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PURINES—III[1]

REARRANGEMENT OF 1-ALKOXY-9-ALKYLADENINES TO 6-ALKOXYAMINO-9-ALKYLPURINES THROUGH ISOLABLE N'-ALKOXY-1-ALKYL-5-FORMAMIDOIMIDAZOLE-4-CARBOXAMIDINES[2]

T. FUJII,[a]* T. ITAYA,[a] C. C. WU[b] and F. TANAKA[a]

[a] Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

[b] Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Tokyo 113, Japan

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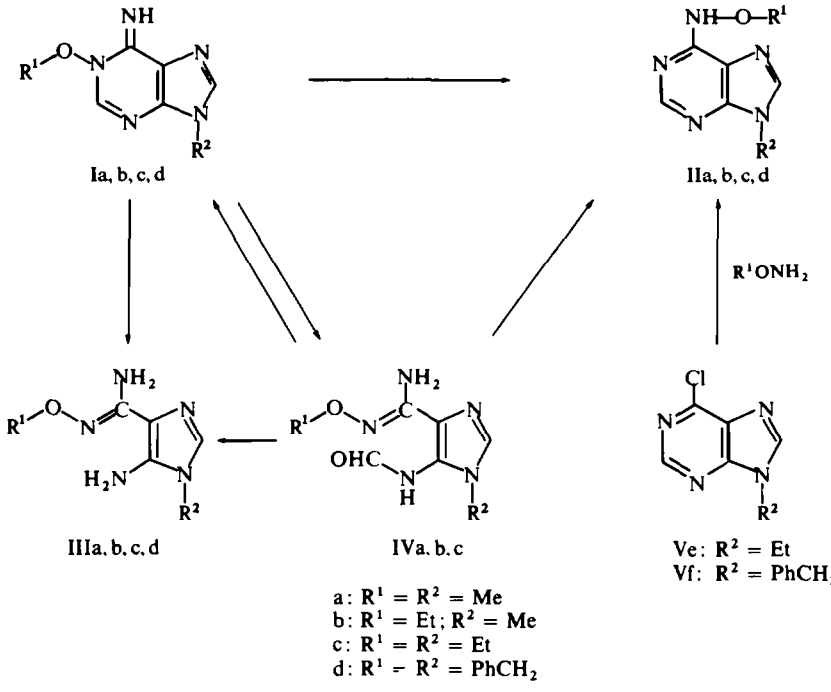
Abstract—The Dimroth rearrangement of 1-alkoxy-9-alkyladenines (Ia, b, c, d) to 6-alkoxyamino-9-alkylpurines (IIa, b, c, d) was readily effected by treating the free bases (I) with boiling water. On the other hand, treatment of the 1-alkoxy derivatives (Ia, b, c) with water at a lower temperature produced N'-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidines (IVa, b, c), the intermediates in the Dimroth rearrangements, in good yields. When heated in water, IVa, b, c were recyclized to the rearranged products (IIa, b, c) with formation of a trace of the reversion products (Ia, b, c). The reaction of I with hot aqueous alkali afforded N'-alkoxy-1-alkyl-5-aminoimidazole-4-carboxamidine (III), the deformylated product of IV, and a small amount of the rearranged product (II). Treatment of IVc with alkali also gave IIIc and a small amount of IIc, whereas the reaction with acid resulted in the rapid reversion to Ic.

SINCE the first observation of Rathke in 1888 on a triazine derivative,[3] the Dimroth rearrangement[4] which involves the apparent migration of an alkyl group from heterocyclic nitrogen to an α-amino or α-imino group has been found in many ring systems. The studies with ^{15}N on the conversion of 1,2-dihydro-2-imino-1-methylpyrimidine into 2-methylaminopyrimidine by Brown[5] and by Goerdeler and Roth[6] support the postulated gross mechanism[7–10] of ring fission followed by rotation and recyclization for the rearrangement in such heterocyclic systems. As part of a study of the synthesis of 1-alkoxy-9-alkyladenines (type I),[1,11–13] we were interested in studying some aspects of the chemistry of such a new class of adenine derivatives. This paper[2] describes a facile Dimroth rearrangement of I into 6-alkoxyamino-9-alkylpurine (II) and isolation and characterization of N'-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidine (IV), an intermediate in the rearrangement.

The free bases (Ia, b, c, d) of 1-alkoxy-9-alkyladenines used in the present work were prepared from the corresponding salts, hydriodide, hydrobromide, or perchlorate, according to the procedure reported previously.[11,12] When 1-ethoxy-9-ethyladenine (Ic) was treated with boiling water for 3 hr, 6-ethoxyamino-9-ethylpurine (IIc) was obtained in 77% yield. Likewise, 1-methoxy-9-methyladenine (Ia) gave 6-methoxyamino-9-methylpurine (IIa) in 74% yield; 1-ethoxy-9-methyladenine (Ib), 6-ethoxyamino-9-methylpurine (IIb) in 74% yield. A similar treatment of 1-benzyloxy-9-benzyladenine (Id) at pH 8 for 1·5 hr afforded 6-benzyloxyamino-9-benzylpurine

* To whom correspondence should be addressed.



Scheme 1

(IId) in a good yield. The 6-alkoxyamino derivatives (IIa, b, c, d) thus obtained were characterized by correct analyses of the free bases and the corresponding hydrochlorides for the respective structures, similarity of their UV spectra at different pH's (Table 1), and identity (for IIc and IId) with the samples synthesized from 6-chloro-9-alkylpurines (Ve, f) and the requisite alkoxyamines. Although compounds I possess the electron-withdrawing alkoxyl groups at the 1-position, they are still strong bases as seen from their high *pKa* values (e.g. 8·62 for Ic),[12] and their aqueous solutions are evidently alkaline. This would have caused to facilitate the above-mentioned rearrangement in boiling water without recourse to any other bases.

On the other hand, the reaction of the 1-alkoxy derivatives (Ia, b, c) with water at a lower temperature was found to result in the ring fission to give the monocyclic derivatives (IVa, b, c). Thus, treatment of Ic with water at 4–5° furnished N'-ethoxy-1-ethyl-5-formamidoimidazole-4-carboxamidine (IVc) in 76% yield. As shown in Table 1, its UV spectra were unlike those of the starting material (Ic) or the rearranged product (IIc) and suggested the breakdown of the adenine ring. The IR spectrum of IVc in a dilute (0·005 M) solution in $CHCl_3$ showed evident absorption bands at 3500 (NH_2), 3390 (NH_2 and CONH), and 1705 cm^{-1} (CONHAr) indicative of the ring-opened structure (IVc), which was also supported by the NMR spectrum obtained in deuterated dimethyl sulfoxide. As illustrated in part in Fig 1, it exhibited two three-proton triplets (J = 7 c/s each) at 8·81 and 8·73 τ and two two-proton quartets (J = 7 c/s each) at 6·18 and 6·10 τ ($N_{(1)}$-Et and OEt), a fairly sharp two-proton peak at 4·37 τ (NH_2, disappeared on addition of D_2O), a sharp one-proton singlet at

2·31 τ ($C_{(2)}$-H), and a combination of a set of two peaks at 1·75 (HCON, *cis*-IVc) and 0·40 τ (CONH, *cis*-IVc) with a pair of AB type doublets (J = 11 c/s) at 1·91 (HCON, *trans*-IVc) and 0·55 τ (CONH, *trans*-IVc) most probably due to *cis-trans* isomerism caused by restricted rotation about the central C—N bond in the formamido group[14] at the 5-position (see Scheme 2). Since the $N_{(1)}$-ethyl, O-ethyl, and/or amino groups are situated in close proximity to the formamido function, chemical shifts for such groups corresponding to *cis*- and *trans*-IVc might be different. In this case, however, it is most likely that the signals for the $N_{(1)}$-ethyl groups of *cis*- and *trans*-IVc are overlaid with those for the O-ethyl groups of both isomers, and chemical shifts for the

TABLE 1. UV SPECTRA OF ADENINES AND IMIDAZOLES

Compound	UV spectra							
	Solvent E[a]		Solvent A[b]		Solvent N[c]		Solvent B[d]	
	λ_{max} (mμ)	$\varepsilon \times 10^{-3}$	λ_{max} (mμ)	$\varepsilon \times 10^{-3}$	λ_{max} (mμ)	$\varepsilon \times 10^{-3}$	λ_{max} (mμ)	$\varepsilon \times 10^{-3}$
IIa	268	13·1	269	13·0	268	13·8	284	11·0
IIb	268	13·2	269	14·7	268	14·6	284	11·1
IIc	268	13·6	269	14·6	268	14·7	284	11·2
IId	271	15·3	272	15·5	—	—	287	12·3
IIIa	263	12·0	281	10·5	263	10·6	263	10·6
IIIb	—	—	282	9·5	263	9·4	263	9·4
IIIc	264	11·9	283	10·9	264	10·8	264	10·8
IIId[e]	267	13·1	288	9·0	265	11·3	265	11·0
IVa	222	13·1	255	7·3	219	11·5	256	10·4
	253[f]	6·1			247[f]	6·7		
IVb	222	12·8	255	8·0	220	11·9	254	11·1
	251[f]	6·7			247[f]	7·1		
IVc	221	12·6	253	7·9	218	11·9	250	10·8
	252[f]	6·3			247[f]	6·9		

[a] 95% EtOHaq.
[b] 0·1 N HClaq (pH 1).
[c] 0·005 M phosphate buffer (pH 7).
[d] 0·1 N NaOHaq (pH 13).
[e] Measured in slightly modified solvents; 95% EtOHaq was added to the extent of 5% (v/v) to each of solvents A, N, and B in order to make a clear solution.
[f] shoulder.

amino groups in both isomers are virtually identical, or they are located in such a manner that the *cis*- and *trans*-formamido groups do not affect them.

Final identification as IVc rested on its simultaneous recyclizations to Ic (minute amount) and IIc (84% yield) when heated in water for 5 hr. To our knowledge, the isolation of the intermediate (IVc) seems to be the first example for the Dimroth rearrangement in the adenine series.*

Treatment of Ia and Ib with cold water in the same way as described above also afforded the corresponding imidazole derivatives (IVa, b). Similarly to the case of IVc,

* In the pyrimidine series, isolation of a ring-opened intermediate[15] (or as oximes[16]) has been reported recently.

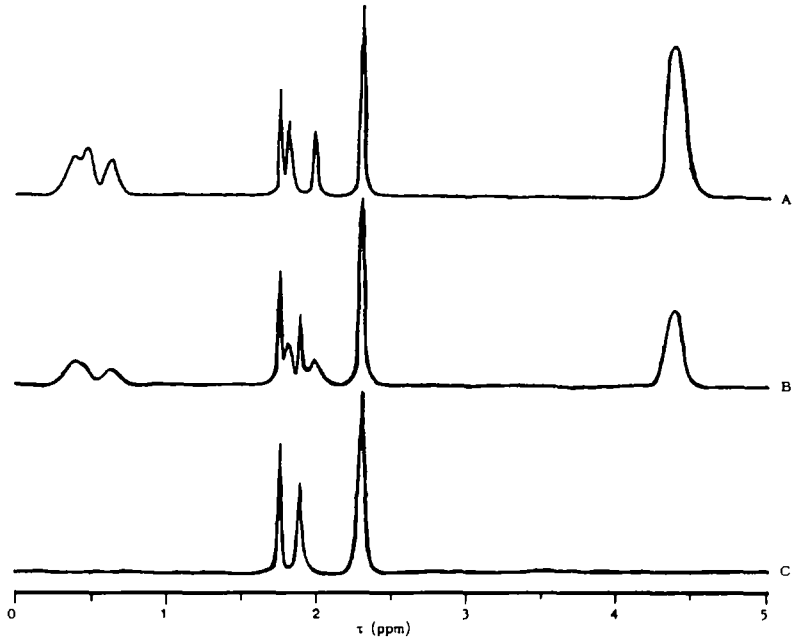
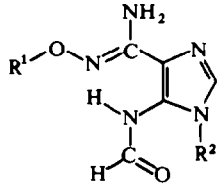
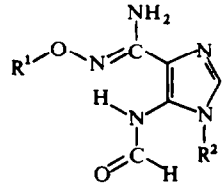


FIG 1. The NMR spectrum of IVc in DMSO-d_6 at 60 Mc/s and 23° (Curve A); Curve B, after addition of an insufficient amount of D_2O; Curve C, after complete addition of a sufficient amount of D_2O.

they were characterized by correct analyses for the ring-opened structure (IV), UV, IR, and NMR spectra. The NMR spectrum of IVa in deuterated dimethyl sulfoxide displayed two singlets at 6·59 and 6·54 τ ($N_{(1)}$-Me's due to *cis-trans* isomerism of IVa), two singlets at 6·38 and 6·34 τ (OMe's due to *cis-trans* isomerism of IVa), a fairly sharp two-proton peak at 4·42 τ (NH_2), a sharp one-proton singlet at 2·43 τ ($C_{(2)}$-H), two peaks at 1·95 (dull, HCON of *trans*-IVa) and 1·80 τ (sharp, HCON of *cis*-IVa), and a broad one-proton peak at 0·55 τ (CONH's of *cis*- and *trans*-IVa). Compound IVb showed a similar pattern in the NMR spectrum, but the two singlets at 6·38 and 6·34 τ for the O-methyl groups of *cis*- and *trans*-IVa were replaced with a three-proton triplet at 8·80 τ (overlapped OCH_2Me's of *cis*- and *trans*-IVb) and two quartets at 6·11



cis-IVa, b, c



trans-IVa, b, c

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

SCHEME 2

and 6·06 τ (OCH_2Me's due to *cis-trans* isomerism of IVb). When heated in water for 5·5 hr, IVa also gave a trace of Ia and a large amount (76% yield) of IIa simultaneously.

In ample precedents for the Dimroth rearrangement, the reactions have been accomplished in hot aqueous alkali, and sometimes they give degraded products derived from the postulated intermediates.[4] Accordingly, we next turned our attention to the reaction of I at a higher pH. When a solution of Ic in dilute NaOHaq was refluxed for 15 min, N′-ethoxy-1-ethyl-5-aminoimidazole-4-carboxamidine (IIIc), the deformylated product, was obtained in 71% yield with a small amount (7% yield) of the rearranged product (IIc). The assignment of structure IIIc was based on correct analysis for $C_8H_{15}ON_5$, UV spectra at various pH's (Table 1), and NMR spectrum. The NMR spectrum in deuterated dimethyl sulfoxide revealed two three-proton triplets (J = 7 c/s each) at 8·78 and 8·73 τ and two two-proton quartets (J = 7 c/s each) at 6·15 and 6·07 τ ($N_{(1)}$-Et and OEt), two considerably sharp two-proton peaks at 4·66 and 4·51 τ (two NH_2's, disappeared on addition of D_2O), and a sharp one-proton singlet at 2·83 τ ($C_{(2)}$-H). Since IIIc was also obtained from IVc by treating it with aqueous alkali under the same reaction conditions, it would be reasonable to assume that the conversion of Ic into IIIc might proceed through IVc. Treatment of Ia, Ib, and Id with alkali in a similar manner also furnished the corresponding primary amine (IIIa, b, d)[17] as the major product and the rearranged product (IIa, b, d) as the minor product.

Further interest in the intermediate (IV) stems from its behavior at a lower pH. When IVc was treated with 0·2 N perchloric acid at 20°, Ic was produced in 75% yield with the formation of a trace of IIc and IIIc. The half life of the reversion to Ic at pH 1 (HCl) and 25° was roughly estimated at *ca* 4 hr by following the progress of the reaction spectrophotometrically. It is of interest to note that much more rapid reversion in acid has been observed for few acyclic intermediates of the Dimroth rearrangements in the pyrimidine series.[15]

In conclusion, the isolation of the intermediate (IV) in the rearrangement of I to II described above indicates that the rate of reaction I → IV is much faster than that of reaction IV → II, and the latter reaction is slow enough to enable IV to come out of the reaction mixture. The facile ring-opening of 1-alkoxy-9-alkyladenines (I), coupled with the reaction sequence[1,12] by which they are readily synthesized, may find ways to be utilized for chemical modification of adenine derivatives* and nucleic acids in the pyrimidine moieties of adenine residues.

EXPERIMENTAL

All m.ps are corrected. Paper chromatographies were developed as described previously.[1] See also Refs 1 and 12 for details of instrumentation and measurement.

6-Ethoxyamino-9-ethylpurine (IIc)

(i) *Rearrangement of* Ic. A soln of 1-ethoxy-9-ethyladenine hydriodide (Ic·HI)[1,12] (3·02 g, 9 mmoles) in H_2O (150 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (15 ml), and eluted with H_2O. The eluate (1 liter) was concentrated *in vacuo* to a small volume (100 ml), and the resulting soln was refluxed for 3 hr and evaporated *in vacuo* to leave a solid. The residue was washed with a small amount of EtOH and dried to give a paper chromatographically pure sample of IIc (1·44 g, 77%). Recrystallization from H_2O afforded colorless prisms, m.p. 189–190° (dec); pKa (at 20°) 3·21 ± 0·12, 11·53 ± 0·06; UV (Table 1).

* See, for example, the recent synthesis of 2-aza-adenosine from 1-benzyloxyadenosine (type I) reported by Montgomery and Thomas.[17]

(Found: C, 51·96; H, 6·20; N, 33·95. $C_9H_{13}ON_5$ requires: C, 52·16; H, 6·32; N, 33·80%).

The *hydrochloride* of IIc was prepared from a portion (300 mg) of IIc by dissolving it in EtOH (50 ml) and adding 8·7% (w/v) ethanolic HCl (10 ml). The mixture was concentrated to *ca* 10 ml and Et_2O (50 ml) was added to separate colorless needles in 97% yield. Recrystallization from EtOH furnished an analytical sample, m.p. 215–216° (dec). (Found: C, 44·32; H, 5·98; N, 28·80. $C_9H_{14}ON_5Cl$ requires: C, 44·35; H, 5·79; N, 28·74%).

(ii) *Metathesis of* Ve *with ethoxyamine.* A mixture of 6-chloro-9-ethylpurine (Ve)[18] (300 mg, 1·64 mmoles) and ethoxyamine[19] (1·2 ml) was refluxed for 3 hr. The crystals that separated were filtered, washed successively with a small amount of EtOH and Et_2O, and dried to give IIc (250 mg), m.p. 189–190° (dec). The filtrate and washings were combined and evaporated *in vacuo* to dryness. The residue was dissolved in H_2O and passed through a column of Amberlite IRA-402 (HCO_3^-) (4 ml), and the column was eluted with H_2O. The eluate (300 ml) was evaporated *in vacuo* to dryness to leave almost colorless prisms (50 mg) as the second crop. Total yield, 300 mg (88%). For purification, the crude sample was recrystallized from EtOH to yield IIc as colorless prisms, m.p. 189–190° (dec). Identity of this sample with the one obtained by method-(i) was established by m.m.p. and comparison of their UV and IR spectra.

(iii) *Cyclization of* IVc. A suspension of IVc (1·04 g, 4·62 mmoles) in H_2O (40 ml) was refluxed for 5 hr, and the resulting soln was evaporated *in vacuo* to leave a solid. The solid was washed with EtOH (3 ml) and dried to give IIc (800 mg, 84%), m.p. 189–190° (dec). Recrystallization from H_2O provided a pure sample as colorless prisms, m.p. 189–190° (dec), undepressed in m.p. on admixture with the sample obtained by method-(i). The IR spectra of both samples were also identical. The formation of a trace of the reversion product (Ic) during the reaction was evidenced by paper chromatographies using three different solvent systems.

6-*Methoxyamino*-9-*methylpurine* (IIa)

(i) *Rearrangement of* Ia. By treating 1-methoxy-9-methyladenine hydriodide (Ia·HI)[1,12] as described above for IIc [method-(i)], IIa was obtained in 74% yield. Recrystallization from H_2O furnished an analytical sample as colorless prisms, m.p. 239° (dec); pKa (at 20°) 3·06 ± 0·05, 11·26 ± 0·07; UV (see Table 1). (Found: C, 47·15; H, 5·10; N, 38·86. $C_7H_9ON_5$ requires: C, 46·92; H, 5·06; N, 39·09%).

The *hydrochloride* of IIa, prepared in the same way as described for that of IIc, was recrystallized from EtOH–Et_2O to give colorless needles, m.p. 225–226° (dec). (Found: C, 38·99; H, 4·95; N, 32·78. $C_7H_{10}ON_5Cl$ requires: C, 38·99; H, 4·67; N, 32·48%).

(ii) *Cyclization of* IVa. The cyclization of IVa in boiling H_2O was carried out as described above for that of IVc, and IIa, m.p. 239° (dec), was obtained in 76% yield. The presence of the reversion product (Ia) in the mother liquor of recrystallization of the crude IIa was indicated by paper chromatographies using three different solvent systems.

6-*Ethoxyamino*-9-*methylpurine* (IIb)

This was prepared from 1-ethoxy-9-methyladenine hydriodide (Ib·HI)[1,13] in 74% yield in the same manner as described above. Recrystallization from 70% EtOH aq gave IIb as colorless prisms, m.p. 212–214° (dec); *pKa* (at 20°) 3·19 ± 0·07, 11·49 ± 0·05; UV (Table 1). (Found: C, 49·92; H, 5·67; N, 36·11. $C_8H_{11}ON_5$ requires: C, 49·73; H, 5·74; N, 36·25%).

6-*Benzyloxyamino*-9-*benzylpurine* (IId)

(i) *Rearrangement of* Id. The monohydrate (1·48 g, 3·44 mmoles) of 1-benzyloxy-9-benzyladenine hydrobromide (Id·HBr)[1,12] was dissolved in H_2O (150 ml) by warming. The soln was basified with sat $NaHCO_3$ aq to pH 8 and heated at reflux for 1·5 hr. The colorless crystals that resulted were filtered, washed with H_2O, and dried. The crystals (980 mg, 86%), m.p. 197–200° (dec), were recrystallized from EtOH to afford IId as colorless plates, m.p. 210–211° (dec); UV (Table 1). (Found: C, 68·94; H, 5·16; N, 21·31. $C_{19}H_{17}ON_5$ requires: C, 68·86; H, 5·17; N, 21·14%).

The *hydrochloride* of IId, m.p. 210–211° (dec), was prepared and recrystallized in the same way as described for that of IIc. (Found: C, 62·06; H, 5·11; N, 19·21. $C_{19}H_{18}ON_5Cl$ requires: C, 62·04; H, 4·93; N, 19·04%).

(ii) *Reaction of* Vf *with benzyloxyamine.* A mixture of 6-chloro-9-benzylpurine (Vf)[18] (300 mg, 1·23 mmoles) and benzyloxyamine[19] (3·00 g, 24·4 mmoles) was heated at 80° (bath temp) for 4 hr. The crystals that separated were filtered, washed with EtOH, and recrystallized from EtOH to give IId (400 mg, 98%) as colorless plates, m.p. 210–211° (dec). This sample was identical (m.m.p., TLC, and UV and IR spectra) with the one obtained by method-(i).

Isolation of the intermediates (IVa, b, c)

The procedure employed for IVc will be described in detail. The isolations of the other intermediates (IVa, b) were accomplished similarly.

N'-*Ethoxy*-1-*ethyl*-5-*formamidoimidazole*-4-*carboxamidine* (IVc). A soln of 1-ethoxy-9-ethyladenine hydriodide (Ic·HI)[1,12] (2·01 g, 6 mmoles) in H_2O (100 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (14·5 ml), and the column was eluted with H_2O. The eluate (400 ml) was concentrated *in vacuo* to a volume of *ca* 50 ml and kept standing in a refrigerator for 48 hr. The soln was then concentrated *in vacuo* to a small volume (*ca* 5 ml) and kept in a refrigerator overnight. The ppts that resulted were filtered to give IVc (570 mg), m.p. 161–164°. The mother liquor was evaporated *in vacuo* to dryness, and a few drops of H_2O was added to the residue. The resulting soln was kept at room temp overnight, and the crystals that separated were collected as the second crop (460 mg). Total yield, 1·03 g, (76%). Recrystallization from EtOH produced IVc as colorless prisms, m.p. 164–166°; pKa (at 20°) 3·78 ± 0·04, 10·97 ± 0·08; UV (Table 1); IR and NMR (see Theoretical part and Fig 1); Mass Spectrum *m/e*: 225 (M^+). (Found: C, 47·90; H, 6·71; N, 31·27. $C_9H_{15}O_2N_5$ requires: C, 47·99; H, 6·71; N, 31·09%).

N'-*Methoxy*-1-*methyl*-5-*formamidoimidazole*-4-*carboxamidine* (IVa). This was obtained from the hydriodide[1,12] of Ia in 61% yield and recrystallized from EtOH to give colorless prisms, m.p. 178° (dec); *pKa* (at 20°) 3·57 ± 0·04, 10·90 ± 0·03; UV (Table 1); $IR\nu_{max}^{CHCl_3}$ (in 0·005 M soln) cm^{-1}: 3505 (NH_2), 3400 (NH_2 and CONH), 1705 (CONHAr); NMR (see Theoretical part). (Found: C, 42·83; H, 5·86; N, 35·48. $C_7H_{11}O_2N_5$ requires: C, 42·63; H, 5·62; N, 35·52%).

N'-*Ethoxy*-1-*methyl*-5-*formamidoimidazole*-4-*carboxamidine* (IVb). Compound IVb was prepared from the hydriodide[1,13] of Ib in 72% yield and recrystallized from EtOH to afford colorless minute needles, m.p. 152–153°; *pKa* (at 20°) 3·77 ± 0·06, 10·95 ± 0·06; UV (Table 1); $IR\nu_{max}^{CHCl_3}$ (in 0·005 M soln) cm^{-1}: 3505 (NH_2), 3395 (NH_2 and CONH), 1705 (CONHAr); NMR (DMSO-d_6) τ: 8·80 (3H, t, J = 7 c/s, overlapped OCH_2Me's of *cis*- and *trans*-IVb), 6·56 and 6·52 (s each, $N_{(1)}$-Me's due to *cis-trans* isomerism of IVb), 6·11 and 6·06 (q each, J = 7 c/s, OCH_2Me's due to *cis-trans* isomerism of IVb), 4·46 (2H, NH_2), 2·39 (1H, s, $C_{(2)}$-H), 1·91 (dull, HCON of *trans*-IVb), 1·78 (s, HCON of *cis*-IVb), 0·57 (broad, CONH of both isomers). (Found: C, 45·36; H, 6·17; N, 33·38. $C_8H_{13}O_2N_5$ requires: C, 45·49; H, 6·20; N, 33·16%).

N'-*Ethoxy*-1-*methyl*-5-*aminoimidazole*-4-*carboxamidine* (IIIb)

A mixture of 1-ethoxy-9-methyladenine hydriodide (Ib·HI)[1,13] (6·42 g, 0·02 mole) and NaOH (5 g) in H_2O (100 ml) was refluxed for 15 min. The soln was neutralized with 10% HCl aq and evaporated *in vacuo* to dryness. The residual solid was continuously extracted with benzene by using a Soxhlet extractor. The benzene extracts were evaporated *in vacuo* to leave a solid, which was triturated with AcOEt (20 ml). The insoluble crystals were filtered, washed with AcOEt (5 ml), and dried to give IIb (179 mg, 5%), m.p. 209–211° (dec). Recrystallization from 70% EtOH aq produced a pure sample of IIb as colorless prisms, m.p. 212–213° (dec), identified with the sample described above by m.m.p. and IR spectrum.

The AcOEt soln and washings, which were obtained when IIb was filtered, were combined and evaporated to dryness, and the residue was purified by column chromatography [silica gel (200 g), AcOEt—EtOH (4:1)]. The fractions shown to be homogeneous by TLC were combined and evaporated to give slightly brownish prisms (2·66 g, 73%), m.p. 85–91°. Recrystallizations from C_6H_6 gave IIIb as colorless prisms, m.p. 90–92°; UV (Table 1); NMR (DMSO-d_6) τ: 8·80 (3H, t, J = 7 c/s, OCH_2Me), 6·60 (3H, s, $N_{(1)}$-Me), 6·12 (2H, q, J = 7 c/s, OCH_2Me), 4·71 (2H, slightly dull, NH_2), 4·54 (2H, slightly dull, NH_2), 2·91 (1H, s, $C_{(2)}$-H); Mass Spectrum *m/e*: 183 (M^+). (Found: C, 45·62; H, 7·15; N, 38·32. $C_7H_{13}ON_5$ requires: C, 45·89; H, 7·15; N, 38·23%).

N'-*Methoxy*-1-*methyl*-5-*aminoimidazole*-4-*carboxamidine* (IIIa)

A similar treatment of the hydriodide[1,12] of Ia with NaOH aq to that described for IIIb gave IIa (3%), m.p. 239° (dec), and IIIa (56%) as colorless prisms (recrystallized from AcOEt), m.p. 153–155°; UV (Table 1); NMR (DMSO-d_6) τ: 6·57 (3H, s, $N_{(1)}$-Me), 6·32 (3H, s, OMe), 4·69 (2H, NH_2), 4·47 (2H, NH_2), 2·91 (1H, s, $C_{(2)}$-H); Mass Spectrum *m/e*: 169 (M^+). (Found: C, 42·87; H, 6·60; N, 41·41. $C_6H_{11}ON_5$ requires: C, 42·59; H, 6·55; N, 41·40%).

N'-*Ethoxy*-1-*ethyl*-5-*aminoimidazole*-4-*carboxamidine* (IIIc)

(i) *From* Ic. A mixture of 1-ethoxy-9-ethyladenine hydriodide (Ic·HI)[1,12] (10·06 g, 0·03 mole) and NaOH (7·5 g) in H_2O (150 ml) was refluxed for 15 min. The pH of the resulting soln was adjusted to 8 with 10% HCl aq, and the soln was concentrated *in vacuo* to a volume of *ca* 30 ml. The ppts that resulted were filtered,

washed with H_2O (50 ml), and dried to give crude IIIc (4·22 g, 71%), m.p. 129–134°. Recrystallization from H_2O furnished an analytical sample as colorless prisms, m.p. 134–135°; UV (Table 1); NMR (see Theoretical part); Mass Spectrum *m/e*: 197 (M^+). (Found: C, 48·89; H, 7·60; N, 35·43. $C_8H_{15}ON_5$ requires: C, 48·71; H, 7·67; N, 35·51%).

The filtrate and washings, which were obtained when the crude IIIc was filtered, were combined and evaporated *in vacuo* to dryness. The residual solid was continuously extracted with C_6H_6 by the use of a Soxhlet extractor, and the extracts were evaporated *in vacuo* to dryness leaving a solid, which was successively washed with AcOEt and C_6H_6 to give crude IIc (422 mg, 7%), m.p. 188–189° (dec). Recrystallization from H_2O gave a pure sample of IIc, m.p. 189–190° (dec), identical (by m.m.p. and comparison of the IR spectra) with the one prepared from Ve and ethoxyamine.

(ii) *From* IVc. A suspension of IVc (2·25 g, 0·01 mole) in a soln of NaOH (2·5 g) in H_2O (50 ml) was heated at reflux for 15 min. The soln was neutralized with 20% HCl aq and concentrated *in vacuo* to a volume of *ca* 20 ml. The ppts that resulted were extracted with $CHCl_3$, and the $CHCl_3$ soln was dried over anhyd. Na_2SO_4, evaporated *in vacuo* leaving a solid. The solid was recrystallized from H_2O (10 ml) to give IIIc (1·25 g) as the first crop. The mother liquor of the recrystallization was evaporated *in vacuo* to dryness, and the residue was submitted to column chromatography [silica gel (50 g), C_6H_6–EtOH (6:1)] to collect an additional crop (0·17 g) of IIIc. Total yield, 1·42 g (72%). Recrystallization from H_2O gave a pure sample of IIIc as colorless prisms of m.p. 134–135°, undepressed in m.p. on admixture with the sample obtained by method-(i). The IR spectra of both samples were also identical.

Further elution of the column yielded IIc (126 mg, 6%), m.p. 188–189° (dec). Recrystallization from EtOH provided a pure sample as colorless prisms, m.p. 189–190° (dec), shown to be identical with the authentic IIc by mixed melting-point test and comparison of the IR spectra.

N'-Benzyloxy-1-benzyl-5-aminoimidazole-4-carboxamidine (IIId)

A mixture of 1-benzyloxy-9-benzyladenine perchlorate (Id·$HClO_4$)* (2·93 g, 6·79 mmoles), NaOH (3·5 g) in H_2O (20 ml), and 2-methoxyethanol (20 ml) was refluxed for 15 min. The pH of the mixture was brought to 8 with 10% HCl aq, and the ppts that resulted were filtered, washed with H_2O, and dried. The solid was dissolved in *ca* 1% ethanolic HCl (50 ml), and Et_2O (200 ml) was added. The ppts that formed were filtered and recrystallized from EtOH (45 ml) to give the hydrochloride (1·47 g, 60%) of IIId, m.p. 177–178° (dec), shown to be homogeneous by TLC. The mother liquor of the recrystallization was evaporated *in vacuo* to dryness leaving a solid, which was recrystallized from EtOH to give the hydrochloride (0·30 g, 12%) of IId, m.p. 210–211° (dec).

When recrystallized from EtOH, the hydrochloride of IIId formed an analytical sample as colorless pillars, m.p. 177–178° (dec). (Found: C, 60·67; H, 5·79; N, 19·64. $C_{18}H_{20}ON_5Cl$ requires: C, 60·41; H, 5·63; N, 19·57%).

The free base (IIId) was prepared by dissolving the hydrochloride in warm H_2O and neutralizing the soln with 28% NH_4OH aq. Recrystallization from 70% EtOH aq gave IIId as colorless plates, m.p. 131–133°; UV (Table 1); NMR (DMSO) τ: 5·12 (2H, s, CH_2Ph), 4·97 (2H, s, CH_2Ph), 4·66 (2H, NH_2), 4·37 (2H, NH_2), 2·7 (11H, m, phenyl protons and $C_{(2)}$-H); Mass Spectrum *m/e*: 321 (M^+). (Found: C, 67·43; H, 6·09; N, 22·00. $C_{18}H_{19}ON_5$ requires: C, 67·27; H, 5·96; N, 21·79%).

Reversion of IVc *to* Ic *in acid*

A soln of IVc (225 mg, 1 mmole) in 0·2 N $HClO_4$ aq (10 ml) was allowed to stand at room temp (20°) for 26 hr. The ppts that formed were filtered, washed with H_2O (2 ml), and dried to give the perchlorate (231 mg, 75%) of Ic as colorless needles, m.p. 271–272° (dec), identified with the authentic perchlorate[12] by m.m.p. and IR spectrum. The presence of a trace of IIc and a small amount of IIIc in the reaction mixture was suggested by TLC [Merck silica gel GF_{254}, AcOEt–EtOH (6:1)].

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* The perchlorate, m.p. 191–193° (dec), has been prepared from the corresponding hydrobromide by Mr. S. Moro of Kanazawa University.

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