Irreversible Enzyme Inhibitors. CLIII.[1,2] Proteolytic Enzymes. XI.[2] Inhibition of Guinea Pig Complement by Substituted Phenoxyacetamides

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A series of 89 compounds derived from phenoxyacetamide and phenoxyacetone were investigated as inhibitors of the guinea pig complement system. Only two of the compounds without a terminal SO_2F moiety showed 30–50% inhibition at 1–3 mM, namely, α-naphthoxyacetone (**14**) and N-benzyl-N-carboxymethyl-3,4-dichlorophenoxyacetamide (**70**); however, these concentrations were lower than the 10–20 mM needed for N-acetyl-L-tyrosine ethyl ester (**1**) and N-tosyl-L-arginine methyl ester (**4**). Several compounds derived from N-benzyl- and N-phenylphenoxyacetamide with a COOH group *ortho* to the ether linkage (**37–39**, **66**) accelerated complement-induced lysis, perhaps by inhibition of the destruction of one or more of the sensitive components of complement such as C′1, C′4, or C′6. When the N-phenyl- or N-benzyl-2-carboxy-4-chlorophenoxyacetamides were bridged to benzenesulfonyl fluoride with a ureido moiety (**76–87**), some excellent "irreversible" inhibitors emerged such as N-[*m*-(3-chloro-4-fluorosulfonylphenylureido)benzyl]-2-carboxy-4-chlorophenoxyacetamide (**85**) which at 0.25 mM gave 82% inhibition of the complement system; it was further established that the SO_2F moiety on a molecule such as **85** was necessary for activity, but the abbreviated *p*-acetamidobenzenesulfonyl fluoride showed no activity.

Complement consists of nine components which arise from eleven distinct proteins, all of which are required for lysis of a foreign cell;[4a] thus, inhibition of complement could be useful for voiding organ transplant rejection, providing other enzymes of serum are not inhibited.[5] Some of the components of complement are either "tryptic" or "chymotryptic" or both in character.[4a] For example, the activation of C′2 by C′1a is inhibited by N-tosyl-L-arginine methyl ester (TAME);[6] TAME as well as N-acetyl-L-tyrosine ethyl ester (ATEE) are substrates for C′1a[7] and thus could act as inhibitors of the whole complement system. Furthermore, cell-bound C′3 can utilize glycyl-L-tyrosine as a substrate,[8] and ϵ-aminocaproic acid can inhibit the activation of C′1 to C′1a.[9] That TAME (**4**), ATEE (**1**), and related esters (**2**, **3**) at high concentration (10–20 mM) could inhibit whole-complement lysis of sheep red blood cells (RBC) in the assay used in this laboratory was confirmed (Table I); however, ϵ-aminocaproic acid (**5**) was not an inhibitor at 5 mM.

The best inhibitor of whole complement reported in the literature is maleopimaric acid (**6**);[10] actually maleopimaric acid was assayed as the Na salt of the corresponding tricarboxylic acid.[2] Since some of the components of complement have "tryptic" character, the inhibition of whole complement by a series of tryspin inhibitors was described in the previous paper.[2] Furthermore, one or more components of complement also have "chymotryptic" character. Therefore, the chymotrypsin inhibitors previously reported from this laboratory[11–15] were assayed on whole complement; the results with these chymotrypsin inhibitors as well as some additional synthetics are the subject of this paper.

Inhibition Results.—Phenoxyacetone (**7**) (Table II) is a weak inhibitor of chymotrypsin; the inhibition is considerably enhanced by introduction of *m*-Cl (**9**), *o*-C_6H_5 (**13**), 3,4-benzo (**15**), 3,4-Cl_2 (**11**), or 2,3-Cl_2 (**10**) substituents by factors of 11-, 8-, 7-, 16-, and 23-fold, respectively, but only twofold by 2,3-benzo (**14**).[11] Although no inhibition of complement was observed with the highest concentration (3 mM) run with phenoxyacetone, it was noted that the 2,3-Cl_2 (**10**) and 2,3-benzo (**14**) derivatives considerably enhanced the inhibition of complement, in contrast to the other substituents that enhanced binding to chymotrypsin; of course, the lack of solubility of **13** and **15** may have precluded observable activity.

A series of phenoxyacetanilides[11–14] were then investigated for inhibition of complement. No inhibition was observed by the parent phenoxyacetanilide (**21**) or 18 of its derivatives (Table III); the lack of inhibition in many cases may have been due to low solubility. However, it was noted that the *o*-carboxy derivatives (**37–39**) accelerated the complement-induced lysis, since no lysis by these compounds occurred in the absence of complement.[5a] Thus, it is possible that **37–39** inhibit the enzymatic destruction of some components of complement such as C′1, C′4, or C′6.[4,5a]

Although no inhibition of complement was observed with N-benzylphenoxyacetamide (**40**) a number of its derivatives showed low, but reproducible, activity such as the 3-Cl (**45**), 3-Cl-4′-NH_2 (**50**), and 3,4,4′-Cl_3 (**54**) derivatives (Table IV). Therefore, a series of 12 derivatives related to **54** were synthesized (**55–67**) where the substituents on both phenyl moieties were varied to see if the weak inhibition could be enhanced. None were

(1) This work was generously supported by Grant CA-08695 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper in this series see B. R. Baker and E. H. Erickson, *J. Med. Chem.*, **12**, 408 (1969).

(3) NDEA predoctoral fellow.

(4) (a) H. J. Muller-Eberhard, *Advan. Immunol.*, **8**, 1 (1968); (b) N. Tamura and R. A. Nelson, Jr., *J. Immunol.*, **99**, 582 (1967).

(5) For a more complete discussion (a) see ref 2; (b) B. R. Baker and E. H. Erickson, *J. Med. Chem.*, **10**, 1123 (1967), paper CVI of this series.

(6) R. M. Stroud, K. F. Austen, and M. M. Mayer, *Immunochemistry*, **2**, 219 (1965).

(7) A. L. Haines and I. H. LePow, *J. Immunol.*, **92**, 456 (1964).

(8) N. R. Cooper and E. L. Becker, *ibid.*, **98**, 119 (1967).

(9) F. B. Taylor, Jr., and H. Fudenberg, *Immunology*, **7**, 319 (1964).

(10) M. M. Glovsky, E. L. Becker, and N. J. Halbrook, *J. Immunol.*, **100**, 979 (1968).

(11) B. R. Baker and J. A. Hurlbut, *J. Med. Chem.*, **10**, 1129 (1967), paper CVII of this series.

(12) B. R. Baker and J. A. Hurlbut, *ibid.*, **11**, 233 (1968), paper CXIII of this series.

(13) B. R. Baker and J. A. Hurlbut, *ibid.*, **11**, 241 (1968), paper CXIV of this series.

(14) B. R. Baker and J. A. Hurlbut, *ibid.*, **11**, 1054 (1968), paper CXXXII of this series.

(15) B. R. Baker and J. A. Hurlbut, *ibid.*, **12**, 118 (1969), paper CXLV of this series.

Table I

Inhibition[a,b] of Guinea Pig Complement by Amino Acid Esters and Related Compounds

No.	Compound	Concn, mM	% inhibn
1	N-Acetyl-L-tyrosine ethyl ester	20	83
		5	0
2	N-Benzoyl-L-tyrosine ethyl ester	2.5[d]	10
3	N-Benzoyl-L-arginine ethyl ester	20	78
		10	38
		1	5
4	N-Tosyl-L-arginine ethyl ester	20	83
		10	38
5	ε-Aminocaproic acid	5[d]	0
6	Maleopimaric acid[c]	1	81
		0.5	45
		0.25	3

[a] The technical assistance of Sharon Lalhr, Diane Shea, and Susan Black with these assays is acknowledged. [b] See ref 2 for the method of assaying sheep RBC lysis by hemolysin and guinea pig complement. [c] Assayed as the Na salt of the corresponding tricarboxylic acid; data from ref 2. [d] Maximum solubility.

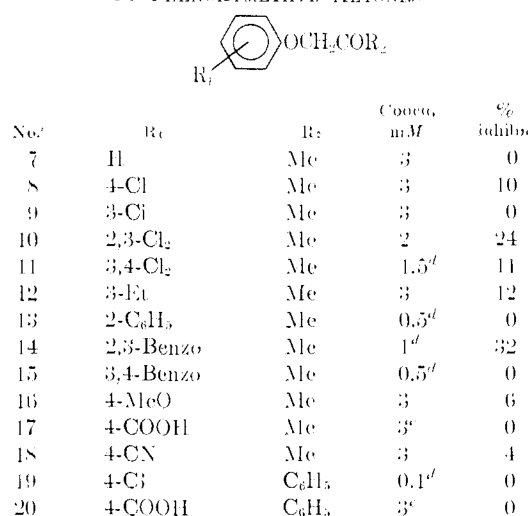


Table II

Inhibition[a,b] of Guinea Pig Complement by Phenoxymethyl Ketones

No.[c]	R_1	R_2	Concn, mM	% inhibn
7	H	Me	3	0
8	4-Cl	Me	3	10
9	3-Cl	Me	3	0
10	2,3-Cl_2	Me	2	24
11	3,4-Cl_2	Me	1.5[d]	11
12	3-Et	Me	3	12
13	2-C_6H_5	Me	0.5[d]	0
14	2,3-Benzo	Me	1[d]	32
15	3,4-Benzo	Me	0.5[d]	0
16	4-MeO	Me	3	6
17	4-COOH	Me	3[e]	0
18	4-CN	Me	3	4
19	4-Cl	C_6H_5	0.1[d]	0
20	4-COOH	C_6H_5	3[e]	0

[a,b] See corresponding footnotes in Table I. [c] See ref 11 for compounds. [d] Maximum solubility. [e] Dissolved in MeOEtOH + 1 equiv of Tris base.

better than **54**, although lack of solubility was again a problem. The more soluble 2-carboxy derivative (**66**) could be assayed at 1 mM where it showed acceleration of complement-induced lysis, but little lysis in the absence of complement. However, when the carboxyl was moved to the amide N as an N-carboxymethyl derivative (**70**), good inhibition of complement was observed at 3 mM, but complete lysis occurred in the absence of complement.

A series of quaternized pyridylacrylanilides and pyridylpropionanilides (**71–75**) at 1–2 mM showed no useful amount of inhibition of complement (Table V).

When a series of active-site-directed irreversible inhibitors[16] of chymotrypsin derived from 2-carboxy-4-chlorophenoxyacetamide[15] were investigated (Table VI), some excellent inhibitors of complement emerged. These were assayed as the Tris salt, and solubility in the assay solution varied from 0.12 mM to over 1 mM;[17] thus, in some cases direct comparisons between com-

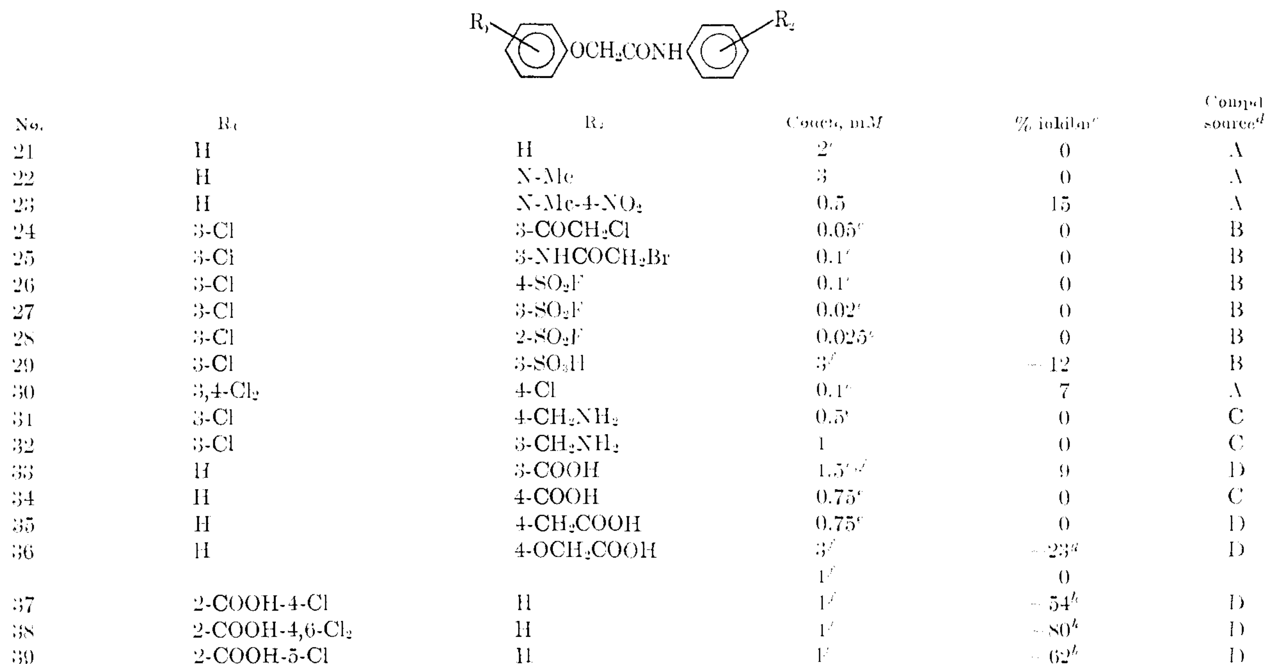


Table III

Inhibition[a,b] of Guinea Pig Complement by Phenoxyacetanilides

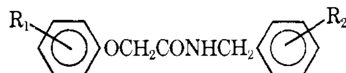
No.	R_1	R_2	Concn, mM	% inhibn[c]	Compd source[d]
21	H	H	2[e]	0	A
22	H	N-Me	3	0	A
23	H	N-Me-4-NO_2	0.5	15	A
24	3-Cl	3-$COCH_2Cl$	0.05[e]	0	B
25	3-Cl	3-$NHCOCH_2Br$	0.1[e]	0	B
26	3-Cl	4-SO_2F	0.1[e]	0	B
27	3-Cl	3-SO_2F	0.02[e]	0	B
28	3-Cl	2-SO_2F	0.025[e]	0	B
29	3-Cl	3-SO_3H	3[f]	−12	B
30	3,4-Cl_2	4-Cl	0.1[e]	7	A
31	3-Cl	4-CH_2NH_2	0.5[e]	0	C
32	3-Cl	3-CH_2NH_2	1	0	C
33	H	3-COOH	1.5[e,f]	9	D
34	H	4-COOH	0.75[e]	0	C
35	H	4-CH_2COOH	0.75[e]	0	D
36	H	4-OCH_2COOH	3[f]	−23[g]	D
			1[f]	0	
37	2-COOH-4-Cl	H	1[f]	−54[h]	D
38	2-COOH-4,6-Cl_2	H	1[f]	−80[h]	D
39	2-COOH-5-Cl	H	1[f]	−62[h]	D

[a,b] See corresponding footnotes in Table I. [c] A minus number indicates more lysis than the complement control without compound. [d] A, ref 11; B, ref 12; C, ref 13; D, ref 14. [e] Maximum solubility. [f] Dissolved in 1:1 H_2O–MeOEtOH containing 1 equiv of Tris base. [g] 20% lysis observed in the absence of complement. [h] Near total lysis, but no lysis in the absence of complement.

(16) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors. The Organic Chemistry of the Enzymic Active-Site," John Wiley and Sons, Inc., New York, N. Y., 1967.

(17) A series of seven compounds related to **76–81** without the COOH group[15] were only soluble up to 0.02 mM and no inhibition of complement was seen.

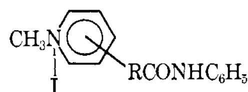
TABLE IV
INHIBITION[a,b] OF GUINEA PIG COMPLEMENT BY N-BENZYLPHENOXYACETAMIDES



No.	R_1	R_2	Concn, mM	% inhibn[c]	Compd source[d]
40	H	H	1	0	A
41	H	2-Cl	1	0	A
42	H	3-Cl	0.5[e]	8	A
43	H	4-Cl	0.5[e]	9	A
44	H	4-NO_2	0.5[e]	8	A
45	3-Cl	H	1	15	A
46	3-Cl	2-NO_2	0.2[e]	0	C
47	3-Cl	4-NO_2	0.2[e]	0	C
48	3-Cl	2-NH_2	0.5[e]	9	C
49	3,4-Cl_2	3-NH_2	0.25[e]	0	C
50	3-Cl	4-NH_2	0.5	18	C
51	3-Cl	2-$NHCOCH_2Br$	0.2[e]	0	C
52	3,4-Cl_2	3-$NHCOCH_2Br$	0.1[e]	0	C
53	3-Cl	4-$NHCOCH_2Br$	0.025[e]	0	C
54	3,4-Cl_2	4-Cl	0.1[e]	16	A
55	2-Cl	4-Cl	0.1[e]	5	E
56	3-Cl	4-Cl	0.1[e]	5	E
57	4-Cl	4-Cl	0.1[e]	0	E
58	2,4-Cl_2	4-Cl	0.02[e]	0	E
59	2,3-Cl_2	4-Cl	0.05[e]	10	E
60	2,5-Cl_2	4-Cl	0.05[e]	0	E
61	3,5-Cl_2	4-Cl	0.05[e]	0	E
62	2,4,6-Cl_3	4-Cl	0.05[e]	0	E
63	3,4-Benzo-6-COOH	4-Cl	0.12[e]	5	E
64	3,4-Cl_2	2,3-Benzo	0.012[e]	−13	E
65	2-COOH	4-Cl	3[e,f]	8	E
66	2-COOH-4-Cl	4-Cl	1[f]	−48[g]	E
67	2-COOH-4-Cl	2,3-Benzo	0.12[e]	8	E
68	2-COOH-4-Cl	3-NH_2	1[f]	11[h]	D
69	3,4-Cl_2	N-Me	0.12[e]	0	E
70	3,4-Cl_2	N-CH_2COOH	3[f]	45[i]	E

[a,b] See corresponding footnotes in Table I. [c] See footnote c in Table III. [d] A, ref 11; B, ref 12; C, ref 13; D, ref 14; E, Experimental Section. [e] Maximum solubility. [f] Dissolved in MeOEtOH plus 1 equiv of Tris base. [g] 10% lysis in the absence of complement. [h] 14% lysis in the absence of complement. [i] Complete lysis in the absence of complement.

TABLE V
INHIBITION[a,b] OF GUINEA PIG COMPLEMENT BY PYRIDYLACYLANILIDES



No.[c]	Isomer	R	Concn, mM	% inhibn
71	2	CH=CH	1	0
72	3	CH=CH	1	5
73	4	CH=CH	1	7
74	2	$(CH_2)_2$	2	5
75	4	$(CH_2)_2$	2	5

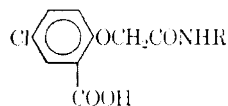
[a,b] See corresponding footnotes in Table I. [c] See ref 14 for compounds.

pounds could not be made. For example, **79** showed no inhibition at 0.12 mM, but 75% inhibition at 1 mM; in contrast, **83** showed 54% inhibition at its maximum solubility of 0.12 mM. Thus **83** is a more effective compound than **79** if comparison of the concentration needed for 50% inhibition is made, but **79** is more effective than **83** if maximum inhibition at any concentration is made.

That the ureidobenzenesulfonyl moiety of the anilides and benzylamides in Table VI was necessary for activity was indicated by comparison with compounds (**37**, **66**) not having this moiety; **37** and **66** accelerated lysis. Furthermore, that the SO_2F moiety was needed for activity was indicated by comparison of **80** with the corresponding sulfonamide (**88**). At its maximum solubility of 0.5 mM, **80** showed 70% inhibition of complement and only 7% lysis in the absence of complement; in contrast, **88** at 0.5 mM showed no inhibition, but at 1 mM accelerated complement-induced lysis. That the $C_6H_4SO_2F$ moiety had to be bridged to a phenoxyacetamide for activity was indicated by lack of activity of *p*-acetamidobenzenesulfonyl fluoride.[5a]

Covalent bond formation *via* the SO_2F moiety to give irreversible inhibition of one or more of the components of complement is a good probability. However, the difference in effectiveness between the SO_2NH_2 and SO_2F moieties could be due to point binding to a component of complement by the SO_2F moiety where the F: forms a donor–acceptor complex, although this explanation is considered less likely. It is unlikely that these two explanations can be differentiated by structure–activity relationships, but could be differentiated by determining whether irreversible inhibition of one or

Table VI
Inhibition[a,b] of Guinea Pig Complement by Sulfonyl Fluorides Derived from



No.[d]	R	Concn,[e] mM	% inhibn[e]	% lysis[f]
76	m-$C_6H_4NHCONHC_6H_4SO_2F$-4	0.12[g]	15	0
77[i]	m-$C_6H_4NHCONHC_6H_4SO_2F$-3	0.5[g]	82	8
		0.25	43	
		0.17	29	
78	p-$CH_2C_6H_4NHCONHC_6H_4SO_2F$-4	0.5	70	
		0.25	26	
79	p-$CH_2C_6H_4NHCONHC_6H_4SO_2F$-3	1	75	16
		0.5	55	
		0.33	26	
		0.12	0	
80	m-$CH_2C_6H_4NHCONHC_6H_4SO_2F$-4	0.5[g]	70	7
		0.25	18	
81	m-$CH_2C_6H_4NHCONHC_6H_4SO_2F$-3	1	82	0
		0.5	50	
		0.25	2	
82	m-$C_6H_4NHCONHC_6H_3$-4-Me-3-SO_2F	0.25[g]	80	0
		0.10	17	
83	m-$C_6H_4NHCONHC_6H_3$-2-Cl-5-SO_2F	0.12[g]	54	0
		0.06	12	
84	p-$CH_2C_6H_4NHCONHC_6H_3$-4-Me-3-SO_2F	0.25[g]	37	6
		0.12	0	
85	m-$CH_2C_6H_4NHCONHC_6H_3$-3-Cl-4-SO_2F	0.25[g]	82	8
		0.12	24	
86	m-$CH_2C_6H_4NHCONHC_6H_3$-4-Me-3-SO_2F	0.5[g]	86	9
		0.25	39	
87	m-$CH_2C_6H_4NHCONHC_6H_3$-2-Cl-5-SO_2F	0.5	89	12
		0.25	54	
		0.17	23	
88[h]	m-$CH_2C_6H_4NHCONHC_6H_4SO_2NH_2$-4	1	−68	0
		0.5	−8	0

[a,b] See corresponding footnotes in Table I. [c] See footnote c in Table III. [d] See ref 15 for synthesis unless other indicated. [e] Compounds dissolved in MeOEtOH containing 1 equiv of Tris base. [f] Lysis in the absence of complement corrected for 2–5% lysis in the absence of compound. [g] Maximum solubility. [h] See Experimental Section for synthesis. [i] See ref 14 for synthesis.

more of the separated components of complement[4a,18] is seen with the SO_2F-type inhibitors in Table VI.

Substitution on the benzenesulfonyl fluoride moiety was beneficial to inhibition in several cases as seen by comparison of **82** and **83** with **77**, **85** with **80**, and **86** and **87** with **81**. Although both anilides and benzylamides were effective inhibitors, the benzylamides have the advantage of being more soluble.

The inhibition pattern of the compounds in Table VI is different for complement and chymotrypsin; for example, **82** and **85** are excellent inhibitors of complement, but only **85** is a good irreversible inhibitor of chymotrypsin.

The most effective compound in Table VI from the standpoint of 50% inhibition at the lowest concentration is **83** at 0.12 mM. The most effective compounds based on giving >80% inhibition are **77**, **82**, and **85–87**; of these, **82** and **85** are the best since they give >80% inhibition at the lowest concentration (0.25 mM). Although **82**, **83**, and **85** are the best inhibitors of the complement system yet observed, many questions remain unanswered with the compounds in Table VI.

(1) Although the COOH group on the phenoxy moiety is necessary for solubility, can this carboxyl group be placed elsewhere in the basic structure (compare **70**) or can other solubilizing groups such as quaternary salts bridged to the amide N be used to get enhanced activity? Furthermore, other substituents on the phenoxy moiety might give enchanced activity.

(2) Would replacement of the phenoxyacetyl moiety by phenylpropionyl with or without α-acylamido substituents lead to enhanced activity?

(3) Would change of bridge length between the amide nitrogen and its phenyl substituent or between the benzene ring on the amide and the ureido group be beneficial?

(4) Would other bridges to the terminal benzenesulfonyl fluoride moiety give greater inhibition of complement at lower concentration?

(5) Since substitution on the $C_6H_4SO_2F$ moiety has been beneficial to inhibition in several cases, can other or more substituents give even more favorable inhibition?

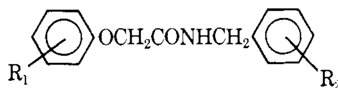
Studies to answer some of these questions are proceeding in this laboratory.

(18) E. L. Becker, *Biochim. Biophys. Acta*, 147, 289 (1967), and references therein.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. All analytical samples gave appropriate ir spectra, moved as a single spot on Brinkmann silica gel GF, and gave analyses for C, H, and N within 0.4% of the theoretical. The physical properties of new compounds are given in Table VII.

TABLE VII
PHYSICAL PROPERTIES OF



No.	R1	R2	Method[a]	Yield, %	Mp, °C	Formula[b]
55	2-Cl	4-Cl	A	78[c]	107–110	$C_{15}H_{13}Cl_2NO_2$
56	3-Cl	4-Cl	A	70[c]	90–92	$C_{15}H_{13}Cl_2NO_2$
57	4-Cl	4-Cl	A	67[c]	101–103	$C_{15}H_{13}Cl_2NO_2$
58	2,4-Cl_2	4-Cl	A	82[c]	131–134	$C_{15}H_{12}Cl_3NO_2$
59	2,3-Cl_2	4-Cl	A	95[c]	130–134	$C_{15}H_{12}Cl_3NO_2$
60	2,5-Cl_2	4-Cl	B	65[d,e]	126–129	$C_{15}H_{12}Cl_3NO_2$
61	3,5-Cl_2	4-Cl	B	61[d,e]	121–124	$C_{15}H_{12}Cl_3NO_2$
62	2,4,6-Cl_3	4-Cl	A	73[c]	104–106	$C_{15}H_{11}Cl_4NO_2$
63	3,4-Benzo-6-CO_2H	4-Cl	C	81[c,f]	216–220	$C_{20}H_{16}ClNO_4$
64	3,4-Cl_2	2,3-Benzo	A	24[e,g]	151–153	$C_{19}H_{15}Cl_2NO_2$
65	2-CO_2H	4-Cl	C	59[c]	169–172	$C_{16}H_{14}ClNO_4$
66	4-Cl-2-CO_2H	4-Cl	C	92[c]	185–188	$C_{16}H_{13}Cl_2NO_4$
67	4-Cl-2-CO_2H	2,3-Benzo	C	86[c]	212–215	$C_{20}H_{16}ClNO_4$
69	3,4-Cl_2	N-Me	A	58[e]	76–78	$C_{16}H_{15}Cl_2NO_2$
70	3,4-Cl_2	N-CH_2CO_2H	A,C[h]	73[i]	122–125	$C_{17}H_{15}Cl_2NO_4$
88	4-Cl-2-CO_2H	*m*-$NHCONHC_6H_4SO_2NH_2$-*p*	D	46[j,c]	165–187	$C_{23}H_{21}ClN_4O_7S \cdot 0.5C_2H_5OH$[k]
91	3,4-Benzo-6-CO_2Me	4-Cl	B[l]	58[c]	147–149	$C_{21}H_{18}ClNO_4$
92	4-Cl-2-CO_2Me	4-Cl	B[l]	63[c]	145–147	$C_{17}H_{15}Cl_2NO_4$
93	2-CO_2Me	4-Cl	B[l]	56[c]	91–92	$C_{17}H_{16}ClNO_4$

[a] A: condensation of amine with acid chloride; see ref 11, method E; B: alkylation of appropriate phenol with N-(*p*-chlorobenzyl)-chloroacetamide; see ref 14, method E; C: by saponification of the corresponding ester; see ref 14, method F; D: by condensation of **90** with the appropriate arylamine.[15] [b] All compounds showed a correct analysis for C, H, N. [c] Recrystallized from EtOH. [d] Recrystallized from EtOH–H_2O. [e] Recrystallized from petroleum ether (bp 60–110°). [f] Recrystallized from Me_2CO. [g] Recrystallized from $CHCl_3$–petroleum ether (bp 60–110°). [h] Over-all yield for method A, then C; the intermediate ester was an oil. [i] Recrystallized from PhMe. [j] Recrystallized from MeOEtOH–H_2O. [k] EtOH solvate verified by nmr. [l] Intermediate phenolic ester made from the acid with $POCl_3$–MeOH; see J. Klosa, *Arch. Pharm.*, **289**, 143 (1956).

N-(α-Naphthylmethyl)-2-carbomethoxy-4-chlorophenoxyacetamide (89).—To a stirred solution of 1.23 g (5 mmoles) of 2-carbomethoxy-4-chlorophenoxyacetic acid[15] and 0.51 g (5 mmoles) of Et_3N in 5 ml of THF was added 0.55 g (5 mmoles) of ethyl chloroformate in 5 ml of THF over a period of 2 min maintaining the temperature at −5 to 0°. After being stirred at this temperature for an additional 45 min, the solution was treated with 0.79 g (5 mmoles) of α-naphthylmethylamine in 20 ml of THF over a period of 20 min. The mixture was stirred at ambient temperature for 12 hr, then filtered. The filtrate was evaporated *in vacuo*. Two recrystallizations from EtOH gave 0.89 g (47%) of analytical sample as white crystals, mp 160–163°. *Anal.* ($C_{21}H_{18}ClNO_4$) C, H, N.

O-(*p*-Nitrophenyl) N-(*p*-Sulfamylphenyl)carbamate (90).—To a stirred solution of 2.02 g (10 mmoles) of *p*-nitrophenyl chloroformate[19] in 20 ml of THF was added dropwise over 45 min a solution of 3.4 g of sulfanilamide in 30 ml of THF.[20] After being stirred for an additional 30 min, the solution was saturated with dry HCl, then filtered. To the filtrate was added several volumes of petroleum ether (bp 60–110°). The product was collected and recrystallized from toluene–Me_2CO; yield, 1.9 g (56%) of white crystals, mp 195–203°. *Anal.* ($C_{13}H_{11}N_3O_6S$) C, H, N.

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(20) B. R. Baker and N. M. J. Vermeulen, *J. Med. Chem.*, **12**, 74 (1969), paper CXXXIV of this series.