was added via a serum cap to a mixture of **30** (3.0 g, 11 mmol) in dry THF (150 mL). The mixture was allowed to stir under nitrogen at room temperature for 30 min, and excess diborane was carefully destroyed with MeOH (10 mL). The solvents were removed in vacuo to afford a yellow solid (2.4 g). Crystallization from MeOH yielded colorless **31**: yield 2.3 g (81.6%); mp 82–84 °C; NMR ($CDCl_3/Me_4Si$) δ 6.70–7.50 (m, 6 H, 4 aromatic, 1-H, 3-H), 4.30 (q, 2 H, J = 7.0 Hz, $COOCH_2CH_3$), 2.83 (s, 3 H, 6-NCH_3), 1.33 (t, 3 H, J = 7.0 Hz, $COOCH_2CH_3$).

2-(Hydroxymethyl)-6-methyl-5,6-dihydropyrrolo[1,2-*c*]quinazoline (32). A solution of ester **31** (27.92 g, 109 mmol) in ether (500 mL) was added to a slurry of $LiAlH_4$ (16.75 g, 442 mmol). The reaction mixture was stirred at ambient temperature for 1.5 h. To the reaction mixture was added dropwise and successively H_2O (17.0 mL), NaOH (17.0 mL of 15% aqueous solution) and H_2O (51 mL). The precipitate was filtered and washed with ether. After the solution was dried ($MgSO_4$), the solvent was removed in vacuo to yield **32** as a colorless solid: yield 22.56 g (96.6%); mp 74–76 °C; NMR ($CDCl_3/Me_4Si$) δ 6.30–7.58 (m, 6 H, 4 aromatic H, 1-H, 3-H), 4.80 (s, 2 H, 5-CH_2), 4.58 (s, 2 H, 1-H), 2.85 (s, 2 H, CH_2OH), 2.10 (s, 1 H, OH).

2-Carboxy-5,6-dihydropyrrolo[1,2-*c*]quinazoline-6-propionic Acid (33). A solution of the free base of **25** (2.75 g, 8 mmol) and KOH (4.0 g, 71 mmol) in MeOH (40 mL) and H_2O (40 mL) was refluxed for 4 h. The ethanol was removed under vacuum and the resulting aqueous solution was acidified with HCl (10% aqueous). The greenish solid which formed was filtered, washed (H_2O), and dried to yield 2.2 g of crude product. Crystallization from MeOH afforded **33**: yield 1.8 g (80%); mp 234–236 °C; NMR (Me_2SO-d_6/Me_4Si) δ 10.70–11.50 (m, 2 H, 2-COOH and 6-CH_2CH_2COOH), 6.70–7.70 (m, 6 H, 1-, 3-, 7-, 8-, 9-, 10-H), 5.16 (s, 2 H, 5-CH_2), 3.61 (t, 2 H, J = 6.5 Hz, 2′-H), 2.57 (t, 2 H, J = 6.5 Hz, 1′-H).

6-(3-Hydroxypropyl)-2-methyl-5,6-dihydropyrrolo[1,2-*c*]quinazoline (34). $LiAlH_4$ (2.88 g, 76 mmol) was slurried in ether (250 mL) and to this was added a solution of **52** (5.5 g, 9 mmol) in ether (100 mL). The reaction mixture was stirred at room temperature for 0.5 h. Water (3.0 mL), NaOH (3.0 mL of 15% aqueous), and H_2O (9.0 mL) were added to the reaction mixture. The precipitate was filtered and washed with ether. The solvent was removed in vacuo and the residue crystallized from pentane to yield **34** as a pale yellow solid: yield 2.06 g (44.8%); mp 77–78 °C: NMR ($CDCl_3/Me_4Si$) δ 7.30–7.52 (m, 1 H, 7-H), 7.20 (d, 1 H, $J_{3,1}$ = 1.0 Hz, 3-H), 6.60–7.10 (m, 3 H, 8-, 9-, 10-H), 6.35 (s, 1 H, 3′-OH), 6.25 (d, 1 H, $J_{1,3}$ = 1.0 Hz, 1′-H), 4.92 (s, 2 H, 5-H), 3.72 (t, 2 H, J = 7.0 Hz, 3′-H), 3.35 (t, 2 H, J = 7.0 Hz, 1′-H), 2.15 (s, 3 H, 2-CH_3), 1.60–2.10 (m, 2 H, 2′-H).

3-Bromo-2-methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one Hydrate (55). Bromine (1.6 g, 10 mmol) was added dropwise to a solution of **43** (2.0 g, 10 mmol) in CCl_4 (600 mL) at reflux. The reaction mixture was refluxed for 1 h, and the solvent was removed in vacuo to yield a dark solid residue (2.4 g). Trituration with MeOH (50 mL) and crystallization from benzene (500 mL) afforded **55** as an off-white solid: yield 2.05 g (89.0%); mp >300 °C: NMR (Me_2SO/Me_4Si) δ 11.28 (s, 1 H, NH), 7.53–7.80 (m, 1 H, 7-H), 6.93–7.27 (m, 3 H, 8-, 9-, 10-H), 6.87 (s, 1 H, C_1 H), 2.10 (s, 3 H, 2-CH_3).

9-(2′,3′-Epoxypropoxy)-2-methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (56). Compound **40** (6.10 g, 27 mmol), NaOH (1.28 g, 32 mmol), EtOH (409 mL), and H_2O (656 mL) were combined, and the resulting yellow solution was stirred at room temperature, protected from light with Al foil, under nitrogen for 3 h. Epibromohydrin (4.79 g, 35 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 40 h. During this time, a white solid formed. The reaction mixture was cooled to 0 °C, and the white solid was filtered, washed (H_2O), and dried to give 2 g of crude product. The crude product was chromatographed on a 175-g SilicAR column prepared in CH_2Cl_2. Elution with 1% $MeOH/CH_2Cl_2$ yielded **56** as a white solid: yield 0.49 g (6.7%); mp 208–210 °C: NMR (Me_2SO-d_6/Me_4Si) δ 11.76 (s, 1 H, N-H), 7.20–7.40 (m, 2 H, 3-H, 8-H), 7.08 (d, 1 H, $J_{7,8}$ = 9 Hz, 7-H), 6.88 (d, 1 H, $J_{8,10}$ = 3 Hz, 10-H), 6.73 (d, 1 H, $J_{1,3}$ = 2 Hz, 1-H), 3.83 (J/gem = 11 Hz, J_{vic} = 6 Hz), 4.30 (J_{gem} = 11 Hz, J_{vic} = 4 Hz, (AB quartet, 2 H, i), 3.23 (m, 1 H, ii), 2.71 (m, 2 H, iii), 2.18 (s, 3 H, 2-CH_3).

i ii iii

9-[3′-(Isopropylamino)-2′-hydroxy-1′-propoxy]-2-methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (57). A solution of **56** (1.42 g, 5 mmol) in isopropylamine (50 mL) and acetonitrile (50 mL) was placed in a pressure bottle. The bottle was heated in an oil bath at 95 °C for 16 h. During this time, a white solid formed. It was filtered, washed (cold acetonitrile), and dried to give **57** as a white solid: yield 1.20 g (72.7%); mp 206–208 °C; NMR (CF_3COOH/Me_4Si) δ 7.55–8.20 (m, 4 H, 1-, 7-, 8-, 10-H), 7.20 (br s, 2 H, 2 NH), 5.30–5.80 (m, 2 H, 3-H), 4.70–5.10 (m, 1 H, 2′-H), 4.30–4.70 (m, 2 H, 1′-H), 3.50–4.10 (m, 3 H, 3′-, 5′-H), 2.80 (s, 3 H, 2-CH_3), 1.70 (d, 6 H, 5′-CH_3), 1.60 (br s, 1 H, OH).

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2-(Isoxazolylethenyl)phenoxypropanolamines: A New Class of β-Receptor Antagonists with Antihypertensive Activity

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The synthesis of a series of (*E*)-1-amino-3-[2-(2-isoxazolylethenyl)phenoxy]-2-propanols is described. These compounds were found to have β- and α-adrenergic blocking properties, as well as hypotensive and antihypertensive properties. The β-adrenoceptor antagonism of all these compounds was more pronounced than their α-sympatholytic and hypotensive activity. **3a** was 16 times more potent than labetalol in β-adrenergic receptor blockade and was effective in lowering blood pressure in acute trials on spontaneously hypertensive rats at a dosage of 15 mg/kg. Structure–activity considerations showed that antihypertensive potency was more sensitive to structural variations than β-adrenoceptor antagonistic activity. However, in general, those compounds having the most potent β-adrenoceptor blocking activity also lowered blood pressure most effectively.

β-Adrenoceptor antagonists alone[1-8] or in combination with peripheral vasodilators[5,6,9-12] are of great importance in antihypertensive pharmacotherapy. Combination of both these activities results in an enhancement of antih-

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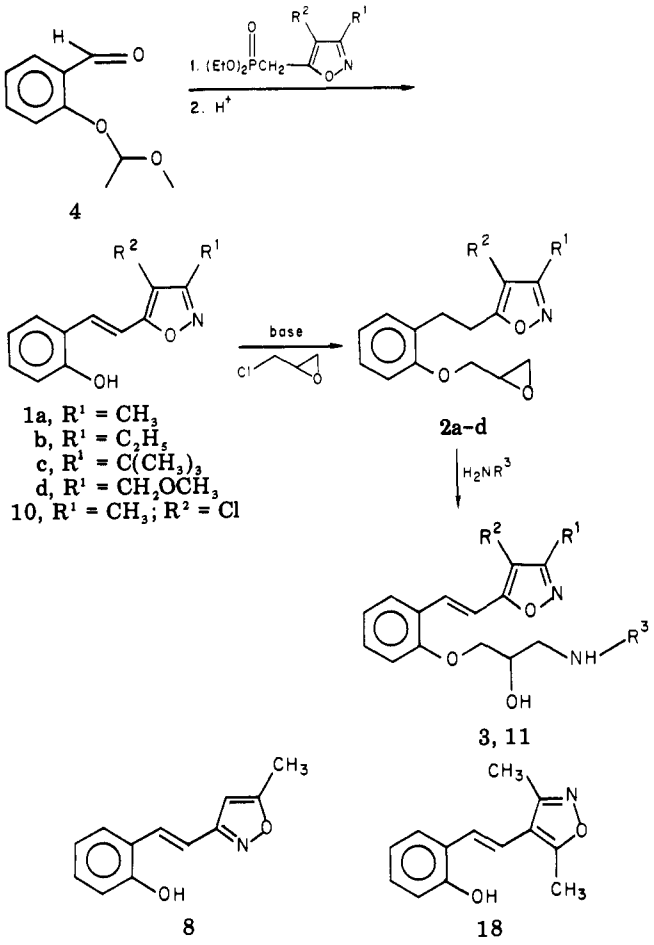
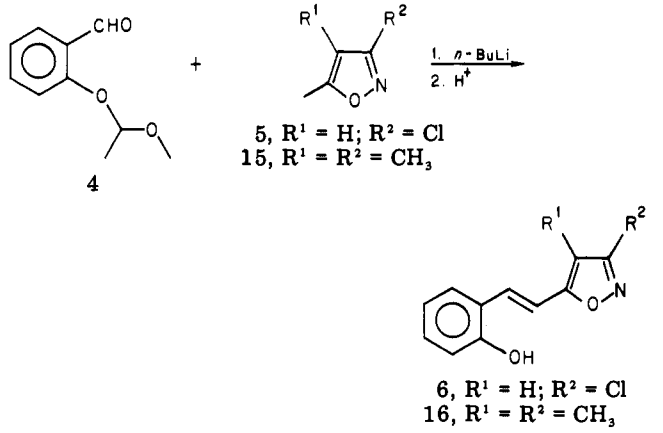
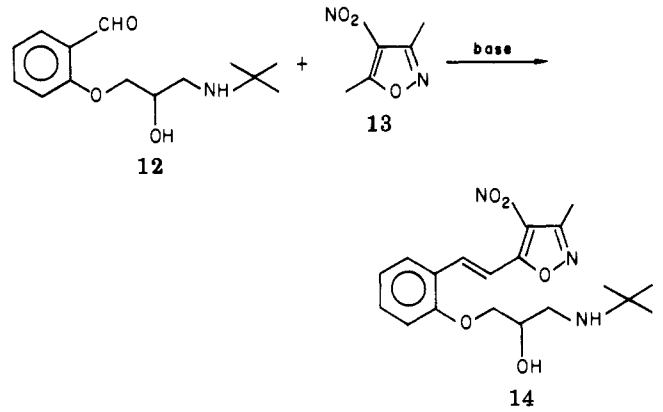
Scheme I



Scheme II



Scheme III



ypertensive potency[10-12] and in a decrease of side effects.[10-13] In particular, the reflux tachycardia induced by peripheral vasodilators is diminished.[10-12]

Recently, starting with labetalol (5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide),[14,15] compounds have been developed which, in contrast to classical β-adrenoceptor antagonists like propranolol, exhibit vasodilating as well as α-adrenergic blocking activity. Labetalol and bucindolol (1-[2-cyanophenoxy]-3-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-2-propanol)[16,17] induce peripheral vasodilation by blocking vascular α-adrenoceptors. Another compound, MK-761 (2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine), displays similar effects, i.e., β-adrenoceptor blockade and acute vasodilation,[18-20] with the latter mechanism still unknown.

This report describes the synthesis and the pharmacological properties of 2-(2-isoxazolylethenyl)phenoxypropanolamines exemplified by **3**, a new class of β-adrenoceptor blocking compounds with antihypertensive activity.

Chemistry. The compounds discussed in this report are listed in Table I. With the exception of **14**, all compounds are prepared by addition of the corresponding amines to 2-(2,3-epoxypropoxy)phenylethenylisoxazoles[21] (Scheme I). The corresponding glycidic ethers were isolated only in a few cases (**2a** and **19**) and were usually used without purification as crude products from the reaction of epibromo- or epichlorohydrin with phenols **1a–d**, **6**, **8**, **10**, **16**, and **18**. The 2-hydroxyphenylethenylisoxazoles **1a–d**, **8**, **10**, and **18** were synthesized as described[22] by the

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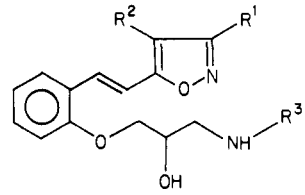
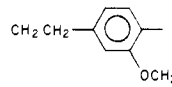
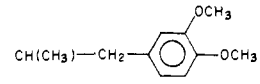
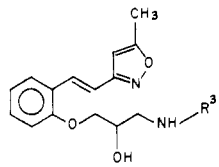
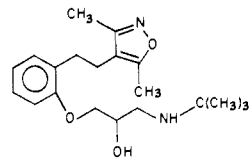
Table I. Physical Properties of (*E*)-1-Amino-3-[2-(2-isoxazolylethenyl)phenoxy]-2-propanols



no.	R^1	R^2	R^3	formula[a]	mp, °C	yield, %
3a	CH_3	H	$C(CH_3)_3$	$C_{19}H_{26}N_2O_3 \cdot HCl$	217	79
3b	CH_3	H	$CH(CH_3)_2$	$C_{18}H_{24}N_2O_3$	106-108	57
3c	CH_3	H	c-C_3H_5	$C_{18}H_{22}N_2O_3$	137-139	21
3d	CH_3	H	$C(CH_3)_2C{\equiv}CH$	$C_{20}H_{24}N_2O_3 \cdot HCl$	191	55
3e	CH_3	H		$C_{25}H_{30}N_2O_5$[b]	80-83	27
3f	CH_3	H	$CH(CH_3)CH_2CH_2\text{-}C_6H_5$	$C_{25}H_{30}N_2O_3$	90-91	25
3g	CH_3	H		$C_{26}H_{32}N_2O_5$	121-125	12
3h	CH_3	H	$CH(CH_3)CH_2CH_2\text{-}C_6H_4\text{-}OH\text{-}p$	$C_{25}H_{30}N_2O_4$	110-112	30
3i	CH_3	H	$C(CH_3)_2CH_2CH_2\text{-}C_6H_4\text{-}OH\text{-}p$	$C_{26}H_{32}N_2O_4$	139-140	38
3j	CH_3	H	$C(CH_3)_2CH_2CH_2\text{-}C_6H_4\text{-}OCH_3\text{-}p$	$C_{27}H_{34}N_2O_4$[b]	83-85	27
3k	C_2H_5	H	$C(CH_3)_3$	$C_{20}H_{28}N_2O_3 \cdot HCl$	163-164	67
3l	C_2H_5	H	$CH(CH_3)_2$	$C_{19}H_{26}N_2O_3 \cdot HCl$	134-135	52
3m	$C(CH_3)_3$	H	$C(CH_3)_3$	$C_{22}H_{32}N_2O_3 \cdot HCl$	207-208	71
3n	CH_2OCH_3	H	$CH(CH_3)_2$	$C_{19}H_{26}N_2O_4 \cdot HCl$	123	30
3o	CH_2OCH_3	H	$C(CH_3)_3$	$C_{20}H_{28}N_2O_4 \cdot HCl$	152	52
3p	CH_2OCH_3	H	c-C_3H_5	$C_{19}H_{24}N_2O_4$	93	45
3q	Cl	H	$CH(CH_3)_2$	$C_{17}H_{21}ClN_2O_3$	114-116	74
11	CH_3	Cl	$C(CH_3)_3$	$C_{19}H_{25}ClN_2O_3$	109	51
14	CH_3	NO_2	$C(CH_3)_3$	$C_{19}H_{25}N_3O_5$	98-102	43
17	CH_3	CH_3	$C(CH_3)_3$	$C_{20}H_{28}N_2O_3$[c]	197	77
9a			$CH(CH_3)_2$	$C_{18}H_{24}N_2O_3 \cdot HCl$	155	46
9b			$C(CH_3)_3$	$C_{19}H_{26}N_2O_3 \cdot HCl$	181	39
20				$C_{20}H_{28}N_2O_3 \cdot HCl$	200	60

[a] C, H, and N values were within ±0.4% of the theoretical values. [b] $0.5H_2O$. [c] 0.5-Fumaric acid.

Wittig-Horner reaction of diethyl isoxazolylmethylphosphonates with the protected salicylaldehyde 4 and subsequent acidic cleavage of the protecting group. The diethyl phosphonates were prepared by a Michaelis-Arbusov reaction[23] from triethyl phosphite and chloromethylisoxazoles. Cycloaddition of nitrile oxides to propargyl chloride yielded 3-alkyl-5-methylisoxazoles.[24] 3-(Chloromethyl)-5-methylisoxazole[25] and 4-(chloromethyl)-3,5-dimethylisoxazole[26] were synthesized by

Table II. Physical Properties of 2-(2-Hydroxyphenyl)ethenylisoxazoles and 2-[2-(2,3-Epoxypropoxy)phenyl]ethenylisoxazoles

no.	formula[a]	mp, °C	yield, %	crystn solv
1a	$C_{12}H_{11}NO_2$	236-238	85	MeOH-H_2O
1b	$C_{13}H_{13}NO_2$	175-176	48	MeOH-H_2O
1c	$C_{15}H_{17}NO_2$	152-155	78	MeOH-H_2O
1d	$C_{13}H_{13}NO_3$	154	34	Me_2CO-cyclohexane
6	$C_{11}H_8ClNO_2$	183-186	51	EtOH
8	$C_{12}H_{11}NO_2$	174-175	55	EtOH
10	$C_{12}H_{10}ClNO_2$	184	26	EtOH
16	$C_{13}H_{13}NO_2$	208-210	47	MeOH
2a	$C_{15}H_{15}NO_3$	100	87	EtOH
2b	oil[b]		92[c]	
2c	oil[b]		96[c]	
2d	oil[b]		79[c]	

[a] C, H, Cl, and N analyses were within ±0.4% of the theoretical values. [b] Characterized by ^1H NMR spectroscopy. [c] Yield of crude product.

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Table III. Pharmacological Activity of 2-(Isoxazolylethenyl)phenoxypropanolamines

	inhibn of isoproterenol-induced tachycardia in pithed rats[a]			hypotensive act. in anesthetized rats[a]			antihypertensive act. in SH rats[c]		
compd	no. of rats	ED_{50},[b] mg/kg	rel potency[d]	no. of rats	ED_{20},[b] mg/kg	rel potency[d]	no. of rats	ED_{20},[b] mg/kg	rel potency[d]
3a	9	0.0088 (0.0054-0.014)	15.9	15	0.40 (0.35-0.45)	13.0	28	14.5 (8.62-24.6)	3.3
3b	9	0.0060 (0.0049-0.0074)	23.3	6	~0.65 (0.55-0.77)	8.0	4	>21.5	
3c	9	0.0091 (0.0077-0.011)	15.4	4	~1.47	~3.5	4	~21.5	~2.2
3d	4	~0.0681	~2.1	8	~1.25 (0.69-2.3)	4.2	8	~46.4	~1.0
3e	4	~0.0215	~6.5	4	~1.0	~5.2	4	~21.5	~2.2
3f	3	~0.0464	~3.0	4	~1.0	~5.2	8	~46.4	~1.0
3g	4	~0.0464	~3.0	4	~2.15	~2.4	4	>21.5	
3h	12	0.011 (0.0090-0.013)	12.7	9	0.49 (0.38-0.64)	10.6	24	~46.4	~1.0
3i	4	~0.0215	~6.5	2	~1.0	~5.2	4	~21.5	~2.2
3j	5	~0.215	~0.7	2	~1.0	~5.2	4	~21.5	~2.2
3k	4	~0.0215	~6.5	9	0.93 (0.79-1.1)	5.6	4	>21.5	
3l	4	~0.0215	~6.5	6	0.41 (0.39-0.44)	12.7	20	9.38 (6.02-14.6)	5.1
3m	4	~0.0215	~6.5	2	>1.0		4	>46.4	
3n	12	0.0064 (0.0056-0.0073)	21.9	8	~1.0	~5.2	12	18.2 (13.5-24.5)	2.6
3o	9	0.0074 (0.0066-0.0084)	18.9	6	~0.80	~6.5	12	~21.5	~2.2
3p	5	~0.01	~14.0	6	~1.0	~5.2	12	~10	~4.8
3q	4	~0.0464	~3.0	3	~0.68	~7.6	4	>21.5	
9a	6	0.0034 (0.0026-0.0045)	41.2	4	~2.15	~2.4	4	~46.4	~1.0
9b	9	0.013 (0.011-0.014)	10.8	4	~2.15	~2.4	4	~21.5	~2.2
11	9	0.014 (0.0072-0.026)	10.0	4	~1.0	~5.2	4	>21.5	
14	4	~0.0681	~2.1	2	~1.0	~5.2	4	>21.5	
17	4	~0.0215	~6.5	4	~0.68	~7.6	4	>21.5	
20	2	~0.0464	~3.0	6	~1.0	~5.2	4	>21.5	
labetalol	12	0.14 (0.13-0.16)	1.0	15	5.2 (4.1-6.4)	1.0	12	47.7 (28.3-80.5)	1.0

[a] Intravenous administration. [b] 95% confidence limits in parentheses. [c] Oral administration. [d] Labetalol = 1.0.

chlorination of the corresponding hydroxymethylisoxazoles and 5-(bromomethyl)-4-chloro-3-methylisoxazole by bromination of 4-chloro-3,5-dimethylisoxazole.[27] Deprotonation of 3-chloro-5-methylisoxazole (**5**)[28] and trimethylisoxazole (**15**)[29] with butyllithium, addition of the carbanions to **4**, and cleavage of the protecting group provided phenols **6** and **16**, respectively (Scheme II). The physical data of the phenols and glycidic ethers prepared in this study are listed in Table II. Direct condensation of 3,5-dimethyl-4-nitroisoxazole (**13**)[30] with 2-[2-hydroxy-3-(*tert*-butylamino)propoxy]benzaldehyde (**12**)[31] provided **14** (Scheme III).

Results and Discussion

Three main activities were observed in acute pharmacological experiments in rats: β-sympatholytic, α-sympatholytic, and hypotensive or antihypertensive activity (Tables III and IV).

Cardiac β-receptor blockade was most pronounced. Tachycardia in pithed rats induced by intravenous administration of 0.1 μg/kg isoproterenol (increase in heart rate in 100 control animals from 268 ± 3.9 to 389 ± 4.7 min^{-1}) was inhibited in a dose-related manner. Doses effecting a 50% reduction in heart-rate increase (ED_{50}) were up to 40 times lower than those for labetalol (Table III).

Table IV. α-Sympatholytic Activity

	inhibn of *l*-phenylephrine-induced pressor response in pithed rats[a]		
compd	no. of rats	ED_{50},[b] mg/kg	rel potency[c]
3a	20	0.12 (0.11-0.14)	3.9
3c	9	0.63 (0.56-0.72)	0.8
3e	9	~1.0	~0.5
3n	12	0.61 (0.49-0.76)	0.8
3o	9	0.21 (0.17-0.24)	2.2
3p	12	0.73 (0.62-0.86)	0.6
labetalol	20	0.47 (0.42-0.53)	1.0

[a] Intravenous administration. [b] 95% confidence limits in parentheses. [c] Labetalol = 1.0.

Stimulation of postsynaptic adrenergic α-receptors was antagonized by all compounds tested. The pressor effect of *l*-phenylephrine (1.47 μg/kg iv = 34 ± 0.7 mmHg in 40 untreated animals) was inhibited by 50% in doses which were in the same order of magnitude as that of labetalol. The effective doses of compounds **3a** and **3o** were 3.9 and 2.2 times lower, respectively, while that of the other com-

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pounds were 1.3 to 2 times higher, compared to that of labetalol (Table IV).

The arterial blood pressure of rats anesthetized with urethane was attenuated. All 2-(isoxazolylethenyl)phenoxypropanolamines, except 3m, were 2 to 13 times more active than labetalol. The dose range of the hypotensive activity (Table III) was similar to the dose exerting α-sympatholytic activity.

In analogy to the hypotensive action in normotensive rats, an antihypertensive activity was observed in spontaneously hypertensive rats (SHR). The active compounds showed the same activity (compounds **3h** and **9a**) or were 2 (compounds **3c,e,o** and **9b**) to 5 times (compound **3l**) more active than labetalol. Other compounds (**3b** and **11**) with a high β-sympatholytic activity exhibited only low antihypertensive effects. This may have been due to the limiting influence of absorption and/or first pass clearance after the oral application used here.

As expected, the compounds with an isopropyl or *tert*-butyl group attached to the nitrogen in the side chain were the most potent β-adrenoceptor antagonists. Of the aralkyl-substituted derivatives only, **3h** exhibited a comparable activity. Substituent modification of the isoxazole ring lead to potent compounds only for $R^1 = CH_2OCH_3$ and CH_3, whereas higher alkyl groups (**3k**,m), chlorine (**3q**), or the additional introduction of a methyl or nitro group into the 4 position attenuated activity. However, compounds **9a** and **9b**, isomeric to **3a** and **3b**, exhibited high β-sympatholytic activity.

In general, antihypertensive activity did not exactly parallel β-sympatholic activity. Nevertheless, most compounds with the highest antihypertensive activity were also potent β-adrenoceptor antagonists (**3a,c,n,p**). Moreover, it is noticeable that antihypertensive activity was more sensitive to modifications in the isoxazole ring than β-sympatholytic activity (**9**, **11**, **14**, and **20**).

Experimental Section

NMR spectra were obtained with Varian HR 220 and Brukker WH 270 FT instruments (internal standard tetramethylsilane). Melting points were determined on a Buchi melting point apparatus and are uncorrected. Silica gel 60 (E. Merck, Darmstadt) was used for column chromatography. In the ^1H NMR spectra, the two doublets of the olefinic hydrogen atoms showed a characteristic vicinal trans coupling constant of 16 Hz.

General Procedure for the Preparation of 2-[2-(2,3-Epoxypropoxy)phenyl]ethenylisoxazoles. The preparation of **2a** is presented as an example. A mixture of 3-methyl-5-[2-(2-hydroxyphenyl)ethenyl]isoxazole[22] (**1a**; 20 g, 0.1 mol), epibromohydrin (21 g, 0.15 mol), and K_2CO_3 (28 g) was stirred at 50 °C for 4 h, poured onto 200 mL of ice–water, and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated. The residue was recrystallized from EtOH to yield 23.3 g (87%) of **2a**, mp 100 °C. Anal. ($C_{15}H_{15}NO_3$) C, H, N.

General Procedure for the Preparation of (*E*)-1-Amino-3-[2-(2-isoxazolylethenyl)phenoxy]-2-propanols 3a–q, 9a,b, 11, 17, and 20, Using (*E*)-[(1,1-Dimethylethyl)amino]-3-[2-[2-(3-methyl-5-isoxazolyl)ethenyl]phenoxy]-2-propanol (3a) as the Example. *tert*-Butylamine (50 mL) was added to **2a** (23 g, 0.09 mol) in EtOH (100 mL). The solution was refluxed for 1 h and then stirred at 25 °C overnight and concentrated. The residue was recrystallized from EtOH and treated with HCl in EtOH to yield 33.8 g (79%) of **3a**, mp 217 °C. Anal. ($C_{19}H_{26}N_2O_3 \cdot HCl$) C, H, N, Cl. The compounds **3b–q**, **9a,b**, 11, 17, and 20 were prepared in a similar manner. The following required amines were commercially available or were prepared by literature procedures: 4-(3-aminobutyl)phenol,[32] α-methylbenzenepropanamine,[33] and 3,4-dimethoxy-α-methylbenzeneethanamine.[34] 4-(3-Amino-3-methylbutyl)phenol and α,α-dimethyl-4-methoxybenzenepropanamine were prepared according to the procedure of Ritter and Kalish[35] for α,α-dimethylbenzeneethanamine.

3-Chloro-5-[2-(2-hydroxyphenyl)ethenyl]isoxazole (6). *n*-Butyllithium (1.6 N in hexane, 0.095 mol) was added to a stirred solution of 3-chloro-5-methylisoxazole (**5**)[28] in absolute THF (100 mL) at −78 °C. After 30 min at −78 °C, 2-(1-methoxyethoxy)-benzaldehyde (**4**; 160 g, 0.089 mol) was added, and the mixture was stirred for 15 min at −50 °C, poured onto ice–water, and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 (120 mL)/Et_3N (70 mL) and then methanesulfonyl chloride (18.5 g, 0.162 mol) was added dropwise. The suspension was stirred for 12 h at 25 °C and poured into ice–water. The yellow oil, obtained by concentration of the organic layer, was dissolved in MeOH (40 mL) and acidified with 2 N HCl. Water was added until the formation of a yellow precipitate of **6**: yield 9.4 g (51%); mp 183–186 °C. 3,4-Dimethyl-5-[2-(2-hydroxyphenyl)ethenyl]isoxazole (**16**) was prepared in a corresponding manner. Phenols **1a–d**, **8**, and **10** were synthesized according to the method of Franke et al.[22]

(*E*)-1-[(1,1-Dimethylethyl)amino]-3-[2-[2-(3-methyl-4-nitro-5-isoxazolyl)ethenyl]phenoxy]-2-propanol (14). 2-[2-Hydroxy-3-(*tert*-butylamino)propoxy]benzaldehyde[31] (**12**; 5.5 g, 0.023 mol) and 3,5-dimethyl-4-nitroisoxazole[30] (**13**; 3.3 g, 0.023 mol) were stirred in MeOH (60 mL)/piperidine (1 mL) for 18 h at 25 °C. The mixture was filtered and the solid residue was recrystallized from EtOH to yield 3.7 g (43%) of **14**: mp 98–102 °C. Anal. ($C_{19}H_{25}N_3O_5$) C, H, N.

Pharmacological Methods. β-Sympatholytic Activity in Pithed Rats. The β-sympatholytic activity was determined in groups of two to five male, pithed, Sprague–Dawley rats, 200–240 g, anesthetized by intraperitoneal injection of 120 mg/g amobarbital. The trachea was cannulated for artificial respiration. Blood pressure was recorded from the right carotid artery by means of Statham transducers. Heart rate was measured with a rate meter (Hellige) from the distance of the pulse amplitude.

Isoproterenol (0.1 μg/kg) was injected intravenously before and 5 min after iv administration of the drugs. The dose which inhibited the isoproterenol-induced increase in heart rate by 50% was determined as the ED_{50}.

α-Sympatholytic Activity in Pithed Rats. The α-sympatholytic activity was tested in groups of three to five male Sprague–Dawley rats per dose, 200–240 g, which were prepared in the same manner as above.

l-Phenylephrine (1.47 μg/kg; 34 ± 0.7 mmHg in 40 animals) was injected iv before and 5 min after iv administration of the test compounds. The dose which inhibited the *l*-phenylephrine-induced rise in blood pressure by 50% was determined as the ED_{50}.

Hypotensive Activity in Anesthetized Rats. The substances were administered intravenously to groups of two to five male Sprague–Dawley rats, 230–280 g, anesthetized by urethane, 1.78 g/kg ip. The blood pressure in the carotid artery was measured as above. The dose which lowered the mean carotid pressure by 20% was determined as the ED_{20}.

Antihypertensive Activity in Conscious SH Rats. The substances were administered orally to groups of four to eight male, SH rats, 250–380 g, from the Okamoto strain. Systolic blood pressure was measured, before and 2 h after administration, using a tail cuff method at an ambient temperature of 35 °C. The dose which lowered the systolic blood pressure by 20%, taking into account the values found in placebo-treated control animals, was determined as the ED_{20}. The effective doses were calculated from the linear relationship between the logarithm of the doses (mg/kg) and the relative effects (Δ%) by means of regression analysis.

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