Purines. XXXII.[1] Synthesis and Ring Fission of 3,9-Dialkyladenines

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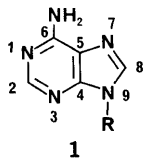
A detailed account is given of the general synthetic route to 3,9-dialkyladenine salts (3d—l·HX) from *N'*-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidines (type 8 or 9), obtainable by ring opening of 1-alkoxy-9-alkyladenines (type 6 or 7). Alkylations of 8a and 9b, c with alkyl halides in $HCONMe_2$ in the presence of NaH or anhydrous K_2CO_3 produced *N'*-alkoxy-1-alkyl-5-(*N*-alkylformamido)imidazole-4-carboxamidines (10d—f and 11g—l) in good yields. Hydrogenolyses of 10d—f and 11g—l using hydrogen and Raney Ni catalyst in the presence of one molar eq of HCl afforded 1-alkyl-5-(*N*-alkylformamido)imidazole-4-carboxamidines (12d—l·HCl). On treatment with HCl, $HClO_4$, or Et_3N in boiling MeOH or EtOH, the amidines 12d—l·HCl cyclized to give 3,9-dialkyladenines (3d—l), which were isolated as the HCl or $HClO_4$ salts. 9-Alkyl-3-methyladenine salts (3d, g, j·HX) were alternatively synthesized from 8a and from 9b, c through a 3-step route, which consisted of $LiAlH_4$ reduction of the formamido group, cyclizations of the resulting 5-(methylamino)imidazoles (15a and 16b, c) with $CH(OEt)_3$ to give N^6-alkoxy-9-alkyl-3-methyladenines (17a and 18b, c), and dealkoxylation of 17a and 18b, c by catalytic hydrogenolysis. 3,9-Dialkyladenine salts (3d—l·HX) thus prepared were found to be unstable in alkaline aqueous solution. In 0.1 M aqueous $NaHCO_3$, 3d·HCl and 3f·$HClO_4$ were equilibrated with their ring-opened derivatives, 12d and 12f, respectively, and their equilibrium constants and rates of ring opening and cyclization at 25 °C were determined.

Keywords 3,9-dialkyladenine synthesis; formamido group *N*-alkylation; lithium aluminum hydride reduction; hydrogenolytic dealkoxylation; ethyl orthoformate cyclization; amidine formamido cyclization; alkaline hydrolysis; ring–chain equilibrium; kinetic study; UV

The title compounds, 3,9-dialkyladenines (**3**), constitute one of the 11 possible groups of positional isomers of N^x,N^y-disubstituted adenines. Such 3,9-disubstitution has previously been known only in cyclic derivatives[2] (*e.g.*, **23**[2a]), N^6,N^6-dialkyl derivatives,[2b,3] an N^6-monomethylated derivative,[4] or an N^6-methyl-8-oxo derivative (caissarone).[5] It is also assumed to occur as a part structure, in the form of 3-alkyl-2'-deoxyadenosine (**4**), in alkylated deoxyribonucleic acid·(DNA) molecules.[6] Although the prototype of this disubstitution is 3,9-dimethyladenine (**3d**), neither **3d** itself nor its homologues had been known at the time when the present study was undertaken. In connection with our continuing interest in fission and reclosure of the adenine ring,[7] we thus investigated the synthesis and stability of all nine 3,9-dialkyladenines (**3d**—**l**) that carry any one of the methyl, ethyl, and benzyl groups at each of the 3- and 9-positions. Brief accounts of the results recorded here have been published in preliminary form.[8,9]

The desired 3,9-dimethyladenines (**3**) would be readily accessible from either 3-alkyladenines (**2**) or 9-alkyladenines (**1**) by alkylation if the alkyl group at the 3- or 9-position could direct an incoming alkyl group to the 9- or 3-position, respectively, as in the case of the N^6-methyl,[4,10] N^6,N^6-dimethyl,[3b,c,f] or N^6,N^6-diethyl derivatives.[3a,c] However, such a concise synthetic route is not feasible since an alkyl group at the 3- or 9-position of adenine itself orients further alkylation mainly to the 7-[11] or 1-position,[12] respectively. In reaching 3,9-dimethyladenine (**3d**), we therefore tried to take advantage of the "fission and reclosure" technology[7] developed in our laboratory for modification of the adenine ring. This technology features the use of 1-substituted *N'*-alkoxy-5-formamidoimidazole-4-carboxamidines (type **8** or **9**), the readily isolable ring-opened intermediates in the Dimroth rearrangements of 9-substituted 1-alkoxyadenines (type **6** or **7**) leading to the N^6-alkoxy isomers (type **14**),[12h,13] as the starting materials.

Thus, the formamidoimidazole **8a**[12h,13a] was reduced with $LiAlH_4$ in tetrahydrofuran (THF) at room temperature for 2.5 h to give the methylamino derivative **15a** in 74% yield. In order to cyclize **15a** with introduction of a C_1-unit by application of the method of Shealy and O'Dell,[14] **15a** was treated with ethanolic HCl, and the resulting hydrochloride **15a**·HCl (98% yield) was heated in boiling ethyl orthoformate for 4 h, affording the cyclized product **17a** in 75% yield. The formation of the free base **17a** instead of the hydrochloride **17a**·HCl is not unlikely, because HCl reacts with ethyl orthoformate at elevated temperatures to give ethyl chloride and ethyl formate.[15] Although the above cyclization result was not always reproducible owing to the incidental formation of an intractable tarry substance, this difficulty was overcome when the reaction was carried out at 80 °C for 4 h or in MeOH at room temperature for 40 min, furnishing **17a**·HCl in 87% or 94% yield, respectively. Hydrogenolysis of the perchlorate **17a**·$HClO_4$, prepared in 91% yield from **17a** and aqueous $HClO_4$ in EtOH, or of the hydrochloride **17a**·HCl using hydrogen and 10% Pd–C catalyst in EtOH or in 70% (v/v) aqueous EtOH at room temperature gave the first target **3d**·$HClO_4$ or **3d**·HCl in 56% or 61% yield, respectively. In the permutation **15a**→**21**·HCl→**3d**·HCl (Chart 2), removal of the methoxy group from **15a** was effected at the first stage by catalytic



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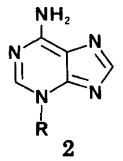

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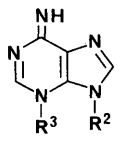
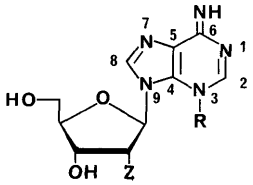


3: R^2 and R^3 = alkyl
3d: R^2 = R^3 = Me



4: Z = H
5: R = Me; Z = OH

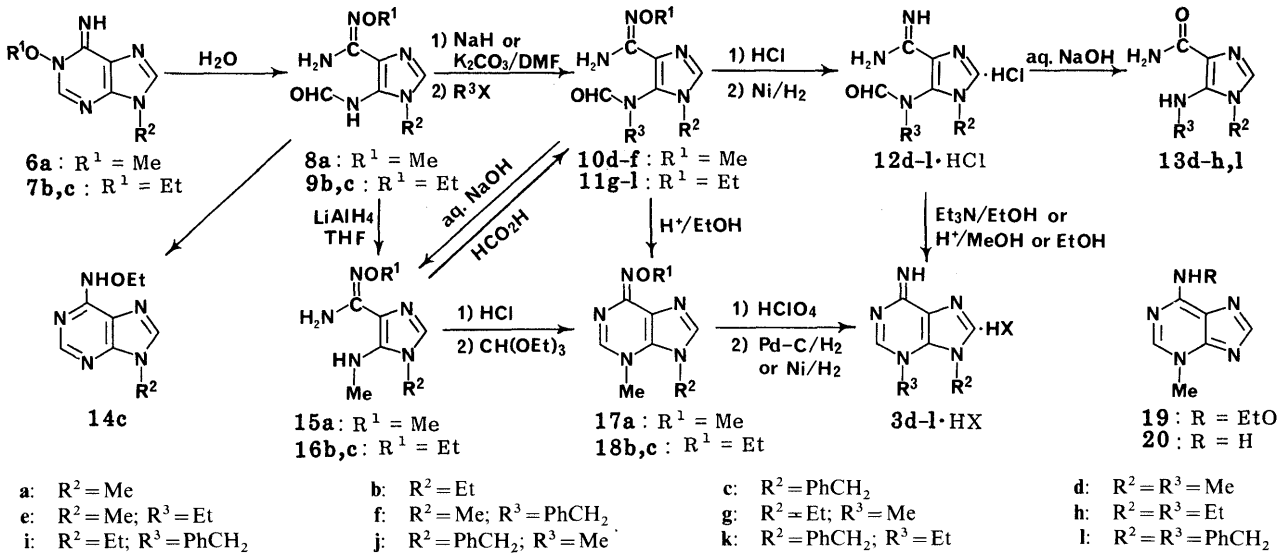


Chart 1

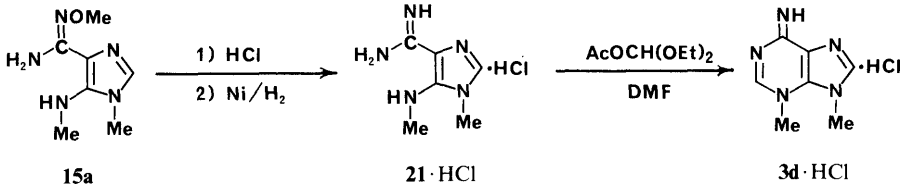
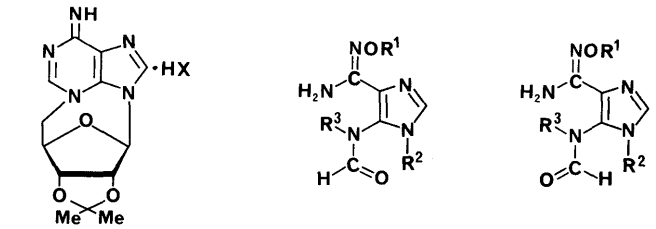


Chart 2

hydrogenolysis under conditions which we featured[16] in our previous hydrogenolytic cleavage of *N'*-alkoxy group in a similar amidine system. Thus, hydrogenation of **15a** over Raney Ni catalyst in H_2O containing one molar eq of HCl proceeded smoothly at room temperature, producing the amidine hydrochloride **21**·HCl in 84% yield. Reaction of **21**·HCl with diethoxymethyl acetate,[17] a C_1-unit-introducing cyclization reagent often used for synthesis of purines from pyrimidine or imidazole precursors,[17b,18] in $HCONMe_2$ (DMF) at room temperature for 80 min afforded the target compound **3d**·HCl in 89% yield. The 3,9-dimethyl structure of **3d**·$HClO_4$ and **3d**·HCl thus obtained was assignable on the basis of the above self-consistent reaction sequence through which they were formed, as well as the similarity of their ultraviolet (UV) spectra with that of 3,5′-cyclo-2′,3′-*O*-isopropylideneadenosine perchlorate (**22**) prepared from the corresponding *p*-toluenesulfonate (**23**).[2a]



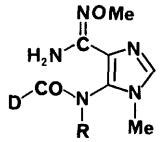
A parallel sequence of reactions starting with the ethyl homologue **9b**[12h,13a] provided **16b** (83% yield), **16b**·2HCl (97%), **18b** (44%) or **18b**·$HClO_4$ (84%), and **3g**·$HClO_4$ (52%). In an attempt to cyclize **16b** with an alternative C_1-unit,[13g] **16b** was treated with boiling 90% formic acid for 3.5 h. However, the product isolated in 59% yield was not the expected one (**18b**) but the *N*-formylated monocycle **11g**. The benzyl analogue **9c**, prepared in 84% yield [together with the rearranged product **14c** (8%)] from **7c**·HI by treatment with H_2O at pH 10—11, similarly gave the methylamino derivative **16c** (87% yield), which was then converted into the hydrochloride **16c**·2HCl. Cyclization of **16c**·2HCl with ethyl orthoformate in MeOH at room temperature for 2 h and conversion of the product into a perchlorate furnished **18c**·$HClO_4$ in 92% overall yield (from **16c**·2HCl). Although hydrogenolysis of **18c**·$HClO_4$ using hydrogen and 10% Pd–C catalyst in MeOH at room temperature resulted in debenzylation to form N^6-ethoxy-3-methyladenine (**19**) (38% yield) as well as 3-methyladenine (**20**) (25%), replacement of the catalyst by Raney Ni afforded the desired compound **3j**·$HClO_4$ in 34% yield.

The above synthetic route has thus proved to be generally applicable to synthesis of 9-alkyl-3-methyladenine salts (**3**·HX, R^2 = alkyl; R^3 = Me), but it suffers from the intrinsic defect that the 3-substituent (R^3) of the resulting 3,9-disubstituted adenine salts (type **3**·HX) is confined to only the methyl group. In order to remove such a drawback, we next developed an alternative route which featured *N*-alkylation of the formamido group in the monocycle **8** or **9** and did not require an exogenous C_1-unit in the cyclization step (Chart 1). Methylation of the Na salt of **8a**, generated *in situ* from the formamido derivative **8a** and NaH in DMF at room temperature, with MeI in DMF at room temperature for 1 h produced the *N*-methylformamido derivative **10d** in 87% yield. Methylation of **9b** with NaH and MeI in a

similar manner gave **11g** (85% yield), which was identical with the product from the reaction of the methylamino derivative **16b** with formic acid (*vide supra*). Apart from these favorable results, the unusually strong acidity (pK_a 10.36 ± 0.04 at 40 °C) observed[13d] for the formamido group of **8a** suggested the use of a weaker base for generation of the formamido anion prior to alkylation. When **8a** was treated with anhydrous K_2CO_3 in DMF at room temperature and the resulting mixture was methylated as described above, the desired *N*-methylformamido derivative **10d** was obtained in 84% yield. Alkylations of **8a** with EtI and $PhCH_2Br$ and those of **9b** and **9c** with the above three alkyl halides were also found to proceed equally well under similar reaction conditions, giving the corresponding *N*-alkylformamido derivatives (**10e, f** and **11g—l**) in good yields. The results are summarized in Table I.

The *N*-alkylformamido structure of **10** and **11** thus prepared was further supported by the alkaline hydrolysis (1 N aqueous NaOH, reflux, 15 min) of **10d** and **11g** to give **15a** and **16b** in 97% and 99% yields, respectively, and by their proton nuclear magnetic resonance (^{1}H-NMR) spectral data (Table II). In all ^{1}H-NMR spectra, two sets of signals, all with identical ratios (from 3 : 1 to 7 : 1) of relative integral intensities, were observed for most of the different species of protons in **10d—f** and **11g—l**. The complexity of these signals is probably a result of *cis–trans* equilibration (**24**⇌**25**) of the *N*-alkylformamido group, as we have experienced previously in similar structures.[13a-d,f,19] In any case, however, we were unable to determine which isomer it was that predominated. The assignments of the imidazole ring and formyl proton signals, as shown in Table II, were based on comparison of the ^{1}H-NMR spectral data for **10d** and **10f** with those for the corresponding deuteroformamido derivatives (**26** and **27**)[20] and on a deuterium labeling experiment in which signals to be ascribed to the C(2)-proton disappeared after **10d** and **11j—l** had separately been treated with boiling D_2O (of 99.8% isotopic purity) for 4 h.[21]

In reaching 3,9-dimethyladenine (**3d**) from **10d**, two synthetic routes may be considered: **10d**→**17a**→**3d** ("early" cyclization and "late" demethoxylation) and **10d**→**12d**→**3d** ("early" demethoxylation and "late" cyclization) (Chart 1). In the first permutation, treatment of **10d** with boiling H_2O or with 0.1 N aqueous HCl at 25 °C[19b] did not give the desired cyclization product (**17a**). This failure presents a contrast to the fairly easy cyclization of the *N*-(unsubstituted)-formamido analogues (type **8** or **9**→type **14**) under



26: R = Me
27: R = $PhCH_2$

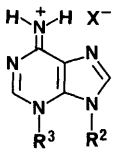


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TABLE I. Alkylation of *N'*-Alkoxy-1-alkyl-5-formamido-1*H*-imidazole-4-carboxamidines (**8a** and **9b, c**) in $HCONMe_2$ at Room Temperature

Substrate			Base	Alkylating agent	Reaction time (h)	Product	
No.	R^1	R^2				No.	Yield (%)
8a	Me	Me	NaH	MeI	1	**10d**	87
			K_2CO_3	MeI	2	**10d**	84
			K_2CO_3	EtI	3	**10e**	92
			K_2CO_3	$PhCH_2Br$	2	**10f**	97
9b	Et	Et	NaH	MeI	1	**11g**	85
			K_2CO_3	MeI	2	**11g**	83
			K_2CO_3	EtI	3	**11h**	88
			K_2CO_3	$PhCH_2Br$	2	**11i**	91
9c	Et	$PhCH_2$	K_2CO_3	MeI	3	**11j**	91
			K_2CO_3	EtI	5	**11k**	95
			K_2CO_3	$PhCH_2Br$	3	**11l**	94

TABLE II. ^{1}H-NMR Spectral Data for *N'*-Alkoxy-1-alkyl-5-(*N*-alkylformamido)-1*H*-imidazole-4-carboxamidines (**10d—f** and **11g—l**)

Compd.	Chemical shift (δ)[a] in Me_2SO-d_6															
	R^1			R^2				R^3					NH_2	C(2)-H	CHO[b]	
	Me	Et		Me	Et		$PhCH_2$		Me	Et		$PhCH_2$				
		Me	CH_2		Me	CH_2	CH_2	Ph		Me	CH_2	CH_2	Ph				
10d	3.60			3.50					3.01					5.66	7.72	8.01	(5)
	3.66			3.40					3.27					5.66	7.68	8.26	(1)
10e	3.62			3.51						0.99[c]	3.4—4.0[d]			5.63	7.74	7.99	(10)
	3.67			3.42						1.03[c]	3.4—4.0[d]			5.63	7.71	8.31	(3)
10f	3.67			3.05								4.5—5.1[d]	7.23[d]	5.65	7.57	8.13	(3)
	3.75			2.79								4.5—5.1[d]	7.23[d]	5.70	7.50	8.55	(1)
11g		1.16[c]	3.6—4.0[d]		1.32[c]	3.6—4.0[d]			3.03					5.60	7.81	8.04	(4)
		1.18[c]	3.6—4.0[d]		1.28[c]	3.6—4.0[d]			3.27					5.60	7.77	8.26	(1)
11h		1.16[c]	3.2—4.0[d]		1.34[c]	3.2—4.0[d]				1.00[c]	3.2—4.0[d]			5.57	7.83	8.01	(4)
		1.18[c]	3.2—4.0[d]		—[e]	3.2—4.0[d]				1.04[c]	3.2—4.0[d]			5.57	7.81	8.31	(1)
11i		1.20[c]	3.75—4.1[d]		0.98[c]	3.34[f]						4.2—5.1[d]	7.21[d]	5.57	7.65	8.12	(4)
		1.25[c]	3.75—4.1[d]		0.80[c]	3.40[f]						4.2—5.1[d]	7.21[d]	5.60	7.59	8.54	(1)
11j		1.12[c]	3.65—4.0[d]				5.13	7.0—7.5[d]	2.74					5.61	7.92	7.77	(6)
		1.16[c]	3.65—4.0[d]				5.13	7.0—7.5[d]	2.84					5.61	7.84	8.18	(1)
11k		1.13[c]	3.6—4.0[d]				4.85—5.2[d]	7.0—7.4[d]		0.89[c]	3.1—3.6[d]			5.61	7.91	7.66	(7)
		1.17[c]	3.6—4.0[d]				4.85—5.2[d]	7.0—7.4[d]		0.81[c]	3.1—3.6[d]			5.61	7.70	8.30	(1)
11l		1.16[c]	3.7—4.05[d]				4.1—5.15[d]	6.7—7.45[d]				4.1—5.15[d]	6.7—7.45[d]	5.60	7.74	7.68	(6)
		1.25[c]	3.7—4.05[d]				4.1—5.15[d]	6.7—7.45[d]				4.1—5.15[d]	6.7—7.45[d]	5.66	—[e]	8.58	(1)

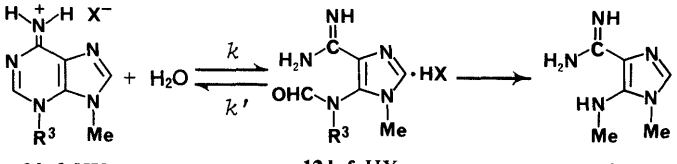
a) Measured at 0.02—0.22 M concentration and expressed in ppm downfield from internal Me_4Si. *b*) The figures in parentheses indicate relative integral intensities for a pair of isomers. *c*) Triplet with $J = 7$ Hz. *d*) Multiplet. *e*) Unidentified. *f*) Quartet with $J = 7$ Hz.

similar reaction conditions[12h,13a-d,f,19a] and may be explained in terms of the effect of product development control associated with steric repulsion between the methyl groups at the 3- and 9-positions in the expected bicyclic product **17a**. Nevertheless, treatment of **10d** with ethanolic HCl at room temperature for 9 h afforded **17a**·HCl in 47% yield, and demethoxylation of **17a**·HCl was effected by catalytic hydrogenolysis to give **3d**·HCl in 61% yield (*vide supra*), the overall yield from **10d** being 29%. In the second permutation (**10d**→**12d**→**3d**), demethoxylation of **10d** was carried out (Raney Ni/H_2, H_2O containing 1 molar eq of HCl, 1 atm, room temp., 3 h) as described above for **15a**→**21**·HCl (Chart 2), producing **12d**·HCl in 66% yield. Although cyclization of **12d**·HCl in boiling MeOH was extremely slow, addition of 2 molar eq of HCl (method A) or $HClO_4$ (method B) accelerated the reaction to give **3d**·HCl or **3d**·$HClO_4$ in 73% or 81% yield, respectively. Alternatively, **12d**·HCl readily cyclized in boiling EtOH in the presence of 0.1 molar eq of Et_3N (method C), furnishing **3d**·HCl in 89% yield.

The above favorable results obtained from the permutation **10d**→**12d**→**3d** led us to synthesize the other 3,9-dialkyladenine salts through parallel routes. Thus, similar catalytic hydrogenolyses of **10e,f** and **11g—l** yielded the corresponding amidines **12e—l**·HCl. The structures of **12d—h**·HCl and **12l**·HCl were confirmed by their alkaline hydrolyses (1 N aqueous NaOH, reflux, 30—60 min) which led to the known carboxamide derivatives (**13d—h,l**).[22] Interestingly, the reaction sequence **6** or **7**→**8** or **9**→**10** or **11**→**12**·HCl→**13** (Chart 1) represents an alternative route to the key intermediates utilized in the syntheses of 3,9-dialkylhypoxanthines,[18d] 3,9-dialkylguanines,[23] 3,9-dimethylisoguanine,[24] and 3,9-dimethylxanthine.[23b] The amidine hydrochlorides **12e—l**·HCl were then cyclized by method B or C (*vide supra*) to provide the desired 3,9-dialkyladenine salts (**3e—l**·HX) in 36—86% overall yields [from the alkylation products (**10e,f** and **11g—l**)].

It may be seen from Table III that the 3,9-dialkyladenine salts thus obtained had similar UV spectra, indicative of identical positional disubstitution. The ^{1}H-NMR spectra of these salts in Me_2SO-d_6 revealed that the C(2)-proton signal falls within the range of 8.53—8.79 δ, and the C(8)-proton signal lies in the 8.26—8.49 δ region,[20,25] suggesting the importance of resonance structures with the positive charge in the pyrimidine part. Indeed, our recent X-ray crystallographic structure analysis[1] of 3-methyladenosine *p*-toluenesulfonate (**5**·TsOH)[26] indicated that this salt has the exocyclic iminium structure (type **28**). From analogy with this as well as the results[1] of the semiempirical calculation of the atomic orbital coefficients for the HOMO of 6-imino-3,9-dimethylpurine (**3d**), similar exocyclic iminium structures (type **28**) are inferred for the salts of 3,9-dialkyladenines described above.

In an attempt to isolate the free base of 3,9-dimethyladenine (**3d**), an aqueous solution of **3d**·HCl was passed through a column of Amberlite IRA-402 (HCO_3^-). However, the substance isolated from the eluate in 97% yield was the bicarbonate salt **3d**·H_2CO_3, suggesting that the basicity of the free base is considerably high, in contrast to the rather low basicity of the N^6-methoxy derivative **17a** [pK_a 5.09±0.03 (at 20 °C) for **17a**·$HClO_4$]. On the other hand, replacement of the ion-exchange resin by Amberlite CG-400 (OH^-) in the above neutralization resulted in the formation of the methylaminoimidazole **21**, which was characterized as the hydrochloride **21**·HCl (61% yield). Since the same hydrochloride was obtained from **12d**·HCl by a similar treatment, the observed conversion of **3d**·HCl into **21** seemed to proceed through hydrolytic ring opening followed by deformylation, as delineated in Chart 3. It was found that in aqueous $NaHCO_3$ the UV spectral changes of both **3d**·HCl and **12d**·HCl with time went through the same isosbestic point at 256 nm, converging on an identical spectrum.[27] Actually, 3,9-dimethyladenine was isolated in 66% yield as the perchlorate **3d**·$HClO_4$ from a solution of **12d**·HCl in 0.5 M aqueous $NaHCO_3$ which had been kept at 25 °C for 6 h. All these observations indicated the existence



d: R^3=Me **f**: R^3=$PhCH_2$

Chart 3

TABLE III. UV Spectra of 3,9-Dialkyladenine Salts (**3**·HX)

Compound No.	R^2	R^3	UV spectra[a] 95% EtOH λ_{max} (nm)	ε	H_2O (pH 1)[b] λ_{max} (nm)	ε	H_2O (pH 7)[c] λ_{max} (nm)	ε
3d·HCl	Me	Me	272	15500	270	15700	270	15600
3d·$HClO_4$	Me	Me	272	15400	270	15600	270	15400
3e·HCl	Me	Et	273	15400	271	15700	271	15600
3e·$HClO_4$	Me	Et	273	15300	271	15700	271	15500
3f·$HClO_4$	Me	$PhCH_2$	274	16100	272	15900	272	15900
3g·$HClO_4$	Et	Me	271	14300	270	16000	270	16000
3h·$HClO_4$	Et	Et	272.5	14600	271	15800	271	15800
3i·$HClO_4$	Et	$PhCH_2$	272.5	14600	272	16100	272	16000
3j·$HClO_4$	$PhCH_2$	Me	273	16400	271.5	17900	271.5	17900
3k·$HClO_4$	$PhCH_2$	Et	273.5	15900	272	17300	272	17400
3l·$HClO_4$	$PhCH_2$	$PhCH_2$			273	17800	273	17800

a) Unstable in the alkaline region in H_2O. *b*) Measured in 0.1 N aqueous HCl. *c*) Measured in 0.005 M phosphate buffer (pH 7).

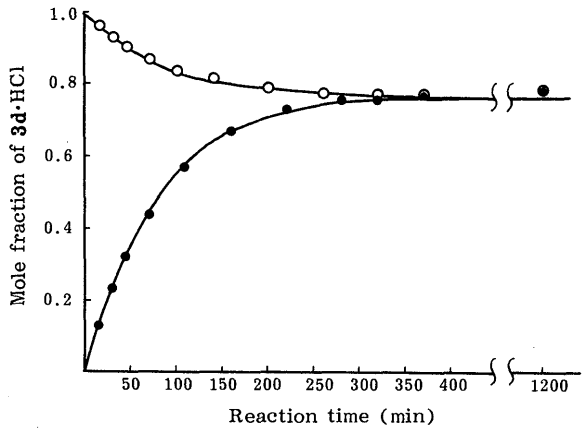


Fig. 1. Variation of the Concentration of **3d**·HCl with Time in the Ring Opening of **3d**·HCl (—○—) and in the Cyclization of **12d**·HCl (—●—) in 0.1 M Aqueous $NaHCO_3$ (pH 8.32) at 25°C

of an equilibrium between 3,9-dimethyladenine (**3d**) and the ring-opened derivative **12d** in H_2O, and this was confirmed by following spectrophotometrically the time-courses of the ring-opening reaction of **3d**·HCl and of cyclization of **12d**·HCl in 0.1 M aqueous $NaHCO_3$ (pH 8.32) at 25 °C. It may be seen from Fig. 1 that equilibrium between **3d**·HCl (77%) and **12d**·HCl (23%) was established in *ca.* 8 h. On treatment of these kinetic data in the usual manner,[28] the reactions in both directions (Chart 3) were found to obey pseudo-first-order kinetics ($k=2.88\times10^{-3}\,min^{-1}$; $k'=9.63\times10^{-3}\,min^{-1}$; $K_{eq}=k/k'=0.30$). For the reversible reactions between **3f**·$HClO_4$ and **12f**·$HClO_4$ were obtained $k=3.98\times10^{-3}\,min^{-1}$, $k'=0.82\times10^{-3}\,min^{-1}$, and $K_{eq}=k/k'=4.85$. Kinetic results obtained with the other 3,9-dialkyladenine salts (**3e, g—l**·$HClO_4$) in H_2O at pH 8.98 and 25 °C have been reported[29] by us in preliminary form.[25] It is of particular interest to note that among the four possible N^x,9-dimethyladenines (*i.e.*, the 1,9-, 3,9-, 7,9-, and N^6,9-dimethyl isomers), the 3,9-dimethyl isomer (**3d**) has been found to undergo hydrolytic fission of the adenine ring most rapidly under alkaline conditions.[30] The N^6-methoxy derivative **17a** was also reported to give the monocycle **10d** in H_2O at pH 7.72 and 25 °C at a rate of $4.96\times10^{-4}\,min^{-1}$.[19b]

In conclusion, the above results have established a general synthetic route to 3,9-dialkyladenine salts (**3**·HX) for the first time. Successful applications of this route to the nucleoside level are seen in our previous syntheses of 3-methyladenosine *p*-toluenesulfonate (**5**·TsOH)[26] and 3-methyl-2′-deoxyadenosine *p*-toluenesulfonate (**4**·TsOH, R=Me),[13e] the cation moiety of the latter being assumed to occur in methylated DNA molecules as a part structure.[6] It is hoped that the easy ring-opening observed for the 3,9-dialkyladenine salts will find its significance and utility in studies of DNA molecules after alkylation, *e.g.*, DNA sequencing, enzymatic work, chemical modification, and so forth.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. Paper partition chromatographies (PPC) were developed on Toyo Roshi No. 51 filter paper by the ascending method with solvent system A [1-butanol–H_2O–AcOH (75:20:5, v/v)], solvent system B [1-butanol–28% aqueous NH_3–H_2O (4:1:1, v/v)], or solvent sytem C [2-propanol–1% aqueous $(NH_4)_2SO_4$ (2:1, v/v)], and spots were located under UV rays. Spectra reported herein were recorded on a Hitachi EPS-2U or a Hitachi model 323 UV spectrophotometer [on solutions in 95% (v/v) aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13)], a JASCO DS-402G or a JASCO IRA-2 infrared (IR) spectrophotometer, a JEOL JMS-01SG mass spectrometer, or a JEOL JNM-C-60 or a JEOL JNM-PS-100 nuclear magnetic resonance (NMR) spectrometer at 25 °C with Me_4Si as an internal standard. Spectrophotometric determinations were carried out with a Hitachi model 181 spectrophotometer, and pH's were measured on a Hitachi-Horiba F-5 or a Toa HM-18ET pH meter. The pK_a determination was made spectrophotometrically at 20 °C and ionic strength 0.10 as described previously.[13d] 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.

1-Benzyl-*N*′-ethoxy-5-formamido-1*H*-imidazole-4-carboxamidine (9c) and 9-Benzyl-N^6-ethoxyadenine (14c) 9-Benzyl-1-ethoxyadenine hydriodide (**7c**·HI)[31] (1.99 g, 5 mmol) was dissolved in H_2O (75 ml) at 60 °C, and the solution was made alkaline (pH 10—11) with 10% aqueous Na_2CO_3 while hot, then cooled in an ice bath without delay, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a yellow oil. The oil was dissolved in 20% (v/v) aqueous EtOH (50 ml), and the solution was kept at 40 °C for 42 h and then concentrated *in vacuo* to leave a solid. The solid was chromatographed on a silica gel column using AcOEt and AcOEt–EtOH (10:1, v/v) as the eluents. Earlier fractions gave **9c** (1.21 g, 84%) as a colorless solid, mp 132—133 °C. Recrystallization from benzene furnished an analytical sample as colorless pillars, mp 132.5—133 °C; UV $\lambda_{max}^{95\%\,EtOH}$ 250 nm (sh) (ε 7700); $\lambda_{max}^{H_2O}$ (pH 1) 254.5 (9300); $\lambda_{max}^{H_2O}$ (pH 7) 247 (sh) (7800); $\lambda_{max}^{H_2O}$ (pH 13) 256 (12300); IR $\nu_{max}^{CHCl_3}$ (in 0.005 M solution) cm^{-1}: 3535 (NH_2), 3415 (NH_2, CONH), 1704 (CONHAr); NMR (Me_2SO-d_6) δ: 1.18 and 1.20 (3H, t each, J=7 Hz, OCH_2 Me), 3.88 and 3.90 (2H, q each, J=7 Hz, OCH_2Me), 5.05 and 5.14 (2H, slightly dull s each, CH_2Ph), 5.56 and 5.60 (2H, br each, NH_2), 7.09—7.45 (5H, m, CH_2Ph), 7.75 and 7.79 [1H, s each, C(2)-H], 7.92 (d, J=10 Hz, *trans*-**9c**) and 8.20 (s, *cis*-**9c**) (1H, HCON), 9.46 (d, J=10 Hz, *trans*-**9c**) and 9.63 (br, *cis*-**9c**) (1H, CONH).[32] *Anal.* Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.37. Found: C, 58.54; H, 5.87; N, 24.28.

Later fractions in the above chromatography afforded **14c** (112 mg, 8%) as a colorless solid, mp 231.5—233 °C (dec.). This sample was identical [by comparison of the IR spectrum and thin-layer chromatographic (TLC) mobility] with authentic **14c**.[13b,16]

***N*′-Methoxy-1-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamidine (15a)** i) By Reduction of **8a**: To a stirred suspension of $LiAlH_4$ (3.4 g, 90 mmol) in dry tetrahydrofuran (THF) (50 ml) was added dropwise in 20 min a solution of **8a**[12h,13a] (3.35 g, 17 mmol) in dry THF (325 ml) at such a rate that the inner temperature did not exceed 37 °C. After the resulting mixture had been stirred at 25 °C for 2.5 h, a mixture of H_2O (3.4 ml) and THF (3.4 ml), 15% aqueous NaOH (3.4 ml), and H_2O (10.2 ml) were added in that order under ice-cooling and stirring, and stirring was continued for 2.5 h. The insoluble material that resulted was removed by filtration and washed with THF (60 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave a yellow solid. Purification of the solid by column chromatography [silica gel (180 g), benzene–EtOH (8:1, v/v)] furnished **15a** (2.31 g, 74%) as a colorless solid, mp 135—136 °C. Recrystallization from benzene gave an analytical sample as colorless prisms, mp 135—136 °C; MS *m/z*: 183 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 226.5 nm (ε 11500), 256 (8400); $\lambda_{max}^{H_2O}$ (pH 1) 257 (sh) (5700), 287 (7600); $\lambda_{max}^{H_2O}$ (pH 7) 225 (12800), 250 (sh) (8500); $\lambda_{max}^{H_2O}$ (pH 13) 225 (12500), 250 (sh) (8500); NMR (Me_2SO-d_6) δ: 2.71 (3H, br s, NHMe), 3.49 [3H, s, N(1)-Me], 3.63 (3H, s, NOMe), 4.90—5.35 (1H, br, NHMe), 5.53 (2H, s, NH_2), 7.21 [1H, s, C(2)-H]. *Anal.* Calcd for $C_7H_{13}N_5O$: C, 45.89; H, 7.15; N, 38.23. Found: C, 46.11; H, 7.10; N, 38.52.

ii) By Hydrolysis of **10d**: A solution of **10d** (2.11 g, 10 mmol) in 1 N aqueous NaOH (50 ml) was heated under reflux for 15 min. The reaction mixture was first neutralized with 10% aqueous HCl, then made alkaline with 28% aqueous NH_3, and concentrated *in vacuo*. The residue was dried and extracted with boiling benzene. The benzene extracts were concentrated *in vacuo* to leave **15a** (1.78 g, 97%) as a colorless solid, mp 135—136 °C. This sample was identical (by comparison of the IR spectrum and TLC behavior) with the one obtained by method (i).

***N*′-Methoxy-1-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamidine Hydrochloride (15a·HCl)** To a solution of **15a** (928 mg, 5.07 mmol) in EtOH (10 ml) were added 10% (w/w) ethanolic HCl (5 ml) and ether (50 ml) in that order. The precipitate that resulted was filtered off and dried to give **15a**·HCl (1.09 g, 98%), mp 179—181 °C (dec.). Recrystallization from EtOH yielded an analytical sample as colorless pillars, mp 180—182 °C (dec.); UV $\lambda_{max}^{95\%\,EtOH}$ 222 nm (ε 9950), 252 (7300); $\lambda_{max}^{H_2O}$ (pH 1) 259 (sh) (5400), 287 (7300); $\lambda_{max}^{H_2O}$ (pH 7) 224 (12000), 249 (sh) (8100); $\lambda_{max}^{H_2O}$ (pH 13) 224 (12000), 249 (sh) (8100); NMR (Me_2SO-d_6) δ: 2.85, 3.68, and 3.82 [3H each, s, NHMe, N(1)-Me, and NOMe], 6.65—7.80 (br, NH's), 8.53 [1H, s, C(2)-H]. *Anal.* Calcd for $C_7H_{13}N_5O$·HCl: C, 38.27; H, 6.42; N, 31.88. Found: C, 38.25; H, 6.53; N, 31.91.

***N*′-Ethoxy-1-ethyl-5-(methylamino)-1*H*-imidazole-4-carboxamidine (16b)** i) By Reduction of **9b**: The formamidoimidazole **9b**[12h,13a] (3.35 g, 16 mmol) was reduced with $LiAlH_4$ (3.0 g, 79 mmol) in a manner similar to that described above for **15a**, giving **16b** in 83% yield. Recrystallization of **16b** from H_2O furnished an analytical sample as colorless prisms, mp 89—91 °C; UV $\lambda_{max}^{95\%\,EtOH}$ 226 nm (ε 11100), 255 (8500); $\lambda_{max}^{H_2O}$ (pH 1) 259 (sh) (5100), 288 (7300); $\lambda_{max}^{H_2O}$ (pH 7) 224 (11300), 249 (sh) (7900); $\lambda_{max}^{H_2O}$ (pH 13) 224 (11500), 249 (sh) (8000); NMR (Me_2SO-d_6) δ: 1.20 (3H, t, J=7 Hz, OCH_2Me), 1.33 [3H, t, J=7 Hz, N(1)-CH_2Me], 2.50 (3H, dull s, NHMe), 3.89 [4H, q, J=7 Hz, OCH_2Me and N(1)-CH_2Me], 5.07 (1H, br, NHMe), 5.52 (2H, dull s, NH_2), 7.33 [1H, s, C(2)-H]. *Anal.* Calcd for $C_9H_{17}N_5O$: C, 51.16; H, 8.11; N, 33.15. Found: C, 51.49; H, 8.06; N, 33.07.

ii) By Hydrolysis of **11g**: The *N*-methylformamido derivative **11g**

(957 mg, 4 mmol) was hydrolyzed as described above for **15a** under item (ii) to afford **16b** (839 mg, 99%), mp 87.5—89.5 °C. Recrystallization from H_2O produced colorless prisms, mp 89.5—90.5 °C, identical with a sample of **16b** prepared by method (i).

***N'*-Ethoxy-1-ethyl-5-(methylamino)-1*H*-imidazole-4-carboxamidine Dihydrochloride (16b·2HCl)** To a solution of **16b** (2.54 g, 12 mmol) in EtOH (15 ml) were added successively 10% (w/w) ethanolic HCl (20 ml) and dry ether (150 ml). The precipitate that resulted was filtered off and dried to give **16b**·2HCl (3.30 g, 97%), mp 179—180 °C (dec.). Recrystallization from EtOH produced an analytical sample as colorless prisms, mp 179—180 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 222 nm (ε 10200), 250 (sh) (7600); $\lambda_{max}^{H_2O}$ (pH 1) 258 (sh) (5100), 287 (7600); $\lambda_{max}^{H_2O}$ (pH 7) 224 (11400), 248 (sh) (8100); $\lambda_{max}^{H_2O}$ (pH 13) 224 (11400), 248 (sh) (8100); NMR (Me_2SO-d_6) δ: 1.25 and 1.35 [3H each, t, J=7 Hz, $OCH_2\underline{Me}$ and N(1)-$CH_2\underline{Me}$], 2.77 (3H, s, NH$\underline{Me}$), 4.02 and 4.08 [2H each, q, J=7 Hz, $OC\underline{H}_2Me$ and N(1)-$C\underline{H}_2Me$], 7.20—8.10 (br, NH's), 8.66 [1H, s, C(2)-H]. *Anal.* Calcd for $C_9H_{17}N_5O\cdot 2HCl$: C, 38.04; H, 6.74; N, 24.64. Found: C, 38.08; H, 6.85; N, 24.54.

1-Benzyl-*N'*-ethoxy-5-(methylamino)-1*H*-imidazole-4-carboxamidine (16c) Reduction of **9c** (2.87 g, 10 mmol) with $LiAlH_4$ (1.90 g, 50 mmol) in THF (200 ml) and work-up of the reaction mixture were performed as described above for **15a** under item (i), and the crude product was purified by column chromatography (silica gel, AcOEt) to yield **16c** (2.37 g, 87%) as a slightly brownish solid, mp 98.5—102 °C. Recrystallization from hexane gave an analytical sample as colorless pillars, mp 103.5—104.5 °C; UV $\lambda_{max}^{95\%\ EtOH}$ 225 nm (sh) (ε 11800), 258 (9700); $\lambda_{max}^{H_2O}$ (pH 1) 286 (7600); $\lambda_{max}^{H_2O}$ (pH 7) 225 (sh) (11600), 250 (sh) (8700); $\lambda_{max}^{H_2O}$ (pH 13) 225 (sh) (11400), 250 (sh) (8650); IR ν_{max}^{Nujol} cm^{-1}: 3495, 3300 (NH_2, NH), 1626 (C=N); NMR (Me_2SO-d_6) δ: 1.20 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 2.60 (3H, dull s, NH$\underline{Me}$), 3.90 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.76—5.28 (1H, br, NH), 5.14 (2H, s, $C\underline{H}_2Ph$), 5.55 (2H, dull s, NH_2), 7.08—7.44 [6H, m, $CH_2\underline{Ph}$ and C(2)-H]. *Anal.* Calcd for $C_{14}H_{19}N_5O$: C, 61.52; H, 7.01; N, 25.62. Found: C, 61.55; H, 6.93; N, 25.55.

1-Benzyl-*N'*-ethoxy-5-(methylamino)-1*H*-imidazole-4-carboxamidine Dihydrochloride (16c·2HCl) To a solution of **16c** (410 mg, 1.5 mmol) in EtOH (2 ml) were added successively 10% (w/w) ethanolic HCl (5 ml) and dry ether (35 ml). The precipitate that resulted was filtered off and dried to afford **16c**·2HCl (521 mg, 100%), mp 177—178 °C (dec.). Recrystallization from EtOH produced an analytical sample as faintly brownish prisms, mp 177—178 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 258 nm (ε 7700); $\lambda_{max}^{H_2O}$ (pH 1) 285.5 (7500); $\lambda_{max}^{H_2O}$ (pH 7) 225 (sh) (11600), 250 (sh) (8700); $\lambda_{max}^{H_2O}$ (pH 13) 225 (sh) (11500), 250 (sh) (8700); NMR (Me_2SO-d_6) δ: 1.27 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 2.70 (3H, s, NMe), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.46 (2H, slightly dull s, $C\underline{H}_2Ph$), 7.44 (5H, s, $CH_2\underline{Ph}$), 7.84 (5H, br, NH's), 8.80 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{14}H_{19}N_5O\cdot 2HCl$: C, 48.56; H, 6.11; N, 20.23. Found: C, 48.45; H, 6.15; N, 20.24.

Alkylations of the Na or K Salts of 8a and 9b,c All alkylations were carried out under the reaction conditions specified in Table I in a manner similar to that described below for the methylation of the Na or K salt of **8a**, and the results are summarized in Table I. The *N*-alkylformamido derivatives (**10d—f** and **11g—l**) thus obtained were characterized as follows.

***N'*-Methoxy-1-methyl-5-(*N*-methylformamido)-1*H*-imidazole-4-carboxamidine (10d)** i) By Methylation of the Na Salt of **8a**: An oil dispersion (115 mg) containing 50% NaH (2.4 mmol) was added to a stirred solution of **8a**[12h,13a] (394 mg, 2 mmol) in $HCONMe_2$ (9 ml), and stirring was continued at room temperature for 30 min. A solution of MeI (340 mg, 2.4 mmol) in $HCONMe_2$ (1 ml) was then added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to leave a yellowish brown jelly, which was extracted with boiling benzene. The benzene extracts were combined and concentrated *in vacuo*, and the residue was washed with AcOEt (1.5 ml) to leave **10d** (368 mg, 87%) as a colorless solid, mp 159—161 °C. Recrystallization from AcOEt gave an analytical sample as colorless prisms, mp 162—163 °C; MS *m/z*: 211 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 5500); $\lambda_{max}^{H_2O}$ (pH 1) 253 (7600); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (5700); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (5700); IR ν_{max}^{Nujol} cm^{-1}: 3435, 3315 (NH_2), 1683 (HCON); NMR (Table II). *Anal.* Calcd for $C_8H_{13}N_5O_2$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.65; H, 6.43; N, 32.87.

ii) By Methylation of the K Salt of **8a**: A mixture of **8a**[12h,13a] (4.34 g, 22 mmol), anhydrous K_2CO_3 (4.56 g, 33 mmol), and $HCONMe_2$ (100 ml) was stirred at room temperature for 1 h, and then a solution of MeI (3.75 g, 26.4 mmol) in $HCONMe_2$ (10 ml) was added. After having been stirred at room temperature for 2 h, the reaction mixture was worked up as described above for **10d** under method (i), yielding **10d** (3.89 g, 84%) as colorless prisms, mp 160—161 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one prepared by method (i).

5-(*N*-Ethylformamido)-*N'*-methoxy-1-methyl-1*H*-imidazole-4-carboxamidine (10e) The reaction mixture from **8a**[12h,13a] (1.38 g, 7 mmol) and EtI in the presence of anhydrous K_2CO_3 was concentrated *in vacuo*, and the residue was chromatographed [silica gel, AcOEt–EtOH (8:1, v/v)]. The resulting crude **10e** was recrystallized from hexane–AcOEt (1:1, v/v) to furnish an analytical sample as colorless prisms, mp 95—96 °C; MS *m/z*: 225 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 5500); $\lambda_{max}^{H_2O}$ (pH 1) 253 (7500); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (5700); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (5900); IR ν_{max}^{Nujol} cm^{-1}: 3400, 3315 (NH_2), 1683 (HCON); NMR (Table II). *Anal.* Calcd for $C_9H_{15}N_5O_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 48.06; H, 6.59; N, 30.85.

5-(*N*-Benzylformamido)-*N'*-methoxy-1-methyl-1*H*-imidazole-4-carboxamidine (10f) The reaction mixture from equimolar amounts of **8a**[12h,13a] and $PhCH_2Br$ in the presence of anhydrous K_2CO_3 was concentrated *in vacuo*, and the residue was chromatographed (silica gel, AcOEt) to give **10f** as a colorless glass; MS *m/z*: 287 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh); $\lambda_{max}^{H_2O}$ (pH 1) 251; $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh); NMR (Table II). For further characterization, a small sample (100 mg) of crude **10f** was dissolved in EtOH (1 ml), and a saturated solution (2 ml) of picric acid in EtOH was added. The precipitate (163 mg, 91%) that resulted was filtered off and recrystallized from MeOH to provide the picrate of **10f** as orange pillars, mp 161—162 °C. *Anal.* Calcd for $C_{14}H_{17}N_5O_2\cdot C_6H_3N_3O_7$: C, 46.52; H, 3.90; N, 21.70. Found: C, 46.46; H, 3.90; N, 21.50.

***N'*-Ethoxy-1-ethyl-5-(*N*-methylformamido)-1*H*-imidazole-4-carboxamidine (11g)** i) The reaction mixture from **9b**[12h,13a] and MeI in the presence of NaH or anhydrous K_2CO_3 was concentrated *in vacuo*, and the residue was chromatographed (alumina, AcOEt) or extracted with boiling AcOEt to isolate crude **11g**. Recrystallization from H_2O afforded an analytical sample as colorless prisms, mp 147—148 °C; UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 5900); $\lambda_{max}^{H_2O}$ (pH 1) 252 (8000); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (5800); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (5800); IR $\nu_{max}^{CHCl_3}$ (in 0.005 M solution) cm^{-1}: 3510, 3395 (NH_2), 1690 (HCON); NMR (Table II). *Anal.* Calcd for $C_{10}H_{17}N_5O_2$: C, 50.20; H, 7.16; N, 29.27. Found: C, 50.28; H, 6.87; N, 29.00.

ii) By Formylation of **16b**: A mixture of **16b** (211 mg, 1 mmol) and 90% formic acid (1 ml) was heated under reflux for 3.5 h. The reaction mixture was concentrated *in vacuo*, and the residue was co-evaporated *in vacuo* 5 times with a little H_2O. The resulting residue was triturated with a little H_2O, and the insoluble solid was collected by filtration and dried to give **11g** (142 mg, 59%), mp 145—146.5 °C. Recrystallization from H_2O produced a pure sample as colorless prisms, mp 147—147.5 °C, identical (by comparison of the IR spectrum and TLC mobility) with the one obtained by method (i).

***N'*-Ethoxy-1-ethyl-5-(*N*-ethylformamido)-1*H*-imidazole-4-carboxamidine (11h)** The reaction mixture from the K salt of **9b**[12h,13a] and EtI was concentrated *in vacuo*, and the residue was extracted with boiling AcOEt to isolate crude **11h**. Recrystallization from H_2O yielded an analytical sample as colorless pillars, mp 132—133 °C; UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 5700); $\lambda_{max}^{H_2O}$ (pH 1) 251.5 (7900); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (5700); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (5800); IR ν_{max}^{Nujol} cm^{-1}: 3430, 3330 (NH_2), 1678 (HCON); NMR (Table II). *Anal.* Calcd for $C_{11}H_{19}N_5O_2$: C, 52.16; H, 7.56; N, 27.65. Found: C, 52.11; H, 7.73; N, 27.48.

5-(*N*-Benzylformamido)-*N'*-ethoxy-1-ethyl-1*H*-imidazole-4-carboxamidine (11i) This was isolated by column chromatography (silica gel, AcOEt) and recrystallized from H_2O to form colorless prisms, mp 69.5—71 °C; UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 6500); $\lambda_{max}^{H_2O}$ (pH 1) 250 (7200); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (5900); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (5900); IR ν_{max}^{Nujol} cm^{-1}: 3470, 3330 (NH_2), 1677 (HCON); NMR (Table II). *Anal.* Calcd for $C_{16}H_{21}N_5O_2$: C, 60.94; H, 6.71; N, 22.21. Found: C, 61.09; H, 6.97; N, 22.19.

1-Benzyl-*N'*-ethoxy-5-(*N*-methylformamido)-1*H*-imidazole-4-carboxamidine (11j) This was isolated by extraction of the residue, obtained by concentration of the reaction mixture from the K salt of **9c** and MeI, with boiling AcOEt and recrystallized from 10% (v/v) aqueous EtOH to give colorless prisms, mp 82.5—84.5 °C; UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 6500); $\lambda_{max}^{H_2O}$ (pH 1) 252.5 (8900); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (6100); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (6200); IR ν_{max}^{Nujol} cm^{-1}: 3510, 3340 (NH_2), 1677 (HCON); NMR (Table II). *Anal.* Calcd for $C_{15}H_{19}N_5O_2$: C, 59.78; H, 6.36; N, 23.24. Found: C, 59.49; H, 6.43; N, 23.08.

1-Benzyl-*N'*-ethoxy-5-(*N*-ethylformamido)-1*H*-imidazole-4-carboxamidine (11k) This was isolated by extraction of the residue, obtained by concentration of the reaction mixture from the K salt of **9c** and EtI, with boiling AcOEt and recrystallized from benzene–hexane (1:1, v/v) to provide colorless prisms, mp 102.5—103 °C; UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 6300); $\lambda_{max}^{H_2O}$ (pH 1) 251 (8800); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (5900); $\lambda_{max}^{H_2O}$ (pH 13)

250 (sh) (6000); IR ν_{max}^{Nujol} cm^{-1}: 3495, 3350 (NH_2), 1682 (HCON); NMR (Table II). *Anal.* Calcd for $C_{16}H_{21}N_5O_2$: C, 60.94; H, 6.71; N, 22.21. Found: C, 60.89; H, 6.99; N, 21.99.

1-Benzyl-5-(*N*-benzylformamido)-*N'*-ethoxy-1*H*-imidazole-4-carboxamidine (11l) This was isolated by column chromatography (alumina, AcOEt) and recrystallized from benzene–hexane (1 : 4, v/v) to furnish colorless needles, mp 97—98 °C; UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 6900); $\lambda_{max}^{H_2O}$ (pH 1) 246 (8000); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (5950); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (6100); IR ν_{max}^{Nujol} cm^{-1}: 3425, 3320 (NH_2), 1681 (HCON); NMR (Table II). *Anal.* Calcd for $C_{21}H_{23}N_5O_2$: C, 66.82; H, 6.14; N, 18.56. Found: C, 67.00; H, 6.26; N, 18.80.

Catalytic Hydrogenolyses of 10d—f and 11g—l The procedure employed for the hydrogenolysis of **10d** will be described below in detail. The other hydrogenolyses were accomplished similarly, and the resulting dealkoxylated amidines were, in most cases, used directly in the next cyclization step without purification. However, four of them were purified and characterized as follows.

1-Methyl-5-(*N*-methylformamido)-1*H*-imidazole-4-carboxamidine Hydrochloride (12d·HCl) A solution of **10d** (1.69 g, 8 mmol) in H_2O (200 ml) containing 1 N aqueous HCl (8 ml) was hydrogenated over Raney Ni W-2 catalyst[33] (3 ml) at atmospheric pressure and room temperature for 3 h. The catalyst was removed by filtration and washed with H_2O (40 ml). The combined filtrate and washings were concentrated *in vacuo*, and the residue was washed with EtOH (10 ml) to leave **12d**·HCl (1.14 g, 66%) as a colorless solid, mp 278—279 °C (dec.). Recrystallization of the solid by dissolving it in MeOH and adding AcOEt to the resulting methanolic solution gave an analytical sample as colorless pillars, mp 278—279 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 257 nm (ε 8900); $\lambda_{max}^{H_2O}$ (pH 1) 254 (8400); $\lambda_{max}^{H_2O}$ (pH 7) 254 (8600); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.14 and 3.26 (3H, s each, HCONMe), 3.53 and 3.59 [3H, s each, N(1)-Me], 8.06 [1H, s, C(2)-H], 8.23 and 8.28 (1H, s each, HCONMe), 8.40—8.80 (2H, br, NH_2), 9.05—9.45 (2H, br, NH_2^+).[32] *Anal.* Calcd for $C_7H_{11}N_5O$·HCl: C, 38.63; H, 5.56; N, 32.18. Found: C, 38.63; H, 5.67; N, 32.15.

5-(*N*-Benzylformamido)-1-methyl-1*H*-imidazole-4-carboxamidine Hydrochloride (12f·HCl) This was obtained in 65% yield from **10f** by hydrogenolysis (for 6 h) and recrystallized as in the case of **12d**·HCl, affording colorless prisms, mp 201 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 258 nm (ε 8800); $\lambda_{max}^{H_2O}$ (pH 1) 252 (7100); $\lambda_{max}^{H_2O}$ (pH 7) 252 (7300); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 2.90 and 3.11 [3H, s each, N(1)-Me], 4.20—5.30 (2H, br m, CH_2Ph), 7.00—7.45 (5H, m, CH_2Ph), 7.85 and 7.88 [1H, s each, C(2)-H], 8.33 and 8.60 (1H, s each, HCON), 8.54 (2H, br, NH_2), 9.22 (2H, br, NH_2^+).[32] *Anal.* Calcd for $C_{13}H_{15}N_5O$·HCl: C, 53.15; H, 5.49; N, 23.84. Found: C, 53.27; H, 5.57; N, 23.84.

1-Benzyl-5-(*N*-methylformamido)-1*H*-imidazole-4-carboxamidine Hydrochloride (12j·HCl) This was obtained in 54% yield from **11j** by hydrogenolysis (for 8 h) and recrystallized as in the case of **12d**·HCl, forming colorless fine crystals, mp 253—254 °C (dec.). *Anal.* Calcd for $C_{13}H_{15}N_5O$·HCl: C, 53.15; H, 5.49; N, 23.84. Found: C, 52.92; H, 5.42; N, 23.55.

1-Benzyl-5-(*N*-benzylformamido)-1*H*-imidazole-4-carboxamidine Hydrochloride (12l·HCl) This was prepared in 21% yield from **11l** by hydrogenolysis (for 9 h). Recrystallization as in the case of **12d**·HCl and drying over P_2O_5 at 2 mmHg and 50 °C for 15 h gave an analytical sample as colorless prisms, mp 193—194 °C; UV $\lambda_{max}^{95\%\ EtOH}$ 256 nm (ε 8500); $\lambda_{max}^{H_2O}$ (pH 1) 249 (7300); $\lambda_{max}^{H_2O}$ (pH 7) 249 (7400); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 4.50—4.90 [4H, br m, N(1)-CH_2Ph and HCONCH_2Ph], 6.85—7.45 (10H, m, CH_2Ph's), 7.74 and 7.95 [1H, s each, C(2)-H], 8.07 and 8.64 (1H, s each, HCON), 8.30—8.60 (2H, br, NH_2), 8.80—9.10 (2H, br, NH_2^+).[32] *Anal.* Calcd for $C_{19}H_{19}N_5O$·HCl·1/3H_2O: C, 60.72; H, 5.45; N, 18.63. Found: C, 60.70; H, 5.73; N, 18.43.

Alkaline Hydrolyses of 12d—h, l·HCl The procedure employed for the hydroysis of **12d**·HCl will be described below in detail. The other amidine hydrochlorides **12e—h,l**·HCl, obtained by the above catalytic hydrogenolyses of **10e, f** and **11g, h, l**, were similarly hydrolyzed (but reflux for 60 min in the case of **12l**·HCl) without purification to give 5-(ethylamino)-1-methyl-1*H*-imidazole-4-carboxamide (**13e**) (80% overall yield from **10e**), 5-(benzylamino)-1-methyl-1*H*-imidazole-4-carboxamide (**13f**) (44% from **10f**), 1-ethyl-5-(methylamino)-1*H*-imidazole-4-carboxamide (**13g**) (90% from **11g**), 1-ethyl-5-(ethylamino)-1*H*-imidazole-4-carboxamide (**13h**) (90% from **11h**), and 1-benzyl-5-(benzylamino)-1*H*-imidazole-4-carboxamide (**13l**) (56% from **11l**), which were shown to be identical (by comparison of the IR spectra and TLC mobilities) with authentic samples.[22]

1-Methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide (13d) A solution of **12d**·HCl (218 mg, 1 mmol) in 1 N aqueous NaOH (10 ml) was heated under reflux for 30 min. The reaction mixture was first neutralized with 10% aqueous HCl, then made alkaline with 28% aqueous NH_3, and concentrated to dryness *in vacuo*. The residual solid was dried and extracted with six 15-ml portions of boiling AcOEt. The AcOEt extracts were concentrated *in vacuo* to leave **13d** (126 mg, 82%) as almost colorless prisms, mp 207—210 °C. This sample was identical (by comparison of the IR spectrum and TLC behavior) with authentic **13d**.[22]

***N*⁶-Methoxy-3,9-dimethyladenine (17a)** A stirred suspension of **15a**·HCl (989 mg, 4.5 mmol) in ethyl orthoformate (45 ml) was heated under reflux for 4 h. After cooling, the reaction mixture was filtered to collect an insoluble solid, which was then washed with ether and dried to give **17a**·1/4H_2O (664 mg, 75%) as a slightly brownish solid, mp 210—211.5 °C (dec.). This sample showed a negative reaction in the Beilstein test for halogen, supporting its existence in the free base form. Recrystallization from EtOH and drying over P_2O_5 at 1 mmHg and room temperature for 24 h yielded an analytical sample of **17a**·1/4H_2O as faintly yellowish needles, mp 266.5—267 °C (dec.); MS *m/z*: 193 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 275 nm (ε 11500), 315 (sh) (5400); $\lambda_{max}^{H_2O}$ (pH 1) 282 (15900); $\lambda_{max}^{H_2O}$ (pH 7) 278 (12200), 314 (sh) (5600); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.65, 3.69, and 3.86 (3H each, s, NMe's and OMe), 7.45 and 7.51 (1H each, s, ring protons). *Anal.* Calcd for $C_8H_{11}N_5O$·1/4H_2O: C, 48.60; H, 5.86; N, 35.42. Found: C, 49.00; H, 6.04; N, 35.16.

***N*⁶-Methoxy-3,9-dimethyladenine Hydrochloride (17a·HCl)** i) By Cyclization of **15a**·HCl in $CH(OEt)_3$: A suspension of **15a**·HCl (7.03 g, 32 mmol) in ethyl orthoformate (320 ml) was stirred at 80 °C for 4 h. After cooling, the precipitate that resulted was filtered off, washed with ether, and dried to give **17a**·HCl (6.38 g, 87%), mp 217—218 °C (dec.). Recrystallization from EtOH produced an analytical sample as colorless fine prisms, mp 218—219 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 281 nm (ε 14200); λ_{max}^{HO} (pH 1) 281.5 (15700); $\lambda_{max}^{H_2O}$ (pH 7) 277 (12000), 314 (sh) (5300); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.85, 4.13, and 4.25 (3H each, s, NMe's and OMe), 8.41 (1H, s, ring proton), 8.75 (1H, dull s, ring proton). *Anal.* Calcd for $C_8H_{11}N_5O$·HCl: C, 41.84; H, 5.27; N, 30.49. Found: C, 41.71; H, 5.18; N, 30.54.

ii) By Cyclization of **15a**·HCl with $CH(OEt)_3$ in MeOH: A mixture of **15a**·HCl (220 mg, 1 mmol) and ethyl orthoformate (15 ml) in MeOH (5 ml) was stirred at room temperature for 40 min. Evaporation of the MeOH from the reaction mixture under reduced pressure and addition of ether (10 ml) to the residue resulted in the formation of a precipitate, which was filtered off, washed with ether, and dried to give **17a**·HCl (217 mg, 94%) as a colorless solid, mp 218—219 °C (dec.). This sample was identical (by comparison of the IR spectrum and PPC mobility) with the one obtained by method (i).

iii) By Cyclization of **10d**: A stirred suspension of **10d** (148 mg, 0.7 mmol) in 5% (w/w) ethanolic HCl (10 ml) was kept at room temperature for 9 h. The reaction mixture was concentrated *in vacuo*, and the residue was washed with EtOH (2 ml) and dried to yield **17a**·HCl (75 mg, 47%) as a colorless solid, mp 218—219 °C (dec.), which was identical (by comparison of the IR spectrum and PPC mobility) with a sample prepared by method (i).

***N*⁶-Methoxy-3,9-dimethyladenine Perchlorate (17a·HClO₄)** i) From **17a**·HCl: A solution of $NaClO_4$ (3.92 g, 32 mmol) in H_2O (5 ml) was added to a solution of **17a**·HCl (4.00 g, 17.4 mmol) in H_2O (4 ml). The precipitate that resulted was filtered off, washed with a little H_2O, and recrystallized from EtOH to furnish **17a**·$HClO_4$ (4.18 g, 82%) as colorless prisms, mp 244.5—245.5 °C (dec.). Further recrystallization from EtOH gave an analytical sample, mp 245—247 °C (dec.); pK_a 5.09 ± 0.03 (at 20 °C); UV $\lambda_{max}^{95\%\ EtOH}$ 283 nm (ε 15800); $\lambda_{max}^{H_2O}$ (pH 1) 282 (16400); $\lambda_{max}^{H_2O}$ (pH 7) 278 (12500), 314 (sh) (5800); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.85, 4.11, and 4.22 (3H each, s, NMe's and OMe), 8.35 and 8.68 (1H each, s, ring protons). *Anal.* Calcd for $C_8H_{11}N_5O$·$HClO_4$: C, 32.72; H, 4.12; N, 23.85. Found: C, 32.66; H, 4.20; N, 23.92.

ii) From **17a**: A solution of **17a**·1/4H_2O (386 mg, 1.95 mmol) in EtOH (65 ml) was acidified (pH 1—2) by addition of a solution of 70% aqueous $HClO_4$ (0.5 g) in EtOH (2 ml). Ether (60 ml) was added to the resulting mixture, and the precipitate that resulted was collected by filtration and dried to afford **17a**·$HClO_4$ (521 mg, 91%), mp 240—242.5 °C (dec.). Recrystallization from EtOH gave a pure sample as colorless prisms, mp 244—245 °C (dec.), identical (by comparison of the IR spectrum and PPC mobility) with the one prepared by method (i).

***N*⁶-Ethoxy-9-ethyl-3-methyladenine (18b)** A suspension of **16b**·2HCl (124 mg, 0.436 mmol) in ethyl orthoformate (5 ml) was stirred at 50—60 °C for 5 h. After cooling, the precipitate that resulted was filtered off, washed with ether, and dissolved in H_2O (20 ml). The resulting aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (2 ml), and

the column was eluted with H_2O (10 ml). The eluate was concentrated *in vacuo* to leave a yellowish solid (80 mg). The solid was recrystallized from benzene (15 ml) to give **18b**·H_2O (46 mg, 44%). Further recrystallization from benzene and drying over P_2O_5 at 2 mmHg and 40 °C for 24 h yielded an analytical sample as colorless needles, mp 245—248 °C (dec.) (softened at *ca.* 110 °C); MS *m/z*: 221 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 272 nm (ε 13700), 320 (4500); $\lambda_{max}^{H_2O}$ (pH 1) 282 (17400); $\lambda_{max}^{H_2O}$ (pH 7) 276 (13500), 311 (sh) (6300); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 1.19 (3H, t, *J*=7 Hz, $OCH_2\underline{Me}$), 1.41 [3H, t, *J*=7 Hz, N(9)-$CH_2\underline{Me}$], 3.72 [3H, s, N(3)-Me], 3.93 (2H, q, *J*=7 Hz, $OC\underline{H}_2Me$), 4.29 [2H, q, *J*=7 Hz, N(9)-$C\underline{H}_2Me$], 7.50 and 7.66 (1H each, s, ring protons). *Anal.* Calcd for $C_{10}H_{15}N_5O\cdot H_2O$: C, 50.20; H, 7.16; N, 29.27. Found: C, 50.25; H, 6.88; N, 29.47.

N^6-Ethoxy-9-ethyl-3-methyladenine Perchlorate (18b·$HClO_4$) i) By Cyclization of **16b**·2HCl in $CH(OEt)_3$: A suspension of **16b**·2HCl (1.42 g, 5 mmol) in ethyl orthoformate (100 ml) was stirred at 80 °C for 4 h. After cooling, the precipitate that resulted was filtered off, washed with ether, and dissolved in H_2O (3 ml). To the resulting aqueous solution was added a solution of $NaClO_4\cdot H_2O$ (850 mg, 6 mmol) in H_2O (1 ml), and the precipitate that deposited was filtered off, washed with a little H_2O, and dried to give **18b**·$HClO_4$ (1.27 g, 79%), mp 178—179 °C (dec.). Recrystallization from 90% (v/v) aqueous EtOH produced an analytical sample as colorless prisms, mp 180—181 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 283 nm (ε 15300); $\lambda_{max}^{H_2O}$ (pH 1) 283 (16400); $\lambda_{max}^{H_2O}$ (pH 7) 276 (12700), 310 (sh), (5900); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 1.27 (3H, t, *J*=7 Hz, $OCH_2\underline{Me}$), 1.49 [3H, t, *J*=7.3 Hz, N(9)-$CH_2\underline{Me}$], 4.07 (2H, q, *J*=7 Hz, $OC\underline{H}_2Me$), 4.18 [3H, s, N(3)-Me], 4.52 [2H, q, *J*=7.3 Hz, N(9)-$C\underline{H}_2Me$], 8.46 (1H, s, ring proton), 8.67 (1H, dull s, ring proton). *Anal.* Calcd for $C_{10}H_{15}N_5O\cdot HClO_4$: C, 37.33; H, 5.01; N, 21.77. Found: C, 37.39; H, 4.97; N, 21.61.

ii) By Cyclization of **16b**·2HCl with $CH(OEt)_3$ in MeOH: A mixture of **16b**·2HCl (284 mg, 1 mmol) and ethyl orthoformate (15 ml) in MeOH (5 ml) was stirred at room temperature for 2 h. The reaction mixture was worked up as described below for **18c**·$HClO_4$, yielding **18b**·$HClO_4$ (270 mg, 84%) as a colorless solid, mp 180—181 °C (dec.). This sample was identical (by comparison of the IR spectrum) with the one obtained by method (i).

iii) From **18b**: The free base **18b**·H_2O (341 mg, 1.43 mmol) was treated with $HClO_4$ in a manner similar to that described above for **17a**·$HClO_4$ under item (ii), and **18b**·$HClO_4$ (425 mg, 93%) was obtained as a colorless solid, mp 180—181 °C (dec.).

9-Benzyl-N^6-ethoxy-3-methyladenine Perchlorate (18c·$HClO_4$) A stirred mixture of **16c**·2HCl (346 mg, 1 mmol) and ethyl orthoformate (15 ml) in MeOH (5 ml) was kept at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was washed with ether (20 ml), dried, and then dissolved in H_2O (0.5 ml). To the resulting aqueous solution was added a solution of $NaClO_4\cdot H_2O$ (210 mg, 1.5 mmol) in H_2O (0.5 ml), and the precipitate that resulted was filtered off, washed with H_2O (1 ml), and dried to afford **18c**·$HClO_4$ (354 mg, 92%), mp 175—179 °C (dec.). Recrystallization from EtOH produced an analytical sample as colorless plates, mp 182—183 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 282 nm (ε 15000); $\lambda_{max}^{H_2O}$ (pH 1) 283.5 (17500); $\lambda_{max}^{H_2O}$ (pH 7) 277 (12900), 315 (sh) (5500); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 1.28 (3H, t, *J*=7 Hz, $OCH_2\underline{Me}$), 3.95 (3H, s, NMe), 4.09 (2H, q, *J*=7 Hz, $OC\underline{H}_2Me$), 5.81 (2H, slightly dull s, $C\underline{H}_2Ph$), 7.00—7.60 (5H, m, $CH_2\underline{Ph}$), 8.48 (1H, s, ring proton), 8.59 (1H, dull s, ring proton). *Anal.* Calcd for $C_{15}H_{17}N_5O\cdot HClO_4$: C, 46.94; H, 4.73; N, 18.25. Found: C, 46.89; H, 4.88; N, 18.31.

3,9-Dimethyladenine Hydrochloride (3d·HCl) i) By Hydrogenolysis of **17a**·HCl: A solution of **17a**·HCl (500 mg, 2.18 mmol) in 70% (v/v) aqueous EtOH was hydrogenated over 10% Pd–C (750 mg) at atmospheric pressure and room temperature for 7 h. The catalyst was removed by filtration and washed with 70% (v/v) aqueous EtOH (60 ml). The filtrate and washings were combined and concentrated to dryness *in vacuo*, and the residual solid was washed with EtOH (5 ml) and dried to give **3d**·HCl·0.4H_2O (276 mg, 61%), mp 281—282 °C (dec.). Recrystallization from 90% (v/v) aqueous EtOH and drying over P_2O_5 at 2 mmHg and 100 °C for 3.5 h yielded an analytical sample as colorless fine prisms, mp 281—282 °C (dec.); UV (Table III). *Anal.* Calcd for $C_9H_9N_5\cdot HCl\cdot 0.4H_2O$: C, 40.65; H, 5.26; N, 33.86. Found: C, 40.52; H, 5.14; N, 33.93.

ii) Cyclization of **12d**·HCl by Method A: A mixture of **12d**·HCl (218 mg, 1 mmol) and 10% (w/w) methanolic HCl (2 ml) in MeOH (28 ml) was heated under reflux for 8 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was washed with EtOH (3 ml) and dried to give a colorless solid (152 mg, 73%), mp 281—282 °C (dec.), which was identical (by comparison of the IR spectrum and PPC mobility) with the sample of **3d**·HCl·0.4H_2O described above under item (i).

iii) Cyclization of **12d**·HCl by Method C: A stirred suspension of **12d**·HCl (762 mg, 3.5 mmol) in EtOH (60 ml) containing Et_3N (0.05 ml, 0.36 mmol) was heated under reflux for 30 min. After cooling, the precipitate that resulted was filtered off, washed with a little EtOH, and dried to give **3d**·HCl·0.4H_2O (644 mg, 89%) as a colorless solid, mp 281—282 °C (dec.). This sample was identical (by comparison of the IR spectrum and PPC mobility) with the one described above under item (i).

iv) By Cyclization of **21**·HCl with $AcOCH(OEt)_2$: A mixture of **21**·HCl (*vide infra*) (190 mg, 1 mmol), diethoxymethyl acetate[17] (1 ml), and $HCONMe_2$ (5 ml) was stirred at room temperature for 80 min. The reaction mixture was diluted with ether (10 ml), and the precipitate that resulted was collected by filtration, washed with ether (15 ml), and dried to give **3d**·HCl·0.4H_2O (185 mg, 89%), mp 278—280 °C (dec.). This sample was shown to be identical (by comparison of the IR spectrum and PPC behavior) with the one described above under item (i).

3,9-Dimethyladenine Perchlorate (3d·$HClO_4$) i) By Hydrogenolysis of **17a**·$HClO_4$: A solution of **17a**·$HClO_4$ (200 mg, 0.68 mmol) in EtOH (320 ml) was hydrogenated over 10% Pd–C (400 mg) at atmospheric pressure and room temperature for 4 h. The catalyst was removed by filtration and washed thoroughly with hot H_2O. The combined filtrate and washings were concentrated to dryness *in vacuo* to leave **3d**·$HClO_4$ (101 mg, 56%) as a colorless solid, mp >300 °C. Recrystallization from H_2O provided an analytical sample as colorless prisms, mp >300 °C; UV (Table III); NMR (Me_2SO-d_6) δ: 4.10 [3H, s, N(9)-Me], 4.19 [3H, s, N(3)-Me], 8.32 [1H, s, C(8)-H], 8.58 [1H, s, C(2)-H], 9.10 and 9.17 (1H each, s, $=NH_2^+$).[20,25] *Anal.* Calcd for $C_7H_9N_5\cdot HClO_4$: C, 31.89; H, 3.82; N, 26.56. Found: C, 31.58; H, 3.80; N, 26.36.

ii) Cyclization of **12d**·HCl by Method B: A stirred solution of **12d**·HCl (218 mg, 1 mmol) in MeOH (30 ml) containing 70% aqueous $HClO_4$ (290 mg, 2 mmol) was heated under reflux for 7 h. After cooling, the precipitate that deposited was collected by filtration and washed with a little MeOH to give **3d**·$HClO_4$ (213 mg, 81%) as a colorless solid, mp >300 °C. This sample was identical (by comparison of the IR spectrum and PPC behavior) with the one described above under item (i). When a crude sample of **12d**·HCl, obtained by the hydrogenolysis of **10d** (1.27 g, 6 mmol) according to the procedure described above for **12d**·HCl, was similarly cyclized, **3d**·$HClO_4$ was isolated in 75% overall yield (from **10d**).

3-Ethyl-9-methyladenine Hydrochloride (3e·HCl) A solution of crude **12e**·HCl, obtained by the hydrogenolysis of **10e** (338 mg, 1.5 mmol) according to the procedure described above for **12d**·HCl, in EtOH (25 ml) containing Et_3N (0.03 ml, 0.2 mmol) was heated under reflux for 8 h (method C). The reaction mixture was concentrated to dryness *in vacuo*, and the residual solid was washed with EtOH (5 ml) and dried to give **3e**·HCl [169 mg, 53% (from **10e**)], mp 243—244 °C (dec.). Recrystallization from EtOH yielded an analytical sample as colorless prisms, mp 251—252 °C (dec.); UV (Table III). *Anal.* Calcd for $C_8H_{11}N_5\cdot HCl$: C, 44.97; H, 5.66; N, 32.78. Found: C, 44.90; H, 5.74; N, 33.04.

3-Ethyl-9-methyladenine Perchlorate (3e·$HClO_4$) A solution of crude **12e**·HCl, obtained from the hydrogenolysis of **10e** (338 mg, 1.5 mmol) according to the procedure described above for **12d**·HCl, in EtOH (15 ml) containing 70% aqueous $HClO_4$ (250 mg, 1.74 mmol) was heated under reflux for 8 h (method B). After cooling, the precipitate that resulted was filtered off, washed with a little EtOH, and dried to give **3e**·$HClO_4$ [326 mg, 78% (from **10e**)], mp >300 °C. Recrystallization from MeOH furnished an analytical sample as colorless plates, mp >300 °C; UV (Table III). *Anal.* Calcd for $C_8H_{11}N_5\cdot HClO_4$: C, 34.61; H, 4.36; N, 25.22. Found: C, 34.68; H, 4.39; N, 25.20.

9-Ethyl-3-methyladenine Perchlorate (3g·$HClO_4$) i) By Hydrogenolysis of **18b**·$HClO_4$: A solution of **18b**·$HClO_4$ (200 mg, 0.62 mmol) in EtOH (300 ml) was hydrogenated over 10% Pd–C (300 mg) at atmospheric pressure and room temperature for 5 h. The catalyst was removed by filtration and washed with hot EtOH (300 ml). The filtrate and washings were combined and concentrated to dryness *in vacuo*, leaving **18b**·$HClO_4$ (90 mg, 52%), mp >300 °C. Recrystallization from 70% (v/v) aqueous EtOH gave an analytical sample as colorless prisms, mp >300 °C; UV (Table III). *Anal.* Calcd for $C_8H_{11}N_5\cdot HClO_4$: C, 34.61; H, 4.36; N, 25.22. Found: C, 34.77; H, 4.38; N, 25.11.

ii) Cyclization of crude **12g**·HCl in EtOH containing $HClO_4$ (method B) was effected as described above for **3e**·$HClO_4$, giving **3g**·$HClO_4$ (mp >300 °C) in 62% overall yield (from **11g**). This sample was identical (by comparison of the IR spectrum and PPC mobility) with the one obtained by method (i).

9-Benzyl-3-methyladenine Perchlorate (3j·$HClO_4$) i) By Hydrogenolysis of **18c**·$HClO_4$ Using Raney Ni and Hydrogen: A solution of **18c**·$HClO_4$ (300 mg, 0.782 mmol) in MeOH (40 ml) was hydrogenated over Raney Ni W-2 catalyst[33] (300 mg) at atmospheric pressure and room

temperature for 9 h. Hydrogenation was continued for a further 7 h after addition of more (600 mg) catalyst and MeOH (10 ml), and for a further 8 h after another addition of Raney Ni W-2 catalyst (900 mg) and MeOH (10 ml). The catalyst was removed from the reaction mixture by filtration and washed with hot MeOH (50 ml). The filtrate and washings were combined and concentrated to dryness *in vacuo*, leaving a pale greenish solid (188 mg). Recrystallization of the solid from EtOH–MeOH (1 : 1, v/v) afforded **3j**·$HClO_4$ (89 mg, 34%) as slightly greenish pillars, mp 247—248 °C (dec.). This sample was identical (by comparison of the IR spectrum and PPC behavior) with the one prepared by method (ii).

ii) By Cyclization of **12j**·HCl: A solution of crude **12j**·HCl, obtained by the hydrogenolysis of **11j** (301 mg, 1 mmol) according to the procedure described above for **12j**·HCl, in EtOH (5 ml) containing 70% aqueous $HClO_4$ (0.13 ml) and Et_3N (25 μl) was heated at 80 °C for a while and then kept in a refrigerator overnight. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give **3j**·$HClO_4$ (252 mg), mp 236.5—239 °C (dec.), as a first crop. The filtrate and washings were combined and concentrated to a volume of *ca.* 2.5 ml to deposit a second crop (8 mg) of **3j**·$HClO_4$, mp 229—235 °C (dec.). The total yield was 260 mg (77% from **11j**). Recrystallization from MeOH furnished an analytical sample as colorless prisms, mp 248—249 °C (dec.); UV (Table III). *Anal.* Calcd for $C_{13}H_{13}N_5 \cdot HClO_4$: C, 45.96; H, 4.15; N, 20.61. Found: C, 46.17; H, 4.20; N, 20.86.

Cyclizations of 12f, h, i, k, l·HCl Crude samples of **12f, h, i, k, l**·HCl prepared by the hydrogenolyses of **10f** and **11h, i, k, l** according to the procedure described above for **12d**·HCl, were treated with $HClO_4$ in boiling EtOH (but MeOH for **12f**·HCl) (method B) as described above for **3e**·$HClO_4$ or for **3d**·$HClO_4$ under item (ii), and the cyclized products (**3f, h, i, k, l**·$HClO_4$) were characterized as follows.

3-Benzyl-9-methyladenine Perchlorate (3f·$HClO_4$) This was obtained in 68% overall yield from **10f** and recrystallized from EtOH to form colorless prisms, mp 223—224 °C[34]; UV (Table III). *Anal.* Calcd for $C_{13}H_{13}N_5 \cdot HClO_4$: C, 45.96; H, 4.15; N, 20.61. Found: C, 45.82; H, 4.12; N, 20.55.

3,9-Diethyladenine Perchlorate (3h·$HClO_4$) This was obtained in 86% overall yield from **11h** and recrystallized from MeOH to give colorless prisms, mp > 300 °C; UV (Table III). *Anal.* Calcd for $C_9H_{13}N_5 \cdot HClO_4$: C, 37.06; H, 4.84; N, 24.01. Found: C, 36.95; H, 4.91; N, 23.89.

3-Benzyl-9-ethyladenine Perchlorate (3i·$HClO_4$) This was prepared in 67% overall yield from **11i** and recrystallized from MeOH to afford colorless prisms, mp 226—227 °C (dec.); UV (Table III). *Anal.* Calcd for $C_{14}H_{15}N_5 \cdot HClO_4$: C, 47.53; H, 4.56; N, 19.80. Found: C, 47.52; H, 4.45; N, 19.53.

9-Benzyl-3-ethyladenine Perchlorate (3k·$HClO_4$) This was prepared in 61% overall yield from **11k** and recrystallized from MeOH to give colorless needles, mp 256—256.5 °C (dec.); UV (Table III). *Anal.* Calcd for $C_{14}H_{15}N_5 \cdot HClO_4$: C, 47.53; H, 4.56; N, 19.80. Found: C, 47.62; H, 4.60; N, 19.91.

3,9-Dibenzyladenine Perchlorate (3l·$HClO_4$) This was obtained in 36% overall yield from **11l** and recrystallized from EtOH to furnish colorless plates, mp 206—206.5 °C (dec.); UV (Table III). *Anal.* Calcd for $C_{19}H_{17}N_5 \cdot HClO_4$: C, 54.88; H, 4.36; N, 16.84. Found: C, 54.82; H, 4.42; N, 17.11.

Catalytic Hydrogenolysis of 18c·$HClO_4$ to Form N^6-Ethoxy-3-methyladenine (19) and 3-Methyladenine (20) A solution of **18c**·$HClO_4$ (384 mg, 1 mmol) in MeOH (50 ml) was hydrogenated over 10% Pd–C (400 mg) at atmospheric pressure and room temperature for 7 h. The catalyst was removed by filtration and washed with MeOH (50 ml). The combined filtrate and washings were concentrated to dryness *in vacuo* to leave an almost colorless solid (276 mg). The solid was chromatographed on an alumina column using AcOEt and AcOEt–EtOH [8 : 1 (v/v), 6 : 1 (v/v), and then 4 : 1 (v/v)] as the eluents. Concentration of earlier fractions under reduced pressure left an almost colorless glass (88 mg), which was triturated with benzene (0.5 ml). The insoluble solid that resulted was filtered off, washed with benzene (1 ml), and dried to give **19** (73 mg, 38%), mp 160—165 °C (dec.). Recrystallization from AcOEt yielded an analytical sample of **19** as slightly brownish prisms, mp 164.5—165.5 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 295.5 nm (ε 15100); $\lambda_{max}^{H_2O}$ (pH 1) 223.5 (10500), 285.5 (19400); $\lambda_{max}^{H_2O}$ (pH 7) 294 (15500); $\lambda_{max}^{H_2O}$ (pH 13) 285 (11900); NMR (Me_2SO-d_6) δ: 1.21 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 3.48 [3H, s, N(3)-Me], 3.94 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$), 7.59 and 7.74 (1H each, s, ring protons), 11.85—12.45 (1H, br, NH). *Anal.* Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.84; H, 5.75; N, 36.03.

Later fractions in the above chromatography furnished **20** (38 mg, 25%) as a slightly yellowish solid, mp 290—300 °C (dec.). Recrystallization from a little H_2O produced a pure sample as colorless needles, mp 301.5—302.5 °C (dec.); this product was identical (by mixture melting point test and comparison of the IR spectrum and PPC behavior) with authentic **20**.[35]

1-Methyl-5-(methylamino)-1*H*-imidazole-4-carboxamidine Hydrochloride (21·HCl) A solution of **15a** (916 mg, 5 mmol) in H_2O (100 ml) containing 1 N aqueous HCl (5 ml) was hydrogenated over Raney Ni W-2 catalyst[33] (900 mg) at atmospheric pressure and room temperature for 3 h. The catalyst was removed by filtration and washed with H_2O (20 ml). The combined filtrate and washings were concentrated to dryness *in vacuo* to leave a pale orange solid (906 mg), which was triturated with boiling EtOH (10 ml). After cooling, the ethanolic mixture was filtered to remove an insoluble solid, and the filtrate was concentrated *in vacuo* to leave **21**·HCl (796 mg, 84%) as a slightly violet solid, mp 180—182 °C. Recrystallization from EtOH yielded an analytical sample as colorless plates, mp 182—183 °C; UV $\lambda_{max}^{95\%\ EtOH}$ 275 nm (ε 6400); $\lambda_{max}^{H_2O}$ (pH 1) 260 (sh) (4300), 290 (8850); $\lambda_{max}^{H_2O}$ (pH 7) 277 (6000); $\lambda_{max}^{H_2O}$ (pH 13) 252 (sh) (7050); NMR (Me_2SO-d_6) δ: 2.74 (3H, dull d, J = 3.3 Hz, NH$\underline{Me}$), 3.58 [3H, s, N(1)-Me], 5.88 (1H, br, N$\underline{H}$Me), 7.62 [1H, s, C(2)-H], 8.50 (4H, br, NH_2 and NH_2^+). *Anal.* Calcd for $C_6H_{11}N_5 \cdot HCl$: C, 38.00; H, 6.38; N, 36.93. Found: C, 37.89; H, 6.65; N, 36.91.

3,5′-Cyclo-2′,3′-*O*-isopropylideneadenosine Perchlorate (22) A solution of $NaClO_4 \cdot H_2O$ (190 mg, 1.3 mmol) in H_2O (1 ml) was added to a hot solution of 3,5′-cyclo-2′,3′-*O*-isopropylideneadenosine *p*-toluenesulfonate (**23**)[2a] (400 mg, 0.87 mmol) in H_2O (3 ml). After cooling, the crystals that deposited were filtered off, washed with a little H_2O, and dried to give **22** (308 mg, 91%), mp 277—278 °C (dec.). Recrystallization from 50% (v/v) aqueous EtOH provided an analytical sample as colorless plates, mp 277—278 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 274 nm (ε 14200); $\lambda_{max}^{H_2O}$ (pH 1) 272 (15700); $\lambda_{max}^{H_2O}$ (pH 7) 272 (14900); $\lambda_{max}^{H_2O}$ (pH 13) unstable. *Anal.* Calcd for $C_{13}H_{15}N_5O_3 \cdot HClO_4$: C, 40.06; H, 4.14; N, 17.97. Found: C, 40.17; H, 4.24; N, 17.91.

Conversion of 3d·HCl into 3,9-Dimethyladenine Bicarbonate (3d·H_2CO_3) A solution of **3d**·HCl·0.4H_2O (60 mg, 0.29 mmol) in H_2O (1 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (1 ml), and the column was eluted with H_2O (15 ml). The eluate was concentrated to dryness *in vacuo* below 40 °C to leave **3d**·H_2CO_3 (63 mg, 97%) as a colorless solid, mp 159—161 °C (dec.). The solid was dissolved in a little H_2O, and EtOH was added to the resulting aqueous solution to deposit a pure sample as fine prisms, mp 161—162 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 272 nm (ε 15400); $\lambda_{max}^{H_2O}$ (pH 1) 270 (15600); $\lambda_{max}^{H_2O}$ (pH 7) 270 (15500); $\lambda_{max}^{H_2O}$ (pH 13) unstable. *Anal.* Calcd for $C_7H_9N_5 \cdot H_2CO_3$: C, 42.67; H, 4.92; N, 31.10. Found: C, 42.60; H, 4.93; N, 31.02.

Treatment of 3d·HCl with Amberlite CG-400 (OH^-) in H_2O A solution of **3d**·HCl·0.4H_2O (207 mg, 1 mmol) in H_2O (3 ml) was passed through a column of Amberlite CG-400 (OH^-) (16 ml), and the column was eluted with H_2O (26 ml). The eluate was concentrated to dryness *in vacuo*, and the residue was dissolved in MeOH (10 ml). After addition of Et_3N·HCl (151 mg, 1.1 mmol), the methanolic solution was concentrated *in vacuo*, and the residue was washed with cold EtOH (0.5 ml) and dried to give **21**·HCl (115 mg, 61%), mp 180—181 °C. Recrystallization from EtOH gave a pure sample as colorless plates, mp 182—183 °C, shown to be identical (by mixture melting point test and comparison of the IR spectrum and PPC mobility) with the one obtained by hydrogenolysis of **15a** (*vide supra*).

Treatment of 12d·HCl with Amberlite CG-400 (OH^-) in H_2O A solution of **12d**·HCl (218 mg, 1 mmol) in H_2O (1 ml) was passed through a column of Amberlite CG-400 (OH^-) (16 ml), and the column was eluted with H_2O (26 ml). The eluate was worked up as in the case of **3d**·HCl (*vide supra*), giving **21**·HCl (138 mg, 73%), mp 181—182 °C, identical with an authentic sample.

Cyclization of 12d·HCl in 0.5 M Aqueous $NaHCO_3$ A solution of **12d**·HCl (152 mg, 0.7 mmol) in 0.5 M aqueous $NaHCO_3$ (14 ml) was kept at 25 °C for 6 h. The pH of the reaction mixture was adjusted to 6 by addition of 70% aqueous $HClO_4$. The precipitate that resulted was filtered off, washed with a little H_2O, and dried to give **3d**·$HClO_4$ (122 mg, 66%), mp > 300 °C, identical with an authentic sample.

Kinetic Procedure The ring-opening reactions of **3d**·HCl and **3f**·$HClO_4$ and cyclizations of **12d**·HCl and **12f**·$HClO_4$ in 0.1 M aqueous $NaHCO_3$ (pH 8.32) at 25 °C were followed by UV spectrophotometry. The substrates were separately dissolved, at a concentration of *ca.* 5×10^{-4} M, in 0.1 M aqueous $NaHCO_3$ kept at 25 ± 0.05 °C in a thermoregulated constant-temperature bath. At intervals, 2-ml samples were withdrawn and diluted with 0.2 M aqueous KH_2PO_4 by a factor of 10 in order to quench the reaction. The optical densities of the diluted solutions at 270 or

272 nm were determined, and the concentration of the substrate was then calculated in the usual manner. In all cases, good pseudo-first-order kinetics were obtained,[28] and the results are summarized in the text and Fig. 1.

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27) The instability of **3d**·HCl in the alkaline region made the pK_a measurement extremely difficult. According to a private communication from Professor W. Pfleiderer (Konstanz), he has also encountered a similar difficulty with a sample of **3d**·HCl obtained from us.
28) *a*) K. J. Laidler, "Chemical Kinetics," McGraw-Hill, New York, 1965, pp. 19—21; *b*) S. S. Jones and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2762.
29) T. Fujii, T. Saito, and T. Nakasaka, *Heterocycles*, **15**, 195 (1981).
30) T. Fujii, T. Saito, I. Inoue, Y. Kumazawa, and K. Tamura, *Chem. Pharm. Bull.*, **36**, 107 (1988).
31) T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.*, **19**, 1368 (1971).
32) The observed complexity of the proton signals is interpretable in terms of *cis–trans* isomerism of the formamido moiety.[13a–d,f,19]
33) R. Mozingo, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, New York, 1955, p. 181.
34) In our preliminary communication,[9] the melting point of **3f**·$HClO_4$ was erroneously reported as "mp > 300°C." See also footnote 11 in ref. 11*f* for the correction to the melting point.
35) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 1914 (1962).