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Irreversible Enzyme Inhibitors.[1] Inhibitors of Guinea Pig Complement Derived by Quaternization of Substituted Pyridines with Benzyl Halides

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A series of 83 compounds derived from hydrocarbon-substituted pyridines by quaternization with $PhCH_2Br$ usually containing a 2-SO_2F or 6-Cl-2-SO_2F group was synthesized and evaluated as inhibitors of guinea pig complement and in most cases its $C\bar{1}$ component. The most active compounds were 3-(4-phenylphenylbutyl)-*N*-(6-chloro-2-fluorosulfonylbenzyl)pyridinium bromide (**43**) and 3-(4-phenylphenylbutyl)-*N*-(2-fluorosulfonylbenzyl)pyridinium bromide (**44**), each showing 50% inhibition at 7.8 μM. The most effective irreversible inhibitor of the $C\bar{1}$ component was *N*-(6-chloro-2-fluorosulfonylbenzyl)-5,6-benzoquinolinium bromide (**87**), which showed 50% inhibition at 4 μM.

The serum complement system is a mixture of 11 distinct proteins[3,4] which has protease activity that is both "tryptic" and "chymotryptic". Acting in concert with antibodies, the complement system represents one of the two aspects of the mammalian immune system. Inhibitors of the complement system have potential medicinal use in preventing tissue and organ rejection as well as in the treatment of arthritis.[5,6] Also, complement inhibitors have been useful in supplying information about the molecular biology of the complement system itself.[7] Complement inhibition is readily measured by the antibody mediated complement lysis of sheep red blood cells (RBC).[5,8]

Studies in this laboratory have utilized the qualitative approach of designing biologically active compounds which was developed by the late Bernard R. Baker. This four step modus operandi[9,10] employs hydrophobic interactions, hydrogen bonding, anionic–cationic interactions, and charge-transfer complexes to selectively enhance inhibitor–enzyme binding, thereby selectively inhibiting target enzymes. Slight evolutionary differences outside the active site are then exploited to provide dimensions of specificity when target pathways are also used by host cells, such as in cancer, or when several enzymes have similar active sites, such as with proteolytic enzymes.

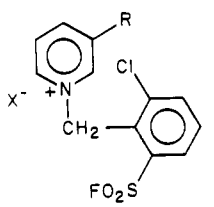
In the first step the binding points of a reversible inhibitor are determined; some binding points can be eliminated if stronger binding can be found in another area on the inhibitor.

The second step consists of a search for bulk tolerance areas in the enzyme–inhibitor complex. These are areas where a portion of the inhibitor, usually a modified substrate molecule, does not contact the enzyme.

The third step involves the placement of an alkylating group in a noncontact area. If the dimensions between the inhibitor-attached alkylating group and an enzyme nucleophilic group are correct, then irreversible inhibition by a facile neighboring-group reaction may occur.

The final step of the sequence is the modification of the irreversible inhibitor so that differences in enzymes from different species or tissues can be found and exploited.

Since the serum complement is a complex, multienzyme system, the above modus operandi has not been rigidly applied. The initial studies involved the preparation of potent trypsin[11-13] and chymotrypsin[14-19] inhibitors which were then tested on the complement system.[5,20,21] This preliminary information was then used as a starting point in designing potent complement inhibitors.[8,22-25] The most effective chymotryptic type inhibitors thus developed have been quaternized pyridines (I).[1b]



I

1, R = $C_6H_5(CH_2)_2$
2, R = $C_6H_5(CH_2)_4$
3, R = 3,4-$Cl_2C_6H_3OCH_2CONH$

Compound **1** showed 40% inhibition of whole complement at 125 μM while **2** and **3**, each with a slightly larger R group, showed 50% inhibition at 62 and 31 μM, respectively.[1b] These results suggested that a slightly larger and/or different type of R group might achieve greater hydrophobic binding to a complement enzyme, thereby maximizing inhibition of the whole complement system. Consequently, compounds related to I were prepared and evaluated as inhibitors of whole guinea pig complement and, in most cases, its $C\bar{1}$ component[26] as well. The results are the subject of this paper.

Assay Results. When the phenyl ring of **1** was substituted with a 4-phenyl group, the resulting compound

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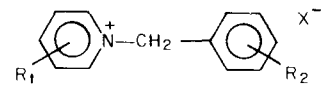
Table I. Inhibition[a] of Guinea Pig Complement and Irreversible Inhibition of the $\overline{C1}$ Component by 

No.	R_1	R_2	X	Whole complement			$\overline{C1}$, %	Yield,[e,f] %	Mp, °C
				mM inhibn	% inhibn[b]	% lysis[c]	inactn[d]		
1[g]	3-$C_6H_5CH_2CH_2$	6-Cl-2-SO_2F	Br	0.25	75	0	70		
				0.125	40		45		
2[g]	3-$C_6H_5(CH_2)_4$	6-Cl-2-SO_2F	Br	0.125	80		75		
				0.062	50		40		
3[g]	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	6-Cl-2-SO_2F	Br	0.125	85		70		
				0.062	65		35		
				0.031	25				
4	3-(4-$C_6H_5C_6H_4CH_2CH_2$)	6-Cl-2-SO_2F	Br	0.062	75		70	40[h]	187–189
				0.031	60		15		
				0.015	15				
5	4-(4-$C_6H_5C_6H_4CH_2CH_2$)	6-Cl-2-SO_2F	Br	0.062	90		80	33[i]	183–184
				0.031	60		40		
6	4-(3-$C_6H_5C_6H_4CH_2CH_2$)	6-Cl-2-SO_2F	Br	0.062	50		90	40[i]	190–191
				0.031			40		
7	3-[4-($C_6H_5CH_2CH_2$)$C_6H_4CH_2CH_2$]	6-Cl-2-SO_2F	Br	0.125	100		60	25[h]	175–176
				0.062	85		25		
				0.031	30				
8	3-(2-$C_{10}H_7CH_2CH_2$)	6-Cl-2-SO_2F	Br	0.125	70		60	30[h]	148–150
				0.062	35		30		
9	3-[$(C_6H_5)_2CH$]	6-Cl-2-SO_2F	Br	0.125	75		80	30[h]	172–174
				0.062	35		50		
10	3-[$C_6H_5CH_2(C_6H_5)CHCH_2CH_2$]	6-Cl-2-SO_2F	Br	0.125	95		80	33[h]	162–164
				0.062	60		45		
11	3-[$(C_6H_5)_2CHCH_2CH_2CH_2$]	6-Cl-2-SO_2F	Br	0.125	85		75	33[j]	130–132
				0.062	75		45		
				0.031	35		15		
12	4-[$(C_6H_5)_2CHCH_2CH_2$]	6-Cl-2-SO_2F	Br	0.125	70		90	37[h]	147–150
				0.062	25		50		
13	3-$C_6H_5(CH_2)_6$	6-Cl-2-SO_2F	Br	0.125	90	0	35	60[k]	103–104
				0.062	65		20		
				0.031	35				
14	3-$C_6H_5(CH{=}CH)_3$	6-Cl-2-SO_2F	Br	0.125			70	75[i]	193–195
				0.062	65		25		
				0.031	30				
15	3-$C_6H_5(CH{=}CH)_2$	6-Cl-2-SO_2F	Br	0.125	95	0	75	24[l]	203–205
				0.062	65		45		
				0.031	15				
16	3-[3-$NO_2C_6H_4(CH{=}CH)_2$]	6-Cl-2-SO_2F	Br	0.125	85	10	75	75[i]	224–226
				0.062	70		40		
				0.031	25		20		
17	3-[4-$NO_2C_6H_4(CH{=}CH)_2$]	6-Cl-2-SO_2F	Br	0.125	90	0	90	19[i]	220–222
				0.062	45		80		
				0.031	10		40		
18	3-[3,4-$Cl_2C_6H_3(CH{=}CH)_2$]	6-Cl-2-SO_2F	Br	0.062	70		60	23[i]	138–140
				0.031	30		30		
19[g]	3-[3,4-$Cl_2C_6H_3(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.062	75		65		
				0.031	20		40		

20	3-[2-$CH_3C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	85		75	39[h]	114–115
				0.062	45		50		
				0.031	10		25		
21	3-[3-$CH_3C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	90		75	32[i]	145–147
				0.062	45		35		
22	3-[4-$CH_3C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	80		85	52[h]	154–156
				0.062	55		50		
				0.031	15				
23	3-[3,4-$(CH_3)_2C_6H_3(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	85		75	74[h]	149–150
				0.062	60		30		
				0.031	15				
24	3-[2-$ClC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.062	65		65	53[i]	132–134
				0.031	25		40		
25	3-[3-$ClC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	95		90	45[h]	113–115
				0.062	35		65		
				0.031	15		35		
26	3-[4-$ClC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.062	90		95	33[h]	165–167
				0.031	45		65		
				0.016	15		15		
27	3-[4-$FC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	95		85	38[h]	124–125
				0.062	40		50		
				0.031	5		15		
28	3-[2,4-$Cl_2C_6H_3(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.062	100		80	37[c]	131–132
				0.031	45		25		
29	3-[2,6-$Cl_2C_6H_3(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.062	85		70	42[i]	148–150
				0.031	25		40		
30	3-[4-$(CH_3CONH)C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	85		45	55[i]	176–177
				0.062	45				
31	3-[4-$(C_6H_5CONH)C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	95	6	60	74[i]	178–179
				0.062	80	1	25		
				0.031	40				
32	3-[4-(4-$NO_2C_6H_4CONH)C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.25	40		65	35[i]	187–188
				0.125	55	20	30		
				0.062	65	10	15		
				0.031	35				
33	3-[4-$(C_6H_5OCH_2CONH)C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	90		50	85[h]	109–111
				0.062	55	1	10		
				0.031	20				
34	3-[4-$(C_6H_5CH_2CH_2CONH)C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	60	20	90	59[i]	173–174
				0.062	55	10	60		
				0.031	20		15		
35	3-[4-$(CH_3)_2CHC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	95	3	60	50[h]	149–150
				0.062	75	3	35		
				0.031	50	3			
				0.016	15				
36	3-[1-$C_{10}H_7(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.062	70		50	31[h]	125–127
				0.031	25		15		
37	3-[2-$C_{10}H_7(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	95	3	80	22[m]	151–153
				0.062	80		40		
				0.031	50		10		
38	3-[4-$C_6H_5CH_2C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125		100	65	38[h]	118–119
				0.062	90	1	25		
				0.031	70				
				0.016	20				

Table I (*Continued*)

No.	R_1	R_2	X	Whole complement: mM inhibn	Whole complement: % inhibn[b]	Whole complement: % lysis[c]	$\overline{C1}$, % inactn[d]	Yield,[e,f] %	Mp, °C
39	3-[3-$C_6H_5CH_2C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125	85		65	13[h]	157–159
				0.062	85	3	30		
				0.031	35	1			
40	3-[4-$C_6H_5CH_2CH_2C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125		100	60	52[i]	150–151
				0.062		100	20		
				0.031	60				
				0.016	15				
41	3-[3-$C_6H_5CH_2CH_2C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125		100	60	57[h]	98–100
				0.062	60	15	25		
				0.031	50	0			
				0.016	20				
42	3-[3-$C_6H_5C_6H_4(CH_2)_4$]	2-SO_2F	Br	0.125	30	30	30	90[h]	80–82
				0.062	10	0	20		
43	3-[4-$C_6H_5C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	Br	0.125		100		61[i]	163–165
				0.062	100	0	65		
				0.031	100		20		
				0.016	85				
				0.012	60				
				0.0078	50				
				0.0039	10				
44	3-[4-$C_6H_5C_6H_4(CH_2)_4$]	2-SO_2F	Br	0.062	85		40	75[i]	158–160
				0.031	80		20		
				0.016	65				
				0.0078	50				
45	3-[4-$C_6H_5C_6H_4(CH{=}CH)_2$]	6-Cl-2-SO_2F	Br	0.125			40	27[i]	198–200
				0.062	80		10		
				0.031	55				
				0.016	10				
46	3-(4-$C_6H_5C_6H_4OCH_2CONH$)	6-Cl-2-SO_2F	Br	0.125	70			51[i]	184–185
				0.062	35		60		
				0.031	15		40		
47	3-(4-$C_6H_5C_6H_4CONHCH_2$)	6-Cl-2-SO_2F	Br	0.062	85	3	70	35[h]	86–89
				0.031	50		10		
				0.016	15				
48	3-(4-$C_6H_5C_6H_4CH_2CH_2CONH$)	6-Cl-2-SO_2F	Br	0.062	85	0	60	50[i]	175–177
				0.031	50		15		
49	3-(4-$C_6H_5C_6H_4CH_2CH_2CONHCH_2$)	6-Cl-2-SO_2F	Br	0.125	65			49[h]	116–118
				0.062	45	1	40		
50	3-(3-$C_6H_5C_6H_4OCH_2CONH$)	2-SO_2F	Br	0.062			65	50[i]	171–173
				0.031	0		35		
51	3-[4-$C_6H_5C_6H_4(CH_2)_4$]	H	Br	0.25		100		30[i]	134–135
				0.125	20	15	0		
				0.062	0		0		
52	3-[4-$C_6H_5C_6H_4(CH_2)_4$]	2-SO_3^-		0.25			10	80[o]	187–189
				0.125[n]	0	10			
				0.062	0				
53	4-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	H	Br	0.5	35	65		62[p]	170–172
				0.25	40	5			
				0.125	10	2			
54	3-[4-(C_6H_5CONH)$C_6H_4(CH_2)_4$]	H	Br	1.0	35	3		31[p]	148–150
				0.5	15	4			

55	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	CH_3, no benzyl	I	1.0	20	2	85[h]	135–136
				0.5	10			
56	3-[3-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	CH_3, no benzyl	I	1.0	20	3	80[h]	137–138
				0.5	15			
57	3-[4-(3-$SO_2FC_6H_4CONH$)$C_6H_4OCH_2CONH$]	H	Br	0.125[n]	0	1	55[p]	185–186
				0.062	0			
58	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	H	Br	0.250[n]	20	2	60[p]	205–207
				0.125	10			
59	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_2$]	H	Br	1.0	40		65[p]	217–219
				0.5	15	5		
60	4-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_2$]	H	Br	1.0	40		54[p]	215–217
				0.5	15	2		
61	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4OCH_2CONHCH_2$]	H	Br	1.0	30	3	56[p]	184–186
				0.5	25	2		
				0.25	20			
62	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4CH_2CH_2CONHCH_2$]	H	Br	1.0	35	2	50[h]	128–130
				0.5	20			
63	3-[4-(4-$SO_2FC_6H_4CH_2CONH$)$C_6H_4(CH_2)_4$]	H	Br	0.25[n]	30	1	58[k]	118–120
				0.125	25			
64	3-[4-(4-$SO_2FC_6H_4CH_2CH_2CONH$)$C_6H_4(CH_2)_4$]	H	Br	0.25[n]		60	45[p]	193–195
				0.125	20	0		
				0.062	15			
65	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	4-NO_2	Br	0.062[n]	5	1	67[p]	215–217
66	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	3-NO_2	Br	0.031[n]	0	0	56[p]	230–233
67	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	3-CF_3	Cl	0.125		60	10[p]	172–174
				0.062	0	3		
68	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	4-Cl	Cl	0.062[n]	0		70[p]	217–220
				0.031	10			
69	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	3-Cl	Cl	0.062[n]	0	0	35[p]	195–198
70	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	2-Cl	Cl	0.125[n]	10	2	73[p]	164–166
				0.062	0	0		
71	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	3,4-Cl_2	Cl	0.062[n]	0	0	51[p]	213–215
				0.031	5	0		
72	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	4-CH_3O	Br	0.125[n]	10	0	57[p,q]	144–146
				0.062	15	0		
73	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	3-CH_3O	Br	0.125[n]	10	0	73[p,q]	175–176
				0.062	5	0		
74	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	2-CH_3O	Br	0.125[n]	5	6	64[p,q]	159–160
				0.062	5	0		
75	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	4-$C_6H_5CH_2O$	Cl	0.062		60	63[p]	153–155
				0.031		30		
				0.016	0			
76	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	C_6H_5CO, no benzyl	Br	0.062[n]	10	0	34[p]	174–176
77	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	3,4-$(CH{=}CH)_2$	Br	0.125[n]		30	58[p]	153–155
				0.062	5	1		
78	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	2,3-$(CH{=}CH)_2$	Cl	0.062[n]	20		75[p]	165–168
79	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	4-C_6H_5	Br	0.125[n]		80	56[p,r]	131–134
				0.062	20	20		
				0.031	10			
80	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	3-C_6H_5	Br	0.062[n]		50	21[p,r]	175–177
				0.031	0	5		
				0.016	10			
81	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	2-C_6H_5	Br	0.062[n]		30	33[p,r]	171–173
				0.031	5	0		
82	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	2-SO_2F	Br	0.125	50		63[p]	107–108
				0.062	30			

Table I (*Continued*)

No.	R_1	R_2	X	mM inhibn	Whole complement % inhibn[b]	Whole complement % lysis[c]	$\bar{C}l$, % inactn[d]	Yield,[e,f] %	Mp, °C
83	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	Free amine, no benzyl		0.031[n]	3	10			
				0.016	0	10			
84[g]	2,3-Benzo	6-Cl-2-SO_2F	Br	0.125	85		95		
				0.062	45		90		
				0.031	10		90		
				0.016			55		
				0.008			30		
85	2,3-Benzo	2-SO_2F	Br	0.50	60			22[i]	184–185
				0.25	30				
				0.125	10				
				0.062			50		
				0.031			35		
86	2,3-1',2'-Naphtho	2-SO_2F	Br	0.25	50			45[i]	204–205
				0.125	30		100		
				0.062	15		70		
				0.031			50		
				0.016			25		
87	2,3-1',2'-Naphtho	6-Cl-2-SO_2F	Br	0.062	95		85	36[i]	180–182
				0.031	40		85		
				0.016	10		85		
				0.008			75		
				0.004			50		
				0.002			10		
88	2,3-Benzo-4-$C_6H_5CH_2CH_2$	2-SO_2F	Br	0.5	60		90	33[i]	218–220
				0.25	25		75		
				0.125	10		50		
				0.062			35		

[a] The technical assistance of Pauline Minton, Julie Beardslee, Nancy Middleton, and Daniel Dawson with these assays is gratefully acknowledged. [b] Inhibition of lysis of sheep red blood cells by guinea pig complement and antibody determined as previously described;[5] average of three or more determinations, each within five absolute percent of the average. [c] Lysis by the compound in the absence of complement expressed as percent of total lysis possible;[5] average of two or more determinations. [d] Inhibitor incubated 10 min at 37° with $\bar{C}l$, then whole complement restored and assayed as previously described;[5] average of three or more determinations, each within five absolute percent of the average. [e] Prepared by method A, quaternization,[1b,22] except for 52 which was prepared from 44 by treatment with NaOH in 50:50 EtOH–H_2O; product separated as an oil and was recrystallized from EtOH–H_2O. [f] Analyses for C, H, N. [g] Data from ref 1b. [h] Recrystallized from Me_2CO–petroleum ether (bp 60–110°). [i] Recrystallized from Me_2CO containing about 5% MeOH–petroleum ether (bp 60–110°). [j] Recrystallized from Me_2CO. [k] Recrystallized from Me_2CO–EtOAc. [l] Recrystallized from Me_2CO containing about 5% MeOH–Et_2O. [m] Recrystallized from Me_2CO–Et_2O. [n] Maximum solubility. [o] Recrystallized from EtOH–H_2O. [p] Recrystallized from Me_2CO containing about 15% MeOH–petroleum ether (bp 60–110°). [q] Substituted benzyl bromide prepared from appropriate benzyl alcohol and PBr_3. [r] Substituted benzyl bromide prepared from appropriate phenyltoluene and NBS.

(4) was five times more potent than the parent compound and twice as effective as 2. When 1 was 4-phenethyl substituted, the resultant 7 was threefold more potent than 1. This suggested a large area of binding and bulk tolerance which might be explored for further inhibition enhancement. First, large hydrophobic substituents along the aliphatic chain of 2 were studied with compounds 8–12, but these changes were only moderately effective, as were both the extension of the chain to six carbon atoms (13) and the replacement by unsaturated chains (14–18).

The terminal phenyl group of 2 was then investigated for the optimum placement of small substituents and later for larger groups. The 4-Cl (26) and 2,4-Cl_2 (28) compounds were twice as effective as 2 while the 2,6-Cl_2 and 3,4-Cl_2 compounds 29 and 19 were slightly more effective than the parent compound 2. The 3-benzyl and 3-phenethyl groups of 39 and 41 slightly increased inhibition, while a 3-phenyl group (42) caused a threefold loss of inhibition. The 4-benzyl and 4-phenethyl groups of 38 and 40 were responsible for twofold increases in inhibition while the 4-phenyl-substituted compound 43 was eight times as effective as 2, showing 50% inhibition at 7.8 μM.

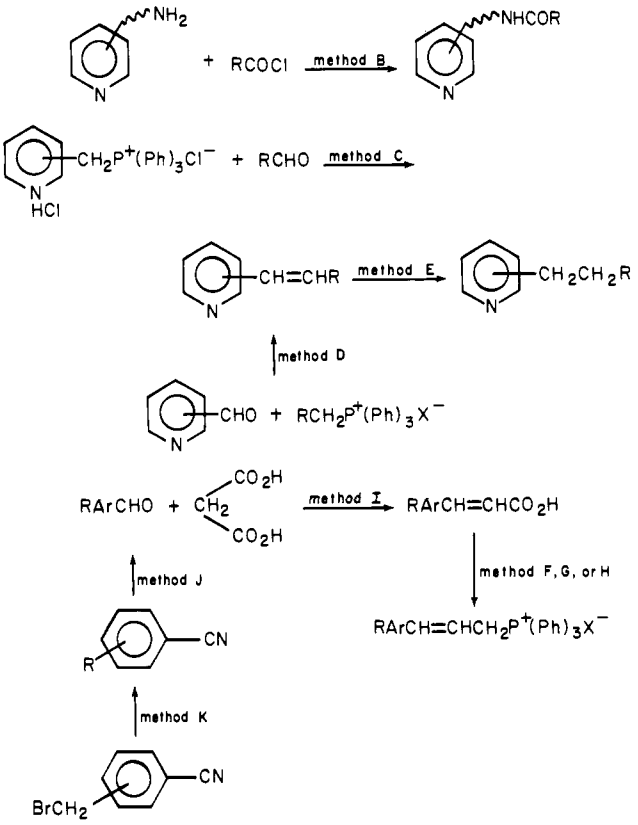
At this point changes in the aliphatic bridge of 43 were made in an attempt to more favorably position the biphenyl moiety. Four- and tenfold losses of inhibition resulted when the $(CH_2)_4$ bridge of 43 was replaced by $(CH{=}CH)_2$ in 45 and OCH_2CONH in 46, respectively. Other bridge changes were also made but the resulting compounds (47–50) were far less potent than 43. The removal of the 6-Cl of 43, previously resulting in enhancement,[1b] had no effect (44 vs. 43).

The SO_2F moiety has previously been found to be required for inhibition in compounds like I.[21] When the SO_2F group of 44 was removed, the resulting 51 was about 20-fold less effective. To exclude the possibility that the SO_2F was being hydrolyzed and the resulting SO_3^- moiety was responsible for all or part of the enhancement, 52 was prepared by hydrolysis of 44 and then tested; 52 showed no inhibition at its maximum solubility.

The area of bulk tolerance adjacent to the terminal phenyl group of 2 was then explored with compounds 53–64 for a possible alternate location to effectively place a SO_2F group. None of the new compounds were as effective as 2, indicating the absence of an appropriate nucleophilic group on the enzyme and confirming the hydrophobicity of the area where the 4-$C_6H_5C_6H_4(CH_2)_4$ moiety of 43 rests. Additionally, compounds 65–82 were prepared to explore the binding of the benzyl ring of I. These were too insoluble and/or impotent to supply meaningful information.

Compounds 1–52 were also tested as irreversible inhibitors of the $C\bar{1}$ component[26] of complement. The assay, which uses a rate-limiting quantity of $C\bar{1}$, has been described.[8] Within a factor of 2, compounds 1–42 had similar potencies on the two assays. Compounds with bulky substituents on the terminal phenyl ring of 2 (38, 40, 41, and 43–45) generally showed a larger disparity between the two assays. Due to the large excess of the $C\bar{1}$ component in whole complement (90% of $C\bar{1}$ can be inhibited with little loss in whole complement activity[27]), it is unlikely that a compound whose sole action was on $C\bar{1}$ would be as potent in the whole complement assay as in the $C\bar{1}$ assay. Conversely, a potent inhibitor of a C2–C9 component, but with no real $C\bar{1}$ potency, would show $C\bar{1}$ assay inhibition at only one-tenth of its whole complement level. This is a consequence of the one to ten $C\bar{1}$ and inhibitor dilution before reconstitution of the complement system with the C2–C9 components.[8] It should be noted, then, that to obtain the real $C\bar{1}$ inhibition one must subtract the whole complement activity at one-tenth the inhibitor concentration of the $C\bar{1}$ assay. In most cases this factor is negligible. Compounds 43 and 44, however, appear to have little or no real $C\bar{1}$ activity and therefore show very strong selectivity between the two assays. The other compounds, 1–42 and 45–50, appear to act on $C\bar{1}$ as well as another component having a similar active site.

Scheme I



Since the $C\bar{1}$ component had been strongly inhibited by a quaternized quinoline (84),[1b] several similar compounds (85–88) were prepared. A fourfold increase in inhibition in the $C\bar{1}$ assay was observed in 87 by a simple benzo substitution. Thus 87 showed 50% inhibition of $C\bar{1}$ at 4 μM. Compounds 85 and 86, analogous to 84 and 87 but without the 6-Cl groups, are each fourfold less active, indicating a strong preference for this moiety on potent $C\bar{1}$ inhibitors. This 6-Cl enhancement was not observed with the potent whole complement inhibitors, 43 vs. 44.

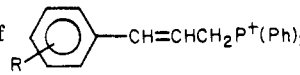
Since the preparation of the compounds reported here, there have been two studies by Hansch et al. utilizing quantitative structure–activity relationships (QSAR) to correlate complement inhibitors derived from quaternized pyridines. The first paper[6] correlated previously reported compounds,[1b,21,22] while the later[28] demonstrates the utility of the approach by showing that the previously derived equation predicts, with uncanny accuracy, the potencies of the compounds presented here. The equations derived from these studies also suggest areas to be explored for designing more potent complement inhibitors. Work is currently underway to prepare new inhibitors which should be more potent and should further demonstrate the utility and validity of QSAR in designing active molecules.

Chemistry. The quaternary salts in Table I were prepared by reaction[1b,22] of the appropriate benzyl bromides[22] or alkyl halides with the appropriate pyridines. The substituted pyridines necessary for 9 and 85–87 were commercially available. Those needed for the remainder

Table II. Physical Properties of Substituted Pyridines, RC_5H_4N

No.	R	Method[a]	Yield, %	Mp, °C	Formula[b]
83	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	B (from 132)	61[c]	184–185	$C_{22}H_{21}FN_2O_3S$
89	3-(4-$C_6H_5C_6H_4CH_2CH_2$)	C + E	20[d,e]	84–88	$C_{19}H_{17}N$
90	4-(4-$C_6H_5C_6H_4CH_2CH_2$)	C + E	88[d,f]	126–128	$C_{19}H_{17}N$[g]
91	4-(3-$C_6H_5C_6H_4CH_2CH_2$)	D[h] + E	32[d,i]	180–182[j]	$C_{19}H_{17}N$·HCl
92	3-[4-($C_6H_5CH_2CH_2$)$C_6H_4CH_2CH_2$]	C[k] + E	33[d,l]	92–94	$C_{21}H_{21}N$
93	3-(2-$C_{10}H_7CH_2CH_2$)	C + E	26[d]	160–162[m]	$C_{17}H_{15}N$·HCl
94	3-[$C_6H_5CH_2(C_6H_5)CHCH_2CH_2$]	D + E	28[d,i]	171–173[j]	$C_{21}H_{21}N$·HCl
95	3-[$(C_6H_5)_2CH(CH_2)_3$]	C + E	20[d,i]	170–172[j]	$C_{21}H_{21}N$·HCl
96	4-[$(C_6H_5)_2CH(CH_2)_2$]	C + E	35[d]	68–70	$C_{20}H_{19}N$
97	3-$C_6H_5(CH_2)_6$	E	25	101–103[j]	$C_{17}H_{21}N$·HCl
98	3-$C_6H_5(CH{=}CH)_3$	D	43[f]	149–150	$C_{17}H_{15}N$
99	3-$C_6H_5(CH{=}CH)_2$	D[n]	40[o]	101–102[p]	
100	3-[3-$NO_2C_6H_4(CH{=}CH)_2$]	C[q]	59[f]	128–130	$C_{15}H_{12}N_2O_2$
101	3-[4-$NO_2C_6H_4(CH{=}CH)_2$]	C	70[f]	173–175	$C_{15}H_{12}N_2O_2$
102	3-[3,4-$Cl_2C_6H_3(CH{=}CH)_2$]	C[r]	6[i,l]	109–111	$C_{15}H_{11}NCl_2$
103	3-[2-$CH_3C_6H_4(CH_2)_4$]	D + E	36[d,s]	117–119[j]	$C_{16}H_{19}N$·HCl
104	3-[3-$CH_3C_6H_4(CH_2)_4$]	D + E	26[d,i]	121–123[j]	$C_{16}H_{19}N$·HCl
105	3-[4-$CH_3C_6H_4(CH_2)_4$]	D + E	35[d,i]	144–146[j]	$C_{16}H_{19}N$·HCl
106	3-[3,4-$(CH_3)_2C_6H_3(CH_2)_4$]	D + E	31[d,s]	148–150[j]	$C_{17}H_{21}N$·HCl
107	3-[2-$ClC_6H_4(CH_2)_4$]	D + E	30[d,s]	115–117[j]	$C_{15}H_{16}ClN$·HCl
108	3-[3-$ClC_6H_4(CH_2)_4$]	D + E	30[d,s]	118–120[j]	$C_{15}H_{16}ClN$·HCl
109	3-[4-$ClC_6H_4(CH_2)_4$]	D + E	47[d,i]	170–172[j]	$C_{15}H_{16}ClN$·HCl
110	3-[4-$FC_6H_4(CH_2)_4$]	D + E	36[d,i,t]	49–51	$C_{15}H_{16}NF$
111	3-[2,4-$Cl_2C_6H_3(CH_2)_4$]	D + E	40[d,i,t]	31–32	$C_{15}H_{15}Cl_2N$
112	3-[2,6-$Cl_2C_6H_3(CH_2)_4$]	D + E	50[d,i]	134–136[j]	$C_{15}H_{15}Cl_2N$·HCl
113	3-[4-(CH_3CONH)$C_6H_4(CH_2)_4$]	B (from 132)	60[f]	107–108	$C_{17}H_{20}N_2O$
115	3-[4-(4-$NO_2C_6H_4CONH$)$C_6H_4(CH_2)_4$]	B (from 132)	61[c]	167–168	$C_{22}H_{21}N_3O_3$
116	3-[4-($C_6H_5OCH_2CONH$)$C_6H_4(CH_2)_4$]	B (from 132)	62[f]	94–96	$C_{23}H_{24}N_2O_2$
117	3-[4-($C_6H_5CH_2CH_2CONH$)$C_6H_4(CH_2)_4$]	B (from 132)	80[f]	130–131	$C_{24}H_{26}N_2O$
118	3-[4-$(CH_3)_2CHC_6H_4(CH_2)_4$]	D + E	40[d,s]	141–142[j]	$C_{18}H_{19}N$·HCl
119	3-[1-$C_{10}H_7(CH_2)_4$]	D + E	37[d,i]	144–146[j]	$C_{19}H_{19}N$·HCl
120	3-[2-$C_{10}H_7(CH_2)_4$]	C + E	86[d,i,u]	67–69	$C_{19}H_{19}N$
121	3-[4-$C_6H_5CH_2C_6H_4(CH_2)_4$]	D + E	15[d,s]	117–118[j]	$C_{22}H_{23}N$·HCl
122	3-[3-$C_6H_5CH_2C_6H_4(CH_2)_4$]	D + E	44[d,i]	139–141[j]	$C_{22}H_{23}N$·HCl
123	3-[4-($C_6H_5CH_2CH_2$)$C_6H_4(CH_2)_4$]	D + E	48[d,e]	65–66	$C_{23}H_{25}N$[g]
124	3-[3-($C_6H_5CH_2CH_2$)$C_6H_4(CH_2)_4$]	D + E	36[d,s]	109–110[j]	$C_{23}H_{25}N$·HCl
125	3-[3-$C_6H_5C_6H_4(CH_2)_4$]	D + E	50[d,s]	121–122[j]	$C_{21}H_{21}N$·HCl
126	3-[4-$C_6H_5C_6H_4(CH_2)_4$]	D + E	42[d,e]	66–67	$C_{21}H_{21}N$
127	3-[4-$C_6H_5C_6H_4(CH{=}CH)_2$]	D	60[c]	175–176	$C_{21}H_{17}N$
128	3-(4-$C_6H_5C_6H_4OCH_2CONH$)	B	75[c]	143–145	$C_{19}H_{16}N_2O_2$
129	3-(4-$C_6H_5C_6H_4CONHCH_2$)	B	49[c]	178–180	$C_{19}H_{16}N_2O$
130	3-(4-$C_6H_5C_6H_4CH_2CH_2CONH$)	B + E	85[f]	151–152	$C_{20}H_{19}N_2O$
131	3-(4-$C_6H_5C_6H_4CH_2CH_2CONHCH_2$)	B + E	75[f]	149–150	$C_{21}H_{20}N_2O$
132	3-(3-$C_6H_5C_6H_4OCH_2CONH$)	B	67[c]	153–155	$C_{19}H_{16}N_2O_2$
133	3-[4-$NH_2C_6H_4(CH_2)_4$]	E (from 101)	60[v]	229–233[j]	$C_{15}H_{18}N$·2HCl
134	3-(4-$C_6H_5C_6H_4CH{=}CHCONHCH_2$)	B	83[f]	180–181	$C_{21}H_{18}N_2O$
135	3-(4-$C_6H_5C_6H_4CH{=}CHCONH$)	B	95[f]	200–202	$C_{20}H_{16}N_2O$
136	3-[4-(3-$SO_2FC_6H_4CONH$)$C_6H_4OCH_2CONH$]	B (from 141)	33[f]	151–153	$C_{20}H_{16}FN_3O_5S$
137	4-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_4$]	B (from 142)	38[f]	165–167	$C_{22}H_{21}FN_2O_3S$
138	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_2$]	B (from 145)	35[f]	198–200	$C_{20}H_{17}FN_2O_3S$
139	4-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4(CH_2)_2$]	B	33[f]	194–196	$C_{20}H_{17}FN_2O_3S$
140	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4OCH_2CONHCH_2$]	B (from 147)	34[w]	215–217	$C_{21}H_{18}FN_3O_5S$
141	3-[4-(4-$SO_2FC_6H_4CONH$)$C_6H_4CH_2CH_2CONHCH_2$]	B (from 149)	41[c]	200–202	$C_{22}H_{20}FN_3O_4S$
142	3-(4-$NH_2C_6H_4OCH_2CONH$)	E (from 142)	85[f]	134–135	$C_{13}H_{13}N_3O_2$
143	3-(4-$NO_2C_6H_4OCH_2CONH$)	B	66[w]	197–198	$C_{13}H_{11}N_3O_4$
144	4-[4-$NH_2C_6H_4(CH_2)_4$]	E (from 144)	86[e]	75–77	$C_{15}H_{18}N_2$[g]
145	4-[4-$NO_2C_6H_4(CH{=}CH)_2$]	C	47[f]	193–195	$C_{15}H_{12}N_2O_2$
146	3-(4-$NH_2C_6H_4CH_2CH_2$)	E (from 146)	88[f]	118–120	$C_{13}H_{14}N_2$[g]
147	3-(4-$NO_2C_6H_4CH{=}CH$)	C	40[c]	143–145	$C_{13}H_{10}N_2O_2$
148	3-(4-$NH_2C_6H_4OCH_2CONHCH_2$)	E (from 146)	65[x]	231–233[j]	$C_{14}H_{15}N_3O_2$·2HCl
149	3-(4-$NO_2C_6H_4OCH_2CONHCH_2$)	B	48[w]	135–137	$C_{14}H_{13}N_3O_4$
150	3-(4-$NH_2C_6H_4CH_2CH_2CONHCH_2$)	E (from 150)	82[y]	104–106	$C_{15}H_{17}N_3O$
151	3-(4-$NO_2C_6H_4CH{=}CHCONHCH_2$)	B	68[w]	231–233	$C_{15}H_{13}N_3O_3$

[a] Methods: B, amide synthesis, amine plus acid chloride (see Experimental Section); C,[1b] Wittig reaction, 3- or 4-picolyltriphenylphosphonium chloride hydrochloride and appropriate RCHO; D,[1b] Wittig reaction, $RCH_2P^+(Ph)_3X^-$ and 3- or 4-pyridinecarboxaldehyde; E,[1b] catalytic reduction. [b] Analyses for C, H, N unless otherwise indicated. [c] Recrystallized from EtOH. [d] Overall yield for Wittig reaction and catalytic reduction. [e] Recrystallized from petroleum ether (bp 60–110°). [f] Recrystallized from EtOH–H_2O. [g] Analyses for C and H only. [h] 3-Phenylbenzyltriphenylphosphonium bromide was prepared by the procedure of Baker and Bramhall, *J. Med. Chem.*, 15, 937 (1972). [i] HCl salt was recrystallized by dissolving in boiling Me_2CO containing about 5% MeOH followed by the addition of petroleum ether (bp 60–110°) to cloudiness. [j] HCl salt. [k] 4-Stilbenecarboxaldehyde prepared by the procedure of Baker and Gibson, *J. Med. Chem.*, 14, 315 (1971). [l] Recrystallized from MeOH–H_2O. [m] Free amine, mp 59–60°. [n] Cinnamyltriphenylphosphonium bromide prepared by the method of McDonald and Campbell, *J. Org. Chem.*, 24, 1969 (1959). [o] Recrystallized from *i*-PrOH–H_2O. [p] R. Bodalski, A. Malkiewicz, and J. Michalski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 13, 139 (1965), reported mp 101–102°. [q] *m*-Nitrocinnamaldehyde obtained from Starks Associates, Buffalo, N.Y. [r] Preparation of 3,4-dichlorocinnamaldehyde is described in ref 1b. [s] Recrystallized from Me_2CO–petroleum ether (bp 60–110°). [t] Purified by recrystallization of HCl salt and then treating an ether solution with gaseous NH_3 to obtain the free amine. [u] HCl salt, mp 175–177°. [v] Recrystallized from Me_2CO. [w] Recrystallized from MeOEtOH–EtOH. [x] Di-HCl salt recrystallized from MeOH–petroleum ether (bp 60–110°). [y] Recrystallized from $CHCl_3$–petroleum ether (bp 60–110°).

Table III. Physical Properties of 

No.	R	X	Method[a]	Yield, %	Mp, °C	Formula[b]
152	2-CH_3	Cl	F	25[c,d]	154-157	$C_{28}H_{26}ClP$
153	3-CH_3	Cl	F	31[c,e]	180-182	$C_{28}H_{26}ClP \cdot 0.25H_2O$
154	4-CH_3	Cl	F	38[d,f]	184-186	$C_{28}H_{26}ClP \cdot 0.5H_2O$
155	3,4-$(CH_3)_2$	Cl	F	16[e,g]	200-202	$C_{29}H_{28}ClP \cdot H_2O$
156	2-Cl	Cl	F	30[d,f]	203-205	$C_{27}H_{23}Cl_2P$
157	3-Cl	Cl	F	17[c,d]	135-137	$C_{27}H_{23}Cl_2P \cdot 0.5H_2O$
158	4-Cl	Cl	F	28[e,f]	198-200	$C_{27}H_{23}Cl_2P \cdot 0.5H_2O$
159	4-F	Br	G	46[d,f]	187-189	$C_{27}H_{23}BrFP$
160	2,4-Cl_2	Cl	F	24[d,f]	146-148	$C_{27}H_{22}Cl_3P \cdot H_2O$
161	2,6-Cl_2	Cl	F	25[d,f]	252-254	$C_{27}H_{22}Cl_3P$
162	4-$(CH_3)_2CH$	Br	G	52[d,f]	200-202	$C_{30}H_{30}BrP$
162	4-$(CH_3)_2CH$	Br	H	47[d,f]	200-202	$C_{30}H_{30}BrP$
163	2,3-Benzo	Cl	F	27[c,d]	180-182	$C_{31}H_{26}ClP$
164	4-$C_6H_5CH_2$	Br	G	40[d,f]	167-169	$C_{34}H_{30}BrP$
165	3-$C_6H_5CH_2$	Br	H	55[d,f]	228-229	$C_{34}H_{30}BrP$
166	4-$C_6H_5CH{=}CH$	Br	G	36[d,f]	203-204	$C_{35}H_{30}BrP$
167	3-$C_6H_5CH{=}CH$	Br	G	40[d,f]	175-176	$C_{35}H_{30}BrP$
168	3-C_6H_5	Br	H	35[d,f]	217-218	$C_{33}H_{28}BrP$
169	4-C_6H_5	Br	G	60[d,f]	238-240	$C_{33}H_{28}BrP$

[a] Methods (see Experimental Section): F,[1b] $RCO_2H \xrightarrow{SOCl_2} RCOCl \xrightarrow{NaBH_4} RCH_2OH \xrightarrow{SOCl_2} RCH_2Cl \xrightarrow{(Ph)_3P} RCH_2P^+(Ph)_3Cl^-$; G, $RCO_2H \xrightarrow{SOCl_2} RCOCl \xrightarrow{NaBH_4} RCH_2OH \xrightarrow{HBr\ (g)} RCH_2Br \xrightarrow{(Ph)_3P} RCH_2P^+(Ph)_3Br^-$; H, $RCO_2H \xrightarrow{SOCl_2} RCOCl \xrightarrow{NaBH_4} RCH_2OH \xrightarrow{(Ph)_3PHBr} RCH_2P^+(Ph)_3Br^-$. [b] Analyses for C and H. [c] Yield from appropriate benzaldehyde (see Table IV and method J). [d] Recrystallized from Me_2CO containing about 5% MeOH-petroleum ether (bp 60-110°). [e] Recrystallized from Me_2CO-petroleum ether (bp 60-110°). [f] Yield from appropriate cinnamic acid. [g] Yield from 3,4-dimethylbenzonitrile.

Table IV. Physical Properties of Miscellaneous Compounds

No.	Structure	Method[a]	Yield, %	Mp, °C	Formula[b]
170	2-$CH_3C_6H_4CH{=}CHCO_2H$	I	95[c]	171-174[d]	
171	3-$CH_3C_6H_4CH{=}CHCO_2H$	I	98[c]	115-117[e]	
172	3,4-$(CH_3)_2C_6H_3CH{=}CHCO_2H$	J + I	82[c,f]	172-174[g]	
173	1-$C_{10}H_7CH{=}CHCO_2H$	I	97[c]	207-210[h]	
174	3-$ClC_6H_4CH{=}CHCO_2H$	I	95[c]	159-161[i]	
175	3-$C_6H_5C_6H_4CH{=}CHCO_2H$	I	14[j,k]	177-179	$C_{15}H_{12}O_2$
176	3-$(C_6H_5CH_2)C_6H_4CH{=}CHCO_2H$	K + J + I	70[l,m]	120-122	$C_{16}H_{14}O_2$
177	3-$(C_6H_5CH{=}CH)C_6H_4CH{=}CHCO_2H$	L + I	94[l]	183-185	$C_{17}H_{14}O_2$
178	4-$C_6H_5C_6H_4CH{=}CHCO_2H$	I	96[c]	220-222[n]	
179	4-$(C_6H_5CH_2)C_6H_4CH{=}CHCO_2H$	K + J + I	65[l,m]	165-167[o]	
180	4-$(C_6H_5CH{=}CH)C_6H_4CH{=}CHCO_2H$	L + I	95[j]	254-257[p]	
181	4-$C_6H_5C_6H_4OCH_2CO_2H$	M	40[c]	186-190[q]	
182	4-$(C_6H_5CH{=}CH)C_6H_4CHO$	L	87	111-113[r]	
183	3-$(C_6H_5CH{=}CH)C_6H_4CHO$	L	55	95-97[s]	

[a] Methods (see Experimental Section): I, $RArCHO + HO_2CCH_2CO_2H \rightarrow RArCH{=}CHCO_2H$; J, RArCN + Red-Al → RArCHO; K, $RArCH_2Br + C_6H_6 + AlCl_3 \rightarrow RArCH_2C_6H_5$; L, prepared from benzyltriphenylphosphonium chloride and the appropriate benzenedicarboxaldehyde by the general procedure of Baker and Gibson *J. Med. Chem.*, 14, 315 (1971); M, $RArOH + t\text{-}BuO_2CCH_2Cl \rightarrow \rightarrow RArOCH_2CO_2H$. [b] Analyses for C and H. [c] Crystallized from reaction, used without further purification. [d] J. Frederick, J. Dippy, and J. E. Page, *J. Chem. Soc.*, 357 (1938), reported mp 169°. [e] J. Frederick, J. Dippy, and J. E. Page, *J. Chem. Soc.*, 357 (1938), reported mp 119°. [f] Overall yield from 3,4-dimethylbenzonitrile. [g] S. Sugasawa and S. Sugimoto, *J. Pharm. Soc. Jpn.*, 61, 62 (1941), reported mp 172°. [h] B. West, *J. Am. Chem. Soc.*, 42, 1656 (1920), reported mp 209-212°. [i] K. Pandya and R. Pandya, *Proc. Indian Acad. Sci., Sect. A*, 14, 112 (1941), reported mp 163°. [j] Recrystallized from MeOEtOH-H_2O. [k] Overall yield from 3-phenylbromobenzene. [l] Recrystallized from EtOH-H_2O. [m] Overall yield from appropriate α-bromotolunitrile. [n] G. Cavallini, E. Massarani, D. Nardi, and R. D'Ambrosia, *J. Am. Chem. Soc.*, 79, 3514 (1957), reported mp 225°. [o] J. Gilbert, *J. Rech. C. N. R. S.*, No. 36, 271 (1956) [*Chem. Abstr.*, 51, 8702q (1957)], reported mp 167°. [p] G. Cavallini, E. Massarini, D. Nardi, and R. D'Ambrosia, *J. Am. Chem. Soc.*, 79, 3514 (1957), reported mp 256-258°. [q] M. Synerholm and P. Zimmerman, *Contrib. Boyce Thompson Inst.*, 14, 91 (1945), reported mp 189-190°. [r] B. R. Baker and R. E. Gibson, *J. Med. Chem.*, 14, 315 (1971), reported mp 115-116°. [s] R. Heck, *J. Am. Chem. Soc.*, 90, 5518 (1968), reported mp 94.5-95°.

of the compounds were prepared by one of the following general routes (see Scheme I).

Compounds **89**, **90**, **92**, **93**, **95**, **96**, and **120** (see Table II) were prepared by a Wittig reaction with 3- or 4-picolyltriphenylphosphonium chloride[1b] and the appropriate benzaldehyde or cinnamaldehyde, followed by catalytic reduction.[1b] Compounds **91**, **94**, **103-112**, **118**, **119**, and **121-126** were similarly prepared from 3- or 4-pyridinecarboxaldehyde and the appropriate benzyl- or cinnamyltriphenylphosphonium halides listed in Table III, followed by catalytic reduction. Compounds **97-102** and **127** were similarly prepared. When **133** was treated with the appropriate acid chloride, compounds **83** and **113-117** were formed. The amides **128-132**, **134-143**, and **148-151** were similarly prepared from 3-aminopyridine, 3-aminomethylpyridine, or from **133**, **142**, **144**, **146**, **148**, or **150**.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. Each analytical sample had an ir

spectrum compatible with its structure and moved as a single spot on TLC on Brinkman silica gel GF. All analytical samples gave combustion values for C, H, or C, H, N within 0.4% of theoretical values.

3-(4-Benzamidophenylbutyl)pyridine (114) (Method B). A solution of 0.8 g (3.5 mmol) of 133, 0.5 g (3.5 mmol) of benzoyl chloride, and 0.5 g (5 mmol) of Et_3N in 40 ml of DMF was heated at 100° for 10 min and allowed to cool to room temperature before 50 ml of H_2O was added. The crystalline product was collected, washed with H_2O, air-dried, and recrystallized from EtOH–H_2O: yield, 0.8 g (69%); mp 114–115°. Anal. ($C_{22}H_{22}N_2O$) C, H, N.

4-Fluorocinnamyltriphenylphosphonium Bromide (159) (Method G). A solution of 4.0 g (26 mmol) of 4-fluorocinnamyl alcohol [prepared from 4-fluorocinnamic acid by the general method of Baker and Doll[1b] and recrystallized from petroleum ether (bp 60–110°)] was dissolved in 75 ml of dry Et_2O which had been saturated with dry HBr. The solution was stirred at room temperature for 3 h; the organic layer was decanted, dried (Na_2SO_4), and evaporated to a purple solid which was heated overnight in a benzene solution containing 7.0 g of $(Ph)_3P$. The crystalline product was collected by filtration and recrystallized by dissolving in hot Me_2CO containing about 5% MeOH and adding petroleum ether (bp 60–110°) to cloudiness: yield, 5.7 g (46%); mp 187–189°. Anal. ($C_{27}H_{23}BrFP$) C, H.

5-Phenyl-2,4-pentadienyltriphenylphosphonium Bromide (Method H). A solution of 6.7 g (42 mmol) of 5-phenyl-2,4-pentadienol (prepared in 90% yield from 5-phenyl-2,4-pentadienoic acid by the general method of Baker and Doll[1b] and used without further purification) and 13.0 g (38 mmol) of triphenylphosphonium bromide[29] in 60 ml of MeOH was stirred at room temperature for 72 h, poured into H_2O, and twice extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and evaporated to a light yellow oil which crystallized upon trituration in Me_2CO: yield, 11.9 g (65%); white solid; mp 229–230° (lit.[30] 236–240°).

3-Styrylcinnamic Acid (177) (Method I, See Table IV). A solution of 3.8 g (18 mmol) of 3-stilbenecarboxaldehyde (183), 3.6 g (35 mmol) of malonic acid, and 0.5 ml of piperidine in 25 ml of pyridine was heated on a steam bath for 4 h and then poured into a solution of 75 g of ice and 40 ml of concentrated HCl. The product was separated by filtration and washed with dilute HCl and H_2O: yield 4.3 g (94%); mp 183–185°. Anal. ($C_{17}H_{14}O_2$) C, H.

4-Benzylbenzaldehyde (Method J). A benzene solution of 4-benzylbenzonitrile was treated with Red-Al according to the general procedure of Baker and Gibson.[31] The crude product was used without further purification.

4-Benzylbenzonitrile (Method K). Upon mixing, a stirred solution of 23.1 g (0.12 mol) of α-bromo-*p*-tolunitrile and 13.3 g (0.10 mol) of $AlCl_3$ in 120 ml of PhH became warm and evolved HCl gas. After 15 min 5.3 g (0.04 mol) of additional $AlCl_3$ was added. After stirring at ambient temperature overnight, the solution was poured into ice water; the organic layer was twice extracted with H_2O, dried ($MgSO_4$), and evaporated to a brown solid (21.3 g, 90%) which was treated by method J without further purification.

3-Phenylphenoxyacetic Acid (Method M). A solution of 4.75 g (28 mmol) of 3-phenylphenol, 4.2 g (28 mmol) of *tert*-butylchloroacetate, and 3.9 g (28 mmol) of K_2CO_3 in 30 ml of DMF was stirred overnight at 70°, poured into H_2O, and twice extracted with PhMe. The organic layers were combined, washed with H_2O, and dried ($MgSO_4$). After 50 mg of TsOH was added the solution was heated at 100° overnight, evaporated to 25 ml, and treated with petroleum ether (bp 60–110°) to promote crystallization; yield, 2.7 g (42%); mp 100–102° (lit.[32] mp 108–109.5°).

β-Phenylcinnamyltriphenylphosphonium chloride (184) was prepared from 5.0 g of β-phenylcinnamic acid by the general method of Baker and Doll[1b] and was recrystallized from acetone: yield, 7.1 g (60%); white solid; mp 253–255°. Anal. ($C_{33}H_{28}ClP$) C, H.

3-Phenylbenzaldehyde. A solution of 3-phenylphenylmagnesium bromide was prepared from 3-phenylbromobenzene and Mg in the usual manner and then treated with ethyl orthoformate. The crude acetal was heated for 1.5 h in a refluxing solution of 90 ml of EtOH and 10 ml of 3 N H_2SO_4. This solution was poured into water and extracted with Et_2O. The organic layers were combined, dried (Na_2SO_4), and evaporated to an amber oil which was treated by method I to prepare 175 in 14% yield overall.

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References and Notes

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