

[54] N-(2-DIALKYLAMINOALKYLENE)AMIDES OF 1,1-DIHYDROPERFLUOROALKOXY-SUBSTITUTED ARYL ACIDS AND SALTS THEREOF

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[22] Filed: July 22, 1970

[21] Appl. No.: 57,352

[52] U.S. Cl.260/326.3, 260/239 A, 260/239 E, 260/293.77, 260/520, 260/521 A, 260/544 M, 260/559 R, 260/559 S, 260/560, 424/244, 424/267, 424/274, 424/324, 260/239 B

[51] Int. Cl.C07c 103/30, C07d 27/02
[58] Field of Search.....260/559, 239, 326.3, 293.77

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UNITED STATES PATENTS

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[57] ABSTRACT

N-(2-Dialkylaminoalkylene)amides of aromatic acids. Also included are pharmaceutically acceptable acid addition salts thereof. These compounds have valuable antiarrhythmic activity.

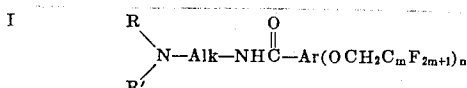
16 Claims, No Drawings

N-(2-DIALKYLAMINOALKYLENE)AMIDES OF 1,1-DIHYDROPERFLUOROALKOXY-SUBSTITUTED ARYL ACIDS AND SALTS THEREOF

DETAILED DESCRIPTION

The present invention relates to N-(2-dialkylaminoalkylene)amides of aromatic acids. Also included are pharmaceutically acceptable acid addition salts thereof. These compounds have valuable antiarrhythmic activity.

A preferred class of compounds of the invention are those having the formula:



where R and R' are alkyl of one to three carbon atoms, or together form an alkylene group of two to six carbon atoms, Alk is an ethylene group optionally substituted by a methyl group, Ar is an aromatic group containing from six to ten carbon atoms, m is one to tree and n is one to three, and pharmaceutically acceptable acid-addition salts thereof. The group $\text{C}_m\text{F}_{2m+1}$ is straight or branched chain and optionally contains one divalent oxygen atom as part of the chain.

When R and R' are alkyl, the alkyl may be straight or branched and R and R' may be the same or different. When R and R' together form an alkylene group it may be straight or branched, but unbranched is presently preferred. R and R' are presently preferred to contain a total of four carbon atoms. It is presently preferred that Alk be ethylene and that Ar be a benzene or naphthalene ring system. Compounds wherein m is 1 are also presently preferred as are those wherein n is 1 or 2.

The compounds can be used directly or in the form of pharmaceutically acceptable acid-addition salts, especially as soluble hydrochloric, sulfuric or phosphoric acid salts. Other such salts include combinations with hydrobromic acid, sulfamic acid, methanesulfonic acid, benzenesulfonic acid, ethanedisulfonic acid, acetic acid, citric acid, malic acid, oxalic acid, succinic acid, maleic acid, fumaric acid, tartaric acid and benzylic acid.

The compounds of the invention are generally active as antiarrhythmics, although it will be appreciated that some appear to be more active than others using the test methods presently available, and some have better therapeutic indices than others.

Antiarrhythmic activity of compounds of the invention is detected using a well-known screening method. Activity is manifested in the ability to block chloroform-induced ventricular fibrillation in mice. This test method is described in detail by J. W. Lawson, J. Pharmacol. Exp. Therap. 160:22-31, 1968

Presently preferred compounds of the invention having high antiarrhythmic activity are:

- N-(2-diethylaminoethyl)-2-(2,2,2-trifluoroethoxy)-benzamide
- N-(2-diethylaminoethyl)-3-(2,2,2-trifluoroethoxy)-benzamide
- N-(2-diethylaminoethyl)-4-(2,2,2-trifluoroethoxy)-benzamide

N-(2-diethylaminoethyl)-2,4-di-(2,2,2-trifluoroethoxy)-benzamide

N-(2-diethylaminoethyl)-2,5-di-(2,2,2-trifluoroethoxy)-benzamide

5 N-(2-diethylaminoethyl)-2,6-di-(2,2,2-trifluoroethoxy)-benzamide

N-(2-diethylaminoethyl)-3,4-di-(2,2,2-trifluoroethoxy)-benzamide

10 N-(2-diethylaminoethyl)-1-(2,2,2-trifluoroethoxy)-2-naphthamide

N-(2-diethylaminoethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide

N-(2-pyrrolidinylethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide

15 and pharmaceutically acceptable salts of these compounds.

Antiarrhythmics are commonly administered parenterally, frequently by intravenous titration. The compounds of this invention are effective by this mode of administration, and have also been found active orally, particularly as their salts but also as the free bases. When given intravenously the compounds will generally be formulated in saline solution. When given orally the form of administration will generally be tablets, as is known to the art.

25 In addition, some of the compounds of the present invention exhibit a high degree of activity as local anesthetics, the duration of that activity being quite extensive. These compounds can be administered by topical application to produce surface anesthesia and used to relieve itching, burning and surface pain or by local injection for surgical procedures. When they are administered topically the compounds are generally administered from aqueous solutions, in pharmaceutical cream or salve bases, etc. When injected as anesthetics the compounds can be conveniently used as solutions, for example, in aqueous or saline solutions.

30 The local anesthetic activity has been observed using the corneal reflex test using rabbits as test animals. This test method is described by F. P. Luduena and J. O. Hoppe, J. Pharmacol. Ex. Therap., 104:40, 1952.

Presently preferred among the compounds active as local anesthetics are those compounds in which R and R' are alkyl (especially ethyl), Alk is unsubstituted and m and n are 1. Particularly preferred are:

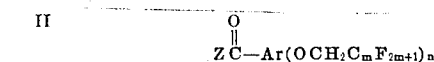
N-(2-diethylaminoethyl)-1-(2,2,2-trifluoroethoxy)-2-naphthamide,

N-(2-diethylaminoethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide,

50 N-(2-diethylaminoethyl)-3-(2,2,2-trifluoroethoxy)-benzamide

and pharmaceutically acceptable salts of these compounds.

55 The compounds of the invention can be prepared by reacting an acid halide of the formula:



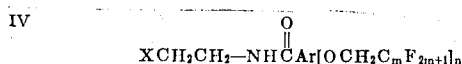
(wherein Z is halogen, preferably chlorine) with a 2-dialkylaminoalkylamine of the formula:



in an inert solvent such as benzene, toluene or diethyl ether. Compounds of Formula II are conveniently prepared by refluxing the corresponding acids (that is, compounds of Formula II where Z = OH) with an excess of thionyl chloride in the presence of a small amount of dimethylformamide. The excess thionyl chloride is then removed by distillation.

An alternative procedure involves reaction of 2-dialkylaminoalkylamines of Formula III in an aminolysis with esters of Formula II where Z is alkoxy or 1,1-dihydroperfluoroalkoxy, of one to four carbon atoms. The reaction is generally carried out by refluxing the reactants without solvent, followed by isolation of the product.

A further refinement of the above procedures involves reaction of the compounds of Formula II wherein Z is chlorine or bromine with ethyleneimine followed by cleavage with isopropanolic-hydrochloric acid to give the compounds of the formula



wherein X is chlorine or bromine. The halogen of the haloethyl group can then be displaced by reaction with an appropriate secondary amine to give a compound of Formula I.

The compounds of Formula III are generally known to the art, or can be conveniently prepared by methods known in the art. The compounds of Formula II are novel but can be prepared from well-known compounds. The compounds of Formula II wherein Z is alkoxy or 1,1-dihydroperfluoroalkoxy (that is, esters) are prepared by reaction of the hydroxy and polyhydroxyaromatic acids with the alkylating agents of the formula:



in the presence of sodium bicarbonate, potassium bicarbonate or other metal bicarbonates in an inert solvent such as acetone. The resulting 1,1-dihydroperfluoroalkoxy-substituted aromatic ester (i.e. a compound of Formula II wherein Z is alkoxy or 1,1-dihydroperfluoroalkoxy) can be hydrolyzed to the free acid (compounds of Formula II wherein Z is OH) which can in turn be converted to the acid halides (compounds of Formula II wherein Z is halogen) by e.g. thionyl chloride and the like.

The following examples will more fully illustrate the preparation of the compositions of the invention. All temperatures in the examples are given in degrees Centigrade. Examples 1–40 relate to the preparation of intermediate compounds and the remaining examples relate to the preparation of compounds of the invention.

EXAMPLE 1

Preparation of Methyl 2-(2,2,2-Trifluoroethoxy)benzoate

A mixture of methyl salicylate (6.4 ml., 7.6 g., 0.05 mole), 2,2,2-trifluoroethyl trifluoromethanesulfonate

(13.9 g., 0.06 mole), anhydrous potassium carbonate (13.8 g., 0.1 mole) and acetone (150 ml.) is heated under reflux with efficient stirring for 3 days. The product is filtered and the filtrate is concentrated to a small volume. It is diluted with cold water and the resulting precipitate is collected and washed successively with cold dilute sodium hydroxide solution and water. The desired material is recrystallized then from aqueous ethanol to afford white solid, m.p. 61°–62° C.

Analysis:

Calculated for $\text{C}_{10}\text{H}_9\text{F}_3\text{O}_3$: C, 51.3; H, 3.9; F, 24.3

Found: C, 51.2; H, 4.1; F, 25.0

EXAMPLE 2

Preparation of Methyl 1-(2,2,2-Trifluoroethoxy)-2-Naphthoate

A mixture containing 20.2 g. (0.1 mole) of methyl 1-hydroxy-2-naphthoate, 29 g. (0.125 mole) of 2,2,2-trifluoroethyl trifluoromethanesulfonate, 20 g. (0.2 mole) of anhydrous potassium bicarbonate and 200 ml. of dry acetone is refluxed for 3 days. Acetone is removed by distillation (steam bath). The residue is cooled and diluted with water. The resulting white solid is collected by filtration and washed successively with cold dilute sodium hydroxide solution and water. The solid is further purified by several recrystallizations from aqueous alcohol followed by sublimation (oil bath, 60°–75°/0.2 mm. Hg.) to give white solid, m.p. 69.5°–70.5° C.

Analysis:

Calculated for $\text{C}_{14}\text{H}_{11}\text{F}_3\text{O}_3$: C, 59.2; H, 3.9; F, 20.0

Found: C, 58.9; H, 4.0; F, 21.1

Additional compounds of Formula II, where Z is alkoxy or 1,1-dihydroperfluoroalkoxy and m is one are prepared according to the procedures described in Examples 1 and 2 and are described in Table I.

TABLE I

Example No.	Compound	Melting Point (in ° C.)
3.	Methyl 3-(2,2,2-trifluoroethoxy)benzoate	57.5–59
4.	Methyl 4-(2,2,2-trifluoroethoxy)benzoate	59.5–60.6
5.	Ethyl 2,3-di-(2,2,2-trifluoroethoxy)benzoate	30–31
6.	Methyl 2,4-di-(2,2,2-trifluoroethoxy)benzoate	70.5–71.5
7.	Methyl 2,5-di-(2,2,2-trifluoroethoxy)benzoate	42–44
8.	Methyl 2,6-di-(2,2,2-trifluoroethoxy)benzoate	52–54
9.	Methyl 3,4-di-(2,2,2-trifluoroethoxy)benzoate	57–59
10.	Methyl 3,5-di-(2,2,2-trifluoroethoxy)benzoate	81.5–82.5
11.	2',2',2'-trifluoroethyl 2,4,6-tri-(2,2,2-trifluoroethoxy)benzoate	64.8–65.8
12.	Methyl 3,4,5-tri-(2,2,2-trifluoroethoxy)benzoate	86–87
13.	Methyl 3-(2,2,2-trifluoroethoxy)-2-naphthoate	77–77.5

Compounds of Formula II where Z is alkoxy prepared according to the procedures described in Examples 1 and 2 but utilizing compounds of Formula V other than 2,2,2-trifluoroethyl trifluoromethanesulfonate are shown in Table II.

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TABLE II

Example No.	Starting Materials	Product
14.	methyl 2-hydroxybenzoate	
	1,1-dihydroperfluoro-n-propyl trifluoromethanesulfonate	methyl 2-(1,1-dihydroperfluoro-n-propoxy)benzoate
15.	ethyl 1-hydroxy-2-naphthoate	
	1,1-dihydroperfluoro-n-butyl trifluoromethanesulfonate	ethyl 1-(1,1-dihydroperfluoro-n-butoxy)-2-naphthoate
16.	methyl 2,4,6-trihydroxybenzoate	
	1,1-dihydroperfluoro-n-propyl trifluoromethanesulfonate	methyl 2,4,6-tri-(1,1-dihydroperfluoro-n-propoxy)-benzoate
17.	n-propyl 2,5-dihydroxybenzoate	
	1,1-dihydroperfluoroisobutyl trifluoromethanesulfonate	n-propyl 2,5-di-(1,1-dihydroperfluoroisobutoxy)benzoate
18.	methyl 4-hydroxybenzoate	
	2,2-difluoro-2-(trifluoromethylthoxy)ethyl trifluoromethanesulfonate	methyl 4-[2,2-difluoro-2-(trifluoromethylthoxy)ethoxy]

An example of preparation of compounds of Formula II wherein Z is 1,1-dihydroperfluoroalkoxy is given in Example 19.

EXAMPLE 19

Preparation of 2',2',2'-Trifluoroethyl 2,5-di-(2,2,2-trifluoroethoxy)benzoate

To a stirred refluxing suspension of 2,5-dihydroxybenzoic acid (88.3 g., 0.573 mole), potassium bicarbonate (573 g., 5.73 mole) and acetone (2.4 l.) is added dropwise 2,2,2-trifluoroethyl trifluoromethanesulfonate (564 g., 2.43 mole) in acetone (230 ml.). The mixture is maintained at reflux temperature for 48 hours, then additional 2,2,2-trifluoroethyl trifluoromethanesulfonate (139 g., 0.60 mole) in acetone is added and refluxing is continued for 24 hours. The acetone is removed by evaporation in vacuo, then the residue is added to water (2 l.). The aqueous layer is extracted with diethyl ether, and the ether layer is washed with saturated aqueous sodium chloride, then dried over sodium sulfate. The ether is evaporated in vacuo, then the residue is distilled to give 2',2',2'-trifluoroethyl 2,5-di-(2,2,2-trifluoroethoxy)benzoate, b.p. 91°-96° C./0.2 mm.

6
EXAMPLE 20

Preparation of 2-(2,2,2-Trifluoroethoxy)benzoic Acid

Methyl 2-(2,2,2-trifluoroethoxy)-benzoate (8 g., 34.2 mmoles) potassium hydroxide (3.3 g., 350 mmoles), water (50 ml.) and alcohol (25 ml.) are heated together under reflux for 1.5 hours, and distilled until ca. 25 ml. of distillate is removed. The cooled residue is acidified (pH 3) and the resulting white solid is collected and recrystallized (aqueous alcohol) to give fluffy white solid, m.p. 85°-86.5° C.

Analysis:

Calculated for $C_9H_7F_3O_3$: C, 49.1; H, 3.2; F, 25.9

Found: C, 48.8; H, 3.3; F, 26.2

EXAMPLE 21

Preparation of 1-(2,2,2-trifluoroethoxy)-2-Naphthoic Acid

A mixture of 10 g. (35 mmoles) of methyl 1-(2,2,2-trifluoroethoxy)-2-naphthoate, 2.6 g., (42 mmoles) of potassium hydroxide, 50 ml. of ethanol and 40 ml. of water is refluxed for one hour, chilled and acidified. The fluffy precipitate is collected, water washed, and air-dried. It is purified by recrystallization first from chloroform and then from aqueous alcohol, m.p. 171.5°-172°.

Analysis:

Calculated for $C_{13}H_9F_3O_3$: C, 57.8; H, 3.4; F, 21.1

Found C, 57.8; H, 3.6; F, 21.7 products 25.

Compounds of Formula II where Z is OH are obtained from each of the products of Examples 3 through 17 by the methods described in detail in Examples 20 and 21. Such Products where m is one are listed in Table III.

TABLE III

Example No.	Compound	Melting Point (in ° C.)
22.	3-(2,2,2-trifluoroethoxy)benzoic acid	105-105.5
23.	4-(2,2,2-trifluoroethoxy)benzoic acid	200-200.5
24.	2,3-di-(2,2,2-trifluoroethoxy)-benzoic acid	141-143
25.	2,4-di-(2,2,2-trifluoroethoxy)-benzoic acid	143.5-144
26.	2,5-di-(2,2,2-trifluoroethoxy)-benzoic acid	122-124
27.	2,5-di-(2,2,2-trifluoroethoxy)-benzoic acid	158-159
28.	3,4-di-(2,2,2-trifluoroethoxy)-benzoic acid	143-144
29.	3,5-di-(2,2,2-trifluoroethoxy)-benzoic acid	141.5-143
30.	2,4,6-tri-(2,2,2-trifluoroethoxy)benzoic acid	140.5-141.5
31.	3,4,5-tri-(2,2,2-trifluoroethoxy)benzoic acid	196-197
32.	3-(2,2,2-trifluoroethoxy)-2-naphthoic acid	149-150

Compounds of Formula II where Z is alkoxy are prepared according to the procedure described in Examples 20 and 21 where m is 2 or 3 and are listed in Table IV.

TABLE IV

Example No.	Starting Material	Product
33.	methyl 2-(1,1-dihydroperfluoro-n-propoxy)benzoate	2-(1,1-dihydroperfluoro-

34. ethyl 1-(1,1-dihydroperfluoro-n-butoxy)-2-naphthoate n-propoxybenzoic acid
35. n-propyl 2,5-di-(1,1-dihydroperfluoroisobutoxy)benzoate- 1-(1,1-dihydroperfluoro-n-butoxy)-2-naphthoic acid
36. methyl 4-[2,2-difluoro-2-(trifluoromethoxy)ethoxy]benzoic acid 2,5-di-(1,1-dihydroperfluoroisobutoxy)-benzoic acid
- 4-[2,2-difluoro-2-(trifluoromethoxy)ethoxy]benzoic acid

EXAMPLE 37

Preparation of N-(2-Chloroethyl)-2,5-di(2,2,2-trifluoroethoxy)benzamide

Ethyleneimine (2.9 g., 0.068 mole), triethylamine (6.8 g., 0.068 mole) and diethyl ether (250 ml.) are cooled to 0° C. and stirred while adding 2,5-di-(2,2,2-trifluoroethoxy)benzoyl chloride (22.8 g., 0.068 mole). The mixture is allowed to warm to room temperature and filtered. The filtrate is treated with 6.6 N isopropanol-hydrochloric acid mixture and filtered and the solvent evaporated in vacuo to give N-(2-chloroethyl)-2,5-di-(2,2,2-trifluoroethoxy)benzamide hydrochloride, n.p. 87°-88.5° C.

Analysis:

Calculated for $C_{13}H_{12}ClF_6NO_3$: C, 41.5; H, 3.2; N, 3.6

Found: C, 41.1; H, 3.2; N, 3.7

Additional compounds of Formula IV are prepared as described in Example 37 and are listed in Table V.

TABLE V

Example No.	Compound
38.	N-(2-chloroethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide
39.	N-(2-chloroethyl)-2-(2,2,2-trifluoroethoxy)-benzamide
40.	N-(2-chloroethyl)-3-(2,2,2-trifluoroethoxy)-benzamide

EXAMPLE 41

Preparation of N-(2-Diethylaminoethyl)-1-(2,2,2-trifluoroethoxy)-2-naphthamide Dimaleate

A mixture of 10 g. (37 mmoles) of 1-(2,2,2-trifluoroethoxy)-2-naphthoic acid, 21.8 ml. (35.7 g., 300 mmoles) of purified thionyl chloride and 3 drops of dimethylformamide is refluxed for 1 hour. Excess thionyl chloride is removed as described in Example 43. The residue is diluted with ether (ca. 250 ml.) and ca. 1 g. of a white solid is removed by filtration. To the chilled filtrate is added dropwise with stirring 5.25 ml. (4.3 g., 37 mmoles) of β -diethylaminoethylamine. The mixture is then diluted with water, made alkaline (NaOH — pH 10) and separated. The organic extract is dried (anhydrous $MgSO_4$), filtered, and the filtrate evaporated to leave ca. 5 g. of yellow oil. It is taken up in 15 ml. of carbon tetrachloride and chromatographed on 75 g. of activated magnesium silicate (available from the Floridin Company of Hancock, W. Va. under

the trade designation "Florasil"). Elution with ether and acetone, respectively, afford the basic amide. An equal weight of maleic acid is added to the amide in ca. 10 ml. of absolute ethanol. Subsequent chilling and dilution with anhydrous ether afford the dimaleate salt. It is recrystallized from absolute alcohol-absolute ether to give the desired salt, m.p. 82.5°-84° C.

Analysis:

Calculated for $C_{27}H_{30}F_3N_2O_{10}$: C, 54.0; H, 5.2; F, 9.5

Found: C, 54.3; H, 5.3; F, 9.3

EXAMPLE 42

Preparation of N-(2-Diethylaminoethyl)-2,5-di-(2,2,2-trifluoroethoxy)Benzamide Phosphate

A mixture of 2',2',2'-trifluoroethoxy 2,5-di-(2,2,2-trifluoroethoxy)benzoate (216 g., 0.54 mole) and 2-diethylaminoethylamine (166 g., 1.43 mole) is heated at reflux temperature for four days. The resulting oil is dissolved in diethyl ether, and the ether solution is washed with water, then extracted with 6N hydrochloric acid. The acid extract is washed with ether, then the pH of the aqueous solution is adjusted to 8 with ten per cent aqueous sodium hydroxide. The aqueous solution is extracted with ether, and the ether layer is washed with water and saturated aqueous sodium chloride, then dried over sodium sulfate. The solvent is evaporated in vacuo, and the residue is distilled (b.p. 166°-176° C./24 mm.). The product (207.1 g., 0.498 mole) solidifies on standing and is dissolved in 2.1 l. of diethyl ether. Phosphoric acid (48.9 g., 0.498 mole) in diethyl ether (1225 ml.) is added, as a 325 ml. portion followed by stirring until crystals form, then the remainder is added in three portions over a period of 20 hours. The product, white crystals of N-(2-diethylamino-ethyl)-2,5-di-(2,2,2-trifluoroethoxy)benzamide phosphate is recrystallized from an ethanol-ethyl acetate mixture with treatment with decolorizing charcoal and dried to give pure product, m.p. 152°-153° C.

Analysis:

Calculated for $C_{17}H_{22}F_6N_2O_3 \cdot H_3PO_4$: C, 39.7; H, 4.9; N, 5.4

Found: C, 39.4; H, 4.7; N, 5.4

EXAMPLE 43

Preparation of N-(2-Diethylaminoethyl)-2,5-di-(2,2,2-trifluoroethoxy)benzamide

To 9.4 g. (30 mmoles) of 2,5-di-(2,2,2-trifluoroethoxy)benzoic acid are added 2 drops of dimethylformamide and 7.2 ml. (11.9 g., 100 mmoles) of purified thionyl chloride. The product is refluxed for 3 hours and excess thionyl chloride is removed (steam bath/water aspirator pressure). Last traces of thionyl chloride are removed by similar vacuum distillation of added benzene. The residue is taken up in 75 ml. of absolute diethyl ether, chilled, and to it is added dropwise with stirring 4.25 ml. (3.5 g., 30 mmoles) of 2-diethylaminoethylamine. The gummy material is diluted with water, made alkaline (pH 10-11) with dilute sodium hydroxide and separated in a separatory funnel. The separated and dried (anhydrous $MgSO_4$) ether solution is filtered and the filtrate is evaporated to leave 11.8 g. of viscous yellow liquid. It is dissolved in 25 ml. of carbon tetrachloride and chromatographed on 300 g. of basic alumina, activity II. Elution of the

column with ether affords after recrystallization (pet. ether, b.p. 30–60°) 9.3 g. of white amide, m.p. 54°–55° C.

Analysis:

Calculated for $C_{17}H_{22}ClF_3NO_4$: C, 49.0; H, 5.3; F, 27.4

Found: C, 49.2; H, 5.3; F, 27.1

Additional compounds of the invention of Formula I are prepared according to the methods of Examples 41, 42 and 43 are given in Table VI.

TABLE VI

Example No.	Product	M.P. (in °C.) or B.P. (in °C./mm Hg)
44	N-(2-diethylaminoethyl)-3,5-di-(2,2,2-trifluoroethoxy)benzamide	163–164
45	N-(2-diethylaminoethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide	71–72
46	N-(2-diethylaminoethyl)-2,3-di-(2,2,2-trifluoroethoxy)benzamide	155/0.2
47	N-(2-diethylaminoethyl)-2,6-di-(2,2,2-trifluoroethoxy)benzamide	83.5–85
48	N-(2-diethylaminoethyl)-2-(2,2,2-trifluoroethoxy)benzamide hydrochloride	141–142
49	N-(2-diethylaminoethyl)-4-(2,2,2-trifluoroethoxy)benzamide	69–70.5
50	N-(2-diethylaminoethyl)-3-(2,2,2-trifluoroethoxy)benzamide oxalate	137–138
51	N-(2-diethylaminoethyl)-2,4-di-(2,2,2-trifluoroethoxy)benzamide	77–79.5
52	N-(2-diethylaminoethyl)-3,4-di-(2,2,2-trifluoroethoxy)benzamide oxalate	146.5–147
53	N-(2-diethylaminoethyl)-3,4,5-tri-(2,2,2-trifluoroethoxy)benzamide hydrochloride	214.5–215.5
54	N-(2-diethylaminoethyl)-2,4,6-tri-(2,2,2-trifluoroethoxy)benzamide	112–113
55	N-(2-diethylaminoethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide hydrochloride	157–159

EXAMPLE 56

Preparation of N-[2-(2-methylpiperidinyl)ethyl]-2,5-di-(2,2,2-trifluoroethoxy)benzamide

Excess 2-methylpiperidine (25 ml.) and N-(2-chloroethyl)-2,5-di-(2,2,2-trifluoroethoxy)benzamide (5.0 g., 0.013 mole) are heated to reflux temperature and maintained at reflux overnight. The mixture is washed with 10 per cent sodium hydroxide solution and the organic layer is separated and dissolved in diethyl ether, washed again with base, then water and finally with saturated aqueous sodium chloride. After drying over magnesium sulfate the ether is evaporated in vacuo and the residue is steam distilled to remove excess 2-methylpiperidine. The residue is separated from the water, dissolved in ether and dried. The ether is evaporated in vacuo, the residue is treated with a mixture of isopropanol and hydrochloric acid, then water is added to precipitate the product as the hydrochloride. The salt is reconverted to the free base with ten per cent aqueous sodium hydroxide, extracted with ether, dried and the ether evaporated in vacuo. The residue is recrystallized from a 4/1 petroleum ether/cyclohexane mixture with treatment with decolorizing charcoal. A white powder of N-[2-(2-methylpiperidinyl)ethyl]-2,5-di-(2,2,2-trifluoroethoxy)benzamide, m.p. 69.5°–71° C. is obtained.

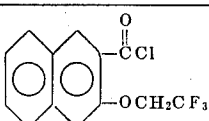
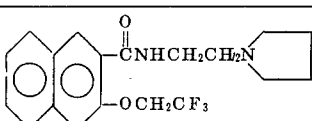
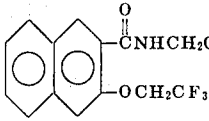
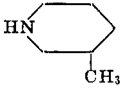
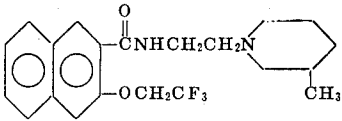
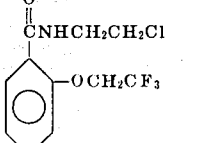
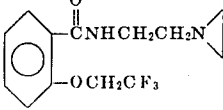
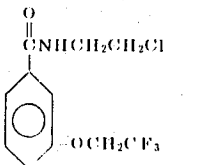
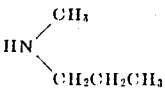
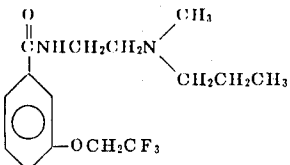
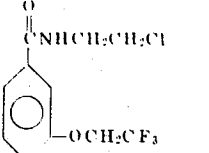
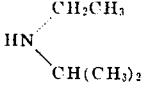
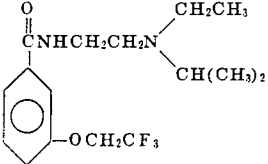
Analysis:

Calculated for $C_{19}H_{24}F_6N_2O_3$: C, 51.6; H, 5.5; N, 6.3

Found: C, 51.5; H, 5.4; N, 6.3

Other compounds of Formula I wherein R and R₁ are varied are prepared using starting materials which are known or described herein and are given in Table VII.

TABLE VII

Example No.	Starting materials	Product
57	 $NH_2CH_2CH_2N$ 	
58	 HN 	
59	 H 	
60	 HN 	
61	 HN 	

EXAMPLE 62

Preparation of N-(2-Diethylaminoethyl)-3-(1,1-dihydroperfluoro-n-butoxy)-2-naphthamide

Triethylamine (1.8 g., 0.018 mole), 2-diethylaminoethylamine (2.1 g., 0.018 mole) and chloroform (30 ml.) are cooled with an ice bath. To the stirred solution is added 3-(1,1-dihydroperfluoro-n-butyl)-2-naphthoyl chloride (6.6 g., 0.018 mole) in chloroform (40 ml.). The mixture is then allowed to warm ambiently and excess 10 percent cent aqueous sodium hydroxide is added. The mixture is extracted with diethyl ether, the ether layer is washed with water and saturated aqueous sodium chloride and dried over magnesium sulfate. Evaporation of the ether in vacuo gives a solid residue which is recrystallized from cyclohexane with treatment with decolorizing charcoal to give white needles of N-(2-diethylaminoethyl)-3-(1,1-dihydroperfluoro-n-butoxy)-2-naphthamide, m.p. 58°-59.5° C.

Analysis:

Calculated for $C_{21}H_{23}F_3N_2O_2$: C, 53.9; H, 5.0; N, 6.0

Found: C, 54.0; H, 4.8; N, 5.9

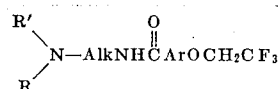
Other compounds of Formula I are prepared using starting materials which are known or may be prepared as described herein and are given in Table VIII.

wherein R and R' are alkyl of one to three carbon atoms each, or together form an alkylene group of two to six carbon atoms, Alk is an ethylene group optionally substituted by a methyl group, Ar is phenylene or naphthylene, provided that when Ar is naphthylene, only one ring thereof is substituted and the N-(aminoalkylene)amide group thereon is oriented ortho to a fluoroalkoxy group, m is one to three and n is one to three, or a pharmaceutically acceptable acid-addition salt thereof.

2. A compound according to claim 1 wherein n is two.

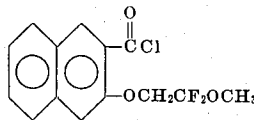
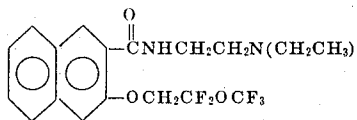
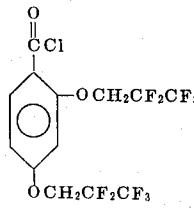
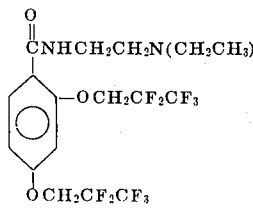
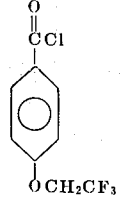
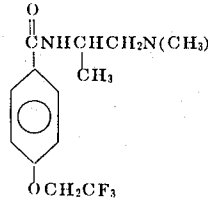
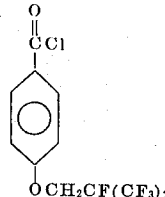
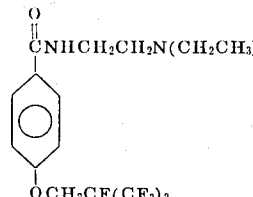
3. A compound according to claim 1 wherein n is one.

4. An N-(aminoalkylene)amide of a fluoroalkoxy aromatic acid of the formula:



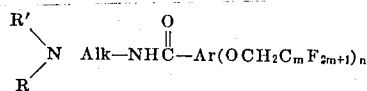
wherein R and R' are alkyl of one to three carbon atoms each, Alk is ethylene and Ar is a naphthalene group, the N-(aminoalkylene)amide group and the fluoroalkoxy group being oriented ortho to one another

TABLE VIII

Example No.	Starting materials	Product
63	 + $\text{NH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$	
64	 + $\text{NH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$	
65	 + $\text{NH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2$	
66	 + $\text{NH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$	

What is claimed is:

1. An N-(aminoalkylene)amide of a fluoroalkoxy aromatic acid of the formula:

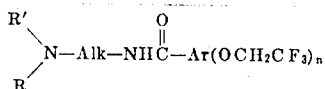


on the same ring of the naphthalene group, or a pharmaceutically acceptable acid-addition salt thereof.

5. N-(2-diethylaminoethyl)-1-(2,2,2-trifluoroethoxy)-2-naphthamide according to claim 4.

65 6. N-(2-diethylaminoethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide according to claim 4.

7. A compound of the formula:



wherein R and R' are alkyl of one to three carbon atoms each and having a total of four carbon atoms, or together form a tetramethylene group, Alk is an ethylene group, Ar is a benzene ring and n is one or two, or a pharmaceutically acceptable acid-addition salt thereof.

8. N-(2-diethylaminoethyl)-2-(2,2,2-trifluoroethoxy)benzamide according to claim 16.

9. N-(2-diethylaminoethyl)-3-(2,2,2-trifluoroethoxy)benzamide according to claim 16.

10. N-(2-diethylaminoethyl)-4-(2,2,2-trifluoroethoxy)benzamide according to claim 16.

11. N-(2-diethylaminoethyl)-2,4-di-(2,2,2-trifluoroethoxy)benzamide according to claim 16.

12. N-(2-diethylaminoethyl)-2,5-di-(2,2,2-trifluoroethoxy)benzamide according to claim 16.

12. N-(2-diethylaminoethyl)-2,6-di-(2,2,2-trifluoroethoxy)benzamide according to claim 16.

14. N-(2-diethylaminoethyl)-3,4-di-(2,2,2-trifluoroethoxy)benzamide according to claim 16.

15. A compound according to claim 2 wherein Alk is ethylene, m is one and R and R' together form an alkylene group.

16. N-(2-pyrrolidinylethyl)-3-(2,2,2-trifluoroethoxy)-2-naphthamide.

* * * * *