2-Amino-1-methyl-1*H*-imidazole-4,5-dione: Synthesis and the Dimroth Type Rearrangement to Creatone (2-Methylamino-1*H*-imidazole-4,5-dione)

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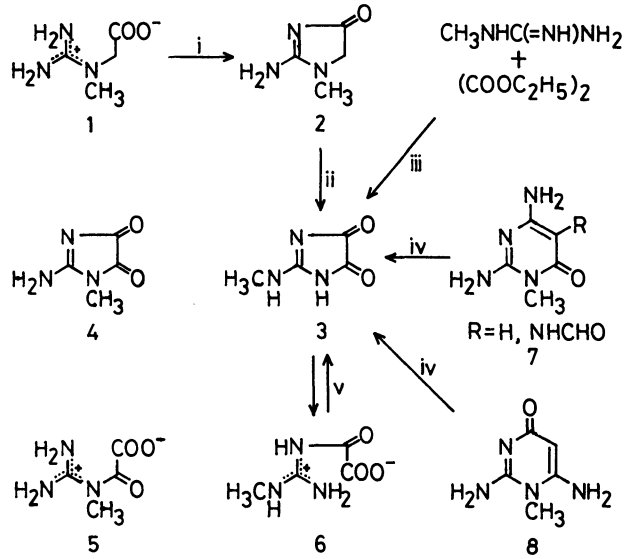
Treatment of creatinine with BOC-ON gave 2-*t*-butoxycarbonylamino-1-methyl-1,5-dihydro-4*H*-imidazol-4-one, which was oxidized with mercury(II) acetate to the corresponding 1*H*-imidazole-4,5-dione. Deprotection of the amino group of this dione afforded the title compound **4**, which in turn was shown to undergo a facile, Dimroth-type rearrangement under weakly acidic conditions to give creatone, thus proving **4** to be the key intermediate in the formation of creatone from various starting materials. The equilibria among these compounds are discussed.

Creatine (**1**) and its dehydrated form creatinine (**2**) are present in the muscular tissue of many vertebrates and play important roles in energy transfer and storage.[1,2] We reported[3] that the oxidation product (creatone) of **1** and **2** with mercury(II) acetate possessed the structure **3** (2-methylamino-1*H*-imidazole-4,5-dione) rather than the previously presented ring-open formula **5**[4,5] (Scheme 1). Furthermore, it was suggested[3] that the previous structures **4** and **6** which had been respectively presented for the condensation product[6] of methylguanidine with diethyl oxalate and for the peroxyacid oxidation product[7] of 2,6-diamino-3-methyl-4(3*H*)-pyrimidones **7** or 2,6-diamino-1-methyl-4(1*H*)-pyrimidone (**8**) ought to be replaced by the revised formulation **3**, because all of these products were found to be identical with creatone (Scheme 1). It was also confirmed[8] that the acyclic compound **6** prepared from **3** reverted to **3** without producing any other isomers **4** and **5**. We have now prepared **4** (2-amino-1-methyl-1*H*-imidazole-4,5-dione) and confirmed a facile, Dimroth-type rearrangement of **4** to **3**, thus proving that **4** is the key intermediate in the formation of **3** from various precursors.

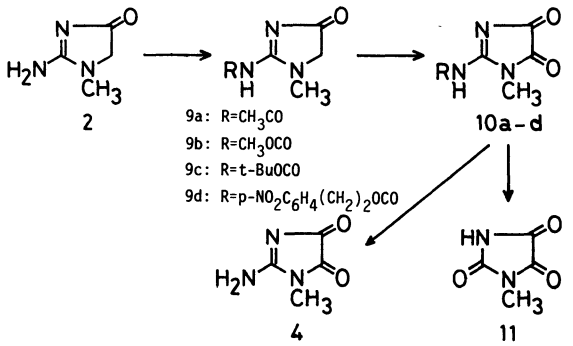


Scheme 1. Formation of creatone **3** from various starting materials, i. H^+, Ref. 21. ii. $Hg(OAc)_2$, Refs. 3—5. iii. reflux in EtOH, Ref. 6. iv. H_2O_2–HCOOH, Ref. 7. v. H_2O, Ref. 8.

Results and Discussion

As the oxidation of **1** and **2** with mercury(II) acetate resulted[3,8] in the exclusive formation of **3** without affording any of the postulated intermediates such as **4** and **5**, we had to devise a new scheme for preparing **4** by an alternative route: namely, the protection of the 2-amino group of creatinine (**2**), followed by the oxidation and then deprotection of the amino group of the resulting imidazoledione. Thus, in order to find a suitable protecting group, **2** was led to various kinds of NH(2)-substituted derivatives (see Scheme 2): 2-acetamido- (**9a**,[9] with acetic anhydride, 74% yield), 2-methoxycarbonylamino- (**9b**, with 1-methoxycarbonyl-3-methylimidazolium chloride, 71%), 2-*t*-butoxycarbonylamino- (**9c**, with 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON),[10] 75%), and 2-[2-(*p*-nitrophenyl)ethoxycarbonylamino]-1-methyl-1,5-dihydro-4*H*-imidazol-4-one (**9d**, with 1-methyl-3-[2-(*p*-nitrophenyl)ethoxycarbonyl]imidazolium chloride,[11] 95%).

The structures of these compounds were readily verified by the spectral data and the elemental analyses



Scheme 2. Preparation of **4**.

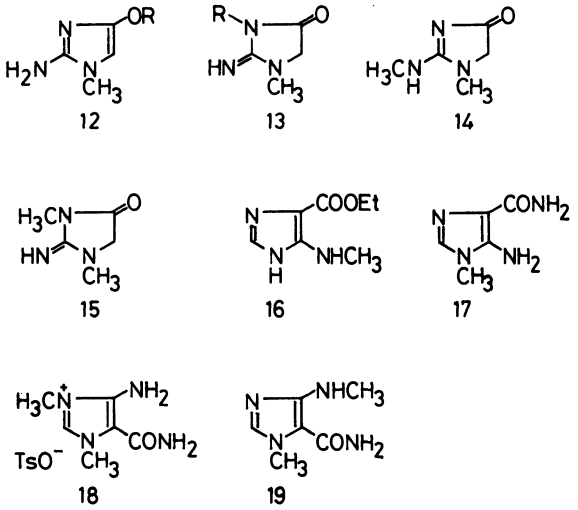
Table 1. Physical Properties of Some Imidazole Derivatives

Compd.	^{1}H NMR parameter[a]				Ionization and UV spectra in water			
	CH_3-1	RNH-2	H_2-5	b)	h)	pK_a	λ_{max}/nm(log ε)	pH
2	3.05 s	7.3 brm	3.92 s	C[c]	+	4.85[l]		
	3.11 s	4.78 brs	4.22 s	D[c]	0		235(3.88)[j]	
	3.37 s	8.03 brm	4.66 s	T[d]				
3		2.98 d[e]	—	C	+	0.62[d]	212(3.97)[d]	−0.05
		2.96 s	—	D	0		204(4.13)[d]	4
		3.31 d[e]	—	T[d]	−	7.87[d]	234(4.00)[d]	10
4	3.22 s	7.4 brm	—	C	+	1.89±0.19	223, 270 sh (4.03, 3.06)[k]	0
	3.21 s		—	D	0		232, 296(4.05, 3.15)[k]	4
	3.57 s		—	T	−[l]	8.0±0.2	237(3.97)[k]	10
9a	3.13 s	2.19 s	3.93 s	C	+	3.37±0.01	232(3.935)	1
		8.5 brm			0		220, 252(4.13, 4.15)	6
	3.08 s	2.17 s	4.11 s	D	−	8.76±0.01	249(4.295)	12
9b	3.11 s	3.76 s	3.93 s	C	+	2.09±0.02	238(3.895)	0
		6.5 brm			0		212, 242(4.29, 4.125)	6
					−	9.13±0.01	236(4.43)	12
9c	3.12 s	1.50 s	3.91 s	C	+	2.22±0.06	227(3.84)	0
		7.6 brm			0		240(3.99)	7
					−	8.79±0.05	238(4.11)	12
9d	3.09 s	3.10 t[f]	3.92 s	C[c]	+	1.97±0.01	210, 230 sh, 278	0
		4.34 t[f]					(4.12, 4.02, 4.00)	
		7.40 brd[g]			0		214, 244, 279	5
		8.14 brd[g]					(4.45, 4.22, 4.00)	
		10.26 brm			−	9.18±0.03	237, 280 sh(4.47, 4.04)	12

a) δ values (at 60 MHz unless otherwise specified): s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. b) Solvent: C, $CDCl_3$; D, D_2O; T, TFA. c) At 250 MHz. d) From Ref. 3. e) J=5 Hz. f) J=7 Hz, $ArCH_2$-CH_2OOC. g) J=9 Hz, O_2N-C_6H_4C. h) Species: monocation (+), neutral species (0), monoanion (−). i) From Ref. 22. j) From Ref. 23. k) Extrapolated value since the species gradually decomposes during the measurement. l) Likely for the ring-open species **6a**.

(see Table 1 for ^{1}H NMR and UV spectra as well as pK_a values, and the Experimental section for other data). The presence of a singlet (2H) at δ 3.9—4.0 (due to H_2-5) in the ^{1}H NMR spectra of **9a—d** eliminated the possibility of the enolated O(4)-substituted structure **12** for these compounds. Also the rather low, basic pK_a values (3.4—2.0) of **9a—d** were in agreement with the 2-amino-4-oxo form rather than the 2-imino-3-substituted form **13** which would be expected to have much higher pK_a values by analogy with those of related compounds (e.g. acetylguanidine, pK_a 8.26).[2b,12,13]

The 2-carbonyamino derivatives **9a—d** were then subjected to the oxidation with mercury(II) acetate. However, the oxidation conducted in water (as in the case of **1** and **2**)[3-5] gave no satisfactory results in general but appeared to cause decomposition into smaller fragments. After various attempts, the oxidation of **9b** and **9c** was accomplished by employing a two-layer system ($CHCl_3$–water), thus giving the 4,5-dioxo compounds **10b** (80% yield) and **10c** (50%), respectively (Scheme 2). Compound **9a**, however, did not give the expected product **10a** but yielded creatone (**3**) and a low yield of 1-methylparabanic acid (**11**)[14] under these conditions, whereas the



oxidation of **9d** gave only a low yield of unstable **10d** which was contaminated by a small amount of the inseparable starting material. The structures of these 4,5-dioxo compounds **10b—d** were established on the evidences of the spectral data (see Experimental section).

Deprotection of the 2-amino group of **10b—d** was

then examined under various conditions. Acid hydrolysis of **10b** (in 2 M†† HCl) resulted in the formation of a 60% yield of **11**, whereas treatment of **10b** with sodium benzenethiolate in HMPA caused profound decomposition. The desired compound **4** was, however, obtained in a 67% yield on heating **10c** in anhydrous trifluoroacetic acid (TFA) at 60 °C. A less satisfactory deprotection to obtain **4** was also accomplished by the treatment of **10d** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in pyridine.[11]

The IR spectrum of **4** showed absorptions due to NH and C=O groups (3200, 3000, 1793, 1720, and 1700 cm^{-1}) but apparently differed from that[3] of **3** particularly in the fingerprint regions. Compound **4** showed a singlet at δ 3.22 due to N-Me and a broad multiplet at 7.4 due to NH_2 groups in $CDCl_3$; the N-Me singlet signal appeared at δ 3.57 and 3.21 in TFA and in D_2O, respectively. As the high-resolution MS confirmed the molecular formula $C_4H_5N_3O_2$, the 2-amino-1-methyl-1*H*-imidazole-4,5-dione structure was unequivocally assigned to **4**. It should be noted that the Me-1 signal of **4** appears at a slightly down-field when compared with the N-Me signals of **2** and **3** in the same solvent system; the conclusive N-Me parameters of **2** and **3** for the additional structural proof have been obtained for the first time in the present study in $CDCl_3$ (and D_2O) (see Table 1).

The UV spectra of the neutral and monocationic species of **4** are shown in Fig. 1; for their absorption maxima, see Table 1. It was found that **4** possessed a low, basic pK_a value (1.89) similar to that of **3** (0.6).[3] These figures indicate that the neutral species of **4** exists exclusively in the 2-amino-1*H*-imidazol-4-one form rather than in the 2-imino-2,3-dihydro-1*H*-imidazol-4-one form **4a** (Scheme 3) in water, taking into account the notable difference of the known pK_a values between the 2-amino-4-oxo and the 2-imino-4-oxo forms of such related compounds as **14** (4.55) and **15** (8.07),[2b] respectively.

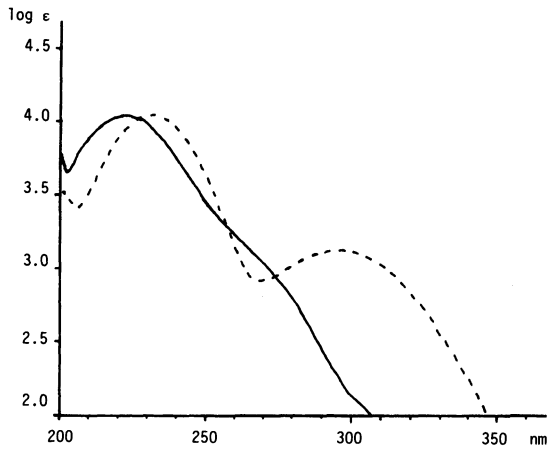


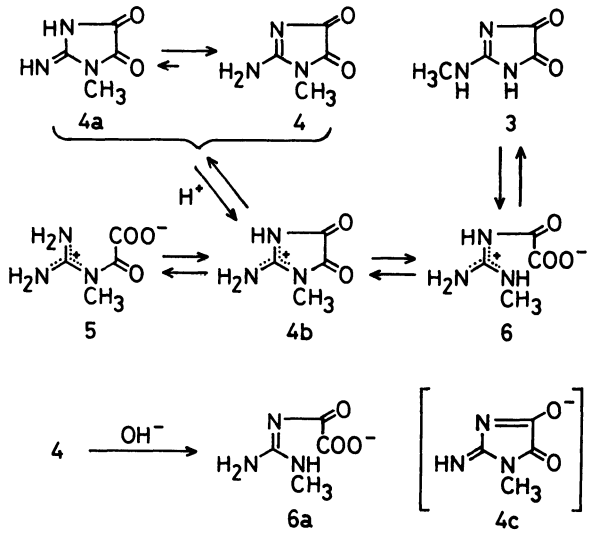
Fig. 1. UV Spectra of **4**: ——, pH 0; ------, pH 4.

†† 1 M=1 mol dm^{-3}.

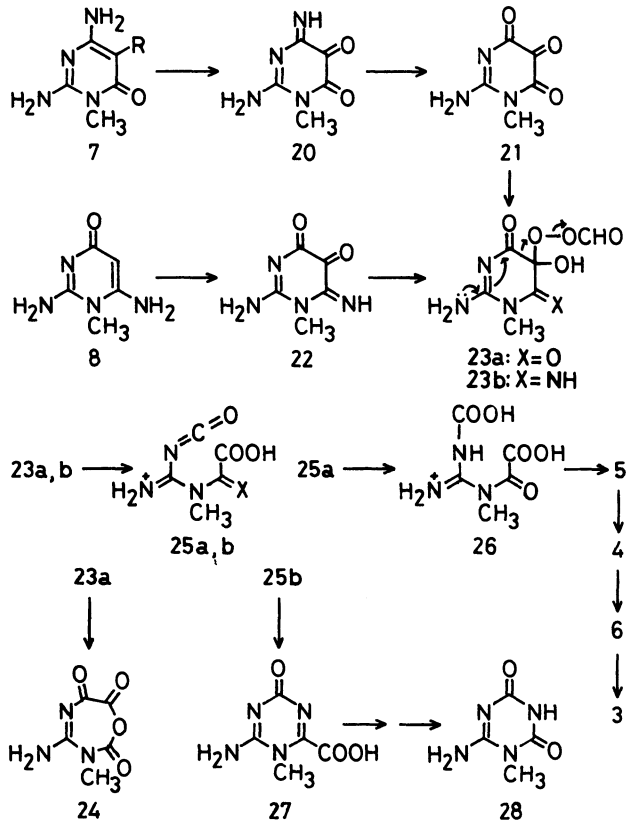
Although **4** remained stable as solid or in anhydrous aprotic solvents, it was found to undergo rearrangement rapidly in aqueous acid ($t_{1/2}$ ca. 5 min at pH 4) and more slowly even at pH 7 ($t_{1/2}$ ca. 30 min), giving creatone **3** exclusively; it was possible to follow this rearrangement either by ^1H NMR in D_2O or by UV spectrometry in various pH buffer solns.[15] Thus, the protonation of an equilibrium mixture of the neutral species **4** and **4a** affords the resonance-stabilized monocation **4b** in acid, which in turn is readily transformed into an equilibrium with the ring-open forms **5** and **6**. Recyclization of the latter provides apparently the thermodynamically more stable product **3** in a manner similar to the Dimroth rearrangement[16] as illustrated in Scheme 3.

Even in weak alkaline regions, **4** was found to change into a transient species which showed a UV absorption maximum at 237 nm (at pH 10, with an apparent pK_a value of 8.0) but underwent a gradual decomposition into smaller fragments exhibiting virtually no UV absorptions ($t_{1/2}$=ca. 60 min). On the grounds of these spectral data and the pK_a value, the short-lived intermediate is presumed to be a ring-open, anionic species such as **6a** rather than the equilibrated 2,5-dihydro-2-imino-5-oxo-1*H*-imidazol-4-olate form **4c** which is expected normally to have a much higher pK_a value.

It has now become obvious that compound **4** is the initially formed key intermediate by the oxidation of creatine (**1**) and creatinine (**2**) to give creatone (**3**), the reaction of which proceeds at ca. pH 3.[3] The oxidized pyrimidone intermediates **20**—**23a** (Scheme 4) and then the seven-membered ring intermediate **24** derived by a Baeyer-Villiger reaction were previously suggested[3] for the possible reaction pathways for the



Scheme 3. Tautomeric forms and equilibria of **4** and the rearrangement to **3**.



Scheme 4. Revised reaction pathways for the formation of **3** from 2,6-diamino-3-methyl-4(3*H*)-pyrimidones **7** and the 1-methyl-4(1*H*) isomer **8**.

oxidative ring-contraction of **7** and **8** to **3**. We now present here a slightly modified common, ring-open intermediates **25a** (instead of **24**) and **26** as illustrated in Scheme 4. Decarboxylation from **26** would afford **5** which subsequently is converted into **3** through the equilibrium shown in Scheme 3, while in the case of the peroxyacid oxidation of **8** the major product 1,3,5-triazine **28** is produced by the oxidative rearrangement through the previously presented intermediates[3] **22**, **23b**, **25b**, and then **27** (Scheme 4).

Many rearrangements have been known[17] involving the fission of a heterocyclic ring and ring closure in the alternate direction catalyzed by acid, base, heat, light, or miscellaneous reagents. As for the imidazole ring system, only a few examples of such rearrangements have been reported, to the best of our knowledge: i.e. **15**→**14** (in boiling methanol),[2b] **16**→**17** (in aq ammonia at 120 °C),[18] and **18**→**19** (with a basic ion-exchange resin).[19] The present rearrangement which takes place extremely fast under such mild conditions is certainly a unique example of the thermodynamically controlled ring transformation. Moreover, as creatone **3** has been isolated[20] from beef and regarded as a constituent of muscle tissue, the present findings are believed to be of value in connection with a biological implication, particularly in clarifying the possibility and mechanism of the reversible reaction between creatine and creatone (or an intermediate shown above), participating in an oxido-reductive process of organism.

Experimental

Melting points were determined with a Yanagimoto MP-S3 instrument and are uncorrected. All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with 2-propanol–AcOEt–water (5:3:1) or MeOH–$CHCl_3$ (1:9) as eluant. Column chromatography was performed with Wako C-200 silica gel. The IR spectra were taken with a Hitachi 215 spectrometer (as KBr disk). The ^1H NMR spectra were measured in $CDCl_3$ (unless otherwise stated) with a Hitachi R-600 (60 MHz, FT) or Bruker AM-250 cryospectrometer (250 MHz) at 27 °C. Chemical shifts (at 60 MHz unless otherwise specified) are recorded as δ values relative to tetramethylsilane [or sodium 3-(trimethylsilyl)-1-propanesulfonate in D_2O] as internal standard. The mass spectra were taken on a Shimadzu LKB-9000 low resolution or a JEOL JMX-HX100 high-resolution instrument, and are given in terms of *m/z* (rel intensity) compared with the base peak. The microanalyses were performed at University of Konstanz. The measurements of the ionization constants were carried out spectrophotometrically at 25 °C in 0.01 M buffers by the usual method.[12]

2-Acetamido-1-methyl-1,5-dihydro-4*H*-imidazol-4-one (9a). A better yield of **9a** was obtained by employing a slightly modified procedure of Ing.[9] Thus, a mixture of **2**[21] (0.50 g) and acetic anhydride (1 cm^3) was heated at 70 °C (oil bath) with swirling until the white suspension became a pale yellow soln (ca. 5 min), and then, after cooling with water, diluted with diethyl ether (10 cm^3). The mixture was allowed to stand overnight at 5 °C. The ppt was filtered and recrystd from EtOH/ether, giving **9a** as colorless needles (0.51 g, 74%): mp 124—125 °C (Ref. 9, 124—125 °C); IR 3170 (NH), 1770, 1740, and 1615 cm^{-1} (C=O, C=N); MS *m/z* 155 (M^+; 4.4), 154 (37.8), 140 (75.3), 113 (27.0), and 44 (100).

2-Methoxycarbonylamino-1-methyl-1,5-dihydro-4*H*-imidazol-4-one (9b). To a soln of 1-methylimidazole (0.44 cm^3) in dry ether (8 cm^3) was added methyl chloroformate (0.43 cm^3, 1.0 equiv) at 0 °C under nitrogen. After 5 min, the solvent was evaporated in vacuo and the white viscous tar (1-methoxycarbonyl-3-methylimidazolium chloride) was dissolved in dry DMF (7 cm^3) with stirring at 0 °C under nitrogen. To this soln was added **2** (0.50 g, 1.0 equiv) and the mixture was stirred at 20 °C under nitrogen. After 2 h, water (1 cm^3) was added. The solvent was evaporated in vacuo and the residue was triturated with AcOEt. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was recrystd from AcOEt–ether, giving **9b** as pale yellow crystals (0.53 g, 71%): mp 132—133 °C; IR 3230 (NH), 1780, 1750, 1660, and 1620 cm^{-1} (C=O, C=N); MS *m/z* 171 (M^+; 45.9), 140 (63.8), 112 (24.7), 69 (33.9), 44 (100), and 42 (52.9).

Found: C, 42.07; H, 5.35; N, 24.25%. Calcd for $C_6H_9N_3O_3$: C, 42.10; H, 5.30; N, 24.55%.

2-*t*-Butoxycarbonylamino-1-methyl-1,5-dihydro-4*H*-imidazol-4-one (9c). A soln of **2** (240 mg), triethylamine (0.45 cm^3, 1.6 equiv), and BOC-ON (260 mg, 0.5 equiv) in dry DMF (16 cm^3) was heated at 60 °C for 4 d with stirring

under argon; more BOC-ON (3×260 mg) was added every 1 d. The solvent was evaporated in vacuo and the residue was triturated with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed in a column of silica gel with AcOEt–hexane, giving **9c** as a pale yellow syrup (338 mg, 75%), which became colorless needles on recrystallization from ether-light petroleum: mp 33—34 °C; IR 3230 (NH), 1760, and 1655 cm^{-1} (C=O); MS *m/z* 213 (M^+; 0.7), 158 (100), 140 (57.1), 57 (57.0), 44 (20.7), and 18 (51.9).

Found: *m/z* 158.0562. Calcd for $C_5H_8N_3O_3$: M−C_4H_7, 158.0566.

1-Methyl-2-[2-(*p*-nitrophenyl)ethoxycarbonylamino]-1,5-dihydro-4*H*-imidazol-4-one (9d). To a suspension of **2** (23 mg) in dry DMF (0.5 cm^3) was added 1-methyl-3-[2-(*p*-nitrophenyl)ethoxycarbonyl]imidazolium chloride[11] (69 mg, 1.1 equiv) in one portion at 20 °C with stirring. After 45 min, cold water (3 cm^3) was added to the mixture at 5 °C. The resultant suspension was extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo and the residue was recrystd from AcOEt to give **9d** as almost colorless needles (60 mg, 95%): mp 146—147 °C; IR 3220 (NH), 1755, 1710, 1650, and 1620 cm^{-1} (C=O); MS *m/z* 307 (M+1; 4.53), 306 (M^+; 2.39), 260 (2.87), 167 (4.07), 157 (42.7), 149 (19.3), 140 (83.7), 139 (13.7), 137 (11.3), 112 (20.6), 91 (7.7), 69 (18), 44 (100), 43 (43.7), 42 (52.2), 31 (40.2), 30 (43.8), and 18 (28).

Found: C, 50.87; H, 5.02; N, 18.16%. Calcd for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29%.

Oxidation of 9a. To a soln of **9a** (31 mg) in water (2 cm^3) was added mercury(II) acetate (128 mg, 2.0 equiv). The resultant mixture was set aside at 20—25 °C for 3 d. The ppt was filtered off and washed with a small amount of water. The combined filtrate and washings were saturated with H_2S (gas). The ppt was filtered off and washed with water. The combined filtrate and washings were once more filtered (with gravity) and evaporated in vacuo to give a white solid, which was triturated with $CHCl_3$ to give crude **11**; the solid which remained undissolved in $CHCl_3$ was identified by chromatography and spectroscopy (NMR, IR, and MS) to be mostly creatone **3** (10 mg, 39%). The former product **11** was chromatographed in a column of silica gel with 2% MeOH–$CHCl_3$, giving pure **11** as colorless needles (2 mg, 8%): mp 151—152 °C (from AcOEt–hexane, Ref. 14, 150—152 °C); pK_a 5.99±0.1; UV λ_{max} (pH 2) 213 nm (log ε 3.88), (pH 8) 221 and 285 nm (log ε 3.95 and 2.50); IR 3220, 1790, 1745, 1715, and 1660 cm^{-1}; ^1H NMR (250-MHz) δ=3.21 (3H, s, Me-1) and 7.98 (1H, brm, NH), (in D_2O) 3.11 (s, Me-1); MS *m/z* 128 (M^+; 48.6), 100 (44.3), 72 (21.9), 57 (83.6), 56 (100), 44 (25.0), 43 (26.6), 29 (51.1), and 28 (69.6). (Found: *m/z* 128.0235).

Even by employing the two-layer system (see below), oxidation of **9a** with $Hg(OAc)_2$ resulted in the formation of **3** and **11** only; no desired compound **10a** was obtained.

2-Methoxycarbonylamino-1-methyl-1*H*-imidazole-4,5-dione (10b). To a soln of **9b** (105 mg) in water (10 cm^3) was added $CHCl_3$ (20 cm^3) and then mercury(II) acetate (395 mg, 2.0 equiv). The mixture was stirred at 20 °C under the protection of light. After 90 min, it was separated and the aq layer was extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed in a column of silica gel with 5% MeOH–CH_2Cl_2, giving crude **10b** as a pale yellow solid. This was dissolved in CH_2Cl_2 (50 cm^3), washed with cold 0.5 M HCl (20 cm^3), dried (Na_2SO_4), and evaporated in vacuo. The residue was recrystd from CH_2Cl_2–hexane to give pure **10b** as colorless needles (89 mg, 80%): mp 192—193 °C; IR 3280, 1790, 1690, and 1650 cm^{-1}; ^1H NMR 3.26 (s, Me-1) and 3.84 (s, MeO); MS *m/z* 185 (M^+; 50.0), 157 (85.4), 155 (36.5), 126 (100), 99 (26.5), 83 (81.0), 69 (45.5), and 59 (19.6).

Found: *m/z* 185.0464. Calcd for $C_6H_7N_3O_4$: M, 185.0446.

2-*t*-Butoxycarbonylamino-1-methyl-1*H*-imidazole-4,5-dione (10c). A mixture of **9c** (68 mg) and mercury(II) acetate (225 mg, 2.2 equiv) in $CHCl_3$ (15 cm^3) and water (15 cm^3) was stirred at 20 °C for 6 h in the dark. After separation the aq layer was extracted with $CHCl_3$. The combined organic layers were washed with aq $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed in a column of silica gel with AcOEt–hexane, giving **10c** as pale yellow needles (37 mg, 50%): mp 157—159 °C (from AcOEt–hexane); IR 3290, 1800, 1790, 1770, 1690, 1670, and 1650 cm^{-1}; ^1H NMR 1.55 (s, *t*-BuO) and 3.27 (s, Me-1); MS *m/z* 227 (M^+; ≃0), 212 (1.5), 172 (47.8), 154 (50.4), and 57 (100).

Found: *m/z* 172.0388. Calcd for $C_5H_6N_3O_4$: M−C_4H_7, 172.0357.

1-Methyl-2-[2-(*p*-nitrophenyl)ethoxycarbonylamino]-1*H*-imidazole-4,5-dione (10d). To a suspension of **9d** (32 mg) in water (30 cm^3) was added mercury(II) acetate (90 mg, 2.5 equiv), and the mixture was stirred at 20 °C for 3 d. Then more mercury(II) acetate (50 mg, 1.5 equiv) and water (10 cm^3) were added, and stirring was continued for 7 d (total). The pale yellow precipitate was filtered off and triturated with 5% MeOH–$CHCl_3$; the above filtrate was extracted with $CHCl_3$. The combined organic layers were evaporated in vacuo and the residue was chromatographed in a column of silica gel with $CHCl_3$→5% MeOH–$CHCl_3$, giving **10d** as pale yellow crystals (10 mg, 30%) (which, however, contained a small amount of inseparable **9d**): mp 182—184 °C (from $CHCl_3$–hexane); IR 3300, 1789, 1740, 1685, 1635 cm^{-1}; ^1H NMR (250-MHz) 3.17 (2H, t, *J*=6.8 Hz, $ArCH_2$), 3.27 (3H, s, Me-1), 4.49 (2H, t, *J*=6.8 Hz, CH_2OOC), 7.44 (2H, brd, *J*=8.9 Hz, H-2′,6′), 8.20 (2H, brd, *J*=8.9 Hz, H-3′,5′), and 10.29 (1H, brm, NH-2); MS *m/z* 320 (M^+; ≃0), 167 (4.0), 154 (47.3), 149 (100), 137 (17.7), 126 (27.8), 103 (17.0), 83 (67.3), and 28 (100). Compound **10d** was liable to decompose (presumably by hydrolysis or methanolysis) during the purification.

Found: C, 49.16; H, 4.12; N, 17.76%. Calcd for $C_{13}H_{12}N_4O_6$: C, 48.75; H, 3.78; N, 17.50%.

Attempted Deprotection of 10b. A soln of **10b** (22 mg) in 2 M HCl (10 cm^3) was stirred at 20 °C for 10 min, and then extracted with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed in a column of silica gel with 10% ether–CH_2Cl_2, giving **11** (by IR, ^1H NMR, and TLC) as colorless plates (10 mg, 66%), mp 153—154 °C (Ref. 14, 150—152 °C).

2-Amino-1-methyl-1*H*-imidazole-4,5-dione (4). A. A soln of **10c** (4.5 mg) in anhyd TFA (1 cm^3) was heated at 60 °C for 1 h with stirring under argon. The mixture was diluted with dry $CHCl_3$ and then evaporated in vacuo to remove TFA, which was repeated several times. The residue

was washed with dry $CHCl_3$ and then with a small amount of dry AcOEt, giving **4** as a colorless crystalline powder (2.0 mg, 67%): mp 208—209 °C decomp; IR 3200, 3000, 1793, 1720, and 1700 cm^{-1}; MS *m/z* 127 (M^+; 88.0), 99 (M—CO, 87,7), 71 (M—2CO, 44.8), 56 (61.0), 42 (59.8), and 28 (100).

Found: *m/z* 127.0418. Calcd for $C_4H_5N_3O_2$: M, 127.0382.

B. A soln of **10d** (9 mg) and DBU (15 mg) in dry pyridine was stirred at 20 °C for 12 h under argon. The solvent was evaporated in vacuo below 20 °C (pump) and the residue was washed with dry cyclohexane, and then with a small amount of dry $CHCl_3$, giving crude **4** (by IR, ^1H NMR, and TLC) as a colorless powder (1 mg, ca. 25%), mp 205—208 °C decomp.

Rearrangement of 4 to 3. A soln of **4** (2.6 mg) in 1 M acetic acid (0.15 cm^3) was allowed to stand at 20 °C for 20 h. The ppt was filtered off and washed with cold water, giving colorless crystals which were identified by IR and ^1H NMR to be **3** (1.6 mg, 62%), mp 198—201 °C decomp (Ref. 3, 197—199 °C decomp).

The rearrangement of **4** (0.8 mg) in D_2O (0.6 cm^3) was pursued by ^1H NMR measurement (following a gradual decrease of the singlet signal of **4** at δ 3.21 with a simulaneous increase of the singlet of **3** at δ 2.98; $t_{1/2}$ ca. 14 min at pH 5).

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