Acknowledgment. This work was supported by the National Institutes of Health (HL 38048 to W.C.G. and HL 37616 to J.R.H.).

† Wichita State University.
‡ University of Utah Health Sciences Center.
§ University of Minnesota.

**W. C. Groutas,*,† J. R. Hoidal,*,‡ M. J. Brubaker†
M. A. Stanga,† R. Venkataraman†
B. H. Gray,§ N. V. Rao‡**

*Department of Chemistry
Wichita State University
Wichita, Kansas 67208
School of Medicine
Division of Respiratory, Critical Care and Occupational Medicine
University of Utah Health Sciences Center
Salt Lake City, Utah 84132
Department of Microbiology and Medicine
University of Minnesota
Minneapolis, Minnesota 55455*

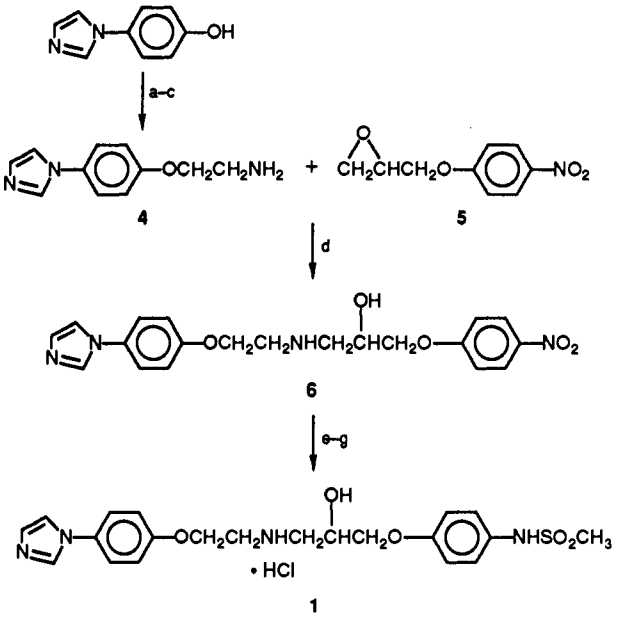
Received November 29, 1989

Synthesis and Pharmacological Studies of *N*-[4-[2-Hydroxy-3-[[2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl]amino]propoxy]phenyl]methanesulfonamide, a Novel Antiarrhythmic Agent with Class II and Class III Activities

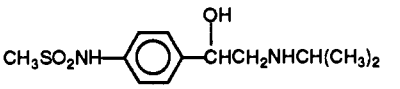
Sir:

Sudden cardiac death (SCD) claims approximately 400 000 lives annually in the United States.[1] Most of these deaths are due to reentrant ventricular arrhythmias.[2] No single antiarrhythmic agent is effective in a majority of arrhythmia patients due to the variety of etiologies contributing to SCD. Our approach to the treatment of SCD was to design compounds with multiple focussed activities in order to obtain agents with a broader therapeutic application. We chose to combine Class III electrophysiological activity (prolonging cardiac refractoriness)[3] with Class II (β-blocking) activity. Class III antiarrhythmic agents have been shown to be effective in models of reentrant arrhythmias.[4-8] These arrhythmias are thought to be major contributors to SCD.[8-10] Class II agents reduce enhanced sympathetic activity which has been implicated as a potential trigger for reentrant arrhythmias.[11,12] In fact, β-blockers are the only agents approved for the purpose of reducing mortality after a myocardial infarction. Thus, a combination Class II/III agent should not only decrease the opportunity for a triggering event, but should also prevent the establishment of a reentrant rhythm by increasing cardiac refractoriness. (±)-Sotalol can be considered as a prototype of these agents; however, this compound lacks potency as a Class III agent relative to its Class II activity and is a nonselective β-blocker.

Scheme I. Synthesis of Compound 1[a]



[a] (a) 2-Ethyl-2-oxazoline; (b) 6 N HCl; (c) NaOH; (d) $(CH_3)_3Al/CH_2Cl_2$; (e) H_2, Pd–C/EtOH; (f) CH_3SO_3H, CH_3SO_2Cl/H_2O (pH = 5–6); (g) HCl/MeOH.



(±)-sotalol

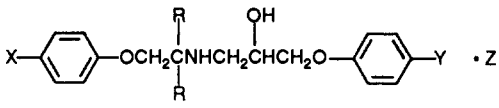
Our goal was to design potent Class III agents with a *balanced* amount of cardioselective β-blockade which would be effective against reentrant arrhythmias and catecholamine dependent arrhythmias without adverse conduction slowing or hemodynamic activity. The approach to these agents was to combine a Class III pharmacophore with a β-blocking pharmacophore using a common nitrogen moiety. We describe the synthesis and pharmacology of the most interesting compound from this work, **1**, its enantiomers and a limited series of related analogues. A full report of the compounds which led to **1** will be given in a subsequent publication.

We had observed that *N*,*N*-diethyl-2-[4-(1*H*-imidazol-1-yl)phenoxy]ethanamine (**2**) and *N*-[4-[3-(diethylamino)-2-hydroxypropoxy]phenyl]methanesulfonamide (**3a**) were potent Class III electrophysiological agents in canine Purkinje fibers (see Table II). Further, Smith[13] has

(1) Kaplan, H. R. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1986**, *45*, 2184.
(2) Savage, D. D.; Castelli, W. P.; Anderson, S. J.; Kannel, W. B. *Am. J. Med.* **1983**, *74*, 148.
(3) Vaughan Williams, E. M. In *Symposium on Cardiac Arrhythmias*; Sandoe, E., Flensted-Jansen, E., Olesen, K. H., Eds.; AB Astra: Sodertalje, Sweden, 1970; pp 449–72.
(4) Lumma, W. C., Jr.; Wohl, R. A.; Davey, D. D.; Argentieri, T. M.; De Vita, R. J.; Gomez, R. P.; Jain, V. K.; Marisca, A. J.; Morgan, T. K., Jr.; Reiser, H. J.; Sullivan, M. E.; Wiggins, J.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 755.
(5) Morgan, T. K., Jr.; Wohl, R. A.; Lumma, W. C., Jr.; Wan, C.-N.; Davey, D. D.; Gomez, R. P.; Marisca, A. J.; Briggs, M.; Sullivan, M. E.; Wong, S. S. *J. Med. Chem.* **1986**, *29*, 1398.
(6) Morgan, T. K., Jr.; Lis, R.; Marisca, A. J.; Argentieri, T. M.; Sullivan, M. E.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 2259.
(7) Lis, R.; Morgan, T. K., Jr.; De Vita, R. J.; Davey, D. D.; Lumma, W. C., Jr.; Wohl, R. A.; Diamond, J.; Wong, S. S.; Sullivan, M. E. *J. Med. Chem.* **1987**, *30*, 696.
(8) Reiser, H. J.; Sullivan, M. E. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1986**, *45*, 2206.
(9) Josephson, M. E.; Horowitz, L. N.; Farshidi, A. *Circulation* **1978**, *57*, 659.
(10) Josephson, M. E.; Horowitz, L. N.; Farshidi, A.; Kastor, J. A. *Circulation* **1978**, *57*, 431.
(11) Lynch, J. J.; Lucchesi, B. R. In *Life-Threatening Arrhythmias During Ischemia and Infarction*; Hearse, D. J., Manning, A. S., Janse, M. J. Eds.; Raven Press: New York, NY, 1987; pp 169–196.
(12) Frishman, W. H.; Laifer, L. I. In *Mechanisms and Treatment of Cardiac Arrhythmias; Relevance of Basic Studies to Clinical Management*; Reiser, H. J., Horowitz, L. N., Eds.; Urban and Schwarzenberg: Baltimore, MD, 1985; pp 263–281.

0022-2623/90/1833-1087$02.50/0

Table I. Structure and Physical Properties of Compound 1 and Analogues



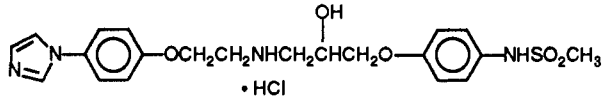
compd	X	Y	R	Z	melting range, °C	recryst solvent	elemental analysis
1	1*H*-imidazol-1-yl	$NHSO_2CH_3$	H	HCl	163–167	MeOH/EtOH	C,H,Cl,N,S
1-(***S***)	1*H*-imidazol-1-yl	$NHSO_2CH_3$	H	HCl	201–203	MeOH	C,H,Cl,N,S
1-(***R***)	1*H*-imidazol-1-yl	$NHSO_2CH_3$	H	HCl	201–202	MeOH/H_2O	C,H,Cl,N,S
7	2-methyl-1*H*-imidazol-1-yl	$NHSO_2CH_3$	H	H_3PO_4	215–218	MeOH	C,H,N
8	1*H*-imidazol-1-yl	$N(CH_3)SO_2CH_3$	H	2HCl	190–192	MeOH/2-PrOH	C,H,N
9	2-methyl-1*H*-imidazol-1-yl	$N(CH_3)SO_2CH_3$	H		42–45		C,H,N
10	1*H*-imidazol-1-yl	$NHSO_2CH_3$	CH_3	2HCl·H_2O	156–160		C,H,Cl,N,S

Table II. In Vitro Pharmacology

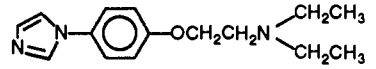
	electrophysiology[a]		β-receptor affinity[b]		contractile function[c]	
compd	n[d]	$C_{20}APD_{95}$,[e] μM	n (β_1/β_2)	$IC_{50}(\beta_1,\beta_2)$,[f] μM	n	%ΔF at 10 μM[g]
1	6	0.4 (0.2–4.0)	10/9	2.4 ± 0.3/47 ± 9.2	8	+53 (6–124)
1-(***S***)	4	0.8 (0.4–1.8)	5/6	1.7 ± 0.4/ca. 100	8	+75 (−17–365)
1-(***R***)	4	0.8 (0.4–1.6)	5/6	38 ± 7.6/>100	4	+27 (5–41)
7	2	7.3 (6.6, 8.0)	3/3	2.8 ± 0.1/57 ± 8	4	+9 (4–14)
8	6	1.4 (0.1–5.1)	4/3	21 ± 9.8/>100	4	−15 (−28–0)
9	2	>30 (ca. 18% at 30)	3/3	18 ± 1/>100	4	−16 (−29–10)
10	2	0.5 (0.2, 1.1)	5/3	2.6 ± 0.5/23 ± 10	3	+69 (0–162)
(±)-sotalol	7	18 (9–63)	3/3	9 ± 5/5 ± 1	8	−12 (−27–11)
2	2	3.4 (2.8, 4.1)		–		–
3a	2	4.8 (2.1, 11)		–		–

[a] Electrophysiological activity was assessed in isolated canine cardiac Purkinje fibers using standard microelectrode techniques. No significant change from control was observed for the rate of rise of phase 0 of the action potential ($\dot{V}_{max}$) at the $C_{20}APD_{95}$, indicating selective Class III activity. [b] β-Receptor affinities were determined in partially purified membrane fractions from canine ventricular muscle (β_1-receptors; β_2-receptors were blocked with 1 μM zinterol) and canine lung tissue (β_2-receptors; β_1-receptors were blocked with 0.1 μM metoprolol). [c] Effects on contractile function were determined in isolated ferret papillary muscle. [d] n = number of experiments. [e] $C_{20}APD_{95}$ = concentration of drug which increased action potential duration at 95% full repolarization by 20% over control. Reported is the log mean average of n experiments with the range given in parentheses. [f] $IC_{50}(\beta_1/\beta_2)$ = concentration of drug which inhibited the binding of [^{3}H]dihydroalprenolol (4.5 nM) by 50%. Reported is the average ±SEM of n experiments. β_1-Receptor data is listed first. [g] %ΔF = percent change in force of contraction from control value at a 10 μM concentration of the drug. Reported is the average of n experiments with the range given in parentheses.

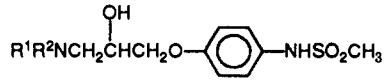
reported that a secondary amine analogue of **3a** (**3b**, R^1 = H, R^2 = $CH(CH_3)_2$) is a β_1-selective receptor antagonist. Combination of the pharmacophores of **2** and **3b** provided **1** as a synthetic target with putative dual activity. The synthesis of **1** is outlined in Scheme I. The key intermediates in the preparation of **1** were amine **4** and epoxide **5** (Sigma Chemical Co.).



1



2



3a: $R^1 = R^2 = CH_2CH_3$
b: R^1 = H, $R^2 = CH(CH_3)_2$

Compound **4** was synthesized in three steps from 4-(1*H*-imidazol-1-yl)phenol. Addition of the phenol to 2-ethyl-2-oxazoline at 130 °C provided *N*-[2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl]propanamide. Hydrolysis of the amide with 6 N hydrochloric acid followed by treatment of the resulting dihydrochloride salt with sodium hydroxide solution gave amine **4**.

Trimethylaluminum-assisted[14] opening of epoxide **5** by amine **4** afforded amino alcohol **6**. Hydrogenation of the nitro group in **6** followed by selective mesylation of the aromatic amino group and salt formation provided **1**. The enantiomers of **1** [1-(***S***) and 1-(***R***)] were prepared in an analogous manner from optically active epoxides **5**-(***R***) and **5**-(***S***). Preparation of **5**-(***S***) and **5**-(***R***) was accomplished by reaction of (*R*)- or (*S*)-glycidol, respectively, with 4-fluoronitrobenzene under basic conditions. X-ray structure analysis of the (*S*)-malic acid salt of 1-(***S***) confirmed the absolute stereochemistry (Figure 1). A limited number of analogues (**7**–**10**) of **1** were prepared to examine the contribution of some of the key structural features of **1** to its pharmacological activity (Table I).[15]

Class III electrophysiological activities were assessed in isolated canine cardiac Purkinje fibers using standard microelectrode techniques.[16] β-Adrenergic receptor affinities were determined by standard competition binding studies using 4.5 nM [^{3}H]dihydroalprenolol as the ligand in partially purified membrane fractions from canine cardiac tissue (β_1) and canine lung tissue (β_2).[17] Effects on contractility were measured in isolated ferret papillary muscles.[18] The new compounds were compared to sotalol

(13) Smith, L. H *Int. Cong. Symp. Ser.—R. Soc. Med.* **1980**, *19*, 93.
(14) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195.
(15) Full experimental details for the synthesis of the new compounds can be found in the supplementary material.
(16) Davis, L. D.; Temte, J. V. *Circ. Res.* **1969**, *24*, 639.
(17) Modified from the procedure of Beer et al.: Beer, M.; Richardson, A.; Poat, J.; Iversen, L. L.; Stahl, S. M. *Biochem. Pharmacol.* **1988**, *37*, 1145.

Table III. In Vivo Pharmacology

study	1	1-(*S*)	1-(*R*)	sotalol
PES efficacy in conscious dogs[a]				
no. effective/no. tested	8/8	7/8	not tested	7/9
mean effective dose	~1 mg/kg iv	~0.4 mg/kg iv		~2 mg/kg iv
halothane/epinephrine induced arrhythmias in anesthetized dogs[b]				
no. effective/no. tested	0/2 (0.3 mg/kg) 6/8 (1 mg/kg)	2/4 (0.3 mg/kg) 4/4 (1 mg/kg)	1/4 (1 mg/kg) 1/4 (3 mg/kg)	4/4 (1 mg/kg) 6/6 (3 mg/kg)
hemodynamics: normal anesthetized dog,[c]				
dose 30 mg/kg			not tested	
MAP	−25 ± 9%	−30 ± 6%		−42 ± 10%[d]
CO	−28 ± 5%	−32 ± 10%		−61 ± 11%
TPR	3 ± 7%	6 ± 8%		78 ± 38%
LV dP/dt	−38 ± 10%	−28 ± 6%		−52 ± 8%
cor flow	−29 ± 6%	−41 ± 8%		−51 ± 11%
HR	−49 ± 5%	−48 ± 1%		−51 ± 3%
ISO (0.08 μg/kg) challenge: normal conscious dogs,[e] % Δ from control response				
dose (mg/kg) 0.3	(+) 30 ± 30	(+) 10 ± 29	(+) 40 ± 17	(−) 72 ± 10[f]
1.0	(−) 0.75 ± 15	(−) 25 ± 6*	(+) 62 ± 42	(−) 42 ± 19
3.0	(−) 74 ± 1*	(−) 45 ± 14*	(−) 6 ± 27	(−) 79 ± 6*
10.0	(−) 78 ± 5*	(−) 64 ± 7*	(+) 41 ± 39	

[a] Mongrel dogs were studied in a programmed electrical stimulation (PES) protocol 3–8 days after a surgically produced occlusion/reperfusion-induced infarction.[19] Two control arrhythmias were induced prior to drug administration; sustained ventricular tachycardia (SVT) was terminated by burst pacing and ventricular fibrillation (VF) was terminated by DC countershock. To be considered effective, the animal must have been noninducible after drug administration. [b] Mongrel dogs were anesthetized with thiopental and respired with 1.5 vol% halothane in O_2. After a 15–30-min stabilization period, the drug was administered intravenously over 10 min. Following a 20-min equilibration period, an infusion of epinephrine (1.5 μg/kg per min) was started. SVT/VF was induced in saline-treated controls within 2–4 min of epinephrine infusion. A drug was considered effective if SVT/VF could not be induced during the 15-min time course of the epinephrine infusion. [c] Mongrel dogs were anesthetized with pentobarbital and hemodynamic parameters (MAP = mean arterial pressure; CO = cardiac output; TPR = total peripheral resistance; LV dP/dt = left ventricular change in pressure with respect to time; cor flow = coronary flow; HR = heart rate) were determined after a 30-min stabilization period. Drug was administered intravenously over a 5-min period (cumulative doses of 3, 10, and 30 mg/kg), and effects were monitored at 5-min intervals for 15 min and then the next dose was given. Reported in the table are the percent change ± SEM from control for the hemodynamic parameters for the 30 mg/kg dose determined at 15 min postdose (n = 4). [d] One dog died during this study. [e] Lead II electrocardiograms were monitored on conscious mongrel dogs (n = 4). After a stabilization period, increasing doses (0.04, 0.08, and 0.16 μg/kg) of isoproterenol (ISO) were given intravenously (left cephalic vein) and percent changes in heart rate (% ΔHR) were determined. HR was allowed to return toward control values between each dose. The ISO challenge was repeated after administration of cumulative doses (0.3, 1.0, 3.0, and 10.0 mg/kg) of test compound and % ΔHR redetermined. Reported is the percent change from control response [(% $\Delta HR_{no\ drug}$ − % ΔHR_{drug}/% $\Delta HR_{no\ drug}$) × 100] ± SEM for the 0.08 μg/kg dose of ISO. Asterisk indicates significant ($P < 0.05$, paired Student's t test) difference from % $\Delta HR_{no\ drug}$; (−) represents inhibition of the ISO response. [f] n = 2 for this dose.

in these in vitro studies (Table II).

Compounds 1, 1-(*S*), and sotalol were studied in two models of antiarrhythmic efficacy and hemodynamic effects were evaluated in anesthetized dogs. Efficacy against programmed electrical stimulation (PES) induced arrhythmias were assessed in conscious dogs 3–8 days after an occlusion/reperfusion induced infarction according to the method of Karagueuzian.[19] In the second efficacy model, arrhythmias were induced by infusion of epinephrine in halothane-anesthetized dogs.[20] Compound 1-(*R*) was also studied in the halothane/epinephrine dog model. In vivo β-blockade was assessed in conscious dogs by inhibition of the positive chronotropic response to isoproterenol.[21]

Results and Discussion

The results of the in vitro studies (Table II) illustrate the effect of altering key structural features of 1. All of the new compounds except 9 exhibited potent Class III activity in canine Purkinje fibers; indeed 1 was ca. 45 times more potent than sotalol. Compound 9, which contains methyl substituents on the sulfonamide nitrogen and on the imidazole ring, showed only marginal activity. We had observed this effect previously in a series of benzamide Class III antiarrhythmic agents.[4,22] Compounds 7 and 8, with only one methylated substituent, had Class III potencies intermediate between 1 and 9, which indicated that both pharmacophores contribute to the Class III activity of 1. Dimethylation of the connecting chain, as in 10, did not affect Class III activity.

Compound 1 demonstrated selective β_1-receptor affinity, and as expected, the (*S*)-enantiomer was the major contributor to receptor affinity. Methylation of the sulfonamide (8 and 9) reduced the β_1-receptor affinity by nearly 1 order of magnitude. Compound 10 with dimethyl substitution α to the basic nitrogen maintained affinity for the β_1-receptor but was less selective than 1. In contrast to 1, sotalol bound with equal affinity to both β_1 and β_2 receptors.

Compounds 1, 1-(*S*), 1-(*R*), and 10, the more potent Class III agents, demonstrated moderate positive inotropic activity in the ferret papillary muscle. Among the less potent Class III agents (7–9 and sotalol), compounds 8, 9, and sotalol exhibited negative inotropic activity in this preparation. The positive inotropic effects of 1 and 1-(*S*), possibly due to the potent Class III activity,[23] may help

(18) Hagedorn, A. A., III; Erhardt, P. W.; Lumma, W. C., Jr.; Wohl, R. A.; Cantor, E.; Chou, Y.-L.; Ingebretsen, W. R.; Lampe, J. W.; Pang, D.; Pease, C. A.; Wiggins, J. *J. Med. Chem.* **1987**, *30*, 1342.
(19) Karagueuzian, H. S.; Fenoglio, J. J., Jr.; Weiss, M. B.; Wit, A. L. *Circ. Res.* **1979**, *44*, 833.
(20) Adapted from Mitsuhashi, H.; Akiyama, K.; Hashimoto, K. *Jpn. J. Pharmacol.* **1987**, *43*, 179.
(21) Experimental details for this model can be found in the supplementary material.
(22) Morgan, T. K., Jr.; Lis, R.; Lumma, W. C., Jr.; Nickisch, K.; Wohl, R. A.; Phillips, G. B.; Gomez, R. P.; Lampe, J. W.; Di Meo, S. V.; Marisca, A. J.; Forst, J. *J. Med. Chem.* **1990**, *33*, 1091.

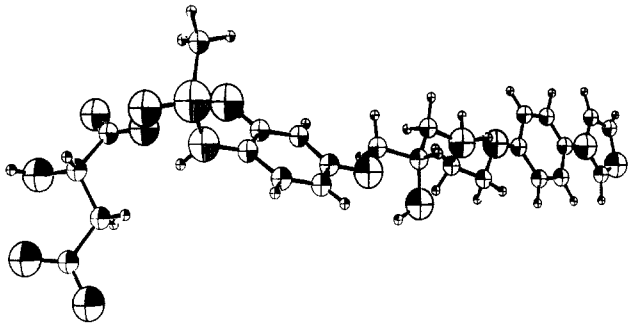


Figure 1. ORTEP drawing of a fragment of the X-ray structure of the (*S*)-malic acid salt of 1-(***S***) showing a single molecule of 1-(***S***) and the (*S*)-malic acid dianion.

offset any negative inotropic influence of β-blockade.

The in vivo results (Table III) parallel the in vitro results for 1, 1-(***R***), 1-(***S***), and sotalol. Compounds 1, 1-(***S***), and sotalol were all highly effective in the PES efficacy model in conscious dogs. Selective Class III agents are very efficacious in the PES model, whereas β-blockers, in general, are not efficacious. Compound 1-(***S***) was ca. 5 times more potent than sotalol in this model. In the halothane/epinephrine dog model, in which β-blockers, but not Class III agents, are effective, compounds 1, 1-(***S***), and sotalol were equieffective. Compound 1-(***R***), which lacks β-receptor affinity, was not effective. Although 1 and 1-(***S***) were effective in preventing sustained ventricular tachycardia and ventricular fibrillation in the halothane/epinephrine model, they, as well as 1-(***R***) (not effective), produced ecotopic activity in some animals prior to epinephrine administration. This is due to the potent Class III activity of these compounds and has been observed for other Class III agents in halothane-sensitized preparations.[24,25]

The hemodynamic effects of 1, 1-(***S***), and sotalol in normal pentobarbital anesthetized dogs at a dose of 30 mg/kg are given. In general, the profiles for the new compounds were similar to that for sotalol in this model. However, sotalol was, on average, more depressant than 1 or 1-(***S***) on most of the hemodynamic parameters. In particular, sotalol caused a large increase in total peripheral resistance (TPR) while 1 and 1-(***S***) caused little change. One animal in the sotalol group died during this study. The increased potency of 1-(***S***) in the PES studies coupled with the hemodynamic results suggests that compound 1-(***S***) will have a significantly better therapeutic ratio than sotalol in this respect.

Both the racemic 1 and 1-(***S***) produced a dose-dependent decrease in the positive chronotropic response to isoproterenol (ISO) in conscious dogs. The onset of β-blocking activity was between 1 and 3 mg/kg for 1 and approximately 1 mg/kg for 1-(***S***). As expected, 1-(***R***), which had a much lower affinity for β-receptors, did not decrease the positive chronotropic response to ISO. No overt CNS effects were observed in any of the conscious dogs either in this model or in the PES efficacy model.

On the basis of the above results, 1 and 1-(***S***) were selected for further studies. Compound 1 was negative in the Ames test (mutagenicity) and the LD_{50} in rats after intravenous administration was between 200 and 300 mg/kg. Compound 1 showed no CNS activity in mice at doses up to 300 mg/kg (ip). The absolute bioavailability of both 1 and 1-(***S***) is ca. 60% (determined by comparison of areas under the plasma–time curve after intravenous and oral administration of 3 mg/kg to dogs). The duration of both the Class III activity and β-blocking activity in dogs after a 3 mg/kg intravenous dose of 1-(***S***) was ca. 4 h. This parallels the half-life of ca. 3 h found during the bioavailability studies. Thus, compound 1-(***S***) holds promise for the treatment of arrhythmias which may lead to SCD, and this compound is continuing in development as a clinical candidate.

Registry No. (±)-1, 125228-82-2; (±)-1·HCl, 125228-72-0; (*R*)-1, 125279-80-3; (*R*)-1·HCl, 125279-78-9; (*S*)-1, 125279-79-0; (*S*)-1·HCl, 125279-77-8; (*S*)-1 (*S*)-malic acid salt (2:1), 125279-87-0; **2**, 122958-17-2; **2**·HCl, 125228-73-1; (±)-**3a**, 125228-74-2; (±)-**3b**, 125228-81-1; **4**, 122958-36-5; **4**·2HCl, 122958-35-4; (±)-**5**, 125228-75-3; (*R*)-**5**, 125279-81-4; (*S*)-**5**, 125279-82-5; (±)-**6**, 125228-76-4; (*R*)-**6**, 125279-83-6; (*S*)-**6**, 125279-84-7; (±)-**7**, 125228-77-5; (±)-**7**·H_3PO_4, 125228-78-6; (±)-**8**, 125228-83-3; (±)-**8**·2HCl, 125228-79-7; (±)-**9**, 125228-80-0; (±)-**10**, 125228-84-4; (±)-**10**·2HCl, 125249-53-8; 4-(1*H*-imidazol-1-yl)phenol, 10041-02-8; 4-(2-methyl-1*H*-imidazol-1-yl)phenol, 81376-54-7; 2-chloro-*N*,*N*-diethylethanamine hydrochloride, 869-24-9; 2-ethyl-2-oxazoline, 10431-98-8; 3-chloro-2-methylpropene, 563-47-3; (±)-*N*-[4-(oxiranylmethoxy)phenyl]methanesulfonamide, 125228-85-5; *N*-[2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl]propanamide, 125228-86-6; *N*-[2-[4-(2-methyl-1*H*-imidazol-1-yl)phenoxy]ethyl]propanamide, 125228-87-7; *N*-[1,1-dimethyl-2-[4-(1*H*-imidazol-1-yl)phenoxy]-ethyl]acetamide, 125228-88-8; 2-[4-(2-methyl-1*H*-imidazol-1-yl)-phenoxy]ethanamide dihydrochloride, 125228-89-9; 1,1-dimethyl-2-[4-(1*H*-imidazol-1-yl)phenoxy]ethanamine dihydrochloride, 125228-90-2; 1,1-dimethyl-2-[4-(1*H*-imidazol-1-yl)-phenoxy]ethanamine, 125228-91-3; (*S*)-oxiranemethanol, 60456-23-7; (*R*)-oxiranemethanol, 57044-25-4; 4-fluoro-1-nitrobenzene, 350-46-9; (±)-1-[[2-[4-(2-methyl-1*H*-imidazol-1-yl)phenoxy]-ethyl]amino]-3-(4-nitrophenoxy)-2-propanol, 125228-92-4; (±)-1-(4-aminophenoxy)-3-[[2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl]-amino]-2-propanol, 125228-93-5; (*R*)-1-(4-aminophenoxy)-3-[[2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl]amino]-2-propanol, 125279-85-8; (*S*)-1-(4-aminophenoxy)-3-[[2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl]amino]-2-propanol, 125279-86-9; (±)-1-(4-aminophenoxy)-3-[[2-[4-(2-methyl-1*H*-imidazol-1-yl)phenoxy]-ethyl]amino]-2-propanol, 125228-94-6; (±)-*N*-methyl-*N*-[4-(oxiranylmethoxy)phenyl]methanesulfonamide, 125228-95-7; 1-[4-(2-methyl-2-propenyloxy)phenyl]-1*H*-imidazole, 125228-96-8; (*R*)-α-methylbenzyl isocyanate, 33375-06-3.

Supplementary Material Available: Full synthetic procedures for the preparation of 1–10, X-ray crystallographic data, and additional information on pharmacological protocols (32 pages). Ordering information is given on any current masthead page.

(23) Positive inotropic responses in ferret papillary muscle have been observed in our laboratory for a variety of selective Class III agents, e.g. sematilide, at the same concentrations which prolong action potential duration in cardiac tissue. Partial β-agonist activity seems unlikely in the absence of any positive chronotropic response in either isolated spontaneously beating guinea pig atria or intact animals (unpublished results). Inhibition of cAMP-PDE can be ruled out as a positive inotropic mechanism since 1-(***S***) caused only 19 ± 9% (100 μM) inhibition of activity of the particulate cAMP-PDE fraction from dog heart (unpublished results).

(24) Steinberg, M. I.; Lindstrom, T. D.; Fasola, A. F. In *New Drugs Annual—Cardiovascular Drugs, Volume 2*; Scriabine, A.; Ed.; Raven Press: New York, NY 1984; pp 103–121.

(25) Hashimoto, K.; Haruno, A.; Matsuzaki, T. *J. Mol. Cell. Cardiol* **1989**, *21* (Suppl. II), S12.

† Medicinal Chemistry Department.
§ Present address: Schering AG, D-1000, Berlin (West) 65, Federal Republic of Germany.
‡ Pharmacology Department.

Thomas K. Morgan, Jr.,*,† Randall Lis†
William C. Lumma, Jr.,† Ronald A. Wohl†
Klaus Nickisch,†,§ Gary B. Phillips,† Joan M. Lind†
John W. Lampe,† Susan V. Di Meo,† H. Joseph Reiser‡
Thomas M. Argentieri,‡ Mark E. Sullivan‡
Elinor Cantor‡
Berlex Laboratories, Inc.
Cedar Knolls, New Jersey 07927

Received November 3, 1989