Purines. XLI.[1] An Alternative Synthesis and the Chemical Behavior of 7,9-Dialkyladeninium Salts

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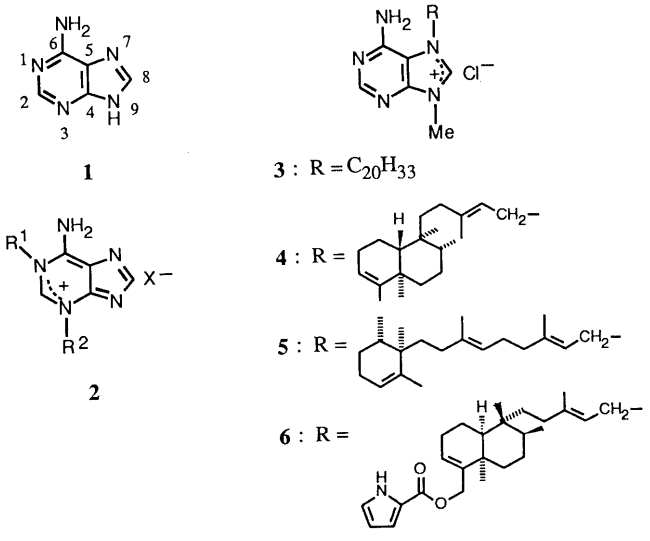
A full account is given of the chemical behavior observed for 7,9-dialkyladeninium salts (16). On treatment with boiling 1 N aqueous NaOH for 60 min, 16a, b, d, e (X = I), 16c (X = Br), and 16f (X = ClO_4) rearranged to isomeric N^6,7-dialkyladenines (21a—f) in 50—91% yields. Treatment of the salts with 0.5 N aqueous Na_2CO_3 at room temperature for 30—90 min or with Amberlite CG-400 (OH^-) in H_2O at room temperature gave the ring-opened derivatives 22a—f (in the *trans*-formamide form) in 56—83% yields, and rate constants for the ring-opening reactions of 16a, b, d—g (X = ClO_4) and 16c (X = Br) leading to 22a—g were determined in H_2O at pH 9.84 and ionic strength 0.50 at 25 °C. Cyclization of 22a with NaH in $AcNMe_2$ at room temperature or with boiling 1 N aqueous NaOH produced 21a in 84% or 72% yield, respectively.

In solution, the *trans*-formamides 22 seemed to transform slowly into the *cis*-formamides 23, attaining equilibria. The existence of such an equilibrium in D_2O or Me_2SO-d_6 at 25 °C or in H_2O at pH 9.84 and ionic strength 0.50 at 25 °C was kinetically confirmed in the case of 22a, and the mechanism of the rearrangement of 16 to 21 through 22 is discussed on the basis of the above kinetic results and Deslongchamps' theory of stereoelectronic control. On treatment with $NaBH_4$ in MeOH at room temperature, 16a (X = I) furnished the 7,8-dihydro derivative 28 (84% yield), which slowly decomposed in H_2O at 60 °C to give 22a in 49% yield.

The 7,9-dialkyladeninium salts (16) were found to be obtainable from *N'*-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidines (9) through an alternative synthetic route: Alkylations of 9 with alkyl halides in $HCONMe_2$ in the absence of base, followed by hydrogenolysis of the *N'*-alkoxy group and cyclization (or *vice versa*) produced 16 in acceptable yields. In order to interpret the proton nuclear magnetic resonance spectrum of 22a, the 2-deuterated species 26 was also synthesized from 24 *via* 25 and 27.

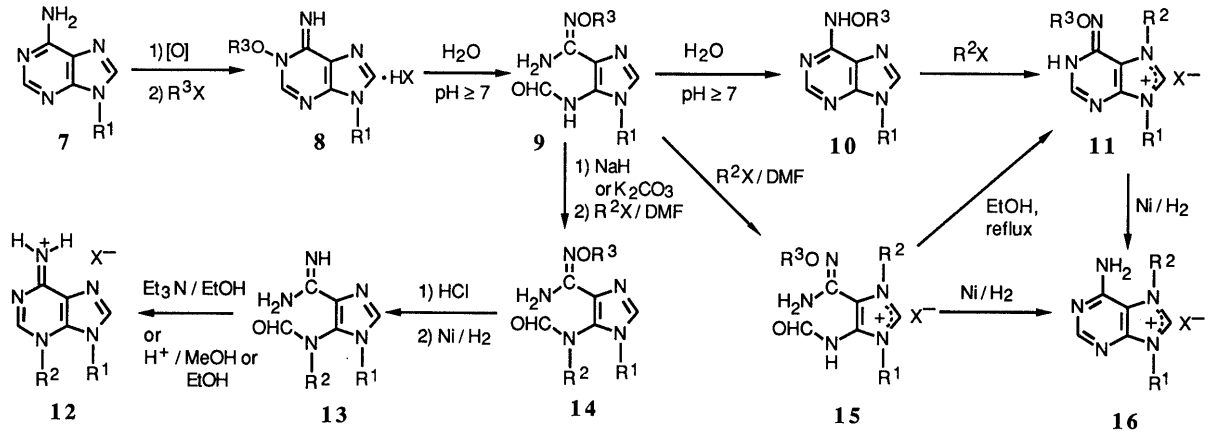
Keywords 7,9-dialkyladenine synthesis; 2-deuterio-7,9-dialkyladenine; imidazole *N*-alkylation; hydrogenolytic dealkoxylation; amidine formamido cyclization; ring opening; formamidopyrimidine *trans–cis* equilibration; rearrangement; N^6,7-dialkyladenine; kinetic study

An important structural feature of the adenine ring system (**1**) is that it carries five nitrogen atoms, one exocyclic and four endocyclic, so that 11 types of N^x,N^y-disubstitution are possible in principle. Such disubstitutions are now all known to exist except for 1,3-disubstitution (type **2**).[2] The existence of the 7,9-disubstituted adenine structure (type **16**) was first shown by us in 1973 as a result of the synthesis of 7,9-dimethyladeninium perchlorate (**16a**: X = ClO_4)[3] or 7-methyladenosine sulfate (**16h**: $X^- = 1/2\,SO_4^{2-}$)[3a] from N^6-methoxy-9-methyladenine (**10a**: R^3 = Me) or N^6-methoxyadenosine (**10h**: R^3 = Me), respectively. The synthesis consisted of preferential N(7)-methylation of **10a** (R^3 = Me) or **10h** (R^3 = Me) and hydrogenolytic removal of the methoxy group from the resulting 7-methylated product **11a** (R^3 = Me) or **11h** (R^3 = Me).[3] This synthetic route was then extended to cover other N(7)-alkylations of 9-alkyl analogues, establishing a general synthetic route to 7,9-dialkyladeninium salts (type **16**)[4] (see Chart 1). In the meantime, the natural occurrence of the 7,9-disubstitution in the form of agelasine (from the sea sponge *Agelas dispar*),[5] agelasines A—F (from the Okinawan sea sponge *A. nakamurai*),[6,7] and agelines A (agelasine F[6]) and B (from a Pacific sea sponge *Agelas* sp.),[8] all with diterpene or modified diterpene units at the 7-position (type **3**), was reported. The existence of the 7-methyladenosine structure (**16h**) in transfer ribonucleic acids of *Bacillus stearothermophilus*[9] and *B. subtilis*[10] as a modified nucleoside component was also suggested, and 7-methyl- or 7-ethyladenosine (type **16h** or **16i** with unspecified X) was reported to be a by-product of methylation or ethylation of adenosine in neutral aqueous solution.[11] Interestingly, several of these biochemically significant compounds were synthesized by application of the above general method for the synthesis of 7,9-dialkyladeninium salts: 7-methyladenosine perchlorate (**16h**: X = ClO_4)[12] and 7-ethyladenosine perchlorate (**16i**: X = ClO_4)[12] by us; agelasine B (**4**)[13] and (±)-ageline A [(±)-agelasine F)] (**5**)[14] by Tokoroyama's group. In the present study, we investigated an alternative synthesis and the chemical behavior of 7,9-dialkyladeninium salts (**16**). A brief account of the results described here has been published in a preliminary form.[15]



Synthetic Routes

The monocycles **9**, readily obtainable from 9-substituted



a: $R^1 = R^2 = Me$ **b**: $R^1 = Me$; $R^2 = Et$ **c**: $R^1 = Me$; $R^2 = PhCH_2$

d: $R^1 = Et$; $R^2 = Me$ **e**: $R^1 = R^2 = Et$ **f**: $R^1 = Et$; $R^2 = PhCH_2$

g: $R^1 = PhCH_2$; $R^2 = Et$ **h**: $R^1 = \beta$-D-ribofuranosyl; $R^2 = Me$ **i**: $R^1 = \beta$-D-ribofuranosyl; $R^2 = Et$

Chart 1

adenines (**7**) in three steps involving N(1)-oxidation, *O*-alkylation, and hydrolytic ring opening of the 1-alkoxy derivatives **8** under mild conditions[16] (Chart 1), occupy a key position in our "fission and reclosure" technology[17] developed for modification of the adenine ring (**1**). They have been shown[4] to produce 7,9-disubstituted adeninium salts (**16**) through **10** and **11**, as described above. On the other hand, alkylations of **9** with alkyl halides in $HCONMe_2$ (DMF) in the presence of NaH or anhydrous K_2CO_3 give the 5-(*N*-alkylformamido) derivatives **14**, which can be led to 3,9-disubstituted adenines (**12**) through the dealkoxy derivatives **13**.[18] If these alkylations of **9** were effected in the absence of the inorganic base, the site of alkylation could be different since the amidine moiety and the N(3) atom of the imidazole ring would also be susceptible to alkylation.[19,20]

In order to study this problem, methylation of the formamidoimidazole **9a** ($R^3 = Me$)[21] with MeI in DMF was carried out at 30 °C for 41 h. When a crude product presumed to be the N(3)-methyl derivative **15a** ($R^3 = Me$; X = I) was treated with boiling EtOH for 5 h, N^6-methoxy-7,9-dimethyladeninium iodide [**11a** ($R^3 = Me$; X = I)] was obtained in 61% overall yield [from **9a** ($R^3 = Me$)]. The structure of this iodide salt was confirmed by direct comparison with an authentic sample.[3] Similar alkylations of **9a** ($R^3 = Me$) with EtI (50 °C, 93 h) and $PhCH_2Br$ (30 °C, 46 h or 100 °C, 4 h) and those of **9d** ($R^3 = Et$)[21] with MeI (30 °C, 3 d) and EtI (50 °C, 3 d) afforded the corresponding 3-substituted imidazolium salts [**15b** ($R^3 = Me$; X = I), **15c** ($R^3 = Me$; X = Br), **15d** ($R^3 = Et$; X = I), and **15e** ($R^3 = Et$; X = I)] as crude products. On heating in boiling EtOH for 5 h, these imidazolium salts cyclized to give **11b** ($R^3 = Me$; X = I), **11c** ($R^3 = Me$; X = Br), **11d** ($R^3 = Et$; X = I), and **11e** ($R^3 = Et$; X = I) in 41—53% overall yields (from the corresponding formamidoimidazoles **9**). The cyclized products were also identified by comparison with authentic samples.[4]

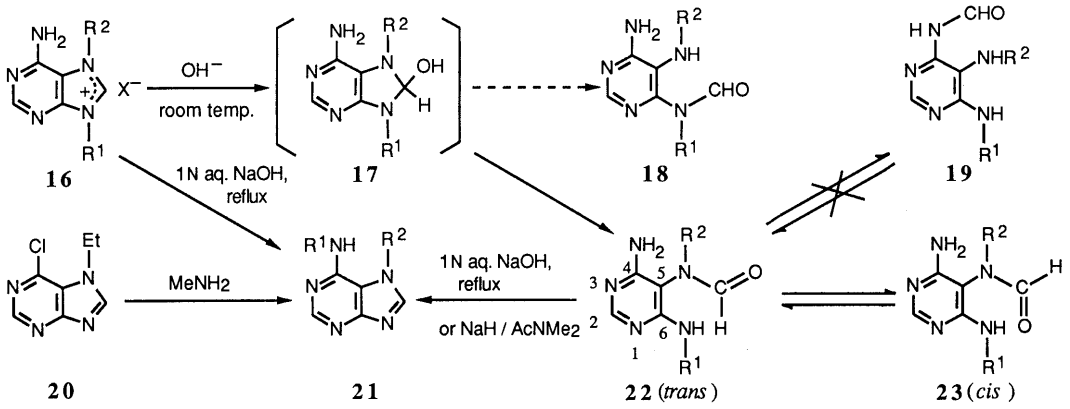
Since the N^6-methoxy derivatives **11a, b** ($R^3 = Me$; X = I) and **11c** ($R^3 = Me$; X = Br) have been converted by us into the demethoxy derivatives **16a, b** (X = I) and **16c** (X = Br) in 51—81% yields by catalytic hydrogenolysis (Raney Ni/H_2, H_2O, 1 atm, room temperature, 18—52 h),[4] the above syntheses of **11a, b** ($R^3 = Me$; X = I) and **11c** ($R^3 = Me$; X = Br) from **9a** ($R^3 = Me$) through **15a, b** ($R^3 = Me$; X = I) and **15c** ($R^3 = Me$; X = Br), respectively, are tantamount to new formal syntheses of these 7,9-dialkyladeninium salts (**16**). The N^6-ethoxy derivatives **11d, e** ($R^3 = Et$; X = I) likewise underwent catalytic hydrogenolysis to afford the known 7,9-dialkyladeninium salts **16d, e** (X = I) in 82% and 63% yields, respectively. Alternatively, similar hydrogenolyses of crude **15a, b** ($R^3 = Me$; X = I), **15c** ($R^3 = Me$; X = Br), and **15d** ($R^3 = Et$; X = I) and spontaneous cyclizations of the resulting dealkoxy derivatives directly produced the desired 7,9-dialkyladeninium salts **16a, b** (X = I), **16c** (X = Br), and **16d** (X = I) in 19—45% overall yields (from the corresponding formamidoimidazoles **9**).

The observed preferential N(3)-substitution on the imidazole ring of **9** ($R^3 = Me$ or Et) presents a marked contrast to the previous finding[18] that **9** is alkylated almost exclusively on the 5-formamido nitrogen atom to give **14** when treated with alkyl halide in the presence of NaH or anhydrous K_2CO_3.

Chemical Behavior

Ring Opening and Reclosure Leading to Isomeric N^6,7-Dialkyladenines The imidazolium structure of **16** suggests an electron deficiency at the C(8) atom, which may allow nucleophiles to attack this position.[22] In practice, the adeninium salts **16** were all unstable under mild alkaline conditions. On treatment with 0.5 N aqueous Na_2CO_3 at room temperature for 30 min, 7,9-dimethyladeninium iodide [**16a** (X = I)] produced the ring-opened derivative **22a** in 56% yield (Chart 2). Replacement of the inorganic base by Amberlite CG-400 (OH^-) in the above treatment also afforded **22a** in 83% yield. Similar treatments of other 7,9-dialkyladeninium salts, such as **16b, d, e** (X = I), **16c** (X = Br), and **16f** ($X = ClO_4$),[3] with aqueous Na_2CO_3 or the ion-exchange resin gave the corresponding ring-opened derivatives **22b—f** in 58—83% yields.

Characterization of all the ring-opened derivatives as 4-amino-6-alkylamino-5-(*N*-alkylformamido)pyrimidines (type **22**) was based on their ultraviolet (UV) spectra, which



a: $R^1 = R^2 = Me$ **b**: $R^1 = Me$; $R^2 = Et$ **c**: $R^1 = Me$; $R^2 = PhCH_2$

d: $R^1 = Et$; $R^2 = Me$ **e**: $R^1 = R^2 = Et$ **f**: $R^1 = Et$; $R^2 = PhCH_2$

g: $R^1 = PhCH_2$; $R^2 = Et$

Chart 2

turned out to be similar to that of 4-amino-5-(ethoxycarbonylamino)-6-(propylamino)pyrimidine[23] or of its 6-(ribofuranosylamino) analogue,[23] and on their proton nuclear magnetic resonance (^{1}H-NMR) spectra in Me_2SO-d_6. For example, **22b** exhibited proton signals at δ 0.99 [3H, t, J=7.3 Hz, C(5)-NCH$_2$Me], 2.75 [3H, d, J=4.6 Hz, C(6)-NHMe], 3.20—3.65 [2H, m, C(5)-NCH$_2$-Me],[24] 6.18 [2H, dull s, C(4)-NH$_2$], 6.47 [1H, q, J=4.6 Hz, C(6)-NHMe], 7.77 (1H, s, CHO), and 7.89 [1H, s, C(2)-H]. The observation of the presence of a vicinal interproton coupling with J=4.6 Hz in the C(6)-NHMe proton system as well as the two-proton dull singlet at δ 6.18, assignable to the C(4)-NH$_2$ protons, supported the correctness of the 5-(*N*-ethylformamido) structure and ruled out the possibility of the alternative, isomeric structures **18b** and **19b** (the latter may be formed from **22b** through intramolecular transformylation) and of the pseudo-base structure **17b**. The distinction between the formyl and C(2)-H proton signals was made by analogy with the case of **22a**, which displayed proton signals in Me_2SO-d_6 at δ 2.74 (minor, s)[25] and 2.74 (major, d, J=4.6 Hz) [3H, C(6)-NMe], 2.90 [3H, d, J=0.5 Hz, C(5)-N(CHO)Me], 6.22 [2H, dull s, C(4)-NH$_2$], 6.54 [1H, q, J=4.6 Hz, C(6)-NHMe], 7.76 [1H, d, J=0.5 Hz, C(5)-N(CHO)Me], and 7.87 [1H, s, C(2)-H]. Comparison of this spectrum of **22a** with that of the C(2)-deuterated species **26** (*vide post*) permitted unambiguous assignments of the formyl and C(2)-H proton signals. The *trans* configuration (carbonyl oxygen *trans* to pyrimidine ring) of the formamido moiety in **22a**—**f** was assigned on the basis of the evidence and discussion presented in the next subsection.

The C(2)-deuterated species **26** utilized in the above NMR spectroscopic study was prepared, as shown in Chart 3, by a similar ring opening of 7,9-dimethyladeninium-*2-d* iodide (**27**), which was obtained from N^6-methoxy-9-methyladenine-*2-d* (**24**)[26] by means of an isotopic version of the previously reported synthetic route[4] to **16a** (X=I) from **10a** (R^3=Me). Thus, treatment of **24** with MeI in AcNMe$_2$ at 30 °C for 6 h gave the N(7)-methylated product **25**

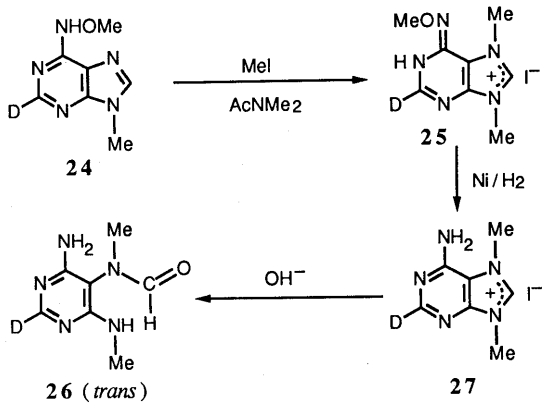
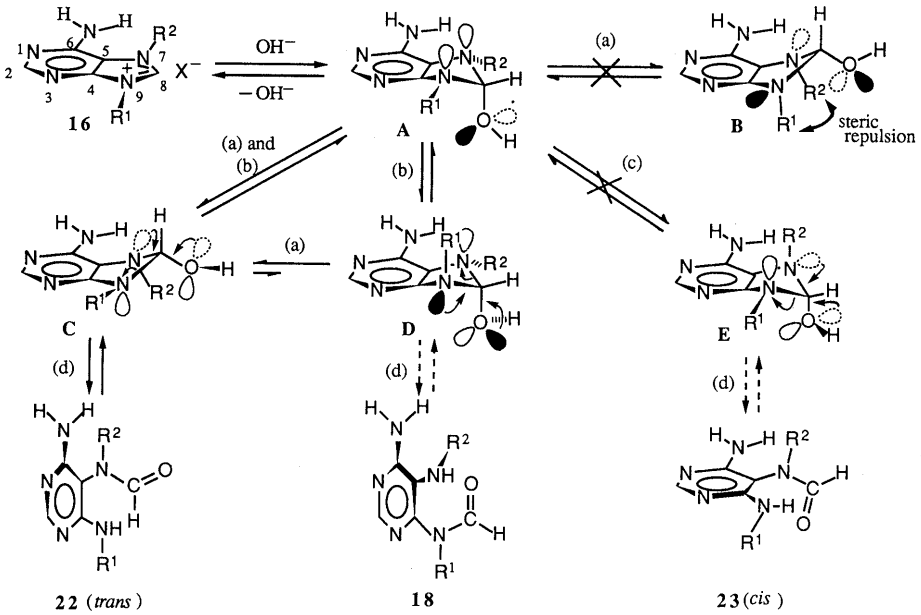


Chart 3

[^{1}H-NMR (Me_2SO-d_6) δ: 9.27 (C(8)-H)] in 55% yield. Demethoxylation of **25** by catalytic hydrogenolysis (Raney Ni/H$_2$, H$_2$O, 1 atm, room temperature, 6 h) furnished **27** [^{1}H-NMR (Me_2SO-d_6) δ: 9.56 (C(8)-H)] in 62% yield. Comparison of the ^{1}H-NMR spectra of **25** and **27** in Me_2SO-d_6 with those of the isotopically unmodified species **11a** (X=I) and **16a** (X=I) verified the correctness of our previous assignments[3b,4b] of the C(2)-H and C(8)-H proton signals of the latter two. Finally, treatment of **27** with Amberlite CG-400 (OH^-) in H$_2$O at room temperature produced the desired ring-opened derivative **26** [^{1}H-NMR (Me_2SO-d_6) δ: 7.77 (C(5)-N(CHO)Me)] in 51% yield.

It seems most likely that the formation of **22** from **16** proceeds through the tetrahedral intermediate **17** (Chart 2). A reasonable interpretation of the exclusive formation of the *trans*-formamide **22** may be given by Deslongchamps' theory of stereoelectronic control.[27] According to the theory, preferential cleavage or formation of a tetrahedral intermediate occurs when there are two lone pairs of electrons antiperiplanar to the leaving or incoming group. When the reactant cannot attain such a conformation or when the "reactive conformation" is not energetically favored, the rate of reaction will be lower. Thus, the reaction



process (a), ring reversal[28]; (b) pyramidal nitrogen [N(9)] inversion; (c) pyramidal nitrogen [N(7)] inversion; (d) bond cleavage with stereoelectronic assistance

Chart 4

TABLE I. UV Spectra of N^6,7-Dialkyladenines (**21a—f**)

Compound			UV spectra							
			95% EtOH		H_2O (pH 1)[a]		H_2O (pH 7)[b]		H_2O (pH 13)[c]	
No.	R^1	R^2	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
21a[d]	Me	Me	273[e]	13.8	279	16.8	276	15.1	276	15.0
			278	14.1						
21b	Me	Et	272.5[e]	13.7	279	16.9	276	14.9	276	14.9
			277	14.0						
21c	Me	$PhCH_2$	274[e]	12.5	280	16.0	277	13.7	277	13.6
			278	12.7						
21d	Et	Me	274[e]	14.3	282	17.7	278	16.0	278	15.8
			279	14.7						
21e	Et	Et	275[e]	13.9	281	18.0	278	15.5	278	15.8
			280	14.2						
21f	Et	$PhCH_2$	275[e]	13.1	283	17.0	279	14.8	279	14.4
			280	13.4						

a) Measured in 0.1 N aqueous HCl. *b*) Measured in 0.005 M phosphate buffer (pH 7). *c*) Measured in 0.1 N aqueous NaOH. *d*) Reported[32] data: λ_{max}^{EtOH} 272 nm (log ε 4.11), 278 (4.12); $\lambda_{max}^{0.1NHCl}$ 278 (4.24). *e*) Appeared as a shoulder.

of the 7,9-dialkyladeninium salt (**16**) with hydroxide ion must first give conformer **A** of the tetrahedral intermediate **17** under stereoelectronic control, as shown in Chart 4. Conformer **A** would be unstable because its substituents are all *cis* to each other in the five-membered ring, but the N(9)–C(8) or N(7)–C(8) bond cannot be cleaved since the bond does not lie antiperiplanar to the lone pair of electrons on the neighboring N(7) or N(9) atom, respectively, even though it could lie antiperiplanar to one of the lone pairs on the neighboring C(8)–O atom. If ring reversal[28] of conformer **A** occurs without pyramidal atomic inversions[29] about N(7) and N(9), it would produce conformer **B** in which the two alkyl groups at N(7) and N(9) are *cis* to each other and quasi-axial. However, such a conformational change should not be favored because of a severe steric repulsion between the two *N*-alkyl groups. Alternatively, if pyramidal nitrogen inversion[29] occurs at N(7) in conformer **A**, it would give conformer **E**, leading to the formation of the *cis*-formamide **23** through the N(9)–C(8) bond cleavage with stereoelectronic assistance. The process **A**→**E**, however, requires coplanarity of the N^6-NH_2 and N(7)–R^2 bonds in the transition state, and steric strain induced by the two *peri*-substituents[27f,30] should make this process improbable. Among the remaining two alternatives for the possible process of conformational change of **A**, pyramidal N(9) inversion would give conformer **D**, and ring reversal synchronized with N(9) inversion[31] would give conformer **C**. Although **D** should be able to yield the 6-formamidopyrimidine **18** through N(7)–C(8) bond cleavage, it would be more rapidly converted through ring reversal into **C**, which should be more stable than **D** because of lower steric strain induced at the *peri*-positions and of its

N(9) atom (with the lone-pair electrons almost perpendicular to the pyrimidine ring) that constitutes a part of a resonance-stabilized 4,6-diaminopyrimidine structure. Conformer **C** would then undergo cleavage of its N(9)–C(8) bond easily under stereoelectronic control to afford exclusively the *trans*-formamide **22**.

Under more drastic alkaline conditions, 7,9-dialkyladeninium salts (**16**) were found to undergo rearrangement. On treatment with boiling 1 N aqueous NaOH for 60 min, **16a, b, d, e** (X=I), **16c** (X=Br), and **16f** ($X=ClO_4$)[3] rearranged to the isomeric N^6,7-dialkyladenines (**21a—f**) in 50—91% yields (Chart 2). The assignment of the N^6,7-disubstituted structures to the rearranged products was based on their UV spectra (Table I), which were similar to that reported[32] for N^6,7-dimethyladenine (**21a**), and on the identity of **21b** with a sample synthesized from 6-chloro-7-ethylpurine (**20**)[33] and $MeNH_2$. Since the ring-opened derivative **22a** was found to cyclize to **21a** (72% yield) under the same conditions as those employed for the above direct conversion of **16a** (X=I) into **21a**, it is most likely that the rearrangement of **16** to **21** proceeds through the intermediates **17** and **22**. Cyclization of **22a** was alternatively effected with NaH in $AcNMe_2$ at room temperature for 40 min, furnishing **21a** in 84% yield.

***trans* to *cis* Isomerization of the Ring-Opened Intermediate (22)** The ring-opened derivatives **22** were also unstable in solution at room temperature. For example, **22a** was found to transform slowly into an unknown substance in H_2O at room temperature, attaining equilibrium with only a slight change in the UV spectrum of the aqueous solution. Concentration of the reaction mixture left only **22a** that was apparently less soluble, and we were unable to isolate the counterpart from the equilibrated mixture in spite of the clear detection of its presence by thin-layer chromatography (TLC). In our preliminary communication,[15] we presumed this counterpart to be the 4-formamidopyrimidine **19a**, a positional isomer derivable from **22a** by transformylation (Chart 2). However, it turned out to be the *cis*-

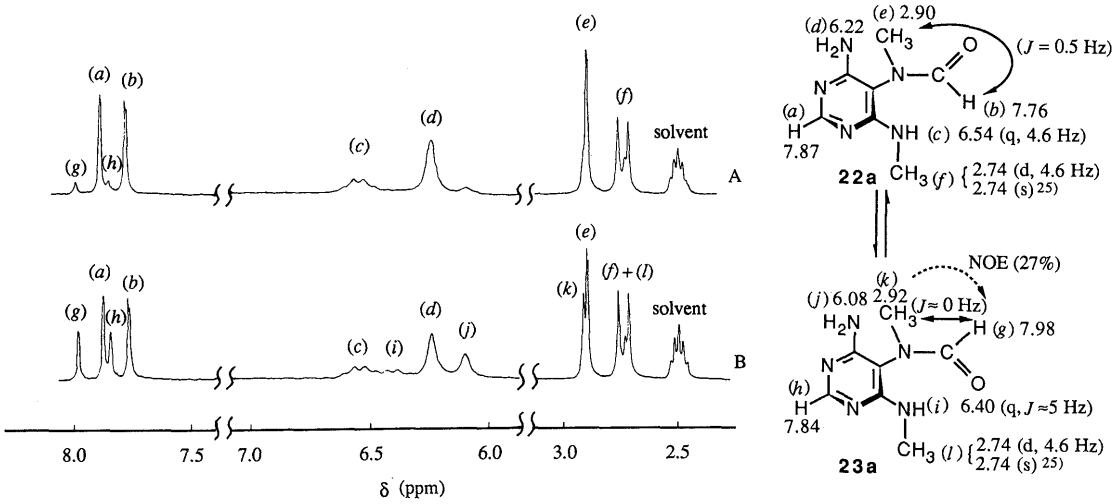


Fig. 1. The ^{1}H-NMR Spectrum of 4-Amino-6-methylamino-5-(*N*-methylformamido)pyrimidine (**22a**) in Me_2SO-d_6 at 0.06 M Concentration and 25 °C (with Magnification in Peak Height of the Signals in the δ 6.0—8.0 Region, for Clarity)

Curve A, 15 min after dissolution; curve B, 7 h after dissolution.

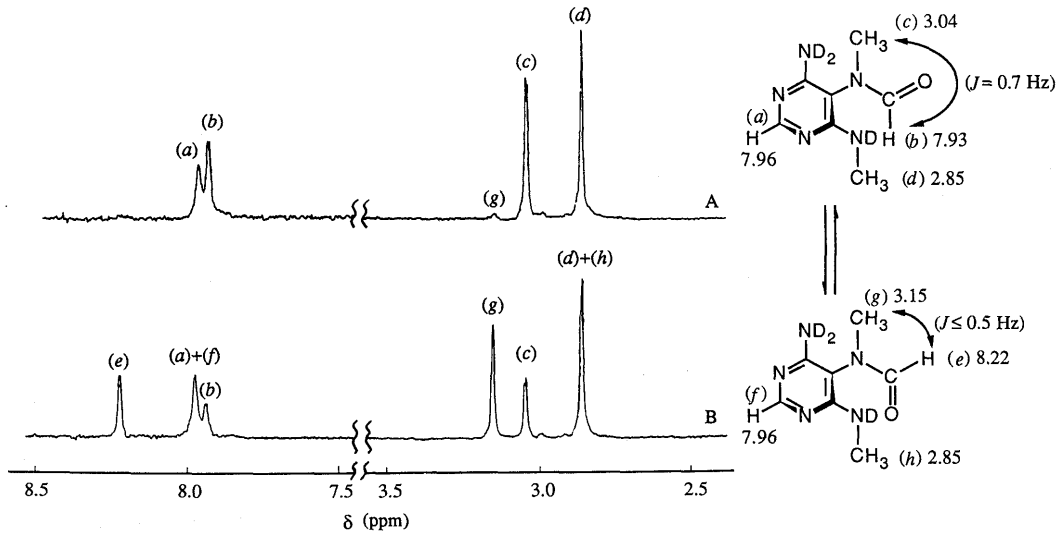


Fig. 2. The ^{1}H-NMR Spectrum of 4-Amino-6-methylamino-5-(*N*-methylformamido)pyrimidine (**22a**) in D_2O at 0.06 M Concentration and 25 °C (with Magnification in Peak Height of the Signals in the δ 7.5—8.5 Region, for Clarity)

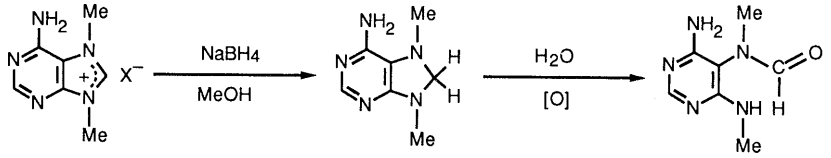
Curve A, 15 min after dissolution; curve B, 63 h after dissolution.

formamide **23a** (with carbonyl oxygen *cis* to the pyrimidine ring) rotationally isomerized from the *trans*-formamide **22a** (with carbonyl oxygen *trans* to the pyrimidine ring) on the basis of the following ^{1}H-NMR spectroscopic study.

In Me_2SO-d_6 at 25 °C, **22a** was also unstable, as indicated by changes in the ^{1}H-NMR spectrum with time. It may be seen from Fig. 1 that the spectral change during 7 h is interpretable in terms of the formation and coexistence of the isomeric *cis*-formamide **23a**, and the correctness of the structures of **22a** and **23a** is supported by the signal assignments, nuclear Overhauser effect (NOE) data, and coupling constants represented in the attached formulas. A 27% NOE observed for the signal (*g*) of **23a** on irradiation of the signal (*k*) clearly demonstrates the *cis*-formamide structure in which the formyl and *N*-methyl protons are in close proximity. The *trans* coupling with $J=0.5$ Hz found for the signals (*b*) and (*e*) of **22a** and virtually no coupling between (*g*) and (*k*) of **23a** are in general agreement with the *trans* and *cis* coupling constants reported for other *N*-methylformamides.[34,35] An upfield shift of the formyl proton signal of **22a** by 0.22 ppm, relative to that of **23a**, is most likely due to the proximity of the aromatic ring[27h,35e,36] which is considered[36b-e,37] to lie perpendicular to the plane of the formamide moiety. Although the difference in chemical shift between the C(5)-NMe signals [(*e*) and (*k*)] of **22a** and **23a** is only 0.02 ppm, the observed shielding in **22a** may be explained in terms of the effect of the carbonyl group[34,36e,38] in close proximity. The spectral changes observed at 80 °C did not differ significantly from those at 25 °C. Figure 2 shows a change in the ^{1}H-NMR spectrum of **22a** in D_2O at 25 °C during 63 h, which also implies a partial formation of the *cis*-formamide **23a** in deuterated form. All signals could reasonably be assigned, as indicated in the attached formulas, by analogy with the above case in Me_2SO-d_6. The absence of any signals in the δ 7.9—4.5 region except for that of HDO excludes the possibility of an alternative pseudo-base structure (**17a** or **33a**).[27i,39]

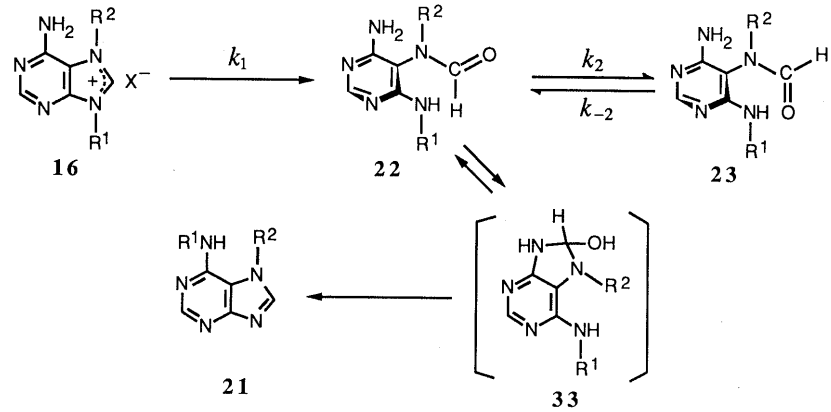
In Me_2SO-d_6 at 25 °C, compounds **22b—f** also underwent similar ^{1}H-NMR spectral changes indicative of equilibration with the corresponding *cis*-isomers **23b—f**, and equilibration between **22a** and **23a** in several solvents was confirmed by a kinetic study (*vide post*). It is of interest to note that a similar *trans–cis* isomerization has recently been reported for 2,6-diamino-4-hydroxy-5-(*N*-methylformamido)pyrimidine, a structurally related formamide system.[40] However, it is remarkable that we were able to isolate the *trans*-formamides **22a—f** at room temperature in pure, crystalline form[37e] in the present study. The reason for such ready isolation of the *trans*-isomers will be discussed in the subsection on the kinetic study.

Reduction with $NaBH_4$ On treatment with $NaBH_4$ in MeOH at room temperature for 20 min, 7,9-dimethyladeninium iodide [**16a** (X = I)] furnished the 7,8-dihydro derivative **28** in 84% yield (Chart 5). The ^{1}H-NMR spectrum of **28** in Me_2SO-d_6 showed signals at δ 2.64 and 2.73 (3H each, s, NMe's), 4.33 [2H, s, C(8)-H's], 5.70 (2H, br s, NH_2), and 7.67 [1H, s, C(2)-H]. The upfield shift of the two N-Me signals, relative to those of **16a**,[4b] supported the structure **28** saturated in the imidazole moiety. In H_2O at 60 °C, **28** slowly decomposed to give the ring-opened



16a (X = I) **28** **22a**

Chart 5



16 **22** **23**

21 **33**

a: $R^1 = R^2 = Me$ **b**: $R^1 = Me$; $R^2 = Et$

c: $R^1 = Me$; $R^2 = PhCH_2$ **d**: $R^1 = Et$; $R^2 = Me$

e: $R^1 = R^2 = Et$ **f**: $R^1 = Et$; $R^2 = PhCH_2$

g: $R^1 = PhCH_2$; $R^2 = Et$

Chart 6

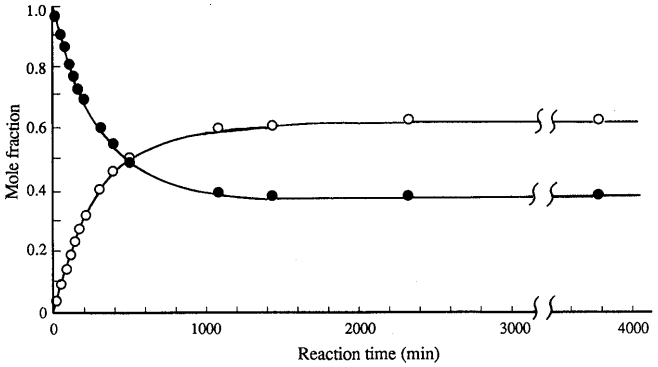


Fig. 3. Variation of the Concentrations of the Two Components with Time in the Isomerization of **22a** (—●—) to **23a** (—○—) in D_2O at 25 °C

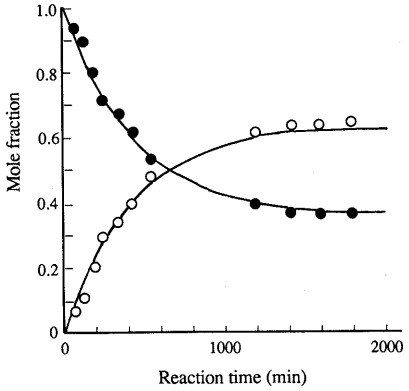


Fig. 4. Variation of the Concentrations of the Two Components with Time in the Isomerization of **22a** (—●—) to **23a** (—○—) in 0.1 M Carbonate Buffer (pH 9.84) at Ionic Strength 0.50 and 25 °C

derivative **22a** in 49% yield. This conversion seems most likely to proceed through initial dehydrogenation in the dihydroimidazole moiety followed by hydrolytic cleavage. The above result of the $NaBH_4$ reduction of **16a** (X=I) is in line with those[41] reported for 7,9-disubstituted purines.

Kinetic Study Chart 6 represents the system of reactions that produces **21** from **16** through **22** and includes the competitive isomerization of **22** to equilibrate with **23**. First of all, the time-course of the isomerization of **22a** to **23a** in D_2O at 25 °C was followed by means of ^{1}H-NMR spectroscopic analysis. It may be seen from Fig. 3 that equilibrium between **22a** and **23a**, where they existed in a ratio of 38 : 62, was established in *ca.* 25 h. On treatment of these kinetic data in the usual manner,[42] the reactions in both directions (Chart 6) were found to obey pseudo-first-order kinetics with $k_2^* = 2.10 \times 10^{-3}\,\mathrm{min}^{-1}$ ($3.50 \times 10^{-5}\,\mathrm{s}^{-1}$), $k_{-2} = 1.28 \times 10^{-3}\,\mathrm{min}^{-1}$ ($2.14 \times 10^{-5}\,\mathrm{s}^{-1}$), and $K_{eq} = k_2/k_{-2} = 1.64$. The free energies of activation for this interconversion were then calculated by use of the Eyring equation,[43] $k = \boldsymbol{k}T/h \cdot \exp(-\Delta G^{\ddagger}/RT)$ where $\boldsymbol{k}$ is the Boltzmann constant and h is Planck's constant, giving $\Delta G^{\ddagger}$ (**22a**→**23a**) = 23.5 kcal/mol and $\Delta G^{\ddagger}$ (**23a**→**22a**) = 23.8 kcal/mol. A similar approach revealed that in Me_2SO-d_6 at 25 °C **22a** came to equilibrium with **23a** in 3 h, where the *trans*-formamide **22a** was favored over the *cis*-formamide **23a** in a ratio of 67 : 33 ($K_{eq} = 0.49$).

Figure 4 shows the time-course of the same isomerization in H_2O at pH 9.84 (ionic strength 0.50) and 25 °C as followed by high-performance liquid chromatographic (HPLC) analysis. It may be seen that equilibrium (**22a** : **23a** = 36 : 64) was established within *ca.* 30 h. Treatment of these kinetic data in a manner similar to that described above for the case in D_2O gave the values $k_2 = 1.49 \times 10^{-3}\,\mathrm{min}^{-1}$, $k_{-2} = 0.84 \times 10^{-3}\,\mathrm{min}^{-1}$, $K_{eq} = k_2/k_{-2} = 1.78$, $\Delta G^{\ddagger}$ (**22a**→**23a**) = 23.7 kcal/mol, and $\Delta G^{\ddagger}$ (**23a**→**22a**) = 24.0 kcal/mol. Barriers to rotation about the C–N bond of carboxamides are known to be affected by the nature of the solvent, and polar solvents tend to increase the barrier by stabilizing the dipolar resonance structures of the amides.[37e] The observed slow isomerization in D_2O or in H_2O (pH 9.84), relative to that in Me_2SO-d_6, is in general agreement with this tendency. The free energies of activation calculated for **22a**→**23a** (23.7 kcal/mol) and **23a**→**22a** (24.0 kcal/mol) in H_2O at pH 9.84 and 25 °C provide a theoretical basis for our success in isolation of the *trans* isomer **22a** in pure, crystalline form from the reaction mixture, reflecting the steric effect exerted in this formamide system. However, our lack of success in isolation of a pure *cis* isomer (**23a**) is probably owing to its higher solubility in H_2O and in recrystallization solvents, which allows only the less soluble *trans* isomer **22a** to crystallize out of a mixture solution, resulting in a complete shift of equilibrium to the *trans* isomer side.

In the above kinetic run in H_2O, the formation of **21a** was not detected at all, indicating that the cyclization of **22a** to **21a** is slow enough to allow the other steps to be treated separately from it. Thus, the hydrolytic ring opening of **16a** (X=ClO_4)[3] in H_2O at pH 9.84 (ionic strength 0.50) and 25 °C was followed by means of HPLC or UV spectrophotometric analysis, leading to the results illustrated in Fig. 5. The semilogarithmic plots of mole fractions of the residual substrate [**16a** (X=ClO_4)] against time indicated that the reaction obeyed a fairly good pseudo-first-order kinetics with $k_1 = 5.47 \times 10^{-3}\,\mathrm{min}^{-1}$. The observed variation of the concentration of each of the three components [**16a** (X=ClO_4), **22a**, and **23a**] with time is in

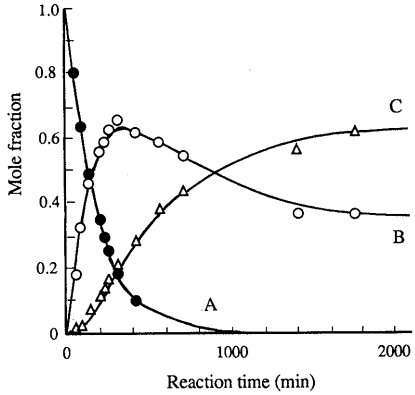


Fig. 5. Variation of the Concentrations of the Three Components with Time in the Hydrolysis of **16a** (X=ClO_4) in 0.1 M Carbonate Buffer (pH 9.84) at Ionic Strength 0.50 and 25 °C

●, **16a** (X=ClO_4); ○, **22a**; △, **23a**.
Solid lines A, B, and C represent mole fractions calculated from the following equations:

curve A: $[\mathbf{16a}]/[\mathbf{16a}]_0 = \exp(-5.47 \times 10^{-3}t)$
curve B: $[\mathbf{22a}]/[\mathbf{16a}]_0 = 1 - ([\mathbf{16a}]/[\mathbf{16a}]_0) - ([\mathbf{23a}]/[\mathbf{16a}]_0)$
curve C: $[\mathbf{23a}]/[\mathbf{16a}]_0 = 0.475 \cdot \exp(-5.47 \times 10^{-3}t) - 1.11 \cdot \exp(-2.33 \times 10^{-3}t) + 0.639$

where the quantities in square brackets represent the concentrations; $[\mathbf{16a}]_0$ is the initial concentration of **16a** (X=ClO_4); and t is the reaction time in min.

Table II. Rate Constants (k_1) for the Ring Opening of 7,9-Dialkyladeninium Salts (**16**) in H_2O at pH 9.84, 25 °C, and Ionic Strength 0.50

Substrate				Ring opening	
No.	R^1	R^2	X	$k_1 \times 10^4$ (min^{-1})	Relative rate
16a	Me	Me	ClO_4	54.7	1
16b	Me	Et	ClO_4	6.72	0.12
16c	Me	$PhCH_2$	Br	190	3.47
16d	Et	Me	ClO_4	23.8	0.44
16e	Et	Et	ClO_4	2.63	0.05
16f	Et	$PhCH_2$	ClO_4	79.4	1.45
16g	$PhCH_2$	Et	ClO_4	83.1	1.52

good agreement with that calculated from the equations shown in the legend to Fig. 5. These equations were obtained by assuming that the system of reactions is composed of consecutive first-order reactions, **16a** (X = ClO_4)→**22a**⇌**23a** (Chart 6) where $k_1 = 5.47 \times 10^{-3}\ min^{-1}$, $k_2 = 1.49 \times 10^{-3}\ min^{-1}$, and $k_{-2} = 0.84 \times 10^{-3}\ min^{-1}$ (*vide supra*).[44] Accordingly, it is clear that the rearrangement of **16** to **21** involves the reaction sequence represented in Chart 6, where the pseudo-base **33** must be another intermediate. The conversion **22**→**33**→**21** should proceed under stereoelectronic control according to a process parallel to that shown in Chart 4 for **22**→**C**→**A**→**16**, and the conversion **23**→**33**→**21** (without passing through **22**) would not be probable for a reason analogous to the reason why the process **23**⇄**E**⇌**A**⇄**16** (Chart 4) is unfavored (*vide supra*).

We next determined the rates of the ring openings of other 7,9-dialkyladeninium salts (type **16**) in order to investigate the effect of alkyl groups at the 7- and 9-positions. Kinetic runs with **16b** (X = ClO_4), **16c** (X = Br),[4] **16d—f** (X = ClO_4),[4b] and **16g** (X = ClO_4)[4] were handled as in the case of **16a** (X = ClO_4), giving typical first-order plots. Table II lists the rate constants (k_1) obtained from these plots. It may be seen that the replacement of the methyl group at the 7- or 9-position by the ethyl group retards the ring opening, and the effect of the N(7)-Et group is even greater. Since there could be little difference in electron-donating character between the methyl and ethyl groups,[45] the observed retardation is probably owing to the steric bulk of the latter, hindering attack by hydroxide ion at the C(8) atom. On the other hand, the benzyl group at either position accelerates the reaction. This rate enhancement may be attributed to the electron-withdrawing nature, relative to an alkyl group, of the benzyl group,[45,46] lowering the electron density of C(8).

Knowing the rate constant for the ring opening of **16a** (X = ClO_4) under alkaline conditions, we can now compare it with those of the other three of the four possible N^x,9-dimethyladenines. As reported previously,[18b,47] the relative ease with which the adenine ring undergoes hydrolytic fission has been found to decrease in the order 3,9- > 7,9- > 1,9- ≫ N^6,9-dimethyladenine.

Conclusion

An alternative synthesis of 7,9-dialkyladeninium salts (**16**) has now become feasible through a generally applicable route starting from *N'*-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidine (**9**). The route consists of alkylation of **9** in the absence of base, followed by hydrogenolysis of the *N'*-alkoxy group and cyclization (or *vice versa*).[48]

The observed facile ring opening of **16** under mild alkaline conditions and the ready cyclization of the resulting formamidopyrimidines **22** to give N^6,7-dialkyladenines (**21**) form a part of a newly established synthetic route to **21** from 9-alkyladenine (**7**) (Charts 1 and 2). They also afford a better understanding of similar reactions of agelasine (type **3**),[5] ageline A (agelasine F[6b]) (**5**),[8] ageline B (**6**),[8] N^6-benzoyl-9-benzyl-7-methyladeninium iodide,[41c,d] and N^6-benzoyl-9-benzyl-7-phenacyladeninium bromide,[41c,d] upon which the correctness of their 7,9-disubstituted adenine structures has relied. Moreover, a facile isomerization reported[8] for the ring-opened derivatives (type **22**) of ageline A (**5**) and ageline B (**6**) may be explained in terms of *trans–cis* equilibration similar to that described above for the *trans*-formamide **22a** and the *cis*-formamide **23a**.

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 18*b* for details of instrumentation and measurements. However, the internal standard used for measurements of ^{1}H-NMR spectra in D_2O was sodium 3-(trimethylsilyl)propanesulfonate. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

N^6-Methoxy-7,9-dimethyladeninium Iodide [11a (R^3 = Me; X = I)] A mixture of **9a** (R^3 = Me)[21] (3.94 g, 20 mmol) and MeI (14.2 g, 100 mmol) in $HCONMe_2$ (DMF) (20 ml) was stirred at 30 °C for 41 h. The precipitate that resulted was filtered off, washed successively with a little DMF and EtOH, and dried to yield a first crop (2.02 g, 31%) of **11a** (R^3 = Me; X = I), mp 251—253 °C (dec.). The filtrate and washings were combined and concentrated *in vacuo* to leave crude **15a** (R^3 = Me; X = I) as a yellow oil, which was dissolved in EtOH (50 ml). The resulting ethanolic solution was heated under reflux for 5 h and then kept in a refrigerator for 24 h. The precipitate that deposited was filtered off and dried to give a second crop (1.93 g, 30%) of **11a** (R^3 = Me; X = I), mp 251—253 °C (dec.). The total yield of **11a** (R^3 = Me; X = I) was 3.95 g (61%). Recrystallization of the crude product from EtOH afforded a pure sample as colorless needles, mp 251—253 °C (dec.). This sample was identical [by comparison of the infrared (IR) spectrum and paper partition chromatographic (PPC) mobility] with authentic **11a** (R^3 = Me; X = I).[3]

7-Ethyl-N^6-methoxy-9-methyladeninium Iodide [11b (R^3 = Me; X = I)] A mixture of **9a** (R^3 = Me)[21] (197 mg, 1 mmol) and EtI (780 mg, 5 mmol) in DMF (1 ml) was stirred at 50 °C for 93 h. The reaction mixture was worked up as described above for **11a** (R^3 = Me; X = I), giving **11b** (R^3 = Me; X = I), mp 249.5—250.5 °C (dec.), in 44% yield. This sample was identical (by comparison of the IR spectrum and PPC mobility) with authentic **11b** (R^3 = Me; X = I).[4]

7-Benzyl-N^6-methoxy-9-methyladeninium Bromide [11c (R^3 = Me; X = Br)] A mixture of **9a** (R^3 = Me)[21] (197 mg, 1 mmol) and $PhCH_2Br$ (513 mg, 3 mmol) in DMF (1 ml) was stirred at 30 °C for 46 h or at 100 °C for 4 h. Either reaction mixture was worked up as described above for **11a** (R^3 = Me; X = I), affording **11c**·H_2O (R^3 = Me; X = Br), mp 227.5—232.5 °C (dec.), in 41% or 51% yield, respectively. Recrystallization from EtOH gave colorless needles, mp 235—236 °C (dec.), identical (by comparison of the IR spectrum and PPC mobility) with an authentic sample.[4]

N^6-Ethoxy-9-ethyl-7-methyladeninium Iodide [11d (R^3 = Et; X = I)] A mixture of **9d** (R^3 = Et)[21] (680 mg, 3 mmol) and MeI (2.13 g, 15 mmol) in DMF (3 ml) was stirred at 30 °C for 3 d. The reaction mixture was worked up as described above for **11a** (R^3 = Me; X = I), giving crude **11d** (R^3 = Et; X = I), mp 232.5—233.5 °C (dec.), in 53% yield. Recrystallization from EtOH furnished an analytical sample as colorless needles, mp 239—241.5 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 291 nm (ε 8100); $\lambda_{max}^{H_2O}$ (pH 1) 284 (10000); $\lambda_{max}^{H_2O}$ (pH 7) 284 (9700); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me_2SO-d_6) δ: 1.28 (3H, t, *J* = 7 Hz, N^6-$OCH_2\underline{Me}$), 1.44 [3H, t, *J* = 7 Hz, N(9)-$CH_2\underline{Me}$], 3.99 [3H, s, N(7)-Me], 4.09 (2H, q, *J* = 7 Hz, N^6-$O\underline{CH_2}Me$), 4.23 [2H, q, *J* = 7 Hz, N(9)-$\underline{CH_2}Me$], 7.82 [1H, d, *J* = 3.4 Hz, C(2)-H], 9.32 [1H, s, C(8)-H], 11.20 [1H, br, N(1)-H]. *Anal.* Calcd for $C_{10}H_{16}IN_5O$: C,

34.40; H, 4.62; N, 20.06. Found: C, 34.16; H, 4.64; N, 20.10.

N^6-Ethoxy-7,9-diethyladeninium Iodide [11e (R^3 = Et; X = I)] A mixture of **9d** (R^3 = Et)[21] (680 mg, 3 mmol) and EtI (2.34 g, 15 mmol) in DMF (3 ml) was stirred at 50 °C for 3 d. The reaction mixture was worked up as described above for **11a** (R^3 = Me; X = I), producing crude **11e** (R^3 = Et; X = I), mp 228—231 °C (dec.), in 47% yield. Recrystallization from EtOH gave an analytical sample as colorless prisms, mp 233.5—235 °C (dec.). *Anal.* Calcd for $C_{11}H_{18}IN_5O$: C, 36.38; H, 5.00; N, 19.28. Found: C, 36.15; H, 5.13; N, 19.07.

7,9-Dimethyladeninium Iodide [16a (X = I)] A mixture of **9a** (R^3 = Me)[21] (394 mg, 2 mmol) and MeI (1.42 g, 10 mmol) in DMF (2 ml) was stirred at 30 °C for 41 h. The reaction mixture was concentrated *in vacuo*, and the residue [presumed to contain **15a** (R^3 = Me; X = I)] was dissolved in 30% (v/v) aqueous EtOH (30 ml). The resulting solution was hydrogenated over Raney Ni W-2 catalyst[49] (1 ml) at atmospheric pressure and room temperature for 22 h. The catalyst was removed by filtration and washed with 30% (v/v) aqueous EtOH. The filtrate and washings were combined and concentrated to dryness *in vacuo* to leave a greenish solid. Recrystallization of the solid from 90% (v/v) aqueous EtOH furnished a first crop (162 mg) of **16a** (X = I) as colorless needles, mp 253—255 °C (dec.), identical (by comparison of the IR spectrum and PPC mobility) with an authentic sample.[4] The mother liquor from this recrystallization was then concentrated *in vacuo*, and the residual solid was recrystallized from 90% (v/v) aqueous EtOH to yield a second crop (100 mg) of **16a** (X = I), mp 253—255 °C (dec.). The total yield of **16a** (X = I) was 262 mg [45% from **9a** (R^3 = Me)].

7-Ethyl-9-methyladeninium Iodide [16b (X = I)] A mixture of **9a** (R^3 = Me)[21] (394 mg, 2 mmol) and EtI (1.56 g, 10 mmol) in DMF (2 ml) was stirred at 50 °C for 93 h. The reaction mixture was concentrated *in vacuo* to leave an oil presumed to contain **15b** (R^3 = Me; X = I), which was dissolved in 20% (v/v) aqueous EtOH (90 ml). The resulting solution was hydrogenated for 11 h as described above for **16a** (X = I), and the crude product was recrystallized from 95% (v/v) aqueous EtOH to give **16b** (X = I) in 42% yield [from **9a** (R^3 = Me)] as colorless scales, mp 236.5—239 °C (dec.). This sample was identical (by comparison of the IR spectrum and PPC mobility) with authentic **16b** (X = I).[4]

7-Ethyl-9-methyladeninium Perchlorate [16b (X = ClO_4)] A solution of $NaClO_4$ (184 mg, 1.5 mmol) in H_2O (0.5 ml) was added to a solution of **16b** (X = I) (305 mg, 1 mmol) in warm H_2O (1.5 ml). After cooling, the precipitate that resulted was filtered off, washed with a little H_2O, and dried to give **16b** (X = ClO_4) (228 mg, 82%), mp 261.5—262.5 °C (dec.). Recrystallization from H_2O furnished an analytical sample as colorless prisms, mp 279—280 °C (dec.); UV $\lambda_{max}^{95\%\,EtOH}$ 272 nm (ε 11600); $\lambda_{max}^{H_2O}$ (pH 1) 268 (11800); $\lambda_{max}^{H_2O}$ (pH 7) 269 (12100); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me_2SO-d_6) δ: 1.46 [3H, t, J = 7 Hz, N(7)-CH_2Me], 3.88 [3H, s, N(9)-Me], 4.58 [2H, q, J = 7 Hz, N(7)-CH_2Me], 7.96 (2H, dull s, NH_2), 8.47 [1H, s, C(2)-H], 9.62 [1H, s, C(8)-H]. *Anal.* Calcd for $C_8H_{12}ClN_5O_4$: C, 34.61; H, 4.36; N, 25.22. Found: C, 34.63; H, 4.39; N, 25.13.

7-Benzyl-9-methyladeninium Bromide [16c (X = Br)] A mixture of **9a** (R^3 = Me)[21] (394 mg, 2 mmol) and $PhCH_2Br$ (1.03 g, 6 mmol) in DMF (2 ml) was stirred at 30 °C for 46 h. The precipitate that resulted was collected by filtration and washed with a little DMF. The filtrate and washings were combined and concentrated *in vacuo* to leave an orange oil, which was triturated with ether several times in order to remove the unaltered $PhCH_2Br$. The residual oil and the above precipitate were combined and dissolved in H_2O (90 ml), and the resulting aqueous solution was hydrogenated over Raney Ni W-2 catalyst[49] (1 ml) at atmospheric pressure and room temperature for 50 h. The reaction mixture was then worked up as described above for **16a** (X = I), giving crude **16c** (X = Br) (250 mg, 37%) as a greenish solid, mp 217—218 °C (dec.). Recrystallization from 95% (v/v) aqueous EtOH yielded a pure sample as colorless prisms, mp 224.5—225.5 °C (dec.), identical (by comparison of the IR spectrum and PPC mobility) with authentic **16c** (X = Br).[4]

9-Ethyl-7-methyladeninium Iodide [16d (X = I)] i) From **11d** (R^3 = Et; X = I): A solution of **11d** (R^3 = Et; X = I) (210 mg, 0.6 mmol) in H_2O (25 ml) was hydrogenated over Raney Ni W-2 catalyst[49] (1 ml) at atmospheric pressure and room temperature for 6 h. The catalyst was removed by filtration and washed with H_2O. The filtrate and washings were combined and concentrated to dryness *in vacuo* to leave crude **16d** (X = I) (150 mg, 82%) as a colorless solid, mp 260—262 °C (dec.). Recrystallization from 90% (v/v) aqueous EtOH yielded a pure sample as colorless needles, mp 268—270 °C (dec.), identical (by comparison of the IR spectrum) with authentic **16d** (X = I).[4]

ii) From **15d** (R^3 = Et; X = I): A mixture of **9d** (R^3 = Et)[21] (2.25 g, 10 mmol) and MeI (7.10 g, 50 mmol) in DMF (10 ml) was stirred at 30 °C for 72 h. The reaction mixture was concentrated *in vacuo*, and the residue [presumed to contain **15d** (R^3 = Et; X = I)] was dissolved in H_2O (100 ml). Hydrogenation of the resulting aqueous solution (at 50—60 °C for 14 h) and work-up of the reaction mixture were carried out in a manner similar to that described above under item (i), and the crude product was recrystallized from 90% (v/v) aqueous EtOH to yield **16d** (X = I) (580 mg) in 19% yield [from **9d** (R^3 = Et)].

7,9-Diethyladeninium Iodide [16e (X = I)] A solution of **11e** (R^3 = Et; X = I) (145 mg, 0.4 mmol) in H_2O (20 ml) was hydrogenated over Raney Ni W-2 catalyst[49] (1.5 ml) at atmospheric pressure and room temperature for 10 h. The reaction mixture was worked up as described above for **16d** (X = I) under method (i), giving crude **16e** (X = I) (80 mg, 63%) as a colorless solid, mp 249—251 °C (dec.). Recrystallization from EtOH afforded a pure sample as colorless needles, mp 264.5—265.5 °C (dec.), identical (by comparison of the IR spectrum) with authentic **16e** (X = I).[4]

(*E*)-4-Amino-6-methylamino-5-(*N*-methylformamido)pyrimidine (22a) i) By Treatment of **16a** (X = I) with Aqueous Na_2CO_3: A mixture of **16a** (X = I)[4] (262 mg, 0.9 mmol) and 0.5 N aqueous Na_2CO_3 (18 ml) was stirred at room temperature for 30 min. After addition of 1 N aqueous HCl (8 ml), the reaction mixture was concentrated to dryness *in vacuo*. The residue was washed with H_2O (2 ml) and dried to give **22a** (92 mg, 56%) as a colorless solid, mp 242—244 °C (dec.). For purification, the solid was dissolved in MeOH (25 ml) at room temperature, and the resulting methanolic solution was concentrated *in vacuo* to a volume of *ca.* 1 ml and then cooled in a refrigerator, producing **22a** as colorless prisms, mp 247—248 °C (dec.); MS *m/z*: 181 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 223 nm (ε 44800), 257 (5620); $\lambda_{max}^{H_2O}$ (pH 1) 223 (29500), 268 (12900); $\lambda_{max}^{H_2O}$ (pH 7) 221 (41200), 258 (6080); $\lambda_{max}^{H_2O}$ (pH 13) 221 (41200), 257 (6050); IR ν_{max}^{Nujol} cm^{-1}: 3420, 3370, 3340, and 3230 (NH_2 and NH), 1660 (HCON); ^{1}H-NMR (see the text and Figs. 1 and 2). *Anal.* Calcd for $C_7H_{11}N_5O$: C, 46.40; H, 6.12; N, 38.65. Found: C, 46.54; H, 6.24; N, 38.89.

ii) By Treatment of **16a** (X = I) with Amberlite CG-400 (OH^-): A solution of **16a** (X = I)[4] (873 mg, 3 mmol) in H_2O (18 ml) was passed through a column of Amberlite CG-400 (OH^-) (45 ml), and the column was eluted with H_2O. The eluate (130 ml) was concentrated *in vacuo* to leave a colorless solid, which was washed with MeOH (5 ml) to leave **22a** (374 mg, 69%) as a colorless solid, mp 247—248 °C (dec.). The washings were concentrated *in vacuo* to a volume of *ca.* 1 ml and then cooled in a refrigerator, yielding a second crop (75 mg, 14%) of **22a**, mp 247—248 °C (dec.). The total yield of **22a** was 449 mg (83%). These samples were identical [by comparison of the IR spectra and thin-layer chromatographic (TLC) mobilities] with the one obtained by method (i).

(*E*)-4-Amino-5-(*N*-ethylformamido)-6-methylaminopyrimidine (22b) A solution of **16b** (X = I)[4] (458 mg, 1.5 mmol) in H_2O (3 ml) was treated with Amberlite CG-400 (OH^-) in a manner similar to that described above for **22a** under method (ii), yielding **22b** (230 mg, 78%) as a colorless solid, mp 204—208 °C (dec.). Recrystallization of the solid by dissolving it in EtOH (40 ml) and concentrating the ethanolic solution to a volume of *ca.* 3 ml gave a pure sample as colorless prisms, mp 206—208 °C (dec.); MS *m/z*: 195 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 223 nm (ε 43700), 258 (5660); $\lambda_{max}^{H_2O}$ (pH 1) 224 (28700), 268 (12900); $\lambda_{max}^{H_2O}$ (pH 7) 222 (40400), 258 (6160); $\lambda_{max}^{H_2O}$ (pH 13) 222 (38900), 258 (6190); IR ν_{max}^{Nujol} cm^{-1}: 3450, 3355, and 3240 (NH_2 and NH), 1666 (HCON). *Anal.* Calcd for $C_8H_{13}N_5O$: C, 49.22; H, 6.71; N, 35.87. Found: C, 49.36; H, 6.83; N, 35.90. The ^{1}H-NMR spectrum of this sample in Me_2SO-d_6 at 25 °C indicated the formation of the *cis* isomer (**23b**) from **22b** in a ratio of **22b** : **23b** = 77 : 23 (at 10 min after dissolution) or 56 : 44 (at 23 h); δ (**22b**) (see the text); δ (**23b**): 1.03 [t, J = 7.1 Hz, C(5)-N(CHO)CH$_2$Me], 2.75 [d, J = 4.6 Hz, C(6)-NHMe], 3.20—3.65 [m, C(5)-N(CHO)CH_2Me],[24] 6.01 [dull s, C(4)-NH_2], 6.32 [q, J = 4.6 Hz, C(6)-NHMe], 7.86 [s, C(2)-H], 8.06 [s, C(5)-N(CHO)CH$_2$Me].

(*E*)-4-Amino-5-(*N*-benzylformamido)-6-methylaminopyrimidine (22c) A mixture of **16c**·H_2O (X = Br)[4] (169 mg, 0.5 mmol) and 0.5 N aqueous Na_2CO_3 (10 ml) was stirred at room temperature for 30 min. The precipitate that resulted was filtered off, washed with a little H_2O, and dried to give **22c** (107 mg, 83%) as a colorless solid, mp 191—192 °C (dec.). Recrystallization from MeOH in a manner similar to that described above for **22a** produced a pure sample as colorless prisms, mp 191—192 °C (dec.); MS *m/z*: 257 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 223 nm (ε 40300), 258 (5620); $\lambda_{max}^{H_2O}$ (pH 1) 223 (25000), 269 (11800); $\lambda_{max}^{H_2O}$ (pH 7) 222 (36400), 259 (5770); $\lambda_{max}^{H_2O}$ (pH 13) 222 (37000), 258 (5970); IR ν_{max}^{Nujol} cm^{-1}: 3495, 3400, 3265, and 3130 (NH_2 and NH), 1666 (HCON). *Anal.* Calcd for $C_{13}H_{15}N_5O$: C, 60.69; H, 5.88; N, 27.22. Found: C, 60.51; H, 5.89; N, 27.26. The ^{1}H-NMR spectrum of this sample in Me_2SO-d_6 at 25 °C indicated the formation of the *cis* isomer (**23c**) from **22c** in a ratio of **22c** : **23c** = 67 : 33 (at 7 min after

dissolution), 63:37 (at 32 min), 64:36 (at 50 min), or 64:36 (at 69 h); δ (**22c**): 2.61 [3H, d, J=4.5 Hz, C(6)-NHMe], 4.52 and 4.64 [1H each, d, J=13.5 Hz, C(5)-N(CHO)CH$_2$Ph],[24] 5.88 [dull s, C(4)-NH$_2$], 6.12 [1H, q, J=4.5 Hz, C(6)-NHMe], 7.25 (5H, m, Ph), 7.77 [1H, s, C(2)-H], 7.89 [1H, s, C(5)-N(CHO)CH$_2$Ph]; δ (**23c**): 2.61 [d, J=4.5 Hz, C(6)-NHMe], 4.50 [dull s, C(5)-N(CHO)CH$_2$Ph],[24] 5.77 [2H, dull s, C(4)-NH$_2$], *ca.* 5.88 [dull, C(6)-NHMe], 7.25 (m, Ph), 7.75 [1H, s, C(2)-H], 8.34 [s, C(5)-N(CHO)CH$_2$Ph].

(*E*)-4-Amino-6-ethylamino-5-(*N*-methylformamido)pyrimidine (22d) Ring opening of **16d** (X=I)[4] and recrystallization of the crude product (58% yield) were effected as in the case of **22b**, affording a pure sample of **22d** as colorless prisms, mp 205—207 °C (dec.); MS *m/z*: 195 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 226 nm (ε 44000), 258 (6000); $\lambda_{max}^{H_2O}$ (pH 1) 225 (29400), 269 (13900); $\lambda_{max}^{H_2O}$ (pH 7) 224 (41500), 259 (6700); $\lambda_{max}^{H_2O}$ (pH 13) 223 (42100), 259 (6400); IR ν_{max}^{Nujol} cm^{-1}: 3410, 3330, and 3230 (NH$_2$ and NH), 1667 (HCON). *Anal.* Calcd for $C_8H_{13}N_5O$: C, 49.22; H, 6.71; N, 35.87. Found: C, 49.17; H, 6.91; N, 36.08. The ^{1}H-NMR spectrum of this sample in Me$_2$SO-d_6 at 25 °C indicated the formation of the *cis* isomer (**23d**) from **22d** in a ratio of **22d**:**23d**=88:12 (at 20 min after dissolution) or 67:33 (at 24 h); δ (**22d**): 1.05 [t, J=7 Hz, C(6)-NHCH$_2$Me], 2.90 [3H, s, C(5)-N(CHO)Me], 3.1—3.5 [m, C(6)-NHCH$_2$Me], 6.22 [2H, dull s, C(4)-NH$_2$], 6.59 [1H, t, J=6 Hz, C(6)-NHCH$_2$Me], 7.76 [1H, s, C(5)-N(CHO)Me], 7.86 [1H, s, C(2)-H]; δ (**23d**): 1.05 [t, J=7 Hz, C(6)-NHCH$_2$Me], 2.92 [s, C(5)-N(CHO)Me], 3.1—3.5 [m, C(6)-NHCH$_2$-Me], 6.08 [dull s, C(4)-NH$_2$], 6.40 [t, J=6 Hz, C(6)-NHCH$_2$Me], 7.83 [s, C(2)-H], 7.98 [s, C(5)-N(CHO)Me].

(*E*)-4-Amino-6-ethylamino-5-(*N*-ethylformamido)pyrimidine (22e) Ring opening of **16e** (X=I)[4] and recrystallization of the crude product (62% yield) were carried out as in the case of **22b**, giving a pure sample of **22e** as colorless pillars, mp 161.5—162.5 °C (dec.); MS *m/z*: 209 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 226 nm (ε 43900), 258 (6100); $\lambda_{max}^{H_2O}$ (pH 1) 225 (28300), 270 (13800); $\lambda_{max}^{H_2O}$ (pH 7) 224 (41000), 259 (6600); $\lambda_{max}^{H_2O}$ (pH 13) 223 (41100), 259 (6500); IR ν_{max}^{Nujol} cm^{-1}: 3420, 3370, 3335, and 3230 (NH$_2$ and NH), 1658 (HCON). *Anal.* Calcd for $C_9H_{15}N_5O$: C, 51.66; H, 7.23; N, 33.47. Found: C, 51.41; H, 7.42; N, 33.29. The ^{1}H-NMR spectrum of this sample in Me$_2$SO-d_6 at 25 °C indicated the formation of the *cis* isomer (**23e**) from **22e** in a ratio of **22e**:**23e**=70:30 (at 20 min after dissolution) or 55:45 (at 24 h); δ (**22e**): 1.00 [t, J=7 Hz, C(6)-NHCH$_2$Me or C(5)-N(CHO)CH$_2$Me], 1.04 [t, J=7 Hz, C(5)-N(CHO)CH$_2$Me or C(6)-NHCH$_2$Me], 3.0—3.5 [m, C(5)-N(CHO)CH$_2$Me and C(6)-NHCH$_2$Me], 6.17 [2H, dull s, C(4)-NH$_2$], 6.50 [1H, t, J=6 Hz, C(6)-NHCH$_2$Me], 7.77 [1H, s, C(5)-N(CHO)CH$_2$Me], 7.87 [1H, s, C(2)-H]; δ (**23e**): 1.00 [t, J=7 Hz, C(6)-NHCH$_2$Me or C(5)-N(CHO)CH$_2$Me], 1.04 [t, J=7 Hz, C(5)-N(CHO)CH$_2$Me or C(6)-NHCH$_2$Me], 3.0—3.5 [m, C(5)-N(CHO)-CH$_2$Me and C(6)-NHCH$_2$Me], 6.01 [dull s, C(4)-NH$_2$], 6.21 [t, J=6 Hz, C(6)-NHCH$_2$Me], 7.84 [s, C(2)-H], 8.06 [s, C(5)-N(CHO)CH$_2$Me].

(*E*)-4-Amino-5-(*N*-benzylformamido)-6-ethylaminopyrimidine (22f) A mixture of **16f** (X=ClO$_4$)[4] (354 mg, 1 mmol) and 0.5 N aqueous Na$_2$CO$_3$ (20 ml) was stirred at room temperature for 90 min. The reaction mixture was worked up as in the case of **22c**, producing crude **22f** (190 mg, 70%) as a colorless solid, mp 155—155.5 °C (dec.). Recrystallization of the solid from EtOH in a manner similar to that described above for **22b** furnished a pure sample as colorless prisms, mp 155—155.5 °C (dec.); MS *m/z*: 271 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 225 nm (ε 42500), 258 (6100); $\lambda_{max}^{H_2O}$ (pH 1) 225 (25800), 271 (12700); $\lambda_{max}^{H_2O}$ (pH 7) 224 (36400), 260 (6300); $\lambda_{max}^{H_2O}$ (pH 13) 224 (36600), 260 (6300); IR ν_{max}^{Nujol} cm^{-1}: 3450, 3345, and 3230 (NH$_2$ and NH), 1655 (HCON). *Anal.* Calcd for $C_{14}H_{17}N_5O$: C, 61.98; H, 6.32; N, 25.81. Found: C, 61.80; H, 6.42; N, 26.11. The ^{1}H-NMR spectrum of this sample in Me$_2$SO-d_6 at 25 °C indicated the formation of the *cis* isomer (**23f**) from **22f** in a ratio of **22f**:**23f**=80:20 (at 3 min after dissolution), 66:34 (at 20 min), or 62:38 (at 24 h); δ (**22f**): 0.84 [3H, t, J=7 Hz, C(6)-NHCH$_2$Me], 2.9—3.3 [m, C(6)-NHCH$_2$Me], 4.43 and 4.73 [1H each, d, J=14 Hz, C(5)-N(CHO)CH$_2$Ph],[24] 5.83 [1H, t, J=5.6 Hz, C(6)-NHCH$_2$Me], 6.02 [2H, dull s, C(4)-NH$_2$], 7.26 (5H, m, Ph), 7.76 [1H, s, C(2)-H], 7.88 [1H, s, C(5)-N(CHO)CH$_2$Ph]; δ (**23f**): 0.81 [t, J=7 Hz, C(6)-NHCH$_2$Me], 2.9—3.3 [m, C(6)-NHCH$_2$Me], 4.41 and 4.57 [d, J=14 Hz, C(5)-N(CHO)CH$_2$Ph],[24] 5.59 [t, J=5.6 Hz, C(6)-NHCH$_2$Me], 5.88 [dull s, C(4)-NH$_2$], 7.26 (m, Ph), 7.74 [s, C(2)-H], 8.35 [s, C(5)-N(CHO)CH$_2$Ph].

***N*^{6}-Methoxy-7,9-dimethyladeninium-2-*d* Iodide (25)** A mixture of **24**[26] (1.08 g, 6 mmol) and MeI (3.41 g, 24 mmol) in AcNMe$_2$ (12 ml) was stirred at 30 °C for 6 h. The reaction mixture was then cooled in an ice bath for 1 h, and the precipitate that resulted was filtered off, washed with a little EtOH, and dried to give crude **25** (1.07 g, 55%), mp 242.5—244 °C (dec.). Recrystallization from 90% (v/v) aqueous EtOH afforded an analytical sample of **25** as colorless needles, mp 242.5—245.5 °C (dec.); UV $\lambda_{max}^{95\%\,EtOH}$ 291 nm (ε 7400); $\lambda_{max}^{H_2O}$ (pH 1) 226 (18000), 283 (8600); $\lambda_{max}^{H_2O}$ (pH 7) 226 (18400), 283 (8500); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me$_2$SO-d_6) δ: 3.80 [3H, s, N(9)-Me or OMe], 3.86 [3H, s, OMe or N(9)-Me], 4.00 [3H, s, N(7)-Me], 9.27 [1H, s, C(8)-H], 12.01 (1H, br, NH). *Anal.* Calcd for $C_8H_{11}DIN_5O$ (by H$_2$O/HDO gas volume analysis): C, 29.83; H, 3.75; N, 21.74. Found: C, 29.72; H, 3.75; N, 21.52.

7,9-Dimethyladeninium-2-*d* Iodide (27) A solution of **25** (322 mg, 1 mmol) in H$_2$O (30 ml) was hydrogenated over Raney Ni W-2 catalyst[49] (1 ml) at atmospheric pressure and room temperature for 6 h. The catalyst was removed by filtration and washed with H$_2$O. The filtrate and washings were combined and concentrated to dryness *in vacuo* to leave a solid, mp 247.5—253.5 °C (dec.). Recrystallization of the solid from 90% (v/v) aqueous EtOH gave **27** (180 mg, 62%) as colorless needles, mp 256—259 °C (dec.). Further recrystallizations in the same manner yielded an analytical sample, mp 266.5—269.5 °C (dec.); UV $\lambda_{max}^{95\%\,EtOH}$ 272 nm (ε 11800); $\lambda_{max}^{H_2O}$ (pH 1) 268 (12100); $\lambda_{max}^{H_2O}$ (pH 7) 269 (12300); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me$_2$SO-d_6) δ: 3.88 [3H, s, N(9)-Me], 4.18 [3H, s, N(7)-Me], 7.95 (2H, br, NH$_2$), 9.56 [1H, s, C(8)-H].[50] *Anal.* Calcd for $C_7H_9DIN_5$ (by H$_2$O/HDO gas volume analysis): C, 28.78; H, 3.45; N, 23.98. Found: C, 28.54; H, 3.45; N, 24.18.

(*E*)-4-Amino-6-methylamino-5-(*N*-methylformamido)pyrimidine-2-*d* (26) A solution of **27** (117 mg, 0.4 mmol) in H$_2$O (10 ml) was passed through a column of Amberlite CG-400 (OH$^-$) (7 ml), and the column was eluted with H$_2$O (60 ml). The eluate (*ca.* 70 ml) was concentrated to dryness *in vacuo* to leave a colorless solid, which was dissolved in EtOH–MeOH (1:1, v/v) (10 ml). The resulting solution was concentrated *in vacuo* to a volume of *ca.* 1 ml and then cooled in an ice bath for 1 h, depositing **26** (37 mg, 51%) as colorless prisms, mp 236—240 °C (dec.); MS *m/z*: 182 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 225 nm (ε 45200), 258 (5500); $\lambda_{max}^{H_2O}$ (pH 1) 225 (29700), 269 (12600); $\lambda_{max}^{H_2O}$ (pH 7) 222 (41300), 258 (6000); $\lambda_{max}^{H_2O}$ (pH 13) 222 (42500), 258 (6000); ^{1}H-NMR (Me$_2$SO-d_6) δ: 2.74 (minor, s)[25] and 2.74 (major, d, J=4 Hz) [3H, C(6)-NMe], 2.90 [3H, s, C(5)-N(CHO)Me], 6.22 (2H, br, NH$_2$), 6.54 [1H, q, J=4 Hz, C(6)-NHMe], 7.77 [1H, s, C(5)-N(CHO)Me].[51] *Anal.* Calcd for $C_7H_{10}DN_5O$ (by H$_2$O/HDO gas volume analysis): C, 46.14; H, 6.08; N, 38.44. Found: C, 46.14; H, 6.33; N, 38.34.

***N*^{6},7-Dimethyladenine (21a)** i) From **16a** (X=I): A stirred mixture of **16a** (X=I)[4] (291 mg, 1 mmol) and 1 N aqueous NaOH (5 ml) was heated under reflux for 60 min. The reaction mixture was passed through a column of Amberlite CG-120 (Type I, H$^+$) (10 ml), and the column was eluted with H$_2$O (20 ml) followed by 5% aqueous NH$_3$ (50 ml). The ammoniacal eluate was concentrated *in vacuo* to leave **21a** (142 mg, 87%) as a colorless solid, mp 297—300 °C. Recrystallization from 90% (v/v) aqueous EtOH produced an analytical sample as colorless prisms, mp 309—310 °C (lit.[32] mp 311 °C); UV (Table I). *Anal.* Calcd for $C_7H_9N_5$: C, 51.52; H, 5.56; N, 42.92. Found: C, 51.37; H, 5.64; N, 42.84.

ii) From **22a** by Treatment with Aqueous NaOH: A stirred mixture of **22a** (127 mg, 0.7 mmol) and 1 N aqueous NaOH (3.5 ml) was heated under reflux for 60 min. The reaction mixture was worked up in a manner similar to that described above under item (i), giving **21a** (82 mg, 72%) as a colorless solid, mp 296—299 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one obtained by method (i).

iii) From **22a** by Treatment with NaH: An oil dispersion (34 mg) containing 50% NaH (0.7 mmol) was added to a stirred suspension of **22a** (127 mg, 0.7 mmol) in AcNMe$_2$ (2 ml), and stirring was continued at room temperature for 40 min. The reaction mixture was concentrated *in vacuo*, and the residue was washed with EtOH (2 ml) to leave **21a** (96 mg, 84%) as a colorless solid, mp >300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one prepared by method (i).

7-Ethyl-*N*^{6}-methyladenine (21b) i) From **16b** (X=I): Hydrolysis of **16b** (X=I)[4] with 1 N aqueous NaOH was effected as described above for **21a** under method (i), affording **21b** in 86% yield. Recrystallization from EtOH gave an analytical sample of **21b** as colorless pillars, mp 254—255 °C; UV (Table I). *Anal.* Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.29; H, 6.18; N, 39.24. This sample was identical (by comparison of the IR spectrum and TLC behavior) with the one described below under item (ii).

ii) From **20**: A mixture of 6-chloro-7-ethylpurine (**20**)[33] (183 mg, 1 mmol) and 40% aqueous MeNH$_2$ (11 ml) was heated at 100 °C for 40 min. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in H$_2$O (3 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$_2$O. Concentration of the eluate (50 ml) under reduced pressure and recrystallization of the residual solid from EtOH provided **21b** (69 mg, 39%) as colorless pillars, mp 253—254 °C.

7-Benzyl-*N*^{6}-methyladenine (21c) A stirred suspension of **16c**·H$_2$O

(X=Br)[4] (169 mg, 0.5 mmol) in 1 N aqueous NaOH (2.5 ml) was heated under reflux for 60 min. After cooling, the reaction mixture was adjusted to pH 6 by addition of 10% aqueous HCl and then made alkaline by addition of 28% aqueous NH_3. The precipitate that resulted was filtered off, washed with H_2O, and dried to give **21c** (109 mg, 91%) as a colorless solid, mp 178—180 °C. Recrystallization from benzene yielded an analytical sample as colorless needles, mp 181—182 °C; UV (Table I). *Anal.* Calcd for $C_{13}H_{13}N_5$: C, 65.26; H, 5.48; N, 29.27. Found: C, 65.15; H, 5.46; N, 29.02.

N^6-Ethyl-7-methyladenine (21d) This compound was obtained in 55% yield from **16d** (X=I)[4] in a manner similar to that described above for **21a** under method (i). Recrystallization from AcOEt furnished an analytical sample of **21d** as colorless prisms, mp 184.5—185.5 °C; UV (Table I). *Anal.* Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.16; H, 6.28; N, 39.76.

N^6,7-Diethyladenine (21e) Hydrolysis of **16e** (X=I)[4] with 1 N aqueous NaOH was carried out as described above for **21a** under method (i), producing **21e** in 50% yield. Recrystallization from AcOEt gave an analytical sample of **21e** as colorless plates, mp 160—162 °C; UV (Table I). *Anal.* Calcd for $C_9H_{13}N_5$: C, 56.53; H, 6.85; N, 36.62. Found: C, 56.41; H, 7.09; N, 36.49.

7-Benzyl-N^6-ethyladenine (21f) A stirred mixture of **16f** ($X=ClO_4$)[4] (283 mg, 0.8 mmol) and 1 N aqueous NaOH (4 ml) was heated under reflux for 60 min. After cooling, the crystals that deposited were filtered off, washed with H_2O, and dried to give **21f** (148 mg, 73%), mp 119.5—124 °C. Recrystallization from AcOEt yielded an analytical sample as colorless prisms, mp 129—130.5 °C; UV (Table I). *Anal.* Calcd for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.29; H, 6.04; N, 27.91.

7,8-Dihydro-7,9-dimethyladenine (28) A suspension of **16a** (X=I)[4] (146 mg, 0.5 mmol) in MeOH (8 ml) was stirred at room temperature, and $NaBH_4$ (28 mg, 0.75 mmol) was added portionwise to the suspension. After having been stirred for 20 min, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in H_2O (0.5 ml), and the aqueous solution was extracted with $CHCl_3$ after addition of saturated aqueous K_2CO_3 (1 ml). The $CHCl_3$ extracts were washed with saturated aqueous K_2CO_3, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave **28** (70 mg, 84%) as a colorless solid, mp 148—150 °C (dec.). Recrystallization from benzene gave an analytical sample as pale yellowish prisms, mp 148—153 °C (dec.); MS *m/z*: 165 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 223.5 nm (ε 25600), 293 (5890); IR ν_{max}^{Nujol} cm^{-1}: 3312 and 3140 (NH_2); ^{1}H-NMR (Me_2SO-d_6) δ: 2.64 [3H, s, N(7)-Me or N(9)-Me], 2.73 [3H, s, N(9)-Me or N(7)-Me], 4.33 [2H, s, C(8)-H's], 5.70 (2H, br, NH_2), 7.67 [1H, s, C(2)-H]. *Anal.* Calcd for $C_7H_{11}N_5$: C, 50.89; H, 6.71; N, 42.39. Found: C, 50.92; H, 6.74; N, 42.40.

Hydrolysis of 28 A solution of **28** (99 mg, 0.6 mmol) in H_2O (2 ml) was heated at 60 °C for 9 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography [alumina (10 g), $CHCl_3$–EtOH (15:1, v/v)] to give **22a** (53 mg, 49%) as a colorless solid, mp 247—248 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC behavior) with authentic **22a** (*vide supra*).

Kinetic Procedure i) Equilibrium between **22a** and **23a** in D_2O: The *trans*-formamide **22a** was dissolved in D_2O at 0.06 M concentration. The resulting solution was kept at 25 °C, and the ^{1}H-NMR spectrum of the solution was measured at intervals. For determination of **22a** and **23a** in the solution, relative areas of the C(5)-NMe signals at δ 3.04 and 3.15 (Fig. 2) were obtained. The descrease of the concentration of **22a** was found to obey good pseudo-first-order kinetics. The results are summarized in the text and Fig. 3.

ii) Equilibrium between **22a** and **23a** in Me_2SO-d_6: The *trans*-formamide **22a** was dissolved in Me_2SO-d_6 at 0.06 M concentration, and the change of the isomer ratio in the solution was followed as in the case of the above D_2O solution but by measuring the relative areas of the formyl protons at δ 7.76 and 7.98. The results are summarized in the text.

iii) Equilibrium between **22a** and **23a** in H_2O at pH 9.84: The *trans*-formamide **22a** was dissolved, at a concentration of 6.098×10^{-4} M, in 0.1 M aqueous $NaHCO_3$–Na_2CO_3 (pH 9.84) brought to ionic strength 0.50 with KCl, and the resulting solution was kept at 25±0.05 °C in a thermoregulated constant-temperature bath. At intervals, aliquots (1 ml) of the reaction mixture were withdrawn and diluted with 0.05 M KH_2PO_4–MeOH (90:10, v/v) by a factor of 5. Small portions (15 μl) of the diluted solutions were then analyzed by means of high-performance liquid chromatography (HPLC). The HPLC analyses were carried out on a Waters ALC/GPC 204 liquid chromatograph by using a μBondapak C_{18} column [0.05 M KH_2PO_4–MeOH (90:10, v/v), 1950 p.s.i., 1.5 ml/min],[52] and the peak height of the substrate, located by using a UV absorbance detector operated at 254 nm, was determined. The concentration of the unaltered substrate in the reaction mixture was then estimated from a calibration curve which had been obtained with substrate solutions of known concentration, and the decrease of the concentration of the substrate was found to obey good pseudo-first-order kinetics. The results are summarized in the text and Fig. 4.

iv) Ring Opening of 7,9-Dialkyladeninium Salts [**16a, b, d—g** (X=ClO_4) and **16c** (X=Br)]: The substrates were separately dissolved, at a concentration of 5.9×10^{-4}—6.1×10^{-4} M, in 0.1 M aqueous $NaHCO_3$–Na_2CO_3 (pH 9.84) brought to ionic strength 0.50 with KCl, and the resulting solutions were kept at 25±0.05 °C. In the case of the ring opening of **16a** (X=ClO_4), the decrease of **16a** (X=ClO_4) in the reaction solution was followed by HPLC in the same manner as described above under item (iii) or by UV spectrophotometry. For the UV spectrophotometric analysis, aliquots of the reaction solution were withdrawn at intervals and diluted with 0.2 M aqueous KH_2PO_4–Na_2HPO_4 (pH 6.89 at 25 °C) by a factor of 10. The optical densities of the diluted solutions at 270 nm were then determined,[53] and concentration of **16a** (X=ClO_4) was then calcuated in the usual manner. The results were comparable to those from the above HPLC analysis. Similar UV spectroscopic analyses were applied to the cases of **16c** (X=Br), **16d** (X=ClO_4), and **16f** (X=ClO_4), and similar HPLC analyses, to the cases of **16b, e** (X=ClO_4) (with modification of the flow rate to 2.0 ml/min) and **16g** (X=ClO_4) [with modifications of the diluent and eluent to 0.05 M aqueous KH_2PO_4–MeOH (50:50, v/v) and of the flow rate to 1.2 ml/min]. All ring-opening reactions were followed through at least two half-lives with at least six measurements, and good pseudo-first-order kinetics were obtained in all cases. The results are shown in Fig. 5 and Table II.

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