Studies on Imidazole Derivatives and Related Compounds. I. Synthesis of Novel Antineoplastic Derivatives of 4-Carbamoylimidazolium-5-olate

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Acylation of 4-carbamoylimidazolium-5-olate (**2**) with a variety of acid chlorides produced 4(5)-carbamoyl-1*H*-imidazol-5-(4)yl acid carboxylates (**3a-j**). Treatment of esters **3a,c** with sodium hydroxide gave imides, **4a,c**. Methylation of **3a** and **2** with diazomethane gave the *N*-3 methyl derivative (**6**) and a mixture of the *N*-3, *O*-dimethyl derivative (**9**), the *N*-1, *N*-3-dimethyl derivative (**10**) and the *O*-methyl derivative (**11**), respectively. 5-Carbamoyl-1-methylimidazolium-4-olate (**7**) and its 4-carbamoyl isomer (**16**) were prepared from 2-aminopropanediamides **8** and **15**, respectively. Treatment of the imidazolium compound (**10**) with aqueous potassium hydroxide gave the recyclized product, 1-methyl-5-methylcarbamoylimidazolium 4-olate (**18**). Methyl derivatives **6, 7,** and **9** except **16** demonstrated the complete lack of antitumor activity against Lewis lung carcinoma or sarcoma 180 in mice.

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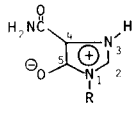
Bredinin (**1**) is an imidazole nucleoside which was isolated from the culture filtrate of *Eupenicillium brefeldianum* by K. Mizuno (1) in 1974; its structure has been determined by X-ray crystallographic study to be 4-carbamoyl-1-β-D-ribofuranosylimidazolium-5-olate (**1**) (2). The aglycone, 4-carbamoylimidazolium-5-olate (**2**) (3), of bredinin was as strongly cytotoxic to L5178y cells as bredinin (1).

Meanwhile, N. Yoshida, *et al.* (4), found that compound **2** had an antitumor activity against Sarcoma 180 and Ehrlich carcinoma. These cytotoxic and antitumor activities of **2** invoked in us a great deal of interest in the synthesis and evaluation of novel derivatives of **2**.

The purpose of the present investigation was to prepare acyl derivatives of **2** with increased lipophilicity. We expected that these derivatives would be distributed in tissues better than the parent compound (**2**) and metabolic hydrolysis of an acyl function would lead to their intracellular conversion into the active **2**. We also prepared several methyl derivatives of **2** and **3a** with the intent to delineate more accurately the specificity of action of **2**.



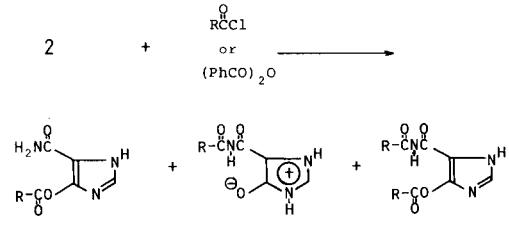
1 R= 1-β-D-ribofuranosyl

2 R= H

Figure 1

I. Acyl Derivatives of **2**.

Treatment of **2** with a variety of acid chlorides in pyridine principally gave the *O*-acylated products (**3a-j**) as shown in Scheme 1. The yields of the isolated products were 65-100%. The production of esters (**3a-j**) was consistent with the results reported by Y. Y. Usaevich, *et al.* (5), who conducted acylation of 2-(3,4-dimethoxyphenyl)-4-(5)-alkyl-5-(4)imidazolones with acetyl chloride, benzoyl chloride and *p*-nitrobenzoyl chloride to yield esters.



3a-j 4a,c 5a

a R= 1-adamantyl
b R= Phenyl
c R= 3,4-methylenedioxyphenyl
d R= 4-methylphenyl
e R= 4-(bis-2-chloroethyl)aminophenyl
f R= 4-t-butylphenyl
g R= 4-methoxyphenyl
h R= 2-thienyl
i R= 4-n-octyloxyphenyl
j R= 4-pyridinyl

Scheme 1

The same authors (5) obtained the *N*-3 acylated products by the use of acetic anhydride and benzoic anhydride. In contrast, acylation of **2** with benzoic anhydride in dimethyl sulfoxide afforded the *O*-benzoyl derivative (**3b**) in 81% yield. This different result may be attributed to the decrease of basicity of the nitrogen atom at the 3-position in **2**.

Most derivatives of compound **3a-j** exhibited more potent antitumor activity than the parent **2** in an experimental animal test. Among them, 1-adamantanecarbonyl (**3a**) and 3,4-methylenedioxybenzoyl derivatives (**3c**) were most active against both ascites and solid forms

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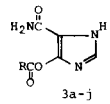
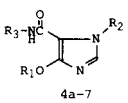
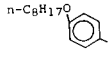
Table 1

Analytical Data for the Ester Derivatives **3** of Compound **2** and their Related Compounds


3a-j


4a-7

Compound No.	R	M.p. °C (Solvent)	Yield % (c)	Formula (Molecular Weight)	Analysis, %	Ms (M/e)
3a	Adm	221 dec. (a)	81.0 (A)	$C_{15}H_{19}N_3O_3$ (289.33)	Calcd. C, 62.26; H, 6.62; N, 14.52; Found C, 62.23; H, 6.68; N, 14.56	289, 261, 163, 135, 127
3b		203.5 dec. (a)	75.2 (A) 81.3 (B)	$C_{11}H_9N_3O_3$ (231.21)	Calcd. C, 57.14; H, 3.92; N, 18.18 Found C, 56.97; H, 3.79; N, 18.20	231, 127, 105, 77
3c		215.5 dec. (a)	78.0 (A)	$C_{12}H_9N_3O_5$ (275.22)	Calcd. C, 52.37; H, 3.30; N, 15.27 Found C, 52.70; H, 3.30; N, 15.20	275, 165, 149, 121
3d		203.5 dec. (a)	75.0 (A)	$C_{12}H_{11}N_3O_3$ (245.24)	Calcd. C, 58.77; H, 4.52; N, 17.14 Found C, 58.65; H, 4.49; N, 16.97	245, 127, 119, 91
3e		177-178 (methanol-water)	93.0 (A)	$C_{15}H_{16}Cl_2N_4O_3$ (371.22)	Calcd. C, 48.53; H, 4.34; Cl, 19.10; N, 15.09 Found C, 48.17; H, 4.30; Cl, 18.91; N, 15.22	288 (e), 286, 263, 261, 244, 242, 211, 127
3f		198 dec. (a)	77.6 (A)	$C_{15}H_{17}N_3O_3$ (287.31)	Calcd. C, 62.70; H, 5.96; N, 14.63 Found C, 62.17; H, 5.93; N, 14.39	287, 272, 244, 227, 188, 178, 161
3g		216 dec. (a)	83.0 (A)	$C_{12}H_{11}N_3O_4$ (261.23)	Calcd. C, 55.17; H, 4.24; N, 16.09 Found C, 54.71; H, 4.17; N, 16.00	261, 177, 152, 135, 127
3h		199-199.5 (*N,N*-dimethyl-formamide-water)	83.7 (A)	$C_9H_7N_3O_3S$ (237.24)	Calcd. C, 45.57; H, 2.97; N, 17.71; S, 13.52 Found C, 45.36; H, 2.77; N, 17.94; S, 13.14	237, 127, 111, 39
3i		213 dec. (b)	95.2 (A)	$C_{19}H_{25}N_3O_4$ (359.41)	Calcd. C, 63.49; H, 7.01; N, 11.69 Found C, 63.29; H, 7.10; N, 11.75	359, 316, 275, 250, 233, 127
3j		192.5 dec. (a)	Quantitative (A)	$C_{10}H_8N_4O_3 \cdot \frac{1}{4}H_2O$ (232.20)	Calcd. C, 50.74; H, 3.62; N, 23.67 Found C, 50.80; H, 3.60; N, 23.50	232, 127, 106, 78, 51, 28
4a	R_1 H R_2 H R_3 AdmCO	233 dec. (methanol)	33.5 based on **3a** 2.0 based on **2**	$C_{15}H_{19}N_3O_3 \cdot \frac{3}{4}CH_3OH$ (289.33)	Calcd. C, 60.36; H, 7.08; N, 13.41 Found C, 60.41; H, 7.10; N, 13.39	289, 261, 179, 135
4c	R_1 H R_2 H R_3 	235 dec. (a)	57.2 based on **3c**	$C_{12}H_9N_3O_5 \cdot \frac{1}{2}H_2O$ (275.22)	Calcd. C, 48.56; H, 3.87; N, 14.16 Found C, 48.44; H, 3.61; N, 14.17	(d)
5a	R_1 AdmCO R_2 H R_3 AdmCO	217 dec. (chloroform-diisopropyl ether)	3.0 based on **2**	$C_{26}H_{33}N_3O_4 \cdot \frac{1}{3}H_2O$ (451.55)	Calcd. C, 68.25; H, 7.42; N, 9.18 Found C, 68.00; H, 7.50; N, 9.50	451, 423, 395, 341, 250, 179
6	R_1 AdmCO R_2 CH_3 R_3 H	182.5-183.5 (chloroform-diisopropyl ether)	70.3 based on **7** 65.0 based on **3a**	$C_{16}H_{21}N_3O_3$ (303.15)	Calcd. C, 63.35; H, 6.98; N, 13.85 Found C, 63.2; H, 7.0; N, 13.8	303, 275, 163, 135
7	R_1 H R_2 CH_3 R_3 H	241 dec. (aqueous methanol)	96.8 based on **6** 94.3 based on **8**	$C_5H_7N_3O_2$ (141.13)	Calcd. C, 42.55; H, 5.00; N, 29.78 Found C, 42.39; H, 5.08; N, 29.64	141, 124, 97, 69, 42, 28, 15

(a) Dimethyl sulfoxide-water. (b) Analyzed without recrystallization. (c) Yield without purification. A-B in parenthesis refers to the method of acylation (see Experimental). (d) Hard to measure due to its extremely low vapor pressure. (e) $M^+ - CH_2Cl - Cl + 2H$.

of Ehrlich carcinoma (6).

Our interest in the antitumor activity of **3a** and **3c** led us to examine acylation of **2** with 1-adamantanecarbonyl chloride and with 3,4-methylenedioxybenzoyl chloride in detail.

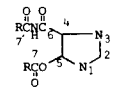
After the precipitated **3a** was removed from the reaction mixture by filtration, the filtrate was submitted to column chromatography, and an imide **4a** and a diacyl derivative (**5a**) were separated.

With 3,4-methylenedioxybenzoyl chloride, the corresponding imide (**4c**) and diacyl derivative could not be isolated, but the presence of **4c** was confirmed by comparing its retention time in hplc with that of an authentic sample, prepared by the method described later in this paper. The structure of **3a-j** was determined as follows.

The results of elemental analyses and molecular ions in the mass spectra proved **3a-j** to be mono-acylated products (Table 1). Although the carbonyl absorption observ-

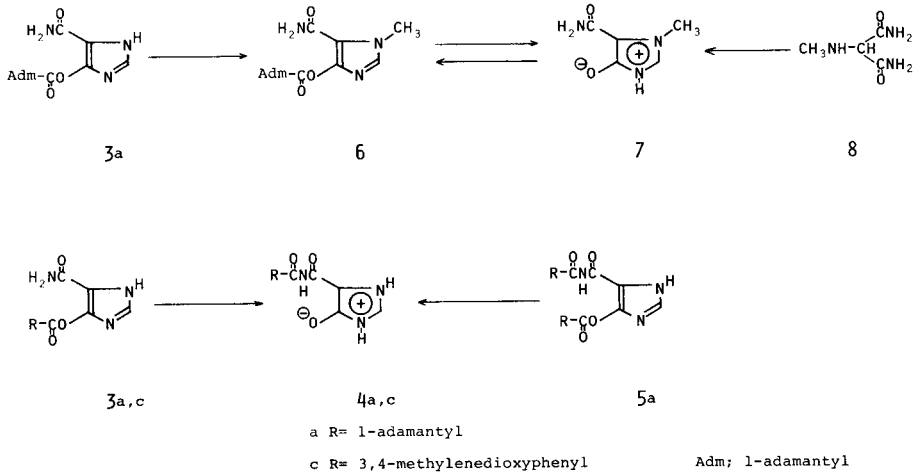
Table 2

^{13}C and ^{1}H Nmr Chemical Shifts (a) and Carbonyl Stretching Absorption for Esters and their Related Compounds



Compound No.	^{13}C Chemical Shifts (ppm) C-2	C-4	C-5	C-6	C-7	C-7'	N-3-CH_3	^{1}H Chemical Shifts (ppm) C-2-*H*	-CONH_2	CONH-	N-3or1-*H*	N-3-CH_3	Ir (Nujol) $\nu_{C=O}$ cm^{-1}
2	126.3	100.3	156.3	162.0				7.6	6.9				
3a	132.7	112.6	146.6	160.1	174.2			7.6	6.9		12.7		1770
3b	133.0	112.9	146.5	160.2	163.9			7.6	7.2		12.8		1740
3c	132.9	112.5	146.3	159.8	163.1			7.6	7.0		12.9		1740
3d	132.9	112.9	146.4	160.0	163.8			7.6 (c)	7.0		12.8		1745
3e	133.0	112.4	146.8	159.9	163.6			7.5	6.8		12.6		1735
3f	133.1	112.4	146.6	159.8	163.7			7.6	7.1		12.8		1750
3g	133.0	112.5	146.5	159.9	163.5			7.7	7.5		12.7		1735
3h	133.2	112.6	146.3	159.9	159.4			7.6	7.1		12.7		1730
3i	133.0	112.7	146.3	159.9	163.4			7.7	7.2		13.0		1740
3j	133.1	112.4	146.0	159.6	162.9			7.6	7.2		12.7		1760
4a	128.3	99.8	158.2	156.9		175.3		8.2		11.0			1725 (d)
4c	(e)							8.5		12.0			1720 (d)
5a	127.5	99.4	145.1	157.5	174.5	177.5		7.7		9.6	13.0		1780
													1725 (d)
6	136.5	113.2	146.9	160.3	174.3		34.0 (b)	7.6	7.2			3.8	1780
7	128.6	100.4	157.1	162.2			35.6 (b)	7.9	6.9			3.8	

(a) In δ units (ppm) in deuteriodimethylsulfoxide with TMS as internal standard. (b) Quartet, $^{1}J_{C\text{-}H}$ = 143 Hz. (c) Hard to assign due to the overlap of phenyl protons. (d) Imide carbonyl stretching absorptions. (e) Could not be measured due to decomposition during measurement.



Scheme 2

ed at 1730-1770 cm^{-1} in their ir spectra seemed to support the ester structure of **3a-j**, the *N*-acylated structure could not be eliminated because the infrared spectrum of *N*-acetylimidazole displays a carbonyl band in the 1747 cm^{-1} region (7). In the ^{13}C nmr spectra of **3a-j** (Table 2), there exist large upfield shifts for C-5 (*ca.* − 10 ppm) and large downfield ones for C-4 (*ca.* + 12 ppm) compared with those of **2**. These shifts seem to be ascribable to a decrease of polarizability of the bond between C-5 and a neighboring oxygen atom or nitrogen atom.

On the basis of these data, the site of acylation might be either the nitrogen atom at position 1 or the oxygen atom bonded to C-5.

As there remained uncertainty as to the structure of **3a-j**, X-ray crystallographic analysis of **3a** was carried out; its crystals suitable for X-ray analysis were grown from a mixture of methanol and water. The structure of **3a** was finally determined as 5-carbamoyl-1*H*-imidazol-4-yl 1-adamantanecarboxylate (8). The ester structure of **3b-j**, therefore, was concluded by analogy.

Table 3

Analytical Data for the Alkyl Derivatives of Compound **2**

Compound No.	M.p. °C (solvent)	Yield (%) (a)	Formula (Molecular Weight)		Analysis, % C	H	N	Ms (m/e)
9	157.5-159 (ethyl acetate-*n*-hexane)	61.5 based on **7**	$C_6H_9N_3O_2$ (155.16)	Calcd.	46.44	5.85	27.08	155, 139, 137, 110,
				Found	46.47	5.69	27.19	42
10	226-230 (methanol-diisopropyl ether)	30.5 based on **7** 78.1 based on tri-*n*-butyltin derivatives of **7**	$C_6H_9N_3O_2$ (155.16)	Calcd.	46.44	5.85	27.08	155, 138, 42
				Found	46.08	5.67	27.14	
11	199 dec. (methanol-diisopropyl ether)	23.4	$C_5H_7N_3O_2$ (141.13)	Calcd.	42.55	5.00	29.78	141, 124, 95, 44,
				Found	42.4	4.9	30.0	42, 28
16	222.5 dec. (methanol)	24.6	$C_5H_7N_3O_2$ (141.13)	Calcd.	42.55	5.00	29.78	141, 124, 96, 42
				Found	42.6	5.1	29.5	
17	237 dec. (methanol)	14.8	$C_5H_7N_3O_2$	Calcd.	42.55	5.00	29.78	141, 123, 111, 84
				Found	42.3	5.1	29.4	59, 44, 27
18	236 dec. (methanol-diisopropyl ether)	94.2	$C_6H_9N_3O_2 \cdot 1/6H_2O$ (155.16)	Calcd.	45.56	5.95	26.57	155, 137, 125, 97,
				Found	45.9	5.7	26.6	69, 58, 42, 28

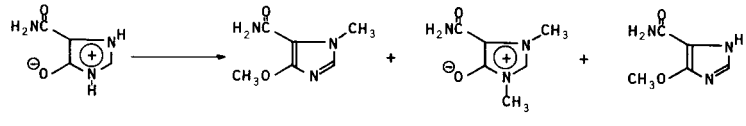
(a) Yield without purification.

Table 4

^{13}C Nmr Chemical Shifts (a) of the Alkyl Derivatives of Compound **2**

Compound No.	C-2	C-4	C-5	C-6	X-CH_3 (X)	^1JC-H (b)
9	135.9	105.3	157.0	161.4	34.4 (N-3)	141
					56.0 (O)	146
10	128.0	98.9	156.7	162.5	27.9 (N-1)	142
					36.0 (N-3)	143
11	132.3	105.0	155.3	160.6	56.0 (O)	147
16	126.1	98.4	155.9	162.1	28.1 (N-1)	141
18	128.2	100.8	156.8	161.5	35.7 (N-3)	144
					24.5 (amide)	137
1-methylimidazole	138.3	128.9	120.8		32.8 (N)	143
1,3-dimethylimidazolium iodide	136.9	123.2	123.2		35.9 (N)	143

(a) In δ units (ppm) in deuteriodimethyl sulfoxide with TMS as internal standard. (b) Coupling constants between methyl carbon and methyl protons in Hz.



2 9 10 11

Scheme 3

The second product (**4a**) in the acylation of **2** proved to be identical with the product of the base catalyzed rearrangement reaction of **3a**. Their ^1H nmr spectra, which showed the presence of acyl amide protons integrated for one proton, indicated that **4a** and **4c** were 4-(1-adamantylcarbonyl)carbamoyl and 4-(3,4-methylenedioxybenzoyl)-carbamoylimidazolium-5-olate, respectively.

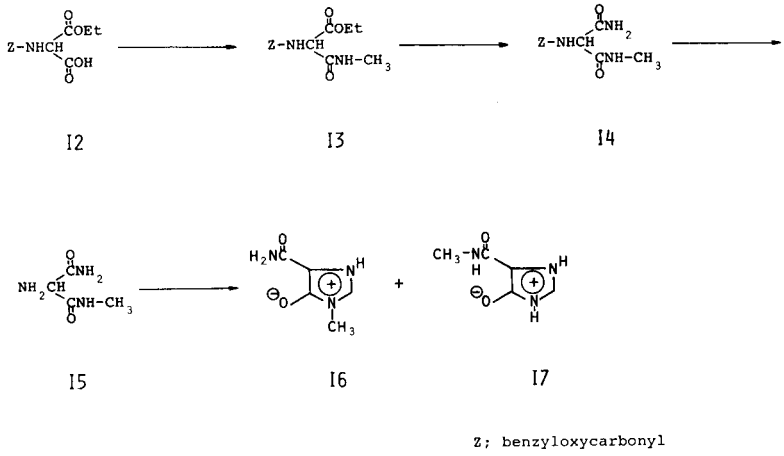
Alcoholysis of the third product (**5a**) in refluxing methanol afforded the deacylated product, which was identified with compound **4a** prepared from **3a**, by com-

Table 5

^{1}H Nmr Chemical Shifts (a) of the Alkyl Derivatives of Compound **2**

	C-2-*H*	X-C*H*$_3$ (X)	CON*H*$_2$	CON*H*-
9	7.45	3.81 (N-3) 3.95 (O)	6.48, 7.08	
10	8.13	3.29 (N-1) 3.80 (N-3)	6.54, 7.44	
11	7.42	3.93 (O)	6.47, 7.10	
16	8.13	3.30 (N-1)	7.0	
18	7.88	2.73 (amide, d (b), J = 4.9 Hz) 3.81 (N-3)		7.8
1-methylimidazole	7.50			
1,3-dimethylimidazolium iodide	9.19			

(a) In δ units in deuteriodimethyl sulfoxide with TMS as internal standard. (b) d: doublet.



Scheme 4

parison of ir spectra. Compound **5a** was assumed to possess the structure as shown in Scheme 2 due to the presence of the ester carbonyl absorption at 1780 cm^{-1} in its ir spectrum and the peak of an imino-hydrogen atom at 13.0 ppm in its ^{1}H nmr spectrum.

In the view of the potent antitumor activity of **3a**, it was of interest to investigate a further modification of **3a**. Compound **3a** was methylated with large excess of diazomethane in *N,N*-dimethylformamide, yielding **6** in 65% yield after purification. The position of the methyl substituent in **6** was determined unequivocally as shown in Scheme 2.

Cyclization of 2-methylaminopropanediamide **8** with triethyl orthoformate gave 5-carbamoyl-1-methylimidazolium-5-olate **7**. Silylation of **7** with hexamethyldisilazane, followed by acylation of the resultant trimethylsilyl derivative with 1-adamantanecarbonyl chloride yielded compound **6**. Moreover, hydrolysis of **6** with dilute hydrochloric acid gave **7** in turn.

D. J. Brown (9) conducted cyclization of 2-methylaminopropanediamide **8** with ethyl formate in the presence of sodium ethoxide to yield 4,6-dihydroxy-5-methylaminopyrimidine. The reaction was repeated by the present authors and the product proved to be identical with compound **7**. On the basis of ^{13}C nmr study for **7** (Table 2), the authentic 4,6-dihydroxypyrimidine (9), and the above fact (conversion of **7** to the authentic imidazole derivative **6**), the structure of 4,6-dihydroxy-5-methylaminopyrimidine has been disproved.

II. Alkyl Derivatives of **2**.

During the course of the investigation related to the syntheses of novel derivatives of **2**, we examined methylation of **2** with diazomethane. Treatment of **2** with large excess of diazomethane gave a mixture of dimethyl derivatives (**9** and **10**), and monomethyl derivative (**11**).

The structure of **10** was determined as follows. The 1-methyl derivative (**16**) of **2** was synthesized in a four-step sequence of reactions starting with Ethyl hydrogen (benzyloxycarbonylamino)propanedioate (**12**) (11) as shown in Scheme 4.

Compound **14** was prepared by condensation of **12** with

methylamine in the presence of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole, followed by treatment of the resultant methylamide (**13**) with ammonia in methanol. Catalytic hydrogenation of **14** over 10% palladium on calcium carbonate as a catalyst gave **15** successfully.

Cyclization of **15** with triethyl orthoformate produced a mixture of 4-carbamoyl-1-methylimidazolium-5-olate (**16**) and 4-methylcarbamoylimidazolium-5-olate (**17**), which was separated into the respective pure forms on the basis of differing solubility in methanol. The structural assignment of the two products was based on their ^1H and ^{13}C nmr studies.

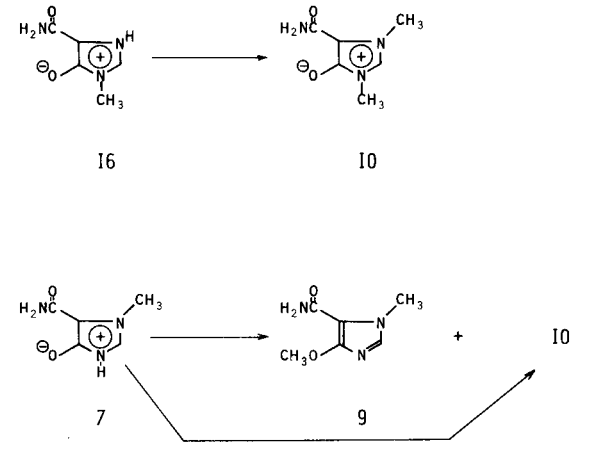
Methylation of the 1-methyl derivative (**16**) obtained above and the 3-methyl isomer (**7**) was then studied. Methylation of the former (**16**) with diazomethane gave a single dimethyl product (**10**), while the latter (**7**) gave two dimethyl derivatives on treatment with the same reagent. A minor product, which was prepared exclusively from **7** by successive treatment with bis(tri-*n*-butyltin) oxide in boiling toluene and methyl iodide, was identical in all respects with the dimethyl product (**10**) from **16**. Therefore, this product is 4-carbamoyl-1,3-dimethylimidazolium-5-olate; it was also identical with the dimethylated product (**10**) from **2**.

A major dimethyl product (**9**) from **7** proved to be identical with **9** from **2**, and its assumed structure in Schemes 3 and 5 was verified by nmr spectral study. The third product (**11**) from the methylation reaction of **2**, unidentical with any of its isomers (**7**, **16** and **17**) must be 4(5)-methoxy-1*H*-imidazole-5-(4)-carboxamide; its spectral data was consistent with the assigned structure (12).

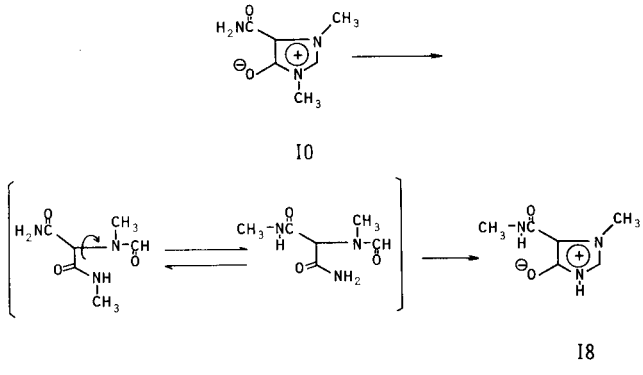
Tables 4 and 5 summarize the pertinent ^{13}C and ^1H nmr spectral data for the alkyl imidazole derivatives described in section II (10). In the nmr spectra, C-2 and C-2 proton of **10** shifted upfield and downfield, respectively, compared to those of **9**. The same tendency for chemical shift was observed in the comparison of **6** with **7**, and of authentic *N*-methylimidazole with 1,3-dimethylimidazolium iodide (13). These phenomena have been explained in terms of the σ-bond polarization, which means the variation of electron density: an increase at C-2 and a decrease at the proton bonded to C-2 (14).

It was previously shown that imidazolium compounds occasionally gave ring-opened products or rearranged ones under basic conditions (15a-c). On heating in aqueous potassium hydroxide, compound **10** afforded **18** in good yield. The ^1H and ^{13}C nmr spectra of **18** showed almost the same absorption peaks as those of **7**, except for a doublet at 2.73 ppm (^1J CH_3-NH = 4.9 Hz) for the amide of *N*-methyl protons. These results were compatible with the structure of **18**. The formation of **18** can be explained by a Dimroth-type rearrangement (15c,16a-b) as shown in Scheme 6.

The methyl derivatives **6**, **7**, **9** and **16** were tested



Scheme 5



Scheme 6

against Lewis lung carcinoma or Sarcoma 180 in mice. The methyl derivatives, except for **16** which displayed a similar degree of activity against Sarcoma 180 to that of the parent **2**, demonstrated the complete lack of activity against Lewis lung carcinoma or Sarcoma 180.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined for Nujol mulls on a Hitachi type-285 grating spectrophotometer. Nuclear magnetic resonance spectra were obtained in DMSO-d_6 on a JEOL EX-100 FT-NMR spectrometer at 99.60 (^1H) and 25.2 (^{13}C) MHz using tetramethylsilane as an internal standard. Electron impact mass spectra were obtained on a shimazu LKB-9000 mass spectrometer operating at 12 and 70eV.

4-Carbamoylimidazolium-5-olate (**2**) (3), m.p. 237° dec., and 2-methylaminopropanediamide (**8**) (9), m.p. 205° dec., were prepared by the method described in the literature. The preparation of ethyl hydrogen (benzyloxycarbonylamino)propanedioate (**12**) (11), m.p. 68-70°, was slightly modified (potassium carbonate was used in the place of potassium hydroxide).

Acylation of **2**.

The esters (**3a-j**) were prepared by the following methods.

A. With Acid Chloride in Pyridine

The two examples given below are representative for the preparation of the compounds **3a-j**.

5-(4)Carbamoyl-1*H*-imidazol-4-(5)yl 1-Adamantanecarboxylate (**3a**), 4-(1-Adamantylcarbonyl)carbamoylimidazolium-5-olate (**4a**) and 5(4)-(1-Adamantylcarbonyl)carbamoyl-1*H*-imidazol-4-(5)yl 1-Adamantanecarboxylate (**5a**).

To a solution of 21.86 g. (110 mmoles) of 1-adamantanecarbonyl chloride in 260 ml. of pyridine, was added 12.71 g. (100 mmoles) of **2** and the reaction mixture was stirred at 41-43° for 3.5 hours. After removal of the pyridine *in vacuo*, 300 ml. of ethyl acetate and 300 ml. of water were added to the residue and the mixture was vigorously stirred for 1 hour. The insoluble solid was collected by filtration and washed with ethyl acetate to give 23.44 g. (81.0%) of almost pure **3a**, m.p. 205° dec. Evaporation of the filtrate and washings left a viscous oil which was dissolved in a small amount of *N,N*-dimethylformamide and the solution was charged on a silica gel column for chromatography. The initial fraction eluted with chloroform-methanol (30:1) mixture gave 1.35 g. (3.0%) of **5a**. The analytically pure sample of **5a** was obtained by recrystallization from chloroform-diisopropyl ether. The following fraction eluted with chloroform-methanol (4:1) mixture afforded 580 mg. (2.0%) of **4a** which showed an identical ir spectrum with that of the sample prepared

5-(4)Carbamoyl-1*H*-imidazol-4-(5)yl 3,4-methylenedioxybenzoate (**3c**).

To a mixture of 76.26 g. (600 mmoles) of **2**, 840 ml. of dry tetrahydrofuran and 140 g. of dry pyridine, was added 121.82 g. (660 mmoles) of 3,4-methylenedioxybenzoyl chloride and the reaction mixture was stirred at 40-45° for 4 hours. After the mixture was cooled to 20°, 66.79 g. (660 mmoles) of triethylamine was added and then the mixture was further stirred at 5° for 1 hour. The precipitates were collected by filtration, washed successively with 300 ml. of tetrahydrofuran, 1200 ml. of 1,2-dichloroethane and 800 ml. of chloroform to give 144.75 g. (87.7%) of almost pure **3c**, m.p. 200° dec. The presence of 4-(3,4-methylenedioxybenzoyl)carbamoylimidazolium-5-olate (**4c**) in the filtrate and washings was confirmed by comparing the retention time (*ca.* 8.5 minutes under the conditions described below) in high pressure liquid chromatogram with that of an authentic sample prepared by treatment of **3c** with 3*N* aqueous sodium hydroxide in *N,N*-dimethylformamide.

The hplc conditions were as follows: column, μ Bondapak C_{18}, 30 × 0.4 cm ID; mobile phase, 0.01 *M* phosphate buffer/1,4-dioxane (5/1); flow rate, 1.0 ml./minute; detector, 254 nm; temperature, ambient. We could not succeed in the isolation of **4c** from the filtrate and washings by means of silica gel column chromatography eluted with a mixture of chloroform and methanol as in the case of **4a**.

B. With Benzoic Anhydride.

5-(4)Carbamoyl-1*H*-imidazol-4-(5)yl Benzoate (**3b**).

To a suspension of 254 mg. (2.00 mmoles) of **2** in 5 ml. of dry dimethyl sulfoxide, was added 457 mg. (2.02 mmoles) of benzoic anhydride. The mixture was stirred at room temperature for 50 minutes and at 60° for 75 minutes to give a greenish solution. After cooling, the solution was poured into 15 ml. of ice-cold water. The product that separated was filtered and washed with 2 ml. of tetrahydrofuran to yield 376 mg. (81.3%) of **3b**. The ir spectrum of this product was identical with that of the authentic sample prepared by Method A.

4-(1-Adamantylcarbonyl)carbamoylimidazolium-5-olate (**4a**).

A. From **3a**.

To a solution of 1.000 g. (3.456 mmoles) of **3a** in 10 ml. of *N,N*-dimethylformamide, was added 2.0 ml. of 3*N* aqueous sodium hydroxide and the mixture was stirred for 1 hour. The precipitates were collected by filtration, washed with ethyl acetate and diisopropyl ether to give 719 mg. of the sodium salt of **4a**. To the solution of this salt in 180 ml. of methanol was added 6*N* hydrochloric acid and the *p*H of the solution was adjusted to 1. After 300 ml. of diisopropyl ether was added to the solution, the crystals that separated were collected by filtration, washed with diisopropyl ether to give 335 mg. (33.5%) of **4a**, m.p. 222°. An analytically pure sample was obtained by recrystallization from methanol.

B. From **5a**.

A solution of 452 mg. (1.00 mmole) of **5a** in 30 ml. of chloroform and 5 ml. of methanol was refluxed for 3 hours. After the solvent was evaporated *in vacuo*, 40 ml. of diisopropyl ether was added to the residue. An insoluble solid was collected by filtration, washed with diisopropyl ether to give 280 mg. (96.9%) of **4a**. The ir spectrum of the product was identical with that of the authentic sample prepared by Method A.

4-(3,4-Methylenedioxybenzoyl)carbonylimidazolium-5-olate (**4c**) from **3c**.

The *p*H of a solution of 500 mg. (1.82 mmoles) of **3c** in 15 ml. of *N,N*-dimethylformamide was adjusted to 9 by the addition of 3*N* aqueous sodium hydroxide and the mixture was stirred for 5 hours. The precipitates were collected by filtration and washed with diethyl ether to give 454 mg. of the sodium salt of **4c**. To the solution of this salt in 150 ml. of methanol, was added 6*N* hydrochloric acid and the *p*H of the solution was adjusted to 2. The precipitates were collected by filtration and washed with methanol to give 286 mg. (57.2%) of **4c**, m.p. 230° dec.

5-Carbamoyl-1-methyl-1*H*-imidazol-4-yl 1-Adamantanecarboxylate (**6**).

(A) Methylation of **3a**.

To a solution of 1.445 g. (5.00 mmoles) of **3a** in 80 ml. of dry *N,N*-dimethylformamide, was added an excess of diazomethane in diethyl ether at 0-5°. After the solution had been stirred for 2 hours in an ice bath and at room temperature for 18 hours, the solvent was evaporated *in vacuo*. The oily residue was chromatographed on a column of silica gel eluted with chloroform-methanol (9:1) to give 977 mg. (64.5%) of **6**, m.p. 176-179°. The ir spectrum of this product was identical with that of the authentic sample prepared by the Method (B).

(B) Acylation of **7**.

A mixture of 141 mg. (1.00 mmole) of **7**, 5 ml. of hexamethyldisilazane and 2 mg. of anhydrous ammonium sulfate was refluxed for 2 hours to give a clear solution. After the solution was concentrated to dryness *in vacuo*, the residue was dissolved in 10 ml. of dry tetrahydrofuran and the solution was allowed to cool to −10°. To the solution was added 199 mg. (1.00 mmole) of 1-adamantanecarbonyl chloride in 2 ml. of dry tetrahydrofuran. After the reaction mixture had been stirred for 2 hours, 1 ml. of methanol was added. Further, 0.15 ml. (1.07 mmoles) of triethylamine was added after additional stirring for 0.5 hour. Then, the mixture was allowed to come to room temperature and stirred overnight. After the removal of the precipitates by filtration, the filtrate was directly chromatographed on a column of silica gel, eluted with tetrahydrofuran to give 213 mg. (70.3%) of **6**, m.p. 177.5°. The analytically pure sample was obtained by recrystallization from chloroform-diisopropyl ether.

5-Carbamoyl-1-methylimidazolium-4-olate (**7**).

(A) Hydrolysis of **6**.

To a solution of 100 mg. (0.33 mmole) of **6** in 10 ml. of methanol, was added 0.46 ml. (0.46 mmole) of *N* hydrochloric acid and the solution was stirred at room temperature for 63 hours. Then, the *p*H of the reaction mixture was adjusted to 6.5 by the addition of *N* aqueous sodium hydroxide. After evaporation of the solvent *in vacuo*, the residue was chromatographed on a column of silica gel to afford 45.0 mg. (96.8%) of **7**, m.p. 238.5° dec.

(B) Cyclization of **8**.

A mixture of 6.557 g. (50.0 mmoles) of **8**, 130 g. (880 mmoles) of triethyl orthoformate and a catalytic amount of acetic acid was stirred for 2 hours under reflux. The mixture was allowed to cool down to room temperature. The crystals were collected by filtration and washed with ethanol and diisopropyl ether to give 6.652 g. (94.3%) of **7**. The ir spectrum of this product was identical with that of the authentic sample prepared by the Method (A).

Melting points, yields and analytical data of the compounds **3a-j**, **4a**, **4c**, **5a**, **6** and **7** are listed in Table 1. ^1H and ^{13}C nmr data are also listed in Table 2.

Methylation of **2**.

4-Methoxy-1-methyl-1*H*-imidazole-5-carboxamide (**9**), 4-Carbamoyl-1,3-dimethylimidazolium-5-olate (**10**) and 4-(5)Methoxy-1*H*-imidazole-5-(4)-carboxamide (**11**).

To a solution of 636 mg. (5.00 mmoles) of **2** in 50 ml. of water and 75 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 was removed *in vacuo*, the residual solid was chromatographed on a column of silica gel. The initial fraction eluted with chloroform-methanol (15:1) mixture afforded 238 mg. (30.7%) of **9**. The following fraction eluted with (9:1) mixture gave 165 mg. (23.4%) of **11** and then 236 mg. (30.4%) of **10**. The ir spectrum of **9** was identical with that of the authentic sample prepared from **7**. The ir spectrum of **10** was identical with that of the authentic sample prepared from tri-*n*-butyltin derivative of **7**. An analytically pure sample of **11** was obtained by recrystallization from methanol-diisopropyl ether.

Ethyl 2-Benzyloxycarbonylamino-3-methylamino-3-oxopropanoate (**13**).

To a solution of 2.81 g. (10.0 mmoles) of **12**, 1.00 g. (10.0 mmoles) of 30% ethanolic methylamine solution and 1.48 g. (11.0 mmoles) of 1-hydroxybenzotriazole in 25 ml. of dry tetrahydrofuran, was added dropwise 2.06 g. (10.0 mmoles) of dicyclohexylcarbodiimide in 15 ml. of tetrahydrofuran at −7°. After the mixture had been stirred at room temperature for 19 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 2.86 g. (97.0%) of **13**, m.p. 120-122°. The analytically pure product was obtained by recrystallization from chloroform-diisopropyl ether, m.p. 123.5-124.5°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.17; N, 9.52. Found: C, 57.2; H, 6.2; N, 9.6.

2-Benzyloxycarbonylaminopropane-*N*-methyldiamide (**14**).

To a solution of 10.3 g. (35.0 mmoles) of **13** in 120 ml. of methanol, was added 120 ml. of 16% methanolic ammonia. The reaction vessel was completely sealed and was allowed to stand at 5° for 44 hours. The crystals that separated were collected by filtration to give 8.05 g. (86.7%) of **14**. Further, the filtrate was condensed to dryness and the residue was recrystallized from methanol-diisopropyl ether, yielding 350 mg. (3.8%) of **14** (total yield 90.5%). The analytically pure product was obtained by recrystallization from methanol, m.p. 178.5-179.5°.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.1; H, 5.8; N, 16.0.

2-Aminopropane-*N*-methyldiamide (**15**).

A solution of 5.31 g. (20.0 mmoles) of **14** 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 17 hours. After the catalyst was filtered off, the filtrate was evaporated to dryness *in vacuo*. The residual product was purified by recrystallization from ethanol-diisopropyl ether to give 2.21 g. (84.4%) of **15**, m.p. 121-122.5°.

Anal. Calcd. for $C_4H_9N_3O_2$: C, 36.63; H, 6.92; N, 32.05. Found: C, 36.5; H, 6.9; N, 32.4.

Cyclization of **15**.

4-Carbamoyl-1-methylimidazolium-5-olate (**16**) and 4-Methylcarbamoylimidazolium-5-olate (**17**).

A mixture of 1.57 g. (12.0 mmoles) of **15**, 8.95 g. (60.4 mmoles) of triethyl orthoformate and 50 ml. of dry ethanol was refluxed for 1.5 hours. The crystals that separated were collected by filtration to give 1.302 g. (76.4%) of a mixture of **16** and **17**. The ratio of **17**/**16** was determined to be 40/60 by ^{1}H nmr analysis. Recrystallization from methanol gave 417 mg. (24.6%) of **16**, m.p. 222.5° dec., as greenish cubics. The methanolic filtrate was condensed to a small volume, and cooled, whereupon **17** separated out as greenish needles, which were collected by filtration and washed with a small amount of cold methanol to give 250 mg. (14.8%) of **17**, m.p. 237° dec.

Methylation of **16**.

4-Carbamoyl-1,3-dimethylimidazolium-5-olate (**10**).

To a solution of 73 mg. (0.52 mmole) of **16** in 5 ml. of methanol, was added an excess of diazomethane in diethyl ether and the solution was stirred at room temperature for 1 hour. After the excess of diazomethane was removed, the solution was treated with decolorizing charcoal and evaporated to dryness to give 58 mg. (72%) of **10**, m.p. 220-221°.

Methylation of **7**.

4-Methoxy-1-methyl-1*H*-imidazole-5-carboxamide (**9**) and 4-Carbamoyl-1,3-dimethylimidazolium-5-olate (**10**).

To a solution of 141 mg. (1.00 mmole) of **7** in 70 ml. of methanol, was added an excess of diazomethane in diethyl ether and this solution was stirred at room temperature for 1 hour. 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 a mixture of chloroform and methanol (9:1) afforded 660 mg. (42.6%) of **9**, m.p. 157.5-159°. The following fraction eluted with a mixture of the same solvents (4:1) gave 660 mg. (42.6%) of **10**, m.p. 213° dec. Analytically pure samples of **9** and **10** were obtained by recrystallization from ethyl acetate-*n*-hexane and methanol-diisopropyl ether, respectively.

Methylation of the tri-*n*-butyltin Derivative of **7**.

4-Carbamoyl-1,3-dimethylimidazolium-5-olate (**10**).

A mixture of 141 mg. (1.00 mmole) of **7**, 10 ml. of dry toluene and 596 mg. (1.00 mmole) of bis(tri-*n*-butyltin)oxide was refluxed for 1 hour to give a clear solution. After removal of the toluene *in vacuo*, 10 ml. of methyl iodide was added, the mixture was refluxed for 2.5 hours. The reaction mixture was allowed to cool down to room temperature and the crystals were collected by filtration, washed with diisopropyl ether to give 121 mg. (78.1%) of **10**, m.p. 213° dec.

1-Methyl-5-methylcarbamoylimidazolium-4-olate (**18**).

To a solution of 155 mg. (1.00 mmole) of **10** in 50 ml. of methanol, was added 5 ml. (67 mmoles) of 50% aqueous potassium hydroxide. The reaction mixture was stirred for 1.5 hours, cooled down to room temperature and neutralized by the addition of 6*N* hydrochloric acid. The potassium chloride that precipitated was filtered and the filtrate was concentrated to dryness. This residue was chromatographed on a column of silica gel, eluted with chloroform-methanol (4:1) to afford 146 mg. (94.2%) of **18**.

Melting points, recrystallization solvent, yields and analytical data of the compounds **9-11** and **16-18** are listed in Table 3. ^{13}C and ^{1}H nmr data are also listed in Tables 4 and 5, respectively, except for those of **17**.

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