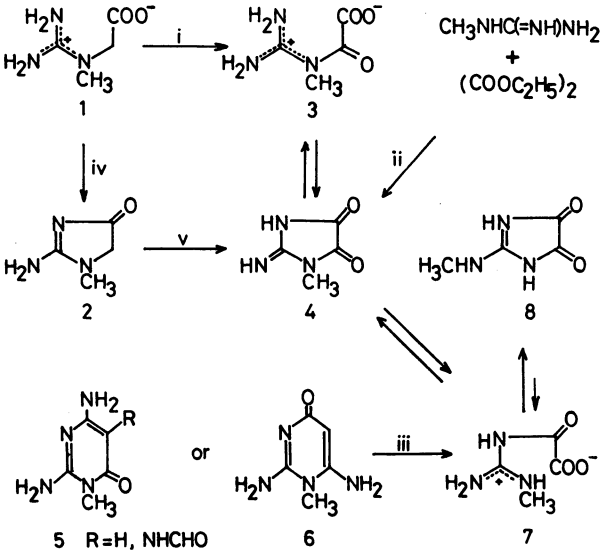
2-Methylamino-4,5-imidazoledione. A Revised Structure for Creatone, Methylparabanic Acid Imide, and (3-Methylguanidino)glyoxylic Acid

Hiroshi YAMAMOTO* and Wolfgang PFLEIDERER†
Department of Chemistry, Faculty of Science, Okayama University, Okayama 700
†*Universität Konstanz, Facultät für Chemie, D-7750 Konstanz, Germany*
(Received November 18, 1981)

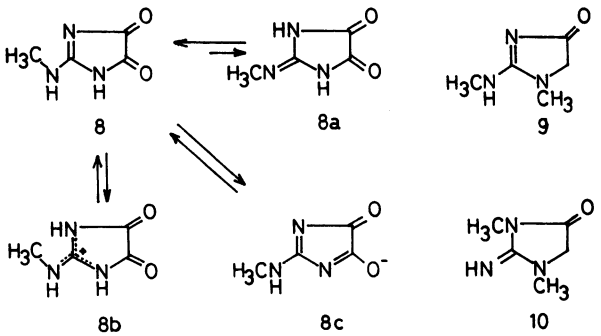
The previous structures presented for the $Hg(OAc)_2$ oxidation product of creatine, the condensation product of methylguanidine and diethyl oxalate, and the peracid oxidation product of 1-methyl-2-amino-dihydropyrimidines are all replaced by a revised formulation, 2-methylamino-1*H*-imidazole-4,5-dione on the basis of the pK_a values (0.62 and 7.87) and the spectra. The equilibria between this thermodynamically controlled product and the previous formulations are discussed.

Creatine (**1**) is present in the muscular tissue of many vertebrates, mostly as phosphocreatine, which plays an important role in energy transfer and storage.[1] It has been reported[2,3] that the action of mercury(II) acetate on **1** afforded a single product (creatone) (mp 203—204°C decomp), to which the structure of (1-methylguanidino)-glyoxylic acid (**3**) was assigned (Scheme 1). The same product was also isolated from beef and regarded as a constituent of muscle tissue.[4] Traube and Gorniak,[5] meanwhile, briefly reported a condensation product (mp 205—207 °C decomp) of methylguanidine and diethyl oxalate; the structure of "1-methylparabanic acid imide" (2-imino-1-methylimidazolidine-4,5-dione) (**4**) was simply presented for this product, without any proof.

During our study of the oxidative pyrimidine→1,3,5-triazine rearrangement, we found that the action of performic acid on 2,4-diamino-1-methyl-1,6-dihydro-pyrimidin-6-ones (**5**) and the 6-amino-4-oxo isomer (**6**) afforded a 20—25% yield of colorless needles (mp 200 °C decomp), to which the Zwitter ion structure, (3-methylguanidino)glyoxylic acid (**7**), was assigned on the evidences of the elemental analysis and spectral data



Scheme 1. Reaction pathways for the formation of **8** from **1**, **2**, **5**, **6**, and methylguanidine–diethyl oxalate. i, $Hg(OAc)_2$, Refs. 2, 3. ii, Ref 5. iii, H_2O_2/HCOOH. Ref. 6. iv, H^+. v, $Hg(OAc)_2$.



Scheme 2. Tautomeric forms and equilibria of **8**.

(UV, IR, and ^{1}H-NMR).[6] However, the close similarity of the melting points and the solubilities (in water) among the products, **3**, **4**, and **7**, led us to reinvestigate those structures.

We have now found that both creatone (**3**) prepared[3] from **1** and the condensation product[5] (**4**) were identical with our specimen,[6] derived from **5** and **6**, on the evidence of the spectroscopic data (IR, NMR) and the mixed melting points. Creatinine (**2**), an important end product of nitrogen metabolism,[7] also produced the identical substance more rapidly than **1** upon treatment with mercury(II) acetate. The revised structure of 2-methylamino-1*H*-imidazole-4,5-dione (**8**) was then assigned to the common product on the basis of the spectral data, as will be shown below.

The repeated elemental analysis of the specimen of **8** dried at 120 °C/0.05 Torr** over P_2O_5 showed an analytical figure corresponding to $C_4H_5N_3O_2$ instead of $C_4H_7N_3O_3$, which had previously been reported.[2,3,6] The EI high-resolution and chemical-ionization mass spectra clearly confirmed the molecular formula ($C_4H_5N_3O_2$), and the characteristic fragmentation peaks were those at *m/e* 99 and 71 due to the successive loss of two CO groups from the molecular ion. The presence of imino and two kinds of carbonyl groups were confirmed by the IR spectrum (3200, 1710, and 1630 cm^{-1}). Because of the sparing solubility in other suitable solvents (*e.g.*, DMSO-d_6, D_2O, or pyridine-d_5), the NMR spectrum of **8** was taken in trifluoroacetic acid (TFA); the signals are recorded in Table 1. In TFA-*d*, the doublet at 3.31 collapsed into a singlet,

** 1 Torr≈133.332 Pa.

Table 1. Physical properties of some imidazole derivatives

Compd	^{1}H-NMR parameters[a]				Ionization and UV spectra[l] in water(25 °C)			
	CH_3-1* or H-1	H_2N-2* or CH_3NH-2	H-3	2H-5	Species[l]	pK_a	λ_{max}/nm (ε)	pH
1[b]	3.37*s	6.54*bm	6.54bm[c]	4.54s	+	2.54[k]		
					−	14.28[k]		
2	3.37*s	8.03*bm	8.03bm[d]	4.66s	+	4.83[l]		
					0		235(7060)[m]	
8[e]	7.70bm	3.31d[f,g]	7.70bm	—	+	0.62±0.10[n]	212(9380)	−0.05
		8.65bq[f,h]			0		204(13600)	4.0
					−	7.87±0.04[n]	234(10100)[o]	9.8
9					+	4.55[p]		
					0		212(18400)[p]	
							235(shoulder)	
10					+	8.07[p]		
					0		205(13 600)[p]	

a) δ values in TFA at 30 °C, with TMS as the internal standard; s, singlet; d, doublet; q, quartet; m, multiplet; b, broad. b) The numbering of **1** corresponds to that of **2** for the purpose of comparison. On setting aside the sample solution in TFA at 25 °C, **1** gradually changes to **2** ($t_{1/2}$ *ca.* 3 d), which, in contrast, remains unchanged. c) 2H. d) The assignment has been made because **2** probably exists as the monocation in TFA. e) The spectra are of compounds, **3**, **4**, and **7**, all of which are identical and exist as the monocation **8b** in TFA. f) J=5.0 Hz. g) 3H. h) 1H. i) Measured with a Hitachi EPS 3T Recording Spectrophotometer. j) Monocation (+), neutral species (0), monoanion(−). k) From Ref. 17. l) From Ref. 8. m) From Ref. 9. n) Determined spectroscopically according to Ref. 16. o) Extrapolated value since the anionic species gradually decomposes during the measurement. p) From Ref. 10.

and the broad multiplet and the quartet disappeared, suggesting the presence of a CH_3NH– (or $CH_3\overset{+}{N}H$=) group in the molecule. Structures **3** and **4** were thus eliminated because their *N*-methyl signal may be expected to be a singlet, as was observed in the spectra of the two starting materials, **1** and **2**, in the same solvent (see Table 1).

Creatinine (**2**) was shown to exist mainly in the amino-oxo form rather than the universally written 2-imino-1-methylimidazolidin-4-one form by comparing the pK_a value and other physical properties with those of such related compounds as **9** and **10** (see Table 1).[8-11] The pK_a values and UV spectra of **8** were thus measured; the results are summarized in Table 1. Although the neutral species of **8** was completely stable in water at 25 °C, both cationic and anionic species were gradually degraded——*e.g.*, $t_{1/2}$ 3 d (in 1 mol dm^{-3} HCl) and 70 min (at pH 9—13). The extremely low value (0.6) of the basic pK_a of **8** and the stability of its neutral species in water point to the amino-oxo form (**8**) rather than the tautomeric imino form (**8a**) (Scheme 2), since the exocyclic imono group may be expected to be more basic and unstable in a protic solvent, as is shown in the case of **10**, which gradually isomerized to **9** in boiling methanol.[10] The UV absorption maximum of **8** in acid and the NMR doublet signal of the methyl group in TFA suggest the resonance-stabilized form **8b** for the monocation. The large bathochromic shift (30 nm) observed in the UV absorption maximum in alkaline solutions indicates that **8** probably becomes a fully conjugated diazacyclopentadienone form, **8c**, which in turn tends to decompose readily to oxalic acid and methylguanidine.

The oxidation of **1** and **2** with mercury(II) acetate presumably proceeds in a manner similar to that of the dehydrogenation of cyclic tertiary amines[12] to give **4**, which is in equilibrium with the ring-opened forms **3** and **7** (Scheme 1). The latter should provide **8** upon a recyclization similar to the Dimroth rearrangement,[13] and the predominant formation of the final product **8** could be explained by its thermodynamical stability compared with other isomers (**3**, **4**, and **7**). The formation of **8** from the pyrimidines, **5** and **6**, is initiated by the peroxy acid degradation to afford a common intermediate **4** or **7**, followed by a similar equilibrium transformation. The same equilibrium scheme was also applied to the condensation product of methylguanidine and diethyl oxalate, as is shown in Scheme 1.

Many rearrangements have been known[14] involving the fission of a heterocyclic ring and ring closure in the alternate direction catalyzed by acid, base, heat, light, or miscellaneous reagents. The present rearrangement at such a low temperature can be classified, to the best of our knowledge, as a rare example of thermodynamically controlled ring transformation of the imidazole-ring system.[15]

Experimental

The ^{1}H-NMR spectra were measured in TFA with a Hitachi High-resolution NMR Spectrometer, R-20A (60 MHz), at 30 °C. The IR spectra were taken with a Nihon-Bunko IR-S spectrometer. The mass spectra were measured at the Department of Chemistry, the University of Alberta, with an A. E. I. MS 50 ultra-high-resolution instrument (for the accurate mass measurement) and an A. E. I. MS 12 appararus (for the chemical ionization with NH_3). The measurements of the ionization constants were carried out spectrophotometrically in 0.01 mol dm^{-3} buffers by the usual method.[16]

The microanalyses were performed using a Yanagimoto CHN Corder, MT-2. Substances stated to be identical were compared by means of mixed-melting-point determinations, their spectra (IR, NMR), and TLC (silica gel; developed with DMF–MeOH–$CHCl_3$, 1 : 5 : 15). The melting points are uncorrected.

The Oxidation of Creatinine (2). To a solution of 1.13 g (10 mmol) of **2** in 80 ml of water was added 11.2 g (35 mmol) of mercury(II) acetate, after which the mixture was allowed to stand at room temperature; after *ca.* 3 h, colorless leaflets began to separate, and 4.82 g (15 mmol) more of $Hg(OAc)_2$ was added after 1 d. The precipitate was filtered off after 3 d and washed with a small amount of cold water; the pH of the supernatant solution was 3 throughout this period. The filter cake was suspended in 100 ml of water and saturated with hydrogen sulfide gas with stirring. The black mercury sulfide was filtered by gravity and washed with boiling water (20 ml). The combined filtrate and washings were evaporated to dryness *in vacuo*, and the residue was washed with 80% aq *t*-BuOH, giving 0.56 g (38%) of **8** as a colorless powder: mp 197—199 °C decomp (from 50% aq ethanol); IR (KBr), 3200 (NH), 1710 (C=O), 1630 (C=N–CO=), 1450, 1370, 1190, 1160, 790, and 680 cm^{-1}; EI high-resolution MS, *m/e* (rel intensity), 127 (89; M^+), 99 (100; M−CO), 71 (54; M−2CO), 58 (34), 56 (75; MeNHC≡N), and 55 (71; MeNCN); CI (NH_3) MS, *m/e* (rel intensity), 147 (0.8; P+2), 146 (5.5; P+1), 145 [100; P($M+NH_4^+$)], 128 (2.8), 102 (1.0), and 86 (6.9).

Found (for material dried over P_2O_5 at 120 °C/0.05 Torr for 7 h): C, 37.42; H, 4.21; N, 32.83%; *m/e*, 127.0381. Calcd for $C_4H_5N_3O_2$: C, 37.81; H, 3.97; N, 33.06%; *m/e*, 127.0382.

The product was identical with the specimen[6] obtained from **5** and **6**.

The Oxidation of Creatine (1). The procedure fo Greenwald[3] was followed; after *ca.* 10 h, colorless leaflets began to separate. The product similarly obtainep after 8 d (20%yield, mp 197—199 °C decomp) was identical with **8**.

The Condensation of Methylguanidine and Diethyl Oxalate. Traube and Gorniak[5] reported the product **4** without describing the experimental procedure in detail. Thus, the reaction was carried out as follows: a solution of sodium ethoxide was prepared by dissolving 0.30 g (13 mmol) of sodium in 10 ml of absolute ethanol. To this were added, under argon at 5 °C, 1.42 g (13 mmol) of methylguanidine hydrochloride and 1.9 g (13 mmol) of diethyl oxalate. The resulting white suspension was stirred at 20 °C for 5 h. The mixture was taken to pH 4 by the careful addition of 5 mol dm^{-3} AcOH at 5 °C and subsequently concentrated *in vacuo*. The residue was suspended in methanol (20 ml) and filtered off, giving 0.80 g (47%) of **8** as colorless leaflets; mp 203—205 °C decomp (from 50% aq ethanol).

We wish to thank Dr. M.-A. Armour of the University of Alberta for the high-resolution mass spectra.

References

1) For reviews of the chemistry and biology of creatine, see a) S. Schipper and A. R. Day, "Hetetrocyclic Compounds," ed by R. C. Elderfield, Wiley, New York (1957), Vol. 5, p. 263; b) M. Cohn, *Quart. Rev. Biophys.*, **3**, 61 (1970).

2) L. Baumann and T. Ingvaldsen, *J. Biol. Chem.*, **35**, 277 (1918).

3) I. Greenwald, *J. Am. Chem. Soc.*, **41**, 1109 (1919).

4) V. S. Gulevich, *C. R. A. Sci. U. R. S. S.*, **1930A**, 559; *Z. Phys. Chem.*, **217**, 63 (1933).

5) W. Traube and K. Gorniak, *Z. Angew. Chem.*, **42**, 379 (1929).

6) H. Yamamoto and W. Pfleiderer, *Chem. Ber.*, **106**, 3194 (1973); the material dried at 100 °C/15 Torr gave an analytical figure corresponding to $C_4H_7N_3O_3$.

7) A. H. Ennor and J. F. Morrison, *Phys. Rev.*, **38**, 631 (1958).

8) A. K. Grzybowski and S. P. Datta, *J. Chem. Soc.*, **1964**, 187.

9) K. Matsumoto and H. Rapoport, *J. Org. Chem.*, **35**, 552 (1968).

10) G. L. Kenyon and G. L. Rowley, *J. Am. Chem. Soc.*, **93**, 5552 (1971).

11) J. Elguero, C, Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles," (Adv. Heterocyclic Chem. Supplement 1), Academic Press, New York (1976), pp. 479—481.

12) N. J. Leonard, L. A. Miller, and P. D. Thomas, *J. Am. Chem. Soc.*, **78**, 3463 (1956); J. Knabe and H. Roloff, *Chem. Ber.*, **97**, 3452 (1964).

13) See D. J. Brown, "Mechanisms of Molecular Migrations" ed by B. S. Thyagarajan, Interscience-Wiley, New York (1968), Vol. 1, p. 202.

14) H. C. van der Plas, "Ring Transformation of Heterocycles," Academic Press, New York (1973).

15) A closer mechanistic study is currently in progress.

16) A. Albert and E. P. Serjeant, "Ionization Constants of Acid and Base," Methuen, London (1962).

17) A. Hahn and H. Fasold, *Z. Biol.*, **82**, 473 (1925); C. F. Failey and E. Brand, *J. Biol. Chem.*, **102**, 767 (1933).