1, H-1'). Anal. ($C_{18}H_{17}N_3O_6$) C, H, N.

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Antiarrhythmics. 2. Synthesis and Antiarrhythmic Activity of *N*-(Piperidylalkyl)trifluoroethoxybenzamides

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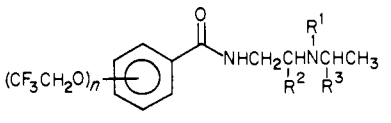
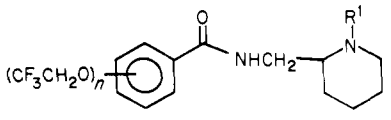
Benzamides characterized by one or more 2,2,2-trifluoroethoxy ring substituents and a heterocyclic amide side chain have been prepared and evaluated for oral antiarrhythmic activity in mice. The most potent compounds are derived from 2,5-bis(2,2,2-trifluoroethoxy)benzamide, and, within this group, both tertiary as well as secondary benzamides are active. Considerable variation in the heterocyclic ring is permissible, but antiarrhythmic activity is strongly influenced by the basicity of the amine nitrogen and the nature of the link between heterocycle and amide nitrogen. One of these compounds, *N*-(2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate (flecainide acetate, USAN), was studied extensively in animals and selected for clinical trial as an antiarrhythmic.

In a previous paper[1] we described a series of *N*-(aminoalkyl)trifluoroethoxybenzamides which possessed potent antiarrhythmic properties. Within this series considerable variation of the amide side chain was possible without significant reduction in activity, but a structural feature common to a majority of the most potent compounds was an amide side chain with branching α to the basic nitrogen atom (I). We now wish to report a series of *N*-(piperidylalkyl)trifluoroethoxybenzamides, typified by the general structure II, which can be formally derived from I by linking R^2 and R^3.



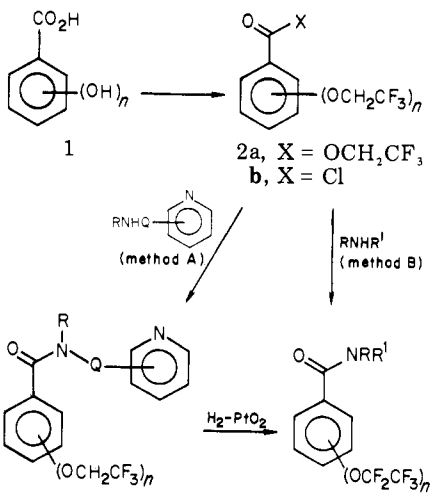
I



II

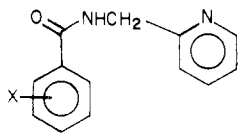
Chemistry. The trifluoroethoxybenzamides studied in this investigation were prepared by the general routes outlined in Scheme I. Trifluoroethylation of hydroxy acids

Scheme I



3-15 (Table I) **28-40** (Table III)
16-27 (Table II) **41-64** (Table IV)

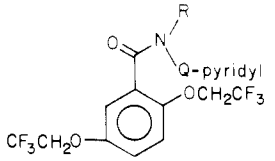
Table I. Ring-Substituted *N*-(2-Pyridylmethyl)benzamide Intermediates



Compd	X	Mp, °C	Formula[a]	Recrystn solvent
3	2-OCH_2CF_3	86-88	$C_{15}H_{13}F_3N_2O_2$	Cyclohexane
4	3-OCH_2CF_3	98-99	$C_{15}H_{13}F_3N_2O_2$	EtOAc
5	4-OCH_2CF_3	128-130.5	$C_{15}H_{13}F_3N_2O_2$	EtOH-H_2O
6	2,3-$(OCH_2CF_3)_2$	144-146	$C_{17}H_{14}F_6N_2O_3$	*i*-PrOH
7	2,4-$(OCH_2CF_3)_2$	103-105.5	$C_{17}H_{14}F_6N_2O_3$	Cyclohexane-benzene
8	2,5-$(OCH_2CF_3)_2$	103-105	$C_{17}H_{14}F_6N_2O_3$	Benzene-hexane
9	2,6-$(OCH_2CF_3)_2$	137-138.5	$C_{17}H_{14}F_6N_2O_3$	Cyclohexane
10	3,4-$(OCH_2CF_3)_2$	117-118	$C_{17}H_{14}F_6N_2O_3$	CCl_4
11	3,5-$(OCH_2CF_3)_2$	103-104.5	$C_{17}H_{14}F_6N_2O_3$	Toluene-heptane
12	2,4,6-$(OCH_2CF_3)_3$	155.5-157	$C_{19}H_{15}F_9N_2O_4$	Cyclohexane-benzene
13	2-OCH_2CF_3, 5-CH_3	99-100.5	$C_{16}H_{15}F_3N_2O_2$	EtOH-H_2O
14	2-OCH_2CF_3, 5-Cl	119-121	$C_{15}H_{12}ClF_3N_2O_2$	Cyclohexane-benzene
15	2-OCH_2CF_3, 5-F	114.5-116	$C_{15}H_{12}F_4N_2O_2$	EtOH-H_2O

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

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



Compd	R	Q-Pyridyl	Mp, °C	Formula[a]	Recrystn solvent
16	H	2-Pyridyl	166-179	$C_{16}H_{12}F_6N_2O_3 \cdot HCl$	*i*-PrOH
17	H	3-Pyridyl	114-117	$C_{16}H_{12}F_6N_2O_3 \cdot 0.5CCl_4$	*i*-PrOH-CCl_4
18	H	4-Pyridyl	164.5-166.6	$C_{16}H_{12}F_6N_2O_3 \cdot HCl$	EtOAc-*i*-PrOH
19	H	3-Pyridylmethyl	181-188	$C_{17}H_{14}F_6N_2O_3 \cdot HCl$	*i*-PrOH
20	H	6-Methyl-3-pyridylmethyl	113-114.5	$C_{18}H_{16}F_6N_2O_3$	CCl_4-cyclohexane
21	H	1-(2-Pyridyl)ethyl	98-100.5	$C_{18}H_{16}F_6N_2O_3$	Cyclohexane
22	*n*-Bu	2-Pyridylmethyl	82-84	$C_{21}H_{22}F_6N_2O_3$	Heptane
23	CH_3	2-Pyridylmethyl	89-91	$C_{18}H_{16}F_6N_2O_3$	Heptane-benzene
24	CH_3	6-Methyl-3-pyridylmethyl	83-86	$C_{19}H_{18}F_6N_2O_3$	Heptane-benzene
25	CH_3CH_2	2-Pyridylmethyl	68-74	$C_{19}H_{18}F_6N_2O_3$	Glass
26	C_5H_{11}	2-Pyridylmethyl	113-114	$C_{23}H_{24}F_6N_2O_3$	Cyclohexane
27	*t*-Bu	2-Pyridylmethyl	122-123.5	$C_{21}H_{22}F_6N_2O_3$	Cyclohexane-hexane

[a] See corresponding footnote in Table I.

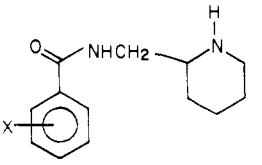
1 by methods previously described[1] gave the intermediate trifluoroethyl esters 2a. Usually these activated esters could be converted directly into benzamides, but in certain cases it was necessary to use the corresponding acid chloride 2b, obtained from 2a by saponification followed by chlorination with thionyl chloride.

Most of the compounds were obtained from 2a and 2b in two steps (Scheme I, method A). Treatment of either intermediate with RNHQ-pyridine yielded a series of *N*-(Q-pyridyl)trifluoroethoxybenzamides (3–27, Tables I and II). In this scheme Q represents a methylene link, a substituted methylene link (21), or a carbon–nitrogen bond (16–18). With pyridines bearing a primary amine function (R = H), the method of choice was direct aminolysis of ester 2a with excess amine. In cases where valuable amine had to be conserved, it was necessary to use acid chloride 2b. The *tert*-*N*-alkyl-*N*-(Q-pyridyl)-trifluoroethoxybenzamides 22–27, derived from pyridines with a bulky secondary amino group (R = alkyl), also required the use of 2b. In either case, subsequent catalytic hydrogenation of the pyridine ring gave the desired piperidine compounds. The availability of required pyridines and lack of complications made the two-step synthesis a preferred route.

One-step conversion of 2a and 2b into *N*-(piperidylalkyl)trifluoroethoxybenzamides (method B) was achieved with certain fully saturated amine components $RNHR^1$ (R^1 = piperidyl or piperidylmethyl). With acid chloride 2b this method is clearly limited to cases where no mixed products are possible, i.e., the ring nitrogen must be tertiary. In contrast, aminolysis of ester 2a is highly selective and occurs preferentially with primary amines (R = H). Thus even if the ring nitrogen is secondary, aminolysis of 2a with an excess of NH_2R^1 involves reaction at the exocyclic amine function only to give the desired products. All *N*-(piperidylalkyl)trifluoroethoxybenzamides (28–64) which were prepared by either method are collected in Tables III and IV.

Most of the amines required for the preparation of benzamides described in this paper are readily available. Exceptions include the 2-(alkylaminomethyl)pyridines which were used to synthesize benzamides 22–27. These amines were obtained by condensing the appropriate primary amine with 2-pyridinecarboxaldehyde and hydrogenating the intermediate Schiff base without isolation according to a modification of the procedure described by Profft.[2] The isomeric diamines, 2-aminomethyl-1,2,3,4-tetrahydroquinoline and 1-aminomethyl-1,2,3,4-tetra-

Table III. Ring-Substituted N-(2-Piperidylmethyl)benzamides



Compd	X	Mp, °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)
28	2-OCH_2CF_3	196-197.5	$C_{15}H_{19}F_3N_2O_2 \cdot HCl$	*i*-PrOH	A (65)[c]	283 (212-394)
29	3-OCH_2CF_3	107.5-109	$C_{15}H_{19}F_3N_2O_2$	Cyclohexane	A (37)	76 (54-107)
30	4-OCH_2CF_3	226-228	$C_{15}H_{19}F_3N_2O_2 \cdot HCl$	*i*-PrOH-EtOH	A (47)	190 (128-278)
31	2,3-$(OCH_2CF_3)_2$	199-201	$C_{17}H_{20}F_6N_2O_3 \cdot HCl$	*i*-PrOH-$(i\text{-Pr})_2O$	A (80)	149 (111-202)
32	2,4-$(OCH_2CF_3)_2$	271-272	$C_{17}H_{20}F_6N_2O_3 \cdot HCl$	MeOH	A (64)	244 (182-328)
33	2,5-$(OCH_2CF_3)_2$	145-147	$C_{17}H_{20}F_6N_2O_3 \cdot C_2H_4O_2$	*i*-PrOH-$(i\text{-Pr})_2O$	A (76)	48 (36-65)
34	2,6-$(OCH_2CF_3)_2$	266-268	$C_{17}H_{20}F_6N_2O_3 \cdot HCl$	EtOH	A (71)	271 (211-348)
35	3,4-$(OCH_2CF_3)_2$	157.5-159.5	$C_{17}H_{20}F_6N_2O_3 \cdot HCl$	CH_3CN-$(i\text{-Pr})_2O$	A (65)	277 (200-388)
36	3,5-$(OCH_2CF_3)_2$	202-204	$C_{17}H_{20}F_6N_2O_3 \cdot HCl$	*i*-PrOH-$(i\text{-Pr})_2O$	A (16)	388 (284-532)
37	2,4,6-$(OCH_2CF_3)_3$	264-265	$C_{19}H_{21}F_9N_2O_4 \cdot HCl$	EtOH	A (74)	95 (73-124)
38	2-OCH_2CF_3, 5-CH_3	193-196	$C_{16}H_{21}F_3N_2O_2 \cdot HCl$	*i*-PrOH-$(i\text{-Pr})_2O$	A (79)	>600
39	2-OCH_2CF_3, 5-Cl	157-160	$C_{15}H_{18}ClF_3N_2O_2 \cdot HCl$	*i*-PrOH-$(i\text{-Pr})_2O$	A (82)	230 (173-287)
40	2-OCH_2CF_3, 5-F	200-201.5	$C_{15}H_{18}F_4N_2O_2 \cdot HCl$	*i*-PrOH-$(i\text{-Pr})_2O$	A (81)	270 (186-391)

[a] All compounds analyzed for C, H, and N within ±0.4% of the theoretical value. [b] 95% confidence limits. [c] Yields listed for method A refer only to the final hydrogenation step.

hydroisoquinoline, were synthesized by the method of Rupe et al.[3] and Katz and Popp,[4] respectively.

Pharmacology. Prevention of chloroform-induced ventricular fibrillation in female mice (18–24 g) of Swiss–Webster origin was used for preliminary identification and quantification of antiarrhythmic activity.[5] Control mice when exposed to chloroform vapors until cessation of respiration exhibit ventricular fibrillation upon visual inspection of the heart. Prevention of this response was taken as evidence of antiarrhythmic action. Sometimes after drug administration the response to subsequent chloroform exposure resulted in alternating periods of arrhythmia and/or fast ventricular rate (>200/min) with periods of normal rhythm and/or slow ventricular rate (<200/min). When this occurred, a predominance of normal rhythm and/or slow ventricular rate was taken as an indication of antiarrhythmic action. 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 dose (range finding). Compounds which lacked potency compared to standard reference agents were disqualified from further testing. Compounds showing good activity at the initial 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.[6] Results are expressed in Tables III and IV 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 III.

Discussion

Our earlier structure–action studies on N-(aminoalkyl)trifluoroethoxybenzamides[1] revealed that antiarrhythmic potency varied widely depending on the pattern of trifluoroethoxy ring substitution. Among N-(2-diethylaminoethyl)benzamides, the most potent activity was observed with compounds bearing two trifluoroethoxy groups, one of which was ortho to the carboxamide function. A similar trend was found in the present study although the variation in potency with substituent changes was somewhat less pronounced.

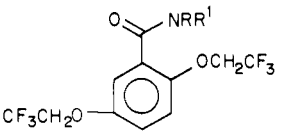
The effect of ring substituent changes was evaluated with a set of N-(2-piperidylmethyl)benzamides (**28–37**, Table III). These compounds differ only in the number and position of trifluoroethoxy groups, and many have ED_{50} values of 200–300 μmol/kg, putting them roughly in the same range as the reference agent quinidine in this test.

Among the monosubstituted compounds, a trifluoroethoxy group meta (**29**) to the carboxamide function is superior to substitution at either the ortho (**28**) or para (**30**) position. Of the six possible disubstituted isomers (**31–36**), four have at least one CF_3CH_2O group meta to the carboxamide. Two of the four, **31** [2,3-$(OCH_2CF_3)_2$; ED_{50} = 149 μmol/kg] and **33** [2,5-$(OCH_2CF_3)_2$; ED_{50} = 48 μmol/kg], are considerably more potent than the others. These are the only two isomers which have one CF_3CH_2O ortho and one CF_3CH_2O meta to the carboxamide function and this clearly represents the most favorable configuration. Replacement of the *m*-CF_3CH_2O in compound **33** with other substituents (**38–40**) results in substantial reduction in activity.

Since the best aromatic substitution pattern is unmistakably 2,5-$(OCH_2CF_3)_2$, all additional compounds designed to explore modification of the amide side chain were based on this ring nucleus. The various N-substituted 2,5-bis(2,2,2-trifluoroethoxy)benzamides **41–64** which were prepared and studied are collected in Table IV. Compounds **41–47** illustrate effects of altering the chain length between amide and amine nitrogen atoms. A two-carbon link between these sites is a common characteristic among many compounds with local anesthetic or antiarrhythmic activity.[7] Although the amine nitrogen in the present series is part of a heterocyclic ring, a two-carbon link is still optimum whether the amide is bonded to a methylene (**33**, **41**, **42**) or directly to the ring (**43**). Extension of the chain to three (**44**, **45**) or four carbons (**46**) results in marked reduction in activity, and this reduction is even more dramatic when the chain is shortened to one carbon atom (compare **33** and **47**).

Most of the compounds reported here are secondary amines, but tertiary amines are also active. Thus **48**

Table IV. N-Substituted 2,5-Bis(2,2,2-trifluoroethoxy)benzamides



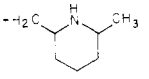
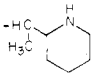
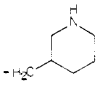
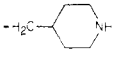
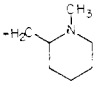
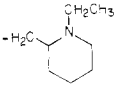
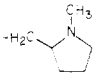
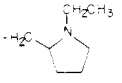
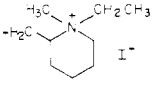
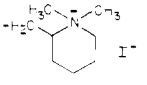
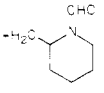
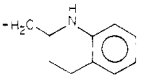
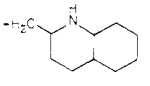
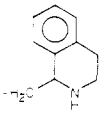
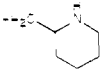
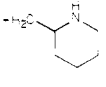
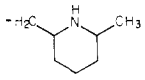
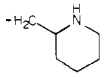
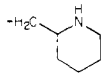
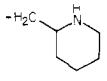
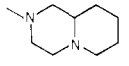
Compd	R	R^1	Mp or bp (mm), °C	Formula[a]	Recrystn solvent	Synthetic method (yield, %)	Mouse protection screen, ED_{50}, μmol/kg po
41	H		215-222	$C_{18}H_{22}F_6N_2O_3 \cdot HCl$	EtOH	A (46)[b]	22 (15-30)[c]
42	H		95-97.5	$C_{18}H_{22}F_6N_2O_3$	Cyclohexane	A (55)	19 (9-35)
43	H		224-225	$C_{16}H_{18}F_6N_2O_3 \cdot HCl$	EtOH-*i*-PrOH	A (18)	57 (39-82)
44	H		189-191.5	$C_{17}H_{20}F_6N_2O_3 \cdot HCl$	*i*-PrOH	A (65)	82 (58-118)
45	H		193.5-195	$C_{18}H_{18}F_6N_2O_3 \cdot HCl$	*i*-PrOH-$(i\text{-Pr})_2O$	A (42)	144 (89-234)
46	H		179-180	$C_{17}H_{20}F_6N_2O_3 \cdot HCl$	EtOAc-*i*-PrOH	B (67)	149 (73-304)
47	H		Glass	$C_{16}H_{18}F_6N_2O_3 \cdot HCl \cdot 0.75H_2O$		A (88)	>500
48	H		99-102	$C_{18}H_{22}F_6N_2O_3$	Cyclohexane	C (61)[d]	44 (30-61)
49	H		98-99	$C_{19}H_{24}F_6N_2O_3$	Petr ether-cyclohexane	B (62)	102 (59-151)
50	CH_2CH_3		163 (0.2)	$C_{19}H_{24}F_6N_2O_3$		A (80)	29 (20-43)
51	H		78-80	$C_{18}H_{22}F_6N_2O_3$	Petr ether-cyclohexane	B (59)	70 (47-105)
52	H		162-165	$C_{20}H_{27}F_6IN_2O_3$	MeOH-$(i\text{-Pr})_2O$	D (76)[d]	>380
53	H		170-172.5	$C_{19}H_{25}F_6IN_2O_3$	EtOAc-*i*-PrOH	D (71)	>395
54	H		90-94	$C_{18}H_{20}F_6N_2O_4$	Benzene-hexane	E (58)[d]	>510
55	H		196-206	$C_{21}H_{20}F_6N_2O_3 \cdot HCl$	MeOH	B (48)	>450
56	H		241-246	$C_{21}H_{26}F_6N_2O_3 \cdot HCl$	CH_3CN-EtOH	B (24)	27 (14-53)
57	H		103-109	$C_{21}H_{20}F_6N_2O_3$	Cyclohexane	B (69)	380 (223-647)
58	*n*-Bu		119-120	$C_{21}H_{28}F_6N_2O_3 \cdot C_2H_4O_2$	MIBK	A (49)	32 (25-40)
59	CH_3		113-115	$C_{18}H_{22}F_6N_2O_3 \cdot C_2H_4O_2$	MIBK-*i*-PrOH	A (81)	24 (20-27)

Table IV (*Continued*)

Compd	R	R'	Mp or bp (mm), °C	Formula[a]	Recrystn solvent	Synthetic method (yield, %)	Mouse protection screen, ED_{50}, μmol/kg po
60	CH_3		130-131	$C_{19}H_{24}F_6N_2O_3 \cdot C_2H_4O_2$	MIBK	A (72)	9 (7-12)
61	CH_2CH_3		93-96	$C_{19}H_{24}F_6N_2O_3$	Hexane	A (65)	<2
62	c-C_6H_{11}		132-135	$C_{23}H_{30}F_6N_2O_3 \cdot 0.86C_4H_4O_4$	EtOAc-*i*-PrOH	A (33)	36 (23-47)
63	*t*-Bu		110-112.5	$C_{21}H_{28}F_6N_2O_3$	Cyclohexane-hexane	A (45)	17 (13-22)
64			101-105	$C_{19}H_{22}F_6N_2O_3$	Cyclohexane-hexane	B (62)	>510

[a] All compounds analyzed for C, H, and N within ±0.4% of the theoretical values. [b] Yields listed for method A refer only to the final hydrogenation step. [c] 95% confidence limits. [d] See Experimental Section.

(*N*-methyl) is comparable to **33** although **49** (*N*-ethyl) is less than one-half as potent. While no clear superiority can be demonstrated for either secondary or tertiary amines in the side chain, the need for an amino group of relatively strong basic strength is unmistakable. Thus quaternization (**52**, **53**) or formylation (**54**) of the amine is unfavorable. Similarly compound **55**, bearing a weakly basic arylamino group in the side chain, shows lower activity. The effect of basicity is dramatically illustrated by comparing **55** (ED_{50} > 450 μmol/kg) with its saturated counterpart **56** (ED_{50} = 27 μmol/kg). The presence of a six-membered heterocycle, however, is not essential since the two *N*-alkylpyrrolidines **50** and **51** show good activity.

As a class, the most active compounds in this entire series are the tertiary amides **50** and **58–63**. All compare favorably with **33** in potency, but some also show increased toxicity (CNS depression). A curious exception to the general observation of excellent activity among tertiary amides is compound **64**. The amide function in **64** is part of a rigid bicyclic ring system, and this structural alteration results in a significant reduction in activity.

The work reported here demonstrates that 2,5-bis-(2,2,2-trifluoroethoxy)benzamides bearing a piperidine ring as part of the amide side chain possess interesting and potent antiarrhythmic activity. Considerable latitude in the nature of the piperidine side chain is possible without loss of activity. On the basis of this preliminary work, several compounds were studied more extensively in canine model arrhythmias (e.g., ouabain-induced ectopic ventricular tachycardia and coronary ligation induced ventricular arrhythmia). One of these compounds, *N*-(2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate (**33**; flecainide acetate, USAN), is currently being evaluated for antiarrhythmic activity in man. A short description of the pharmacological properties of **33** has already appeared,[8] and a more detailed account will be published elsewhere.

Experimental Section

Boiling points are uncorrected. Melting points, determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus, are uncorrected. The general procedures outlined in Scheme I and listed in Tables III and IV are illustrated by the following examples.

Method A. ***N*-(2-Pyridylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide** (**8**). 2,2,2-Trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate[1] (21.6 g, 0.054 mol) was added neat over a period of 1 h to a stirred solution of 7.06 g (0.0648 mol) of 2-aminomethylpyridine in 100 mL of glyme under N_2 at 25 °C. The clear solution was stirred for 20 h at 25 °C and slowly brought to reflux. After 3 h the solution was cooled and concentrated in vacuo. Crystallization of the residue from benzene–hexane afforded **8** as an off-white solid: mp 103–105 °C; yield 20.1 g (91%).

***N*-(*n*-Butyl)-*N*-(2-pyridylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide** (**22**). A solution of 10.1 g (0.03 mol) of 2,5-bis(2,2,2-trifluoroethoxy)benzoyl chloride[1] in 30 mL of benzene was added dropwise at room temperature to a stirred suspension of 4.9 g (0.03 mol) of 2-(*n*-butylaminomethyl)pyridine, 13.7 g (0.12 mol) of Na_2CO_3, and 90 mL of benzene. After the addition was complete the mixture was heated under gentle reflux for 5 h, cooled, and concentrated under reduced pressure to remove benzene. Water and CH_2Cl_2 were added to the residue. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Recrystallization of crude product from heptane gave **22** as white flakes: mp 82–84 °C; yield 10.5 g (75.5%).

***N*-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)-benzamide Acetate** (**33**). A solution of 40.8 g (0.01 mol) of compound **8** in 600 mL of HOAc was added under N_2 to a paste of 0.4 g of PtO_2 in HOAc and hydrogenated on a Parr apparatus. After the theoretical amount of H_2 had been taken up, the mixture was filtered to remove catalyst and the filtrate was refiltered with added Super Cel. Evaporation of the filtrate under vacuum left a viscous syrup which solidified on trituration with $(i\text{-Pr})_2O$. The solid was collected by suction filtration and dissolved in hot *i*-PrOH. Crystallization was induced by adding $(i\text{-Pr})_2O$ to the cloud point. The purified product was collected as a white granular solid: mp 145–147 °C; yield 35.8 g (76%). This reduction can also be carried out in EtOH using a preformed HCl salt of the starting pyridylmethylbenzamide.

Method B. ***N*-(4-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide Hydrochloride** (**46**). 2,2,2-Trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate (10.0 g, 0.025 mol) was added neat over a period of 1 h to a stirred solution of 28.5 g (0.25 mol) 4-aminomethylpiperidine in 25 mL of glyme. The mixture was stirred overnight at room temperature and poured into H_2O. Most of the glyme was removed by concentrating the aqueous mixture on a rotary evaporator. The solid which separated was collected by suction filtration, dried, and dissolved in EtOAc. 2-Propanolic HCl was added and the solution was cooled. The HCl salt was collected and recrystallized from EtOAc–*i*-PrOH: mp 179–180 °C; yield 7.4 g (67%).

Method C. ***N*-(1-Methyl-2-piperidylmethyl)-2,5-bis-(2,2,2-trifluoroethoxy)benzamide** (**48**). 1-Methylpiperidine derivatives were prepared by the Eschweiler–Clarke reaction. Formalin (1.44 g, 0.048 mol), *N*-(2-piperidylmethyl)-2,5-bis-

(2,2,2-trifluoroethoxy)benzamide (8.3 g, 0.02 mol), and excess 88% formic acid (5.5 g, 0.12 mol) were combined and stirred under reflux. After 12 h the mixture was cooled and 2.8 mL of concentrated HCl was added. Heating under reflux was continued for another 5 h. The solution was then cooled, made strongly basic with 10% NaOH, diluted with H_2O, and extracted with CH_2Cl_2. Evaporation of solvent yielded 6 g of crude product which was purified by recrystallization from cyclohexane: mp 99–102 °C; yield 5.2 g (61%). Compounds of this type were also conveniently prepared by the Borch reductive amination procedure.[9]

Method D. 2-[2,5-Bis(2,2,2-trifluoroethoxy)benzamidomethyl]-1,1-dimethylpiperidinium Iodide (53). Compound 48 (2.7 g, 0.0063 mol) was heated with 10 mL of CH_3I in a sealed tube at 55 °C. After 1.5 h the tube was opened and the contents rinsed out with CH_3OH. Solvents were removed under vacuum and the residue was recrystallized from EtOAc–*i*-PrOH to give **53** as a white powder: mp 170–172.5 °C; yield 2.4 g (71%).

Method E. *N*-(1-Formyl-2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide (54). Trichloroacetaldehyde (2.82 g, 0.019 mol) was added dropwise at 0 °C to a stirred solution of compond **33** (7.24 g, 0.0175 mol) in 70 mL of $CHCl_3$. After the addition was complete, the solution was allowed to warm to room temperature, stirred for 1 h, and then heated under reflux for 3 h. The solution was cooled, washed with 5% HCl, dried, and concentrated. The residual gummy solid was dissolved in hot benzene. Slow addition of hexane to the cloud point induced crystallization of **54** as a finely divided ivory powder: mp 90–94 °C; yield 4.6 g (58%).

2-(*tert*-Butylaminomethyl)pyridine. The general procedure used to prepare various 2-(alkylaminomethyl)pyridines is illustrated by the following example. A solution of 21.9 g (0.3 mol) of *tert*-butylamine in 30 mL of absolute EtOH was added dropwise over 1.5 h to a stirred solution of 32.1 g (0.3 mol) of 2-pyridinecarboxaldehyde in 40 mL of absolute EtOH maintained at 10–20 °C. After the addition was complete, the mixture was stirred 1 h at 25 °C, heated to reflux for 6 h and cooled. GLC analysis showed that conversion to the Schiff base was essentially quantitative. The mixture was diluted with 150 mL of absolute EtOH and hydrogenated over 1 g of 10% Pd/C in a Parr apparatus. After removal of catalyst and solvent, the crude product was purified by distillation: bp 75–80 °C (1.2 mm); yield 40.4 g (82%). Purity was established by NMR and comparative GLC traces.

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Notes

Synthesis of 5-Chloro-3′-nitro-4′-substituted Salicylanilides, a New Series of Anthelmintic and Antimicrobial Agents[1]

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A number of 5-chloro-3′-nitro-4′-substituted salicylanilides (**6–23**) have been synthesized by treating 4′,5-dichloro-3′-nitrosalicylanilide (**5**) with various sodium aryl oxides, alkoxides, or amines. These compounds have been tested against *Hymenolepis nana* infection in rats and have also been evaluated for their in vitro antimicrobial activity against various strains of bacteria and fungi. In the former test 17 was the most active cestodicidal agent showing activity at 30 mg/kg. In the antimicrobial screening, **22** inhibited the growth of all the bacteria and fungi used while 6 was active against the pencillin resistant *Staphylococcus aureus* at a minimum inhibitory concentration of 0.00609 μg/mL.

It has been observed that introduction of a phenoxy group in a biologically active molecule may lead to compounds with enhanced activity.[2,3] One example is the discovery of 3′-chloro-4′-(*p*-chlorophenoxy)-3,5-diiodosalicylanilide (rafoxanide, **1**).[4] Based on this observation, the synthesis of various 5-chloro-3′-nitro-4′-aryloxysalicylanilides (**6–9**), as the structural analogues of the well-known cestodicide, 2,5′-dichloro-4′-nitrosalicylanilide (**2**),[5] has been carried out. Unlike **2**, in which ring B is substituted by two electron-withdrawing groups (Cl and NO_2) at the 2 and 4 positions, respectively, the compounds reported in this communication carry one electron-withdrawing NO_2 group at the 3 position and one electron-donating aryloxy group in the 4 position of ring B. Compounds **10–23** with other electron-donating groups like ethoxy, dialkylamino, and cyclic imino have also been prepared for structure–activity relationship studies. These compounds have been tested for their in vivo cestodicidal activity. In addition, they have also been subjected to in vitro antimicrobial screening and the results are reported