Synthesis and Antiarrhythmic Activity of Novel 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium Salts and Related Compounds[1]

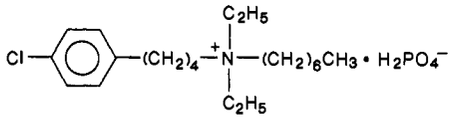
Randall Lis,*† Thomas K. Morgan, Jr.,† Robert J. DeVita,† David D. Davey,† William C. Lumma, Jr.,† Ronald A. Wohl,† Julius Diamond,‖ Samuel S. Wong,§ and Mark E. Sullivan‡

Berlex Laboratories, Inc., Cedar Knolls, New Jersey 07927. *Received November 24, 1986*

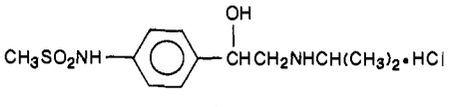
Novel 3-alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium salts were synthesized and investigated for their class III electrophysiological activity on isolated canine cardiac Purkinje fibers and ventricular muscle tissue. Structure–activity relationships are discussed for a series of 25 compounds. Compound **3**, 1-[2-hydroxy-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-3-methyl-1*H*-imidazolium chloride, prolonged the functional refractory period in anesthetized dogs when given intraduodenally and was also effective in preventing reentrant ventricular tachycardia induced by programmed electrical stimulation when administered intravenously in anesthetized dogs 24 h after an acute myocardial infarction. Both enantiomers of **3** were synthesized. No enantioselectivity was found in the electrophysiological effects of **3**.

Our goal has been to develop novel antiarrhythmic agents that selectively prolong the action potential duration (APD) and concomitantly increase the refractory period (FRP) of heart cells without significant effects on cardiac conduction. Compounds that exhibit these effects are termed class III antiarrhythmic agents in the Vaughan Williams classification.[2] In addition, for clinical utility, our goal was to find such a compound that would be orally available and devoid of unwanted side effects, such as cardiotoxicity, gastrointestinal complications, or central nervous system (CNS) stimulation.

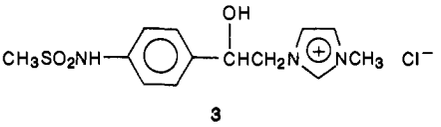
Clofilium phosphate (LY 150378) (**1**) has been shown to be an effective class III antiarrhythmic agent in animals[3] and efficacious against programmed electrical stimulation (PES) induced ventricular tachyarrhythmias in man[4a,b] but has limited bioavailability.[5] The orally available agent sotalol hydrochloride (MJ 1999) (**2**) was originally developed as a β-adrenergic blocking agent[6] (class II)[2] for therapeutic application in the treatment of hypertension. Other studies have demonstrated that sotalol also exhibits class III antiarrhythmic activity.[7]



1



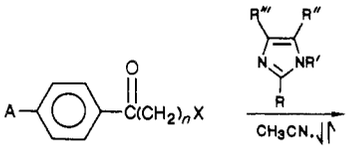
2



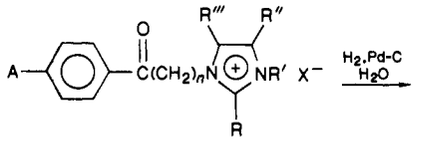
3

Since β-blockade may produce unwanted side effects (e.g., diminished myocardial function in certain patient groups with ventricular arrhythmias), we wanted to develop analogues of sotalol with little or no β-blocking activity. Prior studies have shown that quaternization of the amino moiety in certain β-blocking drugs greatly diminishes β-blocking activity.[8] Thus, we decided to explore a series of imidazolium salts related to sotalol as antiarrhythmic agents.

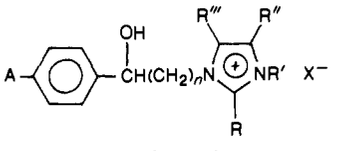
Scheme I



4a: A = CH_3SO_2NH, n = 1
b: A = $CH_3CH_2SO_2NH$, n = 1
c: A = CF_3SO_2NH, n = 1
d: A = CH_3SO_2NH, n = 2



5-14



3, 15-23

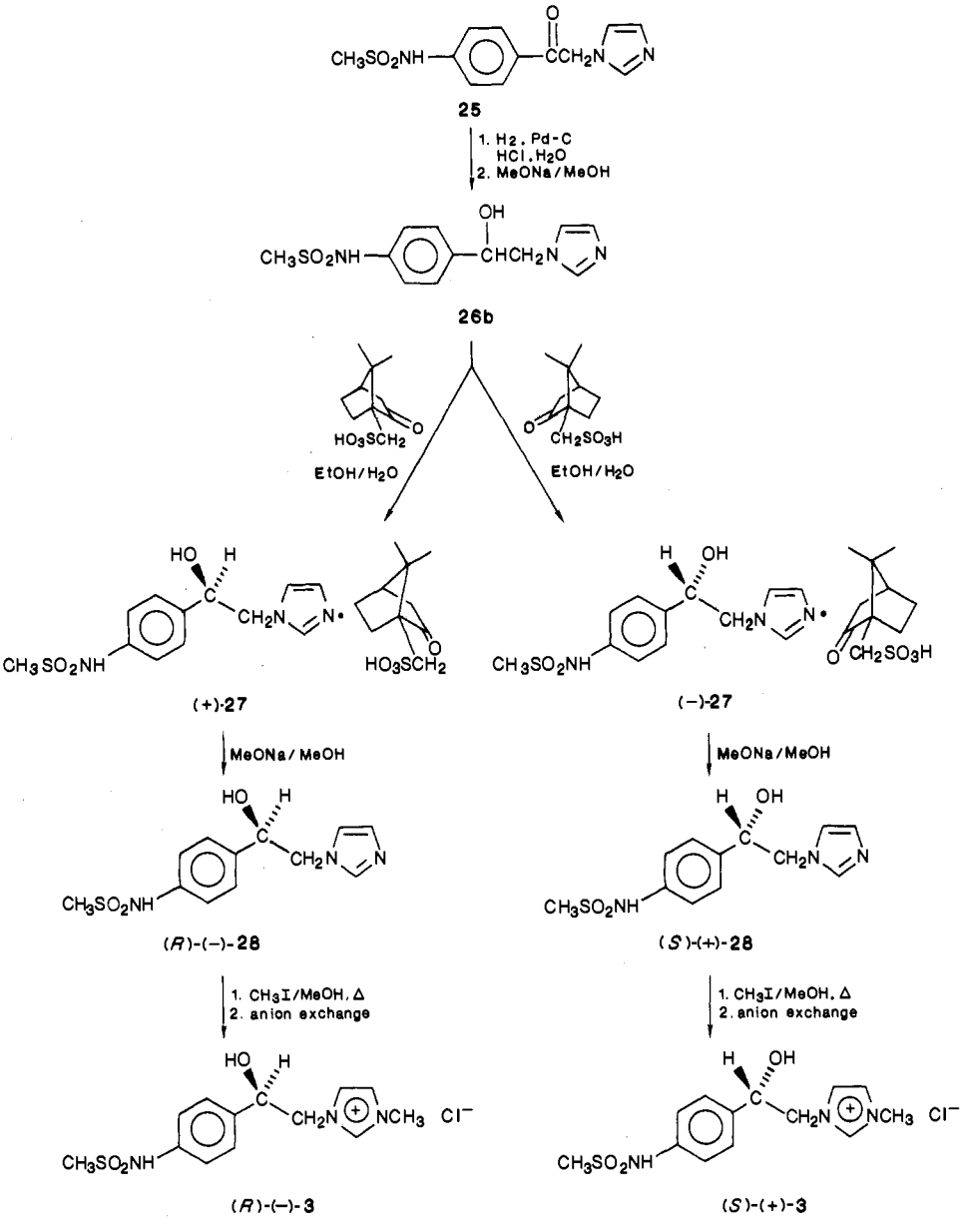
We report here a new series of 3-alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium salts (**3**, **15–23**), which represent imidazolium analogues

† Department of Medicinal Chemistry.
‡ Department of Pharmacology.
§ Present address: Pfizer International, New York, New York 10017.
‖ Present address: Key Pharmaceuticals, Inc., Miami, Florida 33137.

(1) A preliminary account of this work has appeared: Lis, R.; Morgan, T. K., Jr.; DeVita, R. J.; Davey, D. D.; Lumma, W. C., Jr.; Wohl, R. A.; Diamond, J.; Wong, S. S.; Sullivan, M. E.; Reiser, H. J.; Wiggins, J.; Hill, J. L. *Pharmacologist* **1985**, *27*, 112 (Abstr 28).
(2) Vaughan Williams, E. M. In *Symposium on Cardiac Arrhythmias*; Sandoe, E., Flensted-Jansen, E., Olsen, K. H., Eds.; AB Abstra: **1970**; pp 449–472.
(3) Steinberg, M. I.; Molloy, B. B. *Life Sci.* **1979**, *25*, 1397.
(4) (a) Greene, H. L.; Werner, J. A.; Gross, B. W.; Sears, G. K.; Trobaugh, G. B.; Cobb, L. A. *Am. Heart J.* **1983**, *106*, 492. (b) Platia, E.; Reid, P. R. *Clin. Pharmacol. Ther.* **1984**, *35*, 193.
(5) Steinberg, M. I.; Lindstrom, L. D.; Fasola, A. F. In *New Drugs Annual: Cardiovascular Drugs* Scriabine, A., Ed.; Raven: New York, 1984; pp 103–121.
(6) Larsen, A. A.; Uloth, R. H. U.S. Patent 3 478 149, 1969.
(7) Singh, B. N.; Vaughan Williams, E. M. *Br. J. Pharmacol.* **1970**, *39*, 675.
(8) Gibson, J. K.; Lucchesi, B. R. *J. Pharmacol. Exp. Ther.* **1980**, *214*, 449.

0022-2623/87/1830-0696$01.50/0

Scheme II

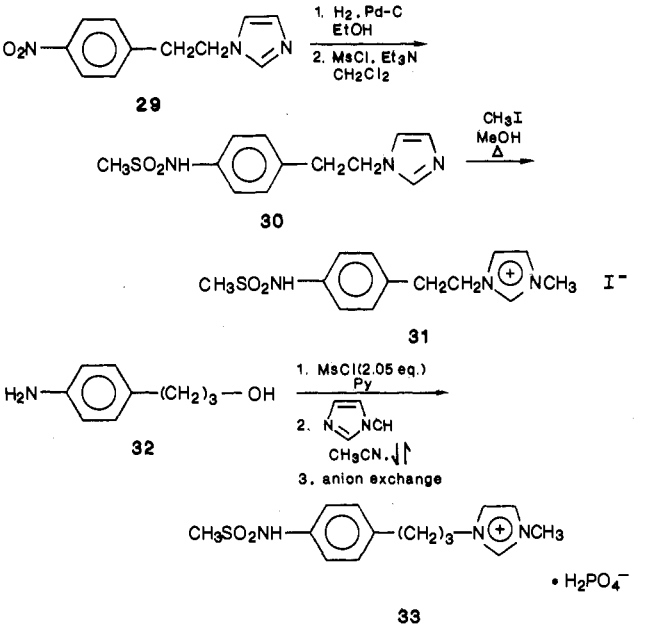


of sotalol. These compounds were screened in vitro to determine their class III electrophysiological effects. Some of these compounds were chosen for further evaluation with in vivo models. Of these, 1-[2-hydroxy-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-3-methyl-1*H*-imidazolium chloride (**3**) was selected for further development as a potential orally active antiarrhythmic agent.

Chemistry

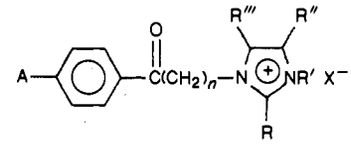
The synthetic routes to the target compounds **3**, **5–24**, **33**, and **35** are illustrated in Schemes I–III. The required chloroacetophenones **4a–d** were obtained by modification of the known procedure[9] (see Experimental Section). Treatment of the chloroacetophenone derivatives with 1-alkylimidazoles in refluxing acetonitrile afforded the keto imidazolium salts **5–13**. Compound **14** was prepared by the method of Boekelheide and Fedoruk.[10] Catalytic hydrogenation[11] of keto imidazolium salts **5–14** gave the

Scheme III



(9) Uloth, R. H.; Kirk, J. R.; Gould, W. A.; Larsen, A. A. *J. Med. Chem.* **1966**, *9*, 88.
(10) Boekelheide, V.; Fedoruk, N. A. *J. Am. Chem. Soc.* **1968**, *90*, 3830.

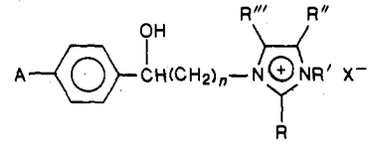
Table I. 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-oxoalkyl]-1*H*-imidazolium Salts **5–14**



no.	A	*n*	R	R′	R″	R‴	yield, %	mp,[a] °C (solv)	formula	anal.[b]
5	CH_3SO_2NH	1	H	CH_3	H	H	84	257–261 (A)	$[C_{13}H_{16}N_3O_3S]^+Cl^-\cdot 0.25H_2O$	CHNSCl
6	CH_3SO_2NH	1	H	CH_2CH_3	H	H	89	252–254 (B)	$[C_{14}H_{18}N_3O_3S]^+Cl^-$	CHN
7	CH_3SO_2NH	1	H	$CH(CH_3)_2$	H	H	76	239–241 (B)	$[C_{15}H_{20}N_3O_3S]^+Cl^-$	CHN
8	CH_3SO_2NH	1	H	$(CH_2)_6CH_3$	H	H	60	78–80 (E)	$[C_{19}H_{28}N_3O_3S]^+Br^-$	CHNSBr
9	CH_3SO_2NH	1	CH_3	CH_3	H	H	72	252–253 (C)	$[C_{14}H_{18}N_3O_3S]^+Cl^-$	CHN
10	CH_3SO_2NH	1	CH_3	CH_3	CH_3	CH_3	67	294–297 (F)	$[C_{16}H_{22}N_3O_3S]^+Cl^-$	CHN
11	$CH_3CH_2SO_2NH$	1	H	CH_3	H	H	76	218–220 (B)	$[C_{14}H_{18}N_3O_3S]^+Cl^-$	CHN
12	CF_3SO_2N[c]	1	H	CH_3	H	H	42	226–229 (B)	$C_{13}H_{12}F_3N_3O_3S$[c]	CHN
13	CH_3SO_2NH	2	H	CH_3	H	H	68	174–176 (B)	$[C_{14}H_{18}N_3O_3S]^+Cl^-$	CHN
14[d]	H	1	H	CH_3	H	H	87	155–156.5[d] (D)	$[C_{12}H_{13}N_2O]^+Br^-\cdot HBr\cdot {}^2/_3H_2O$	CHNBr

[a] Recrystallization solvent: A = 75% aqueous EtOH, B = 95% aqueous EtOH, C = 80% aqueous EtOH, D = 95% aqueous *i*-PrOH, E = CH_3CN/EtOAc, and F = acetone. [b] Elemental analyses are within ±0.4% of the calculated values. [c] Zwitterion. [d] Reference 10.

Table II. 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium Salts **3** and **15–24**



no.[a]	A	*n*	R	R′	R″	R‴	yield, %	mp,[b] °C (solv)	formula	anal.[c]
3	CH_3SO_2NH	1	H	CH_3	H	H	78	206–207 (A)	$[C_{13}H_{18}N_3O_3S]^+Cl^-$	CHNSCl
(*S*)-(+)-**3**	CH_3SO_2NH	1	H	CH_3	H	H	77	230–231 (A)	$[C_{13}H_{18}N_3O_3S]^+Cl^-$	CHN
(*R*)-(−)-**3**	CH_3SO_2NH	1	H	CH_3	H	H	76	229–230 (A)	$[C_{13}H_{18}N_3O_3S]^+Cl^-$	CHN
24	CH_3SO_2N[e]	1	H	CH_3	H	H	80	257–260 (A)	$C_{13}H_{17}N_3O_3S$[e]	CHN
15	CH_3SO_2NH	1	H	CH_2CH_3	H	H	81	188–189 (A)	$[C_{14}H_{20}N_3O_3S]^+Cl^-$	CHN
16	CH_3SO_2NH	1	H	$CH(CH_3)_2$	H	H	82	187–190 (A)	$[C_{15}H_{22}N_3O_3S]^+Cl^-$	CHN
17	CH_3SO_2NH	1	H	$(CH_2)_6CH_3$	H	H	66	*d*	$[C_{19}H_{30}N_3O_3S]^+$ $H_2PO_4\cdot 0.5H_2O$	CHNSP
18	CH_3SO_2NH	1	CH_3	CH_3	H	H	83	223.5–225 (B)	$[C_{14}H_{20}N_3O_3S]^+Cl^-$	CHN
19	CH_3SO_2NH	1	CH_3	CH_3	CH_3	CH_3	83	244–247 (A)	$[C_{16}H_{24}N_3O_3S]^+Cl^-$	CHN
20	$CH_3CH_2SO_2NH$	1	H	CH_3	H	H	66	143.5–145.5 (C)	$[C_{14}H_{20}N_3O_3S]^+Cl^-$	CHN
21	CF_3SO_2N[e]	1	H	CH_3	H	H	35	240–242 (A)	$C_{13}H_{14}F_3N_3O_3S$[e]	CHN
22	CH_3SO_2NH	2	H	CH_3	H	H	70	*d*	$[C_{14}H_{20}N_3O_3S]^+Cl^-\cdot 0.6C_2H_5OH$	CHNSCl
23	H	1	H	CH_3	H	H	87	195–198 (A)	$[C_{12}H_{15}N_2O]^+Br^-$	CHN

[a] All compounds are optically inactive or racemic unless otherwise indicated. [b] Recrystallization solvent: A = EtOH, B = 95% aqueous isopropyl alcohol, C = 95% aqueous EtOH. [c] Elemental analyses are within ±0.4% of the calculated values. [d] Isolated as a white foam. [e] Zwitterion.

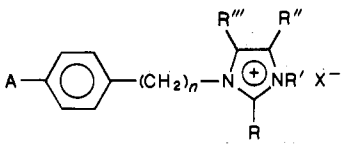
hydroxy imidazolium salts **3**, **15–23**. Zwitterion **24** was prepared by passing hydroxy imidazolium salt **3** through a hydroxide ion-exchange column.

In order to investigate if there was any enantioselectivity in the electrophysiological activity of **3**, the enantiomers (+)-**3** and (−)-**3** were synthesized as depicted in Scheme II. Catalytic hydrogenation of keto imidazole **25**[12] in aqueous hydrochloric acid gave hydroxy imidazole **26a** as the hydrochloride salt in good yield. The free base of **26a**, prepared by treatment of the hydrochloride salt with methanolic sodium methoxide, was treated with (+)- and (−)-camphorsulfonic acid in aqueous ethanol and gave the enantiomeric camphorsulfonates (+)-**27** and (−)-**27**, respectively. A single-crystal X-ray analysis of camphorsulfonate (−)-**27** unambiguously determined its structure[13] (Figure 1). The enantiomeric hydroxy imidazolium chlorides (*R*)-(−)-**3** and (*S*)-(+)-**3**[14] were prepared from the (+)-**27** and (−)-**27** camphorsulfonates, respectively, by treatment with methanolic sodium methoxide, heating the resulting free base with methyl iodide in methanol, and subsequent anion exchange. The synthetic routes to imidazolium salts **31** and **33** are depicted in Scheme III. Catalytic reduction (H_2/Pd–C) of nitro imidazole **29**[15] followed by methanesulfonylation using mesyl chloride in cold triethylamine/methylene chloride afforded methanesulfonamide **30** in good overall yield. Heating **30** with methyl iodide in methanol gave imidazolium salt **31**.

Amino alcohol **32**[16] was treated with 2.05 equiv of mesyl chloride in cold pyridine and afforded the dimethane-

(11) Breitner, E.; Roginski, E.; Rylander, P. N. *J. Org. Chem.* **1959**, *24*, 1855.
(12) Nardi, D.; Tajana, A.; Leonardi, A.; Pennini, R.; Portioli, F.; Magistretti, M. J.; Subissi, A. *J. Med. Chem.* **1981**, *24*, 727.
(13) We thank Dr. Cynthia Day of Crystalytics Co., Lincoln, NE, for performing the X-ray structure determination of (−)-**27**.
(14) The enantiomeric excess of (*S*)-(+)-**3** and (*R*)-(−)-**3** was determined by subjecting their corresponding (*S*)-(−)-α-methylbenzyl carbamates (prepared by treating (*S*)-(+)-**28** and (*R*)-(−)-**28** with (*S*)-(−)-α-methylbenzyl isocyanate in 1-methyl-2-pyrrolidinone) to HPLC analysis. (*S*)-(−)-α-Methylbenzyl isocyanate (Aldrich Chemical Co., Lot #7717EK, $[\alpha]_D$ −90° (*c* = neat)) was also assayed for its enantiomeric purity according to the method of Gat et al. (*Drug Metab. Dispos.* **1981**, *9*, 557) with (−)-menthol as the chiral alcohol. By this method, both (*S*)-(+)-**3** and (*R*)-(−)-**3** were at least 98% ee.
(15) Kabara, J. J.; Vrable, R.; Baggaley, K. H. *Artery* **1977**, *3*, 489.
(16) Oki, M.; Iwamura, H. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 1135.

Table III. 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]alkyl]-1*H*-imidazolium Salts **31** and **33**



no.	A	*n*	R	R′	R″	R‴	yield, %	mp,[a] °C (solv)	formula	anal.[b]
31	CH_3SO_2NH	2	H	CH_3	H	H	48	163–165 (A)	$[C_{13}H_{18}N_3O_2S]^+I^-$	CHN
33	CH_3SO_2NH	3	H	CH_3	H	H	41	199–202 (B)	$[C_{14}H_{20}N_3O_2S]^+H_2PO_4^-$	CHN

[a] Recrystallization solvent: A = methanol, B = 95% aqueous ethanol. [b] Elemental analyses are within ±0.4% of the calculated values.

Table IV. Effects of Various 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium Salts, Related Compounds, and the Standards Clofilium (1) and Sotalol (2) on Action Potential Characteristics of Isolated Canine Cardiac Purkinje Fibers and Refractory Period of Isolated Canine Cardiac Ventricular Muscle

	Purkinje fiber[a,c]			ventricular muscle fiber[b,c]		
compound[i]	*n*[j]	$C_{20}APD_{95}$[d] μM	maxΔAPD_{95} (concn, μM)[e]	*n*[j]	$C_{20}FRP$,[f] μM	maxΔFRP (concn, μM)[g]
clofilium (1)	6	0.26 (0.08–0.82)[p]	39 ± 8% (10)	3	NR[h]	7 ± 9% (100)
sotalol (**2**)	6	14.4 (11.2–18.6)	48 ± 3% (100)	3	24.7 (3.7–162)	23 ± 4% (100)
3	4	1.6 (1.3–1.9)	50 ± 5% (100)	8	5.9 (2.3–15.2)	31 ± 4% (100)
(*S*)-(+)-**3**	2	0.7, 0.6	74%, 80% (100)	4	7.5 (1.2–48.0)	31 ± 8% (100)
(*R*)-(−)-**3**	2	0.3, 0.9	58%, 65% (100)	4	14.0 (4.0–47.0)	25 ± 4% (100)
24	2	0.6, 1.5	55% (100), 47% (10)	1	8.7	24% (100)
5[q]	2	2.3,[o] 2.9	38%, 46% (10)	1	NR[h,r]	15% (100)
6	2	49.4,[s] NR[h]	26%, 19% (100)	2	28.2, 17.2	26%, 27% (100)
7	1	NR[h,n,t]	min[k]	1	NR[h]	14% (100)
8	2	9.0,[o] 25.1	21% (10), 40% (100)	1	NR[h,u]	14% (100)
9	2	24.8, 6.2	33%, 43% (100)	2	14.7, NR[h]	32%, 14% (100)
10	2	NR,[h] NR[h]	min[k]	2	15.8, 100	26%, 20% (100)
11	2	29.0, 35.4[w]	33%, 30% (100)	1	40.0	26% (100)
12	1	NR[h]	min[k]	1	NR[h]	min[l]
13	2	38.3, 25.6	26%, 29% (100)	1	17.8	29% (100)
14	2	(−) 69.0, (−) 52.0	NA[m]	1	NR[h]	min[l]
15	3	6.2 (0.9–40.7)	65 ± 12% (100)	1	28.2	26% (100)
16	1	NR[h]	min[k]	1	NR[h]	17% (100)
17	2	2.8, 1.0	50%, 84% (100)	1	9.0	24% (100)
18	2	0.8, 0.2	51% (10), 110% (100)	2	0.2, 0.6	44% (10) 56% (100)
19	3	NR,[h,y] 1.3, 1.6[z]	13%, 64%, 58% (100)	2	2.5, 14.1	29%, 29% (100)
20	2	30.0, 8.9	27%, 35% (100)	2	14.5, 11.7	27%, 32% (100)
21	1	NR[h]	min[k]	1	NR[h]	min[l]
22	1	NR[h]	min[k]	1	100[v]	20% (100)
23	2	NR,[h] NR[h]	12%, 14% (100)	1	50	22% (100)
31	4	2.6 (0.6–11.2)	45 ± 14% (100)	1	10.0	24% (100)
33	4	7.2 (0.9–46)	47 ± 12% (100)	1	NR[h]	13% (100)

[a] The change in the rate of rise of phase 0 of the action potential (V_{max}) was less than 10% unless otherwise noted. [b] The change in conduction time (CT) was less than 10% unless otherwise noted. [c] Dose range 0.1–100 μM unless otherwise noted. [d] The concentration of drug (in micromoles) that causes a 20% increase (+) or decrease (−) in APD_{95} (action potential duration at 95% repolarization) from control value, when $n > 2$, log mean and 90% confidence interval reported. [e] The maximum observed change in APD_{95} from control value and concentration (in micromoles) where this occurred. [f] The concentration of drug (in micromolar units) which causes a 20% increase (+) or decrease (−) in the functional refractory period from control value, when $n > 2$, log mean and 90% confidence interval reported. [g] The maximum change from control in functional refractory period that was observed (frequency of 1.0 Hz) and the concentration at which this effect was observed. [h] NR = never reached. [i] Compounds are optically inactive or racemic unless otherwise noted. [j] Number of experiments. [k] Minimal effects on APD_{95} observed at the concentrations studied. [l] Minimal effects on FRP observed at the concentrations studied. [m] NA = not available. [n] A 20% decrease in V_{max} observed at 63.0 μM. [o] Dose range 0.1–10 μM. [p] Dose range 0.01–10 μM. [q] Tested as the bromide salt. [r] A 20% decrease in CT was observed at 100 μM. [s] A 16% decrease in V_{max} was observed at 100 μM. [t] A 23% increase in V_{max} was observed at 100 μM. [u] Variable effects in CT were observed over the dose range. [v] A 14% decrease in CT was observed at 100 μM. [w] Variable effects in V_{max} were observed over the dose range. [x] A 27% decrease in V_{max} was observed at 100 μM. [y] A very long control APD_{95} (475 ms) was observed in this experiment. [z] A 28% decrease in V_{max} was observed at 100 μM.

sulfonate in excellent yield. Heating this product with 1-methylimidazole in acetonitrile followed by anion exchange afforded imidazolium salt **33**.

Pharmacology

The initial screening for electrophysiological activity was carried out in two in vitro systems, an intracellular screen using canine cardiac Purkinje fibers and an extracellular screen using canine ventricular muscle tissue.

In the intracellular screen the action potential characteristics of canine cardiac Purkinje fibers were recorded by using standard microelectrode recording techniques.[17]

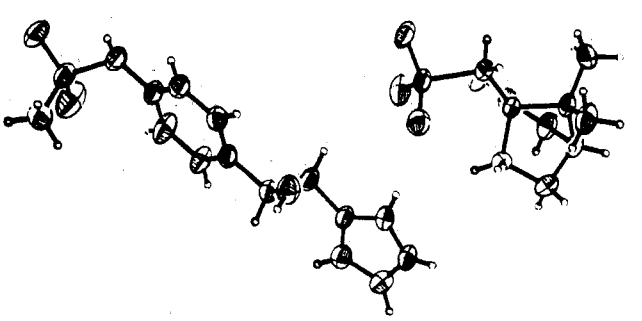


Figure 1. ORTEP view of camphorsulfonate (−)-**27**.

For a compound to be considered active as a class III agent in this model, it must prolong the action potential duration

(17) Davis, L. D.; Temte, J. V. *Circ. Res.* **1969**, *24*, 639.

Table V. In Vivo Test Results for Clofilium (1), Sotalol (2), and Selected Imidazolium Salts

	intraduodenal activity				antiarrhythmic efficacy (PES model)					
compound[a]	n[b]	active dose,[c] mg/kg, id	HR[d]	BP[e]	n[b]	number effective	dose range, mg/kg, iv	mean effective dose,[h] mg/kg, iv	HR[d]	BP[e]
clofilium (1)	3	10	−18 ± 7	−4 ± 8	10	7	0.1–10	0.63 ± 0.40	−12 ± 7	2 ± 5
sotalol (2)	7	10	−11 ± 1	8 ± 8	10	3	0.1–30	1.4 ± 0.8	−23 ± 14	−23 ± 21
3[f]	3	10	−10 ± 4	5 ± 3	3	2	0.3–10	6.5 ± 3.5	−23 ± 6	0 ± 0
5[g]	2	30	−19 ± 1	3 ± 3	3	0	0.3–30			
13	2	10	−2 ± 3	6 ± 4						
17	2	10	−10 ± 1	6 ± 5						
18	2	10	−20 ± 6	3 ± 1	3	0	0.3–30			
19	2	10	−12 ± 3	19 ± 11						
31	2	30	−13 ± 1	3 ± 6	2	2	1.0–10	6.5 ± 3.5	NR[i]	+13 ± 6

[a] All compounds are optically inactive or racemic unless otherwise noted. [b] Number of experiments. [c] FRP ≥ 12% from control. [d] Percent change in heart rate at active or effective dose (mean ± SEM). [e] Percent change in blood pressure at active or effective dose (mean ± SEM). [f] Tested as the iodide salt. [g] Tested as the bromide salt. [h] Mean ± SE. [i] NR = not recorded.

at 95% repolarization (APD_{95}) by at least 20% with minimal effects on the rate of rise of phase 0 of the action potential ($\dot{V}_{max}$). In Table IV, we report the concentration of drug that causes a 20% increase in APD_{95} ($C_{20}APD_{95}$), the maximum observed increase in APD_{95} ($max\Delta APD_{95}$), the effects on $\dot{V}_{max}$, and the dose range studied.

In the extracellular screen, conduction interval curves were determined on isolated pieces of ventricular muscle tissue. This in vitro method was developed at Berlex and is an adaptation of the method of Carson and Dresel used in whole animals.[18] An active compound in the extracellular screen must prolong the functional refractory period (FRP) by 20% with minimal effects on conduction time (CT). In Table IV, we report the concentration of drug that causes a 20% increase in FRP ($C_{20}FRP$), the maximum observed increase in FRP ($max\Delta FRP$), the effects on CT, and the dose range studied.

Changes in $\dot{V}_{max}$ or CT of ≤10% from control were considered minimal (no class I activity). The majority of the compounds tested (Table IV) showed little effect on both of these parameters and are therefore considered selective class III agents.[2] Some compounds did show variable changes or significant changes (>10% from control) at high doses (i.e., 100 μM) on $\dot{V}_{max}$ or CT and these are shown in Table IV.

Our screening strategy was to perform duplicate experiments in canine cardiac Purkinje fiber in order to access electrophysiological activity. Ventricular muscle tissue was used as a secondary in vitro screen. Compounds that were considered active (vide supra) below ca. 10 μM in one of these screens were usually evaluated for intraduodenal activity in anesthetized mongrel dogs (Table V). For a compound to be considered intraduodenally active it must have prolonged the cardiac functional refractory period (FRP) by at least 12% in two of three animals.

Some of the intraduodenally active compounds were then examined for efficacy in a programmed electrical stimulation (PES) model.[19] This model is similar to that used to determine the most effective antiarrhythmic agent for use in certain clinical subjects.[20] In this model, mongrel dogs were subjected to ligation of the left anterior descending coronary artery according to the method of Harris.[21] After a 24-h recovery period, the animals were anesthesized and their chests reopened, and recording and stimulating electrodes were attached to the myocardium. Before administration of the test compound, the animals were subjected to a PES protocol to induce either sustained ventricular tachycardia (SVT) or ventricular fibrillation (VF). SVT was terminated by burst pacing and VF was terminated by DC cardioversion. After demonstrating the reproducibility of the induced arrhythmia, the test compound was administered and the stimulation protocol was repeated. A compound was considered effective if SVT or VF could not be reinduced in two of three animals. The results of the PES efficacy studies are listed in Table V.

Table VI. β-Adrenergic Receptor Binding Activity

compound	IC_{50},[a] μM
3	2350 ± 1020
sotalol (2)	7.2 ± 1.5
propranolol	0.004 ± 0.001

[a] IC_{50} values represent the concentration that is effective in displacing [^{3}H]dihydroalprenolol from canine ventricular tissue and are expressed as mean ± SEM from at least six experiments.

Results and Discussion

Both intracellular (canine cardiac Purkinje fibers) and extracellular (canine ventricular muscle tissue) electrophysiology screens were used for primary in vitro evaluation (Table IV). The standards clofilium (1) and sotalol (2) were also tested by this protocol for comparison of relative electrophysiological properties.

The electrophysiological effects in Purkinje fiber complemented those in ventricular muscle fiber for most compounds tested. Compounds tested in Purkinje fiber ($n \geq 2$) showed little variability in results. A difference of factor of ca. 5 between compounds was taken as evidence of greater or lesser potency. Greater variability was observed in the ventricular muscle screen ($n > 2$). Up to a 10-fold difference in potency was observed for a given compound by this protocol. A difference of a factor of >10 between compounds was, therefore, taken to assess greater or lesser potency in this screen. No differences were observed in the effects on the refractory period and the action potential characteristics between **3**, its zwitterion **24**, or enantiomers (*S*)-(+)-**3** and (*R*)-(−)-**3**[22] (Table IV).

The electrophysiological effects of **3**, **5**, **13**, **17–19**, and **31** were investigated following intraduodenal administration (Table V). All of these compounds showed intra-

(18) Carson, D. L.; Dresel, P. F. *J. Cardiovasc. Pharmacol.* **1981**, *3*, 924.
(19) Scherlag, B. J.; Kabell, G.; Brachmann, J., Harrison, L.; Lazzara, R. *Am. J. Cardiol.* **1983**, *51*, 207.
(20) Horowitz, L. N.; Spielman, S. R.; Greenspan, A. M.; Josephson, M. E. *Am. Heart J.* **1982**, *103*, 604.
(21) Harris, A. S. *Circulation* **1950**, *1*, 1318.

(22) Compounds **3**, (*S*)-(+)-**3**, and (*R*)-(−)-**3** were tested with use of Purkinje fibers and ventricular muscle fibers from the same dog's heart in each case.

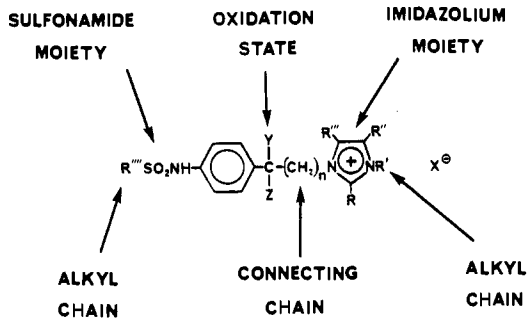


Figure 2.

duodenal activity similar to that of clofilium and sotalol.

Compounds **3**, **5**, **18**, and **31**, which showed class III electrophysiologic activity at a dose of 10 or 30 mg/kg (id), were selected for further studies in in vivo models. Both **3** and **31** were found to be ca. 10 times less potent than clofilium but more efficacious than sotalol at suppressing ventricular tachycardia in anesthetized infarcted dogs.

To determine potential β-blocking activity, compound **3** was examined for its ability to displace the β-receptor antagonist [^{3}H]dihydroalprenolol from canine cardiac tissue (Table VI). Sotalol (**2**) and propranolol were also used as standards in this assay. These results clearly demonstrate that replacement of the isopropylamino group of sotalol with an imidazolium moiety leads to a compound (**3**) with reduced affinity for β-receptors.

Structure–activity relationships (SAR) within this series of compounds[23] were established through variation of six parameters (Figure 2): (1) the influence of the alkyl chain of the sulfonamide moiety, (2) the sulfonamide moiety itself, (3) the oxidation state of the benzylic carbon, (4) the connecting chain length between the aromatic ring and the imidazolium moiety, (5) substitution on the imidazolium moiety, and (6) the alkyl chain on the imidazolium moiety.

Alkyl Chain on Sulfonamide. Replacing the methyl group with the electronegative trifluoromethyl group (analogues **12** and **21**) resulted in inactive compounds. Also replacing the alkyl group from methyl to ethyl leads to less potent analogues (i.e., **3** and **20**; **5** and **11**).

Sulfonamide Moiety. The inactivity of compounds **14** and **23** indicates that the sulfonamide group is essential for activity.

Oxidation State. The in vitro (Purkinje fiber) data demonstrate a general trend that the secondary alcohols are more potent than their keto precursors. Possible exceptions are compounds **20** vs. **11**, **3** vs. **5**, and **22** vs. **13**. In vivo results also support this trend. Alcohol **3** and analogue **31** were effective in the prevention of ventricular tachycardia in anesthetized infarcted dogs (PES model) while keto analogue **5** was ineffective. Compounds **3**, **31**, and **5** also showed comparable activity in the Purkinje fiber screen.

Connecting Chain. Examination of compound pairs **3**, **22** and **5**, **13**, which differ only by the length of their connecting chain, indicates that the two-carbon chain in each case is more active than the corresponding three-carbon analogue. Compounds **31** and **33**, however, show comparable activity in the Purkinje fiber screen.

Substitution on the Imidazolium Moiety. Compounds **9** and **18**, with two methyl groups on the imidazolium moiety, show comparable activity to the corresponding analogues (**5** and **3**) with one methyl group. Although analogue **18** was found to be intraduodenally active, it was ineffective in our PES model. Complete substitution of the imidazolium moiety with methyl groups afford compounds (**10** and **19**) with no clear-cut differences from the other compounds in this series.

Alkyl Chain on Imidazolium Moiety. Increasing the lipophilicity and the steric bulk of the alkyl group on the imidazolium moiety results in inactive compounds **7** and **16**. Increasing the chain length to a heptyl group affords compounds (**8** and **17**) that have comparable activity to that of **5** and **3**.

Conclusions

We have shown that various novel 3-alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium salts possess potent class III electrophysiological activity in our in vitro screens. A number of these compounds also showed intraduodenal activity in anesthetized mongrel dogs (10 or 30 mg/kg, id). Both **3** and **31** were also effective in our PES model in preventing ventricular tachycardia in anesthetized infarcted dogs (3, 10 mg/kg, iv). Further investigation of these compounds is warranted.

Experimental Section

Chemistry. Proton nuclear magnetic resonance (NMR) spectra were taken at either 60 MHz (Varian EM-360) or 300 MHz (Varian XL-300) as indicated. Chemical shifts are reported in parts per million (δ) downfield from an internal standard of tetramethylsilane (Me_4Si) for $CDCl_3$, Me_2SO-d_6, and CF_3COOD or sodium 3-(trimethylsilyl)propionate (TSP) for D_2O. Infrared (IR) spectra were taken on a Sargent-Welch 3-300 or a Beckman Acculab 2 spectrophotometer as a KBr pellet or as a Nujol mull as indicated. Elemental analyses were performed by the analytical department of Berlex Laboratories, Inc., Galbraith Laboratories, Inc., Knoxville, TN, or Microlit Laboratories, Inc., Caldwell, NJ. Optical rotations ($[\alpha]_D$) were obtained on a Perkin-Elmer 241 variable-wavelength polarimeter. Circular dichroism spectra were measured with a JASCO J500A instrument at room temperature. Melting points were obtained on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Woelm silica gel (63–200 mesh) and Fisher alumina (neutral, activity III) were used for column chromatography.

***N*-[4-(2-Chloro-1-oxoethyl)phenyl]methanesulfonamide (4a).** To a well-stirred solution of *N*-phenylmethanesulfonamide[24] (128.4 g, 0.75 mol) and chloroacetyl chloride (169.5 g, 1.50 mol) in 1 L of methylene chloride at ca. −10 °C under nitrogen was added aluminum chloride (300.0 g, 2.25 mol) in three equal portions. The resulting tan to dark brown mixture was stirred for 2 h at ca. −10 °C, then warmed to room temperature, and stirred for an additional 5 h. The reaction mixture was quenched by pouring it onto 2 kg of ice containing 600 mL of concentrated hydrochloride acid. The resulting precipitate was collected and washed with methanol (3 × 300 mL). Drying in vacuo at 80 °C overnight gave 173.6 g (93%) of **4a** as white crystals: mp 197.5–199 °C; IR (KBr) 3275, 1690, 1600, 1330, 1255, 1220, 970 cm^{-1}; NMR (60 MHz, Me_2SO-d_6) δ 3.16 (s, 3), 5.15 (s, 2) 7.40 (d, 2, J = 8.5 Hz), 8.06 (d, 2, J = 8.5 Hz), 10.48 (br s, 1).

Compounds **4b**, **4c**, and **4d** were prepared in a similar manner in 88%, 31%, and 91% yield, respectively.

4b: mp 157–159 °C (EtOH); IR (KBr) 3250, 2985, 2945, 1690, 1660, 1335 cm^{-1}; NMR (300 MHz, Me_2SO-d_6) δ 1.21 (t, 3), 3.23 (quar, 2), 5.13 (s, 2), 7.32 (d, 2), 7.98 (d, 2), 10.25 (br s, 1). Anal. ($C_{10}H_{12}ClNO_3S$) C, H, N.

4c: mp 148–150 °C; IR (Nujol) 3180, 1685, 1660, 1415 cm^{-1}; NMR (300 MHz, Me_2SO-d_6) δ ca. 4.0 (br s, 1), 5.16 (s, 2), 7.37 (d, 2), 7.99 (d, 2). Anal. ($C_9H_7ClF_3NO_3S$) C, H, N.

4d: mp 156–158 °C (MeOH + H_2O, 4 + 1); IR (Nujol) 3240, 1670, 1660, 1595, 1330 cm^{-1}; NMR (60 MHz, Me_2SO-d_6) δ 3.10 (s, 3), 3.47 (m, 2), 3.90 (m, 2), 7.23 (d, 2), 7.90 (d, 2), 10.18 (br s,

(23) The SAR follows from the test results of the in vitro canine cardiac Purkinje fiber screen.

(24) Marvel, C. S.; Melfrick, M. D.; Belsley, J. P. *J. Am. Chem. Soc.* **1929**, *51*, 1272.

1). Anal. ($C_{10}H_{12}ClNO_3S$) C, H, N.

3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-oxoalkyl]-1*H*-imidazolium Halides 5–13. General Method. 3-Methyl-1-[2-[4-[(methylsulfonyl)amino]phenyl]-2-oxoethyl]-1*H*-imidazolium Chloride (5). A 5-L, four-necked, round-bottom flask was equipped with a mechanical stirrer, thermometer, and condenser and charged with chloro ketone **4a** (160.0 g, 0.646 mol) and 2.1 L of acetonitrile. To this slurry was added 1-methylimidazole (55.7 g, 0.678 mol) and the resulting mixture refluxed for 17 h. After the mixture was cooled to room temperature, the white to tan solid was collected, washed with 2 L of acetonitrile, and air-dried. Recrystallization from 75% aqueous ethanol (0.1 g/mL) gave 157.3 g (84%) of **5** as white crystals: mp 257–261 °C; IR (KBr) 3400, 3090, 2920, 2850, 1690, 1605, 1330, 1240, 1175, 1150, 985, 925, 835 cm^{-1}; NMR (300 MHz, Me_2SO-d_6) δ 3.14 (s, 3), 3.95 (s, 3), 5.98 (s, 2), 7.36 (d, 2, J = 8.8 Hz), 7.69 (t, 1, J = 1.8 Hz), 7.76 (t, 1, J = 1.8 Hz), 8.02 (d, 2, J = 8.8 Hz), 9.06 (s, 1), 10.66 (br s, 1).

Compounds **6–13** were prepared in a similar manner. Compound **14** was prepared by the method of Bolkelheide and Fedoruk.[10]

3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium Halides 3, 15–23. General Method. (±)-1-[2-Hydroxy-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-3-methyl-1*H*-imidazolium Chloride (3). A 2-L Parr bottle was charged with keto imidazolium salt **5** (152.3 g, 0.463 mol), 7.62 g of 10% palladium on activated carbon, and 1.1 L of distilled water. The mixture was hydrogenated at ca. 50 psi for 5 h at room temperature. The catalyst was collected by filtration through 50 g of Celite and washed with 250 mL of distilled water. The filtrate was concentrated in vacuo to give white crystals. Recrystallization from absolute ethanol afforded 121.0 g (78%) of **3**: mp 206–207 °C; IR (Nujol) 3350 (br), 1610, 1560, 1505, 1330, 1150, 1085, 950 cm^{-1}; NMR (300 MHz, Me_2SO-d_6) δ 2.98 (s, 3), 3.87 (s, 3), 4.22 (dd, 1, J = 8.6, 13.7 Hz), 4.42 (dd, 1, J = 3.1, 13.7 Hz), 4.89 (ddd, 1, J = 3.1, 4.7, 8.6 Hz), 6.10 (d, 1, J = 4.7 Hz), 7.23 (d, 2, J = 8.5 Hz), 7.37 (d, 2, J = 8.5 Hz), 7.69 (t, 1, J = 1.7 Hz), 7.72 (t, 1, J = 1.7 Hz), 9.16 (s, 1), 9.84 (s, 1).

Compounds **15–23** were prepared in a similar manner.

(±)-1-[2-Hydroxy-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-3-methyl-1*H*-imidazolium Hydroxide Inner Salt (24). A solution of 2.0 g (6.03 mmol) of **3** in 10 mL of water was passed through 50 g of hydroxide ion exchange resin (Bio-Rad, AG 1-X8, 20–50 mesh). Fractions were collected with a pH > 8 and combined and concentrated in vacuo to give 1.42 g (80%) of zwitterion **24**, which was recrystallized from ethanol: mp 257–260 °C; IR (Nujol) 3200, 1605, 1570, 1310, 1290, 1270, 1230, 1180, 1100, 940, 840 cm^{-1}; NMR (300 MHz, Me_2SO-d_6) δ 3.29 (s, 3), 3.85 (s, 3), 4.17 (dd, 1, J = 8.5, 12.0 Hz), 4.29 (dd, 1, J = 3.4, 12.0 Hz) 4.69 (br dd, 1, J = 3.4, 8.5 Hz), 5.62 (br s, 1), 6.78 (d, 2, J = 8.5 Hz), 6.97 (d, 2, J = 8.5 Hz), 7.65 (s, 1), 7.67 (s, 1), 9.04 (s, 1).

(±)-*N*-[4-[1-Hydroxy-2-(1*H*-imidazol-1-yl)ethyl]phenyl]methanesulfonamide Hydrochloride (26a). A 2-L Parr bottle was charged with *N*-[4-[2-(1*H*-imidazol-1-yl)-1-oxoethyl]-phenyl]methanesulfonamide (**25**)[12] (31.2 g, 112 mmol), 3.12 g of 10% palladium on activated carbon, and 12 N hydrochloric acid (9.32 mL, 112 mmol) in 850 mL of distilled water. The mixture was hydrogenated at ca. 50 psi for 24 h at room temperature. The catalyst was collected by filtration through 25 g of Celite and washed with 100 mL of water. Concentrating the filtrate at reduced pressure afforded crystals, which were recrystallized from absolute ethanol. This gave 32.1 g (90%) of **26a** as white crystals: mp 158–160 °C; IR (Nujol) 3500, 3330, 2600, 1605, 1570, 1535, 1505, 1320, 1280, 1215, 1195, 1135, 1070, 1025, 1000, 950, 900, 820, 730 cm^{-1}; NMR (60 MHz, CF_3COOD) δ 3.25 (s, 3), 4.55–4.90 (m, 2), 5.20–5.50 (m, 1), 7.51 (s, 6), 8.71 (s, 1). Anal. ($C_{12}H_{15}N_3O_3S$·HCl) C, H, N, S, Cl.

(+)-*N*-[4-[1-Hydroxy-2-(1*H*-imidazol-1-yl)ethyl]phenyl]methanesulfonamide *d*-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic Acid Salt ((+)-27). To a slurry of hydroxy imidazole **26a** (31.8 g, 100 mmol) in 100 mL of methanol at room temperature was added sodium methoxide (5.41 g, 100 mmol), and the solution was stirred for 17 h. The solution was filtered and the filtrate concentrated in vacuo to give crystals. Recrystallization from absolute ethanol afforded 25.7 g (91%) of **26b** as white crystals: mp 158–160 °C; IR (Nujol) 3200, 1615, 1595, 1505, 1325, 1150, 1080, 850 cm^{-1}; NMR (300 MHz, Me_2SO-d_6) δ 2.96 (s, 3), 4.04 (dd, 1, J = 8.2, 13.4 Hz), 4.15 (dd, 1, J = 3.9, 13.4 Hz), 4.79 (dd, 1, J = 3.9, 8.2 Hz), 5.60 (br s, 1), 6.92 (s, 1), 7.16 (d, 2, J = 7.6 Hz), 7.17 (s, 1), 7.29 (d, 2, J = 7.6 Hz), 7.66 (s, 1), 9.74 (s, 1). Anal. ($C_{12}H_{15}N_3O_3S$·0.5H_2O) C, H, N, S. To a solution of hydroxy imidazole **26b** (27.3 g, 94.0 mmol) in 200 mL of ethanol and 200 mL of water was added (+)-*d*-camphorsulfonic acid (21.84 g, 94.0 mmol) in one portion. The mixture was stirred until homogeneous and then concentrated in vacuo, and the residue was recrystallized from methanol to give 20.8 g of crystals. Three more recrystallizations from 95% aqueous methanol, 90% aqueous methanol, and 80% aqueous methanol, respectively, gave 14.56 g of (+)-**27** as white flakes: mp 247–249 °C; $[\alpha]_D$ +14.9° (c 1.95, 2 N aqueous NaOH); IR (Nujol) 3400 (br), 3190, 3120, 2700 (br), 1730, 1585, 1560, 1520, 1380, 1155, 770 cm^{-1}; NMR (300 MHz, Me_2SO-d_6) δ 0.75 (s, 3), 1.05 (s, 3), 1.26–1.29 (m, 2), 1.83–1.93 (m, 2), 1.97 (m, 1), 2.20 (m, 1), 2.39 (d, 1, J = 14.7 Hz), 2.61 (m, 1), 2.87 (d, 1, J = 14.7 Hz), 2.98 (s, 3), 4.25 (dd, 1, J = 8.3, 13.5 Hz), 4.42 (dd, 1 J = 3.5, 13.5 Hz), 4.92 (br dd, 1, J = 3.4, 8.3 Hz), 5.92 (br s, 1), 7.20 (d, 2, J = 8.3 Hz), 7.35 (d, 2, J = 8.3 Hz), 7.65 (s, 1), 7.70 (s, 1), 9.02 (s, 1), 9.77 (s, 1), 14.30 (br s, 1). Anal. ($C_{12}H_{15}N_3O_3S·C_{10}H_{16}O_4S$) C, H, N.

The enantiomeric salt (−)-**27** was produced in a similar fashion with (−)-*l*-camphorsulfonic acid: $[\alpha]_D$ −14.9° (c 1.95, 2 N aqueous NaOH); the melting point, IR, NMR, and TLC behavior were identical with those of the (+) enantiomeric salt. Anal. ($C_{12}H_{15}N_3O_3S·C_{10}H_{16}O_4S$) C, H, N.

Single-Crystal X-ray Analysis of (−)-27. The crystal of (−)-**27** produced above were recrystallized from 80% aqueous methanol to provide crystals for the X-ray study: mp 247–249 °C. The crystals were monoclinic and of the space group $P2_1$–C_2^2 in cell dimensions a = 7.491 (2) Å, b = 9.398 (3) Å, c = 17.211 (6) Å, α = 90.00°, β = 91.54 (2)°, γ = 90.00°, V = 1211.3 (7) Å^3, and ρ_{calcd} = 1.408 g cm^{-3} for Z = 2. A computer-controlled Four-Circle Nicolet autodiffractometer equipped with Cu K_α radiation (λ = 1.54184 Å) was used to measure 2366 unique reflections with 2θ > 84°. Of these 2285 were observed ($I > 3\sigma(I)$) and corrected for Lorentz and polarization effects. The structure was solved by using the SHELXTL Direct Methods programs and refined by using a cascade-block diagonal-matrix least-squares procedure. The function minimization was $\sum\omega(|F_0| - |F_c|)^2$ with = $1/(\sigma F_0)^2$ to give an unweighted residual value of $R(F)$ = 0.034 and a weighted residual value of $R_w(F)$ = 0.043. Tables I–VI in the supplementary material contain the final fractional coordinates, temperature parameters, bond distances, and bond angles.

(*R*)-(−)-*N*-[4-[1-Hydroxy-2-(1*H*-imidazol-1-yl)ethyl]phenyl]methanesulfonamide ((*R*)-(−)-28). To a suspension of salt (+)-**27** (14.3 g, 27.8 mmol) in 60 mL of methanol was added sodium methoxide (1.50 g, 27.8 mmol). The mixture was heated until dissolved, cooled to room temperature, and chromatographed on 150 g of alumina. Elution with methylene chloride–methanol (4:1) afforded 7.76 g (99%) of (*R*)-(−)-**28** as white crystals: mp 189–191 °C; $[\alpha]_D$ −59.5° (c 1.715, 1 N aqueous HCl); IR (Nujol) 3200, 3120, 1610, 1595, 1505, 1330, 1305, 1150, 1080, 850 cm^{-1}; NMR (300 MHz, Me_2SO-d_6) δ 2.96 (s, 3), 4.00–4.20 (m, 2), 4.80 (m, 1), 5.66 (d, 1, J = 4.7 Hz), 6.82 (s, 1), 7.10 (s, 1), 7.16 (d, 2, J = 8.3 Hz), 7.29 (d, 2, J = 8.3 Hz), 7.47 (s, 1), 9.70 (s, 1). Anal. ($C_{12}H_{15}N_3O_3S$) C, H, N.

(*S*)-(+)-**28** was produced in a similar fashion from (−)-**27**: $[\alpha]_D$ +59.7° (c 1.740, 1 N aqueous HCl); the melting point, IR, NMR, and TLC behavior were identical with those of the (−) enantiomer. Anal. ($C_{12}H_{15}N_3O_3S$) C, H, N.

(*S*)-(+)-1-[2-Hydroxy-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-3-methyl-1*H*-imidazolium Chloride ((*S*)-(+)-3). To a solution of (*S*)-(+)-**28** (5.00 g, 17.7 mmol) in 80 mL of methanol was added methyl iodide (11.02 mL, 177.0 mmol), and the solution was stirred in a pressure bottle at ca. 50 °C for 48 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in 25 mL of water and passed through 300 g of hydroxide ion exchange resin (Bio-Rad, AG 1-X5, 20–50 mesh). Fractions were collected with a pH > 9 and combined and concentrated at reduced pressure to afford crystals of the zwitterion. Filtration of the crystals followed by trituration with hot ethanol (100 mL) afforded 4.20 g (80%) of the zwitterion. This was dissolved in water (100 mL), treated with

1 N aqueous HCl (14.23 mL), and concentrated in vacuo to give crystals. Recrystallization from ethanol gave 4.54 g (77% from (*S*)-(+)-**28**) as white crystals: mp 230–231 °C; $[\alpha]_D$ +55.6° (c 1.78, H_2O); IR (Nujol) 3260 (br), 1605, 1560, 1505, 1330, 1145, 1080, 965, 930, 860 cm^{-1}; NMR (300 MHz, Me_2SO-d_6) δ 2.98 (s, 3), 3.87 (s, 3), 4.21 (dd, 1, *J* = 8.6, 13.7 Hz), 4.41 (dd, 1, *J* = 3.3, 13.7 Hz), 4.89 (ddd, 1, *J* = 3.3, 4.8, 8.6 Hz), 6.06 (d, 1, *J* = 4.8 Hz), 7.22 (d, 2, *J* = 8.5 Hz), 7.36 (d, 2, *J* = 8.5 Hz), 7.68 (t, 1, *J* = 1.7 Hz), 7.70 (t, 1, *J* = 1.7 Hz), 9.13 (s, 1), 9.83 (s, 1); CD(CH_3OH) λ 276 nm, $\Delta\epsilon$ = +0.143, λ 230 nm, $\Delta\epsilon$ = +3.2.

(*R*)-(−)-**3** was prepared in a similar fashion from (*R*)-(−)-**28**: $[\alpha]_D$ −55.9° (*c* 1.77, H_2O); CD(CH_3OH) λ 276 nm, $\Delta\epsilon$ = −0.166; λ 230 nm, $\Delta\epsilon$ = −3.4; the melting point IR, NMR, and TLC behavior were identical with those of the (+) enantiomer.

***N*-[4-[2-(1*H*-Imidazol-1-yl)ethyl]phenyl]methanesulfonamide (32).** A Parr bottle was changed with 1-[2-(4-nitrophenyl)ethyl]-1*H*-imidazole[15] (**29**) (18.0 g, 82.9 mmol) and 1.0 g of 10% palladium on activated carbon in 200 mL of ethanol. The mixture was hydrogenated at ca. 50 psi for 1 h at room temperature. The catalyst was collected by filtration and the filtrate concentrated in vacuo to give 15.5 g of the corresponding amine. This amine was dissolved in 150 mL of methylene chloride and 20 mL of triethylamine and cooled to −10 °C as methanesulfonyl chloride (11.0 mL, 142.2 mmol) was added dropwise. The reaction mixture was stirred at −10 °C for 0.5 h and then at room temperature for 1 h. The solution was then extracted with ammonium hydroxide (100 mL) and then water (100 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give crude **30**. Recrystallization from tetrahydrofuran gave 15.0 g (68%) of **30** as white crystals: mp 149–151 °C; IR (Nujol) 3110, 2700, 1610, 1500, 1410, 1325, 1280, 1225, 1145, 1100, 1075, 965, 915, 845, 825, 780, 725 cm^{-1}; NMR (60 MHz, CF_3COOD) δ 3.20 (s, 3), 3.27 (t, 2, *J* = 7.0 Hz), 4.59 (t, 2, *J* = 7.0 Hz), 7.10–7.60 (m, 6), 8.40 (s, 1). Anal. ($C_{12}H_{15}N_3O_2S$) C, H, N.

3-Methyl-1-[2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-1*H*-imidazolium Iodide (31). A mixture of **30** (5.0 g, 18.8 mmol) and methyl iodide (5.0 mL, 80.3 mmol) in 25 mL of methanol was heated in a pressure bottle for 24 h at ca. 75 °C. After cooling to room temperature, the solution was concentrated at reduced pressure and the resulting solid slurried with acetone (100 mL). The crystals were filtered and washed with acetone (100 mL). Recrystallization from methanol afforded 3.7 g (48%) of **31** as white crystals: mp 163–164 °C; IR (Nujol) 3060, 1605, 1570, 1555, 1500, 1390, 1320, 1290, 1215, 1150, 955, 885, 835, 820, 760, 745 cm^{-1}; NMR (300 MHz, D_2O) 3.10 (s, 3), 3.17 (t, 2, *J* = 6.8 Hz), 4.05 (s, 3), 4.47 (t, 2, *J* = 6.8 Hz), 7.19 (d, 2, *J* = 8.7 Hz), 7.24 (d, 2, *J* = 8.7 Hz), 7.37 (s, 1), 7.38 (s, 1), 8.65 (s, 1).

3-Methyl-1-[3-[4-[(methylsulfonyl)amino]phenyl]propyl]-1*H*-imidazolium Dihydrogen Phosphate (33). To a solution of 4-aminobenzenepropanol[16] (**32**) (1.90 g, 12.56 mmol) in 25.0 mL of pyridine at 0 °C under nitrogen was added 1.99 mL (25.76 mmol) of methanesulfonyl chloride. The solution was stirred for 17 h at 0 °C and then poured into 75 mL of cold water. The aqueous solution was extracted with methylene chloride (3 × 100 mL), and the combined organic extracts were washed with cold 5% aqueous hydrochloric acid and dried over sodium sulfate. Concentration at reduced pressure afforded 3.78 g (98%) of the dimethanesulfonate as yellow crystals: mp 101–103 °C; IR (Nujol) 3320, 1615, 1515, 1345, 1225, 1170, 1150, 985, 925, 835 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.06 (m, 2), 2.74 (t, 2, *J* = 7.9 Hz), 3.00 (s, 3), 3.01 (s, 3), 4.23 (t, 2, *J* = 6.2 Hz), 6.57 (br s, 1), 7.18 (s, 4). To a solution of the dimethanesulfonate (7.10 g, 23.1 mmol) in 50 mL of acetonitrile was added 1.93 mL (24.2 mmol) of 1-methylimidazole and the solution heated to reflux for 17 h. After cooling to room temperature, the solution was concentrated in vacuo. To the residue was added 50 mL of water and the resulting solution extracted with methylene chloride (3 × 100 mL). The aqueous extracts were concentrated at reduced pressure, and the residue was chromatographed on 400 g of alumina. Elution with methylene chloride–methanol (9:1) provided 6.2 g of an oil, which was passed through 85 g of hydroxide anion exchange resin (Bio-Rad, AG 1-X8, 20–50 mesh). The basic fractions (pH >8.0) were combined, and the pH was adjusted to 4.5 with 0.2 N phosphoric acid. Concentrating this solution at reduced pressure afforded crystals. Recrystallization from 95% aqueous ethanol gave 3.73 g (41%) of **33** as white crystals: mp 199–202 °C; IR (Nujol) 1590, 1340, 1270, 1165, 940, 870 cm^{-1}; NMR (300 MHz, D_2O) δ 2.24 (m, 2), 2.73 (t, 2, *J* = 7.1 Hz), 3.09 (s, 3), 3.82 (s, 3), 4.23 (t, 2, *J* = 6.6 Hz), 7.21 (d, 2, *J* = 8.5 Hz), 7.25 (d, 2, *J* = 8.5 Hz), 7.34 (s, 1), 7.42 (s, 1), 8.60 (s, 1).

Pharmacology. Intracellular Electrophysiological Profile. Canine cardiac Purkinje fibers (free running false tendons) were anchored in a tissue bath and perfused at a rate of 6 mL/min with modified Tyrode's solution containing the following ions in mmol/L: Na^+, 149.8; K^+, 4.0; Mg^{2+}, 0.5; Ca^{2+}, 2.5; Cl^-, 134.0; $H_2PO_4^-$, 1.8; HCO_3^-, 24.0; and glucose, 5.5). The solution was gassed with a mixture of 95% oxygen–5% carbon dioxide (pH 7.35–7.40) and maintained at 36 ± 0.5 °C. The tissues were stimulated at a control rate of 1.0 Hz through bipolar Teflon-coated platinum electrodes with square wave pulses of 2 ms duration and twice the diastolic threshold current. Intracellular action potentials were recorded with glass microelectrodes (3 M KCl) by using standard recording techniques.[17] Parameters measured were resting membrane potential, threshold current, action potential amplitude, maximum upstroke velocity, and action potential duration at 50% and 95% repolarization. Fibers were stabilized for up to 1 h before control measurements were taken. Test compounds were screened in the range of 10^{-8} to 10^{-3} molar concentrations. Data were collected for each compound after 30 min of exposure to a given concentration. Only one compound was tested per Purkinje fiber preparation, and the appropriate vehicle controls were conducted in every experiment.

Extracellular Electrophysiological Profile. Canine ventricular muscle strips taken from the right ventricle papillary muscle near the base (5–6 mm long × 1–2 mm wide) were mounted on a silicone washer and placed in a 3.5-mL tissue bath. The preparation was continuously superfused with warmed (36 ± 0.5 °C), physiological saline equilibrated with a gas mixture of 95% oxygen–5% carbon dioxide. The preparation was stimulated at one end through bipolar, stainless steel, teflon-coated electrodes (0.005 in.) impaled into the muscle. A bipolar electrogram was recorded at the opposite end of the muscle strip with the same type of bipolar electrodes described above. The output of the electrical signal was amplified and displayed on an oscilloscope. The diastolic threshold (DT) of the muscle preparation was determined with bipolar stimuli 2 ms in duration at a cycle length of 4000 ms. The muscle tissue was then stimulated at 4 times the diastolic threshold for an initial equilibration period of 60 min. The functional refractory period was determined at a cycle length of 1000 ms by applying a premature stimulus (S2) of the same duration and strength after every tenth basic stimulus (S1) at decreasing S1–S2 intervals until refractoriness occurred. Conduction time (CT), measured as the time interval from the stimulus to the peak of the electrogram, was determined for each S1–S2 interval that produced a propagated response. The relationship between the degree of prematurity (S1–S2 interval) and conduction time of the premature stimulus (S2) was constructed as a conduction–interval curve. The tissue was then superfused with various concentrations of test compound. Only one compound was tested per ventricular muscle strip preparation, and the appropriate vehicle controls were conducted in every experiment.

Intraduodenal Bioavailability. Normal healthy dogs (8–20 kg) of either sex were anesthetized with sodium pentobarbital (30 mg/kg, iv), intubated, and mechanically respired. Respiratory parameters were adjusted to maintain blood gasses within acceptable limits. Lead II ECG and esophogeal temperature were monitored throughout the experiment. Body temperature was maintained at 36 ± 0.5 °C by means of a heating pad placed under the animal. The right femoral artery and vein were cannulated to monitor blood pressure and for the administration of fluids, respectively. A longitudinal incision (2 in.) was made at the umbilicus along the linea alba and the duodenum isolated. A small incision was made into the duodenum and a catheter was inserted for compound administration. The heart was exposed through a lateral thoracotomy, and silver bipolar plaque electrodes were sutured onto the surface of the right atrium and the left ventricle (LV). Unipolar Teflon-coated stainless steel plunge electrodes were positioned close to the endocardial surface under the left ventricular recording plaque. The animal was then allowed to equilibrate 15–30 min before any experimental determinations were made.

Heart rate (HR) and blood pressure (BP) measurements were determined prior to stimulation. The LV functional refractory period (FRP) was obtained by sequential pacing of the atria and ventricles at a basic cycle length of 300–450 ms with unipolar cathodal stimulation pulses 2 ms in duration at a stimulus intensity 4 times the diastolic threshold (4 × DT).[25] A single premature stimulus (S2) was delivered at the same ventricular site following 15 driving stimuli (S1) at decreasing intervals (S1–S2) until ventricular refractoriness occurred. Transmural myocardial conduction time was determined for each S1–S2 interval that produced a propagated ventricular response. Transmural conduction time was measured as the time interval from the stimulus to the peak of the local LV electrogram. The test compound was administered via the intraduodenal catheter as a homogeneous suspension with 0.5% tragacanth as the vehicle. Vehicle controls conducted with 0.5% tragacanth have shown it to have no significant effect on any of the parameters measured in these experiments. After administration of the test compound, HR, BP, and FRP were determined at 45 min postdose. If there was a greater than 12% change in FRP and/or conduction time after 45 min postdose, no second dose was administered. If the test compound failed to produce an effect on FRP and/or conduction time (i.e., 12% change from control), a second intraduodenal dose was administered and the above procedure repeated.

Antiarrhythmic Efficacy (PES Model). Evaluation of the antiarrhythmic efficacy of several of the class III agents against PES-induced reentrant ventricular tachyarrhythias was determined similar to the procedure outlined by Scherlag et al.[19] Briefly, mongrel dogs (8–17 kg) that underwent a two-stage total occlusion of the left anterior descending coronary artery 24 h previously were anesthetized with sodium thiopental (15 mg/kg), intubated with a cuffed endotracheal tube, and mechanically respired. Lead II ECG and esophogeal temperature were monitored throughout the experiment. Body temperature was maintained at 36 ± 0.5 °C by means of a heating pad placed under the animal. The right femoral artery and vein were cannulated to monitor BP and for the administration of fluids, respectively. The heart was exposed through a left lateral thoracotomy. Defibrillator pads were sutured onto the exterior surface of the pericardium and a silver, bipolar stimulating electrode was sutured onto the noninfarcted surface of the right ventricle. After completion of surgery, an equilibration period of 15–30 min was allowed before any experimental determinations were made.

Following the equilibration period, arrhythmias were induced with right ventricular bipolar stimulation by delivering three to five impulses at a cycle length (CL) of 200–120 ms at 5 or 10 mA. The investigation started with three impulses at 5 mA and a CL of 200 ms, delivered up to 10 times 5–6 s apart. If no sustained arrhythmia was induced, the CL was decreased in 10-ms steps and the above procedure repeated until the CL was 120 ms. At this point the procedure was repeated using five beats, 5 mA, 200–120 ms, then three beats, 10 mA, 200–120 ms, and finally five beats, 10 mA, 200–120 ms, until a sustained ventricular arrhythmia was induced. Sustained ventricular tachycardia (SVT) was defined as ventricular tachycardia lasting greater than 30 s in duration and a rate > 240 bpm. SVT was terminated after 30–40 s with ventricular burst pacing or electrical DC countershock. Ventricular fibrillation was treated immediately with DC countershock.

After two control arrhythmias were induced 30 min apart, the test material was given as an intravenous infusion over 10 min. Twenty minutes after the infusion, the PES protocol was repeated to attempt to induce an arrhythmia. If an arrhythmia could be induced, then the next dose of the test agent was administered and the above procedure repeated. If an arrhythmia could not be induced with the entire spectrum of the PES protocol, then the animal was considered noninducible and the test agent considered to be effective in that experiment. Placebo administration (vehicle controls) was found to be ineffective in preventing PES-induced tachyarrhythmias.

β-Adrenergic Receptor Binding Studies. Cardiac membranes were prepared from canine ventricular tissue.[26] Ventricular muscle was homogenized with Tissuemizer in 5 volumes of a solution containing 0.25 M sucrose, 1 mM $MgCl_2$, and 5 mM Tris, pH 7.5. After removal of the nuclear (700*g* for 1 min) and mitochondrial (10000*g* for 15 min) fractions, a microsomal fraction was collected by centrifugation at 100000*g* for 30 min. The final pellet was resuspended in 50 mM Tris, pH 7.5, at a protein concentration of 4 mg/mL and stored at −80 °C until used. Binding of [^{3}H]dihydroalprenolol (DHA)[27] to cardiac membranes was performed according to the method of Cantor et al.[28] Total DHA binding was measured in the presence of 4.5 nM [^{3}H]DHA, 0.1 mg protein, and 50 mM Tris, pH 7.5, in a total volume of 0.25 mL. Reaction was carried out for 15 min at 37 °C. Bound complexes were separated by rapid vacuum filtration over glass fiber filters (Whatman, GF/C). The filters were washed with 15 mL of cold 50 mM Tris, pH 7.5, and counted for radioactivity in 5 mL of Aquasol[27] in a liquid scintillation spectrometer. Test compounds were added at a concentration range from 0.1 nM to 10 mM.

Acknowledgment. We thank Dr. Walton B. Caldwell and members of the Analytical Chemistry Section of our department for interpretation of the NMR spectra, elemental analyses, and a HPLC method to determine the enantiomeric purity of (*S*)-(+)-**3** and (*R*)-(−)-**3**. Special thanks go to Drs. G. Cleve and G.-A. Hoyer (Schering AG, Berlin) for the circular dichroism spectra of (*S*)-(+)-**3** and (*R*)-(−)-**3**. We thank Ron Barbati, Roy H. Winters, C. Michael Doroshuk, Ellen Ambelas, and Hannah Hom-Troy of our Pharmacology Department for technical assistance during the course of this study. Appreciation is also given to Drs. H. Joseph Reiser, Jay Wiggins, Elinor H. Cantor, and Jeffrey L. Hill for their collaboration during the course of this investigation.

Supplementary Material Available: Full X-ray crystallographic data for camphorsulfonate (−)-**27** (12 pages). Ordering information is given on any current masthead page.

(25) Four times the diastolic threshold (4 × DT) has been stated by some authors (Michelson, E. L.; Spear, J. F.; Moore, E. N. *Circulation* 1981, *63*, 1158) to yield much more consistent values for FRP because one is on a "steeper" portion of the strength–interval curve. The release of "local" catecholamines are a potential problem with any suprathreshold stimulation of the heart. However, the shorter pulse duration of 2 ms tends to minimize this problem. Pulse durations of 10 ms or 60-Hz trains of impulses, similar to the techniques used to determine ventricular fibrillation thresholds, are much more associated with catecholamine release than are the techniques we describe.

(26) Khatter, J. C.; Michiel, D. F.; Lamers, J. M. J. In *Methods in Studying Cardiac Membranes*; Dhalla, N. S., Ed.; CRC: Boca Raton, 1984; Vol. II, p 131.

(27) Available from New England Nuclear, Boston, MA.

(28) Cantor, E. H.; Greenberg, L. H.; Weiss, B. *Mol. Pharmacol.* 1981, *19*, 21.