4,5-Dihydro-1-phenyl-1*H*-2,4-benzodiazepines: Novel Antiarrhythmic Agents

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A series of 4,5-dihydro-1-phenyl-1*H*-2,4-benzodiazepines has been identified as potential antiarrhythmic agents that interact with sodium and potassium channels and prolong the ventricular effective refractory period (ERP) in anesthetized guinea pigs. Concomitant displacement of radiolabeled bactrachotoxin from site II in Na^+ channels and of radiolabeled dofetilide from delayed rectifier K^+ channels was evident with all members of this chemical series at a concentration of 10 μM. Structure–activity relationship (SAR) studies using a paced guinea pig model to assess prolongation of the ERP indicated that methyl or ethyl at the 1-position had little effect on activity, while larger groups caused a diminution of activity. Compounds with substituents at either the 3- or 4-position that increased lipophilicity generally were more potent; however, too many lipophilic substituents simultaneously at positions 1, 3, and 4 resulted in less active compounds. Substituents on either aromatic ring had little influence on activity, and phenyl at the 5-position resulted in a significant reduction in antiarrhythmic activity. When two sets of enantiomerically pure compounds were tested in the guinea pig, chirality was shown to be important for activity of **8**, where the (*R*)-enantiomer was the more active, but not in the case of **15**, where the enantiomers were equiactive. Several compounds in this series increased the threshold for vertricular fibrillation and refractoriness in myocardially-infarcted anesthetized cata and delayed the onset of aconitine-induced arrhythmias in anesthetized guinea pigs following intravenous dosing. Moreover, these compounds possessed oral antiarrhythmic activity in conscious myocardially-infarcted dogs. Compound *R*-**15** has been advanced for further biological and toxicological evaluations.

Complex arrhythmias degenerating into ventricular fibrillation have been proposed as a primary cause of cardiac death.[1] Agents used to prevent arrhythmias have been classified by Vaughan Williams[2] as class I (membrane-stabilizing local anesthetics that primarily block cardiac Na^+ channels), class II (β-blockers), class III (agents that prolong refractoriness by primarily blocking cardiac delayed rectifier K^+ channels), and class IV (Ca^{2+} channel entry blockers). Until recently, class I agents were the most frequently used antiarrhythmics; however, their utility has been called into question on the basis of the results of the cardiac arrhythmia suppression trial (CAST)[3] which revealed that class I therapy with encanide, flecanide, or moricizine leads to decreased patient survival.[4] As a result of the CAST findings, research directions have focused on discovering pure class III agents,[5-8] or agents with a combination of different antiarrhythmic mechanisms.[9-11] Drugs having class III/I activity with the combined activities of prolonging refractoriness and abolishing ventricular ectopic impulses could have a greater impact upon this unmet therapeutic need than either class of drug alone.[10] In this report we describe the synthesis and biological activity of a novel series of 4,5-dihydro-1-phenyl-1*H*-2,4-benzodiazepines that (a) interact with both Na^+ and K^+ channels, (b) increase ventricular refractoriness in vivo with minimal effects on cardiac contractility, and (c) possess functional parenteral and oral antiarrhythmic activity in myocardially-infarcted animals.

Chemistry

The necessary intermediate for the synthesis of all target 2,4-benzodiazepines (Table I) was the appropriate 1,2-phenylenedimethanamine **1**.[12] Ring closure of **1** with either ortho esters in acetic acid[13] (method A), or imino esters in MeOH (method B) afforded benzodiazepines **6–22**, **27**, **33–39**, and **54–56** (Scheme I). The determination of the (*Z*)-positioning of the two phenyl groups of **55** was made by appropriate NOE experiments at 270 MHz, which showed a 23% enhancement of the 1-benzhydryl hydrogen when the 5-benzhydryl hydrogen was irradiated. This result answers the previously unresolved question concerning the stereochemistry of the starting diamine **1a** (**1**: $R^1 = R^5 = Ph$, $R^4 = Me$, $X = H$),[12] which can now be reported as a mixture of (*RS*) and (*SR*).

Compounds with amino substitutents at the 3-position of the benzodiazepines were prepared via several routes. The unsubstituted 3-amino group was prepared by reaction of diamine **1b** (**1**: $R^1 = Ph$, $R^4 = Me$, $R^5 = X = H$) with BrCN to give **23**. To obtain 3-alkylamino substituents, three different routes were investigated, and none was completely satisfactory. The thiourea **2**, from the reaction of **1b** with carbon disulfide, was either methylated with MeI to give **3** which was reacted with 2-(diethylamino)-

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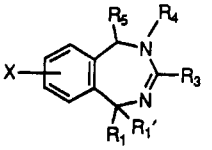
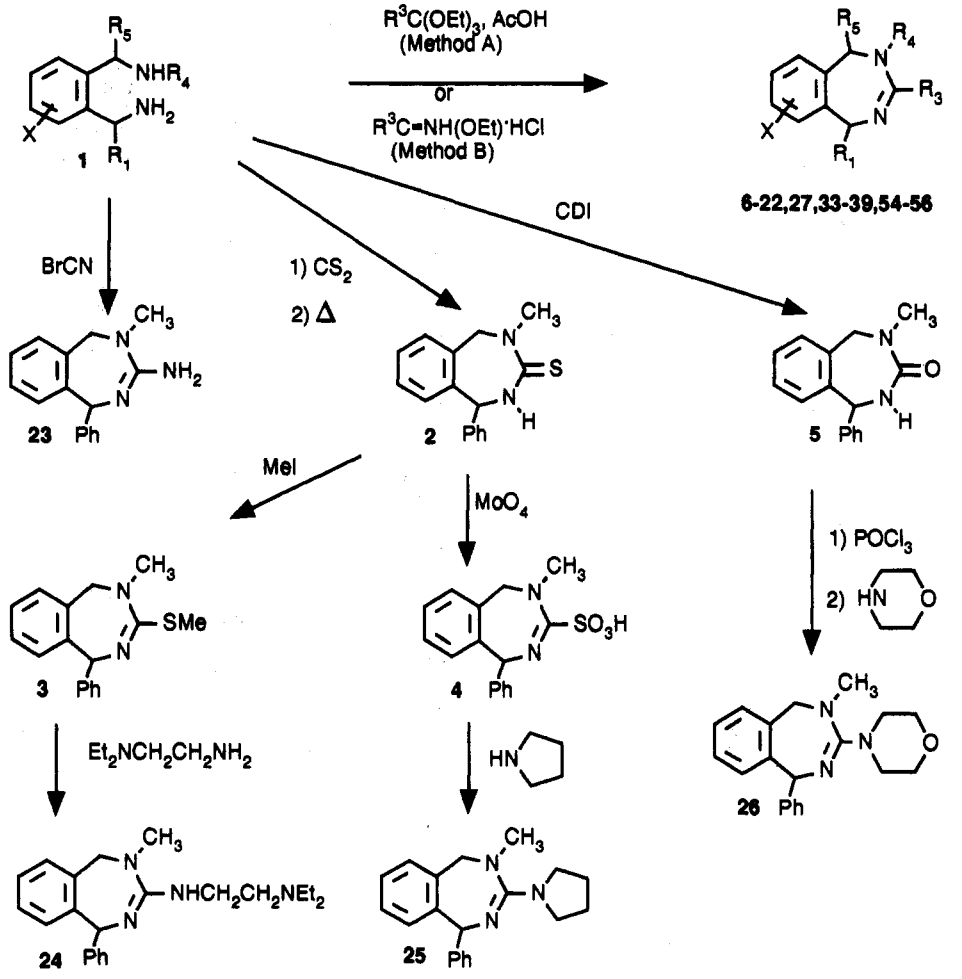
Table I. 4,5-Dihydro-1-phenyl-1*H*-2,4-benzodiazepines: Structure, Method of Synthesis, and Physical Properties



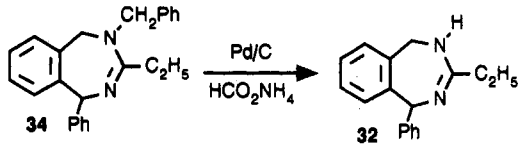
compd	X	R_1,R_1'	R_3	R_4	R_5	method[a]	mp °C	yield, %[b]	recrystn solvent	formula[c]
6	H	C_6H_5,H	H	CH_3	H	A	149–151	74	EtOH	$C_{16}H_{16}N_2$·Z-$C_4H_4O_4$
7	H	C_6H_5,H	CH_3	CH_3	H	A	177–178	45	MeCN	$C_{17}H_{18}N_2$·Z-$C_4H_4O_4$
8	H	C_6H_5,H	C_2H_5	CH_3	H	A	198–200	40	MeCN/*t*-BuOMe	$C_{18}H_{20}N_2$·HCl
R-8	H	(*R*)-C_6H_5,H	C_2H_5	CH_3	H	*d*	244–247	22[e]	EtOH/Et_2O	$C_{18}H_{20}N_2$·HCl
S-8	H	(*S*)-C_6H_5,H	C_2H_5	CH_3	H	*d*	247–249	37[e]	EtOH/Et_2O	$C_{18}H_{20}N_2$·HCl
9	H	C_6H_5,H	*n*-C_3H_7	CH_3	H	A	218–221	69	MeCN/*t*-BuOMe	$C_{19}H_{22}N_2$·HCl
10	H	C_6H_5,H	*n*-C_4H_9	CH_3	H	A	212–214	46	MeCN/*t*-BuOMe	$C_{20}H_{24}N_2$·HCl
11	H	C_6H_5,H	*n*-C_5H_{11}	CH_3	H	B	197.0–197.5	27	acetone/Et_2O	$C_{21}H_{26}N_2$·HCl
12	H	C_6H_5,H	*n*-C_8H_{17}	CH_3	H	B	159–161	28	MeCN/Et_2O	$C_{24}H_{32}N_2$·HCl·1.25H_2O
13	H	C_6H_5,H	C_6H_5	CH_3	H	A	114–115	29	CH_2Cl_2/hexane	$C_{22}H_{20}N_2$
14	H	C_6H_5,H	$CH_2C_6H_5$	CH_3	H	A	236–237	78	MeCN	$C_{23}H_{22}N_2$·HCl
15	H	C_6H_5,H	$(CH_2)_2C_6H_5$	CH_3	H	A	132–133	62	MeCN	$C_{24}H_{24}N_2$·HCl
R-15	H	(*R*)-C_6H_5,H	$(CH_2)_2C_6H_5$	CH_3	H	*d*	198–199.5	77	MeCN/Et_2O	$C_{24}H_{24}N_2$·HCl
S-15	H	(*S*)-C_6H_5,H	$(CH_2)_2C_6H_5$	CH_3	H	*d*	198–199.5	71	MeCN/Et_2O	$C_{24}H_{24}N_2$·HCl
16	H	C_6H_5,H	$(CH_2)_3C_6H_5$	CH_3	H	A	204–206	9	MeOH/Et_2O	$C_{25}H_{26}N_2$·HCl
17	H	C_6H_5,H	$(CH_2)_2$-4-OCH_3-C_6H_4	CH_3	H	B	131–133	53	MeOH/Et_2O	$C_{25}H_{26}N_2$·HCl·1.25H_2O
18	H	C_6H_5,H	$(CH_2)_2$-4-Cl-C_6H_4	CH_3	H	B	185–187	48	MeOH/acetone/Et_2O	$C_{24}H_{23}ClN_2$·E-$C_4H_4O_4$
19	H	C_6H_5,H	(CH_2)-*c*-C_6H_{11}	CH_3	H	B	141–142	43	MeCN/Et_2O	$C_{24}H_{30}N_2$·HCl
20	H	C_6H_5,H	$CH_2OC_6H_5$	CH_3	H	B	153–155	74	EtOH/Et_2O	$C_{23}H_{22}N_2O$·HCl·H_2O
21	H	C_6H_5,H	$CH_2OC_6H_4$-4-OCH_3	CH_3	H	B	224.5–225.5	17	EtOH/Et_2O	$C_{24}H_{24}N_2O_2$·HCl
22	H	C_6H_5,H	$CH_2OC_6H_4$-4-Cl	CH_3	H	B	166–168	15	EtOH/Et_2O	$C_{23}H_{21}ClN_2$·HCl·0.5 H_2O
23	H	C_6H_5,H	NH_2	CH_3	H	*d*	259–261	13	EtOH	$C_{16}H_{17}N_3$·HCl
24	H	C_6H_5,H	$NH(CH_2)_2N(C_2H_5)_2$	CH_3	H	*d*	160–162	4	*i*-PrOH	$C_{22}H_{30}N_4$·2E-$C_4H_4O_4$·0.5H_2O
25	H	C_6H_5,H	$N(CH_2)_4$	CH_3	H	*d*	188.0–119.5	22	hexane	$C_{20}H_{23}N_3$
26	H	C_6H_5,H	$N(CH_2CH_2)_2O$	CH_3	H	*d*	245–246	14	CH_2Cl_2/hexane	$C_{20}H_{23}N_3O$·HCl
27	H	C_6H_5,H	CH_2Cl	CH_3	H	B	129–131	30	*t*-BuOMe/hexane	$C_{17}H_{17}ClN_2$
28	H	C_6H_5,H	$CH_2N(CH_3)_2$	CH_3	H	E	184–186	45	EtOH/Et_2O	$C_{19}H_{23}N_3$·E-$C_4H_4O_4$
29	H	C_6H_5,H	$CH_2N(CH_2)_5$	CH_3	H	E	202–204	43	EtOH/Et_2O	$C_{22}H_{27}N_3$·1.5E-$C_4H_4O_4$
30	H	C_6H_5,H	$CH_2N(CH_2CH_2)_2O$	CH_3	H	E	206–208	28	MeOH/Et_2O	$C_{21}H_{25}N_3$·E-$C_4H_4O_4$·0.5 H_2O[f]
31	H	C_6H_5,H	$CH_2N(CH_2CH_2)_2NCH_3$	CH_3	H	E	233.0–234.5	65	MeOH/Et_2O	$C_{22}H_{28}N_4$·2E-$C_4H_4O_4$
32	H	C_6H_5,H	C_2H_5	H	H	*d*	203–204	61	*i*-PrOH/Et_2O	$C_{17}H_{18}N_2$·HCl
33	H	C_6H_5,H	C_2H_5	$CH(CH_3)_2$	H	A	232–234	71	EtOAc/Et_2O	$C_{20}H_{24}N_2$·HCl
34	H	C_6H_5,H	C_2H_5	$CH_2C_6H_5$	H	A	222–224	38	*i*-PrOH	$C_{24}H_{24}N_2$·HCl·0.25H_2O
35	H	1-naphthyl,H	C_2H_5	CH_3	H	A	145–148	50	EtOH	$C_{22}H_{22}N_2$
36	H	$CH_2C_6H_5$,H	C_2H_5	CH_3	H	A	137–138	25	EtOH/Et_2O	$C_{19}H_{22}N_2$·$C_6H_{13}O_3NS$
37	H	$CH_2C_6H_5$,H	$(CH_2)_2C_6H_5$	CH_3	H	B	139–140	47	EtOH	$C_{25}H_{26}N_2$·E-$C_4H_4O_4$
38	H	4-Cl-C_6H_4,H	$(CH_2)_2C_6H_5$	CH_3	H	B	202–203	31	MeCN/EtOH	$C_{24}H_{23}ClN_2$·HCl
39	H	4-OCH_3-C_6H_4,H	$(CH_2)_2C_6H_5$	CH_3	H	B	203–204	35	MeOH/Et_2O	$C_{25}H_{26}N_2O$·HCl
40	H	$C_6H_5CH_3$	CH_3	CH_3	H	C	228–230	46	*i*-PrOH	$C_{18}H_{20}N_2$·E-$C_4H_4O_4$
41	H	$C_6H_5CH_3$	C_2H_5	CH_3	H	C	244–246	66	EtOH	$C_{19}H_{22}N_2$·E-$C_4H_4O_4$[g]
42	H	$C_6H_5CH_3$	$(CH_2)_2C_6H_5$	CH_3	H	D	167.5–168.5	82	MeCN/Et_2O	$C_{25}H_{26}N_2$·Z-$C_4H_4O_4$
43	H	$C_6H_5CH_3$	$CH_2CHOHC_6H_5$	CH_3	H	D	170–171	35	EtOH/Et_2O	$C_{25}H_{26}N_2O$·Z-$C_4H_4O_4$
44	H	$C_6H_5CH_3$	CH_2Cl	CH_3	H	D	117.5–119.5	68	*h*	$C_{18}H_{19}ClN_2$
45	H	$C_6H_5CH_3$	$CH_2N(CH_3)_2$	CH_3	H	E	89–90	64	*h*	$C_{20}H_{25}N_3$
46	H	$C_6H_5CH_3$	$CH_2N(CH_2CH_2)_2O$	CH_3	H	E	137–140	14	MeOH/acetone	$C_{22}H_{27}N_3O$·2H_2SO_4[i]
47	H	$C_6H_5C_2H_5$	C_2H_5	CH_3	H	C	234–235	67	EtOH	$C_{20}H_{24}N_2$·E-$C_4H_4O_4$
48	H	$C_6H_5CO_2C_2H_5$	C_2H_5	CH_3	H	C	162 dec	57	EtOH	$C_{21}H_{24}N_2O_2$·E-$C_4H_4O_4$
49	H	$C_6H_5COCH_3$	C_2H_5	CH_3	H	C	183.5–184.5	22	EtOH	$C_{20}H_{22}N_2O$·E-$C_4H_4O_4$
50	H	$C_6H_5CH_2OCH_3$	C_2H_5	CH_3	H	C	155–156	16	EtOAc/hexane	$C_{19}H_{22}N_2O$[j]
51	H	$C_6H_5CH_3$	$CH_2N(C_2H_5)_2$	CH_3	H	E	200–206 dec	11	MeCN/Et_2O	$C_{22}H_{29}N_3$·2HCl
52	H	$C_6H_5CH_3$	$CH_2CO_2C_2H_5$	CH_3	H	D	100.0–101.5	11	CH_2Cl_2/hexane	$C_{21}H_{24}N_2O_2$
53	H	$C_6H_5CH_3$	$CH(CH_3)_2$	CH_3	H	D	223–225	28	EtOH	$C_{20}H_{24}N_2$·E-$C_4H_4O_4$
54	8,9-benzo	C_6H_5,H	C_2H_5	CH_3	H	A	149–141	40	*h*	$C_{22}H_{22}N_2$
55	H	C_6H_5,H	C_2H_5	CH_3	C_6H_5	A	121.5–123.0	27	hexane	$C_{24}H_{24}N_2$
56	H	H,H	C_2H_5	$CH_2C_6H_5$	C_6H_5	A	209–210	49	EtOAc/Et_2O/hexane	$C_{24}H_{24}N_2$·HCl

[a] Refers to the general method used and is described in the Experimental Section. [b] Yields were not optimized. [c] Analyses within ±0.4% for C, H, and N were obtained for all indicated formulas, unless otherwise stated. [d] See Experimental Section. [e] Yield is of DBT salt. [f] C: calcd, 65.20; found, 64.79. [g] N: calcd, 7.10; found, 6.69. [h] Compd purified by chromatography and did not require recrystallization. [i] N: calcd, 7.70; found, 7.25. [j] C: calcd, 77.52; found, 77.11.

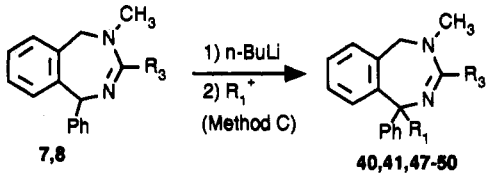
Scheme I



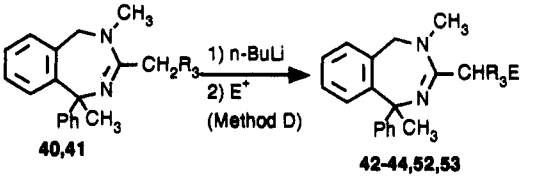
Scheme II



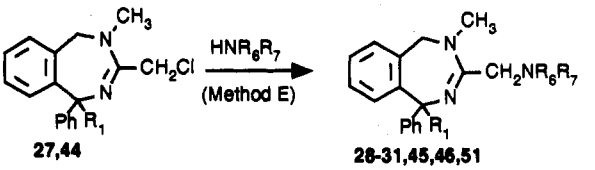
Scheme III



Scheme IV



Scheme V



ethylamine to give **24**, or reacted with MoO_4 to give the sulfonic acid **4** which was reacted with pyrrolidine to give **25**. The reaction of **1b** with 1,1'-carbonyldiimidazole (CDI) gave urea **5**, which was sequentially treated with $POCl_3$ and morpholine to give **26** (Scheme I).

Debenzylation of **34** using a palladium catalyst and ammonium formate gave **32**, the analog without substitution at either the 2- or 4-nitrogen (Scheme II).

In order to prepare compounds that were quaternary at the benzhydryl carbon, the trisubstituted benzodiazepines **7** and **8** were reacted with *n*-butyllithium and then with an electrophile to give compounds **40**, **41**, and **47–50** (Scheme III, method C). If the benzhydryl carbon was already tertiary and a hydrogen was present on a carbon at the 3-position, then the sequential treatment of this material **40** or **41** with *n*-butyllithium and then electrophiles gave compounds **42–44**, **52**, and **53** (Scheme IV, method D).

Substituted aminomethyl compounds were prepared by reacting the appropriate 3-(chloromethyl)benzodiazepine **27** or **44**, prepared by either method B or method D, with secondary amines to give **28–31**, **45**, **46**, and **51** (Scheme V, method E).

Although the initially prepared compounds were racemic, two compounds, **8** and **15**, were separated into their respective enantiomers as their dibenzoyl-D-tartaric acid salts. The absolute configuration of the pure enantiomer *R*-**8** was determined by X-ray crystal analysis of the dibenzoyltartaric acid salt. Hydrolysis of *R*-**8** gave enantiomerically pure diamine *R*-**1b** which was converted to

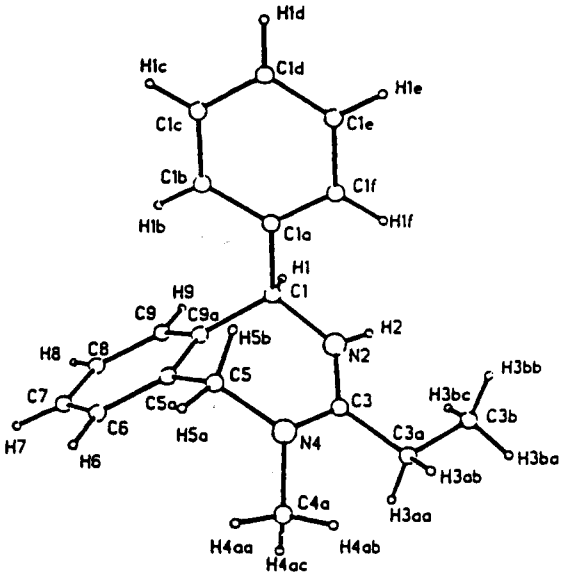
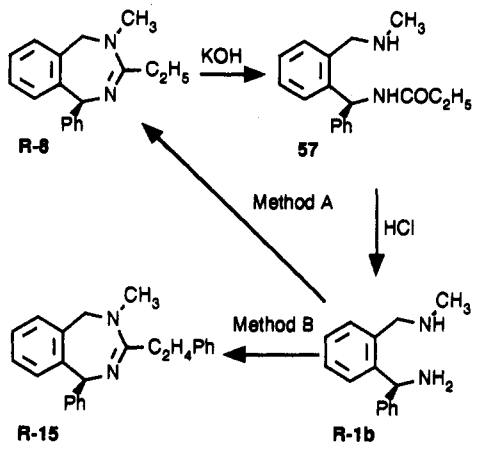


Figure 1. The X-ray structure of compound *R*-8.

Scheme VI



either *R*-8 or *R*-15 using method A or B, respectively (Scheme VI).

The X-ray analysis of *R*-8 indicated that the positioning of the 1-phenyl ring was pseudo axial and that the plane of the 1-phenyl ring was parallel to the line joining C9a and N2 (see Figure 1). A more thorough analysis of the conformation of this class of compounds will be forthcoming.

Results and Discussion

Interactions at two relevant ion channels which regulate cardiac rhythm (Na^+ channel, delayed rectifier K^+ channel) were quantitated for all members of this series of compounds (Table II). Displacement of [^{3}H]batrachotoxin (^{3}H-BTX) binding from site II in sodium channels (either neuronal or cardiac) has previously been linked to blockade of sodium current in cardiac myocytes for antiarrhythmic agents possessing class I activity.[14] Similarly, more recent studies have demonstrated a strong positive correlation for displacement of [^{3}H]dofetilide (UK-68798) from cardiac myocytes with blockade of the delayed rectifier K^+ channel.[15] All agents from this current chemical series affected ^{3}H-BTX binding and [^{3}H]dofetilide binding (Table II). In general, a greater effect on Na^+ channels was evident when all compounds were tested at 10 μM. Differences in displacement for some compounds indicated

Table II. Effects of 4,5-Dihydro-1-phenyl-1*H*-2,4-benzodiazepines on Na^+ and K^+ Channels and in the Paced Guinea Pig Assay

	% inhibn of specific binding		in vivo paced guinea pig	
cmpd	^{3}H-BTX at 10 μM[a]	^{3}H-dofetilide at 10 μM[a]	ED_{20}[b]	dP/dt_{20}[c]
6	68	38	1.4	0.9
7	52	44	1.2	0.9
8	50	27	0.6	0.8
R-8	42	26	0.3	0.3
S-8	45	34	7.1	0.09
9	72	30	0.4	0.8
10	83	48	0.1	0.1
11	95	62	0.1	0.08
12	81	77	0.2	0.1
13	85	35	0.3	1.1
14	95	67	0.3	0.15
15	92	62	0.04	0.02
R-15	95	35	0.03	0.03
S-15	96	37	0.02	0.02
16	100	56	0.2	0.12
17	91	47	0.1	0.06
18	97	35	0.1	0.85
19	98	82	0.1	0.66
20	98	45	0.3	no estimate
21	98	59	0.1	0.48
22	100	51	0.2	0.17
23	91	41	1.7	1.0
24	98	61	0.7	0.9
25	100	43	0.2	no estimate
26	49	16	0.6	0.4
28	44	30	0.6	no estimate
29	94	50	0.4	0.002
30	57	26	0.25	0.11
31	38	20	0.4	0.1
32	84	35	1.1	0.2
33	87	45	0.2	0.15
34	98	67	1.0	0.2
35	94	26	0.6	0.2
36	84	48	0.2	0.1
37	97	86	0.2	0.04
38	96	47	0.2	0.2
39	95	45	0.1	0.1
40	71	21	0.8	0.9
41	60	17	0.7	1.2
42	97	48	0.34	0.9
43	92	38	0.1	0.1
44	82	14	0.4	0.002
45	57	16	0.8	0.02
46	51	22	2.4	0.1
47	78	27	0.2	0.1
48	56	12	0.4	0.1
49	28	12	0.9	0.45
50	45	12	2.5	0.1
51	90	31	0.2	0.05
52	79	40	0.3	0.007
53	50	23	0.8	0.7
54	98	23	0.3	0.06
55	97	31	≥20	0.01
56	97	46	≥3	0.3
disopyramide[d]	17	14	0.2	0.03
quinidine[d]	68	40	7.2	2.5
lidocaine[d]	10	5	8	4.3
encainide[d]	55	22	0.7	0.003
flecainide[d]	74	15	12.8	1.8
d,l-sotalol[d]	0	8	1.3	1.9
sematilide[d]	0	17	1.9	18.7
dofetilide[d]	NT[e]	92	NT	NT

[a] Run in duplicate or triplicate and reported as the average. [b] ED_{20}, reported in mg/kg, is the dose estimated from linear regression of dose response that increases ERP by 20 ms. [c] dP/dt_{20} is the dose, in mg/kg, at which the rate of pressure development in the left ventricle is reduced by 20%. Both ERP and dP/dt were evaluated in the same animals (n = 3–5 per compound). [d] Using the Vaughn Williams classification system (ref 2), disopyramide, quinidine, lidocaine, encainide, and flecainide are considered class I antiarrhythmic agents, and *d,l*-sotalol, sematilide, and dofetilide are class III antiarrhythmic agents. [e] NT = not tested.

greater or less activity at one or both channels. These data show that agents from this series interact with sites on Na^+ and K^+ channels which are predictive of blockers of Na^+ and K^+ current.

In addition to radioligand displacement, the effects of selected agents upon cardiac refractoriness (ERP) were evaluated using an in vivo paced guinea pig model modified from classical dog studies.[16] In this model, class III agents such as sematilide and *d,l*-sotalol, as well as some class I agents such as quinidine and lidocaine, prolonged ERP (Table II). Thus, this model detects potential antiarrhythmic agents that block Na^+ channels, K^+ channels, or both. We also measured cardiac dP/dt as an index of cardiac contractility in this model. Typically, selective Na^+ channel blockers (class I agents), such as encainide and flecainide, depress dP/dt at doses below those which increase ERP (Table II). Moreover, selective blockers of the delayed rectifier K^+ channel (class III agents), such as sematilide or dofetilide, increase ERP with little or no effect on dP/dt (Table II). For purposes of SAR development, we prioritized compounds on the basis of potency at which a biologically relevant increase of 20 ms in ERP was determined from dose–response studies (ED_{20}) and compared this dose to that which induced modest reduction in inotropy as indexed by a 20% reduction in the rate of pressure development in the left ventricle (dP/dt_{20}).

Several members of this new series (such as examples, **18**, **19**, **20**, **25**, and **28**) that demonstrated a separation of dosages affecting cardiac refractoriness (ERP) and contractility (dP/dt) suggesting that the effects upon ERP were observed prior to an influence upon left ventricular function (Table II) were identified. Several other members of this series were identified with the opposite profile (reduction in inotropy at doses lower than ERP changes). Among these were examples *S*-**8**, **29**, **32**, **37**, **44**, and **46**. The majority of compounds in this series affected both parameters at approximately the same dosages.

The SAR discussion that follows utilizes the ED_{20} (ERP) in the paced guinea pig model for evaluating in vivo activity of compounds in this new series.

The most studied substituent position on the 1-aryl-4,5-dihydro-1*H*-2,4-benzodiazepines has been the 3-position. To explore the importance of aliphatic chain length on activity, compounds **6**–**12** were prepared. Compounds with different alkyl chain length **8**–**12** showed little apparent difference in activity ranging from ethyl to *n*-octyl; although the longer chains appeared to be slightly more active (Table II). Activity fell off for **7** and **6** where there was only a methyl or hydrogen, respectively, at the 3-position. In a small series of phenyl analogs **13**–**16**, phenylethyl was more potent when compared with phenylpropyl, phenylmethyl, or phenyl. Substitution on the phenyl ring as in **17** (4-MeO) and **18** (4-Cl) of the phenylethyl compound **15** had little effect on activity. Similar results were observed for **21** (4-MeO) and **22** (4-Cl) relative to **20**. Replacement of the phenylethyl of **15** with a cyclohexylethyl group to give **19** seemed also to retain activity.

A more drastic substitution at the 3-position was found in the amino compounds **23**–**26** and **28**–**31**. These compounds were generally less potent than the more lipophilic compounds discussed above. Within this small series, the relationship of lipophilicity to activity was also apparent in that the unsubstituted guanidine **23** was the least active of these compounds.

The exploration of the 4-position substitution was limited. Three compounds **32**–**34** that were direct analogs of **8** were evaluated. Only **33** with 4-*i*-Pr substitution seemed to retain the activity of **8**.

Replacement of the 1-phenyl of **8** with a 1-naphthyl to give **35** appeared not to affect activity, while replacement with a benzyl group as in **36** may have enhanced activity. By utilizing this possible activity enhancing substitution, the benzyl analog **37** of **15** was prepared and evaluated; however, it was less active than **15**. Substitution on the 1-phenyl ring with either **38** (4-Cl) or **39** (4-MeO) also resulted in compounds no more active than **15**.

In a maneuver to block a potential site of metabolism, several benzhydryl-substituted analogs **40**–**53** were prepared. Benzhydryl methyl **41**, benzhydryl ethyl **47**, benzhydryl ethoxycarbonyl **48**, and benzhydryl acetyl **49**, all analogs of **8**, were as active as **8**, while benzhydryl methoxymethyl **50** was less active than **8**. Analogs **42**–**45**, and **51**–**53** of the benzhydryl methyl compound **41** with a variety of 3-substituents were prepared and evaluated for activity. None of these compounds displayed significant enhancements in activity over **41**, and the non-benzylhydryl-methyl-substituted analog of **42**, which is **15**, was at least 8-fold less active than **15**.

The effect of an 8,9-benzo ring **54** on the activity of **8** was negligible, and placing a 5-phenyl on **8** to give **55** caused a dramatic loss in activity. This finding may be the result of a conformation change caused by the (*Z*)-1,5-diphenyls of **55** where the two phenyls can only exist in pseudoequitorial positions. Another interesting observation was that **56**, the 2-benzyl isomer of **34** also lacked potent activity.

The influence of chirality on activity in the paced guinea pig assay depended on the compound being tested. Thus, the activity of *R*-**8** was at least 10-fold greater than *S*-**8**, while the activities of *R*-**15** and *S*-**15** were equivalent.

Several of these agents were further evaluated in more advanced models to determine functional antiarrhythmic activity (Table III). Delay of arrhythmias induced by the site II Na^+ channel toxin, aconitine in guinea pigs following intravenous administration was evident over the concentration range of 0.1–3 mg/kg, iv for the agents studied. Several of these agents also increased ventricular fibrillation threshold following iv administration to anesthetized, acutely-infarcted cats. In general, activity occurred over this same concentration range. These agents were also orally bioavailable by virtue of their ability to suppress spontaneous arrhythmias in infarcted dogs over the dose range of 3–10 mg/kg. In general, these compounds were 3–10-fold more potent than reference antiarrhythmics such as quinidine, flecainide, or disopyramide in this model.

One of these agents, *R*-**15**, has been advanced for further biological and toxicological evaluation. Blockade of I_K (IC_{50} = 90 nM) with modest effects on I_{Na} (IC_{50} = 2.1 μM) has been demonstrated for *R*-**15**, and dose-related increases in ERP (13–33 ms) and QT interval (13–41 ms), with moderate changes in QRS interval (1–4 ms) and A-V conduction (0–5 ms) have been observed in anesthetized dogs (n = 4) following intravenous administration of 0.1–1.6 mg/kg (unpublished observations). Higher dosages of 3.6 mg/kg increased monophasic action potential duration and ventricular ERP (63–73 ms), while having minimal effects upon conduction (mean QRS interval increased 9 ms). The 3.6 mg/kg dose was well tolerated hemodynamically.

Table III. In Vivo Antiarrhythmic Activity of 1-Aryl-4,5-dihydro-1*H*-2,4-benzodiazepines in Guinea Pig (Aconitine-Induced), Conscious Infarcted Dog, and Myocardially-Infarcted Cat Arrhythmia Models

compd	guinea pig aconitine: MED,[a] mg/kg iv	conscious infarcted dog: MED,[a] mg/kg po	myocardially-infarcted cat[b] dose, mg/kg	VFT, mamps	ERP, ms
saline	inactive	inactive	inactive	−5 ± 3	−14 ± 8
8	3	10	1	84 ± 11	13 ± 4
R-**8**	3	10	0.3	63 ± 14	16 ± 5
S-**8**	3	>10		NT[c]	NT
15	<3	3	1	95 ± 1	61 ± 14
R-**15**	0.1	3	0.3	37 ± 19	13 ± 5
S-**15**	0.1	10	1	82 ± 8	21 ± 4
18	3	3	1	93 ± 2	45 ± 4
41	<3	10	3	81 ± 18	78 ± 4
43	<3	10		NT	NT
48	<3	3	0.3	84 ± 9	47 ± 7
quinidine	1	30		NT	NT
flecainide	3	10	3	30 ± 19	5 ± 4
disopyramide	1	40	5	73 ± 24	26 ± 16
dofetilide	NT	NT	0.03	43 ± 7	85 ± 2

[a] MED = minimal effective dose as defined in an ascending semilogarithmic dose escalation that resulted in significant delay in the onset of arrhythmias in guinea pigs challenged with aconitine hydrochloride or a significant reduction in PVC frequency in conscious dogs administered test agents (po) 24 h after coronary artery ligation. [b] The myocardially-infarcted cat model reflects data obtained in anesthetized cats dosed intravenously with selected test agents. Mean maximum changes over a 5-h test period were recorded for changes in ventricular fibrillation threshold (VFT in mamps) and ventricular refractoriness (ERP in ms) determined. [c] NT = not tested.

In summary, on the basis of the data presented, it appears that the 4,5-dihydro-1-aryl-1*H*-2,4-benzodiazepines series is a family of novel compounds that possess antiectopic activity and are agents that increase ventricular refractoriness. As such, these compounds may be useful as antiarrhythmic agents.

Experimental Section

Reactions involving organometallic reagents were run under a N_2 atmosphere. Solvents and reagents from commercial sources were used without further purification. Melting points (Pyrex capillary) are uncorrected. For ^{1}H NMR spectra, multiplicity is denoted by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sep (septet), m (multiplet), and br (broad). Coupling constants are in hertz (Hz). ^{1}H NMR spectra were run on either a 200-, 270-, or 300-MHz instrument. Infrared spectra (IR) were measured as KBr pellets. If the requisit ortho esters for general method A were not available commercially, they were prepared by literature procedures.[17] All imino esters used in general method B were also prepared by literature procedures.[18,19]

General Method A. (*RS*)-3-Ethyl-4,5-dihydro-4-isopropyl-1-phenyl-1*H*-2,4-benzodiazepine (33). This procedure illustrates the general method for preparation of **6–10, 13–16, 33–36,** and **54–56.** A mixture of *N*-isopropyl-α′-phenyl-1,2-phenylenedimethanamine dihydrochloride[12] **1c** (24.0 g, 73.3 mmol), NaOAc (12.6 g, 154 mmol), triethyl orthopropionate (66.5 g, 367 mmol), and HOAc (22 g, 367 mmol) was stirred at room temperature for 24 h. Analysis of the reaction mixture by TLC (SiO_2 plates with eluting solvent 5% diethylamine in EtOAc) indicated a single new spot at R_f = 0.28, more polar than starting diamine. After another 24 h at room temperature, 150 mL of H_2O was added and the resulting liquid was filtered through Solca Floc. After the filtrate was concentrated on a rotary evaporator to remove most of the AcOH, 250 mL of 1 N NaOH was added and the mixture extracted 4× with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4), concentrated, and treated with ethereal HCl to give a pale green solid which was recrystallized from EtOAc/Et_2O to give 17.1 g (71%) of the HCl salt of **33**: mp 232–234 °C; ^{1}H NMR ($CDCl_3$) δ 1.25–1.50 (m, 9H), 2.80–3.20 (m, 2H), 3.82 (d, 1H, *J* = 15.2), 4.20 (quin, 1H, *J* = 6.7), 4.50 (d, 1H, *J* = 15.2), 5.95 (d, 1H, *J* = 6.7), 7.15–7.50 (m, 9H). Anal. ($C_{20}H_{24}N_2$·HCl) C, H, N.

General Method B. (*RS*)-4,5-Dihydro-4-methyl-3-(phenoxymethyl)-1-phenyl-1*H*-2,4-benzodiazepine (20). This procedure illustrates the general method for the preparation of **11, 12, 17–22, 27,** and **37–39.** A mixture of *N*-methyl-α′-phenyl-1,2-phenylenedimethanamine (**1b**, 4.53 g, 20 mmol), ethyl phenoxyacetimidate[18] (13.0 g, 60 mmol), AcOH (3.45 mL, 60 mmol), and MeOH (70 mL) was stirred at room temperature for 24 h. The precipitate that had formed was collected and washed with Et_2O. Et_2O was added to the filtrate until no more solid precipitated, and then this solid was collected. The combined solids were recrystallized from EtOH/Et_2O to give 5.6 g (74%) of **15** as the HCl salt: mp 153–155 °C; ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 3H), 3.61 (d, 1H, *J* = 15.0), 4.92 (d, 1H, *J* = 15.0), 5.00 (d, 1H, *J* = 15.0), 5.91 (d, 1H, *J* = 15.0), 6.05 (d, 1H, *J* = 7.5), 7.05–7.55 (m, 14H), 13.20 (br, 1H). Anal. ($C_{23}H_{22}N_2O$·HCl·H_2O) C, H, N.

(*RS*)-4,5-Dihydro-4-methyl-1-phenyl-1*H*-2,4-benzodiazepin-3-amine (23). A solution of *N*-methyl-α′-phenyl-1,2-phenylenedimethanamine (**1b**; 15 g, 66 mmol) in 85 mL of MeOH was stirred while CNBr (7.5 g, 68 mmol) was added in portions over 10 min while using a cold water bath to keep the temperature at 30–40 °C. The mixture was stirred at room temperature overnight and then concentrated on a rotary evaporator. The concentrate was dissolved in a minimum amount of warm MeOH and *i*-PrOAc was added to the cloud point. Upon cooling crystals formed and were collected (4.5 g). This HBr salt was dissolved in warm MeOH, and 2N NaOH was added until the solution was basic, and then H_2O was added to the cloud point. This mixture was extracted with EtOAc two times. The combined EtOAc extracts were washed with saturated NaCl and concentrated to dryness. The HCl salt was prepared in EtOH and gave 2.4 g (13%) of **23**: mp 259–261 °C; ^{1}H NMR (DMSO-d_6) δ 3.07 (s, 3H), 3.43 (br, 2H), 4.32 (d, 1H, *J* = 13.2), 4.45 (d, 1H, *J* = 13.2), 5.95 (, 1H, *J* = 5.3), 7.20–7.45 (m, 9H), 7.65 (s, 2H), 9.10 (d, 1H, *J* = 5.3). Anal. ($C_{16}H_{17}N_3$·HCl) C, H, N.

(*RS*)-*N*-[2-(Diethylamino)ethyl]-4,5-dihydro-4-methyl-1-phenyl-1*H*-2,4-benzodiazepin-3-amine (24). A solution of *N*-methyl-α′-phenyl-1,2-phenylenedimethanamine (**1b**; 25.3 g, 112 mmol) in 170 mL of 2-propanol was stirred while carbon disulfide (6.7 mL, 8.5 g, 112 mmol) in 60 mL of *i*-PrOH was added dropwise. A gummy solid formed. The mixture was heated under reflux 2 h and cooled, and the crude precipitate was collected (28.9 g). This solid was combined with 1.5 mL of concentrated HCl and 180 mL of 95% EtOH and heated under reflux 20 h. The mixture was cooled and the precipitated (*RS*)-1,2,4,5-tetrahydro-2-methyl-5-phenyl-3*H*-2,4-benzodiazepine-3-thione (**2**) was collected (18.2 g): mp 208–209 °C; ^{1}H NMR (CF_3COOH) δ 3.53 (s, 3H), 4.40 (d, 1H, *J* = 15.4), 4.85 (d, 1H, *J* = 15.4), 6.00 (s, 1H), 7.25–7.55 (m, 9H), 11.60 (s, 1H). Anal. ($C_{16}H_{16}N_2S$) C, H, N.

This material was slurried in 225 mL of EtOH and stirred at 50 °C while 6.2 mL (14.2 g, 100 mmol) of MeI in 60 mL of EtOH was added dropwise. After 20 h of stirring at room temperature, the crude solid, (*RS*)-4,5-dihydro-4-methyl-3-(methylthio)-1-phenyl-1*H*-2,4-benzodiazepine hydroiodide, was collected (22.7 g, 55 mmol, 50% yield from **1b**): mp 204–208 °C. The methanesulfonate salt **3** was prepared and crystallized from EtOH: mp 195–196 °C, ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3H), 2.95 (s, 3H), 3.40 (s, 3H), 3.90 (d, 1H, *J* = 14.7), 4.90 (d, 1H, *J* = 14.7), 6.50 (d, 1H, *J* = 6.4), 7.18–7.65 (m, 9H), 10.40 (d, 1H, *J* = 5.9). Anal. ($C_{17}H_{18}N_2S$·CH_4SO_3) C, H, N. The crude HI salt was combined with *N*,*N*-diethylethylenediamine (7.8 mL, 6.45 g, 55 mmol) and 285 mL of MeOH and heated under reflux 20 h, filtered hot, and concentrated on a rotary evaporator to an oil. This oil was dissolved in methylene dichloride, washed with 2 N NaOH three times, saturated NaCl two times, dried ($MgSO_4$), and concentrated. The concentrate was combined with 2 equiv of fumaric acid in *i*-PrOH to give **24** (2.35 g, 4% from **1b**) as the difumarate hemihydrate: mp 160–162 °C; ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 6H, *J* = 6.6), 2.45 (q, 4H, *J* = 6.6), 3.00 (s, 3H), 3.30 (br, 2H), 4.38 (d, 1H, *J* = 15.5), 4.50 (d, 1H, *J* = 15.5), 6.00 (s, 1H), 6.50 (s, 4H), 7.20–7.45 (m, 10H), 10.21 (br, 1H). Anal. ($C_{22}H_{30}N_4$·2-E-$C_4H_4O_4$·$^1/_3H_2O$) C, H, N.

(*RS*)-4,5-Dihydro-4-methyl-1-phenyl-3-pyrrolidinyl-1*H*-2,4-benzodiazepine (25). To a suspension of **2** (29.0 g, 108

mmol), prepared as in the synthesis of **24**, in 50 mL of H_2O and 10 mL of *t*-BuOH, was added NaCl (2.4 g, 42 mmol) and $Na_2MoO_4 \cdot 2H_2O$ (0.42 g, 1.7 mmol). The mixture was cooled with stirring at 2–5 °C while 30% H_2O_2 (35 mL, 340 mmol) was added dropwise over 70 min. The resulting mixture was stirred at room temperature 16 h and was then heated to 70 °C. An exotherm raised the reaction temperature to 88 °C before cooling brought the temperature back to 70 °C. Heating at 70–80 °C was cautiously continued 1.5 h. The suspension was cooled in an ice bath, and the solid was collected, washed with H_2O, and then dried in a vacumn oven at 85 °C overnight to give (*RS*)-4,5-dihydro-4-methyl-1-phenyl-1*H*-2,4-benzodiazepine-3-sulfonic acid (**4**, 30.6 g, 90% yield): mp 188–190 °C; ^{1}H NMR (DMSO-d_6) δ 3.59 (s, 3H), 4.19 (d, 1H, J = 16.8), 4.66 (d, 1H, J = 16.5), 6.01 (s, 1H), 7.04–7.63 (m, 10H), 10.14 (br, 1H). Anal. ($C_{16}H_{16}N_2O_3S$) C, H, N. A portion of the sulfonic acid (4.75 g, 15 mmol) was combined with 20 mL of pyrrolidine and heated with stirring under reflux 18 h. The reaction mixture was concentrated to dryness on a rotary evaporator and placed on a 340-g SiO_2 column packed wet with EtOAc/diethylamine 95/5 and eluted with the same solvent system. The initial 1.5 L of eluate contained traces of high R_f impurities. The next 1250 mL of eluate contained the desired product and was concentrated to dryness on a rotary evaporator. Recrystallization of the residue from hexane gave **25** (2.14 g, 47% yield): mp 118–119.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.75–1.88 (m, 4H), 2.75 (s, 3H), 3.19–3.40 (m, 4H), 3.95 (d, 1H, J = 15.0), 4.42 (d, 1H, J = 15.0), 6.10 (s, 1H), 6.75 (m, 1H), 7.10–7.58 (m, 8H). Anal. ($C_{20}H_{23}N_3$) C, H, N.

(*RS*)-4,5-Dihydro-4-methyl-3-morpholinyl-1-phenyl-1*H*-2,4-benzodiazepine (26). To a solution of *N*-methyl-α-phenyl-1,2-phenylenedimethanamine (**1b**; 11.3 g, 50 mmol) in 75 mL of $CHCl_3$ was added 1,1′-carbonyldiimidaole (8.9 g, 50 mmol). The resulting solution was stirred 20 h, washed four times with H_2O, dried (Na_2SO_4), and concentrated on a rotary evaporator. The residual solid was triturated with boiling EtOAc (200 mL) and cooled in ice. Two crops of crystals were collected of (*RS*)-1,2,4,5-tetrahydro-4-methyl-1-phenyl-3*H*-2,4-benzodiazepin-3-one **5** (9.10 g, 72% yield): mp 198–199.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.02 (s, 3H), 3.95 (d, 1H, J = 15.4), 4.31 (d, 1H, J = 15.4), 5.37 (br, 1H), 5.55 (d, 1H, J = 5.4), 7.06–7.40 (m, 9H). Anal. ($C_{16}H_{16}N_2$) C, H, N. This benzodiazepine (7.0 g, 28 mmol) was dissolved in 35 mL of $POCl_3$, and 100 mg of P_2O_5 was added. After stirring at room temperature for 0.5 h, the mixture was heated under reflux for 18 h and then concentrated on a rotary evaporator to give 14.4 g of viscous oil. Morpholine (75 mL) was added to the viscous oil giving an exothermic reaction that was controlled by use of an ice bath. This mixture was stirred until the exotherm was over, and then it was placed in a sonicator for 2–3 min and left at room temperature overnight. The mixture was concentrated on a rotary evaporator and then dissolved in 200 mL of warm H_2O. After filtering this solution, the filtrate was extracted three times with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator to give 13.7 g of viscous oil. This oil was dissolved in 100 mL of warm EtOAc and cooled in ice, and the resultant precipitate was collected. Recrystallization from CH_2Cl_2/hexane gave **26** (2.01 g, 20% yield) as the HCl salt: mp 245–246 °C; ^{1}H NMR ($CHCl_3$) δ 2.89 (s, 3H), 3.12 (br, 1H), 3.30–3.79 (m, 5H), 3.93, (br, 2H), 4.11 (d, 1H, J = 16.2), 4.75 (d, 1H, J = 16.5), 6.25 (d, 1H, J = 6.1), 7.09–7.35 (m, 9H), 10.84 (d, 1H, J = 6.1). Anal. ($C_{20}H_{23}N_3O \cdot HCl$) C, H, N.

(*RS*)-4,5-Dihydro-3-ethyl-1-phenyl-1*H*-2,4-benzodiazepine (32). A mixture of **34** (1.36 g, 3.6 mmol), 10% Pd/C (136 mg), and ammonium formate (257 mg, 4 mmol) in 50 mL of MeOH was heated under reflux for 30 h. At 5-h intervals, 23 mg additional ammonium formate was added giving a total of 372 mg (5.9 mmol). After the 30 h, TLC on SiO_2 plates eluted with EtOAc/diethylamine (95/5) showed no **34**, and only one new spot at lower R_f. The Pd/C was removed by filtration and the filtrate concentrated on a rotary evaporator. The residue was combined with H_2O and enough 35% NaOH to give a basic aqueous layer which was extracted three times with Et_2O. The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated on a rotary evaporator. The HCl salt was prepared by dissolving the residue in EtOAc/Et_2O (3/2) and adding ethereal HCl. The precipitate was collected and recrystallized from *i*-PrOH to give 610 mg of **32** (61%) as the HCl salt: mp 203–204 °C; ^{1}H NMR (DMSO-d_6) δ 1.29 (t, 3H, J = 7.3), 2.62 (q, 2H, J = 7.6), 4.07 (d, 1H, J = 14.5), 4.15 (d, 1H, J = 14.2), 5.85 (d, 1H, J = 6.6), 7.12–7.64 (m, 9H), 10.47 (br, 1H), 10.77 (d, 1H, J = 6.6). Anal. ($C_{17}H_{18}N_2 \cdot HCl$) C, H, N.

General Method C. (*RS*)-4,5-Dihydro-3-ethyl-1,4-dimethyl-1-phenyl-1*H*-2,4-benzodiazepine (41). This procedure illustrates the general method for preparation of **40**, **41**, and **47–50**. A solution of **8** (10.9 g, 41.2 mmol) in 200 mL of THF was cooled to −78 °C and *n*-BuLi (22.7 mL of 2.0 M solution in hexanes, 45.3 mmol) was added. The mixture was stirred 1.5 h at −78 °C and then MeI (6.40 g, 45.3 mmol) was added. Stirring at −78 °C was continued 10 min, and then the mixture was warmed to room temperature over 1 h, poured into H_2O, and extracted three times with Et_2O. The combined extracts were washed with saturated NaCl, dried (K_2CO_3), and concentrated to an oil. This oil was treated with fumaric acid, and the resulting salt was recrystallized from EtOH to give **41** (10.8 g, 66%) as the fumarate: mp 244–246 °C; ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 3H, J = 7.4), 1.97 (s, 3H), 2.78 (q, 2H, J = 7.2), 3.24 (s, 3H), 3.93 (d, 1H, J = 15.3), 4.40 (d, 1H, J = 14.9), 4.55–5.55 (br, 5H), 6.44 (s, 2H), 7.06–7.79 (m, 9H). Anal. ($C_{19}H_{22}$E-$C_4H_4O_4$) C, H, N.

General Method D. (*RS*)-4,5-Dihydro-1,4-dimethyl-1-phenyl-3-(phenylethyl)-1*H*-2,4-benzodiazepine (42). This procedure illustrates the general method for the preparation of **42–44**, **52**, and **53**. The benzyl bromide used in the preparation of **42** was replaced with benzaldehyde for **43**, hexachloroethane for **44**, ethyl chloroformate for **52**, and MeI for **53**. A solution of **40** (4.22 g, 16 mmol) in 65 mL of THF was stirred at −65 °C while 2.5 N *n*-BuLi in hexanes (7.04 mL, 17.6 mmol) was added in 10 min. After this solution was stirred for another 1.25 h, benzyl bromide (3.15 g, 18.4 mmol) in 16 mL of THF was added in 5 min. The mixture was stirred at −65 °C for 20 min, warmed to room temperature in over 0.75 h, poured into H_2O containing 2 mL of 2 N NaOH, and extracted three times with Et_2O. The combined organic extracts were washed with saturated NaCl containing 1 mL of 2 N NaOH, dried (Na_2SO_4), and concentrated on a rotary evaporator to give 7.3 g of a yellow oil. The maleic acid salt was prepared in acetone using 1.25 equiv of maleic acid and recrystallized from MeCN/Et_2O in three crops to give **42** as the maleate salt (6.14 g, 82%): mp 167.5–168.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.00 (s, 3H), 2.93–3.42 (m, 4H), 3.47 (d, 1H, J = 15.2), 4.72 (d, 1H, J = 14.9), 6.33 (s 2H), 6.92–7.74 (m, 14H), 10.95 (br, 1H). Anal. ($C_{25}H_{26}N_2$-Z-$C_4H_4O_4$) C, H, N.

General Method E. (*RS*)-4,5-Dihydro-4-methyl-1-phenyl-3-[(1-piperidinyl)methyl]-1*H*-2,4-benzodiazepine (29). This procedure illustrates the general method used to prepare **29**, **28–31**, **45**, **46**, and **51**. A mixture of **27** (16.7 g, 50 mmol) and piperidine (12.8 g, 150 mmol) in 225 mL of $CHCl_3$ was heated under reflux for 2.5 h. After sitting at room temperature for 60 h, the mixture was poured into 2 N NaOH. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and 2 N NaOH, dried (Na_2SO_4), and concentrated on a rotary evaporator to give an oil. A solution of the oil and 2.2 equiv of fumaric acid in EtOH was treated with Et_2O to give a precipitate which was recrystallized from EtOH/Et_2O to give 9.63 g (43%) of **29** as the fumarate (2:3) salt: mp 202–204 °C; ^{1}H NMR (DMSO-d_6) δ 1.32–1.65 (m, 6H), 2.42–2.62 (m, 4H), 3.27 (s, 3H), 3.55 (s, 2H), 4.40 (d, 1H, J = 15.2), 4.64 (d, 1H, J = 14.8), 6.28 (s, 1H), 6.49 (s, 2H), 7.17–7.56 (m, 9H). Anal. ($C_{22}H_{27}N_3 \cdot 1.5$-E-$C_4H_4O_4$) C, H, N.

Resolution of (*RS*)-4,5-Dihydro-3-ethyl-4-methyl-1-phenyl-1*H*-2,4-benzodiazepine (8). To a solution of racemic **8** (90.5 g, 358 mmol) in 4 L of MeOH was added dibenzoyl-L-tartaric acid (128.4 g, 358 mmol). The mixture was warmed to obtain a solution and then allowed come to room temperature. The crystals that formed were collected (62 g) and recrystallized once from MeOH to give *S*-**8** dibenzoyl-L-tartrate methanolate (43.5 g, 37%) with constant rotation and constant mp: mp 161–163 °C; $[\alpha]^{25}_D$ = −130.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7), 2.74 (q, 2H, J = 7), 3.23 (s, 3H), 3.48 (s, 3H), 3.62 (d, 1H, J = 14), 4.83 (d, 1H, J = 14), 5.95 (s, 1H), 6.00 (s, 2H), 7.00–7.55 (m, 15H), 7.93–8.09 (m, 4H). Anal. ($C_{18}H_{20}N_2 \cdot C_{18}H_{14}O_8 \cdot CH_4O$) C, H, N. The mother liquors were combined, concentrated on a rotary evaporator, and partitioned between saturated Na_2CO_3 and EtOAc. The organic layer was separated, dried (Na_2SO_4), and concentrated on a rotary evaporator to give

41.9 g of the free base enriched with the (*R*)-enantiomer. A portion of this material (34.2 g, 135 mmol) was dissolved in 700 mL of MeOH and dibenzoyl-D-tartaric acid (48.5 g, 135 mmol) was added. After warming the mixture to achieve solution, it was left to return to room temperature. The crystals that had formed were collected and recrystallized from MeOH to give *R*-8 dibenzoyl-D-tartarate methanolate (21 g, 22%): mp 157–159 °C; $[\alpha]^{25}_D$ = +139.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 1.25 (t, 3H, *J* = 7), 2.70 (q, 2H, *J* = 7), 3.20 (s, 3H), 3.45 (s, 3H), 3.65 (d, 1H, *J* = 14), 4.78 (d, 1H, *J* = 14), 5.91 (s, 1H), 5.98 (s, 2H), 7.00–7.53 (m, 15H), 7.94–8.08 (m, 4H). Anal. ($C_{18}H_{20}N_2 \cdot C_{18}H_{14}O_8 \cdot CH_4O$) C, H, N.

For pharmacological testing, both *R*-8 and *S*-8 monohydrochlorides were prepared by treating their respective dibenzoyltartarate salts with saturated Na_2CO_3, extracting with EtOAc, drying (Na_2SO_4), concentrating on a rotary evaporator, treating the residue with EtOH and ethereal HCl, and recrystallizing from EtOH/Et_2O. In this way *R*-8 HCl salt was prepared: mp 244–247 °C; $[\alpha]^{25}_D$ = +346.9° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, *J* = 8), 2.92 (q, 2H, *J* = 8), 3.33 (s, 3H), 3.80 (d, 1H, *J* = 16), 4.85 (d, 1H, *J* = 16), 5.86 (d, 1H, *J* = 6), 7.10–7.55 (m, 9H). Anal. ($C_{18}H_{20}N_2 \cdot HCl$) C, H, N. Also prepared was *S*-8 HCl salt: mp 247–249 °C; $[\alpha]^{25}_D$ = −343.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.38 (t, 3H, *J* = 8.0), 2.95 (q, 2H, *J* = 8), 3.28 (s, 3H), 3.72 (d, 1H, *J* = 16), 4.85 (d, 1H, *J* = 16), 5.90 (d, 1H, *J* = 6), 7.05–7.55 (m, 9H). Anal. ($C_{18}H_{20}N_2 \cdot HCl$) C, H, N.

The assignment of enantiomer structure was by X-ray analysis of the *R*-8 dibenzoyl-D-tartarate methanolate.

Single-Crystal X-ray Analysis of *R*-8 Dibenzoyl-D-tartrate Methanolate. A single-crystal X-ray diffraction study was performed on *R*-8 dibenzoyl-D-tartarate methanolate, $C_{18}H_{20}N_2 \cdot C_{18}H_{14}O_8 \cdot 0.87CH_4O$, FW = 650.55, which was crystallized from MeOH. A clear colorless fragement of a prism, 0.40 × 0.35 × 0.68 mm was used for the study. A triclinic unit cell with dimensions: *a* = 7.467(1) Å; *b* = 10.532(2) Å; *c* = 11.225(1) Å; α = 104.44(1)°; β = 93.63(1)°; γ = 98.44(1)° was found by centering 25 reflections. *Z* = 1; *V* = 841.0(2) Å^3, D_{cal} = 1.285 g/cm^3. The absorption coefficient for Cu radiation is 0.72 mm^{-1}. No absorption correction was applied.

The data were collected on a Siemens R3m/V diffractometer using Cu K_α radiation (graphite monochromator; λ = 1.541 78 Å) in an ω-scan mode (ω-range: 1.2° + [2θ($K_{\alpha1}$) − 2θ($K_{\alpha2}$)]; 2θ range: 3–130°). A total of 2680 independent reflections were collected, of which 2510 were considered as observed [$F > 4.0\sigma(F)$]. The programs of Siemens SHELXTL (Release 5.1) were used for data reduction and all other calculations.

The structure was solved by direct methods of phase determination. Atomic coordinates and anisotropic temperature factors for all non-hydrogen atoms were refined by a "blocked cascade" least-squares method. Hydrogen atoms were included in the refinement in calculated positions with isotropic temperature factors. The refinement converged at *R* = 3.82% and R_w = 4.36%. The largest peak in the final "Fourier difference map" was 0.18 eÅ^3.

Hydrolysis of (*R*)-4,5-Dihydro-3-ethyl-4-methyl-1-phenyl-1*H*-2,4-benzodiazepine [*R*-8], and Reconversion into [*R*-8]. A solution of KOH (105.0 g, 1.61 mol) was added to *R*-8 HCl salt (99.3 g, 0.33 mol) in 1290 mL of MeOH. The mixture was stirred at room temperature for 30 h, concentrated on a rotary evaporator, combined with saturated NaCl, and extracted with CH_2Cl_2/Et_2O. The organic extracts were combined, washed with saturated NaCl, dried (Na_2SO_4), and concentrated on a rotary evaporator. The resultant solid was treated with methanolic HCl and enough Et_2O to initiate crystallization. The product, (*R*)-*N*-[[2-[(methylamino)methyl]phenyl]phenylmethyl]propanecarboxamide (**57**; 41.4 g, 80%) was collected: mp 207.5–208.5 °C; $[\alpha]^{25}_D$ = +46.6° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$) δ 1.13 (t, 3H, *J* = 7), 2.38 (sep, 2H, *J* = 7), 2.69 (s, 3H), 4.00 (d, 1H, *J* = 15), 4.40 (d, 1H, *J* = 15), 6.18 (d, 1H, *J* = 8), 7.10–7.50 (m, 8H), 7.55–7.68 (m, 1H), 8.82 (d, 1H, *J* = 8), 10.18 (br, 2H). Anal. ($C_{18}H_{22}N_2O$) C, H, N. A solution of **57** in 505 mL of concentrated HCl was heated under reflux for 50 h. After filtering the mixture, it was concentrated on a rotary evaporator, made basic with 35% NaOH and extracted with Et_2O/hexane. The organic extracts were combined, dried (Na_2SO_4), and concentrated to give the crude chiral diamine *R*-**1b** (29.2 g, 99%) which showed the same R_f on SiO_2 TLC eluted with 30% IPA in *t*-BuOMe as the racemic diamine, and the ^1H NMR spectrum was identical to racemic diamine.[12] This material (870 mg, 2.91 mmol) was reacted with triethyl orthopropionate following general method A to give *R*-8 (387 mg, 44%); mp 245–246 °C; $[\alpha]^{25}_D$ = +343.8° (*c* 1.0, $CHCl_3$).

Resolution of (*RS*)-4,5-Dihydro-4-methyl-1-phenyl-3-(2-phenylethyl)-1*H*-2,4-benzodiazepine (15). To a solution of racemic **15** (46.9 g, 138 mmol) in 110 mL of MeOH was added dibenzoyl-D-tartaric acid monohydrate (51.8 g, 138 mmol). After heating to obtain a solution, the salt was allowed to crystallize at room temperature overnight. The crystals were collected, giving pure *R*-**15** dibenzoyl-D-tartarate (41.9 g, 87%): mp 159–160 °C; $[\alpha]^{25}_D$ = +186° (*c* 1.0, MeOH). Anal. ($C_{24}H_{24}N_2 \cdot C_{18}H_{14}O_8$) C, N; H: calcd 5.85; found, 5.42. The free base was regenerated by stirring the salt with a mixture of 1 N NaOH and *t*-BuOMe. NaCl was added to saturate the aqueous phase and the organic layer was separated, washed with saturated NaCl, dried (Na_2SO_4), and concentrated to give 21.75 g of oil. The HCl salt was prepared in MeCN/Et_2O with ethereal HCl to give *R*-**15** as the HCl salt (20.15 g, 77% from racemic **15**): mp 198–199.5 °C; $[\alpha]^{25}_D$ = +261° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.68 (s, 1H), 2.95 (s, 3H), 3.00–3.25 (m, 2H), 3.25–3.42 (m, 2H), 3.50 (d, 1H, *J* = 14), 4.87 (d, 1H, *J* = 14), 6.00 (d, 1H, *J* = 6), 7.00–7.70 (m, 14H). Anal. ($C_{24}H_{24}N_2 \cdot HCl$) C, H, N. The mother liquors containing the dibenzoyl-D-tartaric acid were concentrated on a rotary evaporator. The residue was converted to the free base as above to give 31.1 g (91 mmol) as an oil. This oil was dissolved in 100 mL of MeOH, treated with dibenzoyl-L-tartaric acid monohydrate (34.3 g, 91 mmol), and heated to give solution. After the solution was heated at room temperature for 20 h, the crystals were collected giving *S*-**15** dibenzoyl-L-tartarate (37.2 g, 77%): mp 169–170 °C; $[\alpha]^{25}_D$ = −198° (*c* 1.0, MeOH). The free base was regenerated as above and the HCl salt was prepared and recrystallized from MeCN/Et_2O to give *S*-**15** as the HCl salt (18.45 g, 71% from racemic **15**): mp 198–199.5° C; $[\alpha]^{25}_D$ = −249° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.75 (s, 1H), 2.92 (s, 3H), 3.00–3.25 (m, 2H), 3.25–3.45 (m, 2H), 3.50 (d, 1H, *J* = 14), 4.85 (d, 1H, *J* = 14), 6.00 (d, 1H, *J* = 7), 7.00–7.70 (m, 14 H). Anal. ($C_{24}H_{24}N_2 \cdot HCl$) C, N; H: calcd, 5.85; found, 5.40.

(*R*)-4,5-Dihydro-4-methyl-1-phenyl-3-(2-phenylethyl)-1*H*-2,4-benzodiazepine [*R*-15]. By following general method B, the crude chiral diamine *R*-**1b** (31.9 g, 141 mmol) was converted to *R*-**15** (4.99 g, 9%) isolated as the HCl salt: mp 195–197 °C; $[\alpha]^{25}_D$ = +262° (*c* 1.0, $CHCl_3$).

Biological Studies. The animal care, use of tissue, and in vivo experimentation conform to the NIH Guide for the Care and Use of Laboratory Animals (NIH Publication no. 86-23, 1985), the Animal Welfare Act (P.L. 89-544, as amended). All research involving animals described in this publication was performed in accord with the Sterling Winthrop Pharmaneuticals Research Division's (SWPRD) Policy on Animal Use and all national and federal legislation. All SWPRD animal facilities and programs are accredited by the American Association for Accreditation of Laboratory Animal Care (AALAC).

In Vitro Pharmacology. A. Radioligand Binding to Potassium Channels. Ventricular myocytes were enzymatically dissociated from the hearts of adult male guinea pigs (400–500 g; Charles River Labs, Wilmington, MA) and radioligand studies performed as previously described.[15] Myocytes (1–12 mg of protein/mL were incubated with [^{3}H]dofetilide (10–15 nM) for 1 h at 34 °C in 0.10 mL of high-K^+ buffer containing 0.1% bovine serum albumin. All incubations were performed in triplicate and nonspecific binding was determined by incubation with 10 μM unlabeled dofetilide. Myocyte-bound [^{3}H]dofetilide was determined by filtration on Whatman GF/C filters.

B. Radioligand Binding to Sodium Channels. Homogenates of neuronal membrane vesicles were freshly prepraed from the cortex of male Sprague–Dawley rats as previously described.[20] Vesicular homogenate (100 μL; ca. 150–300 μg of protein) were added to an incubation buffer containing [^{3}H]batrachotoxinin benzoate (^{3}H-BTX-B) (56.8 Ci/mmol; 10 nM final concentration); *Leiurus quinquestriatus* (Lqq) North African scorpion venom (17 μM); tetrodotoxin (1.0 μM), and unlabeled test compounds. Incubation buffer (pH 7.4 at 25 °C) contained choline chlorine (130 mM), HEPES (50 mM), Tris-base (23 mM), glucose (5.5 mM, $MgSO_4 \cdot 7H_2O$ (0.8 mM), KCl (5.4 mM), and 0.1% bovine

serum albumin. Preparations were incubated at 37 °C for 2 h, followed by rapid filtration through Whatman GF/C filters using 10 mL per tube of ice cold wash buffer (163 mM choline Cl^-; 50 mM HEPES adjusted with TRIS base to pH 7.4; 1.8 mM $CaCl_2$; 0.8 mM $MgSO_4$; 1.0 mg/mL of bovine serum albumin).

Total radioactivity bound to neural membranes was determined by liquid scintillation spectrometry. Assays were done in parallel with preparations exposed to either 0.3 mM veratridine or 0.3 mM aconitine. These alkaloid toxins reportedly compete with BTX for specific binding at site 2 of the sodium channel,[21] and in the presence of these saturating concentrations, the remaining BTX radioactivity remaining trapped on the filter is a measure of nonspecific binding. Percent inhibition of specific binding was computed as the ratio of radioactivity bound in the presence and absence of selected test agents, minus nonspecific binding. Values reported in the text and tables are means of duplicate determinations where each compound was tested at a final concentration of 10 μM.

In Vivo Pharmacology. A. Aconitine-Induced Arrhythmias in Guinea Pigs. Delay in the onset of aconitine induced arrhythmias was used as an index of antiarrhythmic activity in anesthetized guinea pigs. Lead II electrocardiograms were continuously recorded from male Duncan–Hartley guinea pigs (600–900 g), anesthetized with urethane HCl (1.2 g/kg, ip). Guinea pigs were pretreated with selected doses of various antiarrhythmic agents or saline (1 mL/kg, iv), administered 10 min prior to challenge with a lethal dose of aconitine hydrochloride (LD_{100} = 34 μg/kg, iv). Dose–response studies were conducted in parallel groups (n = 6 per dose) with the maximally tolerated dose of the test agent determined by the appearance of normal sinus rhythm within 1 min after bolus injection. The average time (in min) for each dose group was monitored for the appearance of the first premature ventricular contraction (PVC), sustained runs of ventricular tachycardia (VT), and ventricular fibrillation (VF) lasting longer than 15 s. Data were compared to concurrent controls using a one-way analysis of variance.[22] Dose–response relationships were determined using a least-square linear regression. Protection against aconitine-induced arrhythmias was defined as a significant delay ($p < 0.05$) in the onset time for PVC, VT, and VF time.

B. Ventricular Refractoriness (ERP) Measurements in Guinea Pigs. ERP determination in anesthetized guinea pigs was modified from standard programmed electrophysiological techniques.[23,24] Male Duncan–Hartley guinea pigs (600–800 g) were anesthetized with sodium pentobarbital (30 mg/kg, ip) and ventilated with a small animal respirator and the left ventricle exposed via a lateral thoracotomy. Bipolar plunge electrodes were used to deliver stimuli (2 ms pulses at 2× threshold, at 5 Hz) from a Bloom DTU-2 stimulator (Bloom Electronics, Inc., Reading, PA). Ventricular refractoriness was determined by premature stimulation (S2) following an 8 beat S1 train. The interval between the last S1 and the premature S2 pulse was reduced in 10 ms increments until a ventricular response was not initiated. ERP was defined as the longest S1–S2 interval that failed to produce a ventricular response. Pacing stimuli and the ECG were digitized by an 8-bit A/D converter (R. C. Electronics, Santa Barbara, CA) and displayed on an Apple IIe microcomputer.

Measurement of cardiac function was modified from techniques previously described in anesthetized guinea pigs.[25] A fluid-filled polyethylene catheter, connected to a Millar Micro-tip transducer (Model 4F, Millar Inst. Inc., Houston, TX), was inserted through the anterior wall of the left ventricle to monitor left ventricular pressure (LVP). The first derivative of the LVP (dP/dt), obtained from a Grass differentiator (Model 7P20B), was used as an index of contractile function. Hemodynamic parameters were continuously recorded on a Grass polygraph (Model 7B).

Hemodynamic function was evaluated during normal sinus rhythm. Ventricular refractoriness was determined during brief periods of pacing during baseline and 10 min after drug administration. Test compounds were administered (1 mL/kg) as a bolus injection via the left ventricular catheter for doses < 10 mg/kg. Higher doses (>10 mg/kg) were slowly infused over a 1-min interval. Doses were cumulatively increased every 15 min until a maximally tolerated dose which reduced dP/dt by >50% was noted. Data (n = 6 per treatment group) were analyzed using an analysis of variance for repeated measures. Effective doses to increase ERP by a minimum of 20 ms (ERP_{20}) or decrease dP/dt by 20% (dP/dt_{20}) are presented as treatment means and were derived from a linear regression of individual dose response curves. Activity in increasing ERP or decreasing dP/dt was defined if significance of these changes was established at a $p <$ 0.05.

C. Coronary-Ligated Dog Model. Oral activity of selected antiarrhythmic agents was evaluated in conscious male mongrel dogs 24 h after occlusion of the left anterior coronary artery (LAD). Colony bred dogs (8.0–19.1 kg) were prepared as previously described[26] using aseptic procedures under halothane anesthesia. Subcutaneous silver electrodes were sutured to the chest to Holter monitor the precordial V1 and V6 cardiac electrograms. Following surgery, animals were given morphine sulfate (1 mg/kg im), Combiotic (0.1 mL/kg), 20 000 units/kg procaine penicillin G, and dihydrostreptomycin base (25 mg/kg, Pfizer Labs) and following recovery were returned to their living quarters. Animals were given free access to water, but food was withheld for 30 h after surgery. Twenty-four hours after LAD occlusion, animals with PVCs in excess of 50% the heart rate were subjected to electrocardiographic monitoring and drug treatment (n = 4 per group). All test agents were dissolved in water and administered by gavage. Holter tapes were recorded for 1 h prior to medication and 12–24 h following oral medication and analyzed in a blinded manner. Antiarrhythmic activity was defined as a significant reduction in the density of arrhythmias for the first 5 h following oral medication expressed as density per hour compared to baseline density and statistically analyzed using analysis of variance.

D. Efficacy in Anesthetized Cats Following Acute Myocardial Infarction. Adult cats (1.5–4.0 kg) were anesthetized with 30–50 mg/kg ip sodium pentobarbital and respired with room air. Two pair of subdermal Grass electrodes were plunged into the left ventricle for cardiac pacing to determine refractoriness using standard pacing techniques. One pair of electrodes were positioned in the left ventricle in an area perfused by the distal branches of the LAD that would become ischemic after total ligation of the LAD. A second pair of electrodes was placed high on the lateral region of the left ventricle where the myocardium would remain perfused following anterior LAD occlusion. Lead II and modified V1 electrocardiograms and blood pressure were monitored continuously throughout the experiment. Following instrumentation the animals were allowed to stabilize for at least 15 min prior to commencement of electrophysiological study. The left ventricle was paced at twice diastolic threshold using a Bloom (model DTU 201) stimulator (Bloom Assoc., Reading, PA) at a frequency fast enough to overdrive sinus rhythm. The typical interspike pacing interval utilized (S1) was 300 ms (3.3 Hz). The effective refractory period (ERP) was defined in both the normal region and the region destined to be infarcted using standard techniques. Following determination of refractoriness, ventricular fibrillation threshold (VFT) was induced by high frequency burst pacing using a train of 20 pulses at 100 Hz triggered 10 ms after the ERP. The stimulating current was increased until fibrillation was induced. The entire sequence was repeated three times at approximately 15 min intervals to obtain baseline values. Animals were medicated with a slow intravenous bolus of test agent and 10 min later subjected to a single-stage LAD occlusion. The pacing sequence was then repeated at 15-min intervals for 2 h following LAD occlusion and thereafter, at 30-min intervals for a total study duration of 5 h. Electrical cardioversion was performed using a Liteguard 9 portable defibrillator (Survival Technology Inc., Bethesda, MD) at pediatric settings (14–50 J). Data were analyzed for statistical significance using an analysis of variance for ranked data. Additional comparisons were made using an analysis of variance on maximal changes within each treatment group (n = 4–6 cats) in addition to the monotonic trend analysis. Maximum changes were noted immediately following intravenous injection and all maximum values were noted at the 15–min time period. Biological significance was established at a probability of error less than 0.05.

Supplementary Material Available: A listing of atomic coordinates, isotropic and anisotropic thermal parameters, bond

lengths and angles, and H atom coordinates for *R*-8 (6 pages). Ordering information is given on any current masthead page.

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