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Syntheses of 2-Aryl-4-(3-thienyl)imidazole Derivatives with Antiinflammatory Properties[1)]

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A series of 2-substituted 4-(3-thienyl)imidazoles (**6**, **11**, and **14**) was synthesized and evaluated for antiinflammatory activity. Among them, **6g**, **14a**, and **14g** exhibited strong activity, comparable to that of ibuprofen. The acute toxicity and the ulcerogenicity were low as compared with those of standard acidic antiinflammatory agents. The structure–activity relationships are discussed.

Keywords——3-thiophenecarbonylmethylamine; *N*-aroyl-3-thiophenecarbonylmethylamine; 2-substituted 4-(3-thienyl)imidazole; 2-aryl-4-(3-thienyl)-5-alkylimidazole; alkylation; antiinflammatory activity; ulcerogenicity

Many kinds of nonsteroidal antiinflammatory agents have been reported, and those having an acidic moiety often exhibit gastrointestinal toxicities. A chief object of recent studies, therefore, has been the search for a safe drug without this characteristic side effect.[3)] In this context, nonacidic imidazole derivatives have been studied.[4)] We have also been interested in imidazole derivatives, and reported the synthesis of various 2-mercaptoimidazoles **2** with antiinflammatory activities in our preceding paper.[5)] We found that the derivatives **3** having a 3-thienyl moiety at the 4 position of the imidazole moiety showed considerably stronger activity than mefenamic acid.

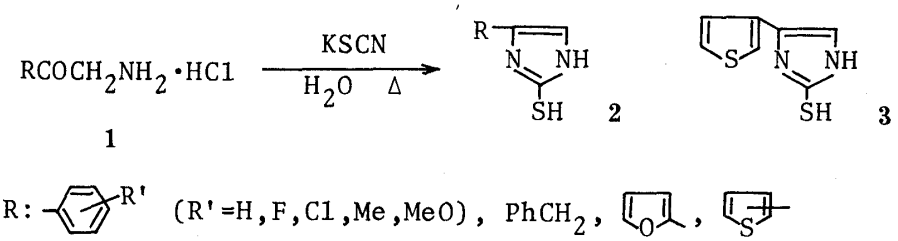


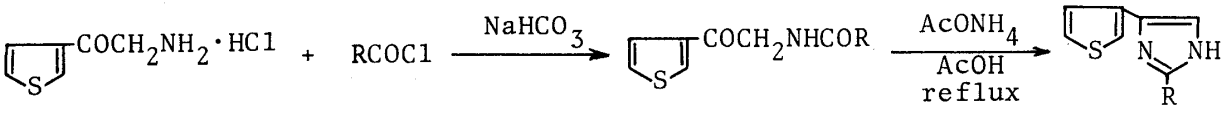
Chart 1

As a continuation of that study, we synthesized more imidazole analogs containing a 3-thienyl moiety and evaluated their antiinflammatory activities. It was found that 2-aryl-4-(3-thienyl)-5-alkyl(alkenyl)imidazoles[6)] exhibited good antiinflammatory activity.

Structure and Activities

2-Substituted 4-(3-Thienyl)imidazoles——We synthesized a series of 2-substituted 4-(3-thienyl)imidazoles in which the mercapto group at the 2-position of the former imidazole compound **3** was replaced by other substituents such as aryl, hetaryl, and alkyl groups. First, 3-thiophenecarbonylmethylamine hydrochloride (**4**)[5)] as the starting material was led to the corresponding N-acyl derivatives **5** under the Schotten–Baumann conditions using various

acyl halides in high yields (Table VI).[7] Subsequently, the *N*-acylamino ketones **5** were converted to the desired 2-substituted 4-(3-thienyl)imidazoles **6** by the conventional treatment[8] as shown in Chart 2 (Table I).



4 **5a—p** **6a—p**

a—p: see Table I

Chart 2

TABLE I. Physicochemical Properties and Antiinflammatory Activity of 4-(3-Thienyl)imidazoles **6**

6	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)				AI[a]
					C	H	N	S	
6a	iso-Pr	81	106—108	$C_{10}H_{12}N_2S$	62.46	6.29	14.57	16.68	−
					(62.37	6.51	14.52	16.53)	
6b		62	150—151	$C_{12}H_{14}N_2S$	66.02	6.46	12.83	14.69	±
					(66.15	6.47	12.96	14.72)	
6c	 [b]	47	219—220 (dec.)	$C_{13}H_{16}N_2S \cdot HCl$	58.09	6.37	10.42	11.93	−
					(58.21	6.33	10.32	11.68)	
6d	C_6H_5	54	151—153	$C_{13}H_{10}N_2S \cdot H_2O$	63.91	4.95	11.47	13.12	±
					(63.88	4.60	11.42	13.07)	
6e	2-F-C_6H_4	63	126—128	$C_{13}H_9FN_2S$	63.92	3.71	11.47	13.13	−
					(63.89	3.76	11.73	13.02)	
6f	2-Cl-C_6H_4	55	111—114	$C_{13}H_9ClN_2S \cdot H_2O$	56.01	3.98	10.05	11.50	−
					(55.88	3.68	10.24	11.51)	
6g	4-F-C_6H_4	54	178—180	$C_{13}H_9FN_2S$	63.92	3.71	11.47	13.13	+++
					(63.74	3.64	11.65	13.28)	
6h	4-Cl-C_6H_4	67	177—179	$C_{13}H_9ClN_2S$	59.88	3.48	10.74	12.30	+++
					(60.03	3.76	10.76	12.28)	
6i	4-Br-C_6H_4	54	199—200	$C_{13}H_9BrN_2S$	51.15	2.97	9.18	10.51	++
					(51.09	3.33	9.18	10.44)	
6j	4-Me-C_6H_4	53	162—164	$C_{14}H_{17}N_2S$	69.97	5.03	11.66	13.34	+
					(70.07	5.14	11.55	13.45)	
6k	4-MeO-C_6H_4	57	142—143	$C_{14}H_{12}N_2OS$	65.60	4.72	10.93	12.51	+
					(65.54	4.84	10.92	12.49)	
6l	3-CF_3-C_6H_4	60	148—151	$C_{14}H_9F_3N_2S$	57.14	3.08	9.52	10.09	−
					(56.92	3.23	9.51	10.23)	
6m	3-Pyridyl	43	193—197	$C_{12}H_9N_3S$	63.41	3.99	18.49	14.17	+
					(63.32	4.17	18.13	14.52)	
6n	2-Thienyl	60	215—216	$C_{11}H_3N_2S_2 \cdot 1/2\,H_2O$	54.74	3.76	11.08	26.57	+
					(54.69	3.67	11.48	26.38)	
6o	3-Thienyl	64	210—211	$C_{11}H_8N_2S_2$	56.87	3.47	12.06	27.60	+
					(56.79	3.82	11.73	26.98)	
6p	5-Cl-3-Thienyl	31	159—164	$C_{11}H_7ClS_2$	49.52	2.64	10.50	24.04	+
					(49.38	2.63	10.53	24.32)	
2-Mercapto-4-(3-thienyl)imidazole (**3**)									++[3]

a) AI: Antiinflammatory activity represented by the ED_{30} value (mg/kg, *p.o.*) for rat carrageenan-induced paw edema; +++ 10—19.9, ++ 20—29.9, + 30—39.9, ± 40—50, − >50. *b*) HCl salt.

The various thienylimidazoles **6** thus obtained were examined for antiinflammatory activities on carrageenan-induced paw edema in rats by oral administration. These results are summarized in Table I. Compounds **6g** and **6h** bearing a 4-halogenophenyl moiety at the 2

position on the imidazole ring exhibited significantly stronger activity than the 2-mercaptoimidazole **3**. In contrast, other aromatic and heteroaromatic substituents at the 2 position (*i.e.* **6d** and **6j**—**p**) diminished the activity in comparison with that of **3**. On the other hand, the imidazole derivatives **6a**—**c**, **6e**, and **6f** substituted with alkyl or 2-halogenophenyl groups at the 2 position scarcely showed activity at the dose of 50 mg/kg, *p.o.* The 4-fluorophenyl **6g** and 4-chlorophenyl **6h** derivatives having strong antiinflammatory activity were subjected to an analgesic test by the phenylquinone writhing method. The 4-fluoro compound **6g** exhibited a marked analgesic effect (ED_{50}: 28 mg/kg, *p.o.*) in mice, while the 4-chloro compound **6h** was considerably weaker (ED_{50}: 150 mg/kg, *p.o.*). Therefore, 2-(4-fluorophenyl)-3-thienylimidazole (**6g**) was selected as the most effective compound from a series of 2-substituted imidazole derivatives **6**.

Further modifications of the thienylimidazole **6g** were made in order to clarify the structure–activity relationships. For example, 2-(4-chlorophenyl)-4-phenyl (**8a**) and 2-(4-fluorophenyl)-4-(2-thienyl)imidazoles (**8b**) in which the 3-thienyl group of **6g** or **6h** was replaced by a phenyl or a 2-thienyl group, were synthesized from the corresponding N-acyl compounds **7** in a similar way, as shown in Chart 2 (Table II). Furthermore, 2-(3-thienyl)-4-(4-fluorophenyl)imidazole (**8c**), in which the substituents at the 2 and 4 positions of **6g** are interchanged, was also synthesized from the 4-fluorobenzoylmethylamine derivative **7c**[7] in good yield. On the other hand, in order to confirm the importance of the imidazole skeleton

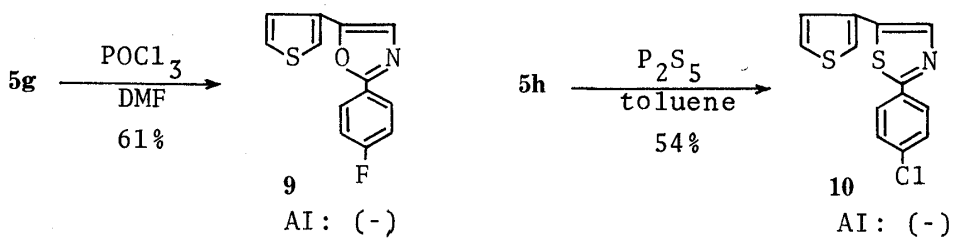
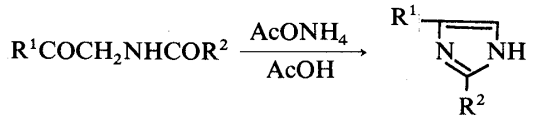


Chart 3

TABLE II. Physicochemical Properties and Antiinflammatory Activity of 2,4-Disubstituted Imidazoles **8**



7a—e **8a—e**

8	R^1	R^2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)				AI[a]
						C	H	N	S	
8a	C_6H_5	4-Cl-C_6H_4	75	197—198	$C_{15}H_{11}ClN_2$	70.73	4.35	11.00		—
						(70.70	4.44	10.78)		
8b	2-Thienyl	4-F-C_6H_4	56	185—187	$C_{13}H_9FN_2S$	63.92	3.71	11.47	13.13	—
						(63.73	3.91	11.42	13.32)	
8c	4-F-C_6H_4	3-Thienyl	67	197—198	$C_{13}H_9FN_2S$	63.92	3.71	11.47	13.13	—
						(63.78	3.81	11.52	13.33)	
8d	5-Cl-3-Thienyl	4-F-C_6H_4	46	198—200 (dec.)	$C_{13}H_8ClFN_2S$	56.02	2.89	10.05	11.50	++
						(56.21	2.77	10.31	11.62)	
8e	5-Br-3-Thienyl	4-F-C_6H_4	36	204—205	$C_{13}H_8BrFN_2S$	48.31	2.50	8.67	9.92	++
						(48.52	2.55	8.73	10.03)	

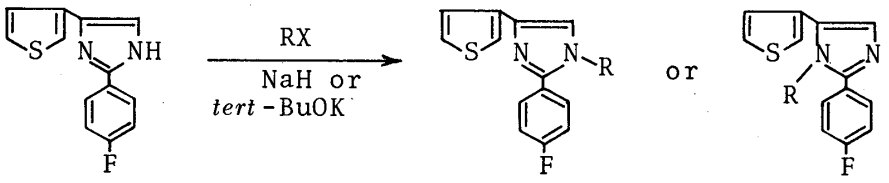
a) AI: Antiinflammatory activity represented by the ED_{30} value (mg/kg, *p.o.*) for rat carrageenan-induced paw edema; +++ 10—19.9, ++ 20—29.9, + 30—39.9, ± 40—50, − >50.

for the activity, the oxazole **9** and thiazole **10** congeners corresponding to **6g** and **6h** were synthesized by the reactions of *N*-aroyl-3-thiophenecarbonylmethylamines **5g** and **5h** with phosphoryl chloride[7] or phosphorus pentasulfide,[9] respectively. Antiinflammatory tests of **8a—c**, **9**, and **10** indicated that these modifications resulted in considerable loss of activity. Thus, it is clear that the imidazole moiety of 2-(4-halogenophenyl)-4-(3-thienyl)imidazole **6g—j** is essential for the antiinflammatory activity in this series.

We continued with the syntheses of **8d** and **8e**, introducing a chloro or bromo group onto the thienyl ring of **6g**, in order to examine some substituent effects. These compounds **8d** and **8e** were prepared from the corresponding *N*-acylamino ketones **7d** and **7e** by a method similar to that used for **6**. From the results of the bioassay, it was found that the introduction of a substituent onto the thienyl ring slightly diminished the antiinflammatory activity (Table II).

N-Substituted 3-Thienylimidazole Compounds——In order to investigate the effect of the NH group in the imidazole skeleton, various substituents were introduced onto the NH group of **6g** by using alkyl halides and acyl chlorides in the presence of NaH or *tert*-BuOK in tetrahydrofuran (THF) or dimethylformamide (DMF), as summarized in Table III (Chart 4).

All the N-substituted products were found to be single isomers from the nuclear magnetic resonance (NMR) spectra, but the structural elucidation of the imidazole compounds **11** or **12**



6g **11a—h** **12a—h**

a—h: see Table III

Chart 4

TABLE III. Physicochemical Properties and Antiinflammatory Activity of N-Substituted 4-(3-Thienyl)imidazoles **11** or **12**

11 or 12	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)				AI[a]
					C	H	N	S	
a	Me	81	143—145	$C_{14}H_{11}FN_2S$	65.09 (64.98	4.29 4.31	10.85 10.99	12.41 12.35)	±
b	Et	62	90—92	$C_{15}H_{13}FN_2S$	66.15 (65.80	4.81 4.81	10.29 10.43	11.77 11.97)	−
c	*n*-Bu	75	Syrup[b]						−
d	$C_6H_5CH_2$	67	125—126	$C_{20}H_{15}FN_2S$	71.83 (71.69	4.52 4.52	8.38 8.26	9.59 9.42)	+
e	COMe	52	Syrup[c]						++
f	COOEt	62	88—89	$C_{16}H_{13}FN_2O_2S$	60.75 (60.58	4.14 4.35	8.86 8.99	10.14 10.43)	+++
g	C_6H_5CO	34	135—137	$C_{20}H_{13}FN_2OS$	68.95 (68.90	3.76 4.07	8.04 8.12	9.20 9.17)	++
h	SO_2Me	19	175—183 (dec.)	$C_{14}H_{11}FN_2O_2S_2$	52.16 (52.12	3.44 3.62	8.69 8.82	19.89 19.90)	−

a) AI: Antiinflammatory activity represented by the ED_{30} value (mg/kg, *p.o.*) for rat carrageenan-induced paw edema; +++ 10—19.9, ++ 20—29.9, + 30—39.9, ± 40—50, − >50. *b*) This compound was isolated by column chromatography using $CHCl_3$ as the eluent; IR ν_{max}^{film} cm^{-1}: 1605, 1595. MS *m/e*: 300 (M^+). *c*) This compound was isolated by column chromatography using $CHCl_3$ as the eluent; IR ν_{max}^{film} cm^{-1}: 1740, 1605, 1595. MS *m/e*: 244 (M^+).

was not attempted in this study. The antiinflammatory activities of these compounds **11** or **12** were also examined. The N-alkyl compounds **11a—d** or **12a—d** showed remarkably reduced activity; on the other hand, the N-acyl compounds **11e—g** or **12e—g**, showed activity almost as strong as that of the unsubstituted compound **6g**. The results may be explained as follows: the amide (C–N) bond (acetyl, ethoxycarbonyl, or benzoyl group) of **11e—g** or **12e—g** would be cleaved in the body of the rat, generating the original imidazole derivative **6g**, which exhibits the activity.

5-Alkyl Substituted Imidazole Compounds——To obtain more effective agents, the introduction of alkyl groups at the 5 position of the imidazole compound **6g** was performed. A variety of 5-alkylimidazole derivatives **14** were synthesized as follows: *N*-4-fluoro- and 4-chlorobenzoyl-3-thiophenecarbonylmethylamines (**5g** and **5h**) were allowed to react with

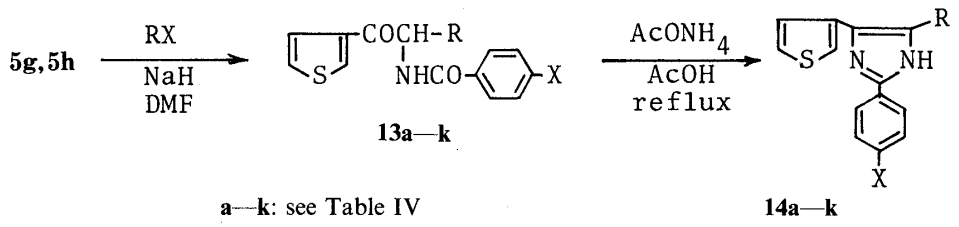


Chart 5

various alkyl halides in the presence of NaH in DMF to afford the corresponding C-alkyl derivatives **13** in good yields (Table VII). In this reaction, the expected C-alkylation predominantly proceeded and undesired products such as N- or O-alkylated compounds were scarcely formed.[7] Subsequently, **13** was converted to 2-(4-fluoro- or 4-chlorophenyl)-4-(3-thienyl)-5-alkylimidazoles **14** with ammonium acetate ($AcONH_4$) by the conventional method[8] as shown in Chart 5. These results are summarized in Table IV. Similarly, the antiinflammatory activities of these compounds were examined. As shown in Table IV, the imidazole derivatives **14a—d**, **14g**, and **14h** substituted by lower alkyl groups such as methyl, propyl, or allyl exhibited strong activities. In particular, the 5-methyl derivative **14a** was more effective than the unsubstituted compound **6g**, while the butyl or cyclohexyl group of **14f** and **14k** reduced the antiinflammatory effect. From these results, it was concluded that the introduction of a lower alkyl group at the 5 position of the imidazole skeleton tends to increase the antiinflammatory activity.

Biological Evaluations——The 3-thienyl imidazole derivatives **6g**, **14a**, and **14g** showed very strong antiinflammatory activity against carrageenan-induced rat paw edema. The ED_{30} values of these compounds were 15, 12, and 16 mg/kg, *p.o.*, respectively. More detailed pharmacological examinations of these compounds were performed in comparison with some non steroidal antiinflammatory drugs (NSAIDs).

Analgesic activities were estimated by two different methods: the phenylquinone-induced writhing test in mice and the Randall–Selitto test in rats. The 5-allylimidazole **14g** exhibited a very strong analgesic effect in the Randall–Selitto test, whereas **6g** showed hardly any activity. On the other hand, **14a** showed strong activity (similar to that of ibuprofen) in both analgesic tests.

Moreover, the ulcerogenic activity of these compounds was examined by using restraint and water-immersion-stressed mice. There were no detectable gastric ulcers in the mice given these derivatives at the dose level of 500 mg/kg, *p.o.* On the other hand, the acidic NSAIDs such as indomethacin, ibuprofen, and mefenamic acid showed ulcerogenic activity at much lower doses (0.2—35 mg/kg, *p.o.*).

Furthermore, in the acute toxicity test, these compounds did not kill any animals at the maximal dose given (1 g/kg, *p.o.*).

TABLE IV. Physicochemical Properties and Antiinflammatory Activity of 5-Substituted 4-(3-Thienyl)imidazoles **14**

14	R	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)				AI[a]
						C	H	N	S	
14a	Me	F	86	171—172	$C_{14}H_{11}FN_2S$	65.09 (65.28	4.29 4.48	10.85 10.91	12.41 12.46)	+++
14b	Et	F	71	155—157	$C_{15}H_{13}FN_2S$	66.15 (66.05	4.81 4.71	10.29 10.41	11.77 11.75)	+++
14c	Et	Cl	64	195—196	$C_{15}H_{13}ClN_2S$	62.38 (62.23	4.54 4.49	9.70 9.76	11.10 11.09)	+++
14d	*n*-Pr	F	49	135—137	$C_{16}H_{15}FN_2S$	67.11 (67.38	5.28 5.31	9.78 9.76	11.20 11.32)	+++
14e	iso-Pr	F	85	182—184	$C_{16}H_{15}FN_2S$	67.11 (67.38	5.28 5.31	9.78 9.76	11.20 11.32)	++
14f	*n*-Bu	F	80	140—142	$C_{17}H_{17}FN_2S$	67.97 (68.00	5.70 5.78	9.32 9.35	10.67 10.75)	+
14g	$CH_2=CHCH_2$	F	76	144—145	$C_{16}H_{13}FN_2S$	67.58 (67.50	4.61 4.51	9.85 9.95	11.28 11.11)	+++
14h	$CH_2=CHCH_2$	Cl	66	150—152	$C_{16}H_{13}ClN_2S$ $1/3\,H_2O$	62.64 (62.50	4.49 4.68	9.13 8.95	10.45 10.48)	+++
14i	$CH_2=C(Me)CH_2$	F	91	173—174	$C_{17}H_{15}FN_2S$	68.43 (68.52	5.07 5.13	9.39 9.22	10.75 10.71)	++
14j	$CH\equiv CCH_2$	F	39	227—229	$C_{16}H_{11}FN_2S$	68.06 (68.32	3.93 3.91	9.92 9.68	11.36 11.32)	±
14k		F	61	171—172	$C_{19}H_{19}FN_2S$	69.90 (69.62	5.87 5.79	8.58 8.55	9.82 9.60)	−

a) AI: Antiinflammatory activity represented by the ED_{30} value (mg/kg, *p.o.*) for rat carrageenan-induced paw edema; +++ 10—19.9, ++ 20—29.9, + 30—39.9, ± 40—50, − >50.

TABLE V. Pharmacological Properties of Thienylimidazoles[a]

Antiinflammatory agent	AI ED_{30}	Analgesic PQ-W[b] ED_{50}	Analgesic R.S[c] ED_{30}	Ulcerogenicity UD_2	Acute toxicity LD_{50}
6g	15	28	>200	>500	>1000
14a	12	16	10	>500	>1000
14g	16	80	1	>500	>1000
Mefenamic acid	33	57	59	35	1880
Ibuprofen	16	15	40	7	1300
Indomethacin	3	3	2	0.2	32

a) Data are shown as mg/kg, *p.o.* *b*) Phenylquinone writhing method. *c*) Randall–Selitto method.

From these results (Table V), it was concluded that these imidazole derivatives **6g**, **14a**, and **14g** showed strong antiinflammatory and analgesic activities, comparable to those of ibuprofen. Moreover, the acute toxicity was weak and the ulcerogenicity was very low.

At present, further detailed pharmacological tests are being performed in order to select a candidate for a new and effective antiinflammatory agent from among these imidazole compounds.

Experimental

Melting points, which were measured with a Yamato melting point apparatus, are uncorrected. The infrared (IR) spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. The NMR spectra were obtained using a Hitachi Perkin-Elmer R-20A high-resolution NMR spectrometer with tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a Hitachi RMU-6M spectrometer at an ionizing potential of 30 eV. Column chromatography was carried out on silica gel (Kieselgel 60, 0.063—0.200 mm, E. Merck).

3-Thiophenecarbonylmethylamine Hydrochloride (4)——This compound was prepared by acid hydrolysis of 5-(3-thienyl)oxazole-4-carboxylate according to our previous report.[5] The newly prepared 5-halogeno substituted compounds showed the following physicochemical properties.

5-Chloro-3-thiophenecarbonylmethylamine Hydrochloride: mp 206—207 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1665, 1595. NMR (DMSO-d_6) δ: 8.6 (3H, br, NH_2HCl), 8.59 (1H, d, J=1.5 Hz, thiophene-H), 7.57 (1H, d, J=1.5 Hz, thiophene-H), 4.43 (2H, s, CH_2). *Anal.* Calcd for $C_6H_7Cl_2NOS$: C, 33.98; H, 3.33; N, 6.60; S, 15.11. Found: C, 34.21; H, 3.18; N, 6.59; S, 14.93.

5-Bromo-3-thiophenecarbonylmethylamine Hydrochloride: mp 184—189 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1685, 1675. NMR (DMSO-d_6) δ: 8.71 (1H, d, J=1.8 Hz, thiophene-H), 8.65 (3H, br, NH_2 HCl), 7.66 (1H, d, J=1.8 Hz, thiophene-H), 4.45 (2H, s, CH_2). *Anal.* Calcd for $C_6H_7BrClNOS$: C, 28.09; H, 2.75; N, 5.46; S, 12.50. Found: C, 28.12; H, 2.66; N, 5.53; S, 12.38.

***N*-Acylaminomethylarylketones (5 and 7)**——These compounds were prepared by N-acylation of the amino ketone hydrochlorides[5] according to our previous report.[7] The properties of **5d**, **5f—h**, **5j**, **5k**, and **7a—c** were reported in that paper.

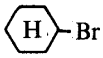
The physicochemical properties of the other new N-acyl products are summarized in Table VI.

Typical Procedure for Preparation of Imidazoles (6 and 8)——$AcONH_4$ (20 g, 0.26 mol) was added gradually to a solution of **5g**[7] (2.63 g, 0.01 mol) and AcOH (2 ml) at 130—140 °C (bath temperature) over a period of 2 h. The reaction mixture was cooled in an ice bath, then AcOEt (100 ml), Et_2O (50 ml), and water (100 ml) were added. The organic layer was separated, washed with water, dried over $MgSO_4$ and then evaporated *in vacuo*. The residue was purified by column chromatography using $CHCl_3$ as an eluent. Recrystallization from a mixture of $CHCl_3$ and

TABLE VI. Physicochemical Properties of *N*-Acyl-3-thiophenecarbonylmethylamines **5**, **7d**, and **7e**

Compd.	Yield (%)	mp (°C)	IR ν_{max}^{Nujol} cm^{-1}	Analysis (%) Calcd (Found)			
				C	H	N	S
5a	95	109—110	3280, 3100, 1687, 1660, 1640, 1560	56.85	6.20	6.63	15.18
				(56.99	6.25	6.58	15.03)
5b	94	109—110	3350, 3100, 1680, 1635	60.73	6.37	5.90	13.51
				(60.67	6.18	6.11	13.38)
5c	90	109—111	3340, 3250, 3100, 1685, 1670, 1630	62.12	6.82	5.57	12.76
				(61.99	7.02	5.38	12.81)
5e	97	121—122	3430, 3100, 1675, 1660, 1650, 1615	59.30	3.83	5.32	12.18
				(59.22	3.81	5.42	12.00)
5i	99	164—166	3350, 1680, 1630, 1590	48.16	3.11	4.32	9.89
				(48.11	3.30	4.29	9.95)
5l	95	118—119	3370, 3110, 1680, 1650, 1644, 1610	53.67	3.22	4.47	10.23
				(53.92	3.33	4.28	10.13)
5m	65	141—142	3300, 3100, 1675, 1625, 1590	58.52	4.09	11.38	13.02
				(58.51	4.22	11.18	12.88)
5n	93	152—154	3380, 3080, 1678, 1635	52.57	3.61	5.57	25.52
				(52.38	3.82	5.51	25.63)
5o	93	125—126	3370, 3100, 1685, 1630	52.57	3.61	5.57	25.52
				(52.51	3.71	5.52	25.38)
5p	93	152—154	3360, 3110, 1685, 1630	46.23	2.82	4.90	22.44
				(46.38	6.81	4.72	22.67)
7d	84	139—141	3400, 3080, 1680, 1640, 1600, 1590	52.44	3.05	4.70	10.77
				(52.19	3.21	4.82	10.68)
7e	96	124—127	3310, 3090, 1685, 1650, 1645, 1605	45.63	2.65	4.09	9.37
				(45.71	2.72	4.22	9.43)

TABLE VII. Physicochemical Properties of *N*-Aroyl-2-(3-thiophenecarbonyl)methylamines **13**

13	RX	Yield (%)	mp (°C)	IR ν_{max}^{Nujol} cm^{-1}	Analysis (%) Calcd (Found)			
					C	H	N	S
13a	MeI	61	99—100	3370, 3100, 1650, 1600	60.63	4.37	5.05	11.56
					(60.59	4.44	5.22	11.75)
13c	EtI	72	114—116	3320, 3100, 1682, 1650, 1600	58.53	4.58	4.55	10.42
					(58.37	4.72	4.56	10.29)
13d	*n*-PrI	68	92—94	3350, 1680 (sh), 1640, 1600	62.93	5.28	4.59	10.50
					(63.21	5.12	4.62	10.38)
13e	iso-PrI	55	114—115	3430, 3120, 1675, 1650, 1600	62.93	5.28	4.59	10.50
					(62.77	5.33	4.63	10.71)
13f	*n*-BuI	71	101—102	3300, 3110, 1684, 1633, 1605	63.93	5.68	4.39	10.04
					(64.00	5.53	4.38	10.17)
13h	$CH_2=CHCH_2Br$	86	91—93	3340, 3120, 1660, 1630, 1595	63.84	4.41	4.38	10.03
					(63.88	4.39	4.21	10.11)
13i	$CH_2=\underset{Me}{C}CH_2Br$	63	114—115	3320, 3090, 1680, 1635, 1608	64.33	5.08	4.41	10.10
					(64.56	5.07	4.19	10.23)
13j	$CH\equiv CCH_2Br$	85	87—89	3300, 3100, 1690, 1642, 1610	63.77	4.01	4.65	10.64
					(63.81	4.22	4.44	10.81)
13k		42	127—129	3150, 1675, 1638, 1605	66.06	5.84	4.06	9.28
					(65.82	5.88	4.21	9.52)

hexane gave **6g** as colorless prisms (1.32 g, 54%), mp 178—180 °C. IR ν_{max}^{Nujol} cm^{-1}: 1610, 1597, 1560, 1510. NMR (DMSO-d_6) δ: 12.50 (1H, br, NH), 7.1—8.2 (8H, m, CH, arom-H, thiophene-H).

Other imidazole compounds **6** and **8** were prepared in the same way. The results are summarized in Tables I and II.

2-(4-Fluorophenyl)-5-(3-thienyl)oxazole (9)——Phosphoryl chloride (2.27 g, 0.015 mol) was added dropwise to a solution of *N*-(4-fluorobenzoyl)aminomethyl(3-thienyl)ketone (**5g**,[7] 3.0 g, 0.011 mol) in DMF (13 ml) at 3—8 °C, and the mixture was stirred overnight at room temperature. Then, the mixture was poured into ice water (50 ml) and the resulting oily products were extracted with AcOEt. The extract was washed successively with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* and the product was separated by column chromatography using $CHCl_3$ as an eluent. Recrystallization from a mixture of AcOEt and hexane gave **9** as colorless prisms (1.7 g, 61%), mp 65—67 °C. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1610, 1600. NMR (DMSO-d_6) δ: 7.2—8.3 (8H, m, CH, arom-H, thiophene-H). *Anal.* Calcd for $C_{13}H_8FNOS$: C, 63.66; H, 3.29; N, 5.71; S, 13.07. Found: C, 63.57; H, 3.41; N, 5.82; S, 12.93.

2-(4-Chlorophenyl)-5-(3-thienyl)thiazole (10)——Phosphorus pentasulfide (3.33 g, 0.015 mol) was added portionwise to a mixture of *N*-(4-chlorobenzoyl)aminomethyl(3-thienyl)ketone (**5h**,[7] 2.8 g, 0.01 mol) and toluene (10 ml) at 100 °C over a period of 10 min. The mixture was refluxed for 2 h, then the reaction mixture was cooled and 10% HCl (30 ml) was added. The insoluble materials were filtered off, and the filtrate was extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and then evaporated *in vacuo*. The residual solid was triturated with hexane, collected by suction, and then recrystallized from a mixture of AcOEt and iso-Pr_2O to give **10** as colorless prisms (1.5 g, 54%), mp 143—144 °C. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1595. NMR ($CDCl_3$+DMSO-d_6) δ: 7.9 and 7.41 (4H, A_2B_2q, J=3 Hz, arom H), 7.78 (1H, s, thiazole-H), 7.2—7.5 (3H, m, thiophene-H). *Anal.* Calcd for $C_{13}H_8ClNS_2$: C, 56.21; H, 2.90; N, 5.04; Cl, 12.76; S, 23.08. Found: C, 56.11; H, 2.84; N, 5.08; Cl, 12.99; S, 22.75.

Typical Procedure for Preparation of N-Substituted 2-(4-Fluorophenyl)-4-(3-thienyl)imidazoles (11 or 12)——**6g** (2.44 g, 0.01 mol) was added gradually to a suspension of NaH (60% in oil, 0.6 g, 0.015 mol) in DMF (20 ml) at 20—25 °C over a period of 15 min, and then methyl iodide (2.13 g, 0.015 mol) was added dropwise. The mixture was stirred for 2 h at room temperature, 10% AcOH was added to neutralize the solution under ice cooling, and the whole was evaporated *in vacuo*. The residue was extracted with AcOEt and the extract was washed with water, dried over $MgSO_4$, and then evaporated *in vacuo*. The residual crystals were recrystallized from a mixture of AcOEt and hexane to give **11a** or **12a** as colorless prisms (2.1 g, 81%), mp 143—145 °C. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1605, 1592. NMR ($CDCl_3$) δ: 6.9—7.8 (8H, m, CH, arom-H, thiophene-H), 3.70 (3H, s, CH_3).

Other N-substituted imidazoles **11** or **12** were prepared in the same way and the results are summarized in Table III.

***N*-Aroyl-2-(3-thiophenecarbonyl)methylamines (13)**——These compounds were prepared by the reaction of **5g** or **5h** with alkyl halides in the presence of NaH in DMF according to the previous report.[7] The properties of **13b** and **13g** were reported in that paper. The physicochemical properties of the other new alkylated products **13** are summarized in Table VII.

Typical Procedure for Preparation of 5-Substituted Imidazoles (14)——Treatment of **13a** (2.77 g, 0.01 mol), $AcONH_4$ (20 g, 0.26 mol), and AcOH (2 ml) as described for the synthesis of **6g** gave **14a** as colorless prisms (2.21 g, 86%), mp 171—172 °C. IR ν_{max}^{Nujol} cm^{-1}: 1610, 1590. NMR (DMSO-d_6) δ: 6.9—8.2 (m, 7H, arom-H, thiophene-H), 2.42 (3H, s, CH_3).

In the same way, **14g** (2.16 g, 76%) was obtained by using **13g** (3.03 g, 0.01 mol), $AcONH_4$ (20 g, 0.26 mol), and AcOH (2 ml), mp 144—145 °C. IR ν_{max}^{Nujol} cm^{-1}: 1640, 1610. NMR ($CDCl_3$) δ: 6.8—7.9 (7H, m, arom-H, thiophene-H), 5.5—6.2 (1H, m, CH=), 4.8—5.2 (2H, m, $=CH_2$), 3.48 (2H, d, J=6 Hz, CH_2).

Other imidazole compounds **14** were prepared in the same way. The results are summarized in Table IV.

Antiinflammatory Activity[10]——The same test as described in the previous paper[5] was employed.

Analgesic Activity——Phenylquinone Writhing Test[11]: Male mice of ddY strain, weighing 18—22 g, were used. The test compound or vehicle (0.25% carboxymethyl cellulose (CMC)) was administered (1 ml/100 g) orally (4—12 animals/group), and 15 min later 0.25 ml of 0.02% phenylquinone solution was injected intraperitoneally. The number of writhes induced in each mouse was observed for a 5 min period beginning 5 min after injection of phenylquinone.

The analgesic activity was expressed in terms of % inhibition (I),

I (%) = (1 − the mean number of writhes in mice administered a test compound/the mean number of writhes in mice administered the vehicle) × 100

The value of ED_{50}, the dose required to produce 50% inhibition, was assessed graphically.

Randall–Selitto Test[12]: Male rats of SD strain, weighing 75—110 g, were used after being fasted overnight. The test compound or vehicle was administered orally (5—10 animals/group) and immediately 0.1 ml of 20% dry yeast suspension was injected into the subplantar area of the left hind paw of each rat. After 2 h, the pain threshold of each foot was measured by means of an analgesia meter (Ugo Basili) and the difference in the threshold between the inflamed foot and the normal foot was calculated.

The analgesic activity was expressed in terms of % inhibition (I),

I (%) = (1 − the mean difference in rats administered a test compound/the mean difference in rats administered the vehicle) × 100

The value of ED_{30}, the dose required to produce 30% inhibition, was assessed graphically.

Ulcerogenic Activity——Male mice of ddY strain, weighing 18—22 g, were used. Immediately after oral administration of a test compound or vehicle (5—10 animals/group), each mouse was restrained in a wire mesh cage, immersed vertically in water at 25 °C for 15 min, and kept at room temperature (23—24 °C) for 105 min. Then the mouse was sacrificed and the stomach was isolated, inflated with saline, immersed in 70% EtOH and opened along the greater curvature. The mucosa was observed under a dissecting microscope and the degree of ulceration was grossly assessed according to an arbitrary scoring system ranging from 0 to 4 (0 = no ulcer, 4 = most severe). The ulcerogenic activity of test compounds was expressed as UD_2, the dose required to produce ulceration assessable as 2.0.

Acute Toxicity——Male mice of ddY strain, weighing 18—22 g, were used. The test compound was administered orally (5—15 animals/group). The animals were kept under observation at 23—24 °C for 1 week, and LD_{50} was determined.[13]

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References and Notes

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