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Syntheses of 3-Substituted Pyrrole Derivatives with Antiinflammatory Activity[1)]

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Various dimethyl 3-substituted pyrrole-2,4-dicarboxylates (**3**) were synthesized by the reaction of methyl isocyanoacetate (**2**) with methyl α-isocyanoacrylates (**5**) in the presence of base. This type of reaction was also applicable to the preparation of 3-substituted pyrrole-2,4-dicarboxamides (**10**) by employing appropriate amide compounds (**8**) or (**9**) and (**12**) as reactants. Hydrolysis followed by decarboxylation of the pyrrole diester compounds (**3**) gave 3-substituted pyrroles (**14**) in good yields. A series of these compounds (**14**) showed antiinflammatory activities against carrageenan-induced rat paw edema. Among the compounds tested, 3-(2-chlorophenyl)pyrrole (**14d**) was found to be more potent than mefenamic acid.

Keywords——isocyano compound; pyrrole synthesis; decarboxylation; antiinflammatory; structure-activity relationship; adrenalectomized rats

Pyrrole compounds have often been isolated from natural sources,[3)] and a great many synthetic studies have been reported.[4)] We previously exploited a one-step synthesis of 3-substituted pyrrole-2,4-dicarboxylic acid diesters using α-isocyanoacetate,[5)] and in preliminary pharmacological screening, it was observed that some compounds obtained by this method possessed antiinflammatory activity. In the present study, we have investigated in detail the syntheses of various kinds of 3-substituted pyrrole derivatives in order to develop a useful antiinflammatory agent.

3-Substituted Pyrrole-2,4-dicarboxylic Acid Derivatives

We previously reported a synthetic method for dimethyl 3-substituted pyrrole-2,4-dicarboxylates (**3**) by the reaction of aldehydes (**1**) with methyl isocyanoacetate (**2**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[5)] By this method (Method A), many pyrrole compounds have been synthesized, though in the case of benzaldehydes substituted by halogens, the yields of the pyrrole compounds were low.

Next, we investigated in detail an alternative synthetic method (Method B) using α-isocyanoacrylate (**5**), a key intermediate for the formation of the pyrroles (**3**),[5b)] as a starting material as shown in Chart 1.

As a typical example, the reaction using methyl α-isocyano-4-chlorocinnamate (**6**), which was synthesized by the method described in the previous paper,[6)] will be described. First,

1) This paper constitutes Part VI of the series entitled "Synthesis of Heterocyclic Compounds using Isocyano Compounds," Part V: K. Nunami, M. Suzuki, and N. Yoneda, *J. Org. Chem.*, **44**, 1887 (1979). This study was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980.

2) Location: *a) 16-89, Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan*; *b) 2-2-50, Kawagishi, Toda, Saitama 335, Japan.*

3) For example: K. Arima, H. Imanaka, K. Kousaka, A. Fukuta, and G. Tamura, *Agr. Biol. Chem.* (Tokyo), **28**, 575 (1964); O. Salcher, F. Lingens, and P. Fischer, *Tetrahedron Lett.*, **1978**, 3097.

4) J.M. Patterson, *Synthesis*, **1975**, 281.

5) *a)* M. Suzuki, M. Miyoshi, and K. Matsumoto, *J. Org. Chem.*, **39**, 1980 (1974); *b)* K. Matsumoto, M. Suzuki, Y. Ozaki, and M. Miyoshi, *Agr. Biol. Chem.* (Tokyo), **40**, 2271 (1976).

6) M. Suzuki, K. Nunami, T. Moriya, K. Matsumoto, and N. Yoneda, *J. Org. Chem.*, **43**, 4933 (1978).

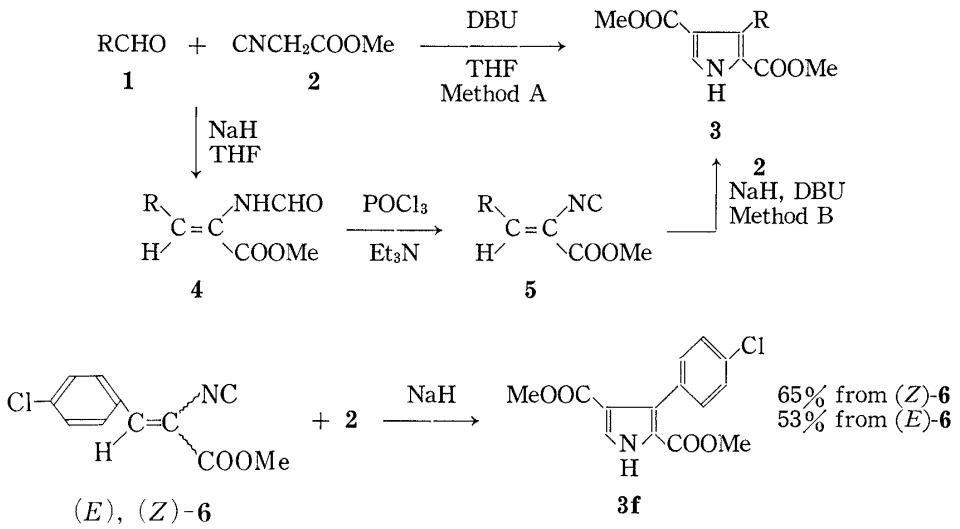


Chart 1

TABLE I. Formation of Dimethyl 3-Substituted Pyrrole-2,4-dicarboxylates (**3**) from (*Z*)-Methyl α-Isocyanoacrylates (**5**) (Method B)

Compd.	R	Yield (%)	mp (°C) [Lit., mp(°C)]	Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
3a	Ph	70[a]	183—184 (183—185[5a])	MeOH				
3b	2-F–Ph	58[b]	145—146	MeOH	$C_{14}H_{12}FNO_4$	60.65 (60.32	4.36 4.49	5.05 5.35)
3c	4-F–Ph	72[a]	179—181	MeOH–Et_2O	$C_{14}H_{12}FNO_4$	60.65 (60.61	4.36 4.30	5.05 5.14)
3d	2-Cl–Ph	56[b]	116—118	Benzene–hexane	$C_{14}H_{12}ClNO_4$	57.25 (57.29	4.12 4.23	4.77 4.73)
3e	3-Cl–Ph	63[b]	136—139	MeOH–H_2O	$C_{14}H_{12}ClNO_4$	57.25 (57.21	4.12 4.25	4.77 4.69)
3f	4-Cl–Ph	70[a] 65[b]	180—183	Benzene	$C_{14}H_{12}ClNO_4$	57.25 (57.42	4.12 4.23	4.77 4.73)
3g	2-Br–Ph	60[b]	117—119	MeOH–H_2O	$C_{14}H_{12}BrNO_4$	49.72 (49.62	3.58 3.64	4.14 4.11)
3h	2,4-diCl–Ph	72[b]	142—143	MeOH–H_2O	$C_{14}H_{11}Cl_2NO_4$	51.24 (51.13	3.38 3.31	4.27 4.17)
3i	2,6-diCl–Ph	42[b]	212—214	MeOH–H_2O	$C_{14}H_{11}Cl_2NO_4$	51.24 (51.22	3.38 3.51	4.27 4.37)
3j	3,4-diCl–Ph	73[b]	159—161	MeOH–H_2O	$C_{14}H_{11}Cl_2NO_4$	51.24 (51.20	3.38 3.44	4.27 4.15)
3k	4-Me_2N–Ph	68[b]	166—169	MeOH	$C_{16}H_{18}N_2O_4$	63.56 (63.43	6.00 5.97	9.27 9.21)
3q	4-Me–Ph	70[a]	157—158 (157—158[5b])	EtOH–H_2O				
3r	4-isoPr–Ph	48[b]	111—113	EtOH–H_2O	$C_{17}H_{19}NO_4$	67.76 (67.70	6.36 6.44	4.65 4.58)
3t	3,4-OCH_2O–Ph	62[a]	175—177 (176—178[5b])	MeOH				
3w	2-Thienyl	72[a]	146—148 (147—148[5b])	EtOH–H_2O				

a) DBU as a base.
b) NaH as a base.

in order to examine the reactivity of the (*E*)- or (*Z*)-isomer, each compound [(*E*)-6, (*Z*)-6] was allowed to react with **2** in the presence of sodium hydride (NaH). As a result, dimethyl 3-(4-chlorophenyl)pyrrole-2,4-dicarboxylate (**3f**) was obtained in 53% and 65% yields from (*E*)-6 and (*Z*)-6, respectively; no marked differences in reactivity of the geometrical isomers were observed. In a similar way, various dimethyl 3-substituted pyrrole-2,4-dicarboxylates (**3**) were prepared by the reaction of **2** with methyl α-isocyanoacrylates (**5**), which were easily derived by the reaction of aldehydes with **2** in the presence of sodium hydride followed by treatment with phosphoryl chloride and triethylamine,[6-8] in the presence of NaH or DBU. These results are summarized in Table I.

Furthermore, we attempted the synthesis of the amide derivatives to obtain higher anti-inflammatory activity. An initial attempt to achieve the direct amidation of pyrrole diester compounds (**3**) with amines in the usual way was unsuccessful because of low reactivity of the ester groups; the starting material (**3**) was recovered. As an alternative method, the reaction using isocyanoacetamide (**8**, **9**) as a starting material was investigated. In fact, reaction of 4-methoxybenzaldehyde with isocyanoacetylpyrrolidine (**8**) in the presence of DBU was attempted according to the one-step pyrrole synthetic method (Method A), but the reaction did not proceed. Next, we attempted a stepwise method *via* α-isocyanocinnamamides (**12**). As a typical example, (*Z*)-α-formylamino-4-chlorocinnamoylpyrrolidine (**11a**) was synthesized by the reaction of **7** (R=4-Cl) with **8** in the presence of NaH in DMF, followed by recrystallization from EtOH. Subsequently compound **11a** was converted to the corresponding α-isocyanocinnamamide (**12a**), which was reacted with **8** in the presence of NaH to afford 3-(4-chlorophenyl)pyrrole-2,4-dicarboxamoylpyrrolidine (**10a**) in good yield. Other pyrrole compounds (**10b**—**d**) having amide groups were similarly prepared, as shown in Chart 2 (Table II).

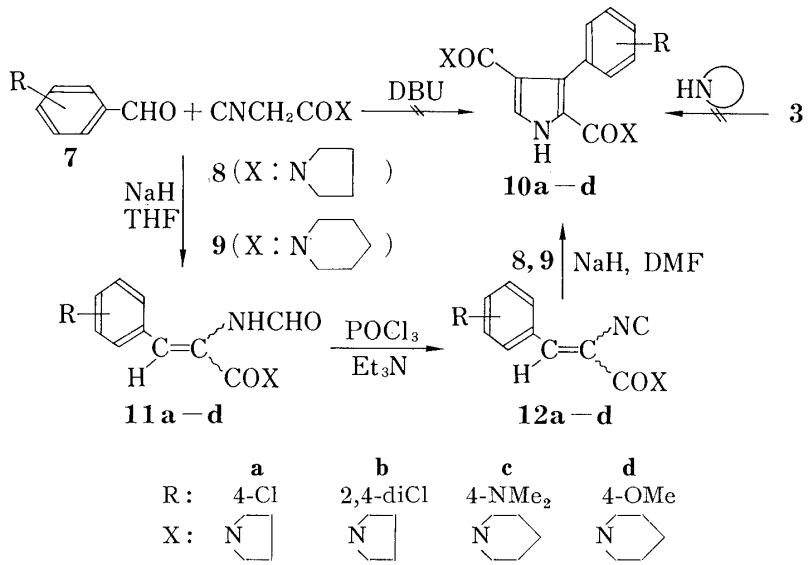


Chart 2

In pharmacological tests, the series of 3-substituted pyrrole-2,4-dicarboxylic acid esters (**3**) and amides (**10**) obtained as described above or by Method A did not exhibit strong anti-inflammatory activity, with only a few exceptions (Table V). Furthermore, we hydrolyzed the pyrrole diester compounds (**3**) to afford pyrrole carboxylic acid compounds (**13**) in the

7) U. Schöllkopf, F. Gerhart, R. Schröder, and D. Hoppe, *Ann. Chem.*, **763**, 1 (1972).
8) M. Suzuki, K. Nunami, K. Matsumoto, N. Yoneda, O. Kasuga, H. Yoshida, and T. Yamaguchi, *Chem. Pharm. Bull.*, **28**, 2374 (1980).

Table II. Formation of 3-Substituted Pyrrole-2,4-dicarboxamides (**10a—d**)

Compd.	Yield (%)	mp (°C)	Recryst. solvent	IR ν_{max}^{Nujol} cm^{-1}	Formula	Analysis (%) Calcd (Found) C	H	N
10a	65	260—262	EtOH	3140, 1610, 1576	$C_{20}H_{22}ClN_3O_2$	64.60 (64.67	5.96 6.13	11.30 11.34)
10b	76	230—231	EtOH	3130, 1615, 1600	$C_{20}H_{21}Cl_2N_3O_2$	59.12 (58.97	5.21 5.48	10.34 10.31)
10c	63	139—142	Benzene	3150, 1620, 1590	$C_{24}H_{32}N_4O_2$	70.56 (70.25	7.90 8.21	13.71 13.94)
10d	79	202—203	AcOEt	3230, 1610, 1595	$C_{23}H_{29}N_3O_3$	69.85 (69.87	7.39 7.45	10.63 10.72)

Table III. Formation of 3-Substituted Pyrrole-2,4-dicarboxylic Acids (**13**)

Compd.	R	Yield (%)	mp[a] (°C, dec.)	IR ν_{max}^{Nujol} cm^{-1}	Formula	Analysis (%) Calcd (Found) C	H	N
13a	Ph	85	210—211	3420, 1675	$C_{12}H_9NO_4$	62.34 (62.21	3.92 3.99	6.06 6.01)
13c	4-F–Ph	85	239—240	3410, 1660	$C_{12}H_8FNO_4$	57.84 (57.80	3.24 3.29	5.62 5.53)
13d	2-Cl–Ph	83	248—249	3320, 1660	$C_{12}H_8ClNO_4$	54.25 (54.23	3.04 3.11	5.27 5.20)
13f	4-Cl–Ph	92	252—254	3420, 1660	$C_{12}H_8ClNO_4$	54.25 (54.03	3.04 3.00	5.27 5.21)
13k	4-Me_2N–Ph	87	236—237	3240, 1660	$C_{14}H_{14}N_2O_4$	61.30 (60.98	5.14 5.31	10.21 10.26)
13r	4-isoPr–Ph	87	204—206	3320, 1660	$C_{15}H_{15}NO_4$	65.92 (65.57	5.53 5.62	5.12 5.14)
13s	4-MeO–Ph	91	229—230	3400, 1655	$C_{13}H_{11}NO_5 \cdot 1/2H_2O$	57.77 (57.87	4.47 4.61	5.18 5.11)
13t	3,4-OCH_2O–Ph	93	223—224	3310, 1670	$C_{13}H_9NO_6 \cdot 1/2H_2O$	54.94 (55.19	3.55 3.72	4.93 4.73)
13u	3-Pyridyl	95	232—233	3410, 1690	$C_{11}H_8N_2O_4 \cdot H_2O$	52.80 (53.10	4.02 4.40	11.19 11.09)
13v	4-Pyridyl	83	255—256	1655	$C_{11}H_8N_2O_4 \cdot 3/4H_2O$	53.77 (53.96	3.58 3.74	11.40 11.49)
13w	2-Thienyl	89	207—209	3420, 1675	$C_{10}H_7NO_4S$	50.63 (50.30	2.97 3.19	5.90 5.84)

a) Recrystallized from MeOH or MeOH–H_2O.

hope of obtaining higher activity (Table III), but satisfactory activity was not observed. Thus, we next attempted the synthesis of 3-monosubstituted pyrrole compounds, since this is the simplest skeleton.

3-Substituted Pyrroles

As regards the preparation of 3-substituted pyrroles, especially 3-arylpyrroles, only a few synthetic methods have so far been reported.[9] However, these methods lack generality because of their low yields, multiple reaction steps, and complicated handling.

9) *a*) T. Severin, P. Adhikary, E. Dehmal, and I. Eberhard, *Chem. Ber.*, **104**, 2856 (1971); *b*) K. Tanaka, K. Kariyone, and S. Umino, *Chem. Pharm. Bull.*, **17**, 611 (1969).

In order to develop a more versatile synthesis of 3-arylpyrroles, we attempted decarboxylation of the dicarboxylic acid at 170—200° in glycerine or ethanolamine; the desired 3-substituted pyrroles (**14**) were obtained in good yields. Further, refluxing of the pyrrole diesters (**3**) in alkaline solution gave **14** directly. The identity of these products was confirmed by the

Table IV. Formation of 3-Substituted Pyrroles (**14**)

Compd.	Method[a]	Yield (%)	mp (°C)	Recryst. solvent	IR ν_{max}[b] cm^{-1} NH	NMR δ NH	Formula	Analysis (%) Calcd (Found) C	H	N
14a	A	60	42— 44[c]	Hexane	3425	8.35[d]				
14b	A	68	Syrup[f]		3430	8.25[d]	$C_{10}H_8FN$	74.51 (74.45	5.00 5.11	8.69 8.60)
14c	A	95	77—78.5	Et_2O–hexane	3470	8.25[d]	$C_{10}H_8FN$	74.51 (74.39	5.00 5.10	8.69 8.72)
14d	A	64	Syrup[f]		3400	8.40[d]	$C_{10}H_8ClN$	67.61 (67.41	4.54 4.74	7.89 7.94)
14e	A	52	62— 63	Et_2O–hexane	3450	8.30[d]	$C_{10}H_8ClN$	67.61 (67.38	4.54 4.74	7.89 7.96)
14f	A	83	116—118	Hexane	3450	8.10[e]	$C_{10}H_8ClN$	67.61 (67.41	4.54 4.70	7.89 7.99)
14g	A	48	Syrup[f]		3400	11.05[e]	$C_{10}H_8BrN$	54.08 (54.00	3.63 3.69	6.31 6.15)
14h	A	78	Syrup[f]		3400	11.10[e]	$C_{10}H_7Cl_2N$	56.63 (56.49	3.33 3.40	6.60 6.59)
14i	A	43	49— 50	Hexane	3400	11.00[e]	$C_{10}H_7Cl_2N$	56.63 (56.67	3.33 3.51	6.60 6.62)
14j	A	60	99—100	Benzene–hexane	3400	10.90[e]	$C_{10}H_7Cl_2N$	56.63 (56.59	3.33 3.31	6.60 6.48)
14k	B	86	146—147	Benzene–hexane	3400	8.10[d]	$C_{12}H_{14}N_2$	77.38 (77.28	7.57 7.80	15.04 14.95)
14l[g]	B	78	202—204 (dec.)	Et_2O	3200	11.10[e]	$C_{14}H_{18}N_2 \cdot HCl$	67.05 (67.00	7.64 7.80	11.17 10.99)
14m	A	42	159—160	AcOEt	3300	10.00[e]	$C_{14}H_{16}N_2$	79.20 (79.23	7.59 7.68	13.19 13.11)
14n	A	68	99—101	Benzene–hexane	3440	7.95[d]	$C_{15}H_{18}N_2$	79.60 (79.77	8.01 7.99	12.37 12.19)
14o	A	64	159—161	Benzene	3590	10.75[e]	$C_{15}H_{19}N_3 \cdot 1/2H_2O$	71.97 (72.40	8.05 7.92	16.79 16.72)
14p	A	78	Syrup[f]		3450	8.10[d]	$C_{11}H_{11}N$	84.04 (83.98	7.05 7.11	8.91 8.90)
14q	C	58	93— 95	Hexane	3440	8.10[d]	$C_{11}H_{11}N$	84.04 (84.14	7.05 7.10	8.91 8.82)
14r	B	77	Syrup[f]		3420	8.10[d]	$C_{13}H_{15}N$	84.27 (84.02	8.16 8.07	7.56 7.59)
14s	B	85	99—100	MeOH–H_2O	3370	8.10[d]	$C_{11}H_{11}NO$	76.27 (75.99	6.40 6.45	8.09 8.00)
14t	B C	74 58	82— 83	iso-Pr_2O–hexane	3440	10.80[e]	$C_{11}H_9NO_2$	70.57 (70.48	4.84 4.81	7.48 7.49)
14u	B	72	133—134	Benzene	3180	9.00[d]	$C_9H_8N_2$	74.98 (74.79	5.59 5.79	19.43 19.09)
14v	B	76	222—224	AcOEt	3100	11.25[e]	$C_9H_8N_2$	74.98 (74.80	5.59 5.49	19.43 19.29)
14w	B	67	13— 14	Hexane	3420	8.00[d]	$C_8H_7NS \cdot 1/4H_2O$	62.50 (62.61	4.91 4.71	9.11 9.26)

a) See the experimental section.
b) Taken in Nujol or as a film.
c) Ref. 9*a*, mp 40—42°.
d) Taken in $CDCl_3$.
e) Taken in DMSO-d_6.
f) Purified by column chromatography.
g) Hydrochloride.

infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy and elemental analysis. The results are summarized in Table IV. Thus, it appears that this method represents a general synthetic procedure for 3-monosubstituted pyrroles.

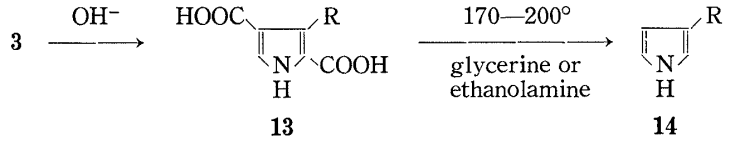
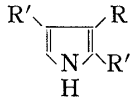
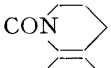


Chart 3

TABLE V. Antiinflammatory Activity of the Pyrrole Compounds (**3**, **10**, **13**, **14**)



Series A				Series B			
Compd.	R	R′	Inhibition[a] (%)	Compd.	R	R′	Inhibition[a] (%)
3a	Ph	COOMe	−0.5	**14a**	Ph	H	19.3
3b	2-F–Ph	COOMe	2.7	**14b**	2-F–Ph	H	8.3
3c	4-F–Ph	COOMe	−6.1	**14c**	4-F–Ph	H	−2.1
3d	2-Cl–Ph	COOMe	7.0	**14d**	2-Cl–Ph	H	45.3
3f	4-Cl–Ph	COOMe	11.7	**14e**	3-Cl–Ph	H	24.3
3k	4-Me_2N–Ph	COOMe	−9.7	**14f**	4-Cl–Ph	H	31.0
3m	4- 	COOMe	−10.8	**14g**	2-Br–Ph	H	28.1
3n	4- 	COOMe	11.2	**14h**	2,4-diCl–Ph	H	27.2
3o	4- 	COOMe	41.3	**14i**	2,6-diCl–Ph	H	35.9
3p	2-Me–Ph	COOMe	20.8	**14j**	3,4-diCl–Ph	H	34.8
3q	4-Me–Ph	COOMe	4.8	**14k**	4-Me_2N–Ph	H	47.6
3r	4-iso-Pr–Ph	COOMe	−9.5	**14l**[b]	4-Et_2N–Ph	H	49.8
3s	4-MeO–Ph	COOMe	−3.1	**14m**	4- 	H	9.4
3u	3-Pyridyl	COOMe	0.2	**14n**	4- 	H	19.8
3w	2-Thienyl	COOMe	−0.2	**14o**	4- 	H	42.1
10a	4-Cl–Ph	CO 	−6.8	**14p**	2-Me–Ph	H	27.7
10b	2,4-diCl–Ph	CO 	3.2	**14q**	4-Me–Ph	H	20.2
10c	4-Me_2N–Ph	CO 	0.2	**14r**	4-iso-Pr–Ph	H	17.3
10d	4-MeO–Ph	CO 	6.1	**14s**	4-MeO–Ph	H	1.0
13a	Ph	COOH	12.4	**14t**	3,4-OCH_2O–Ph	H	9.1
13d	2-Cl–Ph	COOH	13.8	**14u**	3-Pyridyl	H	10.2
13f	4-Cl–Ph	COOH	12.2	**14v**	4-Pyridyl	H	9.4
13k	4-Me_2N–Ph	COOH	8.2	**14w**	2-Thienyl	H	12.2
13w	2-Thienyl	COOH	1.5				

Mefenamic acid: 30.8%, Control: 0.952 ± 0.0013 (ml)[c]

a) % Inhibition of the carrageenan-induced paw edema.
b) Hydrochloride.
c) The volume of the carrageenan-induced paw edema of the control rats.

Pharmacology

The antiinflammatory activities of the pyrrole compounds are summarized in Table V. Many active compounds were found among the 3-substituted pyrrole derivatives (Series B) but only a few among the 2,4-dimethoxycarbonyl-3-substituted ones (Series A).

In Series A, only compound **3o** was more active than the standard drug, mefenamic acid (MA), and its activity was comparable to that of compound **14o**, which possesses the same substituent in Series B. Compound **3p** exhibited a higher activity in this series but was less active than MA. Preliminary oral acute toxicity tests using mice revealed that these two compounds were toxic, *i.e.*, **5** out of **5** mice died within two hours at 500 mg/kg, although no mice died at 1000 mg/kg of MA.

In Series B, the anti-edema activity was markedly increased by the introduction of Cl or Br (**14d—j**), while the introduction of F did not enhance the activity (**14b, c**). Furthermore, a marked increase in the activity was obtained by the introduction of such substituents as dimethylamino, diethylamino, 4-methylpiperazino, or methyl into the phenyl ring at position 3 of the pyrrole. It was found that substitution of a hetero ring for the phenyl ring at position 3 of the pyrrole scarcely increased the activity.

Although the 4-dimethylamino (**14k**) and 4-diethylamino (**14l**) derivatives were more active than MA, excitatory behavioral changes such as hypermotor activity and hyperresponsiveness to external stimuli were produced by these compounds on oral administration of 50 mg/kg.

As shown in Table V, compounds **14f, 14g, 14h, 14i, 14j,** and **14p** were as active as, and **14d** was more active than, MA. On the other hand, the acute toxicities of these compounds were not great; no mice died at an oral dosage of 1000 mg/kg.

According to the results of antiinflammatory activity tests on adrenalectomized rats, **14d, 14f, 14i,** and **14p** did not exhibit anti-edema activity, indicating that the activities were dependent on adrenal gland stimulation. In contrast, the standard drug (MA) showed the same antiinflammatory activity on the adrenalectomized rats as on normal ones (Table VI).

Table VI. Antiinflammatory Activities of Pyrrole Derivatives in Adrenalectomized Rats

Compound	Number[a)]	Volume of swelling (ml)
Control, normal	20	0.989±0.028
Control, adrex.[b)]	20	0.993±0.031
14d	8	0.924±0.042
14f	8	1.033±0.049
14i	8	0.957±0.037
14p	8	0.977±0.037
Mefenamic acid, normal	20	0.640±0.026
Mefenamic acid, adrex.[b)]	12	0.669±0.044

a) Number of animals used.
b) Adrenalectomized rats were used.

Based on these results, we concluded that none of the compounds examined in the present work would be useful as an antiinflammatory drug for therapeutic purposes, even though some of them showed high anti-edema activity in the preliminary animal experiments.

Experimental

Melting points (which were measured with a Yamato melting point apparatus) and boiling points are uncorrected. IR spectra were recorded with a Shimadzu IR-27G spectrophotometer and NMR spectra with a Hitachi Perkin-Elmer R-20A high resolution NMR spectrometer using tetramethylsilane as an internal

standard. Column chromatography was carried out on silica gel (Kieselgel 60, 0.063—0.200 mm, E. Merck).

Materials——Methyl α-formylaminoacrylates (**4**) and methyl α-isocyanoacrylates (**5**) were prepared according to the reported method.[6,8]

Typical Procedure for the Preparation of Dimethyl 3-Substituted Pyrrole-2,4-dicarboxylates (3) (Method B)——i) A mixture of (*Z*)-methyl α-isocyano-4-chlorocinnamate[6] (**6**) (1.1 g, 0.005 mol) and **2** (0.6 g, 0.006 mol) in THF (10 ml) was added dropwise to a suspension of NaH (65% in oil) (0.22 g, 0.006 mol) in THF (5 ml) at 45—50°. After stirring for 3 hr at the same temperature, the reaction mixture was neutralized with 10% AcOH and then the solvent was evaporated off *in vacuo*. The resulting residue was extracted with AcOEt and the extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crystals were recrystallized from benzene to give dimethyl 3-(4-chlorophenyl)pyrrole-2,4-dicarboxylate (**3f**) (0.96 g, 65%) as yellow prisms, mp 180—183°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1728, and 1690. NMR (in $CDCl_3$) δ: 9.90 (1H, broad, NH), 7.50 (1H, d, $J=3$ Hz, CH), 7.28 (4H, s, arom-H), 3.78 (3H, s, OMe), and 3.77 (3H, s, OMe).

In the same way, **3f** was prepared from (*E*)-6[6] in 53% yield.

ii) A solution of **2** (0.6 g, 0.006 mol) in THF (10 ml) was added dropwise to a mixture of (*Z*)-methyl α-isocyano-4-fluorocinnamate[8] (1.0 g, 0.005 mol) and DBU (0.91 g, 0.006 mol) dissolved in THF (10 ml) at 45—50°. After stirring for 2 hr at the same temperature, treatment as described above was carried out to afford dimethyl 3-(4-fluorophenyl)pyrrole-2,4-dicarboxylate (**3c**) (1.0 g, 72%) as colorless prisms, mp 179—181°. IR ν_{max}^{Nujol} cm^{-1}: 3360, 1730, and 1690. NMR (in $CDCl_3$) δ: 7.51 (1H, d, $J=3$ Hz, CH), 6.80—7.53 (5H, m, arom-H, NH), and 3.65 (6H, s, 2×OMe).

Other pyrrole compounds (**3**) were prepared similarly, and the results are summarized in Table I.

General Procedure for the Preparation of Dimethyl 3-Substituted Pyrrole-2,4-dicarboxylates (3) (Method A)——These compounds were prepared by reaction of **1** (0.01 mol) and **2** (2.2 g, 0.022 mol) in the presence of DBU (3.5 g, 0.023 mol) in THF (30 ml) by a method similar to that described in the previous report.[5a] The yields and the physical data are summarized in Table VII.

Table VII. Formation of Dimethyl 3-Substituted Pyrrole-2,4-dicarboxylates (3) by the Direct Method (Method A)

Compd.	R	Yield (%)	mp (°C)[a]	IR ν_{max}^{Nujol} cm^{-1}	Formula	Analysis (%) Calcd (Found) C	H	N
3m	4-  -Ph	37	186—188	3400, 1700, 1620	$C_{18}H_{20}N_2O_4$	65.84 (65.45	6.14 6.26	8.53 8.48)
3n	4-  -Ph	36	138—139	3310, 1725, 1695	$C_{19}H_{22}N_2O_4$	66.65 (66.72	6.48 6.37	8.18 8.01)
3o	4-MeN  -Ph	35	116—118	3560, 1695, 1680	$C_{19}H_{23}N_3O_4$	63.85 (64.12	6.49 6.13	11.76 11.82)
3p	2-Me-Ph	45	140—142	3350, 1730, 1695	$C_{15}H_{15}NO_4$	65.92 (66.10	5.53 5.63	5.13 5.28)
3v	4-Pyridyl	52	225—226 (dec.)	1712, 1690	$C_{13}H_{12}N_2O_4$	60.00 (59.89	4.65 4.71	10.76 10.71)

a) Recrystallized from MeOH or MeOH-H_2O.

α-Formylaminocinnamamides (11a—d)——These compounds were prepared by the reaction of benzaldehydes (**7**) and isocyanoacetylpyrrolidine (**8**)[10] or isocyanoacetylpiperidine (**9**)[10] in the presence of NaH in DMF by a method similar to that in the previous report.[8] The yields and the physical data are listed in Table VIII.

α-Isocyanocinnamamides (12a—d)——These compounds were prepared by the reaction of **11a—d** and phosphoryl chloride in the presence of triethylamine in CH_2Cl_2 by a method similar to that described in the previous report.[8] The yields and the physical data are listed in Table VIII.

Typical Procedure for the Preparation of 3-Substituted Pyrrole-2,4-dicarboxamides (10)——A mixture of (*Z*)-**11a** (2.6 g, 0.01 mol) and **8** (1.38 g, 0.01 mol) in DMF (20 ml) was added dropwise to a suspension of NaH (65% in oil) (0.44 g, 0.012 mol) in DMF (10 ml) at 45—50°. After stirring for 3 hr at room temperature, the reaction mixture was neutralized with 10% AcOH and the solvent was evaporated off *in vacuo*. The resulting residue was extracted with $CHCl_3$ and the extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crystals were recrystallized from EtOH to give 3-(4-chlorophenyl)-

10) Y. Ozaki, K. Matsumoto, and M. Miyoshi, *Agr. Biol. Chem* (Tokyo), **42**, 1565 (1978).

Table VIII. Formation of α-Formylaminocinnamamide (**11a—d**) and α-Isocyanocinnamamide (**12a—d**)

Compd.	Yield (%)	Config.	mp (°C) (Recryst. solv.)	IR ν_{max}^{Nujol} cm^{-1}	Formula	Analysis (%) Calcd (Found) C	H	N
11a	70	*Z*	174—175 (EtOH)	3200, 1700, 1650, 1610	$C_{14}H_{15}ClN_2O_2$	60.32 (60.63	5.42 5.50	10.05 10.08)
11b	66	*Z*	149—150 (AcOEt)	3100, 1695, 1650, 1615	$C_{14}H_{14}Cl_2N_2O_2$	53.68 (53.42	4.50 4.49	8.94 9.03)
11c	77	*Z*/*E*=2	123—127 (AcOEt)	3250, 1690, 1642, 1600	$C_{17}H_{23}N_3O_2$	67.75 (67.63	7.69 7.75	13.94 13.85)
11d	35	*Z*	165—167 (EtOH)	3120, 1690, 1642, 1612	$C_{16}H_{20}N_2O_3$	66.65 (66.71	6.99 6.97	9.72 9.48)
12a	87	*Z*	56—58 (C_6H_6–hexane)	2110, 1645, 1605	$C_{14}H_{13}ClN_2O$	64.49 (64.40	5.03 5.11	10.75 10.65)
12b	81	*Z*	71—73 (C_6H_6–hexane)	2100, 1640, 1610	$C_{14}H_{12}Cl_2N_2O$	56.97 (56.81	4.10 4.05	9.49 9.38)
12c	81	*Z*/*E*=2	93—96 (C_6H_6–hexane)	2200, 1641, 1590	$C_{17}H_{21}N_3O$	72.05 (72.01	7.47 7.50	4.83 4.76)
12d	75	*Z*	79—80 (C_6H_6–hexane)	2100, 1640, 1600	$C_{16}H_{18}N_2O_2$	71.09 (71.00	6.71 6.75	10.36 10.30)

pyrrole-2,4-dicarboxamoylpyrrolidine (**10a**) (2.4 g, 65%) as colorless needles, mp 260—262°. NMR (in DMSO-d_6) δ: 11.75 (1H, broad, NH), 7.05—7.50 (5H, m, arom-H, CH), 2.70—3.60 (8H, m, $4\times NCH_2$), and 1.40—2.05 (8H, m, $4\times CH_2$).

Other pyrrole compounds (**10b—d**) were prepared in a similar way; the results are summarized in Table II.

General Procedure for the Preparation of 3-Substituted Pyrrole-2,4-dicarboxylic Acids (13)——After stirring a solution of **3** (0.01 mol) and NaOH (4.1 g, 0.1 mol) in MeOH (50 ml) and H_2O (10 ml) for 18 hr at 50°, H_2O was added to the mixture and MeOH was removed *in vacuo*. The residue was adjusted to pH 2 with 10% HCl under ice cooling and the resulting precipitates were filtered off by suction and washed with H_2O. Recrystallization from MeOH or aqueous MeOH gave **13**, as summarized in Table III.

Typical Procedure for the Preparation of 3-Substituted Pyrroles (14)——Method A: A suspension of **13f** (2.7 g, 0.01 mol) in ethanolamine (30 ml) was stirred for 1 hr at 170° under an N_2 atmosphere. After cooling, AcOEt (200 ml) was added and the solution was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crystals were recrystallized from hexane to give 3-(4-chlorophenyl)pyrrole (**14f**) (1.5 g, 83%) as colorless needles, mp 116—118°.

Method B: A suspension of **13s** (3.4 g, 0.013 mol) in glycerine (25 ml) was stirred for 30 min at 200° under an N_2 atmosphere. After cooling, H_2O (200 ml) was added to the solution, and the whole was extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was recrystallized from aqueous MeOH to give 3-(4-methoxyphenyl)pyrrole (**14s**) (1.85 g, 85%) as colorless leaflets, mp 99—100°.

Method C: A mixture of **3q** (2.73 g, 0.01 mol), KOH (85%, 2.7 g, 0.04 mol), and H_2O (10 ml) was refluxed for 5.5 hr under an N_2 atmosphere. After cooling, H_2O (20 ml) was added to the solution and the whole was extracted with Et_2O. The extract was washed with 2% HCl, 5% $NaHCO_3$, and H_2O, and then dried over $MgSO_4$. The solution was evaporated down *in vacuo* and the resulting residue was recrystallized from hexane to give 3-(4-methylphenyl)pyrrole (**14q**) (0.91 g, 58%) as colorless leaflets, mp 93—95°.

Other pyrrole compounds (**14**) were prepared similarly, and the results are summarized in Table IV.

Pharmacological Testing——The carrageenan-induced rat paw edema assay was carried out by a modification of Winter's method.[11] Male Sprague-Dawley rats, in groups of four animals weighing 160—180 g, were fasted overnight. One group served as the control and the others as experimental groups. Carrageenan (0.05 ml of 1% solution in sterile 0.9% saline) was injected into the plantar surface of the rat's hind paw 1 hr after oral administration of the test compound (50 mg/kg) as a 0.25% CMC suspension. For very active compounds, the experiments were repeated two or three times to confirm the results. Results were expressed as percent inhibition of swelling, relative to the control group given the vehicle.

The antiinflammatory activities were also examined using bilaterally adrenalectomized rats, which were maintained on a normal diet with 1% saline for 3 days prior to the experiments.

11) C.A. Winter, E.A. Risely, and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

The acute toxicities of very active compounds were determined by oral administration to groups of five male mice (ddY strain, weighing 18—22 g).

Mefenamic acid was used as a standard drug.

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