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.



A number of papers and patents have appeared describing the antiallergic activity of relatives of disodium cromoglycate (1),¹⁻³ 4-0x0-4H-[1]benzothieno[3,2-*b*]pyran-2-carboxylic acid (2),⁴ 4-0x0-4H-[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-4-0x0quinolinecarboxylic acid (6).⁹ Only one compound, AH-7725⁸ (5), has been shown to be effective when given by mouth.



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.



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.



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

$$\frac{\text{RNH}_2 + \text{CICOCO}_2 \text{R}^1}{10} \xrightarrow{\text{I}_1} \frac{\text{RNH}_2 + \text{CICOCO}_2 \text{R}^1}{11}$$

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-toluenesulfonamide¹¹ 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



					R_4	Ý	NHCOCOR			%	%	inhib	nª po
						R ₅				inhibn,"			<u> </u>
								- .		200	200	25	
	_	-	-	-	-	-	Mp or bp	Crystn	Anal-	mg/	mg/	mg/	10
Compd	R	R ₁	R_2	\mathbf{R}_3	R_4	R_5	(mm), °C	solvent	yses	кg ıр	ĸg	кg	mg/kg
	Dicodiur	n anomog	Ivanto							86			
24	OFt	n cromog.	lycate				64-67°	EtOH		100	64		7
25	OFt	Мо					$126(0.05)^{4}$	2.011		75	01	14	, 0
26	OEt	me	Me				56-60 ^e	Benzene-		85	51	11	õ
20	OL							hexane			01		Ŭ
27	OEt			Me			65-674	Benzene-		100	13		
-	•							hexane					
28	OEt	OMe					81-85ª	Benzene-		100	11		
								hexane					
29	OEt		OMe				95–98 [†]	MeOH-		38			0
								H ₂ O					
30	OEt			OMe			100-104	EtOH		75	76		27
31	OEt	OH					182–184 ^h	EtOAc		100		0	
32	OEt		F				85-89	EtOH	C, H, N'	78		2°	0
33	OEt		CF_3				120–123 ^{<i>j</i>}	EtOH		64	12		
34	OEt			CONH ₂			259–264	DMF	C, H, N*	55			0
35	OEt			NO_2			169–172°	HOAc		75		16	0
36	OEt			C_6H_5			128–132'	EtOH		0			
37	OEt			OC ₆ H ₅			$97 - 100^{m}$	EtOH	_	2			
38	OEt			$N = NC_6H_5$			157-160	EtOH	C, H, N"	41			
39	OEt	SO_2NH_2			Cl		183-187	EtOH	C, H, N, S	5° 36	17		
40	OEt	NO ₂		OMe			154-160	EtOH		84	8		
41	OEt	NO ₂		\mathbf{CF}_3		~.	124-126	EtOH	C, H, N ⁴	29			
42	OEt	Cl	o			CI	128-130	Et ₂ O		100	15		
43	OEt	Сн—Сн	CH==C	H GUGU GU			105-107*	Et ₂ O		97	55		44
44	OEt			CHCH=CH			118-120-		C II NI	76	2		0.0
45	OEt			NO ₂	014		100-110	EtOH	С, п, м	100	73		30
40	OEt		OMe	OMe	Ome		132-134"	EtOH Et O		03		44	U
47							113-110-			100	10		U
40	<i>n</i> -OPr						90-92 51_52#	El ₂ U Dentanc		84	60 10		0
40	OC H						31-33 136-130°	Fentane FiOu		100	20		U
51	NHC.H						249-251 ^w	Benzene		09	49		
91	MIC605						240-201	Denzene		U			

^aInhibition of greater than 35% considered statistically significant by Student's t test (p < 0.05). ^bDose 20 mg/kg. ^cG. Tierie. Recl. Trav. Chim. Pays-Bas, **52**, 420 (1933). ^aP. E. Todesco and P. Vivarelli, Boll. Sci. Fac. Chim. Ind. Bologna, **22** (1), 1 (1964); Chem. Abstr., **61**, 4192f (1964). ^eP. A. Petyunin, V. S. Shklyaev, and I. S. Berdinskiy, Zh. Obshch. Khim., **24**, 1078 (1954); Chem. Abstr., **49**, 8888d (1955). ^fP. A. Petyunin and I. S. Berdinskiy, Zh. Obshch. Khim., **21**, 1859 (1951). ^sA. Piutti and R. Piccoli, Chem. Ber., **31**, 330 (1898). ^hK. Dickoré, K. Sasse, and K.-D. Bode, Justus Liebigs Ann. Chem., **733**, 70 (1970). ^fYield 88%. ^fA. Baruffini, P. Borgna, and G. Pagani, Farmaco. Ed. Sci., **22** (9), 717 (1967). ^kYield 40%. ^fA. G. Richardson, J. S. Pierce, and E. E. Reid, J. Am. Chem. Soc., **74**, 4011 (1952). ^mP. A. Petyunin, V. P. Razuvaeva, and G. P. Petyunin, Khim.-Farm. Zh., 1 (12), 7 (1967); Chem. Abstr., **68**, 95474v (1968). ⁿYield 83%. ^oYield 50%. ^pI. L. Knunyants and Z. V. Benevolenskaya, J. Gen. Chem. USSR, **7**, 2471 (1937). ^rP. A. Petyunin and Z. G. Kalugina, Zh. Obshch. Khim., **33**, 2835 (1963); Chem. Abstr., **60**, 1620f (1964). ^sP. P. T. Sah, J.-M. Yang, H.-C. Chin and C. Wang, J. Chin. Chem. Soc. (Peking), 14, 101 (1946); Chem. Abstr., **43**, 6973g (1949). ^tYield 66%. ^aR. Anschütz, Justus Liebigs Ann. Chem., **254**, 11 (1889). ^eR. Stollé and E. Knebel, Chem. Ber., **54**, 1213 (1921). ^wJ. 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.

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $							R,								
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $						1		Ŗ				<i>A</i>)	57	inhibn ^a	od
							∕ }≃	NHCOCO	R			inhibn,"	200	9r	4
	Compd	R	\mathbf{R}_1	\mathbf{R}_{2}	\mathbf{R}_3	\mathbf{R}_{i}	$\mathbf{R}_5 \%$	yield	Mp, °C	Crystn solvent	Analyses	kg ip	kg kg	∠.J mg/kg	nu mg/kg
	52	OEt	CO ₂ H						182–183°	Toluene		50			
	53	OEt	CONH ₂						160161 ^c	EtOH		91			
	54	OEt	CN				-	15^d	90 - 91	EtOH	С, Н, N	53			
	55	\mathbf{NH}_2	CONH ₂					••	247–251°	MeOH		0			
	56	OEt	CO_2H	OMe				37	142144	EtOH	С, Н, N	54			
57 01b CN OME 01c CN 00c CI, N 00c 11 01c	ი	OEt	$CONH_2$	OMe)	30	170173	EtOH	С, Н, N	100	91	35	
	57	OEt	CN	OMe			J	54	142145	Toluene	С, Н, N	80	11		20
	58	OEt	CO ₂ Me	OMe			-	52	6696	EtOH	C, H, N	76			5
	59	OEt	CONHMe	OMe			••	27	119–121	EtOAc-hexane	С, Н, N	72	42		
	60	OEt	COMe	OMe			-	31	70-73	Benzene-hexane	С, Н, N	46			
	16	НО	$CONH_2$	OMe			•	62	220 dec	MeO(CH ₂) ₂ OH	С, Н, N	48			
	17	\mathbf{NH}_2	CONH ₂	OMe			**	38	252-255	H_2O	С, Н, N	26			
	61	OMe	CONH ₂	OMe				56	195198	MeOH	С, Н, N	96	12		
	62	n-OPr	CONH ₂	OMe				57	158161	MeCN	С, Н, N	96	12		
	63	<i>i</i> -OPr	CONH ₂	OMe				56	128-132	Benzene	C, H, N	57			0
	64	n-OBu	CONH ₂	OMe			-	10	126-129	Benzene	C, H, N	98	12		
	65	sec-OBu	$CONH_2$	OMe				46	119–122	Benzene	C, H, N	100	02		40
	66	c-OC ₆ H ₁₁	CONH ₂	OMe			-	69	166 - 169	Benzene	С, Н, N	91	20		
	67	OEt	CONH ₂	OEt			-	71	142–145	EtOH	С, Н, N	80	44		
69OEICONH2 i^{-} OPr i^{-} OPr73123-125EtOHC, H, N i^{6} 71OEICONH2 u^{-} OBu $0CH_{5}CH_{5}OC_{4}H_{5}$ i^{-} OBu73123-125EtOHC, H, N75073OEICONH2 $0CH_{5}CH_{5}OC_{4}H_{5}$ 78130-134EtOHC, H, N75073OEICONH2 $0CH_{5}CH_{5}OC_{4}H_{5}$ 71130-134EtOHC, H, N75074OEICONH2 $0CH_{5}CH_{5}OK_{4}$ 71130-134EtOHC, H, N75074OEICONH2 $0CH_{5}CH_{5}OK_{4}$ 78130-134EtOHC, H, N75075OEICONH2 $0CH_{5}CH_{5}OK_{4}$ 78130-133EtOHC, H, N75075OEICONH2 $COH_{5}CH_{5}OK_{4}$ NO_{7} 78209-210'MeOHC, H, N75076OEICONH2 COH_{6} NO_{7} 78209-210'MeOHC, H, N75076OEICONH2 OOH_{7} NO_{7} 78209-210'MeOHC, H, N75077OEI OOH_{7} NO_{7} 78209-210'MeOHC, H, N7076OEI OOH_{7} NO_{7} 78209-210'MeOHC, H, N7077OEI OOH_{7} OOH_{7} NO_{7} 78209-210'MeOHC, H, N<	68	OEt	CONH ₂	n-OPr			-	73	130-133	EtOH	С, Н, N	52			13
700ElCONH3 $n-OBu70120-123EtOHC,H,N750710ElCONH30CH_2OL_4H_30CH_2OL_6H_4770CH_2OL_6H_37730ElCONH30CH_2OL_6H_47120-123EtOHC,H,N750730ElCONH3C10CH_2OL_6H_3142-145EtOHC,H,N750740ElCONH3C10CH_2OL_6H_60CH_2OL_6H_60CH_2OL_6H_6750750ElCONH3C1120-133EtOHC,H,N10032750ElCONH3C1R190-130ROCH - CH,NR10032760ElCONH3C1R100-130100-10020-210^{\circ}MeOHC,H,N10032760ElCONH3C1R100-100R100-10010032770ElCONH30CH0OHC1,N,N59100780ElCOH0OHC,H,N66129-133EtOHC,H,N112710ElCOH0OH0OHC,H,N10012710El0OH0OH0OH0OH0OH0OH110700OH0OH0OH0OH0OH0OH0OH0OH7$	69	OEt	CONH ₂	i-OPr			-	73	123-125	EtOH	С, Н, N	99			
71OEtCONH2OCH2CH3OC6H378142-145EtOHC,H,N75072OEtCONH2OCH2CH0Me31130-134EtOAc-hexaneC,H,N75073OEtCONH2OCH2CH3Me231130-134EtOAc-hexaneC,H,N75074OEtCONH2OCH2CH3Me265209-210 ⁶ MeOHC,H,N,C(185075OEtCONH2OCH2CH3Me278190-193EtOHC,H,N,C(155076OEtCONH2CI84204-210MeCNC,H,N,C(155076OEtCONH2NO278190-193EtOHC,H,N,C(155077OEtCO3HNO278206-209EtOHC,H,N76078OEtCO3HNO278206-209EtOHC,H,N76079OEtCO3HNO278206-209EtOHC,H,N76070OHNO278206-209EtOHC,H,N56070OHNO2NO2NO278206-209EtOHC,H,N7370OHNO2NO2NO278206-209EtOHC,H,N1270OHNO2NO2NO2NO2130-133EtOHC,H,N1280OEtCO3HNEMeMeMe85190-193EtOH<	22	OEt	$CONH_2$	n-OBu				70	120-123	EtOH	C, H, N	75	0		
72 OEt CONH2 OCH2/CHOHMe 31 130-134 EtOAc -hexane C,H,N 100 32 73 OEt CONH2 OCH2/CHOHMe 31 130-134 EtOAc -hexane C,H,N,Cl 85 20 74 OEt CONH2 OCH2/CH3/NMe2 G 73 00H C,H,N,Cl 85 26 75 OEt CONH2 OCH2/CH3/NMe2 G 73 130-133 EtOH C,H,N,Cl 85 26 76 OEt CONH2 OC NO2 78 130-133 EtOH C,H,N,Cl 85 0 77 OEt CONH2 NO2 78 206-209 EtOH C,H,N,Cl 85 0 12 71 OEt CO2 MeC MeC MeC C,H,N,Cl 55 0 7 OEt CO3H 7 238-243 EtOH C,H,N 11 10 12 7 OEt OMe </th <th>11</th> <th>OEt</th> <th>CONH₂</th> <th>OCH2CH2OC6H5</th> <th></th> <th></th> <th>-</th> <th>78</th> <th>142145</th> <th>EtOH</th> <th>С, Н, N</th> <th>75</th> <th></th> <th></th> <th>0</th>	11	OEt	CONH ₂	OCH2CH2OC6H5			-	78	142145	EtOH	С, Н, N	75			0
73OEICONH3OCH3CCH3/CH3/NMe374OEICONH3CI $C(H, N, CI)$ 8575OEICONH3CI78190–193EtOHC, H, N, CI8576OEICONH3CI78204–210MeCNC, H, N, CI55076OEICONH3CI78204–210MeCNC, H, N, CI55077OEICO3HNO278206–209EtOHC, H, N, CI55077OEICO3HNO278206–209EtOHC, H, N, CI55078OEICO2HNO278206–209EtOHC, H, N, CI55079OEICO2Me49238–243EtOHC, H, N58079OEICO2HOMe49238–243EtOHC, H, N58070OEICO2HOMe49238–243EtOHC, H, N58070OEICO2HOMe49238–233EtOHC, H, N3380OEICO2HMeMeMe80235–239EtOHC, H, N1081OEICONH3MeMeMeMeMe00082OEICONH3MeMeMeMe00083OEICONH3MeMeMeMe00084 <t< th=""><th>72</th><th>OEt</th><th>$CONH_2$</th><th>OCH₂CHOHMe</th><th></th><th></th><th></th><th>31</th><th>130-134</th><th>EtOAc – hexane</th><th>C, H, N</th><th>100</th><th>32</th><th></th><th></th></t<>	72	OEt	$CONH_2$	OCH ₂ CHOHMe				31	130-134	EtOAc – hexane	C, H, N	100	32		
74OEtCONH2C178190-193EtOHC,H,N2675OEtCONH2C1 NO_2 C1 84 $204-210$ MeCNC,H,N,C1 55 0 76OEtCONH2NO2T 84 $204-210$ MeCNC,H,N,C1 55 0 76OEtCONH2NO2T 78 $206-209$ EtOHC,H,N 59 0 77OEtCO2H $0Me$ 49 $238-243$ EtOHC,H,N 59 0 78OEtCO2H $0Me$ Me Me 49 $238-243$ EtOH C,H,N 59 0 78OEtCO2H $0Me$ Me Me 49 $238-243$ EtOH C,H,N 59 0 79OEt CO_2Me $0Me$ Me Me Me Me 10 110 0 79OEt CO_2H Me Me Me Me 80 $235-239$ $EtOH$ C,H,N 33 80OEt $CONH277232-236MeCNC,H,N100781OCH2OOH_2MeMeMeMeCNC,H,N100782OEHCONH277232-236MeCNC,H,N100783OCH_2OOH_2MeMeMeMeCNC,H,N1001084CONH2COH2COH2$	73	OEt	CONH ²	OCH ₂ CH ₂ NMe ₂			-	65	$209-210^{b}$	MeOH	C, H, N, CI	85			
75OEtCONH2CI84 $204-210$ MeCNC,H,N,CI55076OEtCONH2NO2T78 $206-209$ EtOHC,H,N,CI55077OEtCO2HOMe49 $238-243$ EtOHC,H,N591278OEtCO2Me49 $238-243$ EtOHC,H,N59079OEtCO2Me0Me48 $186-188$ EtOHC,H,N58080OEtCO2HMeMeMe80 $235-239$ EtOHC,H,N3381OEtCO3HMeMeMe80 $235-239$ EtOHC,H,N3381OEtCONH2MeMeMe80 $235-236$ MeOH7782OEtCONH2MeMeMeMeMe77 $232-236$ MeOH7783OEtCONH2MeMeMeMe45177-179EtOHC,H,N0	74	OEt		G			-	78	190 - 193	EtOH	С, Н, N	26			
76OEI $CONH_2$ NO_2 NO_2 78 $206-209$ $EtOH$ C,H,N 59 77OE CO_2H OMe 49 $238-243$ $EtOH$ C,H,N 59 78OE CO_2Me OMe 49 $238-243$ $EtOH$ C,H,N 59 79OE CO_2Me OMe 49 $238-243$ $EtOH$ C,H,N 58 0 79OE CO_2H OMe 48 $186-188$ $EtOH$ C,H,N 31 10 80OE CO_2H MeMeMe80 $235-239$ $EtOH$ C,H,N 33 81OE COH_2 MeMeMe80 $235-236$ $MeOH$ 0 7 82OEI COH_2 OCH_2O 77 $232-236$ $MeCN$ 0 7 83OEI COH_2 Me MeMe 45 $177-179$ C,H,N 0	75	OEt	$CONH_2$		IJ			84	204-210	MeCN	C, H, N, CI	55			0
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 CO_2Me OMe 48 $186-188$ $EtOH$ C,H,N 58 0 80 OEt CO_2H Me Me 80 $235-239$ $EtOH$ C,H,N 33 81 OEt CO_2H Me Me 80 $235-239$ $EtOH$ C,H,N 33 82 OEt $CONH_2$ Me Me 80 $235-236$ $MeCN$ C,H,N 100 7 82 OEt $CONH_2$ OCH_2O 77 $232-236$ $MeCN$ C,H,N 100 7 83 OEt $CONH_2$ $0.6H,N$ $0.6H$ $0.6H,N$ $0.6H,N$ $0.6H,N$ $0.6H,N$ $0.6H,N$ $0.6H,N$	76	OEt	$CONH_2$		NO_2		-	78	206–209	EtOH	C, H, N	59			
78 OEt CO ₂ Me OMe 66 129–133 EtOH C,H,N 58 0 79 OEt CONH ₂ OMe 48 186–188 EtOH C,H,N 58 0 0 80 OEt CO ₂ H Me Me 80 235–239 EtOH C,H,N 33 0 0 0 81 OEt CONH ₂ Me Me 80 235–239 EtOH C,H,N 33 0 81 OEt CONH ₂ Me Me 85 190–193 EtOH C,H,N 100 7 82 OEt CONH ₂ OCH ₂ O 77 232–236 MeCN C,H,N 0 7 83 OEt CONH ₂ OCH ₂ O 77 232–236 MeCN C,H,N 0 7 83 OEt CONH ₂ Me Me 45 177–179 EtOH C,H,N 0	77	OEt	CO_2H		OMe		•	49	238-243	EtOH	С, Н, N	61			12
79 OEt CONH2 OMe 48 186–188 EtOH C,H,N 91 10 0 80 OEt CO2 _H Me Me 80 235–239 EtOH C,H,N 33 91 10 0 81 OEt CO2 _H Me Me 85 190–193 EtOH C,H,N 33 82 OEt CONH2 Me Me 85 190–193 EtOH C,H,N 100 7 82 OEt CONH2 OCH2O 77 232–236 MeCN C,H,N 0 83 OEt CONH2 Me 45 177–179 EtOH C,H,N 0	78	OEt	CO_2Me		OMe		-	66	129-133	EtOH	С, Н, N	58			0
80 OEt CO ₂ H Me Me Me 80 235–239 EtOH C,H,N 33 81 OEt CONH2 Me Me 85 190–193 EtOH C,H,N 100 7 82 OEt CONH2 OCH2O 77 232–236 MeCN C,H,N 0 0 7 83 OEt CONH2 Me Me 45 177–179 EtOH C,H,N 0	62	OEt	$CONH_2$			OMe		48	186188	EtOH	C, H, N	91	10		0
81 OEt CONH2 Me Me Me 85 190–193 EtOH C,H,N 100 7 82 OEt CONH2 OCH2O 77 232–236 MeCN C,H,N 0 83 OEt CONH2 Me 45 177–179 EtOH C,H,N 0	80	OEt	CO_2H		Me	Me		80	235-239	EtOH	С, Н, N	33			
82 OEt CONH2 OCH2O 77 232–236 MeCN C, H, N 0 83 OEt CONH2 Me 45 177–179 EtOH C, H, N 0	81	OEt	$CONH_2$		Me	Me		85	190193	EtOH	C, H, N	100		7	
83 OEt CONH ₂ Me Me 45 177–179 EtOH C, H, N 0	82	OEt	$CONH_2$		00	H ₂ O	-	77	232-236	MeCN	C, H, N	0			
	83	OEt	CONH		Me		Me	45	177-179	EtOH	C, H, N	0			
	YIUUIT.	DILION OF BREALER	UNAL 35176 COUSIGE	ereu statusticany signific	nic vo lue:	Sell S Lest		Jelermine	on the nya.	TOCHIOTIGE SEPTEM TEL US TOT	non appyage mo	I of a.S in rell	DX DOC 4	0.5	

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

% inhibn,^a % inhibn^a po

Compd	А	Mp, °C	Crystn solvent	Analyses	200 mg/kg ip	200 mg/kg	10 mg/kg
84		214-217	EtOH		72	0	
85	$1,4-C_{6}H_{4}CH_{2}$	149–151°	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	$1,4-C_{6}H_{4}O$	159–162 [»]	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'	9		
91	$1,4-C_6H_4OCH_2CH(OCOCO_2-Et)CH_2O$	168-170	EtOAc–hexane	C, H, N ^g	13		

Table III. Bisoxanilic Acid Esters, EtO2CCONH-A-1,4-C6H4NHCOCO2Et

^aInhibition of greater than 35% considered statistically significant by Student's t test (p < 0.05). ^bA. Rio, French Patent 1,338,399 (1963); *Chem. Abstr.*, **60**, 3012b (1964). ^cYield 75%. ^aYield 56%. ^eFrench Patent 1,567,434 (1969); *Chem. Abstr.*, **71**, 112653 n (1969). ^fYield 36%. ^aYield 30%.

Table IV. N-Heteroaryl Oxamic Acid Esters, RNHCOCO₂R₁

							76	% i	nhibnª	po
Compd	R	R ₁	% yield	Mp or bp (mm), °C	Crystn solvent	Analyses	inhibn, ^a 200 mg/ kg ip	200 mg/ kg	15 mg/ kg	10 mg/ kg
	9 Didia1			70 756			100			
92 01	2-Pyriullyi		41	13-13	Et ₂ O	CUN	100	00		30
21	5-Pyriainyi	EL Di	41	98-100		C, H, N	90	04		11
93	4-Pyriainyi	Et	22	110113		C, H, N	100	34		
94	6-Methyl-2-pyri- dinyl	Et	66	61-63	Et_2O	С, Н, N	777	74		25
95	3-Cyano-2-pyri- dinyl	Et	26	9597	$Et_2O-CH_2Cl_2$	C, H, N	100		0°	
22	1-Methylpyridi- nium-3-yl iodide	Et	84	138–140	EtOH	C, H, I, N	0			
96	2-Pyrimidinyl	Et	35	9699	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	4H-1,2,4-Triazol- 4-vl	Et	53	206-209	EtOH	С, Н, N	7			
100	2-Pyridinyl	Ме	59	102-106	Et₀O	C. H. N	77	100		25
101	2-Pyridinyl	n-Pr	35	5659	Et ₀ O	C. H. N	58	77		
102	2-Pyridinyl	<i>i</i> -Pr	37	Oil	2-	C. H. N	100	••	0	
103	2-Pyridinyl	n-Bu	61	35-37	Et _o O	CHN	100		õ	
104	2-Pyridinyl	sec-Bu	46	112-116 (0.05)	2.20	C, H, N	100		0	
105	2-Pyridinyl	Cyclohexyl	67	62-64	Et ₂ O-hexane	C, H, N	53			

^aInhibition of greater than 35% considered statistically significant by Student's t test (p < 0.05). ^bDose 20 mg/kg. ^cP. A. Petyunin and A. V. Storozheva, Zh. Obshch. Khim., **32**, 1395 (1962); Chem. Abstr., **58**, 4449b (1963). ^aP. A. Petyunin and M. V. Zakalyuzhnyi, Zh. Obshch. Khim., **34** (1), 28 (1964); Chem. Abstr., **60**, 10591c (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-dione¹⁶ 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 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-

					9	c inhibn° j	00
Compd		Mp or bp (mm), °C	Crystn solvent	‴e inhibn,ª 200 mg∕kg ip	2 00 mg/kg	25 mg/kg	10 mg/kg
106	NH ₂ COCO ₂ Et	113-116		0			*** *
107	C ₆ H ₅ CH ₂ NH- COCO ₂ Et	47–50 ^{<i>b</i>}	Et ₂ O-pentane	16			
108	C ₆ H ₁₁ NHCO- CO₅Et	6063°	Hexane	24			
20	C ₆ H₅CONH- COCO₂Et	48-51 ^d	Et ₂ O-hexane	71		0	
109	C ₆ H ₅ COCO ₂ - Et	73 (0.2) ^e		2			
110	C ₆ H ₅ OCOCO ₂ - Et	98–100 (0.05) ^f		0			4
111	C ₆ H₅NMe- COCO₀Et	108 (0.25) [#]		2			
112	$C_5H_{10}NCO-$	92–96 (0.25) ^h		9			
113	C ₆ H ₅ NHCS- CO ₅ Et	39–40 <i>°</i>	Petroleum ether	28			
114	C ₆ H ₅ NHCO- CN	129–132'	Benzene- cvclohexane	Toxic at ≥25 mg/kg ip			
115	C ₆ H ₅ NHCO- CCl ₂	90—95 [*]	EtOH	25			0
116	C ₆ H ₅ NHCO- CONHOH	165–167 ¹	H ₂ O	92		0	
117	C ₆ H ₅ NHCO- CHN ₄	216–21 8 ^{<i>m</i>}	EtOH-H ₂ O	100	85		24

Table V. Radical Changes of the Simple Oxanilic Acids

^aInhibition of greater than 35% considered statistically significant by Student's t test (p < 0.05). ^bT. Curtius and K. Raschig, J. Prakt. Chem., 125, 466 (1930). ^cK. A. de Vries, Recl. Trav. Chim. Pays-Bas, 61, 223 (1942). ^dAnal. C, H, N. Yield 11%. ^eB. 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. ^(Y)Y. N. Ivashchenko, S. D. Moshchitskii, and A. V. Kirsanov, Zh. Obshch. Khim., 32, 3765 (1962); Chem. Abstr., 58, 12452h (1963). ^eP. A. Petyunin, V. S. Shklyaev, and A. S. Pesis, Zh. Obshch. Khim., 27, 1554 (1957); Chem. Abstr., 52, 3763i (1958). ^hH. E. Ungnade and L. W. Kissinger, J. Org. Chem., 24, 666 (1959). ^(A)A. Reissert, Chem. Ber., 37, 3708 (1904). ^JR. Malachowski and J. Jankiewicz-Wasowska, Rocz. Chem., 25, 35 (1951); Chem. Abstr., 47, 10483f (1953). ^kY. V. Svetkin, Zh. Obshch. Khim., 32, 1037 (1962); Chem. Abstr., 58, 1378g (1963). ^(O)O. Dimroth and L. Taub, Chem. Ber., 39, 3912 (1906). ^mB. 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

			MeO CO NH	NH ₂ IR		
Compd	R	% yield	Mp, °C	Crystn solvent	Analyses	% inhibn,⁴ 200 mg∕kg ip
118	CO ₂ Et	72	173-176	МеОН	C, H, N	0
119	n-COPr	36	145-148	EtOAc-hexane	C, H, N	0
120	COCH ₂ CO ₂ Et	77	143-146	EtOH	C, H, N	17
121	COCCI3	69	165168	EtOH	C, H, N	0

^aInhibition 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 Me₄Si in CDCl₃ and DMSO- d_6 and DSS in D₂O. 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		Intra	wenous	^h
	Dose, mg/kg	N°	Av wheal size, $\frac{4}{\text{mm}^2 \pm \text{SE}}$	Dose, mg/kg	N^{ε}	Av wheal size, ^d mm ² ± SE
Control	Water, 5 ml/kg	4	115.5 ± 2.9	Saline, 5 ml/kg	4	114.6 ± 5.4
MeO CONH:	25	4	75.6+7.6*	1	٨	79.9 + 7*
NHCOCO.E1	50	5	68±8.3*	3	4	25 + 7.8*
9	100	4	$19.4 \pm 7.6*$	5	4	$21.4 \pm 1.2*$
MeO_CONH	25	4	105 ± 3.4	1	4	81 4 + 12 7*
NHCOCO Na	50	5	91 ± 6.2*	ŝ	5	$76.4 \pm 7*$
16	100	4	$98 \pm 6.5^*$	Ş	5	$43.8 \pm 5.7*$
MeO_CONH_	25	4	109 ± 4.2	4	4	64 9 + 10*
	50	5	113.6 ± 4.2	3	5	$29.3 \pm 6*$
16	100	4	114.3 ± 3.5	5	5	9.8 ± 3*

^aDrug administered 5 min prior to antigen challenge. ^aDrug administered simultaneously with antigen challenge. ^cN = number of rats/point - 2 wheals/rat. ^aAn asterisk indicates p < 0.05.

Table VIII. Intermediate 2-Nitrobenzonitriles

				N 0,		
Compd	R	% yield	Formula	Analyses	Mp, °C	Crystn solvent
122 123 124	$\begin{array}{c} \mathbf{CH}_{2}\mathbf{CH}_{2}\mathbf{OC}_{6}\mathbf{H}_{5}\\ \mathbf{CH}_{2}\mathbf{CHOHMe}\\ \mathbf{CH}_{2}\mathbf{CH}_{2}\mathbf{NMe}_{2} \end{array}$	70 39 45	$\begin{array}{c} C_{15}H_{12}N_2O_4\\ C_{10}H_{10}N_2O_4\\ C_{11}H_{13}N_3O_3\end{array}$	C, H, N C, H, N C, H, N	127130 121124 8991	MeCN Benzene Benzene-hexane

Table IX. Intermediate 2-Aminobenzamides

			OR CON NH.	H ₂		
Compd	R	% yield	Formula	Analyses	Mp, °C	Crystn solvent
125	Et	51	C ₉ H ₁₂ N ₂ O ₂	C, H, N	173-174	MeCN
126	<i>n</i> -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	<i>n-</i> Bu	61	$C_{11}H_{16}N_2O_2$	C, H, N	119-122	EtOH
129	CH ₂ CH ₂ OC ₆ H ₅	50	$C_{15}H_{16}N_2O_3$	C, H, N	127-130	EtOH
130	CH ₂ CHOHMe	78	$C_{10}H_{14}N_2O_3$	C, H, N	115-118	EtOAc-hexane
131	$CH_2CH_2NMe_2$	31	$\mathbf{C}_{11}\mathbf{H}_{17}\mathbf{N}_{3}\mathbf{O}_{2}$	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 PCl₅ 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 $160-165^{\circ}$, causing about 80 ml of POCl₃ to distill off. The temperature was then raised to $185-187^{\circ}$ and an additional 70 ml of POCl₃ was slowly distilled off. (*Caution:* at the point where the temperature is $185-187^{\circ}$ 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-H₂O and the flask was rinsed out with another 1 l. of H₂O. 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 H₂O, added to a solution of 750 ml of Me₂CO and 750 ml of 14% NH₄OH, and stirred for 0.5 hr at room temperature. The Me₂CO was removed on a rotary evaporator at 60° and ~500 ml of H₂O was added to the residue. The solid was filtered, washed with H₂O, and added to 800 ml of 10% NaOH. The mixture was stirred for 0.5 hr and the solid was filtered, washed with at 70° in vacuo, and crystallized (toluene), giving 139 g (72%) of 13: mp 143-146° (lit.¹⁹ mp 145°). Anal. (C₇H₃N₃O₄) 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 $0-5^{\circ}$, and filtered. The solid was slurried in H₂O 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% NH₂NH₂·H₂O was added, followed immediately by small amounts of washed (three times with H₂O 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 (H₂O), giving 59 g (72%) of 15: mp 150–153° (lit.²⁰ mp 155–156°). Anal. (C₈H₁₀N₂O₂) 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 CH₂Cl₂ was cooled to \sim 5-.10° and 6.2 ml (0.0554 mol) of EtO₂CCOCl was added dropwise over \sim 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 \sim 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. (C₁₃H₁₄N₂O₅) 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 H₂O, 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. (C₁₀H₉N₂NaO₅) C, H, N.

Acidification of 10 g (0.038 mol) of 16 dissolved in 100 ml of H₂O with 100 ml of 1 N HCl gave 7.6 g of 16 free acid after crystallization (MeOCH₂CH₂OH): 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 NH₃ at 0-5° and stirred at \sim 5-10° for 2 hr. The mixture was filtered, washed with EtOH, and crystallized (H₂O), giving 1.41 g (28%) of 17: mp 252-255°. Anal. (C₁₀H₁₁N₃O₄) 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 Et₂O 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-H₂O 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-2H-3,1-benzoxazine-2,4(1H)-dione: mp >300°. The isatoic anhydride was then added to 435 ml of 1 M NH₄OH. 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. (C₉H₁₂N₂O) 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.

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