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Purines. XXVI.[1,2] The Dimroth Rearrangement of 9-Substituted 1-Methyladenines: Accelerating Effect of a β-D-Ribofuranosyl Group at the 9-Position

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The reaction rates in the Dimroth rearrangements of 9-substituted 1-methyladenines (**5a**—**i**) were measured in H_2O at various pH's and ionic strength 1.0 at 40 °C. In all cases, attack of hydroxide ion on the protonated species of **5** at the 2-position was faster than that on the neutral species by a factor of 90—180. Among nine kinds of 9-substituents in these compounds, the β-D-ribofuranosyl group was found to accelerate both modes of hydroxide attack most significantly. It has been concluded that this rate enhancement is attributable solely to the electron-withdrawing effect of the furanose ring oxygen and not to the 5′-hydroxy group, a potential participant in intramolecular catalysis for the hydroxide attack on the adenine ring at the 2-position.

Keywords——9-substituted 1-methyladenine; 1-methyladenosine carbocyclic analogue; adenine ring-opening; Dimroth rearrangement rate study; 9-substituted N^6-methyladenine; 1,9-disubstituted adenine acid dissociation constant; 9-(ω-ethoxycarbonylalkyl)adenine; 9-(ω-hydroxyalkyl)adenine

Introduction

The Dimroth rearrangement is an isomerization process proceeding through ring-opening and subsequent recyclization whereby a heterocyclic nitrogen and its attached substituent exchange places with an α-amino or α-imino group.[3] Under basic conditions, 1-alkyladenines and their derivatives (*e.g.*, type **5**) usually undergo this type of rearrangement to produce isomeric N^6-alkyladenine derivatives (type **8**), and no ring-opened intermediates (type **6**) are detectable.[3,4] The rearrangement in these cases 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 **5**·HX) and the neutral species (type **5**) at the 2-position, and a subsequent fast ring closure (Chart 1).[4] 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.[4e] It is particularly noteworthy that a β-D-ribofuranosyl group at the 9-position accelerates the ring-opening of both the protonated and the neutral species.[4e,5] However, it has so far been uncertain whether this is attributable purely to the electron-withdrawing effect of the ribosyl group and/or to intramolecular participation of the hydroxy group at the 5′-position.[6]

In the present work, we prepared some ten 9-substituted 1-methyladenines (**5a**—**i** or **5a**—**i**·HX), in which most of the 9-substituents carry the essential partial structures of the ribosyl group, and determined the rates of their Dimroth rearrangements with a view to finding out which factor(s) is responsible for the rate-accelerating effect of a β-D-ribofuranosyl group at the 9-position.

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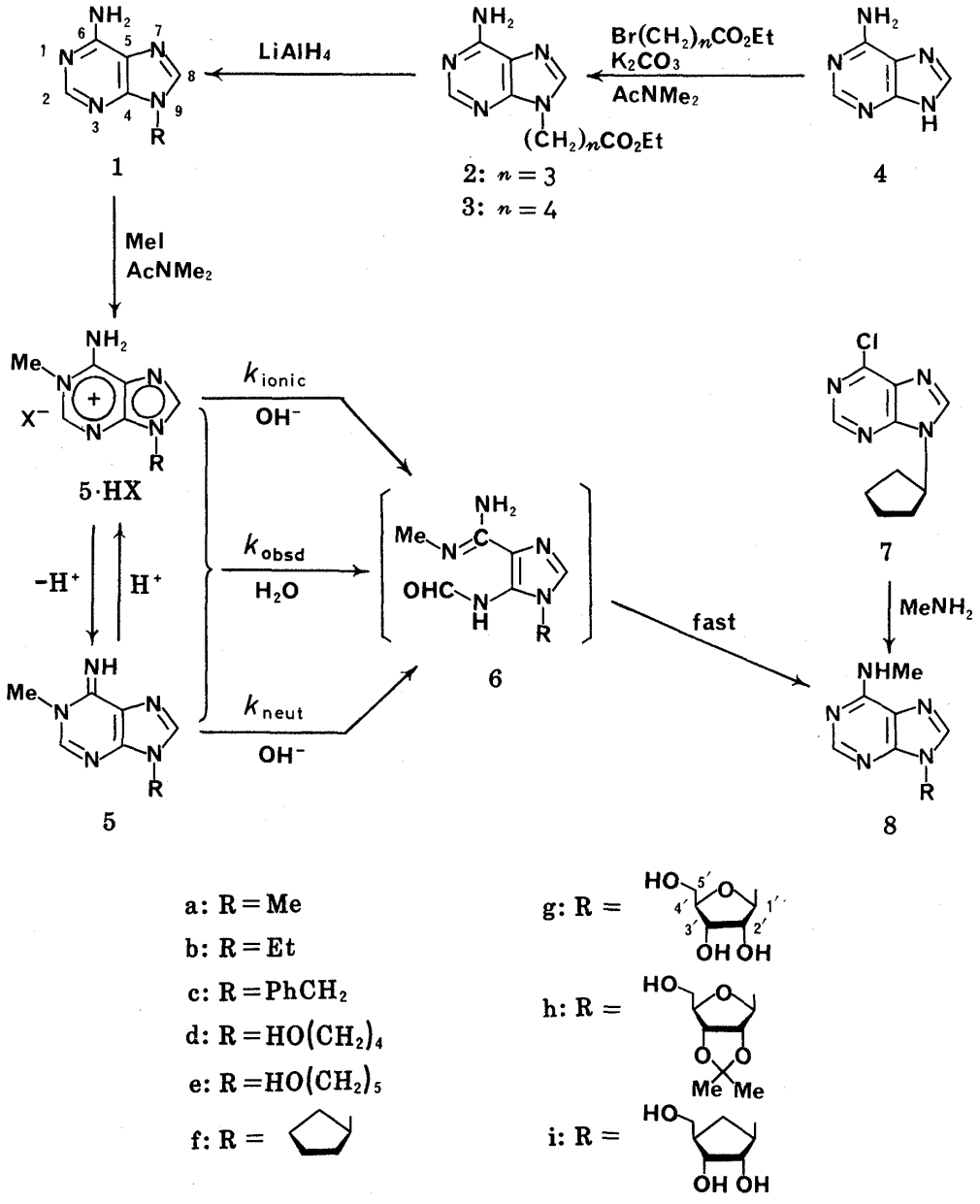

Chart 1

Results

Synthesis of Compounds

The substrates selected for the present kinetic study were the free bases or the perchlorate salts of **5a**—**i**, which all possess a methyl group at the 1-position for uniformity, but carry a β-D-ribofuranosyl group or its structural unit(s) at the 9-position. They were prepared by methylation of the corresponding 9-substituted adenines [**1a**—**h** and (−)-aristeromycin (**1i**)[7]] with MeI in $AcNMe_2$, a well-established general 1-alkylation procedure,[4b,8] followed by conversion of the resulting hydriodide salts (**5**·HI) into the perchlorates or the free bases (Chart 1). The syntheses of **5a**·$HClO_4$,[4b] **5g**,[4e,8a] and **5c**·HI[8b] by this procedure and the rearrangements of the free bases of the first two compounds to the N^6-methyl isomers **8a**[4b] and **8g**[4e,8a] in boiling H_2O have already been reported.

Treatments of **5b**—**e**, **h**, **i** or their perchlorates with boiling H_2O or 0.2 N aqueous NaOH

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gave the corresponding N^6-methyl isomers **8b—e, h, i**, among which **8h, i** were characterized in the form of the hydrochlorides. On the other hand, **8f** was prepared in 92% yield from **7** and aqueous $MeNH_2$. Among the starting 9-substituted adenines (**1**), **1d, e** were synthesized from adenine (**4**) by alkylation with the corresponding ω-bromo esters in $AcNMe_2$ in the presence of K_2CO_3 and subsequent reduction of **2** and **3** with $LiAlH_4$.

The structures of the 9-substituted 1-methyl- and N^6-methyladenines thus obtained were supported by the way in which they were generated,[8] microanalytical data, and the ultraviolet (UV) spectral features shown in Table I. Table II lists the acid dissociation constants of the substrates **5a—i**.

TABLE I. UV Spectra of 9-Substituted 1-Methyl- (**5a—i**) and N^6-Methyladenines (**8a—i**)

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)	$\varepsilon \times 10^{-3}$
5a·$HClO_4$[e]	261	13.5	261	13.6	261	13.3	261	14.1
5b·$HClO_4$	261	12.8	261	12.8	261	12.9	261	13.9
5c·$HClO_4$	261	15.5	260	13.9	260	14.5	261	14.7
5d	260	13.5	260	13.4	260	13.4	260	14.3
5e	260	13.4	261	13.3	261	13.3	261	14.3
5f·$HClO_4$	261	13.5	261	13.5	261	13.4	260	14.7
5g[f]	258	13.0	258	13.3	258	13.3	259	14.0
5h	259	13.7	259	13.9	259	13.9	259	14.6
5i	260	13.6	260	13.4	260	13.3	260	14.5
8a[e]	268	14.7	265	16.0	268	15.1	268	15.1
8b	—	—	265	17.5	269	16.5	269	16.5
8c	268	17.9	264	19.0	268	17.8	268	17.7
8d	268	16.4	265	18.0	268	16.9	268	16.9
8e	267	15.3	264	16.7	267	15.9	267	15.9
8f	268	16.7	265	18.2	268.5	17.2	268.5	17.2
8g[f]	266	16.2	262	17.7	266	16.5	266	16.7
8h·HCl	266	17.1	262	18.8	266	17.4	266	17.4
8i·HCl	267	16.9	264	18.6	268	17.5	268	17.5

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*) From ref. 4*b*. *f*) From ref. 4*e*.

TABLE II. Acid Dissociation Constants of 1,9-Disubstituted Adenines (**5a—i**)

Compound		pK_a at 40 °C and ionic strength 1.0
No.	9-Substituent	
5a·$HClO_4$	Me	8.96±0.04[a]
5b·$HClO_4$	Et	8.99±0.05
5c·$HClO_4$	$PhCH_2$	8.81±0.05
5d	$HO(CH_2)_4$	8.90±0.04
5e	$HO(CH_2)_5$	8.94±0.02
5f·$HClO_4$	Cyclopentyl	9.00±0.04
5g	β-D-Ribofuranosyl	8.55±0.07[a]
5h	2,3-*O*-Isopropylidene-β-D-ribofuranosyl	8.56±0.03
5i	2α,3α-Dihydroxy-4β-(hydroxymethyl)-1β-cyclopentyl	8.90±0.02

a) From ref. 4*e*.

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Kinetic Study

Chart 1 includes the scheme of the reaction system that produces the N^6-methyl isomers **8** from the 1-methyl isomers **5** or **5**·$HClO_4$. In a typical experiment, the rearrangement of **5c**·$HClO_4$ in 0.02—0.1 M buffer solutions of pH 7.04 to 11.42 at ionic strength 1.0 at 40 °C was followed by measuring the increase in UV absorption at 268 nm which occurs on formation of **8c**. Semilogarithmic plots of mole fraction of the residual substrate (**5c**·$HClO_4$) against time indicated that the reaction obeyed fairly good pseudo-first-order kinetics at all pH's through at least two half-lives. Kinetic runs with the other substrates were also handled in a similar manner, affording typical first-order plots at various pH's. Table III assembles the rate constants (k_{obsd}) obtained from these plots. It may be seen that in all cases the reaction rate increases with increasing pH of the reaction medium. As a good approximation, these rate constants may be regarded as the limiting rate constants for zero buffer concentration becuase we have already found that the catalytic coefficients of the buffer components are small in this type of reaction.[4e,5]

Figure 1 shows a pH–rate profile, which was obtained by plotting the rate constants for the rearrangement of **5c**·$HClO_4$ as a function of pH. As reported previously for similar cases,[2,4b,e,5] a theoretical pH–rate profile may be calculated from Eq. 1, where v is the reaction

TABLE III. The Rate Constants for the Rearrangement of **5b—f, h, i** to **8b—f, h, i** at 40 °C and Ionic Strength 1.0

Substrate	Pseudo-first-order rate constant, $k_{obsd} \times 10^4$ (min^{-1})					
	pH value					
	7.04	8.04	9.12	10.08	10.98	11.42
5b·$HClO_4$	0.21	1.3	8.3	14	30	47
5c·$HClO_4$	0.25	1.7	9.1	14	35	52
5d	0.20	1.6	8.2	13	29	45
5e	0.17	1.4	7.9	12	29	42
5f·$HClO_4$	0.14	0.99	7.1	12	25	36
5h	0.56	4.5	16	31	66	109
5i	0.24	1.8	8.7	14	34	52

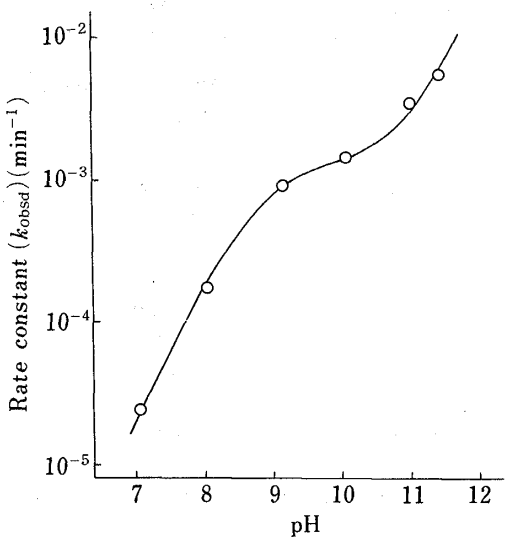

Fig. 1. pH–Rate Profile for the Rearrangement of **5c** to **8c** at 40 °C and Ionic Strength 1.0

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TABLE IV. Effect of Substituents on the Dimroth Rearrangement of the Protonated and Neutral Species of 9-Substituted 1-Methyladenines at 40 °C and Ionic Strength 1.0

Substrate	Second-order rate constant ($M^{-1}\,min^{-1}$)	
	k_{ionic}	k_{neut}
1,9-Dimethyladenine (**5a**)[a]	50 (1.0)[b]	0.55 (1.0)[b]
9-Ethyl-1-methyladenine (**5b**)	50 (1.0)	0.50 (0.9)
9-Benzyl-1-methyladenine (**5c**)	70 (1.4)	0.60 (1.1)
9-(4-Hydroxybutyl)-1-methyladenine (**5d**)	55 (1.1)	0.50 (0.9)
9-(5-Hydroxypentyl)-1-methyladenine (**5e**)	53 (1.1)	0.45 (0.8)
9-Cyclopentyl-1-methyladenine (**5f**)	40 (0.8)	0.37 (0.7)
1-Methyladenosine (**5g**)[a]	250 (5.0)	1.4 (2.5)
1-Methyl-2′,3′-*O*-isopropylideneadenosine (**5h**)	200 (4.0)	1.3 (2.4)
1-Methylaristeromycin (**5i**)	65 (1.3)	0.60 (1.1)

a) From ref. 4*e*. *b*) The figures in parentheses represent the relative rates.

$$v = k_{obsd}[\mathbf{5c}]_{total} = k_{ionic}[\mathbf{5c}\cdot H^+][OH^-] + k_{neut}[\mathbf{5c}][OH^-] \quad (1)$$

rate; $[\mathbf{5c}]_{total}$, the total concentration of **5c** and its protonated species; $[\mathbf{5c}\cdot H^+]$, the concentration of the protonated species of **5c**; [**5c**], the concentration of the neutral species of **5c**; $[OH^-]$, 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 **5c** is 8.81 (Table II). When k_{ionic} of 70 and k_{neut} of 0.60 (time in minutes) were adopted, the theoretical pH–rate profile that resulted corresponded to the curve plotted in Fig. 1. A similar treatment of the pseudo-first-order rate constants in Table III provided the second-order rate constants listed in Table IV.

Discussion

We have previously suggested that the site of protonation in the conjugate acids of 1,9-disubstituted adenines (type **5**) is the N^6-position,[4e] and this may explain the influence of both 1- and 9-substituents on the acid dissociation constant, as observed in the previous[2,4b,e,5] and present studies. Table II indicates that the 9-alkyl analogues **5a**, **b**, **f** 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 9-psoition. On the other hand, the observed decrease in base strength of **5c** and **5g** is attributable to the electron-withdrawing nature, relative to a *n*-alkyl group, of the benzyl group[9] and of the β-D-ribofuranosyl group.[10] Introduction of the electron-withdrawing hydroxy group as in the cases of **5d**, **e**, **i** causes only a small decrease in base strength. Comparison of the pK_a's of 1-methyladenosine (**5g**), its 2′,3′-*O*-isopropylidene derivative (**5h**), and the carbocyclic analogue 1-methylaristeromycin (**5i**) makes it clear that the electron-withdrawing nature of the β-D-ribofuranosyl group is attributable to the endocyclic oxygen atom.

The results shown in Fig. 1 and Table IV reveal that all the substrates (**5a**—**i**) undergo rearrangement to give the corresponding N^6-methyl isomers (**8a**—**i**) according to the rate law given by Eq. 1, in line with previous results[2,4a,b,e,5] obtained with other 1,9-disubstituted adenines. It follows that in the ring-opening of **5**, attack of the hydroxide ion on the protonated species (**5**·HX) at the 2-position is dominant in the pH region lower than the pK_a of **5** and is superseded in importance at higher pH's by attack on the neutral species at the 2-position.

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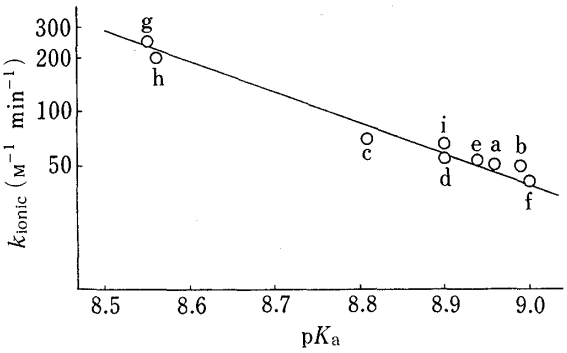

Fig. 2. pK_a–Rate Profile for Hydroxide Attack on the Protonated Species of **5a**—**i** in H_2O at 40 °C and Ionic Strength 1.0

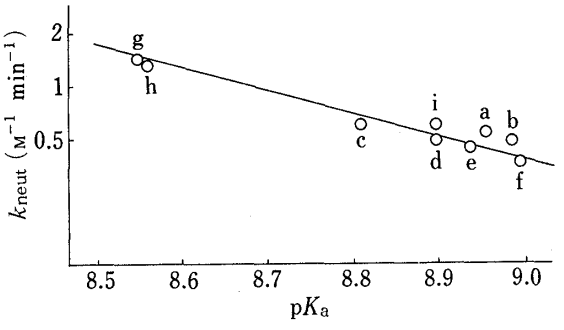

Fig. 3. pK_a–Rate Profile for Ring-Opening of the Neutral Species of **5a**—**i** in H_2O at 40 °C and Ionic Strength 1.0

It may be seen from Table IV that in all cases the hydroxide attack on the protonated species is much faster than that on the neutral species (by a factor of 90—180). In the reaction of the protonated species, there are no significant differences in rate among **5a**, **b**, **d**, **e**, **f**, **i**, whereas the 9-benzyl analogue **5c** rearranges 1.4 times as fast as the 9-methyl analogue **5a**; the nucleosides **5g** and **5h** rearrange 5 and 4 times more rapidly than **5a**. Figure 2 shows semilogarithmic plots of the second-order rate constants for the protonated species of **5a**—**i** against pK_a. It is clear from the linear relation that the rate increases with decreasing pK_a, reflecting the effect of the electron-withdrawing property of a 9-substituent on the 2-position. A similar approach to the analysis of the rate data on the neutral species (Table IV) is illustrated in Fig. 3. It may be seen from the gently sloping linear relation that the hydroxide attack on the neutral species at the 2-position is also accelerated by an electron-withdrawing 9-substituent, but to a lesser extent than that on the protonated species.

In conclusion, the present results reveal that the rate enhancement of the Dimroth rerrangement of 1-methyladenosine (**5g**) is attributable solely to the electron-withdrawing effect caused by the furanose ring oxygen. Thus, the possibility[4e] of intramolecular participation of the 5′-OH group[6] in the rearrangement may now be excluded.

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 on 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). Nuclear magnetic resonance (NMR) spectra were obtained with a JEOL JNM-PS-100 or -FX-100 spectrometer at 24 °C using Me_4Si as an internal standard; circular dichroism (CD) spectra, with a JASCO J-500C spectropolarimeter; and optical rotations, with a JASCO DIP-181 polarimeter. 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.

Ethyl 4-(9-Adenyl)butyrate (2)——A stirred mixture of adenine (**4**) (2.70 g, 20 mmol) and anhydrous K_2CO_3 (2.76 g, 20 mmol) in $AcNMe_2$ (80 ml) was heated at 110 °C for 30 min. After addition of a solution of ethyl 4-bromobutyrate (7.80 g, 40 mmol) in $AcNMe_2$ (10 ml), stirring was continued at 105—110 °C for 30 min. The reaction mixture was concentrated to dryness *in vacuo*. The residue was washed with two 60-ml portions of hexane and the washings were removed by decantation. The insoluble solid was then extracted with hot benzene (1 × 50 ml, 2 × 25 ml). The benzene extracts were combined, washed with saturated aqueous NaCl (10 ml), dried over anhydrous Na_2SO_4, and concentrated to dryness *in vacuo* to give **2** (2.25 g, 45%) as a colorless solid, mp 106—107 °C. Recrystallization from benzene–hexane (2 : 1, v/v) gave an analytical sample as colorless needles, mp 110—111 °C (lit.[11] mp 108—109 °C); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 261.5 nm (ε 14900); $\lambda_{max}^{H_2O}$ (pH 1) 259 (14400); $\lambda_{max}^{H_2O}$ (pH 7) 262 (14500); $\lambda_{max}^{H_2O}$ (pH 13) 262 (14800). *Anal.* Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.09. Found: C, 53.05; H, 6.34; N, 27.91.

Ethyl 5-(9-Adenyl)valerate (3)——This was prepared in 56% yield from adenine (**4**) and ethyl 5-bromovalerate in

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a manner similar to that described above for **2** and obtained as colorless minute prisms, mp 107—108 °C; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 261 nm (ε 14900); $\lambda_{max}^{H_2O}$ (pH 1) 260 (14800); $\lambda_{max}^{H_2O}$ (pH 7) 262 (15000); $\lambda_{max}^{H_2O}$ (pH 13) 262 (15000). *Anal.* Calcd for $C_{12}H_{17}N_5O_2$: C, 54.74; H, 6.51; N, 26.60. Found: C, 54.69; H, 6.79; N, 26.62.

9-(4-Hydroxybutyl)adenine (1d)——A solution of ethyl 4-(9-adenyl)butyrate (**2**) (2.12 g, 8.5 mmol) in tetrahydrofuran (THF) (100 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.61 g, 42.4 mmol) in THF (50 ml) over a period of 15 min. After having been refluxed for 80 min, the resulting greenish-gray mixture was treated successively with H_2O (1.6 ml), 15% aqueous NaOH (1.6 ml), and H_2O (4.8 ml) under ice-cooling and stirring. The precipitate that resulted was filtered off and washed with THF (50 ml). The combined filtrate and washings were concentrated to dryness *in vacuo*, and the residual solid was dissolved in boiling EtOH (50 ml). The ethanolic solution was treated with charcoal and filtered while hot. The filtrate was concentrated to a volume of *ca.* 25 ml and kept in a refrigerator. The crystals that separated were filtered off, washed with a little EtOH, and dried to give **1d** (1.01 g, 57%) as slightly yellowish minute prisms, mp 197—199 °C. The filtrate and washings were combined and concentrated to dryness *in vacuo*, and the residue was recrystallized from EtOH (7 ml) to give a second crop (237 mg, 13%), mp 195—197 °C. The total yield was 70%. Recrystallization of the first crop of the crystals from EtOH furnished an analytical sample as colorless minute prisms, mp 200—201 °C (lit.[12] mp 196—197 °C); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 262 nm (ε 15000); $\lambda_{max}^{H_2O}$ (pH 1) 260 (14700); $\lambda_{max}^{H_2O}$ (pH 7) 262 (15000); $\lambda_{max}^{H_2O}$ (pH 13) 262 (14900); NMR (Me_2SO-d_6) δ: 1.40 (2H, m, CH_2CH_2OH), 1.85 (2H, m, NCH_2CH_2), 3.42 [2H, m (converted into t with J=7 Hz on addition of D_2O), CH_2OH], 4.15 (2H, t, J=7 Hz, NCH_2), 4.43 (1H, dull t, OH, exchangeable with D_2O), 7.16 (2H, s, NH_2, exchangeable with D_2O), 8.13 (2H, s, purine protons). *Anal.* Calcd for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.79. Found: C, 52.19; H, 6.47; N, 33.76.

9-(5-Hydroxypentyl)adenine (1e)——This was prepared from **3** in 60% yield in the same manner as described above for **1d**, giving colorless prisms, mp 194—195 °C; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 261 nm (ε 14300); $\lambda_{max}^{H_2O}$ (pH 1) 259 (13900); $\lambda_{max}^{H_2O}$ (pH 7) 261 (14200); $\lambda_{max}^{H_2O}$ (pH 13) 261 (14300); NMR (Me_2SO-d_6) δ: 1.0—1.65 (4H, m, $CH_2CH_2CH_2OH$), 1.83 (2H, m, NCH_2CH_2), 3.39 (CH_2OH, overlapped with a signal of H_2O contained in the solvent), 4.15 (2H, t, J=7 Hz, NCH_2), 4.38 (1H, br, OH), 7.20 (2H, s, NH_2), 8.13 and 8.15 (1H each, s, purine protons). *Anal.* Calcd for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.65. Found: C, 54.23; H, 7.04; N, 31.67.

9-Ethyl-1-methyladenine Hydriodide (5b·HI)——A mixture of 9-ethyladenine (**1b**)[13] (3.26 g, 20 mmol), MeI (14.5 g, 100 mmol), and $AcNMe_2$ (30 ml) was stirred at 50 °C for 90 min. The reaction mixture was cooled to room temperature, and the precipitate was filtered off, washed with a little EtOH, and dried to give a colorless solid (5.31 g). Recrystallization from 70% (v/v) aqueous EtOH (120 ml) furnished a chromatographically pure sample of **5b**·HI (4.67 g, 77%) as colorless plates, mp 291—292 °C (dec.), which were further recrystallized in a similar manner to produce an analytical sample, mp 292.5—293.5 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 260 nm (ε 13000); $\lambda_{max}^{H_2O}$ (pH 1) 260 (13000); $\lambda_{max}^{H_2O}$ (pH 7) 260 (13000); $\lambda_{max}^{H_2O}$ (pH 13) 260 (13900). *Anal.* Calcd for $C_8H_{12}IN_5$: C, 31.49; H, 3.96; N, 22.95. Found: C, 31.73; H, 3.89; N, 22.85.

9-Ethyl-1-methyladenine Perchlorate (5b·$HClO_4$)——This salt was prepared from **5b**·HI (3.66 g, 12 mmol) by dissolving it in hot H_2O (35 ml) and adding a solution of $NaClO_4 \cdot H_2O$ (3.37 g, 24 mmol) in H_2O (2 ml). The precipitate that resulted was filtered off, washed with a little H_2O, and dried to give colorless pillars (3.31 g, 99%), mp 301—301.5 °C (dec.). Recrystallization from H_2O and drying over P_2O_5 at 100 °C and 4 mmHg for 3 h yielded an analytical sample, mp 305—306 °C (dec.); UV (Table I); pK_a (Table II); NMR (Me_2SO-d_6) δ: 1.46 (3H, t, J=7 Hz, CH_2Me), 3.84 (3H, s, NMe), 4.30 (2H, q, J=7 Hz, CH_2Me), 8.54 and 8.64 (1H each, s, purine protons), 8.75—9.4 and 9.4—10.1 (1H each, br, NH's). *Anal.* Calcd for $C_8H_{12}ClN_5O_4$: C, 34.61; H, 4.36; N, 25.22. Found: C, 34.71; H, 4.37; N, 25.28.

9-Benzyl-1-methyladenine Hydriodide (5c·HI)——The following procedure was based on the method of Leonard and Fujii.[8b] A mixture of 9-benzyladenine (**1c**)[13] (3.38 g, 15 mmol) and MeI (16.9 g, 75 mmol) in $AcNMe_2$ (40 ml) was stirred at 50 °C for 2 h. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give a colorless solid (3.15 g, 57%) as a first crop, mp 259.5—260.5 °C (dec.). The filtrate and washings were combined and concentrated to dryness *in vacuo*. Two recrystallizations of the residual solid from 30% (v/v) aqueous EtOH (20 ml each) yielded a second crop (1.51 g, 27%), mp 259.5—260.5 °C (dec.). The total yield was 84%. Recrystallization of the crude **5c**·HI from H_2O provided an analytical sample as colorless needles, mp 260.5—261.5 °C (dec.) [lit.[8b] mp 268—270 °C (dec.)]; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 260 nm (ε 13900); $\lambda_{max}^{H_2O}$ (pH 1) 260 (13900); $\lambda_{max}^{H_2O}$ (pH 7) 260 (13900); $\lambda_{max}^{H_2O}$ (pH 13) 260 (14800); NMR (Me_2SO-d_6) δ: 3.82 (3H, s, NMe), 5.52 (2H, s, CH_2Ph), 7.38 (5H, s, Ph), 8.72 (2H, s, purine protons), 8.9—9.4 and 9.6—10.1 (1H each, br, NH's). *Anal.* Calcd for $C_{13}H_{14}IN_5$: C, 42.52; H, 3.84; N, 19.07. Found: C, 42.70; H, 3.97; N, 19.28.

9-Benzyl-1-methyladenine Perchlorate (5c·$HClO_4$)——To a hot solution of **5c**·HI (2.94 g, 8 mmol) in H_2O (60 ml) was added a solution of $NaClO_4 \cdot H_2O$ (2.25 g, 16 mmol) in H_2O (2 ml). The precipitate that resulted was filtered off, washed with H_2O, and dried to give colorless needles (2.72 g, 100%). Recrystallization from H_2O furnished an analytical sample, mp 286—288 °C (dec.); UV (Table I); pK_a (Table II); NMR (Me_2SO-d_6) δ: 3.78 (3H, s, NMe), 5.44 (2H, s, CH_2Ph), 7.32 (5H, s, Ph), 8.62 (2H, s, purine protons), 8.8—9.25 and 9.5—10.0 (1H each, br, NH's). *Anal.* Calcd for $C_{13}H_{14}ClN_5O_4$: C, 45.96; H, 4.15; N, 20.61. Found: C, 45.92; H, 4.01; N, 20.47.

9-(4-Hydroxybutyl)-1-methyladenine (5d)——A mixture of **1d** (746 mg, 3.6 mmol) and MeI (2.56 g, 18 mmol) in $AcNMe_2$ (6 ml) was stirred at room temperature for 24 h. The precipitate that separated was filtered off, washed with

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a little EtOH, and dried to give a colorless solid (868 mg), mp 244—245 °C (dec.). This hydriodide salt was dissolved in H_2O (10 ml) and the aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (10 ml). The column was eluted with H_2O, and the eluate (80 ml) was concentrated under reduced pressure to leave crude **5d** (557 mg, 70%), mp 152—156 °C. Recrystallization from MeCN produced an analytical sample as colorless prisms, mp 167.5—168.5 °C; UV (Table I); pK_a (Table II); NMR (Me_2SO-d_6) δ: 1.33 (2H, m, CH_2CH_2OH), 1.80 (2H, m, NCH_2CH_2), 3.40 (2H, t, J=6.5 Hz, CH_2OH), 3.45 (3H, s, NMe), 4.06 (2H, t, J=7 Hz, NCH_2), 4.2—4.75 (1H, br, OH or NH, exchangeable with D_2O), 6.5—7.2 (1H, br, NH or OH, exchangeable with D_2O), 7.88 and 8.01 (1H each, s, purine protons). *Anal.* Calcd for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.65. Found: C, 54.15; H, 6.95; N, 31.87.

9-(5-Hydroxypentyl)-1-methyladenine (5e)——A mixture of **1e** (553 mg, 2.5 mmol) and MeI (1.77 g, 12.5 mmol) in $AcNMe_2$ (5 ml) was stirred at room temperature for 24 h. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give a colorless solid (605 mg), mp 244—245 °C (dec.). The solid was dissolved in H_2O (10 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (7 ml), and the column was eluted with H_2O. Concentration of the eluate (80 ml) under reduced pressure left crude **5e** (394 mg, 67%), mp 151—153 °C. Recrystallizations from MeCN gave an analytical sample as colorless prisms, mp 155.5—156.5 °C; UV (Table I); pK_a (Table II). *Anal.* Calcd for $C_{11}H_{17}N_5O$: C, 56.15; H, 7.28; N, 29.76. Found: C, 55.87; H, 7.18; N, 29.85.

9-Cyclopentyl-1-methyladenine Perchlorate (5f·HClO$_4$)——A mixture of 9-cyclopentyladenine (**1f**)[14] (813 mg, 4 mmol) and MeI (2.84 g, 20 ml) in $AcNMe_2$ (10 ml) was stirred at 45 °C for 2 h. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give a colorless solid of **5f**·HI (1.00 g), mp 272.5—273.5 °C (dec.). A portion (897 mg) of the solid was dissolved in hot H_2O (17 ml), and a solution of $NaClO_4 \cdot H_2O$ (730 mg, 5.2 mmol) in H_2O (1 ml) was added. The resulting precipitate was filtered off, washed with a little H_2O, and dried to give **5f**·$HClO_4$ (802 mg, 70% from **1f**), mp 284—286 °C (dec.). Recrystallization from H_2O provided an analytical sample as colorless pillars, mp 292—293 °C (dec.); UV (Table I); pK_a (Table II); NMR (Me_2SO-d_6) δ: 1.5—2.4 (8H, m, CH_2's), 3.80 (3H, s, NMe), 4.90 (1H, m, CH), 8.56 and 8.61 (1H each, s, purine protons), 8.8—9.2 and 9.55—10.0 (1H each, br, NH's, exchangeable with D_2O). *Anal.* Calcd for $C_{11}H_{16}ClN_5O_4$: C, 41.58; H, 5.08; N, 22.04. Found: C, 41.54; H, 4.98; N, 22.11.

1-Methyl-2′,3′-*O*-isopropylideneadenosine (5h)——A mixture of **1h**[15] (922 mg, 3 mmol) and MeI (2.13 g, 15 mmol) in $AcNMe_2$ (6 ml) was stirred at room temperature for 24 h. The resulting reddish-brown solution was concentrated to dryness *in vacuo*, and the residue was washed with two 5-ml portions of EtOH to give a colorless solid (1.17 g). The solid was dissolved in H_2O (45 ml) and the solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (7 ml). The column was eluted with H_2O, and the eluate (200 ml) was concentrated *in vacuo* to leave a colorless solid of **5h** (820 mg, 85%), mp 162—165 °C. Recrystallizations from MeCN gave an analytical sample as colorless plates, mp 176.5—177.5 °C; UV (Table I); pK_a (Table II). *Anal.* Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.79. Found: C, 52.08; H, 5.89; N, 21.94.

1-Methylaristeromycin (5i)——A mixture of (−)-aristeromycin (**1i**) (398 mg, 1.5 mmol) and MeI (1.07 g, 7.5 mmol) in $AcNMe_2$ (3 ml) was stirred at room temperature for 28 h. The resulting yellow solution was concentrated to dryness *in vacuo*, and the residue was recrystallized from EtOH to afford **5i**·HI (370 mg) as colorless crystals, mp 230—232 °C (dec.). The hydriodide salt was dissolved in H_2O (5 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (2.5 ml), and the column was eluted with H_2O. Concentration of the eluate (50 ml) and recrystallization of the residue from EtOH furnished an analytical sample of **5i** as colorless needles, mp 199—200 °C; $[\alpha]_D^{23}$ −48.5° (c=0.71, H_2O); UV (Table I); pK_a (Table II). *Anal.* Calcd for $C_{12}H_{17}N_5O_3$: C, 51.61; H, 6.14; N, 25.07. Found: C, 51.56; H, 6.11; N, 25.13.

9-Ethyl-N^6-methyladenine (8b)——A mixture of **5b**·$HClO_4$ (555 mg, 2 mmol) and 0.2 N aqueous NaOH (20 ml) was heated under reflux for 20 min. The reaction mixture was adjusted to pH 8 with 10% aqueous HCl and concentrated to dryness *in vacuo*. The residue was extracted with eight 20-ml portions of boiling benzene. The benzene extracts were combined and evaporated to dryness *in vacuo* to leave crude **8b** (338 mg, 95%), mp 137—140 °C. Recrystallizations from AcOEt gave an analytical sample as colorless prisms, mp 142—143 °C; UV (Table I). *Anal.* Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.32; H, 6.30; N, 39.60.

9-Benzyl-N^6-methyladenine (8c)——A mixture of **5c**·HI (1.84 g, 5 mmol) and 0.2 N aqueous NaOH (50 ml) was heated under reflux for 15 min. The reaction mixture was neutralized with 10% aqueous HCl and extracted with three 30-ml portions of AcOEt. The AcOEt extracts were combined, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo*. Recrystallization of the residual solid from benzene gave **8c** (988 mg, 82%) as colorless prisms, mp 133—134 °C. Further recrystallization in the same way produced an analytical sample, mp 134—135 °C; UV (Table I); NMR (Me_2SO-d_6) δ: 3.04 (3H, dull, NHMe), 5.38 (2H, s, CH_2Ph), 7.32 (5H, s, Ph), 7.66 (1H, br, NH, exchangeable with D_2O), 8.24 (2H, s, purine protons). *Anal.* Calcd for $C_{13}H_{13}N_5$:C, 65.26; H, 5.48; N, 29.27. Found: C, 65.37; H, 5.47; N, 29.11.

9-(4-Hydroxybutyl)-N^6-methyladenine (8d)——A solution of **5d** (221 mg, 1 mmol) in H_2O (3 ml) was heated under reflux for 4 h. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was purified on a column of alumina (13 g) using $CHCl_3$–EtOH (10 : 1, v/v) as eluent. Concentration of the eluate left crude **8d** (155 mg, 70%), mp 109—110 °C. Recrystallization from AcOEt furnished an analytical sample as colorless plates, mp 109—110 °C; UV (Table I). *Anal.* Calcd for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.65. Found: C, 54.10; H, 6.82; N, 31.60.

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9-(5-Hydroxypentyl)-N^6-methyladenine (8e)——A mixture of **5e** (59 mg, 0.25 mmol) and 0.2 N aqueous NaOH (2.5 ml) was refluxed for 15 min. The reaction mixture was adjusted to pH 9 with 10% aqueous HCl and concentrated to dryness *in vacuo*. The residual solid was extracted with four 5-ml portions of boiling benzene. The benzene extracts were combined and concentrated to dryness *in vacuo* to leave crude **8e** (57 mg, 97%), mp 99—100 °C. Recrystallizations from AcOEt gave an analytical sample as colorless prisms, mp 99—100 °C; UV (Table I). *Anal.* Calcd for $C_{11}H_{17}N_5O$: C, 56.15; H, 7.28; N, 29.76. Found: C, 56.02; H, 7.41; N, 29.49.

9-Cyclopentyl-N^6-methyladenine (8f)——A mixture of 6-chloro-9-cyclopentylpurine (**7**)[14] (400 mg, 1.8 mmol) and 40% aqueous $MeNH_2$ (20 ml) was heated in an oil bath kept at 100 °C for 80 min. The reaction mixture was concentrated to dryness *in vacuo*. The residual oil was triturated with H_2O (1 ml). The resulting crystals were filtered off, washed with a little H_2O, and dried to give **8f** (360 mg, 92%) as an almost colorless solid, mp 103—104 °C. Recrystallizations from hexane yielded an analytical sample as colorless plates, mp 104—105 °C; UV (Table I); NMR (Me_2SO-d_6) δ: 1.4—2.3 (8H, m, CH_2's), 2.98 (3H, dull, NHMe), 4.80 (1H, m, CH), 7.57 (1H, br, NH, exchangeable with D_2O), 8.13 and 8.17 (1H each, s, purine protons). *Anal.* Calcd for $C_{11}H_{15}N_5$: C, 60.81; H, 6.96; N, 32.23. Found: C, 61.10; H, 6.99; N, 32.01.

N^6-Methyl-2′,3′-*O*-isopropylideneadenosine Hydrochloride (8h·HCl)——A solution of **5h** (760 mg, 2.37 mmol) in H_2O (6 ml) was heated under reflux for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was purified on a column of silica gel (60 g) using $CHCl_3$–EtOH (10 : 1, v/v) as eluent. Concentration of the eluate left a colorless glass (492 mg), which was dissolved in EtOH (4 ml), and 10% ethanolic HCl (1 ml) was added. The precipitate that separated was filtered off, washed with a little EtOH, and dried to give **8h**·HCl (392 mg, 46%) as a colorless solid. The solid was dissolved in warm MeOH and reprecipitated by addition of ether, yielding an analytical sample as colorless needles, mp 191—192 °C (dec.); UV (Table I). *Anal.* Calcd for $C_{14}H_{20}ClN_5O_4$: C, 47.00; H, 5.63; N, 19.57. Found: C, 46.97; H, 5.64; N, 19.77.

N^6-Methylaristeromycin Hydrochloride (8i·HCl)——A solution of **5i** (106 mg, 0.38 mmol) in H_2O (5 ml) was heated under reflux for 4 h. The reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in MeOH, and 10% methanolic HCl was added to adjust the pH of the solution to 1. The mixture was then kept in a refrigerator, and the crystals that resulted were filtered off, washed with a little MeOH, and dried to give **8i**·HCl (32 mg, 25%), mp 226—228 °C. Recrystallization from MeOH gave an analytical sample as colorless needles, mp 226—228 °C; CD [$c = 5.69 \times 10^{-5}$ M, 0.005 M phosphate buffer (pH 7)] $[\theta]^{20}$ (nm): 0 (300), −790 (268) (neg. max), 0 (242), +180 (235) (pos. max), 0 (229); UV (Table I). *Anal.* Calcd for $C_{12}H_{18}ClN_5O_3$: C, 43.18; H, 6.04; N, 20.98. Found: C, 43.07; H, 6.13; N, 20.74.

Spectrometric Determination of Acid Dissociation Constants——The pK_a's of **5b**, **c**, **f**·$HClO_4$ and **5d**, **e**, **h**, **i** at 40 °C and ionic strength 1.0 were determined in a manner similar to that described previously.[4e] The results are listed in Table II.

Kinetic Procedure——The rearrangement reactions of **5** to **8**, shown in Chart 1, in aqueous solution at various pH's and ionic strength 1.0 at 40 °C were followed by UV spectrophotometry. Buffer solutions employed for kinetic runs were 0.02 M NaH_2PO_4–Na_2HPO_4 (pH 7.04 and 8.04 at 40 °C); 0.02 M $NaHCO_3$–Na_2CO_3 (pH 9.12 and 10.08 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 substrates (**5b**—**f**, **h**, **i**), in the form of the perchlorate salt or free base, were separately dissolved in the buffer solutions at concentrations ranging from 4.1×10^{-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 ±0.02 unit. The concentrations of the substrates were calculated in the usual manner[16] by utilizing the molecular extinction coefficients at the analytical wavelength, obtained from solutions of analytically pure samples of the substrates and **8b**—**f**, **h**, **i** in the appropriate buffer solutions. Except for the slow reactions of **5b**—**f**, **h**, **i** 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.

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References and Notes

1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.
2) Paper XXV in this series, T. Fujii, T. Itaya, T. Saito, and S. Kawakatsu, *Chem. Pharm. Bull.*, **32**, 4842 (1984).
3) For reviews, see *a*) D. J. Brown, "Mechanisms of Molecular Migrations," Vol. 1, ed. by B. S. Thyagarajan, Interscience Publishers, New York, 1968, pp. 209—245; *b*) J. H. Lister, "Fused Pyrimidines. Part II. Purines," ed. by D. J. Brown, Wiley–Interscience, New York, 1971, pp. 313—315; *c*) T. Fujii, T. Itaya, and T. Saito, *Yuki*

NII-Electronic Library Service

Gosei Kagaku Kyokai Shi, **41**, 1193 (1983).
4) *a*) J. B. Macon and R. Wolfenden, *Biochemistry*, **7**, 3453 (1968); *b*) T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, **28**, 535 (1972); *c*) E. R. Garrett and P. J. Mehta, *J. Am. Chem. Soc.*, **94**, 8542 (1972); *d*) T. Fujii, F. Tanaka, K. Mohri, and T. Itaya, *Chem. Pharm. Bull.*, **22**, 2211 (1974); *e*) T. Fujii, T. Itaya, and T. Saito, *ibid.*, **23**, 54 (1975); *f*) T. Fujii, T. Saito, and T. Nakasaka, *ibid.*, **31**, 3521 (1983).
5) T. Itaya, T. Saito, S. Kawakatsu, and T. Fujii, *Chem. Pharm. Bull.*, **23**, 2643 (1975).
6) For the primed numbers, see the nucleoside numbering system shown in the part structure **g** (Chart 1).
7) T. Kishi, M. Muroi, T. Kusaka, M. Nishikawa, K. Kamiya, and K. Mizuno, *Chem. Pharm. Bull.*, **20**, 940 (1972). For (±)-aristeromycin, see Y. F. Shealy, M. C. Thorpe, W. C. Coburn, Jr., and J. D. Clayton, *ibid.*, **28**, 3114 (1980).
8) *a*) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963); *b*) N. J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U.S.A.*, **51**, 73 (1964).
9) *a*) H. C. Brown, D. H. McDaniel, and O. Häfliger, "Determination of Organic Structures by Physical Methods," ed. by E. A. Braude and F. C. Nachod, Academic Press, New York, 1955, pp. 581—582 and p. 584; *b*) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt & Co., New York, 1959, pp. 206—207.
10) *a*) C. D. Jardetzky and O. Jardetzky, *J. Am. Chem. Soc.*, **82**, 222 (1960); *b*) R. P. Panzica, R. J. Rousseau, R. K. Robins, and L. B. Townsend, *ibid.*, **94**, 4708 (1972).
11) N. J. Leonard and K. Ito, *J. Am. Chem. Soc.*, **95**, 4010 (1973).
12) M. Ikehara, E. Ohtsuka, S. Kitagawa, K. Yagi, and Y. Tonomura, *J. Am. Chem. Soc.*, **83**, 2679 (1961).
13) T. Fujii, S. Sakurai, and T. Uematsu, *Chem. Pharm. Bull.*, **20**, 1334 (1972).
14) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **80**, 409 (1958).
15) A. Hampton, *J. Am. Chem. Soc.*, **83**, 3640 (1961).
16) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley & Sons, Inc., New York, 1962, pp. 556—560.

NII-Electronic Library Service