was cooled to 0–5° and 1 N HCl (100 ml) was added. The organic layer was separated, washed well with water, and dried ($MgSO_4$). The solvent was evaporated (aspirator) and the unreacted isobutyraldehyde and low-boiling by-products were removed in vacuo [bp 100° (0.3 mm)]. The oil residue crystallized slowly on standing. Recrystallization from petroleum ether (bp 30–60°) afforded 11.5 g (56%) of beige crystals, mp 50–53°. Anal. ($C_{15}H_{13}F_6NO$) C, H, N.

2,8-Bis(trifluoromethyl)-4-quinolyl Isopropyl Ketone. A mixture of the above alcohol (6.8 g, 0.02 mol), potassium dichromate (6.8 g, 0.023 mol), and glacial acetic acid (100 ml) was heated on a steam bath for 15 min. The mixture was cooled, diluted with water, and extracted with ether. The ether layer was washed consecutively with water, 10% aqueous $NaHCO_3$, and water and dried ($MgSO_4$). After the removal of the solvent, the oily ketone (6.1 g, 90%) was obtained which was suitable for the next step.

2,6-Bis(trifluoromethyl)-4-quinolyl α-Bromoisopropyl Ketone. The preceding ketone (6.1 g, 0.018 mol) was converted to the title compound (4.8 g, 66%), mp 108–110°, after recrystallization from petroleum ether (bp 30–60°) in the same manner as described above as part of the sequence to **3**. Anal. ($C_{15}H_{10}BrF_6NO$) C, H, Br.

1-[2,8-Bis(trifluoromethyl)-4-quinolyl]-1-methoxy-2,2-dimethyloxirane. To a suspension of sodium methoxide (5.4 g, 0.1 mol) in dry ether (100 ml), a solution of the above α-bromo ketone (4.1 g, 0.01 mol) in ether (50 ml) was added at 0–5°. The suspension was stirred at room temperature for 48 hr, water was added, and the layers were separated. The ether layer was dried (K_2CO_3) and concentrated. The residue was crystallized from MeOH to give 2.9 g (80%) of the title compound, mp 98–100°. Anal. ($C_{16}H_{13}F_6NO_2$) C, H, N.

α-(2-Ethylamino-2-propyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride (10). A solution of the above epoxy ether (3.65 g, 0.01 mol) in EtOH (80 ml) containing ethylamine (20 ml) was refluxed 72 hr. The solvent and excess amine were removed under reduced pressure. The residue was dissolved in EtOH (50 ml) containing concentrated HCl (10 ml) and heated for 5 hr on a steam bath to hydrolyze any imine. The solution was concentrated and the residue was diluted with water. The crystalline product was filtered and recrystallized from 2-propanol to yield 3.1 g (70%), mp 237–239°, of α-2-ethylamino-2-propyl-2,8-bis(trifluoromethyl)-4-quinolyl ketone. Anal. ($C_{17}H_{17}ClF_6N_2O$) C, H, N. To a slurry of the ethylamino ketone (2.2 g, 5 mmol) in EtOH (100 ml) was added a solution of $NaBH_4$ (0.6 g in 5 ml of H_2O). The mixture was stirred at room temperature for 3 hr. The solution was concentrated and made acidic with 10% HCl. The product was filtered, washed with cold water, and recrystallized from 2-propanol. The yield of the title carbinolamine **10** was 65%, mp 239–241°.

α-[2-(1-Butylamino)-2-propyl]-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride (11). The required precursor butylamino ketone (65%, mp 240–243°) was prepared from the epoxy ether and butylamine using the procedure described above for the ethyl analog. Anal. ($C_{19}H_{21}ClF_6N_2O$) C, H, N. The butylamino ketone was converted to the title carbinolamine **11** (81%, mp 238–240°) by the procedure described above for the ethyl analog.

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3-Arylquinolizidines, Potential Antidepressant Agents†

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The synthesis, structure elucidation, and pharmacological evaluation of some 3-arylquinolizidines as semirigid phenethylamines are described. Many of the derivatives possess antidepressant activity. Some anticonvulsant effects are noted.

In a continuation of our investigation of 3-substituted quinolizidines as semirigid phenethylamines, a series of 3-arylquinolizidines (**2**, Table I) was prepared from the appropriate 3-aryl-3-hydroxyquinolizidines[1] either by hydrogenolysis of **1** or by the dehydration of **1** followed by hydrogenation of the unsaturated intermediate **3** (Scheme I).

It was anticipated that the hydrogenolysis of **4** and **5** over Pd/C would proceed stereospecifically to give prod-

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Table I. 3-Arylquinolizidines

No.	R	Method	Yield,[a] %	Mp, °C	Mol formula[b]
6a	H	D	75	210–212	$C_{15}H_{21}N \cdot HCl$
6b	2′-OCH_3	E, B, C, D	53	192–194	$C_{16}H_{23}NO \cdot HCl$
6c	3′-OCH_3	B, C	49[c]	181–182	$C_{16}H_{23}NO \cdot HCl$
6e	4′-OCH_3	B, D, E	25	213–215	$C_{16}H_{23}NO \cdot HCl$
6f	3′,4′-OCH_3	B, E	38	201–203	$C_{17}H_{25}NO_2 \cdot HCl$
7a	H	B, D	89	174–176	$C_{15}H_{21}N \cdot HCl$
7b	2′-OCH_3	E, B, C, D	55	94–95	$C_{16}H_{23}NO$
7c	3′-OCH_3	B, C	10[c]	168–170	$C_{16}H_{23}NO \cdot HCl$
7d	4′-OH	D, B	29	118–119	$C_{15}H_{21}NO$
7e	4′-OCH_3	E, D, B	89	167–169	$C_{16}H_{23}NO \cdot HCl$
7f	3′,4′-OCH_3	E, B	50	44–45	$C_{17}H_{25}NO_2$

[a]Yield is for the first method listed. [b]Analyzed for C, H, and N; results are within ±0.4% of the theoretical value except for 6e (C: calcd, 68.19; found, 67.66) and 7f (C: calcd, 74.14; found, 74.57). [c]Yield is for the sample isolated from crude products obtained from B and C and is not indicative.

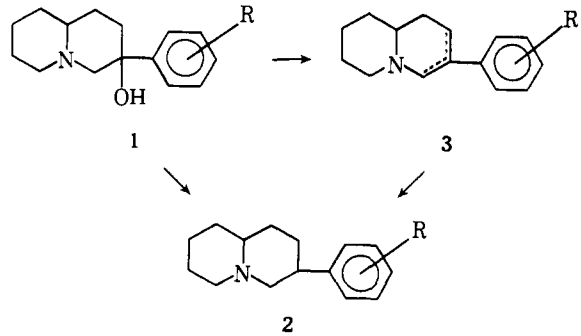
Table II. Ratio of Epimers Obtained from the Hydrogenolysis of 3-Aryl-3-hydroxyquinolizidines

Starting alcohol	R	Method	Ratio[a] of 7:6	% completion of rxn[b]
4a	H	D	10:90	100
4b	2′-OCH_3	E	29:71	100
4c	3′-OCH_3	D	100:0	5
4d	4′-OH	D	100:0[c]	<50[d]
4e	4′-OCH_3	D	76:24	54
		E	50:50	100
4f	3′,4′-OCH_3	E	85:15	100
5a	H	D	95:5	87
5b	2′-OCH_3	E	89:11	100
5c	3′-OCH_3	D	100:0	50
5d	4′-OH	D	100:0[c]	50[d]
5e	4′-OCH_3	D	77:23	30
		E	94:6	100
5f	3′,4′-OCH_3	E	95:5	100

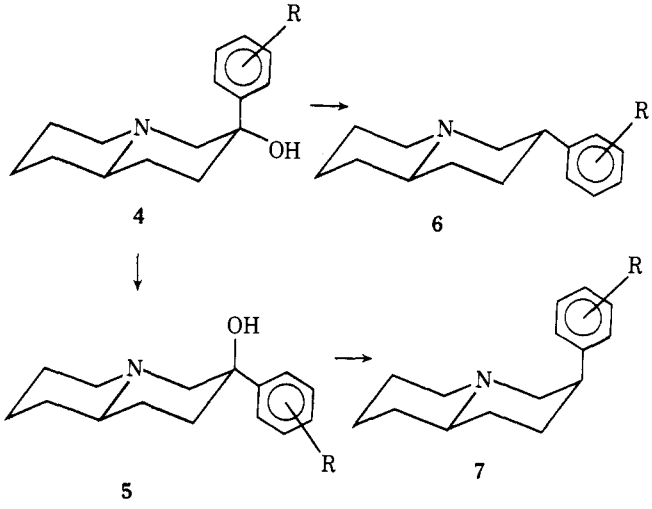
[a]Determined by GLC of crude product except for 4d and 5d. [b]Percent of crude product represented by 7 and 6. [c]Product recovery data. [d]Estimated from TLC.

ucts (Table II) inverted at C-3,[2] i.e., 6 and 7, respectively (Scheme II). Although this occurred in most cases, some of the axial aryl epimers, however, were epimerized under the acidic reaction conditions to the more stable equatorial aryl derivatives. The product(s), therefore, from the hydrogenolysis of 4 actually result from the hydrogenolysis of 4 and/or 5.

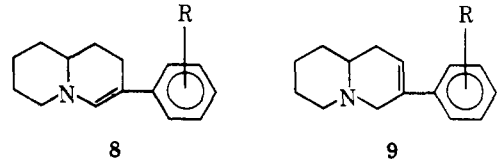
Scheme I



Scheme II



Two isomeric olefins 8 and 9 are possible from the dehydration of the alcohols. It was expected that 8 would be formed predominantly because of the conjugated enamine system; however, it was found that either 8 or 9 could be



obtained preferentially. Compounds 4b and 5b (Scheme III) were dehydrated individually in refluxing 25% sulfuric acid and the course of the reactions was followed by GLC.

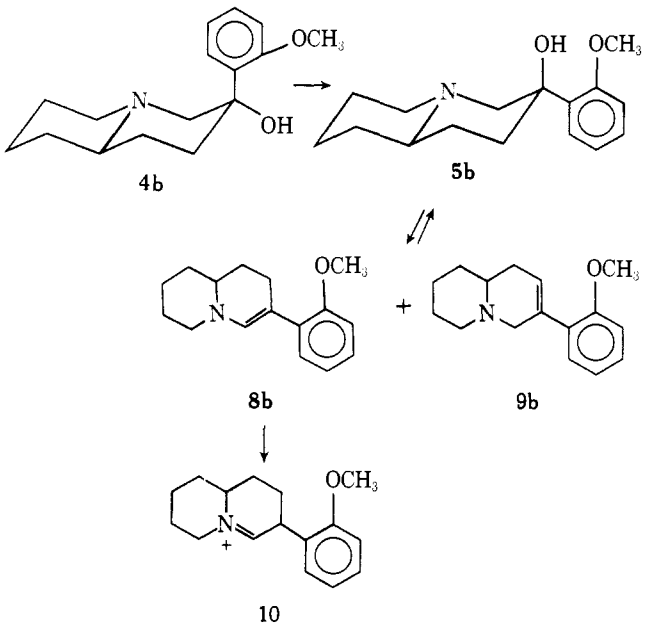
The initial product of dehydration of either alcohol (30 min) consists of 8b and 9b in the ratio of 8:92. Prolonged heating of the reaction mixture reverses this ratio so that the olefins 8b and 9b are now present in the proportion of 94:4 (48 hr). Enamines, though initially protonated at the nitrogen, are slowly converted to the more thermodynamically stable iminium ions.[3,4] Protonated 8b, therefore, is converted to the more stable iminium ion 10 which in strongly acidic solution prevents this species from reacting further. Meanwhile, the protonated 9b and possibly any existing protonated 8b are in equilibrium with protonated 5b. The protonated 8b formed from this equilibrium is re-

Table III. Unsaturated 3-Arylquinolizidines (8 and 9)[a]

No.	R	Rxn time, hr; H_2SO_4 concn, %	Yield, %	Mp, °C (recrystn solvent)[b]	Mol formula
8a	H	4; 50	85	69–70 (E)	$C_{15}H_{19}N$
8b	2′-CH_3O	96; 25	64	Oil	$C_{16}H_{21}NO$
9b	2′-CH_3O	1; 25	67	191–193 (A)	$C_{16}H_{21}NO \cdot HCl$[c]
9c	3′-CH_3O	10; 25	84	Oil	$C_{16}H_{21}NO$
8d	4′-CH_3O	4; 10	*d*	Oil	$C_{16}H_{21}NO$
9d	4′-CH_3O	4; 10	*d*	Oil	$C_{16}H_{21}NO$
8e	3′,4′-$(CH_3O)_2$	1; 10	13	116–117 (PE)	$C_{17}H_{23}NO_2$[c]
9e	3′,4′-$(CH_3O)_2$	1; 10	47	119–120 (PE)	$C_{17}H_{23}NO_2$[c]

[a]Prepared by method A. [b]E = ethanol, A = acetonitrile, PE = petroleum ether. [c]Analyzed for C, H, and N. [d]Unidentified mixture of 8d and 9d.

Scheme III



moved via **10**. Over a period of time protonated **8b** is converted to **10** which yields the enamine **8b** on work-up.

In general, the formation of the enamine is favored by longer reaction periods, reaction mediums containing a greater percentage of sulfuric acid, and by ease of dehydration of the alcohol (ortho- and para-directing groups on the ring promoting dehydration). Refluxing in 10% sulfuric acid is sufficient for the dehydration of **5c** but not **5e**. The dehydration of **5e** is effected with 25% sulfuric acid. The use of 50% sulfuric acid causes the demethylation of isomers containing ring methoxy groups. Although the crude product in most cases was used without further work-up, some of the olefins were isolated and characterized (Table III).

Table IV. Ratio of Epimers Obtained from the Hydrogenation of Unsaturated 3-Arylquinolizidines

Starting olefin	R	Method	Ratio of 7:6[a]
8a	H	B	98:2
8b	2′-OCH_3	B	73:27
8b	2′-OCH_3	C	52:48
8c	3′-OCH_3	F	64:36
9b	2′-OCH_3	B	11:89
9b	2′-OCH_3	C	52:48
9c	3′-OCH_3	B	19:81
9c	3′-OCH_3	C	76:24
9e	3′,4′-OCH_3	B	12:88

[a]Determined by GLC of crude product.

Table V. CNS Properties of 3-Arylquinolizidine

Compd no.	Approx mouse LD_{50}, mg/kg po	Approx mouse LD_{50}, mg/kg ip	Dopa response,[a] act. at 100 mg/kg po[c]	Serotonin potentiation,[b] act. at 100 mg/kg po[c]
6a	300	100	2	1
6b	300	100	0	0
6c	300	100	0	0
6e	300	100	0	1
6f	750	300	2	0
7a	300	100	3	1
7b	100	100	2	0
7c	300	100	0	1
7d		100	0	0
7e	300	100	3	0
7f	750	100	2	0
8a	750	750	2	0
Imipramine	400	100	3	2

[a]See ref 12. [b]See ref 13. [c]Ratings: 0 = inactive, 1 = slight potentiation, 2 = moderate, 3 = marked.

Catalytic hydrogenation of the enamines (**8**) yields predominantly the axial aryl epimer (Table IV) while hydrogenation of the isomeric olefin (**9**) gives mainly the equatorial aryl epimer. The reduction of **8c** with potassium borohydride[5] also provides a greater yield of the axial aryl epimer. As noted in Table V acidic hydrogenation conditions (method C) give a different ratio of products from that obtained with neutral conditions (method B).

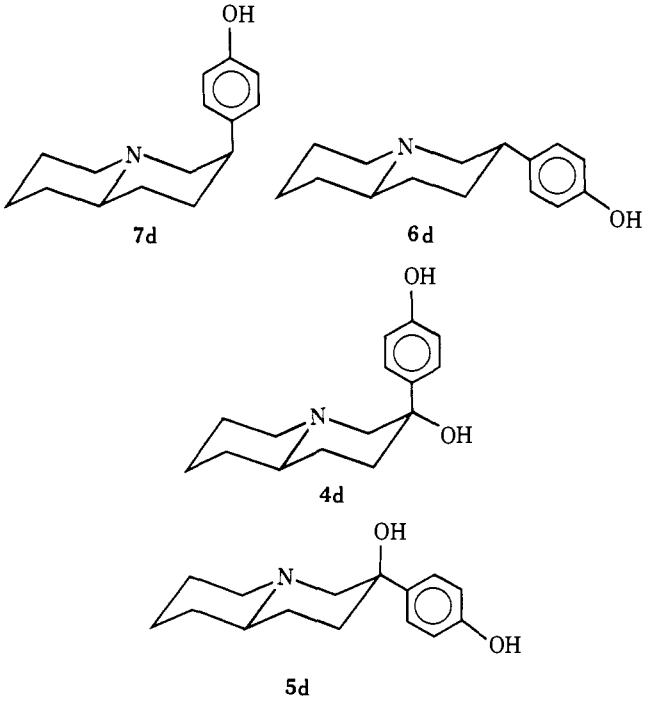
The procedure described by Boekelheide and coworkers[6] also was used in the preparation of **6a** and **7a**; however, only a 27% yield of a 30:60 mixture was obtained in the reductive cyclization step.

Though Okhi and Yamakawa[7] reported that a mixture of **6a** and **7a** is isomerized to the trans compound in 50% sulfuric acid, in our hands the individual isomers were stable to these conditions. Compound **7a** similarly proved isomer-

ically stable to conditions reported to effect isomerization of 1(a)-(4′-methoxyphenyl)quinolizidine.[8]

All 3-arylquinolizidines show Bohlman bands[9] characteristic of the transoid ring fusion. The stereochemistry of the aromatic ring was assigned on the basis of the downfield shift of the aromatic protons previously shown to be characteristic of quinolizidines bearing a benzene ring in the axial position.[1,10,11]

Both epimers of the 3-arylquinolizidines were obtained with the exception of the 4′-hydroxyphenyl derivative **6d**. The epimer of the latter that was obtained was assigned structure **7d** by comparing its NMR values with NMR values for 3(a)-hydroxy-3(e)-(4′-hydroxyphenyl)quinolizidine (**5d**) and 3(e)-hydroxy-3(a)-(4′-hydroxyphenyl)quinolizidine (**4d**). The $\Delta\delta$ for the ortho and meta protons of **7d** is less than that for **4d** but greater than that for **5d**. The $\Delta\delta$ for **4d** is increased by the anisotropy of the lone pair on nitrogen and by the alcohol group; the $\Delta\delta$ for **7d** is increased only by the nitrogen effect and that for **5d** is increased only by the effect of the alcohol group. The $\Delta\delta$ of **6d** should be less than that of **5d** since none of the aforementioned effects increase its value.



Biological Data. The potential antidepressant activity of the compounds listed in Table V was evaluated by their effects in animals in the modified Dopa test, potentiation of serotonin, and protecting against audiogenic seizures. The Dopa test[12] consists of a potentiated motor response in mice (four per dose) pretreated with a low dose of a monoamine oxidase inhibitor (pargyline, 40 mg/kg ip), a challenging dose of *dl*-Dopa (20 mg/kg ip), and the test compound (administered orally). As noted in Table V only **7a** and **7e** exhibit marked activity in the Dopa test. In general, the axial isomer is more potent than the equatorial isomer. None of the compounds, however, is as active as imipramine.

The serotonin test[13] determines a potentiated motor response in mice (four per dose) pretreated with pargyline (40 mg/kg ip) followed by the test compound and then challenged with serotonin (100 mg/kg ip). The compounds listed in Table V possess little or no effect in the serotonin test.

The audiogenic seizure test[14] consists of administering the test drug orally to ten O'Grady strain mice per dose and 1 hr later determining protection against convulsions. Protection against audiogenic seizures was determined for all compounds except **6b, 6e,** and **7b.** At 50 mg/kg po only **6a** and **8b** exhibit activity; 20% of the mice are protected.

In determining approximate LD_{50}'s it was noted that acute toxicity symptoms were generally those associated with CNS stimulation. Approximate LD_{50}'s were determined utilizing three mice per dose and five different dose levels.

Additional studies are underway in order to more clearly define the relationship of the biological activity to the chemical structure of this series of compounds.

Experimental Section

All melting points were taken on a Mel-Temp and are corrected. Infrared spectra were determined on a Perkin-Elmer Model 257 spectrometer. The NMR spectra were taken on a Jeolco Model C-60-HL spectrometer (Me_4Si). Ultraviolet spectra were determined on a Beckmann Model DU spectrophotometer using 95% ethanol as solvent. TLC of the unsaturated 3-arylquinolizidines was performed using silica gel thin-layer sheets (Brinkman, polygram sil G) and petroleum ether–ethyl ether (90:10); TLC of the 3-arylquinolizidines was performed using basic alumina thin-layer sheets (Eastman) and petroleum ether–Et_2O (90:10). Gas chromatographic analyses were performed on a Varian Aerograph Model 600D fitted with a flame ionization detector and a 5 ft by ⅛ in. column packed with Varaport No. 30 (100–120 mesh) coated to a concentration of 3% with SE-30; column temperatures of 180–225° were used with injection temperatures 80–100° above the column temperature; a nitrogen carrier flow rate of approximately 30–40 ml/min was used; quantitative measurements were made using the ratio of peak heights method and are not corrected for detector response. Column chromatography was performed using neutral alumina (Woelm), basic alumina (Brockman), or silica gel (Woelm, 0.05–0.20 mm); the chromatograms were monitored by TLC or GLC; like fractions were combined and concentrated. Unless otherwise indicated all solvents were evaporated and all reaction mixtures concentrated at water aspirator pressure on a spin evaporator. Elemental analyses were performed by the A. H. Robins Co., Richmond, Va.

3-Aryl-1,6,7,8,9,9a-hexahydro-2*H*-quinolizines (8) and 3-Aryl-1,6,7,8,9,9a-hexahydro-4*H*-quinolizines (9) (Table III). Method A. A solution of 5 g (0.02 mol) of appropriate alcohol (1) in 50 ml of 10–50% sulfuric acid was refluxed with stirring for 1 hr to 4 days, cooled in an ice bath, and basified to pH 11–13 with 20% NaOH. The alkaline solution was extracted with three 100-ml portions of Et_2O; the extract was dried over $MgSO_4$ and evaporated to give the unsaturated 3-arylquinolizidines. The ratio of isomeric olefins was determined by GLC. The isomers were separated by fractional recrystallization or column chromatography.

3-Arylquinolizidines (Table I). Method B. The appropriate unsaturated compound (**3**, 5 g, 0.02 mol), 0.5 g of 10% Pd/C, and 100 ml of absolute EtOH were hydrogenated at room temperature and 46 psi for 3 hr. The catalyst was removed by filtration and the EtOH evaporated to give the epimeric arylquinolizidines. The ratio of epimers was determined by GLC. The epimers were separated by fractional recrystallization and/or column chromatography.

Method C. The appropriate unsaturated compound (**3**, 5 g, 0.02 mol), 0.5 g of 10% Pd/C, 1 ml of concentrated sulfuric acid, and 100 ml of absolute EtOH were hydrogenated at room temperature and 46 psi for 3 hr. The catalyst was removed by filtration and the EtOH evaporated. The residue was dissolved in 50 ml of cold water and basified to pH 11–13 with 20% NaOH. The mixture was extracted with three 100-ml portions of Et_2O; the extract was dried over $MgSO_4$ and evaporated to yield the epimeric 3-arylquinolizidines.

Method D. The method of Rosemund and Karg[15] was used. The appropriate alcohol (1, 5 g, 0.02 mol), 1 g of 10% Pd/C, 3 ml of concentrated sulfuric acid, and 100 ml of water were hydrogenated at 55–60° and 46 psi for 48 hr. The product was isolated as described in method C.

Method E. The reaction was conducted as in method D using absolute EtOH as solvent. After the catalyst was removed by fil-

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

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

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

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

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

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

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

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