Bamberger Fission and Reclosure of 1-Alkyl-5-(alkylamino)imidazole-4-carbonitriles Leading to Their 2-Oxo Derivatives

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1-Methyl-5-(methylamino)imidazole-4-carbonitrile (4a) afforded three minor ring-opened products (5a, 6a, 10a) besides its 2-oxo derivative 3a on treatment with ethyl chloroformate in aqueous sodium bicarbonate. The geometrical isomers of these trisubstituted propenenitriles (5a, 6a, 10a) can be separated from each other by means of TLC, but equilibrate rapidly in solution. Because these compounds were converted into 3a in aqueous sodium hydroxide, alkaline treatment of the reaction mixture of 4a afforded a higher yield of 3a; although 3a also rapidly changed into other compounds in 0.1 N aqueous sodium hydroxide at room temperature, it could be recovered from the solution in high yield.

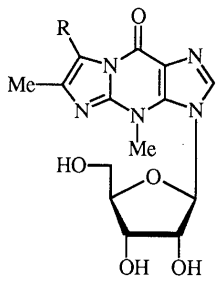
5-Alkylamino homologues 3b, c were also prepared in 64% and 46% yields, respectively, by similar treatment of the substrates 4b, c having the 5-alkylamino substituents. The same products 3b, c were obtainable from the positional isomers 4d, e in 83% and 51% yields, respectively. These outcomes are interpretable by supposing that the reactions proceed through common intermediates, equilibrated mixtures of (*E*)- and (*Z*)-[2-(alkylamino)-1-cyano-2-(methylamino)ethenyl]carbamic acid ethyl esters (7).

Key words imidazole-4-carbonitrile; 2-oxoimidazole-4-carbonitrile; Bamberger fission; triaminopropenenitrile; geometrical isomerization

The putative structures **1**[1] for a nucleoside family isolated from tRNAs are unique in that they have a 3,9-disubstituted purine skeleton as a partial structure. No other naturally occurring 3,9-disubstituted purine derivative was known until the isolation of caissarone hydrochloride (**2**) from the sea anemone *Bunodosoma caissarum* CORREA 1964.[2] In connection with the synthesis of **1**,[1] we have reported syntheses of several types of 3,9-dialkylpurines[3] and 3-alkyl-9-β-D-ribofuranosylpurines.[3d,4] In the course of those studies, 1-methyl-5-(methylamino)-2-oxoimidazole-4-carbonitrile (**3a**) was obtained in 56% yield through the Bamberger fission of 1-methyl-5-(methylamino)imidazole-4-carbonitrile (**4a**).[3d] Compound **3a** might be a good synthon for an alternative access to **2**, which was synthesized for the first time in our laboratory by regioselective methylation of *N*, 9-dimethyl-8-oxoadenine.[5] This paper reports more detailed studies on the reactions of **4a** and preparation of the 5-alkylamino homologues **3b, c** of **3a**.

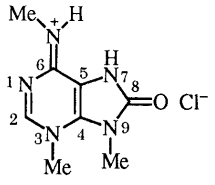
Compound **4a** afforded a complex mixture of products on treatment with ethyl chloroformate in aqueous sodium bicarbonate at room temperature according to the reported procedure.[3d] Compound **3a** was obtained from the mixture in 49% yield. Careful separation of the remainder by chromatography on silica gel afforded **6a** (1.7%), **11a**[3d] (0.6%), **5a** (20%), and **10a** (7.1%) in decreasing order of mobility. Compound **5a** behaved chromatographically as if it were a mixture of two different substances. However, it was shown by means of TLC and ^{1}H-NMR spectroscopy that even quick extraction of each of the two bands with deuterated chloroform from the silica gel plate afforded a mixture of the same composition as that of the original one. This was also the case for **6a** and **10a**. The observed complexity is probably due to rapid equilibrium of geometrical isomers [*e.g.*, (*Z*)-**5a**⇌(*E*)-**5a**] in solution, as shown in Chart 1. Another rotational isomerism arising from the formamido group[6] is possible for **5a** and **10a**. These compounds were indeed shown to be composed of four ^{1}H-NMR-spectrometrically distinguishable isomers. In addition to the reasonable ^{1}H-NMR spectra, the IR and high-resolution mass spectra supported the correctness of the structures **5a**, **6a**, and **10a**. Final identification of **5a** rested on its transformation into **3a** in 70% yield by treatment of **5a** with 0.1 N aqueous sodium hydroxide at room temperature for 1 h. This result, however, posed a puzzle, because **3a** has been reported to be unstable under these conditions.[3d] We therefore reexamined the reaction of **3a** in 0.1 N aqueous sodium hydroxide.

The UV spectrum of **3a** in 0.1 N aqueous sodium hydroxide showed the absorption maximum at 276 nm (ε *ca.* 9000) and the absorption minimum at 237 nm (ε *ca.* 3500). The latter increased with time to become an



1a—c

a: R = H
b: R = Me
c: R = CH_2CH_2—C(H, CO_2Me, $NHCO_2Me$)



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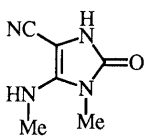

3a

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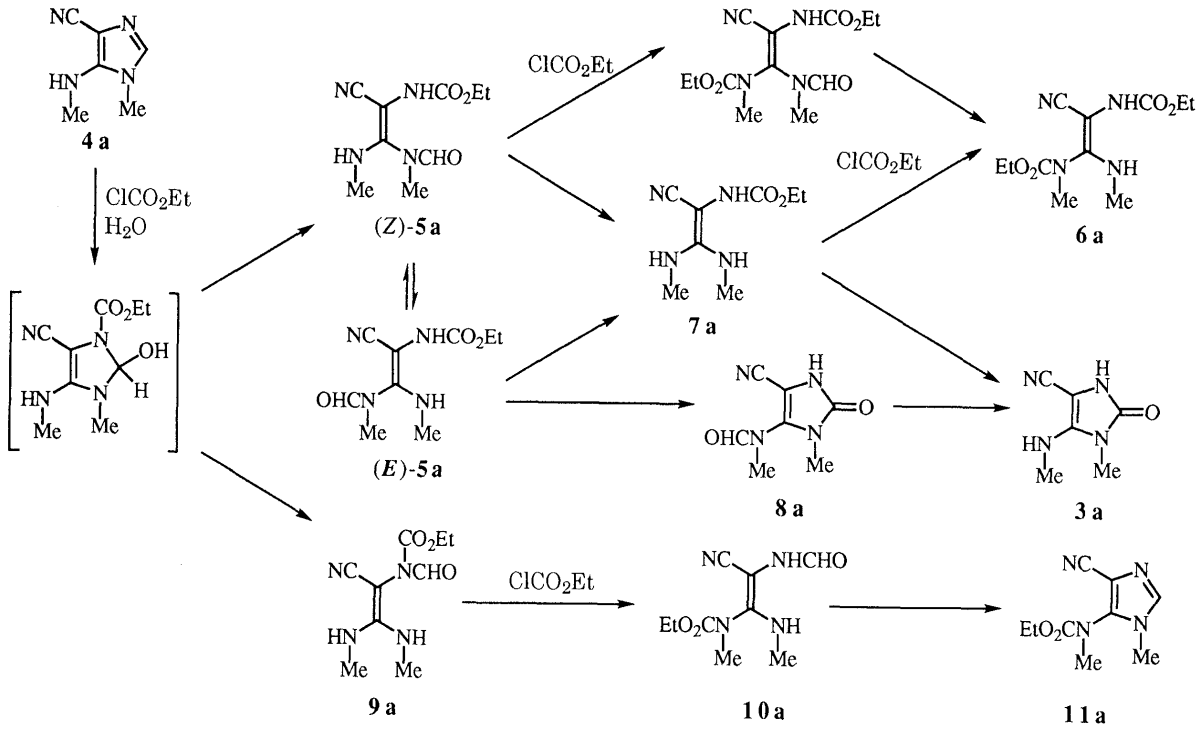


Chart 1

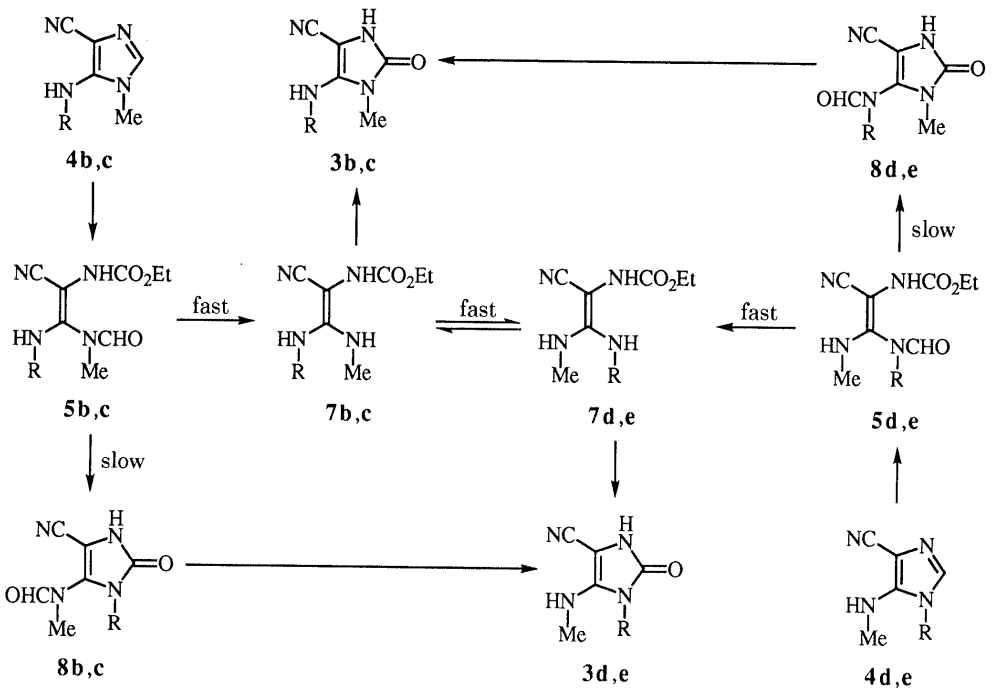
absorption maximum at 237 nm (ε *ca.* 7500) after storage of the solution at room temperature for 30 min, during which time ε at 276 nm decreased to *ca.* 3500. These changes showed no isosbestic point. Thereafter, the absorbance slowly decreased until the solution became almost transparent over the whole range 5.5 h after dissolution of **3a**. It did not recover absorbance on neutralization. No product other than **3a** was detected by means of TLC, and **3a** was recovered in 82% yield upon concentration of the solution. The recovery decreased to 53% after storage of the alkaline solution at room temperature for 50 h. These results suggest that **3a** comes to equilibrium with a compound x, which has the absorption maximum at 237 nm, and a non-UV-absorbing compound y in 0.1 N aqueous sodium hydroxide; although compound y exists almost exclusively in the equilibrated mixture, the rapid rate of the reverse reaction and the relatively small solubility of **3a** permit the recovery of **3a**; the ultimate product(s) z is slowly formed from the equilibrated mixture. Unfortunately, we have not yet elucidated any of the structures of compounds x, y, and z.

Compounds **6a** and **10a** also produced **3a** on treatment with aqueous sodium hydroxide. These results suggested that ethoxycarbonylation of **4a** in the presence of sodium hydroxide instead of sodium bicarbonate might afford a higher yield of **3a**. Contrary to our expectation, **4a** was recovered unchanged on treatment with ethyl chloroformate in 0.2 N aqueous sodium hydroxide at room temperature for 1 h, probably owing to the instability of the reagent under these conditions. We then treated **4a** with ethyl chloroformate in aqueous sodium bicarbonate, followed by addition of sodium hydroxide after complete consumption of **4a**, obtaining **3a** in 87% yield.

The above results suggest that compound **5a** is the main precursor for the formation of **3a**, notwithstanding other routes may lead to the end product **3a**. Chart 1 summarizes our proposal for the formation of the five isolable products (**3a**, **5a**, **6a**, **10a**, and **11a**), although some variations are of course possible. Assuming that (*Z*)-**5a** cyclizes to **8a** through (*E*)-**5a** prior to hydrolysis to **7a**, the transformation of **4a** into **3a** should be accompanied with apparent transposition of the methyl groups. In order to visualize such a phenomenon we performed the reactions with the heterogeneously alkylated substrates **4b**—**e**. The requisite compounds **4b**, **c**, **e** were prepared according to the reported procedure for the preparation of **4a**, **d**.[7]

5-(Ethylamino)-1-methyl-2-oxoimidazole-4-carbonitrile (**3b**) and 1-ethyl-5-(methylamino)-2-oxoimidazole-4-carbonitrile (**3d**) were obtained in 64% and 8% yields, respectively, on treatment of 5-(ethylamino)-1-methylimidazole-4-carbonitrile (**4b**) with ethyl chloroformate in the presence of sodium bicarbonate and then with sodium hydroxide (Chart 2). The correctness of the structures of **3b**, **d** was supported by the close resemblance of their UV spectra to those of **3a**. Compounds **3b**, **d** were easily discriminated from each other by the coupling patterns of the 5-alkylamino groups in the ^{1}H-NMR spectra measured in hexadeuterated dimethyl sulfoxide. Compound **3d** was not transformed into **3b** under conditions similar to those employed for their production. These outcomes suggest that cyclization of **5b** to **8b** is a slower reaction than its hydrolysis leading to an equilibrated mixture of **7b** and **7d**. Probably, the difference in size between the methylamino and ethylamino groups not only shifted the equilibrium, but also favored the cyclization of **7** to **3b**.

When 1-ethyl-5-(methylamino)imidazole-4-carbonitrile (**4d**),[7] the regioisomer of **4b**, was similarly treated with ethyl chloroformate and then with sodium hydroxide, **3b**, **3d**, and **4d** were obtained in 83%, 1.4%, and 2.9% yields, respectively. Compound **3b** was expected to be the major



b,**d**: R = Et
c,**e**: R = $PhCH_2$

Chart 2

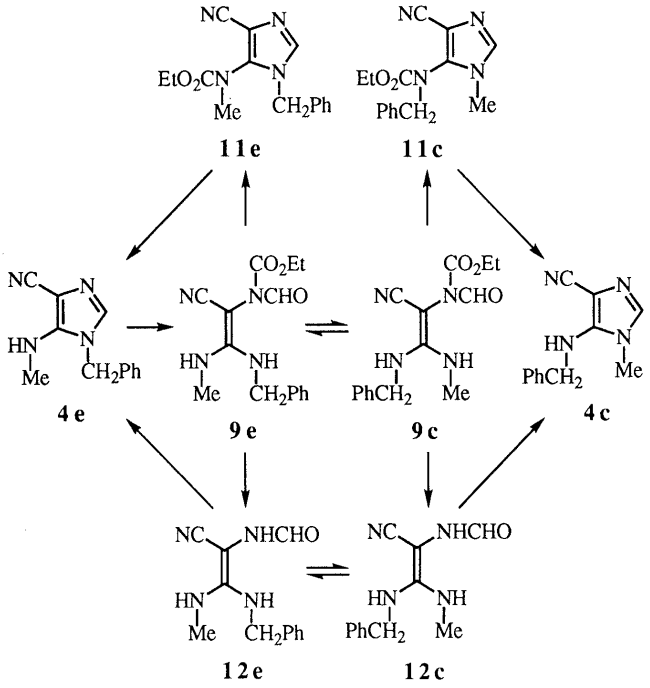


Chart 3

product again, because **4d** should afford the same equilibrated mixture of **7b** and **7d** as that formed from **4b**. The secondary route through **8d** also leads to **3b**, in contrast with the reaction of **4b**, contributing to the higher selectivity for the formation of the major product **3b**.

The chemoselectivity observed for the formation of **3b** was also realized in the formation of the 5-benzylamino analogue **3c**. The reaction of 5-(benzylamino)-1-methylimidazole-4-carbonitrile (**4c**) was carried out in a mixture of dioxane and water (1 : 2, v/v) because of its poor solubility in water. It was somewhat slower than those of **4a**, **b**, **d** carried out in water. After treatment with sodium hydroxide, we obtained an equilibrated mixture of **7c** and **7e** (35%), **3c** (46%), and **3e** (8%). The structure of **7c(e)** was assignable on the basis of the ^{1}H-NMR spectrum. Although the formation of this type of compound **7a** was postulated for the reaction with **4a** as shown in Chart 1, attempts at isolation were unsuccessful.[8]

Similar treatment of the regioisomer **4e** produced **4c** (5.6%) and **7c(e)** (1.6%) besides **3c** (51%), **3e** (4.9%), and **4e** (2.4%). The starting material **4e** was so stable in 0.2 N sodium hydroxide solution in dioxane–water (1 : 2, v/v) that **4c**, **e** were most likely produced from **9c**, **e** through **11c**, **e** and/or **12c**, **e** as illustrated in Chart 3. Although **11c**, **e** were not obtained in this reaction, the 1-methyl analogue **11a** was isolated in the reaction of **4a** (Chart 1).

In conclusion, we have established the reaction pathways of ethoxycarbonylation of **4** leading to **3** and have shown that the reactions of either **4b**, **c** or **4d**, **e** afford **3b**, **c** as the main products, and **4d**, **e** are the better substrates for the preparation of **3b**, **c**. The observed reactivity of **3** implies potential utility as intermediates for syntheses of purine derivatives and other heterocycles.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus, and values are corrected. MS and UV spectra were recorded on a Hitachi M-80 or a JEOL JMS-SX102A mass spectrometer and a Hitachi model 320 UV spectrophotometer [for solutions in 95% aqueous ethanol, 0.1 N hydrochloric acid (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous sodium hydroxide (pH 13)]. IR spectra were measured with a JASCO A-202 or a Shimadzu FTIR-8100 IR spectrophotometer. ^{1}H-NMR spectra were measured with a JEOL JNM-FX-100 or a JEOL JNM-EX-270 NMR spectrometer. Elemental analyses and MS measurements were performed by Mr. Y. Itatani, Dr. M. Takani, and

their associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.[9] The following abbreviations are used: br = broad, d = doublet, dq = doublet-of-quartets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

3-Benzyl-*N*,*N*,9-trimethyladeninium Iodide This compound was prepared according to the procedure[10] reported for the general synthesis of *N*,*N*,3,9-tetraalkyladeninium salts. A mixture of 3-benzyl-*N*,*N*-dimethyladenine[11] (1.01 g, 3.99 mmol), methyl iodide (1.80 g, 12.7 mmol), and *N*,*N*-dimethylacetamide (DMAc, 4.5 ml) was stirred at 40 °C for 124 h and concentrated *in vacuo*. The residue was washed with ethanol (4 ml) and dried to afford the iodide (1.51 g, 96%), mp 183—197 °C (dec.). Recrystallization of this sample from ethanol afforded an analytical sample as colorless pillars, mp 197—201 °C (dec.); UV $\lambda_{max}^{95\%\,EtOH}$ 291 nm (ε 18500); $\lambda_{max}^{H_2O}$ (pH 1) 289 (18400); $\lambda_{max}^{H_2O}$ (pH 7) 289 (18400); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me_2SO-d_6) δ: 3.45 and 3.89 (3H each, s, NMe_2), 3.77 [3H, s, N(9)-Me], 5.91 (2H, s, $PhC\underline{H}_2$), 7.15—7.25 (2H) and 7.34—7.50 (3H) (m each, $\underline{Ph}CH_2$), 8.28 and 8.82 (1H each, s, purine protons). *Anal.* Calcd for $C_{15}H_{18}IN_5$: C, 45.58; H, 4.59; N, 17.72. Found: C, 45.75; H, 4.63; N, 17.76.

5-(Benzylamino)-1-methyl-1*H*-imidazole-4-carboxamide 3-Benzyl-*N*,*N*,9-trimethyladeninium iodide (2.37 g, 6 mmol) was heated in 1 N aqueous sodium hydroxide (50 ml) under reflux for 15 min, and the mixture was cooled in ice-water. The precipitate that resulted was collected by filtration, washed with water, and dried to afford the carboxamide (1.07 g), mp 159—160.5 °C. The filtrate and washings were combined and concentrated to a volume of *ca.* 30 ml to afford a second crop of the carboxamide (0.11 g; the total yield was 86%). These samples were identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.[7]

1-Alkyl-5-(alkylamino)-1*H*-imidazole-4-carbonitriles (4) These compounds were prepared by treatment of 1-alkyl-5-(alkylamino)-1*H*-imidazole-4-carboxamides with phosphorus oxychloride according to the procedure[7] reported for the preparation of **4a**, **d**.

5-(Ethylamino)-1-methyl-1*H*-imidazole-4-carbonitrile (4b) Recrystallization of **4b** (1.07 g, 89%), mp 149—150 °C, which was obtained from 5-(ethylamino)-1-methyl-1*H*-imidazole-4-carboxamide[7] (1.34 g, 7.97 mmol), from water afforded an analytical sample as colorless scales, mp 150—151 °C; MS *m/z*: 150 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 252 nm (ε 12600); $\lambda_{max}^{H_2O}$ (pH 1) 241 (10300), 262 (7900); $\lambda_{max}^{H_2O}$ (pH 7) 252 (11400); $\lambda_{max}^{H_2O}$ (pH 13) 252 (11400); IR ν_{max}^{Nujol} cm^{-1}: 3210, 2200; ^{1}H-NMR (Me_2SO-d_6) δ: 1.19 (3H, t, J = 7 Hz, $\underline{Me}CH_2$), 3.31 (2H, dq, J = 6, 7 Hz, $MeC\underline{H}_2NH$), 3.36 [3H, s, N(1)-Me], 6.23 (1H, br t, J = 6 Hz, $MeCH_2N\underline{H}$), 7.19 [1H, s, C(2)-H]. *Anal.* Calcd for $C_7H_{10}N_4$: C, 55.98; H, 6.71; N, 37.31. Found: C, 55.86; H, 6.82; N, 37.48.

5-(Benzylamino)-1-methyl-1*H*-imidazole-4-carbonitrile (4c) 5-(Benzylamino)-1-methyl-1*H*-imidazole-4-carboxamide[7] (161 mg, 0.699 mmol) afforded **4c** (115 mg, 78%), mp 124—126 °C. Recrystallization of crude **4c** from benzene afforded an analytical sample as slightly brown needles, mp 126—127 °C; MS *m/z*: 212 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 251 nm (ε 12600); $\lambda_{max}^{H_2O}$ (pH 1) 242 (10600), 257 (sh) (8500); $\lambda_{max}^{H_2O}$ (pH 7) 253 (10800); $\lambda_{max}^{H_2O}$ (pH 13) 253 (11300); IR ν_{max}^{Nujol} cm^{-1}: 3200, 2200; ^{1}H-NMR ($CDCl_3$) δ: 3.41 [3H, s, N(1)-Me], 3.95 (1H, br t, J = 6 Hz, $PhCH_2N\underline{H}$), 4.58 (2H, d, J = 6 Hz, $PhC\underline{H}_2NH$), 7.01 [1H, s, C(2)-H], 7.37 (5H, s, $\underline{Ph}CH_2$). *Anal.* Calcd for $C_{12}H_{12}N_4$: C, 67.91; H, 5.70; N, 26.40. Found: C, 67.88; H, 5.49; N, 26.56.

1-Benzyl-5-(methylamino)-1*H*-imidazole-4-carbonitrile (4e) This compound **4e** (1.53 g, 90%), mp 167—172 °C, was prepared from 1-benzyl-5-(methylamino)-1*H*-imidazole-4-carboxamide[7] (1.84 g, 7.99 mmol). Recrystallization of crude **4e** from ethanol (treated with activated charcoal powder) afforded an analytical sample as slightly yellow prisms, mp 174.5—175.5 °C; MS *m/z*: 212 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 253 nm (ε 13500); $\lambda_{max}^{H_2O}$ (pH 1) 243 (10500), 257 (sh) (8400); $\lambda_{max}^{H_2O}$ (pH 7) 253 (12700); $\lambda_{max}^{H_2O}$ (pH 13) 253 (12500); IR ν_{max}^{Nujol} cm^{-1}: 3250, 2200; ^{1}H-NMR (Me_2SO-d_6) δ: 2.92 (3H, d, J = 5 Hz, $\underline{Me}NH$), 5.04 (2H, s, $PhC\underline{H}_2$), 6.36 (1H, br q, J = 5 Hz, $MeN\underline{H}$), 7.0—7.4 [6H, m, $\underline{Ph}CH_2$ and C(2)-H]. *Anal.* Calcd for $C_{12}H_{12}N_4$: C, 67.91; H, 5.70; N, 26.40. Found: C, 67.76; H, 5.58; N, 26.31.

2,3-Dihydro-1-methyl-5-(methylamino)-2-oxo-1*H*-imidazole-4-carbonitrile (3a) i) From **4a** without Treatment with Sodium Hydroxide: Ethyl chloroformate (1.0 ml, 10.5 mmol) was added to a solution of **4a**[7] (409 mg, 3 mmol) and sodium bicarbonate (1.0 g, 12 mmol) in water (100 ml), and this solution was stirred at room temperature for 2 h, then concentrated *in vacuo* to a volume of *ca.* 20 ml. The resulting precipitate was collected by filtration, washed with a little water, and dried to give **3a** (166 mg), mp 234—239 °C (dec.). The filtrate and washings were combined, concentrated *in vacuo* to a volume of *ca.* 10 ml, and continuously extracted with dichloromethane. The precipitate that separated from the organic layer was collected by filtration to afford a second crop of **3a** (59 mg; the total yield was 49%), mp 236—241 °C (dec.). Recrystallization of crude **3a** from ethanol gave colorless needles, mp 239—241 °C (dec.), identical (by comparison of the IR spectrum and TLC mobility) with authentic **3a**.[3d]

The dichloromethane solution was concentrated, and the residue was purified by flash chromatography [chloroform–methanol (10 : 1, v/v)] to give a mixture (23 mg) of [2-cyano-2-(ethoxycarbonylamino)-1-(methylamino)ethenyl]methylcarbamic acid ethyl ester (**6a**) and (4-cyano-1-methyl-1*H*-imidazol-5-yl)methylcarbamic acid ethyl ester (**11a**), [1-cyano-2-(methylamino)-2-(*N*-methylformamido)ethenyl]carbamic acid ethyl ester (**5a**) (165 mg), and [2-cyano-2-formamido-1-(methylamino)-ethenyl]methylcarbamic acid ethyl ester (**10a**) (75 mg). The mixture of **6a** and **11a** was further purified by repeated preparative TLC on silica gel [chloroform–methanol (10 : 1, v/v) and then ethyl acetate–ethanol (10 : 1, v/v)] to afford **6a** (14 mg, 1.7%) and **11a** (4 mg, 0.6%), each as a colorless syrup. The latter was identical (by comparison of the ^{1}H-NMR spectrum and TLC mobility) with authentic **11a**.[3d] Compound **6a** showed two well-separated spots on TLC. Preparative TLC of a portion of this sample on silica gel [benzene–ethanol (5 : 1, v/v)] afforded 0.9 mg from the higher band and 6.8 mg from the lower band, each as a colorless syrup. These materials, however, showed two identical spots on TLC and gave indistinguishable ^{1}H-NMR spectra, MS *m/z*: 270.1335 (M^+, $C_{11}H_{18}N_4O_4$ requires 270.1328); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3418, 3327, 2193, 1725, 1640; ^{1}H-NMR ($CDCl_3$) δ: 1.28 and 1.31 (3H each, t, J = 7 Hz, two $\underline{Me}CH_2$'s), 2.79 (13/15 × 3H) and 2.84 (2/15 × 3H) (d each, J = 5.3 Hz, $\underline{Me}NH$), 3.03 (2/15 × 3H) and 3.18 (13/15 × 3H) (s each, $\underline{Me}NCO_2Et$), 4.18 and 4.24 (2H each, q, J = 7 Hz, two $MeC\underline{H}_2$'s), 4.98 (2/15H) and 5.18 (13/15H) (br each, $MeN\underline{H}$), 5.47 (2/15H) and 5.68 (13/15H) (br each, $N\underline{H}CO_2Et$).

Repeated flash chromatography [chloroform–methanol (10 : 1, v/v) and then benzene–ethanol (5 : 1, v/v)] of crude **5a** gave a colorless syrup (138 mg, 20%). This compound also showed two spots on silica gel TLC, and preparative TLC on silica gel [benzene–ethanol (5 : 1, v/v)] of a portion of this sample gave 4 mg from the upper zone and 37 mg from the lower zone. These two samples were also shown to be the same mixtures by TLC (two spots) and ^{1}H-NMR spectroscopy, MS *m/z*: 226.1073 (M^+, $C_9H_{14}N_4O_3$ requires 226.1066); UV $\lambda_{max}^{95\%\,EtOH}$ 268 nm; $\lambda_{max}^{H_2O}$ (pH 1) (unstable) 269; $\lambda_{max}^{H_2O}$ (pH 7) 270; $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 270; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3414, 3330, 2195, 1721, 1694, 1636; ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J = 7 Hz, $\underline{Me}CH_2$), 2.79 (4/50 × 3H), 2.81 (39/50 × 3H), 2.87 (1/50 × 3H), and 2.92 (6/50 × 3H) (d each, J = 5 Hz, $\underline{Me}NH$), 3.03 (6/50 × 3H), 3.13 (39/50 × 3H), 3.16 (1/50 × 3H), and 3.30 (4/50 × 3H) (s each, $\underline{Me}NCHO$), 4.19 (a total of 2H overlapping with small q's, q, J = 7 Hz, $MeC\underline{H}_2$), 5.49 (1H, br, $MeN\underline{H}$), 6.05 (6/50H), 6.24 (4/50H), and 6.28 (40/50H) (br each, $N\underline{H}CO_2Et$), 8.16 (1/50H), 8.20 (4/50H), 8.22 (6/50H), and 8.34 (39/50H) (s each, $MeNC\underline{H}O$). The ^{1}H-NMR spectrum suggests that **5a** is a 39 : 6 : 4 : 1 mixture of four interconvertible isomers.

Purification of crude **10a** by flash chromatography [ethyl acetate–ethanol (10 : 1, v/v)] afforded a colorless syrup (48 mg, 7.1%), which showed two spots on TLC. Separation by preparative TLC on silica gel [chloroform–methanol (5 : 1, v/v)] gave 3 mg from the upper zone and 27 mg from the lower zone. These two samples were identical on the basis of TLC and ^{1}H-NMR spectroscopy, MS *m/z*: 226.1065 (M^+, $C_9H_{14}N_4O_3$ requires 226.1066); UV $\lambda_{max}^{95\%\,EtOH}$ 270 nm; $\lambda_{max}^{H_2O}$ (pH 1) (unstable) 271; $\lambda_{max}^{H_2O}$ (pH 7) 271; $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 275; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3308, 2195, 1705, 1640; ^{1}H-NMR ($CDCl_3$) δ: 1.32 (a total of 3H overlapping with small signals, t, J = 7 Hz, $\underline{Me}CH_2$), 2.79 (16/28 × 3H), 2.81 (9/28 × 3H), 2.86 (2/28 × 3H), and 2.90 (1/28 × 3H) (d each, J = 5 Hz, $\underline{Me}NH$), 3.03 (2/28 × 3H), 3.06 (1/28 × 3H), 3.18 (9/28 × 3H), and 3.19 (16/28 × 3H) (s each, $\underline{Me}NCO_2Et$), 4.24 and 4.25 (a total of 2H, q each, J = 7 Hz, $MeC\underline{H}_2$), 5.49 (3/28H, m), 5.68 (16/28H, br), and 6.29 (9/28H, br) ($MeN\underline{H}$), 6.80 (1/28H) and 7.13 (9/28H) (br d each, J = 12 Hz, *trans*-$N\underline{H}CHO$), 7.52 and 7.75 (a total of 18/28H, br, *cis*-$N\underline{H}CHO$), 7.99 (1/28H) and 8.04 (9/28H) (d each, J = 12 Hz, *trans*-$NHC\underline{H}O$), 8.13 (2/28H) and 8.16 (16/28H) (d each, J = 1 Hz, *cis*-$NHC\underline{H}O$).

ii) From **4a** with Sodium Hydroxide: Ethyl chloroformate (2 ml, 21 mmol) was added to a solution of **4a** (681 mg, 5 mmol) and sodium bicarbonate (2 g, 24 mmol) in water (200 ml), and this solution was stirred at room temperature for 3 h, by which time **4a** had been completely

consumed. A 2 N aqueous solution of sodium hydroxide (30 ml, 60 mmol) was then added to the solution, and the whole was kept at room temperature for 10 min, neutralized with 2 N hydrochloric acid, and concentrated *in vacuo* to a volume of *ca.* 30 ml. The resulting precipitate was collected by filtration, washed with water (3 ml), and dried to give **3a** (591 mg) as colorless needles, mp 236—241 °C (dec.). The filtrate and washings were combined, concentrated *in vacuo* to a volume of *ca.* 10 ml, and extracted with dichloromethane using a continuous extractor. The extracts were concentrated *in vacuo*, and the resulting solid was washed with water (2 ml) and then dried to afford a second crop of **3a** (63 mg; the total yield was 87%), mp 239—241 °C (dec.). Recrystallization of crude **3a** from ethanol gave colorless pillars, mp 240—241 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.[3d]

iii) From **5a**: A solution of **5a** (30 mg, 0.13 mmol) in 0.1 N aqueous sodium hydroxide (4 ml) was kept at room temperature for 1 h, brought to pH 7 with 1 N hydrochloric acid, and concentrated *in vacuo*. The resulting solid residue was washed with a small volume of water, and dried to afford **3a** (14 mg, 70%), mp 232—237 °C (dec.).

iv) From **6a**: A solution of **6a** (11 mg, 0.041 mmol) in 0.1 N aqueous sodium hydroxide (1 ml) was kept at room temperature for 25 min, neutralized with 1 N hydrochloric acid, and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel [ethyl acetate–ethanol (5 : 1, v/v)] to afford **3a** (3 mg, *ca.* 50%), mp 198—221 °C (dec.).

v) From **10a**: A solution of **10a** (12 mg, 0.053 mmol) in 0.1 N aqueous sodium hydroxide (2 ml) was kept at room temperature for 45 min, neutralized with 1 N hydrochloric acid, and concentrated *in vacuo*. The residue was washed with a little water and dried to afford **3a** (5 mg, *ca.* 60%), mp 221—232 °C (dec.).

2,3-Dihydro-5-(ethylamino)-1-methyl-2-oxo-1*H*-imidazole-4-carbonitrile (3b) i) From **4b**: A mixture of **4b** (150 mg, 1 mmol), ethyl chloroformate (0.4 ml, 4.2 mmol), and sodium bicarbonate (400 mg, 4.76 mmol) in water (40 ml) was stirred at room temperature for 2 h. A 2 N aqueous solution of sodium hydroxide (6 ml) was added to the solution, and the whole was kept at room temperature for a further 30 min. The solution was neutralized with 2 N hydrochloric acid and then concentrated *in vacuo* to a volume of *ca.* 10 ml. The precipitate that resulted was collected by filtration, washed with a little water, and dried to afford **3b** (78 mg), mp 212—224 °C (dec.). The filtrate and washings were combined, and extracted with dichloromethane using a continuous extractor. The organic layer was concentrated *in vacuo* and the residue was purified by preparative TLC on silica gel [ethyl acetate–ethanol (10 : 1, v/v)] to afford a second crop of **3b** (29 mg; the total yield was 64%) and 2,3-dihydro-5-(methylamino)-1-ethyl-2-oxo-1*H*-imidazole-4-carbonitrile (**3d**) (13 mg, 8%), mp 165—182 °C (dec.).

ii) From **4d**: Compound **4d**[7] (376 mg, 2.5 mmol) was treated with ethyl chloroformate in a manner similar to that described under method (ii) for the preparation of **3a**. The disappearance of **4d** was confirmed by TLC, then 2 N aqueous sodium hydroxide (15 ml) was added to the mixture, and the whole was kept at room temperature for a further 30 min, neutralized with 2 N hydrochloric acid, and concentrated *in vacuo* to a volume of *ca.* 15 ml. The resulting precipitate was collected by filtration, washed with a little water, and dried to afford **3b** (283 mg), mp 225—229 °C (dec.). The filtrate and washings were combined and extracted with dichloromethane using a continuous extractor. Removal of the solvent from the extract by evaporation left a colorless solid (100 mg). Purification of this material by preparative TLC on silica gel [chloroform–methanol (10 : 1, v/v)] afforded **3d** (6 mg, 1.4%), mp 165—182 °C (dec.), **4d** (11 mg, 2.9%), mp 162—164 °C, and a second crop of **3b** (61 mg; the total yield was 83%), mp 230—233 °C (dec.). Recrystallization of crude **3b** from ethanol afforded an analytical sample as colorless scales, mp 236—237 °C (dec.); MS *m/z*: 166 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 221 nm (ε 3600), 272 (12200); $\lambda_{max}^{H_2O}$ (pH 1) (unstable) 227 (*ca.* 6000), 271 (*ca.* 7000); $\lambda_{max}^{H_2O}$ (pH 7) 223 (4000), 271 (13600); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 277 (*ca.* 10000); IR ν_{max}^{Nujol} cm^{-1}: 3321, 2191, 1746; ^{1}H-NMR (Me_2SO-d_6) δ: 1.18 (3H, t, J=7 Hz, MeCH$_2$), 2.99 [3H, s, N(1)-Me], 3.23 (2H, dq, J=6, 7 Hz, MeCH$_2$), 6.55 (1H, br t, J=6 Hz, MeCH$_2$NH), 9.88 [1H, br s, N(3)-H]. *Anal.* Calcd for $C_7H_{10}N_4O$: C, 50.59; H, 6.07; N, 33.71. Found: C, 50.48; H, 6.15; N, 33.71.

Recrystallization of crude **3d** from ethanol afforded **3d** as colorless needles, mp 186—200 °C (dec.); MS *m/z*: 166.0853 (M^+, $C_7H_{10}N_4O$ requires 166.0855); IR ν_{max}^{Nujol} cm^{-1}: 3379, 2185, 1722, 1690, 1622; ^{1}H-NMR (Me_2SO-d_6) δ: 1.05 (3H, t, J=7 Hz, MeCH$_2$), 2.86 (3H, d, J=5 Hz, MeNH), 3.52 (2H, q, J=7 Hz, MeCH$_2$), 6.63 (1H, br q, J=5 Hz, MeNH), 9.85 [1H, br s, N(3)-H].

2,3-Dihydro-5-(benzylamino)-1-methyl-2-oxo-1*H*-imidazole-4-carbonitrile (3c) i) From **4c**: A mixture of **4c** (212 mg, 1 mmol), ethyl chloroformate (0.4 ml, 4.2 mmol), sodium bicarbonate (400 mg, 4.76 mmol), dioxane (20 ml), and water (40 ml) was stirred at room temperature for 3 h and then 2 N aqueous sodium hydroxide (6 ml) was added. The mixture was stirred at room temperature for a further 30 min, neutralized with 2 N hydrochloric acid, concentrated *in vacuo* to a volume of *ca.* 10 ml, and then extracted with chloroform (3 × 40 ml). The extracts were dried over magnesium sulfate and concentrated *in vacuo*. The residue was triturated with chloroform (2 ml), and the insoluble solid was collected by filtration and dried to afford **3c** (82 mg), mp 205—210 °C (dec.). The filtrate was purified by repeated flash chromatography and preparative TLC on silica gel [chloroform–methanol (15 : 1, v/v)] to provide [2-(benzylamino)-1-cyano-2-(methylamino)ethenyl]carbamic acid ethyl ester [**7c(e)**] (96 mg, 35%), mp 149—154 °C (dec.), 2,3-dihydro-1-benzyl-5-(methylamino)-2-oxo-1*H*-imidazole-4-carbonitrile (**3e**) (19 mg, 8%), mp 188—197 °C (dec.), and a second crop of **3c** (24 mg; the total yield was 46%). Recrystallization of **7c(e)** from water afforded an analytical sample as colorless plates, mp 156—158 °C (dec.); MS *m/z*: 274.1434 (M^+, $C_{14}H_{18}N_4O_2$ requires 274.1430); UV $\lambda_{max}^{95\%\,EtOH}$ 266 nm (ε 18100); $\lambda_{max}^{H_2O}$ (pH 1) 210 (16700); $\lambda_{max}^{H_2O}$ (pH 7) 264 (16200); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 266 (*ca.* 9500); IR ν_{max}^{Nujol} cm^{-1}: 3364, 3297, 2147, 1709; ^{1}H-NMR (Me_2SO-d_6) δ: 1.16 (3H, t, J=7 Hz, MeCH$_2$), 2.65 (2/5 × 3H) and 2.78 (3/5 × 3H) (d each, J=5 Hz, MeNH), 3.98 (2H, q, J=7 Hz, MeCH$_2$), 4.25 (3/5 × 2H) and 4.38 (2/5 × 2H) (d each, J=6 Hz, PhCH$_2$NH), 5.79 (1H, br q, J=5 Hz, MeNH), 6.09 (1H, br t, J=6 Hz, PhCH$_2$NH), 7.25 (3/5 × 5H) and 7.30 (2/5 × 5H) (s each, PhCH$_2$), 7.47 (1H, br s, NHCO$_2$Et); ^{1}H-NMR ($CDCl_3$) δ: 1.25 and 1.27 (a total of 3H, t, J=7 Hz, MeCH$_2$), 2.84 (4/9 × 3H, d, J=5.5 Hz) and 2.97 (5/9 × 3H, br d, J=5.5 Hz) (MeNH), 4.15 and 4.17 (a total of 2H, overlapping with a broad 4/9H signal arising from NH, q, J=7 Hz, MeCH$_2$), 4.30 (5/9 × 2H, overlapping with a broad 4/9H signal arising from NH, d, J=5.5 Hz) and 4.43 (4/9 × 2H, d, J=5.5 Hz) (PhCH$_2$NH), 4.52 (5/9H, br q, J=5.6 Hz, MeNH), 4.80 (5/9H, br, PhCH$_2$NH), 5.30 (1H, br, NHCO$_2$Et), 7.21—7.46 (5H, m, PhCH$_2$). *Anal.* Calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.28; H, 6.65; N, 20.42.

Compound **3e** was recrystallized from water to provide an analytical sample as colorless needles, mp 203—207.5 °C (dec.); MS *m/z*: 228 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 273 nm (ε 14100); $\lambda_{max}^{H_2O}$ (pH 1) (unstable) 271 (*ca.* 13000); $\lambda_{max}^{H_2O}$ (pH 7) 271 (14000); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 278 (*ca.* 10000); IR ν_{max}^{Nujol} cm^{-1}: 3368, 3162, 2172, 1721, 1694; ^{1}H-NMR (Me_2SO-d_6) δ: 2.84 (3H, d, J=5 Hz, MeNH), 4.74 (2H, s, PhCH$_2$), 6.66 (1H, br q, J=5 Hz, MeNH), 7.15—7.39 (5H, m, PhCH$_2$), 10.03 [1H, br s, N(3)-H]. *Anal.* Calcd for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.07; H, 5.30; N, 24.50.

Recrystallization of **3c** from water gave an analytical sample as colorless needles, mp 212—213 °C (dec.); MS *m/z*: 228 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 274 nm (ε 12400); $\lambda_{max}^{H_2O}$ (pH 1) (unstable) 272 (*ca.* 11000); $\lambda_{max}^{H_2O}$ (pH 7) 272 (12200); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 277 (*ca.* 9000); IR ν_{max}^{Nujol} cm^{-1}: 3289, 3146, 2190, 1757, 1678; ^{1}H-NMR (Me_2SO-d_6) δ: 3.06 [3H, s, N(1)-Me], 4.42 (2H, d, J=6.3 Hz, PhCH$_2$NH), 7.18 (1H, br t, J=6.3 Hz, PhCH$_2$NH), 7.23—7.41 (5H, m, PhCH$_2$), 9.89 [1H, br s, N(3)-H]. *Anal.* Calcd for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.02; H, 5.09; N, 24.55.

ii) From **4e**: Compound **4e** (531 mg, 2.5 mmol) was dissolved in dioxane (50 ml). Ethyl chloroformate (1.0 ml, 10.5 mmol), sodium bicarbonate (1.0 g, 11.9 mmol), and water (100 ml) were added to the solution, and the mixture was stirred at room temperature for 3.5 h. More ethyl chloroformate (1.0 ml) and sodium bicarbonate (1.0 g) were added, and the whole was stirred at room temperature for a further 3 h. At this time **4e** was no longer detectable in the reaction mixture. This mixture was stirred for 1 h after addition of 2 N aqueous sodium hydroxide (15 ml), neutralized with 2 N hydrochloric acid, and concentrated *in vacuo* to a volume of *ca.* 80 ml. The resulting precipitate was collected by filtration and recrystallized from water to give **3c** (241 mg), mp 205—208.5 °C (dec.). The aqueous filtrate of the reaction mixture and mother liquor of recrystallization were combined, and extracted with dichloromethane (3 × 80 ml). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo* to leave a yellow syrup. This was purified by flash chromatography [chloroform–methanol (15 : 1, v/v)] to afford **7c(e)** (24 mg), **4e** (16 mg), **3e** (40 mg), **4c** (46 mg), and **3c** (65 mg). Crude **7c(e)**, **4e**, and **3c,e** were further purified by preparative TLC on

silica gel [chloroform–methanol (15 : 1, v/v)] to afford **7c(e)** (11 mg, 1.6%), mp 147—151 °C, **4e** (13 mg, 2.4%), mp 171—174 °C, **3e** (28 mg, 4.9%), mp 198—202 °C (dec.), and a second crop of **3c** (50 mg; the total yield was 51%), mp 203—206 °C (dec.). Crude **4c** (32 mg) was further purified by preparative TLC on silica gel [ethyl acetate–ethanol (15 : 1, v/v)] to afford **4c** (30 mg, 5.6%) as colorless needles, mp 121—125 °C, identical (by comparison of the MS, IR, and ^{1}H-NMR spectra) with authentic **4c**.

References and Notes

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