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Syntheses of 2-Mercapto-4-substituted Imidazole Derivatives with Antiinflammatory Properties[1)]

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Various 2-mercapto-4-substituted-5-imidazolecarboxylates (**5**) were synthesized by the reaction of *C*-acylamino acid methyl esters (**4**) with potassium thiocyanate. Hydrolysis followed by decarboxylation of the imidazole carboxylates (**5**) gave 2-mercapto-4-substituted imidazoles (**8**) in good yields. Furthermore, the imidazoles (**8**) were also directly obtained by the reaction of aminoketones (**9**) with potassium thiocyanate. These compounds (**8**) exhibited antiinflammatory activities against carrageenan-induced rat paw edema. Among the compounds tested, 2-mercapto-4-(3-thienyl)imidazole (**8r**) showed the best therapeutic index value, giving a value comparable to that of mefenamic acid.

Keywords——*C*-acylamino acid ester; α-amino ketone; 2-mercapto-4-substituted imidazole; 2-mercapto-4-substituted-5-imidazole-carboxylate; decarboxylation; antiinflammatory

We previously established a convenient synthetic method for *C*-acylamino acid derivatives,[2)] which are of interest from a physiological point of view and also have synthetic utility, being convertible into heterocyclic compounds.[3)] In the course of our investigations on the synthetic applications of the *C*-acylamino acids, our interest was focussed on synthesizing 2-mercaptoimidazole derivatives, since it is known that some imidazole compounds exhibit potent antiinflammatory and analgesic activities.[4)] We describe here the synthesis of various kinds of 2-mercaptoimidazole derivatives for antiinflammatory activity testing.

Synthesis

Prior to the synthesis of the title compound, we prepared a number of *C*-acylamino acid methyl esters (**4**) as starting materials, according to our previous report.[2)] The first attempt to synthesize 2-mercapto-4-substituted imidazole-5-carboxylic acid esters (**5**) was made by reacting various *C*-acylamino acid esters (**4**) with potassium thiocyanate. In such reactions, the product is known to be an imidazolinone compound.[5)] However, the corresponding 2-mercapto-4-acyl-imidazoline (**6**) was not detected in the present reaction, but the desired 2-mercaptoimidazole compounds (**5**) were obtained in good yields, as shown in Table I.[6)] The reaction process may be as follows: the thioureido group formed in the first step reacted predominantly with the keto group rather than the ester group of **4**, resulting in the formation of imidazole compound (**5**).[7)] The identities of these products were confirmed by the infrared (IR) spectra and elemental analyses (Table I). In addition, the intermediate thioureido compound (**10**) was obtained under mild conditions in high yield. Subsequently, **10** was easily converted to the imidazole (**5g**) by heating in acetic acid.

Unfortunately, the mercaptoimidazole compounds (**5**) thus obtained exhibited almost no potency in antiinflammatory test. Thus, the ester compounds (**5**) were converted into the corresponding carboxylic acids (**7**) by hydrolysis (Table I). As an alternative method,

TABLE I. Properties and Antiinflammatory Activity of 2-Mercaptoimidazole-4(5)-carboxylic Acids (**5** and **7**)

Compd.	R	Yield (%)	mp (°C) (dec.)	IR ν_{max}^{Nujol} cm^{-1}, CO	Formula	Analysis (%) Calcd (Found) C	H	N	S	Inhibition[a] (%)
5a	Ph	92	186—187	1724	$C_{11}H_{10}N_2O_2S$	56.39 (55.76	4.30 4.22	11.96 11.92	13.69 13.86)	16
5d	4-F-Ph	86	209—210	1730	$C_{11}H_9FN_2O_2S$	52.37 (52.20	3.60 3.52	11.11 10.85	12.91 12.48)	0
5e	2-Cl-Ph	94	211—212	1700	$C_{11}H_9ClN_2O_2S$	49.16 (49.11	3.38 3.47	10.43 10.51	11.93 11.72)	0
5g	4-Cl-Ph	85	220—221	1725	$C_{11}H_9ClN_2O_2S$	49.16 (49.34	3.38 3.40	10.43 10.56	11.93 11.77)	0
5h	4-Me-Ph	96	203	1721	$C_{12}H_{12}N_2O_2S$	58.05 (57.74	4.87 4.99	11.28 10.92	12.91 12.45)	0
5k	4-MeO-Ph	87	191—192	1724	$C_{12}H_{12}N_2O_3S$	54.53 (54.62	4.58 4.65	10.60 10.47	12.13 11.91)	5
5l	$PhCH_2$	83	209—210	1717	$C_{12}H_{12}N_2O_2S$	58.05 (57.73	4.87 4.96	11.28 11.09	12.91 12.80)	1
5q	2-Thienyl	58	204—205	1726	$C_9H_8N_2O_2S_2$	44.98 (44.70	3.37 3.27	11.66 11.56	26.69 26.58)	0
7a	Ph	82	226—227	1690	$C_{10}H_8N_2O_2S$	54.53 (55.30	3.66 4.04	12.72 12.63	14.56 14.24)	1
7e	2-Cl-Ph	87	220—222	1685	$C_{10}H_7ClN_2O_2S$	47.16 (47.42	2.77 2.95	11.00 10.88	12.59 12.50)	3
7g	4-Cl-Ph	83	278—280	1685	$C_{10}H_7ClN_2O_2S$	47.16 (47.18	2.77 2.74	11.00 10.83	12.59 12.51)	0
7h	4-Me-Ph	69	267	1670	$C_{11}H_{10}N_2O_2S$	56.39 (56.35	4.80 4.38	11.96 11.58	13.09 13.26)	5
7l	$PhCH_2$	78	214—215	1680	$C_{11}H_{10}N_2O_2S \cdot H_2O$	52.37 (52.38	4.79 5.00	11.10 11.11	12.71 12.45)	1

a) % inhibition of the carrageenan-induced paw edema.

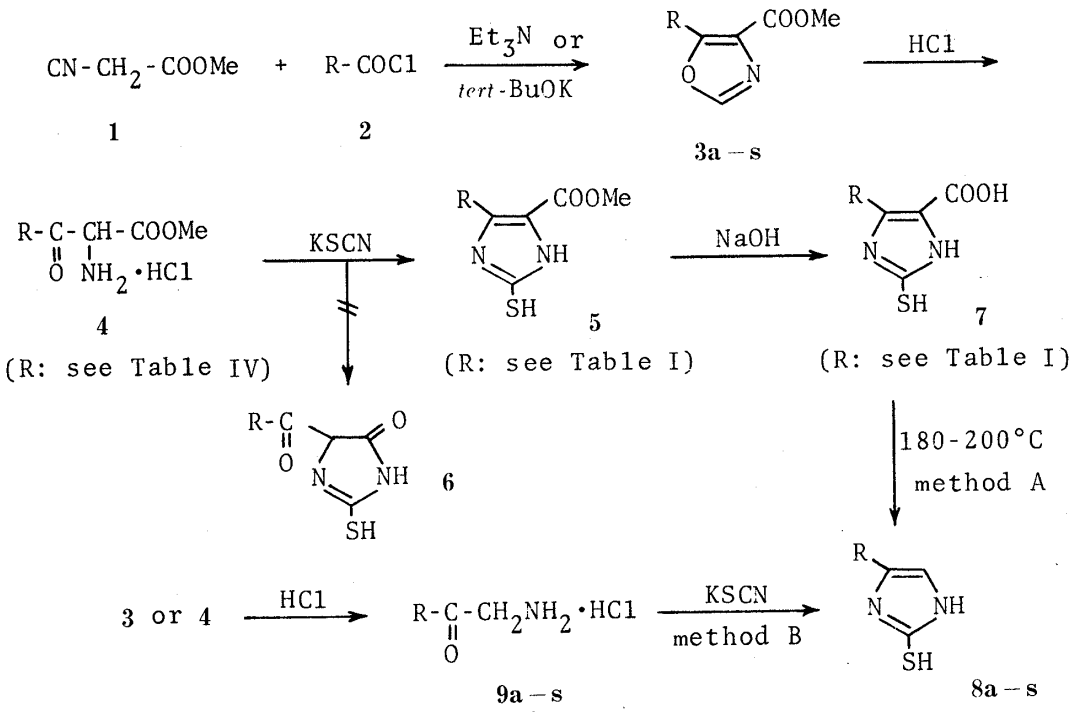
treatment of the thioureido compound (**10**) with KOH–aqueous MeOH directly gave the corresponding imidazole carboxylic acid (**7g**) in 80% yield. However, these acid compounds were not active either.

Next, we attempted the synthesis of 2-mercapto-4-substituted imidazole compounds (**8**) without an ester or acid moiety in order to investigate the structure–activity relationship for antiinflammatory activities. Only a few synthetic methods have been reported for such compounds,[8] though many methods for 1,4-disubstituted and 1,4,5-trisubstituted-2-mercaptoimidazole compounds are available.[9]

Here, for the syntheses of **8**, we attempted decarboxylation of the imidazole carboxylic acids (**7**) obtained above. The reaction was carried out at 180 to 200 °C in glycerin (method A) and the desired compounds (**8**) were obtained in fairly good yields. These compounds were also synthesized according to a conventional method,[8b,10] by the reaction of the amino ketone compounds (**9**), which were readily prepared from oxazole esters (**3**) or *C*-acylamino acid esters (**4**),[2] with potassium thiocyanate (method B). Physicochemical properties and yields of the imidazole compounds (**8**) obtained by methods A and B are summarized in Table II.

Antiinflammatory Activity

All of the 2-mercapto-imidazoles obtained in this study were examined for antiin-



a: R=Ph **b**: R=2-F–Ph **c**: R=3-F–Ph **d**: R=4-F–Ph
e: R=2-Cl–Ph **f**: R=3-Cl–Ph **g**: R=4-Cl–Ph **h**: R=4-Me–Ph
i: R=4-iso-Pr–Ph **j**: R=4-*tert*-Bu–Ph **k**: R=4-MeO–Ph **l**: R=$PhCH_2$
m: R=4-F–$PhCH_2$ **n**: R=4-Cl–$PhCH_2$ **o**: R=$PhCH_2CH_2$ **p**: R=2-furyl
q: R=2-thienyl **r**: R=3-thienyl **s**: R=3-pyridyl

Chart 1

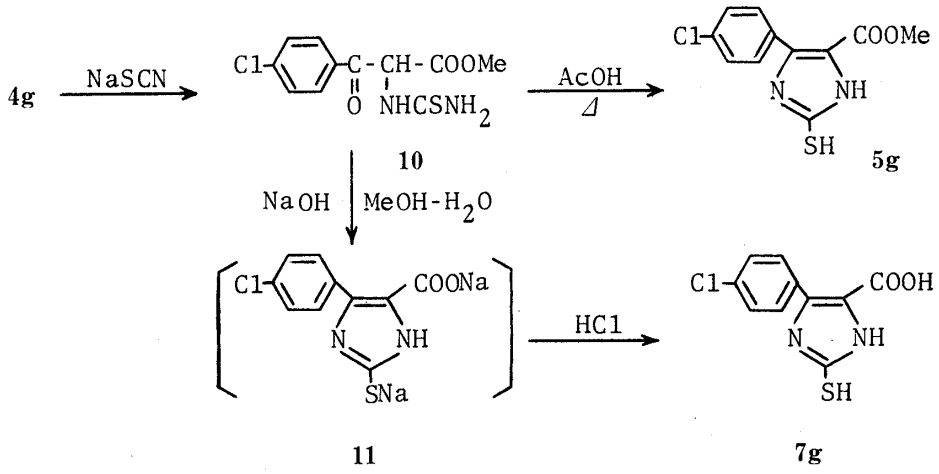


Chart 2

flammatory activities on carrageenan-induced paw edema in rats as described in the experimental section. These results are summarized in Tables I and II. As shown in Table I, methyl 2-mercapto-4-substituted-imidazole-5-carboxylates (**5**) exhibited very little antiinflammatory activity. Further, the corresponding acid derivatives (**7**), which may be regarded as structure analogues of α-imino acid, were also inactive. However, 2-mercapto-4-phenylimidazole (**8a**) tested as a typical compound without an ester or a carboxyl group, showed higher activity than a standard drug, mefenamic acid (MA). Therefore, we continued to investigate this series of compounds (**8b—s**) synthesized by method A or B (Table II).

TABLE II. Properties and Antiinflammatory Activity of 2-Mercaptoimidazoles (**8**)

8	Method	Yield (%)	mp (°C) (dec.)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Inhibition[a] (%)	Mortality[b]
a	A	90	255—257[c]	$C_9H_8N_2S$	61.33	4.58	15.90	18.19	50	5/5
					(61.24	4.65	16.02	18.18)		
b	B	64	262—263	$C_9H_9FN_2S$	55.65	3.63	14.42	16.51	18	CNS depress.
					(55.61	3.57	14.22	16.47)		
c	B	37	268—270	$C_9H_7FN_2S$	55.65	3.63	14.42	16.51	28	1/5
					(55.35	3.63	14.28	16.50)		
d	B	78	253—254	$C_9H_7FN_2S$	55.65	3.63	14.42	16.51	40	CNS depress.
					(55.55	3.65	14.41	16.75)		
e	A	76	257—259	$C_9H_7ClN_2S$	51.31	3.35	13.30	15.22	5	
	B	79			(51.16	3.41	13.37	14.93)		
f	B	57	274	$C_9H_7ClN_2S$	51.31	3.35	13.30	15.22	7	
					(50.94	3.36	13.30	15.34)		
g	B	56	270[d]	$C_9H_7ClN_2S$	51.31	3.35	13.30	15.22	31	1/5
					(51.51	3.57	13.23	15.14)		
h	B	95	267	$C_{10}H_{10}N_2S$	63.13	5.30	14.72	16.85	27	0/5
					(63.03	5.36	14.54	16.75)		
i	B	85	267—270	$C_{12}H_{14}N_2S$	66.02	6.46	12.83	14.69	0	
					(66.35	6.73	12.54	14.08)		
j	B	98	286	$C_{13}H_{16}N_2S$	67.20	6.94	12.06	13.80	11	
					(67.17	7.00	11.82	13.71)		
k	B	98	244[e]	$C_{10}H_{10}N_2OS$	58.23	4.89	13.58	15.55	12	
					(58.45	4.85	13.34	15.23)		
l	A	74	219—222	$C_{10}H_{10}N_2S$	63.13	5.30	14.72	16.83	27	0/5
	B	85			(63.00	5.41	14.65	16.84)		
m	B	71	242—244	$C_{10}H_9FN_2S$	57.67	4.36	13.45	15.40	27	1/5
					(57.32	4.27	13.37	15.28)		
n	B	68	251—255	$C_{10}H_9ClN_2S$	53.45	4.04	12.47	14.27	17	0/5
					(53.23	3.91	12.53	14.04)		
o	B	78	183—184	$C_{11}H_{12}N_2S$	64.67	5.92	13.71	15.70	29	2/5
					(64.78	5.72	13.98	15.43)		
p	A	66	251—252	$C_7H_6N_2OS$	50.59	3.64	16.86	19.29	30	5/5
					(50.80	3.61	16.74	19.44)		
q	B	81	255—258	$C_7H_6N_2S_2$	46.13	3.32	15.37	35.18	20	0/5
					(46.31	3.22	15.18	35.03)		
r	B	62	244—247	$C_7H_6N_2S_2$	46.13	3.32	15.37	35.18	42	0/5
					(45.95	3.23	15.21	35.08)		
s	B	62	>250	$C_8H_7N_3S$	54.22	3.98	23.71	18.09	26	0/5
					(53.95	3.71	23.50	18.24)		
Mefenamic acid (MA)									30	0/5

a) % inhibition of the carrageenan-induced paw edema.
b) (No. of mice died)/(No. of mice used) after 1000 mg/kg, *p.o.*
c) Lit.[11] mp 267.5 °C.
d) Lit.[12] mp 293—295 °C (dec.).
e) Lit.[13] mp 240 °C.

In a series of 4-phenylimidazole derivatives (**8a—j**), the fluoro compounds (**8b—d**) showed high activities, whereas the chloro derivatives (**8e—g**) did not exhibit marked activities. Among the fluorophenyl imidazoles, the 4-substituted compound (**8d**) exhibited the highest activity. On the other hand, among the 4-alkyl derivatives (**8h—j**) tested, only the methyl compound (**8h**) showed activity, while the isopropyl or *tert*-butyl derivative was

ineffective. Moreover, compound (**8l**) with a benzyl group was as active as compound (**8h**), and the fluorobenzyl compound (**8m**) was also active. Compounds (**8p—s**) substituted with a hetero aromatic ring such as furan, thiophene, or pyridine in place of the phenyl group at position 4 of the imidazole also showed fairly good activities. The 3-thienyl analogue (**8r**) was almost as active as the phenyl one (**8a**).

On the other hand, the acute toxicity of the compounds showing significant antiinflammatory activities was examined using mice as described in the experimental section. As summarized in Table II, compounds **8a** and **8p** were highly toxic; all mice orally given a dose of 1000 mg/kg died. In the case of compounds **8b** and **8d**, though no mice died at this dosage, apparent behavioral changes indicating central nervous system depression were observed.

Based on these results, compounds **8h**, **8l**, **8m** and **8r** seemed to have large therapeutic index values, comparable to that of MA. Among these, 2-mercapto-4-(3-thienyl)imidazole (**8r**), showing the most effective antiinflammatory activity, was selected for further pharmacological tests.

Experimental

Melting points, which were measured with a Yamato melting point apparatus, are uncorrected. The IR spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. The nuclear magnetic resonance (NMR) spectra were obtained using a Hitachi Perkin-Elmer R-20A high resolution NMR spectrometer with tetramethylsilane as an internal standard. Column chromatography was carried out on silica gel (Kieselgel 60, 0.063—0.200 mm, E. Merck).

Methyl 5-Substituted Oxazole-4-carboxylates (3)——These compounds were prepared by the reaction of methyl isocyanoacetate (**1**) with acyl chlorides (**2**) in the presence of Et_3N or *tert*-BuOK by methods similar to those described by Schöllkopf *et al.*[13] and the authors.[2]

Physicochemical properties of the oxazoles (**3a—k**, **3p** and **3q**) were reported previously.[14] The other oxazole compounds are listed in Table III.

***C*-Acylamino Acid Methyl Ester Hydrochlorides (4)**——These compounds were prepared by acid hydrolysis of the oxazole compounds (**3**) according to the method described by the authors.[2] The results are summarized in Table IV.

α-Amino Ketone Hydrochlorides (9)——These compounds were prepared by acid hydrolysis of the oxazole compounds (**3**) (method A) or the *C*-acylamino acid esters (**4**) (method B) according to the method described by the authors.[2] The results are summarized in Table V.

Typical Procedure for Preparation of Methyl 2-Mercaptoimidazole-5-carboxylates (5)——A mixture of methyl α-benzoylglycinate hydrochloride (**4a**, 6.0 g, 0.02 mol) and potassium thiocyanate (2.3 g, 0.024 mol) in water (6 ml) was heated at 80—90 °C for 4 h, then the mixture was cooled in an ice bath and the resulting precipitates were filtered off by suction and washed with cold water. Recrystallization from MeOH gave methyl 2-mercapto-4-phenylimidazole-5-carboxylate (**5a**) as colorless prisms (4.3 g, 92%). NMR (in DMSO-d_6) δ: 12.65 (2H, br s, NH and SH), 7.9—7.3 (5H, m, arom-H), 3.72 (3H, s, CH_3).

Other methyl 2-mercaptoimidazole-5-carboxylates (**5**) were prepared in the same way. The results are

Table III. Properties of Methyl 5-Substituted Oxazole-4-carboxylates (**3**)

3	Yield (%)	mp (°C)	IR ν_{max}^{Nujol} cm^{-1}	NMR δ in $CDCl_3$	
				CH=N (s, 1H)	OMe (s, 3H)
l	82	Syrup[a]	3125, 1720, 1610	7.83	4.43
m	55	Syrup[a]	3160, 1730, 1610	7.95	3.90
n	84	Syrup[a]	3160, 1730, 1608	8.04	3.93
o	84	Syrup[a]	3140, 1720, 1607	7.75	3.85
r	70	62—64[b]	3140, 1700, 1590	7.85	4.00
s	42	82—84[c]	3120, 1730, 1620	8.06	3.97

a) Purified by column chromatography.
b) *Anal.* Calcd for $C_9H_7NO_3S$: C, 51.67; H, 3.27; N, 6.70. Found: C, 51.47; H, 3.28; N, 6.68.
c) *Anal.* Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.65; H, 3.87; N, 13.83.

TABLE IV. Properties of *C*-Acylamino Acid Methyl Ester Hydrochlorides (**4**)

4	R	Yield (%)	mp (°C) (dec.)	IR ν_{max}^{Nujol} cm^{-1}	Formula	Analysis (%) Calcd (Found)		
						C	H	N
a	Ph	80	185—186[a]					
d	4-F–Ph	75	183—184	1743, 1695	$C_{10}H_{11}ClFNO_3$	48.50	4.48	5.66
						(48.46	4.43	5.66)
e	2-Cl–Ph	48	158—161	1762, 1709	$C_{10}H_{11}Cl_2NO_3$	45.48	4.20	5.30
						(45.67	4.03	5.24)
g	4-Cl–Ph	60	182—185	1740, 1690	$C_{10}H_{11}Cl_2NO_3$	45.48	4.20	5.30
						(45.53	4.17	5.30)
h	4-Me–Ph	76	142—144	1740, 1685	$C_{11}H_{14}ClNO_3$	54.22	5.79	5.75
						(54.11	5.75	5.89)
k	4-MeO–Ph	67	165—166	1740, 1678	$C_{11}H_{14}ClNO_4$	50.87	5.43	5.39
						(50.85	5.39	5.35)
l	Ph–CH_2	51	168—169	1738, 1675	$C_{11}H_{13}ClNO_3$	54.22	5.79	5.75
						(54.35	5.82	6.90)
p	2-Furyl	89	181—183	1750, 1677	$C_8H_{10}ClNO_4$	43.75	4.59	6.38
						(43.52	4.58	6.54)
q	2-Thienyl	79	172—173	1753, 1660	$C_8H_{10}ClNO_3S$	40.77	4.28	5.94
						(40.36	4.27	5.94)

a) Lit.[2] mp 185—186 °C.

summarized in Table I.

Typical Procedure for Preparation of 2-Mercaptoimidazole-5-carboxylic Acids (7)——A solution of **5a** (5.0 g, 0.021 mol) and 8% NaOH (30 ml) was stirred for 18 h at room temperature, then 6 N HCl was added to the mixture to adjust the pH to 3 and the resulting precipitates were filtered off by suction. Recrystallization from MeOH gave 2-mercapto-4-phenylimidazole-5-carboxylic acid (**7a**) as colorless needles (3.6 g, 81.6%). NMR (in DMSO-d_6) δ: 12.85 (1H, br s, COOH), 12.55 (1H, br s, NH), 7.8—7.3 (5H, m, arom-H).

Other 2-mercaptoimidazole-5-carboxylic acids (**7**) were prepared in the same way. The results are summarized in Table I.

Methyl 1-(4-Chlorobenzoyl)-1-thioureidoacetate (10)——A mixture of **4g** (2.64 g, 0.03 mol) and sodium thiocyanate (2.42 g, 0.03 mol) in water (40 ml) was heated at 40—50 °C for 3 h under stirring, then the crystals formed were filtered off by suction and recrystallized from MeOH to give **10** as colorless prisms (2.4 g, 84%), mp 220—222 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3250, 3230, 3100, 1730, 1695, 1640. NMR (in $CDCl_3$+DMSO-d_6) δ: 12.80 (3H, br s, thiourea), 7.70 and 7.45 (4H, A_2B_2q, J=9 Hz, arom-H), 3.78 (3H, s, CH_3). *Anal.* Calcd for $C_{11}H_{11}ClN_2O_3S$: C, 46.08; H, 3.87; N, 9.77; Cl, 12.37; S, 9.42. Found: C, 46.12; H, 3.57; N, 9.64; Cl, 12.54; S, 9.98.

Methyl 4-(4-Chlorophenyl)-2-mercaptoimidazole-4-carboxylate (5g)——A mixture of **10** (0.57 g, 0.002 mol) and AcOH (10 ml) was refluxed for 1 h, then the solvent was removed *in vacuo*. The resulting crystals were washed with sat. $NaHCO_3$ and then recrystallized from MeOH to give **5g** as colorless prisms (0.5 g, 93%). This product was identical with **5g** directly derived from **4g** in physicochemical properties.

General Procedure for Preparation of 2-Mercapto-4-substituted Imidazole (8)——Method A: A 2-mercapto-4-substituted imidazole-5-carboxylic acid (**7**, 0.01 mol) was added to preheated glycerin (25 ml) at 180—200 °C under a nitrogen atmosphere and the mixture was stirred for 30 min at the same temperature. The reaction mixture was cooled, ice water (70 ml) was added, and the resulting precipitates were filtered off by suction and washed with cold water. Recrystallization from 50% aqueous MeOH gave the corresponding 2-mercapto-4-substituted imidazole (**8**) as summarized in Table II.

Method B[10]: A mixture of an amino ketone (**9**, 0.02 mol) and potassium thiocyanate (2.3 g, 0.024 mol) in water (6 ml) was heated at 80—90 °C for 4 h, then the mixture was cooled at 0 °C and the resulting precipitates were filtered off by suction and washed with cold water. Recrystallization from 50% aqueous MeOH gave the corresponding 2-mercapto-4-substituted imidazole (**8**) as summarized in Table II.

4-(4-Chlorophenyl)-2-mercaptoimidazole-5-carboxylic Acid (7g)——A mixture of **10** (0.57 g, 0.002 mol), NaOH (0.32 g, 0.008 mol), water (2 ml), and MeOH (10 ml) was heated at 60—70 °C for 2 h, then the MeOH was evaporated off *in vacuo* and 10% HCl was added to the residue to neutralize it. The resulting precipitates were filtered off by

TABLE V. Properties of α-Amino Ketone Hydrochlorides (**9**)

3 $\xrightarrow{\text{method A}}$ R–CO–$CH_2NH_2 \cdot HCl$ (**9**) $\xleftarrow{\text{method B}}$ **4**

9	Method	Yield (%)	mp (°C) (dec.)	IR ν_{max}^{Nujol} cm^{-1}, CO	Formula	Analysis (%) Calcd (Found)		
						C	H	N
a	B	92	190—191[a]	1700				
b	A	83	206—208	1680	C_8H_9ClFNO	50.67	4.78	7.38
						(50.43	4.91	7.36)
c	A	99	153—157	1680	C_8H_9ClFNO	50.67	4.78	7.38
						(50.32	4.76	7.35)
d	A	60	237—240	1690	C_8H_9ClFNO	50.67	4.78	7.38
						(50.75	4.71	7.42)
e	B	92	171—172	1697	$C_8H_9Cl_2NO$	46.63	4.40	6.80
						(46.50	4.33	6.86)
f	B	93	220—221	1687	$C_8H_9Cl_2NO$	46.63	4.40	6.80
						(47.04	4.51	6.82)
g	B	96	263—265[b]	1680	$C_8H_9Cl_2NO$	46.63	4.40	6.80
						(46.47	4.36	6.77)
h	B	94	205[c]	1680	$C_9H_{12}ClNO$	58.22	6.52	7.54
						(58.24	6.47	7.54)
i	A	61	184—189	1685	$C_{11}H_{16}ClNO$	61.82	7.55	6.55
						(61.78	7.36	6.41)
j	B	65	205	1683	$C_{12}H_{18}ClNO$	63.29	7.97	6.15
						(63.38	7.92	6.05)
k	A	81	202—204[d]	1640	$C_9H_{12}ClNO_2$	53.60	6.00	6.95
						(53.55	6.00	7.05)
l	B	64	199—201[e]	1723				
m	A	32	167—169	1727	$C_9H_{11}ClFNO$	53.08	5.44	6.88
						(52.87	5.37	6.93)
n	B	59	206—207	1723	$C_9H_{11}Cl_2NO$	49.11	5.04	6.36
						(49.05	5.02	6.35)
o	A	63	111—114	1720	$C_{10}H_{14}ClNO$	60.15	7.07	7.01
						(60.01	6.87	7.36)
p	B	98	211—213	1730	$C_6H_8ClNO_2$	41.04	4.59	7.98
						(40.72	4.41	7.82)
q	B	91	253—256	1670	C_6H_8ClNOS	37.60	4.21	7.31
						(37.45	4.03	7.20)
r	A	99	179—180	1685	C_6H_8ClNOS	37.60	4.21	7.31
						(37.50	4.03	7.15)
s	A	51	234—245	1710	$C_7H_9ClN_2O$	48.71	5.26	16.23
						(48.53	5.18	16.04)

a) Lit.[2] mp 190—191 °C (dec.).
b) Lit.[15] mp 270—271 °C (dec.).
c) Lit.[15] mp 206—207 °C (dec.).
d) Lit.[15] mp 204 °C (dec.).
e) Lit.[2] mp 200—202 °C (dec.).

suction and recyrstallized from MeOH to give **7g** as colorless prisms (0.4 g, 80%), mp 278—280 °C (dec.). This product was identical with **7g** derived by the hydrolysis of the ester compound (**5g**) in physicochemical properties.

Antiinflammatory Activity Testing——Male Sprague Dawley rats (Charles River, 180 to 190 g) were fasted overnight before use. One hour after oral administration of a test drug (6 to 8 rats/group), 0.05 ml of 1.0% solution of carrageenan (Sigma) was injected into the subplantar pad of the left hind paw. The paw volume was measured by a water displacement technique just before (V_0) and 4 h after (V_4) the carrageenan injection. The percent inhibition of the edema volume was calculated according to the following formula:

$$\% \text{ inhibition} = \left(1 - \frac{V_{4:\text{test}} - V_{0:\text{test}}}{V_{4:\text{cont}} - V_{0:\text{cont}}}\right) \times 100$$

The test compounds (50 ml/kg) were suspended in 0.25% critical micelle concentration (cmc) solution and administered through a metal stomach tube at a volume of 1.0 ml/100 g body weight. Control animals received the vehicle only.

Acute Toxicity——Male ddY mice (Shizuoka Agricultural Coop., 18 to 22 g) were fasted overnight before use. The test compounds (1000 mg/kg) were suspended in 0.25% cmc solution and administered orally (1.0 ml/100 g b.w.). Animals were observed for a 7-day period after a single oral administration of the test compounds.

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References and Notes

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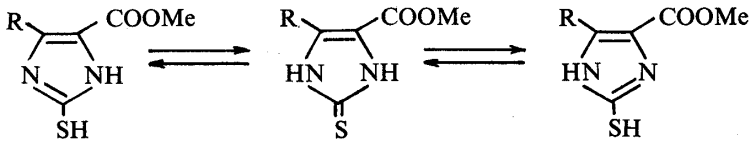
6) The resulting imidazole compounds (**5**) can be regarded as tautomers of 2-mercaptoimidazole and 2(3*H*)-imidazolethione. Moreover, depending upon the position of the imino hydrogen, the nomenclature of the compounds (**5**) should be assigned as methyl 2-mercapto 4(or 5)-substituted-5-(or 4)imidazolecarboxylate.



a b c

In this paper, we adopt the mercaptoimidazole tautomeric form (a) for convenience.
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