Synthesis, Calcium-Channel-Blocking Activity, and Antihypertensive Activity of 4-(Diarylmethyl)-1-[3-(aryloxy)propyl]piperidines and Structurally Related Compounds[1]

James R. Shanklin, Jr.,*,† Christopher P. Johnson, III,†,‡ Anthony G. Proakis,§,∥ and Richard J. Barrett§,‡

Departments of Chemical Research and Pharmacology, A. H. Robins Company, P.O. Box 26609, Richmond, Virginia 23261-6609. *Received May 9, 1991*

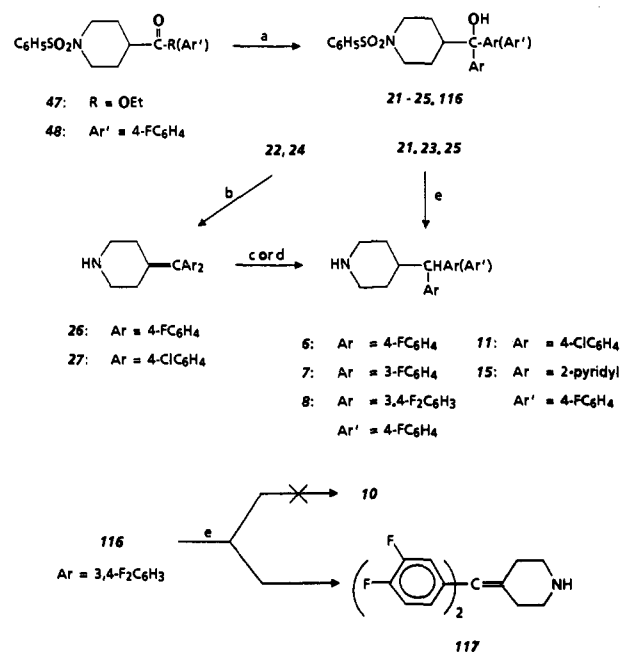
A series of 4-(diarylmethyl)-1-[3-(aryloxy)propyl]piperidines and structurally related compounds were synthesized as calcium-channel blockers and antihypertensive agents. Compounds were evaluated for calcium-channel-blocking activity by determining their ability to antagonize calcium-induced contractions of isolated rabbit aortic strips. The most potent compounds were those with fluoro substituents in the 3- and/or 4-positions of both rings of the diphenylmethyl group. Bis(4-fluorophenyl)acetonitrile analogue **79** was similar in potency to bis(4-fluorophenyl)methyl compound 1. The methylene analogue of 1 (**78**) and derivatives of 1 that contained a hydroxyl (**76**), carbamoyl (**80**), amino (**81**), or acetamido (**82**) substituent on the methyl group were less potent. In most cases, substituents on the phenoxy ring, changes in the distance between the aryloxy group and the piperidine nitrogen, and the substitution of S, $N(CH_3)$, or CH_2 for the oxygen atom of the aryloxy group had only a small to moderate effect on the potency. The best compounds in this series were more potent than verapamil, diltiazem, flunarizine, and lidoflazine, but were less potent than nifedipine. Compounds were evaluated for antihypertensive activity in spontaneously hypertensive rats (SHR) at an oral dose of 30 mg/kg. Of the 55 compounds tested, only nine produced a statistically significant ($p < 0.05$) reduction in blood pressure greater than 20%; all of these compounds had fluoro substituents in both rings of the diphenylmethyl group. One of the most active compounds in the SHR at 30 mg/kg was 1-[4-[3-[4-[bis(3,4-difluorophenyl)methyl]-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (**63**), which produced a 35% reduction in blood pressure and was similar in activity to nifedipine. At lower doses, however, 4-[bis(4-fluorophenyl)methyl]-1-[3-(4-chlorophenoxy)propyl]piperidine (**93**) was one of the most effective antihypertensive agents, producing reductions in blood pressure of 17 and 11% at oral doses of 10 and 3 mg/kg, respectively; **63** was inactive at 10 mg/kg.

Calcium channel blockers are an important class of drugs that are widely used in the treatment of cardiovascular disease. The most frequently prescribed drugs of this type are nifedipine,[2] diltiazem,[3] and verapamil;[4] all are very effective in treating angina and hypertension. In addition, verapamil is useful in correcting superventricular arrhythmias.[5]

Calcium channel blockers are a chemically heterogeneous group of compounds. Many calcium-channel blockers, however, can be placed into one of three major structural classes: the 1,4-dihydropyridines (nifedipine), the benzothiazepines (diltiazem), and the phenylalkylamines (verapamil). Over the past 10 years, these three classes of calcium channel blockers have been extensively investigated and their pharmacology, biochemistry, and electrophysiology have been thoroughly reviewed.[6] On the other hand, a fourth type of calcium channel blocker, the diphenylalkylamines, has received much less attention. Flunarizine[7] and lidoflazine[8] (Chart I), which are marketed outside of the U.S. for the treatment of cerebral and peripheral cardiovascular disorders, belong to this fourth class.

In 1982 we initiated a program in our laboratories to find a calcium channel blocker that would be clinically useful in treating hypertension. Early in this program, 1 (Chart I) was identified as a potent calcium channel blocker, in vitro, and as an effective antihypertensive agent. Compound 1 had been prepared earlier in our laboratories by Duncan and Boswell[9] and was similar in structure to flunarizine and lidoflazine. Accordingly, work was undertaken to synthesize analogues of 1 and to investigate the

Scheme I[a]



[a] Reagents and reaction conditions: (a) ArMgBr or 2-pyrLi, THF; (b) 48% HBr, phenol, reflux, 6 h; (c) for **26**, I_2, phosphorus, $MeSO_3H$, HOAc, reflux; (d) for **27**, 57% HI, phosphorus, HOAc, reflux; (e) 57% HI, phosphorus, HOAc, reflux.

* Author to whom correspondence should be addressed. Present address: The Lubrizol Corp., 29400 Lakeland Blvd., Wickliffe, OH 44092-2298.

† Department of Chemical Research.

‡ Present address: Whitby Research, Inc., P.O. Box 27426, Richmond, VA 23261-7426.

§ Department of Pharmacology.

∥ Present address: Division of Cardio-Renal Drugs, HFD-110, FDA, 5600 Fishers Lane, Rockville, MD 20857.

(1) Shanklin, J. R., Jr.; Johnson, C. P., III; Proakis, A. G. Presented in part at the 193rd National Meeting of the American Chemical Society, Denver, CO, April 1987; paper MEDI 78.
(2) Sorkin, E. M.; Clissold, S. P.; Brogden, R. N. *Drugs* **1985**, *30*, 182-274.
(3) (a) Chaffman, M.; Brogden, R. N. *Drugs* **1985**, *29*, 387-454. (b) Flaim, S. F. In *New Drugs Annual: Cardiovascular Drugs*; Scriabine, A., Ed.; Raven: New York, 1984; Vol. 2, pp 123-156.

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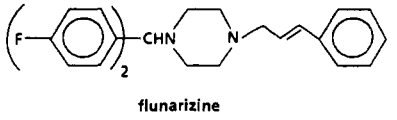
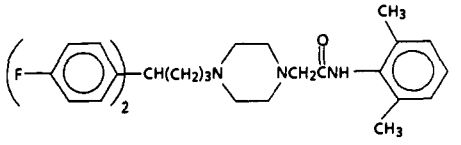
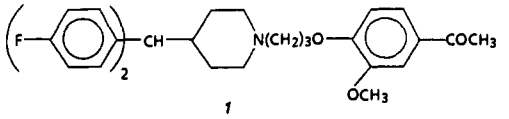
Chart I. Calcium Channel Blockers



flunarizine



lidoflazine



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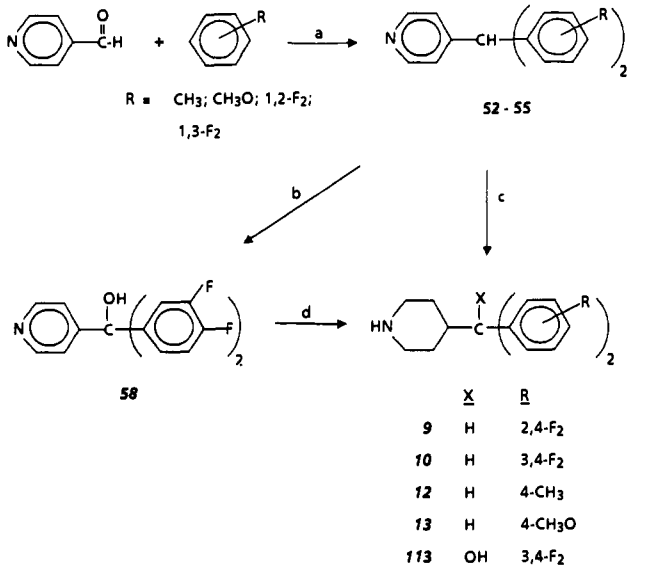
Scheme II[a]

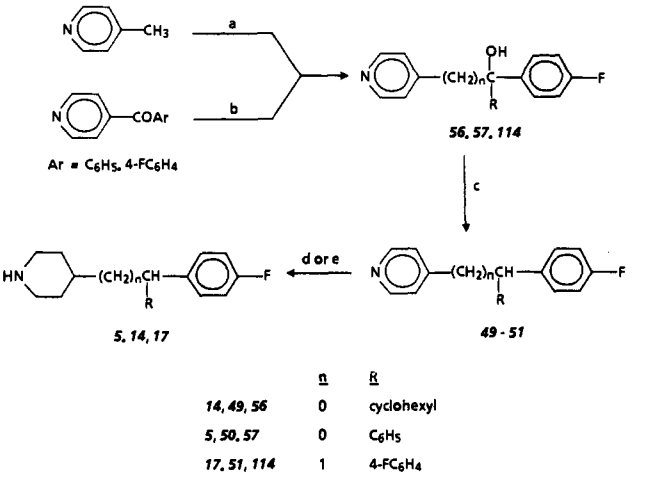


	X	R
9	H	2,4-F_2
10	H	3,4-F_2
12	H	4-CH_3
13	H	4-CH_3O
113	OH	3,4-F_2

[a] Reagents and reaction conditions: (a) concentrated H_2SO_4, 70 °C, 3.5–16 h; (b) for **53**, 50% NaOH, Me_2SO, O_2; (c) H_2, 5% Pt/C or 5% Pd/C, HCl, HOAc, 60–100 °C; (d) H_2, 5% Pt/C, HOAc, 23 °C, 70 h.

structure–activity relationships for this novel group of (diphenylmethyl)piperidine calcium-channel blockers.

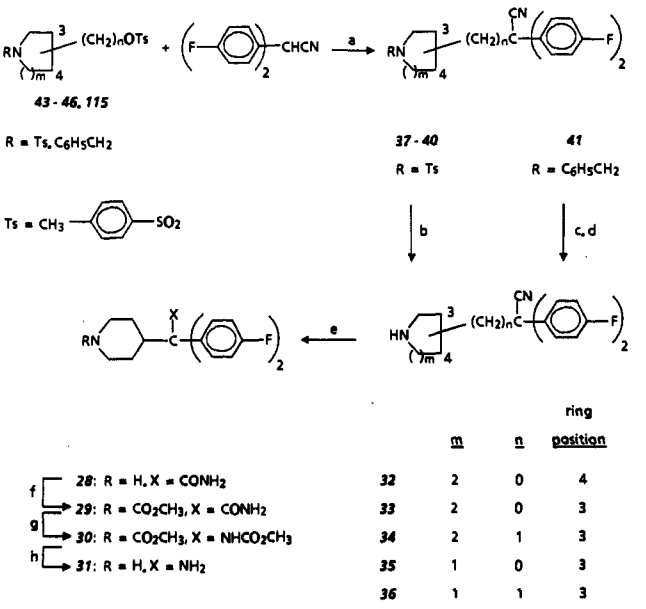
Scheme III[a]



	n	R
14, 49, 56	0	cyclohexyl
5, 50, 57	0	C_6H_5
17, 51, 114	1	4-FC_6H_4

[a] Reagents and reaction conditions: (a) (1) *n*-BuLi, THF, −30 °C, (2) $(4\text{-}FC_6H_4)_2C{=}O$, 23 °C; (b) RMgBr, THF or diethyl ether; (c) 57% HI, phosphorus, HOAc, reflux; (d) for **49**, H_2 (700 psi), 5% Pt/C, HOAc, 60 °C; (e) for **50** and **51**, H_2 (45–49 psi), 5% Pd/C, HOAc, 23 °C.

Scheme IV[a]



		m	n	ring position
f → *28*: R = H, X = $CONH_2$	*32*	2	0	4
f → *29*: R = CO_2CH_3, X = $CONH_2$	*33*	2	0	3
g → *30*: R = CO_2CH_3, X = $NHCO_2CH_3$	*34*	2	1	3
h → *31*: R = H, X = NH_2	*35*	1	0	3
	36	1	1	3

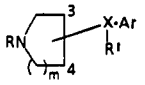
[a] Reagents and reaction conditions: (a) NaH, Me_2SO, 55–80 °C, 16–18 h; (b) 48% HBr, phenol, reflux, 2–4 h; (c) $ClCO_2C_6H_5$, $KHCO_3$, $CHCl_3$, reflux, 16 h; (d) 85% NH_2NH_2, reflux, 16 h; (e) for **32**, 90% H_2SO_4, 85 °C, 16 h; (f) $ClCO_2CH_3$, CH_2Cl_2, 23 °C, 16 h; (g) Br_2, 50% NaOH, MeOH, reflux, 16 h; (h) 50% NaOH, MeOH, reflux, 16 h.

Chemistry

The preparation of 2-(2-bromoethoxy)naphthalene (**2**)[10] and the (aryloxy)chloropropane intermediates **3** and **4** is described in the Experimental Section. The preparation of other (aryloxy)chloropropanes used in this work was described previously by Walsh et al.[11]

(4) Baky, S. In *New Drugs Annual: Cardiovascular Drugs*; Scriabine, A., Ed.; Raven: New York, 1984; Vol. 2, pp 71–102.
(5) Prystowsky, E. N. *J. Clin. Pharmacol.* **1988**, *28*, 6–21.
(6) (a) Janis, R. A.; Silver, P. J.; Triggle, D. J. In *Advances in Drug Research*; Testa, B., Ed.; Academic: San Diego, 1987; Vol. 16, pp 309–591. (b) Katz, A. M.; Pappano, A. J.; Messineo, F. C.; Smilowitz, H.; Nash-Alder, P. In *The Heart and Cardiovascular System*; Fozzard, H. A., Haber, E., Jennings, R. B., Katz, A. M., Morgan, H. E., Eds.; Raven: New York, 1986; Vol. 2, Chapter 67. (c) Meyer, H.; Wehinger, E. In *Cardiovascular Drugs*; Bristol, J. A., Ed.; John Wiley and Sons: New York, 1986; Chapter 4. (d) Soward, A. L.; Vanhaleweyk, G. L. J.; Serruys, P. W. *Drugs* **1986**, *32*, 66–101. (e) Scriabine, A. *J. Cardiovasc. Pharmacol.* **1987**, *9* (*Suppl. 1*), S3–S7. (f) Bossert, F.; Vater, W. *Med. Res. Rev.* **1989**, *3*, 291–324. (g) Godfraind, T. *Am. J. Cardiol.* **1987**, *59*, 11B–23B. (h) Singh, B. N.; Nademanee, K. *Am. J. Cardiol.* **1987**, *59*, 153B–162B.
(7) (a) Holmes, B.; Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1984**, *27*, 6–44. (b) Van Neuten, J. M.; Vanhoutte, P. M. In *New Drugs Annual: Cardiovascular Drugs*; Scriabine, A., Ed.; Raven: New York, 1984; Vol. 2, pp 245–266.
(8) (a) Vanhoutte, P. M.; Van Neuten, J. M. In *New Drugs Annual: Cardiovascular Drugs*; Scriabine, A., Ed.; Raven: New York, 1983; Vol. 1, pp 203–226. (b) *Drug Ther. Bull.* **1983**, *21*, 27–28.
(9) Duncan, R. L., Jr., Boswell, R. F., Jr., U. S. Patent 3 956 296, 1976; *Chem. Abstr.* **1976**, *85*, 108539*b*.
(10) Weinstein, A. H.; Pierson, R. M.; Wargotz, B.; Yen, T. F. *J. Org. Chem.* **1958**, *23*, 363–372.

Table I. Piperidine, Pyrrolidine, and Pyridine Intermediates



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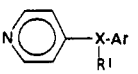

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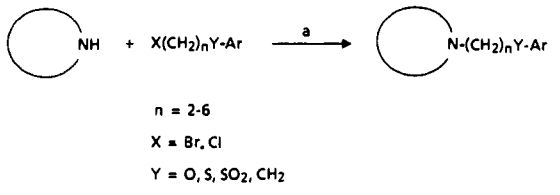
no.	R	m	X	R¹	Ar	ring position	formula[a]	mp, °C (solv)[b]	method of prep[c]	% yield
5[d]	H	2	CH	C_6H_5	$4\text{-}FC_6H_4$	4	$C_{18}H_{20}FN\cdot HCl\cdot 0.5H_2O$	65–68 (kn)	W	85
6[d]	H	2	CH	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{18}H_{18}F_2N\cdot 0.5C_4H_4O_4$[e]$\cdot 0.5H_2O$	208–209 (kn)	R	32
7	H	2	CH	$3\text{-}FC_6H_4$	$3\text{-}FC_6H_4$	4	$C_{18}H_{18}F_2N\cdot HCl$	260–262 (kn)	P	63
8	H	2	CH	$4\text{-}FC_6H_4$	$3,4\text{-}F_2C_6H_3$	4	$C_{18}H_{18}F_3N\cdot C_2H_2O_4\cdot 0.5H_2O$	78–83 (p)	P	22
9	H	2	CH	$2,4\text{-}F_2C_6H_3$	$2,4\text{-}F_2C_6H_3$	4	$C_{18}H_{17}F_4N\cdot HCl$	215–217 (kn)	T	100[f]
10	H	2	CH	$3,4\text{-}F_2C_6H_3$	$3,4\text{-}F_2C_6H_3$	4	$C_{18}H_{17}F_4N\cdot HCl$	263–268 (mn)	T	68[f]
11	H	2	CH	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	4	$C_{18}H_{19}Cl_2N\cdot C_2H_2O_4\cdot 0.5H_2O$	219–220 (kn)	Q	93[f]
12	H	2	CH	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	4	$C_{20}H_{25}N\cdot HCl\cdot 0.2H_2O$	232 (kn)	W	14
13	H	2	CH	$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	4	$C_{20}H_{25}NO_2\cdot HCl\cdot H_2O$	132–135 (kn)	W	89[f]
14	H	2	CH	cyclohexyl	$4\text{-}FC_6H_4$	4	$C_{18}H_{26}FN$	oil (w)	U	55
15	H	2	CH	2-pyridyl	$4\text{-}FC_6H_4$	4	$C_{17}H_{16}FN_2\cdot 2HCl\cdot 0.75H_2O$	182–185 (kn)	P	72
16[g]	H	2	CH	H	$4\text{-}FC_6H_4$	4	$C_{12}H_{16}FN\cdot HCl$	163.5–165.5[g] (kn)	S	75
17	H	2	CH_2CH[h]	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{18}H_{21}F_2N\cdot HCl\cdot 0.5H_2O$	171–173 (kn)	W	72
18	$(CH_2)_3OH$	2	CH	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{21}H_{25}F_2NO\cdot C_2H_2O_4\cdot 0.75H_2O$	89–94 (kn)	FF	67[f]
19	$(CH_2)_3Cl$	2	CH	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{21}H_{24}ClF_2N$	oil (w)	GG	99[f]
20[i]	H	2	C(OH)	H	$4\text{-}FC_6H_4$	4	$C_{12}H_{16}FNO\cdot HCl$	254 dec[i] (l)	O	71
21	$SO_2C_6H_5$	2	C(OH)	$3\text{-}FC_6H_4$	$3\text{-}FC_6H_4$	4	$C_{24}H_{23}F_2NO_3S$	183–185 (n)	D	53
22	$SO_2C_6H_5$	2	C(OH)	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{24}H_{23}F_2NO_3S$	142.5–144 (qr)	D	68
23	$SO_2C_6H_5$	2	C(OH)	$4\text{-}FC_6H_4$	$3,4\text{-}F_2C_6H_3$	4	$C_{24}H_{22}F_3NO_3S$	97–99 (nqr)	F	83[f]
24	$SO_2C_6H_5$	2	C(OH)	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	4		135–140 (nqr)	D	104[j]
25	$SO_2C_6H_5$	2	C(OH)	2-pyridyl	$4\text{-}FC_6H_4$	4	$C_{23}H_{23}FN_2O_3S$	160–163 (vw)	G	54
26[k]	H	2	C=	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{18}H_{17}F_2N\cdot HBr$	216–218 (kn)	X	73[f]
27[l]	H	2	C=	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	4	$C_{18}H_{17}Cl_2N\cdot HBr\cdot H_2O$	106–109 (kn)	X	44
28	H	2	$C(CONH_2)$	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{18}H_{20}F_2N_2O\cdot HCl$	328 dec (mn)	Z	93[f]
29	CO_2CH_3	2	$C(CONH_2)$	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{21}H_{22}F_2N_2O_3$	126–129 (qr)	AA	67[f]
30	CO_2CH_3	2	$C(NHCO_2CH_3)$	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{22}H_{24}F_2N_2O_4\cdot 0.25H_2O$	213 (w)	BB	86[f]
31	H	2	$C(NH_2)$	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{18}H_{20}F_2N_2\cdot 2C_2H_2O_4\cdot 0.5H_2O$	151–154 (kn)	CC	88[f]
32	H	2	C(CN)	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{18}H_{18}F_2N_2\cdot C_2H_2O_4\cdot 0.5C_4H_{10}O$[m]$\cdot 0.25H_2O$	124–127 (kn)	Y	69
33	H	2	C(CN)	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	3	$C_{19}H_{18}F_2N_2\cdot C_4H_4O_4$[n]$\cdot 0.25H_2O$	115–118 (kn)	Y	57
34	H	2	$CH_2C(CN)$[h]	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	3	$C_{20}H_{20}F_2N_2$	oil (w)	Y	67
35	H	1	C(CN)	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	3	$C_{18}H_{18}F_2N_2\cdot C_2H_2O_4\cdot 0.5H_2O$	88.5–90 (kn)	Y	49
36	H	1	$CH_2C(CN)$[h]	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	3		oil (w)	EE	38[j]
37	Ts[o]	2	C(CN)	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	4	$C_{26}H_{24}F_2N_2O_2S$	190–191 (km)	K	97[f]
38	Ts[o]	2	C(CN)	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	3	$C_{26}H_{24}F_2N_2O_2S$	oil (w)	K	77[f]
39	Ts[o]	2	$CH_2C(CN)$[h]	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	3	$C_{27}H_{26}F_2N_2O_2S$	142–143 (m)	K	83[f]
40	Ts[o]	1	C(CN)	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	3	$C_{25}H_{22}F_2N_2O_2S\cdot 0.25H_2O$	181–183 (m)	K	80[f]
41	$CH_2C_6H_5$	1	$CH_2C(CN)$[h]	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	3	$C_{26}H_{24}F_2N_2\cdot 0.5H_2O$	oil (w)	M	81[f]
42	$CO_2C_6H_5$	1	$CH_2C(CN)$[h]	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	3	$C_{26}H_{22}F_2N_2O_2$	oil (w)	DD	70
43[p]	Ts[o]	2	O	Ts[o]	–	3	$C_{18}H_{23}NO_5S_2$	132–133 (nr)	J	101[f]
44[q]	Ts[o]	2	CH_2O[h]	Ts[o]	–	3	$C_{20}H_{25}NO_5S_2$	108–109 (m)	J	78[f]
45	Ts[o]	1	O	Ts[o]	–	3	$C_{18}H_{21}NO_5S_2$	121–122 (u)	J	25[f]
46	$CH_2C_6H_5$	1	CH_2O[h]	Ts[o]	–	3	$C_{18}H_{23}NO_3S\cdot C_2H_2O_4$	147–149 (kn)	L	70[f]
47[r]	$SO_2C_6H_5$	2	C=O	OEt	–	4	$C_{14}H_{19}NO_4S$	85–86.5[s] (ln)	C	24 (78)[s]
48	$SO_2C_6H_5$	2	C=O	–	$4\text{-}FC_6H_4$	4	$C_{18}H_{16}FNO_3S$	156.5–158 (qr)	E	51
49			CH	cyclohexyl	$4\text{-}FC_6H_4$		$C_{18}H_{20}FN$	78–81 (w)	V	92[f]
50			CH	C_6H_5	$4\text{-}FC_6H_4$			oil	V	48[j]
51			CH_2CH[h]	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$		$C_{19}H_{15}F_2N\cdot HCl$	197–199 (np)	V	87
52			CH	$2,4\text{-}F_2C_6H_3$	$2,4\text{-}F_2C_6H_3$		$C_{18}H_{11}F_4N\cdot HCl$	218–222 (mn)	I	45[f]
53			CH	$3,4\text{-}F_2C_6H_3$	$3,4\text{-}F_2C_6H_3$		$C_{18}H_{11}F_4N$	79–82 (qr)	I	74
54[t]			CH	$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$		$C_{20}H_{19}NO_2\cdot 0.2H_2O$	111.5–113.5[u] (qr)	I	48[f]
55			CH	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$			oil	I	99[j,u]
56			C(OH)	cyclohexyl	$4\text{-}FC_6H_4$		$C_{18}H_{20}FNO$	165–167 (v)	H	53
57[v]			C(OH)	C_6H_5	$4\text{-}FC_6H_4$		$C_{18}H_{14}FNO$	190–192[w] (qr)	H	45
58			C(OH)	$3,4\text{-}F_2C_6H_3$	$3,4\text{-}F_2C_6H_3$		$C_{18}H_{11}F_4NO$	147–149 (qr)	N	80

[a] Compounds were analyzed for C, H, and N,and the results were within ±0.4% of theoretical values. A microanalysis was not performed on compounds **24**, **36**, **50**, and **55**. [b] Recrystallization solvents: k = methanol, l = ethanol, m = 2-propanol, n = diethyl ether, o = diisopropyl ether, p = acetonitrile, q = hexanes, r = methylene chloride, s = ligroin, t = acetone, u = ethyl acetate, v = trituration with diethyl ether, and w = purification by flash chromatography on SiO_2. [c] Letters refer to the methods of preparation in the Experimental Section. [d] Reference 9. [e] Fumarate. [f] Crude yield. A small portion of the crude material was used to prepare the analytical sample. The remainder of the crude product was used in the next step of the reaction sequence without further purification. [g] Reference 15; lit. mp 158–160 °C. [h] CH_2 bonded to heterocyclic ring. [i] Reference 16; lit. mp 259–261 °C. [j] Crude yield. A microanalysis was not obtained for this compound. The crude product was used in the next step of the reaction sequence without further purification. [k] Reference 17. [l] Reference 18. [m] Diethyl ether. [n] Maleate. [o] Ts = *p*-toluenesulfonyl group. [p] Reference 19. [q] Reference 20. [r] Reference 21; lit. mp 85.5 °C. [s] In a subsequent preparation with the same method, a 78% yield was obtained, mp 87–89 °C. [t] Reference 22; lit. mp 114–115 °C. [u] ^{13}C NMR indicated that ca. 60% of the crude product was **55**. The remainder was a mixture of isomers. [v] Reference 23; lit. mp 188–190 °C.

Four synthetic routes (Schemes I–IV) were used to prepare the key piperidine and pyrrolidine intermediates **5–15**, **17**, **26–28**, and **31–36** in Table I. In the first route as shown Scheme I, ester **47** or ketone **48** was reacted with

Scheme V[a]



[a] Reagents and reaction conditions: (a) $NaHCO_3$ or Na_2CO_3 or K_2CO_3, KI(trace), 1-butanol, reflux, 8–30 h.

an aryl Grignard reagent or with 2-pyridyllithium to give alcohols **21–25** and **116** in good yield. Heating a solution of **22** or **24** in 48% HBr at reflux[12] gave 4-(diarylmethylene)piperidines **26** and **27**, respectively. These were subsequently reduced with HI/phosphorus or I_2/phosphorus in boiling acetic acid to give 4-(diarylmethyl)-piperidines **6** and **11**. The other alcohols **21**, **23**, and **25** were converted directly to alkylpiperidines **7**, **8**, and **15**, respectively, by heating them at reflux with HI/phosphorus in acetic acid. An attempt to convert **116** to alkane **10** by this latter method failed and gave alkene **117** as the only isolated product. Accordingly, another route (Scheme II) was employed to prepare tetrafluoro analogues **9** and **10** and several other intermediates.

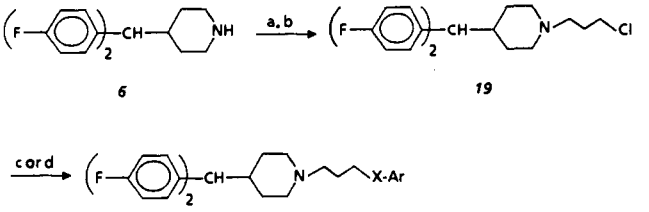
As shown in Scheme II, reacting 4-pyridinecarboxaldehyde with 1,2-difluorobenzene, 1,3-difluorobenzene, anisole, or toluene in concentrated H_2SO_4 at 70 °C[13] gave the 4-(diarylmethyl)pyridines **52–55**. Reducing these catalytically with H_2 over Pt/C or Pd/C yielded piperidines **9**, **10**, **12**, and **13**. Oxidizing **53** (R = 3,4-F_2) by the method of Kress and Moore[14] gave an 80% yield of **58**, which was reacted with H_2 over Pt/C to furnish alcohol **113**.[11]

Intermediate **17** was prepared from the 4-pyridineethanol **114** as shown in Scheme III. The reaction of 4-picolyllithium with 4,4′-difluorobenzophenone produced **114**.[11] Reacting **114** with HI/phosphorus in boiling acetic acid afforded ethylpyridine **51**, which was readily converted to **17** by hydrogenation over Pd/C.

In a related procedure (Scheme III), reacting 4-(4-fluorobenzoyl)pyridine with cyclohexylmagnesium chloride and 4-benzoylpyridine with (4-fluorophenyl)magnesium bromide produced pyridinemethanols **56** and **57**, respectively. These were converted to methylpyridines **49** and **50**; **50** was subjected to a low-pressure (45 psi) catalytic hydrogenation over Pd/C to give an 85% yield of methylpiperidine **5**. An attempt to hydrogenate the more sterically hindered cyclohexyl analogue **49** under the same conditions failed, with only the starting material being recovered. Accordingly, a high-pressure (700 psi) catalytic hydrogenation over Pt/C was required to convert **49** to **14**, which was obtained in a 55% yield.

Nitriles **32–36**, amide **28**, and amino analogue **31** were prepared by the synthetic route depicted in Scheme IV. Reacting **43–46** and **115**[24] with the sodium salt of 4-fluoro-α-(4-fluorophenyl)benzeneacetonitrile in Me_2SO gave the *N*-tosyl compounds **37–40** and *N*-benzyl compound **41**. Treating **37–40** with 48% HBr at reflux removed the *N*-tosyl group to give **32–35**. Reacting **41** with phenyl chloroformate and treating the resulting carbamate **42** (Table I) with hydrazine furnished **36**. Hydration of **32** with 90% H_2SO_4 afforded amide **28**. Finally, converting **28** to methoxycarbonyl derivative **29**, subjecting **29** to a Hofmann rearrangement to give **30**, and then hydrolyzing **30** with 50% NaOH in MeOH produced amino analogue **31**.

Scheme VI[a]



	X	Ar
85	O	2-CH_3O-4-$CO_2CH_3C_6H_3$
87	O	2-CH_3O-4-CNC_6H_3
102	O	1-naphthyl
103	O	2-naphthyl
106	NCH_3	C_6H_5

[a] Reagents and reaction conditions: (a) 3-bromo-1-propanol, $NaHCO_3$, 1-butanol, reflux, 21 h; (b) $SOCl_2$, reflux, 6 h; (c) X = O, ArOH, NaH, Me_2SO, 50–65 °C; 16 h; (d) X = NCH_3, $C_6H_5NHCH_3$ (neat), 100 °C, 30 h.

Most of the target compounds in Tables II–IV were prepared as shown in Scheme V. In this procedure the piperidine or pyrrolidine intermediate was heated with an alkyl halide and an inorganic base in 1-butanol to give the desired target compound, usually in good yield. Five compounds in Table III, however, were prepared by another route as shown in Scheme VI. In this procedure piperidine **6** was converted to chloropropyl intermediate **19**. This was then reacted with the appropriate sodium phenoxide or naphthoxide in Me_2SO to give ethers **85**, **87**, **102**, and **103**. Alternatively, reacting **19** with neat *N*-methylaniline at 100 °C afforded the diamino compound **106**.

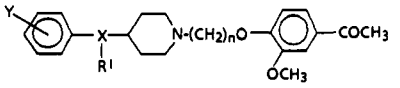
Results and Discussion

The compounds in Tables II–IV were evaluated for calcium-channel-blocking activity by determining their ability to inhibit concentration-dependent, calcium-induced contractions of isolated rabbit aortic strips. As shown in Table II, the lead compound **1** was more potent (larger pA_2 value) than verapamil, diltiazem, flunarizine,

(11) Walsh, D. A.; Franzyshen, S. K.; Yanni, J. M. *J. Med. Chem.* **1989**, *32*, 105–118.
(12) Snyder, H. R.; Heckert, R. E. *J. Am. Chem. Soc.* **1952**, *74*, 2006–2009.
(13) Mathes, W.; Wolf, A. U.S. Patent 3 042 678, 1962; *Chem. Abstr.* **1962**, *57*, 15082e.
(14) Kress, T. J.; Moore, L. L. *J. Heterocycl. Chem.* **1972**, *9*, 1161–1164.
(15) Wick, A.; Frost, J.; Gaudilliere, B.; Bertin, J.; Dupont, R.; Rousseau, J. U. S. Patent 4 690 931, 1987; *Chem. Abstr.* **1984**, *101*, 210992e.
(16) Carr, A. A. U. S. Patent 3 852 455, 1974; *Chem. Abstr.* **1974**, *82*, 125285w.
(17) Duncan, R. L., Jr.; Boswell, R. F., Jr. U. S. Patent 3 922 276, 1975; *Chem. Abstr.* **1976**, *84*, 59224p.
(18) Zivkovic, D. G. B. Patent 1 542 823, 1979; *Chem. Abstr.* **1978**, *89*, 197340c.
(19) Shanklin, J. R., Jr. U. S. Patent 4 593 102, 1986; *Chem. Abstr.* **1986**, *104*, 186309b.
(20) Bettoni, G.; Duranti, E.; Tortorella, V. *Gazz. Chim. Ital.* **1972**, *102*, 189–195.
(21) Skinner, G. S.; Krysiak, H. R.; Perregrino, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 2248–2250.
(22) Posselt, V. K. *Arzneim.-Forsch./Drug Res.* **1978**, *28* (*II*), 1056–1065.
(23) Nagarajan, K.; Talwalker, P. K.; Shah, R. K.; Shenoy, S. J. *Indian J. Chem.* **1985**, *24B*, 112–118.

(24) 4-Methylphenylsulfonic acid ester with 1-[(4-methylbenzene)sulfonyl]-4-piperidinol. See ref 11.

Table II. Calcium-Channel-Blocking Activity in Rabbit Aortic Strips and Antihypertensive Activity in Spontaneously Hypertensive Rats (SHR) of 4-Substituted-*N*-[(4-acetyl-2-methoxyphenoxy)alkyl]piperidines



no.	Y	R^1	X	n	formula[a]	mp, °C (solv)[b]	method of prep[c]	% yield	Ca^{2+} pA_2[d]	SHR, % ΔMABP[e] 0.5–2 h	SHR, % ΔMABP[e] 3–6 h
1	4-F	4-FC_6H_4	CH	3	$C_{30}H_{33}F_2NO_3 \cdot 1.2C_4H_4O_4$[f]	163–164.5 (mo)	HH	72	8.8	−15*	−22*
59[g]	H	C_6H_5	CH	3	$C_{30}H_{35}NO_3 \cdot C_2H_2O_4$	153–155 (q)		64	8.2	−20	−12
60	4-F	C_6H_5	CH	3	$C_{30}H_{34}FNO_3 \cdot C_2H_2O_4$	161–163 (kn)	HH	69	8.2	−8	−12
61	3-F	3-FC_6H_4	CH	3	$C_{30}H_{33}F_2NO_3 \cdot C_4H_4O_4$[f]	181–182 (knp)	HH	40	8.5	−11*	−9*
62	3,4-F_2	4-FC_6H_4	CH	3	$C_{30}H_{32}F_3NO_3 \cdot C_2H_2O_4$	170–171 (kn)	HH	73	8.9	−27*	−30*
63	3,4-F_2	3,4-$F_2C_6H_3$	CH	3	$C_{30}H_{31}F_4NO_3 \cdot HCl \cdot 0.5H_2O$	171–174 (kn)	HH	63	8.6	−28*	−35*
64	2,4-F_2	2,4-$F_2C_6H_3$	CH	3	$C_{30}H_{31}F_4NO_3 \cdot C_2H_2O_4$	151–153 (kn)	HH	58	7.8	−12*	−16*
65	4-Cl	4-ClC_6H_4	CH	3	$C_{30}H_{33}Cl_2NO_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$	169–171 (kn)	HH	30	8.6	−3	−9*
66	4-CH_3	4-$CH_3C_6H_4$	CH	3	$C_{32}H_{39}NO_3 \cdot 0.25H_2O$	oil	HH	30	7.8	+3	−2
67	4-CH_3O	4-$CH_3OC_6H_4$	CH	3	$C_{32}H_{39}NO_5 \cdot C_2H_2O_4$	163.4–165 (kn)	HH	27	8.0	+2	+1
68	4-F	cyclohexyl	CH	3	$C_{30}H_{40}FNO_3$	oil	HH	74	8.3	+3	−6
69	4-F	2-pyridyl	CH	3	$C_{29}H_{33}FN_2O_3 \cdot 0.25H_2O$	oil	HH	62	6.8	−3	+3
70	4-F	H	CH	3	$C_{24}H_{30}FNO_3 \cdot C_4H_4O_4$[h]	113–114.5 (kn)	HH	67	7.7	−7*	−4*
71	4-F	4-FC_6H_4	$CHCH_2$[i]	3	$C_{31}H_{35}F_2NO_3 \cdot C_4H_4O_4$[f]	156–157 (kn)	HH	64	8.5	−13*	−10*
72	4-F	4-FC_6H_4	CH	2	$C_{29}H_{31}F_2NO_3$	129–131 (s)	HH	27	8.2	−4	0
73	4-F	4-FC_6H_4	CH	4	$C_{31}H_{35}F_2NO_3 \cdot 0.5H_2O$	oil	HH	31	8.6	−16*	−21*
74	4-F	4-FC_6H_4	CH	5	$C_{32}H_{37}F_2NO_3 \cdot 0.5H_2O$	oil	HH	25	8.5	−5	−13*
75	4-F	4-FC_6H_4	CH	6	$C_{33}H_{39}F_2NO_3$	oil	HH	54	8.2	−10	−22
76[g]	4-F	4-FC_6H_4	C(OH)	3	$C_{30}H_{33}F_2NO_4$	147–149 (m)		75	8.0	−5	−9
77[g]	3,4-F_2	3,4-$F_2C_6H_3$	C(OH)	3	$C_{30}H_{31}F_4NO_4$	143–146 (m)		48	8.6	−5	−24*
78	4-F	4-FC_6H_4	C=	3	$C_{30}H_{31}F_2NO_3 \cdot C_4H_4O_4$[f]	182–183 (kn)	HH	23	8.4	−9*	−12*[j]
79	4-F	4-FC_6H_4	C(CN)	3	$C_{31}H_{32}F_2N_2O_3 \cdot C_4H_4O_4$[h] $\cdot 0.25H_2O$	158–160 (kn)	HH	52	8.7	−17*	−26*[j]
80	4-F	4-FC_6H_4	$C(CONH_2)$	3	$C_{31}H_{34}F_2N_2O_4 \cdot 0.5C_4H_4O_4$[f] $\cdot 0.5H_2O$	258–260 dec (kn)	HH	67	7.6	+3	+5
81	4-F	4-FC_6H_4	$C(NH_2)$	3	$C_{30}C_{34}F_2N_2O_3 \cdot 2C_4H_4O_4$[f] $\cdot H_2O$	124–128 (k)	HH	61	7.5	+1	−10*
82	4-F	4-FC_6H_4	$C(NHCOCH_3)$	3	$C_{32}H_{39}F_2N_2O_4 \cdot 0.25H_2O$	glass	NN	43	7.2	−3	−7
diltiazem									7.7	−14*	−13*
verapamil									8.0	−19*	−22*
nifedipine									9.8	−30*	−35*
lidoflazine									7.5	−9	−9*
flunarizine									8.3	−1	−1

[a] All compounds were analyzed for C, H, and N, and the results were within ±0.4% of theoretical values. [b] Recrystallization solvents: k = methanol, l = ethanol, m = 2-propanol, n = diethyl ether, o = diisopropyl ether, p = acetonitrile, q = 4-methyl-2-pentanone, r = methylene chloride, and s = trituration with diethyl ether. Oils and glasses were purified by column or flash chromatography on SiO_2. [c] Letters refer to the method of preparation described in the Experimental Section. [d] Antagonism of concentration-dependent, $CaCl_2$-induced contractions of KCl-depolarized rabbit aortic strips. See Experimental Section for details. [e] Average percent change from predose mean arterial blood pressure of conscious SHR, 0.5–2 h and 3–6 h after dosing (30 mg/kg, po). Starred values (*) indicate reductions in MABP that were statistically significant ($p < 0.05$) from pretreatment values as determined by a one-tailed, *t* test for paired observations. Unless otherwise indicated, $n = 3$–6 rats. See Experimental Section for details. [f] Fumarate. [g] Reference 11. [h] Maleate. [i] CH_2 bonded to piperidine ring. [j] $n = 11$ rats.

and lidoflazine, but less potent than nifedipine in this assay. Also, as shown with compounds **59**–**71** and **76**–**82** in Table II, changes in the diarylmethyl group of **1** had a large effect on the calcium-channel-blocking activity. For X, the group linking the two aryl substituents to the piperidine ring, the potency decreased in the following order: X = CH (**1**), C(CN) (**79**) > C= (**78**) > C(OH) (**76**) > C-($CONH_2$) (**80**), $C(NH_2)$ (**81**) > $C(NHCOCH_3)$ (**82**). The only exception to this order was bis(3,4-difluorophenyl)-methanol **77**, which was similar in potency to benzhydryl compound **63**. Finally, **1** was slightly more potent than its one-carbon homologue **71**.

Substituents on the benzene rings of the benzhydryl group had a large effect on the activity. Compounds with fluoro substituents in the 3- and/or 4-positions of both benzene rings of the benzhydryl group (**1** and **61**–**63**) were more potent than the monofluoro (**60**) and unsubstituted (**59**) analogues. In contrast, **64**, the bis(2,4-difluorophenyl)methyl compound, was less potent than **1**, **59**, and **63**, which indicated that fluoro substituents in the 2- and 2′-positions of the benzhydryl group were not well-tolerated. 4,4′-Dichloro analogue **65** was similar in potency to **1**, but the 4,4′-dimethyl (**66**) and the 4,4′-dimethoxy (**67**) analogues were less potent.

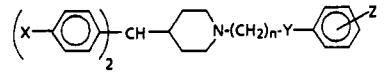
Replacing one of the benzene rings of the benzhydryl moiety with another group had varying effects on the potency. The cyclohexyl analogue **68** was similar in potency to **60**. On the other hand, 2-pyridyl analogue **69** was considerably less potent than **60**, and was one of the least active target compounds prepared in this project. Replacing the phenyl group in **60** with hydrogen gave **70**, which was less potent than **60**, but was similar in potency to lidoflazine.

As shown with **1** and **72**–**75** in Table II, changing the distance between the piperidine nitrogen and the phenoxy group affected the potency. The optimum distance appeared to be that in propyl compound **1**. Ethyl homologue **72** was less potent. Also, as the chain length was successively increased from propyl (**1**) to hexyl (**73**–**75**), the potency decreased.

Compounds **1**, **83**–**99**, and **104** in Table III show the effect that substituents on the phenoxy ring had on calcium-channel-blocking activity. Compound **104** with an unsubstituted phenoxy ring was equipotent to 4-acetyl-2-methoxy analogue **1**. The following modifications of the phenoxy group of **1** had no appreciable effect on the potency: replacing the 4-acetyl group with an ethyl (**84**), a carbomethoxy (**85**), a cyano group (**87**), or with hydrogen (**99**); replacing the 2-methoxy group with hydrogen (**89**); and moving the 2-methoxy group to the 3-position (**88**). However, reducing the 4-acetyl group in **1** to an alcohol (**83**) led to a 6-fold decrease in the potency, whereas replacing the 4-acetyl group with a carboxy group (**86**) produced a 50-fold reduction in the potency.

Comparing **104** with **90**–**98** shows that a fluoro (**92**), chloro (**93**), bromo (**94**), *tert*-butyl (**95**), or methoxy (**98**)

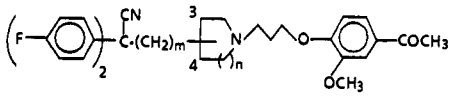
Table III. Calcium-Channel-Blocking Activity in Rabbit Aortic Strips and Antihypertensive Activity in Spontaneously Hypertensive Rats (SHR) of 4-(Diarylmethyl)-*N*-substituted-piperidines



no.	X	*n*	Y	Z	formula[a]	mp, °C (solv)[b]	method of prep[c]	% yield	Ca^{2+} pA_2[d]	SHR, % ΔMABP[e] 0.5–2 h	SHR, % ΔMABP[e] 3–6 h
1	F	3	O	2-OCH_3, 4-$COCH_3$					8.8	−15*	−22*
83	F	3	O	2-OCH_3, 4-$CH(OH)CH_3$	$C_{30}H_{35}F_2NO_3$	132–135 (nr)	LL	49	8.0	−14*	−9[f]
84	F	3	O	2-OCH_3, 4-CH_2Ch_3	$C_{30}H_{35}F_2NO_2{\cdot}C_2H_2O_4$	185–186 (kn)	HH	73	8.6	−9*	−7
85	F	3	O	2-OCH_3, 4-CO_2CH_3	$C_{30}H_{33}F_2NO_4$	oil	JJ	72	8.9	−4	−2
86	F	3	O	2-OCH_3, 4-CO_2H	$C_{29}H_{31}F_2NO_4{\cdot}0.5H_2O$	123–126 (s)	MM	62	7.1	+9	0
87	F	3	O	2-OCH_3, 4-CN	$C_{29}H_{30}F_2N_2O_2{\cdot}0.25H_2O$	oil	JJ	46	8.7	−3	−9*
88	F	3	O	3-OCH_3, 4-$COCH_3$	$C_{30}H_{33}F_2NO_3{\cdot}C_2H_2O_4$	190.5–191 (kn)	HH	60	8.5	−5	−11*
89	F	3	O	4-$COCH_3$	$C_{29}H_{31}F_2NO_2{\cdot}C_2H_2O_4$	141–143 (kn)	HH	75	8.6	−1	0
90	F	3	O	4-$CONH_2$	$C_{28}H_{30}F_2N_2O_2{\cdot}1.5C_4H_4O_4$[g]	193–194 (kn)	HH	58	7.5	−3	−8
91	F	3	O	4-CN	$C_{28}H_{29}F_2N_2O{\cdot}C_4H_4O_4$[g]	167–168 (kn)	HH	53	8.3	+8	−11
92	F	3	O	4-F	$C_{27}H_{29}F_3NO$	oil	HH	53	8.9	−2	−6
93	F	3	O	4-Cl	$C_{27}H_{28}ClF_2NO{\cdot}C_4H_4O_4$[g]	169–170 (kn)	HH	45	8.7	−15*	−25*
94	F	3	O	4-Br	$C_{27}H_{28}BrF_2NO{\cdot}C_4H_4O_4$[g]	185–186 (kn)	HH	79	8.8	−3	−17
95	F	3	O	4-$C(CH_3)_3$	$C_{31}H_{37}F_2NO{\cdot}C_4H_4O_4$[g]$\cdot 0.5H_2O$	194–196 dec (kn)	HH	55	9.0	−15*	−10*
96	F	3	O	4-NH_2	$C_{27}H_{30}F_2N_2O{\cdot}C_4H_4O_4$[g]$\cdot 0.5H_2O$	121.5–124 (kn)	OO	72	7.5	−5	−8
97	F	3	O	4-$NHCOCH_3$	$C_{29}H_{32}F_2N_2O_2{\cdot}HBr$	223–225 (kn)	HH	44	7.9	−12	−12
98	F	3	O	4-OCH_3	$C_{28}H_{31}F_2NO_2{\cdot}C_4H_4O_4$[g]	172–173 (kn)	HH	64	8.6	−2	−3
99	F	3	O	2-OCH_3	$C_{28}H_{31}F_2No_2$	oil	HH	34	8.6	−4	−1
100	F	2	O		$C_{30}H_{29}F_2NO{\cdot}HCl$	155–158 (kn)	II	64	7.9	−19*	−27*
101	F	2	O		$C_{30}H_{29}F_2NO{\cdot}C_2H_2O_4$	168–171 (kn)	II	62	8.4	−16	−30*
102	F	3	O		$C_{31}H_{31}F_2NO{\cdot}HBr{\cdot}0.5H_2O$	219–223 dec (kn)	JJ	19	8.3	−6	−7*
103	F	3	O		$C_{31}H_{31}F_2NO{\cdot}0.5H_2O$	oil	JJ	32	8.1	−7	−4
104	F	3	O	H	$C_{27}H_{29}F_2No{\cdot}C_2H_2O_4$	178–181 (kn)	II	60	8.8	−1	−2
105	F	3	CH_2	H	$C_{28}H_{31}F_2N{\cdot}C_2H_2O_4$	189–190 (kn)	HH	51	8.6	−5	−9*
106	F	3	NCH_3	H	$C_{28}H_{32}F_2N_2$	oil	KK	44	8.7	−3	−6
107	F	3	S	H	$C_{27}H_{29}F_2NS{\cdot}C_6H_8O_7$[h]	149.5–151 (kn)	HH	78	8.5	−5	−3
108	F	3	SO_2	H	$C_{27}H_{29}F_2NO_2S{\cdot}1.5C_4H_4O_4$[g]	172–173 (mn)	HH	26	7.7	+2	+3

[a–e] See corresponding footnotes in Table II. [f] *n* = 8 rats. [g] Fumarate. [h] Citrate.

Table IV. Calcium-Channel-Blocking Activity in Rabbit Aortic Strips and Antihypertensive Activity in Spontaneously Hypertensive Rats (SHR) of 3- and 4-Substituted-*N*-[3-(4-acetyl-2-methoxyphenoxy)propyl]pyrrolidines and -piperidines



no.	*m*	*n*	ring position	formula[a]	mp, °C (solv)[b]	method of prep[c]	% yield	Ca^{2+} pA_2[d]	SHR, % ΔMABP[e] 0.5–2 h	SHR, % ΔMABP[e] 3–6 h
79	0	2	4					8.7	−17*	−26*[f]
109	0	2	3	$C_{31}H_{32}F_2N_2O_3{\cdot}C_2H_2O_4{\cdot}H_2O$	108–109 (kn)	HH	17	8.1	+5	+9
110	1	2	3	$C_{32}H_{34}F_2N_2O_3{\cdot}0.25H_2O$	oil	HH	60	7.9	+2	−5[g]
111	0	1	3	$C_{30}H_{30}F_2N_2O_3{\cdot}0.25H_2O$	oil	HH	68	8.2	−2	+1
112	1	1	3	$C_{31}H_{32}F_2N_2O_3$	oil	HH	52	8.0	+3	−7

[a–e] See corresponding footnotes in Table II. [f] *n* = 11 rats. [g] *n* = 8 rats.

substituent in the 4-position of the phenoxy ring had little effect on the potency. However, the 4-carbamoyl (**90**), 4-cyano (**91**), 4-amino (**96**), and 4-acetamido (**97**) analogues were less potent than **104**. Also, the naphthoxy compounds **100–103** were less potent than **104**.

Replacing the oxygen atom of the phenoxy group in **104** with CH_2 (**105**), $N(CH_3)$ (**106**), or S (**107**) (Table III) had little, if any, effect on the calcium-channel-blocking activity. However, replacing the oxygen with SO_2 (**108**) produced an 13-fold reduction in potency.

The compounds in Table IV were prepared in order to determine if the calcium-channel-blocking activity would be affected by moving the diarylmethyl group to the 3-position of the piperidine ring or by changing the piperidine to a pyrrolidine ring. As shown in Table IV, 4-piperidyl compound **79** was more potent than 3-isomer **109**, the one-carbon homologue of **109** (**110**), and 3-pyrrolidinyl compounds **111** and **112**.

Compounds were evaluated for antihypertensive activity in spontaneously hypertensive rats (SHR) at an oral dose of 30 mg/kg. Only compounds that produced a statistically significant ($p < 0.05$) reduction in blood pressure that was greater than 10% at 0.5–2 h or 3–6 h after administration were considered to be active. Of the 55 target compounds in Tables II–IV that were tested, 17 met these criteria, but only nine of these produced a reduction in blood pressure greater than 20%. Also, many compounds that were potent calcium channel blockers in vitro, were inactive in the SHR.

The antihypertensive activity was very sensitive to

changes in the diarylmethyl portion of the molecule. As shown with 1, 59–71, and 76–82 in Table II, four structure–activity relationships were observed. First, only compounds with fluoro substituents in both rings of the diphenylmethyl group were active. For the benzhydryl compounds 1 and 61–64, the activity decreased in the following order: 3,3′,4,4′-tetrafluoro (63) ≈ 3,4,4′-trifluoro (62) > 4,4′-difluoro (1) ≈ 2,2′,4,4′-tetrafluoro (64) > 3,3′-difluoro (61). For the benzhydrols, bis(3,4-difluorophenyl) compound 77 was active, whereas bis(4-fluorophenyl) analogue 76 was inactive. Second, comparing 1 with 68–70 shows that replacing one of the 4-fluorophenyl groups with a cyclohexyl or a 2-pyridyl group or with a hydrogen abolished the antihypertensive activity. Third, as shown with 1, 63, 71, and 76–82, the most active compounds were those with X = CH (1 and 63) and C(CN) (79). When X was another group, the activity was greatly reduced or abolished. Fourth, comparing 79 with 109 in Table IV illustrates that moving the diarylmethyl group to the 3-position of the piperidine ring eliminated the antihypertensive activity. Also, the one-carbon homologue of 109 (110) as well as pyrrolidine analogues 111 and 112 were inactive (Table IV).

The antihypertensive activity was also affected by changing the distance between the piperidine nitrogen and the phenoxy group. The propyl (1) and butyl (73) homologues (Table II) were similar in activity. On the other hand, pentyl homologue 74 was less active, and the ethyl (72) and hexyl (75) homologues were inactive.

Changes in the aryloxy group had a large effect on the antihypertensive activity. Compound 104 (Table III) with no substituents on the phenoxy group was inactive. Of the 11 derivatives of 104 that contained only one substituent on the phenoxy ring (89–99), only 93 (Z = 4-Cl) and 95 (Z = 4-C$(CH_3)_3$) were effective in lowering blood pressure. The most active compound in Table III with two substituents on the phenoxy ring was 1, which was similar in activity to 93. Reducing the 4-acetyl group of 1 to an alcohol (83) or moving the 2-methoxy group to the 3-position (88) decreased the activity. Replacing the 4-acetyl group with an ethyl (84), carbomethoxy (85), carboxy (86), or cyano (87) group abolished the activity. Finally, naphthoxy compounds 100 and 101 (n = 2) were very effective in lowering blood pressure in the SHR. However, homologues 102 and 103 (n = 3) were inactive.

At an oral dose of 30 mg/kg, one of the most effective antihypertensive agents in this series was 63, which produced a 35% reduction in blood pressure in the SHR. This compound was more active than verapamil, diltiazem, flunarazine, and lidoflazine, but similar in activity to nifedipine. On the other hand, the lead compound, 1, produced a 22% reduction in blood pressure and was similar in activity to verapamil.

Seven compounds that showed good activity in the SHR at 30 mg/kg were tested at lower doses.[25] At an oral dose of 20 mg/kg, 1, 63, 73, 93, 100, and 101 produced reductions in blood pressure of 19–28%, 3–6 h after dosing; 79 gave only a 14% reduction. At an oral dose of 10 mg/kg, 73, 93, and 101 produced 17–23% reductions in blood pressure, but the remaining four compounds were inactive. Finally, at an oral dose of 3 mg/kg, only 93 was active, producing an 11% reduction in blood pressure. Although 63 was one of the most effective antihypertensive agents at our screening dose of 30 mg/kg, it was not one of the best compounds at lower doses. Compound 93 gave a better dose–response profile than 63 and was effective in lowering blood pressure at oral doses of 10 (17% reduction in blood pressure) and 3 mg/kg;[28] 63 was inactive at 10 mg/kg.

An examination of the data in Tables II–IV indicates that there was a poor correlation between the calcium-channel-blocking activity, in vitro, and the antihypertensive activity in the SHR with oral administration of the compounds. For example, 65, 84, 87, 89, 92, 94, 98, 99, and 104–107 were similar in potency to 63 in the calcium-channel-blocking assay, but were inactive in the SHR. Also, in several cases small changes in the structure of a compound had little effect on the calcium-channel-blocking activity, but abolished the antihypertensive activity (1 vs 65, 85, 87, 89, 99, and 104; 93 vs 92 and 94; and 100 and 101 vs 102 and 103). These data suggest that many compounds that were inactive in our SHR test were either poorly absorbed or rapidly converted to inactive metabolites. This was supported by the fact that compounds 60, 65, 68–70, 72, 75, 76, 81, 85, 87, 91, 94, 103, and 110–112, which were inactive in our SHR model, produced a 30–60% reduction in blood pressure when administered to normotensive, anesthetized dogs at an intravenous dose of 1 mg/kg.[25]

In additional studies, 1, 62, 63, 93, and 95 were effective in inhibiting [^{3}H]nimodipine binding to voltage-sensitive calcium channels on rabbit skeletal muscle membranes (IC_{50s} = 10–30 nM).[25] Also, compounds 1 (AHR-5360) and 93 (AHR-12742) were subjected to additional pharmacological and biochemical evaluation, and the results of this work were reported elsewhere.[26-28] Finally, benzhydrol 91, which was a weaker calcium channel blocker than 1 and was inactive in the SHR with oral administration of the compound, produced interesting antiallergy activity in our passive foot anaphylaxis assay. Accordingly, Walsh et al. synthesized a series of benzhydrols for testing for antiallergy activity, and this work was published earlier.[11]

In summary, 4-(diarylmethyl)-1-[3-(aryloxy)propyl]-piperidines and related compounds are a potent group of calcium channel blockers and may be useful for the treatment of hypertension and other cardiovascular diseases.[29] Accordingly, we are continuing to investigate this class of compounds and will present some of this work in future publications.

Experimental Section

General Procedures. Melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian A-60 or Varian EM-360L spectrometer with $CDCl_3$ or Me_2SO-d_6 being used as solvent and with Me_4Si as an internal standard; ^{13}C NMR spectra were recorded on a Varian FT-80A spectrometer with the same solvents. Chemical-ionization mass spectra were determined on a Varian MAT-44 mass spectrometer with isobutane being used as the reagent gas; electron-impact mass spectra were determined on a Hitachi Perkin-Elmer RMU-6H mass spectrometer. IR spectra were recorded as KBr pellets on a Beckman IR8 or a Perkin-Elmer 297 IR spectrophotometer. The spectral data for all compounds were consistent with the assigned structures. Low-pressure catalytic hydrogenations were carried out on a Parr

(25) Data not presented.

(26) Proakis, A. G.; Shanklin, J. R., Jr.; Wright, K. F.; Strand, J. C.; Appell, K. C.; Sancilio, L. F. *Cardiovasc. Drug Ther.* **1987**, *1*, 277.
(27) Barrett, R. J.; Proakis, A. G.; Berger, B. E.; Taylor, D. R.; Sancilio, L. F. *Cardiovasc. Drug Ther.* **1987**, *1*, 214.
(28) Appell, K. C.; Barrett, R. J.; Proakis, A. G.; Shanklin, J. R., Jr. *FASEB J.* **1989**, *3*, A601; abstract 2177.
(29) (a) Fleckenstein, A.; Fleckenstein-Grun, G.; Frey, M.; Zorn, J. *Am. J. Cardiol.* **1987**, *59*, 177B–187B. (b) Boddeke, E.; Hugtenburg, J.; Jap, W.; Heynis, J.; van Zwieten, P. *Trends Pharmacol. Sci.* **1989**, *10*, 397–400.

hydrogenation apparatus. High-pressure catalytic hydrogenations were carried out on a Parr 4563M high-pressure hydrogenation Mini Reactor. Chromatographic purification of compounds was done with column chromatography on Florisil or silica gel and with flash chromatography on silica gel. Elemental analyses were determined on a Perkin-Elmer Model 240 or a Control Equipment Corp. 240-XHA CHN analyzer; all compounds were analyzed for C, H, and N and gave results within ±0.4% of theoretical values.

The preparation of the following intermediates was described previously:[11] 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone, 1-[4-(2-chloroethoxy)-3-methoxyphenyl]ethanone, 1-[4-(4-chlorobutoxy)-3-methoxyphenyl]ethanone, 1-[4-(5-chloropentoxy)-3-methoxyphenyl]ethanone, 1-[4-[(6-chlorohexyl)oxy]-3-methoxyphenyl]ethanone, 1-[4-(3-chloropropoxy)-2-methoxyphenyl]ethanone, 1-[4-(3-chloropropoxy)phenyl]ethanone, 4-(3-chloropropoxy)benzamide, 4-(3-chloropropoxy)benzonitrile, 1-(3-chloropropoxy)-4-fluorobenzene, 1-chloro-4-(3-chloropropoxy)benzene, 1-*tert*-butyl-4-(chloropropoxy)benzene, *N*-[4-(3-chloropropoxy)phenyl]acetamide, 1-(3-chloropropoxy)-4-methoxybenzene, 1-(3-chloropropoxy)-2-methoxybenzene, α,α-bis(4-fluorophenyl)-4-piperidinemethanol, 4-(diphenylmethyl)-piperidine, and 4-(4-fluorobenzoyl)pyridine. [(3-Chloropropyl)-thio]benzene, and [(3-chloropropyl)sulfonyl]benzene were synthesized by published procedures.[30] The synthesis of compounds **59**, **76**, **77**, and **113–115** was described previously.[11] 4-Benzoylpyridine, 1-chloro-4-phenylbutane, and 3-phenoxypropyl bromide were commercially available. Diltiazem, verapamil, nifedipine, lidoflazine, and flunarizine were obtained from Sigma Chemical Co.

Chemistry. Method A. 2-(2-Bromoethoxy)naphthalene (2).[10] A mixture of 144.0 g (1.0 mol) of 2-naphthol and 56.1 g (1.0 mol) of potassium hydroxide in 1 L of 95% ethanol was stirred at room temperature for 0.5 h. To this was added 935 g (5.0 mol) of 1,2-dibromoethane, and the mixture was heated at reflux overnight. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ and 10% NaOH. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give 106.6 g (43%) of **2** as a brown solid. A small portion of this was recrystallized from diethyl ether to give an analytically pure sample of **2** as a light brown solid, mp 91.5–93 °C. Anal. ($C_{12}H_{11}BrO$) C, H.

1-(2-Bromoethoxy)naphthalene[10] was prepared by the same method.

Method B. 1-Bromo-4-(3-chloropropoxy)benzene (3). A mixture of 69.2 g (0.40 mol) of 4-bromophenol, 67.7 g (0.43 mol) of 1-bromo-3-chloropropane, and 55.3 g (0.40 mol) of potassium carbonate in 500 mL of acetone was heated for 16 h at reflux. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and dilute NaOH. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo to give an oil. This was recrystallized from diisopropyl ether to give 79.9 g (80%) of **3** as a white solid: mp 47–48 °C. Anal. ($C_9H_{10}BrClO$) C, H.

1-(3-Chloropropoxy)-4-ethyl-2-methoxybenzene (**4**) was also prepared by this method to give **4** as an oil (52%) after being purified by column chromatography on SiO_2. Anal. ($C_{12}H_{17}ClO_2$) C, H.

Method C. 1-(Phenylsulfonyl)-4-piperidinecarboxylic Acid Ethyl Ester (47). To a solution of 10.1 g (0.064 mol) of ethyl isonipecotate in 300 mL of pyridine and cooled in an ice bath was added 13.2 g (0.075 mol) of benzenesulfonyl chloride. The mixture was stirred for 2 h at room temperature, and the solvent was removed in vacuo. The residue was partitioned between CH_2Cl_2 and dilute NaOH. The CH_2Cl_2 solution was dried ($MgSO_4$), and the solvent was removed in vacuo to give a solid. This was recrystallized from ethanol–diethyl ether to give 4.59 g (24%) of **47** as a crystalline solid, mp 85–86.5 °C. Anal. ($C_{14}H_{19}NO_4S$) C, H, N.

In another preparation of **47**, 100.0 g (0.63 mol) of ethyl isonipecotate and 130.2 g (0.74 mol) of benzenesulfonyl chloride in 800 mL of pyridine were reacted by the above procedure for 4.5 h. Recrystallization from ethanol–diethyl ether gave 148.0 g (78%) of **47**, mp 87–89 °C.

Method D. α,α-Bis(3-fluorophenyl)-1-(phenylsulfonyl)-4-piperidinemethanol (21). To a mechanically stirred suspension of 7.78 g (0.33 mol) of magnesium turnings and a crystal of iodine in 800 mL of anhydrous diethyl ether and under an atmosphere of nitrogen was slowly added a solution of 51.98 g (0.30 mol) of 1-bromo-3-fluorobenzene in 200 mL of diethyl ether. The mixture was stirred for 1.5 h, and 30.6 g (0.10 mol) of **47** was added as a solid. Anhydrous THF (300 mL) was added, and the mixture was stirred at room temperature for 12 h. The mixture was poured into an icy solution of NH_4Cl. The aqueous mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 solution was dried ($MgSO_4$). The solvent was removed in vacuo, and the resulting residue was recrystallized from diethyl ether to give 24.14 g (53%) of **21** as a white, crystalline solid, mp 183–185 °C. Anal. ($C_{24}H_{23}F_2NO_3S$) C, H, N.

Method E. (4-Fluorophenyl)[1-(phenylsulfonyl)-4-piperidinyl]methanone (48). A mixture of 53.3 g (0.22 mol) of 4-(4-fluorobenzoyl)piperidine hydrochloride[31] and 44.0 g (0.25 mol) of benzenesulfonyl chloride in 500 mL of pyridine was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and dilute NaOH. The CH_2Cl_2 solution was extracted with dilute H_2SO_4 and was dried ($MgSO_4$). The volume was reduced in vacuo to 400 mL, hexane was added, and 39.2 g (51%) of **48** was collected as a white, crystalline solid, mp 156.5–158 °C. Anal. ($C_{18}H_{18}FNO_3S$) C, H, N.

Method F. α-(3,4-Difluorophenyl)-α-(4-fluorophenyl)-1-(phenylsulfonyl)-4-piperidinemethanol (23). A three-neck, round-bottom flask, equipped with a mechanical stirrer, flushed with nitrogen, and containing 3.74 g (0.154 mol) of magnesium turnings, was dried with a Bunsen burner. After the flask had cooled, 600 mL of THF (dried over molecular sieves 5A) was added. To this mechanically stirred mixture was slowly added a solution of 29.4 g (0.152 mol) of 4-bromo-1,2-difluorobenzene in 50 mL of THF. The mixture was stirred for 1 h, and 45.11 g (0.130 mol) of **48** was added as a solid. The solution was stirred at ambient temperature for 3 h and was poured into an icy, aqueous solution of NH_4Cl. The aqueous mixture was extracted with CH_2Cl_2, the CH_2Cl_2 solution was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was recrystallized from CH_2Cl_2–hexanes to give 58.89 g (83%) of **23**. A small sample was recrystallized from a mixture of CH_2Cl_2–diethyl ether–hexanes to give an analytically pure sample of **23**, mp 97–99 °C. Anal. ($C_{24}H_{22}F_3NO_3S$) C, H, N.

Method G. α-(4-Fluorophenyl)-α-[1-(phenylsulfonyl)-4-piperidinyl]-2-pyridinemethanol (25). To a solution of 9.26 g (0.059 mol) of 2-bromopyridine in 250 mL of THF (dried over molecular sieves 5A), cooled to −65 °C and under an atmosphere of nitrogen, was slowly added 5.6 mL (0.059 mol) of a 10.5 M solution of *n*-butyllithium in hexanes. The mixture was stirred at −65 °C for 1 h, and 18.2 g (0.053 mol) of **48** was added as a solid. The solution was warmed to room temperature and then was stirred for 72 h. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ and water. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give a brown oil. This was subjected to flash chromatography on SiO_2 with 30–40% ethyl acetate in hexanes being used as the eluent. The resulting white solid was triturated with diethyl ether to give 12.12 g (54%) of **25**, mp 160–163 °C. Anal. ($C_{23}H_{23}FN_2O_3S$) C, H, N.

Method H. α-Cyclohexyl-α-(4-fluorophenyl)-4-pyridinemethanol (56). To a magnetically stirred solution of 23.4 g (0.117 mol) of 4-(4-fluorobenzoyl)pyridine[11] in 400 mL of THF (dried over molecular sieves 4A), cooled in an ice bath and under an atmosphere of nitrogen, was slowly added 70 mL (0.140 mol) of a 2 M solution of cyclohexylmagnesium chloride in diethyl ether. The solution was stirred at room temperature for 0.5 h and then was heated at reflux for 4 h. An aqueous solution of NH_4Cl was added, and the solvent was removed in vacuo. The residue was partitioned between $CHCl_3$ and water, and the organic phase was dried (Na_2SO_4). The solvent was removed in vacuo to give a brown

(30) Zimmerman, H. E.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1960**, *82*, 2505–2511.

(31) Duncan, R. L., Jr.; Helsley, G. C.; Welstead, W. J., Jr.; DaVanzo, J. P.; Funderburk, W. H.; Lunsford, C. D. *J. Med. Chem.* **1970**, *13*, 1–6.

oil. Trituration with diethyl ether gave 17.67 g (53%) of **56** as a white, crystalline solid, mp 165–167 °C. Anal. ($C_{18}H_{20}FNO$) C, H, N.

Compound **57** was prepared by the same procedure except that (4-fluorophenyl)magnesium bromide was reacted with 4-benzoylpyridine.

Method I. 4-[Bis(2,4-difluorophenyl)methyl]pyridine Hydrochloride (52). To a mechanically stirred solution of 45.6 g (0.40 mol) of 1,3-difluorobenzene in 40 mL of concentrated H_2SO_4 at 0 °C was slowly added 21.4 g (0.20 mol) of 4-pyridinecarboxaldehyde.[13] The mixture was warmed to room temperature, was heated at 70 °C overnight, and then was poured over ice. The icy mixture was made basic with 50% NaOH and then was extracted with $CHCl_3$. The organic phase was extracted with 5% NaOH and dried (Na_2SO_4). The solvent was removed in vacuo to give 28.3 g (45%) of the nonsalt form of **52** as a colorless oil. A 1.0-g sample of this was converted to the HCl salt, and the salt was recrystallized from 2-propanol–diethyl ether to give 0.97 g of **52** as a white, crystalline solid, mp 218–222 °C. Anal. ($C_{18}H_{11}F_4N$·HCl) C, H, N.

Method J. 1-[(4-Methylphenyl)sulfonyl]-3-piperidinol 4-Methylbenzenesulfonate Ester (43). A solution of 73.5 g (0.73 mol) of 3-hydroxypiperidine and 350.0 g (1.84 mol) of *p*-toluenesulfonyl chloride in 1 L of pyridine was stirred at room temperature for 17.5 h. The solution was diluted with 1 L of water, and the aqueous mixture was extracted with several portions of CH_2Cl_2. The CH_2Cl_2 solution was extracted with dilute H_2SO_4 and was dried ($MgSO_4$). The solvent was removed in vacuo to give an oil. This was recrystallized from CH_2Cl_2–diethyl ether to give 301.4 g (101%) of a yellow solid, mp 131–133 °C. A 12.7-g sample of this was recrystallized from CH_2Cl_2–diethyl ether to give 9.31 g of an analytically pure sample of **43**, mp 132–133 °C. Anal. ($C_{19}H_{23}NO_5S_2$) C, H, N.

Method K. α,α-Bis(4-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-4-piperidineacetonitrile (37). A suspension of 4.90 g (0.123 mol) of a 60% dispersion of NaH in mineral oil (washed with hexanes) and 28.0 g (0.122 mol) of 4-fluoro-α-(4-fluorophenyl)benzeneacetonitrile[32] in 400 mL of Me_2SO (dried over molecular sieves 4A) and under an atmosphere of nitrogen was stirred for 1 h at room temperature. Then, 50.0 g (0.122 mol) of 4-methylphenylsulfonic acid ester with 1-[(4-methylbenzene)sulfonyl]-4-piperidinol[11] (**115**) was added as a solid, and the mixture was stirred for 15 h at 60 °C. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ and 5% NaOH. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give a solid. This was triturated with diisopropyl ether to give 55.41 g (97%) of **37** as a white solid. A 3-g portion of this was recrystallized from 2-propanol–MeOH to give 2.28 g of an analytical sample of **37**, mp 190–191 °C. Anal. ($C_{26}H_{24}F_2N_2O_2S$) C, H, N.

Method L. 1-(Phenylmethyl)-3-pyrrolidinemethanol 4-Methylbenzenesulfonate Ester Ethanedioate (1:1) (46). A solution of 113.8 g (0.60 mol) of 1-(phenylmethyl)-3-pyrrolidinemethanol,[33] 125.9 g (0.66 mol) of *p*-toluenesulfonyl chloride, and 66.6 g (0.66 mol) of triethylamine in 900 mL of acetonitrile was stirred at room temperature overnight. The reaction mixture was filtered, and the solvent was removed in vacuo. The residue was partitioned between $CHCl_3$ and 5% NaOH, and the organic phase was dried (Na_2SO_4). The solvent was removed in vacuo to give a brown oil. A methanolic solution of this oil was treated with oxalic acid, diethyl ether was added, and 181.6 g (70%) of **46** was collected as a white, crystalline solid. A small portion of this was recrystallized from MeOH–diethyl ether to give an analytically pure sample of **46**, mp 147–149 °C. Anal. ($C_{19}H_{23}NO_3S$·$C_2H_2O_4$) C, H, N.

Method M. α,α-Bis(4-fluorophenyl)-1-(phenylmethyl)-3-pyrrolidinepropanenitrile (41). A suspension of 7.32 g (0.183 mol) of a 60% dispersion of NaH in mineral oil (washed with hexanes) and 41.9 g (0.183 mol) of 4-fluoro-α-(4-fluorophenyl)-benzeneacetonitrile[32] in 600 mL of Me_2SO (dried over molecular sieves 4A) and under an atmosphere of nitrogen was stirred for 3 h at room temperature. Then, 63.18 g (0.183 mol) of **46** was added as a solid, and the solution was stirred at 60 °C overnight. The solvent was removed in vacuo, and the resulting oil was partitioned between $CHCl_3$ and 5% NaOH. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give 59.0 g (81%) of an oil. A 10.0-g portion of this was subjected to flash chromatography on SiO_2 with ethyl acetate–hexanes (1:1) and ethyl acetate being used as the eluent. This gave 4.13 g of **41** as a brown oil. Anal. ($C_{26}H_{24}F_2N_2$·$0.5H_2O$) C, H, N.

Method N. α,α-Bis(3,4-difluorophenyl)-4-pyridinemethanol (58). A solution of 5.66 g (0.018 mol) of **53** and 12 drops of 50% NaOH in 50 mL of Me_2SO and with air bubbling through the reaction mixture was stirred at room temperature for 4.5 h and then was diluted with water.[14] A tan precipitate was collected and recrystallized from CH_2Cl_2–hexanes to give 4.75 g (80%) of **58** as a white, crystalline solid, mp 147–147 °C. Anal. ($C_{18}H_{11}F_4NO$) C, H, N.

As described previously,[11] **58** was converted to α,α-bis(3,4-difluorophenyl)-4-piperidinemethanol (**113**) by catalytic hydrogenation over 5% Pt/C.

Method O. α-(4-Fluorophenyl)-4-piperidinemethanol Hydrochloride (20). To a magnetically stirred solution of 9.95 g (0.25 mol) of sodium borohydride in 200 mL of absolute ethanol was slowly added a solution of 10.2 g (0.042 mol) of 4-(4-fluorobenzoyl)piperidine hydrochloride in 200 mL of absolute ethanol. The mixture was stirred at room temperature for 0.5 h, and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and 2 M NH_4OH, and the solvent was removed in vacuo from the organic phase. The resulting solid was dissolved in 60 mL of absolute ethanol, 3.5 mL of concentrated HCl was added, and a white solid precipitated to give 7.32 g (71%) of **20**, mp 254 °C dec. Anal. ($C_{12}H_{16}FNO$·HCl) C, H, N.

Method P. 4-[Bis(3-fluorophenyl)methyl]piperidine Hydrochloride (7). A mixture of 15.25 g (0.034 mol) of **21**, 50 mL of 57% hydrogen iodide, and 3.4 g (0.11 mol) of phosphorus in 300 mL of glacial acetic acid was heated at reflux for 40 h. The reaction mixture was filtered, and the solvent was removed in vacuo from the filtrate. The residue was partitioned between CH_2Cl_2 and dilute NaOH. The CH_2Cl_2 solution was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was dissolved in MeOH, excess ethereal HCl was added, and anhydrous diethyl ether was added. A precipitate was collected to give 7.04 g (63%) of **7** as a white, crystalline solid, mp 260–262 °C. Anal. ($C_{18}H_{19}F_2N$·HCl) C, H, N.

Method Q. 4-[Bis(4-chlorophenyl)methyl]piperidine Ethanedioate (1:1) (11). A mixture of 13.05 g (0.041 mol) of the nonsalt form of **27** and 45.0 g (1.45 mol) of phosphorus in 300 mL of glacial acetic acid and 230 mL of 57% hydrogen iodide was heated at reflux for 72 h. The mixture was cooled to room temperature and was filtered through Celite, and the filtrate was made basic with 50% NaOH. The basic mixture was extracted with $CHCl_3$, and the organic solution was dried (Na_2SO_4). The solvent was removed in vacuo to give 12.12 g (93%) of the nonsalt form of **11** as a brown oil. A 0.65-g portion of this was converted to the oxalic acid salt, and the salt was recrystallized from MeOH–diethyl ether to give 0.46 g of **11** as a white, crystalline solid, 219–220 °C. Anal. ($C_{18}H_{19}Cl_2N$·$C_2H_2O_4$·$0.5H_2O$) C, H, N.

Method R. 4-[Bis(4-fluorophenyl)methyl]piperidine (*E*)-2-Butenedioate (2:1) (6). A mixture of 30.6 g (0.99 mol) of phosphorus and 15.1 g (0.059 mol) of iodine in 90 mL of glacial acetic acid was stirred at room temperature for 20 min. A solution of 56.2 g (0.197 mol) of the nonsalt form of **26** in a mixture of 70 mL of methanesulfonic acid, 6 mL of H_2O, and 110 mL of glacial acetic acid was added, and the mixture was heated at reflux for 7 h. The solvent was removed in vacuo, and the resulting viscous liquid was poured over ice. The icy mixture was made basic with 50% NaOH and was extracted with CH_2Cl_2. The CH_2Cl_2 solution was extracted with an aqueous solution of sodium thiosulfate and was dried (Na_2SO_4). The solvent was removed in vacuo to give a gum. A methanolic solution of the gum was treated with fumaric acid, and diethyl ether was added. A white solid was collected to give 22.6 g (32%) of **6**, mp 208–209 °C. Anal. ($C_{18}H_{19}F_2N$·$0.5C_4H_4O_4$·$0.5H_2O$) C, H, N.

Method S. 4-[(4-Fluorophenyl)methyl]piperidine Hydrochloride (16). A mixture of 12.0 g (0.057 mol) of the nonsalt form of **20**, 2.2 g (0.071 mol) of phosphorus, and 50 mL of 57%

(32) Jannsen, P. A. J.; Niemegeers, C. J. E. J.; Stokbrockx, R. A.; Vandenberk, J. U. S. Patent 3 884 916, 1975.
(33) Wu, Y. H.; Feldkamp, R. F. *J. Org. Chem.* **1961**, *26*, 1519–1524.

hydrogen iodide in 200 mL of glacial acetic acid was heated at reflux for 10 h. The mixture was filtered through Celite, and the solvent was removed in vacuo. The residue was partitioned between CH_2Cl_2 and dilute NaOH. The CH_2Cl_2 phase was extracted with several portions of dilute H_2SO_4. The acidic extract was made basic with NaOH, and the basic solution was extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried ($MgSO_4$), and the solvent was removed in vacuo to give an oil. This was dissolved in MeOH, excess ethereal HCl was added, and diethyl ether was added. A precipitate was collected to give 9.80 g (75%) of **16** as a white, crystalline solid, mp 163.5–165.5 °C. Anal. ($C_{12}H_{16}FN$·HCl) C, H, N.

Method T. 4-[Bis(2,4-difluorophenyl)methyl]piperidine Hydrochloride (9). A solution of 23.8 g (0.075 mol) of **52** in 400 mL of glacial acetic acid and in the presence of 2.0 g of 5% Pt/C was subjected to catalytic hydrogenation on a Parr apparatus at 60 °C for 3 days and at an initial pressure of 45 psi. The reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The residue was partitioned between $CHCl_3$ and 5% NaOH, and the organic phase was dried (Na_2SO_4). The solvent was removed in vacuo to give 24.4 g (100%) of the nonsalt form of **9** as an oil. A 1.0-g sample was converted to the HCl salt, and the salt was recrystallized from MeOH–diethyl ether to give 1.06 g of **9** as a white, crystalline solid, mp 215–217 °C. Anal. ($C_{18}H_{17}F_4N$·HCl) C, H, N.

Method U. 4-[Cyclohexyl(4-fluorophenyl)methyl]piperidine (14). A solution of 10.42 g (0.039 mol) of **49** and 10 drops of concentrated HCl in 200 mL of glacial acetic acid and in the presence 1.5 g of 5% Pt/C was subjected to catalytic hydrogenation on a Parr high-pressure hydrogenator at 60 °C for 16 h and at an initial pressure of 700 psi. The mixture was filtered through Celite, and the solvent was removed in vacuo. The residue was partitioned between $CHCl_3$ and 5% NaOH, the organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo. The resulting oil was subjected to flash chromatography on SiO_2 with 1–5% NH_4OH in MeOH being used as the eluent. This gave 5.86 g (55%) of **14** as a colorless oil. Anal. ($C_{18}H_{28}FN$) C, H, N.

Method V. 4-[2,2-Bis(4-fluorophenyl)ethyl]pyridine Hydrochloride (51). A mixture of 15.05 g (0.048 mol) of α,α-bis(4-fluorophenyl)-4-pyridineethanol (**114**),[11] 3.2 g (0.10 mol) of phosphorus, and 50 mL of 57% hydrogen iodide in 150 mL of glacial acetic was heated at reflux for 11 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and dilute NaOH. The organic phase was dried ($MgSO_4$), and the solvent was removed in vacuo to give the nonsalt form of **51** as an oil. This was converted to the HCl salt, and the salt was recrystallized from acetonitrile–diethyl ether to give 13.89 g (87%) of **51** as a white, crystalline solid, mp 197–199 °C. Anal. ($C_{19}H_{15}F_2N$·HCl) C, H, N.

Method W. 4-[2,2-Bis(4-fluorophenyl)ethyl]piperidine Hydrochloride (17). A solution of 10.0 g (0.030 mol) of **51** in 200 mL of glacial acetic acid and in the presence of 1.2 g of 5% Pd/C was subjected to catalytic hydrogenation on a Parr apparatus at room temperature for 16 h and at an initial pressure of 49 psi. The solution was filtered through Celite, and the solvent was removed in vacuo. The residue was partitioned between CH_2Cl_2 and dilute NaOH, and the organic phase was concentrated to give an oil. This was dissolved in MeOH, an excess of ethereal HCl was added, and a precipitate was collected to give 7.58 g (72%) of **17** as a white, crystalline solid, mp 171–173 °C. Anal. ($C_{19}H_{21}F_2N$·HCl·0.5H_2O) C, H, N.

Method X. 4-[Bis(4-fluorophenyl)methylene]piperidine Hydrobromide (26). A mixture of 164 g (0.34 mol) of **22** and 80 g (0.85 mol) of phenol in 700 mL of 48% HBr was heated at reflux for 7 h and then was stirred at room temperature for 9 h. The HBr solution was decanted from a gum in the bottom of the reaction flask. The gum was triturated with several portions of diethyl ether to give 91.3 g (73%) of **26** as a tan solid, mp 211–215 °C. A small portion of this was recrystallized from MeOH–diethyl ether to give an analytical sample, mp 216–218 °C. Anal. ($C_{18}H_{17}F_2N$·HBr) C, H, N.

Method Y. α,α-Bis(4-fluorophenyl)-4-piperidineacetonitrile Ethanedioate (1:1) (32). A solution of 52.41 g (0.11 mol) of **37** and 50.0 g (0.53 mol) of phenol in 200 mL of 48% HBr was heated at reflux for 3.5 h and then was poured over ice. The mixture was made basic with 50% NaOH and was extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give a brown oil. This was dissolved in a methanolic solution of oxalic acid, diethyl ether was added, and 34.24 g (69%) of **32** was collected as a white crystalline solid, mp 124–127 °C. ^1H NMR indicated that 0.5 mol of diethyl ether was present. Anal. ($C_{19}H_{18}F_2N_2$·$C_2H_2O_4$·0.5C_4H_{10}·0.25H_2O) C, H, N.

Method Z. α,α-Bis(4-fluorophenyl)-4-piperidineacetamide Hydrochloride (28). A solution of 9.31 g (0.030 mol) of **32** in 100 mL of 90% sulfuric acid was heated at 85 °C overnight. The solution was cooled to room temperature and was poured over ice. The mixture was made basic with 50% NaOH, and was extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give 9.19 g (93%) of a white solid. A 2.25-g portion of this was converted to the HCl salt, and the salt was recrystallized from 2-propanol–diethyl ether to give 0.54 g of **28** as a white, crystalline solid, mp 328 °C dec. Anal. ($C_{19}H_{20}F_2N_2O$·HCl) C, H, N.

Method AA. 4-[2-Amino-1,1-bis(4-fluorophenyl)-2-oxoethyl]-1-piperidinecarboxylic Acid Methyl Ester (29). A mixture of 7.65 g (0.023 mol) of **28**, 2.17 g (0.023 mol) of methyl chloroformate, and 3.36 g (0.023 mol) of sodium bicarbonate in 350 mL of CH_2Cl_2 was stirred at room temperature overnight. The mixture was successively extracted with water, 5% NaOH, and water. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give 5.59 g (67%) of a white solid. A 0.50-g sample was recrystallized from CH_2Cl_2–hexanes to give 0.30 g of **29** as a white, crystalline solid, mp 126–129 °C. Anal. ($C_{21}H_{22}F_2N_2O_3$) C, H, N.

Method BB. 4-[Bis(4-fluorophenyl)[(methoxycarbonyl)amino]methyl]-1-piperidinecarboxylic Acid Methyl Ester (30). To a magnetically stirred solution of 3.88 g (0.010 mol) of **29** and 4.0 g (0.050 mol) of 50% NaOH in 40 mL of MeOH was added dropwise a solution of 4.04 g (0.025 mol) of bromine in 25 mL of MeOH, and the mixture was heated at reflux for 16 h. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ and water. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give 3.60 g (86%) of a white solid. A 0.26-g sample was subjected to flash chromatography on SiO_2 with ethyl acetate–hexanes (1:1) being used as the eluent. This afforded 0.13 g of **30** as a white solid, mp 213 °C. Anal. ($C_{22}H_{24}F_2N_2O_4$·0.25H_2O) C, H, N.

Method CC. α,α-Bis(4-fluorophenyl)-4-piperidinemethanamine Ethanedioate (1:2) (31). A mixture of 2.98 g (0.007 mol) of **30** and 20 g (0.25 mol) of 50% NaOH in 40 mL of MeOH was heated at reflux for 16 h. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ and water. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give 1.90 g (88%) of an oil. A small sample of this was converted to the oxalic acid salt, and the salt was recrystallized from MeOH–diethyl ether to give an analytical sample of **31** as a light yellow solid, mp 151–154 °C. Anal. ($C_{18}H_{20}F_2N_2$·2$C_2H_2O_4$·0.5H_2O) C, H, N.

Method DD. 3-[2-Cyano-2,2-bis(4-fluorophenyl)ethyl]-1-pyrrolidinecarboxylic Acid Phenyl Ester (42). A mixture of 13.48 g (0.034 mol) of **41**, 46.7 g (0.30 mol) of phenyl chloroformate, and 50.0 g (0.50 mol) of $KHCO_3$ in 300 mL of $CHCl_3$ was heated at reflux overnight. The mixture was extracted with 5% NaOH and with water. The organic solution was dried (Na_2SO_4), and the solvent was removed in vacuo to give a brown oil. The oil was subjected to flash chromatography on SiO_2 with 25% ethyl acetate in hexanes being used as the eluent. This gave 10.12 g (70%) of **42** as a yellow oil. Anal. ($C_{26}H_{22}F_2N_2O_2$) C, H, N.

Method EE. α,α-Bis(4-fluorophenyl)-3-pyrrolidinepropanenitrile (36). A suspension of 19.12 g (0.044 mol) of **42** in 150 mL of 85% hydrazine was heated at reflux overnight and was then poured into 3.5 L of water. The aqueous mixture was extracted with $CHCl_3$, and the organic phase was dried ($MgSO_4$). The solvent was removed in vacuo to give a brown oil. This was subjected to flash chromatography on SiO_2 with MeOH and 2% NH_4OH in MeOH being used as the eluent. This gave 5.20 g (38%) of **36** as a red oil. Compound **36** was used in the next step without further purification.

Method FF. 4-[Bis(4-fluorophenyl)methyl]-1-piperidinepropanol Ethanedioate (1:1) (18). A mixture of 10.67 g (0.037 mol) of the nonsalt form of **6**, 5.42 g (0.039 mol) of

3-bromo-1-propanol, and 8.0 g (0.095 mol) of sodium bicarbonate in 400 mL of 1-butanol was heated at reflux for 21 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and dilute NaOH. The CH_2Cl_2 solution was dried ($MgSO_4$), and the solvent was removed in vacuo to give 8.88 g (67%) of the nonsalt form of **18** as an oil. A 1.14-g sample of this oil was converted to the oxalic acid salt, and the salt was recrystallized from MeOH–diethyl ether to give 1.09 g of **18** as a white solid, mp 89–94 °C. Anal. ($C_{21}H_{25}F_2NO\cdot C_2H_2O_4\cdot 0.75H_2O$) C, H, N.

Method GG. 4-[Bis(4-fluorophenyl)methyl]-1-(3-chloropropyl)piperidine (19). A solution of 40.3 g (0.12 mol) of the nonsalt form of **18** and 17.9 g (0.15 mol) of thionyl chloride in 300 mL of $CHCl_3$ was heated at reflux for 6 h, and the solvent was removed in vacuo. The residue was partitioned between $CHCl_3$ and a saturated solution of $NaHCO_3$. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give 42.1 g (99%) of **19** as an oil. An 8.0-g sample of this was subjected to flash chromatography on SiO_2 (elution with 50:50 ethyl acetate–hexanes) to give 6.84 g of an analytically pure sample of **19** as a brown oil. Anal. ($C_{21}H_{24}ClF_2N$) C, H, N.

Method HH. 1-[4-[3-[4-[Bis(2,4-difluorophenyl)-methyl]-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone Ethanedioate (1:1) (64). A mixture of 7.30 g (0.023 mol) of the nonsalt form of **9**, 5.57 g (0.023 mol) of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone, 5.54 g (0.040 mol) of K_2CO_3, and 0.2 g of KI in 350 mL of 1-butanol was heated at reflux overnight. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ and 5% NaOH. The organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give an oil. This was dissolved in a methanolic solution of oxalic acid, diethyl ether was added, and a white solid crystallized to give 8.23 g (58%) of **64**, mp 151–153 °C. Anal. ($C_{30}H_{31}F_4NO_3\cdot C_2H_2O_4$) C, H, N.

Method II. 4-[Bis(4-fluorophenyl)methyl]-1-[2-(1-naphthalenyloxy)ethyl]piperidine Hydrochloride (100). A mixture of 2.84 g (0.010 mol) of **6**, 3.01 g (0.012 mol) of 1-(2-bromoethoxy)naphthalene, and 5.0 g (0.060 mol) of $NaHCO_3$ in 400 mL of 1-butanol was heated at reflux for 16 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and 5% NaOH. The organic solution was dried ($MgSO_4$), and the solvent was removed in vacuo to give an oil. This was dissolved in MeOH, an excess of ethereal HCl was added, and 3.13 g (64%) of **100** crystallized as a white solid, mp 155–158 °C. Anal. ($C_{30}H_{29}F_2NO\cdot HCl$) C, H, N.

Method JJ. 4-[3-[4-[Bis(4-fluorophenyl)methyl]-1-piperidinyl]propoxy]-3-methoxybenzoic Acid Methyl Ester (85). To a magnetically stirred suspension of 2.47 g (0.062 mol) of a 60% dispersion of NaH in mineral oil (washed with hexanes) in 300 mL of Me_2SO (dried over molecular sieves 4A) and under an atmosphere of nitrogen was slowly added 11.26 g (0.062 mol) of methyl vanillate as a solid. The mixture was stirred at room temperature for 0.5 h, and a solution of 21.32 g (0.062 mol) of **19** in 100 mL of Me_2SO was added. The mixture was heated at 60 °C overnight, and the solvent was removed in vacuo. The residue was partitioned between $CHCl_3$ and water, the organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo to give a brown oil. The oil was subjected to flash chromatography on SiO_2 with ethyl acetate being used as the eluent. This gave 22.70 g (72%) of **85** as a brown oil. Anal. ($C_{30}H_{33}F_2NO_4$) C, H, N.

Method KK. *N*-[3-[4-[Bis(4-fluorophenyl)methyl]-1-piperidinyl]propyl]-*N*-methylbenzenamine (106). A mixture of 8.43 g (0.023 mol) of **19** in 100 mL of *N*-methylaniline was stirred at 100 °C for 30 h. The *N*-methylaniline was removed in vacuo, and the residue was partitioned between $CHCl_3$ and 1 M H_2SO_4. The organic phase was extracted with 5% NaOH and was dried (Na_2SO_4). The solvent was removed in vacuo, and the resulting oil was subjected to flash chromatography on SiO_2 with ethyl acetate being used as the eluent. This gave 4.41 g (44%) of **106** as a light brown oil. Anal. ($C_{28}H_{32}F_2N_2$) C, H, N.

Method LL. 4-[3-[4-[Bis(4-fluorophenyl)methyl]-1-piperidinyl]propoxy]-3-methoxy-α-methylbenzenemethanol (83). A mixture of 4.40 g (8.85 mol) of the nonsalt form of **1** and 3.0 g (79.3 mmol) of $NaBH_4$ in 350 mL of 95% ethanol was stirred at room temperature for 2.5 h. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ and water. The solvent was removed in vacuo from the organic phase, and the residue was recrystallized from CH_2Cl_2–diethyl ether to give 2.16 g (49%) of **83** as a white solid, mp 132–135 °C. Anal. ($C_{30}H_{35}F_2NO_3$) C, H, N.

Method MM. 4-[3-[4-[Bis(4-fluorophenyl)methyl]-1-piperidinyl]propoxy]-3-methoxybenzoic Acid (86). A mixture of 18.58 g (0.037 mol) of **85** and 16.80 g (0.30 mol) of KOH in 50 mL of water and 400 mL of ethanol was heated at reflux for 6 h. The solvent was removed in vacuo, and the residue was dissolved in 200 mL of 1 M H_2SO_4. A solution of 5% NaOH was added until a pH of 7 was reached, and the mixture was extracted with $CHCl_3$. The extract was dried (Na_2SO_4), and the solvent was removed in vacuo to give a solid. This was triturated with several portions of diethyl ether to give 11.38 g (62%) of **86** as a white, crystalline solid, mp 123–126 °C. Anal. ($C_{29}H_{31}F_2NO_4\cdot 0.5H_2O$) C, H, N.

Method NN. *N*-[[1-[3-(4-Acetyl-2-methoxyphenoxy)-propyl]-4-piperidinyl]bis(4-fluorophenyl)methyl]acetamide (82). A mixture of 3.53 g (6.95 mmol) of the nonsalt form of **81**, 1.10 g (14.4 mmol) of acetyl chloride, and 0.96 g (6.95 mmol) of K_2CO_3 in 100 mL of acetonitrile was stirred at room temperature overnight. The solvent was removed in vacuo, the residue was dissolved in $CHCl_3$, and water was added slowly. The phases were separated, and the organic phase was extracted with several portions of 5% NaOH and was dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was subjected to flash chromatography on SiO_2 with 20% MeOH in ethyl acetate being used as the eluent. This gave 1.63 g (43%) of **82** as a glass. Anal. ($C_{32}H_{36}F_2N_2O_4\cdot 0.25H_2O$) C, H, N.

Method OO. 4-[3-[4-[Bis(4-fluorophenyl)methyl]-1-piperidinyl]propoxy]benzenamine (*E*)-2-Butenedioate (1:1) (96). A solution of 11.80 g (0.027 mol) of **97** in a mixture of 500 mL of 6 M HCl and 500 mL of MeOH was heated at reflux overnight. The volume was reduced in vacuo, water was added, and the mixture was made basic with 5% NaOH. The mixture was extracted with $CHCl_3$, and the extract was dried (Na_2SO_4). The solvent was removed in vacuo, and the resulting oil was converted to the fumaric acid salt. The salt was recrystallized from MeOH–diethyl ether to give 8.49 g (72%) of **96** as a white solid, mp 121.5–124 °C. Anal. ($C_{27}H_{30}F_2N_2O\cdot C_4H_4O_4\cdot 0.5H_2O$) C, H, N.

α,α-Bis(3,4-difluorophenyl)-1-(phenylsulfonyl)-4-piperidinemethanol (116). To a mechanically stirred mixture of 2.70 g (0.22 mol) of magnesium turnings and a crystal of iodine in 100 mL of dry THF and under an atmosphere of nitrogen was slowly added a solution of 19.6 g (0.10 mol) of 1,2-difluoro-4-bromobenzene in 50 mL of THF. The mixture was stirred at room temperature for 1 h, and 11.88 g (0.040 mol) of **47** was added as a solid. The resulting solution was stirred at room temperature for 23 h and was poured into an icy solution of NH_4Cl. The aqueous mixture was extracted with CH_2Cl_2, and the organic phase was dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was recrystallized from CH_2Cl_2–hexanes to give 17.43 g (90%) of **116** as a white solid, mp 152–154 °C. Anal. ($C_{24}H_{21}F_4NO_3S$) C, H, N.

4-[Bis(3,4-difluorophenyl)methylene]piperidine Ethenedioate (1:1) (117). A mixture of 30.50 g (0.065 mol) of **116**, 100 mL of 57% HI, and 3.0 g (0.097 mol) of phosphorus in 400 mL of glacial acetic acid was heated at reflux for 65 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and dilute NaOH. The organic phase was dried ($MgSO_4$), and the solvent was removed in vacuo to give an oil. A mass spectrum of the oil indicated that it was largely **117** and that only a trace of **10** was present. A methanolic solution of the oil was treated with oxalic acid, diethyl ether was added, and 12.55 g (48%) of **117** crystallized as a white solid, mp 192–195 °C dec. Anal. ($C_{18}H_{15}F_4N\cdot C_2H_2O_4$) C, H, N.

Pharmacology. Antagonism of $CaCl_2$-Induced Contractions of Rabbit Aortic Strips. Spiral strips of thoracic aorta were obtained from nonfasted New Zealand white rabbits. After gently removing the endothelium, the strips were suspended in a modified Krebs solution aerated with 95/5% O_2/CO_2 at 37 °C, pH 7.4. Experiments were conducted according to the method of Godfraind and Kaba.[34] Briefly, the strips were sequentially bathed in a buffer containing $CaCl_2$, a $CaCl_2$-free buffer, and then

(34) Godfraind, T.; Kaba, A. *Br. J. Pharmacol.* **1969**, *36*, 549–560.

in a depolarizing, $CaCl_2$-free buffer. Cumulative addition of $CaCl_2$ to the last buffer induced contractions of the tissue, which were monitored by Grass force-displacement transducers. Contractile responses induced by $CaCl_2$ in the absence and presence of 1–100 nM of test compounds were compared. Responses of at least three tissues were used to calculate pA_2 values according to the method of Van Rossum.[35]

In this experiment, the test compound was also evaluated for α-adrenergic-blocking activity in the isolated rabbit aortic strips by the method of Broekaert and Godfraind[36] with norepinephrine (10^{-8}–10^{-5} M) being used as the agonist. In this procedure none of the compounds in Tables II–IV showed any significant inhibition of the contractions produced by norepinephrine. This indicated an absence of α-adrenergic-blocking activity.

Antihypertensive Activity. At least 24 h prior to compound administration, adult male spontaneously hypertensive rats (SHR) were anesthetized and a polyethylene catheter was implanted in a carotid artery or the abdominal aorta for measurement of arterial blood pressure. The catheter was exteriorized at the nape of the neck and connected through a swivel to a Statham pressure transducer; blood pressure was displayed on a Grass polygraph and simultaneously digitized and collected with a Buxco Electronics Datalogger. Data were collected from conscious, freely moving rats allowed free access to food and water. After obtaining baseline blood pressure data for 1–1.5 h, compounds were administered orally as solutions or uniform suspensions (30 mg/kg in 5 mL/kg of 0.5% Tween 80/distilled H_2O, v/v, or other vehicle as necessary). Blood pressure was measured at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h after dosing. The mean arterial blood pressure (MABP) values obtained at these intervals were used to calculate an average percent change from predose MABP for the 0.5–2-h and the 3–6-h periods. Raw MABP measurements were analyzed by a paired, one-tailed t test; decreases in MABP were considered statistically significant when $p < 0.05$.

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Registry No. 1, 111626-66-5; 1 (free base), 60284-72-2; 2, 13247-80-8; 3, 64010-38-4; 4, 131912-24-8; 5, 60285-02-1; 6, 131911-82-5; 6 (free base), 60285-00-9; 7, 131911-98-3; 8, 131912-06-6; 9, 131912-22-6; 9 (free base), 131950-23-7; 10, 131912-21-5; 11, 131911-94-9; 11 (free base), 131911-93-8; 12, 111627-43-1; 13, 111627-42-0; 14, 131912-01-1; 15, 131911-86-9; 16, 92822-03-2; 17, 131911-90-5; 18, 111627-39-5; 18 (free base), 111627-38-4; 19, 111952-43-3; 20, 38081-58-2; 20 (free base), 54924-33-3; 21, 135256-85-8; 22, 111627-27-1; 23, 135256-86-9; 24, 111627-37-3; 25, 131911-85-8; 26, 111627-29-3; 26 (free base), 58113-36-3; 27, 111627-36-2; 27 (free base), 67853-65-0; 28, 135256-87-0; 29, 135256-88-1; 30, 135256-89-2; 31, 135256-91-6; 32, 111952-37-5; 33, 111952-42-2; 34, 131912-12-4; 35, 131912-09-9; 36, 135256-92-7; 37, 111952-35-3; 38, 111952-40-0; 39, 131912-10-2; 40, 131912-07-7; 41, 111952-52-4; 42, 135256-93-8; 43, 101767-93-5; 44, 101768-07-4; 45, 131912-34-0; 46, 111627-59-9; 47, 111627-26-0; 48, 131912-02-2; 49, 131912-00-0; 50, 135256-94-9; 51, 131911-89-2; 51 (free base), 131911-88-1; 52, 135256-95-0; 53, 131912-17-9; 54, 67916-76-1; 55, 111627-44-2; 56, 131911-99-4; 57, 96835-27-7; 58, 117023-97-9; 59, 60284-70-0; 60, 111626-76-7; 61, 131911-80-3; 62, 131912-35-1; 63, 135256-96-1; 64, 131911-81-4; 65, 131911-79-0; 66, 111626-79-0; 67, 111626-78-9; 68, 131911-58-5; 69, 131911-41-6; 70, 135256-98-3; 71, 131911-76-7; 72, 111626-73-4; 73, 111626-80-3; 74, 111626-90-5; 75, 131911-55-2; 76, 60284-71-1; 77, 117023-24-2; 78, 135256-99-4; 79, 111952-14-8; 80, 135257-01-1; 81, 135257-03-3; 81 (free base), 135257-02-2; 82, 135257-04-4; 83, 111626-70-1; 84, 131911-73-4; 85, 131911-53-0; 86, 131911-56-3; 87, 111951-99-6; 88, 131911-46-1; 89, 111626-32-5; 90, 111626-92-7; 91, 111626-38-1; 92, 111626-10-9; 93, 111626-09-6; 94, 135257-06-6; 95, 111626-49-4; 96, 111626-59-6; 97, 111626-57-4; 98, 111626-12-1; 99, 111626-13-2; 100, 111626-63-2; 101, 111626-65-4; 102, 111952-21-7; 103, 111951-94-1; 104, 111625-93-5; 105, 135257-08-8; 106, 111951-91-8; 107, 135257-10-2; 108, 111952-07-9; 109, 111952-20-6; 110, 131911-61-0; 111, 131950-22-6; 112, 131911-42-7; 113, 117022-56-7; 114, 107071-84-1; 115, 101767-94-6; 116, 131912-11-3; 117, 131912-13-5; 2-naphthol, 135-19-3; 1,2-dibromoethane, 106-93-4; 4-bromophenol, 106-41-2; 1-(2-bromoethoxy)naphthalene, 13247-79-5; 1-bromo-3-chloropropane, 109-70-6; ethylisonipecotate, 1126-09-6; benzenesulfonyl chloride, 98-09-9; 1-bromo-3-fluorobenzene, 1073-06-9; 4-(4-fluorobenzyl)piperidine hydrochloride, 25519-78-2; 4-bromo-1,2-difluorobenzene, 348-61-8; 2-bromopyridine, 109-04-6; 4-(4-fluorobenzoyl)pyridine, 41538-36-7; cyclohexylmagnesium chloride, 931-51-1; (4-fluorophenyl)magnesium bromide, 352-13-6; 4-benzoylpyridine, 14548-46-0; 1,3-difluorobenzene, 372-18-9; 4-pyridinecarboxaldehyde, 872-85-5; 3-hydroxypiperidine, 6859-99-0; 4-fluoro-α-(4-fluorophenyl)-benzeneacetonitrile, 37742-99-7; 1-(phenylmethyl)-3-pyrrolidinemethanol, 5731-17-9; methyl chloroformate, 79-22-1; phenyl chloroformate, 1885-14-9; 3-bromo-1-propanol, 627-18-9; 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone, 58113-30-7; methyl vanillate, 3943-74-6; *N*-methylaniline, 100-61-8.

Supplementary Material Available: Four tables showing the elemental composition, percent yield, melting point, and method of preparation of 1-(aryloxy)-3-chloropropane intermediates 118–125, piperidine intermediates 126–129, and the target compounds 130–152; the biological data for 130–152; and an experimental section describing the preparation of 126, 127, 134, and 152 (8 pages). Ordering information is given on any current masthead page.

(35) Van Rossum, J. M. *Arch. Int. Pharmacodyn.* **1963**, *143*, 299–330.
(36) Broekaert, A.; Godfraind, T. *Eur. J. Pharmacol.* **1979**, *53*, 281–288.