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Purines. XXVII.[1] Hydrolytic Deamination *versus* Dimroth Rearrangement in the 9-Substituted Adenine Ring: Effect of an ω-Hydroxyalkyl Group at the 1-Position

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In H_2O at near neutrality, the 1-(ω-hydroxyalkyl)adenine derivatives **8a**, **b**·HBr and **8c**·$HClO_4$ underwent hydrolytic deamination to give the 1-(ω-hydroxyalkyl)hypoxanthine derivatives **10a**—**c**, in competition with the usual Dimroth rearrangement to produce the N^6-(ω-hydroxyalkyl)adenine derivatives **9a**—**c**. The rates of these competitive reactions were measured in H_2O at various pH's and ionic strength 1.0 at 40 °C, and the relative rate of deamination with respect to Dimroth rearrangement was found to increase as the pH of the reaction medium was decreased. Under similar conditions, the corresponding 1-alkyl analogues **8d**—**g**·$HClO_4$ and the 1-(modified benzyl) analogues **8h**, **i**·HBr underwent only Dimroth rearrangement to afford the N^6-isomers **9d**—**i**. In the Dimroth rearrangements of all of the substrates **8a**, **b**, **d**—**i**·HX (X = Br or ClO_4), attack of hydroxide ion on the protonated species (**8a**, **b**, **d**—**i**·H^+) at the 2-position was faster than that on the neutral species by a factor of 100—640. In the reaction of the protonated species, the 1-(ω-hydroxyalkyl) analogues **8a**, **b**·HBr rearranged faster than the corresponding 1-alkyl analogues **8e**, **f**·$HClO_4$ by a factor of 1.6—2.7. It has been concluded that this rate enhancement is attributable solely to the electron-withdrawing effect, and not to intramolecular participation in catalysis, of the hydroxy group in the 1-substituent chain. In the syntheses of **8a**, **i**·HBr from 9-ethyladenine (**6**) according to a general 1-alkylation procedure, the 7-alkylated products **13** and **16** were also obtained as by-products in 9% and 6% yields, respectively.

Keywords——1,9-disubstituted adenine; 9-substituted 1-(ω-hydroxyalkyl)adenine; Dimroth rearrangement; hydrolytic deamination; 9-substituted 1-(ω-hydroxylalkyl)hypoxanthine; kinetic study; acid dissociation constant; UV; 9-ethyladenine 1-alkylation; 9-ethyladenine 7-alkylation

Introduction

1-Alkyladenines and their derivatives (type **1**) usually undergo Dimroth rearrangement under basic conditions to give the N^6-alkyl isomers (type **3**).[1-3] 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 (type **1**·H^+) and the neutral species (type **1**) at the 2-position, and a subsequent fast ring closure of the putative monocyclic intermediate (type **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—1100), 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.[3e] Interestingly, a β-D-ribofuranosyl group at the 9-position accelerates the ring-opening of both the protonated and the neutral species,[1,3e] and it has been concluded that this rate enhancement is attributable solely to the electron-withdrawing effect of the furanose ring oxygen and not to participation of the 5′-hydroxy group in intramolecular catalysis.[1]

In connection with such unrecognized participation of the β-D-ribofuranosyl group in intramolecular catalysis, we were interested in the Dimroth rearrangement of 1,9-disubsti-

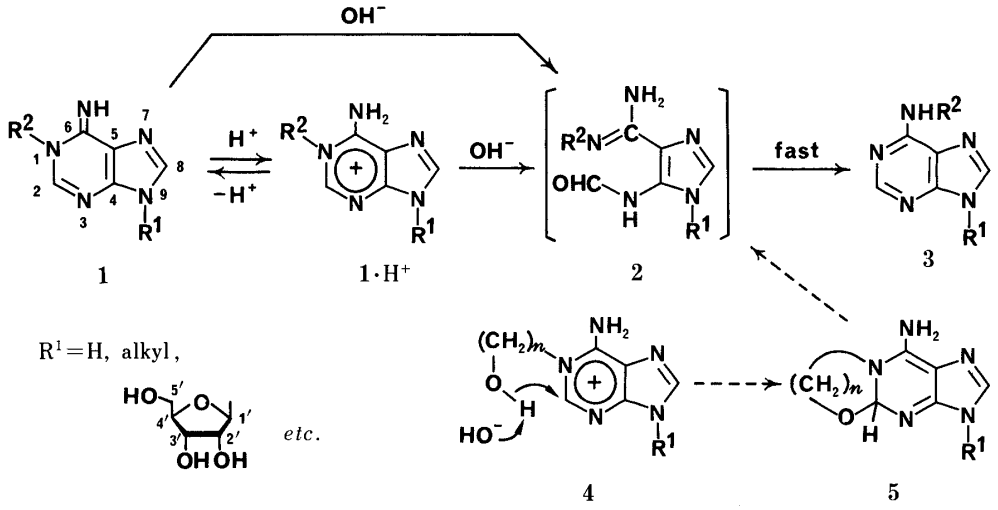

Chart 1

tuted adenines having a hydroxy group in the 1-substituent chain. If the hydroxy group were located properly, it might facilitate the rearrangement of these compounds through intramolecular participation in general-base or nucleophilic catalysis (*e.g.*, **4**→**5**→**2**). The present paper reports a rate study on the Dimroth rearrangement of a series of 9-substituted 1-(ω-hydroxyalkyl)adenines and related compounds [**8a**—**i**·HX (X=Br or ClO_4)] and presents an unusual hydrolytic deamination of the 1-(ω-hydroxyalkyl) analogues **8a**, **b**·HBr and **8c**·$HClO_4$, which has been found to occur, competitively with the usual Dimroth rearrangement, at near neutrality.

Results

Synthesis of Compounds

The substrates selected for the rearrangement study were the hydrobromide or perchlorate salts of **8a**—**i**, which all carry an ethyl group at the 9-position for uniformity except that **8c**·$HClO_4$ possesses a β-D-ribofuranosyl group instead. The hydrobromides **8a**, **b**·HBr were synthesized from 9-ethyladenine (**6**) by treatment with 2-bromoethanol and 3-bromopropanol, respectively, in $AcNMe_2$. The perchlorate **8c**·$HClO_4$ was prepared from adenosine (**7**) and ethylene oxide according to the literature procedure.[4] The perchlorate **8e**·$HClO_4$ was obtained from the corresponding hydriodide **8e**·HI[5] by treating it with sodium perchlorate. The hydriodides **8f**, **g**·HI were obtained by alkylation of **6** with PrI and BuI in $AcNMe_2$ and converted into the perchlorates **8f**, **g**·$HClO_4$. The 1-(modified benzyl) analogues **8h**, **i**·HBr were synthesized by treatment of **6** with 2-(hydroxymethyl)benzyl bromide and 2-methylbenzyl bromide, respectively, in $AcNMe_2$. It is interesting to note that in the above reactions of **6** with 2-bromoethanol and 2-methylbenzyl bromide, the 7-alkylated products **13** and **16** were obtained as by-products in 9% and 6% yields, respectively. The 7,9-disubstituted structures of **13** and **16** were assignable on the basis of the similarity of their ultraviolet (UV) spectra to those of authentic 7,9-dialkyladeninium salts.[6] Attempts to synthesize the higher 1-(ω-hydroxyalkyl) homologue **14** or its equivalent **15** from **6** by similar alkylation with 4-bromobutanol or 4-benzyloxybutyl bromide were all in vain, mostly owing to the decomposition of the alkylating reagent to form tetrahydrofuran under the reaction conditions employed. The syntheses of **8d**·$HClO_4$ and **8e**·HI and their rearrangement to produce the N^6-alkyl isomers **9d**, **e** have already been reported.[1,5,7]

Treatment of **8c**·$HClO_4$ with H_2O at pH 11 and 60 °C for 24 h gave the N^6-(2-

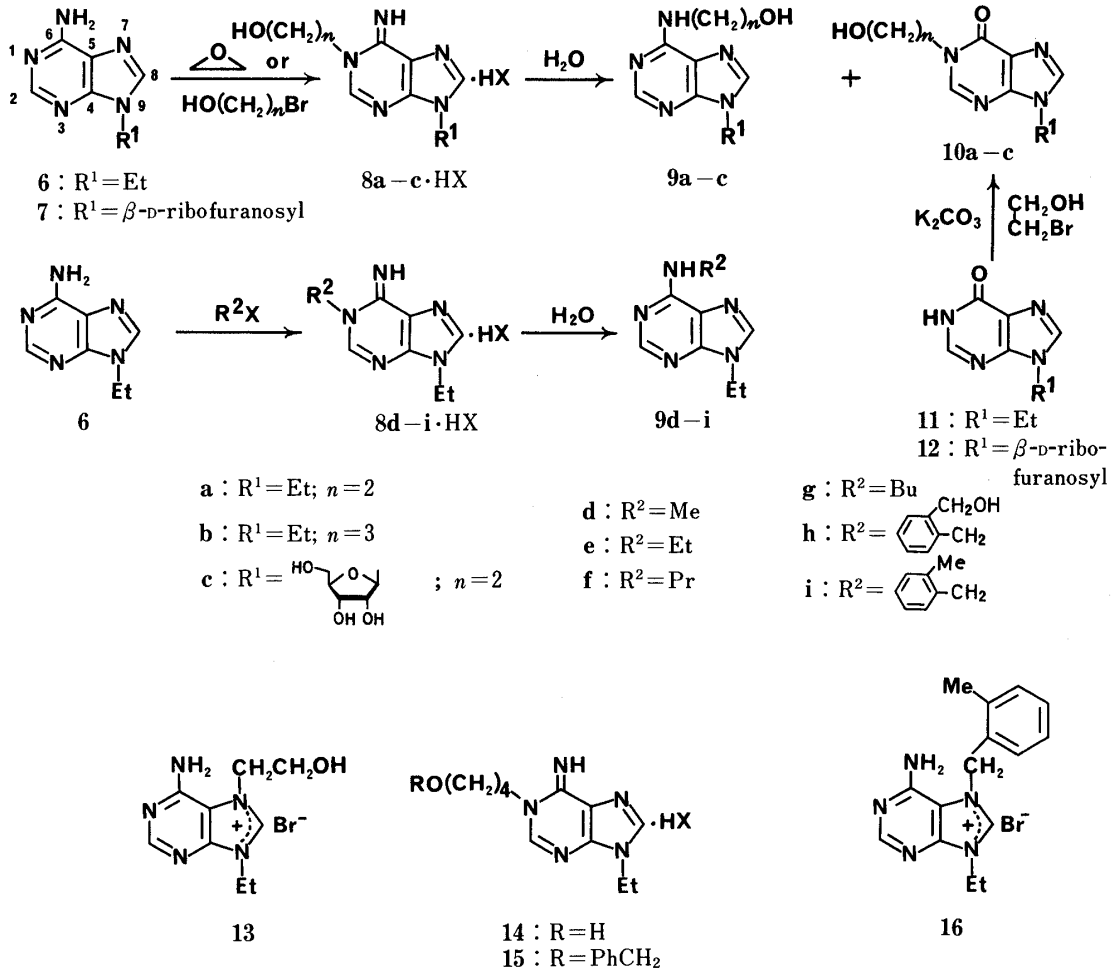

Chart 2

TABLE I. Reaction of 9-Substituted 1-(ω-Hydroxyalkyl)adenines (**8a—c**·HX) in H_2O

Starting material	Reaction conditions			Yield (%)	
	pH or solvent	Temp.[a]	Time	**9**	**10**
8a·HBr	pH 6	A	5 h	38	25
	pH 7	A	2 h	53	10
	0.2 N aq. NaOH	B	15 min	94	0
8b·HBr	pH 6	A	6 h	43	36
	pH 7	A	2 h	45	28
	0.2 N aq. NaOH	B	25 min	90	0
8c·$HClO_4$	pH 6	A	5 h	52	17
	pH 11	60 °C	24 h	93	0

a) The letter A stands for heating in a boiling water bath; B, heating under reflux.

hydroxyethyl)adenosine (**9c**) in 93% yield, in harmony with the finding of Windmueller and Kaplan.[4] In 0.2 N aqueous NaOH, all the other 1,9-disubstituted adenine salts also produced the N^6,9-disubstituted isomers **9a**, **b**, **d—i** exclusively. On the other hand, the rearrangement of the 1-(ω-hydroxyalkyl) analogues **8a**, **b**·HBr and **8c**·$HClO_4$ at near neutrality was found to be accompanied by hydrolytic deamination to give the hypoxanthine derivatives **10a—c** (Table I), whereas that of the simple 1-alkyl analogues **8d—g**·$HClO_4$ and 1-(modified benzyl)

TABLE II. UV Spectra of 1,9-Disubstituted Adenines (**8a, b, d—i**), N^6,9-Disubstituted Adenines (**9a—i**), and 1,9-Disubstituted Hypoxanthines (**10a—c**)

Compound	UV spectra							
	Solvent E[a]		Solvent A[b]		Solvent N[c]		Solvent B[d]	
	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
8a·HBr	260.5	12.5	261	12.5	261	12.5	260.5	13.2
8b·HBr	261	12.8	261	12.5	261.5	12.4	261	13.3
8d·$HClO_4$[e]	261	12.8	261	12.8	261	12.9	261	13.9
8e·$HClO_4$	261.5	13.1	261	12.5	261	12.6	261	13.3
8f·HI	261	12.5	261	12.8	261	12.9	261.5	13.6
8f·$HClO_4$	261	13.0	261.5	12.7	261.5	12.7	261	13.5
8g·HI	261	12.7	261.5	13.1	261.5	13.1	261.5	13.9
8g·$HClO_4$	261.5	13.5	261.5	12.7	261.5	12.7	261.5	13.7
8h·HBr	262	13.5	261.5	13.2	261	13.2	260.5	13.5
8i·HBr	261.5	13.4	262	13.7	262	13.7	261	13.8
9a	268.5	16.8	266	17.4	269	17.6	269	17.6
9b	269	16.4	266	17.8	269.5	17.6	269.5	17.4
9c	266.5	17.7	263	18.3	266	18.1	266	18.3
9d[e]	—	—	265	17.5	269	16.5	269	16.5
9e[f]	269	16.4	265	18.0	269	17.3	269	17.4
9f	269	17.0	265.5	18.1	270	17.4	270	17.4
9g·$HClO_4$	270	17.0	266	18.6	270	17.9	270	17.9
9h·HBr	271	19.0	268	20.1	271	20.4	271	20.5
9i	271	19.7	268	20.0	271.5	19.9	271.5	19.8
10a	254	9.5	253	9.9	253	10.4	253	10.3
10b	254	9.3	253	9.9	253	10.1	253	10.2
10c	251	9.0	250.5	10.1	250	10.2	250	10.0

a) 95% aqueous EtOH. *b*) 0.1 N aqueous HCl (pH 1). *c*) 0.005 M phosphate buffer (pH 7). *d*) 0.1 N aqueous NaOH (pH 13). *e*) Taken from ref. 1. *f*) Taken from ref. 7.

TABLE III. Acid Dissociation Constants of 1,9-Disubstituted Adenines (**8a, b, d—i**)

Compound		pK_a at 40 °C and ionic strength 1.0
No.	1-Substituent	
8a·HBr	$HOCH_2CH_2$	8.60±0.05
8b·HBr	$HOCH_2CH_2CH_2$	8.77±0.02
8d·$HClO_4$	CH_3	8.99±0.05[a]
8e·$HClO_4$	CH_3CH_2	9.04±0.04
8f·$HClO_4$	$CH_3CH_2CH_2$	9.01±0.02
8g·$HClO_4$	$CH_3CH_2CH_2CH_2$	9.02±0.02
8h·HBr	2-(Hydroxymethyl)benzyl	8.37±0.04
8i·HBr	2-Methylbenzyl	8.34±0.03

a) Taken from ref. 1.

analogues **8h, i**·HBr at near neutrality still proceeded exclusively to yield the rearranged products **9d—i**, and the formation of the hydrolytically deaminated products, if any, should have been negligibly small.

The structures of the new 1,9- and N^6,9-disubstituted adenines were supported by the way in which they were generated,[8] microanalytical data, and the UV spectral features shown

in Table II. The deaminated products **10a**, **c** were identified by direct comparison with samples synthesized from 9-ethylhypoxanthine (**11**) and from inosine (**12**) according to a general 1-alkylation procedure for 9-substituted hypoxanthines.[9] The structure of **10b** was assignable on the basis of the UV spectral similarity to **10a**, **c**. Table III assembles the acid dissociation constants of the substrates **8a**, **b**, **d**—**i**·HX (X=Br or ClO_4).

Kinetic Study

The system of reactions shown in Chart 3 is the object of the present kinetic study. The reactions of the 1,9-disubstituted adenine salts **8a**, **b**, **e**—**i**·HX (X=Br or ClO_4) in 0.02 M buffer solutions of pH 7.04 to 10.98 and in 0.05 and 0.1 M buffer solutions of pH 11.42 at ionic strength 1.0 at 40 °C were followed by measuring the increase in UV absorption at 268 nm which occurs on formation of the rearranged products **9a**, **b**, **e**—**i**. The semilogarithmic plots of mole fractions of the residual substrates against time indicated that the rearrangement reactions obey fairly good pseudo-first-order kinetics at all pH's with the simple 1-alkyl analogues **8e**—**g**·$HClO_4$ and 1-(modified benzyl) analogues **8h**, **i**·HBr, but only at pH 9.12—11.42 with the 1-(ω-hydroxyalkyl) analogues **8a**, **b**·HBr.

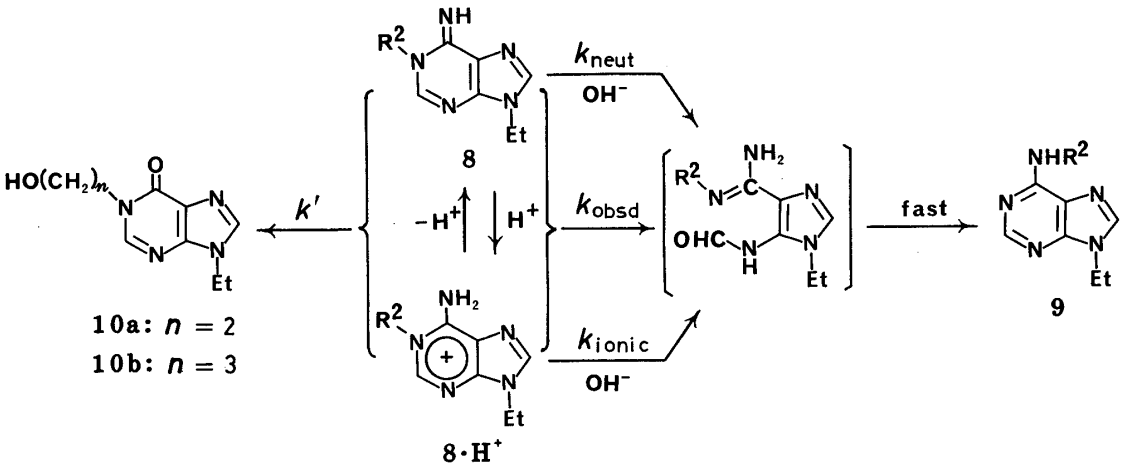

Chart 3

At near neutrality, **8a**·HBr and **8b**·HBr were found to undergo both the Dimroth rearrangement to give **9a**, **b** and the deamination to form the hypoxanthine derivatives **10a**, **b** simultaneously. Thus, these two competitive reactions of **8a**, **b**·HBr were run in 0.05, 0.1, and 0.2 M buffer solutions of pH 6.00 to 9.00 at ionic strength 1.0 at 40 °C, and the change of the concentrations of the substrates was followed by measuring, after dilution with 0.25 M phosphate buffer (pH 11.40), the decrease in UV absorption at 305 nm where the molecular extinction coefficients of **9a**, **b** and **10a**, **b** are negligibly small (relative to those of **8a**, **b**). In the meantime, the changes of the concentrations of **9a**, **b** and **10a**, **b** were followed by measuring, after dilution of the reaction mixtures with 0.3 M phosphate buffer (pH 6.50), the increase in UV absorptions at 284 and 245 nm and by using Eq. 1—3, where $[\mathbf{8}]_0$ is the initial concentration of **8**; [**8**], [**9**], and [**10**], the concentrations of **8**, **9**, and **10**, respectively; ε_8, ε_9, and ε_{10}, the molecular extinction coefficients of **8**, **9**, and **10** at 284 nm [in Eq. 1] or at 245 nm [in Eq. 2]; A_{284} and A_{245}, the absorbances at 284 and 245 nm, respectively. In each case, the ob-

$$[\mathbf{9}]=(\varepsilon_9-\varepsilon_{10})^{-1}\{A_{284}+(\varepsilon_{10}-\varepsilon_8)[\mathbf{8}]-\varepsilon_{10}[\mathbf{8}]_0\} \quad (1)$$

$$[\mathbf{10}]=(\varepsilon_{10}-\varepsilon_9)^{-1}\{A_{245}+(\varepsilon_8-\varepsilon_9)[\mathbf{8}]-\varepsilon_9[\mathbf{8}]_0\} \quad (2)$$

$$\text{or } [\mathbf{10}]=[\mathbf{8}]_0-[\mathbf{8}]-[\mathbf{9}] \quad (3)$$

TABLE IV. The Rate Constants for the Rearrangement of **8a, b, d—i** to **9a, b, d—i** and the Deamination of **8a, b** to **10a, b** at 40 °C and Ionic Strength 1.0

Substrate		Pseudo-first-order rate constant (min^{-1})[a]									
		pH value									
		6.00	7.01	7.04	7.80	8.04	9.00	9.12	10.08	10.98	11.42
8a·HBr	$k \times 10^4$	0.058	0.44	—	2.1	—	13	14	23	29	44
	$k' \times 10^4$	0.058	0.22	—	0.45	—	—	—	—	—	—
8b·HBr	$k \times 10^4$	—	0.32	—	1.5	—	10	13	16	26	24
	$k' \times 10^4$	—	0.38	—	1.4	—	1.0	—	—	—	—
8d·$HClO_4$	$k \times 10^4$	—	0.16	0.21[b]	0.80	1.3[b]	—	8.3[b]	14[b]	30[b]	47[b]
8e·$HClO_4$	$k \times 10^4$	—	—	0.25	—	1.8	—	11	16	25	35
8f·$HClO_4$	$k \times 10^4$	—	—	0.24	—	1.8	—	12	16	26	31
8g·$HClO_4$	$k \times 10^4$	—	—	0.20	—	1.8	—	12	16	26	33
8h·HBr	$k \times 10^4$	—	0.71	0.71	3.0	5.0	13	14	17	25	46
8i·HBr	$k \times 10^4$	—	—	0.77	—	5.3	—	16	19	30	43

a) The values at pH 6.00, 7.01, 7.80, 9.00, and 11.42 are those of the limiting rate constants for zero buffer concentration, which were obtained by extrapolation of the plot of the rate constant (at 0.05, 0.1, and 0.2 M buffer concentration) *versus* buffer concentration to zero buffer concentration, and the others are those of the rate constants at 0.02 M buffer concentration. *b*) Taken from ref. 1.

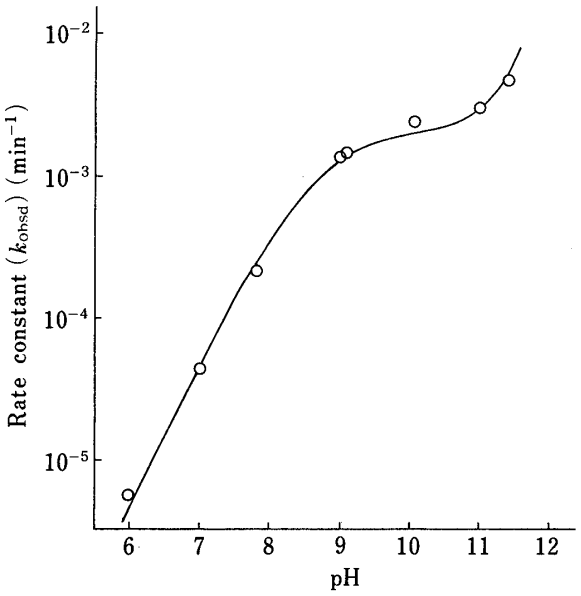

Fig. 1. pH–Rate Profile for the Rearrangement of **8a** to **9a** at 40 °C and Ionic Strength 1.0

served variation of the concentrations of the three components (**8a**, **9a**, and **10a**, or **8b**, **9b**, and **10b**) with time reflected first-order competitive kinetics.[10] Similar kinetic runs with **8d**·$HClO_4$ and **8h**·HBr revealed that the deamination was not significant in such 1-alkyl and 1-(modified ω-hydroxyalkyl) derivatives. Table IV lists the rate constants thus obtained for the rearrangements of **8a**, **b**, **d—i**·HX (X = Br or ClO_4) to **9a**, **b**, **d—i** and for the deaminations of **8a**, **b**·HBr to **10a**, **b**. The listed rate constants at 0.02 M buffer concentration may be regarded as the limiting rate constants for zero buffer concentration since we have already found that the catalytic coefficients of the buffer components are small in this type of reaction.[3e]

Figure 1 shows a pH–rate profile, which was obtained by plotting the rate constants for the rearrangement of **8a**·HBr as a function of pH. As in previous, similar cases,[3b,e,11] a theoretical pH–rate profile may be calculated from Eq. 4, where v is the reaction rate; $[\mathbf{8a}]_{total}$, the total concentration of **8a** and its protonated species; $[\mathbf{8a}\cdot H^+]$, the concentration of the

TABLE V. Effect of Substituents on the Dimroth Rearrangement of the Protonated and Neutral Species of 1,9-Disubstituted Adenines at 40 °C and Ionic Strength 1.0

Substrate	Second-order rate constant ($M^{-1}\,min^{-1}$)	
	k_{ionic}	k_{neut}
9-Ethyl-1-(2-hydroxyethyl)adenine (**8a**)	150	0.40
9-Ethyl-1-(3-hydroxypropyl)adenine (**8b**)	95	0.30
9-Ethyl-1-methyladenine (**8d**)[a]	50	0.50
1,9-Diethyladenine (**8e**)	55	0.25
9-Ethyl-1-propyladenine (**8f**)	60	0.25
1-Butyl-9-ethyladenine (**8g**)	60	0.25
9-Ethyl-1-[(2-hydroxymethyl)benzyl]adenine (**8h**)	230	0.40
9-Ethyl-1-(2-methylbenzyl)adenine (**8i**)	255	0.40

a) Taken from ref. 1.

$$v = k_{obsd}[\mathbf{8a}]_{total} = k_{ionic}[\mathbf{8a}\cdot H^+][OH^-] + k_{neut}[\mathbf{8a}][OH^-] \quad (4)$$

protonated species of **8a**; [**8a**], the concentration of the neutral species of **8a**; [OH^-], hydroxide ion concentration; k_{obsd}, the observed pseudo-first-order rate constant; k_{ionic} and k_{neut}, the rate constants for hydroxide attack on the protonated and the neutral species; the pK_a value of **8a** is 8.60 (Table III). When k_{ionic} of 150 and k_{neut} of 0.40 (time in minutes) were adopted, the resulting theoretical pH–rate profile corresponded to the curve plotted in Fig. 1. A similar treatment of the pseudo-first-order rate constants for the rearrangement reactions in Table IV afforded the second-order rate constants assembled in Table V.

Discussion

Table III indicates that the simple 1-alkyl homologues **8d**—**g** are the strongest bases among the test compounds, and their pK_a's are closely similar, reflecting the small differences in the electron-donating properties of the alkyl groups at the 1-position. On the other hand, the observed decrease in base strength of the 1-(ω-hydroxyalkyl) analogues **8a** and **8b** is attributable to the inductive effect of the hydroxy group. A similar relation has been found to hold between ethanolamine (pK_a 9.50) and ethylamine (pK_a 10.65) or propylamine (pK_a 10.54).[12] The benzyl analogues **8h** and **8i** are the weakest bases among those in Table III, and this is attributable to the electron-withdrawing nature, relative to an alkyl group, of the benzyl moiety.[13] Their pK_a's are closely similar and are almost the same as that of 1-benzyl-9-methyladenine,[3e] reflecting the fact that there is little difference in the electronic properties of the benzyl moieties.

The results shown in Fig. 1 and Table V reveal that all the substrates [**8a**, **b**, **d**—**i**·HX (X=Br or ClO_4)] undergo rearrangement to produce the corresponding N^6-substituted isomers (**9a**, **b**, **d**—**i**) according to the rate law given by Eq. 4. It follows that in the ring-opening of **8**, attack of hydroxide ion on the protonated species (**8**·H^+) at the 2-position is dominant in the pH region lower than the pK_a of **8** and is superseded in importance at higher pH's by attack on the neutral species at the 2-position. It may be seen from Table V that in all cases the hydroxide attack on the protonated species is much faster than that on the neutral species (by a factor of 100—640). These results are in general agreement with those[1,3a,b,e,11] obtained with other 1,9-disubstituted adenines. In the reaction of the protonated species, there is only a little difference in rate among the simple 1-alkyl homologues **8d**—**g**·H^+, whereas the 1-(2-hydroxyethyl) analogue **8a**·H^+ rearranges 2.7 times more rapidly than the 1-ethyl

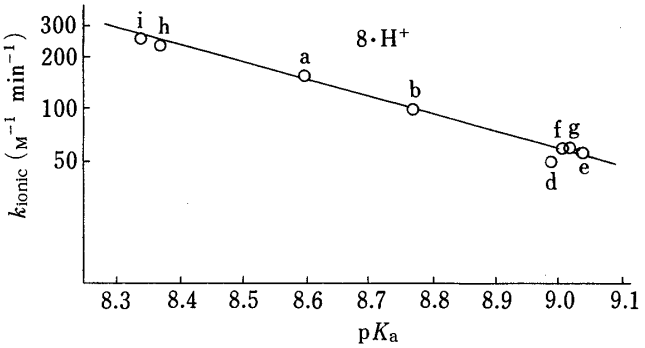

Fig. 2. pK_a–Rate Profile for Hydroxide Attack on the Protonated Species of **8a**, **b**, **d**—**i** in H_2O at 40 °C and Ionic Strength 1.0

analogue **8e**·H$^+$; the 1-(3-hydroxypropyl) analogue **8b**·H$^+$ rearranges 1.6 times as fast as the 1-propyl analogue **8f**·H$^+$. However, comparison of the k_{ionic} value for **8h**·H$^+$ with that for **8i**·H$^+$ indicates that the hydroxy group in **8h**·H$^+$ does not exert such a rate-enhancing effect. Figure 2 shows semilogarithmic plots of the second-order rate constants for the protonated species of **8a**, **b**, **d**—**i** against pK_a. It may be seen from the linear relation that the rate increases with decreasing pK_a, reflecting the effect of the electron-withdrawing property of a 1-substituent on the 2-position. In the reaction of the neutral species, however, such a linear relation does not hold between k_{neut} and pK_a. As in the previous cases,[3e] the hydroxide attack on the neutral species may be influenced by the steric factor of a 1-substituent. Thus, the above results exclude the possibility of intramolecular participation of the hydroxy group in the Dimroth rearrangement of the 1-(ω-hydroxyalkyl) analogues **8a**, **b**·HBr.

The most striking feature that emerged from the present study may be the hydrolytic deamination of the 1-(ω-hydroxyalkyl) analogues **8a**, **b**·HBr and **8c**·$HClO_4$, which occurs at near neutrality in competition with the Dimroth rearrangement. It may be seen from Tables I and IV that the relative rate of deamination with respect to Dimroth rearrangement increases as the pH of the reaction medium decreases. In the case of **8a**·HBr, the rate constants for deamination and rearrangement are comparable to each other at pH 6.00. The 1-(3-hydroxypropyl) analogue **8b**·HBr tends to undergo deamination more favorably than the lower homologue **8a**·HBr. Such a hydrolytic deamination peculiar to the 1-(ω-hydroxyalkyl) analogues **8a**, **b**·HBr and **8c**·$HClO_4$, whose basicities are moderate among the test compounds, suggests that it must be related to an intramolecular catalytic effect, but not the electronic effect, of the hydroxy group in the 1-substituent chain. At present, however, it is uncertain whether the mode of hydrolytic assistance of the hydroxy group is nucleophilic (*e.g.*, **17**→**18**→**19**→**20**→**10** in Chart 4) or involves general-base catalysis (*e.g.*, **21**→**22**→**23**→**10**).

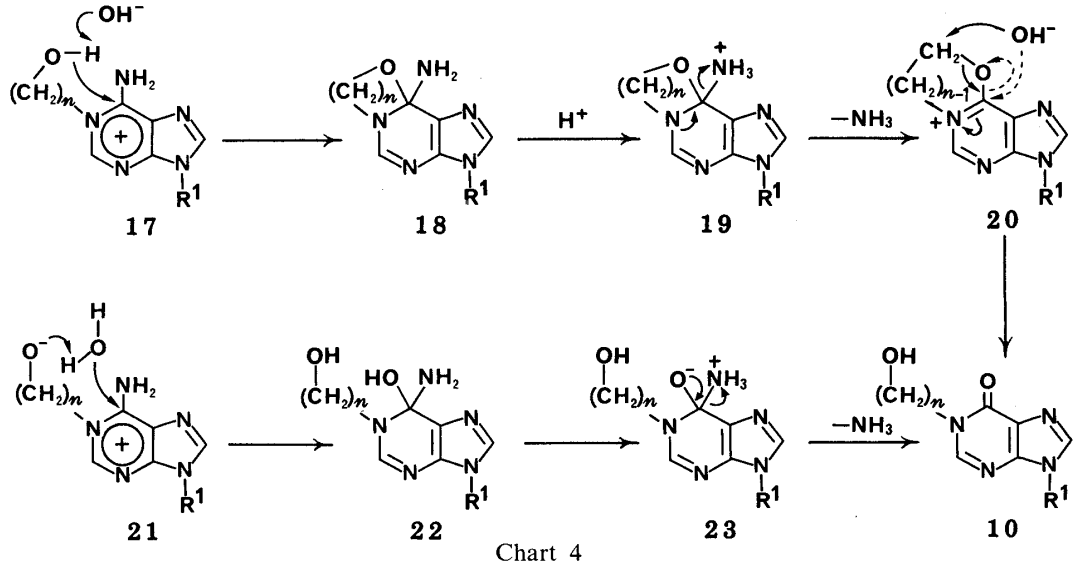

Chart 4

In conclusion, hydrolytic deamination of adenosine (**7**) is an important reaction in the metabolism of the nucleoside. The reaction is catalyzed by adenosine deaminase (adenosine aminohydrolase) which has a widespread distribution in various organisms.[14] Although the full enzyme mechanism,[15] as well as the amino acid residues involved in the catalytic process,[16] still remains obscure, it is believed to be of the addition-elimination type with water attack on the substrate to form a tetrahedral intermediate. The neighboring hydroxy group-assisted, hydrolytic deamination of the adenine ring found in the present work is of particular interest since it is also assumed to proceed by an addition-elimination mechanism through the tetrahedral intermediate **18** or **22**. The present work has also revealed that in the Dimroth rearrangement of 1-substituted 9-ethyladenines, the 1-(2-hydroxyethyl) or 1-(3-hydroxypropyl) group accelerates the ring-opening step through the inductive effect, and not by intramolecular participation in catalysis, of its hydroxy group.

Experimental

General Notes——All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Ultraviolet (UV) spectra were measured with a Hitachi model 323 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-PS-100 spectrometer at 24 °C with Me_4Si as an internal standard. Spectrophotometric determinations were carried out with a Hitachi model 181 spectrophotometer, and pH's were measured on a Hitachi-Horiba F-5 pH meter. Elemental analyses were performed by Mr. Y. Itatani and Miss Y. Arano at Kanazawa University. The following abbreviations are used: br = broad, m = multiplet, q = quartet, s = singlet, t = triplet.

9-Ethyl-1-(2-hydroxyethyl)adenine Hydrobromide (8a·HBr) and 9-Ethyl-7-(2-hydroxyethyl)adeninium Bromide (13)——A mixture of 9-ethyladenine (**6**)[17] (5.87 g, 36 mmol) and 2-bromoethanol (18.0 g, 144 mmol) in $AcNMe_2$ (36 ml) was stirred at 60—65 °C for 24 h. The precipitate that resulted was filtered off, washed with EtOH (*ca.* 10 ml), and dried to give **8a**·HBr (3.46 g, 33%) as a colorless solid. Recrystallization from EtOH furnished an analytical sample as colorless pillars, mp 247—248 °C (dec.); pK_a (Table III); UV (Table II); NMR (Me_2SO-d_6) δ: 1.44 (3H, t, J=7 Hz, N(9)-CH_2Me), 3.73 (2H, m, C$\underline{H}_2$OH), 4.10 (2H, q, J=7 Hz, N(9)-C$\underline{H}_2$Me), 4.44 (2H, m, N(1)-CH_2), 4.8—5.3 (1H, br, OH), 8.56 (2H, s, purine H's), 8.8—10.0 (2H, br, NH's). *Anal.* Calcd for $C_9H_{14}BrN_5O$: C, 37.52; H, 4.90; N, 24.30. Found: C, 37.26; H, 4.82; N, 24.14.

On the other hand, the filtrate and washings, originating from the isolation of the crude **8a**·HBr, were combined and concentrated to dryness *in vacuo*. The residual reddish-brown oil was extracted with four 60-ml portions of boiling AcOEt. Evaporation of the combined AcOEt extracts and recrystallization of the solid residue from EtOH recovered the starting material **6** (973 mg, 17%), mp 194—195 °C. The unextracted, residual matter was dissolved in boiling EtOH (120 ml), and the ethanolic solution was treated with charcoal, concentrated to a volume of *ca.* 60 ml, and kept in a refrigerator. The crystals that separated were filtered off, washed with a little EtOH, and dried to give a second crop of **8a**·HBr (1.09 g). The total yield of **8a**·HBr was 4.55 g (44%). The filtrate and washings, which were obtained on the isolation of the second crop of **8a**·HBr, were combined and allowed to stand at room temperature overnight. The crystals that deposited were filtered off and recrystallized from EtOH to yield **13** (968 mg, 9%) as colorless prisms, mp 230—231 °C; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 273 nm (ε 11000); $\lambda_{max}^{H_2O}$ (pH 1) 270 (11500); $\lambda_{max}^{H_2O}$ (pH 7) 270 (11700); $\lambda_{max}^{H_2O}$ (pH 13) unstable. *Anal.* Calcd for $C_9H_{14}BrN_5O$: C, 37.52; H, 4.90; N, 24.30. Found: C, 37.80; H, 4.89; N, 24.43.

9-Ethyl-1-(3-hydroxypropyl)adenine Hydrobromide (8b·HBr)——A mixture of **6**[17] (5.87 g, 36 mmol) and 3-bromopropanol (10.0 g, 72 mmol) in $AcNMe_2$ (45 ml) was stirred at 60 °C for 24 h. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give a colorless solid (3.62 g, 33%), mp 255—256 °C (dec.). Recrystallization from EtOH provided an analytical sample of **8b**·HBr as colorless needles, mp 255—256 °C (dec.); pK_a (Table III); UV (Table II); NMR (Me_2SO-d_6) δ: 1.46 (3H, t, J=7 Hz, N(9)-CH_2Me), 1.92 (2H, m, N(1)-$CH_2C\underline{H}_2CH_2$), 3.52 (2H, t, J=6 Hz, C$\underline{H}_2$OH), 3.7—4.2 (1H, br, OH), 4.2—4.5 (4H, m, N(1)-CH_2 and N(9)-C$\underline{H}_2$Me), 8.62 and 8.74 (1H each, s, purine H's), 8.9—9.85 (2H, br, NH's). *Anal.* Calcd for $C_{10}H_{16}BrN_5O$: C, 39.75; H, 5.34; N, 23.18. Found: C, 39.46; H, 5.33; N, 23.25.

1,9-Diethyladenine Perchlorate (8e·$HClO_4$)——A solution of $NaClO_4$ H_2O (1.50 g, 11 mmol) in H_2O (4.5 ml) was added to a solution of **8e**·HI[5] (1.00 g, 3.13 mmol) in warm H_2O (7 ml). The precipitate that separated was filtered off, washed with a little H_2O, and dried to yield **8e**·$HClO_4$ (864 mg, 95%), mp 291.5—292 °C (dec.). Recrystallization from H_2O gave an analytical sample as colorless pillars, mp 291.5—292 °C (dec.); pK_a (Table III); UV (Table II); NMR (Me_2SO-d_6) δ: 1.36 (3H, t, J=7.5 Hz, N(1)-CH_2Me), 1.45 (3H, t, J=7.5 Hz, N(9)-CH_2Me), 4.30 (2H, q, J=7.5 Hz, N(1)-C$\underline{H}_2$Me or N(9)-C$\underline{H}_2$Me), 4.35 (2H, q, J=7.5 Hz, N(9)-C$\underline{H}_2$Me or N(1)-C$\underline{H}_2$Me), 8.53 and 8.70 (1H each, s, purine H's), 8.9—9.9 (2H, br, NH's). *Anal.* Calcd for $C_9H_{14}ClN_5O_4$: C, 37.06; H, 4.84; N, 24.01.

Found: C, 36.91; H, 4.92; N, 23.83.

9-Ethyl-1-propyladenine Hydriodide (8f·HI)——A mixture of **6**[17] (3.26 g, 20 mmol) and PrI (10.20 g, 60 mmol) in $AcNMe_2$ (35 ml) was stirred at 70—75 °C for 48 h. The precipitate that resulted was filtered off, washed with EtOH, and dried to give a colorless solid (1.89 g, 28%), mp 262.5—263.5 °C (dec.). The filtrate and washings were combined and allowed to stand at room temperature overnight to afford a second crop (1.03 g), mp 262—263 °C (dec.). The total yield was 2.92 g (44%). Recrystallization from H_2O furnished an analytical sample of **8f**·HI as slightly yellowish pillars, mp 262.5—263.5 °C (dec.); UV (Table II); NMR (Me_2SO-d_6) δ: 0.96 (3H, t, J=7 Hz, N(1)-CH_2CH_2Me), 1.46 (3H, t, J=7 Hz, N(9)-CH_2Me), 1.77 (2H, m, N(1)-CH_2CH_2Me), 4.27 (2H, t, J=7 Hz, N(1)-CH_2), 4.31 (2H, q, J=7 Hz, N(9)-CH_2Me), 8.60 and 8.77 (1H each, s, purine H's), 9.1—9.8 (2H, br, NH's). *Anal.* Calcd for $C_{10}H_{16}IN_5$: C, 36.05; H, 4.84; N, 21.02. Found: C, 36.06; H, 4.97; N, 20.86.

9-Ethyl-1-propyladenine Perchlorate (8f·HClO$_4$)——A solution of $NaClO_4 \cdot H_2O$ (1.15 g, 8.2 mmol) in H_2O (3 ml) was added to a solution of **8f**·HI (900 mg, 2.7 mmol) in warm H_2O (8 ml). The precipitate that resulted was filtered off, washed with a little H_2O, and dried to yield **8f**·$HClO_4$ (777 mg, 94%), mp 270.5—271.5 °C (dec.). Recrystallization from H_2O gave an analytical sample as colorless pillars, mp 271—272 °C (dec.); pK_a (Table III); UV (Table II); NMR (Me_2SO-d_6) δ: 0.96 (3H, t, J=7 Hz, N(1)-CH_2CH_2Me), 1.46 (3H, t, J=7 Hz, N(9)-CH_2Me), 1.77 (2H, m, N(1)-CH_2CH_2Me), 4.25 (2H, t, J=7 Hz, N(1)-CH_2), 4.29 (2H, q, J=7 Hz, N(9)-CH_2Me), 8.54 and 8.68 (1H each, s, purine H's), 9.0—9.8 (2H, br, NH's). *Anal.* Calcd for $C_{10}H_{16}ClN_5O_4$: C, 39.29; H, 5.27; N, 22.91. Found: C, 39.33; H, 5.43; N, 22.97.

1-Butyl-9-ethyladenine Hydriodide (8g·HI)——A mixture of **6**[17] (3.26 g, 20 mmol) and BuI (11.04 g, 60 mmol) in $AcNMe_2$ (30 ml) was stirred at 90 °C for 42 h. The reaction mixture was concentrated *in vacuo* to leave a partially crystallized oil. The residue was triturated with EtOH (10 ml) and the insoluble material was filtered off, washed with a little EtOH, and dried to yield **8g**·HI (4.14 g, 60%), mp 250—251 °C (dec.). Recrystallization from EtOH gave an analytical sample as colorless pillars, mp 251.5—252.5 °C (dec.); UV (Table II); NMR (Me_2SO-d_6) δ: 0.92 [3H, t, J=7 Hz, N(1)-$(CH_2)_3$Me], 1.46 (3H, t, J=7 Hz, N(9)-CH_2Me), 1.1—1.95 (4H, m, N(1)-$CH_2CH_2CH_2$Me), 4.30 (2H, t, J=7 Hz, N(1)-CH_2), 4.32 (2H, q, J=7 Hz, N(9)-CH_2Me), 8.63 and 8.78 (1H each, s, purine H's), 9.0—9.8 (2H, br, NH's). *Anal.* Calcd for $C_{11}H_{18}IN_5$: C, 38.05; H, 5.23; N, 20.17. Found: C, 38.04; H, 5.32; N, 20.00.

1-Butyl-9-ethyladenine Perchlorate (8g·HClO$_4$)——A solution of $NaClO_4 \cdot H_2O$ (1.18 g, 8.4 mmol) in H_2O (3.5 ml) was added to a solution of **8g**·HI (972 mg, 2.8 mmol) in warm H_2O (9 ml). The precipitate that separated was filtered off, washed with a little H_2O, and dried to give **8g**·$HClO_4$ (844 mg, 94%), mp 246—247.5 °C (dec.). Recrystallization from H_2O yielded an analytical sample as colorless needles, mp 250—251 °C (dec.); pK_a (Table III); UV (Table II); NMR (Me_2SO-d_6) δ: 0.92 [3H, t, J=7 Hz, N(1)-$(CH_2)_3$Me], 1.42 (3H, t, J=6.5 Hz, N(9)-CH_2Me), 1.15—1.95 (4H, m, N(1)-$CH_2CH_2CH_2$Me), 4.27 (2H, t, J=7 Hz, N(1)-CH_2), 4.30 (2H, q, J=6.5 Hz, N(9)-CH_2Me), 8.58 and 8.73 (1H each, s, purine H's), 9.1—9.9 (2H, br, NH's). *Anal.* Calcd for $C_{11}H_{18}ClN_5O_4$: C, 41.32; H, 5.67; N, 21.90. Found: C, 41.58; H, 5.61; N, 21.76.

9-Ethyl-1-[(2-hydroxymethyl)benzyl]adenine Hydrobromide (8h·HBr)——A mixture of **6**[17] (4.90 g, 30 mmol) and 2-(hydroxymethyl)benzyl bromide (12.1 g, 60 mmol) in $AcNMe_2$ (50 ml) was stirred at 60 °C for 22 h. The precipitate that resulted was filtered off, washed with EtOH, and dried to yield **8h**·HBr (5.39 g, 49%), mp 195—195.5 °C (dec.). Recrystallization from EtOH gave an analytical sample as colorless needles, mp 195.5—196 °C (dec.); pK_a (Table III); UV (Table II); NMR (Me_2SO-d_6) δ: 1.50 (3H, t, J=7 Hz, N(9)-CH_2Me), 4.37 (2H, q, J=7 Hz, N(9)-CH_2Me), 4.75 (2H, s, ArCH_2OH), 5.70 (2H, s, N(1)-CH_2), 6.65—6.85 (1H) and 7.1—7.65 (3H) (m, phenyl H's), 8.71 and 8.90 (1H each, s, purine H's), 9.0—10.1 (2H, br, NH's). *Anal.* Calcd for $C_{15}H_{18}BrN_5O$: C, 49.46; H, 4.98; N, 19.23. Found: C, 49.62; H, 4.94; N, 19.21.

9-Ethyl-1-(2-methylbenzyl)adenine Hydrobromide (8i·HBr) and 9-Ethyl-7-(2-methylbenzyl)adeninium Bromide (16)——A mixture of **6**[17] (3.92 g, 24 mmol) and 2-methylbenzyl bromide (8.88 g, 48 mmol) in $AcNMe_2$ (50 ml) was stirred at 60 °C for 10 h. The precipitate that deposited was filtered off, washed with EtOH, and dried to yield **8i**·HBr (6.73 g, 80%), mp 240—241.5 °C (dec.). Recrystallization from 90% aqueous EtOH gave an analytical sample as colorless prisms, mp 240—241.5 °C (dec.); pK_a (Table III); UV (Table II); NMR (Me_2SO-d_6) δ: 1.50 (3H, t, J=7 Hz, N(9)-CH_2Me), 2.39 (3H, s, ArMe), 4.35 (2H, q, J=7 Hz, N(9)-CH_2Me), 5.60 (2H, s, N(1)-CH_2), 6.4—6.55 (1H) and 7.05—7.4 (3H) (m, phenyl H's), 8.66 and 8.74 (1H each, s, purine H's), 9.0—10.0 (2H, br, NH's). *Anal.* Calcd for $C_{15}H_{18}BrN_5$: C, 51.74; H, 5.21; N, 20.11. Found: C, 51.78; H, 5.25; N, 20.15.

On the other hand, the filtrate and washings, originating from the above isolation of the crude **8i**·HBr, were combined and the mixture was diluted with benzene (300 ml). The precipitate that separated was filtered off and recrystallized from 90% aqueous EtOH (8 ml) to afford **16** (481 mg, 6%), mp 223—226 °C (dec.). Further recrystallization from 90% aqueous EtOH furnished an analytical sample as colorless prisms, mp 224—227.5 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 274 nm (ε 11000); $\lambda_{max}^{H_2O}$ (pH 1) 271 (11700); $\lambda_{max}^{H_2O}$ (pH 7) 272 (11800); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 1.47 (3H, t, J=7 Hz, N(9)-CH_2Me), 2.37 (3H, s, ArMe), 4.38 (2H, q, J=7 Hz, N(9)-CH_2Me), 5.87 (2H, s, N(7)-CH_2), 6.8—7.1 (1H) and 7.1—7.45 (3H) (m, phenyl H's), 7.88 (2H, s, NH_2), 8.49 (1H, s, C(2)-H), 9.49 (1H, s, C(8)-H). *Anal.* Calcd for $C_{15}H_{18}BrN_5$: C, 51.74; H, 5.21; N, 20.11. Found: C, 51.60; H, 5.32; N, 20.07.

Reaction of 8a·HBr with H_2O——i) In Aqueous NaOH: A mixture of **8a**·HBr (1.35 g, 4.7 mmol) and 0.2 N aqueous NaOH (47 ml) was heated under reflux for 15 min. The mixture was cooled, neutralized to pH 7 with 10%

aqueous HCl, and concentrated to dryness *in vacuo*. The residual solid was extracted with four 40-ml portions of boiling benzene. Evaporation of the benzene extracts left a solid (916 mg, 94%), mp 136.5—137.5 °C. Recrystallization from AcOEt gave an analytical sample of 9-ethyl-N^6-(2-hydroxyethyl)adenine (**9a**) as colorless needles, mp 138—139 °C; MS *m/e*: 207 (M^+); UV (Table II); NMR (Me_2SO-d_6) δ: 1.40 (3H, t, J=7.5 Hz, N(9)-$CH_2\underline{Me}$), 3.62 (4H, m, $OC\underline{H}_2C\underline{H}_2N$), 4.20 (2H, q, J=7.5 Hz, N(9)-$C\underline{H}_2Me$), 4.4—5.0 (1H, br, OH), 8.19 and 8.24 (1H each, s, purine H's). *Anal.* Calcd for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.79. Found: C, 52.12; H, 6.27; N, 34.04.

ii) At pH 6 in Phosphate Buffer: A solution of **8a**·HBr (500 mg, 1.74 mmol) in 0.3 M NaH_2PO_4–Na_2HPO_4 (pH 6.0 at 20 °C) (100 ml) was heated in a boiling water bath for 5 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was extracted with two 20-ml portions of boiling EtOH. The ethanolic extracts were combined and evaporated to dryness *in vacuo*, and the residue was chromatographed on alumina (40 g) using benzene–EtOH (7 : 1, v/v) as the eluent. Earlier fractions gave **9a** (135 mg, 37.5%) as a colorless solid, mp 137—138 °C, which was identical [by comparison of the infrared (IR) spectrum and chromatographic behavior] with the sample obtained by method (i). Later fractions were evaporated to dryness *in vacuo*, and the residue was dried over P_2O_5 at room temperature at 2 mmHg for 20 h. The dried sample was then kept in a closed vessel saturated with H_2O until a constant weight was reached, giving **10a**·H_2O (99 mg, 25%), mp 168—169 °C. This material was identical with that synthesized from **11** by hydroxyethylation (*vide infra*).

iii) At pH 7 in Phosphate Buffer: A solution of **8a**·HBr (922 mg, 3.2 mmol) in 0.25 M NaH_2PO_4–Na_2HPO_4 (pH 7.0 at 25 °C) (320 ml) was heated in a boiling water bath for 2 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was extracted with nine 40-ml portions of boiling AcOEt. The AcOEt extracts were combined and evaporated to dryness *in vacuo*. The residue was chromatographed on alumina (33 g) using benzene–EtOH (6 : 1, v/v) as the eluent. The rearranged product **9a** (354 mg, 53%), mp 137.5—139 °C, was obtained from earlier fractions and identified by direct comparison with the sample prepared by method (i). The deamination product **10a**·H_2O (69 mg, 10%), mp 169—170 °C, was obtained from later fractions.

Reaction of 8b·HBr with H_2O——i) In Aqueous NaOH: A mixture of **8b**·HBr (1.35 g, 4.5 mmol) and 0.2 N aqueous NaOH (45 ml) was heated in a boiling water bath for 25 min. After cooling, the reaction mixture was neutralized to pH 7 with 10% aqueous HCl and concentrated to dryness *in vacuo*. The residue was extracted with four 40-ml portions of boiling benzene. The benzene extracts were combined and concentrated to dryness *in vacuo* to leave **9b** (890 mg, 90%) as a colorless solid, mp 102—104 °C. Recrystallization from benzene gave an analytical sample as colorless pillars, mp 104—105 °C; MS *m/e*: 221 (M^+); UV (Table II); NMR ($CDCl_3$) δ: 1.55 (3H, t, J=7.5 Hz, N(9)-$CH_2\underline{Me}$), 1.87 (2H, m, $CH_2C\underline{H}_2CH_2$), 3.70 (2H, t, J=6 Hz, $C\underline{H}_2OH$), 3.87 (2H, m, NCH_2), 4.28 (2H, q, J=7.5 Hz, N(9)-$C\underline{H}_2Me$), 4.45—4.7 (1H, br, OH), 6.5—6.8 (1H, br, NH), 7.82 and 8.18 (1H each, s, purine H's). *Anal.* Calcd for $C_{10}H_{15}N_5O$: C, 54.29; H, 6.83; N, 31.65. Found: C, 54.54; H, 6.95; N, 31.49.

ii) At pH 6 in Phosphate Buffer: A solution of **8b**·HBr (1.00 g, 3.3 mmol) in 0.3 M NaH_2PO_4–Na_2HPO_4 (pH 6.0 at 20 °C) (200 ml) was heated in a boiling water bath for 6 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was extracted with ten 50-ml portions of boiling AcOEt. The AcOEt extracts were combined and evaporated to dryness *in vacuo*. Recrystallizations of the residue first from AcOEt–EtOH (1 : 1, v/v) and then from EtOH gave a first crop of **10b** (169 mg, 23%) as colorless prisms, mp 161—162 °C; this product was identical with the sample obtained by method (iii).

On the other hand, the mother liquors, which were obtained when the first crop of **10b** was isolated, were combined and evaporated *in vacuo*, and the residual glass was chromatographed on alumina (50 g). Earlier fractions eluted with benzene–EtOH (7 : 1, v/v) gave **9b** (313 mg, 43%), mp 103—104 °C, identical with the sample obtained by method (i). Later fractions afforded a second crop of **10b** (94 mg, 13%), mp 161—162 °C. The total yield of **10b** was 36%.

iii) At pH 7 in Phosphate Buffer: A solution of **8b**·HBr (1.18 g, 3.9 mmol) in 0.25 M NaH_2PO_4–Na_2HPO_4 (pH 7.0 at 26 °C) (410 ml) was heated in a boiling water bath for 2 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residual solid was extracted with six 60-ml portions of boiling AcOEt. The AcOEt extracts were combined and evaporated to dryness *in vacuo*. Two recrystallizations of the residue from EtOH gave a first crop of **10b** (191 mg, 22%) as almost colorless prisms, mp 161—162 °C. Further recrystallization in the same way produced an analytical sample, mp 161—162 °C; MS *m/e*: 222 (M^+); UV (Table II); NMR (Me_2SO-d_6) δ: 1.40 (3H, t, J=7 Hz, N(9)-$CH_2\underline{Me}$), 1.83 (2H, m, $CH_2C\underline{H}_2CH_2$), 3.45 (2H, dull t, J=6 Hz, $C\underline{H}_2OH$), 4.07 (2H, t, J=7 Hz, N(1)-CH_2), 4.17 (2H, q, J=7 Hz, N(9)-$C\underline{H}_2Me$), 4.4—4.7 (1H, br, OH), 8.08 and 8.30 (1H each, s, purine H's). *Anal.* Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.25. Found: C, 54.05; H, 6.55; N, 25.48.

On the other hand, the mother liquors, which were obtained when the first crop of **10b** was isolated, were combined and evaporated *in vacuo*, and the residue was chromatographed on alumina (65 g). Earlier fractions eluted with AcOEt–EtOH (10 : 1, v/v) gave **9b** (388 mg, 45%), mp 103—104 °C, which was identical with the sample obtained by method (i). The later-fraction component was rechromatographed [alumina, benzene–EtOH (6 : 1, v/v)] to provide a second crop of **10b** (54 mg, 6%), mp 158—160 °C. The total yield of **10b** was 28%.

Reaction of 8c·$HClO_4$ with H_2O——i) In Aqueous Alkali: The nucleoside **8c**·$HClO_4$[4] was allowed to react with H_2O at pH 11 and 60 °C for 24 h according to the procedure of Windmueller and Kaplan,[4] and the rearranged product **9c** was obtained in 93% yield as the monohydrate, mp 196—197 °C. Recrystallization from H_2O gave an

analytical sample as colorless minute prisms, mp 196—197 °C (lit.[4] mp 195—196 °C); UV (Table II). *Anal.* Calcd for $C_{12}H_{17}N_5O_5 \cdot H_2O$: C, 43.77; H, 5.82; N, 21.27. Found: C, 43.67; H, 5.56; N, 21.20.

ii) At pH 6 in Phosphate Buffer: A solution of **8c**·$HClO_4$[4] (1.03 g, 2.5 mmol) in 0.3 M NaH_2PO_4–Na_2HPO_4 (pH 6.0 at 20 °C) (150 ml) was heated at 95—100 °C for 5 h. The reaction mixture was cooled and applied to a column of Amberlite CG-120 Type I (H^+) (350 ml). The column was washed with H_2O (650 ml) and then was eluted with 3% aqueous NH_3. A 600-ml fraction eluted after the initial 650-ml eluate was evaporated to dryness *in vacuo*. The residual solid was triturated with hot H_2O (5 ml). After cooling, the mixture was filtered to collect the insoluble material, which was washed with a little H_2O and dried to give **9c**·H_2O (428 mg, 52%), mp 190—192 °C, identical (by comparison of the IR spectrum and chromatographic behavior) with the sample prepared by method (i).

On the other hand, the aqueous filtrate and washings, obtained when **9c**·H_2O was filtered off, were combined and concentrated to dryness *in vacuo*. Recrystallization of the residue from 80% aueous EtOH produced **10c** (130 mg, 17%) as almost colorless prisms, mp 193—194 °C, which were identical with a sample prepared from inosine (**12**) by hydroxyethylation (*vide infra*).

9-Ethylhypoxanthine (11)——A solution of 9-ethyladenine (**6**)[17] (8.16 g, 50 mmol) in 0.8 N aqueous HCl (225 ml) was heated to 90 °C, and a solution of $NaNO_2$ (3.80 g, 55 mmol) in H_2O (125 ml) was added dropwise over a period of 30 min. After the addition, the temperature was maintained at 90 °C for 30 min. The reaction mixture was then concentrated to dryness *in vacuo*. The residue was dissolved in H_2O (15 ml) and the aqueous solution was neutralized to pH 7 with 10% aqueous NaOH. After the mixture had been kept in a refrigerator, the crystals that deposited were filtered off, washed with a little H_2O, and dried to give **11** (3.67 g, 45%), mp 262.5—263.5 °C. The filtrate and washings were combined, treated with charcoal, and concentrated to dryness *in vacuo*. The residual solid was extracted with three 150-ml portions of EtOH, and the ethanolic extracts were evaporated to dryness *in vacuo* to leave a solid. Recrystallization of the solid from H_2O gave a second crop (1.93 g) of **11**, mp 263.5—264.5 °C. The total yield was 68%. Recrystallization of the first and second crops of crystals form H_2O furnished an analytical sample as colorless prisms, mp 265—266 °C; MS *m/e*: 164 (M^+); UV $\lambda_{max}^{H_2O}$ (pH 1) 250.5 nm (ε 11300); $\lambda_{max}^{H_2O}$ (pH 7) 251 (12000); $\lambda_{max}^{H_2O}$ (pH 13) 255.5 (12700); NMR (Me_2SO-d_6) δ: 1.40 (3H, t, J=7 Hz, N(9)-$CH_2\underline{Me}$), 4.16 (2H, q, J=7 Hz, N(9)-$C\underline{H}_2Me$), 8.00 and 8.07 (1H each, s, purine H's), 12.17 (1H, br, NH). *Anal.* Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.41; H, 4.79; N, 33.99.

9-Ethyl-1-(2-hydroxyethyl)hypoxanthine (10a)——A mixture of **11** (3.61 g, 22 mmol) and anhydrous K_2CO_3 (4.56 g, 33 mmol) in $HCONMe_2$ (300 ml) was stirred at 100—110 °C for 30 min. The mixture was cooled to 70 °C and a solution of 2-bromoethanol (5.50 g, 44 mmol) in $HCONMe_2$ (60 ml) was added dropwise over a period of 20 min. After having been stirred at 70 °C for 6 h, the reaction mixture was evaporated to dryness *in vacuo*. The residue was extracted with three 150-ml portions of boiling EtOH. Evaporation of the combined ethanolic extracts and subsequent recrystallization of the resulting solid from H_2O gave **10a**·H_2O (3.65 g, 73%) as colorless prisms, mp 167.5—168.5 °C. Further recrystallization in the same way furnished an analytical sample, mp 169—170 °C (dried over P_2O_5 at 3 mmHg and room temperature for 24 h and then kept in a closed vessel saturated with H_2O until a constant weight was reached); MS *m/e*: 208 (M^+); UV (Table II); NMR (Me_2SO-d_6) δ: 1.40 (3H, t, J=7 Hz, N(9)-$CH_2\underline{Me}$), 3.65 [2H, m (converted into t, J=5.5 Hz, on addition of D_2O), $C\underline{H}_2OH$], 4.07 (2H, t, J=5.5 Hz, N(1)-CH_2), 4.18 (2H, q, J=7 Hz, N(9)-$C\underline{H}_2Me$), 4.90 (1H, t, J=5.5 Hz, OH), 8.10 and 8.24 (1H each, s, purine H's). *Anal.* Calcd for $C_9H_{12}N_4O_2 \cdot H_2O$: C, 47.78; H, 6.24; N, 24.76. Found: C, 47.75; H, 6.08; N, 24.93.

1-(2-Hydroxyethyl)inosine (10c)——A mixture of inosine (**12**) (1.34 g, 5 mmol) and anhydrous K_2CO_3 (1.04 g, 7.5 mmol) in $HCONMe_2$ (40 ml) was stirred at 70 °C for 40 min, and then a solution of 2-bromoethanol (2.50 g, 20 mmol) in $HCONMe_2$ (5 ml) was added dropwise over a period of 20 min. After stirring had been continued at 70 °C for 3 h, the reaction mixture was cooled to room temperature. The inorganic precipitate was removed by filtration and washed with a little $HCONMe_2$. The combined filtrate and washings were concentrated to dryness *in vacuo*. The residue was dissolved in H_2O (10 ml) and the aqueous solution was passed through a column of Amberlite CG-120 Type I (H^+) (100 ml). The column was washed with H_2O (300 ml) and then eluted with 3% aqueous NH_3. A 180-ml fraction eluted after the initial 150-ml eluate was evaporated to dryness *in vacuo*. The residual oil was dissolved in boiling 80% aqueous EtOH (45 ml), and the solution was kept in a refrigerator. The crystals that separated were filtered off, washed with a little 80% aqueous EtOH, and dried to give **10c** (852 mg, 55%) as colorless prisms, mp 194—195 °C. The filtrate and washings were combined and concentrated to dryness *in vacuo*. Recrystallization of the residue from 80% aqueous EtOH yielded a second crop (166 mg), mp 194—195 °C. The total yield was 65%. Recrystallization of the first crop of crystals in the same way furnished an analytical sample as colorless prisms, mp 195—196 °C; UV (Table II). *Anal.* Calcd for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.13; H, 5.16; N, 18.03.

9-Ethyl-N^6-propyladenine (9f)——A mixture of **8f**·HI (1.46 g, 4.4 mmol) and 0.2 N aqueous NaOH (44 ml) was heated in a boiling water bath for 25 min. The reaction mixture was cooled, neutralized to pH 7 with 10% aqueous HCl, and concentrated to dryness *in vacuo*. The residual solid was extracted with four 50-ml portions of boiling benzene. Evaporation of the combined benzene extracts left crude **9f** (840 mg, 93%), mp 98—100 °C. The crude product was dissolved in EtOH, and the ethanolic solution was treated with charcoal and then concentrated to dryness *in vacuo*. Recrystallization of the residue from hexane gave an analytical sample as slightly yellowish prisms,

mp 100—101 °C; UV (Table II); NMR (Me_2SO-d_6) δ: 0.90 (3H, t, J=7.5 Hz, $NCH_2CH_2\underline{Me}$), 1.40 (3H, t, J=7 Hz, N(9)-$CH_2\underline{Me}$), 1.4—1.75 (2H, m, $NCH_2C\underline{H}_2Me$), 3.2—3.7 (2H, br m, NCH_2), 4.18 (2H, q, J=7 Hz, N(9)-$C\underline{H}_2Me$), 7.5—7.8 (1H, br, NH), 8.12 and 8.18 (1H each, s, purine H's). *Anal.* Calcd for $C_{10}H_{15}N_5$: C, 58.52; H, 7.37; N, 34.12. Found: C, 58.38; H, 7.40; N, 33.89.

N^6-Butyl-9-ethyladenine Perchlorate (9g·$HClO_4$)——A mixture of **8g**·HI (1.74 g, 5 mmol) and 0.2 N aqueous NaOH (50 ml) was heated under reflux for 15 min. The reaction mixture was cooled, neutralized to pH 7 with 10% aqueous HCl, and concentrated to dryness *in vacuo*. The residue was extracted with five 50-ml portions of boiling benzene. Evaporation of the benzene extracts left crude **9g** (1.07 g), mp 58—61 °C, which was hygroscopic in nature. The product was dissolved in EtOH, and the ethanolic solution was treated with charcoal and then concentrated to dryness *in vacuo*. The residue was recrystallized from hexane, and the hygroscopic crystals that formed were dissolved in EtOH. The resulting solution was acidified (pH 1) with 70% aqueous $HClO_4$ and then diluted with ether. The precipitate that resulted was filtered off and recrystallized from EtOH to yield **9g**·$HClO_4$ as colorless prisms, mp 128—129 °C (dec.); UV (Table II); NMR (Me_2SO-d_6) δ: 0.93 [3H, t, J=7 Hz, $N(CH_2)_3\underline{Me}$], 1.45 (3H, t, J=7 Hz, N(9)-CH_2Me), 1.1—1.8 [4H, m, $NCH_2(C\underline{H}_2)_2Me$], 3.3—3.7 (2H, br m, NCH_2), 4.29 (2H, q, J=7 Hz, N(9)-$C\underline{H}_2Me$), 8.45 and 8.50 (1H each, s, purine H's). *Anal.* Calcd for $C_{11}H_{18}ClN_5O_4$: C, 41.32; H, 5.67; N, 21.90. Found: C, 41.28; H, 5.85; N, 21.74.

9-Ethyl-N^6-[(2-hydroxymethyl)benzyl]adenine Hydrobromide (9h·HBr)——A mixture of **8h**·HBr (900 mg, 2.47 mmol) and 0.2 N aqueous NaOH (25 ml) in MeOH (10 ml) was heated under reflux for 20 min. After cooling, the reaction mixture was neutralized to pH 7 with 10% aqueous HCl, concentrated to one-half its initial volume, and extracted with AcOEt (30 ml and 2×20 ml). The AcOEt extracts were washed with H_2O (10 ml), dried over anhydrous Na_2SO_4, and concentrated to dryness *in vacuo*. The residual glass was dissolved in EtOH (1 ml), and a solution of 48% aqueous HBr (0.5 ml) in EtOH (1.5 ml) was added. The precipitate that resulted on dilution with ether (10 ml) was filtered off, washed with ether, and dried to yield **9h**·HBr (736 mg, 82%), mp 138—139 °C (dec.). Recrystallization from EtOH afforded an analytical sample as colorless minute needles, mp 165—166.5 °C (dec.); UV (Table II); NMR (Me_2SO-d_6) δ: 1.44 (3H, t, J=7.5 Hz, N(9)-$CH_2\underline{Me}$), 4.30 (2H, q, J=7.5 Hz, N(9)-$C\underline{H}_2Me$), 4.65 (2H, s, $C\underline{H}_2OH$), 4.85 (2H, dull m, NCH_2), 5.1—5.5 (1H, br, OH), 7.0—7.5 (4H, m, phenyl H's), 7.5—8.1 (2H, br, NH's), 8.50 (dull s) and 8.64 (s) (1H each, purine H's). *Anal.* Calcd for $C_{15}H_{18}BrN_5O$: C, 49.46; H, 4.98; N, 19.23. Found: C, 49.18; H, 4.82; N, 19.12.

9-Ethyl-N^6-(2-methylbenzyl)adenine (9i)——A mixture of **8i**·HBr (3.00 g, 8.61 mmol) and 0.2 N aqueous NaOH (86 ml) in MeOH (70 ml) was heated under reflux for 30 min. After cooling, the reaction mixture was neutralized to pH 7 with 10% aqueous HCl and concentrated to one-half its initial volume. The precipitate that resulted was filtered off, washed with H_2O, and dried to yield **9i** (2.24 g, 97%), mp 134.5—135.5 °C. Recrystallization from benzene–hexane (1 : 1, v/v) gave an analytical sample as colorless prisms, mp 134.5—135.5 °C; UV (Table II); NMR (Me_2SO-d_6) δ: 1.42 (3H, t, J=7 Hz, N(9)-$CH_2\underline{Me}$), 2.38 (3H, s, Ar$\underline{Me}$), 4.20 (2H, q, J=7 Hz, N(9)-$C\underline{H}_2Me$), 4.55—5.0 (2H, br, NCH_2), 6.95—7.45 (4H, m, phenyl H's), 8.1 (1H, br, NH), 8.18 and 8.24 (1H each, s, purine H's). *Anal.* Calcd for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.56; H, 6.54; N, 26.06.

Spectrometric Determination of Acid Dissociation Constants——The pK_a's of **8a**, **b**, **h**, **i**·HBr and **8e**—**g**·$HClO_4$ at 40 °C and ionic strength 1.0 were determined in a manner similar to that described previously.[3e] The results are listed in Table III.

Kinetic Procedure——Buffer solutions used for kinetic runs were 0.02 M NaH_2PO_4–Na_2HPO_4 (pH 7.04 and 8.04 at 40 °C); 0.05, 0.1, and 0.2 M NaH_2PO_4–Na_2HPO_4 (pH 6.00, 7.01, and 7.80 at 40 °C); 0.02 M $NaHCO_3$–Na_2CO_3 (pH 9.12 and 10.08 at 40 °C); 0.05, 0.1, and 0.2 M $NaHCO_3$–Na_2CO_3 (pH 9.00 at 40 °C); 0.02 M Na_2HPO_4–Na_3PO_4 (pH 10.98 at 40 °C); 0.05 and 0.1 M Na_2HPO_4–Na_3PO_4 (pH 11.42 at 40 °C), and were brought to ionic strength 1.0 with KCl.

The rate constants for the rearrangement reactions of **8a**, **b**·HBr at pH 9.12, 10.08, 10.98, and 11.42 and of **8e**—**g**·$HClO_4$ and **8h**, **i**·HBr at pH 7.04, 8.04, 9.12, 10.08, 10.98, and 11.42, shown in Table IV, were measured as follows. The substrates were separately dissolved in the buffer solutions at concentrations ranging from 3.1×10^{-5} to 4.8×10^{-5} M. Aliquots (*ca.* 3 ml) of these solutions were sealed in small ampoules and placed in a thermoregulated constant-temperature bath kept at 40 °C (accurate to ±0.05 °C). At intervals the ampoules were removed, cooled, and broken, and the optical densities of the contents at 268 nm were determined at room temperature against blank buffer solutions. During the kinetic runs the pH was never found to vary by more than ±0.03 unit. The concentrations of the substrates were calculated in the usual manner[18] by utilizing the molecular extinction coefficients at the analytical wavelength, obtained from solutions of analytically pure samples of the substrates and **9a**, **b**, **e**—**i** in the appropriate buffer solutions. Except for the slow reactions of **8e**—**i**·HX (X = ClO_4 or Br) at pH 7.04, all rearrangements were followed through at least two half-lives with at least five determinations, and good pseudo-first-order kinetics were obtained in all cases.

For the determination of the reaction rates in the competitive reaction system consisting of the rearrangement of **8a**, **b**·HBr to **9a**, **b** and the deamination of **8a**, **b**·HBr to **10a**, **b**, experiments starting with 5.6×10^{-4} to 6.9×10^{-4} M solutions of **8a**, **b**·HBr in the 0.05, 0.1, and 0.2 M buffer solutions (pH 6.00 to 9.00) were carried out as follows. Aliquots (*ca.* 4.5 ml) of the solutions were sealed in ampoules and ketp at 40 °C. At intervals the ampoules were

removed, cooled, and broken. Aliquots (2 ml) of the contents were diluted with 0.25 M KOH–Na_2HPO_4 (pH 11.40 at 20 °C) by a factor of 10, and the optical densities of the resulting solutions were measured at 305 nm to determine the concentrations of the remaining substrates. The other 2-ml aliquots were diluted ten-fold with 0.3 M KH_2PO_4–Na_2HPO_4 (pH 6.50 at 20 °C), and the optical densities of the resulting solutions were measured at 245 and 284 nm for the calculations of concentrations of the deamination products **10a**, **b** and the rearranged products **9a**, **b**, respectively (see the text). Similar kinetic procedures were adopted for the reactions of **8d**·$HClO_4$ and **8h**·HBr, and the rates of the rearrangement reactions were determined (see Table IV). In these two cases, no appreciable deamination was observed.

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