Synthesis and Antiallergy Activity of 4-(Diarylhydroxymethyl)-1-[3-(aryloxy)propyl]piperidines and Structurally Related Compounds[1]

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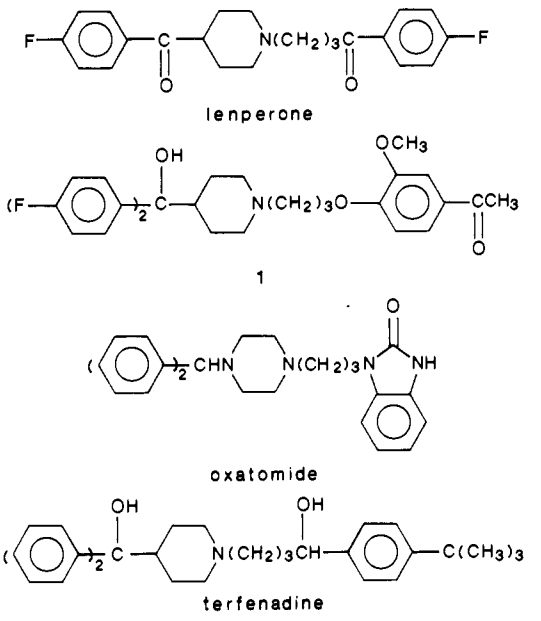
A series of 4-(diarylhydroxymethyl)-1-[3-(aryloxy)propyl]piperidines was synthesized and evaluated for antiallergy activity. Several analogues had potent activity in the passive foot anaphylaxis (PFA) assay, an IgE-mediated model useful in the detection of compounds possessing antiallergic activity. In particular 1-[4-[3-[4-[bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (1, AHR-5333) was more potent than oxatomide and terfenadine in this assay.

In 1982 a program was begun in our laboratories to find a suitable clinical candidate for the treatment of allergic disorders. Initially, file compounds were tested in the passive foot anaphylaxis (PFA) model in rats. This response represents a useful assay for detecting compounds possessing antiallergy activity since it has been shown to be IgE mediated.[2] Lenperone (Chart I), an antipsychotic agent,[3] possessed activity in the PFA model, but its potent central nervous system (CNS) activity precluded its usefulness as an antiallergy agent. Compound 1 (AHR-5333, Chart I), previously prepared by Duncan and Boswell[4] for a CNS project, also possessed excellent activity in the PFA model (Table VI). It was observed that 1 bore structural similarities to the known antiallergy compound oxatomide[5] and the nonsedating antihistamine terfenadine[6] (Chart I). Compound 1 had only minor[7] effects on the electroencephalograph (EEG) of cats with chronically implanted electrodes,[8] indicating a separation of the CNS and antiallergy activities. For these reasons a systematic structure-activity study of derivatives of 1 was undertaken.

Chart I



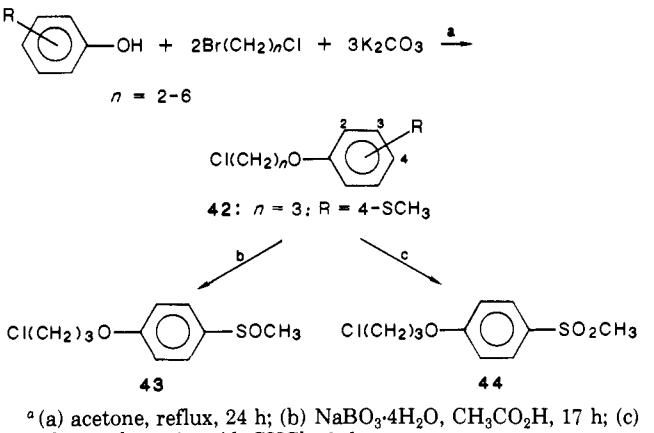
Chemistry

The substituted phenoxychloroalkane intermediates listed in Table I were prepared by the general procedures outlined in Scheme I. One mole of a substituted phenol, 2 mol of a bromochloroalkane, and 3 mol of anhydrous potassium carbonate were heated in acetone to give good yields of the alkylated phenols. Compounds **43** and **44** resulted from the oxidation of the methylthio derivative (**42**).

The piperidinyl and pyrrolidinyl intermediates listed in Table II were prepared by a variety of standard synthetic pathways depicted in Scheme II, and representative procedures are described in the Experimental Section. In general, these procedures employed a Grignard addition to an appropriately substituted ketone or ester to give a tertiary alcohol. The protected amine was then debenzylated by catalytic hydrogenolysis to give the secondary piperidine or pyrrolidine, or the pyridine derivative was reduced catalytically to give a secondary piperidine.

The synthesis of specific amines that are not covered in Scheme II are depicted in Schemes III–VII. The ether derivative **69** was readily prepared from **49** by alkylation with potassium hydride and iodomethane (Scheme III). α,α-Diphenyl-4-piperidineacetonitrile (**72**) and acetamide **73** depicted in Scheme IV were prepared by a procedure described by Shanklin and Wilkinson.[15] The synthesis of the chloro derivative **64** (Scheme V) could not be carried out by the procedures described in Scheme II since the chloro groups could be removed under the catalytic hydrogenation conditions used for debenzylation or reduction. Ethyl isonipecotate was protected with the (di-

Scheme I[a]



[a] (a) acetone, reflux, 24 h; (b) $NaBO_3 \cdot 4H_2O$, CH_3CO_2H, 17 h; (c) *m*-chloroperbenzoic acid, $CHCl_3$, 2 days.

† Department of Chemical Research.
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(1) A preliminary account of the work was presented at the 193rd National Meeting of the American Chemical Society, Denver, CO, April 1987; MEDI 85.
(2) Martel, R. R.; Klicius, J. *Int. Arch. Allergy Appl. Immunol.* **1977**, *54*, 205–209.
(3) Duncan, R. L., Jr.; Helsley, G. C.; Welstead, W. J., Jr.; Da Vanzo, J. P.; Funderburk, W. H.; Lunsford, C. D. *J. Med. Chem.* **1970**, *13*, 1–6.

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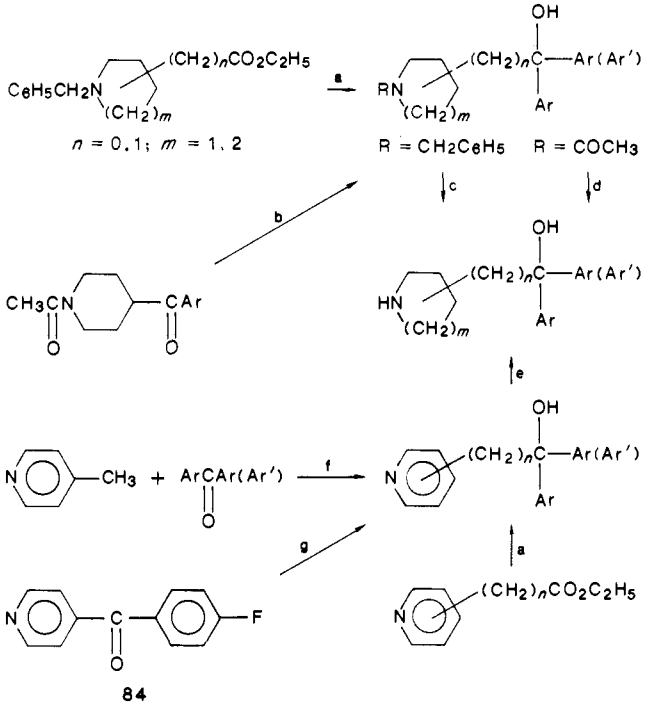
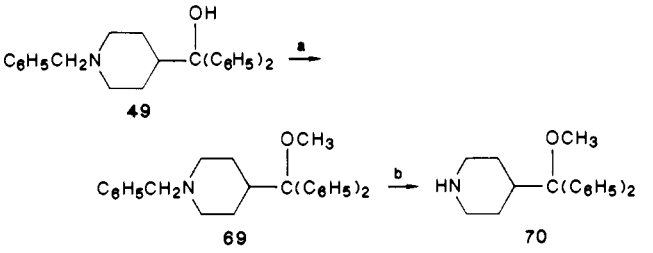
Scheme II[a]



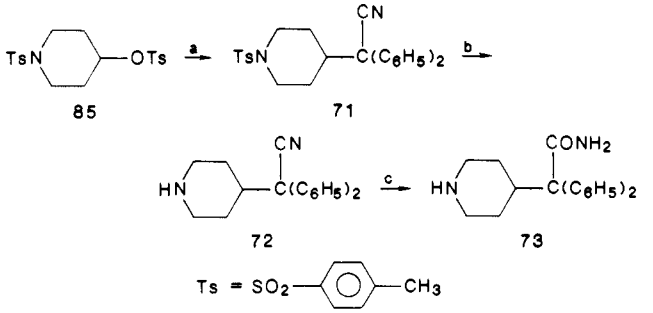
[a] (a) 2ArMgBr, tetrahydrofuran (THF); (b) Ar'MgBr, THF or 2-pyrLi, THF; (c) H_2, 5% Pd/C, C_2H_5OH, 60 °C, 24 h; (d) KOH, H_2O–C_2H_5OH, Δ, N_2; (e) H_2, 5% Pt/C, CH_3CO_2H; (f) *n*-BuLi, THF; (g) 4-$FC_6H_4CH_2MgBr$, THF.

Scheme III[a]



[a] (a) 1. KH, tetrahydrofuran; 2. CH_3I; (b) H_2, 5% Pd/C, 60 °C.

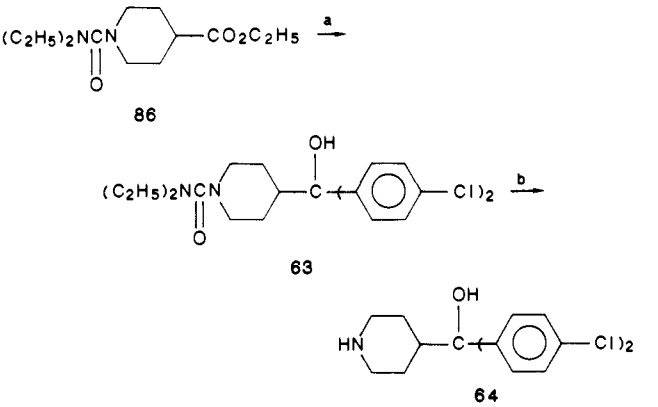
Scheme IV[a]



[a] (a) $(C_6H_5)_2CHCN$, NaH, toluene, 100 °C, 17 h; (b) 48% HBr, phenol; (c) 90% H_2SO_4, 90 °C, 17 h.

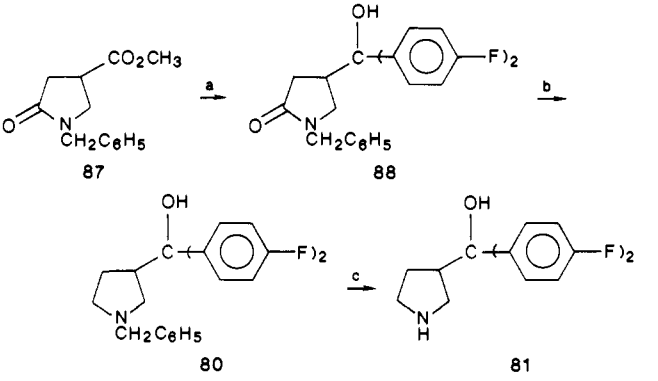
ethylamino)carbonyl group as suggested by Comins and Stroud[16] to give **86**. Grignard addition to **86** gave a good

Scheme V[a]



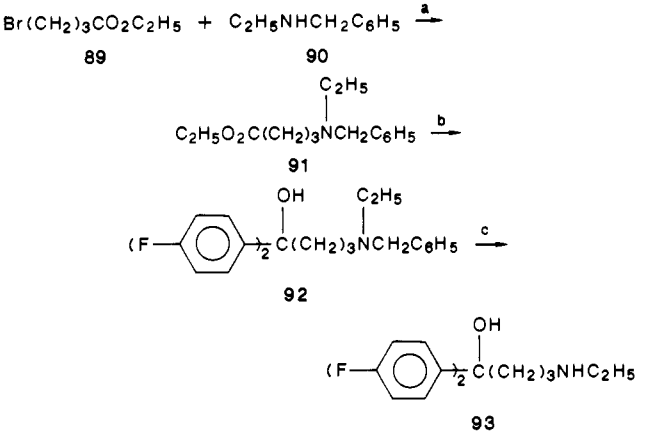
[a] (a) 4-ClC_6H_4MgBr, tetrahydrofuran (THF), 17 h; (b) $LiAlH_4$, THF, Δ, 24 h.

Scheme VI[a]



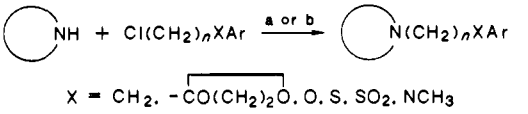
[a] (a) 4-FC_6H_4MgBr, tetrahydrofuran (THF), 17 h; (b) $LiAlH_4$, THF, Δ, 2 h; (c) H_2, 5% Pd/C, C_2H_5OH, 70 °C, 2 days.

Scheme VII[a]



[a] (a) Na_2CO_3, C_2H_5OH, Δ, 2 days; (b) 4-FC_6H_4MgBr, tetrahydrofuran, 17 h; (c) H_2, 10% Pd/C, C_2H_5OH.

Scheme VIII[a]



[a] (a) Na_2CO_3, KI, 1-butanol, Δ, 17 h; (b) Na_2CO_3, KI, DMF, 90–100 °C, 17 h.

yield of **63**. In contrast to the literature report,[16] the (diethylamino)carbonyl group of **63** was resistant to re-

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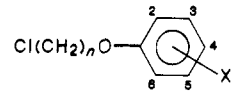
(7) Johnson, D. N. A. H. Robins, Co., unpublished results.

Table I. Substituted Phenoxychloroalkane Intermediates



no.	X[a]	n	mp, °C (solv)[b]	% yield	formula[c]
2	2-OCH_3, 4-$COCH_3$	2	69–70 (k)	42	$C_{11}H_{13}ClO_3$
3	2-OCH_3, 4-$COCH_3$	3	57.5–58.5 (l)	84	$C_{12}H_{15}ClO_3$
4	2-OCH_3, 4-$COCH_3$	4	68.5–70.5 (k)	95	$C_{13}H_{17}ClO_3$
5	2-OCH_3, 4-$COCH_3$	5	57–58 (k)	84	$C_{14}H_{19}ClO_3$
6	2-OCH_3, 4-$COCH_3$	6	35–38 (k)	84	$C_{15}H_{21}ClO_3$
7	2-CH_3, 4-$COCH_3$	3	41.5–42.5 (m)	95	$C_{12}H_{15}ClO_2$
8	3-OCH_3, 4-$COCH_3$	3	47–49 (k)	94	$C_{12}H_{15}ClO_3$
9	2-CH_3	3	oil	62	
10	2-OCH_3	3	oil	84	
11	2-OC_2H_5	3	oil	53	
12	2-$OCH(CH_3)_2$	3	oil	62	
13	2-$OCH_2C_6H_5$	3	oil	84	
14	2,6-$(OCH_3)_2$	3	oil	36	
15	2-$COCH_3$	3	oil	46	
16	2-$CO_2C_2H_5$	3	oil	43	
17	3-CH_3	3	oil	81	
18	3-OCH_3	3	oil	96	
19	3-$COCH_3$	3	oil	96	
20	3-$CO_2C_2H_5$	3	oil	99	
21	4-CH_3	3	oil	95	
22	4-C_2H_5	3	oil	81	
23	4-$CH(CH_3)_2$	3	oil	87	
24	4-$C(CH_3)_3$	3	oil	78	
25	4-C_6H_5	3	65–66 (l)	71	$C_{15}H_{15}ClO$
26	4-OCH_3	3	oil	82	
27	4-F	3	oil	89	
28	4-Cl	3	35–36 (m)	87	$C_9H_{10}Cl_2O$
29	4-$COCH_3$	3	oil	38	
30	4-COC_2H_5	3	41–43 (l)	71	$C_{12}H_{15}ClO_2$
31	4-$COCH(CH_3)_2$[d]	3	oil	98	
32	4-$COC(CH_3)_3$[e]	3	oil	99	
33	4-COC_6H_5	3	oil	98	
34	4-CN	3	40–44 (k)	24	$C_{10}H_{10}ClNO$
35	4-CO_2CH_3	3	56.5–59 (l)	94	$C_{11}H_{13}ClO_3$
36	4-CO_2CH_3	4	28.5–29 (m)	92	$C_{12}H_{15}ClO_3$
37	4-$CO_2C_2H_5$	3	27.5–28.5 (m)	94	$C_{12}H_{15}ClO_3$
38	4-$CONH_2$	3	142–143 (n)	97	$C_{10}H_{12}ClNO_2$
39	4-$CON(CH_3)_2$[f]	3	oil	78	
40	4-$CH_2CO_2CH_3$	3	oil	98	
41	4-$(CH_2)_2CO_2CH_3$	3	38–39.5 (l)	89	$C_{13}H_{17}ClO_3$
42	4-SCH_3	3	oil	98	
43	4-$SOCH_3$	3	oil	49	
44	4-SO_2CH_3	3	84–86 (o)	98	$C_{10}H_{13}ClO_3S$
45	4-SO_2NH_2	3	106–107.5 (o)	34	$C_9H_{12}ClNO_3S$
46	4-NO_2	3	37–39 (mp)	94	$C_9H_{10}ClNO_3$
47	4-$NHCOCH_3$	3	125–127 (q)	23	$C_{11}H_{14}ClNO_2$
48	4-$NHCO_2C_2H_5$[g]	3	91–93 (o)	83	$C_{12}H_{16}ClNO_3$

[a] Starting phenols were either purchased or prepared by literature procedures. [b] k = isopropyl ether, l = petroleum ether (60–110 °C), m = petroleum ether (30–60 °C), n = ethyl acetate, o = 2-propanol, p = ethyl ether, q = acetone. [c] Compounds were analyzed for C, H, and N, and results agreed to ±0.4% of theoretical values. [d] Reference 9. [e] Reference 10. [f] Reference 11. [g] Reference 12.

moval by base hydrolysis. However, **64** was obtained in a fair yield by reaction of **63** with $LiAlH_4$. The pyrrolidine derivative **81** was prepared from **87** in a straightforward manner (Scheme VI). Lactam **88** was reduced with $LiAlH_4$ to give **80**, which was then debenzylated by catalytic hydrogenolysis to yield **81**. Scheme VII illustrates the synthesis of the secondary amine **93** from ethyl 4-bromobutyrate (**89**) and *N*-ethylbenzylamine (**90**).

The preparation of the target compounds is shown in Scheme VIII. One mole of the appropriate secondary amine (substituted piperidine, pyrrolidine, or piperazine) was reacted with 1 mol of the appropriate chloroalkane overnight in 1-butanol with anhydrous sodium carbonate as a base. In cases where 1-butanol could interfere with the reaction (i.e., transesterification), *N*,*N*-dimethylformamide was used as solvent. In general, good to excellent yields of compounds listed in Tables III–VI were obtained. The synthesis of specific target compounds not covered in Scheme VIII are in the Experimental Section.

Results and Discussion

The discovery that **1** possessed antiallergy activity in animal models instigated a synthetic program to investigate the structural requirements for this activity. Initially, the heterocyclic amino portion of **1** was varied and Table III shows data on 15 amines. At 3.16 mg/kg, only three compounds (**99**, **100**, **103**) showed activity in the PFA assay with **99** and **103** being the most potent. Since **99** contained the same 4-benzhydrol-substituted piperidine moiety as **1** which had already been shown to have a good separation between CNS and antiallergy activity, additional analogues incorporating this amine were prepared. Of the four piperazines that were prepared (**105–108**), **107** and **108** possessed activity at 10 mg/kg. Similar piperazine derivatives are ubiquitous in the literature, and compounds structurally related to **107** and **108** have been reported[20,21] to possess antiallergy activity. Thus, further work with these piperazine derivatives was not pursued.

The heteroatom adjacent to the non-benzhydrol aromatic ring in **1** was then varied. Table IV shows data on nine compounds with various substitutions at this point. Clearly, at 10 mg/kg, the compound containing a bridging oxygen (**109**) was the most effective. At 3.16 mg/kg compounds containing a hydroxymethylene (**112**) or a nitrogen (**116**, **117**) retained some activity, but **109** was superior. The phenoxyalkyl group was chosen for further substitution studies.

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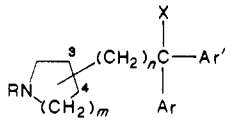
Table II. Substituted Piperidinyl and Pyrrolidinyl Intermediates



no.	Ar	Ar′	X	n	m	pos	R	formula[a]	mp, °C (solv)[b]	method of prep[c]	% yield
49	C_6H_5	C_6H_5	OH	0	2	4	$CH_2C_6H_5$	$C_{25}H_{27}NO$	89.5–90.5 (k)	E	77
50	C_6H_5	C_6H_5	OH	0	2	4	H	$C_{18}H_{21}NO$	160–161 (kl)	F	99
51	C_6H_5	C_6H_{11}[d]	OH	0	2	4	$COCH_3$	$C_{20}H_{29}NO_2$	153–155 (m)	G	43
52	C_6H_5	C_6H_{11}[d]	OH	0	2	4	H	$C_{18}H_{27}NO$[e]	147–149 (no)	H	51
53	C_6H_5	3-$CF_3C_6H_4$	OH	0	2	4	H	$C_{19}H_{20}F_3NO$	97–100 (p)	I	53
54	C_6H_5	4-FC_6H_4	OH	0	2	4	$COCH_3$	$C_{20}H_{22}FNO_2$	173–175 (k)	G	45
55	C_6H_5	4-FC_6H_4	OH	0	2	4	H	$C_{18}H_{20}FNO$	144.5–146 (kl)	H	25
56	3-FC_6H_4	3-FC_6H_4	OH	0	2	4	$CH_2C_6H_5$	$C_{25}H_{25}F_2NO{\cdot}C_4H_4O_4$[f]	212–214 dec (qr)	E	90
57	3-FC_6H_4	3-FC_6H_4	OH	0	2	4	H	$C_{18}H_{19}F_2NO$	117–118 (kl)	F	92
58	4-FC_6H_4	4-FC_6H_4	OH	0	2	4	$CH_2C_6H_5$	$C_{25}H_{25}F_2NO$	113–115 (os)	E	91
59	4-FC_6H_4	4-FC_6H_4	OH	0	2	4	H	$C_{18}H_{19}F_2NO$	159.5–160.5 (kl)	F	92
60	3,4-$F_2C_6H_3$	3,4-$F_2C_6H_3$	OH	0	2	4	H	$C_{18}H_{17}F_4NO{\cdot}0.5C_2H_2O_4{\cdot}0.5H_2O$	278–279 dec (ps)	N	57
61	4-FC_6H_4	2-C_5H_4N[g]	OH	0	2	4	H	$C_{17}H_{19}FN_2O$	228–230 dec (tu)	I	14
62	4-FC_6H_4	4-$FC_6H_4CH_2$	OH	0	2	4	H	$C_{19}H_{21}F_2NO{\cdot}0.5C_2H_2O_4$	317 (p)	N	69
63	4-ClC_6H_4	4-ClC_6H_4	OH	0	2	4	$CON(C_2H_5)_2$	$C_{23}H_{28}Cl_2N_2O_2$	172–175 (k)	U	87
64	4-ClC_6H_4	4-ClC_6H_4	OH	0	2	4	H	$C_{18}H_{19}Cl_2NO$	184–188 (k)	V	35
65	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	OH	0	2	4	$CH_2C_6H_5$	$C_{27}H_{31}NO$	115–117 (k)	E	95
66	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	OH	0	2	4	H	$C_{20}H_{25}NO$	150–153 (k)	F	60
67	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	OH	0	2	4	$CH_2C_6H_5$	$C_{27}H_{31}NO_3{\cdot}C_2H_2O_4{\cdot}0.5EtOH{\cdot}0.5H_2O$	128–131 dec (u)	E	97
68	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	OH	0	2	4	H	$C_{20}H_{25}NO_3$	153–155 (k)	F	30
69	C_6H_5	C_6H_5	OCH_3	0	2	4	$CH_2C_6H_5$	$C_{26}H_{29}NO$	114–115 (l)	O	81
70	C_6H_5	C_6H_5	OCH_3	0	2	4	H	$C_{19}H_{23}NO$	89–90 (v)	F	74
71	C_6H_5	C_6H_5	CN	0	2	4	$SO_2C_6H_4CH_3$	$C_{26}H_{26}N_2O_2S$	183–184 (ow)	Q	92
72	C_6H_5	C_6H_5	CN	0	2	4	H	$C_{19}H_{20}N_2{\cdot}0.5C_2H_2O_4$	275–276 (ps)	R	59
73	C_6H_5	C_6H_5	$CONH_2$	0	2	4	H	$C_{19}H_{22}N_2O{\cdot}1.5C_4H_4O_4$[f]	234–235 (ps)	S	67
74[h]	C_6H_5	C_6H_5		0	2	4	H	$C_{18}H_{19}N$	85–86 (v)		73
75[i]	C_6H_5	C_6H_5	H	0	2	4	H	$C_{18}H_{21}N{\cdot}HCl$	275.5–277 (ps)		80
76	4-FC_6H_4	4-FC_6H_4	OH	1	2	4	H	$C_{19}H_{21}F_2NO$	169–171 (q)	N	85
77	4-FC_6H_4	4-FC_6H_4	OH	0	2	3	$CH_2C_6H_5$	$C_{25}H_{25}F_2NO$	113–115 (k)	E	75
78	4-FC_6H_4	4-FC_6H_4	OH	0	2	3	H	$C_{18}H_{19}F_2NO$	114.5–115.5 (x)	F	72
79	4-FC_6H_4	4-FC_6H_4	OH	1	2	3	H	$C_{19}H_{21}F_2NO{\cdot}HCl$	248 dec (u)	N	71
80	4-FC_6H_4	4-FC_6H_4	OH	0	1	4	$CH_2C_6H_5$	$C_{24}H_{23}F_2NO$	99–100 (k)	X	81
81	4-FC_6H_4	4-FC_6H_4	OH	0	1	4	H	$C_{17}H_{17}F_2NO$	152–153 (k)	F	91
82	4-FC_6H_4	4-FC_6H_4	OH	1	1	4	$CH_2C_6H_5$	$C_{25}H_{25}F_2NO{\cdot}C_2H_2O_4$	154–156 (kms)	E	53
83	4-FC_6H_4	4-FC_6H_4	OH	1	1	4	H	$C_{18}H_{19}F_2NO{\cdot}HCl{\cdot}0.5H_2O$	160–163 (ks)	F	94

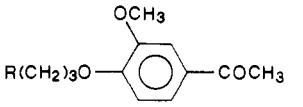
[a] All compounds were analyzed for C, H, and N, and results agreed to ±0.4% of theoretical values. [b] k = 2-propanol, l = isopropyl ether, m = ethyl acetate, n = benzene, o = hexane, p = methanol, q = acetonitrile, r = water, s = ethyl ether, t = pyridine, u = ethanol, v = petroleum ether (30–60 °C), w = methylene chloride, x = cyclohexane. [c] Letters refer to methods of preparation described in the Experimental Section. [d] Aryl group is replaced by a cyclohexyl group. [e] C: calcd, 79.07; found, 78.56. [f] Fumarate. [g] 2-Pyridyl group. [h] Reference 13. [i] Reference 14.

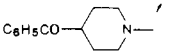
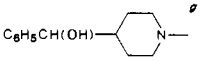
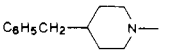
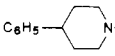
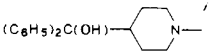
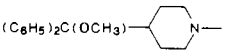
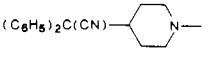
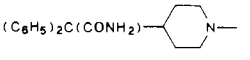
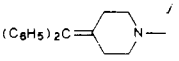
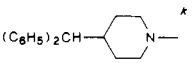
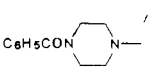
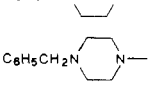
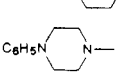
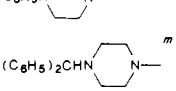
It was observed that the benzhydrol portion of **1** was very sensitive to changes in structure with the result that activity was readily lost. Table V shows six compounds in which the benzhydrol moiety was altered. Addition of a methylene group (**118**) or a change in piperidine ring position from 4 to 3 (**119**, **120**) eliminated activity in the PFA at 10 mg/kg. Exchanging a pyrrolidine ring for the piperidine ring (**121**, **122**) also eliminated activity at the screening dose. Even opening the piperidine ring, which resulted in **123**, a compound that has few steric restrictions, eliminated activity. In this group of compounds the 4-benzyhydrol-substituted piperidine moiety was a requirement for activity at 10 mg/kg in the PFA.

Table VI lists data for **1** and analogues prepared to optimize potency. Substituents on the diaryl portion of the molecule greatly affected activity. Compounds containing phenyl (**99**, **124**), 4-fluorophenyl (**1**, **127**), or 2-pyridyl (**130**) moieties retained activity while compounds containing 3-fluoro (**128**, **129**), 3-trifluoromethyl (**126**), or other 4-substituents such as chloro (**132**), methyl (**133**), and methoxy (**134**) on the phenyl ring were all inactive at 10 mg/kg. Replacing a phenyl group with a cyclohexyl (**125**) or a 4-fluoro benzyl (**131**) group eliminated activity. The activity of compounds containing a hydrogen or a 4-fluoro substituent (**1**, **99**, **127**) on the benzhydrol portion of the molecule was comparable when the aryloxy segment contained the 4-acetyl-2-methoxyphenoxy group. However, when the aryloxy segment was 4-(methoxycarbonyl)-phenoxy, the 4-fluoro-substituted compound (**172**) was clearly superior in activity to the unsubstituted benzhydrol (**173**).

The alkyl chain length between the benzhydrol-substituted piperidine portion of the molecule and the aryloxy portion was varied (Table VI) from two to six carbon atoms (**135**, **1**, **136–138**). Compounds containing three (**1**) or four (**136**) carbon atoms had comparable activity and were superior to the analogues containing two (**135**), five (**137**), or six (**138**) carbon atoms when the aryloxy substituent was 4-acetyl-2-methoxyphenoxy. When the aryloxy substituent was 4-(methoxycarbonyl)phenoxy, the compound containing a three-carbon chain (**172**) was more potent than the analogue containing a four-carbon chain (**174**). From these data it appears that the three-carbon chain length is necessary for optimal activity. Addition of a hydroxyl group to the three-carbon chain gave **191** (Chart II), which had decreased activity when compared to **1**. Compound

Table III. Oral Antiallergy Activity (1-h Pretreatment) in the Passive Foot Anaphylaxis (PFA) Assay of Various Secondary Amines



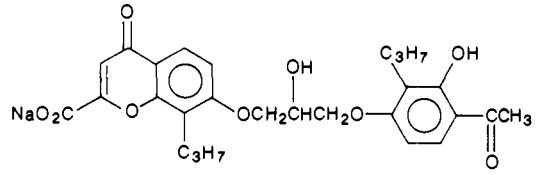
no.	R[a]	formula[b]	mp, °C (solv)[c]	% yield	PFA (mg/kg)[d] 10	3.16	1.0
94		$C_{17}H_{25}NO_3 \cdot C_4H_4O_4$[e]	138–139 (n)	77	–		
95		$C_{24}H_{29}NO_4$	87–89 (n)	66	++	–	
96		$C_{24}H_{31}NO_4$	118–119.5 (n)	64	–		
97		$C_{24}H_{31}NO_3 \cdot C_4H_4O_4$[h]	136–138 (op)	60	–		
98		$C_{23}H_{29}NO_3 \cdot HCl$	179–180.5 (op)	82	–		
99		$C_{30}H_{35}NO_4 \cdot C_2H_2O_4$	174–176 (q)	39	+++	++	–
100		$C_{31}H_{37}NO_4 \cdot C_2H_2O_4$	162.5–164.5 dec (r)	71	+++	+	–
101		$C_{31}H_{34}N_2O_3 \cdot C_2H_2O_4$	226–227 dec (o)	52	–		
102		$C_{31}H_{36}N_2O_4 \cdot 0.5C_4H_4O_4 \cdot H_2O$[e]	211–213 (op)	32	–		
103		$C_{30}H_{33}NO_3 \cdot C_2H_2O_4$	176–178 dec (q)	40	+++	++	–
104		$C_{30}H_{35}NO_3 \cdot C_2H_2O_4$	153–155 (q)	64	++	–	
105		$C_{23}H_{28}N_2O_4 \cdot C_2H_2O_4$	174–175 dec (r)	63	–		
106		$C_{23}H_{30}N_2O_3 \cdot 2C_4H_4O_4$[h]	199–200 (rs)	80	–		
107		$C_{22}H_{28}N_2O_3$	90–92 (n)	73	++	–	
108		$C_{29}H_{34}N_2O_3 \cdot 2C_4H_4O_4$[h]	156–157 (n)	58	++	–	

[a] Secondary amines used as starting materials can be purchased, prepared by literature procedures, or synthesized as described in the Experimental Section. [b] All compounds were analyzed for C, H, and N, and results agreed to ±0.4% of theoretical values. [c] n = 2-propanol, o = methanol, p = ethyl ether, q = 4-methyl-2-pentanone, r = ethanol, s = water. [d] Aminophylline orally at 100 mg/kg was used as a positive control; (–) not significantly different from negative control group at $p < 0.05$ as determined by the Dunnett's t test; (+) activity between positive and negative control groups; (++) activity equivalent to positive control group; (+++) activity greater than positive control group. [e] Fumarate. [f] Reference 3. [g] Reference 17. [h] Maleate. [i] Reference 4. [j] Reference 13. [k] Reference 14. [l] Reference 18. [m] Reference 19.

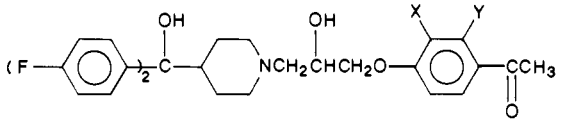
191 had only borderline activity at 10 mg/kg in the PFA assay. Another compound prepared containing a hydroxylated three-carbon chain was **192** (Chart II), which has the same substitution pattern as **190** (FPL-55712). Compound **190** was reported[25] to possess antiallergic properties. At 10 mg/kg, both **190** and **192** were inactive in the PFA assay.

Substituents on the aryloxy portion of **1** did affect activity (Table VI), but in general this portion of the molecule was less sensitive to change than the benzhydrol portion. A wide variety of substituents gave active compounds, but no obvious correlation with electronic, partition, or steric parameters was observed. By use of the unsubstituted analogue, **109**, as a reference, no compound

Chart II



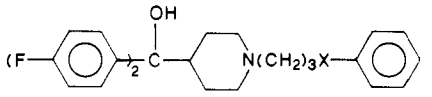
190 (FPL 55712)



191: X = OCH_3; Y = H
192: X = C_3H_7; Y = OH

(22) Fleming, R. W.; Hauck, F. P., Jr. Belg. Patent 668 124, 1965; *Chem. Abstr.* **1966**, *65*, 3801c.
(23) Boddeley, G.; Bennett, G. M. *J. Chem. Soc.* **1933**, 46–48.
(24) Braun, J.; Lotz, R.; Warne, K. C.; Pinkernelle, W.; Rohland, W.; Pohl, A.; Dengel, F.; Arnold, H. *Chem. Ber.* **1937**, *70B*, 979–993.
(25) Sneddon, J. M. *Drugs Future* **1982**, *7*, 472–477.

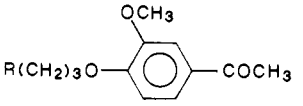
Table IV. Oral Antiallergy Activity (1-h Pretreatment) in the Passive Foot Anaphylaxis (PFA) Assay of Compounds Containing Varied Heteroatoms

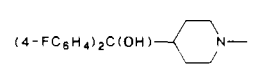
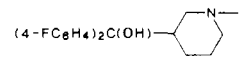
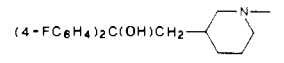
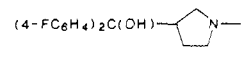
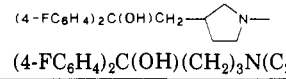


no.	X[a]	formula[b]	mp, °C (solv)[c]	method of prep[d]	% yield	PFA (mg/kg)[e] 10	3.16	1.0
109	O	$C_{27}H_{29}F_2NO_2 \cdot C_2H_2O_4$	151–153 (kl)	BB	66	+++	++	-
110		$C_{30}H_{33}F_2NO_3 \cdot C_2H_2O_4$	219–220 dec (mn)	BB	70	+	-	
111	C(=O)	$C_{28}H_{29}F_2NO_2 \cdot C_4H_4O_4$[g]	166–167 (o)	JJ	72	-		
112	CHOH	$C_{28}H_{31}F_2NO_2 \cdot C_2H_2O_4$	114–119 dec (p)	KK	61	+	+	-
113	CH_2	$C_{28}H_{31}F_2NO$	112–113 (p)	BB	25	+	-	
114	S	$C_{27}H_{29}F_2NOS \cdot C_2H_2O_4$	159–161 (p)	BB	76	+	-	
115	SO_2[h]	$C_{27}H_{29}F_2NO_3S$	138–140 (p)	BB	76	-		
116	NH	$C_{27}H_{30}F_2N_2O \cdot 2C_2H_2O_4$	136–138 (p)	MM	45	+	+	-
117	NCH_3[i]	$C_{28}H_{32}F_2N_2O \cdot 2C_2H_2O_4 \cdot 0.5H_2O$	115–117 (kp)	CC	52	+	+	-

[a] Substituted chloroalkanes used as starting materials can be purchased or prepared by literature procedures. [b] All compounds were analyzed for C, H, and N, and results agreed to ±0.4% of theoretical values. [c] k = methanol, l = ethyl ether, m = ethanol, n = water, o = acetonitrile, p = 2-propanol. [d] Letters refer to methods of preparation described in the Experimental Section. [e] Aminophylline orally at 100 mg/kg was used as a positive control; (-) not significantly different from negative control group at $p < 0.05$ as determined by the Dunnett's t test; (+) activity between positive and negative control groups; (++) activity equivalent to positive control group; (+++) activity greater than positive control group. [f] Reference 22. [g] Fumarate. [h] Reference 23. [i] Reference 24.

Table V. Oral Antiallergy Activity (1-h Pretreatment) in the Passive Foot Anaphylaxis (PFA) Assay of Various Piperidine and Pyrrolidine Derivatives



no.	R	formula[a]	mp, °C (solv)[b]	% yield	PFA (mg/kg)[c] 10	3.16	1.0
1		$C_{30}H_{33}F_2NO_4$	147–149 (k)	75	+++	++	-
118		$C_{31}H_{35}F_2NO_4 \cdot C_4H_4O_4$[d]$\cdot H_2O$	135–136 (lm)	65	-		
119		$C_{30}H_{33}F_2NO_4$	101–105 (k)	78	-		
120		$C_{31}H_{35}F_2NO_4 \cdot C_4H_4O_4$[d]	133–136 (mo)	35	-		
121		$C_{29}H_{31}F_2NO_4 \cdot 0.05CH_2Cl_2$[e]	44–46	34	-		
122		$C_{30}H_{33}F_2NO_4$	oil	46	-		
123	$(4\text{-}FC_6H_4)_2C(OH)(CH_2)_3N(C_2H_5)$	$C_{30}H_{35}F_2NO_4$	oil	80	-		

[a] All compounds were analyzed for C, H, and N, and results agreed to ±0.4% of theoretical values. [b] k = 2-propanol, l = methanol, m = ethyl ether, n = ethyl acetate, o = acetonitrile. [c] Aminophylline orally at 100 mg/kg was used as a positive control; (-) not significantly different from negative control group at $p < 0.05$ as determined by the Dunnett's t test; (+) activity between positive and negative control groups; (++) activity equivalent to positive control group; (+++) activity greater than positive control group. [d] Fumarate. [e] ^1H NMR confirms 0.05 mol of methylene chloride present.

substituted in the ortho or meta position of the aryloxy group was more potent than **109**. At 10 mg/kg generally ortho-substituted compounds (**141–149**) showed greater activity than did meta-substituted compounds (**140**, **150–153**). Certain substituents in the para position eliminated activity. Substitution by halogens (**154**, **155**), large alkyl groups (**159**, **160**), cyano (**176**), and nitro (**183**) led to compounds inactive at 10 mg/kg. Substituents that resulted in compounds equipotent with **109** were methyl (**156**), acetyl (**166**), propionyl (**167**), acetylamino (**185**), and (ethylcarboxy)amino (**186**). The most potent compounds in Table VI were ones substituted in the para position with carboxy (**175**) or carboxy ester groups (**171**, **172**).

Secondary antiallergy testing was done in a classical model of immediate hypersensity, the guinea pig anaphylaxis (GPA) assay.[26] Table VII shows a comparison of four of the most potent compounds from this series with oxatomide and terfenadine. Compounds were screened in the GPA model at three pretreatment times: 1-h pretreatment is an indication of rapid onset of action, 5-h pretreatment is approximately peak effect for this series of compounds, and 24-h pretreatment is an indication of duration of action. The inhibition of tritiated mepyramine binding gives an indication of intrinsic H_1-antihistaminic activity. In the PFA assay, **1**, **99**, **171**, and **172** had excellent activity at 3.16 mg/kg while oxatomide and terfenadine were inactive. In the GPA assay all compounds showed good activity at 1-h pretreatment time, while at 5 h oxatomide was about 3 times less potent and terfe-

(26) Yanni, J. M.; Foxwell, M. H. *Int. Arch. Allergy Appl. Immunol.* **1988**, *85*, 428–433.

nadine about 10 times less potent than **1**, **99**, **171**, or **172**. At 24-h pretreatment **171** was the most potent compound. Compound 1 and oxatomide were equipotent in their ability to displace tritiated mepyramine from a histamine H_1 receptor.

Compound 1, AHR-5333, has been selected for development as an antiallergy agent and is now in phase I clinical studies. The effects of 1 in in vivo models of immediate hypersensitivity have been reported.[26]

Experimental Section

Pharmacology. A. Primary Antiallergy Screen. A passive foot anaphylaxis model[2] in rats was used as the primary test for antiallergy activity. Fed, male, Sprague–Dawley rats were injected in the right hind paw with 0.2 mL of rat anti egg albumin serum at a dilution previously shown to produce significant edema upon antigen challenge. The animals were then fasted but allowed water ad libitum. The next day they were randomized into groups of six by means of tables generated by the IBM scrambler. Random-number tables were also used to determine the groups receiving the control, reference, and test compounds.

On the test day the right foot volume of each rat was determined plethysmographically; the hairline was used as the reference point. The volume of the foot was measured with a mercury filled tube that was connected to a P23A Grass pressure transducer that in turn was connected to a Linear Cole-Parmer recorder (Model No. 255). The instrument was adjusted so that a pen deflection of 25 mm was equivalent to a 1-mL volume.

The reference, test, and control compounds were dissolved or suspended in 0.5% Tween 80 in distilled water. Sonification was used to facilitate solubilization or reduction in particle size. The animals were dosed orally (10 mL/kg) by gavage 1 h prior to the intravenous injection of the antigen: 2 mg of egg albumin in 0.2 mL of sterile saline. Thirty minutes later the foot volume of the right foot was measured again, and edema was determined by difference. Results were expressed as the average foot edema (mL) ± SD. A significant decrease ($p < 0.05$) in the edema of the treated group from that of the control group was considered as indicative of antiallergic activity. The results were acceptable only if the group receiving the reference compound showed a significant decrease in foot edema. The data were analyzed with the Dunnett's t test that compares several treated groups with a control group. Differences between groups were determined by the Studentized Range Test. Regression analysis was used to determine relative potency.

B. Secondary Antiallergy Screen. Secondary antiallegy testing of selected compounds was done in the guinea pig anaphylaxis (GPA) model. Guinea pigs were actively sensitized to egg albumin (EA, Sigma Chemical Co., St. Louis, MO) at least 20 days prior to aerosol challenge by injecting 0.5 mL of EA–$Al(OH)_3$ conjugate (33 μg of EA/mL) intramuscularly in each hind leg.

On the test day, fasted, sensitized, Dunkin–Hartley guinea pigs were randomized by using random-number tables generated by an IBM scrambler into control ($N = 8$) and test ($N = 4$) groups. The control group was always labeled group I. The order in which compounds were administered to the other groups was also determined by random-number tables from the IBM scrambler.

The reference (theophylline at 100 mg/kg, po), test, and control compounds were dissolved or suspended in 0.5% Tween 80 in distilled water, and the concentration was adjusted so that each animal received 10 mL/kg. Compounds were administered by gavage with syringes having rubber catheters attached to their tip.

At a specified time (1–24 h) following the administration of the test, reference, or control compound, each animal was placed in an aerosolization chamber. A 1% solution (w/v) of EA was aerosolized at a flow rate of 10 L of air/min into the chamber for a maximum of 5 min. An electronic timer was started when the aerosolization began. The anaphylactic response consisted of coughing, dyspnea, reeling, collapse, and death. Upon collapsing, the animals were removed from the chamber. The chamber was then flooded with air before the next animal was placed inside. Animals were considered protected if they did not collapse within 5 min of exposure to the aerosolized antigen. The number of animals that collapse in each group is recorded. PD_{50} for collapse is calculated by the method of Litchfield and Wilcoxon[27] for evaluation of dose–effect experiments.

Comparisons of PD_{50}s from different experimental trials and determinations of relative potency are determined by the Litchfield and Wilcoxon method. The following conditions were met before an experiment was acceptable.

1. The control group showed collapse in 7/8 or 8/8 animals.
2. The theophylline referece group showed protection in 3/4 or 4/4 animals.

A compound was judged active if it showed protection in 3/4 or 4/4 animals.

The decision to accept a compound for further study was based on the Fisher's Exact 2 × 2 test. The χ^2 test was used to test similarity between control groups to allow pooling of data.

C. Tritiated Mepyramine Binding to H_1 Histamine Receptors in Guinea Pig Cerebral Cortex. 1. Preparation of Cerebral Cortical Membrane. The procedure was a modification of procedures reported by Wallace and Young[28] and Chang et al.[29] Dunkin–Hartley guinea pigs were killed by decapitation, and the cerebral cortex was quickly removed and weighed. The cerebral cortex was placed in 30 volumes of cold 50 mM Na–K phosphate (pH 7.5) buffer and then processed in a polytron homogenizer for 30 s at a power setting of 6. The homogenate was centrifuged at 48000g for 10 min at 4 °C, and the resultant pellet was resuspended in 30 volumes of fresh buffer. The centrifugation and suspension procedure was repeated twice, and the final pellet was suspended in 30 mL of buffer/g of wet tissue.

2. Procedure for Ligand Binding Assay. Test and reference compounds were dissolved in buffer or the appropriate vehicles at a concentration of 1×10^{-3} M. The assay mixtures consisted of 100 μL of 15 nM tritiated mepyramine (1.5 nM final concentration); 100 μL of test, control, or reference compound; and 800 μL of membrane preparation for a total volume of 1.0 mL. The assay mixture was incubated for 20 min at 25 °C. The reaction was stopped when the assay mixture was washed (3 × 5 mL) with cold buffer and filtered through GF/B glass-fiber filters. The filters were then transferred to vials; scintillation cocktail was added; and the radioactivity in each vial was determined by liquid scintillation counting.

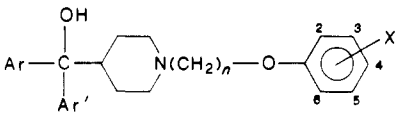
For the determination of an IC_{50} value, six concentrations (1×10^{-5} to 1×10^{-10} M) of the various compounds were tested in triplicate. An IC_{50} value was calculated by means of regression analysis of the logits of the percent of control binding vs the log of the molar compound concentration.

General Procedures. Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected; ^1H NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as internal standard on a Varian A-60 or Varian EM-360L spectrometer; ^{13}C NMR spectra were obtained in the same solvents on a Varian FT-80A spectrometer; mass spectra were determined on a Varian MAT-44 mass spectrometer; IR spectra were run as KBr pellets on a Beckman IR8 or Perkin-Elmer 297 IR spectrophotometer. Spectral data for all reported compounds were consistent with assigned structures. Purification were done by column chromatography on silica gel or Florisil and by high-pressure liquid chromatography with use of a Waters Prep LC-500A apparatus with a PrepPAK-500 silica cartridge. Analytical results for compounds followed by elemental symbols are within ±0.4% of theory and were determined on a Perkin-Elmer Model 240 CHN analyzer. Oxatomide was obtained from Janssen Pharmaceutica, Inc. and terfenadine was obtained from Merrell Dow Pharmaceuticals, Inc.

Method A. General Procedure for the Preparation of (Aryloxy)chloroalkanes (Table I). A mixture of 0.5 mol of a substituted phenol, 1 mol of the appropriate bromochloroalkane, and 207.3 (1.5 mol) of anhydrous K_2CO_3 in 1.5 L of acetone was heated at reflux with mechanical stirring for 24 h. The mixture was cooled to ambient temperature and filtered. The filtrate was

(27) Litchfield, J. T., Jr.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99–113.
(28) Wallace, R. M.; Young, J. M. *Mol. Pharmacol.* **1983**, *23*, 60–66.
(29) Chang, R. S. L.; Tran, V. T.; Snyder, S. H. *Eur. J. Pharmacol.* **1978**, *48*, 463–464.

Table VI. Oral Antiallergy Activity (1-h Pretreatment) in the Passive Foot Anaphylaxis (PFA) Assay of 1 (AHR-5333) and Analogues



no.	Ar	Ar′	*n*	X	formula[a]	mp, °C (solv)[b]	method of prep[c]	% yield	PFA (mg/kg)[d] 10	3.16	1.0	0.5
124	C_6H_5	C_6H_5	3	H	$C_{27}H_{31}NO_2$	87–88 (k)	BB	53	++	–		
99	C_6H_5	C_6H_5	3	2-OCH_3, 4-$COCH_3$	$C_{30}H_{35}NO_4 \cdot C_2H_2O_4$	174–176 (l)	CC	37	+++	+++	–	
125	C_6H_5	C_6H_{11}[e]	3	2-OCH_3, 4-$COCH_3$	$C_{30}H_{41}NO_4 \cdot HCl$	152–155 (l)	CC	54	–			
126	C_6H_5	3-$CF_3C_6H_4$	3	2-OCH_3, 4-$COCH_3$	$C_{31}H_{34}F_3NO_4 \cdot HCl \cdot 0.5H_2O$	95	CC	25	–			
127	C_6H_5	4-FC_6H_4	3	2-OCH_3, 4-$COCH_3$	$C_{30}H_{34}FNO_4$	147–148 (m)	CC	28	+++	++	–	
128	3-FC_6H_4	3-FC_6H_4	3	2-OCH_3, 4-$COCH_3$	$C_{30}H_{33}F_2NO_4$	149–151 (m)	BB	71	–			
1	4-FC_6H_4	4-FC_6H_4	3	2-OCH_3, 4-$COCH_3$	$C_{30}H_{33}F_2NO_4$	147–149 (k)	BB	75	+++	++	–	
129	3,4-$F_2C_6H_3$	3,4-$F_2C_6H_3$	3	2-OCH_3, 4-$COCH_3$	$C_{30}H_{31}F_4NO_4$	143–146 (k)	BB	48	–			
130	4-FC_6H_4	2-C_5H_4N[f]	3	2-OCH_3, 4-$COCH_3$	$C_{29}H_{33}FN_2O_4 \cdot 0.1CH_2Cl_2$[g]	oil	BB	24	+++	+	–	
131	4-FC_6H_4	4-$FC_6H_4CH_2$	3	2-OCH_3, 4-$COCH_3$	$C_{31}H_{35}F_2NO_4$	oil	BB	64	–			
132	4-ClC_6H_4	4-ClC_6H_4	3	2-OCH_3, 4-$COCH_3$	$C_{30}H_{33}Cl_2NO_4 \cdot 1.5C_2H_2O_4$	89–113 dec (m)	BB	30	–			
133	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3	2-OCH_3, 4-$COCH_3$	$C_{32}H_{39}NO_4 \cdot C_2H_2O_4 \cdot H_2O$	92–95 dec (m)	BB	58	–			
134	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	3	2-OCH_3, 4-$COCH_3$	$C_{32}H_{39}NO_6 \cdot C_2H_2O_4$	139–142 dec (m)	BB	53	–			
135	4-FC_6H_4	4-FC_6H_4	2	2-OCH_3, 4-$COCH_3$	$C_{29}H_{31}F_2NO_4$	131–135 (k)	BB	22	++	–		
136	4-FC_6H_4	4-FC_6H_4	4	2-OCH_3, 4-$COCH_3$	$C_{31}H_{35}F_2NO_4$	104–105 (kn)	CC	15	+++	++	–	
137	4-FC_6H_4	4-FC_6H_4	5	2-OCH_3, 4-$COCH_3$	$C_{32}H_{37}F_2NO_4$	117.5–118.5 (k)	BB	65	+	+	–	
138	4-FC_6H_4	4-FC_6H_4	6	2-OCH_3, 4-$COCH_3$	$C_{33}H_{39}F_2NO_4 \cdot HCl$	182–186 dec	BB	17	–			
139	4-FC_6H_4	4-FC_6H_4	3	2-CH_3, 4-$COCH_3$	$C_{30}H_{33}F_2NO_3$	116–117 (k)	BB	76	+	–		
140	4-FC_6H_4	4-FC_6H_4	3	3-OCH_3, 4-$COCH_3$	$C_{30}H_{33}F_2NO_4 \cdot HCl$	196–197 (kn)	BB	40	+	–		
109	4-FC_6H_4	4-FC_6H_4	3	H	$C_{27}H_{29}F_2NO_2 \cdot C_2H_2O_4$	151–153 (op)	BB	24	+++	++	–	
141	4-FC_6H_4	4-FC_6H_4	3	2-CH_3	$C_{28}H_{31}F_2NO_2$	108.5–109 (q)	BB	56	+	–		
142	4-FC_6H_4	4-FC_6H_4	3	2-OCH_3	$C_{28}H_{31}F_2NO_3$	127–128 (k)	BB	66	+++	+	+	–
143	4-FC_6H_4	4-FC_6H_4	3	2-OC_2H_5	$C_{29}H_{33}F_2NO_3$	89–91 (q)	BB	75	+++	+	–	
144	4-FC_6H_4	4-FC_6H_4	3	2-$OCH(CH_3)_2$	$C_{30}H_{35}F_2NO_3$	75–79 (n)	BB	58	++	+	+	–
145	4-FC_6H_4	4-FC_6H_4	3	2-$OCH_2C_6H_5$	$C_{34}H_{35}F_2NO_3 \cdot C_4H_4O_4$[h]	172–174 (r)	BB	64	+	–		
146	4-FC_6H_4	4-FC_6H_4	3	2-OH	$C_{27}H_{29}F_2NO_3 \cdot C_4H_4O_4$[h]$\cdot$ EtOAc[g]	106–116 dec (s)	DD	32	++	–		
147	4-FC_6H_4	4-FC_6H_4	3	2,6-$(OCH_3)_2$	$C_{29}H_{33}F_2NO_4$	136–137 (kn)	BB	40	+	–		
148	4-FC_6H_4	4-FC_6H_4	3	2-$COCH_3$	$C_{29}H_{31}F_2NO_3$	113–114 (k)	BB	71	+	–		
149	4-FC_6H_4	4-FC_6H_4	3	2-$CO_2C_2H_5$	$C_{30}H_{33}F_2NO_4 \cdot 0.75C_4H_4O_4$[h]	138–141 (k)	CC	32	+	+	–	
150	4-FC_6H_4	4-FC_6H_4	3	3-CH_3	$C_{28}H_{31}F_2NO_2$	112.5–114 (k)	BB	62	+	+	–	
151	4-FC_6H_4	4-FC_6H_4	3	3-OCH_3	$C_{28}H_{31}F_2NO_3$	107–108 (k)	BB	66	+	–		
152	4-FC_6H_4	4-FC_6H_4	3	3-$COCH_3$	$C_{29}H_{31}F_2NO_3 \cdot C_2H_2O_4 \cdot H_2O$	95–100 (k)	BB	75	+	–		
153	4-FC_6H_4	4-FC_6H_4	3	3-$CO_2C_2H_5$	$C_{30}H_{33}F_2NO_4 \cdot C_4H_4O_4$[h]	123–131 (r)	CC	67	+	–		
154	4-FC_6H_4	4-FC_6H_4	3	4-F	$C_{27}H_{28}F_3NO_2 \cdot C_4H_4O_4$[h]$\cdot H_2O$	155–157 (k)	BB	39	–			
155	4-FC_6H_4	4-FC_6H_4	3	4-Cl	$C_{27}H_{28}ClF_2NO_2$	92–93 (k)	BB	36	–			
156	4-FC_6H_4	4-FC_6H_4	3	4-CH_3	$C_{28}H_{31}F_2NO_2 \cdot C_4H_4O_4$[h]	193–194 (m)	BB	56	++	++	–	
157	4-FC_6H_4	4-FC_6H_4	3	4-C_2H_5	$C_{29}H_{33}F_2NO_2 \cdot C_2H_2O_4$	132–135 (k)	BB	54	++	+	–	
158	4-FC_6H_4	4-FC_6H_4	3	4-$CH(CH_3)_2$	$C_{30}H_{35}F_2NO_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$	105–109 dec (s)	BB	54	+	–		
159	4-FC_6H_4	4-FC_6H_4	3	4-$C(CH_3)_3$	$C_{31}H_{37}F_2NO_2$	126–127 (k)	BB	41	–			
160	4-FC_6H_4	4-FC_6H_4	3	4-C_6H_5	$C_{33}H_{33}F_2NO_2$	108–109 (k)	BB	69	–			
161	4-FC_6H_4	4-FC_6H_4	3	4-OCH_3	$C_{28}H_{31}F_2NO_3$	107–108 (k)	BB	49	++	–		
162	4-FC_6H_4	4-FC_6H_4	3	4-SCH_3	$C_{28}H_{31}F_2NO_2S$	113–115 (n)	BB	48	++	–		
163	4-FC_6H_4	4-FC_6H_4	3	4-$SOCH_3$	$C_{28}H_{31}F_2NO_3S \cdot C_2H_2O_4 \cdot 1.5H_2O \cdot 0.5i$-PrOH[g]	75–105 dec (k)	BB	40	+	–		
164	4-FC_6H_4	4-FC_6H_4	3	4-SO_2CH_3	$C_{28}H_{31}F_2NO_4S \cdot C_4H_4O_4$[h]	176–178 (r)	BB	48	++	–		
165	4-FC_6H_4	4-FC_6H_4	3	4-SO_2NH_2	$C_{27}H_{30}F_2N_2O_4S \cdot HCl$	152–175 (m)	BB	64	+	–		

Table VI (Continued)

no.	Ar	Ar′	n	X	formula[a]	mp, °C (solv)[b]	method of prep[c]	% yield	PFA (mg/kg)[d] 10	3.16	1.0	0.5
166	4-FC_6H_4	4-FC_6H_4	3	4-$COCH_3$	$C_{29}H_{31}F_2NO_3$·*i*-PrOH[g]	72–84 (k)	BB	71	+++	++	–	
167	4-FC_6H_4	4-FC_6H_4	3	4-COC_2H_5	$C_{30}H_{33}F_2NO_3$·*i*-PrOH[g]	57–62 (k)	BB	76	+++	++	–	
168	4-FC_6H_4	4-FC_6H_4	3	4-$COCH(CH_3)_2$	$C_{31}H_{35}F_2NO_3$·$C_2H_2O_4$	159–161 (r)	BB	73	++	–		
169	4-FC_6H_4	4-FC_6H_4	3	4-$COC(CH_3)_3$	$C_{32}H_{37}F_2NO_3$·$C_4H_4O_4$[h]	162–182 dec (mr)	BB	61	++	–		
170	4-FC_6H_4	4-FC_6H_4	3	4-COC_6H_5	$C_{34}H_{33}F_2NO_3$·$C_4H_4O_4$[h]	200–201 dec (m)	BB	65	+	–		
171	4-FC_6H_4	4-FC_6H_4	3	4-$CO_2C_2H_5$	$C_{30}H_{33}F_2NO_4$·HCl	193.5–194.5 (k)	CC	49		+++	+	+
172	4-FC_6H_4	4-FC_6H_4	3	4-CO_2CH_3	$C_{29}H_{31}F_2NO_4$·$C_4H_4O_4$[h]	140–174 dec (r)	CC	68		+++	+	–
173	C_6H_5	C_6H_5	3	4-CO_2CH_3	$C_{29}H_{33}NO_4$	146–147 (r)	CC	74	–			
174	4-FC_6H_4	4-FC_6H_4	4	4-CO_2CH_3	$C_{30}H_{33}F_2NO_4$·$C_4H_4O_4$[h]	186–188 (rt)	CC	65	+	–		
175	4-FC_6H_4	4-FC_6H_4	3	4-CO_2H	$C_{28}H_{29}F_2NO_4$	132–138 dec (m)	EE	91		+	++	+
176	4-FC_6H_4	4-FC_6H_4	3	4-CN	$C_{28}H_{28}F_2N_2O_2$	107–108 (kn)	BB	30	–			
177	4-FC_6H_4	4-FC_6H_4	3	4-$CONH_2$	$C_{28}H_{30}F_2N_2O_3$	200–204 (m)	BB	63	+++	+	+	–
178	4-FC_6H_4	4-FC_6H_4	3	4-$CON(CH_3)_2$	$C_{30}H_{34}F_2N_2O_3$·$C_4H_4O_4$[h]	166–168 (ru)	BB	65	+++	+	–	
179	4-FC_6H_4	4-FC_6H_4	3	4-CH_2COCH_3	$C_{30}H_{33}F_2NO_3$·$C_2H_2O_4$·0.5EtOAc[g]	93–98 dec (s)	CC	43	+++	–		
180	4-FC_6H_4	4-FC_6H_4	3	4-CH_2CO_2H	$C_{29}H_{31}F_2NO_4$·0.5H_2O	113–121 dec (k)	EE	78	++	+	–	
181	4-FC_6H_4	4-FC_6H_4	3	4-$(CH_2)_2CO_2CH_3$	$C_{31}H_{35}F_2NO_4$·$C_4H_4O_4$[h]	122–129 dec (r)	CC	46	+++	+	+	–
182	4-FC_6H_4	4-FC_6H_4	3	4-$(CH_2)_2CO_2H$	$C_{30}H_{33}F_2NO_4$	131.5–133.5 (mr)	EE	78	+++	++	+	–
183	4-FC_6H_4	4-FC_6H_4	3	4-NO_2	$C_{27}H_{28}F_2N_2O_4$	93.5–94.5 (n)	BB	73	–			
184	4-FC_6H_4	4-FC_6H_4	3	4-NH_2	$C_{27}H_{30}F_2N_2O_2$·2$C_2H_2O_4$	136–139 dec (m)	FF	62	+++	+	–	
185	4-FC_6H_4	4-FC_6H_4	3	4-$NHCOCH_3$	$C_{29}H_{32}F_2N_2O_3$·HCl·H_2O	135–170 dec	BB	38	+++	++	–	
186	4-FC_6H_4	4-FC_6H_4	3	4-$NHCO_2C_2H_5$	$C_{30}H_{34}F_2N_2O_4$·$C_2H_2O_4$·1.5H_2O	70–90 (k)	CC	50	+++	++	–	
187	4-FC_6H_4	4-FC_6H_4	3	4-$NHCOCO_2C_2H_5$	$C_{31}H_{34}F_2N_2O_5$·0.5$C_4H_4O_4$[h]	215–216 dec (mu)	GG	33	–			
188	4-FC_6H_4	4-FC_6H_4	3	4-$NHCONHCH_3$	$C_{29}H_{33}F_2N_3O_3$	177–178 (k)	HH	31	++	–		
189	4-FC_6H_4	4-FC_6H_4	3	4-$NHSO_2CH_3$	$C_{28}H_{32}F_2N_2O_4S$·0.5$C_4H_4O_4$[h]·$CH_3OCH_2CH_2OH$[g]	153–156 (v)	II	61	+++	+	–	
oxatomide									+++	–		
terfenadine									–			

[a] All compounds were analyzed for C, H, and N, and results agreed to ±0.4% of theoretical values. [b] k = 2-propanol, l = 4-methyl-2-pentanone, m = ethanol, n = isopropyl ether, o = methanol, p = ethyl ether, q petroleum ether (60–110 °C), r = acetonitrile, s = ethyl acetate, t = *N*,*N*-dimethylformamide, u = water, v = 2-methoxyethanol. [c] Letters refer to methods of preparation described in the Experimental Section. [d] Aminophylline orally at 100 mg/kg was used as a positive control; (–) not significantly different from negative control group at $p < 0.05$ as determined by the Dunnett's *t* test; (+) activity between positive and negative control groups; (++) activity equivalent to positive control group; (+++) activity greater than positive control group. [e] Aryl group is replaced by a cyclohexyl group. [f] 2-Pyridyl group. [g] ^1H NMR confirms stated amount of solvent present. [h] Fumarate.

concentrated at 70 °C and 2 mm of Hg pressure to remove excess bromochloroalkane. The residue was dissolved in 500 mL of C_6H_6 and stirred for 2 h with KOH pellets to remove any unreacted phenol that was present. The mixture was filtered through Celite and the filtrate was concentrated to give the (aryloxy)chloroalkane. If the product was an oil, the structure was confirmed by NMR and mass spectroscopy and used without further purification. If the product was a solid, it was recrystallized from an appropriate solvent and a combustion analysis was obtained.

Method B. 1-(3-Chloropropoxy)-4-(methylsulfinyl)benzene (43). A mixture of 21.7 g (0.1 mol) of **42**, 18.5 g (0.12 mol) of $NaBO_3·4H_2O$,[30] and 150 mL of glacial CH_3CO_2H was stirred at ambient temperature overnight. The mixture was poured into 1.5 L of ice–H_2O and extracted twice with 250-mL portions of C_6H_6. The combined C_6H_6 extracts were washed once with H_2O, twice with a 2% NaOH solution, once with H_2O, and once with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on 350 g of silica gel with $CHCl_3$ as eluent to yield 11.3 g (49%) of **43** as a clear oil which was used without further purification.

Method C. 1-(3-Chloropropoxy)-4-(methylsulfonyl)benzene (44). To a solution of 21.7 g (0.1 mol) of **42** in 100 mL of $CHCl_3$ was cautiously added a slurry of 51.8 g (0.3 mol) of *m*-chloroperbenzoic acid in 450 mL of $CHCl_3$. The mixture was stirred at ambient temperature for 2 days and then filtered. The filtrate was washed successively with four portions of a solution comprised of 110 mL of saturated $NaHCO_3$, 110 mL of H_2O, and 30 mL of 20% NaOH and then once with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was triturated with petroleum ether (30–60 °C), the suspended solid collected by filtration, and the filter cake dried to yield 24.3 g (98%) of 44 as a white solid. An analytical sample, mp 84–86 °C, was recrystallized from 2-propanol. Anal. ($C_{10}H_{13}ClO_3S$) C, H, N.

Method D. 1-(Phenylmethyl)-4-piperidinecarboxylic Acid Ethyl Ester Hydrochloride (198). To a stirred mixture of 314.4

(30) McKillop, A.; Tarbin, J. A. *Tetrahedron Lett.* **1983**, *24*, 1505–1508.

Table VII. Oral Activity of Selected Compounds in the Passive Foot Anaphylaxis (PFA) Model in Rats and Guinea Pig Anaphylaxis (GPA) Model and Inhibition of Tritiated Mepyramine Binding Specific for H_1 Histamine Receptors

no.	PFA[a] (3.16 mg/kg)	GPA: PD_{50},[b] mg/kg (95% confidence limits) 1 h	5 h	24 h	inhibn of [^{3}H]mepyramine binding: IC_{50}, nM
1	++	1.78 (1.14–2.78)	0.18 (0.08–0.41)	0.78 (0.54–1.13)	8
99	+++	0.57 (0.25–1.31)	0.35 (0.18–0.67)	1.40 (0.51–3.75)	42
171	+++	1.0 (0.64–1.57)	0.44 (0.21–0.92)	0.37 (0.09–3.90)	956
172	+++	0.72 (0.38–1.37)	0.32 (0.21–0.48)	2.04 (1.13–3.67)	63
oxatomide	-	1.25 (0.40–4.0)	1.0 (0.45–2.2)	10.0 (4.35–23.0)	9
terfenadine	-	1.0 (0.7–1.5)	3.2[c] (1.4–7.3)	NT[d]	295

[a] Aminophylline orally at 100 mg/kg was used as a positive control; (-) not significantly different from negative control group at $p < 0.05$ as determined by the Dunnett's t test; (+) activity between positive and negative control groups; (++) activity equivalent to positive control group; (+++) activity greater than positive control group. [b] Dose that protects 50% of the guinea pigs from collapse. [c] 6-h pretreatment time. [d] Not tested.

g (2.0 mol) of ethyl isonipecotate and 265 g (2.5 mol) of anhydrous Na_2CO_3 in 2.5 L of absolute ethanol was added 350.6 g (2.05 mol) of benzyl bromide in a stream over a 20-min period. The mixture was stirred at ambient temperature overnight and filtered, and the filtrate was concentrated. The residue was dissolved in 2 L of CH_2Cl_2 and the solution was washed successively with 1 L of H_2O and 1 L of a 5% NaOH solution, dried (Na_2SO_4), and concentrated to give an oil. The oil was cautiously added to a solution of 2 L of anhydrous ethyl ether and 350 mL of absolute ethanol saturated with HCl gas. A solid crystallized and was collected by filtration, washed with ethyl ether, and dried to yield 454.2 g (80%) of **198**. An analytical sample, mp 154–155 °C, was prepared as a white solid from ethanol–ethyl ether. Anal. ($C_{15}H_{21}NO_2$·HCl) C, H, N.

1-(Phenylmethyl)-3-piperidinecarboxylic Acid Ethyl Ester Hydrobromide (199). With use of the above method, 35.4 g (0.225 mol) of (±)-ethyl nipecotate, 31.8 g (0.30 mol) of anhydrous Na_2CO_3, and 41 g (0.24 mol) of benzyl bromide in 350 mL of absolute ethanol gave 35 g (47%) of **199** as a white solid, mp 148–152 °C (2-propanol). Anal. ($C_{15}H_{21}NO_2$·HBr) C, H, N.

1-(Phenylmethyl)-3-pyrrolidineacetic Acid Ethyl Ester Ethanedioate (1:1) (193). Compound **193**, mp 130–132 °C (2-propanol), was prepared by a published[31] procedure. Anal. ($C_{15}H_{21}NO_2$·$C_2H_2O_4$) C, H, N.

Method E. α,α-Bis-(4-fluorophenyl)-1-(phenylmethyl)-4-piperidinemethanol (58). A Grignard solution was prepared by the addition of 96.3 g (0.55 mol) of 1-bromo-4-fluorobenzene in 250 mL of dry tetrahydrofuran (THF, freshly distilled from $LiAlH_4$) to a mixture of 12.2 g (0.5 mol) of Mg chips in 500 mL of dry THF under a N_2 atmosphere. After the reaction had subsided, the mixture was heated at reflux for 15 min and allowed to cool to ambient temperature to complete Grignard formation. To this solution was added 48.8 g (0.197 mol) of the base of **198** in 250 mL of dry THF in a stream. The solution was stirred at ambient temperature overnight and then poured into 2.5 L of a cold NH_4Cl solution. The mixture was extracted once with 500 mL and twice with 250 mL of CH_2Cl_2. The combined extracts were washed successively with one 250-mL portion of H_2O, one 250-mL portion of a 4% NaOH solution, one 250-mL portion of H_2O, and one 250-mL portion of brine, dried (Na_2SO_4), and concentrated. The residue was triturated with petroleum ether (30–60 °C), and a solid crystallized. The solid was collected by filtration and dried to yield 70.8 g (91%) of **58** as a white solid, mp 113–115 °C (ethyl ether–hexane). Anal. ($C_{25}H_{25}F_2NO$) C, H, N.

Method F. α,α-Bis(*p*-fluorophenyl)-4-piperidinemethanol (59). A solution of 31.2 g (0.079 mol) of **58** in 400 mL of absolute ethanol was hydrogenated at 50 psi and 70 °C over 0.5 tsp of 5% Pd/C over the weekend. The mixture was filtered, and the filtrate was concentrated. Methylene chloride was added to the residue and a solid crystallized. The mixture was diluted with petroleum ether (30–60 °C), and the solid was collected by filtration, washed with petroleum ether (30–60 °C), and dried to yield 22 g (92%) of **59** as a white solid, mp 159.5–160.5 °C (isopropyl ether–2-propanol). Anal. ($C_{18}H_{19}F_2NO$) C, H, N.

Method G. 1-Acetyl-α-cyclohexyl-α-phenyl-4-piperidinemethanol (51). A Grignard reagent was prepared from 282 g (1.72 mol) of bromocyclohexane and 39.7 g (1.72 mol) of Mg chips in 300 mL of anhydrous ethyl ether under a N_2 atmosphere. After the reaction had subsided, the mixture was heated at reflux for 0.5 h and then cooled to 10 °C with an ice bath. A solution of 143.5 g (0.62 mol) of 1-acetyl-4-benzoylpiperidine[3] in 600 mL of dry tetrahydrofuran was added dropwise at such a rate to maintain the temperature at 10 °C. After the addition was complete, the stirred reaction mixture was allowed to warm to ambient temperature and then poured onto a mixture of 1 kg of ice and 159 g (3 mol) of NH_4Cl. The layers were separated, and the organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated. The residue crystallized upon trituration with isopropyl ether. The solid was collected by filtration and recrystallized from ethyl acetate to yield 83.2 g (43%) of **51**, mp 153–155 °C. Anal. ($C_{20}H_{29}NO_2$) C, H, N.

Method H. α-Cyclohexyl-α-phenyl-4-piperidinemethanol (52). A solution of 25 g (0.08 mol) of **51**, 100 mL of 6 N NaOH, and 250 mL of ethanol was heated at reflux for 8 h. The solution was diluted with 500 mL of H_2O and extracted with C_6H_6. The organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was recrystallized from benzene–hexane to yield 11.0 g (51%) of **52**, mp 147–149 °C. Anal. ($C_{18}H_{27}NO$) H, N; C: calcd, 79.07; found, 78.56.

Method I. α-Phenyl-α-[3-(trifluoromethyl)phenyl]-4-piperidinemethanol (53). Compound **53** was prepared by methods G and H as above. By use of method G, a mixture of 419 g (1.86 mol) of 1-bromo-3-(trifluoromethyl)benzene, 45.5 g (1.9 mol) of Mg chips, and 143 g (0.62 mol) of 1-acetyl-4-benzoylpiperidine[3] in 300 mL of anhydrous ethyl ether and 500 mL of dry tetrahydrofuran gave a solid which was indicated by ^{1}H NMR analysis to be a mixture of the *N*-acetyl and NH compounds. By use of method H, this crude solid, 300 mL of ethanol, and 150 mL of 3 N NaOH heated at reflux for 16 h gave 78 g (53%) of **53**, mp 97–100 °C (methanol). Anal. ($C_{19}H_{20}F_3NO$) C, H, N.

Method J. α,α-Bis(4-fluorophenyl)-4-pyridineethanol (194). A solution of 27.8 g (0.30 mol) of 4-picoline in 400 mL of dry tetrahydrofuran (THF) under a N_2 atmosphere was cooled to −30 °C in a dry ice–acetone bath. A solution of 2.5 M of *n*-butyllithium in hexane (119 mL, 0.30 mol) was added over 1 h, and the mixture was stirred for an additional 30 min at −30 °C. The reaction mixture was allowed to warm to ambient temperature over 1.5 h, and 66.7 g (0.30 mol) of 4,4′-difluorobenzophenone in 100 mL of THF was added. The mixture was stirred for 2 h and then was poured into an icy solution of NH_4Cl. A white solid was collected. The aqueous mixture was extracted with several portions of CH_2Cl_2 and the CH_2Cl_2 was removed in

(31) Lindborg, B.; Crona, K.; Dahlbom, R. *Acta Pharm. Suec.* 1984, *21*, 271–294.

vacuo to give additional solid. The solid fractions were combined and recrystallized from a mixture of ether–hexane to give 63.1 g (68%) of **194** as a white, crystalline solid, mp 158–159.5 °C. Anal. ($C_{19}H_{15}F_2NO$) C, H, N.

Method K. α,α-Bis(4-fluorophenyl)-3-pyridineethanol (195). A Grignard solution was prepared from 19.4 g (0.8 mol) of Mg chips and 148.8 g (0.85 mol) of 1-bromo-3-fluorobenzene in 1.25 L of dry tetrahydrofuran (THF). To this solution was added in a stream a solution of 41.3 g (0.25 mol) of ethyl 3-pyridylacetate in 250 mL of THF. The mixture was stirred at ambient temperature overnight and then poured into 2.5 L of a saturated ammonium chloride solution. The layers were separated, and the aqueous layer was extracted once with 500 mL of CH_2Cl_2 and twice with 250 mL of CH_2Cl_2. The combined organic layers were washed successively with 250 mL of H_2O, 250 mL of a 4% NaOH solution, 250 mL of H_2O, and 250 mL of brine. The organic layer was dried (Na_2SO_4) and concentrated to give a gum which crystallized when triturated with a mixture of 100 mL of petroleum ether (30–60 °C) and 100 mL of isopropyl ether. The solid was collected by filtration, air-dried, and slurried with 500 mL of water. The solid was collected by filtration, dissolved in 300 mL of boiling 2-propanol, and filtered to remove insoluble material. The filtrate was concentrated, and recrystallization of the residue from cyclohexane–benzene afforded 24.3 g (31%) of **195** as an off-white solid, mp 137–141 °C. Anal. ($C_{19}H_{15}F_2NO$) C, H, N.

Method L. (4-Fluorophenyl)(4-pyridyl)methanone (84). To a cooled (ice bath) solution of 20.8 g (0.2 mol) of 4-cyanopyridine in 300 mL of dry tetrahydrofuran under a N_2 atmosphere was added 100 mL (0.2 mol) of a commercial solution of (4-fluorophenyl)magnesium bromide (2 M in ethyl ether). The mixture was heated at reflux for 6 h and then concentrated. The residue was treated with a mixture of 100 mL of concentrated HCl and ice. The mixture was made alkaline with a 5% NaOH solution and extracted with $CHCl_3$. The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated to give a brown oil. The oil was purified by flash column chromatography on silica gel with 40–50% ethyl acetate in hexane as eluent. The appropriate fractions were combined and concentrated to yield 25.8 g (64%) of **84** as a light-yellow solid, mp 85–88 °C. Anal. ($C_{12}H_8FNO$) C, H, N.

Method M. α,β-Bis(4-fluorophenyl)-α-4-pyridineethanol (196). A Grignard solution was prepared from 45.4 g (0.24 mol) of benzyl bromide and 5.8 g (0.24 mol) of Mg chips in 500 mL of dry tetrahydrofuran (THF) under a N_2 atmosphere. After the reaction had subsided, the mixture was heated at reflux for 4 h to complete formation. The solution was cooled to ambient temperature and treated dropwise with a solution of 40.2 g (0.2 mol) of **84** in 200 mL of THF. The mixture was stirred at ambient temperature for 16 h and then treated with 75 mL of aqueous NH_4Cl. The layers were separated, and the organic layer was concentrated. The residue was dissolved in $CHCl_3$ and the solution was washed with H_2O and 5% NaOH solution, dried (Na_2SO_4), and concentrated. The residue was triturated with isopropyl ether and cooled, and a brown solid was collected by filtration to yield 10.2 g (16%) of **196**. An analytical sample, mp 195.5–197.5 °C, was recrystallized from isopropyl ether–methylene chloride. Anal. ($C_{19}H_{15}F_2NO$) H, N; C: calcd, 73.30; found, 72.75.

Method N. α,α-Bis(4-fluorophenyl)-3-piperidineethanol Hydrochloride (79). A mixture of 23.8 g (0.076 mol) of **195** in 500 mL of glacial acetic acid was hydrogenated over 2.4 g of 5% Pt/C in a Parr apparatus for 24 h. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was partitioned between 300 mL of CH_2Cl_2 and 300 mL of a 5% NaOH solution, and a solid precipitated. The solid was collected by filtration and partitioned between 200 mL of CH_2Cl_2 and 150 mL of a 5% NaOH solution. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in ethyl ether and converted to the hydrochloride by treatment with ethereal HCl. The white solid was collected by filtration and dried to yield 19.2 g (71%) of **79**, mp 248 °C dec (absolute ethanol). Anal. ($C_{19}H_{21}F_2NO$·HCl) C, H, N.

Method O. 4-(Methoxydiphenylmethyl)-1-(phenylmethyl)piperidine (69). To a slurry of 3.8 g (0.033 mol) of a 35% dispersion of KH in oil in 100 mL of dry tetrahydrofuran (THF) under a N_2 atmosphere was added a solution of 9.9 g (0.027 mol) of **49** in 150 mL of dry THF. The mixture was stirred at ambient temperature for 1.5 h and then heated to reflux. The solution was cooled to ambient temperature and treated dropwise with a solution of 4.1 g (0.029 mol) of CH_3I in 50 mL of dry THF. The mixture was stirred overnight at ambient temperature, then treated with 5 mL of 2-propanol, stirred for 1 h, and filtered. The filtrate was concentrated, and the residue was recrystallized from isopropyl ether to yield 8.3 g (81%) of **69** as a white solid, mp 114–115 °C. Anal. ($C_{26}H_{29}NO$) C, H, N.

Method P. 4-Methylbenzenesulfonic Acid Ester with 1-[(4-Methylphenyl)sulfonyl]-4-piperidinol (85). A solution of 1.6 g (0.016 mol) of 4-hydroxypiperidine and 13.9 g (0.073 mol) of *p*-toluenesulfonyl chloride in 80 mL of pyridine was stirred at 25 °C overnight. The mixture was quenched in 200 mL of H_2O and the aqueous mixture was extracted with several portions of CH_2Cl_2. The combined CH_2Cl_2 layers were extracted successively with several portions of 1 M H_2SO_4 and 1 M NaOH and then were dried ($MgSO_4$). The solvent was removed under reduced pressure to give a solid, which was recrystallized from CH_2Cl_2-ethyl ether to yield 4.8 g (73%) of **85**, mp 140.5–141 °C. Anal. ($C_{19}H_{23}NO_5S_2$) C, H, N.

Method Q. 1-[(4-Methylphenyl)sulfonyl]-α,α-diphenyl-4-piperidineacetonitrile (71). To a slurry of 19.6 g (0.49 mol) of a washed (thrice with toluene), commercial preparation of 60% NaH/oil dispersion in 300 mL of dry toluene under a N_2 atmosphere was added a solution of 94.5 g (0.49 mol) of diphenylacetonitrile in 300 mL of toluene. The mixture was heated at reflux for 2 h, cooled to ambient temperature, and treated portionwise with 200 g (0.49 mol) of **85**. After addition was complete, the mixture was heated at reflux overnight. The mixture was concentrated, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed successively with a 5% NaOH solution, 1 N H_2SO_4, and 5% NaOH, dried ($MgSO_4$), and concentrated to give 194 g (92%) of a reddish-brown oil. The oil crystallized when triturated with toluene. The solid was collected by filtration. An analytical sample, mp 183–184 °C, was recrystallized from CH_2Cl_2–hexane as a white solid. Anal. ($C_{26}H_{26}N_2O_2S$) C, H, N.

Method R. α,α-Diphenyl-4-piperidineacetonitrile Ethanedioate (2:1) (72). A solution of 183.8 g (0.43 mol) of **71** and 150 g (1.6 mol) of phenol in 750 mL of 48% aqueous HBr was heated at reflux with vigorous mechanical stirring for 3.5 h. The mixture was cooled, made basic with 50% NaOH/ice, and extracted with $CHCl_3$. The organic layer was washed with 5% NaOH, dried (Na_2SO_4), and concentrated to give a red oil. The oil was converted to the oxalic acid salt to yield 81.4 g (59%) of **72** as a white solid, mp 275–276 °C (methanol–ethyl ether). Anal. ($C_{19}H_{20}N_2$·$0.5C_2H_2O_4$) C, H, N.

Method S. α,α-Diphenyl-4-piperidineacetamide (*E*)-2-Butenedioate (2:3) (73). A solution of 45.5 g (0.165 mol) of the base of **72**, 280 mL of concentrated H_2SO_4, and 30 mL of H_2O was heated overnight at 90 °C. The reaction was poured onto ice and cautiously made basic with 50% NaOH. The mixture was extracted several times with $CHCl_3$. The combined extracts were dried (Na_2SO_4) and concentrated to yield 32.4 g (67%) of an oil, which crystallized upon standing. A portion of the solid was converted to the fumaric acid salt to yield **73** as a white solid, mp 234–235 °C (methanol–ethyl ether). Anal. ($C_{19}H_{22}N_2O$·$1.5C_4H_4O_4$) C, H, N.

Method T. 1-[(Diethylamino)carbonyl]-4-piperidinecarboxylic Acid Ethyl Ester (86). To a stirred solution of 72.4 g (0.46 mol) of ethyl isonipecotate and 46.5 g (0.46 mol) of $(C_2H_5)_3N$ in 400 mL of CH_2Cl_2 was added dropwise a solution of 62.4 g (0.46 mol) of diethylcarbamoyl chloride in 100 mL of CH_2Cl_2. The mixture was stirred at ambient temperature overnight and then treated with 50 mL of H_2O. The layers were separated, and the organic layer was washed successively with two 25-mL portions of 2 N HCl, once with 50 mL of a saturated $NaHCO_3$ solution, and once with 100 mL of brine, dried (Na_2SO_4), and concentrated. Vacuum distillation of the residue afforded 100.6 g (85%) of **86** as a clear oil, bp 115–119 °C (0.2 mmHg). Anal. ($C_{13}H_{24}N_2O_3$) H, N; C: calcd, 60.91; found, 59.69.

Method U. 4-[Bis(4-chlorophenyl)hydroxymethyl]-*N*,*N*-diethyl-1-piperidinecarboxamide (63). A Grignard solution was prepared by the treatment of a slurry of 8.5 g (0.35 mol) of Mg chips in 200 mL of dry tetrahydrofuran (THF) with a solution of 72.8 g (0.38 mol) of 1-bromo-4-chlorobenzene in 400 mL of THF. After the addition was complete, the mixture was heated at reflux

for 15 min to complete formation. To the Grignard solution at ambient temperature was added in a stream a solution of 38.4 g (0.15 mol) of **86** in 200 mL of THF. The solution was stirred at ambient temperature overnight and poured into 2.5 L of a saturated NH_4Cl solution. The layers were separated, and the aqueous layer was extracted once with 500 mL of CH_2Cl_2 and once with 250 mL of CH_2Cl_2. The combined organic layers were filtered through Celite, and the filtrate was washed successively with 500 mL of H_2O, 750 mL of a 4% NaOH solution, 250 mL of H_2O, and 250 mL of brine. The solution was dried (Na_2SO_4) and concentrated under reduced pressure to give a gum, which gradually crystallized. The solid was triturated with petroleum ether (30–60 °C), collected by filtration, and dried to yield 56.7 g (87%) of **63** as a white solid. An analytical sample, mp 172–175 °C, was prepared from 2-propanol. Anal. ($C_{23}H_{28}Cl_2N_2O_2$) C, H, N.

Method V. α,α-Bis(4-chlorophenyl)-4-piperidinemethanol (64). To a slurry of 8.5 g (0.225 mol) of $LiAlH_4$ in 400 mL of anhydrous tetrahydrofuran (THF) was added in a stream a solution of 39.2 g (0.09 mol) of **63** in 400 mL of THF over a 15-min period. The mixture was heated at reflux for 24 h, cooled, and treated successively with 8.5 mL of H_2O, 25 mL of a 3 N NaOH solution, and 8.5 mL of H_2O. The mixture was stirred for 0.5 h and then filtered. The filtrate was concentrated, the residue was triturated with petroleum ether (30–60 °C), collected by filtration, and recrystallized from benzene to yield 10.5 g (35%) of **64** as a white solid. An analytical sample, mp 184–188 °C (lit.[32] mp 175–177 °C), was prepared from 2-propanol. Anal. ($C_{18}H_{19}Cl_2NO$) C, H, N.

Method W. 4-[Bis(4-fluorophenyl)hydroxymethyl]-1-(phenylmethyl)-2-pyrrolidinone (88). A Grignard solution was prepared by the addition of 96.3 g (0.55 mol) of 1-bromo-4-fluorobenzene in 150 mL of dry tetrahydrofuran (THF) to a mixture of 12.2 g (0.5 mol) of Mg chips in 250 mL of THF. After the reaction had subsided, the mixture was diluted with 350 mL of THF and heated at reflux for 15 min to complete formation. The Grignard solution was added to a solution of 46.7 g (0.2 mol) of **87**[33] in 250 mL of THF and the mixture was stirred at ambient temperature overnight. The solution was poured into 2.5 L of cold, aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted once with 500 mL of CH_2Cl_2 and once with 250 mL of CH_2Cl_2. The combined organic layers were washed once with 250 mL of H_2O, once with 250 mL of a 4% NaOH solution, once with 250 mL of H_2O, and once with 250 mL of brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue crystallized upon trituration with petroleum ether (30–60 °C). The solid was collected by filtration, washed with petroleum ether, and recrystallized from 2-propanol to yield 39.4 g (50%) of **88** as an off-white solid, mp 158–160 °C. Anal. ($C_{24}H_{21}F_2NO_2$) C, H, N.

Method X. α,α-Bis(4-fluorophenyl)-1-(phenylmethyl)-3-pyrrolidinemethanol (80). To a stirred slurry of 7.6 g (0.2 mol) of $LiAlH_4$ in 150 mL of freshly distilled tetrahydrofuran (THF) was added dropwise over a 45-min period a solution of 38.5 g (0.098 mol) of **88** in 150 mL of THF. After the addition was complete, the mixture was heated at reflux for 2 h and then stirred at ambient temperature overnight. The excess $LiAlH_4$ was decomposed by the successive addition of 8 mL of H_2O, 8 mL of a 15% NaOH solution, and 24 mL of H_2O. The mixture was stirred for 30 min and filtered. The filtrate was concentrated under reduced pressure, and the residue crystallized when triturated with petroleum ether (30–60 °C). The solid was collected by filtration and recrystallized from 2-propanol to yield 30.3 g (81%) of **80** as a white solid, mp 99–100 °C. Anal. ($C_{24}H_{23}F_2NO$) C, H, N.

Method Y. 4-[Ethyl(phenylmethyl)amino]butanoic Acid Ethyl Ester (91). A solution of 67.5 g (0.5 mol) of ethyl 4-bromobutyrate (**89**) in 250 mL of absolute ethanol was added dropwise to a stirred mixture of 97.4 g (0.5 mol) of *N*-ethylbenzylamine (**90**) and 265 g (2.5 mol) of anhydrous Na_2CO_3 in 1 L of absolute ethanol. The mixture was heated at reflux for 44 h and filtered, and the filtrate was concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated. The liquid residue was purified by vacuum distillation. The major fraction, bp 96–97 °C (0.20 mmHg), afforded 73.4 g (59%) of a clear liquid. A 22.0-g fraction of this liquid was further purified by column chromatography using 700 g of silica gel on a 30 cm × 10 cm column, eluted with 10% ethyl acetate in hexane solution. The desired fractions were combined and concentrated under pressure to yield 16.0 g of **91** as a clear liquid. Anal. ($C_{15}H_{23}NO_2$) C, H, N.

Method Z. α-[3-[Ethyl(phenylmethyl)amino]propyl]-4-fluoro-α-(4-fluorophenyl)benzenemethanol (92). A Grignard solution was prepared by the addition of 96.3 g (0.55 mol) of 1-bromo-4-fluorobenzene in 250 mL of dry (freshly distilled from $LiAlH_4$) tetrahydrofuran (THF) to a mixture of 12.2 g (0.45 mol) of Mg turnings in 500 mL of THF. To this Grignard reagent at ambient temperature was added in a stream of solution of 49.9 g (0.20 mol) of **91** in 250 mL of THF. The solution was stirred at ambient temperature for 16 h and then poured into 2.5 L of cold, aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted once with 500 mL of CH_2Cl_2 and twice with 250 mL of CH_2Cl_2. The combined organic layers were washed successively with 250 mL of H_2O, 250 mL of a 4% NaOH solution, 250 mL of H_2O, and 250 mL of brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give 76.2 g of an oil. An analysis of the oil by ^1H NMR indicated a 10:1 mixture of **92** and the monofluorophenyl ketone intermediate. Therefore, the oil was dissolved in 250 mL of dry THF and treated with 250 mL of a 1.1 M commercial preparation of (4-fluorophenyl)magnesium bromide in THF. The solution was stirred at ambient temperature for 16 h and then poured into 2 L of aqueous NH_4Cl and treated as above to give 77.5 g of an oil.

A 10.0-g fraction of this oil was purified by column chromatography using 300 g of silica gel on a 69 cm × 4 cm column eluted with 1% CH_3OH in CH_2Cl_2. The fractions containing the desired product were combined and concentrated under reduced pressure. The residue was partitioned between 200 mL of H_2O and 200 mL of ethyl ether. The ethyl ether layer was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 5.6 g (56% recovery) of **92** as a clear, viscous oil. Anal. ($C_{25}H_{27}F_2NO$) C, H, N.

Method AA. α-[3-(Ethylamino)propyl]-4-fluoro-α-(4-fluorophenyl)benzenemethanol (93). A solution of 11.0 g (0.028 mol) of **92** in 200 mL of 95% ethanol was added to a small Parr bottle along with 0.5 tsp of 10% Pd/C catalyst. The reaction mixture was hydrogenated at room temperature until 1 equiv of hydrogen had been used (~8 h). The solution was filtered through Celite and the filtrate concentrated under reduced pressure to yield a viscous, yellow oil which solidified upon standing. The solid was triturated with petroleum ether (30–60 °C) to yield 8.4 g (98%) of **93** as a white solid, mp 69–72 °C. Anal. ($C_{18}H_{21}F_2NO$) C, H, N.

Method BB. 1-[4-[3-[4-[Bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone (1). A stirred mixture of 9.1 g (0.03 mol) of **59**, 7.5 g (0.031 mol) of **3**, 15.9 g (0.15 mol) of anhydrous Na_2CO_3, and 0.4 g of KI in 250 mL of 1-butanol was heated at reflux for 20 h. The mixture was concentrated, and the residue was partitioned between C_6H_6 and H_2O. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue crystallized upon triturated with petroleum ether (30–60 °C). The solid was collected by filtration and recrystallized from 2-propanol to yield 11.4 (75%) of **1** as an off-white powder, mp 147–149 °C. Anal. ($C_{30}H_{33}F_2NO_4$) C, H, N.

Method CC. 4-[3-[4-[Bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]propoxy]benzoic Acid Methyl Ester (*E*)-2-Butenedioate (1:1) (172). A stirred mixture of 9.1 g (0.03 mol) of **59**, 6.7 g (0.03 mol) of **35**, 10.6 g (0.10 mol) of anhydrous Na_2CO_3, and 0.6 g of KI in 125 mL of *N*,*N*-dimethylformamide was heated on a steam bath for 24 h. The mixture was poured into 1.5 L of ice–H_2O, and the solid that precipitated was collected by filtration, washed with H_2O, and dried. The solid was converted to the fumaric acid salt, and this solid was recrystallized from CH_3CN to yield 12.5 g (68%) of **172** as a white solid, mp 140–174 °C dec. Anal. ($C_{29}H_{31}F_2NO_4 \cdot C_4H_4O_4$) C, H, N.

Method DD. α,α-Bis(4-fluorophenyl)-1-[3-(2-hydroxyphenoxy)propyl]-4-piperidinemethanol (*E*)-2-Butenedioate

(32) Zivkovic, D. Brit. Patent 1 542 823, 1979; *Chem. Abstr.* **1978**, *89*, 197340c.

(33) Sugden, J. K. *Pharm. Acta Helv.* **1974**, *49*, 268–269.

(1:1) **Ethyl Acetate (1:1) (146).** A solution of 6.1 g (0.011 mol) of the base of **145** dissolved in 200 mL of absolute ethanol was hydrogenated in a Parr apparatus over 0.25 tsp of 5% Pd/C at 60 °C overnight. The cooled mixture was filtered through Celite, and the filtrate was concentrated. The dark residue was dissolved in ethyl ether and filtered to remove insolubles. The filtrate was concentrated, and the residue was dissolved in ethyl acetate and mixed with an equivalent amount of fumaric acid dissolved in ethyl acetate. The solution was filtered and a solid crystallized from the filtrate. This solid was collected by filtration and dried to yield 2.3 g (32%) of **146** as a white solid, mp 106–116 °C dec. The presence of 1 mol of ethyl acetate was confirmed by ^{1}H NMR. Anal. ($C_{27}H_{29}F_2NO_3 \cdot C_4H_4O_4 \cdot C_4H_8O_2$) C, H, N.

Method EE. 4-[3-[4-[Bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]propoxy]benzeneacetic Acid Hemihydrate (180). A mixture of 3.7 g (0.0073 mol) of the base of **179**, 0.8 g (0.0145 mol) of KOH, 10 mL of H_2O, and 50 mL of 95% ethanol was heated at reflux under a N_2 atmosphere for 1.5 h. The solution was poured into a mixture of 1.3 g (0.022 mol) of glacial CH_3CO_2H in 500 mL of ice–water and let stand at ambient temperature overnight. The solid that had precipitated was collected by filtration, washed with H_2O, dried, and recrystallized from 2-propanol to yield 2.9 g (78%) of **180** as a white solid, mp 113–121 °C dec. Anal. ($C_{29}H_{31}F_2NO_4 \cdot 0.5H_2O$) C, H, N.

Method FF. 1-[3-(4-Aminophenoxy)propyl]-α,α-bis(4-fluorophenyl)-4-piperidinemethanol Ethanedioate (1:2) (184). A solution of 2.6 g (0.0054 mol) of **183** in 50 mL of tetrahydrofuran was hydrogenated at ambient temperature over 0.25 tsp of 5% Pd/C at 40 psi for 4 h. The mixture was filtered, and the filtrate was concentrated. The residue was converted to the dioxalic acid salt, and the solid was recrystallized from 95% ethanol to yield 2.1 g (62%) of **184** as an off-white solid, mp 136–139 °C dec. Anal. ($C_{27}H_{30}F_2N_2O_2 \cdot 2C_2H_2O_4$) C, H, N.

Method GG. [[4-[3-[4-[Bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]propoxy]phenyl]amino]oxoacetic Acid Ethyl Ester (*E*)-2-Butenedioate (2:1) (187). To a solution of 2.4 g (0.0054 mol) of the base of **184** and 1.5 g (0.015 mol) of $(C_2H_5)_3N$ in 50 mL of C_6H_6 was added dropwise a solution of 1.0 g (0.008 mol) of ethoxalyl chloride in 10 mL of C_6H_6. The mixture was stirred at ambient temperature overnight, then treated with 20 mL of H_2O, and vigorously stirred. The layers were separated, and the organic layer was washed with a saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. The residue was dissolved in ethyl ether and filtered to remove insolubles. The filtrate was concentrated, and the residue was converted to the fumaric acid salt. The salt was recrystallized from absolute ethanol–H_2O to yield 1.1 g (33%) of **187** as a white solid, mp 215–216 °C dec. Anal. ($C_{31}H_{34}F_2N_2O_5 \cdot 0.5C_4H_4O_4$) C, H, N.

Method HH. *N*-[4-[3-[4-[Bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]propoxy]phenyl]-*N'*-methylurea (188). To a solution of 4.5 g (0.01 mol) of the base of **184** in 50 mL of C_6H_6 was added dropwise a solution of 0.6 g (0.01 mol) of methyl isocyanate in 10 mL of C_6H_6. The mixture was stirred for 1 h during which time a solid precipitated. The mixture was diluted with 25 mL of cyclohexane, and the precipitate was collected by filtration and recrystallized from 2-propanol to yield 1.6 g (31%) of **188** as a white solid, mp 177–178 °C. Anal. ($C_{29}H_{33}F_2N_3O_3$) C, H, N.

Method II. *N*-[4-[3-[4-[Bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]propoxy]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1) 2-Methoxyethanol (1:1) (189). To a solution of 4.5 g (0.01 mol) of the base of **184** and 1.5 g (0.015 mol) of $(C_2H_5)_3N$ in 50 mL of C_6H_6 and 100 mL of ethyl acetate was added dropwise a solution of 1.2 g (0.01 mol) of methanesulfonyl chloride in 10 mL of C_6H_6. A gum immediately separated. The mixture was stirred at ambient temperature for 2 h, treated with a saturated $NaHCO_3$ solution, and then stirred for 0.5 h during which time all solids dissolved. The layers were separated, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was converted to a solid fumaric acid salt which was recrystallized from 2-methoxyethanol to yield 4.0 g (61%) of **189** as a tan solid, mp 153–156 °C dec. Anal. ($C_{28}H_{32}F_2N_2O_4S \cdot 0.5C_4H_4O_4 \cdot C_3H_8O_2$) C, H, N.

Method JJ. 4-[4-[Bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]-1-phenyl-1-butanone (*E*)-2-Butenedioate (1:1) (111). A solution of 9.8 g (0.02 mol) of the base of **110** in 200 mL of CH_3OH and 20 mL (0.02 mol) of 1 N HCl was stirred at ambient temperature for 4 days. The reaction mixture was poured into a solution of 10 mL (0.05 mol) of a 20% NaOH solution in 2 L of H_2O, and a solid precipitated. The solid was collected by filtration, air-dried, and slurried in 300 mL of ethyl ether. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was converted to the fumaric acid salt which was recrystallized from CH_3CN to yield 8.1 g (72%) of **111** as a white solid, mp 166–167 °C. Anal. ($C_{28}H_{29}F_2NO_2 \cdot C_4H_4O_4$) C, H, N.

Method KK. 4-[Bis(4-fluorophenyl)hydroxymethyl]-α-phenyl-1-piperidinebutanol Ethanedioate (1:1) (112). To a slurry of 0.4 g (0.01 mol) of $LiAlH_4$ in 50 mL of dry tetrahydrofuran (THF) was added a solution of 4.7 g (0.01 mol) of the base of **111** in 100 mL of dry THF, and the mixture was stirred at ambient temperature overnight. The excess $LiAlH_4$ was cautiously decomposed with successive additions of 1 mL of H_2O, 1 mL of a 20% NaOH solution, and 3 mL of H_2O. The mixture was stirred for 1 h and filtered through Celite, and the filtrate was concentrated. The residue was converted to the oxalic acid salt and recrystallized from 2-propanol to yield 3.3 g (61%) of **112** as a white solid, mp 114–119 °°C dec. Anal. ($C_{28}H_{31}F_2NO_2 \cdot C_2H_2O_4$) C, H, N.

Method LL. 4-[Bis(4-fluorophenyl)hydroxymethyl]-*N*-phenyl-1-piperidinepropanamide (197). A mixture of 2.0 g (0.007 mol) of **59**, 2.6 g (0.014 mol) of 3-chloro-*N*-phenylpropanamide, 8.5 g (0.080 mol) of anhydrous Na_2CO_3, and 0.3 g (0.002 mol) of KI in 50 mL of *N,N*-dimethylformamide was heated on a steam bath for 16 h. The mixture was poured into 500 mL of water and extracted twice with 250-mL portions of ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Recrystallization of the residue from methanol–2-propanol afforded 1.9 g (59%) of **197** as a white solid, mp 190–192 °C. Anal. ($C_{27}H_{28}F_2N_2O_2$) C, H, N.

Method MM. α,α-Bis(4-fluorophenyl)-1-[3-(phenylamino)propyl]-4-piperidinemethanol Ethanedioate (1:2) (116). A solution of 6.3 g (0.014 mol) of **197** in 150 mL of dry (freshly distilled from $LiAlH_4$) tetrahydrofuran (THF) was added dropwise to a stirred solution of 1.0 g (0.026 mol) of $LiAlH_4$ in 50 mL of dry THF at ambient temperature under a N_2 atmosphere. The reaction mixture was heated at reflux for 16 h. The solution was allowed to cool, and the excess $LiAlH_4$ was quenched by successive, dropwise additions of 1 mL of H_2O, 1 mL of 15% NaOH, and 3 mL of H_2O. The solution was filtered, and the filtrate concentrated under reduced pressure to give a viscous oil. The oil was purified by high-pressure liquid chromatography (Waters Associates Prep LC/System 500A; PrepPAK-500 silica; ethyl acetate; flow rate 150 mL/min). The fractions containing the desired product were combined and concentrated under reduced pressure. The residue was converted to the dioxalic acid salt and recrystallized from 2-propanol to yield 3.9 g (45%) of **116** as a white solid, mp 136–138 °C. Anal. ($C_{27}H_{30}F_2N_2O \cdot 2C_2H_2O_4$) C, H, N.

Method NN. 1-[4-[3-[4-[Bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]-2-hydroxypropoxy]-3-methoxyphenyl]ethanone Hydrate (191). A solution of 3.0 g (0.01 mol) of **59** and 2.2 g (0.01 mol) of [3-methoxy-4-(oxiranylmethoxy)-phenyl]ethanone[34] in 25 mL of absolute ethanol and 10 mL of ethyl acetate was allowed to stand at ambient temperature for 16 h and then heated at reflux for 3 h. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography on 120 g of Florisil. Fractions eluted with 15% acetone in C_6H_6 were combined and concentrated under reduced pressure to give 2.6 g (48%) of **191** as a pale yellow glass, mp 65–80 °C. Anal. ($C_{30}H_{33}F_2NO_5 \cdot H_2O$) C, H, N.

1-[4-[3-[4-[Bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]-2-hydroxypropoxy]-2-hydroxy-3-propylphenyl]ethanone Hydrochloride (192). By use of the above method, a solution of 3.0 g (0.01 mol) of **59**, 2.5 g (0.01 mol) of 1-[2-hydroxy-4-(oxiranylmethoxy)-3-propylphenyl]ethanone[35] and

(34) Bourgery, G. R.; Lacour, A. P.; Molnet, G. H.; Pourrias, B. M.; Ruch, A. P. U.S. Patent 4178442, 1979; *Chem. Abstr.* **1979**, *90*, 87513z.

20 mL of absolute ethanol was allowed to stand at ambient temperatures for 2 days. The solution was concentrated under reduced pressure, and the glassy residue was dissolved in ethyl ether, filtered through Celite, and treated with ethereal HCl. The solid that precipitated was collected by filtration and recrystallized from 2-propanol–isopropyl ether to yield 2.4 g (41%) of **192** as a white solid, mp 232–233 °C dec. Anal. ($C_{32}H_{37}F_2NO_5$·HCl) C, H, N.

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Registry No. **1**, 60284-71-1; **2**, 3430-03-3; **3**, 58113-30-7; **4**, 117022-40-9; **5**, 111627-49-7; **6**, 111627-52-2; **7**, 111627-47-5; **8**, 111627-55-5; **9**, 117022-41-0; **10**, 90943-48-9; **11**, 93622-35-6; **12**, 117022-42-1; **13**, 117022-43-2; **14**, 24251-51-2; **15**, 82827-55-2; **16**, 93622-59-4; **17**, 62806-87-5; **18**, 117022-44-3; **19**, 104605-75-6; **20**, 117022-45-4; **21**, 79096-53-0; **22**, 117022-46-5; **23**, 117022-47-6; **24**, 100620-48-2; **25**, 99472-05-6; **26**, 20744-03-0; **27**, 1716-42-3; **28**, 64010-37-3; **29**, 91427-23-5; **30**, 65976-48-9; **31**, 117022-48-7; **32**, 117022-49-8; **33**, 117022-50-1; **34**, 111627-46-4; **35**, 69076-29-5; **36**, 104605-71-2; **37**, 75912-94-6; **38**, 111627-48-6; **39**, 117022-51-2; **40**, 69182-96-3; **41**, 117022-52-3; **42**, 7035-53-2; **43**, 111627-56-6; **44**, 111627-51-1; **45**, 111627-53-3; **46**, 79096-54-1; **47**, 104800-03-5; **48**, 111627-61-3; **49**, 114399-88-1; **50**, 115-46-8; **51**, 58113-24-9; **52**, 64061-56-9; **53**, 58113-26-1; **53** (acetyl), 60285-03-2; **54**, 58113-20-5; **55**, 427-40-7; **56**, 117022-53-4; **56**·fumarate, 117022-54-5; **57**, 117022-55-6; **58**, 111627-25-9; **59**, 60284-98-2; **60**, 117022-56-7; **60**·$^1/_2$ oxalate, 117022-57-8; **61**, 116796-12-4; **62**, 117022-58-9; **62**·$^1/_2$ oxalate, 117022-59-0; **63**, 117022-60-3; **64**, 67853-64-9; **65**, 117022-61-4; **66**, 110148-18-0; **67**, 117022-62-5; **67**·oxalate, 117022-63-6; **68**, 117022-64-7; **69**, 117022-65-8; **70**, 117022-66-9; **71**, 111952-29-5; **72**, 111952-30-8; **72**·$^1/_2$ oxalate, 111952-31-9; **73**, 103887-43-0; **73**·$^3/_2$ fumarate, 117022-67-0; **76**, 107071-83-0; **77**, 117022-68-1; **78**, 117022-69-2; **79**, 117022-70-5; **79**·HCl, 117022-71-6; **80**, 117022-72-7; **81**, 117022-73-8; **82**, 117022-74-9; **82**·oxalate, 117022-75-0; **83**, 117022-76-1; **83**·HCl, 117022-77-2; **84**, 41538-36-7; **85**, 101767-94-6; **86**, 117022-78-3; **87**, 51535-00-3; **88**, 117022-79-4; **89**, 2969-81-5; **90**, 14321-27-8; **91**, 117022-80-7; **92**, 117022-81-8; **93**, 117022-82-9; **94**, 117022-83-0; **94**·fumarate, 117022-84-1; **95**, 117022-85-2; **96**, 117022-86-3; **97**, 117022-87-4; **97**·maleate, 117022-88-5; **98**, 117022-89-6; **98**·HCl, 117022-90-9; **99**, 60284-75-5; **99**·oxalate, 60284-76-6; **100**, 107022-91-0; **100**·oxalate, 107022-92-1; **101**, 111951-75-8; **101**·oxalate, 111952-10-4; **102**, 111951-79-2; **102**·$^1/_2$fumarate, 111952-11-5; **103**, 111626-97-2; **103**·oxalate, 111626-98-3; **104**, 60284-69-7; **104**·oxalate, 60284-70-0; **105**, 117022-93-2; **105**·oxalate, 117022-94-3; **106**, 117022-95-4; **106**·dimaleate, 117022-96-5; **107**, 117022-97-6; **108**, 117022-98-7; **108**·dimaleate, 117022-99-8; **109**, 111625-84-4; **109**·oxalate, 111625-85-5; **110**, 117023-00-4; **110**·oxalate, 117023-01-5; **111**, 117023-02-6; **111**·fumarate, 117023-03-7; **112**, 117023-04-8; **112**·oxalate, 117023-05-9; **113**, 117023-06-0; **114**, 117023-07-1; **114**·oxalate, 117023-08-2; **115**, 117023-09-3; **116**, 117023-10-6; **116**·dioxalate, 117023-11-7; **117**, 117023-12-8; **117**·dioxalate, 117023-13-9; **118**, 117023-14-0; **118**·fumarate, 117023-15-1; **119**, 117023-16-2; **120**, 117023-17-3; **120**·fumarate, 117023-18-4; **121**, 117023-19-5; **122**, 117023-20-8; **123**, 117023-21-9; **124**, 117023-22-0; **125**, 111627-18-0; **125**·HCl, 60284-78-8; **126**, 111627-17-9; **126**·HCl, 60284-77-7; **127**, 60284-74-4; **128**, 117023-23-1; **129**, 117023-24-2; **130**, 117023-25-3; **131**, 117023-26-4; **132**, 117023-27-5; **132**·$^3/_2$oxalate, 117039-49-3; **133**, 117023-28-6; **133**·oxalate, 117023-29-7; **134**, 117023-30-0; **134**·oxalate, 117023-31-1; **135**, 111626-71-2; **136**, 111627-19-1; **137**, 111626-72-3; **138**, 117023-32-2; **138**·HCl, 117023-33-3; **139**, 111626-35-8; **140**, 111627-22-6; **140**·HCl, 111627-01-1; **141**, 117023-34-4; **142**, 111626-14-3; **143**, 117039-50-6; **144**, 117023-35-5; **145**, 117023-36-6; **145**·fumarate, 117023-37-7; **146**, 117023-38-8; **146**·fumarate, 117023-39-9; **147**, 117023-40-2; **148**, 117023-41-3; **149**, 111626-87-0; **149**·fumarate, 117023-42-4; **150**, 117023-43-5; **151**, 117023-44-6; **152**, 117023-45-7; **152**·oxalate, 117039-51-7; **153**, 117023-46-8; **153**·fumarate, 117023-47-9; **154**, 117023-48-0; **154**·fumarate, 117023-49-1; **155**, 111626-03-0; **156**, 117023-50-4; **156**·fumarate, 117023-51-5; **157**, 117023-52-6; **157**·oxalate, 117023-53-7; **158**, 117023-54-8; **158**·oxalate, 117023-55-9; **159**, 111626-52-9; **160**, 117023-56-0; **161**, 117023-57-1; **162**, 111626-82-5; **163**, 117023-58-2; **163**·oxalate, 117023-59-3; **164**, 111626-83-6; **164**·fumarate, 111626-84-7; **165**, 111951-95-2; **165**·HCl, 111626-95-0; **166**, 111626-33-6; **167**, 117023-60-6; **168**, 117023-61-7; **168**·oxalate, 117023-62-8; **169**, 117023-63-9; **169**·fumarate, 117039-52-8; **170**, 117023-64-0; **170**·fumarate, 117023-65-1; **171**, 111627-10-2; **171**·HCl, 111626-39-2; **172**, 117023-66-2; **172**·fumarate, 117023-67-3; **173**, 117023-68-4; **173**·fumarate, 117023-69-5; **174**, 117023-70-8; **174**·fumarate, 117023-71-9; **175**, 111627-11-3; **176**, 111626-36-9; **177**, 111626-62-1; **178**, 117023-72-0; **178**·fumarate, 117023-73-1; **179**, 117023-74-2; **179**·oxalate, 117023-75-3; **180**, 117023-76-4; **181**, 117023-77-5; **181**·fumarate, 117023-78-6; **182**, 117023-79-7; **183**, 111626-61-0; **184**, 117023-80-0; **184**·dioxalate, 117023-81-1; **185**, 111627-15-7; **185**·HCl, 111626-60-9; **186**, 117023-82-2; **186**·oxalate, 117023-83-3; **187**, 117023-84-4; **187**·$^1/_2$fumarate, 117023-85-5; **188**, 117023-86-6; **189**, 117023-87-7; **189**·$^1/_2$fumarate, 117023-88-8; **190**, 40786-08-1; **191**, 117023-89-9; **192**, 117023-90-2; **192**·HCl, 117023-93-5; **193**, 95198-67-7; **194**, 107071-84-1; **195**, 110933-18-1; **196**, 117023-91-3; **197**, 117023-92-4; **198**, 24228-40-8; **198**·HCl, 111627-24-8; **199**, 117023-94-6; **199** (free base), 117023-95-7; $Br(CH_2)_2Cl$, 107-04-0; $Br(CH_2)_4Cl$, 6940-78-9; $Br(CH_2)_5Cl$, 54512-75-3; $Br(CH_2)_6Cl$, 6294-17-3; $Br(CH_2)_3Cl$, 109-70-6; *o*-MeC_6H_4OH, 95-48-7; *o*-$MeOC_6H_4OH$, 90-05-1; *o*-$EtOC_6H_4OH$, 94-71-3; *o*-*i*-$PrOC_6H_4OH$, 4812-20-8; *o*-$PhCH_2OC_6H_4OH$, 6272-38-4; *o*-AcC_6H_4OH, 118-93-4; *m*-MeC_6H_4OH, 108-39-4; *m*-$MeOC_6H_4OH$, 150-19-6; *m*-AcC_6H_4OH, 121-71-1; *p*-MeC_6H_4OH, 106-44-5; *p*-EtC_6H_4OH, 123-07-9; *p*-HOC_6H_4Pr-*i*, 99-89-8; *p*-HOC_6H_4Bu-*t*, 98-54-4; *p*-HOC_6H_4Ph, 92-69-3; *p*-HOC_6H_4OMe, 150-76-5; *p*-HOC_6H_4F, 371-41-5; *p*-HOC_6H_4Cl, 106-48-9; *p*-HOC_6H_4Ac, 99-93-4; *p*-HOC_6H_4COPh, 1137-42-4; *p*-HOC_6H_4CN, 767-00-0; *p*-$HOC_6H_4CONH_2$, 619-57-8; *p*-$HOC_6H_4CH_2CO_2Me$, 14199-15-6; *p*-$HOC_6H_4(CH_2)_2CO_2Me$, 5597-50-2; *p*-HOC_6H_4SMe, 1073-72-9; *p*-$HOC_6H_4SO_2NH_2$, 1576-43-8; *p*-$HOC_6H_4NO_2$, 100-02-7; *p*-HOC_6H_4NHAc, 103-90-2; BrPh, 108-86-1; *p*-BrC_6H_4Me, 106-38-7; *p*-BrC_6H_4OMe, 104-92-7; $Cl(CH_2)_3OPh$, 3384-04-1; $Cl(CH_2)_4Ph$, 4830-93-7; $Cl(CH_2)_3SPh$, 4911-65-3; *p*-$FC_6H_4CO(CH_2)_3N(Et)$-CH_2Ph, 117023-96-8; ethyl isonipecotate, 1126-09-6; (±)-ethyl nipecotate, 71962-74-8; 1-bromo-4-fluorobenzene, 460-00-4; bromocyclohexane, 108-85-0; 1-acetyl-4-benzoylpiperidine, 25519-79-3; 1-bromo-3-(trifluoromethyl)benzene, 401-78-5; 4-picoline, 108-89-4; 4,4′-difluorobenzophenone, 345-92-6; 1-bromo-3-fluorobenzene, 1073-06-9; ethyl 3-pyridylacetate, 39931-77-6; 4-cyanopyridine, 100-48-1; (4-fluorophenyl)magnesium bromide, 352-13-6; 4-hydroxypiperidine, 5382-16-1; diphenylacetonitrile, 86-29-3; diethylcarbamoyl chloride, 88-10-8; 1-bromo-4-chlorobenzene, 106-39-8; 3-chloro-*N*-phenylpropanamide, 3460-04-6; [3-methoxy-4-(oxiranylmethoxy)phenyl]ethanone, 69114-02-9; 1-[2-hydroxy-4-(oxiranylmethoxy)-3-propylphenyl]ethanone, 57161-85-0; 2-methoxy-4-acetylphenol, 498-02-2; 2-methyl-4-acetylphenol, 876-02-8; 3-methoxy-4-acetylphenol, 493-33-4; 2,6-dimethoxyphenol, 91-10-1; ethyl 2-hydroxybenzoate, 118-61-6; ethyl 3-hydroxybenzoate, 7781-98-8; 4-propionylphenol, 70-70-2; methyl 4-hydroxybenzoate, 99-76-3; ethyl 4-hydroxybenzoate, 120-47-8; 2-pyridyllithium, 17624-36-1; 1-acetyl-4-(*p*-fluorobenzoyl)-piperidine, 25519-77-1; α,α-bis(3,4-difluorophenyl)-4-pyridinemethanol, 117023-97-9; 4-benzylpiperidine, 31252-42-3; 4-phenylpiperidine, 771-99-3; 1-benzylpiperazine, 2759-28-6; 1-phenylpiperazine, 92-54-6.

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