Oxanilic Acids, a New Series of Orally Active Antiallergic Agents

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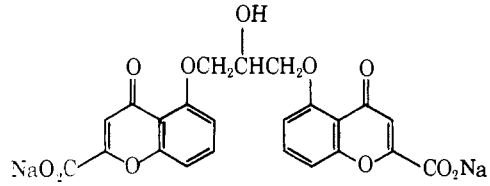
A large number of oxanilic acid esters and N-heteroaryl oxamic acid esters were prepared and found to have antiallergic activity using the rat passive cutaneous anaphylaxis (PCA) test. Many of the oxanilic acid esters are active orally, with the most active species having an aryl 2′-carbamoyl group and a 3′-methoxy group. Hydrolysis of the ester from the oxanilic ester moiety causes a loss of oral activity.

Disodium cromoglycate (1) has been shown to be an effective agent for the treatment of bronchial asthma, and thus far it is the only compound on the market that prophylactically inhibits the liberation of the mediators of allergic reactions initiated by antibody–antigen interactions.



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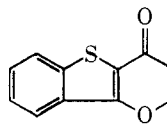
A number of papers and patents have appeared describing the antiallergic activity of relatives of disodium cromoglycate (1),[1-3] 4-oxo-4*H*-[1]benzothieno[3,2-*b*]pyran-2-carboxylic acid (2),[4] 4-oxo-4*H*-[1]benzofuro[3,2-*a*]pyran-2-carboxylic acid (3),[4] 2-nitroindan-1,3-dione (4),[5] 7-(2-hydroxyethoxy)xanthone-2-carboxylic acid (5),[6-8] and 1,4-dihydro-4-oxoquinolinecarboxylic acid (6).[9] Only one compound, AH-7725[8] (5), has been shown to be effective when given by mouth.



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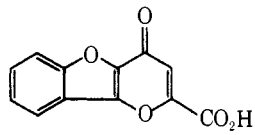

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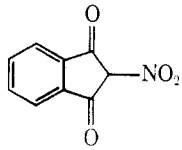

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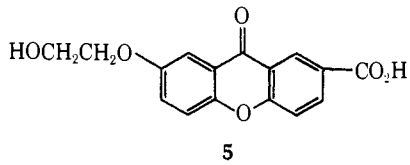

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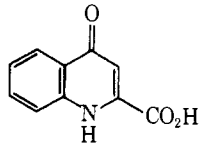

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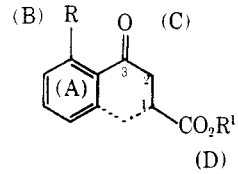
Our objective was to find compounds that had not only antiallergic activity but ones that were also orally active. This paper describes a series of compounds which were found to be active orally and intraperitoneally in the rat passive cutaneous anaphylaxis (PCA) test.

Based on the knowledge of the chemical features of disodium cromoglycate (1), we designed our synthetic efforts around four features that we thought would be essential for activity. As shown in the model compound 7, these are (A) an aromatic nucleus, (B) an R group (optimally an ether group), which should be peri to (C), a carbonyl group, and (D) an acidic group, which should be in a 1,3 relationship to the carbonyl group on the ring.



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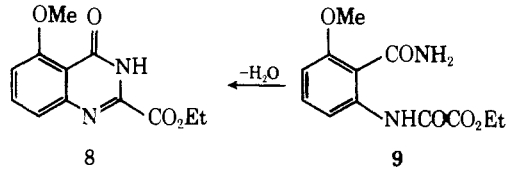
We embarked upon the synthesis of compounds related to 1 which involved the above four features we felt would be essential for activity. One of the compounds that was prepared, the quinazoline 8 in which the -OC=C- group of 1 was replaced with the amidino group (-NC=NH-), was active when given intraperitoneally. However, different batches had rather large variations in potency, and subsequent investigation of these batches by TLC indicated that each had a small amount of contaminant. Investigation of the structure of the contaminant indicated that it was the oxanilic acid ethyl ester 9, the undehydrated intermediate leading to quinazoline 8. A pure sample of ester 9 was then prepared and found to be considerably more potent than quinazoline 8. Thus, as a result of this lead a large number of *N*-aryl and N-heteroaryl oxamic acid esters were prepared and tested for their antiallergy activity.



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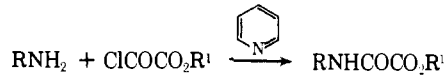
Chemistry. Synthesis of the oxamic acid esters in the series from Tables I–IV was readily carried out (Scheme I) by the acylation of the appropriate amine (10) with various mono esters of oxalyl chloride (11) in the presence of pyridine.

Scheme I



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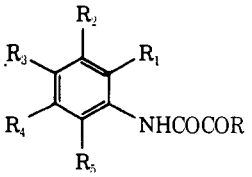
The 2-amino-6-methoxybenzamide intermediate 15 to the oxanilic acid ester 9 was prepared from the precursor 2-nitro-6-methoxybenzonitrile 14 described by Russell and Addison.[10] However, their method suffered from very low yields, and after several attempts we were able to develop a procedure providing nitrile 14 in excellent yield (Scheme II). Treatment of 2,6-dinitrobenzoic acid (12) with phosphorus pentachloride and *p*-toluenesulfonamide[11] provided the common dinitronitrile intermediate 13, having a nitro group that was easily replaced by nucleophiles.[12] The methoxynitrile 14 was readily prepared from dinitronitrile 13 by reaction with sodium methoxide in methanol. Reduction and hydrolysis of methoxynitrile 14 in one step by hydrazine and Raney nickel[13,14] in ethanol yielded the 2-aminobenzamide 15. Reaction of dinitronitrile 13 with other

Table I. Oxanilic Acid Esters



Compd	R	R_1	R_2	R_3	R_4	R_5	Mp or bp (mm), °C	Crystn solvent	Analyses	% inhibn,[a] 200 mg/kg ip	% inhibn[a] po 200 mg/kg	25 mg/kg	10 mg/kg
	Disodium cromoglycate									86			
24	OEt						64–67[c]	EtOH		100	64		7
25	OEt	Me					126 (0.05)[d]			75		14	0
26	OEt		Me				56–60[e]	Benzene–hexane		85	51		0
27	OEt			Me			65–67[d]	Benzene–hexane		100	13		
28	OEt	OMe					81–85[d]	Benzene–hexane		100	11		
29	OEt		OMe				95–98[f]	MeOH–H_2O		38			0
30	OEt			OMe			100–104[g]	EtOH		75	76		27
31	OEt	OH					182–184[h]	EtOAc		100		0	
32	OEt		F				85–89	EtOH	C, H, N[i]	78		2[b]	0
33	OEt		CF_3				120–123[j]	EtOH		64	12		
34	OEt			$CONH_2$			259–264	DMF	C, H, N[k]	55			0
35	OEt			NO_2			169–172[c]	HOAc		75		16	0
36	OEt			C_6H_5			128–132[l]	EtOH		0			
37	OEt			OC_6H_5			97–100[m]	EtOH		2			
38	OEt			$N{=}NC_6H_5$			157–160	EtOH	C, H, N[n]	41			
39	OEt	SO_2NH_2			Cl		183–187	EtOH	C, H, N, S[o]	36	17		
40	OEt	NO_2		OMe			154–160[p]	EtOH		84	8		
41	OEt	NO_2		CF_3			124–126	EtOH	C, H, N[q]	29			
42	OEt	Cl				Cl	128–130[r]	Et_2O		100	15		
43	OEt	CH=CHCH=CH					105–107[s]	Et_2O		97	55		44
44	OEt		CH=CHCH=CH				118–120[s]	Et_2O		76	2		
45	OEt		CF_3	NO_2			106–110	EtOH	C, H, N[t]	100	73		30
46	OEt		OMe	OMe	OMe		132–134[m]	EtOH		63		44	0
47	OMe						113–116[u]	Et_2O		100			0
48	*n*-OPr						90–92[u]	Et_2O		82	10		
49	*i*-OPr						51–53[u]	Pentane		100	60		0
50	OC_6H_5						136–139[v]	EtOH		59	29		
51	NHC_6H_5						249–251[w]	Benzene		0			

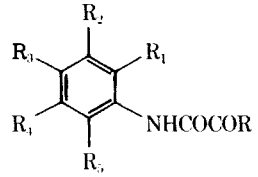
[a]Inhibition of greater than 35% considered statistically significant by Student's t test ($p < 0.05$). [b]Dose 20 mg/kg. [c]G. Tierie, *Recl. Trav. Chim. Pays-Bas*, **52**, 420 (1933). [d]P. E. Todesco and P. Vivarelli, *Boll. Sci. Fac. Chim. Ind. Bologna*, **22** (1), 1 (1964); *Chem. Abstr.*, **61**, 4192*f* (1964). [e]P. A. Petyunin, V. S. Shklyaev, and I. S. Berdinskiy, *Zh. Obshch. Khim.*, **24**, 1078 (1954); *Chem. Abstr.*, **49**, 8888*d* (1955). [f]P. A. Petyunin and I. S. Berdinskiy, *Zh. Obshch. Khim.*, **21**, 1859 (1951). [g]A. Piutti and R. Piccoli, *Chem. Ber.*, **31**, 330 (1898). [h]K. Dickoré, K. Sasse, and K.-D. Bode, *Justus Liebigs Ann. Chem.*, **733**, 70 (1970). [i]Yield 88%. [j]A. Baruffini, P. Borgna, and G. Pagani, *Farmaco. Ed. Sci.*, **22** (9), 717 (1967). [k]Yield 40%. [l]A. G. Richardson, J. S. Pierce, and E. E. Reid, *J. Am. Chem. Soc.*, **74**, 4011 (1952). [m]P. A. Petyunin, V. P. Razuvaeva, and G. P. Petyunin, *Khim.-Farm. Zh.*, **1** (12), 7 (1967); *Chem. Abstr.*, **68**, 95474*v* (1968). [n]Yield 83%. [o]Yield 50%. [p]I. L. Knunyants and Z. V. Benevolenskaya, *J. Gen. Chem. USSR*, **7**, 2471 (1937). [q]P. A. Petyunin and Z. G. Kalugina, *Zh. Obshch. Khim.*, **33**, 2835 (1963); *Chem. Abstr.*, **60**, 1620*f* (1964). [r]P. P. T. Sah, J.-M. Yang, H.-C. Chin and C. Wang, *J. Chin. Chem. Soc. (Peking)*, **14**, 101 (1946); *Chem. Abstr.*, **43**, 6973*g* (1949). [s]Yield 66%. [t]R. Anschütz, *Justus Liebigs Ann. Chem.*, **254**, 11 (1889). [u]R. Stollé and E. Knebel, *Chem. Ber.*, **54**, 1213 (1921). [v]J. Th. Bornwater, *Recl. Trav. Chim. Pays-Bas*, **31**, 105 (1912).

nucleophiles provided compounds **67–73**, the unknown intermediates of which are described in Tables VIII and IX. Preparation of acid **16** was carried out by mild hydrolyses of its precursor ester **9**, and the simple amide **17** was prepared by condensation of the ester **9** with alcoholic ammonia.

A considerable number of compounds from Table I are known, and essentially all of the starting amines (**10**) used to prepare the compounds from Tables I–V are commercially available or easily prepared by literature methods. All of the compounds from Table V are known except **20**, the preparation of which will be described in the Experimental Section. Compounds from Table VI were prepared by acylation of 2-amino-6-methoxybenzamide (**15**) with the corresponding acid chlorides in the presence of pyridine.

The preparation of esters with other than ethyl and methyl on the oxalyl group required the preparation of a half ester–acid chloride of oxalic acid by the method of Frank and Caro,[15] which involves adding 1 mol of an alcohol to 1 mol of oxalyl chloride and careful distillation of the resulting products. All of the acid chlorides used are known in the literature, and compounds **47–50**, **61–66**, and **100–105** were prepared by the standard acylation procedure (Scheme I) using the appropriate acid chloride.

Table II. *N*-Oxalylanthranilic Acids, Esters, and Amides



Compd	R	R_1	R_2	R_3	R_4	R_5	% yield	Mp, °C	Crystn solvent	Analyses	% inhibn,[a] 200 mg/kg ip	% inhibn[a] po 200 mg/kg	25 mg/kg	10 mg/kg
52	OEt	CO_2H						182–183[c]	Toluene		50			
53	OEt	$CONH_2$						160–161[c]	EtOH		91			
54	OEt	CN					15[d]	90–91	EtOH	C, H, N	53			
55	NH_2	$CONH_2$						247–251[c]	MeOH		0			
56	OEt	CO_2H	OMe				37	142–144	EtOH	C, H, N	54			
9	OEt	$CONH_2$	OMe				60	170–173	EtOH	C, H, N	100	91	35	
57	OEt	CN	OMe				64	142–145	Toluene	C, H, N	80	71		20
58	OEt	CO_2Me	OMe				62	96–99	EtOH	C, H, N	76			5
59	OEt	CONHMe	OMe				27	119–121	EtOAc–hexane	C, H, N	72	42		
60	OEt	COMe	OMe				61	70–73	Benzene–hexane	C, H, N	46			
16	OH	$CONH_2$	OMe				79	220 dec	$MeO(CH_2)_2OH$	C, H, N	48			
17	NH_2	$CONH_2$	OMe				28	252–255	H_2O	C, H, N	26			
61	OMe	$CONH_2$	OMe				56	195–198	MeOH	C, H, N	96	12		
62	*n*-OPr	$CONH_2$	OMe				57	158–161	MeCN	C, H, N	96	12		
63	*i*-OPr	$CONH_2$	OMe				56	128–132	Benzene	C, H, N	57			0
64	*n*-OBu	$CONH_2$	OMe				70	126–129	Benzene	C, H, N	98	12		
65	*sec*-OBu	$CONH_2$	OMe				46	119–122	Benzene	C, H, N	100	70		40
66	c-OC_6H_{11}	$CONH_2$	OMe				69	166–169	Benzene	C. H, N	91	20		
67	OEt	$CONH_2$	OEt				71	142–145	EtOH	C, H, N	80	44		
68	OEt	$CONH_2$	*n*-OPr				73	130–133	EtOH	C, H, N	52			13
69	OEt	$CONH_2$	*i*-OPr				73	123–125	EtOH	C, H, N	66			
70	OEt	$CONH_2$	*n*-OBu				70	120–123	EtOH	C, H, N	75	0		
71	OEt	$CONH_2$	$OCH_2CH_2OC_6H_5$				78	142–145	EtOH	C, H, N	75			0
72	OEt	$CONH_2$	$OCH_2CHOHMe$				31	130–134	EtOAc–hexane	C, H, N	100	32		
73	OEt	$CONH_2$	$OCH_2CH_2NMe_2$				65	209–210[b]	MeOH	C, H, N, Cl	85			
74	OEt	$CONH_2$	Cl				78	190–193	EtOH	C, H, N	26			
75	OEt	$CONH_2$		Cl			84	204–210	MeCN	C, H, N, Cl	55			0
76	OEt	$CONH_2$		NO_2			78	206–209	EtOH	C, H, N	59			
77	OEt	CO_2H		OMe			49	238–243	EtOH	C, H, N	61			12
78	OEt	CO_2Me		OMe			66	129–133	EtOH	C, H, N	58			0
79	OEt	$CONH_2$			OMe		48	186–188	EtOH	C, H, N	91	10		0
80	OEt	CO_2H		Me	Me		80	235–239	EtOH	C, H, N	33			
81	OEt	$CONH_2$		Me	Me		85	190–193	EtOH	C, H, N	100		7	
82	OEt	$CONH_2$		OCH_2O			77	232–236	MeCN	C, H, N	0			
83	OEt	$CONH_2$		Me		Me	45	177–179	EtOH	C, H, N	0			

[a] Inhibition of greater than 35% considered statistically significant by Student's *t* test ($p < 0.05$). [b] Determined on the hydrochloride. [c] See ref 10. [d] From dehydration of **53** in refluxing Ac_2O.

Table III. Bisoxanilic Acid Esters, $EtO_2CCONH\text{-}A\text{-}1,4\text{-}C_6H_4NHCOCO_2Et$

Compd	A	Mp, °C	Crystn solvent	Analyses	% inhibn,[a] 200 mg/kg ip	% inhibn[a] po 200 mg/kg	% inhibn[a] po 10 mg/kg
84		214–217[b]	EtOH		72	0	
85	1,4-$C_6H_4CH_2$	149–151[b]	EtOH		16		
86	1,4-$C_6H_4CH_2CH_2$	190–192	MeCN	C, H, N[c]	2		
87	1,4-$C_6H_4CH{=}CH$	282–286	DMF–EtOH	C, H, N[d]	18		
88	1,4-C_6H_4O	159–162[b]	EtOH		34		6
89	1,4-$C_6H_4SO_2$	263–266[e]	EtOH		3		
90	1,4-C_6H_4SS	159–163	MeCN	C, H, N[f]	9		
91	1,4-$C_6H_4OCH_2CH(OCOCO_2Et)CH_2O$	168–170	EtOAc–hexane	C, H, N[g]	13		

[a]Inhibition of greater than 35% considered statistically significant by Student's t test ($p < 0.05$). [b]A. Rio, French Patent 1,338,399 (1963); *Chem. Abstr.*, 60, 3012*b* (1964). [c]Yield 75%. [d]Yield 56%. [e]French Patent 1,567,434 (1969); *Chem. Abstr.*, 71, 112653n (1969). [f]Yield 36%. [g]Yield 30%.

Table IV. *N*-Heteroaryl Oxamic Acid Esters, $RNHCOCO_2R_1$

Compd	R	R_1	% yield	Mp or bp (mm), °C	Crystn solvent	Analyses	% inhibn,[a] 200 mg/kg ip	% inhibn[a] po 200 mg/kg	% inhibn[a] po 15 mg/kg	% inhibn[a] po 10 mg/kg
92	2-Pyridinyl	Et		73–75[c]	Et_2O		100	80		36
21	3-Pyridinyl	Et	41	98–100	Et_2O	C, H, N	96	84		17
93	4-Pyridinyl	Et	22	110–113	Et_2O	C, H, N	100	34		
94	6-Methyl-2-pyridinyl	Et	66	61–63	Et_2O	C, H, N	77	74		25
95	3-Cyano-2-pyridinyl	Et	26	95–97	Et_2O–CH_2Cl_2	C, H, N	100		0[b]	
22	1-Methylpyridinium-3-yl iodide	Et	84	138–140	EtOH	C, H, I, N	0			
96	2-Pyrimidinyl	Et	35	96–99	EtOH	C, H, N	82	9		
97	2-Pyrazinyl	Et	62	134–137	EtOH	C, H, N	100	83		0
98	2-Thiazolyl	Et		174–177[d]	EtOH		100	6		
99	4*H*-1,2,4-Triazol-4-yl	Et	53	206–209	EtOH	C, H, N	7			
100	2-Pyridinyl	Me	59	102–106	Et_2O	C, H, N	77	100		25
101	2-Pyridinyl	*n*-Pr	35	56–59	Et_2O	C, H, N	58	77		
102	2-Pyridinyl	*i*-Pr	37	Oil		C, H, N	100		0	
103	2-Pyridinyl	*n*-Bu	61	35–37	Et_2O	C, H, N	100		0	
104	2-Pyridinyl	*sec*-Bu	46	112–116 (0.05)		C, H, N	100		0	
105	2-Pyridinyl	Cyclohexyl	67	62–64	Et_2O–hexane	C, H, N	53			

[a]Inhibition of greater than 35% considered statistically significant by Student's t test ($p < 0.05$). [b]Dose 20 mg/kg. [c]P. A. Petyunin and A. V. Storozheva, *Zh. Obshch. Khim.*, 32, 1395 (1962); *Chem. Abstr.*, 58, 4449*b* (1963). [d]P. A. Petyunin and M. V. Zakalyuzhnyi, *Zh. Obshch. Khim.*, 34 (1), 28 (1964); *Chem. Abstr.*, 60, 10591*c* (1964).

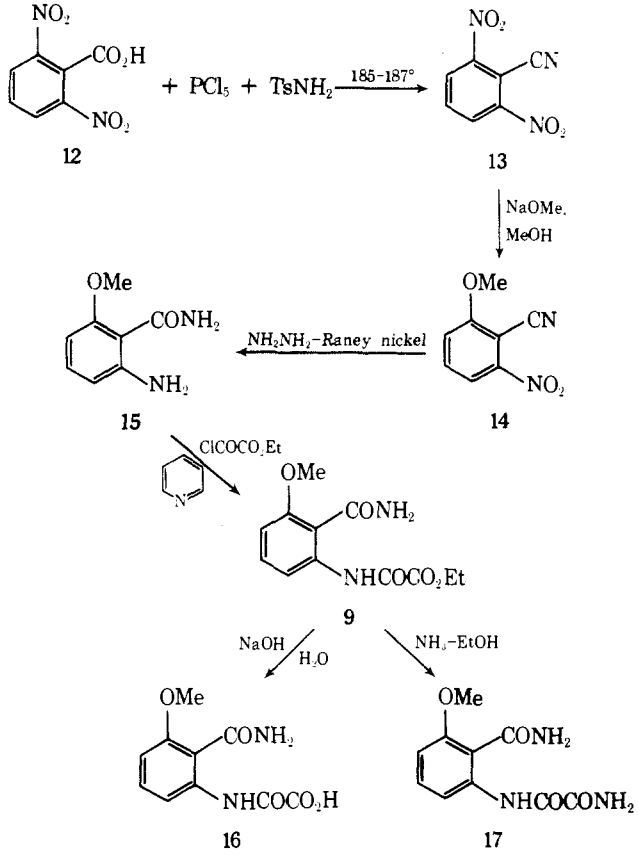
The *N*-methylbenzamide **18**, the amine precursor of **59**, was prepared by methylation of benzamide **15** with sodium hydride and methyl iodide (Scheme III), and amide **19** was prepared (Scheme III) from commercially available 2-amino-3,5-dimethylbenzoic acid through reaction of its corresponding 1,3-benzoxazine-2,4-dione[16] with ammonia.[17] Imide **20** was prepared (Scheme III) by condensation of benzamide with ethyloxalyl chloride. The quaternary salt **22** was prepared (Scheme III) by methylating the pyridineoxamic acid ester **21** with methyl iodide.

Results and Discussion

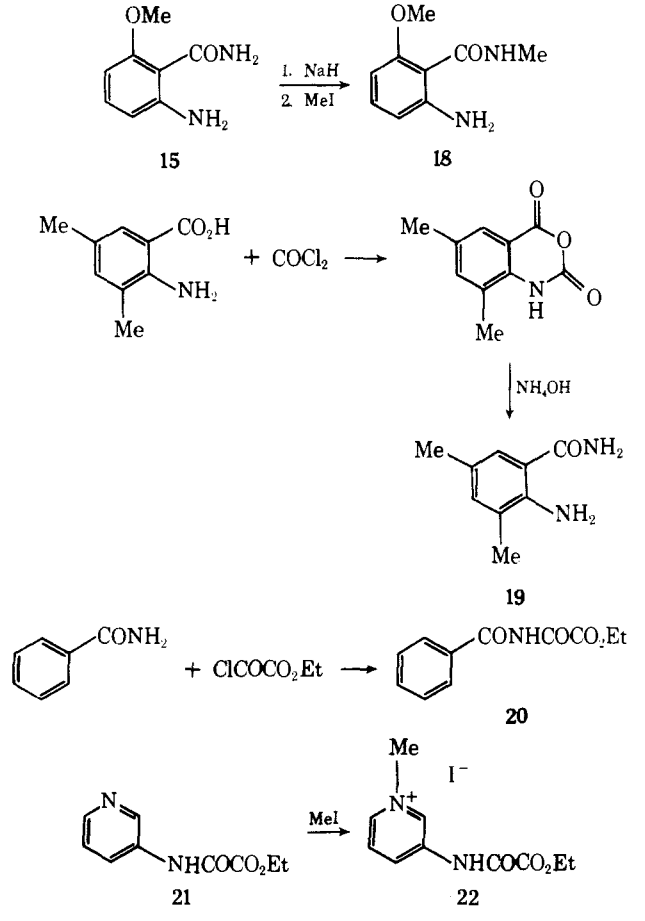
A broad series of oxamic acid derivatives was screened in the rat PCA test, and the results are shown in Tables I–IV. All compounds were initially tested at 200 mg/kg ip to determine general areas of activity and to screen candidates for further oral testing at 200 mg/kg po. If the compound had a significant amount (about 35% inhibition) of activity orally at 200 mg/kg, then the compound was tested orally at lower doses in the 10–25 mg/kg range. It was apparent from the amount of drug needed for oral activity that the series was not highly potent, but the oral activity warranted an extensive investigation of our most promising compounds. Any activity greater than 30–35% inhibition was statistically significant by Student's t test.

When amides **51**, **55**, and **17** were prepared from the active oxalyl esters **24**, **53**, and **9**, they generally lost ip activity. Replacement of the ethyl esters **24**, **9**, and **92** by essen-

Scheme II



Scheme III



tially any other esters in three series (**47–50**, **61–66**, and **100–105**) caused little change in ip activity. Changing the aryl group of the oxanilic acid series (**24**) to essentially any nonaromatic species directly attached to the amide nitrogen (**106**, **107**, **108**, and **112**) resulted in a drastic loss of activity. Any change in or removal of the secondary amide nitrogen (**109**, **110**, and **111**) also resulted in a drastic loss of activity compared to the secondary amide **24**. This loss may reflect the necessity for an acidic nitrogen of a certain pK, as is evident by comparing the difference in ip activity between secondary amides **107** and **20**, two compounds with the same relative size but different nitrogen pK's. Change of the amide **24** to a thioamide **113** caused a loss of activity. Changing the carboxylic acid esters **9** and **24** to any compound less easily hydrolyzed metabolically to an oxamic acid caused a drastic loss of activity (**115**, **118**, **119**, **120**, and **121**). Replacement of the ethyloxalyl moiety of oxamic ester **9** by a group of the same relative size (-NHCOPr) eliminated all activity as in butyramide (**119**), as did lowering the potential acidity of the carboxylic acid ester of the oxamic ester **9** by adding a methylene group between the two carbonyls as in malonamic acid ester **120**. As expected from the paper by Ellis and Shaw,[2] replacing the carboxylic acid ester **24** by an acidic tetrazole moiety (**117**) conferred a still higher degree of activity.

A highly significant observation was that hydrolysis of the ester of the most promising compound (**9**) to a carboxylic acid (**16**) caused loss of oral activity but not of intravenous activity (Table VII). The results shown are in terms of reduction of average wheal size compared to that in the controls.

Many of the starting materials of the most active compounds were tested for activity and found to have none.

With the simple oxanilic acid esters (Tables I and III) it was considerably more difficult to see any clear relationship between aromatic substituents and activity; however, it was evident that making these compounds quite large (**36** and **37**) and making a bis structure (**85–91**) which resembles the bis nature of disodium cromoglycate (**1**) almost eliminated all activity. All of the heteroaryl oxamic acid esters that were prepared (Table IV) except the highly polar type (**22**) and the hydrazo type (**99**) retained a high degree of activity.

The oxalylanthranilic acid compounds (Table II) generally had a moderate amount of ip activity and seemed to be well absorbed orally and quite nontoxic. The most active type had a 2′-carbamoyl moiety (**9**), and essentially any change in this arrangement (**56–60**) lowered the activity. The 3′-methoxy group appeared to be the best substituent, with most changes (**67–71**, **73**, **74**) causing a lowering of activity. Placing a hydroxyl group in the side chain such as in alcohol **72**, like that found in the connecting side chain of disodium cromoglycate (**1**), did not increase the oral activity when compared to **9** or **67**. Placing substituents in other positions on the aromatic ring (**75–83**) did not improve the activity.

Conclusion

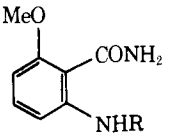
In the present study we have found that a number of oxamic acid esters are active orally at moderate doses in the rat PCA test. We concluded from our structural variations that the oxamic acid esters are needed for oral activity, but when the oxamic acids were tested intraveneously activity was still retained. Making the aryl group of the oxamic acid ester very bulky, or very polar as in a quaternary salt, caused a loss of both oral and intraperitoneal activity. It was also necessary to have the highly acidic oxamic acid in an easily unblocked form such as an ester, because the am-

Table V. Radical Changes of the Simple Oxanilic Acids

Compd		Mp or bp (mm), °C	Crystn solvent	% inhibn,[a] 200 mg/kg ip	% inhibn[a] po 200 mg/kg	25 mg/kg	10 mg/kg
106	NH_2COCO_2Et	113–116		0			
107	$C_6H_5CH_2NHCOCO_2Et$	47–50[b]	Et_2O–pentane	16			
108	$C_6H_{11}NHCOCO_2Et$	60–63[c]	Hexane	24			
20	$C_6H_5CONHCOCO_2Et$	48–51[d]	Et_2O–hexane	71		0	
109	$C_6H_5COCO_2Et$	73 (0.2)[e]		2			
110	$C_6H_5OCOCO_2Et$	98–100 (0.05)[f]		0			4
111	$C_6H_5NMeCOCO_2Et$	108 (0.25)[g]		2			
112	$C_5H_{10}NCOCO_2Et$	92–96 (0.25)[h]		9			
113	$C_6H_5NHCSCO_2Et$	39–40[i]	Petroleum ether	28			
114	$C_6H_5NHCOCN$	129–132[j]	Benzene–cyclohexane	Toxic at ≥25 mg/kg ip			
115	$C_6H_5NHCOCCl_3$	90–95[k]	EtOH	25			0
116	$C_6H_5NHCOCONHOH$	165–167[l]	H_2O	92		0	
117	$C_6H_5NHCOCHN_4$	216–218[m]	EtOH–H_2O	100	85		24

[a]Inhibition of greater than 35% considered statistically significant by Student's t test ($p < 0.05$). [b]T. Curtius and K. Raschig, *J. Prakt. Chem.*, **125**, 466 (1930). [c]K. A. de Vries, *Recl. Trav. Chim. Pays-Bas*, **61**, 223 (1942). [d]Anal. C, H, N. Yield 11%. [e]B. B. Corson, R. A. Dodge, S. A. Harris, and R. K. Hazen in "Organic Syntheses", Collect. Vol. I, 2nd ed, Wiley, New York, N.Y., 1941, pp 241–245. [f]Y. N. Ivashchenko, S. D. Moshchitskii, and A. V. Kirsanov, *Zh. Obshch. Khim.*, **32**, 3765 (1962); *Chem. Abstr.*, **58**, 12452*h* (1963). [g]P. A. Petyunin, V. S. Shklyaev, and A. S. Pesis, *Zh. Obshch. Khim.*, **27**, 1554 (1957); *Chem. Abstr.*, **52**, 3763*i* (1958). [h]H. E. Ungnade and L. W. Kissinger, *J. Org. Chem.*, **24**, 666 (1959). [i]A. Reissert, *Chem. Ber.*, **37**, 3708 (1904). [j]R. Malachowski and J. Jankiewicz-Wasowska, *Rocz. Chem.*, **25**, 35 (1951); *Chem. Abstr.*, **47**, 10483*f* (1953). [k]Y. V. Svetkin, *Zh. Obshch. Khim.*, **32**, 1037 (1962); *Chem. Abstr.*, **58**, 1378*g* (1963). [l]O. Dimroth and L. Taub, *Chem. Ber.*, **39**, 3912 (1906). [m]B. E. Fisher, A. J. Tomson, and J. P. Horwitz, *J. Org. Chem.*, **24**, 1650 (1959).

Table VI. Radical Changes on the Oxamic Acid Moiety of 9



Compd	R	% yield	Mp, °C	Crystn solvent	Analyses	% inhibn,[a] 200 mg/kg ip
118	CO_2Et	72	173–176	MeOH	C, H, N	0
119	*n*-COPr	36	145–148	EtOAc–hexane	C, H, N	0
120	$COCH_2CO_2Et$	77	143–146	EtOH	C, H, N	17
121	$COCCl_3$	69	165–168	EtOH	C, H, N	0

[a]Inhibition of greater than 35% considered statistically significant by Student's t test ($p < 0.05$).

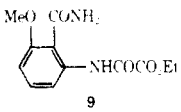
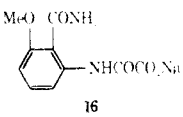
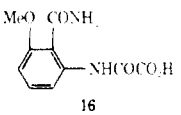
ides were not active, but the 5-carbamyltetrazole was. It also seemed as if a 2-carbamoyl group on the aryl ring of the oxanilic acid ester conferred a higher degree of activity.

Experimental Section

Melting points were taken in an oil bath and are uncorrected. Solvents were removed in vacuo on a Büchi Rotavapor R. Anhydrous sodium sulfate was used for all solution drying. Spectra were obtained under the supervision of Mr. Bruce Hofmann. Ir spectra were determined in KBr pellets using a Perkin-Elmer Model 21 spectrophotometer. NMR spectra were determined with a Varian Model A-60 or a Jeolco Model C-60HL NMR spectrometer using Me_4Si in $CDCl_3$ and DMSO-d_6 and DSS in D_2O. Analyses were carried out on a Perkin-Elmer Model 240 elemental analyzer. The structure of all compounds was confirmed by ir and NMR spectroscopy.

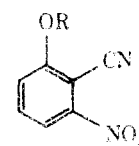
Biological Test Procedure. The PCA test was carried out in a manner similar to that described by Goose and Blair.[18] Male Charles River rats (200–250 g) were injected intracutaneously on their shaved backs with sera from rats immunized with egg albumin and Bordetella pertussis vaccine. After the initial injections (24 hr), test drugs were administered ip, iv, or po. Five minutes later, 1 ml of a 0.5% solution of Evans Blue dye and 8 mg of egg al-

Table VII. Comparative Effects of 9 and Its Free Acid and Sodium Salt in the Rat PCA Test

	Oral[a]			Intravenous[b]		
	Dose, mg/kg	N[c]	Av wheal size,[d] mm² ± SE	Dose, mg/kg	N[c]	Av wheal size,[d] mm² ± SE
Control	Water, 5 ml/kg	4	115.5 ± 2.9	Saline, 5 ml/kg	4	114.6 ± 5.4
 9	25	4	75.6 ± 7.6*	1	4	78.8 ± 7*
	50	5	68 ± 8.3*	3	4	25 ± 7.8*
	100	4	19.4 ± 7.6*	5	4	21.4 ± 1.2*
 16	25	4	105 ± 3.4	1	4	81.4 ± 12.7*
	50	5	91 ± 6.2*	3	5	76.4 ± 7*
	100	4	98 ± 6.5*	5	5	43.8 ± 5.7*
 16	25	4	109 ± 4.2	1	4	64.9 ± 10*
	50	5	113.6 ± 4.2	3	5	29.3 ± 6*
	100	4	114.3 ± 3.5	5	5	9.8 ± 3*

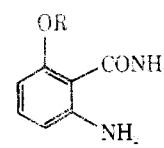
[a] Drug administered 5 min prior to antigen challenge. [b] Drug administered simultaneously with antigen challenge. [c] N = number of rats/point − 2 wheals/rat. [d] An asterisk indicates $p < 0.05$.

Table VIII. Intermediate 2-Nitrobenzonitriles



Compd	R	% yield	Formula	Analyses	Mp, °C	Crystn solvent
122	$CH_2CH_2OC_6H_5$	70	$C_{15}H_{12}N_2O_4$	C, H, N	127–130	MeCN
123	$CH_2CHOHMe$	39	$C_{10}H_{10}N_2O_4$	C, H, N	121–124	Benzene
124	$CH_2CH_2NMe_2$	45	$C_{11}H_{13}N_3O_3$	C, H, N	89–91	Benzene–hexane

Table IX. Intermediate 2-Aminobenzamides



Compd	R	% yield	Formula	Analyses	Mp, °C	Crystn solvent
125	Et	51	$C_9H_{12}N_2O_2$	C, H, N	173–174	MeCN
126	*n*-Pr	72	$C_{10}H_{14}N_2O_2$	C, H, N	159–162	EtOH
127	*i*-Pr	33	$C_{10}H_{14}N_2O_2$	C, H, N	135–138	EtOH
128	*n*-Bu	61	$C_{11}H_{16}N_2O_2$	C, H, N	119–122	EtOH
129	$CH_2CH_2OC_6H_5$	50	$C_{15}H_{16}N_2O_3$	C, H, N	127–130	EtOH
130	$CH_2CHOHMe$	78	$C_{10}H_{14}N_2O_3$	C, H, N	115–118	EtOAc–hexane
131	$CH_2CH_2NMe_2$	31	$C_{11}H_{17}N_3O_2$	C, H, N	118–121	EtOAc–hexane

bumin were injected iv. After an additional 40 min the animals were sacrificed, the skin on their backs was turned back, and the wheal sizes were measured. Four animals were run for each test compound and control group. The mean wheal size for each group was calculated and the percent inhibition compared with that in the control group was obtained. The statistical significance of the data was determined through the use of Student's t test.

2,6-Dinitrobenzonitrile (13). A homogeneous mixture of 212 g (1 mol) of 2,6-dinitrobenzoic acid (12), 183 g (1.07 mol) of $TsNH_2$, and 437 g (2.1 mol) of PCl_5 was stirred in a 2-l. three-neck flask equipped with a thermometer, mechanical stirrer, and an adaptor equipped for vacuum distillation. The stirred mixture was warmed on the steam bath until it became a homogeneous melt, causing HCl to be vigorously evolved. When the initial reaction subsided, the pressure was lowered to ca. 100 mm and the internal temperature was slowly raised to 160–165°, causing about 80 ml of $POCl_3$ to distill off. The temperature was then raised to 185–187° and an additional 70 ml of $POCl_3$ was slowly distilled off. (*Caution:* at the point where the temperature is 185–187° one should be very careful, because with one run a very vigorous exotherm occurred with decomposition when the temperature was not carefully controlled and allowed to raise above 187°.) The molten mass was cooled to ~80° and poured into 1 l. of ice-H_2O and the flask was rinsed out with another 1 l. of H_2O. The lumps were crushed up in a mortar

and pestle and the mixture was stirred for 0.5 hr and filtered. The solid was washed with H_2O, added to a solution of 750 ml of Me_2CO and 750 ml of 14% NH_4OH, and stirred for 0.5 hr at room temperature. The Me_2CO was removed on a rotary evaporator at 60° and ~500 ml of H_2O was added to the residue. The solid was filtered, washed with H_2O, and added to 800 ml of 10% NaOH. The mixture was stirred for 0.5 hr and the solid was filtered, washed with water, dried at 70° in vacuo, and crystallized (toluene), giving 139 g (72%) of **13**: mp 143–146° (lit.[19] mp 145°). Anal. ($C_7H_3N_3O_4$) C, H, N.

2-Methoxy-6-nitrobenzonitrile (14). A solution of NaOMe, obtained from 18.4 g (0.8 mol) of Na and 660 ml of MeOH, was added over 20 min to a mixture of 155 g (0.8 mol) of **13** and 3.1 l. of MeOH, causing the **13** to dissolve and the product (**14**) to begin to crystallize. The mixture was refluxed for 3 hr, cooled to 0–5°, and filtered. The solid was slurried in H_2O and filtered, giving 116 g (81%) of **14**: mp 174–177° (lit.[10] mp 172°).

6-Amino-2-methoxybenzamide (15). A mixture of 88 g (0.5 mol) of **14** and 750 ml of EtOH was stirred at 45° and 62 ml (1.05 mol) of 85% $NH_2NH_2 \cdot H_2O$ was added, followed immediately by small amounts of washed (three times with H_2O followed by three times with EtOH) Grace No. 28 Raney active nickel catalyst in water. The temperature was allowed to go to 65° and the Raney nickel was added continuously until gas evolution and the exothermic reaction ceased. The mixture was then brought to reflux and filtered through Celite and the filter cake was washed with hot EtOH. Evaporation of the filtrate gave a solid that was crystallized (H_2O), giving 59 g (72%) of **15**: mp 150–153° (lit.[20] mp 155–156°). Anal. ($C_8H_{10}N_2O_2$) C, H, N.

[[2-(Aminocarbonyl)-3-methoxyphenyl]amino]oxoacetic Acid Ethyl Ester (9). A solution of 8.75 g (0.0527 mol) of **15** and 8.48 ml (0.1054 mol) of pyridine in 200 ml CH_2Cl_2 was cooled to ~5–10° and 6.2 ml (0.0554 mol) of EtO_2CCOCl was added dropwise over ~10 min. The solution was allowed to warm to room temperature and was stirred for 0.5 hr and evaporated to dryness. The residue was triturated with ~100 ml of water and filtered. The filter cake was layered with ether and crystallized (EtOH), giving 8.35 g (60%) of **9**: mp 170–173°. Anal. ($C_{13}H_{14}N_2O_5$) C, H, N.

[[2-(Aminocarbonyl)-3-methoxyphenyl]amino]oxoacetic Acid (16). A mixture of 26.625 g (0.100 mol) of **9**, 100 ml of H_2O, and 100 ml of EtOH was mechanically stirred while 100 ml of 1.000 *N* NaOH was dripped in over 0.5 hr. The mixture was stirred an additional 0.5 hr, warmed to the point where it became clear, and filtered into 1.2 l. of hot EtOH. It was next brought to boiling, filtered through a rapid filter by gravity, allowed to cool slowly to room temperature, and kept overnight at 5°. It was then filtered once again and the filter cake was washed with EtOH and dried at 65° in vacuo overnight, giving 21 g (79%) of **16**: mp >300°. Anal. ($C_{10}H_9N_2NaO_5$) C, H, N.

Acidification of 10 g (0.038 mol) of **16** dissolved in 100 ml of H_2O with 100 ml of 1 *N* HCl gave 7.6 g of **16** free acid after crystallization ($MeOCH_2CH_2OH$): mp 220° dec. Anal. ($C_{10}H_{10}N_2O_5$) C, H, N.

2-[[2-(Aminocarbonyl)-3-methoxyphenyl]amino]-2-oxoacetamide (17). Compound **9** (5 g, 0.021 mol) was added to 50 ml of EtOH saturated with NH_3 at 0–5° and stirred at ~5–10° for 2 hr. The mixture was filtered, washed with EtOH, and crystallized (H_2O), giving 1.41 g (28%) of **17**: mp 252–255°. Anal. ($C_{10}H_{11}N_3O_4$) C, H, N.

3-[(2-Ethoxy-1,2-dioxoethyl)amino]-1-methylpyridinium Iodide (22). A solution of 3.88 g (0.02 mol) of **21** and 1.44 ml (0.023 mol) of MeI in 50 ml of MeCN was slowly refluxed overnight and then concentrated to dryness. The precipitate was filtered with Et_2O and crystallized (EtOH), giving 5.66 g (84%) of **22**: mp 138–140°. Anal. ($C_{10}H_{13}IN_2O_3$) C, H, I, N.

2-Amino-6-methoxy-*N*-methylbenzamide (18). Slow addition of 4.98 g (0.03 mol) of **15** to a mixture of hexane-washed 57% NaH (1.32 g, 0.0315 mol) in 50 ml of DMF was carried out at room temperature. After the evolution of H_2 ceased, the mixture was cooled to 3° and 2.06 ml (0.033 mol) of MeI was slowly added at 3–5°. The temperature was allowed to go up to room temperature and the mixture was stirred for 2 hr and concentrated. The residue was extracted into EtOAc–H_2O and basified. The EtOAc layer was washed with water and brine and dried. Concentration gave a tan solid that was crystallized (EtOH), giving 0.45 g (8%) of **18**: mp 186–189°. Anal. ($C_9H_{12}N_2O_2$) C, H, N.

2-Amino-3,5-dimethylbenzamide (19). Liquid phosgene (55 g) was added to a stirred solution of 30.1 g (0.182 mol) of 2-amino-3,5-dimethylbenzoic acid in 300 ml of dioxane. The temperature was raised to 40–45° and held for 2 hr. The mixture was stirred overnight at room temperature and filtered. The filter cake was washed with ether, giving 33 g (95%) of 6,8-dimethyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione: mp >300°. The isatoic anhydride was then added to 435 ml of 1 *M* NH_4OH. The mixture was stirred overnight at room temperature, brought to reflux for 2 hr, cooled, filtered, and crystallized (EtOH), giving 13.4 g (47%) of **19**: mp 162–167°. Anal. ($C_9H_{12}N_2O$) C, H, N.

Benzoylaminooxoacetic Acid Ethyl Ester (20). A solution of 12.1 g (0.1 mol) of benzamide and 13.7 g (0.1 mol) of chlorooxoacetic acid ethyl ester in 50 ml of benzene was refluxed for 2 hr and concentrated to dryness. The residual oil was chromatographed on silica gel with 10% Et_2O in hexane and crystallized (Et_2O–hexane), giving 2.4 g (11%) of **20**: mp 48–51°. Anal. ($C_{11}H_{11}NO_3$) C, H, N.

Acknowledgment. The authors wish to thank Mr. W. Budd and Mr. L. Lofton for carrying out the biological tests. They also wish to express deep appreciation to Elizabeth Lilley and Mr. L. Wilson Bicking for help in the preparation of this manuscript.

References and Notes

(1) H. Cairns, C. Fitzmaurice, D. Hunter, P. B. Johnson, J. King, T. B. Lee, G. H. Lord, R. Minshull, and J. S. G. Cox, *J. Med. Chem.*, **15**, 583 (1972).
(2) G. P. Ellis and D. Shaw, *J. Med. Chem.*, **15**, 865 (1972).
(3) G. Barker, G. P. Ellis, and D. Shaw, *J. Med. Chem.*, **16**, 87 (1973).
(4) J. B. Wright and H. G. Johnson, *J. Med. Chem.*, **16**, 861 (1973).
(5) D. R. Buckle, N. J. Morgan, J. W. Ross, H. Smith, and B. A. Spicer, *J. Med. Chem.*, **16**, 1334 (1973).
(6) J. R. Pfister, R. W. Ferraresi, I. T. Harrison, W. H. Rooks, A. P. Roszkowski, A. Van Horn, and J. H. Fried, *J. Med. Chem.*, **15**, 1032 (1972).
(7) D. E. Bays, U.S. Patent 3,706,768 (1972).
(8) E. S. K. Assem, J. A. Evans, and M. McAllen, *Br. Med. J.*, **2**, 93 (1974).
(9) C. M. Hall, H. G. Johnson, and J. B. Wright, *J. Med. Chem.*, **17**, 685 (1974).
(10) A. Russell and L. M. Addison, *J. Am. Chem. Soc.*, **65**, 2379 (1943).
(11) C. S. Miller in "Organic Syntheses," Collect. Vol. III, Wiley, New York, N.Y., 1955, pp 646–649.
(12) During the preparation of this manuscript an identical procedure for replacement of the nitro groups of **13** was described by J. R. Beck, R. L. Sobczak, R. G. Suhr, and J. A. Yahner, *J. Org. Chem.*, **39**, 1839 (1974).
(13) K. Butler and M. W. Partridge, *J. Chem. Soc.*, 2396 (1959).
(14) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).
(15) G. von Frank and W. Caro, *Chem. Ber.*, **63**, 1532 (1930).
(16) Y. Iwakura, K. Uno, and S. Kang, *J. Org. Chem.*, **31**, 142 (1966).
(17) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **13**, 347 (1948).
(18) J. Goose and A. M. J. N. Blair, *Immunology*, **16**, 749 (1969).
(19) S. Reich, *Chem. Ber.*, **45**, 804 (1912).
(20) E. Cortes and F. Walls, *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, **16**, 67 (1964); *Chem. Abstr.*, **63**, 532*f* (1965).