Syntheses and Anti-inflammatory Activity of Novel Oximes and *O*-Acyloximes

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Novel oximes were prepared from the corresponding aldehyde or ketone in the usual way, and a number of oxime esters, *O*-lauroyl, *O*-2-pyridinecarbonyl, *O*-nicotinoyl, and *O*-isonicotinoyl oximes were synthesized by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI)–4-dimethylaminopyridine (DMAP) method or a mixed anhydride method, in our search for potent anti-inflammatory compounds. The anti-inflammatory activity of these compounds was assessed by the carrageenan-induced paw edema assay in rats. The oximes (4, 5, and 13), *O*-lauroyloxime 1L, *O*-nicotinoyloximes (1N, 2N, 3N, and 4N), *O*-isonicotinoyloxime 1I, and *O*-2-pyridinecarbonyloxime 7P showed higher anti-inflammatory potency than aspirin, a prostaglandin cyclooxygenase inhibitor.

Keywords anti-inflammatory activity; oxime; oxime ester; *O*-lauroyloxime; *O*-2-pyridinecarbonyloxime; *O*-nicotinoyloxime; *O*-isonicotinoyloxime

The enzymes that catalyze the metabolism of arachidonic acid have provided an active area for the development of useful therapeutic agents. Inhibitors of the enzymes (cyclooxygenase, 5-lipoxygenase and others), which prevent the formation of prostaglandins, thromboxanes and leukotrienes, are practically useful anti-inflammatory and analgesic agents.

In our previous work, we synthesized malonamic acid, ethyl malonamate and malonamide derivatives, and examined their anti-inflammatory activity,[1] and in the continuing course of our study, we were intrigued by recent reports that oximes, oxime ethers, and oxime esters have a variety of biological activities: analgesic, antipyretic, anticonvulsant activities, and anti-inflammatory activity which might relate to arachidonic acid cascade.[2–5] One of the interesting cases of several 2-adamantanone oxime esters is the detection of anti-inflammatory activity in the carrageenan-induced rat paw edema assay, and the activity is attributed to the intact molecule, oxime ester molecular structure.[3] Another interesting example of *p*-haloacetophenone oxime ethers which possess anti-inflammatory activity is a claim that the oxime ether function is a necessary component of the activity.[4]

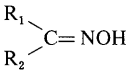
We were interested to clarify the role of the oxime and acyl parts and the ester function in the molecule in pharmacological activity, and also to examine the optimization of these combinations.

In the present investigation, we targeted the anti-inflammatory activity from among the diverse biological activities; oximes including novel oximes and a number of oxime esters were synthesized and examined in the carrageenan-induced rat hind paw edema assay.

As the substantial structure of the oxime moiety (R_1 or R_2), Ar-, Ar-C-, and Ar-C-C-structures and nitrogen-heterocycles were chosen to offer comparison with well known nonsteroidal anti-inflammatory arylacetic acid derivatives, *e.g.*, 4-(2-methylpropyl)benzeneacetic acid (ibufenac), α-methyl-4-(2-methylpropyl)benzeneacetic acid (ibuprofen), and 4-biphenylacetic acid (felbinac). In the other moiety (R_3) of the molecule, the acyl groups were chosen from lipophylic lauric acid and nicotinamide adenine dinucleotide (NAD) related nicotinic acid and its homologues (R_1, R_2, and R_3: See Table II).

The *O*-acyloximes were synthesized from the corresponding oximes with carboxylic acids (lauric acid, picolinic acid, nicotinic acid, or isonicotinic acid) by an 1-eth-

TABLE I. Oximes (**1**—**15**)



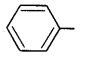
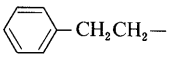
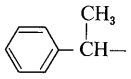
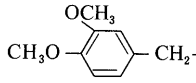
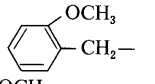
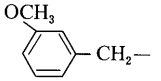
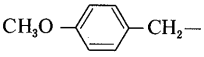
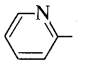
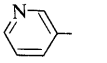
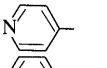
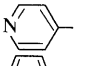
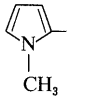
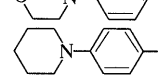
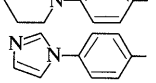
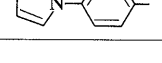
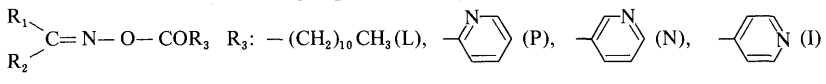
Compd. No.	R_1	R_2	Formula	Ref. and note
1		C_2H_5	$C_9H_{11}NO$	6
2		H	$C_9H_{11}NO$	7
3		H	$C_9H_{11}NO$	8
4		CH_3	$C_{11}H_{15}NO_3$	9
5		CH_3	$C_{10}H_{13}NO_2$	10
6		CH_3	$C_{10}H_{13}NO_2$	11
7		CH_3	$C_{10}H_{13}NO_2$	12
8		CH_3	$C_7H_8N_2O$	13
9		CH_3	$C_7H_8N_2O$	13
10		CH_3	$C_7H_8N_2O$	13
11		H	$C_6H_6N_2O$	14
12		CH_3	$C_7H_{10}N_2O$	15
13		CH_3	$C_{12}H_{16}N_2O_2$	This work
14		CH_3	$C_{13}H_{18}N_2O$	This work
15		CH_3	$C_{11}H_{11}N_3O$	This work

TABLE II. Physical and Spectral Data of *O*-Acyloximes (R_1, R_2: See Table I)



Compd.[a] No.	Method[b]	Yield (%)	mp (°C)	Recrystn. solvent[c]	MS (M^+) m/z	Formula	Elemental analysis (%)[d] Calcd C	H	N	Found C	H	N
1L	A	95.1	<30	H[e]	331	$C_{21}H_{33}NO_2$						
1P	A	36.3	74—75	A	254	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	70.90	5.47	11.05
1N	A	66.8	62.5—63.5	A	254	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	70.71	5.54	11.17
1I	A	41.9	73—75	A	254	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	70.84	5.55	11.01
2P	B	17.2	114—115	B	254	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	70.85	5.56	11.08
2N	B	14.2	93—94	B	254	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	70.75	5.44	11.10
2I	B	21.9	99—100	B	254	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	70.68	5.54	11.00
3L	A	80.2	<30	H[e]	331	$C_{21}H_{33}NO_2$						
3N	A	19.5	59—60	A	254	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	70.97	5.53	11.12
3I	A	19.8	80—81	A	254	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	70.75	5.58	11.00
4L	A	57.7	<30	H[e]	391	$C_{23}H_{37}NO_4$						
4P	A	32.8	91—94	A	314	$C_{17}H_{18}N_2O_4$	64.96	5.77	8.91	64.64	5.65	8.97
4N	A	43.6	95—96.5	A	314	$C_{17}H_{18}N_2O_4$	64.96	5.77	8.91	64.68	5.72	8.97
4I	A	32.9	93—95.5	A	314	$C_{17}H_{18}N_2O_4$	64.96	5.77	8.91	64.90	5.81	9.03
5L	A	86.7	Oil	H[e]	361	$C_{22}H_{35}NO_3$						
5P	A	47.3	Oil	I[e]	284	$C_{16}H_{16}N_2O_3$						
5N	A	63.8	Oil	I[e]	284	$C_{16}H_{16}N_2O_3$						
6L	A	9.9	Oil	H[e]	361	$C_{22}H_{35}NO_3$						
6P	A	23.6	Oil	J[e]	284	$C_{16}H_{16}N_2O_3$						
6N	A	24.4	Oil	I[e]	284	$C_{16}H_{16}N_2O_3$						
7L	A	90.6	32—34	A	361	$C_{22}H_{35}NO_3 \cdot 1/5H_2O$	72.37	9.77	3.84	72.54	9.98	3.96
7P	A	39.9	50	C	284	$C_{16}H_{16}N_2O_3$	67.59	5.67	9.85	67.66	5.66	9.87
7N	A	88.7	67—69	D	284	$C_{16}H_{16}N_2O_3$	67.59	5.67	9.85	67.76	5.67	9.96
8L	A	65.2	38—40	A	318	$C_{19}H_{30}N_2O_2$	71.66	9.49	8.80	71.51	9.78	8.84
8P	A	48.3	132—134	C	241	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42	64.53	4.44	17.35
8N	A	79.0	157—159	E	241	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42	64.67	4.48	17.35
9L	A	78.8	33—34	A	318	$C_{19}H_{30}N_2O_2$	71.66	9.49	8.80	71.33	9.85	8.94
9P	A	44.8	124—126	C	241	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42	64.79	4.43	17.33
9N	A	93.3	152—153	E	241	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42	64.71	4.48	17.35
10L	A	69.1	*ca.* 30	A	318	$C_{19}H_{30}N_2O_2$	71.66	9.49	8.80	71.39	9.78	8.80
10P	A	28.6	136—137	E	241	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42	64.80	4.54	17.15
10N	A	58.7	153—155	E	241	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42	64.70	4.44	17.27
11L	A	66.6	63—64.5	A	304	$C_{18}H_{28}N_2O_2$	71.02	9.27	9.20	70.86	9.57	9.31
11N	A	34.4	155	F	227	$C_{12}H_9N_3O_2$	63.43	3.99	18.49	63.44	3.87	18.31
12L	A	77.6	33—34	A	320	$C_{19}H_{32}N_2O_2$	71.21	10.06	8.74	71.00	10.29	8.80
12N	A	33.3	121—122	D	243	$C_{13}H_{13}N_3O_2$	64.19	5.39	17.27	63.99	5.28	17.25
13L	A	54.5	92—92.5	G	402	$C_{24}H_{38}N_2O_3$	71.60	9.51	6.96	71.51	9.85	7.08
13N	A	71.8	174—176	E	325	$C_{18}H_{19}N_3O_3$	66.45	5.89	12.91	66.34	5.82	12.93
14L	A	57.3	62—63	C	400	$C_{25}H_{40}N_2O_2 \cdot 1/4H_2O$	74.12	10.08	6.92	74.26	10.08	7.08
14N	A	43.2	150—152	E	323	$C_{19}H_{21}N_3O_2$	70.57	6.54	12.99	70.56	6.48	13.02
15L	A	66.6	63—65	D	383	$C_{23}H_{33}N_3O_2 \cdot 1/2H_2O$	70.38	8.73	10.70	70.45	9.01	10.65

a) The initial figure represents oxime number and back alphabet indicates acyl group. *b*) A: EDCI–DMAP method, B: mixed anhydride method. *c*) Solvents: A, Et_2O–*n*-pentane; B, benzene–cyclohexane; C, benzene–*n*-pentane; D, Et_2O; E, benzene; F, CH_2Cl_2–benzene; G, CH_2Cl_2–hexane. *d*) The compounds of low-melting point and the oily compounds are not measured. IR cm^{-1} ($CHCl_3$): **1L**, 1752 (C=O, ester), 1605 (C=N, oxime); **3L**, 1755 (C=O, ester), 1628 (C=N, oxime); **4L**, 1750 (C=O, ester), 1638 (C=N, oxime); **5L**, 1750 (C=O, ester), 1638 (C=N, oxime); **5P**, 1741 (C=O, ester), 1639 (C=N, oxime); **5N**, 1741 (C=O, ester), 1638 (C=N, oxime); **6L**, 1750 (C=O, ester), 1638 (C=N, oxime); **6P**, 1741 (C=O, ester), 1639 (C=N, oxime); **6N**, 1741 (C=O, ester), 1639 (C=N, oxime). *e*) This compound was purified on silica-gel chromatography. Eluting solvents: H, benzene; I, AcOEt–benzene (5:95); J, AcOEt–benzene (2:98).

yl-3-(3-dimethylaminopropyl) carbodiimide (EDCI)–4-dimethylaminopyridine (DMAP) method or a mixed anhydride method. The crude products were purified to homogeneity by silica-gel column chromatography, and/or recrystallization with appropriate solvents. The structures of the oximes and *O*-acyloximes were confirmed by elemental analyses and/or electron impact mass spectrometry. The structural formulas of synthesized and/or assayed oximes are shown in Table I. Table II shows the physical and spectral data of the *O*-acyloximes.

The anti-inflammatory activity was measured as the percentage inhibition of carrageenan-induced rat paw edema. The test compounds (30 mg/kg) were given orally. After 0.5 h, an edema was induced by the subcutaneous injection of λ-carrageenan into the paw pad of the rat. Table III shows the tested anti-inflammatory activity (% inhibition) at 3 h after administration of the oximes, acyl oximes, or related compounds.

Oximes of propiophenone, 3-phenylpropionaldehyde, and 2-phenylpropionaldehyde (**1**, **2**, and **3**) had no activity; however, most of their *O*-acyloximes indicated anti-inflammatory activity, and especially, their *O*-nicotinoyloximes showed significantly potent activity. This significant contrast should be attributed to the intact molecule rather than to a prodrug mode of the action, as suggested by Georgiev, *et al.*[3] Roughly, the esters of oxime **1** had a

TABLE III. Anti-inflammatory Activity (% Inhibition) of the Oximes, *O*-Acyloximes and Related Compounds on Carrageenan-Induced Paw Edema in Rats (at 3 h after; 30 mg/kg, *p.o.*)[a]

Compd.	% inhibition	Compd.	% inhibition	Compd.	% inhibition	Compd.	% inhibition
1	n	**1L**	39[d]	**5P**	n	**10P**	n
2	n	**1P**	28	**5N**	13	**10N**	n
3	n	**1N**	40[c]	**6L**	−13	**11L**	16
4	30[c]	**1I**	33[c]	**6P**	n	**11N**	18
5	46[d]	**2P**	15	**6N**	n	**12L**	22
6	n	**2N**	29[c]	**7L**	−17	**12N**	n
7	n	**2I**	23	**7P**	34[c]	**13L**	26
8	11	**3L**	n	**7N**	16	**13N**	−32
9	18	**3N**	32[c]	**8L**	n	**14L**	25
10	−20	**3I**	11	**8P**	13	**14N**	−16
11	n	**4L**	16	**8N**	n	**15L**	20
12	n	**4P**	16	**9L**	−17	P[b]	n
13	33[c]	**4N**	30[c]	**9P**	n	N[b]	n
14	−24	**4I**	18	**9N**	n	I[b]	n
15	−20	**5L**	19	**10L**	−11	Aspirin	28[c]

a) Percent inhibition showing less than ±10% is indicated as non-active (n). *b*) P: picolinic acid. N: nicotinic acid. I: isonicotinic acid. *c*) Significantly different from control group, $p<0.05$. *d*) Significantly different from control group, $p<0.01$. *Cf.* % inhibition of indomethacin: 46[c] (10 mg/kg, *p.o.*).

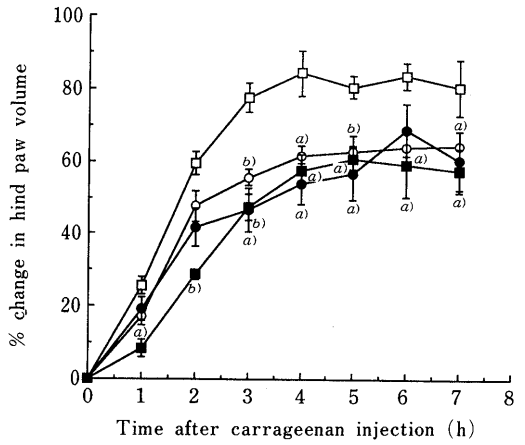


Fig. 1. Effect of Aspirin and Test Compounds (**1L** and **1N**) on Carrageenan-Induced Paw Edema in Rats

Carrageenan edema was induced by injection of 1 mg λ-carrageenan into the pad of the left hind paw of the rats. The drugs (30 mg/kg) were given orally 0.5 h before the injection of carrageenan. Each point represents the mean±S.E. *a*) $p<0.05$ and *b*) $p<0.01$, as compared with the control group. —□—, control; —○—, aspirin; —■—, **1L**; —●—, **1N**.

higher potency than did those of oximes (**2** and **3**).

In the group of mono- and dimethoxyl-substituted benzyl methyl ketone oximes (**4**—**7**), *m*, *p*-disubstituted oxime **4** and *o*-substituted oxime **5** showed significantly potent activity and it is worthy of remark that these oximes have a biologically active phenethylamine-like skeleton. In the case of *m*-substituted oxime **6**, neither the oxime nor its acyl derivatives exhibited activity. Although *p*-substituted oxime **7** was inactive, its picolinic acid ester **7P** actualized potent activity. The structure–activity relations of their methoxyl substituted oximes and its *O*-acyl derivatives are not straightforward.

On the other hand, methyl pyridyl ketone and its analogous oximes (**8**—**12**) and their *O*-acyloximes showed no activity.

In the group of novel oximes (**13**—**15**) in which a hetero ring is substituted at the *para* position of the phenyl group, *p*-morphorinoacetophenone oxime **13** interestingly expressed potent activity; however, their esterification with nicotinic acid resulted in negative activity. Esterification with lauric acid might be effective for the development of activity.

The percentage changes in hind paw volume after administration of representative test compounds (**1L** and **1N**) with the elapse of time are shown in Fig. 1. It was found that the time courses of % change in hind paw volume after administration of these compounds are similar to that of aspirin, a typical arachidonic acid cyclooxygenase inhibitor.

In summary, at the present stage of this study on oxime related compounds, several novel compounds having anti-inflammatory activity were synthesized. The oximes (**4**, **5**, and **13**) and the *O*-acyloximes (**1L**, **1N**, **1I**, **2N**, **3N**, **4N**, and **7P**) showed anti-inflammatory activity comparable to that exhibited by aspirin. It is interesting that *p*-morphorinoacetophenone oxime **13** and propiophenone oxime esters (**1N**, **1L**, and **1I**) show anti-inflammatory activity, because the skeleton of these compounds differ from well known classical nonsteroidal anti-inflammatory drugs having β-phenylacetic acid skeleton. Further synthetic and biochemical studies concerning the mode of action of selected compounds and their (*E*) and (*Z*) stereoisomers are in progress.

Experimental

All melting points were measured with a Yanaco MP-S3 apparatus and are uncorrected. Electron impact mass spectra (EI-MS) were recorded on a JEOL JMS-DX303 spectrometer. Determination and separation of (*E*) and (*Z*) isomers are uncovered in this experiment, although a large excess of (*E*) isomers is expected in case of aryl ketone.

Preparation of Oximes and Physical and Spectral Data of the Novel Oximes 13—15 Oximes (**1**—**10**, **12**—**15**) were synthesized from the corresponding aldehyde or ketone with hydroxylamine.[16]

Oxime **13**: Recrystallization from chloroform; yield, 68.8%; mp 182—185 °C. MS *m/z*: 220 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.28; H, 7.43; N, 12.64.

Oxime **14**: Recrystallization from benzene–*n*-pentane; yield, 91.9%; mp 162—164 °C. MS *m/z*: 218 (M^+). *Anal.* Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.75; H, 8.52; N, 12.77.

Oxime **15**: Recrystallization from EtOH; yield, 94.8%; mp 202—205 °C. MS *m/z*: 201 (M^+). *Anal.* Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.50; H, 5.53; N, 20.63.

General Procedures for the Preparation of *O*-Acyloximes Method A:

The oxime (1 eq), DMAP (0.1 eq), carboxylic acid (1 eq), and EDCI·HCl (1.1 eq) were added to anhydrous CH_2Cl_2 under ice-cooling. The reaction mixture was stirred for 1 h in an ice bath, then overnight at room temperature. Next, CH_2Cl_2 was added to the reaction mixture and this solution was washed with 10% $NaHCO_3$ and water, then dried over $MgSO_4$ and evaporated *in vacuo*. The resultant product was purified to homogeneity by column chromatography on silica gel, and/or recrystallization with appropriate solvents as shown in Table II.

Method B: Carboxylic acid potassium salt (1 eq) suspended in anhydrous CH_2Cl_2 was cooled to $-15\,^{\circ}C$ and treated with ethyl chloroformate (1 eq) and pyridine (1 drop) under stirring at $-15\,^{\circ}C$. After 30 min, oxime **2** (1 eq) in anhydrous CH_2Cl_2 was added to the mixture, stirred for 2 h at room temperature, and filtered. The filtrate was washed with water, then dried over $MgSO_4$ and evaporated *in vacuo*. The resultant product was recrystallized from benzene–cyclohexane.

Anti-inflammatory Activity Groups of six male Sprague-Dawley rats (Japan SLC) weighing 160—180 g were used. Edema was produced in the left hind paw of rats by the subplantar injection of 0.1 ml of a 1% λ-carrageenan suspension in sterile saline. The test compound or its vehicle (0.3% ethylalcohol and 0.3% lecithin in distilled water) was administered orally 30 min before the carrageenan injection. Paw volume was determined with a plethysmometer (TK-101, UNICOM, Chiba) by calculating the amount of water displaced after immersing the paw to the level of the lateral malleolus. Foot volumes were measured just before administration of test compounds and every 1 h for 7 h after carrageenan injection, and the difference was designated as edema volume. The percent change in edema volume of the treated animals relative to the control, and the statistical significance (determined by the Student's *t*-test) were calculated. The evaluation of the anti-inflammatory activity was calculated by the following equations:

$$\%\ \text{change in hind paw volume (\% edema)} = (V_t - V_0)/V_0 \times 100$$

V_t: volume after carrageenan administration
V_0: volume before carrageenan administration

$$\%\ \text{inhibition} = (E_c - E_t)/E_c \times 100$$

E_c: average of the % edema on control animals
E_t: average of the % edema on test animals

References and Notes

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