Purines. XLVII.[1] Dimroth Rearrangement *versus* Hydrolytic Deamination of 1-Ethyladenine

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The Dimroth rearrangement of 1-ethyladenine (6) to give N^6-ethyladenine (11) (91% yield) was accompanied with unusual hydrolytic deaminations to produce hypoxanthine (8) (2%) and 1-ethylhypoxanthine (14) (2%), when carried out in 0.2 N aqueous NaOH at 100 °C for 7 h. Probable pathways leading to these by-products are discussed on the basis of the results of alkaline hydrolysis of 5-amino-*N'*-ethylimidazole-4-carboxamidine dihydrochloride (5), which yielded both 5-aminoimidazole-4-carboxamide (9) and 5-amino-*N*-ethylimidazole-4-carboxamide (12). For structural identification, 14 was alternatively synthesized from inosine (17) through 1-ethylinosine (16), and 12 was synthesized from 16 through 5-amino-*N*-ethyl-1-β-D-ribofuranosylimidazole-4-carboxamide (15). Comparison of the reaction rates in the Dimroth rearrangements of 6·$HClO_4$ and 1-ethyl-9-methyladenine perchlorate [1·$HClO_4$ (R^1 = Et; R^2 = Me)] in H_2O at pH 6.92 and 8.70 (ionic strength 1.0) at 70 °C has revealed that nonsubstitution at the 9-position decreases the rearrangement rate by a factor of 4—30 under these conditions.

Keywords 1-alkyladenine; 1,9-dialkyladenine; imidazole-4-carboxamidine; alkaline hydrolysis; Dimroth rearrangement; hydrolytic deamination; adenine ring-opening; rate study; high-performance liquid chromatography

The most conspicuous chemical behavior of 1-alkyladenines and their derivatives (*e.g.*, type **1**) is that they usually undergo Dimroth rearrangement under basic conditions to produce the N^6-alkyl isomers (type **3**), and no ring-opened intermediates (*e.g.*, type **2**) are detectable.[2] In the case of 9-substituted 1-alkyladenines (**1**), the rearrangement has been found to proceed by a mechanism involving a rate-determining initial ring-opening, caused by attack of hydroxide ion on both the protonated (**1**·H^+) and the neutral species (**1**) at the 2-position, and a subsequent fast ring closure of the putative monocyclic intermediate (**2**) (Chart 1).[3] The hydroxide attack on the protonated species is much faster than that on the neutral species (by a factor of 90—1400),[3] and the former is influenced by the electronic effect of a substituent at the 1-position, whereas the latter is influenced by the steric effect.[3c] In the case of 1-alkyladenines unsubstituted at the 9-position (type **4**), the rearrangement may be said to proceed more slowly than that of the corresponding 9-substituted analogues (type **1**). This statement is based on the following finding. When heated in concentrated aqueous NH_3 at 60 °C for 3 h, 1-(3-methyl-2-butenyl)adenine (**4**: $R^1 = Me_2C=CHCH_2$), a chemical precursor of the cytokinin N^6-(3-methyl-2-butenyl)adenine (**3**: $R^1 = Me_2C=CHCH_2$; R^2 = H),[4] rearranged to the cytokinin to the extent of 27%, whereas the corresponding 9-riboside (**1**: $R^1 = Me_2C=CHCH_2$; R^2 = β-D-ribofuranosyl) rearranged to **3** ($R^1 = Me_2C=CHCH_2$; R^2 = β-D-ribofuranosyl) to the extent of 100%.[5] A more quantitative basis is that the rearrangement of the aglycone **4** ($R^1 = Me_2C=CHCH_2$) in 1 N aqueous KOH at 41 °C displayed first-order kinetics with a time for half reaction ($t_{1/2}$) of 32 h, whereas that of the 9-riboside (**1**: $R^1 = Me_2C=CHCH_2$; R^2 = β-D-ribofuranosyl) in 0.02 N aqueous KOH at 41 °C occurred with $t_{1/2}$ 25 min.[6] In order to check the validity of such statement, we scrutinized the Dimroth rearrangement of 1-ethyladenine (**6**) in H_2O at various pH's. The present paper describes the results including two types of unusual hydrolytic deaminations of **6**, which have been found to occur competitively with the usual Dimroth rearrangement.

Treatment of **6**[1] with 0.2 N aqueous NaOH at 100 °C for 7 h gave N^6-ethyladenine (**11**) in 91% yield, as expected.[7] However, thin-layer chromatographic (TLC) analysis of the reaction mixture indicated the presence of at least two by-products besides a small amount of the starting material (**6**). Separation of the by-products from the reaction mixture by fractional crystallization and column chromatography resulted in the isolation of hypoxanthine (**8**) and 1-ethylhypoxanthine (**14**) in 2% yield each. The structure of **14** was confirmed by comparison with an authentic sample prepared from inosine (**17**) through 1-ethylinosine (**16**) according to a procedure[8] modified slightly from that

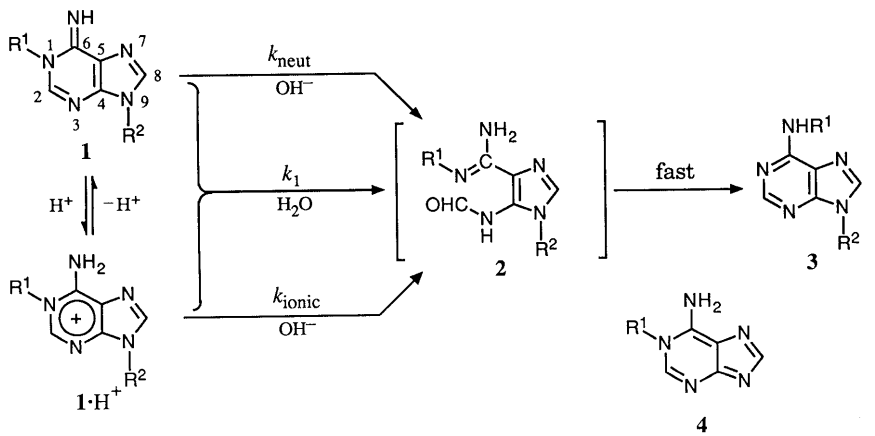

Chart 1

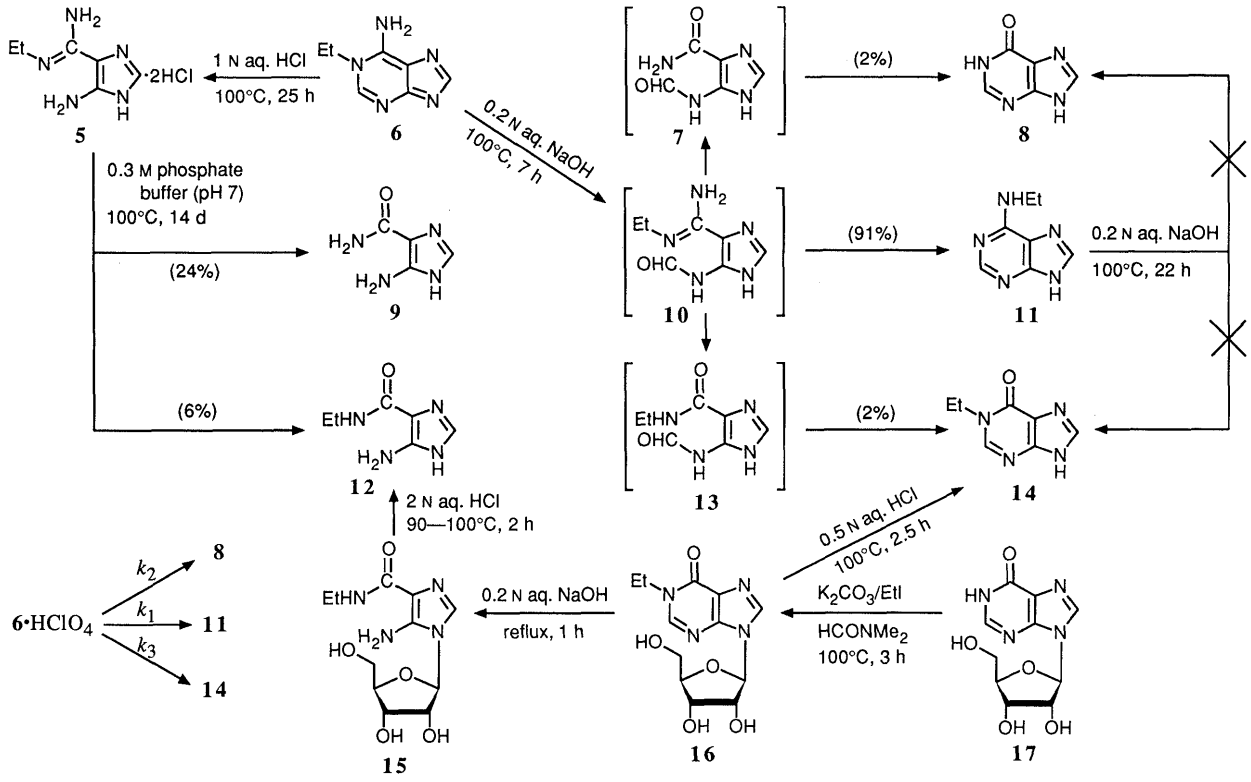

Chart 2

TABLE I. Effect of pH on the Hydrolytic Deamination of 1-Ethyladenine (**6**) in H_2O at 70 °C and Ionic Strength 1.0

Reaction conditions[a]		Yield[b] (%)			
pH[c] or solvent	Time (h)	Unaltered **6**	**11**	**8**	**14**
6.97	240	2	90	<1	3
8.70	150	0	97	<1	3
10.47	96	0	90	6	3.5
0.2 N NaOH	72	0	89	6	2

a) 1-Ethyladenine perchlorate (**6**·$HClO_4$) was dissolved in an appropriate 0.05 M buffer (of ionic strength 1.0) or in 0.2 N aqueous NaOH at 4.7×10^{-4}—5.4×10^{-4} M concentration, and the resulting solution was heated at 70 °C. The details are given in Experimental. *b*) Determined by HPLC analysis. *c*) At 70 °C.

of Balsiger *et al.*[9] It may be seen from Table I that the two by-products also occurred under milder alkaline conditions. At pH 8.70 and below, the formation of **14** was favored over that of **8**, whereas raising the pH to 10.47 and above reversed the situation. The rate of disappearance of **6** seemed to increase as the pH of the medium was increased.

The formation of the two by-products (**8** and **14**) in the Dimroth rearrangement of **6** does not seem to be a result of consecutive reactions of the main product **11**. This is because **11** was recovered in 98% yield, with no indication of the occurrence of **8** and **14**, even after it had been treated with 0.2 N aqueous NaOH at 100 °C for 22 h. We thus presume that both **8** and **14** would have been formed through the monocycle **10**, a putative common intermediate in the Dimroth rearrangement of **6** to give **11**, as shown in Chart 2. Since the monocycle **10** has an unsymmetrical amidine structure, hydrolysis of **10** *via* a tetrahedral intermediate may cleave ethylamine and ammonia competitively,[10] giving **8** (*via* **7**) and **14** (*via* **13**), respectively, if the cyclization of **10** to **11** is sufficiently slow. In the case of the formation of **14**, however, the possibility of a direct hydrolytic deamination of **6** *via* an addition–elimination mechanism may not necessarily be excluded. The possibility of the two directions of hydrolytic cleavage in the amidine system **10** was checked in a similar system. Treatment of the *N'*-ethylamidine salt **5**, prepared from **6** in 66% yield by acid hydrolysis as in the case[11] of the *N'*-methyl homologue, with 0.3 M phosphate buffer (pH 7) at 100 °C for 14 d produced 5-aminoimidazole-4-carboxamide (**9**) and 5-amino-*N*-ethylimidazole-4-carboxamide (**12**) in 24% and 6% yields, respectively. The *N*-ethylcarboxamide **12** was identified by comparison with a sample prepared from **17** through **16** and **15**. The ring opening of **16** to give **15** was analogous to that reported for the 1-benzyl congener.[12] A similar preference for cleavage of ethylamine over ammonia in **5** was also found for its hydrolysis in 0.2 N aqueous NaOH at 70 °C. This preference is in general agreement with the finding of Perrin and Nuñez[10a] and is consistent with a 6:2 preference for the formation of **8** over that of **14** in a similar alkaline hydrolysis of **6** (Table I).

Finally, the reaction rates in the Dimroth rearrangements of 1-ethyladenine perchlorate (**6**·$HClO_4$) and 1-ethyl-9-methyladenine perchlorate [**1**·$HClO_4$ (R^1 = Et; R^2 = Me)] were measured in H_2O at various pH's and ionic strength 1.0 at 70 °C. Chart 2 includes the scheme of the reaction system that produces N^6-ethyladenine (**11**), hypoxanthine (**8**), and 1-ethylhypoxanthine (**14**) from **6**·$HClO_4$ in a competitive manner, and Chart 1 represents the reaction system that produces the N^6-ethyl isomer **3** (R^1 = Et; R^2 = Me) from the 1-ethyl isomer **1**·$HClO_4$ (R^1 = Et; R^2 = Me). In kinetic runs of the former system, the changes of the concentrations of **6** and **11** were followed by means of high-performance liquid chromatographic (HPLC)

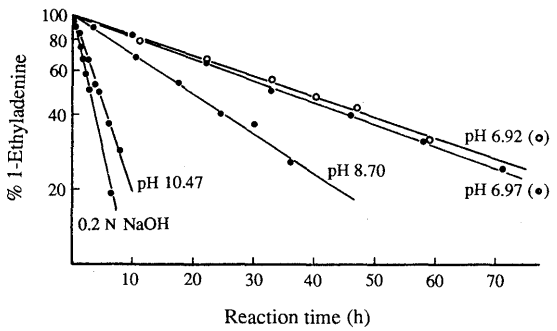

Fig. 1. First-Order Plot for the Reaction of 1-Ethyladenine Perchlorate ($\mathbf{6}\cdot HClO_4$) in H_2O at Various pH's and Ionic Strength 1.0 at 70 °C

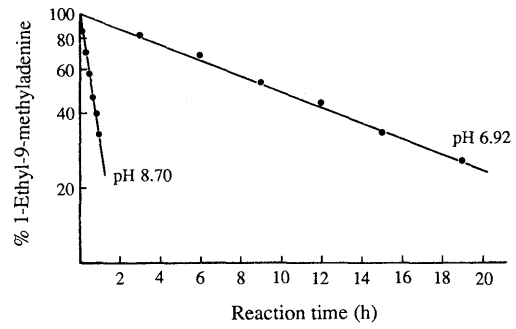

Fig. 2. First-Order Plot for Rearrangement of 1-Ethyl-9-methyladenine Perchlorate [$\mathbf{1}\cdot HClO_4$ ($R^1=Et$; $R^2=Me$)] to N^6-Ethyl-9-methyladenine [**3** ($R^1=Et$; $R^2=Me$)] in H_2O at Various pH's and Ionic Strength 1.0 at 70 °C

TABLE II. The Rate Constants for the Dimroth Rearrangement and Deaminations of 1-Ethyladenine (**6**) and for the Dimroth Rearrangement of 1-Ethyl-9-methyladenine [**1** ($R^1=Et$; $R^2=Me$)] in H_2O at 70 °C and Ionic Strength 1.0

Substrate	pH value or solvent	Pseudo-first-order rate constant (min^{-1})		Half-life[a] (h)
		k_{total}[b]	k_1[c]	
$\mathbf{6}\cdot HClO_4$	6.92	3.2×10^{-4}	2.8×10^{-4}	41
	6.97	3.4×10^{-4}	3.1×10^{-4}	37
	8.70	6.1×10^{-4}	6.0×10^{-4}	19
	10.47	2.8×10^{-3}	2.5×10^{-3}	4.6
	0.2 N NaOH	4.1×10^{-3}	3.7×10^{-3}	3.1
$\mathbf{1}\cdot HClO_4$ ($R^1=Et$; $R^2=Me$)	6.92		1.2×10^{-3}	9.6
	8.70		1.9×10^{-2}	0.61

a) The time for half rearrangement. *b*) $k_{total}=k_1+k_2+k_3$, *etc.* (see Chart 2). *c*) The rate constant for Dimroth rearrangement.

analysis. The semilogarithmic plots of mole fractions of the residual substrate and those of the rearranged product (**11**) against time indicated that all reactions involved obey fairly good pseudo-first-order kinetics at all pH's and are competitive (Fig. 1). Table II lists the rate constants (k_{total} and k_1) and half-lives obtained from such plots in the usual manner.[13] The kinetic experiments in the latter system were carried out in a manner similar to that[3c] described previously for the rearrangement at 40 °C, and the results are included in Fig. 2 and Table II. It may be seen that both substrates increase their rearrangement rates with increasing pH of the reaction medium. Although the pK_a values of $\mathbf{6}\cdot HClO_4$ (7.08 ± 0.06 and 11.40 ± 0.06)[1] and $\mathbf{1}\cdot HClO_4$ ($R^1=Et$; $R^2=Me$) (9.02 ± 0.04)[3c] at 40 °C and ionic strength 1.0 are known, we were unable to determine those at 70 °C (the temperature applied to the Dimroth rearrangement reactions) because of technical difficulty. This hampered the analysis of the above kinetic data, which might reveal the contributions of the protonated, neutral, and anionic (possibly in the case of **6**) species of the substrates to the overall rearrangement rates.[14] However, comparison of the rearrangement rates of $\mathbf{6}\cdot HClO_4$ at pH 6.92 and 8.70 with those of $\mathbf{1}\cdot HClO_4$ ($R^1=Et$; $R^2=Me$) indicated that nonsubstitution at the 9-position slows down the rearrangement rate by a factor of 4—30 under these conditions. Such retardation may be one of the reasons why the competitive deaminations of **6** become not insignificant.

In conclusion, the present results support the validity of the statement that 1-alkyladenines unsubstituted at the 9-position (type **4**) undergo Dimroth rearrangement more slowly than the corresponding 9-substituted analogues (type **1**). The formation of the two deaminated products (**8** and **14**) in the Dimroth rearrangement of 1-ethyladenine (**6**) deserves particular mention because 1,9-dialkyladenines (type **1**) usually do not undergo deamination under Dimroth rearrangement conditions,[3] with the exception of 1-(ω-hydroxyalkyl) analogues.[3g] In addition, there is ultraviolet (UV) spectroscopic and TLC evidence that the Dimroth rearrangement of 1-methyladenine (**4**: $R^1=Me$) is also accompanied with similar side reactions, although we have not yet isolated the by-products. This is suggestive of generality of such deaminations for related 1-substituted adenines (type **4**).

Experimental

General Notes All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. UV spectra reported herein were recorded on a Hitachi model 320 spectrophotometer on solutions in 95% (v/v) aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13). See ref. 1 for details of other instrumentation and measurements. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dq = doublet-of-quartets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

Conversion of 1-Ethyladenine (6) into N^6-Ethyladenine (11), Hypoxanthine (8), and 1-Ethylhypoxanthine (14) A solution of $\mathbf{6}\cdot 1/2H_2O$[1] (3.92 g, 22.8 mmol) in 0.2 N aqueous NaOH (90 ml) was heated in an oil bath kept at 100 °C for 7 h. After cooling, the reaction mixture was brought to pH 7 by addition of 10% aqueous HCl and then kept in a refrigerator overnight. The colorless precipitate that deposited was filtered off, washed with a little H_2O, and dried to furnish a first crop (3.22 g, 87%) of **11**, mp 238.5—239.5 °C (dec.). Recrystallizations from H_2O and drying over P_2O_5 at 2 mmHg and 75 °C for 15 h gave an analytical sample of **11** as colorless, minute needles, mp 238—238.5 °C (dec.) [lit.[15] mp 238—239 °C (dec.)]; UV $\lambda_{max}^{95\%\ EtOH}$ 268 nm (ε 16800); $\lambda_{max}^{H_2O}$ (pH 1) 269 (15500); $\lambda_{max}^{H_2O}$ (pH 7) 267 (16900); $\lambda_{max}^{H_2O}$ (pH 13) 274 (16600).[16] *Anal.* Calcd for $C_7H_9N_5$: C, 51.52; H, 5.56; N, 42.92. Found: C, 51.52; H, 5.55; N, 43.18.

The mother liquor, obtained when the first crop of **11** was filtered off, was concentrated *in vacuo* to leave a pale brownish solid. The solid was dried and extracted with hot MeOH (6 × 20 ml). The MeOH extracts were combined and concentrated *in vacuo*, and the residual solid was triturated with MeOH (20 ml) to separate the insoluble part (fraction A) and the soluble part (fraction B). Recrystallization of fraction A from H_2O (3 ml) afforded hypoxanthine (**8**) (70.9 mg, 2%) as a gray solid, mp > 300 °C. Further recrystallizations from H_2O and drying over P_2O_5 at 2 mmHg and 110 °C for 3 h yielded an analytical sample of **8** as a colorless solid, mp > 300 °C. *Anal.* Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.16. Found: C, 43.90; H, 2.82; N, 40.98. This sample was identical [by comparison of the infrared (IR) spectrum and TLC mobility] with authentic **8**.

Fraction B (*vide supra*) was then subjected to column chromatography [alumina (30 g)]. Earlier fractions eluted with $CHCl_3$–EtOH (30 : 1, v/v) gave a second crop (163 mg, 4%) of **11**, mp 237.5—239 °C (dec.), raising the total yield of **11** to 91%. Later fractions eluted with $CHCl_3$–EtOH (10 : 1, v/v) provided crude 1-ethylhypoxanthine (**14**) (90.6 mg, 2%) as a pale yellow solid. Purification of the solid by means of preparative TLC [alumina, $CHCl_3$–EtOH (6 : 1, v/v)] followed by recrystallization from MeOH afforded **14** as a pale greenish solid, mp 273—276 °C (dec.). This sample was identical (by comparison of the IR and UV spectra and TLC mobility) with authentic **14** (*vide infra*).

Preparation of 1-Ethylhypoxanthine (14) from Inosine (17) through 1-Ethylinosine (16) For the preparation of **14**, the literature procedure[9] was slightly modified in the following manner.[8] A mixture of inosine (**17**) (5.00 g, 18.6 mmol) and anhydrous K_2CO_3 (2.85 g, 20.6 mmol) in $HCONMe_2$ (40 ml) was stirred at 100 °C for 40 min, then allowed to cool. A solution of EtI (3.20 g, 20.5 mmol) in $HCONMe_2$ (10 ml) was added, and the resulting mixture was stirred at 100 °C for 3 h. After cooling, the reaction mixture was filtered to remove the solid that remained insoluble, and the solid was washed with $HCONMe_2$. The filtrate and washings were combined and concentrated *in vacuo* to leave a dark oil, which was dissolved in H_2O (20 ml). The resulting aqueous solution was passed through a column of Amberlite CG-120 (Type I, H^+) (280 ml), and the column was eluted with H_2O followed by 3% aqueous NH_3 (1 l). The ammoniacal eluate was concentrated *in vacuo* to leave crude **16** as a brownish oil, which was dissolved in 0.5 N aqueous HCl (58 ml). The resulting acidic solution was stirred at 100 °C for 2.5 h and then concentrated *in vacuo* to leave a dark oil. The oil was dried and purified by column chromatography [alumina (200 g), $CHCl_3$–EtOH (8 : 1, v/v)], giving **14** (646 mg, 21% yield from **17**) as a pale brownish solid, mp 270—279°C (dec.). Recrystallizations from MeOH produced an analytical sample of **14** as colorless needles, mp 279.5—280 °C (dec.) (lit.[9] mp 275—276 °C); MS *m/z*: 164 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 252 nm (ε 8690); $\lambda_{max}^{H_2O}$ (pH 1) 250 (9780); $\lambda_{max}^{H_2O}$ (pH 7) 251 (9330); $\lambda_{max}^{H_2O}$ (pH 13) 261 (9970); ^{1}H-NMR (Me_2SO-d_6) δ: 1.27 [3H, t, J=7 Hz, N(1)–CH_2Me], 4.04 [2H, q, J=7 Hz, N(1)–CH_2Me], 8.13 and 8.33 (1H each, s, purine protons). *Anal.* Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.19; H, 4.93; N, 34.35.

Earlier fractions of the above alumina column chromatography gave a yellow solid (109 mg, 3%), mp 136—138 °C (dec.). Recrystallizations of the solid from hexane and drying over P_2O_5 at 2 mmHg and 50 °C for 6 h furnished a substance presumed to be 1,7-diethylhypoxanthine as slightly hygroscopic, yellow needles, mp 137—137.5 °C (dec.) (lit.[17] mp 142—144 °C); MS *m/z*: 192 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 257 nm (ε 7980); $\lambda_{max}^{H_2O}$ (pH 1) 252 (8580); $\lambda_{max}^{H_2O}$ (pH 7) 257 (7780); $\lambda_{max}^{H_2O}$ (pH 13) 257 (7830)[18]; ^{1}H-NMR (Me_2SO-d_6) δ: 1.27 and 1.41 (3H each, t, J=7 Hz, CH_2Me's), 4.03 and 4.35 (2H each, q, J=7 Hz, CH_2Me's), 8.23 and 8.30 (1H each, s, purine protons). *Anal.* Calcd for $C_9H_{12}N_4O \cdot 1/10H_2O$: C, 55.72; H, 6.34; N, 28.88. Found: C, 55.61; H, 6.59; N, 28.89.

Stability of N^6-Ethyladenine (11) under Alkaline Conditions A solution of **11** (164 mg, 1 mmol) in 0.2 N aqueous NaOH (4 ml) was stirred at 100 °C for 22 h. The reaction was monitored by TLC and UV spectrophotometry, but there was no indication of the occurrence of any products. After cooling, the reaction mixture was brought to pH 7 by addition of 10% aqueous HCl. The colorless crystals that resulted were filtered off, washed with a little H_2O, and dried to recover **11**, mp 238.5—239 °C (dec.), in 98% yield. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **11**.

5-Amino-*N*′-ethylimidazole-4-carboxamidine Dihydrochloride (5) A solution of **6**·$HClO_4$[1] (942 mg, 3.57 mmol) in H_2O (10 ml) was brought to pH 8 by addition of 10% aqueous Na_2CO_3. The colorless crystals that resulted were filtered off and dissolved in 1 N aqueous HCl (40 ml). The resulting acidic solution was heated at 100 °C with stirring for 25 h. Concentration of the reaction mixture under reduced pressure and co-evaporation of the residue with five 10-ml portions of EtOH left an almost colorless solid. Recrystallization of the solid from EtOH (30 ml) gave a first crop (182 mg, 23%) of **5** as colorless granules, mp 203.5—205 °C (dec.). Concentration of the mother liquor of recrystallization afforded a second crop (352 mg) of **5**, mp 200—203 °C (dec.), raising the total yield of **5** to 534 mg (66%). Further recrystallization from EtOH produced an analytical sample as colorless granules, mp 203—204.5 °C (dec.); UV $\lambda_{max}^{95\%\,EtOH}$ 288 nm (ε 14800); $\lambda_{max}^{H_2O}$ (pH 1) 218 (7500), 278 (10400); $\lambda_{max}^{H_2O}$ (pH 7) 282 (11300); $\lambda_{max}^{H_2O}$ (pH 13) 236 (sh) (3950), 290 (13100); ^{1}H-NMR (Me_2SO-d_6) δ: 1.19 (3H, t, J=7 Hz, NCH_2Me), 3.25—3.53 [2H, m (converted into q with J=7 Hz on addition of D_2O), NHCH_2Me], 5.0—6.4 (4H, br, NH_2 and NH's), 7.94 [1H, s, C(2)-H], 8.53 (2H, s, NH_2), 8.91 (1H, t, J=5 Hz, NHCH_2Me). *Anal.* Calcd for $C_6H_{11}N_5 \cdot 2HCl$: C, 31.87; H, 5.79; N, 30.97. Found: C, 31.95; 5.93; N, 31.17.

Hydrolysis of 5 Leading to 5-Aminoimidazole-4-carboxamide (9) and 5-Amino-*N*-ethylimidazole-4-carboxamide (12) A mixture of **5** (1.13 g, 5 mmol) and 0.3 M aqueous KH_2PO_4–Na_2HPO_4 (pH 7 at 26 °C) (200 ml) was stirred at 100 °C for 14 d. The reaction mixture was concentrated *in vacuo*, and the residue was dried and then extracted with hot EtOH (5 × 30 ml). The ethanolic extracts were combined and concentrated *in vacuo*, and the residue was subjected to flash chromatography[19] [silica gel, CH_2Cl_2–MeOH (3 : 1, v/v)]. Earlier fractions gave **12** as a greenish oil, which was dissolved in EtOH (2 ml). The resulting solution was brought to pH 1 by addition of 10% (w/w) ethanolic HCl, and then ether (20 ml) was added. The yellowish precipitate that resulted was filtered off and dried to give **12**·HCl (61 mg, 6%), mp 195—198 °C (dec.). Further recrystallizations from EtOH yielded a pure sample of **12**·HCl, mp 203—207 °C (dec.), which was identical (by comparison of the UV and IR spectra and TLC mobility) with the one prepared from **15** (*vide infra*).

Later fractions in the above chromatography afforded **9** as a greenish oil, which was dissolved in EtOH (5 ml). The resulting solution was treated with 10% (w/w) ethanolic HCl and then with ether in a manner similar to that described above for **12**·HCl, producing **9**·HCl (192 mg, 24%) as a pale brownish solid, mp 220—225 °C (dec.). Recrystallizations from MeOH and drying over P_2O_5 at 2 mmHg and 75 °C for 23 h furnished an analytical sample of **9**·HCl as a colorless solid, mp 250—255 °C (dec.) (lit.[20] mp 253—254 °C); UV $\lambda_{max}^{95\%\,EtOH}$ 236 nm (sh) (ε 5770), 270 (11500); $\lambda_{max}^{H_2O}$ (pH 1) 240 (7890), 267 (9920); $\lambda_{max}^{H_2O}$ (pH 7) 232 (sh) (4750), 268 (11200); $\lambda_{max}^{H_2O}$ (pH 13) 278 (12700); ^{1}H-NMR (Me_2SO-d_6) δ: 7.54 (2H, s, NH_2), 8.53 [1H, s, C(2)-H]. *Anal.* Calcd for $C_4H_6N_4O \cdot HCl$: C, 29.55; H, 4.34; N, 34.46. Found: C, 29.30; H, 4.31; N, 34.54.

In a separate experiment, a solution of **5** (6.2 mg) in 0.2 N aqueous NaOH (50 ml) was heated at 70 °C. At intervals, an aliquot (15 μl) of the reaction mixture was withdrawn and subjected to HPLC analysis [LiChrosorb RP-18 (7 μm), 0.05 M aqueous KH_2PO_4–MeCN (85 : 15, v/v), 1800 p.s.i., 1.4 ml/min].[21] The results are summarized in the text.

1-Ethylinosine (16) A mixture of inosine (**17**) (5.36 g, 20 mmol) and anhydrous K_2CO_3 (3.04 g, 22 mmol) in $AcNMe_2$ (45 ml) was stirred at 100 °C for 50 min, then allowed to cool. A solution of EtI (3.43 g, 22 mmol) in $AcNMe_2$ (10 ml) was added, and the resulting mixture was stirred at 100 °C for 3 h. The reaction mixture was then cooled in a refrigerator for 1 h. The precipitate that resulted was filtered off and washed with $AcNMe_2$. The filtrate and washings were combined and concentrated *in vacuo* to leave a brown oil. Purification of the oil by flash chromatography[19] [silica gel, CH_2Cl_2–MeOH (6 : 1, v/v)] provided **16** (4.21 g, 71%) as a yellow glass, UV $\lambda_{max}^{95\%\,EtOH}$ 248 nm (sh) (ε 8100), 251 (8300), 266 (sh) (4600); $\lambda_{max}^{H_2O}$ (pH 1) 251 (9300); $\lambda_{max}^{H_2O}$ (pH 7) 250 (9500); $\lambda_{max}^{H_2O}$ (pH 13) 250 (9400); ^{1}H-NMR (Me_2SO-d_6) δ: 1.27 [3H, t, J=7 Hz, N(1)-CH_2Me], 3.61 [2H, m, C(5′)-H_2], 3.85—4.2 [2H, m, C(4′)-H and C(3′)-H], 4.05 [2H, q, J=7 Hz, N(1)-CH_2Me], 4.49 [1H, m, C(2′)-H], 5.06 [1H, dull t, J=5 Hz, C(5′)-OH], 5.19 [1H, dull d, J=5 Hz, C(3′)-OH], 5.46 [1H, dull d, J=6 Hz, C(2′)-OH], 5.85 [1H, d, J=6 Hz, C(1′)-H], 8.33 and 8.44 (1H each, s, purine protons).

5-Amino-*N*-ethyl-1-β-D-ribofuranosylimidazole-4-carboxamide (15) A stirred mixture of **16** (3.98 g, 13.4 mmol) and 0.2 N aqueous NaOH (350 ml) was heated under reflux for 1 h. After cooling, the reaction mixture was brought to pH 8 by addition of 10% aqueous HCl and then concentrated *in vacuo*. The residue was dried and extracted with hot EtOH (5 × 20 ml). The ethanolic extracts were combined and concentrated *in vacuo* to leave a dark glass. Purification of the glassy substance by flash chromatography[19] [silica gel, CH_2Cl_2–MeOH (5 : 1, v/v)] yielded **15** (2.40 g, 62%) as a reddish glass, UV $\lambda_{max}^{95\%\,EtOH}$ 267 nm (ε 13100); $\lambda_{max}^{H_2O}$ (pH 1) 244 (9500), 267 (9500); $\lambda_{max}^{H_2O}$ (pH 7) 265 (12800); $\lambda_{max}^{H_2O}$ (pH 13) 265 (12900); ^{1}H-NMR (Me_2SO-d_6) δ: 1.06 (3H, t, J=7 Hz, $NHCH_2$Me), 3.20 (2H, m, $NHCH_2$Me), 3.58 [2H, m, C(5′)-H_2], 3.88 [1H, m, C(4′)-H], 4.06 [1H, m, C(3′)-H], 4.26 [1H, m, C(2′)-H], 5.1, 5.2, and 5.3 [1H each, br m, C(5′)-OH, C(3′)-OH, and C(2′)-OH], 5.45 [1H, d, J=6 Hz, C(1′)-H], 5.84 (2H, br, NH_2), 7.28 [1H, s, C(2)-H], 7.30 (1H, t, J=6 Hz, NHCH_2Me).

5-Amino-*N*-ethylimidazole-4-carboxamide Hydrochloride (12·HCl) A mixture of **15** (431 mg, 1.5 mmol) and 2 N aqueous HCl (7.5 ml) was stirred at 90—100 °C for 2 h. After cooling, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and then concentrated *in vacuo*. The residue was dried and extracted with hot EtOH (3 × 10 ml). The ethanolic extracts were concentrated *in vacuo*, and the residue was purified by flash chromatography[19] [silica gel, CH_2Cl_2–MeOH (3 : 1, v/v)], giving **12** (101 mg, 44%) as a yellow oil. The oil was dissolved in a little EtOH, and the resulting solution was brought to pH 1 by addition of 10% (w/w) ethanolic HCl. Addition of ether (30 ml) caused crude **12**·HCl (109 mg,

38% yield from **15**) [mp 194—199 °C (dec.)] to crystallize out of the solution. Recrystallization from EtOH–AcOEt and drying over P_2O_5 at 2 mmHg and 75 °C for 6 h furnished an analytical sample of **12**·HCl as almost colorless needles, mp 202—204 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 241 nm (sh) (ε 7100), 268 (12800); $\lambda_{max}^{H_2O}$ (pH 1) 238 (9300), 265 (11100); $\lambda_{max}^{H_2O}$ (pH 7) 235 (sh) (5700), 265 (13200); $\lambda_{max}^{H_2O}$ (pH 13) 276 (14600); ^{1}H-NMR (Me_2SO-d_6) δ: 1.12 (3H, t, J=7 Hz, $NHCH_2\underline{Me}$), 3.29 (2H, dq, J=7, 5.5 Hz, $NHC\underline{H}_2Me$), 8.38 (1H, t, J=5.5 Hz, $N\underline{H}CH_2Me$), 8.51 [1H, s, C(2)-H]. *Anal.* Calcd for $C_6H_{10}N_4O$·HCl: C, 37.80; H, 5.82; N, 29.39. Found: C, 37.93; H, 6.01; N, 29.25.

Kinetic Procedure The Dimroth rearrangement reaction of **1**·$HClO_4$ (R^1=Et; R^2=Me), as depicted in Chart 1, and conversion of **6**·$HClO_4$ into **11**, **8**, and **14**, as shown in Chart 2, in aqueous solution at various pH's and ionic strength 1.0 at 70 °C were followed by means of UV spectrophotometry and HPLC, respectively. Buffer solutions employed for kinetic runs were 0.05 M NaH_2PO_4–Na_2HPO_4 (pH 6.92 and 6.97 at 70 °C); 0.05 M $NaHCO_3$–Na_2CO_3 (pH 8.70 at 70 °C); 0.05 M Na_2HPO_4–Na_3PO_4 (pH 10.47 at 70 °C), and were brought to ionic strength 1.0 with KCl.

The substrates **1**·$HClO_4$ (R^1=Et; R^2=Me) and **6**·$HClO_4$ were separately dissolved in the buffer solutions or in 0.2 N aqueous NaOH at concentrations ranging from 4.3×10^{-5} to 4.5×10^{-5} M and from 4.7×10^{-4} to 5.4×10^{-4} M, respectively. Aliquots (4 ml) of the resulting solutions were sealed in small ampules and placed in a thermoregulated constant-temperature bath kept at 70 °C (accurate to ±0.05 °C). At intervals, ampules were removed, cooled, and broken, and the contents were analyzed, in the case of **1**·$HClO_4$ (R^1=Et; R^2=Me), by UV spectrophotometry in a manner similar to that described previously[3c]; and in the case of **6**·$HClO_4$, by HPLC. For the HPLC analyses, small portions (15 μl) of the reaction mixtures were applied to a Waters ALC/GPC 204 liquid chromatograph equipped with a μBondapak C_{18} column [0.05 M aqueous KH_2PO_4–MeCN (95:5 or 90:10, v/v) or 0.025 M aqueous Na_2HPO_4–MeOH (60:40, v/v), 1500—2600 p.s.i., 0.9—1.0 ml/min][22] or a LiChrosorb RP-18 (7 μm) column [0.025 M aqueous Na_2HPO_4–MeOH (60:40, v/v), 1800 p.s.i., 0.9 ml/min],[23] and the peak heights of the components, located by using a UV absorbance detector operated at 254 nm, were determined. Concentrations of the components in the reaction mixtures were then estimated from calibration curves which had been obtained with authentic samples. All reactions were followed for at least two half-lives with at least six measurements, and good pseudo-first-order kinetics were obtained in all cases. The results are summarized in Figs. 1 and 2 and Tables I and II.

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23) Under these conditions, the retention times of the four components were in the order of **8**<**14**<**6**<**11**.