Studies on Imidazole Derivatives and Related Compounds. 2. Characterization of Substituted Derivatives of 4-Carbamoylimidazolium-5-olate by Ultraviolet Absorption Spectra

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Received January 24, 1983

The representative mono- and dialkyl-substituted derivatives of 4-carbamoylimidazolium-5-olate (**1**) were synthesized unequivocally. On the basis of their spectral data for ultraviolet absorption spectra in acidic, basic and neutral solutions, we have found some spectral characteristics which make it facile to clarify the position of substituents.

J. Heterocyclic Chem., **20**, 875 (1983).

Cytostatic and antitumor activities of 4-carbamoylimidazolium-5-olate (**1**) [1a-b], the aglycone of bredinin (**2**) [1a], have encouraged us to undertake the synthesis and biological evaluation of novel derivatives of **1**. We reported the six methyl derivatives of **1**, N-1 (**3**), N-3 (**4**), N (amide) (**6**) and 5-O (**7**) monomethyl derivatives, and N-1, N-3 (**5**) and N-3, 5-O (**8**) dimethyl derivatives in our previous paper [2].

This paper describes the synthesis of another possible methyl derivative, N-1, 5-O dimethyl derivative (**9a**), and seven kinds of ethyl and benzyl derivatives of **1**. The spectral characteristics of those alkyl derivatives of **1** in ultraviolet absorption spectra make it possible to elucidate the type of substitution.

1. Synthesis of Alkyl Derivatives of **1**.

The alkyl substituted compounds were prepared under similar conditions described in the previous paper [2] as follows.

A. N-3 Monoalkyl (**4b,c**) and N-1, N-3 Dialkyl (**5b,c**) Derivatives.

The compounds **4b,c**, which were obtained by cyclization of 2-alkylaminomalonamide (**11**) with triethyl orthoformate, were further alkylated to give **5b,c** by successive treatment with bis(tri-*n*-butyltin) oxide and ethyl iodide or benzyl chloride as shown in Scheme 1.

B. N-1 (**3b,c**) and N amide (**6b,c**) Monoalkyl Derivatives.

These monosubstituted compounds **3b,c** and **6b,c** were obtained at the same time by cyclization of 2-aminomalonalkylamide (**15**), derived from 2-benzyloxycarbonylaminomalonic acid half ester **12** in three steps, with triethyl orthoformate as depicted in Scheme 2.

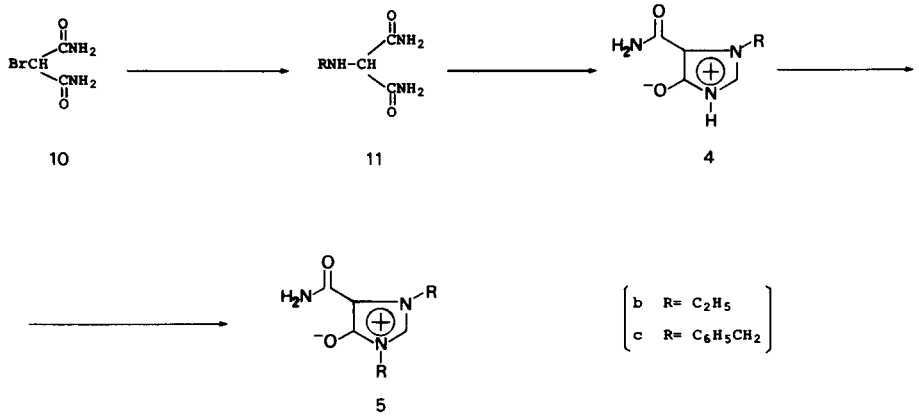
C. N-3, 5-O Dialkyl Derivatives **8b,c**.

The preparation of **8b,c** by treatment of N-3 alkyl derivatives **4b,c** with diazomethane was accompanied by the formation of **5d,e**, respectively as shown in Scheme 3.

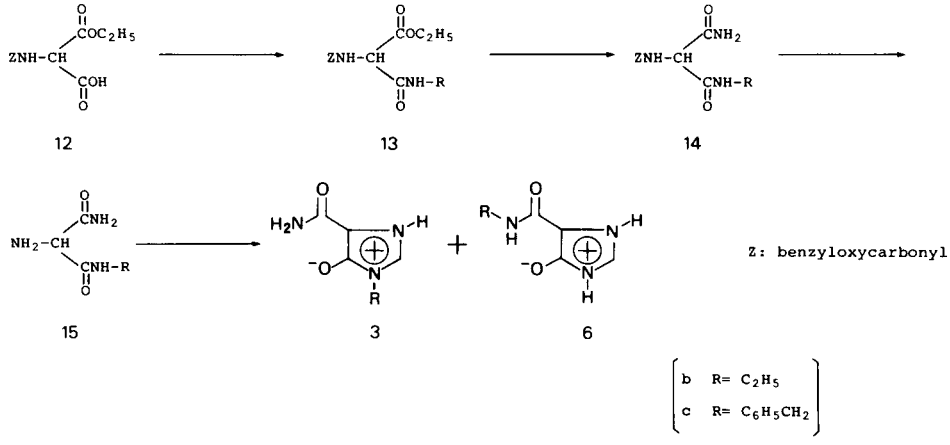
D. N-1, 5-O Dialkyl (**9a-c**) and 5-O Monoalkyl (**7b,c**) Derivatives.

Successive treatment of **1** with bis(tri-*n*-butyltin) oxide in boiling toluene and alkyl halide gave mixtures of 5-O monoalkyl derivatives **7a-c**, N-1, N-3 dialkyl derivatives **5a-c** and N-1, 5-O dialkyl derivatives **9a-c** as shown in Scheme 4. The objective compounds, N-1, 5-O dialkyl derivatives **9**, and other derivatives were separated by column chromatography on silica gel. The results of elemental analyses and molecular ions in the mass spectra proved **9** to be disubstituted products and the structures of **9** were unambiguously verified by leading those to the known N-1 alkyl derivatives **3**. The ether bonds of **9a** and **9b** were

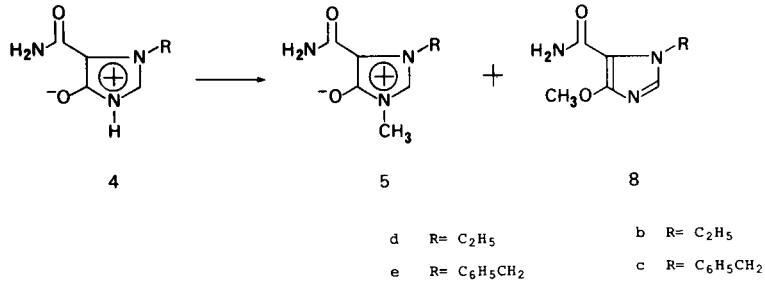
Scheme 1



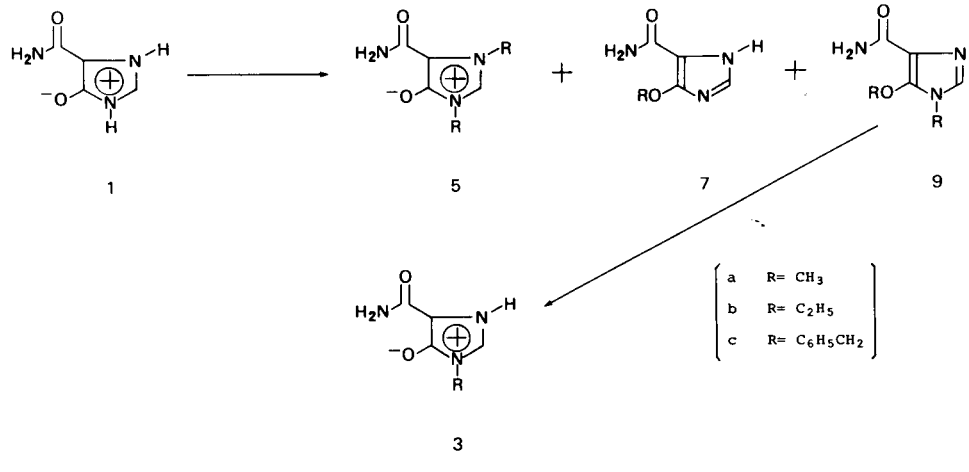
Scheme 2



Scheme 3



Scheme 4



cleaved with trimethylsilyl iodide giving **3a** and **3b**, respectively [3] and the benzyl group of **9c** was removed by hydrogenolysis to afford **3c**. Methyl derivatives, **5a** and **7a** were identical in all respects with the products of methylation of **1** with diazomethane [2]. The monoethyl and monobenzyl derivatives, **7b,c**, unidentical with any of their isomers **3b,c**, **4b,c**, and **6b,c**, respectively, must be 5-O substituted compounds; their spectral data (^{1}H and ^{13}C nmr) were consistent with the assigned structures. Other ethyl and benzyl derivatives **5b,c** proved to be identical with the authentic N-1, N-3 diethyl and dibenzyl derivatives which were prepared as depicted in Scheme 1. Table 3 shows the analytical data for these alkyl derivatives of **1** and Table 4 for the derivatives of malonic acid.

Table.1

Ultraviolet Spectra of Alkyl Derivatives of 1

Compound	Neutral(H_2O) λmax(nm)	Neutral(H_2O) ε x10^{-3}	Acidic(aq. N-HCl) λmax(nm)	Acidic(aq. N-HCl) ε x10^{-3}	Basic(aq. N-NaOH) λmax(nm)	Basic(aq. N-NaOH) ε x10^{-3}
1	275	13.6	277	sh(a)	277	13.3(b)
	236	5.6	241	10.1	232	3.7
2	278	14.3	279	12.3	276	16.3
	244	6.5	243	6.5	240	sh
3a	278	12.8	278	7.3	277	13.3
	239	4.6	240	6.5	240	sh
3b	278	12.4	278	7.4	277	16.0
	238	4.6	239	6.1	240	sh
3c	279	15.3	280	11.1	278	16.2
	241	5.7	241	6.8	(c)	
4a	277	11.7	275	sh	287	12.2
	237	4.0	244	7.7	231	2.5
4b	280	8.4	278	sh	287	12.2
	235	sh	244	7.4	233	2.3
4c	279	11.5	277	4.3	287	12.6
	238	5.2	244	7.5	(c)	
5a	279	11.1	280	7.8	279	10.1(b)
	239	3.5	240	4.5	240	sh
5b	279	11.4	280	8.4	280	11.4(b)
	239	3.3	240	4.1	240	sh
5c	283	12.1	284	10.9	286	12.5(b)
	242	5.0	(c)		(c)	
5d	279	13.2	280	9.7	279	13.3(b)
	236	4.7	241	5.0	239	3.7
5e	281	11.7	282	9.2	285	12.0(b)
	242	4.4	242	4.7	230	4.0
6a	276	12.2	280	sh	276	11.5(b)
	238	4.2	244	9.5		
6b	275	14.0	280	sh	276	11.0(b)
	237	4.8	243	11.3		
6c	278	16.3	280	sh	279	9.7(b)
	236	sh	246	13.8		
7a	256	13.3	241	10.5	268	13.5
7b	257	15.3	241	11.8	268	15.6
7c	256	13.0	237	9.5	268	13.3
8a	258	12.2	243	9.3	258	12.1
8b	258	14.0	244	10.8	258	14.1
8c	258	11.6	245	8.6	258	11.6
9a	245	9.1	227	9.9	244	9.2
9b	246	8.7	228	9.1	245	8.8
9c	247	10.7	230	sh(c)	247	10.6

(a) Shoulder.
(b) The basic solution was prepared just before measurement to avoid its decomposition.
(c) Overlapped with the absorption derived from the phenyl substituent.

2. Results and Discussion.

On the basis of examination of both the ultraviolet and the nmr spectra of the seven differently substituted derivatives of **1**, namely four mono-substituted derivatives and three disubstituted ones, we found some correlations among them. The Figures 3 through 11 are representatives of their ultraviolet spectra and those of **1** and **2** in neutral (full line), acidic (dotted line) and basic (dashed line) solutions. Tables 1 and 2 summarize the pertinent ultraviolet and nmr spectral data for **1**, **2** and the alkyl derivatives of **1**.

Some characteristics can be generalized with respect to the type of substitution. All alkyl derivatives of **1** can be classified into two groups, *i.e.*, 5-O substituted derivatives and 5-O non-substituted ones. All 5-O non-substituted compounds have two bands: main maxima from 275 to 287 nm and second ones from 230 to 246 nm, respectively. Meanwhile 5-O substituted compounds have one band

Table 2

^{13}C and ^{1}H NMR Chemical Shifts[a] for Alkyl Derivatives of 1

Compound	^{13}C Chemical Shifts (in ppm)							^{1}H Chemical Shifts (ppm)				
	C-2	C-4	C-5	C-6	X-$\underline{CH}_3$ (X)	X-$\underline{CH}_2CH_3$ (X)	X-$\underline{CH}_2C_6H_5$ (X)	C-2-$\underline{H}$	$CONH_2$	X-$\underline{CH}_3$ (X)	X-$\underline{CH}_2CH_3$ (X)	X-$\underline{CH}_2C_6H_5$ (X)
1	126.3	100.3	156.3	162.0				7.87	6.9			
2	124.9	99.2	155.3	162.0				8.29	6.9,7.1			
3a	126.1	98.4	155.9	162.1	28.1 (N-1)			8.13	7.0	3.30 (N-1)		
3b	125.5	98.7	155.5	162.3		36.4 (N-1)		8.14	6.6,7.1		3.72 (N-1)	
3c	125.6	98.4	155.4	161.9			44.5 (N-1)	8.24	6.7,7.2(b)			4.93 (N-1)
4a	128.6	100.5	157.0	162.2	35.6 (N-3)			7.87	6.9	3.83 (N-3)		
4b	127.5	99.3	157.7	162.2		43.4 (N-3)		7.99	6.7,7.5		4.24 (N-3)	
4c	129.5	99.8	157.4	162.2			50.1 (N-3)	8.11	7.1,7.9			5.54 (N-3)
5a	127.9	98.7	156.5	162.3	27.9 (N-1) 36.0 (N-3)			8.14	6.6,7.6	3.29 (N-1) 3.80 (N-3)		
5b	126.3	97.9	156.4	162.0		36.2 (N-1) 43.5 (N-3)		8.29	6.6,7.7		3.74 (N-1) 4.29 (N-3)	
5c	127.6	97.9	156.3	162.2			44.5 (N-1) 50.7 (N-3)	8.54	6.7,7.7			4.99 (N-1) 5.60 (N-3)
5d	127.3	97.8	156.9	162.2	28.1 (N-1)	43.7 (N-3)		8.22	6.6,7.7	3.27 (N-1)	4.26 (N-3)	
5e	128.1	97.7	156.7	162.3	28.2 (N-1)		50.5 (N-3)	8.36	6.6,7.7	3.30 (N-1)		5.56 (N-3)
6a	125.5	100.1	156.1	161.3	24.9 (N_{amide})			7.91	7.6	2.80 (N_{amide})		
6b	125.5	100.1	156.2	160.7		32.7 (N_{amide})		7.84	7.6		3.24 (N_{amide})	
6c	125.6	99.6	156.4	160.7			41.4 (N_{amide})	8.08	8.2			4.46 (N_{amide})
7a(c)	132.3	105.0	155.3	160.6	56.0 (5-O)			7.42	6.4,7.1	3.93 (5-O)		
7b(d)	132.5	105.3	154.9	160.8		64.5 (5-O)		7.43	6.4,7.2		4.35 (5-O)	
7c(e)	132.4	105.5	154.6	160.5			70.0 (5-O)	7.44	6.5,7.3			5.38 (5-O)
8a	135.9	105.3	157.0	161.4	34.4 (N-3) 56.0 (5-O)			7.45	6.5,7.1	3.81 (N-3) 3.95 (5-O)		
8b	134.9	103.9	157.0	161.0	55.9 (5-O)	41.9 (N-3)		7.53	6.6,7.2	3.91 (5-O)	4.24 (N-3)	
8c	135.9	104.0	157.0	161.0	55.9 (5-O)		49.1 (N-3)	7.73	6.6,7.2	3.94 (5-O)		5.54 (N-3)
8d	135.9	104.4	156.1	160.9			49.1 (N-3) 70.1 (5-O)	7.77	6.6,7.2(b)			5.55 (N-3) 5.41 (5-O)
9a	130.4	117.2	148.3	163.9	29.2 (N-1) 62.1 (5-O)			7.28	6.9,7.1	3.45 (N-1) 4.08 (5-O)		
9b	129.4	117.4	146.7	164.0		37.7 (N-1) 70.6 (5-O)		7.39	6.9,7.1		3.83 (N-1) 4.42 (5-O)	
9c	130.2	117.9	146.6	164.0			46.2 (N-1) 75.8 (5-O)	7.49	7.2,7.4(b)			4.94 (N-1) 5.35 (5-O)

a) In units (ppm) in deuteriodimethylsulfoxide with TMS as internal standard.
b) Overlapped with phenyl protons.
c) An absorption peak for proton attached to imidazole nitrogen was observed at 12.3 ppm.
d) Ibid. at 12.5 ppm.
e) Ibid. at 12.6 ppm.

shifted toward shorter wave-length compared with the main maxima of 5-O non-substituted ones: from 227 to 258 nm in neutral and acidic solutions, and from 244 to 268 nm in basic solution. Thus the data indicate that the appearance of a second band in the 5-O non-substituted compounds toward the far ultraviolet region and bathochromic shift of main maxima coincide with the presence of 5-oxido group.

While in the case of 4(5)-amino-5(4)-imidazolecarboxamide (**15**), one maximum was observed at 269 nm [4]. According to the suggestion of Cavalieri *et al.*, [4], the C=C-C=O grouping in the 4(5)-amino-5(4)-imidazolecarboxamide (**15**) would not be expected to show two bands because the 4(5)-amino group in **15** has a strong attraction for the π electrons of the C=C group and the interaction between this group and the C=O is minimized. On the other hand, the X-ray crystallographic analysis of bredinin (**2**) [5] suggests that the valence bond structure **16** (Figure 12) in which 5-O electrons enter into the resonating system considerably contributes to the electronic structure of **2**. The fact that all compounds having 5-oxido group exhibit two bands may be successfully explained in terms of the contribution of resonance structure like **16**. 5-O-Alkyl substituted compounds do not have such a resonance structure, therefore they show one band like 4(5)-amino-5(4)-imidazolecarboxamide (**15**). But in the spectra of **7**, the maximum in basic solution considerably shifted toward longer wave-length (268 nm) compared wit that in neutral one. This shift is also explained by the structure **18** in which N-3 electrons enter into the resonating system as depicted in Figure 12.

The position of the double bond in N-1—C-2—N-3 sequence of the non-substituted compounds does not generally localize due to the proton tautomerism. But in **1** and **7**, the position of the double bond was estimated as follows.

There can be considered tautomerism in neutral solution of **7**, and resonance in acidic solutions of **1** and **7** as

Table 3

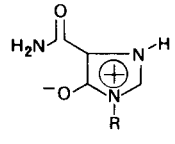
Analytical Data for the Alkyl Derivatives of Compound 1.

Compound	M.p. C (Solvent)	Yield(%)	Formula (Molecular Weight)	Analysis, %	Ms(m/e)
3b	227	33.8 (15b)[a]	$C_6H_9N_3O_2$	Calcd. C, 46.44; H, 5.85; N, 27.08	155, 138, 110,
	(b)	33.0 (9b)	(155.16)	Found C, 46.84; H, 5.95; N, 26.88	66, 28
3c	249 dec.	50.1 (15c)	$C_{11}H_{11}N_3O_2$	Calcd. C, 60.82; H, 5.10; N, 19.35	217, 200, 174,
	(isopropanol)	64.0 (9c)	(217.22)	Found C, 61.13; H, 5.08; N, 19.33	91
4o	189 dec.	63.4	$C_6H_9N_3O_2$	Calcd. C, 46.44; H, 5.85; N, 27.08	155, 140, 110,
	(methanol)		(155.16)	Found C, 46.14; H, 6.04; N, 26.70	83, 28
4c	232 dec.	69.2	$C_{11}H_{11}N_3O_2$	Calcd. C, 60.82; H, 5.10; N, 19.35	217, 200, 174,
	(ethanol-diisopropyl ether)		(217.22)	Found C, 60.44; H, 5.04; N, 19.28	91
5b	221-223	43.0 (4b)	$C_8H_{13}N_3O_2$	Calcd. C, 52.44; H, 7.15; N, 22.94	183, 138, 56,
	(dimethyl sulfoxide)	40.1 (1)	(183.21)	Found C, 52,47; H, 7.15; N, 23.10	28
5c	187-187.5	32.5 (4c)	$C_{18}H_{17}N_3O_2$ $1/5H_2O$	Calcd. C, 69.53; H, 5.64; N, 13.51	307, 290, 106,
	(ethanol-diisopropyl ether)	21.5 (1)	(307.34)	Found C, 69.52; H, 5.55; N, 13.52	91
5d	187-191	37.6	$C_7H_{11}N_3O_2$	Calcd. C, 49.69; H, 6.55; N, 24.84	169, 152, 124,
	(ethyl acetate-n-hexane)		(169.18)	Found C, 49.55; H, 6.70; N, 24.87	42
5e	219.5-220	39.0	$C_{12}H_{13}N_3O_2$	Calcd. C, 62.32; H, 5.67; N, 18.17	231, 214, 91,
	(ethanol-diisopropyl ether)		(231.25)	Found C, 62.31; H, 5.53; N, 18.41	65, 42
6b	237	43.6	$C_6H_9N_3O_2$	Calcd. C, 46.44; H, 5.85; N, 27.08	155, 111, 84,
	(b)		(155.16)	Found C, 46.63; H, 6.14; N, 26.98	44, 28
6c	215	13.7	$C_{11}H_{11}N_3O_2$ $1/4H_2O$	Calcd. C, 59.58; H, 5.23; N, 18.95	217, 106, 91,
	(methanol)		(217.22)	Found C, 60.04; H, 5.13; N, 18.54	28
7b	218-219	6.4	$C_6H_9N_3O_2$	Calcd. C, 46.44; H, 5.85; N, 27.08	155, 140, 127,
	(ethanol)		(155.16)	Found C, 46.29; H, 5.94; N, 27.36	110, 28
7c	212-213	5.5	$C_{11}H_{11}N_3O_2$	Calcd. C, 60.82; H, 5.10; N, 19.35	217, 200, 91,
	(ethanol)		(217.22)	Found C, 60.57; H, 4.88; N, 20.04	65
8b	108.5-111.5	38.5	$C_7H_{11}N_3O_2$	Calcd. C, 49.69; H, 6.55; N, 24.84	169, 154, 137,
	(diisopropyl ether-n-hexane)		(169.18)	Found C, 49.97; H, 6.67; N, 24.18	56, 28
8c	126-127	51.5	$C_{12}H_{13}N_3O_2$	Calcd. C, 62.32; H, 5.67; N, 18.17	231, 214, 91
	(diisopropyl ether-n-hexane)		(231.25)	Found C, 62.24; H, 5.73; N, 18.09	65
9a	191-192	5.7	$C_6H_9N_3O_2$	Calcd. C, 46.44; H, 5.85; N, 27.08	155, 138, 110,
	(methanol-diisopropyl ether)		(155.16)	Found C, 46.17; H, 5.69; N, 27.79	42
9b	136-137	16.0	$C_8H_{13}N_3O_2$	Calcd. C, 52.44; H, 7.15; N, 22.94	183, 168, 155,
	(benzene)		(183.21)	Found C, 52.35; H, 7.26; N, 23.14	138, 110, 56
9c	124-124.5	8.4	$C_{18}H_{17}N_3O_2$	Calcd. C, 70.34; H, 5.58; N, 13.67	307, 290, 106,
	(ethanol-diisopropyl ether)		(307.34)	Found C, 70.75; H, 5.62; N, 13.62	

a) The number in parenthesis indicates the starting material.
b) Analyzed without recrystallization.

shown in Figure 13. But the structures, **20** and **23**, are of minor contribution as judged by the similarity of ultraviolet absorption spectra of **1** and **7** to those of their N-3 substituted compounds, **4** and **8**, respectively. Similarly, tautomerism of 4(5)-alkoxy-1*H*-imidazole-5(4)-carboxamide (**7** and **21**) in neutral solution may lie so far to the left based on the comparison of its spectrum with that of its N-3 substituted compound, **8**.

More specific differences are listed below.



1 : R= H

2 : R= 1-β-D-ribofuranosyl (Rib.)

Figure 1

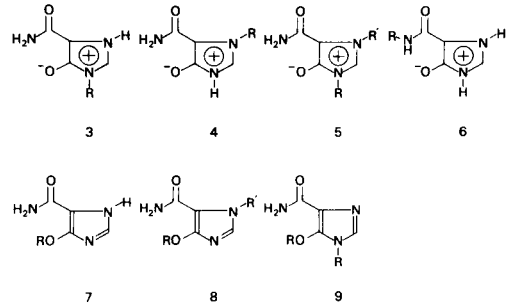


Figure 2

4-Carbamoylimidazolium-5-olate (**1**) (Figure 3).

The absorption maxima for neutral and basic solutions occur at about the same wave length (275-277 nm). Second

Table. 4

Analytical Data for the Derivatives of Malonic acid

Compound	M.P. C (Solvent)	Yield(%)	Formula (Molecular Weight)	Analysis, %
11b	167-170.5 (ethanol-water)	44.1	$C_5H_{11}N_3O_2$ (145.16)	Calcd. C, 41.37; H, 7.64; N, 28.95 Found C, 41.15; H, 7.34; N, 28.72
11c	190.5-192 (ethanol-diiso-propylether)	79.3	$C_{10}H_{13}N_3O_2$ (207.23)	Calcd. C, 57.96; H, 6.32; N, 20.28 Found C, 57.93; H, 6.14; N, 20.29
13b	114.5-116 (ethanol-diiso-propyl ether)	75.4	$C_{15}H_{20}N_2O_5$ (308.33)	Calcd. C, 58.43; H, 6.54; N, 9.09 Found C, 58.46; H, 6.73; N, 9.10
13c	138-139.5 (chloroform-diiso-propyl ether)	74.4	$C_{20}H_{22}N_2O_5$ (370.39)	Calcd. C, 64.85; H, 5.99; N, 7.56 Found C, 64.54; H, 5.84; N, 7.67
14b	173-175 (methanol-diiso-propyl ether)	86.6	$C_{13}H_{17}N_3O_4$ (279.29)	Calcd. C, 55.90; H, 6.14; N, 15.05 Found C, 55.73; H, 6.19; N, 15.04
14c	175.5-176 (chloroform-diiso-propyl ether)	78.8	$C_{18}H_{19}N_3O_4$ (341.36)	Calcd. C, 63.33; H, 5.61; N, 12.31 Found C, 63.29; H, 5.67; N, 12.25
15b	124-124.5 (ethanol-diiso-propyl ether)	85.0	$C_5H_{11}N_3O_2$ (145.16)	Calcd. C, 41.37; H, 7.64; N, 28.95 Found C, 41.30; H, 7.65; N, 28.97
15c	144-148.5 (isopropanol-diiso-propyl ether)	59.3	$C_{10}H_{13}N_3O_2$ (207.23)	Calcd. C, 57.96; H, 6.32; N, 20.28 Found C, 58.27; H, 6.45; N, 19.65

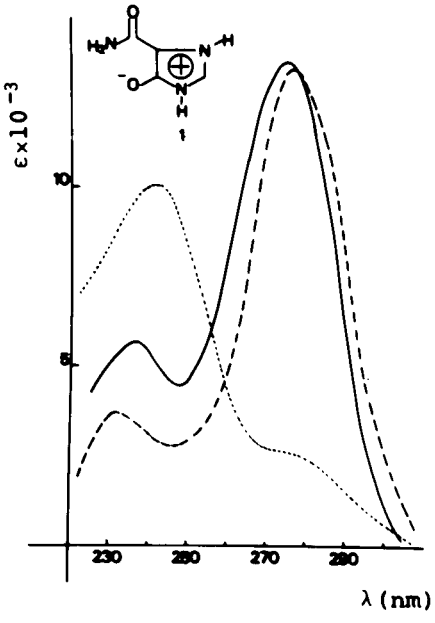


Fig. 3

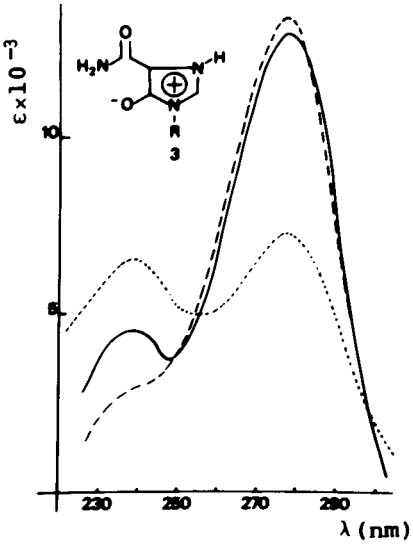


Fig. 5

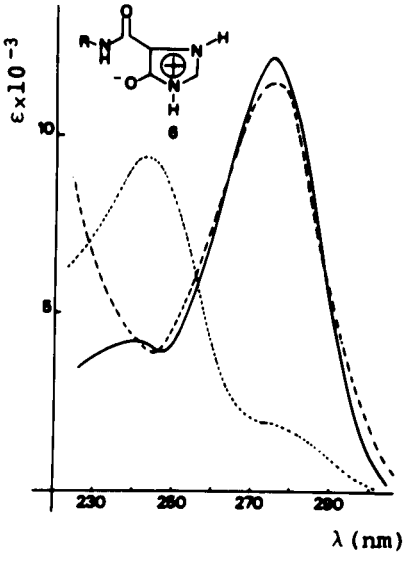


Fig. 4

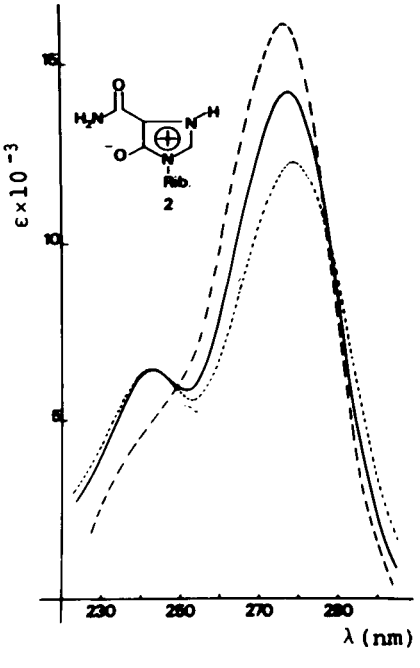


Fig. 6

peaks in neutral and basic solutions occur at shorter wave length (232-236 nm) with low intensity. The acidic maximum shows a pronounced hypsochromic shift and a weak shoulder is present at about 280 nm.

4-Alkylcarbamoylimidazolium-5-olate (**6**) (Figure 4).

The spectra of **6** are essentially identical with those of **1** except the lack of the second peak in basic solution.

1-Alkyl-4-carbamoylimidazolium-5-olate (**3**) (Figure 5).

This compound substituted at N-1 position has almost identical main maxima both in neutral and basic solutions like **1**, but the basic maximum exhibits a slight hyperchromic shift at about 280 nm. The acid spectrum shows a

characteristic pattern; two bands have almost equal intensity at 278-280 nm and at 239-241 nm. The spectrum of bredinin (**2**) (Figure 6) which is one of the compounds of this type is essentially the same as that of **3**, but there is a large hyperchromic shift at about 280 nm in acidic solution.

1-Alkyl-5-carbamoylimidazolium-4-olate (**4**) (Figure 7).

The basic maximum at 287 nm has a slightly higher extinction and longer wave length than the neutral one has, while second peaks in acidic, basic and neutral solutions are essentially similar to those of **1** in shape and in relative intensity.

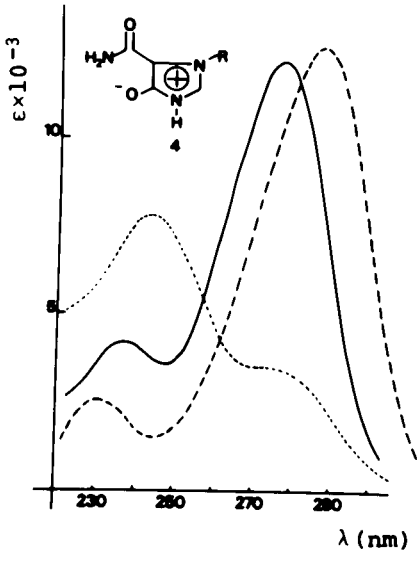


Fig.7

1,3-Dialkyl-4-carbamoylimidazolium-5-olate (**5**) (Figure 8).

The maxima for acidic, basic and neutral solutions occur at about the same wave length. The acidic spectrum shows main maximum at 280 nm like **2**. This is characteristic for **5** compared with those of other 5-O non-substituted compounds, **1**, **3**, **4** and **6**.

4(5)-Alkoxy-1*H*-imidazole-5(4)-carboxamide (**7**) (Figure 9).

The basic maximum exhibits a large bathochromic shift compared with those of other 5-O substituted compounds, **8** and **9**.

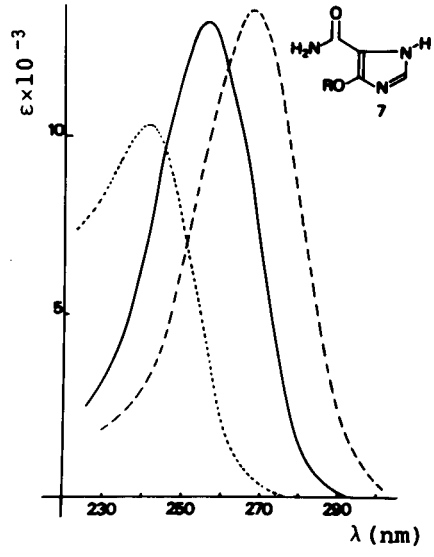


Fig.9

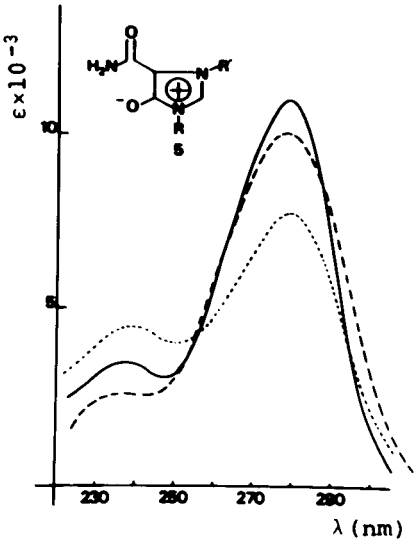


Fig.8

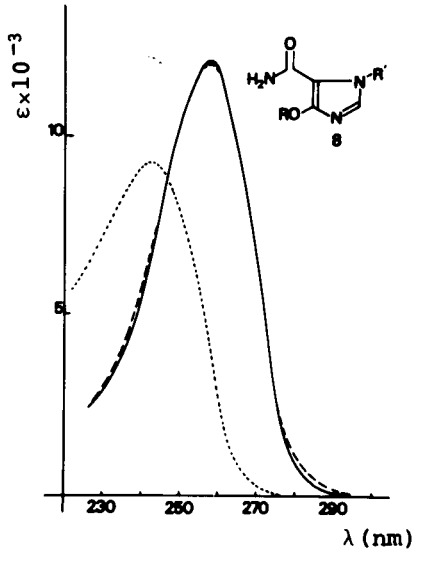


Fig.10

1-Alkyl-4-alkoxy-1*H*-imidazole-5-carboxamide (**8**) (Figure 10).

The spectra in neutral and basic solutions are essentially identical. The maximum for acidic solution shows pronounced hypsochromic and hypochromic shifts like that of **7**.

1-Alkyl-5-alkoxy-1*H*-imidazole-4-carboxamide (**9**) (Figure 11).

The basic, acidic and neutral maxima of this compound show hypsochromic shifts and the neutral and basic ones exhibit hypochromic shift compared with other 5-O substituted compounds, **7** and **8**.

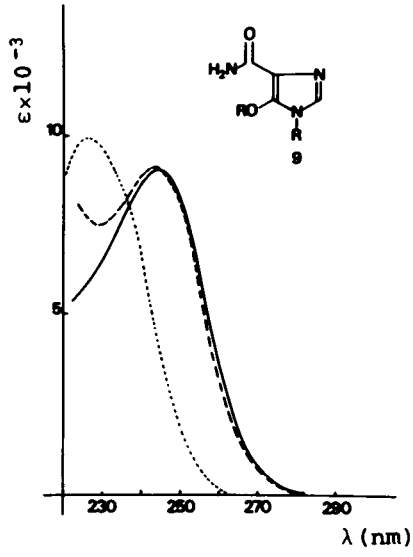
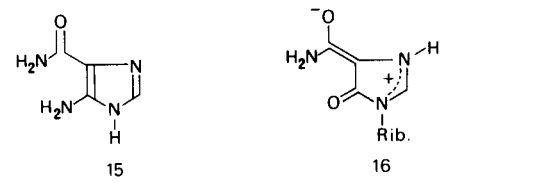


Fig.11

There also exists some differences in ^1H and ^{13}C nmr chemical shifts between 5-O non-substituted compounds and 5-O substituted ones. The peaks for C-2 and C-4 of 5-O non-substituted compounds shift upfield (*ca.* 0 to −11 ppm and −3 to −20 ppm, respectively), while C-2 protons of those shift downfield (*ca.* +0.2 to +1.2 ppm) compared to those of 5-O substituted ones. Concerning the spectra of 5-O substituted compounds, 1-alkyl-5-alkoxy-1*H*-imidazole-4-carboxamide (**9**), the peaks for C-2 and C-5 have tendency to shift upfield (*ca.* −2 to −6 ppm and −6 to −10 ppm, respectively), but the peak for C-4 shifts downfield (*ca.* +11 to +14 ppm) compared with those of **7** and **8**. No prominent differences were observed in chemical shifts for C-2 proton, C-4 and C-5 between **7** and **8** except the peak for C-2 of **8** shifts downfield (*ca.* +2.4 to +3.6 ppm) compared to that of **7**. Not any spectral differences were found among th 5-O non-substituted compounds.



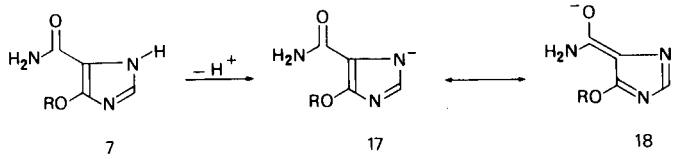


Figure 12

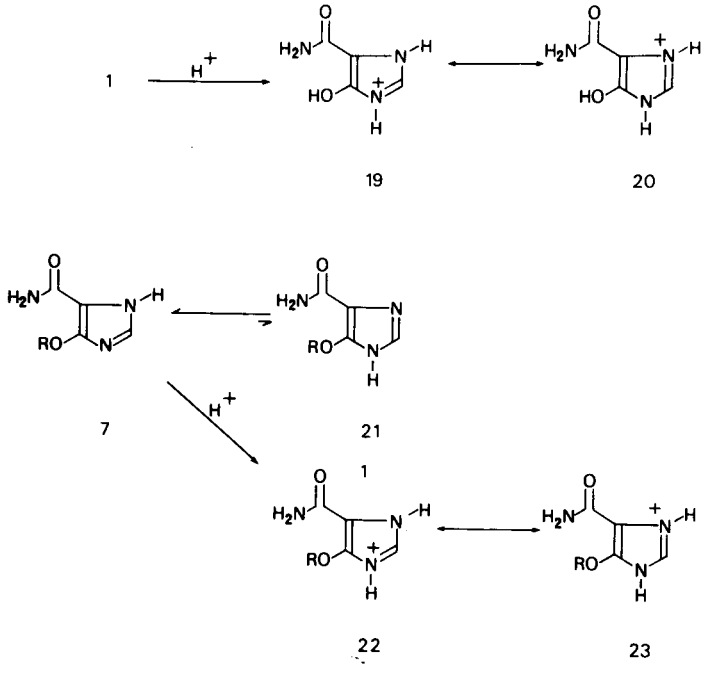


Figure 13

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultraviolet absorption spectra were obtained on a Shimazu UV-300 spectrophotometer. Nuclear magnetic resonance spectra were measured in DMSO-d_6 on a JEOL FX-100 FT-NMR spectrometer at 99.60 (^1H) and 25.20 (^{13}C) MHz using tetramethylsilane as an internal standard. Electron impact mass spectra were determined on a Shimazu LKB-9000 mass spectrometer operating at 12 and 70 eV.

4-Carbamoylimidazolium-5-olate (**1**), mp 237° dec was prepared by the method described in the literature [6]. The ethyl or benzyl derivatives of 4-carbamoylimidazolium-5-olate (**1**), except N-1, 5-O dialkyl ones **9a-c**, were synthesized by the almost same methods previously reported [3].

Melting points, recrystallization solvents and analytical data of those substituted derivatives of **1** and the derivatives of malonic acid are listed in Table 3 and 4, respectively.

2-Ethylaminopropanediamide (**11b**).

A mixture of 4.50 g (25.0 mmoles) of **10**, 2.10 g (25.0 mmoles) of ethylamine hydrochloride, 17 ml (120 mmoles) of triethylamine and 50 ml of dry ethanol was refluxed for 2 hours. The reaction mixture was allowed to cool to room temperature. The precipitates were collected by filtration and washed with ethanol to give 5.45 g of crude product containing triethylamine hydrochloride. This crude product was washed with chloroform to remove the salt and gave 1.60 g (44%) of **11b**, mp 167-170°.

5-Carbamoyl-1-ethylimidazolium-4-olate (**4b**).

A mixture of 1.373 g (9.46 mmoles) of **11b**, 40 mg of *p*-toluenesulfonic acid monohydrate and 15.0 g (102 mmoles) of triethyl orthoformate was stirred for 70 minutes under reflux. The mixture was allowed to cool down to room temperature. The crystals that separated were collected by filtration and washed with ethanol and diisopropyl ether to give 1.60 g of crude product. Recrystallization of this product from methanol-ethyl acetate gave 0.93 g (63%) of **4b**.

4-Carbamoyl-1,3-diethylimidazolium-5-olate (**5b**).

A mixture of 108 mg (0.70 mmoles) of **4b**, 3 ml of dry toluene and 417 mg (0.70 mmoles) of bis(tri-*n*-butyltin) oxide was refluxed for 1 hour to give a clear solution. After removal of the toluene *in vacuo*, 3 ml of ethyl iodide was added and the mixture was refluxed for 13 hours. The crystals were collected by filtration, washed with diisopropyl ether to give 55 mg (43%) of **5b**, mp 202-212°.

Ethyl 2-Benzyloxycarbonylamino-3-ethylamino-3-oxopropanoate (**13b**).

To a solution of 14.05 g (50.0 mmoles) of **12** and 7.40 g (55.0 mmoles) of 1-hydroxybenzotriazole in 225 ml of dry tetrahydrofuran, were added a mixture of 4.06 g (50.0 mmoles) of ethylamine hydrochloride, 7.0 ml (50.0 mmoles) of triethylaminne and 25 ml of dry methanol, and a solution of 10.30 g (50.0 mmoles) of dicyclohexylcarbodiimide in 15 ml of dry tetrahydrofuran at −12°. After the mixture had been stirred at room temperature for 16 hours, the precipitated dicyclohexylurea was filtered off. Evaporation of the filtrate *in vacuo* gave the residue, which was dissolved in ethyl acetate and the solution was washed with *N*-hydrochloric acid, saturated aqueous sodium chloride, aqueous sodium bicarbonate and water, dried over anhydrous sodium sulfate, and the ethyl acetate was removed *in vacuo* to give 16.98 g of crude product. Recrystallization from chloroform-diisopropyl ether gave 11.63 g (75%) of **13a**, mp 109.5-111.5°.

2-Benzyloxycarbonylaminopropane-*N*-ethyldiamide (**14b**).

To a solution of 9.249 g (30.0 mmoles) of **13b** in 60 ml of methanol, was added 60 ml of 16% methanolic ammonia. The reaction vessel was completely sealed and was allowed to stand at 5° for 67 hours. The crystals that separated were collected by filtration to give 4.812 g (57%) of **14b**, and the filtrate was condensed to dryness and the residue was recrystallized from methanol-diisopropyl ether, yielding 2.446 g (29%) of **14b** (total yield 87%).

2-Aminopropane-*N*-ethyldiamide (**15b**).

A solution of 5.586 g (20.0 mmoles) of **14b** in a mixture of 100 ml of tetrahydrofuran and 100 ml of methanol was hydrogenated in the presence of 1.5 g of 10% palladium on calcium carbonate for 2 hours. After the filtration of the catalyst, the filtrate was evaporated to dryness *in vacuo*. The residual product was purified by recrystallization from ethanol-diisopropyl ether to give 2.468 g (85%) of **15b**.

4-Carbamoyl-1-ethylimidazolium-5-olate (**3b**) and 4-Ethylcarbamoylimidazolium-5-olate (**6b**).

A mixture of 1.450 g (10.0 mmoles) of **15b**, 7.460 g (50.0 mmoles) of triethyl orthoformate, 50 mg of *p*-toluenesulfonic acid monohydrate and 50 ml of dry ethanol was refluxed for 30 minutes. To the reaction mixture was added 50 ml of diisopropyl ether. The precipitates were collected to give 1.240 g (80%) of a mixture of **3b** and **6b**. The ratio of **3b/6b** was determined to be 40/60 by ^{1}H nmr analysis. The mixture was separated by reversed phase column chromatography [Merck RP-8 eluted with aqueous 20% methanol containing acetic acid (1%)] to give 515 mg (34%) of **3b**, mp 227° dec and 664 mg (44%) of **6b**, mp 237° dec.

4-Carbamoyl-3-ethyl-1-methylimidazolium-5-olate (**5d**) and 4-Methoxy-1-ethyl-1*H*-imidazole-5-carboxamide (**8b**).

To a solution of 388 mg (2.50 mmoles) of **4b** in 50 ml of methanol, was added large excess of diazomethane in diethyl ether and the reaction mixture was stirred for 1 hour at room temperature. After the excess of diazomethane and the solvent were removed *in vacuo*, the residual solid was chromatographed on a column of silica gel. The initial fraction eluted with chloroform-methanol (9:1) mixture afforded 163 mg (39%) of **8b**, mp 100.5-112°. The following fraction eluted with (4:1) mixture gave 159 mg (38%) of **5d**, mp 172-187°.

These procedures for the preparation of ethyl derivatives **11b, 4b, 5b, 13b, 14b, 15b, 3b, 6b, 5d** and **8b** were also applied to the syntheses of their benzyl derivatives **11c, 4c, 5c, 13c, 14c, 15c, 3c, 6c, 5e** and **8c**, respectively.

Alkylation of **1** *via* Tri-*n*-butylstannylation.

The example given below is representative for the preparation of the compounds **9a-c**.

1-Methyl-5-methoxy-1*H*-imidazole-4-carboxamide (**9a**) and 4-Carbamoyl-1,3-dimethylimidazolium-5-olate (**5a**).

A mixture of 3.18 g (25.0 mmoles) of **1**, 100 ml of dry toluene and 22.35 g (37.5 mmoles) of bis(tri-*n*-butyltin) oxide was refluxed for 2 hours to give a clear solution. After removal of the toluene *in vacuo*, 45 ml of methyl iodide was added and the mixture was refluxed for 6 hours. The reaction mixture was allowed to cool to room temperature and the crystals were collected by filtration and washed with toluene to give 2.24 g (58%) of **5a**, mp 220-222° dec. The ir spectrum and mp of **5a** were identical with those of the authentic sample previously reported [3]. The filtrate and washings were combined and concentrated to give an oily residue. This residue was chromatographed on a column of silica gel eluted with chloroform-methanol (9:1) mixture to afford 220 mg (6%) of **9a**.

Dealkylation of 5-O Substitutents of **9a-c**.

(A) 4-Carbamoyl-1-methylimidazolium-5-olate (**3a**) by Demethylation of **9a**.

To a solution of 78 mg (0.50 mmoles) of **9a** in 7 ml of dry acetonitrile, was added the solution of 100 mg (0.50 mmoles) of trimethylsilyl iodide in 5 ml of dry acetonitrile at room temperature under argon. After the mixture had been stirred at room temperature for three days, the precipitates were collected by filtration to give 33 mg of **3a**. Further, the filtrate was condensed to dryness and the residue was chromatographed on a preparative tlc, developed with chloroform-methanol (4:1) mixture to give 17 mg of the starting material **9a**. Then the demethylated compound **3a** was obtained in the yield of 60%. The ir spectrum of this product was identical with that of the authentic sample previously reported [3].

(B) 4-Carbamoyl-1-ethylimidazolium-5-olate (**3b**) by Deethylation of **9b**.

A solution of 40 mg (0.22 mole) of **9b** and 65 mg (0.33 mmole) of trimethylsilyl iodide in 5 ml of dry acetonitrile was refluxed for 5 hours. The precipitates were collected by filtration to give 11 mg (33%) of **3b**. The ir spectrum of this product was identical with that of the authentic sample prepared from **15b** (Scheme 2).

(C) 1-Benzyl-4-carbamoylimidazolium-5-olate (**3c**) by Debenzylation of **9c**.

A solution of 31 mg (0.10 mmole) of **9c** in 5 ml of 95% ethanol was hydrogenated in the presence of 0.1 ml (0.1 mmole) of *N*-hydrochloric acid and 10 mg of 10% palladium on charcoal for 0.5 hour. After addition of excess sodium bicarbonate, the reaction mixture was filtered. Evaporation of the filtrate *in vacuo* gave the crude product. This residual solid was chromatographed on a column of silica gel, eluted with chloroform-methanol (4:1) mixture to afford 14 mg (64%) of **3c**. The ir spec-

trum of this product was identical with that of the authentic sample prepared from **15c** (Scheme 3).

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