tration, the EtOH was evaporated. The residue was dissolved in 50 ml of cold water and thereafter treated as in method D.

Method F. A modification of the method described by Schroff[5] was used. A solution of 0.5 g (0.002 mol) of 3-(2′-methoxyphenyl)-1,2,6,7,8,9-hexahydro-9a*H*-quinolizine (**8c**) in 25 ml of methanol was treated portionwise with 0.7 g (0.012 mol) of potassium borohydride. Thereafter the mixture was stirred for 12 hr, then poured into ice water, and extracted with ether. Evaporation of the ether gave 0.4 g (80%) of a mixture of **6c** and **7c** as determined by GLC.

Acknowledgment. The authors are grateful to Dr. N. P. Plotnikoff, Abbott Laboratories, for the biological data.

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Antiarrhythmics. *N*-(Aminoalkylene)trifluoroethoxybenzamides and *N*-(Aminoalkylene)trifluoroethoxynaphthamides

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Benzamides and naphthamides characterized by one or more 2,2,2-trifluoroethoxy ring substituents have been prepared and evaluated as antiarrhythmic agents in mice. Structure–action studies reveal that antiarrhythmic activity is highly dependent upon the number and position of 2,2,2-trifluoroethoxy groups. The most potent compounds are derived from 2,5-bis(2,2,2-trifluoroethoxy)benzamide, and, within this group, wide variation of the amide side chain is possible without adversely affecting the antiarrhythmic activity.

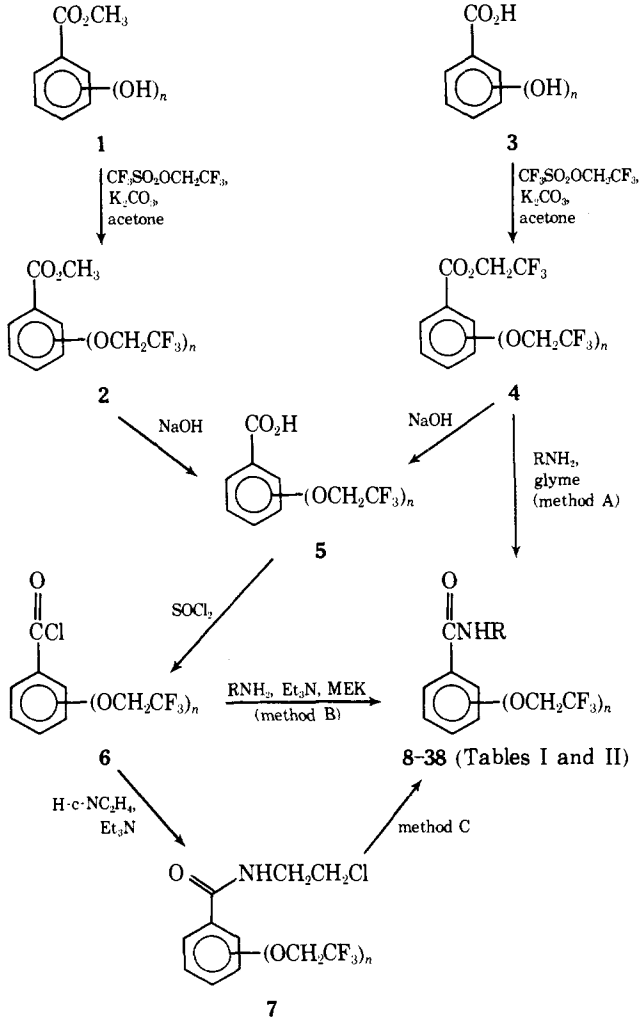
Antiarrhythmic agents as a class include many diverse structural types of compounds. The clinically useful antiarrhythmic drugs today include lidocaine, procainamide, quinidine, and the β-adrenergic blocking agents. Each of these has a somewhat different profile of activity, mechanism of action, and particular utility.[1]

In the past few years, lidocaine has emerged from this group as the drug of choice in coronary care units for treating life-threatening ventricular arrhythmias associated with cardiac emergencies.[2] Its increased use has coincided with a reduction in arrhythmic mortality among patients hospitalized for acute myocardial infarction.[2] Although lidocaine is very effective in such emergency situations when administered by intravenous infusion, it has not found wide use in the prolonged maintenance of patients who have a high risk of sudden, lethal arrhythmias. Factors which limit the usefulness of lidocaine as a prophylactic drug are primarily its extremely short duration of action and the necessity to administer it parenterally.[3] The alternative antiarrhythmic drugs, procainamide and quinidine, are generally not well tolerated during long-term use.[4] Thus a need remains for safer antiarrhythmic agents which may be used orally over prolonged periods of time.

During the course of an investigation of novel fluoroalkoxybenzamides and fluoroalkoxynaphthamides, potent local anesthetic and antiarrhythmic properties were observed. We report here the synthesis of these amides and the preliminary pharmacological evaluation of their antiarrhythmic potential.

Chemistry. Synthesis of a series of trifluoroethoxybenzamides (**8–38**) was achieved as illustrated in Scheme I. Although the various final compounds were synthesized by several different routes, the key step in each method was fluoroalkylation of the appropriate hydroxybenzoic acid or ester. A number of 1,1-dihydroperfluoro alcohols are generally available and are easily converted to trifluoromethanesulfonate esters. These substances are highly reactive alkylating agents. The present study utilized 2,2,2-trifluoroethyl trifluoromethanesulfonate,[5] a triflate which undergoes nucleophilic attack under relatively mild conditions and provides a very convenient medium for trifluoroethylation. Thus the simplest route to the desired benzamides was preparation of the activated trifluoroethyl ester **4** followed by direct aminolysis of **4** in the presence of excess amine (method A). An alternative procedure starting with the appropriately substituted methyl benzoate and proceeding via acid chloride **6** was used in cases where it was desirable to conserve amine (method B). In certain special cases the amide side chain was constructed in two steps by preparing the intermediate *N*-(2-chloroethyl)benzamide **7** and subsequently displacing chloride with the requisite amine (method C). Trifluoroethoxynaphthamides were

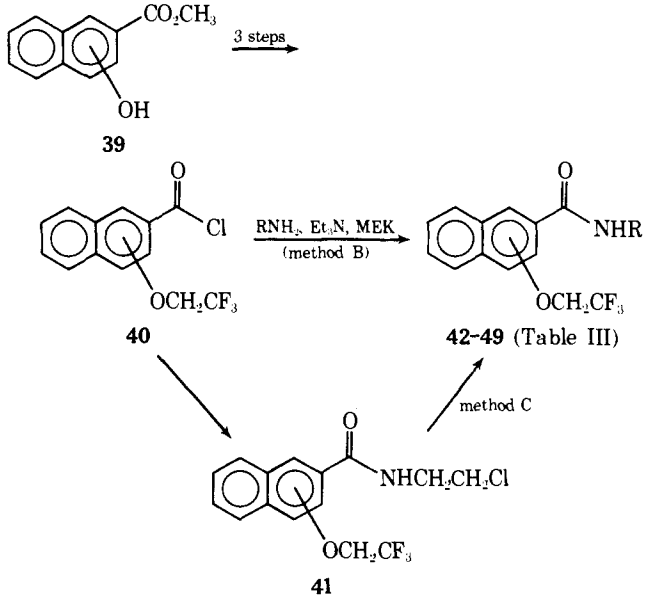
Scheme I



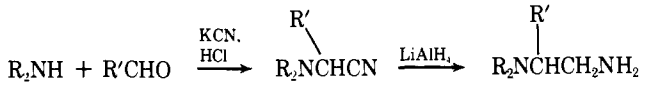
synthesized by analogous reactions as summarized in Scheme II.

The diamines required for many of the amides reported here are readily available. However, the branched diamines needed for compounds **20–24** and **36–38** had to be prepared. A Strecker reaction on the appropriate aldehyde according to the method of Luten[6] followed by $LiAlH_4$ reduction of the product aminonitrile (Scheme III) provided amines with branching β to the primary amine function. This route failed if the β-carbon was fully substituted (e.g., **23**) since $LiAlH_4$ treatment of the intermediate aminonitrile resulted in cleavage of the CCN bond. In this case the more laborious Scheme IV was used. Diamines with

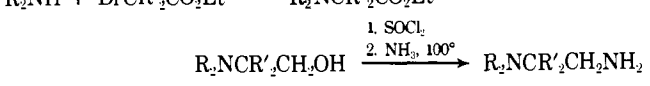
Scheme II



Scheme III

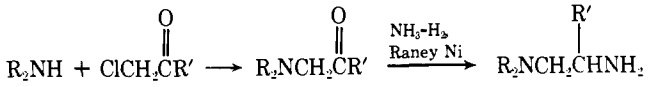


Scheme IV



branching α to the primary amino group were prepared in two steps by reductive amination of the appropriate α-diethylamino ketone[7] (Scheme V).

Scheme V



Since these reactions generally gave the best results with secondary amine starting materials (R = alkyl), the amines required for compounds **36–38** were not prepared directly. Instead *N*-ethylbenzylamine was used as the starting material, and the benzyl group was removed by hydrogenolysis at the amide stage to give the desired *N*-ethylaminoalkylamides.

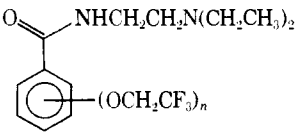
Pharmacology. Prevention of chloroform-induced ventricular fibrillation in the mouse was used for preliminary identification and quantification of antiarrhythmic activity.[8] All test substances were administered orally using 4% acacia as a vehicle. Initially each test compound was given to a group of ten mice at a relatively high range-finding dose. Compounds which lacked potency compared to standard reference agents were disqualified from further testing. Compounds showing good activity at the range-finding dose were subsequently tested in groups of ten mice using 50% increments in dose as necessary to calculate ED_{50} values according to the method of Litchfield and Wilcoxon.[9] Results are expressed in Tables I–III as ED_{50} values (μmol/kg po) together with 95% confidence limits. The ED_{50} values obtained in the same manner for the reference agents quinidine, procainamide, and lidocaine are included in Table I.

Discussion

The structure–activity study produced two distinct sets of benzamides. In the first set (**8–18**, Table I), the number and position of trifluoroethoxy ring substituents were varied while the amide side chain remained the same. In the second set (**19–38**, Table II), alterations of the side chain were explored using the most favorable aromatic substitution pattern.

Compounds **8–18** are all *N*-(2-diethylamino)ethylbenzamides but exhibit a wide variation in activity depending upon the pattern of trifluoroethoxy ring substitution. Among the monosubstituted compounds, a trifluoroethoxy group ortho (**8**) or meta (**9**) to the carboxamide function is clearly superior to substitution at the para position (**10**). Compounds **8** (2-OCH_2CF_3) and **9** (3-OCH_2CF_3) are in the

Table I. Ring-Substituted *N*-(2-Diethylamino)ethylbenzamides



Compd	Position	n	Mp or bp (mm), °C	Formula[a]	Recrystn solvent	Synthetic method (yield, %)	Mouse protection screen, ED_{50}, μmol/kg po
Quinidine							217 (162–291)[b]
Procainamide							1030 (688–1545)
Lidocaine							495 (401–606)
8	2	1	141–142	$C_{15}H_{21}F_3N_2O_2 \cdot HCl$	EtOAc	B (72)	186 (127–276)
9	3	1	137–138	$C_{15}H_{21}F_3N_2O_2 \cdot 1.5C_2H_2O_4$	EtOH	B (53.5)	137 (101–183)
10	4	1	69–70.5	$C_{15}H_{21}F_3N_2O_2$	Hexane	B (79)	>540
11	2,3	2	155 (0.2)	$C_{17}H_{22}F_6N_2O_3$		B (43)	>540
12	2,4	2	77–79.5	$C_{17}H_{22}F_6N_2O_3$	Cyclohexane	B (73)	>540
13	2,5	2	55–56	$C_{17}H_{22}F_6N_2O_3$	Hexane	B (78)	62 (40–97)
14	2,6	2	83.5–85	$C_{17}H_{22}F_6N_2O_3$	Cyclohexane	B (78)	86 (65–118)
15	3,4	2	146.5–147	$C_{17}H_{22}F_6N_2O_3 \cdot C_2H_2O_4$	EtOH	B (48)	>440
16	3,5	2	163–164	$C_{17}H_{22}F_6N_2O_3 \cdot C_2H_2O_4$	EtOH	B (53)	>440
17	2,4,6	3	112–113	$C_{19}H_{23}F_9N_2O_4$	Cyclohexane	B (84)	117 (68–202)
18	3,4,5	3	214.5–215.5	$C_{19}H_{23}F_9N_2O_4 \cdot HCl$	EtOAc–*i*-PrOH	B (69)	>400

[a] All compounds analyzed for C, H, and N within ±0.4% of the theoretical value. [b] 95% confidence limits.

same potency range as the reference agent quinidine. Of more interest, however, are the disubstituted compounds **11–16** since the pattern of substitution produces dramatic differences in activity. Six disubstituted isomers are possible, but two of these, **13** (2,5-OCH_2CF_3) and **14** (2,6-OCH_2CF_3), have potent activity which stands out from all the others. These two exhibited the lowest ED_{50} values (62 and 86 μmol/kg, respectively) in the first set of compounds. The importance of a substituent ortho to the carboxamide group in multisubstituted compounds is further illustrated by the difference between **17** (2,4,6-OCH_2CF_3, ED_{50} = 117 μmol/kg) and **18** (3,4,5-OCH_2CF_3, ED_{50} > 400 μmol/kg).

Since the most favorable aromatic substitution pattern in the initial set was 2,5-OCH_2CF_3, a second group of compounds based on this ring nucleus was designed in order to examine the effect of changes in the amide side chain. The N-substituted 2,5-bis(2,2,2-trifluoroethoxy)benzamides **19–38** which were prepared and studied are collected in Table II. The least active compounds in this set are **26, 27,** and **34**, and all three have an arylamino group in the amide side chain. The reduced basicity associated with an aromatic amine is apparently an important factor, since it does not matter whether the amino group is secondary (**34**), tertiary (**26**), or part of a heterocyclic ring (**27**). Of overall significance is the fact that antiarrhythmic activity was evident among all the remaining compounds in the series. So long as the basic nitrogen does not bear an aromatic substituent, it may be tertiary, secondary, or even primary (**28**). While a two-carbon link between the amide and amine nitrogen atoms is a common characteristic among compounds with antiarrhythmic or local anesthetic activity,[10] extension of this link to three carbons in examples **19** and **35** had no adverse effect on activity. A structural feature shared by a majority of the most potent compounds (e.g., **20, 23, 31, 33, 38**) is a carbon skeleton which is branched α to the basic nitrogen atom. However, this characteristic is not essential (e.g., **22, 32**) and, furthermore, no clear superiority can be demonstrated for either a secondary or tertiary amino group in the side chain.

The trifluoroethoxynaphthamides which were prepared are presented in Table III. Compounds **42** and **43**, bearing a 2-diethylaminoethyl side chain, are the best examples in this set of compounds, but neither compares favorably with the best trifluoroethoxybenzamides. Alteration of the 2-diethylaminoethyl moiety (**44–49**) resulted in a substantial reduction of activity.

We conclude that N-substitued 2,5-bis(2,2,2-trifluoroethoxy)benzamides possess potent antiarrhythmic properties. A variety of alterations in the amide side chain can be made without adverse effects on this activity. Extension of structure–activity studies to related compounds is in progress and will be reported in subsequent publications.

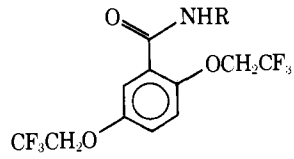
Experimental Section

Boiling points are uncorrected. Melting points, determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus, are uncorrected. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

Methyl 2,5-Bis(2,2,2-trifluoroethoxy)benzoate (2). A mixture of 8.4 g (0.05 mol) of methyl 2,5-dihydroxybenzoate, 27.8 g (0.12 mol) of 2,2,2-trifluoroethyl trifluoromethanesulfonate,[5] 27.6 g (0.2 mol) of anhydrous K_2CO_3, and 300 ml of dry acetone was stirred vigorously under reflux for 72 hr. The mixture was then cooled, filtered, and concentrated by rotary evaporation. Ether was added to the residue, and the solution was washed with H_2O, 5% NaOH, and brine and dried (Na_2SO_4). Concentration of the dried solution yielded an oil which distilled at 96–98° (0.03 mm) to give 12.1 g (73%) of methyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate. The distilled ester hardened on standing to a white solid: mp 43–44°. Anal. ($C_{12}H_{10}F_6O_4$) C, H. Other esters[11] of general structure **2** which were required as intermediates were prepared in similar fashion.

2,2,2-Trifluoroethyl 2,5-Bis(2,2,2-trifluoroethoxy)benzoate (4). A solution of 50 g (0.323 mol) of 2,5-dihydroxybenzoic acid in 600 ml of acetone was added over a period of 2 hr to a stirred mixture of 249 g (1.06 mol) of 2,2,2-trifluoroethyl trifluoromethanesulfonate, 180 g (1.3 mol) of anhydrous K_2CO_3, and 600 ml of acetone at reflux. The mixture was heated under reflux for 24 hr following the addition and then filtered hot. Evaporation of the filtrate under reduced pressure yielded a thick syrup containing suspended salts. Water and $CHCl_3$ were added, and the $CHCl_3$ layer was

Table II. N-Substituted 2,5-Bis(2,2,2-trifluoroethoxy)benzamide



Compd	R	Mp or bp (mm), °C	Formula[a]	Recrystn solvent	Synthetic method (yield, %)	Mouse protection screen, ED_{50}, μmol/kg po
19	$-(CH_2)_3N(CH_2CH_3)_2$	154 (0.05)	$C_{18}H_{24}F_6N_2O_3$		B (39)	33 (23–46)[b]
20	$-CH_2CH(CH_3)N(CH_2CH_3)_2$	50–60	$C_{18}H_{24}F_6N_2O_3 \cdot {}^4/_3H_3PO_4$	Glass	B (55)	13 (8.7–21)
21	$-CH_2CH(CH_2CH_3)N(CH_2CH_3)_2$	160 (0.04)	$C_{19}H_{26}F_6N_2O_3$		A (92)	53 (35–79)
22	$-CH(CH_3)CH_2N(CH_2CH_3)_2$	150 (0.05)	$C_{18}H_{24}F_6N_2O_3$		B (72)	28 (16–51)
23	$-CH_2C(CH_3)_2N(CH_2CH_3)_2$	165 (0.02)	$C_{19}H_{26}F_6N_2O_3$		A (85)	33 (20–54)
24	$-CH_2CH(CH_3)$-c-NC_4H_8	96–97	$C_{18}H_{22}F_6N_2O_3$	Cyclohexane–hexane	A (72)	60 (47–75)
25		69.5–71	$C_{19}H_{24}F_6N_2O_3$	Cyclohexane–hexane	C (48)	79 (56–113)
26	$-CH_2CH_2N(CH_3)C_6H_5$	100–101	$C_{20}H_{20}F_6N_2O_3$	Cyclohexane–CCl_4	C (20)	>495
27		84–85.5	$C_{21}H_{20}F_6N_2O_3$	Cyclohexane	C (64)	>495
28	$-CH_2CH_2NH_2$	200–203	$C_{13}H_{14}F_6N_2O_3 \cdot HCl$	EtOH–*i*-PrOH	A (46)	121 (91–161)
29	$-CH_2CH_2NHCH_3$	179–180	$C_{14}H_{16}F_6N_2O_3 \cdot HCl$	*i*-PrOH	A (66)	78 (62–97)
30	$-CH_2CH_2NHCH_2CH_3$	170–171	$C_{15}H_{18}F_6N_2O_3 \cdot HCl$	*i*-PrOH	A (72)	45 (35–56)
31	$-CH_2CH_2NHCH(CH_3)_2$	196–197	$C_{16}H_{20}F_6N_2O_3 \cdot HCl$	*i*-PrOH	A (65)	20 (12–33)
32	$-CH_2CH_2NH(CH_2)_2CH_3$	170–171	$C_{16}H_{20}F_6N_2O_3 \cdot HCl$	EtOAc–*i*-PrOH	A (50)	34 (23–51)
33	$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	170–171	$C_{17}H_{22}F_6N_2O_3 \cdot HCl$	*i*-PrOH	A (49)	19 (13–28)
34	$-CH_2CH_2NHC_6H_5$	185–190	$C_{19}H_{18}F_6N_2O_3 \cdot HCl$	*i*-PrOH	A (65)	>475
35	$-(CH_2)_3NHCH_2CH_3$	126–128	$C_{16}H_{20}F_6N_2O_3 \cdot HCl$	EtOAc–trichloroethylene	A (58)	50 (40–62)
36	$-CH_2CH(CH_3)NHCH_2CH_3$	168–169.5	$C_{16}H_{20}F_6N_2O_3 \cdot HCl$	*i*-PrOH	A (73)	38 (29–49)
37	$-CH(CH_3)CH_2NHCH_2CH_3$	163–165	$C_{16}H_{20}F_6N_2O_3 \cdot HCl$	EtOAc	A (71)	50 (39–64)
38	$-CH_2C(CH_3)_2NHCH_2CH_3$	139.5–141.5	$C_{17}H_{22}F_6N_2O_3 \cdot C_2H_2O_4$	*i*-PrOH	A (47)	26 (17–39)

[a] All compounds analyzed for C, H, and N within ±0.4% of the theoretical values. [b] 95% confidence limits.

separated, dried ($MgSO_4$), filtered, and concentrated. Distillation of the crude product afforded 111.7 g (86%) of the ester as a clear yellow oil: bp 128° (0.3 mm). Anal. ($C_{13}H_9F_9O_4$) C, H.

2,5-Bis(2,2,2-trifluoroethoxy)benzoic Acid (5). A mixture of either the methyl or 2,2,2-trifluoroethyl ester described above (0.01 mol), NaOH (0.011 mol), and 40 ml of H_2O was heated under reflux for 24 hr. The solution was cooled, acidified, and filtered. Recrystallization of the collected solid from 1:1 EtOH–H_2O gave the acid as white plates: mp 122–124°; yield 2.7 g (85%). Anal. ($C_{11}H_8F_6O_4$) C, H. Other acids[11] of general structure **5** were prepared in similar fashion.

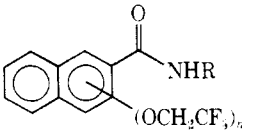
2,5-Bis(2,2,2-trifluoroethoxy)-*N*-(2-chloroethyl)benzamide (7). A mixture of 23.1 g (0.0727 mol) of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid, 21.6 ml (35.7 g, 0.3 mol) of purified $SOCl_2$, and 3 drops of DMF was heated under reflux for 1 hr. Excess $SOCl_2$ was removed in vacuo at reduced pressure. Distillation of the concentrate gave 22.8 g (93%) of 2,5-bis(2,2,2-trifluoroethoxy)-benzoyl chloride as a viscous, yellow oil, bp 100–102° (0.35 mm), which solidified on standing. The acid chloride was dissolved in 250 ml of Et_2O and added with stirring to a solution of 2.91 g (0.0677 mol) of ethylenimine, 6.84 g (0.0677 mol) of Et_3N, and 250 ml of Et_2O kept at 0°. A heavy precipitate consisting mainly of Et_3N·HCl but also some of the aziridinyl amide separated. After the addition was complete, the suspension was warmed to 25°, and the solid was collected by suction filtration. The filtrate was concentrated to dryness. The residue was combined with the collected solid and stirred for 2 hr at 25° with 200 ml of 6 *N* HCl to open the aziridine ring. Water-insoluble 2,5-bis(2,2,2-trifluoroethoxy)-*N*-(2-chloroethyl)benzamide was collected by suction filtration and required no further purification after drying several hours in a vacuum oven at 50°: mp 87.5–88.5°; yield 23.1 g (90%). Anal. ($C_{13}H_{12}ClF_6NO_3$) C, H, N.

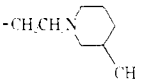
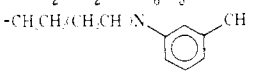
***N*-(2-Chloroethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide (41).** A solution of 25.6 g (0.089 mol) of 3-(2,2,2-trifluoroethoxy)-2-naphthoyl chloride (prepared from methyl 3-hydroxy-2-naphthoate via 2,2,2-trifluoroethylation, saponification, and chlorination as described for the benzamide series) in 200 ml of Et_2O was added with stirring to a solution of 4.6 g (0.089 mol) of ethylenimine, 12.4 g (0.089 mol) of Et_3N, and 450 ml of Et_2O kept at 0°. A heavy precipitate separated. After the addition was complete, the suspension was allowed to warm slowly to 25° and filtered. The filtrate was concentrated to dryness. The residue was combined with the collected solid and stirred for 2 hr at 25° with 200 ml of 6 *N* HCl. Dichloromethane was added, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated to dryness in vacuo. Recrystallization of the crude product from CCl_4–cyclohexane yielded 19.2 g (65.2%) of **41**: mp 125–140°. One recrystallization provided an analytical sample: mp 141–142°. Anal. ($C_{15}H_{13}ClF_3NO_2$) C, H, N.

Preparation of N-Substituted Benzamides and Naphthamides. The general preparative procedures listed in Tables I–III are illustrated by the following examples.

Method A. 2,5-Bis(2,2,2-trifluoroethoxy)-*N*-[(2-methylamino)ethyl]benzamide Hydrochloride (29). 2,2,2-Trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate (10.7 g, 0.0267 mol) was added neat over 10 min to 19.8 g (0.267 mol) of *N*-methylethylenediamine. The solution was stirred 24 hr at 25° and then concentrated to a waxy solid. Excess amine was removed from the res-

Table III. N-Substituted 2,2,2-Trifluoroethoxynaphthamides



Compd	*n*	Position	R	Mp or bp (mm), °C	Formula[a]	Recrystn solvent	Synthetic method (yield, %)	Mouse protection screen, ED_{50}, μmol/kg po
42	1	3	$-CH_2CH_2N(CH_2CH_3)_2$	71–72	$C_{19}H_{23}F_3N_2O_2$	Cyclohexane	B (53)	147 (90–238)[b]
43	1	1	$-CH_2CH_2N(CH_2CH_3)_2$	82.5–84	$C_{19}H_{23}F_3N_2O_2 \cdot 2C_4H_4O_4$	EtOAc	B (31)	147 (103–208)
44	1	3	$-CH_2CH_2$-c-NC_4H_8	107.5–109	$C_{19}H_{21}F_3N_2O_2$	Cyclohexane	B (41)	>600
45	1	3		108–109.5	$C_{21}H_{25}F_3N_2O_2$	Cyclohexane	C (77)	>570
46	1	3	$-CH_2CH_2$-c-$N(CH_2CH_2)_2O$	113–114	$C_{19}H_{21}F_3N_2O_3$	Cyclohexane	B (75)	>590
47	1	3	$-CH_2CH_2NH$-c-C_6H_{11}	188–189	$C_{21}H_{25}F_3N_2O_2 \cdot HCl$	*i*-PrOH	C (75)	>520
48	1	3	$-CH_2CH_2NHC_6H_5$	120–121	$C_{21}H_{19}F_3N_2O_2 \cdot 0.5C_6H_6$	C_6H_6	C (57)	>520
49	1	3		88.5–92	$C_{24}H_{25}F_3N_2O_2$	Cyclohexane	B (29)	>520

[a] All compounds analyzed for C, H, and N within ±0.4% of the theoretical values. [b] 95% confidence limits.

idue by steam distillation, and the nonvolatile amide was extracted from the cooled aqueous solution with CH_2Cl_2. The organic phase was washed with brine and dried ($MgSO_4$). To it was added 3.3 ml of 8.2 *N* 2-propanolic HCl. The HCl salt which slowly separated was collected by suction filtration and recrystallized from *i*-PrOH: mp 179–180°; yield 7.3 g (66%).

Method B. 2,5-Bis(2,2,2-trifluoroethoxy)-*N*-(1-methyl-2-diethylamino)ethylbenzamide (22). 2,5-Bis(2,2,2-trifluoroethoxy)benzoyl chloride (8.0 g, 0.0237 mol) in 40 ml of MEK was added dropwise over 1 hr to a stirred solution of 4.8 g (0.0474 mol) of Et_3N, 3.08 g (0.0237 mol) of 2-amino-1-diethylaminopropane,[7] and 140 ml of MEK which was kept at 0–5°. The mixture was stirred for 30 min at 0–5° after the addition and then for 2 hr at 25° and concentrated in vacuo to remove most of the MEK. Ether and 10% NaOH were added to the residue. The ethereal layer was separated, washed with brine, and dried ($NaSO_4$). Removal of solvent in vacuo afforded an oil which was distilled through a short-path column to give the amide as a viscous liquid: bp 150° (0.05 mm); yield 7.2 g (72%).

***N*-(2-Morpholinoethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide (46).** A solution of 7.5 g (0.0262 mol) of 3-(2,2,2-trifluoroethoxy)-2-naphthoyl chloride in 50 ml of $CHCl_3$ was added dropwise over 80 min to a stirred solution of 5.3 g (0.052 mol) of Et_3N, 3.4 g (0.0262 mol) of *N*-(2-aminoethyl)morpholine, and 30 ml of $CHCl_3$ kept at 0–5°. After the addition was complete, the mixture was stirred at room temperature for 3 hr and concentrated under reduced pressure to remove $CHCl_3$. Ether, EtOAc, and 10% NaOH were added to the residue. The organic layer was separated, washed with brine, dried ($NaSO_4$), and concentrated in vacuo. The crude product was taken up in hot CCl_4–cyclohexane and treated with decolorizing charcoal. Crystalline **46** was obtained on cooling the solution as pink granules: mp 113–114°; yield 7.5 g (75%).

Method C. 2,5-Bis(2,2,2-trifluoroethoxy)-*N*-[2-(methylpiperidino)ethyl]benzamide (25). A solution of 5.0 g (0.0132 mol) of 2,5-bis(2,2,2-trifluoroethoxy)-*N*-(2-chloroethyl)benzamide (**7**) and 25 ml of 2-methylpiperidine was stirred at 100° for 24 hr, cooled, and diluted with Et_2O. The ethereal solution was washed twice with 10% NaOH, twice with H_2O, and concentrated. Excess 2-methylpiperidine was removed from the residue by steam distillation, and the nonvolatile amide was extracted from the cooled aqueous solution with Et_2O. The extract was washed with brine and dried ($MgSO_4$). Removal of solvent in vacuo yielded a thick syrup which crystallized from 1:4 cyclohexane–hexane to give **25** as a fine white powder: mp 69.5–71°; yield 2.8 g (48%).

***N*-[2-(3-Methylpiperidino)ethyl]-3-(2,2,2-trifluoroethoxy)-2-naphthamide (45).** A mixture of 4.0 g (0.0121 mol) of *N*-(2-chloroethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide (**41**) and 20 ml of 3-methylpiperidine was stirred at 100°. After 24 hr the mixture was cooled, diluted, and steam distilled to remove 3-methylpiperidine. The aqueous residue was cooled and extracted twice with Et_2O. The combined Et_2O solution was washed with H_2O and extracted with dilute HCl. Crude **45** was isolated by basification of the acidic solution and extraction with Et_2O. Recrystallization from cyclohexane and treatment with decolorizing charcoal gave **45** as off-white granules: mp 108–109.5°; yield 3.7 g (77%).

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