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]phenyl]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-(2-hydroxyphenyl)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.

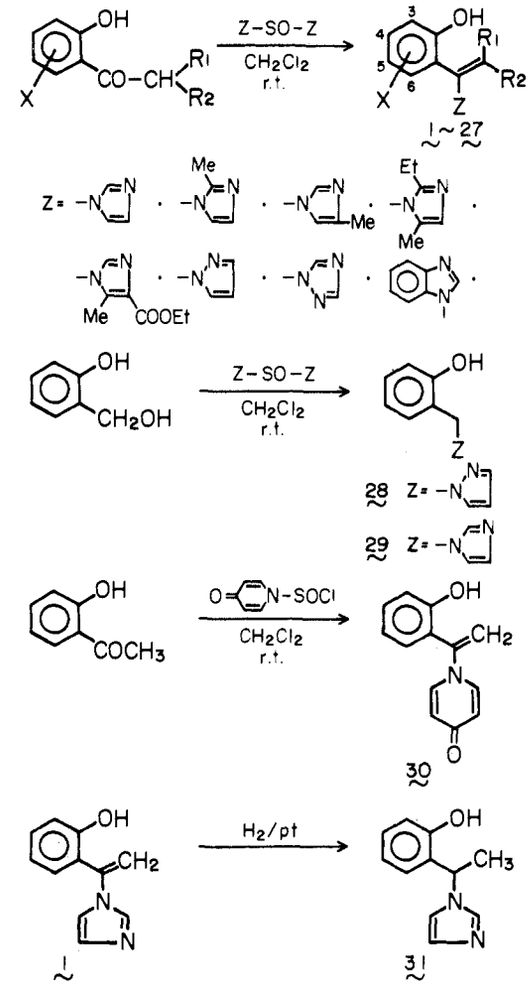
We report here a new series of 1-[1-[2-[3-(alkylamino)-2-hydroxypropoxy]phenyl]vinyl]-1*H*-azoles (**33–81**) containing the (aryloxy)propanolamine structure, which were prepared and screened for potential antiarrhythmic activity. From the results of screening tests, 1-[2,5-dichloro-6-[1-(1*H*-imidazol-1-yl)ethenyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol hydrochloride (**48**) (711389-S) was selected 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-(1*H*-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'*-thionyldiimidazole.[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 synthesis as depicted in Scheme III.

Scheme I



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

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Scheme II

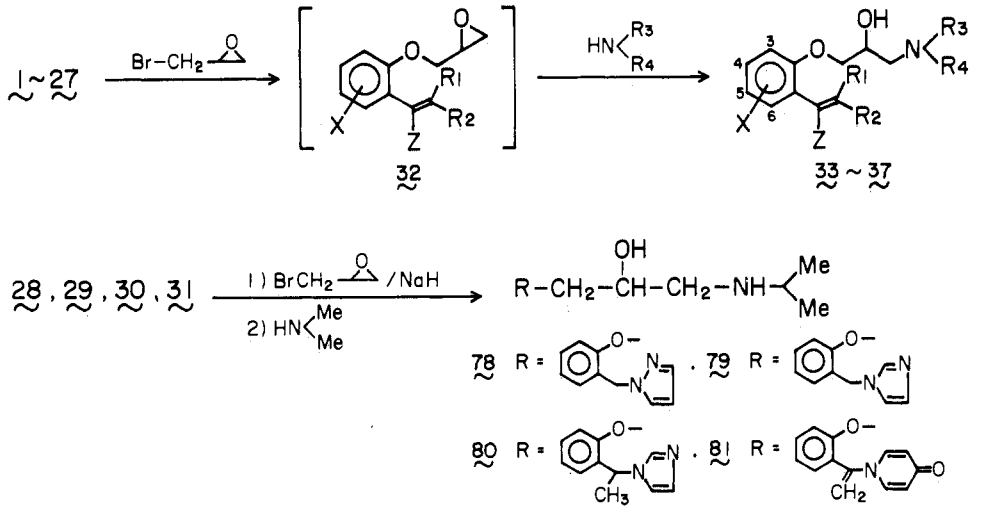
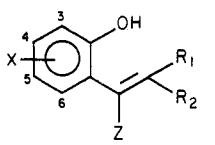


Table I. Physical and Analytical Data for the 1-[1-(2-Hydroxyphenyl)vinyl]-1*H*-azoles



1-27

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

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]-1*H*-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-(1*H*-imidazol-1-yl)ethenyl]-phenoxy]-3-[(1-methylethyl)amino]-2-propanol.[5,6] For-

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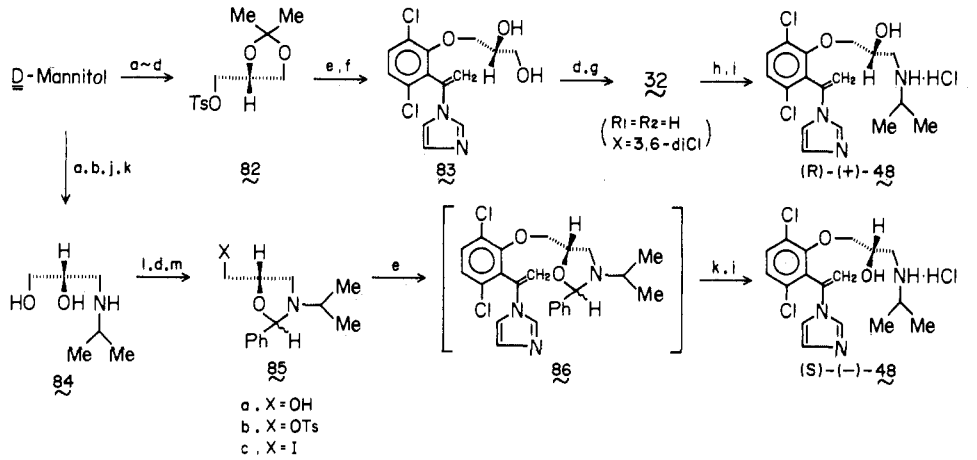
(5) The enantiomeric excess of the free base **48** was determined by ^1H NMR spectroscopy, utilizing tris[3-[(heptafluoropropyl]hydroxymethylene]-*d*-camphorato]europium(III). Nelson, W. L.; Wennerstrom, J. E. *J. Med. Chem.* **1977**, *43*, 3641. Nelson, W. L.; Burke, T. R., Jr. *J. Org. Chem.* **1978**, *43*, 3641. According to this method, both enantiomers were at least 90% ee.

Scheme III



a. $MgCl_2$/2,2-dimethoxypropane/Acetone, refl.
b. $NaIO_4/NaHCO_3/H_2O$/25°C
c. $NaBH_4/H_2O$/25°C
d. $TsCl/Et_3N/CH_2Cl_2$/0°C
e. U/NaH/DMF/100°C
f. 80% AcOH/85°C
g. NaH/THF/25°C
h. i-$PrNH_2$/i-PrOH/refl.
i. HCl-MeOH
j. i-$PrNH_2/H_2$/Pd-C/MeOH/25°C
k. HCl/H_2O/25°C
l. PhCHO/tol./refl.
m. NaI/DMF/80°C

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

Reductive alkylation[7] of (*R*)-glyceraldehyde acetonide with isopropylamine and subsequent hydrolysis[7] 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-(1*H*-imidazol-1-yl)ethenyl]phenoxy]-3-[(1-methylethyl)-amino]-2-propanol,[5] isolated as (*S*)-(-)-1-[2,5-[dichloro-6-[1-(1*H*-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)-2-hydroxypropoxy]benzyl]-1*H*-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]-1*H*-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 intravenous 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 LD_{50} 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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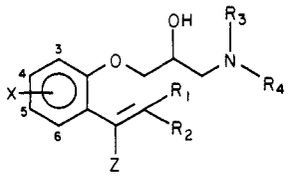
Table II. Physical and Analytical Data for the 1-[2-[3-(Alkylamino)-2-hydroxypropoxy]benzyl]-1*H*-azoles



33–81

no.	R_1	R_2	R_3	R_4	X	Z	recrystn solvent	mp, °C	yield, %	formula
33	H	H	H	*i*-Pr	H	1-imidazolyl		oil	49	$C_{17}H_{23}N_3O_2$
34	H	H	H	*t*-Bu	H	1-imidazolyl	$(i\text{-Pr})_2O$	72–74	17	$C_{18}H_{25}N_3O_2$
35	H	H	pyr[c]		H	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	174–181	21	$C_{18}H_{23}N_3O_2$
36	H	H	Me	Me	H	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	62.5–63.5	28	$C_{16}H_{22}N_3O_2$
37	H	H	H	*i*-Pr	3-Cl	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	64–66	17	$C_{17}H_{22}ClN_3O_2$
38	H	H	H	Me	4-Cl	1-imidazolyl	AcOEt	157–158	20	$C_{15}H_{18}ClN_3O_2\cdot HCl$
39	H	H	H	*i*-Pr	4-Cl	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	72–80	28	$C_{17}H_{22}ClN_3O_2\cdot 0.5H_2O$
40	H	H	H	*i*-Pr	5-Cl	1-imidazolyl	$(i\text{-Pr})_2O$	66.5–67.5	10	$C_{17}H_{22}ClN_3O_2$
41	H	H	H	*t*-Bu	3-Me	1-imidazolyl	MeOH/MeCN	145 dec	48	$C_{19}H_{27}N_3O_2\cdot(COOH)_2\cdot 5H_2O\cdot 0.2MeCN$
42	H	H	H	*i*-Pr	3-OMe	1-imidazolyl		oil	97	$C_{18}H_{25}N_3O_3\cdot H_2O$
43	H	H	H	*i*-Pr	3,4-Cl_2	1-imidazolyl	MeOH/AcOEt	124 dec	16	$C_{17}H_{21}Cl_2N_3O_2\cdot 2(COOH)_2\cdot 0.5H_2O$
44	H	H	H	*i*-Pr	3,5-Cl_2	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	88.5–90	32	$C_{17}H_{21}Cl_2N_3O_2$
45	H	H	H	*t*-Bu	3,5-Cl_2	1-imidazolyl	AcOEt	135–136.5	45	$C_{18}H_{23}Cl_2N_3O_2$
46	H	H	H	*i*-Pr	4,5-Cl_2	1-imidazolyl	$(i\text{-Pr})_2O$	77–78	57	$C_{17}H_{21}Cl_2N_3O_2$
47	H	H	H	*i*-Pr	4,6-Cl_2	1-imidazolyl		oil	18	$C_{17}H_{21}Cl_2N_3O_2$
48	H	H	H	*i*-Pr	3,6-Cl_2	1-imidazolyl	MeOH/AcOEt	151–152	35	$C_{17}H_{21}Cl_2N_3O_2\cdot HCl$
49	H	H	H	*i*-Bu	3,6-Cl_2	1-imidazolyl	AcOEt/pet. ether	104–105.5	31	$C_{18}H_{23}Cl_2N_3O_2$
50	H	H	H	*t*-Bu	3,6-Cl_2	1-imidazolyl	AcOEt	147.5–149.5	27	$C_{18}H_{23}Cl_2N_3O_2$
51	H	H	H	*i*-Pr	3-Me, 5-Cl	1-imidazolyl	MeOH/MeCN	123–127 dec	42	$C_{18}H_{24}ClN_3O_2\cdot 2(COOH)_2\cdot 0.5H_2O$
52	H	H	H	*t*-Bu	3-Me, 5-Cl	1-imidazolyl	MeOH/MeCN	76–78 dec	27	$C_{19}H_{26}ClN_3O_2\cdot 2(COOH)_2$
53	H	H	H	*i*-Pr	3-Cl, 6-Me	1-imidazolyl	EtOH	126 dec	5	$C_{18}H_{24}ClN_3O_2\cdot {}^5/_3(COOH)_2$
54	H	H	H	*t*-Bu	3-Cl, 6-Me	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	131–132	28	$C_{19}H_{26}ClN_3O_2$
55	H	H	H	*i*-Pr	3,6-Me_2	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	109–110	41	$C_{19}H_{27}N_3O_2$
56	H	H	H	*t*-Bu	3,6-Me_2	1-imidazolyl	AcOEt	136.5–140	52	$C_{20}H_{29}N_3O_2$
57	H	H	H	*i*-Pr	3,5-Me_2	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	86–87	68	$C_{19}H_{27}N_3O_2$
58	H	H	H	*t*-Bu	3,5-Me_2	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	111–112	50	$C_{20}H_{29}N_3O_2$
59	H	H	H	*i*-Pr	3-Cl, 5,6-Me_2	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	99–100.5	60	$C_{19}H_{26}ClN_3O_2$
60	H	H	H	*t*-Bu	3-Cl, 5,6-Me_2	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	129–130	54	$C_{20}H_{28}ClN_3O_2$
61	Me	H	H	*i*-Pr	H	1-imidazolyl		oil	17	$C_{18}H_{25}N_3O_2\cdot 0.2H_2O$
62	Me	H	H	*t*-Bu	H	1-imidazolyl		oil	37	$C_{19}H_{27}N_3O_2\cdot 0.2H_2O$
63	Me	Me	H	*i*-Pr	5-Cl	1-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	85–87	37	$C_{19}H_{26}ClN_3O_2$
64	H	H	H	*i*-Pr	H	1-(2-Me)-imidazolyl	AcOEt/$(i\text{-Pr})_2O$	65–66	21	$C_{18}H_{25}N_3O_2\cdot 0.6H_2O$
65	H	H	H	*t*-Bu	H	1-(2-Me)-imidazolyl	$(i\text{-Pr})_2O$	70–71	18	$C_{19}H_{27}N_3O_2$
66	H	H	H	*i*-Pr	H	1-(4-Me)-imidazolyl		oil	45	$C_{18}H_{25}N_3O_2$
67	H	H	H	*i*-Pr	H	1-(2-Et-5-Me)-imidazolyl	$(i\text{-Pr})_2O$/pet. ether	86.5–87	53	$C_{20}H_{29}N_3O_2$
68	H	H	H	*i*-Pr	H	1-(4-COOEt-5-Me)-imidazolyl		oil	27	$C_{21}H_{29}N_3O_4\cdot 0.6H_2O$
69	H	H	H	*i*-Pr	H	1-pyrazolyl	$(i\text{-Pr})_2O$/pet. ether	66.5–67.5	67	$C_{17}H_{23}N_3O_2$
70	H	H	H	*t*-Bu	H	1-pyrazolyl	$(i\text{-Pr})_2O$/*n*-hexane	75–76	3	$C_{18}H_{25}N_3O_2$
71	H	H	H	*i*-Pr	5-Cl	1-pyrazolyl	MeOH/AcOEt	131–132 dec	14	$C_{17}H_{22}ClN_3O_2\cdot(COOH)_2$
72	H	H	H	*t*-Bu	5-Cl	1-pyrazolyl	MeOH/Et_2O	107–109 dec	61	$C_{18}H_{24}ClN_3O_2\cdot(COOH)_2$
73	H	H	H	*i*-Pr	H	1-(1,2,4-triazolyl)	MeOH/AcOEt	156–157 dec	46	$C_{16}H_{22}N_4O_2\cdot(COOH)_2$
74	H	H	H	*i*-Pr	H	1-benzimidazolyl	MeOH/AcOEt	148–149 dec	54	$C_{21}H_{25}N_3O_2\cdot(COOH)_2\cdot 0.5H_2O$
75	H	H	H	*t*-Bu	H	1-benzimidazolyl	AcOEt/$(i\text{-Pr})_2O$	105–106	43	$C_{22}H_{27}N_3O_2$
76	H	H	H	*i*-Pr	3-MeO	1-benzimidazolyl	MeOH/AcOEt	147–148 dec	51	$C_{22}H_{27}N_3O_3\cdot(COOH)_2\cdot 0.2H_2O$
77	H	H	H	*t*-Bu	3-MeO	1-benzimidazolyl	AcOEt/$(i\text{-Pr})_2O$	110–111	32	$C_{23}H_{29}N_3O_3$
78	*b*		H	*i*-Pr	H	1-pyrazolyl	$(i\text{-Pr})_2O$	64–65	44	$C_{16}H_{23}N_3O_2$
79	*b*		H	*i*-Pr	H	1-imidazolyl	MeOH/AcOEt	147.5 dec	31	$C_{18}H_{25}N_3O_6\cdot 0.5H_2O$
80	*b*		H	*i*-Pr	H	1-imidazolyl		oil	37	$C_{17}H_{25}N_3O_2\cdot 0.6H_2O$
81	H	H	H	*i*-Pr	H	1-(4-oxo-1,4-dihydropyridyl)	MeOH/ether	173.5–174.5	46	$C_{19}H_{24}N_2O_3\cdot 1.5(COOH)_2$

[a] Yield based on the last step (1–27 → 33–77). [b] See Scheme II. [c] Pyrrolidinyl.

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. β-Adrenoceptor-Blocking Activities and Effects on the Maximal Follow Rate of Various 1-[2-[3-(Alkylamino)-2-hydroxypropoxy]benzyl]-1*H*-azoles in the Isolated Right Atria of Guinea Pigs[a]

compd no.	β-blocking act.: pA_2			10^{-5}MFR, g/mL		compd no.	β-blocking act.: pA_2			10^{-5}MFR, g/mL	
	n	IE	CE	*n*	% decrease		*n*	IE	CE	*n*	% decrease
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
36	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	**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	2	14.2
52	1	5.04	5.49	2	27.3	**80**	2	6.83	6.90	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*.

Table IV. Effects of Various 1-[2-[3-(Alkylamino)-2-hydroxypropoxy]benzyl]-1*H*-azoles on Aconitine Arrhythmias and Their Acute Toxicities in Mice[a]

compd	iv				po				LD_{50}, mg/kg, iv
	n	dose, mg/kg	VES	VT	*n*	dose, mg/kg	VES	VT	
36	5	10	S	S					45.4
41	5	3	S	S	5	30	S	S	23.1
43	5	3	S	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	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] LD_{50}, 50% lethal doses in mice (up and down method[14]).

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 2-methylimidazole (**64**), 2-ethyl-5-methylimidazole (**67**), and benzimidazole (**74**) decreased the antiarrhythmic effect, with the exception of compounds **65** and **68** (which have

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

compd	iv, dose, mg/kg	iv, % sinus beats before	iv, % sinus beats after	iv, duration, min	po, dose, mg/kg	po, % sinus beats before	po, % sinus beats after	po, duration, min
48	3	5.8	88.9	45	4	10	9.3	69.3	180
49	3	6.5	94.5	60	4	10	9.9	44.8	180
54	3	11.7	59.1	30					
72	2	1.8	14.3						
73	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

[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 ±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-(1*H*-pyrazol-1-yl)ethenyl]phenol (24). To a solution of pyrazole (9.4 g, 0.138 mol) and dry CH_2Cl_2 (47 mL) was added $SOCl_2$ (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 $NaHCO_3$ 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 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 $NaHCO_3$ 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 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 (Me_2SO-d_6) 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-(1*H*-1,2,4-Triazol-1-yl)ethenyl]phenol (25). 1,2,4-Triazole (5.0 g, 0.072 mol) was suspended in CH_2Cl_2 (25 mL), to which $SOCl_2$ (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 $NaHCO_3$ was added, and the mixture was 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 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–CH_2Cl_2 were collected to obtained **25** (702 mg, mp 153–156 °C, from AcOEt, 20.7%): NMR (Me_2SO-d_6) 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-(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-Pyrazolylmethyl)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 $NaHCO_3$, 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. Eluates with CH_2Cl_2 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 ($CDCl_3$) δ 5.23 (2 H, s, CH_2), 6.27–7.53 (7 H, m, aromatic), 10.27 (1 H, br s, OH). Anal. ($C_{10}H_{10}N_2O$) C, H, N.

2-(1-Imidazolylmethyl)phenol (29).[2] $SOCl_2$ (3.30 g, 0.028 mol) was added to a mixture of imidazole (7.56 g, 0.111 mol) and dry CH_2Cl_2 (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 $NaHCO_3$ and extracted with CH_2Cl_2, and the CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was washed with CH_3CN to give **29** (1.06 g, mp 161–164 °C, 32.9%): NMR (Me_2SO-d_6) δ 5.17 (2 H, s, CH_2), 6.83–7.80 (7 H, m, aromatic), 9.87 (1 H, br s, OH). Anal. ($C_{10}H_{10}N_2O$) 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 CH_2Cl_2 (8.4 mL) and stirred under ice cooling. A solution of $SOCl_2$ (1.048 g, 8.8 mmol) in CH_2Cl_2 (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 o-hydroxyacetophenone (1 g, 7.3 mmol), triethylamine (890 mg, 8.8 mmol), and dry CH_2Cl_2 (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 H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was chromatographed on silica gel. Eluates with 7% MeOH/CH_2Cl_2 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) δ 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-Imidazolyl)ethyl]phenol (31). A mixture of 1-[1-(2-hydroxyphenyl)vinyl]-1*H*-imidazole (1) (500 mg), MeOH (20 mL), 14% HCl/MeOH (5 mL), and $PtO_2 \cdot H_2O$ (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 $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, 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 (Me_2SO-d_6) δ 1.75 (3 H, d, J = 7.0, CH_3), 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. ($C_{11}H_{12}N_2O$) 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 = 1-imidazolyl). 3,6-Dichloro-2-[1-(1*H*-imidazol-1-yl)ethenyl]phenyl (**11**) (2 g, 7.8 mmol) was dissolved in dry Me_2SO (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 Na_2SO_4, filtered, and evaporated. The residue was chromatographed on silica gel. The fraction eluted with benzene/CH_3CN (1:1) was collected, giving **32** (1.29 g, 53.3%, oil): NMR (Me_2SO-d_6) δ 2.47–2.87 (2 H, m, methylene), 3.07–3.33 (1 H, m, methine), 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), 7.10–7.60 (5 H, aromatic); IR (neat 1645 (C=C) cm^{-1}; picrate, mp 126–128 °C dec (from CH_3CN/diethyl ether). Anal. ($C_{14}H_{12}Cl_2N_2O_2 \cdot C_6H_3N_3O_7$) C, H, Cl, N.

1-[4-Chloro-2-[1-(1*H*-imidazol-1-yl)-2-methylpropen-1-yl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol (63). 4-Chloro-2-[1-(1*H*-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 Na_2SO_4 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/CH_2Cl_2 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 ($CDCl_3$) 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. ($C_{19}H_{26}ClN_3O_2$) C, H, Cl, N.

Compounds **78–81** were prepared in a similar manner.

(2*R*)-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), $MgCl_2$ (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 CH_2Cl_2, dried over Na_2SO_4, and evaporated to give the 1,2;5,6-diacetonide of D-mannitol (28 g, 53%). An aqueous solution of $NaHCO_3$ (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 H_2O (300 mL). After 0.5 h of stirring at 25 °C, the precipitate was removed by filtration. $NaBH_4$ (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 CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to leave an oil (17.97 g). Et_3N (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 CH_2Cl_2 (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 CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to give the acetonide of **83** as a syrup: IR (neat) 1640, 1560 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (6 H, s, Me_2), 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 CH_2Cl_2. The organic layer was washed with 10% NaOH, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel. The fraction eluted with CH_2Cl_2/MeOH (9:1) gave **83** (1.92 g, 66%) as a syrup: NMR ($CDCl_3$) 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), 6.60–7.60 (5 H, m, aromatic). Hydrochloride of **83**: mp 143–145 °C (from MeOH/AcOEt); IR (Nujol) 3260 cm^{-1}; $[\alpha]^{24}_D$ +11.0° (*c* 1.00, MeOH). Anal. ($C_{14}H_{15}Cl_3N_2O_3$) C, H, Cl, N.

(*R*)-(+)-1-[2,5-Dichloro-6-[1-(1*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), Et_3N (2.34 g, 23.2 mmol), and CH_2Cl_2 (40 mL) at 0 °C and stirred for 2 h. 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 CH_2Cl_2/MeOH (95:1) gave the tosylate of **83** (3.39 g, 66%) as a syrup: NMR ($CDCl_3$) 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 (Na_2SO_4) 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 ($CDCl_3$) 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-Cl_2) (1.85 g, 5 mmol), *i*-$PrNH_2$ (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 CH_2Cl_2/MeOH/28% NH_4OH (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 (*RS*)-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–Et_2O to afford the hydrochloride of (*R*)-(+)-48 (692 mg, 63%): mp 184–186 °C; $[\alpha]^{24}_D$ +16.0° (c 1.00, MeOH).[6] Anal. ($C_{17}H_{22}Cl_3N_3O_2$) 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*-$PrNH_2$ (63 mL) and then hydrogenated (1 atm of H_2) 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 ($CDCl_3$) δ 1.05 (6 H, d, J = 7.0 Hz, $CHMe_2$), 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 K_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to afford an oil, which was chromatographed on alumina (activity II). The fraction eluted with CH_2Cl_2/MeOH/28% NH_4OH (90:10:1) gave the amine **84** (9.5 g, 93%) as an oil: IR (film) 3300 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (6 H, d, J = 7.0 Hz, $CHMe_2$), 2.35–3.85 (9 H, m, methylene, methine, OH, NH); $[\alpha]^{23}_D$ −13.4° (*c* 1.06, MeOH); Hemidi-*p*-toluoyl-D-(−)-tartrate of **84**: mp 160–162 °C (MeOH–acetone). Anal. ($C_{32}H_{48}N_2O_{12}$) 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 ($CDCl_3$) δ 1.05 (6 H, d, J = 7.0 Hz, $CHMe_2$), 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. ($C_{13}H_{19}NO_2$) 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 CH_2Cl_2, washed with aqueous Na_2CO_3, dried (Na_2SO_4), and evaporated to afford **85b** (16.1 g, 95%) as an unstable oil, which was used in the next step without further purification: NMR ($CDCl_3$) δ 0.97 (6 H, d, *J* = 7.0 Hz, $CHMe_2$), 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° (*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/Et_2O).

(*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 Et_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give iodide **86c** (11.5 g, 81%) as an oil, which was used in the next step without further purification: NMR ($CDCl_3$) δ 0.98 (6 H, d, *J* = 7.0 Hz, $CHMe_2$), 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-(1*H*-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 CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to leave an oil, which was chromatographed on alumina (activity II). The fraction eluted with CH_2Cl_2/MeOH/28% NH_4OH (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 Et_2O 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**. $[\alpha]^{23}_D$ −16.6° (c 1.00, MeOH).[6] Anal. ($C_{17}H_{22}Cl_3N_3O_2$) C, H, N, Cl.

Pharmacology. In order to investigate β-adrenoceptor-blocking 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% O_2 and 5% CO_2. 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 pA_2 values[8] 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 μg/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 Downey[11] 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's[14] 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-Cl_2, Z = 1-imidazolyl), 90742-85-1; **32** (R_1, R_2 = H, X = 2,5-Cl_2, Z = 1-imidazolyl)·picrate, 90742-86-2; **32** (R_1, 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; (±)-**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**·$_5/_3(COOH)_2$, 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*-$PrNH_2$, 75-31-0; *t*-$BuNH_2$, 75-64-9; Me_2NH, 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(4-methylimidazole), 90743-06-9; 1,1′-sulfinylbis(2-ethyl-5-methylimidazole), 90743-07-0; 1,1′-sulfinylbis(4-ethoxycarbonyl-5-methylimidazole), 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.