of the compound were identical with those of the product prepared by Method 1.

3′-*O*-Acetyl-5′-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)thymidine (9b). Method 1. The compound was prepared from 3-*O*-acetylthymidine (500 mg) as described for **9a**, Method 1, in 10% yield: ^{1}H NMR (Me_2SO-d_6) δ 7.56 (s, 1 H, C_6 H), 6.17–6.24 (t, 1 H, $C_{1'}$ H), 5.24–5.29 (m, 1 H, $C_{3'}$ H), 4.31–4.36 (m, 5 H, $C_{4'}$ H, $OCH_2CH_2CH_2O$), 4.14–4.28 (m, 2 H, $C_{5'}$ H), 2.25–2.44 (m, 2 H, $C_{2'}$ H), 2.08 (s, 3 H,$COCH_3$), 1.81 (s, 3 H, CH_3), 1.76–2.17 (m, 2 H, $OCH_2CH_2CH_2O$); MS, *m/e* 405 (MH^+); UV (EtOH) λ_{max} 268 (ε 9400). Anal. ($C_{15}H_{21}N_2O_9P$) C, H, N.

Method 2. The compound was prepared from **1d** (200 mg, 0.55 mmol) and acetic anhydride (520 μL) in pyridine (10 mL). The product was purified by preparative chromatography on two thick layers of silica with $CHCl_3$–CH_3OH (95:5) as eluent. The plates were twice developed. The yield was 155 mg (69%). The product was identical with that obtained by method 1.

Enzyme Experiments. 1. Phosphohydrolases. The substrate (0.7 μmol) in water (20 μL) was incubated at 37 °C for 2 h with (a) 5′-nucleotidase (*Crotalus adamanteus*) (20 μL, 2.25 units/mL) in 0.1 M Tris-HCl buffer–0.01 mM $MgCl_2$, pH 9.0 (100 μL); (b) alkaline phosphatase (*Escherichia coli*) (20 μL, 2.18 units/mL) in 0.1 M glycine–sodium hydroxide buffer, pH 10.4 (100 μL); (c) phosphodiesterase I (*Crotalus adamanteus*) (20 μL, 1.69 units/mL) in 0.1 M Tris-HCl buffer–0.01 mM $MgCl_2$, pH 9.0 (100 μL); (d) snake venom (*Crotalus adamanteus*) (20 μL, 1.25 mg/mL) in 0.1 M Tris-HCl buffer–0.1 mM $MgCl_2$, pH 9.0 (100 μL). After incubations were complete, 0.9 mL of EtOH was added, and the solutions were centrifuged at 2000 rpm for 5 min. Aliquots of the supernatants were analyzed by HPLC in the reverse-phase mode (μ-Bondapak C-18) with 0.05 M Tris-HCl buffer, pH 7.0, and methanol (75:25) as eluent.

2. Cytochrome P-450 Dependent Mixed-Function Oxidases. BDF_1 mice were injected intraperitoneally with sodium phenobarbital (75 mg/kg) for 4 consecutive days. The animals were killed 24 h after the last injection, and their livers were excised. A 33% liver homogenate in 0.05 M Tris-HCl/0.15 M KCl/0.01 M $MgCl_2$ buffer, pH 7.4, was centrifuged at 10000*g* for 20 min at 4 °C. The supernatant fraction was aspirated and centrifuged at 105000*g* for 60 min at 4 °C. The microsomal pellet was washed by resuspension in the original volume of buffer containing 0.01 M EDTA and then resedimented at 105000*g* for 30 min. The final pellet was reconstituted in the Tris/KCl/$MgCl_2$ buffer such that each milliliter of suspension contained microsomes from 0.33 g wet weight of liver. Each incubation mixture contained cyclic 5′-nucleotide (1 mM), NADP (0.4 mM), glucose 6-phosphate (5.0 mM), glucose-6-phosphate dehydrogenase (0.6 units/mL), and 0.25 mL of microsomal suspension in a total volume of 1.25 mL. After 1 h at 37 °C, the incubates were transferred to Amicon Centriflo CF 25 membrane cones (Amicon Corp. Lexington, MA) and centrifuged at 2000 rpm (<1000*g*) in a swinging-bucket centrifuge for 75 min at 4 °C. The filtrates were analyzed by HPLC on a μ-Bondapak C-18 column with 0.05 M Tris buffer, pH 7.4, and methanol (85:15) as eluent at a flow rate of 2 mL/min or on a Partisil 10-SAX column (25 cm × 4.6 mm i.d.) (Whatman) with 0.05 M NaOAc buffer, pH 5.0, at a flow rate of 2 mL/min.

Antitumor Screening. Mice weighing 18–20 g were obtained from Jackson Laboratories, Madison, WI. Murine leukemia P-388, both sensitive and resistant to 5-FU (P-388/0 and P-388/5-FU, respectively), was obtained from Dr. Arthur E. Bogden, Mason Research Institute, Worcester, MA. The P-388/0 and the P-388/5-FU tumors were maintained by weekly intraperitoneal passage in female DBA/2 and male BDF_1 mice, respectively. For antitumor screening, 1×10^6 cells were inoculated intraperitoneally into male BDF_1 mice. The test compounds, dissolved in 0.9% salaine, were administered intraperitoneally daily for 5 consecutive days beginning 24 h after tumor transplantation. Animals were observed for 60 days or until the time of death. Antitumor activity was determined by comparing the median survival time of treated animals (*T*) with that of saline-treated controls (*C*) and was expressed as a percentage increase in life span (% ILS), where % ILS = $(T/C - 1) \times 100$.

Acknowledgment. This research was supported by Grant CA 28001 from the National Cancer Institute, National Institutes of Health.

Registry No. β-**1a**, 85954-65-0; α-1a, 85954-66-1; β-**1a** (3′-derivative), 85894-72-0; α-**1a** (3′-derivative), 85894-73-1; **1b**, 78000-60-9; β-1c, 85954-67-2; α-**1c**, 85954-68-3; β-**1c** (3′-derivative), 85894-74-2; α-1c (3′-derivative), 85894-75-3; **1d**, 67803-64-9; **6a**, 156-87-6; **6b**, 504-63-2; **7a**, 50-91-9; **7b**, 50-89-5; **8a**, 2059-38-3; **8b**, 21090-30-2; **9a**, 85894-76-4; **9b**, 85894-77-5; **10**, 13507-10-3; 5′-nucleotidase, 9027-73-0; alkaline phosphatase, 9001-78-9; phosphodiesterase, 9025-82-5.

N-(4-Substituted-thiazolyl)oxamic Acid Derivatives, a New Series of Potent, Orally Active Antiallergy Agents

Karl D. Hargrave,* Friedrich K. Hess, and James T. Oliver

Research and Development, Boehringer Ingelheim Ltd. USA, Ridgefield, Connecticut 06877. *Received July 20, 1982*

A series of *N*-(4-substituted-thiazolyl)oxamic acid derivatives were synthesized and tested for antiallergy activity in the rat PCA model. These compounds were conveniently prepared by treatment of the appropriate acetophenone with thiourea and iodine or by reaction of the chloroacetylbenzene with thiourea to give the corresponding aminothiazoles; subsequent condensation with ethyloxalyl chloride gave the thiazolyloxamates. Many of the analogues showed a 50% inhibition at <2 mg/kg po or <0.4 mg/kg iv and were significantly more potent than disodium cromoglycate, which in the rat PCA model is orally inactive and gives a 50% inhibition at 1.2 mg/kg iv. Hydrolysis of the oxamates generally resulted in enhanced activities, while substitution of the phenyl ring with a variety of substituents (e.g., 4-F, 4-OEt, and 4-$NHCOCH_3$) did not significantly enhance the activity of the unsubstituted phenyl derivative. One of the ethanolamine salts, *N*-[4-(1,4-benzodioxan-6-yl)-2-thiazolyl]oxamic acid ethanolamine salt (**61**, PRH-836-EA), has been selected for further pharmacological evaluation.

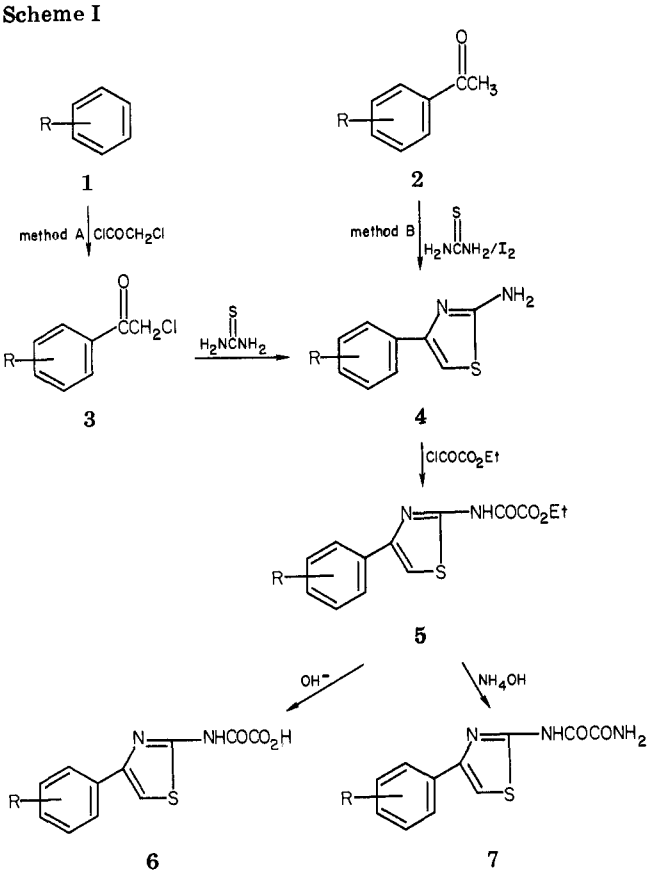
The clinical utility of disodium cromoglycate (DSCG) as a prophylactic antiallergy agent is based on its ability to inhibit the release of mediators initiated by antigen–antibody interactions. DSCG, however, suffers from the fact that it is not orally absorbed but must be administered as a finely powdered aerosol.[1] As a result, the focus of attention for more than a decade has been on the development of more potent, orally active DSCG-like compounds.[2,3]

In 1975, it was reported[4] that a number of oxanilates and *N*-heteroaryloxamates were active in the rat passive cutaneous anaphylaxis (PCA) assay. More recently, *N*,*N*′-

(1) J. S. G. Cox, J. E. Beach, A. M. T. N. Blair, A. J. Clark, J. King, T. B. Lee, D. E. E. Loveday, G. F. Moss, T. S. C. Orr, J. T. Ritchie, and P. Sheard, *Adv. Drug Res.*, **5**, 115 (1970).
(2) J. P. Devlin, *Annu. Rep. Med. Chem.*, 16, 61 (1981).
(3) M. K. Church, *Med. Actual./Drugs Today*, 14, 281 (1978).
(4) J. H. Sellstedt, C. J. Guinosso, A. J. Begany, S. C. Bell, and M. Rosenthale, *J. Med. Chem.*, 18, 926 (1975).

0022-2623/83/1826-1158$01.50/0

Scheme I



phenylenedioxamic acids[5] and *N*-(aminophenyl)oxamic acids[6] have been described. In the patent literature, several series of substituted thiazolyloxamic acids have been claimed.[7a-d]

Our own search for more potent, orally active antiallergy agents led to the selection of *N*-(substituted-thiazolyl)oxamic acids as likely candidates for investigation. This series was chosen on the basis of the earlier report[4] that ethyl *N*-(2-thiazolyl)oxamate was weakly active in the rat PCA model, and because a number of the intermediate aryl-2-aminothiazoles were available from previous studies. Test results for the compounds initially prepared led to the synthesis of the analogues reported herein. Many of these compounds were found to be effective both orally and intravenously in the rat PCA assay. Subsequent evaluation in a range of pharmacological models has led to the selection of *N*-[4-(1,4-benzodioxan-6-yl)-2-thiazolyl]oxamic acid ethanolamine salt (**61**, PRH-836-EA) for further development as an antiallergy agent.

Chemistry. Two standard approaches were utilized for the preparation of most of the aminothiazole intermediates **4** (Scheme I). Friedel–Crafts acylation (method A) of appropriate benzene derivatives resulted in the chloro ketones **3**, which were then converted[8] to **4** by refluxing with thiourea in ethanol. Alternatively, readily available acetophenones **2** were treated with thiourea and iodine to give the aminothiazoles **4** (method B).[9]

The 4-phenyl-5-methylthiazole derivative **11** was prepared from propiophenone via method B. Treatment of phenylacetaldehyde with bromine, followed by refluxing with thiourea in ethanol, led to the 5-phenylthiazoles **88** and **89**. The 4,5-dimethylthiazole derivative **87** was prepared from 3-bromo-2-butanone.

The ethyl esters **5** of the oxamic acids were prepared by stirring the amines **4** with ethyloxalyl chloride in pyridine or triethylamine. Mild alkaline hydrolysis, followed by acidification, gave the oxamic acid **6**, which was often conveniently isolated as the ethanolamine (EA) salt.

The oxamamides **7** were prepared in quantitative yield by overnight stirring of the oxamates with an excess of ammonium hydroxide at room temperature.

Discussion

The *N*-(substituted-thiazolyl)oxamic acids represent a new[7a-d] class of potent, orally active antiallergy compounds as determined by the rat PCA assay. Many of these acids are more potent than the oxanilic acids[4] and with several exceptions are comparable in activity to the *N,N'*-phenylenedioxamic acids[5] and *N*-(aminophenyl)oxamic acids.[6] It can be seen from the data presented in Table I that the oxamic acids in this series are generally more active than their corresponding esters and amides. However, this trend is in contrast to the oxanilic acid series[4] in which the esters are more potent than the acids. That the esters and amides in the present case are acting as prodrugs for the active acids cannot be determined with the available information.

A variety of substituents can be introduced on the phenyl ring of the *N*-(phenylthiazolyl)oxamic acids (Table I) without significantly altering the activity relative to the unsubstituted phenyl analogue **9**. Thus, for example, the monosubstituted 4-F (**13**), 4-OC_2H_5 (**26**), 4-$N(CH_3)_2$ (**35**), and 4-$NHCOCH_3$ (**39**) derivatives all have the same activity (po) as **9**, as do disubstituted analogues, e.g., 3-CH_3 and 4-OH (**51**), 3-$COCH_3$ and 4-OH (**53**), and 3,4-(OCH_2CH_2O) (**61**). However, trisubstituted derivatives (e.g., **82**) and analogues with bulky substituents (e.g., **28**) and nonheteroatom substituents in the 4-phenyl position (e.g., **71**) are significantly less active. A similar loss of activity on introduction of a bulky substituent was noted[4] in the oxanilic acid series.

Neither replacement of the phenyl ring with a heteroaromatic ring [e.g., 4-pyridyl (**93**) or 2-furanyl (**95**)] nor substitution with a methyl group at position 5 of the thiazole ring (**11**) markedly diminishes activity. On the other hand, the 5-phenylthiazole derivative (**89**) is slightly less active than the corresponding 4-isomer (**9**).

Experimental Section

Infrared spectra were determined with a Perkin-Elmer Model 237B or 267 Infrared spectrophotometer, and the NMR spectra were determined with a Varian Model T-60 NMR spectrometer. The structures of the compounds were confirmed in all cases by spectroscopic and elemental analysis.

Method A. To a solution of 0.10 mol of the appropriate benzene derivatives in 100 mL of methylene chloride was added 0.10 mol of chloroacetyl chloride. After the solution was cooled in an ice bath, 0.20 mol of aluminum chloride was added in three portions. The mixture was gently refluxed for 7 h and then allowed to stir overnight at room temperature. After it was poured over ice, the product was extracted with ether, and the extract was dried (sodium sulfate) and filtered. The filtrate was con-

(5) J. B. Wright, C. M. Hall, and H. G. Johnson, *J. Med. Chem.*, 21, 930 (1978).

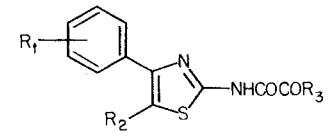
(6) D. H. Klaubert, J. H. Sellstedt, C. J. Guinosso, R. J. Capetola, and S. C. Bell, *J. Med. Chem.*, 24, 742 (1981).

(7) (a) F. K. Hess, P. B. Stewart, and J. T. Oliver, U.S. Patent 4238496 (1980). (b) S. I. Casadio, H. F. Cousse, G. F. Mouzin, and J. P. F. Tarayre, U.S. Patent 4246271 (1981). (c) H. Eilingsfeld, P. Neumann, G. Seybold, D. Lenke, and L. Friedrich, Ger. Offen. 3027527 (1982). (d) H. Eilingsfeld, P. Neumann, G. Seybold, D. Lenke, and L. Friedrich, Ger. Offen. 3027528 (1982).

(8) F. Gagiu, Gh. Savassy, and E. Bebesel, *J. Prakt. Chem.*, 311, 168 (1969).

(9) R. M. Dodson and L. C. King, *J. Am. Chem. Soc.*, 67, 2242 (1945).

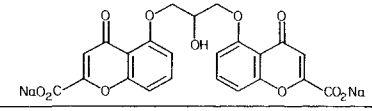
Table I. *N*-(4-Arylthiazolyl)oxamic Acids, Esters, and Amides



no.	R_1	R_2	R_3	mp, °C	method	recrystn solvent[a] (% yield)[b]	formula	anal.	rat PCA ED_{50},[l,m] mg/kg po	rat PCA ED_{50},[l,m] mg/kg iv
8	H	H	OEt	158.5–160	c	I (56)[d]	$C_{13}H_{12}N_2O_3S$	C, H, N	0.61 (0.73–3.6)	
9	H	H	OH	>200 dec	c	II (54)[d]	$C_{11}H_8N_2O_3S$	C, H, N	~1	>3
10	H	H	NH_2	210.5–211.5	c	II (41)[d]	$C_{11}H_9N_3O_2S$	H, N; C[e]	~1	
11	H	CH_3	OH·EA	188–190	B	III (61)[d]	$C_{12}H_{10}N_2O_3S \cdot C_2H_7NO$	C, H, N, O, S	2.5 (1.3–3.3)	
12	4-F	H	OEt	220–223	B	IV (53)	$C_{13}H_{11}FN_2O_3S$	C, H, F, N, S	>10	
13	4-F	H	OH·EA	197–199	B	III (28)	$C_{11}H_7FN_2O_3S \cdot C_2H_7NO$	C, H, F, N, S	0.9 (0.4–2.3)	0.11 (0.04–0.3)
14	2-OH	H	OEt	209–211	B	V (26)	$C_{13}H_{12}N_2O_4S$	C, H, N, S	8.2 (4.7–16.6)	
15	2-OH	H	OH·EA	186–190	B	VI (18)	$C_{11}H_8N_2O_4S \cdot C_2H_7NO$	C, H, N, S	6.7 (2.9–15.4)	0.62 (0.2–1.8)
16	3-OH	H	OEt	231–235	B	VI (32)	$C_{13}H_{12}N_2O_4S$	C, H, N, O, S	>10	
17	3-OH	H	OH·0.5EtOH	211–215	B	II (16)	$C_{11}H_8N_2O_4S \cdot 0.5C_2H_6O$	C, H, N, O, S	~3	~0.1
18	4-OH	H	OEt	230–233	B	VI (45)	$C_{13}H_{12}N_2O_4S$	C, H, N, O, S	~15	
19	4-OH	H	OH	247–250	B	II (36)	$C_{11}H_8N_2O_4S$	C, H, N, O, S	>3	~0.1
20	2-OCH_3	H	OEt	118–122	B	II (63)	$C_{14}H_{14}N_2O_4S$	C, H, N, O, S	>30	~1
21	2-OCH_3	H	OH	195–197	B	VI (35)	$C_{12}H_{10}N_2O_4S$	C, H, N, S		>1
22	3-OCH_3	H	OEt	133–136	B	VII (65)	$C_{14}H_{14}N_2O_4S$	C, H, N, S	~20	
23	3-OCH_3	H	OH	214–217	B	VI (51)	$C_{12}H_{10}N_2O_4S$	C, H, N, O, S	2.1 (1.0–4.1)	0.16 (0.06–0.4)
24	4-OCH_3	H	OEt	164–165	B	VII (54)	$C_{14}H_{14}N_2O_4S$	C, H, N, S	~10	
25	4-OC_2H_5	H	OEt	164–167	B	VIII (53)	$C_{15}H_{16}N_2O_4S$	C, H, N, S	2.1 (1.3–3.2)	
26	4-OC_2H_5	H	OH·EA	195–197	B	III (24)	$C_{13}H_{12}N_2O_4S \cdot C_2H_7NO$	C, H, N, S	0.54 (0.4–0.8)	
27	4-OC_6H_5	H	OEt	181–183.5	A	II (30)	$C_{19}H_{16}N_2O_4S$	C, H, N, S	>30	
28	4-OC_6H_5	H	OH·EA	>166 dec	A	IX (15)	$C_{17}H_{12}N_2O_4S \cdot C_2H_7NO$	C, H, N, O, S	>10	
29	4-SC_6H_5	H	OEt	153–157	A	II (24)	$C_{19}H_{16}N_2O_3S_2$	C, H, N	>3	
30	4-SC_6H_5	H	OH·EA	183–186	A	II (14)	$C_{17}H_{12}N_2O_3S_2 \cdot C_2H_7NO$	C, H, N, O, S	>30	
31	4-NO_2	H	OEt	227–229	B	VI (34)	$C_{13}H_{11}N_3O_5S$	C, H, N, O	>100	
32	4-NO_2	H	OH·EA	230–233	B	III (21)	$C_{11}H_7N_3O_5S \cdot C_2H_7NO$	C, H, N, S	2.5 (1.4–4.6)	
33	3-$N(CH_3)_2$	H	OH·EA	147–150	B	III (12)	$C_{13}H_{13}N_3O_3S \cdot C_2H_7NO$	C, H, N, S	1.7 (0.4–3.0)	0.35 (0.07–1.70)
34	4-$N(CH_3)_2$	H	OEt	210–213	B	X (24)	$C_{15}H_{17}N_3O_3S$	C, H, N, S	~1	~0.3
35	4-$N(CH_3)_2$	H	OH	>220 dec	B	XI (18)	$C_{13}H_{13}N_3O_3S$	C, H, O, S; N[f]	1.1 (0.7–1.6)	0.02 (0.01–0.04)
36	4-c-NC_5H_{10}	H	OEt	207–209	B	XI (14)	$C_{18}H_{21}N_3O_3S$	C, H, N, O, S	3.2 (2.0–5.0)	
37	4-c-$N(CH_2CH_2)_2O$	H	OEt	249–251	B	XI (12)	$C_{17}H_{19}N_3O_4S$	C, H, N, O, S	>100	

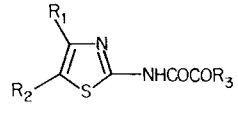
38	4-$NHCOCH_3$	H	OEt	264–265	A	XII (57)	$C_{15}H_{15}N_3O_4S$	C, H, N	0.29 (0.11–0.75)	
39	4-$NHCOCH_3$	H	OH·H_2O	233–234 dec	A	XII (42)	$C_{13}H_{11}N_3O_4S$·H_2O	C, H, N, S	0.37 (0.15–0.94)	0.16 (0.07–0.4)
40	4-$NHCOCH_3$	H	NH_2	279–280	A	II (23)	$C_{13}H_{12}N_4O_3S$	C, H, N	>10	
41	4-$NHCOCF_3$	H	OEt	235–236.5	B	XIII (8)	$C_{15}H_{12}F_3N_3O_4S$	C, H, N	~1	
42	4-$NHCOC_3H_7$	H	OEt	238–241	A	II (30)	$C_{17}H_{19}N_3O_4S$	C, H, N, S	>10	<0.3
43	4-$NHCOCO_2C_2H_5$	H	OEt·0.5H_2O	207–208	B	I (19)	$C_{17}H_{17}N_3O_6S$·0.5H_2O	C, H, N	>30	
44	4-$NHCOCO_2H$	H	OH·2EA	199–201 dec	B	II (5)	$C_{13}H_9N_3O_6S$·$C_4H_{14}N_2O_2$	C, H, N	>10	
45	4-$NHCOCONH_2$	H	NH_2	>320 dec	B	VI (5)	$C_{13}H_{11}N_5O_4S$	C, H; N[g]	~1	
46	2-CO_2CH_3	H	OEt	139–140	B	V (38)	$C_{15}H_{14}N_2O_5S$	C, H, N	>10	
47	4-$CO_2C_2H_5$	H	OMe	209–211	B	V (31)	$C_{15}H_{14}N_2O_5S$	C, H, N, O, S	>10	
48	4-$CO_2C_2H_5$	H	OEt	184–185	B	V (35)	$C_{16}H_{16}N_2O_5S$	C, H, N, O, S	>10	
49	4-$CO_2C_2H_5$	H	OBu	175–177	B	V (27)	$C_{18}H_{20}N_2O_5S$	C, H, N, O, S	>10	
50	3-CH_3, 4-OH	H	OEt	212–215	B	II (14)	$C_{14}H_{14}N_2O_4S$	C, H, N, O, S	2.2 (1.0–4.8)	
51	3-CH_3, 4-OH	H	OH·EA	203–206	B	III (9)	$C_{12}H_{10}N_2O_4S$·C_2H_7NO	C, H, N, S	~1	
52	3-$COCH_3$, 4-OH	H	OEt	185.5–187.5	A	I (13)	$C_{15}H_{14}N_2O_5S$	C, H, N	2.6 (1.0–6.6)	
53	3-$COCH_3$, 4-OH	H	OH·2EA	179.5–181	A	III (6)	$C_{13}H_{10}N_2O_5S$·$C_4H_{14}N_2O_2$	C, H, N	~1	0.71 (0.23–2.24)
54	3,4-$(OH)_2$	H	OEt·0.5H_2O	>300	A	II (18)	$C_{13}H_{12}N_2O_5S$·0.5H_2O	C, H, N	1.4 (0.5–3.5)	
55	3,4-$(OH)_2$	H	OH·EA	224	A	III (4)	$C_{11}H_8N_2O_5S$·C_2H_7NO	C, H, N	~0.1	0.08 (0.02–0.29)
56	3-OCH_3, 4-OH	H	OH·EA	177–180	B	XIV (13)	$C_{12}H_{10}N_2O_5S$·C_2H_7NO	C, H, N, O, S	2.1 (0.64–6.67)	<0.1
57	3,4-$(OCH_3)_2$	H	OEt	131–133	B	VIII (34)	$C_{15}H_{16}N_2O_5S$	C, H, N, O, S	~3	
58	3,4-$(OCH_3)_2$	H	OMe	170–174	B	VIII (27)	$C_{14}H_{14}N_2O_5S$	C, H, N, O, S	1.2 (0.5–3.27)	
59	3,4-$(OCH_3)_2$	H	OH	>200 (dec)	B	VI (6)	$C_{13}H_{12}N_2O_5S$	H, N, S; C[h]	1.48 (1.02–2.15)	
60	3,4-(OCH_2CH_2O)	H	OEt	204–207	B	I (83)	$C_{15}H_{14}N_2O_5S$	C, H, N, O, S	>10	
61	3,4-(OCH_2CH_2O)	H	OH·EA	179–181	B	III (60)	$C_{13}H_{10}N_2O_5S$·C_2H_7NO	C, H, N, O, S	0.6 (0.32–1.04)	0.039 (0.02–0.07)
62	3,4-(OCH_2CH_2O)	H	NH_2	247–249	B	IV (80)	$C_{13}H_{11}N_3O_4S$	C, H, N	>30	
63	3,4-(OCH_2CH_2O)	Me	OH	>226 (dec)	A	XV (4)	$C_{14}H_{12}N_2O_5S$	H, N, O, S; C[i]	0.5 (0.18–1.48)	
64	3,5-$(OCH_3)_2$	H	OEt	166–169	B	XVI (53)	$C_{15}H_{16}N_2O_5S$	C, H, N, O, S	~10	
65	3,5-$(OCH_3)_2$	H	OH	221–223	B	XI (29)	$C_{13}H_{12}N_2O_5S$	C, H, N, S	~1	~0.1
66	2,4-$(OCH_3)_2$	H	OEt	203–207	B	VI (48)	$C_{15}H_{16}N_2O_5S$	C, H, N, O, S	>30	
67	2,4-$(OCH_3)_2$	H	OH	190–193	B	VI (23)	$C_{13}H_{12}N_2O_5S$	C, H, N, S	>10	0.39 (0.2–1.1)
68	2,5-$(OCH_3)_2$	H	OEt	143–144	B	VI (50)	$C_{15}H_{16}N_2O_5S$	C, H, N, O, S	>10	
69	2,5-$(OCH_3)_2$	H	OH·EA	160–162	B	VI (26)	$C_{13}H_{12}N_2O_5S$·C_2H_7NO	C, H, N, O, S	~7	~0.3
70	2-OH, 4-OCH_3	H	OEt	167–170	B	VII (35)	$C_{14}H_{14}N_2O_5S$	C, H, N, S	~1	
71	2-OH, 4-C_6H_5	H	OEt	189–195	B	VIII (6)	$C_{19}H_{16}N_2O_4S$	C, H, N, O, S	>10	
72	2-OH, 4-C_6H_5	H	OH	>225	B	II (5)	$C_{17}H_{12}N_2O_4S$	C, H, N, O, S	>30	
73	2-CH_3, 4-OH	H	OEt	173–176	B	XVII (16)	$C_{14}H_{14}N_2O_4S$	C, H, N, O, S	3.7 (1.5–9.0)	
74	2-CH_3, 4-OH	H	OH·EA	195–197	B	XIV (13)	$C_{12}H_{10}N_2O_4S$·C_2H_7NO	C, H, N, O, S	>10	~1
75	3,4-$(CH_2CH_2CH_2CH_2)$	H	OEt	121.5–122.5	A	XVII (28)	$C_{17}H_{18}N_2O_3S$	C, H, N	>10	

Table I (*Continued*)

no.	R_1	R_2	R_3	mp, °C	method	recrystn solvent[a] (% yield)[b]	formula	anal.	rat PCA ED_{50},[l,m] mg/kg po	rat PCA ED_{50},[l,m] mg/kg iv
76	3,4-($CH_2CH_2CH_2CH_2$)	H	NH_2	226–228	A	XVIII (28)	$C_{15}H_{15}N_3O_2S$	C, H, N	>10	
77	3,4-(S-*o*-C_6H_4S)	H	OEt	234–237	A	XV (61)	$C_{19}H_{14}N_2O_3S_3$	C, H, N	>10	
78	3,4-($COC(CH_3)$=$C(CH_3)O$)	H	OEt	>240 (dec)	A	XIV (1)	$C_{18}H_{16}N_2O_5S$	C, H, N	>3	
79	3,4-[$N(COCH_3)$-*o*-C_6H_4S]	H	OEt	206–207	A	XIX (31)	$C_{21}H_{17}N_3O_4S_2$	H, N; C[j]	>10	
80	3,4-[$N(COCH_3)$-*o*-C_6H_4S]	H	OH·EA	>218 (dec)	A	II (8)	$C_{19}H_{13}N_3O_4S_2 \cdot C_2H_7NO$	C, H, N	~10	
81	3,4-[$OCH_2CH(CH_2$-c-$NC_5H_{10})O$]	H	OEt	153–155	A	XX (14)	$C_{21}H_{25}N_3O_5S$	C, H, N	>10	
82	3,5-$(OCH_3)_2$, 4-OH	H	OEt	164–168	B	VI (18)	$C_{15}H_{16}N_2O_6S$	C, H, N, O, S	~10	
83	3,4,5-$(OCH_3)_3$	H	OEt	141–144	B	II (31)	$C_{16}H_{18}N_2O_6S$	C, H, N, S	14.5 (4.67–21.77)	
84	3,4,5-$(OCH_3)_3$	H	OH·EA	158–161	B	XXI (25)	$C_{14}H_{14}N_2O_6S \cdot C_2H_7NO$	H, N, S; C[k]	5.8 (3.44–9.04)	~1
85	2-OH, 4,6-$(CH_3)_2$	H	OEt	167–170	B	II (12)	$C_{15}H_{16}N_2O_4S$	C, H, N, O, S	~10	
86	2-OH, 4,6-$(CH_3)_2$	H	OH·EA	207–208	B	III (6)	$C_{13}H_{12}N_2O_4S \cdot C_2H_7NO$	C, H, N, S	>10	
DSCG										1.24 (0.56–2.74)

[a] I, $CHCl_3$; II, EtOH; III, EtOH–H_2O; IV, pyridine–EtOH; V, $CHCl_3$–EtOH; VI, DMF–EtOH; VII, acetone–EtOH; VIII, EtOAc; IX, EtOH–H_2O–ether; X, $CHCl_3$–acetone; XI, DMF–MeOH; XII, THF–EtOH; XIII, $CHCl_3$–MeOH; XIV, MeOH; XV, CH_2Cl_2–MeOH; XVI, acetone; XVII, EtOH–petroleum ether; XVIII, THF–cyclohexane; XIX, CH_2Cl_2–EtOH; XX, pyridine–ether; XXI, EtOH–MeOH. [b] Overall yields from 3 (method A) or 2 (method B). [c] Aminothiazole available from Aldrich Chemical Co. [d] Yield from the amine 4. [e] C: calcd, 53.43; found, 53.00. [f] N: calcd, 15.89; found, 16.31. [g] N: calcd, 21.01; found, 20.53. [h] C: calcd, 50.64; found, 50.06. [i] C: calcd, 52.70; found, 51.80. [j] C: calcd, 57.39; found, 56.91. [k] C: calcd, 48.11; found, 47.52. [l] 95% confidence limits are given in parentheses. [m] All ED_{50} values are considered significant at $p < 0.05$ as determined by Student's *t* test.

Table II. Alkyl-, Aryl-, and Heteroarylthiazolyloxamic Acids and Esters



no.	R_1	R_2	R_3	mp, °C	method	recrystn solvent[a] (% yield)[b]	formula	anal.	rat PCA ED_{50},[f,g] mg/kg po	rat PCA ED_{50},[f,g] mg/kg iv
87	Me	Me	OEt	90–90.5	*c*	I (30)	$C_9H_{12}N_2O_3S$	C, H, N	>10	
88	H	Ph	OEt	176–177	*c*	II (92)	$C_{13}H_{12}N_2O_3S$	C, H, N	~10	
89	H	Ph	OH	>233 dec	*c*	III (57)	$C_{11}H_8N_2O_3S$	H, N; C[d]	4.03 (1.3–23)	~0.3
90	2-pyridyl	H	OEt	141–144	B	IV (29)	$C_{12}H_{11}N_3O_3S$	C, H, N, O, S	~10	
91	3-pyridyl	H	OEt	226–228	B	IV (88)	$C_{12}H_{11}N_3O_3S$	C, H, N, O, S	~10	
92	3-pyridyl	H	OH·EA	215–219	B	V (70)	$C_{10}H_7N_3O_3S \cdot C_2H_7NO$	C, H, N, O, S	>10	
93	4-pyridyl	H	OEt	209–211	B	IV (94)	$C_{12}H_{11}N_3O_3S$	H, N, O, S; C[e]	1.2 (0.5–2.9)	
94	4-pyridyl	H	OH·EA·H_2O	167–176	B	V (63)	$C_{10}H_7N_3O_3S \cdot C_2H_7NO \cdot H_2O$	C, H, N	>3	0.06 (0.03–0.1)
95	2-furanyl	H	OEt	117–119	B	VI (65)	$C_{11}H_{10}N_2O_4S$	C, H, N	2.2 (0.91–5.2)	

[a] I, CH_2Cl_2–petroleum ether; II, $CHCl_3$–EtOH; III, acetone–EtOH; IV, $CHCl_3$–hexane; V, EtOH–H_2O; VI, EtOH–petroleum ether. [b] Yield from the amine 4. [c] See text. [d] C: calcd, 53.21; found, 52.75. [e] C: calcd, 51.98; found, 49.27. [f] 95% confidence limits are given in parentheses. [g] All ED_{50} values are considered significant at $p < 0.05$ as determined by Student's *t* test.

centrated in vacuo, and the product was recrystallized to give the chloroacetylbenzene derivative.

A mixture of 15 mmol of the above chloro ketone and 30 mmol of thiourea in 50 mL of ethanol was refluxed for 1 h. After the solvent was evaporated in vacuo, the residue was basified with aqueous potassium hydroxide, the product was extracted with ether, and the extract was dried (sodium sulfate). The solution was then filtered and concentrated in vacuo to give the aminothiazole 4, suitable for use in the next reaction.

Method B. To a resin flask equipped with a mechanical stirrer were added 0.10 mol of the appropriate aryl ketones and 0.20 mol of thiourea, followed by the portionwise addition of 0.10 mol of iodine (exothermic reaction). When the addition was complete, the thick mass was heated for several hours at 100 °C. After the thick mass was cooled, methanol was added, the solid was broken up and treated with warm water, and the lumps were ground with a large mortar and pestle. The crushed solid was then filtered, and the residue was washed successively with water, ethanol, and ether. Drying in vacuo yielded the hydriodide salt of the aminothiazole 4, which was suitable for use in the next reaction.

Synthesis of Compound 5. To a solution of 20 mmol of aminothiazole 4 in 25 mL of pyridine was rapidly added 20 mmol of ethyloxalyl chloride. After stirring overnight at room temperature, the reaction mixture was quenched with saturated sodium bicarbonate, the solid precipitate was filtered, and the residue was washed with water. Recrystallization provided the oxamates 5 (see Tables I and II).

Synthesis of Compound 6. A mixture of the oxamate 5 and 1 N sodium hydroxide was warmed (~40 °C) until the solution was clear. Filtration of this solution, followed by acidification with dilute hydrochloric acid, gave a precipitate, which was collected and washed with water. Recrystallization provided the oxamic acid 6 (see Tables I and II).

Synthesis of Compound 7. A suspension of the ester 5 in an excess of ammonium hydroxide was stirred overnight at room temperature in a stoppered flask. The product was filtered, and the residue was washed with water and dried in vacuo to yield the pure oxamamide 7.

Ethyl *N*-(4,5-Dimethyl-2-thiazolyl)oxamate (87). A solution of 15.1 g (0.10 mol) of 3-bromo-2-butanone, 15.2 g (0.20 mol) of thiourea, and 75 mL of ethanol was refluxed for 2 h. The mixture was then concentrated in vacuo, treated with aqueous sodium bicarbonate, and extracted with methylene chloride, and the extract was dried (sodium sulfate). Removal of the solvent in vacuo gave, after recrystallization from methanol–methylene chloride, 4.7 g (0.037 mol) of 2-amino-4,5-dimethylthiazole, mp 296–298 °C. Anal. ($C_5H_8N_2S$) C, H, N.

The ethyl oxamate 87 was prepared from the above aminothiazole as described for the synthesis of 5.

***N*-(5-Phenyl-2-thiazolyl)oxamic Acid (89) and Its Ethyl Ester (88).** A solution of 16.0 g (0.10 mol) of bromine in 10 mL of methylene chloride was slowly added to a cooled (−10 °C) solution of 12.0 g (0.10 mol) of phenylacetaldehyde in 25 mL of methylene chloride. The resulting solution was allowed to come to room temperature and then warmed to reflux for 30 min. Aqueous sodium bicarbonate was added to the cooled mixture, the product was extracted with methylene chloride, and the extract was dried (sodium sulfate) and concentrated in vacuo. The resulting residue, which was used directly in the next reaction, was treated with 15.2 g (0.20 mol) of thiourea and 75 mL of ethanol. This mixture was refluxed for 2 h, cooled, and filtered, and the solid was treated with aqueous sodium bicarbonate. Recrystallization from methanol–water gave 9.1 g (0.052 mol) of 2-amino-5-phenylthiazole, mp 205–207 °C. Anal. ($C_9H_8N_2S$) C, H, N.

The ethyl oxamate 88 was prepared from the above aminothiazole as described for the synthesis of 5, and the oxamic acid 89 was prepared from the ester 88 as described for the synthesis of 6.

Biological Methods. The potential antiallergic properties of the compounds were ascertained by using a modification[10] of the rat passive cutaneous anaphylaxis (PCA) reaction described by Mota (1964).[11] The anti-ovalbumin (OA) reaginic serum was produced in Sprague–Dawley rats obtained from Taconic Farms (Germantown, NY). Male rats weighing 250–300 g received by ip administration 30×10^9 *Bordetella pertussis* organisms (Armand Frappier Institute, Montreal, Quebec) and by im administration a 0.5-mL suspension containing 1 mg of ovalbumin (recrystallized 5 times) and 10 mg of $Al(OH)_3$. Seven days later, each rat received 2000 *Nippostrongylus brazilensis* larvae, sc. On day 21, the rats were anesthetized with methoxyflurane and exsanguinated via a heart puncture. Blood was then pooled, the serum was collected and filtered (Nalgene 0.45-μm filter), and the filtrate was stored at −20 °C.

A dilution of this serum was used which gave reproducible skin reaction diameters between 13 and 15 mm in unanesthetized rats. This serum dilution was injected in a volume of 0.1 mL id on each side of the shaved backs of male rats 24 h before antigen challenge. Test compounds evaluated by iv administration were dissolved in saline and mixed with 0.5 mL of a solution containing 5 mg of ovalbumin (recrystallized 5 times) and 2% Evans Blue and administered at a final adjusted volume of 1 mL/kg. This mixture was injected 24 h after the rats had been passively sensitized. For evaluation of oral activity, the test compound was suspended in 1% acacia and administered in a volume of 1 mL/kg with an oral feeding needle. The antigenic challenge consisted of 0.02 mg of ovalbumin in 0.5 mL of 2% Evans Blue administered 20–30 min after oral test compound administration. Six rats per group were used for untreated control responses and for each dose tested.

Thirty minutes after antigenic challenge, i.e., for either intravenous or oral administration, the rats were killed by CO_2 asphyxiation. A midline incision was made along the spine, the skin was reflected, and the diameters of the blued areas were measured. The mean area was determined for each spot, and the mean circular area of that test group was calculated. The mean area of the control group was considered as a 100% response, and the results of the test compound groups were expressed as a percent change from the control values. Where applicable, ED_{50}'s (defined as a 50% reduction in area) with 95% confidence limits were determined with the Statistical Analysis System (SAS) program 79.4. In those cases where an ED_{50} with confidence limits could not be calculated, the approximate ED_{50}'s given in Tables I and II were estimated, and a significant difference ($p < 0.05$) from control was verified by Student's t test.

Acknowledgment. The authors gratefully acknowledge the expert technical assistance of E. Dubois.

Registry No. 8, 74531-87-6; 9, 78692-94-1; 10, 78693-00-2; 11, 74605-10-0; 12, 74605-02-0; 13, 74605-06-4; 14, 74604-47-0; 15, 74604-86-7; 16, 74604-57-2; 17, 74604-58-3; 18, 74604-53-8; 19, 74604-59-4; 20, 74604-38-9; 21, 74604-41-4; 22, 74604-51-6; 23, 74604-55-0; 24, 74531-88-7; 25, 74604-99-2; 26, 74605-04-2; 27, 85849-61-2; 28, 85849-63-4; 29, 85849-64-5; 30, 85849-66-7; 31, 74604-45-8; 32, 74604-90-3; 33, 74604-88-9; 34, 74604-63-0; 35, 74604-67-4; 36, 74604-46-9; 37, 74604-44-7; 38, 85849-67-8; 39, 85849-68-9; 40, 85849-69-0; 41, 85849-70-3; 42, 85849-71-4; 43, 85849-72-5; 44, 85849-74-7; 45, 85849-75-8; 46, 74604-75-4; 47, 74604-81-2; 48, 74604-80-1; 49, 74604-82-3; 50, 74604-92-5; 51, 74604-98-1; 52, 85849-76-9; 53, 85849-78-1; 54, 85849-79-2; 55, 85849-81-6; 56, 74604-73-2; 57, 74604-50-5; 58, 74604-84-5; 59, 74604-54-9; 60, 74604-66-3; 61, 74604-77-6; 62, 85849-82-7; 63, 85849-83-8; 64, 74604-48-1; 65, 74604-49-2; 66, 74604-52-7; 67, 74604-56-1; 68, 74604-39-0; 69, 74604-79-8; 70, 74604-61-8; 71, 74604-62-9; 72, 74604-74-3; 73, 74604-65-2; 74, 74604-71-0; 75, 85849-84-9; 76, 85849-85-0; 77, 85849-86-1; 78, 85849-87-2; 79, 85849-88-3; 80, 85849-90-7; 81, 85849-91-8; 82, 74604-60-7; 83, 74604-64-1; 84, 74604-69-6; 85, 74604-91-4; 86, 74604-96-9; 87, 82514-61-2; 88, 85849-92-9; 89, 85849-93-0; 90, 74604-40-3; 91, 74604-43-6; 92, 74604-94-7; 93, 74604-42-5; 94, 74605-01-9; 95, 83089-58-1; $ClCOCH_2Cl$, 79-04-9; $H_2NC{=}S(NH_2)$, 62-56-6; $ClCOCO_2Et$, 4755-77-5; 3-bromo-2-butanone, 814-75-5; 2-amino-4,5-dimethylthiazole, 2289-75-0; phenylacetaldehyde, 122-78-1; 2-amino-5-phenylthiazole, 39136-63-5.

(10) J. El-Azab and P. B. Stewart, *Int. Arch. Allergy Appl. Immunol.*, **55**, 343 (1977).

(11) I. Mota, *Immunology*, **7**, 681 (1964).