and 1.11 (2/3H) (t each, J = 7 Hz, *cis*- and *trans*-NCH₂Me), 3.91 (2H, q, J = 7 Hz, NCH₂Me), 4.96 (1/3 $\times$ 2H) and 4.97 (2/3 $\times$ 2H) (s each, *cis*- and *trans*-OCH₂Ph), 5.97 (1/3 $\times$ 2H) and 6.17 (2/3 $\times$ 2H) (br s each, *cis*- and *trans*-NH₂), 7.25—7.40 (5H, m, OCH₂Ph), 7.57 (2/3H) and 7.59 (1/3H) [s each, *trans*- and *cis*-C(2)-H], 8.12 (1/3H,

d, J = 2 Hz) and 8.38 (2/3H, d, J = 11 Hz) (*cis*- and *trans*-NHCHO), 9.43 (2/3H, d, J = 11 Hz) and 9.68 (1/3H, br s) (*trans*- and *cis*-NHCHO). *Anal.* Calcd for C₁₄H₁₇N₅O₂: C, 58.53; H, 5.96; N, 24.37. Found: C, 58.47; H, 5.95; N, 24.27.

The above crude **18c** was recrystallized from 30% (v/v) aqueous EtOH to afford an analytical sample of 4-[(benzyloxyamino)methylene]amino-1-ethyl-1*H*-imidazole-5-carboxamide (**18c**) as colorless plates, mp 145—146 °C; MS m/z : 287 (M^+); UV $\lambda_{\max}^{95\% \text{ EtOH}}$ 256 nm (sh) (ϵ 9600), 285 (14500); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) (unstable) 255 (ϵ 9000); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 210 (19600), 282 (10300); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) (unstable) 281 (ϵ 7500), 326 (ϵ 11000); IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3383, 3327, 3173 (NH), 1653 (C=O), 1636 (C=N); $^1\text{H-NMR}$ δ : 1.27 (3H, t, J = 7 Hz, NCH₂Me), 4.20 (2H, q, J = 7 Hz, NCH₂Me), 5.00 (2H, s, OCH₂Ph), 7.24 (2H, brs, NH₂), 7.29—7.37 (5H, m, OCH₂Ph), 7.51 (1H, d, J = 11 Hz, N=CHNH), 7.60 [1H, s, C(2)-H], 8.98 (1H, d, J = 11 Hz, N=CHNH). *Anal.* Calcd for C₁₄H₁₇N₅O₂: C, 58.53; H, 5.96; N, 24.37. Found: C, 58.42; H, 6.00; N, 24.34.

1-Benzyl-*N'*-ethoxy-4-formamido-1*H*-imidazole-5-carboxamidine (14d) A suspension of **13d** (*vide supra*) (269 mg, 1 mmol) in H₂O (100 ml) was heated under reflux for 5 h. The resulting colorless solution was extracted with CHCl₃ (7 $\times$ 30 ml). The organic layers were combined, washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to leave an oily residue. This was subjected to flash chromatography [CHCl₃–MeOH (10:1, v/v)]. The compound (5.3 mg, 2%) obtained from the last fraction as a colorless solid (mp 265—267 °C) was recrystallized from H₂O to give colorless plates, mp 266—269 °C. This sample was identical (by comparison of the IR and $^1\text{H-NMR}$ spectra and TLC mobility) with authentic 7-benzylhypoxanthine (**12**; R¹ = PhCH₂).^{5a)}

Repeated flash chromatography and preparative TLC [CHCl₃–AcOEt–MeOH (3:1:1, v/v)] of crude products obtained from other fractions provided crude **14d** (161 mg, 56%), mp 99.5—100.5 °C; crude **15d**; **16d** (5.5 mg, 2%) as a colorless oil, which was identical (by comparison of the $^1\text{H-NMR}$ spectrum and TLC mobility) with authentic **16d** described below; and crude **18d** (18.6 mg, 6%), mp 185—188 °C. Crude **15d** was recrystallized from 30% (v/v) aqueous EtOH, affording a pure sample of **15d** (10.1 mg, 4%), mp 178—179 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **15d** described below. Crude **18d** was recrystallized from AcOEt to afford 1-benzyl-4-[(ethoxyamino)methylene]amino-1*H*-imidazole-5-carboxamide (**18d**) as colorless needles, mp 189.5—190 °C; MS m/z : 287 (M^+); IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3328, 3179, 3088 (NH), 1647 (C=O and C=N); $^1\text{H-NMR}$ δ : 1.19 (3H, t, J = 6.9 Hz, MeCH₂), 3.97 (2H, q, J = 6.9 Hz, MeCH₂), 5.46 (2H, s, PhCH₂), 7.05—7.38 (7H, m, PhCH₂ and NH₂), 7.50 [1H, d, J = 10.6 Hz, N=CHNH], 7.79 [1H, s, C(2)-H], 8.76 (1H, d, J = 10.6 Hz, N=CHNH).

Crude **14d** was further purified by precipitation from AcOEt–hexane to afford an analytical sample of 1-benzyl-*N'*-ethoxy-4-formamido-1*H*-imidazole-5-carboxamidine (**14d**) as colorless prisms, mp 99.5—100.5 °C; MS m/z : 287 (M^+); UV $\lambda_{\max}^{95\% \text{ EtOH}}$ 226 nm (sh) (ϵ 11500), 247 (sh) (9900); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) 250 (sh) (7000); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 225 (sh) (11900); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) (unstable) 263 (ϵ 10500); IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3488, 3357, 3281, 3096 (NH), 1665 (C=O), 1630 (C=N); $^1\text{H-NMR}$ δ : 1.16 (3H, t, J = 7 Hz, MeCH₂), 3.92 (2H, q, J = 7 Hz, MeCH₂), 5.33 (5/7 $\times$ 2H) and 5.38 (2/7 $\times$ 2H) (s each, *trans*- and *cis*-PhCH₂), 5.77 (2/7 $\times$ 2H) and 5.97 (5/7 $\times$ 2H) (br s each, *cis*- and *trans*-NH₂), 7.13—7.38 (5H, m, PhCH₂), 7.74 (5/7H) and 7.76 (2/7H) [s each, *trans*- and *cis*-C(2)-H], 8.14 (2/7H, br s) and 8.41 (5/7H, d, J = 10.9 Hz) (*cis*- and *trans*-NHCHO), 9.45 (5/7H, d, J = 10.9 Hz) and 9.70 (2/7H, br s) (*trans*- and *cis*-NHCHO). *Anal.* Calcd for C₁₄H₁₇N₅O₂: C, 58.53; H, 5.96; N, 24.37. Found: C, 58.51; H, 5.97; N, 24.32.

***N*⁶-Methoxy-7-methyladenine (15a)** i) From the Reaction of **13a** with Aqueous NaOH at 45 °C (Table 1, entry 13): The perchlorate **13a**·HClO₄⁷⁾ (140 mg, 0.5 mmol) was converted into the free base,⁷⁾ which was then dissolved in 0.1*N* aqueous NaOH (10 ml). The solution was kept at 45 °C for 20 h and concentrated *in vacuo* after neutralization with 10% aqueous HCl. The residue was triturated with CHCl₃–EtOH (1:1, v/v) (4 ml), and the insoluble solid was filtered off and washed with EtOH (1 ml). The filtrate and washings were combined and concentrated *in vacuo*, and the residue was subjected to flash chromatography [CHCl₃–EtOH (4:1, v/v and then 3:1, v/v)]. Compound **15a** (43 mg), mp 233—234 °C (dec.), was obtained from earlier fractions. Recrystallization of this sample from EtOH afforded **15a** as colorless prisms, mp 234—235 °C (dec.); this product was identical (by comparison of the IR

and $^1\text{H-NMR}$ spectra) with authentic **15a**.⁸⁾ Crude **12** ($\text{R}^1 = \text{Me}$) (9 mg, 12%) obtained from the last fraction was recrystallized from EtOH to afford a sample of mp $> 300^\circ\text{C}$. This sample was identical (by comparison of the IR and $^1\text{H-NMR}$ spectra and TLC mobility) with authentic 7-methylhypoxanthine (**12**; $\text{R}^1 = \text{Me}$).¹⁰⁾ A mixture (18 mg) containing several compounds, obtained from the middle fractions, was further purified by flash chromatography [CHCl_3 -EtOH (4:1, v/v)] and subsequent preparative TLC on silica gel [CHCl_3 -EtOH (5:1, v/v)] to afford a second crop of **15a** (7 mg; the total yield was 50 mg, 56%) and **16a** (3 mg, 4%).

When **13a** was treated under the same conditions for 5 h, **15a** and **16a** were obtained in 74% and 2% yields, respectively (Table 1, entry 12).

ii) From **13a** by Heating in Aqueous NaOH (Table 1, entry 14): The free base of **13a**⁷⁾ prepared from **13a**·HClO₄ (140 mg, 0.5 mmol) was heated in 0.1 N aqueous NaOH (5 ml) under reflux for 30 min. The resulting solution was neutralized with 10% aqueous HCl and concentrated *in vacuo*. The solid residue was extracted with AcOEt using a Soxhlet extractor. The AcOEt extracts were concentrated *in vacuo*, and the residue was recrystallized from EtOH to yield **15a** (68.7 mg), mp 233–234.5°C. The ethanolic mother liquor was concentrated *in vacuo*, and the residue was subjected to preparative TLC on silica gel [CHCl_3 -AcOEt-MeOH (3:1:1, v/v)] to provide a second crop of **15a** (4.5 mg; the total yield was 73.2 mg, 82%), mp 234.5–235°C. These two samples were identical (by comparison of the IR spectrum and TLC mobility) with authentic **15a**.⁸⁾

iii) From **14a**: A solution of **14a** (29.6 mg, 0.15 mmol) in 0.1 N aqueous NaOH (1.5 ml) was heated under reflux for 30 min, neutralized with 10% aqueous HCl, and concentrated *in vacuo*. The solid residue was extracted with AcOEt using a Soxhlet extractor. The extracts were concentrated *in vacuo*, and the residue was recrystallized from EtOH to provide **15a** (17.9 mg), mp 234.5–235.5°C. The ethanolic mother liquor afforded a second crop of **15a** (6.3 mg; the total yield was 24.2 mg, 90%), mp 223–226°C, by means of preparative TLC on silica gel [CHCl_3 -AcOEt-MeOH (3:1:1, v/v)]. These two samples were identical (by comparison of the IR spectra and TLC mobility) with authentic **15a**.⁸⁾

N⁶-Ethoxy-7-ethyladenine (15b) A solution of **13b**⁷⁾ (311 mg, 1.5 mmol) in 0.1 N aqueous NaOH (15 ml) was heated under reflux for 20 min, neutralized with 1 N aqueous HCl, and cooled to room temperature. The slightly brown pillars that deposited were collected by filtration, washed with H₂O (1 ml), and dried to afford a first crop of **15b** (154 mg), mp 192.5–193.5°C. The filtrate and washings were combined and extracted with AcOEt (5 × 20 ml). The organic layers were combined, dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to leave a partly crystallized residue. This was triturated with benzene (2 ml). The insoluble solid was collected by filtration, washed with benzene (0.5 ml), and dried to afford a second crop of **15b** [112 mg; the total yield was 266 mg (86%)], mp 191.5–192.5°C. Recrystallization of crude **15b** from AcOEt afforded an analytical sample of **15b** as colorless pillars, mp 193–193.5°C; MS m/z : 207 (M^+); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 277 nm (ϵ 13000); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 229 (6800), 279 (10100); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 275 (13800); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 296 (12700); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1661 (C=N); $^1\text{H-NMR}$ δ : 1.25 and 1.36 (3H each, t, $J = 7$ Hz, two MeCH_2 's), 4.00 (2H, q, $J = 7$ Hz, OCH_2Me), 4.21 (2H, q, $J = 7$ Hz, $\text{N(7)-CH}_2\text{Me}$), 7.50 [1H, d, $J = 4$ Hz, C(2)-H], 7.90 [1H, s, C(8)-H], 11.04 (1H, br, NH). *Anal.* Calcd for C₉H₁₃N₅O: C, 52.16; H, 6.32; N, 33.79. Found: C, 52.06; H, 6.41; N, 33.50.

N⁶-Benzyloxy-7-ethyladenine (15c) i) From **13c**: A suspension of **13c**⁷⁾ (269 mg, 1 mmol) in 0.1 N aqueous NaOH (10 ml) was refluxed for 30 min and then cooled in an ice bath. The resulting precipitate was collected by filtration, washed with H₂O (2 ml), and dried to afford a first crop of **15c** (173 mg), mp 160–160.5°C. A second crop of **15c** [41 mg; the total yield was 310 mg (80%)] (mp 166–167°C) was obtained by adjusting the pH of the combined filtrate and washings to 8 with 10% aqueous HCl. Recrystallization of crude **15c** from 30% (v/v) aqueous EtOH afforded **15c** as colorless needles, mp 167–167.5°C. This sample was identical (by comparison of the UV, IR, and $^1\text{H-NMR}$ spectra) with authentic **15c**.⁸⁾

ii) From **14c**: A solution of **14c** (144 mg, 0.5 mmol) in 0.1 N aqueous NaOH (5 ml) was refluxed for 30 min and then cooled to room temperature. The resulting precipitate was filtered off, washed with H₂O (2 ml), and dried to afford a first crop of **15c** (97 mg), mp 166–167°C. The filtrate and washings were combined and brought to pH 8 with 10% aqueous HCl. The precipitate that separated was collected by filtration, washed with H₂O (2 ml), and dried to afford a second crop of **15c** (21 mg;

the total yield was 118 mg, 87%), mp 166–167°C. The filtrate and washings were combined and extracted with CHCl_3 (3 × 10 ml). The organic layers were combined, washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel [CHCl_3 -AcOEt-MeOH (4:4:1, v/v)] to afford **16c** (7 mg, 5%) as a slightly yellow oil, which was identical with a sample obtained from **13c** by hydrolysis with 1 N aqueous HCl at room temperature for 5 h (*vide infra*).

7-Benzyl-N-ethoxyadenine (15d) Compound **13d** (*vide supra*) (135 mg, 0.501 mmol) was heated in 0.1 N aqueous NaOH (5 ml) under reflux for 30 min and allowed to cool to room temperature. The precipitate that resulted was collected by filtration, washed with H₂O (3 ml), and dried to afford a first crop of **15d** (81.4 mg), mp 179–180°C. The filtrate and washings were combined and neutralized with 10% aqueous HCl. The precipitate that deposited was collected by filtration, washed with H₂O (3 ml), and dried to give a second crop of **15d**, which was recrystallized from 30% (v/v) aqueous EtOH to yield **15d** (24.6 mg), mp 179.5–180°C. The mother liquor and washings, which were obtained when the second crop of **15d** was isolated, were combined and extracted with CHCl_3 (4 × 10 ml). The organic layers were combined, washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to leave an oil. This was subjected to preparative TLC on silica gel [CHCl_3 -AcOEt-MeOH (3:1:1, v/v)] to provide a third crop of **15d** (5.5 mg; the total yield was 111.5 mg, 83%) and crude **16d**. Crude **16d** was further purified by preparative TLC on alumina [CHCl_3 -MeOH (30:1, v/v)] to provide **16d** (6.6 mg, 5%) as a slightly yellow oil, which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic sample described below.

Recrystallization of crude **15d** from 30% (v/v) aqueous EtOH afforded an analytical sample of **15d** as colorless needles, mp 179.5–180°C; MS m/z : 269 (M^+); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 280 nm (ϵ 11200); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 225 (sh) (8000), 279 (9100); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 276 (12100); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 299 (11300); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1659 (C=N); $^1\text{H-NMR}$ δ : 1.20 (3H, t, $J = 7$ Hz, MeCH_2), 3.98 (2H, q, $J = 7$ Hz, MeCH_2), 5.46 (2H, s, PhCH_2), 7.24–7.40 (5H, m, PhCH_2), 7.49 [1H, d, $J = 3$ Hz, C(2)-H], 8.07 [1H, s, C(8)-H], 11.08 [1H, br d, $J = 3$ Hz, N(1)-H]. *Anal.* Calcd for C₁₄H₁₅N₅O: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.48; H, 5.60; N, 25.85.

4-Amino-N¹-methoxy-1-methyl-1H-imidazole-5-carboxamide (16a)

i) From **13a** by Heating in Aqueous NaOH (Table 1, entry 15): A solution of **13a**,⁷⁾ which was prepared from **13a**·HClO₄⁷⁾ (140 mg, 0.5 mmol), in 2 N aqueous NaOH (5 ml) was heated under reflux for 10 min, neutralized with 10% aqueous HCl, and concentrated *in vacuo*. The solid residue was extracted with AcOEt using a Soxhlet extractor. The extracts were concentrated *in vacuo*, and the residue was purified by repeated flash chromatography and preparative TLC on silica gel [CHCl_3 -AcOEt-MeOH (3:1:1, v/v)] to afford **15a** (18.5 mg, 21%) (mp 234–235°C) from earlier fractions and **16a** (50 mg, 59%) (mp 107–109°C) from later fractions.

ii) From **13a**·HClO₄ by Treatment with Aqueous HCl (Table 1, entry 3): A solution of **13a**·HClO₄ (280 mg, 1 mmol) in 1 N aqueous HCl (10 ml) was kept at room temperature for 4 h and then passed through a column of Amberlite IRA-402 (HCO_3^-) (22 ml). The column was eluted with H₂O, and the eluate (150 ml) was concentrated *in vacuo*. The oily residue was triturated with a mixture of Et₂O (3 ml) and a little EtOH. The precipitate that separated was collected by filtration and dried to give a first crop of **16a** (126 mg), mp 106.5–108.5°C. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on alumina [CHCl_3 -MeOH (20:1, v/v)] to afford a second crop of **16a** (18 mg; the total yield was 144 mg, 85%), mp 109.5–110.5°C. Recrystallization of crude **16a** from benzene-AcOEt (5:1, v/v) afforded an analytical sample of **16a** as colorless needles, mp 109.5–110.5°C; MS m/z : 169 (M^+); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 232 nm (ϵ 6800), 269 (8900); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 217 (8000), 273 (5700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 225 (7400), 259 (7500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 259 (7500); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3410, 3385, 3244, 3166, 3123 (NH), 1634 (C=N); $^1\text{H-NMR}$ δ : 3.58 [3H, s, N(1)-Me],²³⁾ 3.67 (3H, s, OMe),²³⁾ 4.57 [2H, br, C(4)-NH₂],²⁴⁾ 5.73 (2H, brs, NH₂C=N),²⁴⁾ 7.21 [1H, s, C(2)-H]. *Anal.* Calcd for C₆H₁₁N₅O: C, 42.60; H, 6.55; N, 41.39. Found: C, 42.61; H, 6.69; N, 41.26.

iii) From **14a** by Heating in Aqueous NaOH: A solution of **14a** (19.7 mg, 0.1 mmol) in 2 N aqueous NaOH (1 ml) was heated under reflux for 10 min, neutralized with 10% aqueous HCl, and concentrated *in vacuo*. The solid residue was extracted with AcOEt, and the crude products obtained by concentration of the AcOEt extracts were purified by preparative TLC in the same manner as described above under item

(i) to provide **16a** (12.4 mg, 73%) (mp 106–107 °C) and **15a** (4.3 mg, 24%) (mp 226–229 °C), which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.⁸⁾

iv) From **14a** by Treatment with Aqueous HCl: A solution of **14a** (49.3 mg, 0.25 mmol) in 1 N aqueous HCl (2.5 ml) was kept at room temperature for 4 h. The resulting solution was treated with Amberlite IRA-402 (HCO₃⁻) in a manner similar to that described above under item (ii). The crude products were purified by column chromatography on alumina [CHCl₃–MeOH (20:1, v/v)] to afford **16a** (33.4 mg, 79%) and a mixture of **15a** and **16a**. The latter mixture was further purified by preparative TLC on silica gel [CHCl₃–AcOEt–MeOH (3:1:1, v/v)] to provide **15a** (2.7 mg, 6%) (mp 223–228 °C), which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.⁸⁾

In a separate run, a solution of **14a** (39.4 mg, 0.2 mmol) in 1 N aqueous HCl (2 ml) was kept at room temperature for 30 min, neutralized with saturated aqueous NaHCO₃, and concentrated *in vacuo*. The solid residue was extracted with CHCl₃ using a Soxhlet extractor. The CHCl₃ solution was concentrated, and the residue was subjected to column chromatography on alumina [CHCl₃–MeOH (20:1, v/v)]. Compound **13a** (2.8 mg, 8%) [mp 125–135 °C (dec.)] was obtained from the earlier fractions. Compound **16a** (6.2 mg, 18%) (mp 108–109 °C) was obtained from the middle fractions. A mixture of other products obtained from the later fractions was recrystallized from AcOEt to give a first crop of **14a** (11.1 mg), mp 121–122 °C. The mother liquor of this recrystallization was concentrated *in vacuo*, and the residue was purified by preparative TLC on silica gel [CHCl₃–AcOEt–MeOH (3:1:1, v/v)] to afford crude **15a** and crude **14a**. Recrystallization of crude **15a** from CHCl₃ gave **15a** (1.6 mg, 4%), mp 227.5–230 °C. A second crop of **14a** (7.9 mg; the total recovery was 19 mg, 48%) (mp 120.5–121.5 °C) was obtained by recrystallization of the above crude **14a** from AcOEt.

4-Amino-N'-ethoxy-1-ethyl-1H-imidazole-5-carboxamidinium (16b) A solution of **13b**⁷⁾ (41.4 mg, 0.2 mmol) in 2 N aqueous HCl (2 ml) was kept at room temperature for 2 h and then passed through a column of Amberlite IRA-402 (HCO₃⁻) (8 ml). The column was eluted with H₂O (100 ml). The eluate was concentrated *in vacuo*, and the residue was subjected to column chromatography on alumina [CHCl₃–MeOH (20:1, v/v)] to afford a first crop of **16b** (33.7 mg), mp 41.5–43 °C; MS *m/z*: 197 (M⁺); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3461, 3426, 3355, 3164, 3108 (NH), 1634 (C=N); ¹H-NMR δ : 1.20 and 1.21 (3H each, t, *J* = 7 Hz, two MeCH₂'s), 3.91 (2H, q, *J* = 7 Hz, OCH₂Me),²⁵⁾ 4.03 [2H, q, *J* = 7 Hz, N(1)-CH₂Me],²⁵⁾ 4.47 [2H, br, C(4)-NH₂],²⁴⁾ 5.69 (2H, br s, NH₂C=N),²⁴⁾ 7.27 [1H, s, C(2)-H]. A mixture of two components obtained from the later fractions was purified by preparative TLC on silica gel [CHCl₃–AcOEt–MeOH (3:1:1, v/v)] to afford **15b** (1.9 mg, 5%) (mp 184.5–188.5 °C), which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen described above. A second crop of **16b** (1.6 mg; the total yield was 35.3 mg, 90%) was obtained from the slowly moving band.

4-Amino-N'-benzyloxy-1-ethyl-1H-imidazole-5-carboxamidinium (16c) A solution of **13c**⁷⁾ (269 mg, 1 mmol) in 1 N aqueous HCl (10 ml) was kept at room temperature for 5 h and then neutralized with saturated aqueous NaHCO₃. The precipitate that resulted was collected by filtration, washed with a little H₂O, and dried to give **15c** (11 mg, 4%) (mp 165–166 °C), which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.⁸⁾ The filtrate and washings were combined and extracted with CHCl₃ (3 × 20 ml). The organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was subjected to column chromatography on alumina [CHCl₃–MeOH (30:1, v/v)] to provide **16c** (228 mg, 88%) as a slightly yellow heavy oil, MS *m/z*: 259 (M⁺); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3447, 3331, 3168 (NH), 1634 (C=N); ¹H-NMR δ : 1.09 (3H, t, *J* = 7 Hz, MeCH₂), 3.93 [2H, q, *J* = 7 Hz, N(1)-CH₂Me], 4.41 [2H, br, C(4)-NH₂],²⁴⁾ 4.94 (2H, s, PhCH₂), 5.83 (2H, brs, NH₂C=N),²⁴⁾ 7.15–7.43 [6H, m, PhCH₂ and C(2)-H].

The picrate of **16c** was prepared by mixing a solution of **16c** (223 mg, 0.86 mmol) in EtOH (1 ml) with a saturated ethanolic solution of picric acid (217 mg, 0.947 mmol). The precipitate (381 mg, 91%) that resulted was filtered off and recrystallized from EtOH to afford an analytical sample of the picrate of **16c** as orange plates, mp 145.5–146 °C (dec.). *Anal.* Calcd for C₁₃H₁₇N₅O·C₆H₃N₃O₇: C, 46.72; H, 4.13; N, 22.94. Found: C, 46.71; H, 4.11; N, 22.91.

The free base **16c** was liberated from the picrate in the following manner. A warm solution of the picrate (373 mg, 0.764 mmol) in H₂O

(200 ml) was brought to pH 8 by addition of saturated aqueous NaHCO₃ and then extracted with CHCl₃ (4 × 50 ml). The organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to provide **16c** (198 mg, 100%) as a slightly yellow oil.

4-Amino-1-benzyl-N'-ethoxy-1H-imidazole-5-carboxamidinium (16d) A solution of **13d** (*vide supra*) (135 mg, 0.501 mmol) in 1 N aqueous HCl (5 ml) was kept at room temperature for 4 h, neutralized with saturated aqueous NaHCO₃, and extracted with CHCl₃ (4 × 10 ml). The organic layers were combined, washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The oily residue was purified by column chromatography on alumina [CHCl₃–MeOH (20:1, v/v)] to afford **16d** (125 mg, 96%) as a slightly yellow oil, MS *m/z*: 259 (M⁺); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3445, 3374, 3169 (NH), 1630 (C=N); ¹H-NMR δ : 1.14 (3H, t, *J* = 7 Hz, MeCH₂), 3.87 (2H, q, *J* = 7 Hz, OCH₂Me), 4.54 [2H, br, C(4)-NH₂],²⁴⁾ 5.29 (2H, s, PhCH₂), 5.66 (2H, brs, NH₂C=N),²⁴⁾ 7.07–7.14 (2H) and 7.20–7.34 (3H) (m each, PhCH₂), 7.43 [1H, s, C(2)-H]. Crude **15d** obtained from later fractions was purified by preparative TLC on silica gel [CHCl₃–AcOEt–MeOH (3:1:1, v/v)] to provide **15d** (5 mg, 4%) as a colorless solid, mp 175–177 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **15d** described above.

The picrate of **16d** was prepared by mixing a solution of **16d** (100 mg, 0.386 mmol) in EtOH (0.5 ml) with a saturated ethanolic solution of picric acid (97 mg, 0.423 mmol). The precipitate that resulted was collected by filtration, washed with a little EtOH, and dried to afford the picrate (165 mg, 88%), mp 154–155 °C (dec.). Recrystallization of this sample from EtOH afforded an analytical sample as yellow plates, mp 154.5–155 °C (dec.). *Anal.* Calcd for C₁₃H₁₇N₅O·C₆H₃N₃O₇: C, 46.72; H, 4.13; N, 22.94. Found: C, 46.66; H, 4.06; N, 22.94.

4-[(Methoxyamino)methylene]amino]-1-methyl-1H-imidazole-5-carbonitrile (17a) i) By Pyrolysis of **13a**: Compound **13a**,⁷⁾ prepared from **13a**·HClO₄⁷⁾ (559 mg, 2 mmol), was heated at 150 °C (bath temperature) for 1 h, and the product was extracted with CHCl₃. The CHCl₃ solution was concentrated *in vacuo*, and a brown solid thus obtained was triturated with MeOH (0.5 ml). The insoluble solid was collected by filtration and washed with a little MeOH to provide **17a** (202 mg, 56%), mp 171–171.5 °C. The combined filtrate and washings were concentrated *in vacuo*, and the residue was purified by flash chromatography [CHCl₃–AcOEt–MeOH (3:1:1, v/v)] to recover **13a** (99.2 mg, 28%). Recrystallization of crude **17a** from AcOEt–hexane (2:1, v/v) afforded an analytical sample of **17a** as slightly orange plates, mp 171.5–172 °C; MS *m/z*: 179 (M⁺); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 219 nm (ϵ 16700), 272 (16500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) (unstable) 218 (*ca.* 18000), 266 (*ca.* 12500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 218 (16800), 270 (16500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) (unstable) 263 (*ca.* 11000); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 2207 (C≡N), 1663, 1651 (C=N); ¹H-NMR δ : 3.65 and 3.73 (3H each, s, two Me's), 7.36 (1H, d, *J* = 10.2 Hz, CHNH), 7.73 [1H, s, C(2)-H], 9.58 (1H, brd, *J* = 10.2 Hz, CHNH). *Anal.* Calcd for C₇H₉N₅O: C, 46.92; H, 5.06; N, 39.09. Found: C, 47.07; H, 5.01; N, 39.06.

ii) By Treatment of **13a** with Aqueous NaOH (Table 1, entry 10): A solution of **13a**,⁷⁾ which was prepared from **13a**·HClO₄⁷⁾ (140 mg, 0.5 mmol), in 0.01 N aqueous NaOH (5 ml) was kept in a refrigerator (4 °C) for 35 d. The reaction mixture was neutralized with 10% aqueous HCl and concentrated *in vacuo*. The solid residue was extracted with CHCl₃ using a Soxhlet extractor. The extracts were concentrated *in vacuo*, and the residue was subjected to column chromatography on alumina [CHCl₃–MeOH (20:1, v/v)]. A mixture of products obtained from earlier fractions was subjected to flash chromatography [CHCl₃–MeOH (4:1, v/v)] to afford **17a** (1.4 mg, 2%) [mp 156–168 °C (dec.)], which was identical (by comparison of the ¹H-NMR spectrum and TLC mobility) with authentic **17a** described above, and **13a** (49.1 mg, 55% recovery). A crude product obtained from later fractions was recrystallized from CHCl₃ to afford **15a** (8.1 mg, 9%), mp 234.5–235.5 °C. The mother liquor of this recrystallization was concentrated *in vacuo*, and the residue was purified by preparative TLC on silica gel [CHCl₃–AcOEt–MeOH (3:1:1, v/v)]. The crude product thus isolated was recrystallized from AcOEt to provide **14a** (11.4 mg, 12%), mp 121–121.5 °C.

Reaction of 14a in Boiling H₂O A solution of **14a** (19.8 mg, 0.1 mmol) in H₂O (1 ml) was heated under reflux for 5 h and then concentrated *in vacuo*. Repeated preparative TLC [silica gel, CHCl₃–AcOEt–MeOH (3:1:1, v/v); alumina, CHCl₃–MeOH (20:1, v/v)] of the residue afforded **15a** (5.4 mg, 30%) (mp 229.5–230.5 °C), **16a** (2.0 mg, 12%), and **14a** (10.8 mg, 55% recovery) (mp 120.5–121.5 °C). None of the deaminated

products [**12** ($R^1 = \text{Me}$), **19a**, and **20** ($R^1 = \text{Me}$)] was detectable in the reaction mixture by means of TLC. This was also the case with the reaction of **14a** (3 mg) in boiling 0.1 M acetate buffer (pH 5.2) (1 ml) for 5 h.

Reaction of 15a in 0.1 N Aqueous NaOH at 45°C A solution of **15a** (35.8 mg, 0.2 mmol) in 0.1 N aqueous NaOH (1 ml) was kept at 45°C for 78 h, neutralized with 0.1 N aqueous HCl, and concentrated *in vacuo* to leave a brown solid. This was triturated with EtOH (1 ml), and the insoluble solid was filtered off and washed with EtOH (2 × 0.5 ml). The filtrate and washings were combined and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel [CHCl_3 -MeOH (10:1, v/v)] to afford **15a** (16.7 mg, 47% recovery) (mp 229–231°C) and **12** ($R^1 = \text{Me}$) (4.1 mg, 14%) (mp > 300°C). The latter sample was identical (by comparison of the IR and $^1\text{H-NMR}$ spectra) with authentic **12** ($R^1 = \text{Me}$).¹⁰⁾ Another product (mp > 300°C) obtained from the lower band was inferred to be 7-methyladenine (3.6 mg, 12%) by comparison of its NMR spectrum [$^1\text{H-NMR}$ δ : 3.99 (3H, s, N(7)-Me), 6.91 (2H, brs, NH_2), 8.16 (2H, s, purine protons)] with that of an authentic specimen.²⁶⁾

Reaction of 17a in Boiling H₂O A suspension of **17a** (46 mg, 0.26 mmol) in H₂O (2.5 ml) was heated under reflux for 5 min and concentrated *in vacuo* to leave a semisolid (46 mg), which was shown to be a mixture of **13a**, **14a**, **18a**, and **17a** in a molar ratio of 101:13:3:1 by TLC and $^1\text{H-NMR}$ analyses. The mixture was subjected to column chromatography on alumina [CHCl_3 -MeOH (20:1, v/v)], followed by preparative TLC on silica gel [CHCl_3 -AcOEt-MeOH (3:1:1, v/v)], to afford **13a** (37 mg, 80%). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **13a**.⁷⁾

Reaction of 18a i) In Boiling Acetate Buffer: When **18a** (2.8 mg, 0.014 mmol) was heated in boiling H₂O (1 ml) for 5 h, the formation of a small amount of **12** ($R^1 = \text{Me}$) was detectable by TLC on silica gel [CHCl_3 -AcOEt-MeOH (3:1:1, v/v) or CHCl_3 -MeOH (3:1, v/v)]. Next, a solution of **18a** (9.9 mg, 0.05 mmol) in 0.1 M acetate buffer (pH 5.2 at 24°C) (2 ml) was heated under reflux for 5 h. The reaction mixture was concentrated *in vacuo*, and the solid residue was subjected to preparative TLC on silica gel [CHCl_3 -AcOEt-MeOH (3:1:1, v/v)] to provide **19a** (0.9 mg, 10%), **18a** (3.6 mg, 36% recovery), and **12** ($R^1 = \text{Me}$) (1.7 mg, 23%), mp > 300°C. Compound **19a**, obtained as a colorless solid, was identical (by comparison of the $^1\text{H-NMR}$ spectrum and TLC mobility) with an authentic specimen described above. Compound **12** ($R^1 = \text{Me}$) was identical (by comparison of the IR spectrum and TLC mobility) with an authentic sample.¹⁰⁾ The formation of a trace of **20** ($R^1 = \text{Me}$) was suggested by means of TLC [silica gel, CHCl_3 -AcOEt-MeOH (3:1:1, v/v); alumina, CHCl_3 -MeOH (20:1, v/v)].

ii) In Aqueous HCl: A solution of **18a** (14.7 mg, 0.75 mmol) in 0.1 N aqueous HCl (1 ml) was kept at 50°C for 4 h and then neutralized by adding Amberlite IRA-402 (HCO_3^-) (0.2 ml). The mixture was filtered, and the ion-exchange resin was washed with H₂O (30 ml). The filtrate and washings were combined and concentrated *in vacuo*. The residue was subjected to preparative TLC on silica gel [CHCl_3 -MeOH (4:1, v/v)] to afford **19a** (1.0 mg, 7%), which was identical (by comparison of the $^1\text{H-NMR}$ spectrum and TLC mobility) with an authentic sample described above. The crude product obtained from the lower band was further purified by column chromatography on alumina [CHCl_3 -MeOH (4:1, v/v)] to provide **20** ($R^1 = \text{Me}$) (2.8 mg, 27%) (mp 185–187.5°C), which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.⁹⁾

Acid Hydrolysis of 1-Benzyloxy-9-ethyladenine (1: $R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$) A solution of **1-HBr** ($R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$)²⁷⁾ (2.63 g, 7.51 mmol) in H₂O (200 ml) was passed through a column of Amberlite IRA-402 (Cl^-) (60 ml) and the column was eluted with H₂O. The eluate (700 ml) was concentrated *in vacuo* and the residue was recrystallized from MeOH-Et₂O (1:2, v/v) to provide 1-benzyloxy-9-ethyladenine hydrochloride (**1-HCl**; $R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$) (1.61 g, 70%), mp 225–228.5°C (dec.). Further recrystallization of this product afforded an analytical sample as colorless prisms, mp 227.5–230.5°C (dec.); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 261 nm (ϵ 12400); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 216 (31100), 261 (12200); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 216 (31000), 261 (12200); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) (unstable) 259 (ca. 13000); $^1\text{H-NMR}$ δ : 1.44 (3H, t, $J = 7 \text{ Hz}$, MeCH_2), 4.28 (2H, q, $J = 7 \text{ Hz}$, MeCH_2), 5.43 (2H, s, PhCH_2), 7.44–7.47 (3H) and 7.65–7.68 (2H) (m each, PhCH_2), 8.62 [1H, s, C(8)-H],²²⁾ 8.94 [1H, s, C(2)-H].²²⁾ *Anal.* Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O} \cdot \text{HCl}$: C, 54.99; H, 5.27; N, 22.90. Found: C, 55.07; H, 5.36; N, 22.89. A solution of this hydrochloride salt (306 mg, 1 mmol) in 1 N aqueous HCl (10 ml) was kept at room temperature for 50 h, neutralized with saturated aqueous NaHCO_3 , and extracted with

CHCl_3 (3 × 20 ml). The organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was subjected to column chromatography on alumina [AcOEt-EtOH (20:1, v/v)] to afford **4** ($R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$) (190 mg, 73%), mp 105.5–106.5°C. Compound **3** ($R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$) (22.6 mg, 8%) (mp 187.5–189°C), obtained from the later fractions, was identical (by comparison of the $^1\text{H-NMR}$ spectrum and TLC mobility) with an authentic specimen.^{16b)} Compound **4** ($R^1 = \text{Et}$; $R^2 = \text{PhCH}_2$) was recrystallized from AcOEt-hexane (1:1, v/v) to afford colorless plates (mp 108–108.5°C); this product was identical (by comparison of the UV, IR, and $^1\text{H-NMR}$ spectra and TLC mobility) with an authentic specimen.^{16b)}

Catalytic Hydrogenolysis of 16c Leading to 4-Amino-1-ethyl-1H-imidazole-5-carboxamide (22) A solution of **16c** (130 mg, 0.5 mmol) in a mixture of 1 N aqueous HCl (0.5 ml) and H₂O (12 ml) was shaken under H₂ over Raney Ni W-2 catalyst (0.4 ml) at atmospheric pressure and ca. 50°C for 4 h. The catalyst was filtered off and washed with hot H₂O (50 ml). The filtrate and washings were concentrated *in vacuo* to a volume of ca. 5 ml. The solution was mixed with a solution of picric acid (252 mg, 1.1 mmol) in H₂O (30 ml). The precipitate that resulted was collected by filtration, washed with H₂O (3 ml), and dried to afford **22**·dipicrate (206 mg, 67%), mp 222–225°C (dec.). This was recrystallized from 0.1 M phosphate buffer (pH 6), washed with H₂O, and dried to afford an analytical sample of the dipicrate as yellow pillars, mp 246–246.5°C (dec.); $^1\text{H-NMR}$ δ : 1.24 (3H, t, $J = 7 \text{ Hz}$, MeCH_2), 4.03 (br, $^+\text{NH}_3$ and H₂O), 4.11 (2H, q, $J = 7 \text{ Hz}$, MeCH_2), 8.26 [1H, s, C(2)-H], 8.59 (4H, s, aromatic protons), 8.64 (4H, brs, protonated amide). *Anal.* Calcd for $\text{C}_6\text{H}_{11}\text{N}_5 \cdot 2\text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 35.36; H, 2.80; N, 25.20. Found: C, 35.43; H, 2.72; N, 25.27.

Kinetic Procedure Buffer solutions used for kinetic runs were 0.1 M H_3PO_4 - NaH_2PO_4 (pH 2.00 and 3.00 at 40°C), 0.1 M $\text{HCO}_2\text{H-HCO}_2\text{Na}$ (pH 4.00 at 40°C), 0.1 M AcOH-AcONa (pH 5.00 at 40°C), 0.1 M NaH_2PO_4 - Na_2HPO_4 (pH 6.14, 7.00, and 7.76 at 40°C), 0.1 M NaHCO_3 - Na_2CO_3 (pH 9.00 and 10.00 at 40°C), and 0.1 M Na_2HPO_4 - Na_3PO_4 (pH 11.00 and 11.40 at 40°C) and were brought to ionic strength 1.0 with KCl. The substrate **13c**· HClO_4 was dissolved in the buffer solutions at a concentration of 5.43×10^{-4} – 5.85×10^{-4} M. Aliquots (ca. 2.5 ml) of the resulting solutions were placed in small glass-stoppered tubes and kept in a constant-temperature bath thermoregulated at $40 \pm 0.05^\circ\text{C}$. At intervals, the solutions were cooled to room temperature, and portions (2 ml) were diluted with 0.17 M citrate buffer (pH 5.80 at room temperature; the ionic strength was brought to 1.0 with KCl) to a volume of 20 ml. Portions (20 μl) of the diluted sample solutions were then subjected to HPLC [CH_3CN -0.05 M aqueous KH_2PO_4 (30:70, v/v), 0.5 ml/min]. The HPLC system employed consisted of a Tosoh CCPD pump, an injection valve unit, a UV-8020 detector operated at 254 nm, a Chromatocorder 21 integrator, and a TSK-GEL ODS-80Ts column. Concentrations of **13c** in the reaction mixture were estimated from a calibration curve which had been obtained with authentic **13c**· HClO_4 . All reactions were followed for at least three half-lives with at least eight measurements, and good pseudo-first-order kinetics were obtained in all cases. The results are summarized in Table 3.

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