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N-(2 - DIALKYLAMINOALKYLENE)-ESTERS OF FLUOROALKOXY-SUBSTITUTED ARYL CARBOXYLIC ACID AND SALTS THEREOF

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U.S. Cl. 260—473 R 9 Claims

ABSTRACT OF THE DISCLOSURE

N - (2 - dialkylaminoalkylene)carboxylic esters of polyfluoroalkoxy-substituted aromatic acids. Also included are pharmaceutically acceptable salts of these compounds. These compounds have valuable local anesthetic activity.

DETAILED DESCRIPTION

The present invention relates to N - (2 - dialkylaminoalkylene)esters, which are also sometimes referred to herein as β - dialkylaminoalkyl esters, of polyfluoroalkoxy-substituted aromatic acids, and to salts thereof with pharmaceutically acceptable acids. These compounds have valuable local anesthetic activity.

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

(I) $$RR'N(CHQ)_2O\overset{O}{\overset{\|}{C}}Ar(O\,CH_2R_f)_n$$

wherein R and R' are lower alkyl groups of one to three carbon atoms, Q is hydrogen or a lower alkyl group of one to three carbon atoms, Ar is an aromatic group containing from six to ten carbon atoms, R_f is a fluorocarbon group having from 1 to 3 carbon atoms and *n* is 1–4; and pharmaceutically acceptable salts thereof. The complete fluorocarbon group (R_f) can be a fully or partially fluorinated alkyl group having a straight or branched structure. There can be no more than one hydrogen atom on any carbon atom and two carbon atoms in the R_f group can be linked together by an oxygen atom. Thus, in addition to the optional oxygen atom, R_f can contain only carbon, fluorine and hydrogen. A preferred class of the compounds of the invention is made up of those compounds in which R_f group is trifluoromethyl. The R_f groups can be, but need not be, the same in any particular compound.

A particularly preferred subclass of the compounds are those in which Ar is a condensed ring system containing ten carbon atoms (a naphthalene nucleus) and *n* is 1. These compounds are particularly desirable local anesthetics having activity of long duration. A second preferred subclass consists of those in which Ar is a six-membered aromatic carbocycle (a benzene nucleus) and *n* is 2.

The compounds of the invention can be used in the ester form directly but are also suitably used in the form of pharmaceutically acceptable salts thereof, especially as soluble hydrochlorides or sulfates. Other such salts include combinations with hydrobromic acid, sulfamic acid, phosphoric acid, methanesulfonic acid, benzene sulfonic acid, ethane disulfonic acid, acetic acid, citric acid, malic acid, succinic acid, maleic acid, fumaric acid, tartaric acid and benzylic acid.

The compounds of the invention have not only a high degree of activity compared to other local anesthetics, but, in some cases, the duration of that activity is surprisingly great. They may be administered by topical application to produce surface anesthesia and used to

relieve itching, burning and surface pain. They may also be administered by local injection for surgical procedures. When they are administered topically, the compounds may be administered from aqueous solutions, in pharmaceutical cream or salve bases, etc. The compounds can be conveniently injected in solutions, e.g. in aqueous or saline solutions.

Both the degree and the duration of local anesthetic activity can be conveniently demonstrated by means of a corneal reflex test utilizing rabbits as test animals. In this test the anesthetic solution is instilled in the conjunctival sac of the rabbit eye. The corneal reflex is then tested for insensibility by drawing a thread across the pupil and observing any reflex action.

The results of tests run using this procedure to compare the efficacy of a typical compound of the invention (β - diethylaminoethyl 1 - (2,2,2 - trifluoroethoxy) - 2-naphthoate hydrochloride) and the widely used local anesthetic procaine are presented in the two following tables. The test compound of the invention and the procaine are both used in dilute aqueous solutions. Two to four drops of the solution are placed in the test site and held in situ for one minute. The corneal reflex is tested six times at each of the various elapsed times indicated after administration of the test compound.

TABLE I.—PERCENT INHIBITION OF CORNEAL REFLEX

Time (minutes)	Test compound [1]	Procaine [1]
0	0	0
10	100	84
20	100	50
25	100	50
30	100	----
45	67	----
50	50	----
60	[2]	0

[1] Tested from a 1 percent aqueous solution.
[2] Test discontinued.

TABLE II.—PERCENT INHIBITION OF CORNEAL REFLEX

Time (minutes)	Test compound [1]	Procaine [2]
0	0	0
10	100	50
20	100	67
30	100	84
40	84	33
50	50	33
55	33	0

[1] Tested from a 0.1 percent aqueous solution.
[2] Tested from a 1 percent aqueous solution.

Other compounds showing excellent long term local anesthetic activity are β-diethylaminoethyl 3-(2,2,2-trifluoroethoxy)-2-naphthoate hydrochloride and β-diethylaminoethyl-2,5 di-(2,2,2-trifluoroethoxy) benzoate hydrochloride.

The compounds of Formula I can be produced by converting a hydroxyaryl ester of the formula:

(II) $$R''O\overset{O}{\overset{\|}{C}}Ar(OH)_n$$

to the fluorocarbon ether of the aryl ester:

(III) $$R''O\overset{O}{\overset{\|}{C}}Ar(O\,CH_2R_f)_n$$

by reacting II with an alkylating ester, e.g. a fluorocarbon trifluoromethane sulfonate such as IV

(IV) $$CF_3SO_2OCH_2R_f$$

in the presence of sodium bicarbonate or potassium bicarbonate in an inert solvent such as acetone. The resulting ester (III) is then hydrolyzed to the free acid (III,

R″=H). In these formulas R″ is lower alkyl (usually containing not more than about four carbon atoms), CH_2R_f or H, and R_f, Ar and *n* are as previously defined.

The free acid can be reacted with a β-dialkylaminoalkyl halide or salt thereof, e.g.

(V) $Z(CHQ)_2NRR' \cdot HCl$

(wherein Z is halogen such as chlorine or bromine and Q, R and R′ are as defined above) in the presence of an acid scavenger, such as sodium bicarbonate or potassium bicarbonate, and an inert solvent, such as toluene or benzene, to prepare the β-dialkylaminoalkyl esters of the invention.

An alternative method for the preparation of compounds of Formula I involves the alcoholysis of an ester of the Formula III where R″ is not H with a β-dialkylaminoalkanol of the formula:

(VI) $HO(CHQ)_2NRR'$

The starting materials utilized in the preparation of the compounds of the invention (compounds of types II, IV, V and VI) are well-known to the art. A number of them are utilized in the following preparative examples.

The following examples will more fully illustrate the preparation of the compositions of the invention. All temperatures in the examples are given in ° C. Examples 1–34 relate to the preparation of intermediate compounds and Examples 35–46 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 three 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 $C_{10}H_9F_3O_3$ (percent): C, 51.3; H, 3.9; F, 24.3. Found (percent): 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 three 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 $C_{14}H_{11}F_3O_3$ (percent): C, 59.2; H, 3.9; F, 20.0. Found (percent): C, 58.9; H, 4.0; F, 21.1.

Additional compounds of Formula III, where R″ is not H and R_f is CF_3 are prepared according to the procedures described in Examples 1 and 2 and are described in Table III.

TABLE III

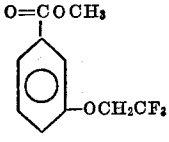
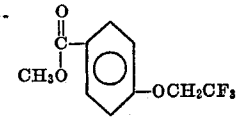
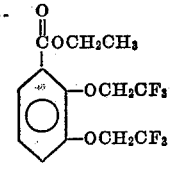
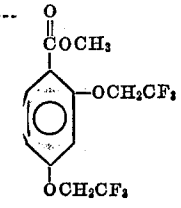
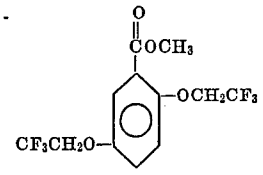
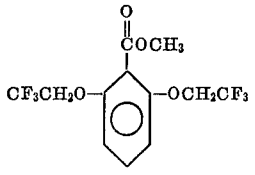
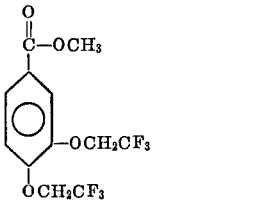
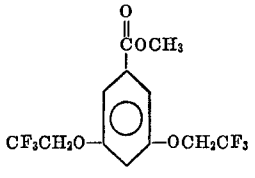
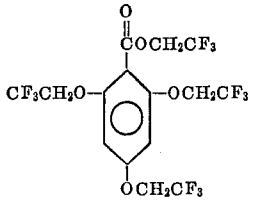
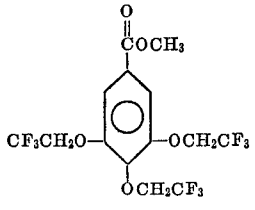
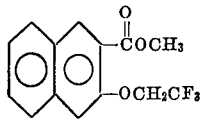
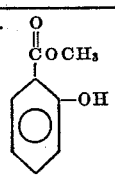
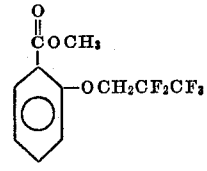
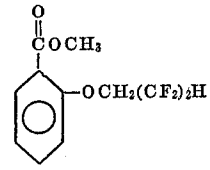
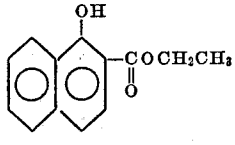
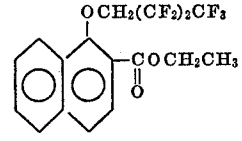
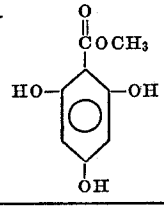
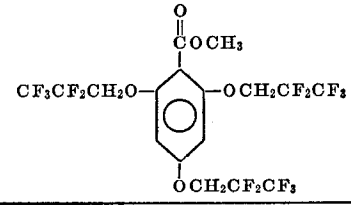
Example No.	Formula	Melting point (in ° C.)	Analysis for— Calculated C	H	F	Found C	H	F
			$C_{10}H_9F_3O_3$					
3		57.5–59	51.3	3.9	24.3	51.2	4.1	25.0
4		59.5–60.5	51.3	3.9	24.3	51.2	4.1	24.8
			$C_{13}H_{12}F_6O_4$					
5		30–31	45.1	3.5	------	45.0	3.7	------
			$C_{12}H_{10}F_6O_4$					
6		70.5–71.5	43.4	3.0	34.3	43.4	3.2	35.3

TABLE III—Continued

Example No.	Formula	Melting point (in °C.)	Analysis for— Calculated C	H	F	Found C	H	F
		42-44	43.4	3.0	34.3	43.4	2.7	34.4
8		52.54	43.4	3.0	34.3	43.2	3.1	34.6
9		57-59	43.4	3.0	34.3	43.6	3.0	34.8
10		81.5-82.5	43.4	3.0	34.3	43.5	3.0	35.4
11		64.8-65.8	$C_{15}H_{10}F_{12}O_5$					
			36.2	2.0	45.8	36.1	2.2	46.1
12		86-87	$C_{14}H_{11}F_9O_5$					
			39.1	2.6	40.0	39.2	2.6	40.3
13		77-77.5	$C_{14}H_{11}F_3O_3$					
			59.2	3.9	20.0	59.2	4.2	21.0

Compounds of Formula III where R'' is not H are prepared according to the procedures described in Examples 1 and 2 but utilizing compounds of Formula IV other than 2,2,2-trifluoroethyl trifluoromethanesulfonate are shown in Table IV.

TABLE IV

Example No.	Srarting materials: Formula II	Formula IV	Product, Formula III
14		$CF_3SO_2OCH_2CF_2CF_2$	
15	Same as above.	$CF_3SO_2OCH_2(CF_2)_2H$	
16		$CF_3SO_2OCH_2(CF_2)_2CF_3$	
17		$CF_3SO_2OCH_2CF_2CF_3$	

Example 18.—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 $C_9H_7F_3O_3$ (percent): C, 49.1; H, 3.2; F, 25.9. Found (percent): C, 48.8; H, 3.3; F, 26.2.

Example 19.—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, 2.9 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° C.

Analysis.—Calculated for $C_{13}H_9F_3O_3$ (percent): C, 57.8; H, 3.4; F, 21.1. Found (percent): C, 57.8; H, 3.6; F, 21.7.

Compounds of Formula III where R'' is H are obtained from each of the products of Examples 3 through 17 by the methods described in detail in Examples 18 and 19. Such products where R_f is CF_3 are listed in Table V.

TABLE V

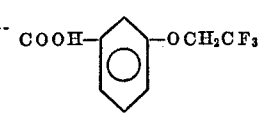
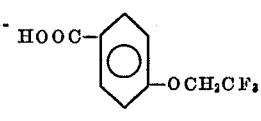
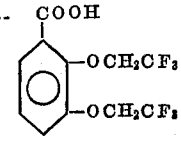
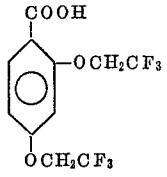
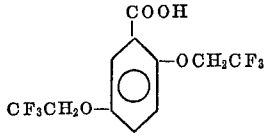
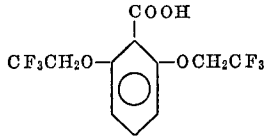
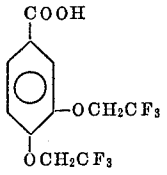
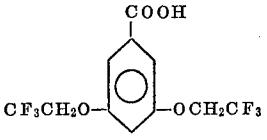
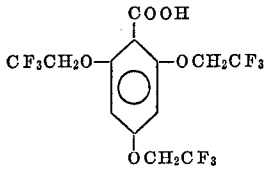
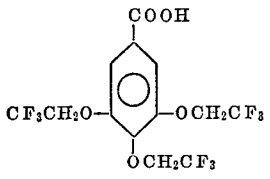
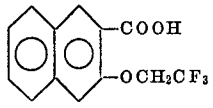
Example No.	Product	Melting point (in° C.)	Analysis for— Calculated C	H	F	Found C	H	F
			$C_9H_7F_3O_3$					
20		105–105.5	49.1	3.2	25.9	49.2	3.1	26.2
21		200–200.5	49.1	3.2	25.9	49.1	3.5	25.8
			$C_{11}H_8F_6O_4$					
22		141–143	41.5	2.5	------	41.9	2.6	------

TABLE V—Continued

Example No.	Product	Melting point (in° C.)	Analysis for— Calculated C	H	F	Found C	H	F
23		143.5–144	41.5	2.5	35.8	40.9	2.6	36.0
24		122–124	41.5	2.5	35.8	41.6	2.8	35.8
25		158–159	41.5	2.5	35.8	41.6	3.1	35.2
26		143–144	41.5	2.5	35.8	41.8	2.5	35.7
27		141.5–143	41.5	2.5	35.8	41.5	2.6	36.0
			$C_{13}H_9F_9O_5$					
28		140.5–141.5	37.5	2.2	41.1	37.7	2.2	41.3
29		196–197	37.5	2.2	41.1	37.5	2.5	41.2
			$C_{13}H_9F_3O_3$					
30		149–150	57.8	3.4	21.1	57.7	3.4	21.4

Several compounds of Formula III where R'' is H are prepared according to the procedure described in Examples 18 and 19 where R_f is other than CF_3 are listed in Table VI.

TABLE VI

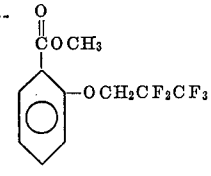
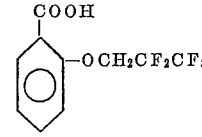
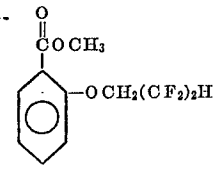
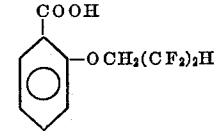
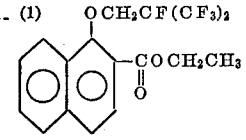
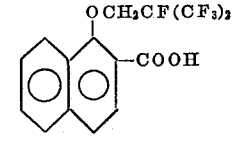
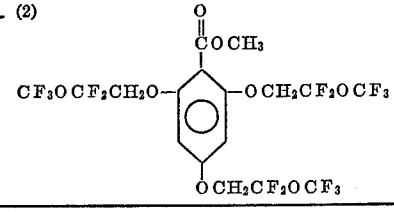
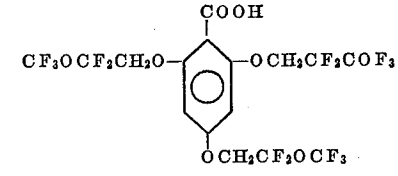
Example No.	Starting material	Product
31		

TABLE VI—Continued

Example No.	Starting material	Product
32		
33 (1)		
34 (2)		

NOTE:

(1) Prepared according to the procedures of Examples 1 and 2 from ethyl 1-hydroxy-2-naphthoate and 1,1-dihydroperfluoroisobutoxy trifluoromethanesulfonate.

(2) Prepared according to the procedures of Examples 1 and 2 from methyl 2,4,6-trihydroxybenzoate and 2,2-difluoro-(2-trifluoromethoxy)ethoxy trifluoromethanesulfonate.

Example 35.—Preparation of β-diethylaminoethyl 2,3-di-(2,2,2-trifluoroethoxy)-benzoate hydrochloride

A mixture containing 9.55 g. (30 mmoles) of 2,3-di-(2,2,2-trifluoroethoxy)-benzoic acid, 9 g. (90 mmoles) of anhydrous potassium bicarbonate and 100 ml. of toluene is well-stirred and refluxed under a water trap for two hours (most of the water separated within the first hour of reaction). The material is cooled and to it added 5.16 g. (30 mmoles) of β-diethylaminoethyl chloride hydrochloride. This product is refluxed under a water trap with efficient stirring for one day. Solvent is removed under diminished pressure and the residue is taken up in an ether-water mixture. The organic layer is separated, water-washed and dried (anhydrous magnesium sulfate). The ethereal solution is filtered and the filtrate is saturated with anhydrous, gaseous hydrogen chloride. The product is protected from moisture and allowed to stand for one day. The resulting white crystals are collected and purified by recrystallization from an absolute alcohol-absolute ether combination. M.P. 72–74.5° C.

Analysis.—Calculated for $C_{17}H_{22}ClF_6NO_4$ (percent): C, 45.0; H, 4.9; F, 25.1. Found (percent): C, 45.0; H, 5.2; F, 25.2.

Example 36.—Preparation of β-diethylaminoethyl 3,4-di-(2,2,2-trifluoroethoxy)-benzoate maleate

Esterification of 3,4 - di-(2,2,2-trifluoroethoxy)-benzoic acid (9.55 g., 30 mmoles) in toluene (100 ml.) under a water trap with potassium bicarbonate (9 g., 90 mmoles) and β-diethylaminoethyl chloride hydrochloride (5.16 g., 30 mmoles) followed by work up is conducted as described in Example 5. The dry ethereal solution is distilled (steam bath) and the resuting viscous yellow oil is taken up in 5 ml. of absolute ethanol. To this solution is added 3.49 g. (30 mmoles) of maleic acid dissolved in the minimum amount of absolute alcohol. This product is then diluted with ether prior to the cloud-point and allowed to stand in the cold. The resulting maleate salt is obtained as white crystals. It was recrystallized from absolute alcohol-absolute ether, M.P. 73.8–74.3° C.

Analysis.—Calculated for $C_{21}H_{25}F_6NO_8$ (percent): C, 47.3; H, 4.7; F, 21.9; N, 4.6. Found (percent): C, 46.3; H, 4.4; F, 20.4; N, 4.3.

Example 37.—Preparation of β-diethylaminoethyl 1-(2,2,2-trifluoroethoxy)-2-naphthoate hydrochloride

Anhydrous potassium bicarbonate (5.2 g., 5.2 mmoles), 1-(2,2,2-trifluoroethoxy)-2-naphthoic acid (4.7 g., 17.4 mmoles) and toluene (100 ml.) are refluxed under a water trap with efficient stirring for 1.5 hours (the theoretical amount of water separated within the first hour). To the cooled product is then added β-diethylaminoethyl chloride hydrochloride and the mixture is refluxed with stirring for one day. The cold material is filtered and the clear filtrate is concentrated to a viscous residue. This residue is taken up in ether and then washed successively with cold dilute aqueous sodium hydroxide and water. The dried ethereal solution is filtered from drying agent (anhydrous magnesium sulfate) and the filtrate is saturated with dry gaseous hydrogen chloride. On standing, white crystals form. They are collected and recrystallized from absolute alcohol-absolute ether, M.P. 124–125.5° C.

Analysis.—Calculated for $C_{19}H_{23}ClF_3NO_3$ (percent): C, 56.2; H, 5.7; F, 14.0; N, 3.4. Found (percent): C, 56.4; H, 6.0; F, 13.9; N, 3.4.

Example 38.—Preparation of β-diethylaminoethyl 1-(1,1-dihydroperfluoroisobutoxy)-2-naphthoate hydrochloride

Anhydrous potassium bicarbonate and 1-(1,1-dihydroperfluoroisobutoxy)-2-naphthoic acid in the molar ratio of 3 to 1 are refluxed in toluene under a water trap with efficient stirring for 1.5 hours (the theoretical amount of water separating within the first hour). To the cooled product is then added β-diethylaminoethyl chloride hydrochloride and the mixture is refluxed with stirring for one day. The cold material is filtered and the clear filtrate is up in ether and then washed successively with cold dilute aqueous sodium hydroxide and water. The dried ethereal solution is filtered from drying agent (anhydrous magnesium sulfate) and the filtrate is saturated with dry gaseous hydrogen chloride. On standing, white crystals of β-diethylaminoethyl 1-(1,1-dihydroperfluoroisobutoxy)-2-naphthoate hydrochloride form. They are collected and recrystallized from absolute alcohol-absolute ether.

Example 39.—Preparation of β-diethylaminoethyl 2,4,6-tri-[2,2 - difluoro-2-(trifluoromethoxy)ethoxy]benzoate hydrochloride

A mixture containing 1 mole of 2,4,6-tri-[2,2-difluoro-2-(trifluoromethoxy)ethoxy]benzoic acid and 3 moles of anhydrous potassium bicarbonate in toluene is well-stirred and refluxed under a water trap for two hours (most of

the water separates within the first hour of reaction). The material is cooled and to it is added 1 mole of β-diethylaminoethyl chloride hydrochloride. This product is refluxed under a water trap with efficient stirring for one day. Solvent is removed under diminished pressure and the residue is taken up in an ether-water mixture. The organic layer is separated, water-washed and dried (anhydrous magnesium sulfate). The ethereal solution is filtered and the filtrate is saturated with anhydrous, gaseous hydrogen chloride. The resulting white crystals of β-diethylaminoethyl 2,4,6 - tri-[2,2-difluoro-2-(trifluoromethoxy)-ethoxy]benzoate hydrochloride are collected and purified by recrystallization from an absolute alcohol-absolute ether combination.

Example 40.—Preparation of β-diethylaminoethyl 2,4-di-(2,2,2-trifluoroethoxy)-benzoate hydrochloride

A mixture containing 9.55 g. (30 mmoles) of 2,4-di-(2,2,2-trifluoroethoxy)benzoic acid, 9 g. (90 mmoles) of anhydrous potassium bicarbonate and 100 ml. of toluene is well-stirred and refluxed under a water trap for two hours (most of the water separates within the first hour of reaction). The material is cooled and to it is added 5.16 g. (30 mmoles) of β-diethylaminoethyl chloride hydrochloride. This product is refluxed under a water trap with efficient stirring for one day. Solvent is removed under diminished pressure and the residue is taken up in an ether-water mixture. The organic layer is separated, water-washed and dried (anhydrous magnesium sulfate). The ethereal solution is filtered and the filtrate is saturated with anhydrous, gaseous hydrogen chloride. The product is protected from moisture and allowed to stand for one day. The resulting white crystals are collected and purified by recrystallization from an absolute alcohol-absolute ether combination, M.P. 128–129° C.

Analysis.—Calculated for $C_{17}H_{22}ClF_6NO_4$ (percent): C, 45.0; H, 4.9; F, 25.1; N, 3.0. Found (percent): C, 45.1; H, 5.1; F, 26.0; N, 3.1.

Example 41.—Preparation of β-diethylaminoethyl 2,5-di-(2,2,2-trifluoroethoxy)-benzoate hydrochloride

A mixture containing 9.55 g. (30 mmoles) of 2,5-di-(2,2,2-trifluoroethoxy)-benzoic acid, 9 g. (90 mmoles) of anhydrous potassium bicarbonate and 100 ml. of toluene is well-stirred and refluxed under a water trap for two hours (most of the water separates within the first hour of reaction). The material is cooled and to it is added 5.16 g. (30 mmoles) of β-diethylaminoethyl chloride hydrochloride. This product is refluxed under a water trap with efficient stirring for one day. Solvent is removed under diminished pressure and the residue is taken up in an ether-water mixture. The organic layer is separated, water-washed and dried (anhydrous magnesium sulfate). The ethereal solution is filtered and the filtrate is saturated with anhydrous, gaseous hydrogen chloride. The product is protected from moisture and allowed to stand for one day. The resulting white crystals are collected and purified by recrystallization from an absolute alcohol-absolute ether combination, M.P. 87–89° C.

Analysis.—Calculated for $C_{17}H_{22}ClF_6NO_4$ (percent): C, 45.0; H, 4.9; F, 25.1; N, 3.0. Found (percent): C, 45.0; H, 4.9; F, 24.2; N, 3.5.

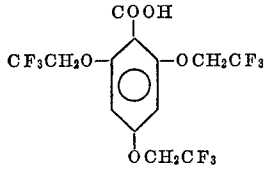
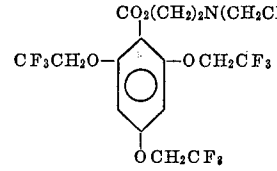
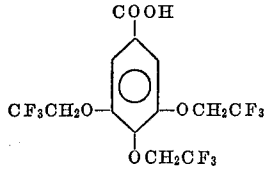
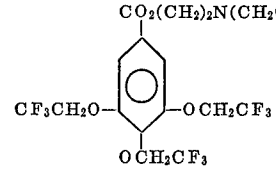
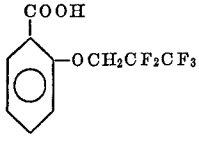
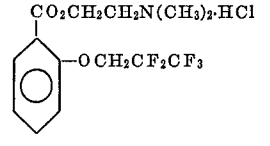
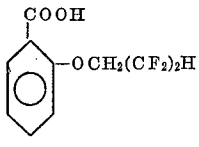
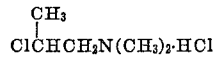
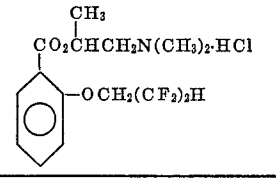
Example 42.—Preparation of β-diethylaminoethyl 3-(2,2,2-trifluoroethoxy)-2-naphthoate hydrochloride

Anhydrous potassium bicarbonate (5.2 g., 62.2 mmoles), 3 - (2,2,2 - trifluoroethoxy)-2-naphthoic acid (4.7 g., 17.4 mmoles) and toluene (100 ml.) are refluxed under a water trap with efficient stirring for 1.5 hours (the theoretical amount of water separates within the first hour). To the cooled product is then added β-diethylaminoethyl chloride hydrochloride and the mixture is refluxed with stirring for one day. The cold material is filtered and the clear filtrate is concentrated to a viscous residue. This residue is taken up in ether and then washed successively with cold dilute aqueous sodium hydroxide and water. The dried ethereal solution is filtered from drying agent (anhydrous magnesium sulfate) and the filtrate is saturated with dry gaseous hydrogen chloride. On standing white crystals form. They are collected and recrystallized from absolute alcohol-absolute ether, M.P. 142–143.5.

Analysis.—Calculated for $C_{19}H_{23}ClF_3NO_3$ (percent): C, 56.2; H, 5.7; F, 14.0; N, 3.4. Found (percent): C, 56.1; H, 5.6; F, 14.0; N, 3.3.

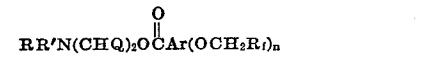
Additional compounds of Formula I (as their salts) are prepared according to the procedures described in Examples 35 through 42 and are listed in Table VII.

TABLE VII

Example No.	Starting material: Formula III	Starting material: Formula V	Product
43		$Cl(CH_2)_2N(CH_2CH_3)_2 \cdot HCl$	
44		$Cl(CH_2)_2N(CH_2CH_3)_2 \cdot HCl$	
45		$ClCH_2CH_2N(CH_3)_2 \cdot HCl$	
46			

What is claimed is:

1. A compound of the formula:



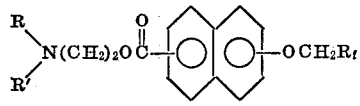
wherein R and R' are alkyl groups of one to three carbon atoms each, each Q is hydrogen or a lower alkyl group, Ar is an aryl group containing from six to ten carbon atoms, each R_f is a fluorocarbon group containing from one to three carbon atoms and *n* is one to four; and pharmaceutically acceptable salts thereof.

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

3. A compound according to claim 1 wherein *n* is 2.

4. A compound according to claim 1 wherein each Q is hydrogen and R_f is trifluoromethyl.

5. A compound of the formula:

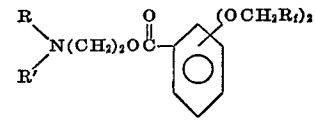


wherein R and R' are lower alkyl groups of from one to three carbon atoms each and R_f is a fluorocarbon group containing from one to three carbon atoms; and pharmaceutically acceptable salts thereof.

6. β - Diethylaminoethyl 1 - (2,2,2-trifluoroethoxy)-2-naphthoate hydrochloride according to claim 5.

7. β - Diethylaminoethyl 3 - (2,2,2,-trifluoroethoxy)-2-naphthoate hydrochloride according to claim 5.

8. A compound of the formula:



wherein R and R' are lower alkyl groups of from one to three carbon atoms each and each R_f is a fluorocarbon group containing from one to three carbon atoms; and pharmaceutically acceptable salts thereof.

9. β - Diethylaminoethyl 2,5-di-(2,2,2-trifluoroethoxy) benzoate hydrochloride according to claim 8.

References Cited

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LORRAINE A. WEINBERGER, Primary Examiner

J. F. TERAPANE, Assistant Examiner

U.S. Cl. X.R.

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