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Syntheses and Anti-Inflammatory and Analgesic Activities of Hydroxamic Acids and Acid Hydrazides[1)]

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On the basis of the generally accepted view that copper ions take part in the occurrence of inflammation, hydroxamic acids and acid hydrazides derived from various substituted cinnamic acids and hydrocinnamic acids, which were expected to chelate with copper ions, were synthesized and evaluated for anti-inflammatory activity by the carrageenin-induced rat paw edema assay and for analgesic activity by the phenylquinone writhing method in mice. Some of the synthesized compounds exhibited both activities, and 3-(3,4-dimethoxyphenyl)propiohydroxamic acid and its Zn complex were more active than aspirin. The Cu(II) complexes of hydroxamic acid derivatives were synthesized and were assumed to have polymeric structures from the results of elemental analysis, molecular weight measurement and determination of magnetic susceptibility.

Keywords——hydroxamic acid; acid hydrazide; cinnamic acid; hydrocinnamic acid; Cu(II) complex; Zn(II) complex; cluster; anti-inflammatory activity; analgesic activity

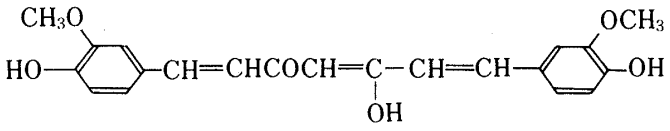
It is well-known that copper ions take part in the occurrence of inflammation and that copper levels in serum and articular synovia in arthritic disease are markedly elevated. On the basis of these observations, D-penicillamine, which has complex forming ability with copper ions, has been used clinically as an anti-arthritic agent.[2)] On the other hand, curcumin, a constituent of rhizomes of *curcuma longa* has a cinnamic acid moiety in its structure **1** and exhibits the same degree of anti-inflammatory activity as phenylbutazone.[3)] In addition, it has been reported that D-phenylalanine and hydrocinnamic acid increase the analgesic activity of enkephalins, by inhibiting the enzymes which rapidly destroy these opiate-like peptides.[4)]

Based on this information, we planned to synthesize hydroxamic acids and acid hydrazides derived from various substituted cinnamic acids and hydrocinnamic acids (*i.e.* 3-phenylpropionic acids) and to test their anti-inflammatory and analgesic activities, as well as their chelating abilities with copper ions.

Chemistry

First of all, the Knoevenagel condensation of appropriately substituted benzaldehydes (**2a**—**f**) with malonic acid furnished cinnamic acid derivatives (**3a**—**f**),[5)] from which the hydroxamic acids were obtained by the two methods illustrated in Chart 1. Namely, acid chlorides (**4b**, **4d**) were allowed to react with hydroxylamine in the presence of triethylamine to afford the hydroxamic acids (**6b**, **6d**) in moderate yields (method A).[6)]

In the other method, the base-catalyzed condensation of esters (**5a**, **5c**) with hydroxylamine was accomplished at room temperature to yield the hydroxamic acids (**6a**, **6c**),



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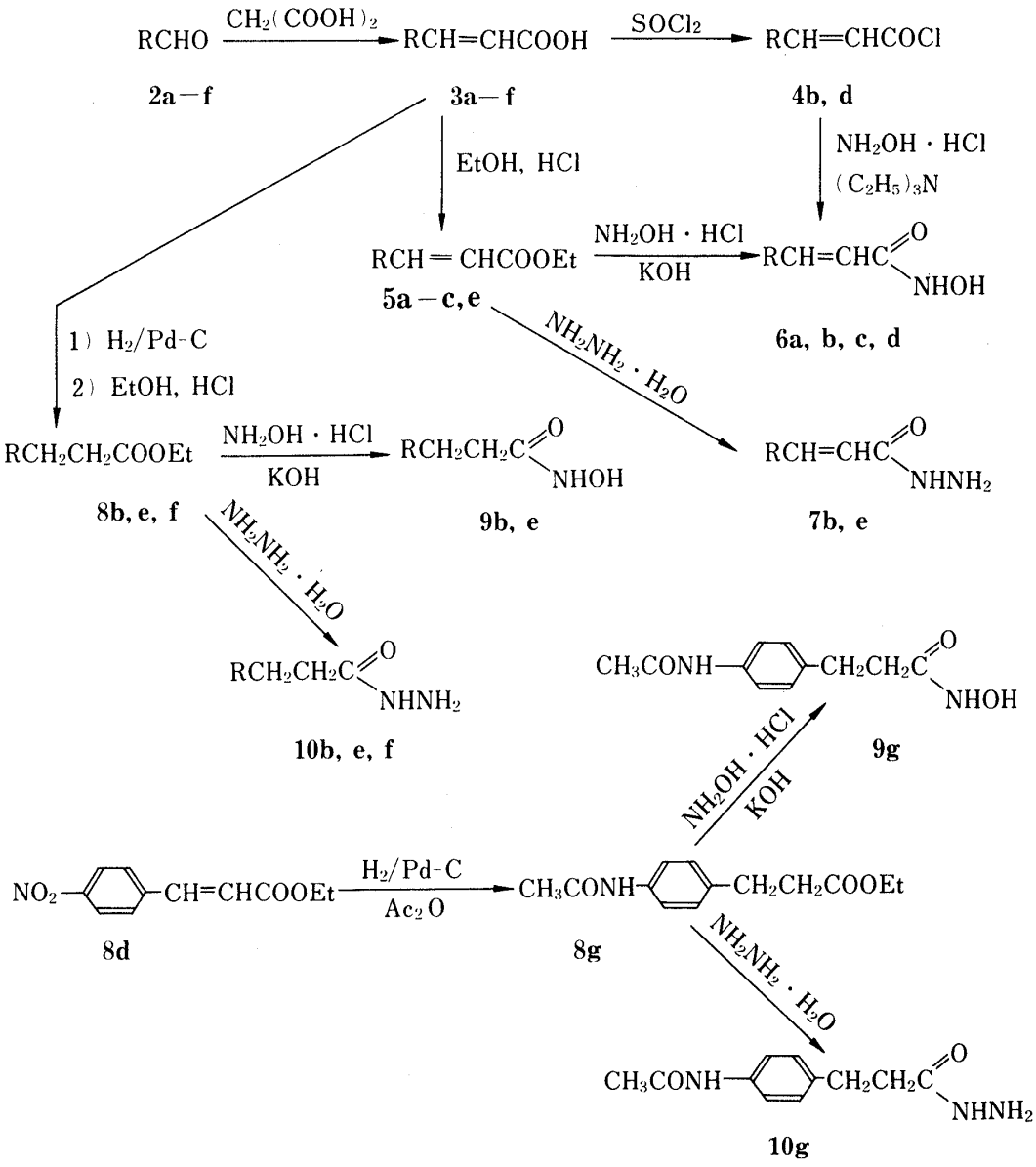
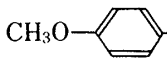
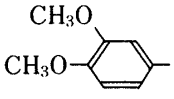


R : **a**,  ; **b**,  ;

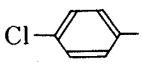
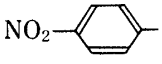
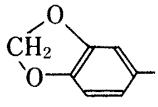
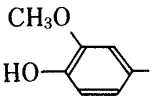
c,  ; **d**,  ; **e**,  ; **f**, 

Chart 1

the formation of which was evidenced by purple coloration with ferric chloride solution (method B).[7]

Acid hydrazides (**7b**, **7e**) were also obtained by heating the corresponding esters (**5b**, **5e**) with hydrazine hydrate. Ethyl 3-phenylpropionates (**8b**, **8e**, **8f**) were prepared by catalytic reduction of cinnamic acids (**3b**, **3e**, **3f**) with palladium-carbon, followed by esterification. 3-Phenylpropiohydroxamic acid derivatives (**9b**, **9e**) were synthesized from **8b** and **8e** through the reaction with hydroxylamine, while acid hydrazides (**10b**, **10e**, **10f**) were obtained by condensation of **8b**, **8e**, **8f** with hydrazine hydrate. Ethyl 3-(4-acetamidophenyl)propionate (**8g**), which was derived from 4-nitrocinnamic acid (**3d**) by catalytic reduction in the presence of palladium-carbon and acetic anhydride in acetic acid, afforded hydroxamic acid (**9g**) or acid hydrazide (**10g**) depending on the method used, as mentioned above.

The Reformatsky reaction of benzophenone with ethyl bromoacetate provided ethyl 3,3-diphenyl-3-hydroxypropionate (**11**)[8] which was dehydrated on heating with formic acid to

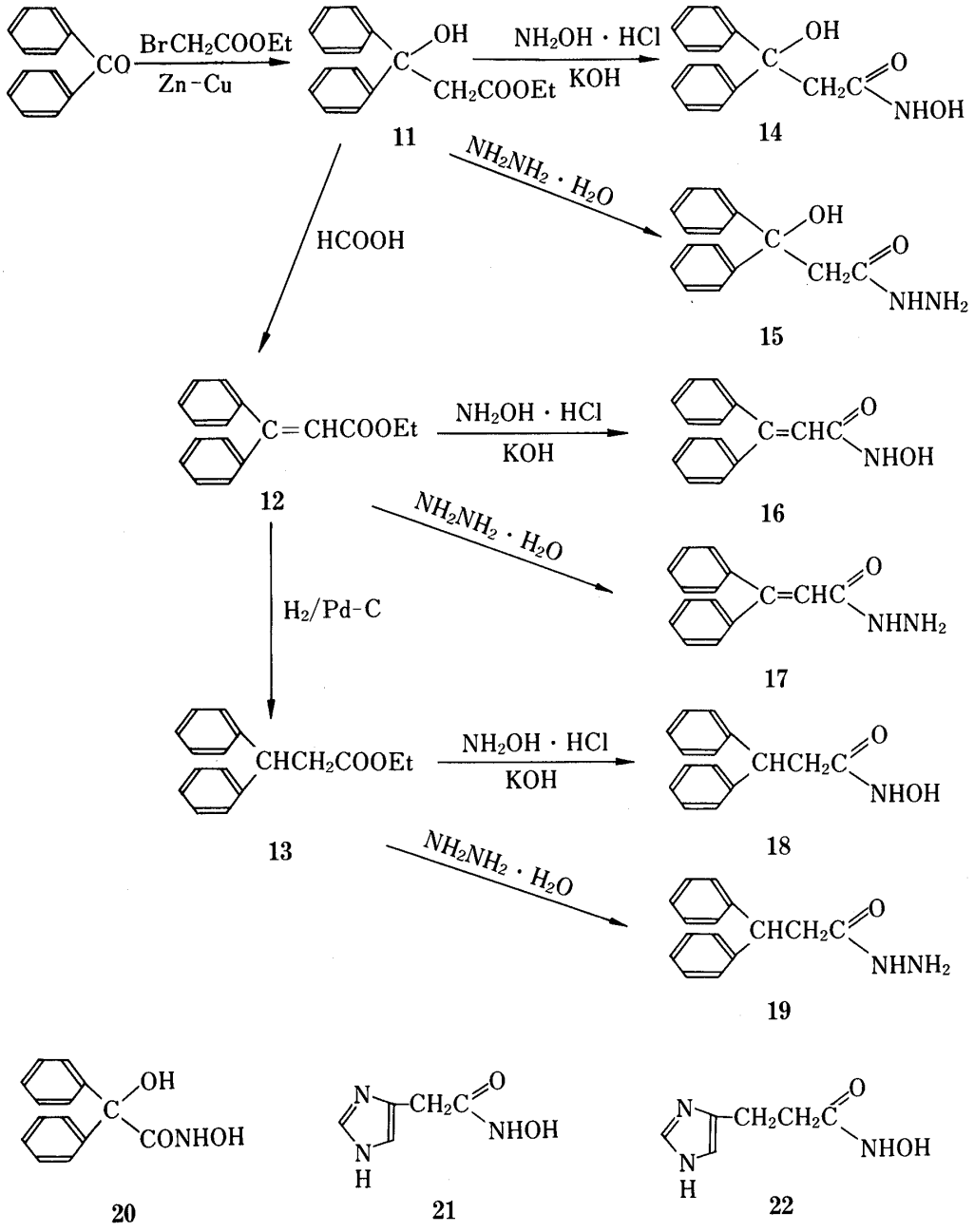


Chart 2

yield ethyl 3,3-diphenylacrylate (**12**). Catalytic reduction of **12** gave ethyl 3,3-diphenylpropionate (**13**). Hydroxamic acids (**14**, **16**, **18**) and acid hydrazides (**15**, **17**, **19**) were prepared from the corresponding intermediates (**11**—**13**) available *via* the standard route (Chart 2).

In addition, the esters of benzilic acid, 4-imidazolylacetic acid and 3-(4-imidazolyl)-propionic acid were reactive enough to undergo condensation with hydroxylamine, yielding the corresponding hydroxamic acids (**20**—**22**).

As expected, the hydroxamic acids and the acid hydrazides thus synthesized readily coordinated to copper ions, when copper acetate was added in equivalent molar ratio. Whereas the Cu(II) complexes of acid hydrazides were unstable and gradually decomposed, those of hydroxamic acids were obtained as stable greenish-blue crystalline powders. The physical data on the Cu(II) complexes of hydroxamic acids are summarized in Table I. Elemental analysis suggested that these complexes were all composed of ligand and Cu(II) in a 1 : 1 ratio. The magnetic susceptibility of these complexes measured by the Gouy method at room temperature indicated the effective magnetic moments to be $\mu_{eff} = 1.22$—1.40 B.M., which are much lower than the normal values, $\mu_{eff} = 1.8$—2.0 B.M., for monomeric structures, suggesting the existence of magnetic exchange between Cu(II), ions as a result of cluster formation. Most of these complexes were insoluble in common solvents, except **14**-Cu and **16**-Cu, which were soluble in chloroform. Their molecular weights measured by the vapor pressure osmotic method in chloroform were found to be 9100 and 6800—7300, respectively. These figures were found to be in accordance with the calculated values of 8852 for a polymeric structure consisting of 27 mol of **14**-Cu and 7230 for the polymer consisting of 23 mol of **16**-Cu. The existence of these polymeric structures was supported by another observation; that is, the temperature dependences of the magnetic susceptibilities of **6b**-Cu and **14**-Cu measured by the Faraday method do not obey the Curie law or theoretical equations for simple clusters such as dimer, trimer and tetramer (Fig. 1).[9]

Furthermore, hydroxamic acids were capable of forming Zn(II) complexes; for example, **9b** reacted with zinc acetate to yield **9b**-Zn as a white crystalline powder soluble in dimethyl sulfoxide but insoluble in chloroform, and this product was assumed to consist of ligand **9b**

TABLE I. Copper(II) Complexes of Hydroxamic Acid Derivatives

Compound	mp (°C)	Formula	Analysis (%) Found (Calcd)			Effective magnetic moment
			C	H	N	μ_{eff} (B.M.)
6a-Cu	251	$C_{10}C_9CuNO_3$	46.65 (47.15	3.69 3.56	5.41 5.50)	1.28
6b-Cu	280	$C_{11}H_{11}CuNO_4$	45.96 (46.40)	4.20 3.89	4.92 4.92)	1.22
6c-Cu	254	$C_9H_6ClCuNO_2$	41.77 (41.71	2.40 2.33	5.53 5.41)	1.30
6d-Cu	246	$C_9H_6CuN_2O_4$	40.20 (40.08	2.48 2.24	10.25 10.39)	1.29
9b-Cu	239—241 (dec.)	$C_{11}H_{13}CuNO_4$	45.94 (46.06	4.64 4.58	4.93 4.88)	1.29
14-Cu	227—229 (dec.)	$C_{15}H_{11}CuNO_3 \cdot 1/2H_2O$	54.81 (54.96	4.26 4.30	4.62 4.27)	1.40
16-Cu	207—210 (dec.)	$C_{15}H_{11}CuNO_2 \cdot 3/4H_2O$	57.15 (57.31	3.72 4.01	4.08 4.46)	1.30

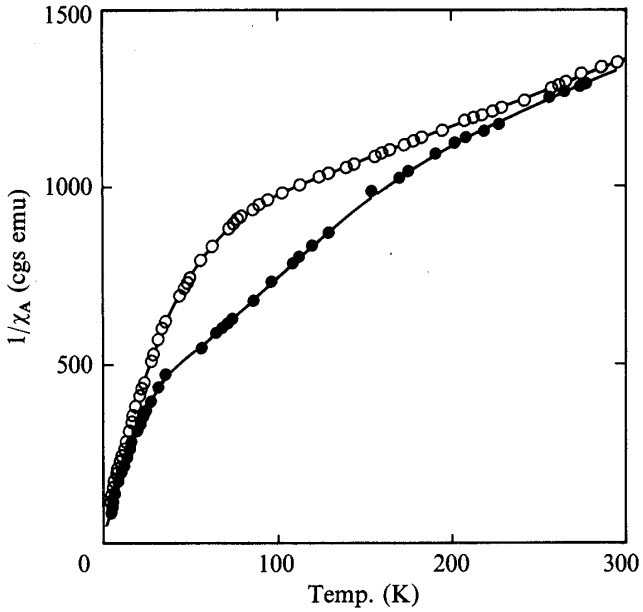
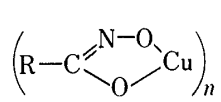
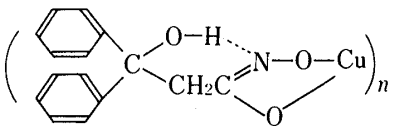


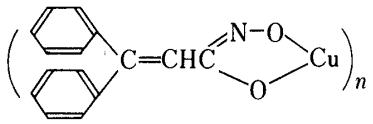
Fig. 1. Temperature Dependence of the Magnetic Susceptibilities of **6b**-Cu (○) and **14**-Cu (●)



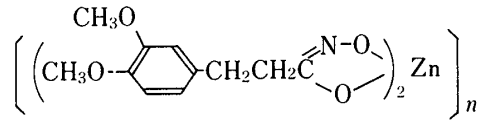
6a, b, c, d-Cu, **9b**-Cu



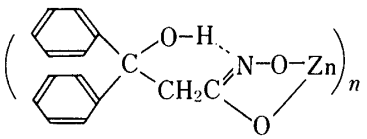
14-Cu



16-Cu



9b-Zn



14-Zn

Chart 3

and Zn(II) in a 2 : 1 ratio, on the basis of its elemental analysis. On the other hand, the Zn(II) complex of **14**, which was soluble in dimethyl sulfoxide and chloroform, appeared to consist of **14** and Zn(II) in a 1 : 1 ratio, forming a cluster which was composed of about 5 mol of **14**-Zn (equivalent to a molecular weight of 2800—3000, measured in chloroform). Thus, the Zn(II) complexes were presumed to form smaller clusters than the Cu(II) complexes.

The nuclear magnetic resonance spectra of the Zn(II) complexes suggested that the hydroxamic acid moiety might contribute to the chelation; that is, the signals at 9.00 and 10.84 ppm in **9b** assigned to the hydroxamic acid group were absent in **9b**-Zn and those at 9.10 and 10.86 ppm due to the hydroxamic acid group in **14** disappeared in **14**-Zn.

The constitutions of these complexes were suggested from these observations to be as shown in Chart 3.

Biology

The synthesized compounds were evaluated for anti-inflammatory activity by the carrageenin-induced rat paw edema assay and for analgesic activity by the phenylbenzoquinone writhing method in mice. As shown in Table II, 3-(3,4-dimethoxyphenyl)propiohydroxamic acid (**9b**) exhibited remarkable anti-inflammatory and analgesic activities,

TABLE II. Anti-Inflammatory and Analgesic Activities of Hydroxamic Acid Derivatives

Compound	Oral dose mg/kg (Rats, $N=6$)	Carrageenin edema inhibition (%)	Oral dose mg/kg (Mice, $N=10$)	PQ-Writhing inhibition (%)
6a	100	14.6	100	−22.6
			200	40.5
6b	100	40.5[b]	50	20.2
			100	63.0[a]
6b-Cu	100	21.6[a]	100	26.9
			200	47.1[a]
6c	100	16.9	100	− 7.5
			200	−23.0
6d	100	19.7	100	−26.4
			200	52.7
9b	50	16.8[a]	25	42.7
	100	35.2[b]	50	64.0[b]
			100	73.2[b]
			200	92.2[b]
9b-Zn	12.5	−10.5	50	51.7[a]
	50	40.8[b]		
	100	41.5[b]		
9e	100	4.8	100	18.5
			200	36.8
9g	100	− 3.0	100	−44.4
			200	−21.2
14	100	8.1	200	47.1[b]
16	100	11.0	100	12.0
			200	6.6
18	100	1.3	100	37.0
			200	86.8[b]
20	100	1.6	200	46.1[b]
21	100	1.6	100	36.0
			200	−29.9
22	100	5.2	50	19.0
			100	55.1[a]
Aspirin	50	8.8	100	45.6
	100	30.7[a]	200	84.3[b]

a) $p<0.05$. b) $p<0.01$.

which were more potent than those of aspirin. It is noteworthy that the zinc complex of **9b** was more effective than the parent compound **9b**, especially as regards anti-inflammatory activity. 3,4-Dimethoxycinnamohydroxamic acid (**6b**) displayed significant anti-inflammatory and analgesic activities similar to those of aspirin, but its Cu(II) complex was less active. Buu-Hoi previously reported the anti-inflammatory activity of **6b**.[10] 3,3-Diphenylpropiohydroxamic acid (**18**) and benzilohydroxamic acid (**20**) were equivalent to, or slightly less effective than aspirin, but only in analgesic potency.

As can seen from Table III, 3,4-dimethoxycinnamic acid hydrazide (**7b**) exhibited anti-

Table III. Anti-Inflammatory and Analgesic Activities of Acid Hydrazide Derivatives

Compound	Oral dose mg/kg (Rats, $N=6$)	Carrageenin edema inhibition (%)	Oral dose mg/mg (Mice, $N=10$)	PQ-Writhing inhibition (%)
7b	50	−3.3	50	52.7[a]
	100	33.4[a]	100	83.0[a]
7e	100	7.8	200	8.4
10b	100	4.5	100	−2.2
			200	76.5[a]
10e	100	−2.3	100	7.6
			200	82.9[b]
10f	100	−14.1	200	5.3
10g	100	20.5	200	22.5
15	100	25.6	50	25.9
17	100	4.8	50	51.5[a]
19	50	22.1[b]	12.5	31.6
	100	34.0[a]		
Aspirin	100	33.2[a]	100	30.3
			200	87.0[b]

a) $p<0.05$. b) $p<0.01$.

inflammatory and analgesic activities similar to those of aspirin. 3,3-Diphenylpropionic acid hydrazide (**19**) showed anti-inflammatory activity, whereas 3-(3,4-dimethoxyphenyl)- and 3-(3,4-methylenedioxyphenyl)propionic acid hydrazides (**10b**, **10e**) as well as 3,3-diphenylacrylic acid hydrazide (**17**) showed analgesic activity. These anti-inflammatory and analgesic activities were also roughly equivalent to those of aspirin.

The above-mentioned results led us to conclude that the hydroxamic acid and acid hydrazide groups capable of forming complexes with copper ions might be the primary determinants in conferring these anti-inflammatory and analgesic activities, while the remaining moieties of the ligand molecules might be the secondary. Cinnamic acids and hydrocinnamic acids having a methoxy group, for example, enhanced these activities as secondary factors, whereas those having a chloro, nitro or acetamido group showed decreased activities.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. Infrared (IR) spectra were measured in Nujol mulls with a Hitachi EPI-S infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were measured with a Hitachi Perkin-Elmer R-20 A (60 MHz) or a JEOL JNM-FX 200 (200 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. Molecular weights were determined with a vapor pressure osmometer (Mechrolab Inc., model 301A). The magnetic susceptibility was determined at room temperature by means of a Gouy magnetic apparatus with a Mettler H51AR microbalance and a Tokyo Giken WM-III electromagnet in a field of about 9000G.

Syntheses of Hydroxamic Acid Derivatives

Method A[6]——$SOCl_2$ (0.12 mol) was added dropwise to a solution of the acid (**3**) (0.1 mol) in $CHCl_3$ (100 ml), and the reaction mixture was heated on a water-bath for half an hour. The solvent was evaporated off *in vacuo* to leave the acid chloride (**4**), which was used immediately for the following reaction without purification. A solution of **4** in $CHCl_3$ (100 ml) was added dropwise to a solution of hydroxylamine hydrochloride (0.12 mol) and triethylamine (0.24 mol) in $CHCl_3$ (100 ml) with stirring and ice-cooling. Stirring was continued at room temperature for 1 h, and then the solvent was removed *in vacuo*. The gummy residue was added to 1 N NaOH aqueous solution (100 ml) and

insoluble materials were filtered off. The filtrate was acidified with conc. HCl to pH 4 with ice-cooling to separate the raw hydroxamic acid as crystalline masses, which were purified by recrystallization from the appropriate solvent.

Method B[7]——A solution of hydroxylamine hydrochloride (0.2 mol) in MeOH (80 ml) was mixed with a solution of KOH (0.3 mol) in MeOH (100 ml) at 40 °C and KCl precipitated during ice-cooling was filtered off. The ester (**5**) (0.1 mol) was added to the filtrate with shaking, and the mixture was allowed to stand at room temperature for several days. The completion of the reaction was confirmed by the detection of a purple spot of hydroxamic acid on spraying $FeCl_3$ solution onto a thin layer chromatogram. When the reaction was over, the solution was concentrated at 35 °C in vacuo and the residue was dissolved in H_2O (100 ml), then insoluble substances were filtered off. The filtrate was acidified with conc. HCl to pH 4 with ice-cooling and the precipitated solid was purified by recrystallization.

4-Methoxycinnamohydroxamic Acid (6a)——**6a** was obtained from ethyl 4-methoxycinnamate (**5a**) (8.6 g, 40 mmol) by method B as colorless plates (from MeOH). mp 143.5—144 °C. Yield 2.44 g (30.3%). IR ν_{max}^{Nujol} cm^{-1}: 3170 (NHOH), 1660 (CO), 1620 (C=C), 1600 (aromatic). NMR (DMSO-d_6) δ: 3.80 (3H, s, CH_3O), 6.37 (1H, d, J=16 Hz, CH=C<u>H</u>CO), 7.46 (1H, d, J=16 Hz, C<u>H</u>=CHCO), 7.46—7.90 (4H, m, aromatic), 8.30 (1H, br s, N<u>H</u>OH), 11.00 (1H, s, NHO<u>H</u>). *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.05; H, 5.72; N, 7.39.

3,4-Dimethoxycinnamohydroxamic Acid (6b)——**6b** was obtaiend from 3,4-dimethoxycinnamic acid (**3b**) (5 g, 24 mmol) *via* the acid chloride (**4b**) by method A as yellowish prisms (from EtOH). mp 187—190 °C (lit.[9] 165—166 °C). Yield 2.06 g (38.5%). IR ν_{max}^{Nujol} cm^{-1}: 3220 (NHOH), 1660 (CO), 1617 (C=C), 1603 (aromatic). NMR (DMSO-d_6) δ: 3.80 (6H, s, CH_3O), 6.35 (1H, d, J=16 Hz, CH=C<u>H</u>CO), 7.41 (1H, d, J=16 Hz, C<u>H</u>=CHCO), 7.18 (3H, m, aromatic), 9.00 (1H, br s, N<u>H</u>OH), 10.60 (1H, s, NHO<u>H</u>). *Anal.* Calcd for $C_{11}H_{13}NO_4$: C, 46.23; H, 4.23; N, 4.90. Found: C, 45.96; H, 4.20; N, 4.92.

4-Chlorocinnamohydroxamic Acid (6c)——**6c** was obtained from ethyl 4-chlorocinnamate (**5c**) (5.6 g, 26 mmol) by method B as colorless plates (from dioxane). mp 171—172 °C. Yield 1.85 g (35.2%). IR ν_{max}^{Nujol} cm^{-1}: 3300 (NHOH), 1670 (CO), 1640 (C=C), 1600, 1560 (aromatic). NMR (DMSO-d_6) δ: 6.55 (1H, d, J=14 Hz, CH=C<u>H</u>CO), 7.55 (1H, d, J=14 Hz, C<u>H</u>=CHCO), 7.65—8.45 (4H, m, aromatic), 9.15 (1H, br s, N<u>H</u>OH), 10.85 (1H, s, NHO<u>H</u>). *Anal.* Calcd for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.50; H, 4.09; N, 7.24.

4-Nitrocinnamohydroxamic Acid (6d)——**6d** was obtained from 4-nitrocinnamic acid (**3d**) (5.8 g, 30 mmol) *via* the acid chloride (**4d**) by method A as yellow needles (from MeOH). mp 185—187 °C. Yield 1.93 g (30.8%). IR ν_{max}^{Nujol} cm^{-1}: 3200 (NHOH), 1660 (CO), 1630 (C=C), 1600 (aromatic), 1500, 1340 (NO_2). NMR (DMSO-d_6) δ: 6.63 (1H, d, J=15 Hz, CH=C<u>H</u>CO), 7.64 (1H, d, J=15 Hz, C<u>H</u>=CHCO), 7.85—8.47 (4H, m, aromatic), 9.5—10.7 (2H, br s, N<u>H</u>O<u>H</u>). *Anal.* Calcd for $C_9H_8N_2O_4 \cdot 1/2H_2O$: C, 49.77; H, 4.17; N, 12.89. Found: C, 49.90; H, 3.96; N, 12.96.

3-(3,4-Dimethoxyphenyl)propiohydroxamic Acid (9b)——**9b** was obtained from ethyl 3-(3,4-dimethoxyphenyl)propionate (**8b**) (20 g, 84 mmol) by method B as colorless fine needles (from AcOEt). mp 103—105 °C. Yield 10.02 g (53.0%). IR ν_{max}^{Nujol} cm^{-1}: 3250 (NHOH), 1648 (CO), 1602 (aromatic). NMR (DMSO-d_6) δ: 2.26 (2H, t, J=8 Hz, CH_2CO), 2.67 (2H, t, J=8 Hz, Ph-CH_2), 3.74 (6H, s, CH_3O), 6.80 (3H, s, aromatic), 9.00 (1H, br s, N<u>H</u>OH), 10.34 (1H, s, NHO<u>H</u>). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58,37; H, 6.67; N, 6.39.

3-(3,4-Methylenedioxyphenyl)propiohydroxamic Acid (9e)——**9e** was obtained from ethyl 3-(3,4-methylenedioxyphenyl)propionate (**8e**) (2.55 g, 15 mmol) by method B as a colorless crystalline powder (from AcOEt). mp 111.5—113 °C. Yield 0.9 g (37.5%). IR ν_{max}^{Nujol} cm^{-1}: 3300 (NHOH), 1660 (CO), 1610 (aromatic). *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.53; H, 5.38; N, 6.77.

3-(4-Acetamidophenyl)propiohydroxamic Acid (9g)——Catalytic reduction of ethyl 4-nitrocinnamate (**8d**) (6.63 g, 30 mmol) in the presence of Pd-C (5%, 1 g) and Ac_2O (10 ml) in AcOH (60 ml) gave ethyl 3-(4-acetamidophenyl)propionate as a colorless crystalline powder (mp 46 °C) (yield 3.5 g, 49.7%). This ester (3.5 g) afforded **9g** (method B) as yellowish plates (from EtOH). mp 148—150 °C. Yield 1.1 g (33.2%). IR ν_{max}^{Nujol} cm^{-1}: 3150 (NHOH, CONH), 1640 (CO), 1600 (aromatic). NMR (DMSO-d_6) δ: 2.05 (3H, s, CH_3CO), 2.30 (2H, d, J=8 Hz, CH_2CO), 2.72 (2H, d, J=8 Hz, Ph-CH_2), 7.08—7.48 (4H, m, aromatic), 8.72 (1H, s, CH_3CONH), 9.72 (1H, s, N<u>H</u>OH), 10.48 (1H, s, NHO<u>H</u>). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.36; N, 12.61. Found: C, 59.35; H, 6.21; N, 12.61.

3,3-Diphenyl-3-hydroxypropiohydroxamic Acid (14)——**14** was obtained from ethyl 3,3-diphenyl-3-hydroxypropionate (**11**)[8] (5 g, 18 mmol) by method B as a colorless crystalline powder (from AcOEt). mp 138—140 °C. Yield 2.2 g (45.8%). IR ν_{max}^{Nujol} cm^{-1}: 3350 (NHOH), 1640 (CO), 1595 (aromatic). NMR (DMSO-d_6) δ: 3.02 (2H, s, CH_2CO), 6.72 (1H, s, $\geq$C–OH), 7.31 (10H, m, aromatic), 9.10 (1H, br s, N<u>H</u>OH), 10.86 (1H, br s, NHO<u>H</u>). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.88; H, 5.91; N, 5.17.

3,3-Diphenylacrylohydroxamic Acid (16)——**16** was obtained from ethyl 3,3-diphenylacrylate (**12**)[8] (colorless oil, bp 150—152 °C/0.2 mmHg) (3 g, 12 mmol) by method B as a colorless crystalline powder (from AcOEt). mp 137—138 °C. Yield 1.5 g (65.2%). IR ν_{max}^{Nujol} cm^{-1}: 3300 (NHOH), 1633 (CO), 1610 (C=C). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.47; N, 5.86. Found: C, 75.56; H, 5.51; N, 5.70.

3,3-Diphenylpropiohydroxamic Acid (18)——**18** was obtained from ethyl 3,3-diphenylpropionate (**13**) (colorless oil, bp 151—153 °C/0.4 mmHg) (2 g, 9 mmol) by method B as a colorless crystalline powder (from AcOEt). mp 151—153 °C. Yield 0.65 g (28.5%). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3250 (NHOH), 1665 (CO), 1628 (C=C), 1600, 1583 (aromatic). *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.49; H, 6.27; N, 5.99.

Diphenylhydroxyacetohydroxamic Acid (Benzilohydroxamic Acid) (20)——**20** was obtained from ethyl benzilate (5.21 g, 20 mmol) by method B as a colorless crystalline powder (from AcOEt). mp 149—150 °C. Yield 1.42 g (28.7%). IR ν_{max}^{Nujol} cm^{-1}: 3450, 3200 (NHOH), 1652 (CO), 1601 (aromatic). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.37; H, 5.44; N, 5.70.

4-Imidazolylacetohydroxamic Acid (21)——**21** was obtained from ethyl 4-imidazolylacetate hydrochloride (2.86 g, 15 mmol) by method B as colorless fine needles (from EtOH). mp 162—163 °C. Yield 0.88 g (41.5%). IR ν_{max}^{Nujol} cm^{-1}: 3480, 3250, 3200 (NHOH, imidazole-NH), 1645 (CO), 1675, 1580, 1530 (imidazole). *Anal.* Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.51; H, 5.10; N, 29.66.

3-(4-Imidazolyl)propiohydroxamic Acid (22)——**22** was obtained from ethyl 3-(4-imidazolyl)propionate hydrochloride (2.43 g, 12 mmol) as a colorless crystalline powder (from EtOH). mp 160—161 °C. Yield 1.07 g (56.6%). IR ν_{max}^{Nujol} cm^{-1}: 3480, 3250, 3170 (NHOH, imidazole-NH), 1643 (CO), 1670, 1575, 1525 (imidazole). NMR (DMSO-d_6) δ: 2.26 (2H, t, J=4 Hz, CH_2CO), 2.70 (2H, t, J=4 Hz, Im-CH_2), 6.72 (1H, s, Im-4-CH), 7.48 (1H, s, Im-2-CH), 10.44 (2H, br s, Im-3-NH, NHOH). *Anal.* Calcd for $C_6H_9N_3O_2$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.42; H, 5.54; N, 26.53.

Syntheses of Acid Hydrazide Derivatives

General Method——A solution of an ester (**5** or **8**) (0.1 mol) and hydrazine hydrate (0.2 mol) in MeOH (50 ml) was refluxed on a water-bath for 3 h. The reaction mixture was concentrated *in vacuo* and added to H_2O (10 ml).

Crystalline masses, that deposited from the solution during ice-cooling were purified by recrystallization from the appropriate solvent.

3,4-Dimethoxycinnamic Acid Hydrazide (7b)——**7b** was obtained from ethyl 3,4-dimethoxycinnamate (**5b**) (2.28 g, 10 mmol) by the general method as colorless fine prisms (from MeOH). mp 217—217.5 °C. Yield 0.93 g (43.5%). IR ν_{max}^{Nujol} cm^{-1}: 3340, 3255 ($NHNH_2$), 1665 (CO), 1613 (C=C), 1593 (aromatic). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.23; H, 6.34; N, 12.67.

3,4-Methylenedioxycinnamic Acid Hydrazide (7e)——**7e** was obtained from ethyl 3,4-methylenedioxycinnamate (**5e**) (7 g, 30 mmol) by the general method as a colorless crystalline powder (from dioxane). mp 151—152.5 °C. Yield 2.3 g (35.1%). IR ν_{max}^{Nujol} cm^{-1}: 3190, 3060 ($NHNH_2$), 1665 (CO), 1610 (C=C). *Anal.* Calcd for $C_{10}H_{10}N_2O_3$: C, 58.52; H, 4.89; N, 13.59. Found: C, 58,47; H, 4.87; N, 13.55.

3-(3,4-Dimethoxyphenyl)propionic Acid Hydrazide (10b)——**10b** was obtained from ethyl 3-(3,4-dimethoxyphenyl)propionate (**8b**) (11.6 g, 50 mmol) by the general method as a colorless crystalline powder (from EtOH). mp 136.5—137 °C. Yield 5.92 g (52.8%). IR ν_{max}^{Nujol} cm^{-1}: 3320, 3200 ($NHNH_2$), 1640 (CO), 1603 (C=C). *Anal.* Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 59.18; H, 7.09; N, 12.53.

3-(3,4-Methylenedioxyphenyl)propionic Acid Hydrazide (10e)——**10e** was obtained from ethyl 3-(3,4-methylenedioxyphenyl)propionate (**8e**) (2 g, 9 mmol) by the general method as colorless needles (from EtOH). mp 146—148 °C. Yield 0.87 g (46.5%). IR ν_{max}^{Nujol} cm^{-1}: 3450, 3300 ($NHNH_2$), 1655 (CO), 1597 (aromatic). *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.78; H, 5.77; N, 13.36.

3-(4-Hydroxy-3-methoxyphenyl)propionic Acid Hydrazide (10f)——**10f** was obtained from ethyl 3-(4-hydroxy-3-methoxyphenyl)propionate (**8f**) (3 g, 13 mmol) by the general method as colorless fine needles (from EtOH). mp 144—145 °C. Yield 1.2 g (42.9%). IR ν_{max}^{Nujol} cm^{-1}: 3300 ($NHNH_2$), 1640 (CO), 1608, 1590 (aromatic). *Anal.* Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.15; H, 6.57; N, 13.52.

3-(4-Acetamidophenyl)propionic Acid Hydrazide (10g)——**10g** was obtained from ethyl 3-(4-acetamidophenyl)propionate (**8g**) (2.24 g, 10 mmol) by the general method as a colorless crystalline powder (from EtOH). mp 172—172.5 °C. Yield 0.7 g (33.3%). IR ν_{max}^{Nujol} cm^{-1}: 3325, 3118 ($NHNH_2$), 1658, 1630 (CO), 1595 (aromatic). *Anal.* Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.33; H, 6.88; N, 18.83.

3,3-Diphenyl-3-hydroxypropionic Acid Hydrazide (15)——**15** was obtained from ethyl 3,3-diphenyl-3-hydroxypropionate (**11**) (3 g, 11 mmol) by the general method as colorless plates (from EtOH). mp 135—136 °C. Yield 2.7 g (95.1%). IR ν_{max}^{Nujol} cm^{-1}: 3340, 3250 ($NHNH_2$), 1635, 1620 (CO), 1600 (aromatic). *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; N, 6.29; N, 10.93. Found: C, 70.36; H, 6.18; N, 10.83.

3,3-Diphenylacrylic Acid Hydrazide (17)——**17** was obtained from ethyl 3,3-diphenylacrylate (**12**) (2.4 g, 10 mmol) by the general method as a colorless crystalline powder (from EtOH). mp 133—136 °C. Yield 2.1 g (92.5%). IR ν_{max}^{Nujol} cm^{-1}: 3270, 3060 ($NHNH_2$), 1680 (CO), 1610 (aromatic). *Anal.* Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.75. Found: C, 75.70; H, 6.05; N, 11.97.

3,3-Diphenylpropionic Acid Hydrazide (19)——**19** was obtained from ethyl 3,3-diphenylpropionate (**13**) (2 g, 8 mmol) by the general method as a colorless crystalline powder (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3370, 3070 ($NHNH_2$), 1640 (CO), 1595 (aromatic). *Anal.* Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.74; H, 6.72; N, 11.85.

Syntheses of Cu(II) Complexes of Hydroxamic Acid Derivatives

General Method——A hydroxamic acid derivative (10 mmol) was dissolved in EtOH (20 ml) and mixed with a solution of $Cu(OAc)_2$ (10 mmol) in EtOH (20 ml); the Cu(II) complex separated immediately as a greenish-blue powder. The reaction mixture was heated on a water-bath at 40 °C for 1 h. The precipitate was filtered off, then washed with H_2O and EtOH. Physical data for the products are listed in Table I. The effective magnetic moment was

calculated using the following equation with correction for the diamagnetism of the ligand. $\mu_{eff} = 2.83\sqrt{\chi_M T}$ B.M., where χ_M is molar susceptibility and T is absolute temperature.

Zn(II) Complex of 3-(3,4-Dimethoxyphenyl)propiohydroxamic Acid (9b-Zn)——**9b** (2.25 g, 10 mmol) was dissolved in EtOH (20 ml) and mixed with a solution of $Zn(OAc)_2 \cdot 2H_2O$ (1.1 g, 5 mmol) in EtOH (50 ml) containing 5 drops of AcOH. The colorless transparent solution was heated at 45 °C for 2 h, then allowed to stand at room temperature overnight, yielding **9b**-Zn as colorless crystalline masses, which were filtered off, washed with EtOH and dried *in vacuo*. mp 263—264 °C (dec.). Yield 1.79 g (53.8%). NMR (DMSO-d_6) δ: 1.98 (3H, s, CH_3COO), 3.80 (6H, s, CH_3O), 6.68 (3H, s, aromatic). *Anal.* Calcd for $C_{22}H_{26}N_2O_8Zn \cdot 2CH_3COOH \cdot 3/2H_2O$: C, 47.39; H, 5.66; N, 4.25. Found: C, 47.16; H, 5.27; N, 4.29.

Zn(II) Complex of 3,3-Diphenyl-3-hydroxypropiohydroxamic Acid (14-Zn)——**14** (2.57 g, 10 mmol) was dissolved in EtOH (20 ml) and mixed with a solution of $Zn(OAc)_2 \cdot 2H_2O$ (2.2 g, 10 mmol) in EtOH (50 ml). The colorless transparent solution was heated at 40 °C for 2 h, then allowed to stand at room temperature overnight, yielding **14**-Zn as colorless needles, which were filtered off, washed with EtOH and dried *in vacuo*. mp 222—224 °C (dec.). Yield 2.29 g (54.1%). NMR (DMSO-d_6) δ: 1.08 (3H, t, J=6 Hz, $C\underline{H}_3CH_2OH$) 1.84 (3H, s, CH_3COO), 2.10 (2H, br s, $CH_2C\lesssim^{O}_{N}$), 3.45 (2H, q, J=6 Hz, $CH_3C\underline{H}_2OH$), 4.30 (1H, br s, $CH_3CH_2O\underline{H}$), 6.70—7.70 (10H, m, aromatic). *Anal.* Calcd for $C_{15}H_{13}NO_3Zn \cdot CH_3COO \cdot 1/2Zn \cdot 1/2H_2O$: C, 48.45; H, 4.07; N, 3.32. Found: C, 48.22; H, 4.25, N, 3.03.

Anti-Inflammatory Assay

Carrageenin Edema——The basic volume of the right hind paw of male rats weighing 160—220 g was estimated. Test compounds were administered *p.o.* in a volume of 1 ml/100 g b.w., followed immediately by oral administration of water to a total of 5 ml/rat. One hour later, the paw was injected *s.c.* with 0.05 ml of 1% carrageenin suspension.[11] The increase in the volume of the foot 3 h after the injection of carrageenin was adopted as a measure of edema.

Analgesic Assay

Phenylquinone Writhing——Male mice weighing 17—24 g were given an aqueous solution of 0.02% phenylquinone (dissolved by adding 5% ethanol) *i.p.* in a volume of 0.1 ml/10 g b.w. 30 min after administration of the test compound.[12] For 20 min after this phenylquinone injection, the frequency of writhing and stretching was counted.

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