A Simple Conversion of Creatinine to Creatol *via* Creatinine Chloramine

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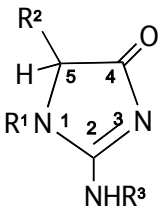
Abstract

Creatinine (2-amino-1,5-dihydro-l-methylimidazol-4-one) (**1a**) was converted in a simple way to creatol (2-amino-1,5-dihydro-5-hydroxy-l-methylimidazol-4-one) (**1b**) *via* creatinine chloramine (2-*N*-chloroamino-1,5-dihydro-l-methylimidazol-4-one) (**3a**), without using protecting groups. The creatinine chloramine exists in the 2-*N-chloroamino* form (**3a**) in aqueous solution, but in the solid state X-ray crystal analysis shows that it has the

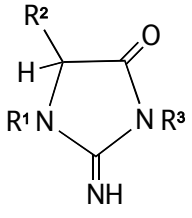
2-*N*-*chloroimino* structure (2-*N*-chloroimino-1,5-dihydro-1-methylimidazol-4-one) (**4a**). Related imidazolones have also been prepared and discussed.

Introduction

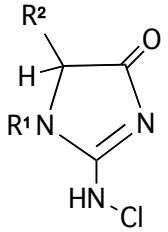
Creatinine (2-amino-1,5-dihydro-l-methylimidazol-4-one) (**1a**) is the cyclisation product of the amino acid creatine, α-(methylguanidino)acetic acid. It occurs in mammalian bodies and is a marker whose level in blood indicates the progression towards renal failure. In a series of investigations we, and others, have discovered other creatinine metabolites in blood and urine which helped to identify the stages (3 to 5) of chronic kidney disease in experimental rats and in humans.[1-7] Creatinine (**1a**) has been reported to react with hydroxyl radicals (•OH) to give a 1:1 mixture of creatol (2-amino-1,5-dihydro-5-hydroxy-l-methylimidazol-4-one) (**1b**),[8,9] and demethylcreatinine (2-amino-1,5-dihydro-imidazol-4-one) (**1c**) quantitatively.[9] That is, C-5 is hydroxylated to the same extent as the



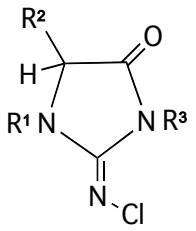
	R¹	R²	R³
1a	Me	H	H
1b	Me	OH	H
1c	H	H	H
1d	H	OH	H
1e	Me	H	Boc
1f	Me	OAc	Boc
1g	Me	OAc	H



	R¹	R²	R³
2a	Me	H	H
2b	Me	OH	H
2c	H	H	H
2d	H	OH	H
2e	H	H	Me
2f	Me	H	Me



	R¹	R²
3a	Me	H
3b	Me	OH
3c	H	H
3d	H	OH



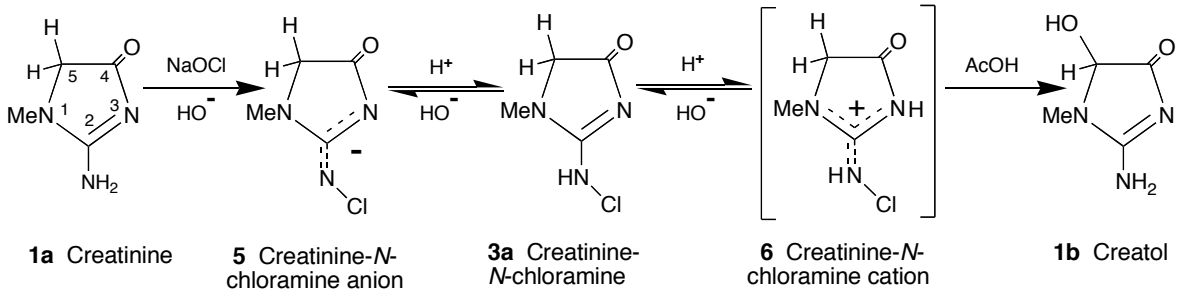
	R¹	R²	R³
4a	Me	H	H
4b	Me	OH	H
4c	H	H	H
4d	H	OH	H
4e	H	H	Me
4f	Me	H	Me

Figure 1

de-methylation of the 1-methylgroup. These reactions, which also generally occur in mammalian bodies, can be observed in test tubes.[9] However, in order to obtain authentic creatol (**1b**), we used the briefly reported procedure from creatinine (**1a**) in four steps by

using a protecting group.[10] On the other hand, creatinine (**1a**) has been reported to be oxidized differently with hypochlorite ($^{-}$OCl) in stimulated neutrophiles to give methylguanidine,[11] although its mechanism remained unclear. We herein report the syntheses[12,13] not only of the creatinine-*N*-chloramine (2-*N*-chloroamino-1,5-dihydro-l-methylimidazol-4-one) (**3a**), but also of its derivatives (**3b-d**, **4e**, **4f**), in order to compare their properties.

We found by accident that the chloramine (**3a**) was converted to creatol (**1b**), when it was dissolved in acetic acid solution. And so, we show herein a simple synthetic procedure for preparing creatol (**1b**), from creatinine (**1a**) *via* the chloramine (**3a**) by reactions (**1a**) → (**3a**) → (**1b**) without using any protecting group which would need to be removed [Scheme 1]. The creatol (**1b**) formed had been known to be further converted to methylguanidine not only i*n vitro* but also *in vivo*.[9]



SCHEME 1. Conversion of creatinine to creatol *via* creatinine-*N*-chloramine

Results and Discussion

Syntheses of authentic specimens

For the preparation of authentic creatol using protective groups,[10] creatinine and *t*-Boc anhydride were reacted to give N^{ε}-*t*-butoxycarbonylcreatinine (**1e**), which was oxidized with lead tetraacetate to form N^{ε}-*t*-butoxycarbonyl-5-acetoxycreatinine (**1f**) as an oil. This was stirred with TFA at room temperature, and the resulting 5-acetoxy-1,5-dihydro-1-methylimidazol-4-one (**1g**) was treated with 1N HCl solution at room temperature to give the HCl salt of creatol (**1b**) quantitatively.

Authentic specimens of the creatinine-*N*-chloramine (**3a**) and creatol-*N*-chloramine (2-*N*-chloroamino-1,5-dihydro-5-hydroxy-l-methylimidazol-4-one) (**3b**) were synthesized according to a method which was described briefly.[12,13] Creatinine (**1a**) reacted with hypochlorite to give the *N*-chloramine (**3a**) quantitatively, although it was isolated in only 70% yield because of decomposition during purification. Similarly, creatol-*N*-chloramine (**3b**) was also prepared from creatol (**1b**). The demethylated creatinine (1,5-dihydroimidazol-4-one) (**1c**) and demethylated creatol (1,5-dihydro-5-hydroxy-imidazol-4-one) (**1d**) were similarly reacted with sodium hypochlorite in aqueous solution to give the corresponding 2-*N*-chloramines, (2-*N*-chloroamino-1,5-dihydroimidazol-4-one) (**3c**) and (2-*N*-chloroamino-1,5-dihydro-5-hydroxyimidazol-4-one) (**3d**). The 3-methylated 2-*N*-chloramines, (2-*N*-chloroamino-1,5-dihydro-3-methylimidazol-4-one) (**4e**) and (2-*N*-chloroamino- 1,5-dihydro-1,3-dimethylimidazol-4-one) (**4f**), were prepared in the same way except that acetone was used as solvent instead of water.

The creatinine-*N*-chloramine (**3a**) and creatol-*N*-chloramine (**3b**), themselves have been known as the chlorination products of creatinine (**1a**) and creatol (**1b**) respectively with free chlorine.[14,15] We have used the general─name of *chloramine* for these *N*-chloro compounds, although we now know that the name *chlorimine* should be used for the compounds in solid the state. The chlorimine structure (**4a**) for the monochloro compound of creatinine (**1a**) in the solid state was confirmed by x-ray analysis, and we deduced that the corresponding derivatives also have chloroimine structures (**4b-4d**) in the solid state. The tautomeric *N*-chloramine structure (**3a**) in alkaline solution was deduced from its u.v. spectra (see below). The structures of the *N*-chloramines (**3c**) and (**3d**) and their *N*-chlorimine tautomers (**4c**) and (**4d**) are also discussed.

Structures in the solid state.

In this study we have determined the X-ray crystal structure of the solid chlorinated product of creatinine which turned out to have the 2-*N*-chlor*imine* structure as shown in formula (**4a**) [Figure 2]. The crystallographic data are reported in the Supplementary Material. The data showed that there is a hydrogen atom on N(2). It also showed that

the lengths of the C(1)—N(2) [1.39A] and C(1)—N(3) [1.35A] bonds are consistent with single bonds, whereas the C(1)—N(1) [1.29A] distance is shorter. This supports a 2-*N*-chlor*imino*- structure. X-ray crystal studies of solid creatinine (**1a**) also showed that the C(1)—N(1) [using Figure 2 numbering of atoms] is the shortest bond,[16,17] supporting structure (**2a**), but that in aqueous solution creatinine is in the amino tautomer which was in agreement with two theoretical studies.[18,19] By analogy, the solid forms of the creatinine derivatives (**2b-d**) which include creatol (**2b**) would have the 2-imino structure, and the chloramines (**3a-d**) should be similar and should have the *N*-chlor*imino* structure (**4b-d**). Moreover the compounds, with methyl groups on N-1 and N-3 like the imidazole-4-ones

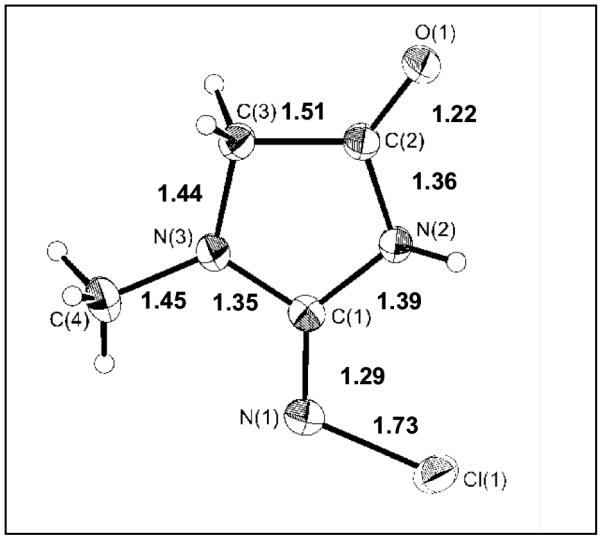
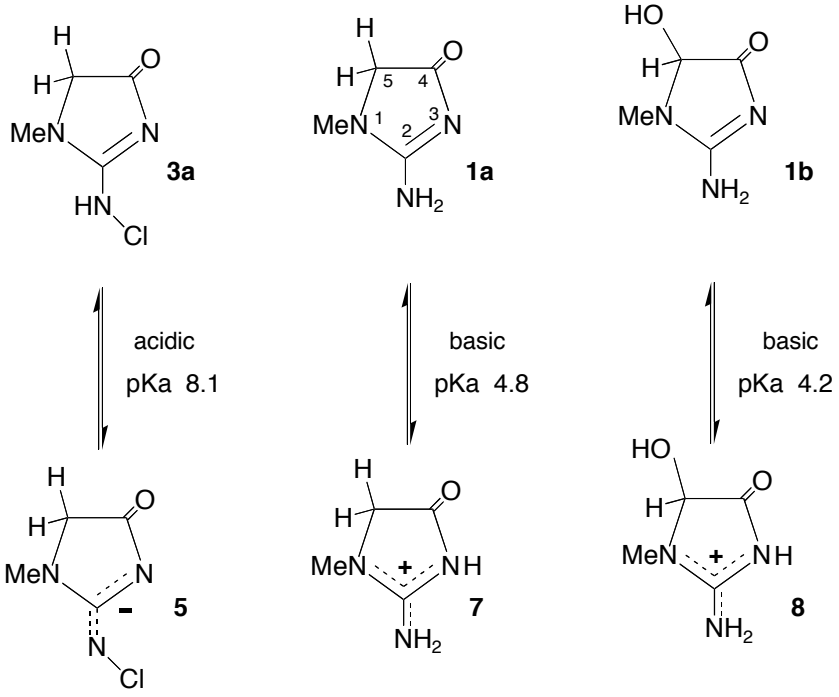


FIGURE 2. Bond lengths of creatinine-*N*-chlorimine (4a) in X-ray analysis
[See Supplementary Material for the true diagram and more accurate bond lengths]

(**2f**) and (**4f**) should *per force* have the 2-imino and the 2-*N*-chlorimino-1,5-dihydro-1,3-dimethylimidazol-4-one structures because the neutral species cannot tautomerise. Analogously, the 3-methyl-*N*-chlor*imino* structure (**4e**) is proposed for the solid form of the 3-methyl derivative (**2e**). These *N*-chloro compounds were prepared by chlorination with the NaOCl or Me_3C-OC1 method (see Experimental).

Structures in solution.

In aqueous solution the species of these dihydroimidazol-4-ones will depend on the pH of the solutions (Scheme 2 and Figure 3a and 3b), and accordingly have different UV spectra. The pKa values and the species of the three dihydro-methylimidazol-4-ones, (**1a**, creatinine), (**1b**, creatol) and (**3a**, creatinine chloramine) in aqueous solutions are shown in Scheme 2, and the titration curves at various pH values are displayed in Figure 3a and 3b (the raw pKa data are in the Suplementary Material). Compounds (numbered within the brackets) with one or no *N*-methyl groups (**1a-d**) and (**2a-d**) as well as compounds (**3a-d**) and (**4a-d**) respectively are tautomeric. By having methyl groups on both the ring nitrogen



SCHEME 2

atoms as in compounds (**2f**) and (**4f**) the neutral species in aqueous solution must have the imino structure fixed without there being any tautomerism (see above). Note that in acidic medium (at least 2 pH units below the basic pKa, see Figure 3a) the species have similar

cationic forms, i.e. neutral tautomeric species (**1a**) and (**2a**) would give the same cation (**7**). Similarly the neutral tautomeric species (**1b**) and (**2b**) give the same cation (**8**). Conversely, the neutral tautomeric species (**3a**) and (**4a**) give the same anion (**5**) at pH values at least 2 units above the acidic pKa (see Scheme 2). Note that we would estimate a basic pKa of < 2.5 for the equilibrium between the *N*-chloramine species (**3a**, **4a**) and cation (**6**) [See Scheme 1]. This pKa could not be measured because in aqueous acidic medium the *N*-chloramines are converted into the respective creatols. The neutral tautomeric species (**3a**) and (**4a**) are also acidic and would give the same anion (**5**) [see

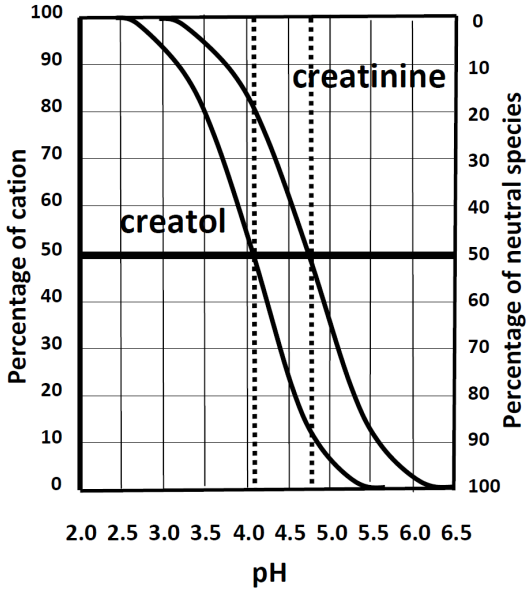


FIGURE 3a. Percentages of neutral and cation species at various pH.

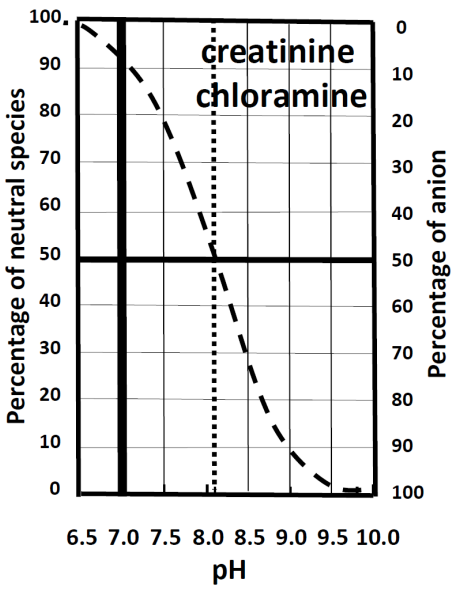
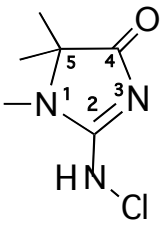
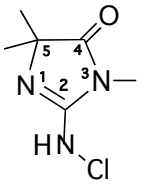
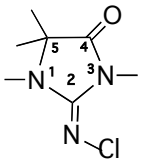


FIGURE 3b. Percentages of neutral and anion species at various pH

Schemes 1 and 2]. Moreover, the neutral species of creatinine (**1a**) and creatol (**1b**) are formed at physiological pH (~ 7) because the solution is at least 2 pH units higher than the pKa values [see Figure 3a] since their basic pKa values are around 4.8 and 4.1 respectively. On the other hand, the *N*-chloro compounds as in (**3a-d**, and **4e,** and **4f**) are weakly basic (see above), but are also distinctly acidic with acidic pKa values of ~8.1 (compare

thiophenol pKa 6.6, and methanethiol pKa10.5). At physiological pH (~7) they are ~90% in the neutral form (**3a**), but at pH >10 the anionic species are in solution (see Figure 3b and Scheme 2).

Table 1. UV spectra and ^{1}H NMR chemical shifts (ppm) of 2-*N*-chloroamino-1,5-dihydroimidazol-4-ones. UV spectra were measured in H_2O at pH 11 (λ_{max} in nm; ε_{max} M^{-1} cm^{-1}). NMR spectra were recorded in acetone-d_6 (TMS internal standard) at 400 MHz.

		3a (1-Me)	**3b** (1-Me)	**3c** (no Me)	**3d** (no Me)	**4e** (3-Me)	**4f** (di Me)
C-5		**2H**	**H & OH**	**2H**	**H & OH**	**2H**	**2H**
		 Type A: UV λ_{max} 223-235 nm*				 Type B: UV λ_{max}~212nm*	 Type C: UV λ_{max}~ 212nm*
UV**		226 nm ε 17300	233 nm ε 16100	226 nm ε 17300	233 nm ε 14550	212 nm ε 15000	212 nm ε 14450
NMR	**1-Me**	2.97 (3H,s)	2.90 (3H,s)				2.92 (3H,s)
	3-Me					2.96 (3H,s)	3.04 (3H,s)
	5-H	4.03 (2H,s)	5.16 (1H,d, *J* =1.9 Hz)	4.04 (2H,s)	5.38 (1H,s)	4.05 (2H,d *J* = 1.5 Hz)	4.01 (2H,s)
	5-OH		5.93 (1H,brs)		5.58 (1H,s)		
	1-H			6,96(1H,brs)	7.79 (1H,s)		
	NH	10.06(1H,s)	10.18(1H,brs)	9.96(1H,brs)	10.05(1H,br)	7.04 (1H,brs)	
$t_{1/2}$ ***		> 5h	> 5h	> 5h		~7 min	~7 min

*Ref 20 gives λ_{max} at 205-208 nm at pH 12 for type B and C spectra and 223-235 nm for type A spectra.

** At pH 11. ***Decomposition rates were measured at the λ_{max} wavelengths of the respective compounds at pH 11.

A general rule of UV spectra and hydrolysis at pH 11 has been reported for related

compounds.[20] UV spectral studies[8-10,12] of the neutral species of 2-amino-1,5-dihydro-imidazol-4-ones of Type A exhibit λ_{max} values at 223-235 nm at pH 11 and slow hydrolysis ($t_{1/2}$ > 5hr). On the other hand, the UV spectra of the neutral species of the 3-methyl derivatives (e.g. **4e**) and compounds where the 2-*imino* structure is fixed (because of 1N,3N-dimethyl groups as in **4f**) are of Type B and C respectively, with fast hydrolysis and with λ_{max} at 205-208 nm at pH 12 (we have found that this value is ~ 212nm at pH 11) [see Table 1]. The UV spectra of the neutral species at pH 11 of the 2-*N*-chloro*imino* derivatives (**3a-d**) show that they are mostly in the 2-*N*-chloro*amino* tautomer (Type A), whereas the spectra of the neutral species of the 3-methyl derivatives (**4e**) and the 1,3-dimethyl derivative (**4f**) are in the 2-*N*-chloro*imino* form (Types B and C). Slow hydrolysis ($t_{1/2}$ >5hr) of 2-*N*-chloroamino derivatives (**3a-c**) also indicated a Type A structure, whereas the fast hydrolysis ($t_{1/2}$ = 7 and 7min, for the imidazolinone **4e** and **4f**

Table 2. **^{1}H and ^{13}C NMR chemical shifts (ppm) of 2-amino-1,5-dihydroimidazol-4-ones**

NMR spectra were recorded in D_2O at 400 MHz with dioxane as internal standard

	^{1}H NMR				**^{13}C NMR***		
	creatinine	creatol	creatinine chloramine		creatinine	creatol	creatinine chloramine
	1a	**1b**	**3a**		**1a**	**1b**	**3a**
#**R^3**	H	H	Cl	#**R^3**	H	H	Cl
Me	3.00 (3H,s)	3.09 (3H,s)	2.84 (3H,s)	**Me**	31.2	29.1	31.3
C-5H	4.00 (2H,s)	5.34 (1H,s)	4.06 (2H,s)	**C2**	170.4	157.5	162.4
				C4	190.0	173.5	175.7
				C5	57.5	82.1	56.7

*Proton decoupled. #Numbering as in Figure 1.

respectively) indicated Types B or C structure in solution [see Table 1]. The blue UV shift of Types C and D spectra may well be because these compounds do not have a double

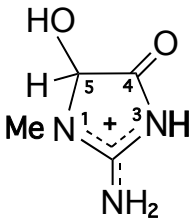
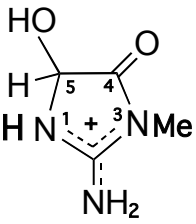
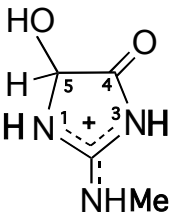
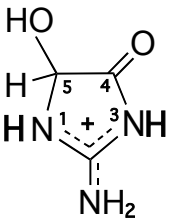
bond conjugated with the 4-carbonyl group as in the neutral species with Type A spectra. The ^{1}H NMR spectra showed no evidence of germinal protons at C-5, i.e. no tautomer with a 1-5-double bond, and no evidence of C-chlorination. Since the 5-methylene protons of 1,3-dimethyl derivative (**4f**) in the ^{1}H NMR spectrum remained after the chlorination reaction, and (**4f**) gave the methylene signal at 4.01 ppm (in d_6-acetone), C-chlorination obviously did not occur, and the *imino*-structure was further confirmed by the Type C UV spectrum[20] with λ_{max} at ~212 nm and rapid hydrolysis ($t_{1/2}$ ~ 7min) at pH 11 (see Table 1).

^{1}H NMR studies in d_6-acetone further confirmed that the 2-*N*-chloramines (**3a-d**) and compound (**4e**) exists in a solution as the amino-form because the proton of the C2-N**H**-Cl portion can be observed as one proton broad singlets at 10.06, 10.18, 9.96, 10.05 and 7.04 ppm respectively. This is not found in the 1,3-dimethyl compound (**4f**). [see Table 1].[12,13] The spectra of four 5-hydroxydihydroimidazolinium salts were determined in d_6DMSO where the exchangeable protons can be observed and assigned. All protons could be assigned and the proton coupling between 5-H and 5-OH in all but the 2-*N*-methylamino-demethyl salt (formula in the fifth column) can be clearly observed. It should be pointed out that in the latter 2-methylamino-demethyl salt the signals from 5-H, 5-OH, 2-NH and 1-H are all doublets with each doublet integrating for a single proton. The differences in chemical shifts of these doublets are far too large (>> 250 Hz) to be couplings. We should like to attribute this to their being rotamers around the C2 and the exocyclic nitrogen bond which, because of a mesomeric structure, there may be *syn* and *anti* forms each with their individual spectra [see Table 3].

Note that C5 in all the dihydroimidazolones that possess a hydroxyl group at C5 are chiral, and each of these compounds is therefore a mixture of optical isomers. All compounds discussed here are synthetic and consequently optically inactive: for example, synthetic creatol (**1b**) showed (R: S = 1 : 1) $[\alpha]^{25}_D$ = 0.0 (c 1.0, H_2O). However, natural creatol isolated from uremic rats was optically active and had $[\alpha]^{25}_D$ = - 5.1 (c 1.0, MeOH).[21]

Table 3. Physical data of 2-amino-1,5-dihydro-5-hydroxyimidazol-4-ones hydrochlorides

^{1}H NMR spectra chemical shifts (ppm) were recorded in d_6-DMSO at 400 MHz with TMS as internal standard

					
		(1-Me) creatol	**(3-Me)**	**(NH-Me)**	**(no Me)**
NMR	**Me**	3.01 (3H,s)	3.07 (3H,s)	2.92 (3H,s)	
	5-H	5.13 (1H,d, *J* =6 Hz)	5.35 (1H,d, *J* =9 Hz)	5.30, 5.36 (1H,d)	4.82 (1H,d, *J* =8 Hz)
	5-OH	7.69 (1H,d, *J* =6 Hz)	7.43 (1H,d, *J* =9 Hz)	7.39, 7.54 (1H,d)	6.21 (1H,d, *J* =8 Hz)
	2-NH	9.28 (1H,s)	7.83 (1H,brs)	9.54, 9.65 (1H,d)	7.07 (1H,brs)
	2-NH	9.42 (1H,s)	8.47 (1H,brs)		7.64 (1H,brs)
	1-H		8.54 (1H,brs)	9.97,10.50 (1H,d)	7.83 (1H,brs)
	3-H	12.5 (1H,brs)		12.5 (1H,brs)	12.5 (1H,brs)
MS	**SIMS m/z**	130 (MH^+)	130 (MH^+)	130 (MH^+)	116 (MH^+)
m.p.		191^{o}C decomp.	186^{o}C decomp.	172^{o}C decomp.	220^{o}C decomp.

Experimental

M.p.s are uncorrected. U.V. spectra were measured on a Cary recording-Spectrometer, Optical rotations were measured with a JASCO DIP-140 spectrometer Model 118. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM-400 instrument with TMS or dioxane as internal standard, and all spectral data are in Tables 1, 2 and 3. Mass spectra were measured on a Hitachi M-80B instrument. The spectra and other data in these tables showed that the compounds were free from impurities and were as predicted from their reactions. All hydrochlorides had sharp decomposition points and their EI-MS spectra had the expected molecular ion peaks.

*Preparation of the authentic creatol **1b***

Creatinine **1a** (10g) and *t*-Boc-anhydride (29g) were dissolved into DMF (300ml), and the solution was heated to 60^{o} and stirred over night. The reaction mixture was evaporated to dryness. Distilled water (100 mL) was added to the residue, and extracted with ethyl acetate (2 x100 mL). The organic layer was evaporated *in vacuo* to dryness. Silica gel column chromatography (70% ethyl acetate/hexane) gave pale yellow crystals, 2-*N*-*t*-butoxycarbonylamino-1-methyl-1,5-dihydroimidazol-4-one **1e** (12.6g), (yield: 67 %) m.p. 109-110 ^{o}C. A solution of the preceding *N*-Boc compound **1e** (11.6g) in dry benzene (300 mL) and lead tetraacetate (36.2 g) was refluxed for 90 min. After cooling to room temperature, a small volume of water was added, the resulting precipitate and water layer was removed. After drying of the organic layer with anhydrous sodium sulfate, filtering and evaporating gave 2-*N*-*t*-butoxycarbonylamino-5-acetoxy-creatinine **1f** as an oil, which was stirred with TFA (100 mL) at room temperature. The resulting 5-acetoxy-creatinine **1g** was treated with 1N HCl solution at room temperature for 2 days. The reaction mixture was evaporated to dryness and the crude crystals were recrystallized from ethanol to give the HCl salt of creatol **1b** [9.0 g: 99% from **1e**], m.p.191^{o}C (decomp) [m.p.190^{o}C (decomp)][8]; Calc for $C_4H_8N_3O_2Cl$: C, 29.0; H, 4.9; N, 25.4. found C, 29.1; H, 4.8; N, 25.7%. Further physical data are in Tables 2 and 3.

*Chlorination of creatinine **1a** and creatol **1b***

a) After addition of creatinine **1a** (100 mmol) or creatol **1b** (100 mmol) into 5% sodium hypochlorite solution (200 ml), the solution was acidified with acetic acid, stirred under ice-cooling and gave the corresponding crystalline mono-chloro derivative, which was recrystallized from water to yield respectively pure **3a**, m.p. 134^{o}C (decomp.) (70%), *m/z* (%) (EI-70eV) 149 (20) [M^{+}+2 for molecule with ^{37}Cl], 147 (62) [M^{+} for molecule with ^{35}Cl], 112 (64), 84 (45), 69 (14), 42 (100). Calc for $C_4H_6N_3OCl$: C 32.6, H 4.2, N 28.2. Found: C 32.6, H 4.1, N 28.5%; and **3b**, m.p. 131^{o}C (decomp.) (67%), %), *m/z* (%) (EI-70eV) 165 (12) [M^{+}+2 for molecule with ^{37}Cl], 163 (38) [M^{+} for molecule with ^{35}Cl], 148 (6), 137 (23), 135 (67), 90 (18), 58(62), 57 (56), 42 (100), 30 (72). Calc for

$C_4H_6N_3O_2Cl$: C 29.4, H 3.7, N 25.7. Found: C 29.5, H 3.7, N 25.7%. NMR data are in Table 2.

b) Creatinine **1a** (10 mmol) or creatol (**1b)** (10 mmol) was chlorinated by Me_3C-OC1 (12 mmol) in H_2O (20 ml) to give the mono-*N*-chloro derivative **3a**, m.p. 134°C (decomp.) (35 %), or the mono-*N*-chloro derivative **3b**, m.p. 131°C (decomp.) (26 %), identical with the above.

*Chlorination of demethylated creatinine **1c** and its 5-hydroxy derivative **1d***

Demethlated creatinine (**1c**) (10 mmol) or demethylated creatol (**1d**) (10 mmol) was chlorinated by Me_3C-OC1 (12 mmol) in aqueous AcOH (20 ml) to give the mono-*N*-chloro derivative (**3c**), m.p. 118°C (decomp.) (40 %), or the mono-*N*-chloro derivative (**3d**), m.p. 138 °C (decomp.) (60 %), respectively. Physical data are in Table 1.

*Chlorination of the 1-methyl derivative **2e** and 1,3-dimethyl-* derivative ***2f***

The monomethyl derivative **2e** (10 mmol), or the dimethyl compound **2f** (10 mmol), was chlorinated by Me_3C-OC1 (12 mmol) in acetone (20 ml) to give the mono-*N*-chloro derivative **4e** (37 %), m.p. 56-59 °C (decomp.), or the di-*N*-chloro derivative **4f** (48 %), m.p. 134°C (decomp.), respectively. Further details of their physical properties are in Table 1.

*Direct conversion of creatinine **1a** to creatol **1b** via chloramine **3a***

Creatinine **1a** (5.4g) was dissolved in 5% aqueous solution of sodium hypochlorite (200mL) and an ice-cooled solution of glacial acetic acid was added to acidify. The crystals that separated were recrystallized from water to yield creatinine-*N*-chloramine **3a** (6.66g) (70%), m. p. 134 °C (decomp.) as above (ref.134 °C).[15] An 80% aqueous acetic acid solution (100 mL) containing creatinine-*N*-chloramine, **3a** (1.0 g) was heated at 40°C for 8 hr. The crude acetate salt of creatol **1b** was formed, and was converted to the hydrochloride salt of creatol **1b** and crystallized from EtOH to give pure HCl salt of **1b** (0.79 g) which was identical to the authentic HCl salt of **1b**, yield: 83%, 191°C decomp.[21] Without purifying the intermediate **3b**, creatinine **1a** was obtained directly by heating with

acetic acid as above and was converted to the hydrochloride salt of **1b** in 73 % yield. Similarly, the hydrochloride salts of 2-amino-5-hydroxy-1,5-dihydroimidazol-4-one (m.p. 220^{o} decomp.), 2-amino-5-hydroxy-3-methyldihydroimidazol-4-one (m.p. 186^{o} decomp.) and 2-methylamino-5-hydroxydihydroimidazol-4-one (m.p. 172^{o} decomp.) were prepared and their spectra are in Table 3.

*X-ray structure determination for **4a***

The intensity data were collected at room temperature by using a Rigaku SCXmini CCD diffractometer with graphite-monochromated Mo *K*α radiation (λ=0.71073 Å). Numerical absorption corrections were applied for the data.[22] The structures were solved by employing direct methods (SHELXS97) and refined on F^2 by using the SHELXL97 software package.[23] All non-H atoms were refined anisotropically, and hydrogen atoms were refined isotropically. All of the calculations were performed with the Crystal Structure software package.[24] Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-1018085 for compound **4a**. Copies of the data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx? from the Cambridge Crystallographic Data Centre.

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