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Studies on the Anti-inflammatory Agents. Synthesis of Carboxamides and Their Anti-inflammatory Activity

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Abstract—Four compounds, *N*-(2, 3-dimethylphenyl)benzamide, *N*-(3-trifluoromethylphenyl) benzamide, *N*-(2, 3-dimethylphenyl) cinnamamide and *N*-(3-trifluoromethylphenyl)cinnamamide, were synthesized and evaluated their activity by the method of the inhibitory effect on the carrageenin-induced rat paw edema, compared with phenylbutazone. All of these exhibited anti-inflammatory activity, and *N*-(2, 3-dimethylphenyl)benzamide exhibited 45.7% edema inhibition *vs.* control when 100 mg/kg of dosage was administered, whereas phenylbutazone, 51.4% for 50 mg/kg.

Among the compounds exhibiting anti-inflammatory activity which have appeared in recent years, *N*-substituted anthranilic acid derivatives were described to exhibit high potencies in anti-inflammatory activity[1,2] and there were some carboxamides[3,4] exhibiting anti-inflammatory activity, but there were no reports on the carboxamides of 2, 3-xylidine and 3-aminobenzotrifluoride. We intended to prepare carboxamides belonging to 2, 3-xylidine and 3-aminobenzotrifluoride which expected to exhibit the activity. Four compounds of these series were synthesized and evaluated for their activity by the method of the inhibitory effect on the carrageenin-induced rat paw edema.

Chemistry—The compounds described in Table I were synthesized by the reaction of appropriate amines with benzoyl chloride and cinnamoyl chloride in the modified condition of Schotten[5] and Baumann[6]. The starting cinnamoyl chloride was synthesized from cinnamic acid and thionyl chloride by the method previously described[7].

Anti-inflammatory activity—The carrageenin-induced rat paw edema assay was carried out using a modified Winter's method[8,9] as a preliminary screening test. The rats, in groups of four animals weighing 150~200 g, young adult female Sprague-Dawley strain, were fasted 16 hours prior to administration of the test compounds. The test compounds and saline (as a control) were administered orally. One hour later, the volume of the right hind paw was

measured plethysmometrically[10], and 0.1ml of a 1% solution of carrageenin in sterile pyrogen-free 0.9% NaCl solution as a phlogistic agent was injected into the paw. Three hours after the injection of carrageenin, the volume of the paw was again measured. Degree of edema was expressed as the rate of volume increased after carrageenin injection to the uninjected paw volume. Phenylbutazone was used as a reference compound.

Table I—Carboxamides

Compd.	Mp	Yield (%)	Appearance	Recryst. solvent	Molecular formula	Analysis(%) Calcd. C	H	N	Found C	H	N
I	184	74.4	White needle	EtOH–Ether (1 : 1)	$C_{15}H_{15}NO$	80.00	6.67	6.22	79.61	6.07	6.32
II	98	67.0	White plate	EtOH–Ether (2 : 1)	$C_{14}H_{10}NOF_3$	63.40	3.77	5.28	62.97	4.01	5.24
III	183	70.2	White needle	EtOH–H_2O (9 : 1)	$C_{17}H_{17}NO$	81.27	6.77	5.58	82.06	7.03	6.03
IV	102	62.0	White plate	EtOH–H_3O (9 : 1)	$C_{16}H_{12}NOF_3$	61.86	4.12	4.81	61.93	4.20	4.51

EXPERIMENTAL

Unless otherwise specified melting points were determined in a Thomas-Hoover capillary melting point apparatus and uncorrected. Infrared spectra were determined in a tablet of KBr with a Beckmann Model 20 A double beam IR spectrophotometer.

***N*-(2, 3-dimethylphenyl)benzamide (I)**—Placed 2.42 g (0.02 mole) of 2, 3-xylidine, 20 ml of 10% NaOH solution in a three-necked flask, added 2.82 g (0.02 mole) of benzoyl chloride, stoppered and stirred vigorously for 15~20 min. Made sure the reaction mixture was alkaline. Diluted with water, filtered off the product, and washed well with water. (Method A). Recrystallized from EtOH and ether (1 : 1). $IR_{max}^{KBr}cm^{-1}$; 3420 (NH, s), 2000-1667(1, 2, 3-trisubstd. phenyl, overtone or combination bands), 1649 (sec. amide I, C=O, s), 1520 (sec. amide II, NH, s), 1450 (CH_3, s), 1300 (sec. amide II, C-N, s), 1280 (amide III, s), 775, 710 (1, 2, 3-trisubstd. phenyl, s).

***N*-(3-trifluoromethylphenyl)benzamide (II)**—The modified procedure of Chun[11] was employed. 2.12 g (0.015 mole) of benzoyl chloride was added to a suspension of 2.42 g (0.015 mole) of 3-aminobenzotrifluoride in 10 ml of pyridine with stirring for 30 min. on the cooling bath. Allow to stand the reaction mixture at room temperature for 30 min. Added 20 ml of water, discarded the water layer, and evaporated on water bath. (Method B). Recrystallized from EtOH and ether (2 : 1). $IR_{max}^{KBr}cm^{-1}$; 3290(NH, s), 2000-1667 (1, 3-disubstd. phenyl, overtone or combination bands), 1655 (sec. amide I, C=O, s), 1550 (sec. amide II, NH, s), 1320, 1262 (sec. amide III, C-N, s), 1320, 1180, 1140 (C-F, broad, s), 795, 690 (1, 3-disubstd. phenyl, s).

***N*-(2, 3-dimethylphenyl)cinnamamide (III)**—Prepared from 3.33g (0.02 mole) of cinnamoyl chloride, 2.42 g of 2, 3-xylidine, and 20 ml of 10% NaOH solution by the method A. Recrystallized from EtOH and water (9 : 1). $IR_{max}^{KBr}cm^{-1}$; 3200 (NH, s), 2000-1667 (1, 2, 3-trisubstd. phenyl, overtone or combination bands), 1660 (sec. amide I, C=O, s), 1545 (sec. amide II, NH, s), 1350, 1275 (sec. amide III, C-N, s), 770, 710 (1, 2, 3-trisubstd. phenyl, s).

***N*-(3-trifluoromethylphenyl)cinnamamide (IV)** — Prepared from 2.50 g (0.015 mole) of cinnamoyl chloride, 2.42 g of 3-aminobenzotrifluoride and 10 ml of pyridine by the method B. Recrystallized from EtOH and water (9 : 1). $IR_{max}^{KBr}cm^{-1}$; 3400 (NH, s), 2000-1667 (1, 3-disubstd. phenyl, overtone or combination bands), 1670 (sec. amide I, C=O, s), 1520 (sec. amide II, NH, s), 1325, 1150, 1110 (C-F, broad, s), 1295, 1280 (sec. amide III, C-N, s), 810, 700 (1, 3-disubstd. phenyl, s).

RESULTS AND DISCUSSION

N-(2, 3-dimethylphenyl)benzamide and *N*-(2, 3-dimethylphenyl)cinnamamide were synthesized by the method A in good yield, and *N*-(3-trifluoromethylphenyl)benzamide and *N*-(3-trifluoromethylphenyl)cinnamamide were synthesized by the method B in better yield.

As shown in Table II all four compounds exhibited inhibitory effect on the carrageenin-induced edema. Of these, *N*-(2, 3-dimethylphenyl)benzamide exhibited 45.7% edema inhibition *vs.* control when 100 mg/kg of dosage was administered, whereas the reference compound phenylbutazone exhibited 51.4% for the dosage of 50 mg/kg.

Table II—Inhibitory effects on carrageenin-induced rat paw edema

Compounds	Dose mg/kg, po	Degree of edema [a]	% Inhibition of edema
Control	—	0.70±.04	—
I	100	0.38±.05[b]	45.7
II	100	0.44±.08[c]	37.1
III	100	0.50±.16[c]	28.6
IV	100	0.46±.09[c]	34.3
Phenylbutazone	50	0.34±.03[b]	51.4

Each figure is average of experiments, 4 rats on each level each day.
[a] Mean±Standard error. [b] $p<0.001$ *vs.* control. [c] $p<0.01$ *vs.* control

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