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2-, 3-, and 4-(α,α,β,β-Tetrafluorophenethyl)benzylamines. A New Class of Antiarrhythmic Agents[1]

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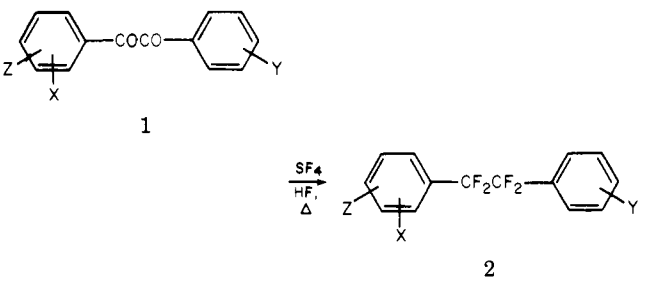
Upon finding 2-(α,α,β,β-tetrafluorophenethyl)benzylamine (4) to be a potent and novel type of antiarrhythmic agent, the title compounds were synthesized. Structure–activity relationships in this series are described.

Among the current drugs for the treatment of cardiac arrhythmias are quinidine and procaine amide, which exhibit similar pharmacologic and electrophysiologic activities. They also share similar disadvantages, especially in terms of myocardial depression. Lidocaine, on the other hand, differs quantitatively in its appreciably less marked alteration of the electrophysiologic properties of the heart. However, it is rapidly metabolized, is usually administered by continuous intravenous infusion, and can cause adverse central nervous system side effects. In the belief that a clinically effective antiarrhythmic agent does not also have to have toxic symptomology, we undertook a search for a nonquinidine type of active structure. This screening program provided a synthetic lead to 2-(α,α,β,β-tetrafluorophenethyl)benzylamine (4), a potent and novel compound. A study pursued to delineate the structure–activity relationships of a series of 2-, 3-, and 4-(α,α,β,β-tetrafluorophenethyl)benzylamines is described.

Chemistry. The key intermediates **2** (Table III) in the synthesis of this series were tetrafluorodiphenylethane derivatives with a substituent (X = Br or CH_3) amenable to further chemical modification. These were obtained conveniently and in good yields from the HF-catalyzed reaction of appropriately substituted benzils with SF_4[2] (Scheme I). The requisite benzils **1** (Table II) were prepared by conventional oxidations of the corresponding deoxybenzoins (Table I) or benzoins.

Reaction sequences used are illustrated for the ortho-substituted derivatives in Scheme II. The aryl bromide **2a** gave the nitrile **3a** with CuCN. Reduction of **3a** with $LiAlH_4$ afforded the lead benzylamine **4**. The 5-fluoro derivative **5**, the 4′-fluoro derivative **6**, and the para-substituted analogue **7** were synthesized similarly from the corresponding nitriles (Table IV). The homologue, 2-

Scheme I



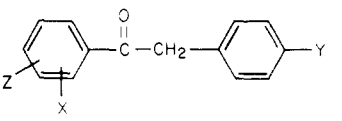
1 2

(α,α,β,β,γ,γ-hexafluorophenylpropyl)benzylamine (**8**), was prepared by an analogous sequence from the corresponding bromide **2j**. The precursor of **2j**, 1-(2-bromophenyl)-3-phenylpropane-1,2,3-trione (**1j**), was obtained from 2-bromobenzaldehyde by conventional procedures.[3] The tertiary amine **9** and the secondary amines **10** and **11** were prepared by standard alkylation procedures.

An α-methyl group was introduced into the benzylamine moiety via the Grignard reaction of the nitrile **3a**. Careful work-up of the reaction mixture with ice-cold aqueous HCl gave the ketimine hydrochloride **12** that was reduced with $LiAlH_4$ in THF to the α-methylbenzylamine **13**. Alternatively, the acetophenone **14** obtained by hydrolysis of **12** was converted to the oxime **15** that was reduced to **13**. Application of the latter sequence to the para-substituted nitrile **3d** gave α-methyl-4-(α,α,β,β-tetrafluorophenethyl)benzylamine (**16**). Alkylation of **13** via reduction of the derived formamide yielded the α,*N*-dimethylbenzylamine **17** that was resolved into its enantiomorphs **18** and **19**.

Under forcing conditions and entrainment, the Grignard reagent was obtained from the bromide **2a** and carbonated

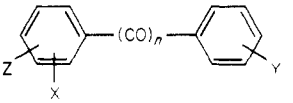
Table I. Intermediates for Table II. Deoxybenzoins



No.	X	Y	Z	Procedure[a]	Yield, %	Bp (mm), °C	Mp, °C	Formula[b]
46	2'-Br	H	H	A	75	154-158 (0.05)[c]		$C_{14}H_{11}BrO$
47	2'-Br	H	4'-F	A	66	112-115 (0.05)		*d*
48	2'-Br	F	H	A	72	130-132 (0.1)	44-46	$C_{14}H_{10}BrFO$
49	3'-Br	H	H	A	42	150-155 (0.1)	62-64[e]	$C_{14}H_{11}BrO$
50	4'-Br	H	H	*h*	55		112-113.5[f]	
51	2'-CH_3	H	3'-CH_3	A	75		52-53[g]	$C_{16}H_{16}O$

[a] See Experimental Section. [b] Analyzed for C, H, and Br if present. [c] Lit.[7] bp 203-206 °C (2 mm). [d] GLC indicated ca. 87.5% purity; sample was not purified for analysis. [e] From hexane. [f] Lit.[8] mp 115 °C. [g] From CH_3OH. [h] See ref 8.

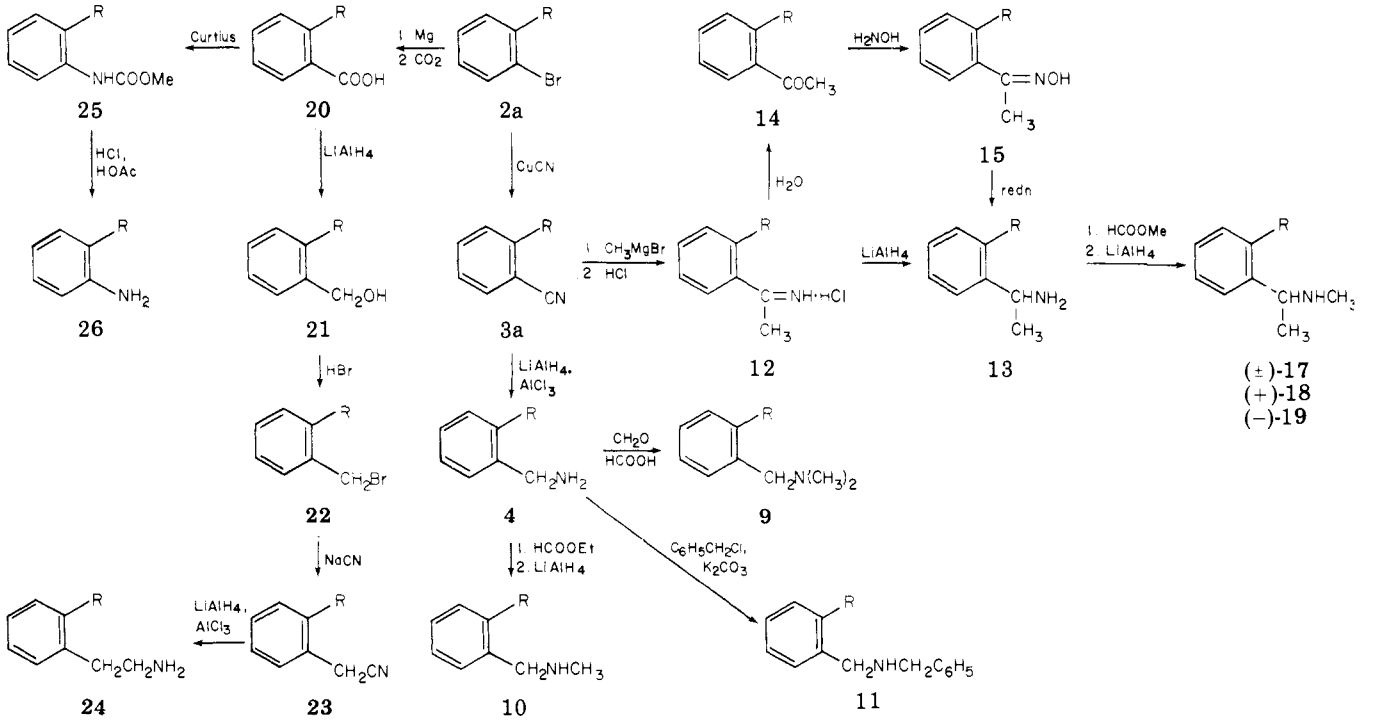
Table II. Intermediates for Table III. Di- and Triketones



No.	X	Y	Z	*n*	Procedure[a]	Yield, %	Bp (mm) or mp, °C	Formula[b]	Starting material[c]
1a	2-Br	H	H	2	B	96	47-48[d]	$C_{14}H_9BrO_2$	46
1b	2-Br	H	4-F	2	B	86	67.5-69[e]	$C_{14}H_8BrFO_2$	47
1c	2-Br	4'-F	H	2	B	84	79-80[d]	$C_{14}H_8BrFO_2$	48
1d	3-Br	H	H	2	B	83	81-82.5[f]	$C_{14}H_9BrO_2$	49
1e	4-Br	H	H	2	B	85	85.5-87.5[g,h]		50
1f	4-Br	4'-CH_3	H	2	*a*	35[i]	136-137[d]	$C_{15}H_{11}BrO_2$	*a*
1g	2-CH_3	2'-CH_3	H	2	*m*	30	89.5-90.5[j]		
1h	2-CH_3	H	3-CH_3	2	B	83	62-64[h]	$C_{16}H_{14}O_2$	51
1i	2-Br	2'-Br	H	2	*a*	32	128-130[k]	$C_{14}H_8Br_2O_2$	
1j	2-Br	H	H	3	*n*	13[l]	174-177 (0.3)	$C_{15}H_9BrO_3$	

[a] See Experimental Section. [b] Analyzed for C, H, and Br if present. [c] If not commercially available. [d] From 95% EtOH. [e] Sublimed in vacuo. [f] From hexane. [g] Lit.[9] mp 86.5 °C. [h] From CH_3OH. [i] Overall from 4'-bromoacetophenone. [j] Lit.[10] mp 96 °C. [k] From cyclohexane. [l] Overall from 2-bromobenzaldehyde. [m] See ref 10. [n] See ref 3.

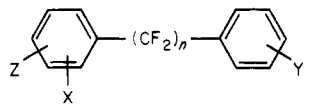
Scheme II



R = $-CF_2CF_2C_6H_5$

to give the benzoic acid **20** in good yield. The acid **20** provided a convenient intermediate to the homologous phenethylamine **24** via $LiAlH_4$ reduction to the benzyl alcohol **21**, conversion to the benzyl bromide **22**, replacement of the bromide with cyanide, and $LiAlH_4$ reduction of the acetonitrile **23**. The next lower homologue

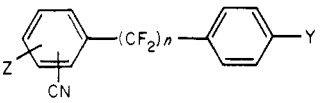
Table III. Intermediate Perfluoro Derivatives



No.	X	Y	Z	n	Procedure[a]	Yield, %	Bp (mm) or mp, °C[b]	Formula[c]	Starting material
2a	2-Br	H	H	2	C	90	54-55	$C_{14}H_9BrF_4$	1a
2b	2-Br	H	4-F	2	C	87.5	47-48	$C_{14}H_8BrF_5$	1b
2c	2-Br	4'-F	H	2	C	85	52-53.5	$C_{14}H_8BrF_5$	1c
2d	3-Br	H	H	2	D	82	74-76[d]	$C_{14}H_9BrF_4$	1d
2e	4-Br	H	H	2	D	77	82-83.5	$C_{14}H_9BrF_4$	1e
2f	4-Br	4'-CH_3	H	2	D	90	103.5-105.5	$C_{15}H_{11}BrF_4$	1f
2g	2-CH_3	2'-CH_3	H	2	D	92.5	73-75[e]	$C_{16}H_{14}F_4$	1g
2h	2-CH_3	H	3-CH_3	2	D	93	110-111.5[e]	$C_{16}H_{14}F_4$	1h
2i	2-Br	2'-Br	H	2	C	78	143-145	$C_{14}H_8Br_2F_4$	1i
2j	2-Br	H	H	3	C	46	83-87 (0.05)	$C_{15}H_9BrF_6$	1j

[a] See Experimental Section. [b] Purification generally was by sublimation in vacuo. [c] Analyzed for C, H, and Br or F. [d] From petroleum ether (bp 30-60 °C). [e] From hexane.

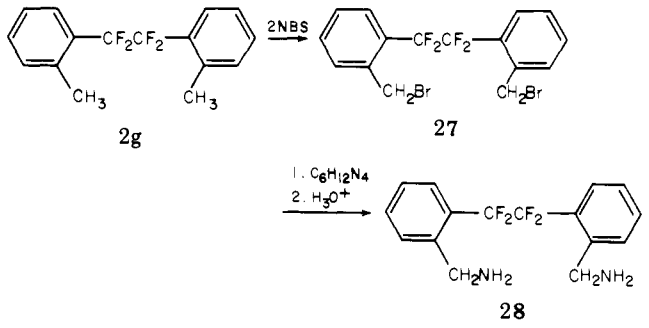
Table IV. Intermediate Benzonitriles



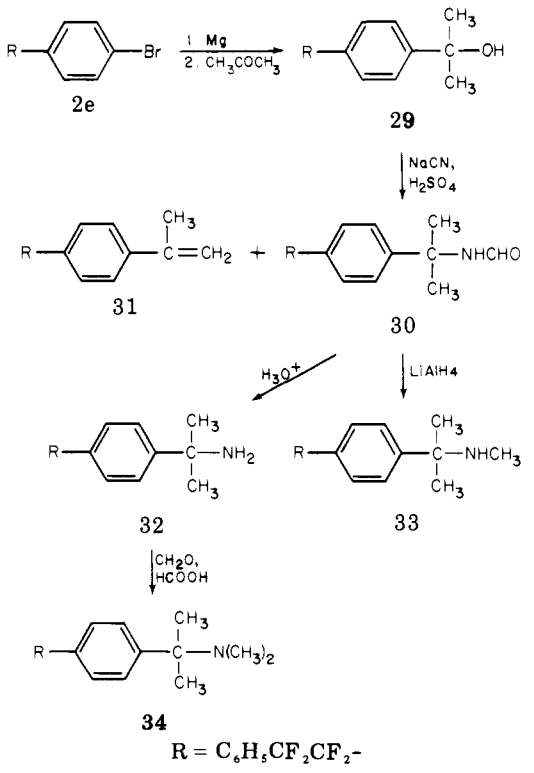
No.	Position of CN	Z	Y	n	Yield,[a] %	Mp, °C	Formula[b]	Starting material
3a	2	H	H	2	85	85-86[c]	$C_{15}H_9F_4N$	2a
3b	2	4-F	H	2	27	68-70[d]	$C_{15}H_8F_5N$	2b
3c	2	H	F	2	41	96.5-97.5[e]	$C_{15}H_8F_5N$	2c
3d	4	H	H	2	61	123.5-125.5[c,f]	$C_{15}H_9F_4N$	2e
3e	2	H	H	3	58	72-73[c,f]	$C_{16}H_9F_6N$	2j

[a] Synthesized by procedure E; see Experimental Section. [b] Analyzed for C, H, and N. [c] Sublimed in vacuo. [d] Purified by chromatography on silica gel, eluting with C_6H_6-CCl_4 (2:1). [e] Purified by chromatography on silica gel, eluting with C_6H_6-hexane (1:1). [f] From hexane.

Scheme III



Scheme IV



also was obtained from the acid **20** via the Curtius reaction and hydrolysis of the urethane **25** to the aniline **26**.

Preparation of a bis(benzylamine) derivative in the ortho-substituted series from the 2,2'-dibromide **2i** failed when **2i** proved to be resistant to reaction with CuCN. Alternatively, the 2,2'-dimethyl compound **2g** was dibrominated successfully with NBS and the bis(benzyl bromide) **27** underwent the Delepine reaction to afford the desired bisamine **28** (Scheme III).

In attempts to introduce a second α-methyl group into the ortho-substituted α-methylbenzylamine, the acetophenone **14** failed to react with a methyl Grignard or the Wittig reagent. Examination of models revealed severe steric hindrance to the accommodation of a second α-methyl in proximity to the ortho CF_2 group. Synthesis of an α,α-dimethylbenzylamine was realized in the para-substituted series (Scheme IV). The reaction of acetone with the Grignard reagent obtained from the bromide **2e** yielded the 2-propanol derivative **29**. The Ritter reaction of **29** gave a fair yield of the formamide **30**. This reaction always yielded the olefin **31** concomitantly under the conditions investigated, but **31** could be resubjected to the Ritter reaction to produce additional formamide. Hydrolysis of **30** afforded the α,α-dimethylbenzylamine **32**

Table V. Effect of Standard Antiarrhythmic Agents in Arrhythmias Due to Acute Myocardial Infarction in Anesthetized Dogs

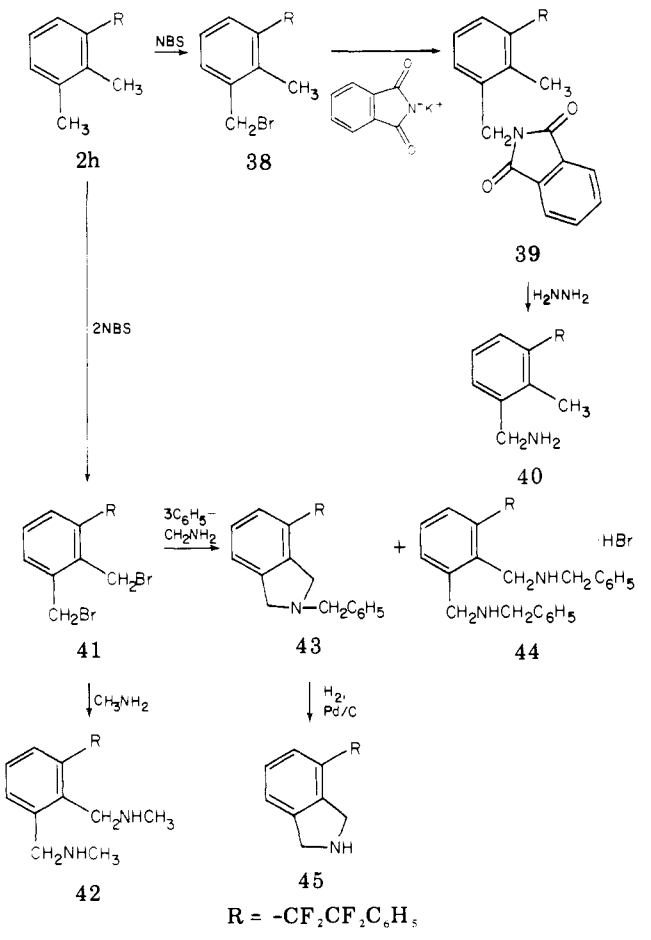
Compound	Dose,[a] mg/kg	% normal ECG complexes[b]	No. of animals	Heart rate		PR interval, ms		QT duration, ms	
				Initial	−Δ	Initial	+Δ	Initial	+Δ
Saline control		19	50	138	6	98	0	213	2
Quinidine,	2.5	25	4	148	21	96	0	200	33
ED_{75} = 9.4 mg/kg[c]	5.0	46	12	132	24	95	8	231	36
	10.0	89	4	136	31	98	15	215	78
Procaine amide[d]	20.0	32	4	148	26	95	10	213	40
	40.0	55	4	129	25	105	23	210	33
Diphenylhydantoin[d]	2.5	17	4	139	11	95	10	210	5
	5.0	40	4	151	13	90	8	200	3
Lidocaine[e]	0.025	75	4	141	7	88	2	208	0
	0.0125	61	4	122	8	88	0	209	0
	0.06	72	4	137	4	96	0	206	0
	0.03	19	4	134	5	90	0	212	0

[a] Compound administered iv prior to infarction; effect on conduction (PR, QT) measured at 0 and 10 min. [b] Recorded during a 1-h period after infarction. [c] ED_{75} is dose estimated to protect the ECG patterns so that 75% are normal. [d] Higher doses not tested due to myocardial depressant and hypotensive action of the compound. [e] Given by continuous infusion, mg/kg/min for 60 min.

and $LiAlH_4$ reduction gave its *N*-methyl derivative **33**. The *N,N*-dimethyl derivative **34** was obtained by conventional dialkylation of **32**. The 4′-methyl (**35**) and 4′,*N*-dimethyl (**36**) derivatives of **32**, as well as the meta analogue, α,α-dimethyl-3-(α,α,β,β-tetrafluorophenethyl)benzylamine (**37**), were prepared analogously from the corresponding bromides.

o-Xylylenediamine derivatives were obtained from 2,3-dimethyl-α,α,α′,α′-tetrafluorobibenzyl (**2h**) (Scheme V). With 1 mol of NBS, **2h** afforded a monobromide that was assigned structure **38** on the basis of NMR comparisons with **2h** and the dibromide **41** obtained from the reaction of **2h** with 2 mol of NBS. The meta derivative **40** was obtained from **38** by the Gabriel reaction. Treatment of **41** with liquid NH_3 gave an intractable mixture, but with liquid CH_3NH_2, the *N,N′*-dimethyl-*o*-xylylenediamine **42** was obtained in fair yield. When **41** was treated with 3 mol of benzylamine, the products, isolated in low yield, were the *N,N′*-dibenzyl-*o*-xylylenediamine hydrobromide **44** and the interesting *N*-benzylisoindoline derivative **43**. Catalytic hydrogenolysis of **43** afforded **45**.

Scheme V



Pharmacology. Antiarrhythmic activity was assessed in an experimental ventricular arrhythmia (VA) in anesthetized dogs. The intracoronary injection of small volumes of a sclerosing agent, tetrafluorohexachlorobutane, into the anterior descending coronary artery produces myocardial damage in the area supplied by the artery and, within a few seconds to 2 min, leads to a severe multifocal VA.[4] It has been found that approximately 33% of saline control animals died following the ventricular fibrillation that occurs soon after the onset of the arrhythmia. Because of this incidence of fibrillation, the activity of compounds was evaluated according to their ability to prevent or modify the development of the VA. Analysis was made from ECG tracings taken in segments during a 1-h postinfarction period. In saline control animals under the experimental conditions, less than 20% of all ECG complexes recorded during this period were of sinus origin (normal).[5]

Quinidine, procaine amide, diphenylhydantoin, and lidocaine were used as reference compounds (Table V). Results for test compounds are given in Tables VI–VIII.

Structure–Activity Relationships. From a comparison of Tables VI–VIII with Table V, it can be seen that all of the benzylamine derivatives were of a higher order of activity than the standard drugs. In general, these compounds did not alter heart rate or conduction (PR, QT). The most active compounds ($ED_{75} \leq 1.0$) were **4**, **5**, **10**, **11**, **17**, **19**, **32**, and **33**. The more extensive structural modifications made in the ortho series clearly defined optimum structural features as an unsubstituted or α-methylated primary or secondary benzylamine (cf. **26** with **4**, **10**, or **17**) and a perfluoroethane bridge (cf. **8** with **4**). Resolution of the racemic α-methyl derivative **17** revealed that the (−) enantiomorph **19** was the more potent component. Nuclear substitution in the terminal aromatic ring reduced activity in both the ortho and para series (e.g., **6** and **35**). Tertiary amines in both series (e.g., **9** and **34**) were of low activity. Meta-substituted analogues, **40** and **37**,

were decidedly less active, as was the isoindoline **45**. From a comparison of the ortho and para series, it would appear that optimum activity required steric crowding around the amino moiety as supplied by the adjacent $-CF_2CF_2-$ chain in the ortho compounds (**4** and its derivatives) and the two α-CH_3 groups in the para compounds **32** and **33**.

Oral activity in the same test situation, dosing 120 min prior to infarction, was determined for a number of the most active compounds. Compounds **4**, **32**, and **33** clearly exhibited good oral potency, producing ≥ 80% normal ECG complexes after infarction at a 10 mg/kg po dose. It was considered on the basis of this evidence and more extensive pharmacological investigation[6] that **32** best achieved our criteria for a safe, effective, and novel type of antiarrhythmic agent, and this drug has been selected for clinical evaluation in man.

Experimental Section

The structures of all compounds are supported by their IR and NMR spectra. IR spectra were recorded on a Perkin-Elmer Model 610 spectrophotometer; NMR spectra on a Varian A-60A spectrometer (Me_4Si); GLC on an F & M 810 flame ionization instrument. Melting points were determined with calibrated thermometers in a Thomas-Hoover apparatus. All concentrations were carried out in a rotary evaporator at reduced pressure. Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Procedure A. 2′-Bromo-2-phenylacetophenone (46). For convenience, two simultaneous 0.16 mol runs were carried out and combined during the work-up. Benzylmagnesium chloride, prepared from 16 g of Mg and 83.3 g (0.66 mol) of benzyl chloride in 325 ml of Et_2O, was stirred at room temperature and under N_2 while a solution of 30 g (0.164 mol) of 2-bromobenzonitrile in 150 ml of Et_2O was added dropwise. The mixture was stirred overnight, then cooled, and hydrolyzed by the dropwise addition of 90 ml of 0.5 M citric acid. The organic phase was decanted and the residue stirred vigorously with another 100 ml of 0.5 M citric acid. This slurry was extracted repeatedly with C_6H_6. Keeping all glassware and solutions ice-cold, the combined organic phases were extracted with four 35-ml portions of 6 N HCl. The crystalline ketimine hydrochloride that separated from the combined acid extracts was collected and washed with Et_2O: combined yield, 60.7 g; mp 180–184 °C. The combined acidic mother liquors were heated on the steam bath for 1.5 h and the dark oil that separated was extracted into C_6H_6. Evaporation of the washed and dried extract and distillation of the residue gave 16.7 g of **46** as a yellow oil, bp 154–158 °C (0.05 mm). Heating a suspension of the crystalline ketimine hydrochloride in 125 ml of 3 N HCl for 1.5 h afforded 51.7 g of **46** after extraction with C_6H_6, washing, drying, and evaporation: combined yield, 75%. A purified sample for analysis was prepared by acid hydrolysis of a recrystallized (cold MeOH–Et_2O) sample of the ketimine hydrochloride: $n^{25.5}D$ 1.6050; homogeneous by GLC.

Procedure B. 2-Bromobenzil (1a). A stirred mixture of 68 g (0.247 mol) of **46** and 38.2 g (0.296 mol) of H_2SeO_3 in 220 ml of *p*-dioxane–44 ml of H_2O was refluxed for 48 h. The precipitate of Se was filtered and washed with C_6H_6. The combined filtrate and washings were concentrated and the residue was partitioned between C_6H_6 and H_2O. Evaporation of the dried extract left 71 g (quantitative) of **1a** as a dark yellow oil that slowly crystallized on standing. GLC indicated ca. 96% purity. A sample was sublimed at 45 °C (0.05 mm) and recrystallized from 95% EtOH for analysis: mp 47–48 °C.

4-Bromo-4′-methylbenzoin. This compound was prepared from the $AlCl_3$-catalyzed condensation of 4-bromophenylglyoxal with toluene by a procedure similar to that described for 4-bromobenzoin:[11] yield, 71%; mp 82–83.5 °C (60% EtOH). Anal. ($C_{15}H_{13}BrO_2$) C, H, Br.

4-Bromo-4′-methylbenzil (1f). This compound was prepared from the above benzoin by an oxidation method similar to that described for benzil:[12] yield, 91%; mp 136–137 °C (95% EtOH).

2,2′-Dibromobenzil (1i). This compound was prepared via the benzoin condensation of 2-bromobenzaldehyde and nitric acid oxidation of the crude intermediate benzoin by a procedure similar to that described for 2,2′-dichlorobenzil.[13] The crude **1i** was purified by chromatography on silica gel (1:1 C_6H_6–hexane elution) followed by recrystallization from cyclohexane: yield, 15%; mp 128–130 °C.

Procedure C. 2-Bromo-α,α,α′,α′-tetrafluorobibenzyl (2a). The benzil **1a** (45.2 g, 0.157 mol), 320 g of SF_4, 10 g of Hg, and ca. 10 ml of HF were charged into a stainless steel bomb and shaken 2 h at 100 °C, 2 h at 120 °C, and 6 h at 140 °C. After cooling and venting the bomb, the solid was removed and the bomb rinsed out with $CHCl_3$. The solid was dissolved in 150 ml of boiling cyclohexane and filtered. Evaporation of the $CHCl_3$ solution left a residue that was triturated with boiling cyclohexane and filtered. The combined cyclohexane solutions were evaporated, leaving an oily, brown solid residue. Sublimation at 80 °C (0.1 mm) gave 52.3 g (90%) of **2a** as white crystals, mp 54–55 °C.

Procedure D. 4-Bromo-α,α,α′,α′-tetrafluorobibenzyl (2e). The benzil **1e** (45.1 g, 0.16 mol), 330 g of SF_4, 4 g of Hg, 4 ml of HF, and 300 ml of C_6H_6 were charged into a stainless steel bomb and shaken 10 h at 80 °C. After cooling and venting the bomb, the solution was filtered and evaporated. The brown residue was sublimed at 80 °C (0.1 mm) to yield 41.2 g (77%) of **2e** as white crystals, mp 80–82 °C. A sample was resublimed for analysis: mp 82–83.5 °C.

Procedure E. 2-(α,α,β,β-Tetrafluorophenethyl)benzonitrile (3a). A stirred mixture of 22.35 g (0.067 mol) of **2a**, 12 g (0.134 mol) of CuCN, 150 ml of freshly redistilled quinoline, and 15 ml of dry DMF was refluxed for 24 h. After dilution with 200 ml of Et_2O, the precipitate was filtered and washed with Et_2O. Evaporation of solvents from the filtrate left an oily brown solid residue that was triturated with petroleum ether to yield 18 g, mp 79–82 °C. The crude **3a** was sublimed at 80–85 °C (0.05 mm). Initially, the sublimate was contaminated with an orange oil and this material was removed, freed from oil by pressing on a porous plate, and returned to the sublimator. The yield of off-white sublimate was 16 g (85%), mp 83.5–85 °C. A sample for analysis was prepared by chromatography on silica gel (3:1 C_6H_6–hexane elution) followed by sublimation at 55 °C (0.05 mm): mp 85–86 °C.

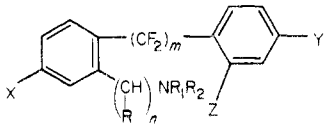
Procedure F. 2-(α,α,β,β-Tetrafluorophenethyl)benzylamine (4). To a stirred mixture of 7.85 g (0.206 mol) of $LiAlH_4$ in 200 ml of Et_2O, under N_2, was added dropwise a solution of 27.4 g (0.206 mol) of $AlCl_3$ in 450 ml of Et_2O. After stirring the mixture that contained a white precipitate for 5–10 min, a solution of 28.85 g (0.103 mol) of the benzonitrile **3a** in 350 ml of Et_2O was added dropwise. The mixture was stirred under N_2 overnight. It then was cooled and hydrolyzed by the dropwise addition of 180 ml of H_2O, and the Et_2O solution was decanted. The gelatinous precipitate was washed with Et_2O and then was stirred thoroughly in 400 ml of 10 N NaOH and 1 l. of H_2O. This mixture was extracted repeatedly with 1:1 C_6H_6–Et_2O. Evaporation of the washed and dried organic layer left 29 g (quant) of crude **4** as an off-white solid, mp 53–56 °C. A sample for analysis was sublimed at 46 °C (0.05 mm): mp 55–57 °C. Anal. ($C_{15}H_{13}F_4N$) C, H, N.

The hydrochloride salt was prepared by treating a 15% solution of the crude base **4** in *i*-PrOH with a 10% excess of EtOH–HCl(g). Two recrystallizations from EtOH yielded 69% of white crystals, mp 257–259 °C.

Procedure G. *N,N*-Dimethyl-2-(α,α,β,β-tetrafluorophenethyl)benzylamine (9). A stirred solution of 1.45 g (0.006 mol) of the primary amine **4** and 1 g (0.013 mol) of 37% HCHO in 3 ml of 88% HCOOH was heated on the steam bath for 18 h. Concentrated HCl (1 ml) was added and the solution was evaporated. A solution of the residual syrup in 25 ml of H_2O was made strongly basic with 40% NaOH and extracted with C_6H_6. Evaporation of the washed and dried extract left 1.5 g of **9** as an oil. The hydrochloride salt was precipitated from a solution of the base in *i*-PrOH by addition of a 10% excess of EtOH–HCl(g) as white crystals: mp 190–192 °C; 1.2 g (58%). The melting point was unchanged by recrystallization from *i*-PrOH.

Procedure H. *N*-Methyl-2-(α,α,β,β-tetrafluorophenethyl)benzylamine (10). A solution of 1.4 g (0.005 mol) of **4** in 100 ml of HCOOEt was refluxed for 20 h. Evaporation of the solution and trituration of the residue with petroleum ether gave 1.4 g (90%) of *N*-[2-(α,α,β,β-tetrafluorophenethyl)benzyl]-

Table VI. Ortho Series. Compounds of Formula



No.	m	R	n	R_1	R_2	X	Y	Z	Procedure[a]	Yield, %	Mp, °C Base[b]	Mp, °C Salt
4	2	H	1	H	H	H	H	H	F	69	55-57	257-259[f]
5	2	H	1	H	H	F	H	H	F	36	53-54.5	
6	2	H	1	H	H	H	F	H	F	91	64-65.5	
8	3	H	1	H	H	H	H	H	F	88		162-163.5[g]
9	2	H	1	CH_3	CH_3	H	H	H	G	57		190-192[h]
10	2	H	1	H	CH_3	H	H	H	H	61		252-253[f]
11	2	H	1	H	$CH_2C_6H_5$	H	H	H	*a*	46		188.5-190[i]
13	2	(±)-CH_3	1	H	H	H	H	H	*a*	70		161-162 dec[j]
17	2	(±)-CH_3	1	H	CH_3	H	H	H	H	65		178-179[i]
18	2	(+)-CH_3	1	H	CH_3	H	H	H	*a*			190-192[f]
19	2	(−)-CH_3	1	H	CH_3	H	H	H	*a*			190-192[f]
24	2	H	2	H	H	H	H	H	F	66		213.5-215.5[k]
26	2		0	H	H	H	H	H	*a*	33		180.5-182.5 dec[h]
28	2	H	1	H	H	H	H	CH_2NH_2	*a*	71	98.5-100	186-187.5[l]

[a] See Experimental Section. [b] Purified by sublimation in vacuo. [c] All compounds were analyzed for C, H, and N. [d] Recorded during a 1-h period after infarction (numbers in parentheses are number of animals tested at each dose). [e] Dose estimated to protect ECG patterns so that 75% are normal; based on estimate at doses tested assuming parallelism to com-

formamide, mp 61–75 °C. Recrystallization from Et_2O–petroleum ether gave mp 84–85.5 °C. Anal. ($C_{16}H_{13}F_4NO$) C, H, F.

To a stirred mixture of 0.29 g (0.0077 mol) of $LiAlH_4$ in 10 ml of Et_2O, under N_2, was added dropwise a solution of 1.2 g (0.00386 mol) of the formamide in 25 ml of Et_2O and the mixture was refluxed overnight. The cooled mixture was hydrolyzed by the successive dropwise addition of 0.3 ml of H_2O, 0.2 ml of 20% NaOH, and 0.6 ml of H_2O, and the precipitate was filtered and washed with Et_2O. Evaporation of the filtrate left 1.0 g of **10** as an oil. The hydrochloride salt was precipitated from a solution of the base in EtOH by addition of a slight excess of EtOH–HCl(g) and recrystallized from EtOH: 0.8 g (62%); mp 251–253 °C. Recrystallization from MeOH–Et_2O gave mp 252–253 °C.

The secondary amine **17** was prepared by procedure H via the intermediate ***N*-[α-methyl-2-(α,α,β,β-tetrafluorophenethyl)-benzyl]formamide**, mp 103–105 °C (*i*-PrOH–H_2O). This intermediate was used after characterization only by its IR and NMR spectra.

***N*-Benzyl-2-(α,α,β,β-tetrafluorophenethyl)benzylamine (11).** A stirred mixture of 3.9 g (0.0138 mol) of **4**, 1.77 g (0.014 mol) of benzyl chloride, 2.5 g of K_2CO_3, and 25 ml of C_6H_6 was refluxed for 40 h. Evaporation of the filtered solution left a mixture of solid and oil that was triturated with $CHCl_3$. The precipitate consisted of 1.1 g of recovered **4**·HCl, mp 251–253 °C. Chromatography of the concentrated $CHCl_3$ filtrate on 250 g of silica gel (1% MeOH in $CHCl_3$ elution) gave 2.6 g of the oily base **11**. The hydrochloride salt was precipitated from a solution of the base in EtOH–HCl(g) by dilution with Et_2O: 1.8 g (46%); mp 188–189.5 °C. Recrystallization from acetone gave mp 188.5–190 °C.

Methyl 2-(α,α,β,β-Tetrafluorophenethyl)phenyl Ketimine (12). To a stirred solution of the Grignard reagent prepared from ca. 25 g (0.26 mol) of CH_3Br and 4.2 g of Mg in 150 ml of Et_2O, under N_2, was added dropwise a solution of 19.3 g (0.0685 mol) of **3a** in 150 ml of Et_2O. After an overnight reflux period, 20 ml of H_2O was added dropwise to the cooled mixture and the organic phase was decanted. The gelatinous precipitate was washed thoroughly with Et_2O and the combined organic layers were extracted with 45 ml of ice-cold 6 N HCl in several portions. The crystalline hydrochloride salt of **12** separated from the acid extract: 3.6 g (33% based on unrecovered nitrile); mp 144–146 °C after prolonged drying at 0.1 mm. Two recrystallizations from *i*-PrOH–Et_2O gave mp 147–148.5 °C. Anal. ($C_{16}H_{13}F_4N$·HCl) C, H, N.

Evaporation of the washed and dried Et_2O extract left a solid that was recrystallized from hexane to recover 10.2 g of **3a**, mp 82–85 °C.

2′-(α,α,β,β-Tetrafluorophenethyl)acetophenone (14). The aqueous acid mother liquor from the crystallization of **12**·HCl in the preceding reaction and that from a similar 0.037 mol run were combined after heating on the steam bath for 1.5 h. The crude oil that separated was extracted into C_6H_6 and chromatographed on 170 g of silica gel. Elution with C_6H_6–hexane (3:1) gave an oily solid that was sublimed at 50 °C (0.1 mm) to yield 3.6 g of white crystalline **14**, mp 58–59.5 °C. Anal. ($C_{16}H_{12}F_4O$) C, H, F.

2′-(α,α,β,β-Tetrafluorophenethyl)acetophenone Oxime (15). A solution of 1.05 g (0.0035 mol) of **14** and 2.5 g (0.007 mol) of H_2NOH·HCl in 7.5 ml of EtOH–1.5 ml of pyridine was refluxed for 6 h and evaporated to dryness. The residue was partitioned between C_6H_6 and H_2O. Evaporation of the dried extract and recrystallization of the residual solid from hexane yielded 615 mg (56%) of **15**, mp 104–108 °C. Recrystallization from hexane gave mp 109–111 °C. Anal. ($C_{16}H_{13}F_4NO$) C, H, N.

α-Methyl-2-(α,α,β,β-tetrafluorophenethyl)benzylamine (13). A solution of 4.3 g (0.013 mol) of the ketimine hydrochloride **12** in 70 ml of THF was added dropwise to a stirred and ice-cold mixture of 1.05 g (0.0276 mol) of $LiAlH_4$ in 25 ml of THF under N_2. The mixture was stirred at room temperature overnight and then worked up as in procedure H to obtain 3.8 g of **13** as a red oil. The hydrogen maleate salt was precipitated from a solution of the base and a slight excess of maleic acid in *i*-PrOH by dilution with Et_2O: 4.2 g (80%); mp 154–155 °C dec. Three recrystallizations from *i*-PrOH–Et_2O gave mp 161–162 °C dec.

The α-methylbenzylamine **13** also was obtained by reduction ($LiAlH_4$–Et_2O) of the corresponding oxime **15**: yield of the hydrogen maleate salt identical with that previously obtained, 7%.

4′-(α,α,β,β-Tetrafluorophenethyl)acetophenone. This compound was obtained from the reaction of the benzonitrile **3d** with MeMgBr by a method similar to that described for **14**. Hydrolysis of the intermediate ketimine occurred in the cold. The oily solid product was sublimed at 95 °C (0.02 mm) to yield 37% of white crystals, mp 128–133 °C. Recrystallization from hexane and resublimation gave mp 134–135.5 °C. Anal. ($C_{16}H_{12}F_4O$) C, H, F.

4′-(α,α,β,β-Tetrafluorophenethyl)acetophenone Oxime. Conversion of the above compound to its oxime was accomplished by the method described for **15**: yield, 95%; mp 140–141 °C (from hexane). Anal. ($C_{16}H_{13}F_4NO$) C, H, N.

α-Methyl-4-(α,α,β,β-tetrafluorophenethyl)benzylamine (16). 4′-(α,α,β,β-Tetrafluorophenethyl)acetophenone oxime, 2.45 g (0.00787 mol), was dissolved in 47 ml of EtOH–3 ml of 8 N HCl (g) in EtOH and hydrogenated at 1 atm and 27 °C over 5% Pd/C

Formula[c]	% normal ECG complexes after infarction[d] 2.5[m]	1.25[m]	0.5[m]	0.25[m]	0.07[m]	ED_{75},[e] mg/kg
$C_{15}H_{13}F_4N \cdot HCl$	98 (2)	91 (1)	86 (9)	81 (2)	58 (5)	0.20
$C_{15}H_{12}F_5N$			48 (2)			0.5
$C_{15}H_{12}F_5N$	74 (3)	52 (3)		20 (2)		3.0
$C_{16}H_{13}F_6N \cdot HCl$	83 (3)	68 (3)		24 (3)		1.8
$C_{17}H_{17}F_4N \cdot HCl$	61 (4)	[At 5 mg/kg, 75 (4)]				4.8
$C_{16}H_{15}F_4N \cdot HCl$	93 (2)		73 (4)	38 (4)		0.84
$C_{22}H_{19}F_4N \cdot HCl$			74 (4)	23 (3)		0.84
$C_{16}H_{15}F_4N \cdot C_4H_4O_4$	87 (4)	82 (4)	43 (6)			1.3
$C_{17}H_{17}F_4N \cdot C_4H_4O_4$	88 (4)	91 (2)	59 (2)	35 (2)		0.88
$C_{17}H_{17}F_4N \cdot 0.5(+)\text{-}C_4H_6O_6$		72 (3)	26 (3)			2.0
$C_{17}H_{17}F_4N \cdot 0.5(-)\text{-}C_4H_6O_6$			84 (3)	44 (3)		0.48
$C_{16}H_{15}F_4N \cdot HCl$	88 (3)		27 (3)			2.0
$C_{14}H_{11}F_4N \cdot HCl$	10 (3)	[At 10 mg/kg, 26 (2)]				Inactive
$C_{16}H_{16}F_4N_2 \cdot 2(\pm)\text{-}C_3H_6O_3$	71 (4)	59 (4)	38 (4)			2.5

pound 4. [f] From EtOH. [g] From EtOAc. [h] From i-PrOH. [i] From acetone. [j] From i-PrOH-Et_2O. [k] From EtOH-Et_2O. [l] From MeOH-Et_2O. [m] mg/kg iv 10 min preinfarction.

(1 g) until uptake ceased. The mixture was filtered and evaporated. Trituration of the residual solid with C_6H_6 and Et_2O yielded 2.45 g (93%) of **16**·HCl, mp 212–215 °C. Successive recrystallizations from EtOH-Et_2O, acetone, and MeOH-Et_2O gave mp 218–219 °C.

The hydrochloride was converted to the free base by suspending in H_2O and adding an excess of 5% NaOH. The white crystalline base **16** was isolated by C_6H_6 extraction followed by sublimation at 60 °C (0.05 mm): mp 64.5–66 °C. Anal. ($C_{16}H_{15}F_4N$) C, H, N.

(+)-α,*N*-Dimethyl-2-(α,α,β,β-tetrafluorophenethyl)benzylamine (18). To a solution of 9.5 g (0.03 mol) of racemic **17** in 25 ml of boiling EtOH was added a solution of 2.3 g (0.0153 mol) of (-)-tartaric acid in 20 ml of EtOH. Crystallization was initiated by seeding and the mixture was held at room temperature until no further precipitation occurred. After collection of the (-)-tartrate, the filtrate was evaporated. The residual salt was converted to the free base by suspending in H_2O and adding an excess of saturated Na_2CO_3. The oily (+) base was isolated by hexane extraction: yield, 1.35 g. To a solution of this base in 4 ml of EtOH was added a solution of 325 mg of (+)-tartaric acid in 3 ml of EtOH. The (+)-tartrate separated in white crystals: mp 183–186 °C; yield, 1.3 g. Five recrystallizations from EtOH gave product of constant specific rotation: $[\alpha]^{24}D$ +18.75°; mp 190–192 °C. Reconversion to the (+) base **18** gave a yellow oil, $[\alpha]^{24}D$ +31.76°.

(-)-α,*N*-Dimethyl-2-(α,α,β,β-tetrafluorophenethyl)benzylamine (19). The (-)-tartrate salt of **17** obtained as the initial precipitate in the preceding preparation, 9.6 g (0.0248 mol), was converted to the free base and a solution of this oil and 1.85 g (0.0123 mol) of (+)-tartaric acid in 40 ml of EtOH was held at room temperature until precipitation was complete. After collection of the (+)-tartrate, the filtrate was evaporated and the residual salt converted to the oily (-) base: yield, 1.09 g. To a solution of this base in 4 ml of EtOH was added a solution of 262 mg of (-)-tartaric acid in 2 ml of EtOH. The (-)-tartrate separated in white crystals: mp 184–187 °C; yield, 1.1 g. Three recrystallizations from EtOH gave product of constant specific rotation: $[\alpha]^{23.5}D$ -21.82°; mp 190–192 °C. Reconversion to the (-) base **19** gave a yellow oil: $[\alpha]^{24}D$ -32.17°.

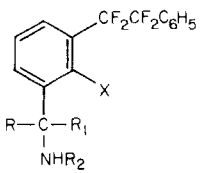
2-(α,α,β,β-Tetrafluorophenethyl)benzoic Acid (20). Under N_2, a mixture of 1.0 g of finely cut Mg, a crystal of I_2, 9.0 g (0.027 mol) of the bromide **2a**, and 50 ml of THF was stirred at reflux for 6 h. During this period, a solution of 1.65 g (0.009 mol) of ethylene bromide in 5 ml of THF was added in several portions and additional freshly cut Mg was added at intervals. Refluxing was continued for 4 h and the mixture was held at room temperature overnight. The Grignard solution was cooled in ice and CO_2(g) was passed over the surface for 30 min and then through the mixture for 2 h. After evaporation of the bulk of the THF, the residue was dissolved in C_6H_6 and hydrolyzed with H_2O and dilute HCl. The C_6H_6 layer was separated, washed with H_2O, and extracted with 5% NaOH. Acidification of the basic extract precipitated 8.0 g (66%) of **20** as white crystals, mp 129–130 °C. A sample for analysis was recrystallized from cyclohexane and sublimed at 100 °C (0.2 mm): mp 131–132 °C. Anal. ($C_{15}H_{10}F_4O_2$) C, H, F.

2-(α,α,β,β-Tetrafluorophenethyl)benzyl Alcohol (21). To a stirred mixture of 0.53 g (0.0139 mol) of $LiAlH_4$ in 15 ml of Et_2O, under N_2, was added dropwise a solution of 4.15 g (0.0139 mol) of the acid **20** in 35 ml of Et_2O and the mixture was held at room temperature overnight. Work-up by hydrolysis with 1 ml of H_2O, filtration, and evaporation of the filtrate left 3.7 g (94%) of **21** as a white solid, mp 80–81 °C. The melting point was unchanged by sublimation at 70 °C (0.1 mm). Anal. ($C_{15}H_{12}F_4O$) C, H, F.

2-(α,α,β,β-Tetrafluorophenethyl)benzyl Bromide (22). A stirred mixture of 3.3 g (0.0116 mol) of **21** and 15 ml of 48% HBr was heated on the steam bath for 3 h. The product that crystallized from the cooled mixture was separated and washed and dried in C_6H_6. Sublimation at 60 °C (0.05 mm) gave 3.55 g (88%) of **22**, mp 70–77 °C. A purified sample was prepared by chromatography on silica gel (2:1 C_6H_6–CCl_4 elution) followed by resublimation at 60 °C (0.05 mm): mp 80.5–82 °C. Anal. ($C_{15}H_{11}BrF_4$) C, H, Br.

2-(α,α,β,β-Tetrafluorophenethyl)phenylacetonitrile (23). A solution of 3.5 g (0.01 mol) of **22** and 2.0 g (0.03 mol) of KCN in 35 ml of acetone–5 ml of H_2O was refluxed for 18 h. The organic phase was separated and evaporated, and the residue dissolved in C_6H_6. Evaporation of the washed and dried extract left 2.9 g (quantitative) of **23** as a brown oil. This product was suitable for further use and was characterized only by its IR and NMR spectra.

Methyl 2-(α,α,β,β-Tetrafluorophenethyl)carbanilate (25). A stirred mixture of 5.7 g (0.019 mol) of the acid **20**, 25 ml of C_6H_6, and 6 ml of $SOCl_2$ was refluxed for 2.5 h and evaporated to dryness. The residue was freed from traces of $SOCl_2$ by repeated dissolution in C_6H_6 followed by evaporation. A solution of the oily acid chloride in 10 ml of Me_2CO was added dropwise to a stirred and ice-cold solution of 2 g (0.03 mol) of NaN_3 in 10 ml of H_2O. After 30 min at room temperature, the mixture was held at ca. 5 °C overnight. The separated oil was extracted into Et_2O and after evaporation of the washed and dried extract, the oil was heated in vacuo at 70 °C until gas evolution was complete (20–30 min). A solution of this product in 30 ml of MeOH was refluxed

Table VII. Meta Series. Compounds of Formula 

No.	R	R_1	R_2	X	Procedure[a]	Yield, %	Mp, °C	Formula[b]	% normal ECG complexes after infarction[c] 2.5[l]	1.25[l]	0.5[l]	0.25[l]	ED_{75},[d] mg/kg
37	CH_3	CH_3	H	H	I	31[e]	179-180[f]	$C_{17}H_{17}F_4N$·HCl	80 (4)	45 (4)			2.7
40	H	H	H	CH_3	*a*	11[g]	209-211.5[h]	$C_{16}H_{15}F_4N$·HCl	49 (4)				
42	H	H	CH_3	CH_2NHCH_3	*a*	26[g]	250-252[i]	$C_{18}H_{20}F_4N_2$·2HBr	92 (4)	65 (4)	61 (4)	30 (4)	1.3
44	H	H	$CH_2C_6H_5$	$CH_2NHCH_2C_6H_5$	*a*	14[g]	176-177.5[j]	$C_{30}H_{28}F_4N_2$·HBr	99 (4)	98 (4)	65 (5)		0.64
45	H	H		$-CH_2-$	*a*	5[g]	192-194[k]	$C_{16}H_{13}F_4N$·HBr	51 (5)	[At 5 mg/kg, 71 (5)]			~7

[a] See Experimental Section. [b] All compounds were analyzed for C, H, and N. [c] See footnote *d*, Table VI. [d] See footnote *e*, Table VI. [e] Overall from **2d**. [f] From MeOH-Et_2O. [g] Overall from **2g**. [h] From EtOH-Et_2O. [i] From EtOH. [j] From acetone. [k] From *i*-PrOH. [l] mg/kg iv 10 min prior to infarction.

Table VIII. Para Series. Compounds of Formula $X-C_6H_4-CF_2CF_2-C_6H_4-C(R)(R_1)-N(R_2)(R_3)$

No.	X	R	R_1	R_2	R_3	Procedure[a]	Yield, %	Mp, °C Base[b]	Mp, °C Salt	Formula[c]	% normal ECG complexes after infarction[d] 2.5[l]	1.25[l]	0.5[l]	0.25[l]	0.06[l]	ED_{75},[e] mg/kg
7	H	H	H	H	H	F	84	101-103	252-253[f]	$C_{15}H_{13}F_4N$·HCl	37 (4)					
16	H	H	CH_3	H	H	*a*	25[g]	64.5-66	218-219[h]	$C_{16}H_{15}F_4N$·HCl	80 (3)	25 (2)				4.0
32	H	CH_3	CH_3	H	H	I	65	82.5-84.5	274-275[i]	$C_{17}H_{17}F_4N$·HCl	98 (3)	89 (3)	75 (10)	50 (4)	35 (9)	0.6
33	H	CH_3	CH_3	H	CH_3	H	50		206-208[f]	$C_{18}H_{19}F_4N$·HCl	99 (2)	86 (5)	65 (5)	68 (5)	27 (6)	0.5
34	H	CH_3	CH_3	CH_3	CH_3	G	73		174-175.5[j]	$C_{19}H_{21}F_4N$·HCl	83 (3)	53 (3)				2.1
35	CH_3	CH_3	CH_3	H	H	I	29		254.5-256.5[f]	$C_{18}H_{19}F_4N$·HCl	88 (3)	75 (3)		52 (4)	15 (3)	1.4
36	CH_3	CH_3	CH_3	H	CH_3	H	73		189-190[k]	$C_{19}H_{21}F_4N$·HCl	67 (3)					

[a] See Experimental Section. [b] Purified by sublimation in vacuo. [c] All compounds were analyzed by C, H, and N. [d] See footnote *d*, Table VI. [e] See footnote *e*, Table VI. [f] From EtOH. [g] Overall from **3d**. [h] From CH_3OH-Et_2O. [i] From EtOH-Et_2O. [j] From *i*-PrOH. [k] From *i*-PrOH-Et_2O. [l] mg/kg iv 10 min prior to infarction.

for 2.5 h. Evaporation left an oily solid residue that was recrystallized from 100 ml of hexane. The by-product, **1,3-bis[2-(α,α,β,β-tetrafluorophenethyl)phenyl]urea**, crystallized and was collected: 2.3 g; mp 132–134 °C. Evaporation of the mother liquor left an oil that was redissolved in 15 ml of MeOH, refluxed for 5 h, and evaporated. Trituration of the residue with petroleum ether gave 2.5 g (40%) of **25** as white crystals, mp 91–98 °C. This material was suitable for further use and was characterized only by its IR and NMR spectra.

2-(α,α,β,β-Tetrafluorophenethyl)aniline (26). A solution of 1.1 g (0.00336 mol) of **25** in 10 ml of HOAc–5 ml of concentrated HCl–5 ml of H_2O was refluxed for 22 h and evaporated. Trituration of the residual sticky solid with Et_2O followed by recrystallization from *i*-PrOH yielded 390 mg (38%) of **26**·HCl, mp 178–180 °C dec. Repeated recrystallization from *i*-PrOH gave mp 180.5–182.5 °C dec.

α,α,α′,α′-Tetrafluoroethylene-2,2′-bis(benzyl bromide) (27). A stirred mixture of 1.41 g (0.005 mol) of **2g**, 1.78 g (0.01 mol) of NBS, a trace of benzoyl peroxide, and 60 ml of CCl_4 was refluxed for 7 h. The precipitate was collected, triturated with 5% NaOH, washed with H_2O, and recrystallized from C_6H_6: yield, 1.5 g (70%); mp 178–183 °C. Repeated recrystallization from C_6H_6 gave mp 187–189 °C. Anal. ($C_{16}H_{12}Br_2F_4$) C, H, Br.

α,α,α′,α′-Tetrafluoroethylene-2,2′-bis(benzylamine) (28). A solution of 6.44 g (0.046 mol) of hexamine and 10.1 g (0.023 mol) of **27** in 75 ml of $CHCl_3$ was refluxed for 8 h. The precipitate of the bis(hexaminium bromide), mp 186–190 °C dec, was washed with Et_2O and dissolved in 25 ml of concentrated HCl–135 ml of EtOH. After 9 h at reflux, the precipitate was collected and the filtrate evaporated. The residue and the precipitate were dissolved in H_2O and the solution was made strongly basic. The white crystalline base was collected, washed with H_2O and Et_2O, and dried by evaporation of a solution in C_6H_6: yield, 4.5 g; mp 96–97 °C. A second crop, 1.5 g, mp 93–95 °C, was recovered from the Et_2O washings: combined yield, 83%. Sublimation at 85 °C (0.1 mm) gave mp 98.5–100 °C. Anal. ($C_{16}H_{16}F_4N_2$) C, H, N.

The (±)-dilactate salt precipitated from a solution of the base in *i*-PrOH upon addition of a slight excess of 85–90% (±)-lactic acid and was recrystallized from EtOH–MeOH: mp 186–187.5 °C.

Procedure I. (i) **Grignard Preparation of α,α-Dimethylbenzyl Alcohols. 2-[4-(α,α,β,β-Tetrafluorophenethyl)phenyl]propan-2-ol (29).** Under N_2, a stirred mixture of 0.5 g of Mg, a crystal of I_2, 5 ml of Et_2O, and a few milliliters of a solution of 6.1 g (0.0183 mol) of the bromide **2e** in 30 ml of Et_2O was heated to reflux. After the reaction was initiated, the remaining solution of **2e** was added dropwise and the mixture was stirred at reflux for 3–5 h. During this period, a solution of 0.2 g of ethylene bromide in 0.5 ml of Et_2O was added in several portions in order to keep the Mg clean. When almost all of the Mg had reacted, the Grignard solution was cooled in ice and a solution of 2.5 g (0.04 mol) of Me_2CO in 5 ml of Et_2O was added dropwise. After 1 h at room temperature and 30 min at reflux, the mixture was hydrolyzed with 2 ml of H_2O. The organic phase was decanted from the gelatinous precipitate that then was extracted with Et_2O. Evaporation of the washed and dried extract left crude **29** as a yellow oil that was chromatographed on silica gel. Elution with $CHCl_3$ gave white crystals: mp 60–62 °C; yield, 3.6 g (63%). A sample for analysis was sublimed at 60 °C (0.02 mm): mp 62–63.5 °C. Anal. ($C_{17}H_{16}F_4O$) C, H, F.

(ii) **Formamides of α,α-Dimethylbenzylamines via the Ritter Reaction. N-[α,α-Dimethyl-4-(α,α,β,β-tetrafluorophenethyl)benzyl]formamide (30) and 2-[4-(α,α,β,β-Tetrafluorophenethyl)phenyl]propene (31).** Glacial HOAc, 3.7 ml, was stirred and cooled in an ice bath until it was about half frozen. In small portions and keeping the temperature at 15–20 °C by cooling as necessary, 0.7 g (0.014 mol) of NaCN followed by an ice-cold solution of 3.45 g of concentrated H_2SO_4 in 1.8 ml of HOAc was added. The alcohol **29**, 3.5 g (0.0112 mol), then was added in portions over 15 min. After stirring 2 h at room temperature and 1 h at 30–35 °C, the mixture was held at room temperature overnight. It was poured into ice and H_2O and neutralized with solid Na_2CO_3, and the product was extracted into Et_2O. Evaporation of the washed and dried extract left 3.55 g of a crystalline mixture of **30** and **31** that was chromatographed on 200 g of silica gel. Elution with $CHCl_3$ yielded 1.4 g (42%) of the olefin **31**, mp 97–104 °C. Sublimation at 80 °C (0.02 mm) gave mp 106.5–111 °C. Anal. ($C_{17}H_{14}F_4$) C, H. Continued elution with MeOH afforded 2.1 g (55%) of the formamide **30**, mp 115–117 °C. Recrystallization from Et_2O–petroleum ether gave mp 116.5–118 °C. Anal. ($C_{18}H_{17}F_4NO$) C, H, N.

Recycling of the olefin **31** through the Ritter reaction by essentially the same procedure yielded a comparable mixture of the formamide (50%) and recovered olefin (30%) that was separated by chromatography.

(iii) **α,α-Dimethylbenzylamines. α,α-Dimethyl-4-(α,α,β,β-tetrafluorophenethyl)benzylamine (32).** A solution of 2.16 g (0.0064 mol) of the formamide **30** in 50 ml of HOAc–35 ml of H_2O–5 ml of concentrated HCl was refluxed for 4 h and evaporated to dryness. The residue was recrystallized from EtOH–Et_2O using charcoal to give a first crop of 1.4 g of white crystalline **32**·HCl, mp 273.5–274.5 °C. Concentration of the mother liquor yielded a second crop of 0.5 g: mp 272–273 °C; combined yield, 85%. A sample of the first crop was dried for analysis.

The hydrochloride salt was converted (saturated Na_2CO_3, hexane) to the crystalline free base, mp 82–84 °C. Sublimation at 75 °C (0.05 mm) gave mp 82.5–84.5 °C. Anal. ($C_{17}H_{17}F_4N$) C, H, N.

The isethionate salt of **32** was prepared by treating a 20% solution of the base in *i*-PrOH with a 5% excess of 3.8 M isethionic acid. Dilution with Et_2O precipitated the hydrated salt that was dissolved in a large volume of C_6H_6. Water was removed by azeotropic distillation of the bulk of the C_6H_6 and the salt was reprecipitated by dilution with Et_2O and recrystallized from *i*-PrOH–Et_2O: mp 135–136.5 °C. Anal. ($C_{17}H_{17}F_4N·C_2H_6O_4S$) C, H, N, S.

Procedure I (i) was applied to the bromide **2f** to obtain the intermediate **2-[4-(*p*-methyl-α,α,β,β-tetrafluorophenethyl)phenyl]propan-2-ol**: mp 88–90 °C [sublimation at 80 °C (0.05 mm) followed by recrystallization from petroleum ether]; yield, 65%. Anal. ($C_{18}H_{18}F_4O$) C, H, F.

The intermediate **2-[3-(α,α,β,β-tetrafluorophenethyl)phenyl]propan-2-ol** was prepared from the bromide **2d** in 74% yield by procedure I (i): mp 76–78 °C (hexane). Anal. ($C_{17}H_{16}F_4O$) C, H, F.

The Ritter reaction [procedure I (ii)] of **2-[4-(*p*-methyl-α,α,β,β-tetrafluorophenethyl)phenyl]propan-2-ol** afforded **N-[α,α-dimethyl-4-(*p*-methyl-α,α,β,β-tetrafluorophenethyl)benzyl]formamide**. Chromatography of the mixture of products on silica gel [MeOH–$CHCl_3$ (2:98) elution] yielded 35% of the formamide, mp 109–119 °C. Recrystallization from EtOH–H_2O and Et_2O–petroleum ether gave the analytical sample, mp 121–122.5 °C. Anal. ($C_{19}H_{19}F_4NO$) C, H, N.

Application of procedure I (ii) to the meta analogue, **2-[3-(α,α,β,β-tetrafluorophenethyl)phenyl]propan-2-ol**, gave **N-[α,α-dimethyl-3-(α,α,β,β-tetrafluorophenethyl)benzyl]formamide** in 50% yield: mp 90–95 °C (chromatography on silica gel, $CHCl_3$ elution). This material was suitable for further use and was characterized only by its IR and NMR spectra.

2-Methyl-3-(α,α,β,β-tetrafluorophenethyl)benzyl Bromide (38). A stirred mixture of 4.0 g (0.0142 mol) of **2h**, 2.52 g (0.0142 mol) of NBS, ca. 50 mg of benzoyl peroxide, and 100 ml of CCl_4 was refluxed for 2.5 h and filtered, and the filtrate was evaporated to dryness. Recrystallization of the residue from petroleum ether yielded 3.8 g (75%) of white crystalline **38**, mp 67–71 °C. Repeated recrystallization from petroleum ether gave mp 69–71 °C: NMR ($CDCl_3$) 2.40 (3 H, br s with fine splitting, 2-CH_3), 4.46 (2 H, s, CH_2Br). Anal. ($C_{16}H_{13}BrF_4$) C, H, Br.

2-Methyl-3-(α,α,β,β-tetrafluorophenethyl)benzylamine (40). A mixture of 8.0 g (0.022 mol) of **38**, 4.1 g (0.022 mol) of potassium phthalimide, and 40 ml of DMF was stirred 30 min at room temperature, 4 h at 95 °C, and 3 h at reflux. The mixture was diluted with $CHCl_3$, washed with H_2O and aqueous NaOH, dried, and evaporated. Recrystallization of the residue from *i*-PrOH yielded 3.1 g (33%) of **N-[2-methyl-3-(α,α,β,β-tetrafluorophenethyl)benzyl]phthalimide (39)**, mp 135–137 °C. This product was used after characterization only by its IR and NMR spectra.

A solution of 3.74 g (0.00876 mol) of the phthalimide **39** and 0.9 ml of 100% hydrazine hydrate in 100 ml of 95% EtOH was refluxed for 7 h. The precipitate of phthalhydrazide was filtered; the filtrate was evaporated to half-volume, filtered, acidified to

pH 2 with concentrated HCl, and evaporated. Recrystallization of the residue from EtOH–Et_2O afforded 1.25 g (43%) of **40**·HCl as white plates, mp 199.5–201 °C. After repeated recrystallizations from EtOH–Et_2O, a purified sample melted at 209–211.5 °C.

3-(α,α,β,β-Tetrafluorophenethyl)-*o*-xylene α,α′-Dibromide (41). A stirred mixture of 6.13 g (0.022 mol) of **2h**, 7.85 g (0.044 mol) of NBS, a trace of benzoyl peroxide, and 175 ml of CCl_4 was refluxed for 6 h and filtered, and the filtrate was evaporated to dryness. Recrystallization of the oily solid residue from petroleum ether gave 4.3 g of white crystals, mp 88–92 °C. The concentrated mother liquor deposited a second crop that was recrystallized from petroleum ether to obtain 1.0 g: mp 85–91 °C; combined yield, 54%. A sample for analysis was sublimed at 85 °C (0.02 mm): mp 90–92 °C; NMR ($CDCl_3$) 4.44 (2 H, br s with fine splitting, 2-CH_2Br), 4.70 (2 H, s, 1-CH_2Br). Anal. ($C_{16}H_{12}Br_2F_4$) C, H, Br.

***N,N′*-Dimethyl-3-(α,α,β,β-tetrafluorophenethyl)-*o*-xylene-α,α′-diamine (42).** The dibromide **41**, 6.0 g (0.0136 mol), was added to 100 ml of $MeNH_2$(l) cooled in a dry ice–Me_2CO bath. After 45 min, the bath was removed and the solution allowed to evaporate. Trituration of the residue with C_6H_6 followed by filtration and evaporation of the filtrate left crude **42** as a gummy solid. A solution of the base in EtOH treated with HBr(g) and diluted with Et_2O yielded the dihydrobromide salt that was recrystallized twice from EtOH: yield, 3.8 g (55%); mp 250–252 °C.

***N,N′*-Dibenzyl-3-(α,α,β,β-tetrafluorophenethyl)-*o*-xylene-α,α′-diamine Hydrobromide (44) and *N*-Benzyl-4-(α,α,β,β-tetrafluorophenethyl)isoindoline (43).** A solution of 10.46 g (0.0238 mol) of **41** and 7.65 g (0.0715 mol) of benzylamine in 240 ml of C_6H_6 was stirred at room temperature for 15 min and at reflux for 3 h. The precipitate of benzylamine hydrobromide was collected and the filtrate evaporated. Trituration of the residual oil with Et_2O yielded crystalline **44**·HBr that was recrystallized from C_6H_6–EtOH–Et_2O to obtain 3.5 g (26%), mp 173–176 °C. Recrystallization from Me_2CO gave mp 176–177.5 °C.

The Et_2O filtrate from the trituration of the diamine **44**·HBr was evaporated. A solution of the residual oil in 25 ml of MeOH–2.5 ml of 48% HBr was diluted with Et_2O to precipitate **43**·HBr that was recrystallized from EtOH: yield, 1.29 g (11%); mp 235–238 °C. Recrystallization from MeOH–Et_2O using charcoal gave white crystals, mp 236.5–238.5 °C. Anal. ($C_{23}H_{19}F_4N$·HBr) C, H, N.

4-(α,α,β,β-Tetrafluorophenethyl)isoindoline (45). A solution of 1.63 g (0.0035 mol) of **43**·HBr in 160 ml of EtOH–14 ml of MeOH was hydrogenated at 1 atm and 25 °C over 5% Pd/C (320 mg) until uptake ceased. The mixture was filtered and evaporated, and the residual solid was recrystallized from EtOH–Et_2O using charcoal to obtain 1.0 g (78%) of **45**·HBr, mp 190–192 °C. Recrystallization from *i*-PrOH gave mp 192–194 °C.

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Quantitative Correlations between Albumin Binding Constants and Chromatographic R_M Values of Phenothiazine Derivatives

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The binding constants of 15 phenothiazine derivatives to bovine serum albumin were obtained by a circular dichroic probe technique. The lipophilicity of the drugs, measured by a reversed-phase thin-layer technique using oleyl alcohol and methanol–water mixtures as the solvents, is expressed as R_{M_w}. The binding constants were of the same order of magnitude as the literature values, and the R_{M_w} values correlated well with log $P_{octanol}$ values from the literature. Correlations of log K with R_{M_w} were found to be more satisfactory when corrections for the state of ionization of the phenothiazines were made, the nonprotonated species accounting for the bulk of the binding. A better correlation was obtained when contributions from both species were taken into account. Similar correlations were attempted between R_{M_w} values and enzyme inhibitory activities of these phenothiazines taken from the literature.

The binding of phenothiazine derivatives to bovine serum albumin (BSA) has been studied by several authors using a variety of techniques.[1-8] Although most of the authors obtained total binding constants of the same order of magnitude, the number of binding sites varied considerably. Janchen et al.[8] found that the number of binding sites on BSA for promazine and chlorpromazine changed with the concentration of the drugs, higher numbers being obtained at higher drug concentrations. They suggested that phenothiazine derivatives are bound by hydrophobic interaction with the aromatic amino acids of the BSA molecule and that, under the influence of high drug concentrations, the number of available sites increased by swelling and unfolding of the BSA molecules in solution. In the literature cited,[1-8] the binding of the phenothiazine drugs to BSA is considered to be the result