Synthesis and Antiarrhythmic Activity of New 1-[1-[2-[3-(Alkylamino)-2-hydroxypropoxy]phenyl]vinyl]-1*H*-imidazoles and Related Compounds

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Various 1-[1-[2-[3-(alkylamino)-2-hydroxypropoxy]pheny]]vinyl]-1*H*-azoles were synthesized and investigated for β -adrenoceptor-blocking and antiarrhythmic activities. Although no compounds showed more potent β -blocking effects than propranolol in the isolated guinea pig right atria, many compounds exhibited significant antiarrhythmic effects against aconitine or ischemic arrhythmia in mice or dogs. 1-[2,5-Dichloro-6-[1-(1*H*-imidazol-1-yl)-ethenyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol hydrochloride (48) (711389-S) was selected as a candidate for clinical evaluation in man, since its antiarrhythmic effects were superior to those of quinidine, disopyramide, or propranolol. Asymmetric synthesis of (*R*)-(+)- and (*S*)-(-)-48 is described, and it is proven that there is no stereospecificity in the antiarrhythmic effect of 48.

In considering possible approaches to the development of new cardiovascular active agents derived from 1-[1-(2hydroxyphenyl)vinyl]-1*H*-azoles,¹ we attempted to introduce the aminohydroxypropoxy side chain, which is thought to be related to the antihypertensive and β -adrenergic blocking effects. The affinity for the β -adrenergic receptor is determined by the aminohydroxypropoxy side chain, and a number of (aryloxy)propranolamines have been shown to be effective as β -blockers. Interestingly, many compounds synthesized on this premise showed little β -blocking effects in isolated guinea pig right atria and exhibited marked antiarrhythmic activity against aconitine arrhythmias in mice.

We report here a new series of 1-[1-[2-[3-(alky]-amino)-2-hydroxypropoxy]phenyl]vinyl]-1H-azoles (33-81) containing the (aryloxy)propanolamine structure, which were prepared and screened for potential antiarrhythmic activity. From the results of screening tests, <math>1-[2,5-di-chloro-6-[1-(1H-imidazol-1-yl)ethenyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol hydrochloride (48) (711389-S) was selected for further pharmacological studies.

Chemistry. The synthetic routes to the target compounds **33–81** are illustrated in Schemes I and II. The o-hydroxyacetophenone derivatives reacted with the N, N'-thionyldiazoles (using imidazoles, pyrazole, 1,2,4-triazole, and benzimidazole as azoles) in dichloromethane at room temperature to give the phenol derivatives 1–27 described in previous literature.¹ Conversion of o-hydroxybenzyl alcohol into 2-[1-(1H-pyrazol-1-yl)-ethenyl]phenol (28) was achieved by using the N,N'-thionyldipyrazole, as well as the reaction of o-hydroxybenzyl alcohol with the N,N'-thionyldimidazole.² N-(Chlorosulfinyl)pyridone reacted with o-hydroxyacetophenone to give the pyridone derivative **30**.³ Catalytic hydrogenation of the double bond in 1 gave the methyl derivative **31** in good yield.

These phenols (1-31) reacted with epibromohydrin in dimethylformamide in the presence of sodium hydride to give the epoxy compounds 32, which were then treated with alkylamine to obtain the target propanolamine derivatives (33-81) (Scheme II and Tables I and II).

In order to examine the pharmacological activities of the two optical isomers, (R)-(+)- and (S)-(-)-1-[2,5-dichloro-6-[1-(1*H*-imidazol-1-yl)ethenyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol hydrochloride, (R)-(+)-48 and (S)-(-)-48, were synthesized by partial asymmetric syn-





thesis as depicted in Scheme III.

The starting material was (2R)-1-(tosyloxy)-2,3propanediol acetonide (82), which was obtained from D-

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New (Aryloxy)propanolamines

Scheme II



Table I. Physical and Analytical Data for the 1-[1-(2-Hydroxyphenyl)vinyl]-1H-azoles

X 5 6 Z R1 R2

				T	-21			
			-		recrystn		yield,	
no.	R_1	R_2	X	\mathbf{Z}	solvent	mp, °C	%	formula
1	H	Н	Н	1-imidazolyl	<i>i</i> -PrOH	152.5-154	75	$C_{11}H_{10}N_2O$
2	н	н	3-C1	1-imidazolyl	i-PrOH	151.5 - 152.5	46	$C_{11}H_9ClN_2O$
3	н	н	4-Cl	1-imidazolyl	$AcOEt/(i-Pr)_2O$	175 - 178	41	$C_{11}H_9ClN_2O$
4	н	н	5-Cl ·	1-imidazolyl	MeOH	191-193	81	$C_{11}H_9ClN_2O$
5	н	н	3-Me	1-imidazolyl	$AcOEt/(i-Pr)_2O$	141 - 143	53	$C_{12}H_{12}N_2O$
6	н	Н	3-OMe	1-imidazolyl	MeOH	153 - 154	62	$C_{12}H_{12}N_2O_2$
7	н	н	$3,4-Cl_2$	1-imidazolyl	i-PrOH	207 - 209	49	$C_{11}H_8Cl_2N_2O\cdot1/6H_2O$
8	н	H	$3,5-Cl_2$	1-imidazolyl	MeOH	217-219	42	$C_{11}H_8Cl_2N_2O$
9	н	н	$4,5-Cl_{2}$	1-imidazolyl	i-PrOH	252 - 253.5	50	$C_{11}H_8Cl_2N_2O$
10	н	н	$4,6-Cl_{2}$	1-imidazolyl	<i>i</i> -PrOH	193–194	59	$C_{11}H_8Cl_2N_2O$
11	н	н	$3,6-Cl_2$	1-imidazolyl	i-PrOH	182 - 184	69	$C_{11}H_8Cl_2N_2O$
12	н	н	3-Me, 5-Cl	1-imidazolyl	MeOH	161 - 161.5	47	$C_{12}H_{11}ClN_2O$
13	н	н	3-Cl, 6-Me	1-imidazolyl	<i>i</i> -PrOH	152.5 - 153.5	39	$C_{12}H_{11}ClN_2O$
14	н	н	$3,6-Me_2$	1-imidazolyl	AcOEt	130–131	16	$C_{13}H_{14}N_2O$
15	н	н	$3,5-Me_2$	1-imidazolyl	MeOH/AcOEt	134–135	59	$C_{13}H_{14}N_2O$
16	н	н	3-Cl, 5,6-Me ₂	1-imidazolyl	MeOH/AcOEt	152 - 153	34	$C_{13}H_{13}CIN_2O$
17	Me	н	Н	1-imidazolyl	MeOH/AcOEt	182 - 186.5	4	$C_{12}H_{12}N_2O$
18	Me	Me	5-C1	1-imidazolyl	AcOEt	194 - 202	12	$C_{13}H_{13}ClN_2O$
19	н	н	Ĥ	1-(2-Me)imidazolyl	MeOH/AcOEt	170-172	72	$C_{12}H_{12}N_2O$
20	н	н	Н	1-(4-Me)imidazolyl	AcOEt	165 - 170	15	$C_{12}H_{12}N_{2}O$
21	н	н	Н	1-(2-Et-5-Me)imidazolyl	MeOH/AcOEt	208 - 210	12	$C_{14}H_{16}N_2O$
22	н	н	H	1-(4-COOEt-5-Me)imidazolyl	MeOH	216 - 218	40	$C_{15}H_{16}N_2O_3$
23	н	н	Н	1-pyrazoyl	AcOEt/pet. ether	107.5 - 109	5	$C_{11}H_{10}N_2O$
24	н	н	5-Cl	1-pyrazolyl	$AcOEt/(i-Pr)_2O$	143–144	15	$C_{11}H_9ClN_2O$
25	н	н	Н	1-(1,2,4-triazolyl)	AcOEt	153 - 156	21	$C_{10}H_9N_3O$
26	н	н	н	1-benzimidazolyl	AcOEt	193–194	59	$C_{15}H_{12}N_2O$
27	H	Н	3-MeO	1-benzimidazolyl	MeOH/AcOEt	192 - 194	60	$\mathrm{C_{16}H_{14}N_2O_2}$

mannitol by modification of the known procedure.⁴ Compound 82 was converted into the phenoxy derivative 83 by treatment with the sodium phenoxide derivative 11 and removal of the acetone-protecting group by 80% acetic acid. The resulting (R)-(+)-1-[2,5-dichloro-6-[1-(1*H*imidazol-1-yl)ethenyl]phenoxy-2,3-propanol (83) was treated with an equimolar amount of tosyl chloride in the presence of triethylamine to give the primary tosyl derivative. Treatment of this tosyl derivative with sodium hydride in tetrahydrofuran at room temperature gave (R)-(+)-1-[1-[2,5-dichloro-6-(2,3-epoxypropoxy)phenyl]-ethenyl]-1H-imidazole (**32**, $R_1 = R_2 = H$, $X = 3,6-Cl_2$), which was then treated with isopropylamine, giving (R)-(+)-1-[2,5-dichloro-6-[1-(1H-imidazol-1-yl)ethenyl]-phenoxy]-3-[(1-methylethyl)amino]-2-propanol.^{5,6} For-

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Scheme III



- TsCI/Et3N/CH2Cl2/O°C d.
- e, U/NaH/DMF/100°C
- 80%AcOH/85°C f.
- g, NaH/THF/25°C

mation as the hydrochloride salt gave (R)-(+)-1-[2,5-dichloro-6-[1-(1H-imidazol-1-yl)ethenyl]phenoxy]-3-[(1methylethyl)amino]-2-propanol hydrochloride [(R)-(+)-48].

Reductive alkylation⁷ of (R)-glyceraldehyde acetonide with isopropylamine and subsequent hydrolysis⁷ gave (S)-(-)-3-(isopropylamino)-1,2-propandiol (84). Treatment of 84 with benzaldehyde in toluene gave the oxazoline derivative 85a, which was then treated with an equimolar amount of tosyl chloride to give the primary tosyl derivative 85b. Compound 85b was converted into the iodo derivative 85c by treatment with sodium iodide. Treatment of 85c with sodium phenoxide derivative 11 gave the phenoxy derivative 86, which was then treated with hydrochloric acid, giving (S)-(-)-1-[2,5-dichloro-6-[1-(1Himidazol-1-yl)ethenyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol,⁵ isolated as (S)-(-)-1-[2,5-[dichloro-6-[1-(1H-imidazol-1-yl)ethenyl]phenoxy]-3-[(1-methylethenyl)amino]-2-propanol hydrochloride [(S)-(-)-48].

Results and Discussion

 β -Adrenoceptor-blocking effects and the effects on refractory periods of various 1-[2-[3-(alkylamino)-2hydroxypropoxy]benzyl]-1H-azoles in the isolated right atria of guinea pigs were investigated, since many β adrenoceptor blockers with an aminopropoxy substituent showed both potent β -adrenoceptor-blocking and antiarrhythmic effects.

Although there were no β -adrenoceptor blockers more potent than propranolol among the various 1-[2-[3-(alkylamino)-2-hydroxypropoxy]benzyl]-1H-azoles, 18 compounds were selected for examination of their antiarrhythmic effects since they significantly prolonged the effective refractory period of the isolated right atria of guinea pig when compared to quinidine (Table III).

The 18 selected compounds showed significant antiarrhythmic effects in aconitine arrhythmias in mice by in-

- k, HCI/H20/25°C
- I, PhCHO/tol./refl.
- m, NaI/DMF/80°C

travenous administration in doses of 1-10 mg/kg (Table IV). The antiarrhythmic effects of 41, 48, 49, 53, 54, 59, 72, and 73 were also investigated by oral administration because they had been observed at intravenous doses of 1-3 mg/kg. Compounds 48, 49, 54, 72, and 73, which showed significant antiarrhythmic effects at an oral dose of 10 or 30 mg/kg, were selected for their antiarrhythmic effects in dogs (Table IV).

In ischemic arrhythmias in dogs, significant antiarrhythmic effects were observed upon intravenous administration of 48, 49, or 54 at a dose of 3 mg/kg (Table V). Antiarrhythmic effects of 48 and 49 in dogs were also markedly observed at an oral dose of 10 mg/kg. Antiarrhythmic effects of 48 and 49 in dogs were superior to those of propanolol, disopyramide, and quinidine in both intravenous and oral administration. However, 48 was selected for preclinical pharmacological studies because LD₅₀ values of 48 and 49 in slc-ddY mice by oral administration were 210 ± 24.6 and 138.1 ± 25.8 mg/kg, respectively.

No significant differences were observed in the β -adrenoceptor-blocking effects and the effects on the refractory period between 48 and its stereoisomers, (R)-(+)-48 and (S)-(-)-48 (Table III). In the aconitine arrhythmias in mice, there were also no differences between 48 and its stereoisomers.

Finally, we describe the influence of chemical modification on the β -adrenoceptor-blocking and antiarrhythmic activities. In many (aryloxy)propanolamine series, replacement of the isopropylamino group by the tert-butylamino group frequently increases β -blocking potency.¹⁶

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Table II. Physical and Analytical Data for the 1-[2-[3-(Alkylamino)-2-hydroxypropoxy]benzyl]-1H-azoles



33-81

	ъ	р	ъ	ъ	v	7	roomusta soluont	mn °C	yield, %	formule
no.	<u>π</u> 1	R ₂	<u>п</u> з	<u>п</u> 4		<u></u>	Tectystil solvent	<u></u>		
33	н	н	H	i-Pr	H	1-imidazolyl	(; D-) ()	011	49	$C_{17}H_{23}N_{3}O_{2}$
34	H	H	н	t-Bu	H	1-imidazolyi	$(l-PI)_2 O$	12-14	17	$C_{18}\Pi_{25}N_{3}O_{2}$
35	H	H	py py	yr ^t	H	1-imidazolyi	$ACUEt/(l-PT)_2U$	1/4-101	21	$C_{18}H_{23}N_{3}O_{2}$
36	H	H	Nie		H	1-imidazolyi	$ACOEt/(i-Fr)_2O$	6466	20 17	$C_{16} H_{22} R_{3} O_{2}$
37	H II	н u	н u	l-PT	3-01	1-imidazolyi	$ACOEt/(t-FT)_2O$	157-158	20	$C_{17}H_{22}OIN_3O_2$
55 90	п u	n u	п U		4-01	1-imidazolyl	$A_{c}OEt/(i_{c}P_{r})_{c}O$	72-80	20	CueHeeClNeOet0 5HeO
99	л U	л U	n u	ι-ΓΓ ; D.,	4-C1 5-C1	1-imidazolyl	$(i_{1}P_{r})_{1}O$	66 5-67 5	10	C ₁₇ H ₂₂ ClN ₃ O ₂
40	п u	и и	п ц	t-F1	3-Mo	1-imidazolyl	MeOH/MeCN	145 dec	48	C ₁₀ H ₂₂ C ₁₁ (COOH) ₀
41	11	11	**	l-Du	0-1110	i minutazoryi		110 400	10	$5H_0O\cdot0.2MeCN$
42	н	н	н	i-Pr	3-OMe	1-imidazolvl		oil	97	C12H25N2O3+H2O
43	Ĥ	Ĥ	Ĥ	<i>i</i> -Pr	3.4-Cl	1-imidazolyl	MeOH/AcOEt	124 dec	16	C ₁₇ H ₂₁ Cl ₂ N ₃ O ₂ ·2(COOH) ₂ ·
					-,2					0.5H ₂ O
44	н	н	н	<i>i</i> -Pr	3.5-Cl ₂	1-imidazolyl	$AcOEt/(i-Pr)_2O$	88.5-90	32	$C_{17}H_{21}Cl_2N_3O_2$
45	Н	н	н	t-Bu	$3,5-Cl_2$	1-imidazolyl	AcOEt	135 - 136.5	45	$C_{18}H_{23}Cl_2N_3O_2$
46	Н	Н	н	<i>i</i> -Pr	$4,5-Cl_2$	1-imidazolyl	(<i>i</i> -Pr) ₂ O	77–78	57	$C_{17}H_{21}Cl_2N_3O_2$
47	н	Η	н	<i>i</i> -Pr	$4,6-Cl_2$	1-imidazolyl		oil	18	$C_{17}H_{21}Cl_2N_3O_2$
48	н	н	н	i-Pr	3,6-Cl ₂	1-imidazolyl	MeOH/AcOEt	151 - 152	35	$C_{17}H_{21}Cl_2N_3O_2$ ·HCl
49	н	Н	н	<i>i</i> -Bu	$3,6-Cl_2$	1-imidazolyl	AcOEt/pet. ether	104 - 105.5	31	$C_{18}H_{23}Cl_2N_3O_2$
50	н	Η	н	t-Bu	$3,6-Cl_2$	1-imidazolyl	AcOEt	147.5 - 149.5	27	$C_{18}H_{23}Cl_2N_3O_2$
51	н	н	Н	i-Pr	3-Me, 5-Cl	1-imidazolyl	MeOH/MeCN	123–127 dec	42	$C_{18}H_{24}CIN_3O_2 \cdot 2(COOH)_2 \cdot$
				_						$0.5H_2O$
52	н	н	н	t-Bu	3-Me, 5-Cl	1-imidazolyl	MeOH/MeCN	7678 dec	27	$C_{19}H_{26}CIN_{3}O_{2}\cdot 2(COOH)_{2}$
53	H	н	н	i-Pr	3-Cl, 6-Me	1-imidazolyl	EtOH	126 dec	5	$C_{18}H_{24}CIN_3O_2$, $/_3(COOH)_2$
54	н	н	H	t-Bu	3-CI, 6-Me	I-imidazolyi	$AcOEt/(i-Pr)_2O$	131-132	28	$C_{19}H_{26}CIN_3O_2$
55	н	н	н	i-Pr	3,6-Me ₂	1-imidazolyl	$AcOEt/(i-Pr)_2O$	109-110	41	$C_{19}H_{27}N_{3}O_{2}$
56	H	н	н	t-Bu	3,6-Me ₂	1-imidazolyl	AcUEt	136.5-140	52	$C_{20}H_{29}N_{3}O_{2}$
57	H	H	H	i-Pr	3,5-Me ₂	1-imidazolyl	$ACOEt/(i-Pr)_2O$	86-87	58	$C_{19}H_{27}N_{3}O_{2}$
98 70	н	н U	H	t-Bu	3, 3	1-imidazolyi	$ACOEt/(l-PT)_2O$	111-112	00 60	$C_{20}\Pi_{29}\Pi_{3}O_{2}$
60 98	п	п U	п u	<i>i</i> -Pr	$3-C1, 5, 6-101e_2$	1-imidazoiyi	$ACOEt/(i-PT)_2O$	190,120	54	$C_{19}\Pi_{26}OIN_{3}O_{2}$
0V 21	п Ма	п u	п u	<i>і-</i> Би ; Ъ.	$3-01, 3, 0-1010_2$	1-imidazolyi	$ACOEt/(t-FT)_2O$	129-130	17	C H N O O 2H O
69	Ma	ម	п u	t-FT	n u	1-imidazolyl		oil	37	$C_{18} H_{26} N_{3} O_{2} O_{2} H_{2} O_{2} O_{2} H_{2} O_{2} O_{2} H_{2} O_{2} O_$
63	Mo	Mo	й	i.Pr	5-CI	1-imidezolyl	A = OEt / (i - Pr) = O	85-87	37	$C_{19} H_{27} R_{3} O_{2} O_{2} O_{2} H_{2} O_{2} O_{2} O_{3} O_{2} O_{3} O_{2} O_{3} O_$
64	H	н	ਸ	<i>i</i> -Pr	H	1-(2-Me)-	$AcOEt/(i-Pr)_{0}O$	65-66	21	C10HarNoOst0.6HaO
	•••		••		**	imidazolvl	1100210/ (0 2 1/20	00 00		01812251302 0101120
65	н	Н	Н	t-Bu	н	1-(2-Me)-	$(i-Pr)_{2}O$	70-71	18	$C_{19}H_{27}N_3O_2$
						imidazolyl				
66	Н	Н	Н	<i>i-</i> Pr	н	1-(4-Me)-		oil	45	$C_{18}H_{25}N_3O_2$
						imidazolyl				
67	Н	Н	н	<i>i</i> -Pr	Н	1-(2-Et-5-Me)-	$(i-Pr)_2O/pet.$ ether	86.5-87	53	$C_{20}H_{29}N_3O_2$
						imidazolyl				
68	н	н	н	ı-Pr	н	1-(4-COOEt-5-Me)-		oil	27	$C_{21}H_{29}N_{3}O_{4}O.6H_{2}O$
<u>~</u> 0	тт	17	TT	: D.,	T T	1midazolyi		00 5 07 5	07	G H NO
09 70	л U	п u	п U	1-Pr	n u	1-pyrazolyi	$(i-Pr)_2O/pet.$ etner	00.0-07.0	67	$C_{17}H_{23}N_{3}U_{2}$
70	л U	л U	л U	<i>i-</i> Би ; Ът	л 5 С1	1-pyrazolyl	$(l \cdot P r)_2 O / n \cdot nexane$ MoOH / A oOE+	/0-/0 191 199 Jac	3 14	$C_{18}\Pi_{25}N_3U_2$
79	пц	и и	п u	<i>t</i> -FT <i>t</i> - D 11	5-C1	1-pyrazolyl	MeOH/ROEL MoOH/Ft O	107-109 dec	14 61	$C_{17}H_{22}CIN_{3}O_{2}(COOH)_{2}$
73	н	н	й	$i_{-}\mathbf{D}\mathbf{u}$	л-Сі ц	1-(1.2 A-triazolyl)	MeOH/MoOEt	107-105 dec	16	C H N O (COOH)
74	н	н	н	$i_{\rm Pr}$	н	1-benzimidazolyl	MeOH/AcOEt MeOH/AcOEt	148-149 dec	54	$C_{16} H_{22} N_4 O_2 (COOH)_2$
			**	<i>v</i> -1 1	11	1-061121111104020191	MEOII/ ACOLI	140 140 000	04	0.5H ₀
75	н	н	н	t-Bu	н	1-benzimidazolvl	AcOEt/(i-Pr) ₂ O	105-106	43	ConHor NoOn
76	н	Н	Н	<i>i</i> -Pr	3-MeO	1-benzimidazolyl	MeOH/AcOEt	147-148 dec	51	C ₂₂ H ₂₇ N ₃ O ₃ ·(COOH) ₂ ·
							,			0.2H ₂ O
77	н	н	н	t-Bu	3-MeO	1-benzimidazolyl	$AcOEt/(i-Pr)_2O$	110-111	32	$C_{23}H_{29}\tilde{N}_{3}O_{3}$
78	Ь		Н	i-Pr	н	1-pyrazolyl	$(i-\mathbf{Pr})_2\mathbf{O}$	64-65	44	$C_{16}H_{23}N_3O_2$
79	Ь		H	i-Pr	н	1-imidazolyl	MeOH/AcOEt	147.5 dec	31	$C_{18}H_{25}N_8O_6.0.5H_2O$
80	<i>b</i>		H	i-Pr	н	1-imidazolyl	14 0114 -	oil	37	$C_{17}H_{25}N_3O_2 \cdot 0.6H_2O$
81	н	н	н	ı-Pr	н	1-(4-0x0-1,4-	MeOH/ether	173.5-174.5	46	$C_{19}H_{24}N_2O_3 \cdot 1.5(COOH)_2$
	_					ainyaropyridyl)				

^a Yield based on the last step $(1-27 \rightarrow 33-77)$. ^bSee Scheme II. ^cPyrrolidinyl.

The same conclusion could be drawn for the compounds of our series; compare compounds 33 and 34, 48 and 50, 61 and 62, 64 and 64 and 65, 69 and 70, 71 and 72, 74 and 75, and 76 and 77.

Modification of the double bond in compound 33 resulted in considerable decrease in its antiarrhythmic activity; namely, compounds 61, 62, 79, and 80 were less potent. This finding demonstrated the importance of the

Table III	A daman a san tan 121 sal-tu u	A	TR.C	1. 1. 1		0 77 1
Table III	p-Adrenoceptor-blocking	Activities and	Effects on t	ine Maximai	Follow Rate	of various
1-12-13-(A)	kyleming)-2-hydroxymrong	with an zull 1 H.	ozolog in the	Incluted Di	abt Atria of I	Cuinas Dias
* [= [0-(21	kylainino/-2-nyuloxyplopo	xyjbenzyij-iii-	azores in the	s isolateu iti	gui Airia oi v	Guinea rigs.

				1	0 ⁻⁵ MFR,						
	ß	8-blocking	act.:		g/mL		ß	8-blocking	act.:	10^{-5} N	AFR, g/mL
compd	pd pA_2		%		compd		$\mathbf{p}A_2$		<u> </u>	76	
no.	n	IE	CE	n	decrease	no.	\overline{n}	IE	CE	$\begin{array}{r c c c c c c c c c c c c c c c c c c c$	
33	2	6.89	6.89	2	27.1	61	2	6.76	6.52	2	18.6
34	2	8.01	7.69	2	14.1	62	2	7.30	7.19	2	14.5
35	2	6.15	6.13	2	16.7	63	2	5.19	4.90	2	21.6
<u>36</u>	2	6.12	5.41	2	30.7	64	2	6.24	6.24	2	15.0
37	2	5.63	5.66	2	28.2	65	2	6.97	6.97	2	27.1
38	2	6.21	6.19	2	17.8	66	2	7.16	7.19	2	36.1
39	2	5.95	5.86	2	26.3	67	2	6.17	5.80	2	9.1
40	2	6.41	6.30	2	27.1	68	2	6.37	6.15	2	31.7
41	2	5.62	5.81	2	46.6	69	2	7.75	7.44	2	21.6
42	1	6.99	6.64	2	29.0	70	2	8.01	8.10	2	39.2
43	2	4.90	4.52	2	35.8	$\overline{71}$	2	6.74	6.76	2	14.3
44	2	6.64	6.50	2	27.5	72	1	6.99	6.90	2	45.7
45	2	6.51	6.30	2	27.1	73	1	6.33	6.12	2	42.8
46	1	6.23	6.64	2	23.8	74	2	6.46	6.67	2	16.8
47	2	6.27	6.44	2	19.6	75	2	7.08	7.29	2	35.8
48	4	5.29	4.86	4	45.7	76	1	6.41	6.26	2	22.3
49	2	5.81	4.89	2	34.9	77	1	7.03	7.03	2	39.2
50	2	5.41	5.27	2	26.3	78	1	7.54	7.42	2	28.7
51	1	5.93	5.22	2	37.9	79	2	6.66	6.69	$\overline{2}$	14.2
52	1	5.04	5.49	2	27.3	80	2	6.83	6.90	$\overline{2}$	15.6
53	1	5.55	5.67	2	50.6	81	2	6.19	6.20	2	13.0
54	1	5.77	5.04	2	49.8	(R)-(+)-48	4	5.19	4.46	5	39.5
55	1	6.43	6.23	2	35.7	(S)-(-)-48	4	5.05	5.08	5	40.3
56	1	6.47	6.36	2	17.1					-	
57	1	6.31	5.55	2	25.9	propranolol	5	8.62	8.44	4	33.5
58	1	6.58	5.55	2	31.8	disopyramide	-			4	15.7
59	1	5.96	5.04	2	29.8	quinidine				12	26.4
60	1	6.21	6.18	2	31.9	•					

^a To evaluate β -adrenoceptor-blocking activities, isoproterenol was used as an agonist. The pA_2 values of the compounds were determined for both the inotropic (IE) and chronotropic (CE) effects 1 h after pretreatment of the right atria with various tested compounds. The maximal follow rate (MFR) shows the maximal contractile frequencies of atria to electrical stimulation. Effects of the compounds on MFR were determined 10 min after their incubation with the right atria. The 18 compounds underlined were selected for examination of antiarrhythmic effects. Number of preparations = n.

		iv	v			ŗ			
compd	n	dose, mg/kg	VES	VT	n	dose, mg/kg	VES	VT	LD ₅₀ , mg/kg, iv
36	5	10	S	s				· · · · · · · · · · · · · · · · · · ·	45.4
41	5	3	S	S	5	30	S	S	23.1
43	5	3	S	\mathbf{s}					33.9
48	7	3	S	S	5	10		S	19.8
49	5	1	S	S	6	10	S	S	15.5
51	6	3	S	S					48.8
53	5	1		S	5	30	S	S	28.5
54	5	3	S	S	5	10	S	S	29.5
55	6	3	S	S					30.7
58	5	3	S	S					15.9
59	6	1	S	S	5	30	s	S	15.5
60	5	3	S	S					18.8
66	5	3		S					36.4
70	5	10	S	s					22.3
72	5	3		s	5	10	S		32.5
73	5	3	s	S	5	30	S	s	36.4
75•	5	3	S	S					26.5
77	5	3	S	s					19.8
(R)-(+)-48	5	3	s	S	5	10		s	
(S) - (-) - 48	5	3	s	s	5	10	S	S	
propranolol	5	10	S	s	7	30	\mathbf{S}		29.2
disopyramide	6	10	S	S	8	30	s	S	30.0
quinidine	11	10	S	S	5	30	s	S	53.6

^a Intravenous (iv) or oral (po) administration of compounds at 3 or 30 min before aconitine infusion, respectively. n, number of mice; VES, ventricular extrasystole; VT, ventricular tachycardia; S, significant antiarrhythmic effect (times to cause VES or VT were significantly prolonged compared with the saline group: Student's t test).¹³ LD₅₀, 50% lethal doses in mice (up and down method¹⁴).

double bond for the antiarrhythmic effect in compounds containing this moiety. Replacement of the imidazole group in compound 33 by pyrazole (compound 69) or 1,2,4-triazol-1-yl (compound 73) did not decrease the antiarrhythmic effect. However, bulky azoles such as 2methylimidazole (64), 2-ethyl-5-methylimidazole (67), and benzimidazole (74) decreased the antiarrhythmic effect, with the exception of compounds 65 and 68 (which have

		dose	iv, % sinus beats		duration.		dose.	po, % sinus beats		duration.
compd	n	mg/kg	before	after	min	n	mg/kg	before	after	min
48	3	3	5.8	88.9	45	4	10	9.3	69.3	180
49	3	3	6.5	94.5	60	4	10	9.9	44.8	180
54	3	3	11.7	59.1	30					
72	2	3	1.8	14.3						
73	3	3	9.8	28.3	15					
propranolol	4	3	11.7	75.0	30	4	60	12.0	51.6	90
disopyramide	3	10	22.4	88.4	30	4	60	10.1	66.2	270
quinidine	5	10	14.1	74.1	60	3	60	4.2	58.3	300

Table V. Effects of Various 1-[2-[3-(Alkylamino)-2-hydroxypropoxy]benzyl]-1*H*-azoles on Ischemic Arrhythmias in Dogs (Glass Bead Method)^a

^a Intravenous administration, iv; oral administration, po; number of dogs, n.

high potency).

Experimental Section

Melting points were determined in a "Büchi" capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Varian T-60 spectrometer. Elemental analyses were performed by the analytical department of Shionogi Research Laboratories and are within $\pm 0.4\%$ of the calculated values.

2-[1-(1*H*-Imidazol-1-yl)ethenyl]phenol (1). The synthesis of this compound was described in ref 1b, and the compounds 2-22 were prepared in a similar manner.

4-Chloro-2-[1-(1H-pyrazol-1-yl)ethenyl]phenol (24). To a solution of pyrazole (9.4 g, 0.138 mol) and dry CH₂Cl₂ (47 mL) was added SOCl₂ (4.08 g, 0.034 mol) dropwise with the temperature maintained at room temperature. After the mixture had been stirred for 10 min, o-hydroxyacetophenone (3.9 g, 0.023 mol) was added at room temperature with stirring. After stirring for 3 h at room temperature, the mixture was diluted with aqueous NaHCO3 and extracted with CH2Cl2. The extract was washed with H₂O, dried over Na₂SO₄, and evaporated to remove the solvent. The residue was refluxed with toluene (98 mL) and p-toluenesulfonic acid (980 mg) for 2.5 h. Toluene was evaporated and the residue was neutralized with aqueous NaHCO₃ and extracted with CH₂Cl₂. The extract was washed with H₂O, dried over Na₂SO₄, and evaporated to remove the solvent. The residue was chromatographed on silica gel and eluted with 1% $MeOH/CH_2Cl_2$ to give the starting o-hydroxyacetophenone (1.19) g, 30.5%). The fractions eluted with 2% MeOH- CH_2Cl_2 were collected to obtained 24 (750 mg, mp 140-142.5 °C, from AcOEt/diisopropyl ether, 14.9%): NMR (Me₂SO- d_{θ}) δ 5.07 (1 H, s, =CH vinyl), 5.77 (1 H, s, =CH) vinyl), 6.83-7.43 (3 H, m, aromatic), 6.40 (1 H, m, pyrazole), 7.63 (2 H, m, pyrazole), 9.95 (1 H, br s, OH). Anal. $(C_{11}H_9N_2OCl)$ C, H, Cl, N.

Compound 23 was prepared in a similar manner.

2-[1-(1H-1,2,4-Triazol-1-yl)ethenyl]phenol (25). 1,2,4-Triazole (5.0 g, 0.072 mol) was suspended in CH₂Cl₂ (25 mL), to which SOCl₂ (2.15 g, 0.018 mol) was added dropwise at 0 °C with stirring. o-Hydroxyacetophenone (2.46 g, 0.018 mol) was then added after 5 min. The mixture was stirred at room temperature for 2.5 h and then aqueous NaHCO₃ was added, and the mixture was extracted with CH₂Cl₂. The extract was washed with H₂O, dried over Na₂SO₄, and evaporated to remove the solvent. The residue was refluxed with toluene (32 mL) and p-toluenesulfonic acid (320 mg) for 2 h. Toluene was evaporated and the residue was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 . The extract was washed with H_2O , dried over Na_2SO_4 , and evaporated to remove the solvent. The residue was chromatographed on silica gel and eluted with CH_2Cl_2 to give the starting o-hydroxyacetophenone (990 mg, 40.2%). The fractions eluted with 3% MeOH-CH₂Cl₂ were collected to obtained 25 (702 mg, mp 153-156 °C, from AcOEt, 20.7%): NMR (Me₂SO-d₆) δ 5.22 (1 H, s, =CH vinyl), 5.82 (1 H, s, =CH vinyl), 6.73-7.43 (4 H, m, aromatic), 8.07 (1 H, s, triazole), 8.35 (1 H, s, triazole), 9.77 (1 H, br s, OH). Anal. $(C_{10}H_9N_3O)$ C, H, N. 2-[1-(1H-Benzimidazol-1-yl)ethenyl]phenol (26). The

2-[1-(1*H*-Benzimidazol-1-yl)ethenyl]phenol (26). The synthesis of this compound was described in ref 1c and the other benzimidazole compound (27) was prepared in a similar manner.

2-(1-Pyrazoly]methyl)phenol (28). Pyrazole (24.68 g, 0.36 mol) was mixed with dry CH_2Cl_2 (123 mL), to which $SOCl_2$ (10.78 g, 0.09 mol) was added with stirring under ice cooling. The mixture

was stirred for 10 min and o-hydroxybenzyl alcohol (7.5 g, 0.06 mol) was added. The mixture was stirred at room temperature for 1.5 h, then neutralized with aqueous NaHCO₃, and extracted with CH₂Cl₂. The extract was washed with H₂O, dried over Na₂SO₄, and evaporated to remove the solvent. The residue was chromatographed on silica gel. Eluates with CH₂Cl₂ were collected, evaporated to remove the solvent, washed with AcOEt/diisopropyl ether, and filtered to give **28** (5.95 g, mp 123–124 °C, from AcOEt/diisopropyl ether, 56.5%): NMR (CDCl₃) δ 5.23 (2 H, s, CH₂), 6.27–7.53 (7 H, m, aromatic), 10.27 (1 H, br s, OH). Anal. (C₁₀H₁₀N₂O) C, H, N.

2-(1-Imidazolylmethyl)phenol (29).² SOCl₂ (3.30 g, 0.028 mol) was added to a mixture of imidazole (7.56 g, 0.111 mol) and dry CH₂Cl₂ (38 mL) at room temperature as above. After 10 min, o-hydroxybenzyl alcohol (2.0 g, 0.018 mol) was added at room temperature. After 30 min of stirring, the mixture was washed with aqueous NaHCO₃ and extracted with CH₂Cl₂, and the CH₂Cl₂ layer was dried over anhydrous Na₂SO₄ and evaporated. The residue was washed with CH₃CN to give **29** (1.06 g, mp 161–164 °C, 32.9%): NMR (Me₂SO-d₆) δ 5.17 (2 H, s, CH₂), 6.83–7.80 (7 H, m, aromatic), 9.87 (1 H, br s, OH). Anal. (C₁₀H₁₀N₂O) C, H, N.

2-[1-(1,4-Dihydro-4-oxo-1*H*-pyridin-1-yl)ethenyl]phenol (30).³ 4-Hydroxypyridine (838 mg, 8.8 mmol) was mixed with a mixture of triethylamine (890 mg, 8.8 mmol) and dry CH₂Cl₂ (8.4 mL) and stirred under ice cooling. A solution of SOCl₂ (1.048 g, 8.8 mmol) in CH₂Cl₂ (3 mL) was added dropwise while the temperature was kept at about 10 °C, and then the mixture was stirred for 30 min and added dropwise to a mixture of ohydroxyacetophenone (1 g, 7.3 mmol), triethylamine (890 mg, 8.8 mmol), and dry CH₂Cl₂ (10 mL) at the same temperature with stirring. The resultant mixture was stirred at room temperature for 15.5 h and then ice water was added. The mixture was made alkaline with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 . The extract was washed with H₂O, dried over Na₂SO₄, and evaporated to remove the solvent. The residue was chromatographed on silica gel. Eluates with 7% MeOH/CH₂Cl₂ were collected and evaporated to remove the solvent. The product was recrystallized from MeOH/AcOEt to give 30 (436 mg, 27.8%, mp 201-203 °C): NMR $(Me_2SO-d_6) \delta 5.33 (1 H, s, =CH vinyl), 5.47 (1 H, s, =CH vinyl),$ 6.10 (2 H, d, J = 8.0 Hz, pyridone), 6.70-7.30 (4 H, m, aromatic), 7.58 (2 H, d, J = 8.0 Hz, pyridone), 10.03 (1 H, br s, OH). Anal. $(C_{13}H_{11}NO_2)$ C, H, N

2-[1-(1-Imidazoly1)ethy1]phenol (31). A mixture of 1-[1-(2-hydroxypheny1)viny1]-1*H*-imidazole (1) (500 mg), MeOH (20 mL), 14% HCl/MeOH (5 mL), and PtO₂·H₂O (100 mg) was stirred in a hydrogen atmosphere and filtered when hydrogen absorption was finished, about 1.5 h later. The filtrate was condensed, neuralized with an aqeuous NaHCO₃, and extracted with CH₂Cl₂. The extract was washed with water, dried over Na₂SO₄, and evaporated to remove the solvent. The residue was recrystallized from AcOEt/diisopropyl ether to give 31 (456 mg, 90.3%, mp 170.5–172 °C): NMR (Me₂SO-d₆) δ 1.75 (3 H, d, J = 7.0, CH₃), 5.70 (1 H, q, J = 7.0 Hz, methine), 6.73–7.70 (7 H, m, aromatic), 9.87 (1 H, br s, OH). Anal. (C₁₁H₁₂N₂O) C, H, N.

1-[1-[2,5-Dichloro-6-(2,3-epoxypropoxy)phenyl]ethenyl]-1*H*-imidazole (32, $R_1 = R_2 = H$, X = H, Z = 1imidazolyl). 3,6-Dichloro-2-[1-(1*H*-imidazol-1-yl)ethenyl]phenyl (11) (2 g, 7.8 mmol) was dissolved in dry Me₂SO (20 mL), to which KOH (770 mg, 86% purity, 11.8 mmol) was added with stirring at 60 °C. After the mixture had been stirred for 1 h, epibromohydrin (1.61 g, 11.8 mmol) was added with stirring and heated at 60 °C for 3 h. The mixture was decomposed with water and extracted with benzene. The organic layer was washed with water, dried over Na₂SO₄, filtered, and evaporated. The residue was chromatographed on silica gel. The fraction eluted with benzene/CH₃CN (1:1) was collected, giving **32** (1.29 g, 53.3%, oil): NMR (Me₂SO-d₆) δ 2.47–2.87 (2 H, m, methylene), 3.07–3.33 (1 H, m, methilene), 3.67–4.23 (2 H, m, methylene), 5.10 (1 H, d, J = 2.0 Hz, =:CH vinyl), 5.75 (1 H, d, J = 2.0 Hz, =:CH vinyl), 5.75 (1 H, d, J = 2.0 Hz, =:CH vinyl), 7.10–7.60 (5 H, aromatic); IR (neat 1645 (C=:C) cm⁻¹; picrate, mp 126–128 °C dec (from CH₃CN/diethyl ether). Anal. (C₁₄H₁₂-Cl₂N₂O₂·C₆H₃N₃O₇) C, H, Cl, N.

1-[4-Chloro-2-[1-(1H-imidazol-1-yl)-2-methylpropen-1yl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol (63). 4-Chloro-2-[1-(1H-imidazol-1-yl)-2-methylpropen-1-yl]phenol (18) (1.2 g, 4.8 mmol) was dissolved in dry DMF (12 mL), to which 50% NaH (350 mg, 7.3 mmol) was added with stirring at room temperature. After the mixture had been stirred for 5 min, epibromohydrin (990 mg, 7.2 mmol) was added with stirring and the mixture heated at 40 °C for 1 h. The mixture was decomposed with water and extracted with benzene. The organic layer was washed with water, dried over Na₂SO₄ and evaporated to remove the benzene; the resulting oily residue (1.67 g of 32, $R_1 = R_2 =$ Me, X = 5-Cl) was mixed with isopropylamine (6 mL), and the mixture was stirred at 50 °C for 19 h and evaporated to remove the isopropylamine. The residue was chromatographed on alumina (activity III). The fraction eluted with 3% MeOH/CH₂Cl₂ was collected and evaporated to remove the solvent. The residue was washed with diisopropyl ether and filtered to give 63 (800 mg, mp 84-87 °C, 45.5%). Recrystallization from AcOEt-diisopropyl ether gave colorless prisms (650 mg, mp 85–87 °C, 37.0%): NMR (CDCl₃) δ (1.07, 6 H, d, J = 7.0 Hz, CH(Me)₂), 1.72 (6 H, s, =(Me)₂), 2.3-3.0 (5 H, m, OH, NH, methylene), 3.7-3.9 (3 H, m, methylene, methine), 6.73-7.57 (6 H, m, aromatic). Anal. (C₁₉H₂₆ClN₃O₂) C, H, Cl, N.

Compounds 78-81 were prepared in a similar manner.

(2R)-1-(Tosyloxy)-2,3-propanediol Acetonide (82). The tosylate 82 was prepared from D-mannitol by the modification of a known procedure.⁴ A mixture of D-mannitol (36.4 g, 0.2 mol), 2,2-dimethoxypropane (49 mL, 0.4 mol), MgCl₂ (anhydrous, 38 g, 0.4 mol), and acetone (200 mL) was refluxed for 7 h and then poured into a mixture of Na_2CO_3 (42.4 g) and H_2O (140 mL). The mixture was extracted with CH₂Cl₂, dried over Na₂SO₄, and evaporated to give the 1,2;5,6-diacetonide of D-mannitol (28 g, 53%). An aqueous solution of NaHCO₃ (12.6 g, 0.15 mol) and $NaIO_4$ (32.1 g, 0.15 mol) was added to a stirred solution of the diacetonide (28 g, 0.107 mol) in H₂O (300 mL). After 0.5 h of stirring at 25 °C, the precipitate was removed by filtration. NaBH₄ (3.0 g, 0.08 mol) was added to the filtrate and the mixture stirred at 25 °C for 1 h. The mixture was extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and evaporated to leave an oil (17.97 g). Et₃N (15.2 g, 0.15 mol) and TsCl (25.9 g, 0.136 mol) was added to a solution of the (S)-glycerol 1,2-acetonide prepared as above (17.97 g, 0.136 mol) in CH₂Cl₂ (200 mL) at 0 °C. After the mixture was stirred for 1 h at 0 °C, the precipitate was removed by filtration and the filtrate was washed with brine, dried (Na_2SO_4) , and evaporated. The residue was chromatographed on silica gel. The fraction eluted with 50% n-hexane/diethyl ether gave the tosylate 82 (26.3 g, 23% from D-mannitol): $[\alpha]^{23}_{D}$ -4.3° (c 13, EtOH), [lit.^{4a} $[\alpha]^{24}_{D}$ –4.6° (c 13, EtOH)].

Racemization of (S)-glycerol 1,2-acetonide was reported.¹⁷

(R)-(+)-1-[2,5-Dichloro-6-[1-(1*H*-imidazol-1-yl)ethenyl]phenoxy]-2,3-propanediol (83). NaH (0.21 g, 8.78 mmol) was added to a stirred solution of the phenol 11 (2.24 g, 8.78 mmol) in DMF (20 mL) at 25 °C. After 10 min of stirring, the tosylate 82 (2.51 g, 8.78 mmol) was added and the mixture was heated at 100 °C for 3 h. The mixture was poured into ice and extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and evaporated to give the acetonide of 83 as a syrup: IR (neat) 1640, 1560 cm⁻¹; NMR (CDCl₃) δ 1.34 (6 H, s, Me₂), 3.60-4.40 (5 H, m, methylene, methine), 5.05 (1 H, d, J = 2.0 Hz, =CH vinyl), 5.70 (1 H, d, J = 2.0 Hz, =CH vinyl), 6.40–7.60 (5 H, m, aromatic). The acetonide of 83 was heated in 80% aqueous AcOH (20 mL) at 85 °C for 1 h. The mixture was evaporated and the residue was extracted with CH₂Cl₂. The organic layer was washed with 10% NaOH, dried (Na₂SO₄), and evaporated. The residue was

10% NaOH, dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel. The fraction eluted with CH₂Cl₂/MeOH (9:1) gave 83 (1.92 g, 66%) as a syrup: NMR (CDCl₃) δ 3.50–4.40 (7 H, m, OH, methylene, methine), 5.10 (1 H, d, J = 2.0 Hz, =-CH vinyl), 5.70 (1 H, d, J = 2.0 Hz, =-CH vinyl), 5.70 (1 H, d, J = 2.0 Hz, =-CH vinyl), 6.60–7.60 (5 H, m, aromatic). Hydrochloride of 83: mp 143–145 °C (from MeOH/AcOEt); IR (Nujol) 3260 cm⁻¹; [α]²⁴_D +11.0° (c 1.00, MeOH). Anal. (C₁₄H₁₅Cl₃N₂O₃) C, H, Cl, N.

(R)-(+)-1-[2,5-Dichloro-6-[1-(1 \dot{H} -imidazol-1-yl)ethenyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol [(R)-(+)-48]. TsCl (2.20 g, 11.6 mmol) was added to a mixture of the diol 83 (3.80 g, 11.6 mmol), Et₃N (2.34 g, 23.2 mmol), and CH₂Cl₂ (40 mL) at 0 °C and stirred for 2 h. Precipitate was removed by filtration, and the filtrate was washed with brine, dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel. The fraction eluted with CH₂Cl₂/MeOH (95:1) gave the tosylate of 83 (3.39 g, 66%) as a syrup: NMR (CDCl₃) δ 2.44 (3 H, s, Me), 3.80-4.20 (6 H, m, methylene, methine, OH), 5.05 (1 H, d, J = 2.0 Hz, ==CH vinyl), 5.70 (1 H, d, J = 2.0 Hz, ==CH vinyl), 6.90-7.90 (9 H, m, aromatic).

A mixture of the tosylate of 83 (3.39 g, 7.02 mmol), NaH (168.5 mg, 7.02 mmol), and THF (35 mL) was stirred at 25 °C for 1 h. The reaction mixture was poured into ice and extracted with CH_2Cl_2 . The organic layer was dried (Na₂SO₄) and evaporated to give the epoxide 32 ($R_1 = R_2 = H, X = 3,6-Cl_2$) (1.85 g, 85%) as a syrup: NMR (CDCl₃) δ 2.40–4.20 (5 H, m, methylene, methine), 5.05 (1 H, d, J = 2.0 Hz, =CH vinyl), 5.70 (1 H, d, J = 2.0 Hz, =CH vinyl), 7.02–7.55 (5 H, m, aromatic).

A mixture of epoxide 32 ($R_1 = R_2 = H$, X = 3.6-Cl₂) (1.85 g, 5 mmol), *i*-PrNH₂ (1 mL), and *i*-PrOH (20 mL) was refluxed for 1 h. After evaporation of the mixture, the residue was chromatographed on silica gel. The fraction eluted with CH₂Cl₂/MeOH/28% NH₄OH (85:15:1) gave the free base of (R)-(+)-48 (1.32 g, 60%), mp 133-134 °C (AcOEt). The compound was identical with the free base of (R)-48 with respect to IR, NMR, and TLC. HCl (6.5%) in MeOH (1.5 mL) was added to a solution of the free base of (R)-(+)-48 (1.0 g, 2.70 mmol) in MeOH (1.0 mL). The mixture was evaporated and the residue was recrystallized from MeOH-Et₂O to afford the hydrochloride of (R)-(+)-48 (692 mg, 63%): mp 184-186 °C; [α]²⁴_D +16.0° (c 1.00, MeOH).⁶ Anal. (C₁₇H₂₂Cl₃N₃O₂) C, H, Cl, N.

(S)-(-)-3-(Isopropylamino)-1,2-propanediol (84). Pb(OAc)₄ (90%, 26.4 g, 53 mmol) was added to a stirred solution of 1,2;-5,6-diisopropylidenemannitol (14 g, 53 mmol) in THF (68 mL) at 25 °C. After 3 h of stirring at 25 °C, the precipitate was removed by filtration and the filtrate was concentrated. The residue was dissolved in MeOH (63 mL) and *i*-PrNH₂ (63 mL) and then hydrogenated (1 atm of H₂) in the presence of 5% Pd-C. The catalyst was removed by filtration and the filtrate was evaporated to give the 1,2-acetonide of 84 (13.3 g, 72%) as an oil: IR (film) 3300 cm⁻¹; NMR (CDCl₃) δ 1.05 (6 H, d, J = 7.0 Hz, CHMe₂), 1.35 and 1.42 (each 3 H, each s, 2 Me), 2.50-4.45 (7 H, m, methylene, methine, NH).

The acetonide of 84 prepared as above was stirred in 6 N HCl (20 mL) at 25 °C for 2 h. The mixture was basified with K₂CO₃ and extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and evaporated to afford an oil, which was chromatographed on alumina (activity II). The fraction eluted with CH₂Cl₂/MeOH/28% NH₄OH (90:10:1) gave the amine 84 (9.5 g, 93%) as an oil: IR (film) 3300 cm⁻¹; NMR (CDCl₃) δ 1.05 (6 H, d, J = 7.0 Hz, CHMe₂), 2.35–3.85 (9 H, m, methylene, methine, OH, NH); $[\alpha]_{D}^{23}$ –13.4° (c 1.06, MeOH); Hemidi-*p*-toluoyl-D-(-)-tartrate of 84: mp 160–162 °C (MeOH–acetone). Anal. (C₃₂H₄₈N₂O₁₂) C, H, N.

(S)-(-)-2-Phenyl-3-isopropyl-5-(hydroxymethyl)oxazolidine (85a). A mixture of the diol amine 84 (22 g, 165 mmol) and benzaldehyde (21 g, 198 mmol) in toluene (110 mL) was refluxed for 3 h, and water was removed azeotropically. The mixture was evaporated to leave an oil, which was distilled to give 85a (30 g, 82%): bp 120-123 °C (0.2 mmHg); IR (film) 3400 cm⁻¹; NMR (CDCl₃) δ 1.05 (6 H, d, J = 7.0 Hz, CHMe₂), 2.65-4.60 (7 H, m, methylene, methine, OH), 5.06 and 5.10 (each 0.5 H, each s, Ar

⁽¹⁷⁾ Baldwin, J. J.; Raab, A. W.; Hensler, K.; Arison, B. H.; McClure, D. E. J. Org. Chem. 1978, 43, 4876.

CH), 7.02–7.60 (5 H, m, aromatic); $[\alpha]^{23}{}_{D}$ –6.1° (c 1.15, MeOH). Anal. (C₁₃H₁₉NO₂) C, H, N.

(S)-(-)-2-Phenyl-3-isopropyl-5-[(tosyloxy)methyl]oxazolidine (85b). TsCl (8.7 g, 45 mmol) was added to a stirred solution of alcohol 86a (10 g, 45 mmol) in pyridine (50 mL) at 0 °C. After stirring at 0 °C for 1.5 h, the mixture was diluted with CH₂Cl₂, washed with aqueous Na₂CO₃, dried (Na₂SO₄), and evaporated to afford 85b (16.1 g, 95%) as an unstable oil, which was used in the next step without further purification: NMR (CDCl₃) δ 0.97 (6 H, d, J = 7.0 Hz, CHMe₂), 2.42 (3 H, s, Ar Me), 2.65-4.45 (6 H, m, methylene and methine), 5.04 and 5.08 (each 0.5 H, each s, Ar CH), 7.18-7.62 (5 H, m, aromatic); $[\alpha]^{23}_{D} - 2.8^{\circ}$ (c 1.10, MeOH).

Racemic tosylate 85b is crystalline (mp 66–67 °C, from Et_2O /petroleum ether) and condensation with the phenol 11 followed by acid treatment gave the free base of racemic 48 (42% after recrystallization from AcOEt/Et₂O).

(S)-2-Phenyl-3-isopropyl-5-(iodomethyl)oxazolidine (85c). A mixture of tosylate 85b (16.1 g 42.9 mmol) and NaI (16.0 g, 107 mmol) in DMF (81 mL) was heated at 80 °C for 3 h under nitrogen. The mixture was poured into ice and extracted with Et₂O. The organic layer was washed with brine, dried (Na₂SO₄), and evaporated to give iodide 86c (11.5 g, 81%) as an oil, which was used in the next step without further purification: NMR (CDCl₃) δ 0.98 (6 H, d, J = 7.0 Hz, CHMe₂), 2.45–4.45 (5 H, m, methylene and methine), 5.22 (1 H, s, ArCH), 7.16–7.60 (5 H, m, aromatic).

(S)-(-)-1-[2,5-Dichloro-6-[1-(1H-imidazol-1-yl)ethyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol Hydrochloride [(S)-(-)-48]. NaH (840 mg, 35 mmol) was added to a stirred solution of the phenol 11 (8.9 g, 35 mmol) in DMF (45 mL) at 25 °C. After 10 min of stirring, iodide 85c (11.5 g, 34.7 mmol) was added and the mixture was heated at 90 °C for 1.5 h. The mixture was cooled to 0 °C, 6 N HCl was added, and the mixture was stirred at 25 °C for 1 h. The mixture was basified with 10% NaOH and extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and evaporated to leave an oil, which was chromatographed on alumina (activity II). The fraction eluted with $CH_2Cl_2/MeOH/28\%$ NH₄OH (85:15:1) gave the free base of (S)-(-)-48 (1.20 g, 7% from 85a), mp 133-134 °C (AcOEt). The free base of (S)-(-)48 was dissolved in 6.5% HCl in MeOH and then Et₂O was added. Recrystallization of the precipitate afforded the hydrochloride (S)-(-)-48 (2.7 g, 77%), mp 184-186 °C, from MeOH/AcOEt. The compound was identical (IR, NMR, TLC) with racemic 48 and (R)-(+)-48. $[\alpha]^{23}{}_{\rm D}$ -16.6° (c 1.00, MeOH).⁶ Anal. (C₁₇H₂₂Cl₃N₃O₂) C, H, N, Cl.

Pharmacology. In order to investigate β -adrenoceptorblocking effects and the effects on refractory periods of tested compounds, isolated right atria of guinea pigs were used. Isolated right atria from male guinea pigs weighing 400-850 g were suspended in a 30-mL organ bath filled with Krebs-Ringer bicarbonate solution at 30 °C, which was aerated with a gas mixture of 95% O₂ and 5% CO₂. With use of FD pick-up (SB-1T, Nihon Kohden, Japan) and preamplifier (RP-3, Nihon Kohden), spontaneous contractions of isolated atria were recorded on a polygraph (WI-260, Nihon Kohden). β -Adrenoceptor-blocking activities of tested compounds were compared on the basis of their pA₂ values⁸ against agonistic effects of isoproterenol in the right atria. In order to observe the effect on the refractory period, effects of tested compounds on the maximal folow rate of isolated right atria to electrical stimulation were determined according to Dawes' method.⁹

Antiarrhythmic effects were investigated in the experimental models of aconitine arrhythmias in mice and ischemic arrhythmias in dogs. Following the procedure of Nwangwu et al.,¹⁰ aconitine arrhythmias were induced in pentobarbital-anesthetized male mice weighing 20–35 g by continuous infusion of aconitine solution into a tail vein (0.685 μ g/min). How intravenous and oral pretreatments with tested compounds prolong the onset of such arrhythmias as ventricular extrasystoles (VES) and ventricular tachycardias (VT) were investigated with recording lead II ECG (AB-620G, Nihon Kohden). Ischemic arrhythmias in dogs were produced according to Wilkerson and Downey¹¹ and Kimoto et

al.¹² Marked ventricular arrhythmias were continuously observed in conscious dogs for 24 h after a glass bead had been inserted into a coronary artery. Antiarrhythmic effects of selected compounds were compared with those of quinidine, disopyramide, and propranolol by intravenous or oral administration. The lead II ECG of a conscious dog was continuously recorded on an ink-writing oscillograph (RJG-4004, Nihon Kohden) by a telemetry system (RZ-5, ZB-141B, Nihon Kohden).

Acute toxicities of tested compounds in male slc-ddY mice were examined according to Brownlee's¹⁴ up and down method or Bliss'¹⁵ probit method.

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Registry No. 1, 74204-47-0; 1 (ketone), 118-93-4; 2, 85128-32-1; 2 (ketone), 3226-34-4; 3, 85128-26-3; 3 (ketone), 6921-66-0; 4, 85128-27-4; 4 (ketone), 1450-74-4; 5, 85128-42-3; 5 (ketone), 699-91-2; 6, 85128-39-8; 6 (ketone), 703-98-0; 7, 85128-36-5; 7 (ketone), 55736-71-5; 8, 85128-25-2; 8 (ketone), 3321-92-4; 9, 3321-92-4; 9 (ketone), 22526-30-3; 10, 85128-37-6; 10 (ketone), 57051-50-0; 11, 85128-28-5; 11 (ketone), 55736-72-6; 12, 85128-43-4; 12 (ketone), 50343-12-9; 13, 85456-98-0; 13 (ketone), 85128-50-3; 14, 85128-45-6; 14 (ketone), 90743-02-5; 15, 85128-46-7; 15 (ketone), 1198-66-9; 16, 85128-44-5; 16 (ketone), 90743-03-6; 17, 85128-30-9; 17 (ketone), 610-99-1; 18, 85128-29-6; 18 (ketone), 90743-04-7; 19, 85128-34-3; 20, 85128-35-4; 21, 85128-33-2; 22, 85128-31-0; 23, 90742-84-0; 24, 85456-97-9; 25, 85128-40-1; 26, 76113-69-4; 27, 85128-41-2; 28, 85137-57-1; 29, 41833-14-1; 30, 82325-04-0; 31, 77175-59-8; 32 (R_1 , R_2 = H, X = 2,5-Cl₂, Z = 1-imidazolyl), 90742-85-1; 32 (R₁, R₂ = H, X = 2,5-Cl₂, Z = 1-imidazolyl)-picrate, 90742-86-2; 32 (\hat{R}_1 , \hat{R}_2 = Me, X = 5-Cl, Z = 1-imidazolyl), 90742-87-3; 33, 85127-67-9; 34, 85127-66-8; 35, 85128-47-8; 36, 85128-48-9; 37, 85127-83-9; 38, 85127-73-7; 38-HCl, 90742-88-4; **39**, 85127-68-0; **40**, 85127-70-4; **41**, 85128-11-6; **41**.(COOH)₂, 85128-12-7; 42, 85127-97-5; 43, 85127-93-1; 43-2(COOH)2, 90742-89-5; 44, 85127-65-7; 45, 85127-69-1; 46, 85127-96-4; 47, 85127-95-3; (\pm) -48, 90742-90-8; (R)-(+)-48, 90821-25-3; (S-(-)-48, 90821-27-5; (±)-48·HCl, 90742-91-9; (R)-(+)-48·HCl, 90821-26-4; (S)-(-)-48·HCl, 90821-28-6; 49, 85127-77-1; 50, 85127-78-2; 51, 85128-15-0; 51-2-(COOH)₂, 85128-16-1; **52**, 85128-13-8; **52**·2(COOH)₂, 90742-92-0; 53, 85127-98-6; 53. (COOH)2, 85127-99-7; 54, 85128-10-5; 55, 85128-20-7; 56, 85128-19-4; 57, 85128-22-9; 58, 85128-21-8; 59, 85128-17-2; 60, 85128-18-3; 61, 85127-75-9; 62, 85127-76-0; 63, 85127-74-8; 64, 85127-85-1; 65, 85127-89-5; 66, 85127-90-8; 67, 85127-84-0; 68, 85127-82-8; 69, 85127-79-3; 70, 85127-92-0; 71, 85127-80-6; 71·(COOH)₂, 85127-81-7; 72, 85128-05-8; 72·(COOH)₂, 85128-06-9; 73, 85128-00-3; 73 (COOH)₂, 85128-01-4; 74, 85127-86-2; 74.(COOH)2, 85127-87-3; 75, 85127-88-4; 76, 85128-07-0; 76. (COOH)₂, 85128-08-1; 77, 85128-09-2; 78, 85128-04-7; 79, 85127-72-6; 79-(COOH)2, 90742-97-5; 80, 85128-49-0; 81, 85128-23-0; 81.1.5(COOH)2, 85128-24-1; 82, 23788-74-1; 82 (alcohol), 22323-82-6; 83, 90742-93-1; 83-HCl, 90742-95-3; 83 (acetonide), 90743-09-2; 83 (tosylate), 90742-96-4; 83 (epoxide), 77046-79-8; 84, 90742-94-2; 84-1/2 di-p-toluoyl-D-(-)-tartrate, 90742-98-6; 87 (1,2-acetonide), 68430-26-2; cis-85a, 90742-99-7; trans-85a, 90743-10-5; cis-(±)-85b, 90821-29-7; trans-(±)-85b, 90821-30-0; cis-85b, 90743-00-3; trans-85b, 90743-11-6; cis-85c, 90743-01-4; trans-85c, 90821-31-1; i-PrNH₂, 75-31-0; t-BuNH₂, 75-64-9; Me₂NH, 124-40-3; pyrrolidine, 123-75-1; pyrazole, 288-13-1; 1,2,4-triazole, 288-88-0; o-hydroxybenzyl alcohol, 90-01-7; 4-hydroxypyridine, 626-64-2; epibromohydrin, 3132-64-7; D-mannitol, 69-65-8; D-mannitol 1,2:5,6-diacetonide, 1707-77-3; 1,1'-sulfinylbisimidazole, 3005-50-3; 1,1'sulfinylbis(2-methylimidazole), 90743-05-8; 1,1'-sulfinylbis(4methylimidazole), 90743-06-9; 1,1'-sulfinylbis(2-ethyl-5-methylimidazole), 90743-07-0; 1,1'-sulfinylbis(4-ethoxycarbonyl-5methylimidazole), 90743-08-1; 1,1'-sulfinylbispyrazole, 50476-18-1; 1,1'-sulfinylbis(1,2,4-triazole), 82969-91-3; 1,1'-sulfinylbisbenzimidazole, 76113-59-2.