Irreversible Enzyme Inhibitors. 185.[1,2] Active-Site-Directed Irreversible Inhibitors of Guanine Deaminase Derived from 9-Phenylguanine Bearing a Terminal Sulfonyl Fluoride. 2[3]

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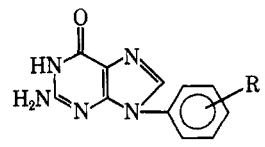
Eleven derivatives of 9-phenylguanine bridged from its meta position and 11 derivatives of 9-(*p*-ethoxyphenyl)-guanine bridged from its terminal Me group by carboxamide or ureido bridges to substituted benzenesulfonyl fluorides were synthesized, then investigated as irreversible inhibitors of Walker 256 guanine deaminase. Four of the compds (**6**, **8**, **10**, **11**) gave essentially complete inactivation of the tumor enzyme, but failed to show tissue specificity in that the rat liver enzyme was also inactivated.

In a previous paper[3] a series of 9-phenylguanines bridged to a terminal SO_2F were investigated as irreversible inhibitors of guanine deaminase from rabbit liver, Walker 256 rat tumor, and rat liver. None of the compds were completely satisfactory in giving good irreversible inhibition of the Walker 256 enzyme with little or no inactivation of the rat liver enzyme. For example, 12 μM **1** gave 100% inactivation of the Walker



1, R = *m*-$NHCOC_6H_3$-2-Cl-5-SO_2F
2, R = *p*-$O(CH_2)_2NHCOC_6H_4SO_2F$-*p*

256 enzyme, but showed no tissue specificity since the rat liver enzyme was inactivated 81%; **2** showed good specificity with no inactivation of the liver enzyme, but only 46% inactivation of the tumor enzyme. When the SO_2F group of **2** was moved to the meta position (**2a**) 47% inactivation of Walker 256 enzyme and 22% inactivation of the rat liver enzyme was seen.[3] Therefore an additional 21 structural variants of **1** and **2** have now been synthesized and evaluated. The results are the subject of this paper.

Enzyme Results.—The compds in Table I can be divided into 4 classes. The first class contains derivatives of 9-(*m*-benzamidophenyl)guanine, 3 of which (**1**, **3**, **9**) were previously reported[3] to be highly effective in inactivating Walker 256 guanine deaminase, but also inactivated the rat liver enzyme; 7 additional analogs were synthesized for evaluation. Replacement of the 2-Cl of **1** by Me (**4**) or MeO (**5**) reduced the irreversible potency, but shift of the 2-Cl to 4-Cl (**6**) gave just as effective an irreversible inhibitor. Introduction of a second Me group (**7**) on **4** destroyed the irreversible activity, but introduction of a second Cl atom (**8**) on **1** did not; these compds (**4**–**6**, **8**) also showed high inactivation of the rat liver enzyme.

Introduction of a 3-Cl (**10**) or 3-Me (**11**) on **9** still allowed retention of high inactivation of the Walker 256 enzyme, but no specificity toward the rat liver enzyme was seen. Removal of SO_2F from **8** and **10** to give **14** and **13**, respectively, destroyed the irreversible inhibition, but not the reversible inhibition; these results would be expected if the SO_2F group is involved in covalent bond formation with the enzyme by the active-site-directed mechanism.[4]

The second series contains derivatives of 9-(*m*-phenylureidophenyl)guanine; the parent compds (**15**, **17**) were previously reported[3] to be poor to fair irreversible inhibitors of guanine deaminase; introduction of Me (**16**, **18**, **20**) or Cl (**19**) substituents did not enhance the inactivation.

The third series contains derivatives of 9-(*p*-benzamidoethoxyphenyl)guanine; the parent *m*-SO_2F (**2a**) and *p*-SO_2F (**2**) compds were previously reported.[3] Introduction of Me (**21**, **24**), MeO (**22**), or Cl (**23**) substituents failed to enhance the inactivation.

The fourth series contains derivatives of 9-(*p*-phenylureidoethoxyphenyl)guanine; the parent *m*-SO_2F (**25**) and *p*-SO_2F (**28**) were poor to ineffective irreversible inhibitors. Introduction of Cl (**27**, **31**) or Me (**26**, **30**) failed to enhance the irreversible inhibition, nor did insertion of a CH_2 group (**32**) in the phenylureido moiety. Introduction of 2,4-Me_2 (**28**) destroyed the already weak irreversible inhibition.

Seven of the compds in the 9-(*m*-benzamidophenyl)-guanine series (**1**, **3**, **6**, **8**, **9**–**11**) show excellent inactivation of Walker 256 guanine deaminase by the active-site-directed mechanism, but also show no specificity since they inactivate the rat liver enzyme. The other 3 series of compds do not inactivate the enzyme sufficiently. Therefore future studies for specificity should focus on 9-(*m*-acylamidophenyl)guanines bridged to a terminal SO_2F, perhaps with longer bridges.

Chemistry.—The two acylamido series (**38**) in Table I were prepared by acylation of 9-(*m*-aminophenyl)-guanine (**34**)[5] or 9-(*p*-aminoethoxyphenyl)guanine (**35**)[6] with the appropriate acid chloride. The two phenylureido series (**37**) were synthesized by condensation of the 2 amines with the appropriate *O*-(*p*-nitrophenyl)-*N*-arylcarbamate (**33**).[7] The acids required for the synthesis of **4**, **6**, **21**, and **23** were previously described.[8] New acids required for **7**, **8**, and **24** were synthesized as follows.

(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 of the series see B. R. Baker and H. U. Siebeneick, *J. Med. Chem.*, **14**, 799 (1971).

(3) For the previous paper on this enzyme see B. R. Baker and W. F. Wood, *ibid.*, **12**, 216 (1969).

(4) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," Wiley, New York, N. Y., 1967.

(5) B. R. Baker and W. F. Wood, *J. Med. Chem.*, **10**, 1101 (1967).

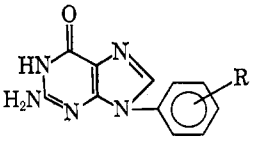
(6) B. R. Baker and W. F. Wood, *ibid.*, **12**, 214 (1969).

(7) B. R. Baker and N. M. J. Vermeulen, *ibid.*, **12**, 74 (1969).

(8) B. R. Baker and R. B. Meyer, Jr., *ibid.*, **12**, 104 (1969).

TABLE I

IRREVERSIBLE INHIBITION[a] OF GUANINE DEAMINASE BY



No.	R	Enzyme source	Reversible I_{50},[b] μM	Irreversible, % inactvn[c]
1[d]	*m*-NHCOC$_6$H$_3$-2-Cl-5-SO$_2$F	W256	0.035	100
		Rat liver		81
2[d]	*p*-O(CH$_2$)$_2$NHCOC$_6$H$_4$SO$_2$F-*p*	W256	0.28	46
		Rat liver		0
2a[d]	*p*-O(CH$_2$)$_2$NHCOC$_6$H$_4$SO$_2$F-*m*	W256	0.70	47
		Rat liver		22
		Rabbit liver[e]		0
3[d]	*m*-NHCOC$_6$H$_4$SO$_2$F-*m*	W256	0.11	93
		Rat liver		73
4	*m*-NHCOC$_6$H$_3$-2-Me-5-SO$_2$F	W256	0.060	59
		Rat liver		81
5	*m*-NHCOC$_6$H$_3$-2-MeO-5-SO$_2$F	W256	0.050	72
		Rat liver		68
6	*m*-NHCOC$_6$H$_3$-4-Cl-3-SO$_2$F	W256	0.080	100
		Rat liver		94
7	*m*-NHCOC$_6$H$_2$-2,4-Me$_2$-5-SO$_2$F	W256	0.042	0
8	*m*-NHCOC$_6$H$_2$-2,4-Cl$_2$-5-SO$_2$F	W256	0.046	100
		Rat liver		100[f]
9[d]	*m*-NHCOC$_6$H$_4$SO$_2$F-*p*	W256	0.064	94
		Rat liver		91
10	*m*-NHCOC$_6$H$_3$-3-Cl-4-SO$_2$F	W256	0.078	100
		Rat liver		84
11	*m*-NHCOC$_6$H$_3$-3-Me-4-SO$_2$F	W256	0.056	94
		Rat liver		82
12	*m*-NHCOC$_6$H$_4$Cl-*o*	W256	0.025	
13	*m*-NHCOC$_6$H$_4$Cl-*m*	W256	0.036	21
14	*m*-NHCOC$_6$H$_3$Cl$_2$-2,4	W256	0.047	0
15[d]	*m*-NHCONHC$_6$H$_4$SO$_2$F-*p*	W256	0.034	13
16	*m*-NHCONHC$_6$H$_3$-3-Me-4-SO$_2$F	W256	0.049	12
17[d]	*m*-NHCONHC$_6$H$_4$SO$_2$F-*m*	W256	0.12	45
		Rat liver		74
18	*m*-NHCONHC$_6$H$_3$-2-Me-5-SO$_2$F	W256	0.29	21
19	*m*-NHCONHC$_6$H$_3$-4-Cl-3-SO$_2$F	W256	0.062	52
		Rat liver		65
20	*m*-NHCONHC$_6$H$_2$-2,4-Me$_2$-5-SO$_2$F	W256	0.35	0
21	*p*-O(CH$_2$)$_2$NHCOC$_6$H$_3$-2-Me-5-SO$_2$F	W256	0.61	13
		Rat liver		20
22	*p*-O(CH$_2$)$_2$NHCOC$_6$H$_3$-2-MeO-5-SO$_2$F	W256	0.16	0
		Rat liver		40
23	*p*-O(CH$_2$)$_2$NHCOC$_6$H$_3$-4-Cl-3-SO$_2$F	W256	0.35	32
24	*p*-O(CH$_2$)$_2$NHCOC$_6$H$_2$-2,4-Me$_2$-5-SO$_2$F	W256	0.24	17
25[d]	*p*-O(CH$_2$)$_2$NHCONHC$_6$H$_4$SO$_2$F-*m*	W256	0.070	43
		Rat liver		28
26	*p*-O(CH$_2$)$_2$NHCONHC$_6$H$_3$-2-Me-5-SO$_2$F	W256	0.089	18
27	*p*-O(CH$_2$)$_2$NHCONHC$_6$H$_3$-4-Cl-3-SO$_2$F	W256	0.10	40
		Rat liver		44
28	*p*-O(CH$_2$)$_2$NHCONHC$_6$H$_2$-2,4-Me$_2$-5-SO$_2$F	W256	0.13	0
29[d]	*p*-O(CH$_2$)$_2$NHCONHC$_6$H$_4$SO$_2$F-*p*	W256	0.067	0
30	*p*-O(CH$_2$)$_2$NHCONHC$_6$H$_3$-3-Me-4-SO$_2$F	W256	0.10	11
31	*p*-O(CH$_2$)$_2$NHCONHC$_6$H$_3$-3-Cl-4-SO$_2$F	W256	0.14	22
32	*p*-O(CH$_2$)$_2$NHCONHCH$_2$C$_6$H$_4$SO$_2$F-*p*	W256	0.20	12

[a] The technical assistance of Julie Beardslee and Pauline Minton with these assays is acknowledged. [b] Assayed with 13.3 μM guanine in pH 7.4 Tris buffer contg 10% DMSO as previously described;[3] I_{50} = concn for 50% inhibn. [c] Incubated 12 μM inhibitor with enzyme at 37° in pH 7.4 Tris buffer contg 10% DMSO, then the remaining enzyme assayed as previously described.[3] [d] Data from ref 3. [e] Result previously reported erroneously[3] as rat liver source. [f] A time study showed inactivation was 100% in <2 min.

2,4-Dimethylbenzoic acid was fluorosulfonated[9] with FSO_3H to give 2,4-dimethyl-5-fluorosulfonylbenzoic acid (method A).

5-Amino-2,4-dichlorobenzoic acid[10] was diazotized and then converted to the sulfonyl chloride.[11] This

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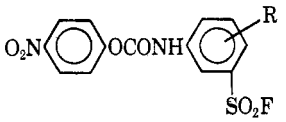
(10) I. Kh. Fel'dman and Ch. S. Frankovskii, *Zh. Obshch. Khim.*, **32**, 2115 (1962); *Chem. Abstr.*, **58**, 10108*a* (1963).

(11) H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).

TABLE II

PHYSICAL PROPERTIES OF



No.[a]	R	Yield,[b] %	Ref to amine	Mp, °C	Formula[f]
33a	2-Me	56	*c*	195–198	$C_{14}H_{11}FN_2O_6S$
33b	4-Cl	67	*d*	159–161	$C_{13}H_8ClFN_2O_6S$
33c	2,4-Me_2	71	*e*	167–170	$C_{15}H_{13}FN_2O_6S$

[a] All compds were prepd by Method C.[7] [b] All compds were recrystd from CH_2Cl_2. [c] See ref 14. [d] See ref 12. [e] Acid hydrolysis of 2,4-dimethyl-5-fluorosulfonylacetanilide. [f] All compds were anal. for C, H, N.

reacted with KF in dioxane[12] to give 2,4-dichloro-5-fluorosulfonylbenzoic acid. 3-Chloro- and 3-methyl-4-fluorosulfonylbenzoic acid were prepared in the same manner.

The carbamates required for the synthesis of **16**, **30**, and **31** were previously reported.[13] New carbamates required for **18**, **19**, **20**, **26**, **27**, and **28** were synthesized as follows: 5-fluorosulfonyl-2-methylaniline[14] and 4-chloro-3-fluorosulfonylaniline[12] were treated with *p*-nitrophenyl chloroformate to give **33a** and **33c** (method C).[7] 2,4-Dimethylacetanilide[15] was fluorosulfonated (method A) and then hydrolyzed to the amine. This reacted with *p*-nitrophenyl chloroformate to give **33c**.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. All anal. samples had ir spectra compatible with their assigned structures and moved as a single spot on tlc with Brinkman silica gel GF; each gave combustion values for C, H, and N or F within 0.4% of theory.

2,4-Dimethyl-5-fluorosulfonylbenzoic Acid (39c) (Method A).—2,4-Dimethylbenzoic acid (7.5 g, 0.05 mmole) was added gradually to 20 ml of FSO_3H over 5 min. The mixt was stirred at 80° for 4 hr, cooled to room temp, then poured on 300 g of ice. The solid was collected, washed (H_2O), and recrystd from EtOH–H_2O; yield, 7.0 g (60%), mp 217–219° (see Table III).

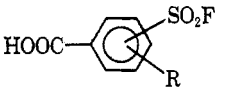
2,4-Dimethyl-5-fluorosulfonylacetanilide.—Fluorosulfonation (method A) of 6.3 g (38.7 mmoles) of 2,4-dimethylacetanilide[15] gave 7.0 g (74%) of pure product, mp 143–145° (EtOH–H_2O). *Anal.* ($C_{10}H_{12}FNO_3S$): C, H, N.

Acid hydrolysis (6 *N* HCl) gave a noncrystalline aniline that was converted to the *O*-(*p*-nitrophenyl)carbamate (**33c**, Table II).

2,4-Dichloro-5-fluorosulfonylbenzoic Acid (39d) (Method B).—A soln of 12.6 g (61 mmoles) of 5-amino-2,4-dichlorobenzoic acid[10] in 44 ml of concd HCl was diazotized with 4.5 g of $NaNO_2$ in 20 ml of H_2O at 0–5°. The soln was poured into 200 ml of HOAc satd with SO_2 contg 1.1 g of $CuCl_2 \cdot 5H_2O$. After the reaction subsided (N_2 evoln), 3 vol of ice water were added. The ppt was collected, washed (H_2O), and recrystd from PhH–petr ether (30–60°); yield, 15.7 g (89%). A mixt of 7.8 g of this crude 5-chlorosulfonyl-2,4-dichlorobenzoic acid, 10 ml of dioxane, 2 ml of DMF, 1.0 ml of H_2O, and 5.5 g of finely powdered KF was stirred and refluxed for 30 min. Then the reaction mixt was poured on ice, and the ppt was collected, washed (H_2O), and recrystd from EtOH–H_2O; yield, 2.9 g (39%), mp 180–182° (see Table III).

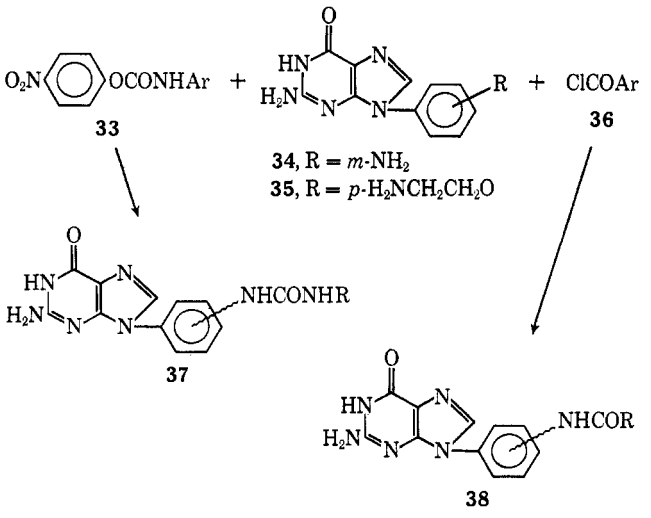
TABLE III

PHYSICAL PROPERTIES OF



No.	R	Position of SO_2F	Yield,[a] %	Ref to amine	Mp, °C	Formula	Analyses
39a[b]	3-Cl	4	38	*c*	216–218	$C_7H_4ClFO_4S$	C, H
39b[b]	3-Me	4	24	*d*	214–216	$C_8H_7FO_4S$	C, H
39c[e]	2,4-Me_2	5	60	Exptl	217–219	$C_9H_9FO_4S$	C, H, F
39d[b]	2,4-Cl_2	5	39	*f*	180–182	$C_7H_3Cl_2FO_4S$	C, H

[a] All compds were recrystd from EtOH–H_2O. [b] Prepd by method B. [c] F. C. Schmelkes and M. Rubin, *J. Amer. Chem. Soc.*, **66**, 1631 (1944). [d] U. Kreusler, *Justus Liebigs Ann. Chem.*, **144**, 179 (1867). [e] Prepared by method A. [f] See ref 10.



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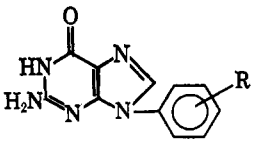
(13) B. R. Baker and N. M. J. Vermeulen, *J. Med. Chem.*, **12**, 79 (1969).
(14) I. Kageyama and S. Nakanishi, Japanese Patent 16 (60) (1960); *Chem. Abstr.*, **54**, 18985*f* (1960).
(15) O. Wallach, *Justus Liebigs Ann. Chem.*, **258**, 330 (1889); **319**, 99 (1901).

TABLE IV
PHYSICAL PROPERTIES OF



No.	R	Method[a]	Yield, %	Mp (dec), °C[b]	Formula[c]
4	*m*-NHCOC$_6$H$_3$-2-Me-5-SO$_2$F	A	34	310	$C_{19}H_{15}FN_6O_4S$
5	*m*-NHCOC$_6$H$_3$-2-MeO-5-SO$_2$F	A	22	290	$C_{19}H_{15}FN_6O_5S$
6	*m*-NHCOC$_6$H$_3$-4-Cl-3-SO$_2$F	A	29	315	$C_{18}H_{12}ClFN_6O_4S \cdot H_2O$
7	*m*-NHCOC$_6$H$_2$-2,4-Me$_2$-5-SO$_2$F	A	18	296	$C_{20}H_{17}FN_6O_4S \cdot H_2O$
8	*m*-NHCOC$_6$H$_2$-2,4-Cl$_2$-5-SO$_2$F	A	20	300	$C_{18}H_{11}Cl_2FN_6O_4S$
10	*m*-NHCOC$_6$H$_3$-3-Cl-4-SO$_2$F	A	26	320	$C_{18}H_{12}ClFN_6O_4S$
11	*m*-NHCOC$_6$H$_3$-3-Me-4-SO$_2$F	A	23	320	$C_{19}H_{15}FN_6O_4S$
12	*m*-NHCOC$_6$H$_4$-Cl-*o*	A	32	320	$C_{18}H_{13}ClN_6O_2$
13	*m*-NHCOC$_6$H$_4$-Cl-*m*	A	21	320	$C_{18}H_{13}ClN_6O_2 \cdot H_2O$
14	*m*-NHCOC$_6$H$_3$-2,4-Cl$_2$	A	28	310	$C_{18}H_{12}Cl_2N_6O_2 \cdot H_2O$
16	*m*-NHCONHC$_6$H$_3$-3-Me-4-SO$_2$F	B	57	258	$C_{19}H_{16}FN_7O_4S$
18	*m*-NHCONHC$_6$H$_3$-2-Me-5-SO$_2$F	B	68	220	$C_{19}H_{16}FN_7O_4S$
19	*m*-NHCONHC$_6$H$_3$-4-Cl-3-SO$_2$F	B	67	320	$C_{18}H_{13}ClFN_7O_4S$
20	*m*-NHCONHC$_6$H$_2$-2,4-Me$_2$-5-SO$_2$F	B	50	300	$C_{20}H_{18}FN_7O_4S \cdot 0.5H_2O$
21	*p*-O(CH$_2$)$_2$-NHCOC$_6$H$_3$-2-Me-5-SO$_2$F	A	27	258–261	$C_{21}H_{19}FN_6O_5S$
22	*p*-O(CH$_2$)$_2$-NHCOC$_6$H$_3$-2-MeO-5-SO$_2$F	A	32	237	$C_{21}H_{19}FN_6O_6S$
23	*p*-O(CH$_2$)$_2$-NHCOC$_6$H$_3$-4-Cl-3-SO$_2$F	A	53	265	$C_{20}H_{16}ClFN_6O_5S$
24	*p*-O(CH$_2$)$_2$-NHCOC$_6$H$_2$-2,4-Me$_2$-5-SO$_2$F	A	40	273–275	$C_{22}H_{21}FN_6O_5S$
26	*p*-O(CH$_2$)$_2$-NHCONHC$_6$H$_3$-2-Me-5-SO$_2$F	B	36	207	$C_{21}H_{20}FN_7O_5S \cdot H_2O$
27	*p*-O(CH$_2$)$_2$-NHCONHC$_6$H$_3$-4-Cl-3-SO$_2$F	B	42	238–242	$C_{20}H_{17}ClFN_7O_5S$
28	*p*-O(CH$_2$)$_2$-NHCONHC$_6$H$_2$-2,4-Me$_2$-5-SO$_2$F	B	34	225	$C_{22}H_{22}FN_7O_5S \cdot H_2O$
30	*p*-O(CH$_2$)$_2$NHCONHC$_6$H$_3$-3-Me-4-SO$_2$F	B	47	241	$C_{21}H_{20}FN_7O_5S \cdot 0.5H_2O$
31	*p*-O(CH$_2$)$_2$NHCONHC$_6$H$_3$-3-Cl-4-SO$_2$F	B	57	229	$C_{20}H_{17}ClFN_7O_5S \cdot 0.5CH_3OCH_2CH_2OH$
32[d]	*p*-O(CH$_2$)$_2$NHCONHCH$_2$C$_6$H$_4$-SO$_2$F-*p*	B	48	286	$C_{21}H_{20}FN_7O_5S$

[a] For method A see B. R. Baker and W. F. Wood, *J. Med. Chem.*, **11**, 650 (1968); for method B see ref 6; yields of anal. pure material. [b] All compds were recrystd from $CH_3OCH_2CH_2OH$–H_2O. [c] All compds were analyzed for C, H, and N. [d] See B. R. Baker and M. Cory, *J. Med. Chem.*, **14**, 805 (1971), for intermediate carbamate.

Irreversible Enzyme Inhibitors. 186.[1,2] Irreversible Inhibitors of the C'1a Component of Complement Derived from *m*-(Phenoxypropoxy)benzamidine by Bridging to a Terminal Sulfonyl Fluoride[3]

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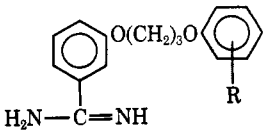
A series of 21 derivatives of *m*-(phenoxypropoxy)-, *m*-(phenoxybutoxy)-, *m*-(phenoxyethoxy)-, and *m*-(phenylbutyl)benzamidine bridged from the ortho position of the Ph moiety to a terminal SO_2F were synthesized, then investigated as irreversible inhibitors of the C'1a component of complement. The 2 most effective compds were *m*-[*o*-(2-chloro-5-fluorosulfonylphenylureido)phenoxybutoxy]benzamidine (**25**) and the corresponding propoxy compd (**17**) which showed 50% irreversible inhibition of C'1a at about 5 and 8 μM, respectively; these 2 compounds were also potent inhibitors of whole complement when assayed by inhibition of lysis of sheep red blood cells by hemolysin and complement.

The possible medicinal utility of inhibitors of serum complement for organ transplantation[4] and in treatment of some arthritic states[4] has been discussed previously.[3,5] The serum complement system involves 11 distinct proteins for killing invading organisms or for lysis of foreign mammalian cells.[4] The most powerful inhibitor of serum complement known to date[3] is the benzamidine meta bridged to SO_2F (**1**); however, **1** is not an irreversible inhibitor of the C'1a component of complement.[3] In contrast, the ortho-bridged SO_2F



1, R = *m*-NHCONHC$_6$H$_4$SO$_2$F-*p*
2, R = *o*-NHCOC$_6$H$_4$SO$_2$F-*m*

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(2) For the previous paper in this series see B. R. Baker and H.-U. Siebeneick, *J. Med. Chem.*, **14**, 802 (1971).

(3) For the previous paper on complement see B. R. Baker and M. Cory, *ibid.*, **14**, 119 (1971).

(4) H. J. Müller-Eberhard, *Advan. Immunol.*, **8**, 1 (1968).

(5) B. R. Baker and E. H. Erickson, *J. Med. Chem.*, **12**, 408 (1969).