activity is, in our view, most interesting.

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References and Notes

(1) On leave from the Department of Medicinal Chemistry, College of Pharmacy, University of Illinois/Medical Center, Chicago, Ill.
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N,N'-(Phenylene)dioxamic Acids and Their Esters as Antiallergy Agents

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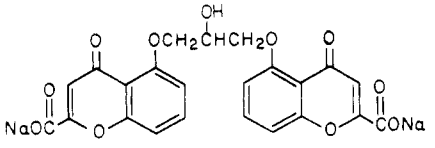
A series of dialkyl *N,N'*-(*m*-phenylene)dioxamates was synthesized by treatment of the requisite *m*-phenylenediamines with an alkyloxalyl chloride in the presence of triethylamine. Hydrolysis with sodium hydroxide solution gave the corresponding *N,N'*-(*m*-phenylene)dioxamic acids. Several *N,N'*-(*p*-phenylene)dioxamic acids were synthesized also in the same manner starting with the requisite *p*-phenylenediamines. These compounds were tested in the rat passive cutaneous anaphylaxis (PCA) assay. When tested iv, activity was found in the *N,N'*-(*m*-phenylene)dioxamic acids up to 2500 times that shown by disodium cromoglycate [50% inhibition at 0.001 mg/kg for *N,N'*-(2-chloro-5-cyano-*m*-phenylene)dioxamic acid (compound **61**)]. Oral activity was seen in this series of compounds with duration of activity up to 120 min. Oral activity was detected in diethyl *N,N'*-(2-chloro-5-cyano-*m*-phenylene)dioxamate (compound **38**) at levels of drug as low as 0.1 mg/kg.

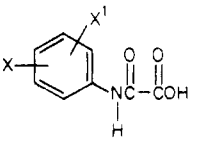
Disodium cromoglycate (**1**) is an antiasthma agent that



1

is thought to act by inhibition of the liberation of the mediators of allergic reactions initiated by antigen–antibody reactions.[1] This activity may be measured conveniently in rats by means of the passive cutaneous anaphylaxis (PCA) reaction.[2]

Previously, we[3] and others[4] have reported that monooxamic acids of the type **2** and **3** possess this same activity to an appreciable extent.



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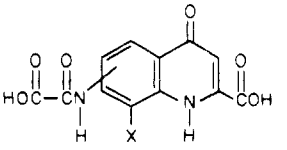


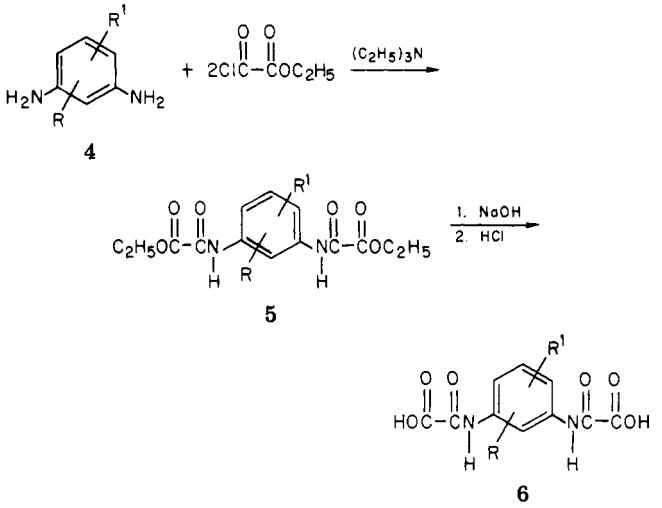
3

Disodium cromoglycate (**1**), as may be seen from its structure, possesses a "bis-functionality". A high order of activity was noted[5] also in the fused-ring quinaldic acids which also possess a bis-functionality. In order to explore the importance of this bis-functionality on the biological activity we synthesized and studied biologically a series of *N,N'*-(phenylene)dioxamic acids and their esters. The results of this study are described below.

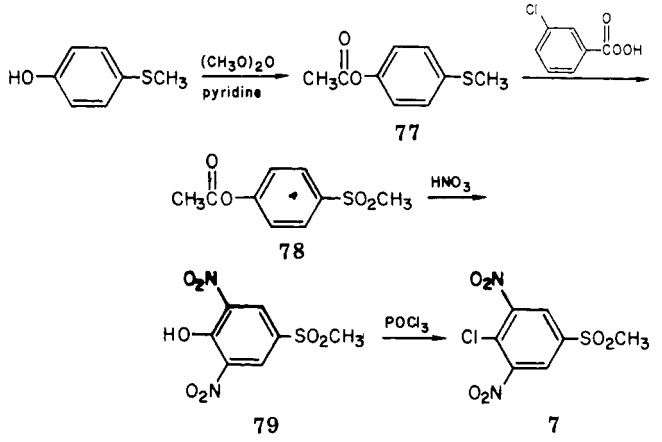
Chemistry. Synthesis of diethyl *N,N'*-(*m*-phenyl-

0022-2623/78/1821-0930$01.00/0

Scheme I



Scheme II



ene)dioxamates **5** (Table I) and the corresponding *N,N'*-(*m*-phenylene)dioxamic acids **6** (Table II) was carried out by a general method[3,4] used to synthesize the monooxamates, namely, treatment of the requisite amine with ethyloxalyl chloride in the presence of triethylamine, followed by hydrolysis of the resulting of ester with sodium hydroxide solution (Scheme I).

It was found that the resulting dioxamic acids **6** in many cases formed hydrates readily or held water very tenaciously. In some cases it was difficult to remove the water by drying before elemental analysis.

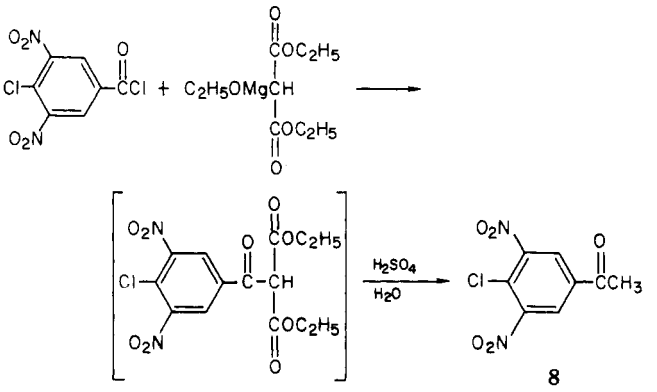
The starting *m*-phenylenediamines **4** that were not commercially available were obtained from the corresponding *m*-dinitrobenzenes either by reduction with stannous chloride in the presence of hydrochloric acid (procedure A), by catalytic hydrogenation in the presence of Raney nickel (procedure B) or palladium on charcoal (procedure C), or by reduction with iron powder and hydrochloric acid in 90% ethanol (procedure D). The previously unreported *m*-phenylenediamines are listed in Table III.

The synthesis of two of the requisite dinitro compounds deserves mention. 4-Chloro-3,5-dinitrophenyl methyl sulfone (**7**) was synthesized as outlined in Scheme II.

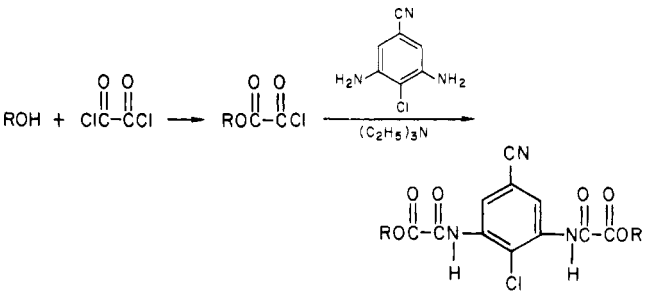
4-Chloro-3,5-dinitroacetophenone (**8**) was synthesized as outlined in Scheme III, utilizing the general method of Krashov.[6]

In view of the very potent activity ultimately shown by diethyl *N,N'*-(2-chloro-5-cyano-*m*-phenylene)dioxamate (**38**), it was felt of interest to investigate some higher esters of **38** in order to determine what effect this variation would

Scheme III



Scheme IV

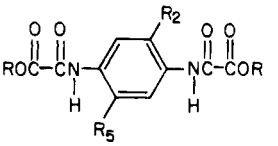


9a, R = *n*-C_4H_9
b, R = *n*-C_6H_{13}
c, R = 1-adamantyl

have upon activity and duration of activity.

These esters were synthesized by the method that was used for the diethyl esters, namely, reaction of the requisite diamine with an alkyloxalyl chloride in the presence of triethylamine. The requisite alkyloxalyl chlorides were prepared by treatment of the requisite alcohols with an excess of oxalyl chloride (Scheme IV).

In addition to the *N,N'*-(*m*-phenylene)dioxamic acids listed in Table II, there were prepared and tested three *N,N'*-(*p*-phenylene)dioxamic acids. These are indicated below (**10–12**).

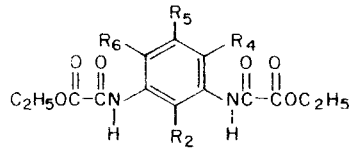


10, R = H; R_2 = H; R_5 = H
11, R = H; R_2 = CN; R_5 = H
12, R = H; R_2 = Cl; R_5 = Cl
80, R = Et; R_2 = H; R_5 = H
82, R = Et; R_2 = CN; R_5 = H
83, R = Et; R_2 = Cl; R_5 = Cl

In general, these compounds were synthesized in the same manner as were the *N,N'*-(*m*-phenylene)dioxamic acids, that is, treatment of the requisite diamine with ethyloxalyl chloride in the presence of triethylamine followed by saponification of the diethyl dioxamate with sodium hydroxide solution. In one case, namely, the preparation of **10**, an alternate method was used for the preparation of the intermediate diethyl *N,N'*-(*p*-phenylene)dioxamate. This involved refluxing of *p*-phenylenediamine with an excess of diethyl oxalate.[7]

Biological Results. The results obtained in the iv rat passive cutaneous anaphylaxis (PCA) assay for the *N,N'*-(*m*-phenylene)dioxamic acids are listed in Table II and those for the *N,N'*-(*p*-phenylene)dioxamic acids are listed in Table IV. The results of the oral PCA assay for the diethyl (*m*-phenylene)dioxamates are listed in Table I and those for the higher alkyl (*m*-phenylene)dioxamates are

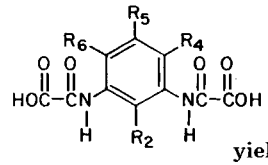
Table I. Diethyl *N,N'*-(*m*-Phenylene)dioxamates



compd	R_2	R_4	R_5	R_6	formula	mp, °C	yield, %	recrystn solvent	analyses	% inhibn of rat PCA, oral dosing: dose, mg/kg	time (min) before challenge: 5	20	60	120	time of peak act.	lowest concn (mg/kg) showing act. >20%
13	H	H	H	H	$C_{14}H_{16}N_2O_6$	155–160	62	MeOH	C, H, N	50	3	94	14	29	20	1.0
14	F	H	H	H	$C_{14}H_{15}FN_2O_6$	164	66	EtOH	C, H, F, N	50			0			
15	Cl	H	H	H	$C_{14}H_{15}ClN_2O_6$	165–166	54	EtOH	C, H, Cl, N	50	53	17	1.8		5	
16	$COOCH_3$	H	H	H	$C_{16}H_{18}N_2O_8$	156–157.5	68	MeOH	C, H, N	50		27	15	0		
17	CH_3	H	H	H	$C_{15}H_{18}N_2O_6$	140–141	32	EtOH	C, H, N	50	28	53				
18	CN	H	H	H	$C_{15}H_{15}N_3O_6$	167–168	62	EtOH	C, H, N							
19	OCH_3	H	H	H	$C_{15}H_{18}N_2O_7$	161.5–163.5		acetone	C, H, N	50	72	11	22			
20	H	CH_3	H	H	$C_{15}H_{18}N_2O_6$	154–155	80	EtOH	C, H, N	50	17	38	12			
21	H	*n*-C_4H_9	H	H	$C_{18}H_{24}N_2O_6$	123–125	26	MeOH–H_2O	C, H, N	50	0	0	5	0		
22	H	OCH_3	H	H	$C_{15}H_{18}N_2O_7$	140–145	55	EtOH	C, H, N	50	50	70	11	45		
23	H	CN	H	H	$C_{15}H_{15}N_3O_6$	138–139	70	EtOH	C, H; N[a]	10	7	19	19			
24	H	F	H	H	$C_{14}H_{15}FN_2O_6$	130	47	EtOH	C, H, F, N	50	74	64	18			
25	H	H	OCH_3	H	$C_{15}H_{18}N_2O_7$	172–173	93	MeOH	C, H, N	50		4	0	29		
26	H	H	COOH	H	$C_{15}H_{16}N_2O_8$	251	44	MeOH	H, N; C[b]	50	14	0	0	20		
27	H	H	$CONH_2$	H	$C_{15}H_{17}N_3O_7$	213–215	57	EtOH–H_2O	C, H, N							
28	H	H	CN	H	$C_{15}H_{15}N_3O_6$	119–121	38	EtOH	C, H, N	10	95	25	0			
29	H	H	NO_2	H	$C_{14}H_{15}N_3O_8$	192.5–195.0	77	acetone	C, H, N	50	0	0	6			
30	H	H	$NHCOCOOC_2H_5$	H	$C_{18}H_{21}N_3O_9$	196–200	55	MeOH	C, H, N	50		0	5	0		
31	H	H	$NHCOCH_3$	H	$C_{16}H_{19}N_3O_7$	210–212	65	EtOH	C, H, N	50	6	1	0	24		
32	Cl	H	CH_3	H	$C_{15}H_{17}ClN_2O_6$	180–181.5	71	acetone	C, H, Cl, N	50		26	0	3		
33	Cl	H	COOH	H	$C_{15}H_{15}ClN_2O_8$	264–265	61	EtOH	C, H, Cl, N	50	15	41	15	9		
34	Cl	H	$COOCH_3$	H	$C_{16}H_{17}ClN_2O_8$	203.5–204.5	50	acetone	C, H, Cl, N	50		7	0	0		
35	Cl	H	$CONH_2$	H	$C_{15}H_{16}ClN_3O_7$	212–213	34	EtOH	C, H, Cl, N	50	85	49				
36	Cl	H	$COCH_3$	H	$C_{16}H_{17}ClN_2O_7$	182–184	98	EtOH	C, H, Cl, N	50		14	37	31		
37	Cl	H	CF_3	H	$C_{15}H_{14}ClF_3N_2O_6$	206–207	92	EtOH–H_2O	C, H, Cl, F, N	50	10	10	4			
38	Cl	H	CN	H	$C_{15}H_{14}ClN_3O_6$	177–179	58	EtOH	C, H, Cl, N	50	100	31	0		5	0.1
39	Cl	H	CH_3SO_2	H	$C_{15}H_{17}ClN_2O_8S$	225	60	*i*-PrOH	C, H, Cl, N, S	50	0	0	0			
40	Cl	H	C_6H_5	H	$C_{20}H_{19}ClN_2O_6$	204–205	78	EtOH	C, H, Cl, N	50	25	25				
41	Cl	NO_2	H	NO_2	$C_{14}H_{13}ClN_4O_{10}$	250–251	76	EtOH	C, H, Cl, N	50		25	0			
42	CH_3	H	COOH	H	$C_{16}H_{18}N_2O_8$	234–235	48	EtOH	C, H, N	50	0	0	0	0		
43	CN	H	CF_3	H	$C_{16}H_{14}F_3N_3O_6$	136–137	39	EtOH	C, H, F, N	50	50	25	0			
44	Cl	Cl	$COOCH_3$	H	$C_{16}H_{16}Cl_2N_2O_8$	129–134	16	benzene–ether	C, H, Cl, N	50		0	0	0		
45	H	Cl	H	Cl	$C_{14}H_{14}Cl_2N_2O_6$	124–125	81	EtOH	C, H, Cl, N	50		50	25			
46	H	NO_2	H	NO_2	$C_{14}H_{14}N_4O_{10}$	227–230	36	benzene	C, H, N	50		17	9			
47	H	Cl	CN	H	$C_{15}H_{14}ClN_3O_6$	153–154	75	EtOH	C, H, Cl, N	50	100	20	0			
48	H	Cl	C_6H_5	H	$C_{20}H_{19}ClN_2O_6$	184–185	83	EtOH	C, H, Cl, N	50	72	10	51			

[a] N: calcd, 12.61; found, 13.09. [b] C: calcd, 51.14; found, 50.65.

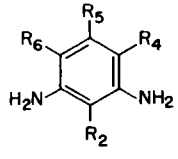
Table II. *N,N'*-(*m*-Phenylene)dioxamic Acids



compd	R_2	R_4	R_5	R_6	formula	mp, °C	yield, %	recrystn solvent	analyses	% inhibn of rat PCA, mg/kg iv 1.0	0.1	0.01	0.001
49	H	H	H	H	$C_{10}H_8N_2O_6$	240 dec	56	EtOH	C, H, N, S	82	73	0	
50	Cl	H	H	H	$C_{10}H_7ClN_2O_6$	>320 dec	64	H_2O	C, H, Cl, N	75	32		
51	H	OCH_3	H	H	$C_{11}H_{10}N_2O_7$	>320	86	H_2O	C, H, N[a]	100	0		
52	H	CN	H	H	$C_{11}H_7N_3O_6 \cdot H_2O$	241 dec	69		C, H, N	87	8		
53	H	F	H	H	$C_{10}H_7FN_2O_6$	>320	83	H_2O	C, H, F, N[b]	100	41		
54	H	H	$CONH_2$	H	$C_{11}H_9N_3O_7 \cdot H_2O$	220 dec	100		C, H, N	91	17		
55	H	H	CN	H	$C_{11}H_7N_3O_6$	230 dec	87		C; H, N[c]		90	57	
56	H	H	$NHCOCH_3$	H	$C_{12}H_{11}N_3O_7$	>320	74	H_2O	H, N; C[d]	47	11	0	
57	Cl	H	CH_3	H	$C_{11}H_9ClN_2O_6$	200-202	52	H_2O	C, H, N, O[e]	100	91	20	2
58	Cl	H	$CONH_2$	H	$C_{11}H_8ClN_3O_7 \cdot H_2O$	>320	70		C, H, Cl, N	90	28	0	
59	Cl	H	$COCH_3$	H	$C_{12}H_9ClN_2O_7 \cdot 0.5H_2O$	208 dec	100	H_2O	C, H, Cl, N	88	22	0	
60	Cl	H	CF_3	H	$C_{11}H_6ClF_3N_2O_6 \cdot 0.5H_2O$	213 dec	98	H_2O	C, H, Cl, F, N		100	90	0
61	Cl	H	CN	H	$C_{11}H_6ClN_3O_6$	212 dec	96		C, H, Cl, N			94	50
62	Cl	H	C_6H_5	H	$C_{16}H_{11}ClN_2O_6$	195 dec	55	H_2O	H, Cl, N; C[f]	94	87	44	
63	H	Cl	H	Cl	$C_{10}H_6Cl_2N_2O_6$	>340	100		C, H, Cl, N	81	25	0	
64	H	Cl	CN	H	$C_{11}H_6ClN_3O_6 \cdot H_2O$	>300	99	H_2O	C, H, Cl, N[g]	100	100	20	0
84	Cl	H	CH_2SO_2	H	$C_{11}H_8ClN_2O_8NaS$	292-294	55		C, H, Cl, N, Na; S[h]	85	10		

[a] Corrected for 1.13% water. [b] Corrected for 6.98% water. [c] H: calcd, 2.55; found, 3.04. N: calcd, 15.16; found, 15.88. [d] Corrected for 2.72% water. C: calcd, 46.60; found, 47.07. [e] Corrected for 6.98% water. [f] C: calcd, 52.98; found, 52.33. [g] C: calcd, 40.08; found, 40.57. H: calcd, 2.44; found, 1.90. N: calcd, 12.75; found, 13.25. Cl: calcd, 10.76; found, 11.36. [h] Analyzed as the monosodium salt. Corrected for 1.18% water. S: calcd, 8.28; found, 9.36).

Table III. *m*-Phenylenediamines



compd	R_2	R_4	R_5	R_6	formula	mp, °C	procedure	yield, %	recrystn solvent	analyses
65	H	CN	H	H	$C_7H_7N_3$	203-204	A	66		C, H, N
66	H	H	CN	H	$C_7H_7N_3$	188-189	A	96	EtOH	C, H, N
67	Cl	H	$COCH_3$	H	$C_8H_6ClN_2O$	123-126	A	90	MeOH	C, H, Cl, N
68	Cl	H	$CONH_2$	H	$C_7H_6ClN_3O$	195-196	A	25	EtOH	C, H, Cl, N
69	Cl	H	CN	H	$C_7H_6ClN_3$	169-170	A	68	EtOH-H_2O	C, H, Cl, N
70	Cl	H	C_6H_5	H	$C_{12}H_{11}ClN_2$	146-147	B	51	EtOH-H_2O	C, H, N; Cl[a]
71	H	H	$HNC(=O)CH_3$	H	$C_8H_{11}N_3O$	112-115	C	80	H_2O	C, H; N[b]
72	CN	H	CF_3	H	$C_8H_6F_3N_3$	65-66	A	43	C_6H_6-C_6H_{14}	C, H, N; F[c]
73	H	Cl	CN	H	$C_7H_6ClN_3$	181-182	A	56	EtOH	C, H, Cl, N
74	Cl	H	CH_3SO_2	H	$C_7H_6ClN_2O_2S$	204-206	D	78	EtOH	C, H, Cl, N, S
76	Cl	Cl	$COOCH_3$	H	$C_8H_6Cl_2N_2O_2$	115.5-117.5	D	55	EtOH	C, H, Cl, N

[a] Cl: calcd, 16.21; found, 15.52. [b] N: calcd, 25.44; found, 24.86. [c] F: calcd, 28.34; found, 29.04.

Table IV. Miscellaneous Dioxamic Acids and Esters

compd	dose	route	% inhibn of rat PCA, mg/kg	time[a] of peak act., min
9a	50	po	100	5
9b	50	po	51	5
9c	50	po	50	60
10	1.0	iv	18	
11	1.0	iv	45	
12	1.0	iv	73	

[a] Optimum time between dosing and challenge.

listed in Table IV. When given by the iv route sodium cromolyn had an ED_{50} of 2.5 mg/kg in the PCA assay.

It is clear from the tables for the dioxamic acids (Tables II and IV) that there are found in this series some extremely active compounds [**61** with 50% inhibition at 0.001 mg/kg represents an activity of 2500 times that shown by disodium cromoglycate (**1**)[8,9]]. It is also equally clear that substitution on the phenyl ring especially at position 5 by electron-attracting substituents is essential for superior activity. A chlorine atom at position 2 also appears to be a favorable substitution, as seen in the comparison of compounds **55**, **61**, and **64**.

For orally administered esters (Tables I and IV), the kinds of activity one sees are both duration of activity (**22**, Table I) and intrinsic activity by the oral route (**38**, Table I) showing greater than 20% inhibition at 0.1 mg/kg.

Experimental Section

Melting points were taken in an oil bath and are uncorrected. The IR spectra were measured on a Perkin-Elmer 421 or Digilab FTS 140 spectrometer. The NMR spectra were measured on a Varian A-60 or a Varian T-60 spectrometer. The IR and NMR spectra were consistent with the assigned structures in all cases. The results of elemental analysis were within ±0.4% of the theoretical values except where noted.

Chemistry. 4-Chloro-3,5-diaminobenzonitrile (Procedure A) (69). To a solution of 352.5 g (1.56 mol) of stannous chloride dihydrate in 860 mL of concentrated hydrochloric acid was added 50 g (0.2195 mol) of 4-chloro-3,5-dinitrobenzonitrile. The mixture was stirred at room temperature for 2 h and cooled to 0 °C in an ice–salt bath, and the mixture was made strongly basic by the addition of a cold 50% sodium hydroxide solution.

The precipitate was removed by filtration and extracted three times with 400-mL portions of ethyl acetate. The extracts were combined and used to extract the aqueous filtrate. The ethyl acetate extracts were dried over anhydrous magnesium sulfate, the solvent was removed, and the residue was recrystallized from a suitable solvent.

2-Chloro-5-phenyl-*m*-phenylenediamine (Procedure B) (70). A solution of 2.79 g (0.01 mol) of 4-chloro-3,5-dinitrobiphenyl in 200 mL of dioxane was hydrogenated at 3 atm of pressure using Raney nickel as the catalyst. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was recrystallized from a suitable solvent.

3,5-Diamino-*p*-toluic Acid (Procedure C) (75). A mixture of 3,5-dinitro-*p*-toluic acid (10.0 g, 0.044 mol), 5% Pd/C (1.0 g), and methanol (300 mL) was shaken on a Parr hydrogenator at 40 psi of hydrogen for 1 h. The catalyst was removed by filtration and the solvent was removed under reduced presssure. The desired product was recrystallized from the appropriate solvent.

4-Methylthiophenyl Acetate (77). A mixture of 4-methylmercaptophenol (20.0 g, 0.14 mol), anhydrous pyridine (150 mL), and acetic anhydride (30.0 g, 0.29 mol) was stirred at room temperature for 18 h. The solvent was removed to leave a residual oil. The oil was dissolved in CH_2Cl_2 and washed with a saturated solution of sodium bicarbonate (2 × 100 mL) and water (100 mL). The organic phase was dried with anhydrous sodium sulfate and the solvent removed. The residue was distilled to give a clear oil (24.04 g, 92%): NMR ($CDCl_3$) δ 7.15 (q, 4 H, aromatic AB), 2.4 (s, 3 H, SCH_3), 2.2 [s, 3 H, $C(=O)CH_3$]; IR (neat) 1760 cm^{-1} (C=O); mass spectrum (70 eV) mol ion m/e^+ 182.

4-Methylsulfonylphenyl Acetate (78). A mixture of methylthiophenyl acetate (10.0 g, 0.055 mol), *m*-chloroperoxybenzoic acid (24.0 g), and methylene chloride (500 mL) was stirred at room temperature for 20 h. The reaction mixture was washed with sodium bisulfite solution (1.0 g in 100 mL of water) and saturated sodium bicarbonate solution (2 × 100 mL). The organic phase was dried with anhydrous sodium sulfate and the solvent was removed to leave a white solid. Recrystallization from Skellysolve B and benzene gave the desired product (11.34 g, mp 97 °C, 96.5%). Anal. ($C_9H_{10}O_4S$) C, H, S.

4-Methylsulfonyl-2,6-dinitrophenol (79). 4-Methylsulfonylphenyl acetate (9.0 g, 0.042 mol) was heated in 20 mL of fuming nitric acid at steam bath temperatures for 2 h. The reaction mixture was cooled to room temperature and was poured into water. The resulting yellow product was dried in a vacuum oven (6.77 g, mp 185–187 °C, 61.5%). Anal. ($C_7H_6N_2O_7S$) C, H, N, S.

4-Chloro-3,5-dinitrophenyl Methyl Sulfone (7). 4-Methylsulfonyl-2,6-dinitrophenol (4.0 g, 0.0153 mol) was heated on a steam bath in a solution of phosphorus oxychloride (20 mL) and DMF (3 mL) for 4 h. The reaction was cooled to room temperature and was poured into water slowly. The resulting white solid was collected by filtration. Recrystallization from ethanol gave a white crystalline product (3.06 g, mp 202–204 °C, 71.5%). Anal. ($C_7H_5ClN_2O_6S$) C, H, N, Cl, S.

2-Chloro-5-methylsulfonyl-1,3-phenylenediamine (Procedure D) (74). A mixture of 4-chloro-3,5-dinitrophenyl methyl sulfone (2.0 g, 0.0071 mol), electrolytically reduced iron powder (4.0 g, 0.072 mol), and 90% ethanol was warmed on a steam bath. A solution of concentrated hydrochloric acid (0.6 mL) in 90% ethanol (10 mL) was added slowly. The reaction was heated at reflux for 2.5 h. The excess iron powder was removed by filtration and the pH of the filtrate was adjusted to 8 with 1.0 N NaOH. The solubilized iron salts precipitated and were removed by filtration. Removal of the solvent, followed by recrystallization, gave the desired product. Anal. ($C_7H_9ClN_2O_2S$) H, Cl, N, S; C: calcd, 38.09; found, 38.51.

Diethyl *N,N'*-(2-Chloro-4,6-dinitro-*m*-phenylene)dioxamate (41). Diethyl *N,N'*-(2-chloro-*m*-phenylene)dioxamate (1.0 g, 0.0029 mol) was stirred in a solution of fuming nitric acid and concentrated sulfuric acid (10 mL, 1:1) at room temperature for 1 h. The reaction mixture was poured into water (200 mL) and the resulting white solid was collected by filtration. Recrystallization from ethanol gave the desired product as a white solid (0.94 g, mp 250–251 °C, 74%).

Diethyl *N,N'*-(2-Chloro-5-cyano-*m*-phenylene)dioxamate (38). To a solution of 56.2 g (0.34 mol) of 4-chloro-3,5-diaminobenzonitrile in 160 mL of dry dimethylformamide was added 82.8 g (0.82 mol) of triethylamine. The solution was cooled to 5 °C and there was added 112 g (0.82 mol) of ethyloxalyl chloride, dropwise. The mixture was stirred at 5 °C for 1 h and then allowed to stand overnight at room temperature. The precipitate was removed by filtration and washed with ethyl acetate, and the ethyl acetate was removed by distillation. The original filtrate was poured into water, and the precipitate was removed by filtration and combined with the material obtained from the ethyl acetate washes. The combined solid was recrystallized from a suitable solvent.

This general procedure was used for the preparation of the diethyl *N,N'*-(*m*-phenylene)dioxamates listed in Table I as well as compounds **82** and **83**.

***N,N'*-(2-Chloro-5-cyano-*m*-phenylene)dioxamic Acid (61).** A solution of 72.4 g (0.197 mol) of diethyl *N,N'*-(2-chloro-5-cyano-*m*-phenylene)dioxamate in 750 mL of methylene chloride was extracted in a separatory funnel with 465 mL of 1 N sodium hydroxide solution. The aqueous phase was separated and acidified with 3 N hydrochloric acid. The precipitate was removed by filtration and washed with water.

Dibutyl *N,N'*-(2-Chloro-5-cyano-*m*-phenylene)dioxamate (9a). To 100 g (0.079 mol) of oxalyl chloride was added over the course of 30 min with stirring 22.24 g of 1-butanol. The mixture was heated under reflux for 3 h, the excess oxalyl chloride was removed by distillation, and the residue was distilled in vacuo through a 15-cm glass helices packed column. There was obtained 39.3 g (80%) of a colorless oil boiling at 64 °C (13 mm).

To a stirred solution of 5.70 g (0.034 mol) of 4-chloro-3,5-diaminobenzonitrile in 16 mL of dry dimethylformamide and 8.30 g (0.082 mol) of triethylamine cooled to 5 °C was added 13.50 g (0.082 mol) of the *n*-butyloxalyl chloride obtained above. After standing for 24 h at room temperature the reaction mixture was poured into 300 mL of water. The precipitate was removed by filtration and recrystallized from a benzene–hexane mixture. There was obtained 10.1 g (52%) of brown needles melting at 120–120.5 °C. Anal. ($C_{19}H_{23}ClN_3O_6$) C, H, Cl, N.

In a similar manner **9b** [mp 83.5–84.5 °C. Anal. ($C_{23}H_{30}ClN_3O_6$) C, H, Cl, N] and **9c** [mp 278 °C dec. Anal. ($C_3H_{34}ClN_3O_6$) C, H, Cl, N] were obtained.

4-Chloro-3,5-dinitroacetophenone (8). The general procedure of Krashov[6] was followed. To a stirred mixture of 8.76 g of magnesium turnings, 80 mL of absolute ethanol, and 2 mL of carbon tetrachloride was added 25 mL of chloroform. The mixture was heated under reflux for 1 h. To the mixture was then added a solution containing 54.5 g of diethyl malonate in 53 mL of chloroform. The mixture was heated under reflux for 3 h and then evaporated to dryness under reduced pressure. The oily residue was dissolved in 62 mL of chloroform and to this solution was added a solution containing 58.2 g (0.22 mol) of 4-chloro-3,5-dinitrobenzoyl chloride in 55 mL of chloroform. The reaction mixture was stirred at room temperature for 12 h and at 33–36 °C for 1 h and then cooled in an ice bath to 5 °C. To this solution was then added 111 mL of 21.5% of sulfuric acid, slowly.

An additional 70 mL of water was added and the chloroform layer was separated and concentrated to dryness. To the oily residue was added 45 mL of water, 67 mL of glacial acetic acid, and 8.3 mL of concentrated sulfuric acid and the mixture was heated under reflux for 8 h. The mixture was evaporated to dryness. The tan residue was triturated with water and the pH was adjusted to 7 with sodium bicarbonate. The precipitate was removed by filtration and recrystallized from ethanol. There was obtained 30.7 g (57%) of fine, tan needles melting at 88–89 °C. Anal. ($C_8H_5ClN_2O_5$) C, H, Cl, N.

Methyl 2,4-Dichloro-3,5-dinitrobenzoate (81). A mixture of 2,4-dichloro-3,5-dinitrobenzoic acid, methanol (75 mL), and concentrated sulfuric acid (1.7 mL) was heated at reflux for 24 h. The desired product precipitated when three-fourths of the solvent was removed under reduced pressure. Recrystallization from MeOH gave a pure product (6.8 g, mp 83.5–85 °C, 65%). Anal. ($C_8H_4Cl_2N_2O_6$) C, H, N, Cl.

Diethyl *N,N'*-(*p*-Phenylene)dioxamate (80). A mixture of *p*-phenylenediamine (10.8 g, 0.10 mol) and diethyl oxalate (50 g) was heated at reflux for 3 h. The cooled reaction mixture was diluted with ether (200 mL) and the solid product was collected by filtration. There was obtained 21.4 g of material melting at 215–218 °C.[7] Anal. ($C_{14}H_{16}N_2O_6$) C, H, N.

***N,N'*-(2-Cyano-*p*-phenylene)dioxamic Acid (11).** A solution of 5.00 g (0.015 mol) of diethyl *N,N'*-(2-cyano-*p*-phenylene)dioxamate in 210 mL of 5% sodium hydroxide solution was stirred for 20 min and then extracted with an equal volume of methylene chloride. The aqueous layer was separated and acidified with 3 N hydrochloric acid. The precipitate was removed by filtration, washed with water, and then recrystallized from water. There was obtained material melting at 210 °C dec. Anal. ($C_{11}H_7N_3O_6$) C, H, N.

This general procedure was used also for the preparation of most of the *N,N'*-(*m*-phenylene)dioxamic acids listed in Table II and *N,N'*-(*p*-phenylene)dioxamic acids listed in Table IV.

Biological Methods. The dioxamic acids synthesized were tested in tris(hydroxymethyl)aminomethane (THAM) solution for their ability to inhibit the passive cutaneous anaphylaxis (PCA) reaction in rats passively sensitized to egg albumin as follows.[10]

Rat homocytotropic antibody was elicited to egg albumin (EA) by the injection (ip) of 0.5 mg of EA + 0.5 cm^3 of *H. pertussis* vaccine (Michigan Department of Public Health, 4.5×10^{10} heat killed organisms) per rat. After 18–20 days the serum was collected and frozen until use. The antibody was shown to be of the 72-h latency type and to be destroyed by heating 1.0 h at 56 °C. Five 0.1-mL volumes of an appropriate dilution of this serum were inoculated into the shaved dorsal surface of a 250-g Sprague–Dawley rat. Saline controls were run and showed less than 4-mm spots. After 72 h the rat was challenged iv with 2 mg per animal of EA + 0.5% Evans blue dye. In the case of acids in drug-treated animals, the materials were given iv at the time of antigen challenge.

For insoluble esters the compounds were administered orally suspended in Vehicle 122 (0.25% methylcellulose, The Upjohn Co., Kalamazoo, Mich.). The oral drug was given at 5, 20, 60, and 120 min before EA challenge by the iv route. After determining the time period between dosing and challenge for optimal inhibition of the reaction, a dose–response curve at that time was run at 50, 10, 5, 1.0, and 0.1 mg/kg. Results were reported as the inhibition of the number of spots per animal (regardless of size) that were seen at five dilutions of serum. The number of spots from a number of sensitization sites in drug-treated animals was compared with the spot score (number of total spots divided by the number of animals) obtained from the same number of sites in untreated animals. Eight animals for control and six for treated were used to calculate the ID_{50}. An iv dose–response curve was established by running three to four doses, six animals each. The percent inhibition of the PCA reaction was then calculated.

It has been found that in repeat runs for disodium cromoglycate the inhibitions can be reproduced with an approximate 8% standard error for duplicate assays. The results are expressed as the percent inhibition for acids and for orally administered esters. A time kinetic curve is given at 50 mg/kg for all compounds, followed by a peak dose response and an indication of the lowest concentration in milligrams per kilogram which gave >20% inhibition of the response.

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