Antihypertensive β-Adrenergic Blocking Agents: *N*-Aralkyl Analogues of 2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-cyanopyridine[1]

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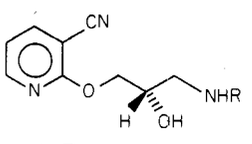
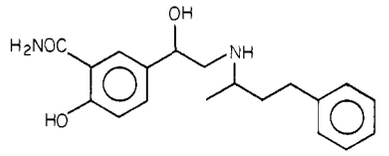
An interest in dual-acting antihypertensive agents, specifically those related to (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine (1), led us to probe the contribution of the side-chain amino substituent in this series. The ability of 1 and its various analogues to displace radiolabeled α_1 (WB-4101 and prazosin) and β (dihydroalprenolol) adrenergic receptor ligands was assessed by receptor-binding techniques. Most of the compounds exhibited high β-adrenoceptor binding affinities, but only the *N*-aralkylamino-substituted compounds showed high α_1-adrenoceptor affinities. Therefore, the vasodilation shown by 1 was not due to an interaction with the α_1 adrenoceptor. The aralkylamino analogues of 1 in spontaneously hypertensive rats and anesthetized dogs exhibited antihypertensive activity and α_1-adrenoceptor blocking properties. Unlike the preference shown by β-adrenoceptors for *S* enantiomers in this oxymethylene class of β blockers, the chirality at the secondary hydroxy center made only a minor contribution to the affinity for the α_1-adrenoceptor and even less of a contribution to the observed antihypertensive effects. This lack of chiral influence at the hydroxy center confirmed what had been previously observed in more limited studies with the isomers of both labetalol and medroxalol.

Adrenergic receptors have been classified as α or β depending upon their relative responses to various adrenergic agonists.[2] This classification was further refined to define α_1, α_2 and β_1, β_2 receptor subtypes.[2] Side effects associated with antihypertensive agents operating via α-adrenergic blockade are reflex tachycardia and postural hypotension.[3] In principle, the reflex tachycardia should be eliminated by concomitant β_1-adrenergic blockade. Problems associated with nonselective β-adrenergic receptor blockade are bronchoconstriction and Raynaud's syndrome;[3,4] these, in principle, should be alleviated by the presence of α_1-adrenergic blocking activity. Thus, the complementary pharmacological profiles suggest that a properly balanced α,β-adrenoceptor antagonist would be free of many of the side effects associated with the use of either type of agent alone.

The application of a strategy considering this complementarity was investigated as part of our program directed toward the development of antihypertensive β-adrenergic receptor antagonists.[5] As a first step, it was necessary to assess the contribution of α_1-adrenergic receptor blockade to the increased peripheral blood flow observed with (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine (1).[5] This analysis was followed by the replacement of the *tert*-butylamino group in 1 with various aralkylamino substituents to determine if such moieties might introduce, or enhance, α-adrenergic blockade. Recently, other dual-acting compounds have been reported. These include labetalol (2),[6,7] medroxalol (3),[8] and sulfinalol



1, R = *tert*-butyl



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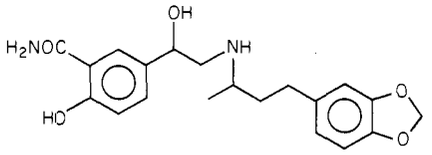

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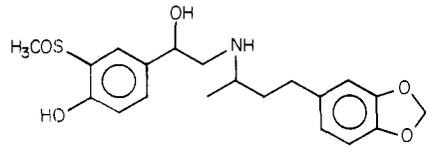

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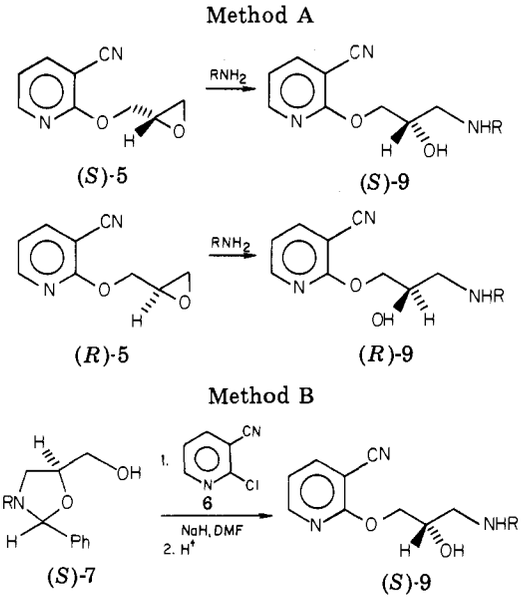
Scheme I



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(1) This paper has been presented in part; see "Abstracts of Papers", 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 29–April 3, 1981; American Chemical Society: Washington, DC, 1981; Abstr MEDI 55.
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(3) Beilin, L. F.; Juel-Jensen, B. E. *Lancet* **1979**, *1*, 979.
(4) Frishman, R.; Silverman, R.; Strom, J.; Elkayam, U.; Sonnenblick, E. *Am. Heart J.* **1979**, *98*, 256.
(5) Baldwin, J. J.; Lumma, W. C., Jr.; Lundell, G. F.; Ponticello, G. S.; Raab, A. W.; Engelhardt, E. L.; Hirschmann, R. *J. Med. Chem.* **1979**, *22*, 1284.
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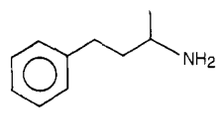
0022-2623/83/1826-0649$01.50/0

(4),[9] all of which bear aralkylamino groups but belong to the ethanolamine class. In this article, we describe the effect of such aralkylamino substitution in the oxymethylene class of β-adrenergic blocking agents. In addition, the influences of chirality on the relative affinities for the [^{3}H]dihydroalprenolol (DHA, β), the [^{3}H]clonidine (α_2), and the [^{3}H]WB-4101 (α_1) or [^{3}H]prazosin (α_1) binding sites were determined.

Chemistry. The compounds summarized in Table I were synthesized by one of two general methods. The first involved the reaction of various amines with (*RS*)-, (*R*)-, or (*S*)-cyanopyridyloxymethyloxiranes (**5**) (Scheme I; method A). These intermediate epoxides were obtained from the respective glycidols and 2-chloro-3-cyanopyridine (**6**).[10] The second approach (method B) involved the reaction of 2-chloro-3-cyanopyridine (**6**) with the N-substituted (*RS*)-, (*R*)-, or (*S*)-substituted-glycolamines protected as their benzaldehyde oxazolidines.[5,11] Although the schemes show the synthesis of enantiomers only, the sequences were also applicable to the preparation of the corresponding racemates.

In addition, the presence of the 1-methyl-3-phenylpropylamino and related chiral groups in **2–4** resulted in diastereomeric mixtures, which presented complications with regard to the interpretation of biological results. Two approaches were considered to resolve this problem in the study of the analogues of **1**; the first involved the preparation of the four individual isomers, while the second focused on the elimination of the chiral center associated with the amino component through the utilization of 1,1-dimethyl-3-phenylpropylamino and related achiral substituents. In order to evaluate the structure–activity relationships in the example bearing the 1-methyl-3-phenylpropylamino substituent (**28**), the individual isomers were prepared. The ready availability of both (*R*)- and (*S*)-**5** and the utilization of the resolved 1-methyl-3-phenylpropylamine (**8**)[12] allowed for the direct synthesis of the individual isomers.



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The resolution of **8** has been reported,[12] but some confusion exists as to the assignment of the absolute configurations[12] due to the change of sign between chirally pure free bases [(*R*)-**8**, $[\alpha]_D$ −18° (*c* = 1, cyclohexane)][12b] and the corresponding hydrochloride salts [(*R*)-**8**·HCl, $[\alpha]_D$ + 13° (*c* = 1, H_2O)].[12b] Following the reported procedure[12a] for the resolution of **8** via the mandelic acid salt, (+)-**8** [$[\alpha]^{25}_D$ +15.8° (*c* = 1.23, cyclohexane)] and (−)-**8** [$[\alpha]^{25}_D$ −14.9° (*c* = 0.996, cyclohexane)] were obtained. Reaction of chiral **8** with (*R*)- or (*S*)-**5** resulted in the formation of each of the individual isomers (**40–43**, Table II).

In order to unambiguously determine the absolute configurations of **40–43**, the amides derived from 1-methyl-3-phenylpropylamine (**8**) and (*S*)-*O*-methylmandelic acid were separated by HPLC and one of these, the *S,S* isomer, was subjected to single-crystal X-ray analysis.[13] This determination also confirmed the assignment of the absolute configuration as (*R*)-(−)-**8**, as assigned in ref 12b,d,e.

The diastereomeric purity of **28** and **40–43** was established by NMR techniques. The methyl region in the ^{1}H NMR exhibited two doublets of about equal intensity in **28**, and several of the ^{13}C peaks also showed doubling in **28** indicative of an approximately 1:1 diastereomeric composition. On the other hand, none of the pure isomers (**40–43**) indicated the presence of any of these doublings by ^{1}H NMR and/or ^{13}C NMR. Thus, the maximum diastereomeric contamination in any of these samples was ≤5%. The evaluation of pure isomers rather than mixtures, as was done with medroxalol,[8] avoided potential problems in interpretation of results. These NMR techniques were also used to ascertain that the diastereomeric mixtures shown in Table I were approximately 1:1 mixtures of the expected diastereomers (**29**, **33–39**).

The enantiomeric purity of the compounds in Table I was taken to be ≥98%. This conclusion stemmed from the analysis of the NMR spectra of the precursor epoxides, (*R*)- or (*S*)-**5**,[10] and several of the compounds in Table I (**25**, **27**, **31**, **32**) in the presence of a chiral shift reagent, Eu(hfbc)$_3$.[10] In all cases examined, none of the opposite enantiomer was detected, indicating a chiral purity of ≥98%.

Pharmacology. Since the blockade at both α- and β-adrenergic receptors could be important in the pharmacology of **1**, the various N-substituted derivatives were assessed by receptor-binding techniques in isolated membrane preparations by using [^{3}H]WB-4101 (α_1) and [^{3}H]-dihydroalprenolol (DHA, β) as radioligands (Table III). The acute antihypertensive effect was also evaluated in the spontaneously hypertensive rat (SH rat, Table IV). Additional in vivo studies in anesthesized dogs were also performed on selected compounds to determine α- and β-adrenoceptor blockade in a whole animal model (Table VI).

Since alteration of the amino substituent usually produced relatively minor changes in β-receptor affinity, these derivatives of the highly potent β-adrenoceptor antagonist **1** would be expected to exhibit relatively low K_I values vs. [^{3}H]DHA (Table III). All of the compounds were rather potent at displacing [^{3}H]DHA from rat neocortical membrane homogenates, although only a few (**27**, **28**, **31**, **34**) approached the affinity of **1**. When comparisons were made between *S* enantiomers and their corresponding racemates (**24**, **25**; **26**, **27**; **30–32**; **33**, **34**), the *S* isomers

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(13) The HPLC separation of the amides was accomplished by Y. Girard, M. Larue, J. Rokach, and J. Atkinson at Merck Frosst Canada, Inc., in Montreal. J. Hirshfield in our Rahway laboratories was responsible for the solution of the X-ray crystal structure. We are indebted to these co-workers for their results, the details of which will be reported in the near future.

exhibited affinities higher than, or at least equal to, the respective racemate as would be expected for oxymethylene β-adrenoceptor antagonists.[14]

The potential of these compounds for α_1-adrenergic receptor blockade was evaluated via the radioligand displacement of [^{3}H]WB-4101 from calf neocortical membrane homogenates, and the dissociation constants (K_I's) were calculated (Table III). Even though this ligand showed biphasic displacement curves,[15] it was still selective for the α_1 adrenoceptor, and it provided comparative data for mechanistic consideration. For the isomeric 1-methyl-3-phenylpropylamino analogues (**28**, **40–43**), the more specific α_1 radioligand, [^{3}H]prazosin, was employed.[15]

Both **1** and the alkylamino analogues **10–19** showed a very low affinity, i.e., high K_I values, for the displacement of [^{3}H]WB-4101 from α_1-adrenoceptors. Compound **19** bearing a 4-*tert*-butylcyclohexylamino substituent had the highest affinity for the α_1 adrenoceptor in this series (K_I = 400 nM). The aralkylamino analogues (**20–39**) represented a demarcation in pharmacological profile; most possessed K_I's ranging from 18–380 nM against [^{3}H]WB-4101. The most active compounds in this series (**27**, **28**, **33**, **34**, **36**) and labetalol (**2**) exhibited similar affinities for α_1-adrenergic receptors. Thus, the presence of an *N*-aralkylamino group induced an interaction with the α_1 adrenoceptor, yielding compounds that showed potencies up to 500 times greater than **1** and related alkylamino analogues with the only exception being **19**. The most obvious aralkylamino exception to this rule was the indanyl derivative **22**; reduction of flexibility may be a causative factor in this result.

Comparisons of pure enantiomers and the corresponding racemates (**24**, **25**; **26**, **27**; **30–32**; **33**, **34**) suggested that structural features other than chirality at the secondary hydroxy center were much more important in determining the α_1-adrenergic receptor binding characteristics. In some cases the *R* enantiomer showed a higher affinity (**24**, **25**; **30–32**), while in others the isomer with higher affinity had the *S* configuration (**26**, **27**; **28**, **40–43**). Comparisons of pure enantiomers and the corresponding racemates (**24**, **25**; **26**, **27**; **30–32**; **33**, **34**) indicated that the antihypertensive activity (Table IV) was not highly dependent upon the chirality at the secondary hydroxy center, which was in agreement with the low chiral influence found in the radioligand displacement studies. Although the influence of chirality on α-adrenoceptor affinity in the related ethanolamine class had been previously probed,[7,8] the mixtures of isomers used in the study of the medroxalol isomers[8] complicated the interpretation of these results, while detailed pharmacology was presented on only one of the isomers of labetalol (*R*,*R* isomer, SCH 19927).[7] The aralkylamino derivatives of **1** provided the first documentation within the oxymethylene class for the importance of chirality at the alcohol center on β-adrenoceptor, but not α_1-adrenoceptor, affinity. Patil et al.[14] had earlier suggested that such may be the case for various α- and β-adrenoceptor antagonists.

None of the alkylamino-substituted analogues (**2**, **10–19**) showed an antihypertensive potency comparable to **1** (Table IV) in the SH rat. In contrast, most of the aralkylamino analogues (**20–39**) exhibited acute antihypertensive activity with a potency somewhat less than the standard **1**. Since β-adrenergic antagonists generally exhibited only modest acute antihypertensive effects,[16] it was attractive to postulate that the observed antihypertensive response in compounds other than **1** resulted from α_1-adrenoceptor blockade. Upon analysis, a statistically significant correlation was found between antihypertensive activity in the SH rat and in vitro α_1-binding affinity.[17] Compounds in the group **20–39** for which there was data available (**21–32**, **34**, **37**) were used to construct a plot of in vitro α_1-adrenoceptor affinity (log K_I vs. [^{3}H]WB-4101) vs. antihypertensive activity in the SH rat at an oral dose of 5 mg/kg, giving a correlation coefficient of 0.673.[17] Although statistically significant, this correlation was not a particularly good one, and other mechanisms may contribute to the observed antihypertensive response. Since **1** was a potent antihypertensive agent[5] via a mechanism that did not involve α-adrenoceptor blockade, these aralkylamino analogues may also reduce blood pressure by mechanisms other than α-adrenergic receptor antagonism. This was somewhat similar to the results observed with the isomers of medroxalol[8] and labetalol,[7] i.e., the isomers exhibited similar antihypertensive activity in the SH rat while showing widely different α-adrenoceptor blocking properties in vitro. In these cases a statistically significant correlation was not observed, perhaps due to the much smaller sample size of their studies. Of course, the absorption, distribution, and metabolism of drugs may also complicate the interpretation of any comparisons of in vivo and in vitro responses.

Based on high α_1- and β-adrenoceptor affinities in radioligand displacements, the diastereomeric mixture **28** was a prime candidate for further pharmacological study. It was of interest to prepare and evaluate each of the four isomers to determine the influence of chirality on the pharmacological profile. While the *S* configuration at the alcohol center had been well established as the biologically active isomer in the aminohydroxypropoxy class of β-adrenergic blocking agents,[14] the influence of chirality on α_1-adrenergic receptor blockade has been only recently described in the ethanolamine class with the isomers of labetalol[7,18] and medroxalol.[8] The configuration at the hydroxy carbon in the potent (*S*)-oxymethylene class of β blockers corresponds to the *R* configuration in the ethanolamine class, each of which corresponds to the absolute configuration found in (*R*)-norepinephrine.

The displacements of various radioligands from mammalian cerebral cortex membrane homogenates allowed for the determination of K_I values at α- and β-adrenergic receptors for the four isomers (**40–43**, Table V). In addition to [^{3}H]WB-4101 as the α_1-adrenoceptor ligand, the displacements of [^{3}H]prazosin (an α_1-selective ligand) and [^{3}H]clonidine (an α_2-selective ligand) were also examined in the binding studies. Since [^{3}H]prazosin appeared to be more selective for the α_1-adrenoceptor and to give monophasic displacement curves,[15] the α_1 results presented were derived from its displacement. Each isomer displaced clonidine with K_I's greater than 1 μM, values much greater than those obtained from the [^{3}H]prazosin studies. Thus, these isomerically related compounds were all selective for the α_1-adrenoceptor. Ratios range from ~25 for the least selective compound (**43**) to ~135 for the most selective

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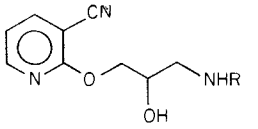
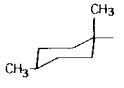
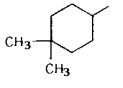
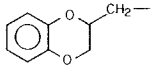
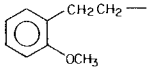
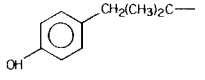
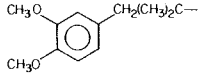
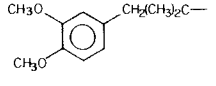
(17) We thank a referee for pointing out that this correlation with 12 degrees of freedom was statistically significant. See George W. Snedecor and William G. Cochran, "Statistical Methods", 7th ed., The Iowa State University Press: Ames, IA, 1980.
(18) Nakagawa, Y.; Shimamoto, N.; Nakazawa, M.; Imai, S. *Jpn. J. Pharmacol.* **1980**, *30*, 743.

Table I. 2-[3-(Substituted-amino)-2-hydroxypropoxy]-3-cyanopyridines 10–39



compd	R	chirality: -CHOH-	method	yield, %	formula	crystn solvent	mp, °C	$[\alpha]^{24}_D$, deg (*c*, solv)	anal.
10	$CH_3CH_2(CH_3)_2C$	*S*	A	18.1	$C_{14}H_{21}N_3O_2 \cdot HCl$	EtOH-Et_2O	141–144		C, H, N, Cl
11	$HC{\equiv}C(CH_3)_2C$	*R,S*	B	9.0	$C_{14}H_{17}N_3O_2 \cdot HCl$	CH_3CN	170–171		C, H, N
12	$HC{\equiv}CCH_2$	*R,S*	B	10.0	$C_{12}H_{13}N_3O_2 \cdot HCl$	*i*-PrOH-Et_2O	155–157		C, H, N
13	$(CH_3)_2CHCH_2CH_2$	*S*	B	47.2	$C_{14}H_{21}N_3O_2 \cdot C_4H_4O_4$	EtOH-Et_2O	95–98	−17.68 (0.92, MeOH)	C, H, N
14		*S*	B	30.7	$C_{15}H_{21}N_3O_2 \cdot C_4H_4O_4$	EtOH-Et_2O	130–134	−17.27 (1.10, MeOH)	C, H, N
15		*S*	B	18.3	$C_{17}H_{25}N_3O_2 \cdot HCl$	EtOH-Et_2O	144–146	−20.08 (0.96, MeOH)	C, H, N, Cl
16		*S*	B	7.0	$C_{19}H_{25}N_3O_2 \cdot HCl \cdot 0.5H_2O$	EtOH-Et_2O	220–221	−17.92 (0.81, MeOH)	C, H, N, Cl
17		*S*	B	15.2	$C_{17}H_{25}N_3O_2 \cdot HCl$	EtOH-Et_2O	165–167	−15.27 (1.02, MeOH)	C, H, N, Cl
18		*S*	B	15.5	$C_{17}H_{25}N_3O_2 \cdot HCl$	EtOH-Et_2O	189–190	−19.24 (1.08, MeOH)	C, H, N, Cl
19		*R,S*	A	12.8	$C_{19}H_{29}N_3O_2 \cdot HCl$	EtOH-Et_2O	161–164		C, H, N, Cl
20		*S*	B	57.2	$C_{18}H_{19}N_3O_4 \cdot C_2H_2O_4 \cdot 0.5H_2O$	EtOH	161–164	−11.67 (1.11, MeOH)	C, H, N
21		*S*	A	18.0	$C_{18}H_{21}N_3O_3$	toluene	97–99	0.00 (0.85, MeOH)	C, H, N
22		*S*	B	15.2	$C_{18}H_{19}N_3O_2 \cdot HCl$	EtOH-Et_2O	130–132	−16.41 (0.59, MeOH)	C, H, N, Cl
23		*R,S*	A	37.0	$C_{19}H_{23}N_3O_3 \cdot HCl$	*i*-PrOH-Et_2O	193–196		C, H, N, Cl
24		*R,S*	A	35.0	$C_{21}H_{27}N_3O_4 \cdot HCl$	EtOH	192–195		C, H, N
25		*S*	A	59.5	$C_{21}H_{27}N_3O_4 \cdot HCl$	EtOH	186–189	−15.79 (1.00, MeOH)	C, H, N, Cl

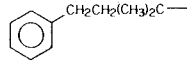
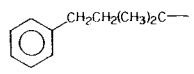
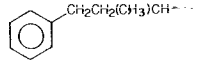
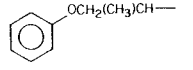
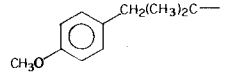
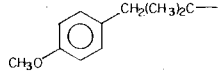
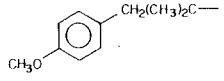
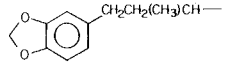
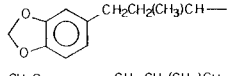
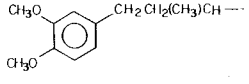
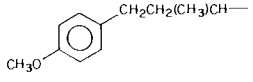
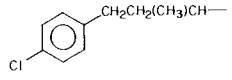
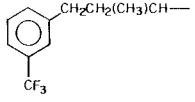
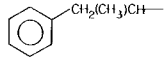
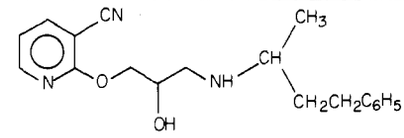
26		*R,S*	A	26.0	$C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$	*i*-PrOH	134–135		C, H, N
27		*S*	A	24.0	$C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$	*i*-PrOH	151–153	−14.44 (1.14, MeOH)	C, H, N
			B	22.3	$C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$		142–145	−13.08	C, H, N
28		*R,S*	A	38.0	$C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$	*i*-PrOH	117–118		C, H, N
29		*R,S*	A	17.5	$C_{18}H_{21}N_3O_3 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	86–89		C, H, N
30		*R,S*	A	51.0	$C_{20}H_{25}N_3O_3 \cdot HCl$	EtOH–Et_2O	153–155		C, H, N, Cl
31		*S*	A	31.0	$C_{20}H_{25}N_3O_3 \cdot HCl$	*i*-PrOH–Et_2O	130–133	−14.05 (1.00, MeOH)	C, H, N
32		*R*	A	75.0	$C_{20}H_{25}N_3O_3 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	128–132	+12.99 (1.22, MeOH)	C, H, N
33		*R,S*	A	34.0	$C_{20}H_{23}N_3O_4 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	122–127		C, H, N
34		*S*	A	37.9	$C_{20}H_{23}N_3O_4 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	113–115	−14.09 (1.01, MeOH)	C, H, N
35		*R,S*	A	15.1	$C_{21}H_{27}N_3O_4 \cdot HCl$	*i*-PrOH–EtOH	183–186		C, H, N
36		*R,S*	A	33.6	$C_{20}H_{25}N_3O_3 \cdot HCl$	EtOH–Et_2O	113–116		C, H, N
37		*R,S*	A	32.8	$C_{19}H_{22}ClN_3O_2 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	112–115		C, H, N
38		*R,S*	A	24.8	$C_{20}H_{22}F_3N_3O_2 \cdot HCl$	EtOH–Et_2O	150–151		C, H, N
39		*R,S*	A	45.3	$C_{18}H_{21}N_3O_2 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	128–132		C, H, N

Table II. 2-[3-[(1-Methyl-3-phenylpropyl)amino]-2-hydroxypropoxy]-3-cyanopyridine Maleate Isomers ($C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$)



compd	chirality: -CHOH-	chirality: —CH(CH3)CH2CH2C6H5	method	yield, %	crystn solvent	mp, °C	$[\alpha]^{24}_D$, deg (c, solv)	anal.
28	*R,S*	*R,S*	A	38	*i*-PrOH	117–118	−0.42 (1.185, MeOH)	C, H, N
40	*S*	*R*	A	31	*i*-PrOH–Et_2O	110–112	−6.32 (1.06, MeOH)	C, H, N
41	*R*	*R*	A	43	*i*-PrOH–Et_2O	113–115	+17.64 (1.015, MeOH)	C, H, N
42	*S*	*S*	A	47	*i*-PrOH–Et_2O	112–114	−18.19 (1.035, MeOH)	C, H, N
43	*R*	*S*	A	47	*i*-PrOH–Et_2O	105–108	+4.91 (1.05, MeOH)	C, H, N

Table III. Inhibition of [^{3}H]WB-4101 and [^{3}H]DHA Binding to Mammalian Neocortical Membranes

compd	chirality: -CHOH-	α_1-receptor K_I,[b] nM, for [^{3}H]WB-4101	β-receptor K_I,[c] nM, for [^{3}H]DHA[a]
1	*S*	9000 ± 2000	0.68 ± 0.10
10	*S*	7000 ± 1000	1.90 ± 0.57
11	*R,S*		11.7 ± 3.0
12	*R,S*		255 ± 40
13	*S*	6000 ± 1000	60.1 ± 2.5
14	*S*	6000 ± 2000	11.6 ± 6.9
15	*S*	3100 ± 500	28.9 ± 6.2
16	*S*	7000 ± 2000	67.1 ± 2.0
17	*S*	6000 ± 2000	1.99 ± 0.09
18	*S*	7000 ± 2000	31.5 ± 3.2
19	*R,S*	400 ± 60	7.16 ± 2.0
20	*S*	89 ± 9	38.5 ± 3.9
21	*S*	210 ± 10	6.85 ± 0.36
22	*S*	1000 ± 100	5.03 ± 1.5
23	*R,S*	72 ± 3	1.54 ± 0.28
24	*R,S*	125 ± 9	4.82 ± 1.0
25	*S*	190 ± 20	5.72 ± 1.5
26	*R,S*	84 ± 9	1.90 ± 0.19
27	*S*	60 ± 10	1.40 ± 0.0
28	*R,S*	63 ± 5	1.45 ± 0.36
29	*R,S*	160 ± 20	8.90 ± 1.0
30	*R,S*	120 ± 10	2.38 ± 0.42
31	*S*	280 ± 20	1.40 ± 0.41
32	*R*	110 ± 20	9.41 ± 2.3
33	*R,S*	40 ± 10	1.88 ± 0.14
34	*S*	18 ± 7	0.58 ± 0.22
35	*R,S*	230 ± 20	14.4 ± 1.9
36	*R,S*	51 ± 7	2.49 ± 0.15
37	*R,S*	73 ± 5	7.01 ± 1.7
38	*R,S*	180 ± 10	6.16 ± 1.4
39	*R,S*	380 ± 40	6.41 ± 1.9
2 (labetalol)		74 ± 9	19.2 ± 2.2

[a] [^{3}H]DHA = [^{3}H]dihydroalprenolol. [b] The results are the mean ± SD for two or more separate determinations. [c] The results are the mean ± SD for three or more separate determinations.

compound (**40**) when [^{3}H]clonidine (α_2) displacement was compared with the results using [^{3}H]prazosin (α_1). The *S* isomers at the hydroxy center (**40**, **42**) showed greater affinities for both the α_1- and β-receptors than did the corresponding isomeric (*R*)-alcohols (**41**, **43**). It was interesting to note that the chirality at each asymmetric carbon was worth about 0.5 kcal/center (Table V); the best bound *S,R* isomer (**40**), which showed the highest affinity vs. [^{3}H]prazosin, had a free energy of binding almost 1 kcal/mol greater than the lowest affinity *R,S* isomer (**43**). Although free-energy differences of this order could be important in overall drug action, they were small compared to the overall free energies for binding. These values were also small when one considers the importance of chirality at the β-adrenergic receptor.[14] The *S* chirality at the hydroxy center led to an approximately tenfold increase in affinity for the β-adrenergic receptor when compared to the corresponding *R* enantiomers (**40** vs. **41**, **42** vs. **43**), amounting to a thermodynamic preference of 1.3 or 1.5 kcal/mol for either *S* isomer.

The most interesting compounds having K_I (α_1) < 100 nM and K_I (β) < 10 nM were examined in anesthetized dogs in order to assess their α- and β-adrenoceptor blockade in a whole animal model (Table VI). However, it should be emphasized that these results are only preliminary. The α-adrenergic receptor blocking activity of these compounds was established by their antagonism of phenylephrine-induced increase in arterial pressure, while their antagonism of isoproterenol-induced tachycardia allowed for a determination of the β-adrenoceptor blockade. In general, the trends observed in the anesthetized dog in terms of α,β-adrenoceptor blockade followed those found in the α_1- and β-radioligand displacement studies. The most interesting compounds in this series were equal to, or slightly more potent than, labetalol (**2**) as α-antagonists and substantially more potent than labetalol as β-antagonists (Tables III, V, and VI). The effect of such an increase in β-adrenoceptor affinity without change in the α-adrenoceptor potency increased the separation between the two activities.

From the K_I values of [^{3}H]WB-4101, it can be concluded that the vasodilation exhibited by **1** was not due to an interaction with the α_1-adrenoceptor; the mode by which **1** produced vasodilation is, therefore, still an open question. The introduction of an aralkylamino substituent into the β-blocking side chain of **1** led to a series of compounds showing in vitro and in vivo α-adrenergic receptor binding properties. With the dual-acting α,β-adrenergic blocking agents from this series as well as labetalol[7] and medroxalol,[8] the chirality at the hydroxy center made only a minor contribution to the affinity for the α_1-adrenoceptor and even less of a contribution to the observed antihypertensive effects.

Experimental Section

Optical rotation measurements were obtained on a Perkin-Elmer 141 polarimeter. NMR spectra were determined in the indicated solvent on a Varian T-60 or EM-390 with tetramethylsilane as Büchi internal standard for proton spectra. Chemical shifts are given in δ units, and coupling constants are in hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; fs s, finely split singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. Chiral shift NMR analyses were conducted on a Varian SC-300 operating in the FT mode. Other high-field NMR spectra were obtained on either a Varian SC-300 or a Nicolet NT-360 spectrometer, and ^{13}C NMR spectra were obtained on a Varian CFT-20 instrument. Melting points were determined on a Thomas-Hoover apparatus, in open capillary tubes, and are uncorrected. Microanalyses are within 0.4% of

Table IV. Comparative Effect of Compounds on Arterial Pressure of Spontaneously Hypertensive Rats

compd	dose, mg/kg	route	no. of SHR	max fall in MAP, mmHg ± SE
1	1.25	po	4	47 ± 5
	0.312	po	8	30 ± 4
	0.078	po	4	19 ± 2
10	5.0	po	3	57 ± 12
	0.312	po	2	4
11	20.0	ip	2	15
12	20.0	ip	2	16
13	20.0	ip	2	17
14	20.0	po	2	24
	5.0	po	2	14
15	20.0	po	8	39 ± 10
	5.0	po	8	22 ± 4
	1.25	po	6	12 ± 5
16	20.0	ip	2	20
17	20.0	po	2	42
	5.0	po	2	31
18	20.0	po	2	30
	5.0	po	2	10
19	20.0	po	2	45
20	20.0	ip	2	40
	20.0	po	2	11
21	5.0	po	2	38
	1.25	po	2	20
	0.312	po	2	11
22	20.0	po	2	33
	5.0	po	2	13
23	5.0	po	2	67
	1.25	po	2	32
	0.312	po	3	17 ± 7
24	5.0	po	2	43
	1.25	po	2	0
25	5.0	po	2	39
	1.25	po	2	30
	0.312	po	3	20 ± 1
26	20.0	ip	2	61
	20.0	po	2	38
	5.0	po	4	27 ± 5
27	5.0	po	4	50 ± 13
	1.25	po	5	28 ± 9
	0.312	po	4	21 ± 4
28	5.0	po	6	38 ± 6
	1.25	po	4	26 ± 5
	0.312	po	2	16
29	20.0	po	2	40
	5.0	po	2	29
	1.25	po	2	8
30	20.0	po	2	54
	5.0	po	2	38
	1.25	po	2	24
	0.312	po	2	26
	0.078	po	2	4
31	5.0	po	2	37
	1.25	po	2	41
	0.312	po	4	24 ± 5
	0.078	po	2	17
32	20.0	po	2	70
	5.0	po	4	73 ± 16
33	20.0	po	2	57
34	5.0	po	2	71
	1.25	po	3	84 ± 6
35	20.0	po	2	38
36	20.0	po	3	58 ± 9
37	20.0	po	2	48
	5.0	po	4	36 ± 9
38	20.0	po	2	29
39	20.0	po	2	50
2	20.0	po	4	38 ± 11
	5.0	po	3	21 ± 1
	1.25	po	4	2 ± 16

theoretical values when indicated by symbols of the elements.

Silica gel 60 (E. Merck, Darmstadt) was used for column chromatography. Organic solutions were dried over Na_2SO_4 and filtered, and the filtrate was concentrated to dryness on a Büchi rotary evaporator under water-aspirator pressure (20 mm).

Method A General Procedure. Reaction of the appropriate epoxide **5**[10] with 1.0–2.0 molar equiv of the required amine was accomplished by heating neat in an oil bath at 60–70 °C overnight. Chromatography on silica gel 60 by eluting with 2–4% $CH_3OH/CHCl_3$ or CH_2Cl_2 separated the desired product from excess residual amine. Salt formation, followed by recrystallization, gave the compounds listed in Tables I and II. The preparation of (*S*)-2-[3-[(1,1-dimethyl-3-phenylpropyl)amino]-2-hydroxypropoxy]-3-cyanopyridine maleate (**27**) is given as an example.

A stirred mixture of (*S*)-**5** (3.52 g, 0.02 mol) and 1,1-dimethyl-3-phenylpropylamine (3.3 g, 0.02 mol) was heated in an oil bath at 60 °C overnight. The mixture was chromatographed on ~250 g of silica gel 60 by eluting with 3% $CH_3OH/CHCl_3$. After isolation of the appropriate fractions, the maleate salt was prepared in 2-propanol. Recrystallization from 2-propanol gave **27** (24.0%): mp 151–153 °C; ^1H NMR (Me_2SO-d_6) δ 1.4 (6 H, s), 1.9 (2 H, m), 2.6 (2 H, m), 3.2 (2 H, m), 4.3 (1 H, m), 4.5 (2 H, d), 6.1 (2 H, s), 7.3 (6 H, m), 8.3 (1 H, dd), 8.5 (1 H, dd).

2-[3-[[1,1-Dimethyl-2-(4-hydroxyphenyl)ethyl]amino]-2-hydroxypropoxy]-3-cyanopyridine Hydrochloride (23). For solid, high-melting amines the following procedure was employed. The epoxide (*RS*)-**5**[10] (1.41 g, 0.008 mol) and 1,1-dimethyl-2-(4-hydroxyphenyl)ethylamine (1.37 g, 0.008 mol) were dissolved in CH_3CN (20 mL) and H_2O (5 mL). This mixture was stirred at room temperature for 1 week. After concentration, the residue was taken up in CH_2Cl_2 and washed with H_2O. Drying and concentration gave the crude product, which was chromatographed on ~200 g silica gel 60 by eluting with NH_3 saturated 5% $CH_3OH/CHCl_3$. The HCl salt was prepared in 2-propanol/ether. Recrystallization from 2-propanol/ether gave **23** (37.0%): mp 193–196 °C; ^1H NMR (Me_2SO-d_6) δ 1.3 (6 H, s), 2.9 (2 H, br s), 3.3 (2 H, m), 5.5 (3 H, br s), 6.7 (2 H, d), 7.1 (2 H, d), 7.2 (1 H, dd), 8.2 (1 H, dd), 8.4 (1 H, dd).

Method B General Procedure. Reaction of the oxazolidine alcohols [(*RS*)- or (*S*)-**7**], prepared as previously described,[5,11] with NaH in DMF formed the sodium alkoxide. To this mixture was added 2-chloro-3-cyanopyridine, and the reaction was stirred overnight. Acid-catalyzed hydrolysis of the oxazolidine ring gave the desired products. The preparation of (*S*)-2-[3-[(3-methylbutyl)amino]-2-hydroxypropoxy]-3-cyanopyridine maleate (**13**) is given as an example.

To (*S*)-2-phenyl-3-(3-methylbutyl)-5-(hydroxymethyl)oxazolidine [(*S*)-**7**, R = $(CH_3)_2CHCH_2CH_2$; 6.01 g, 0.024 mol] in DMF (50 mL) was added NaH (1.16 g, 50% oil dispersion, 0.024 mol) in portions. After heating on a steam bath for 15 min, the mixture was cooled for 1 h prior to the addition of 2-chloro-3-cyanopyridine (3.34 g, 0.024 mol). After stirring overnight, the mixture was poured into 100 mL of ice–water and extracted with ether (4 times). The combined ether extracts were washed with water. The basic materials were extracted into 1.5 N HCl (2 × 50 mL) and H_2O (1 × 100 mL), and the combined aqueous acidic extracts were heated on a steam bath for 0.5 h. After cooling, the mixture was washed with benzene (4 times). The aqueous phase was then basified by adding solid Na_2CO_3 with ice cooling. Extracting with ethyl acetate, drying, and concentrating gave the crude product. The maleic acid salt was prepared in ethanol/ether. Recrystallization from ethanol/ether gave **13** (47.2%): mp 95–98 °C; ^1H NMR (Me_2SO) δ 0.9 (6 H, d), 1.5 (3 H, m), 3.0 (4 H, m), 4.3 (3 H, m), 6.0 (2 H, s), 7.2 (1 H, dd), 8.3 (1 H, dd), 8.5 (1 H, dd).

Pharmacology. α-Adrenergic Receptor Binding Assays. [^3H]Prazosin was obtained from Amersham Corp. at a specific activity of 33 Ci/mmol. [^3H]Clonidine and [^3H]WB-4101 were obtained from New England Nuclear Corp. at specific activities of 23.8 and 25 Ci/mmol, respectively. Radiochemical purity of each radioligand was periodically determined by thin-layer chromatography by using conditions recommended by the manufacturers.

The radioligand displacement assays involved incubating a fixed concentration of the radioligand with calf cerebral cortical membrane suspensions in the presence of five triplicate concentrations of the test compound. The incubation was terminated after 30 min by rapid filtration, and the receptor–radioligand complex was quantitated by means of liquid scintillation spec-

Table V. Inhibition of [^{3}H]Prazosin, [^{3}H]Clonidine, and [^{3}H]DHA Binding to Mammalian Neocortical Membranes

	α_1-receptors		α_2-receptors		β-receptors	
compd	K_I, nM, for [^{3}H]prazosin	ΔG, cal/mol	K_I, nM, for [^{3}H]clonidine	ΔG, cal/mol	K_I, nM	ΔG, cal/mol
28	55 ± 8	−9 900 ± 90	3100 ± 300	−7510 ± 60	1.45 ± 0.36	−12 050 ± 150
40	26 ± 5	−10 340 ± 110	3500 ± 300	−7440 ± 50	0.67 ± 0.09	−12 500 ± 80
41	56 ± 8	−9 890 ± 85	1600 ± 100	−7900 ± 40	5.90 ± 0.42	−11 220 ± 40
42	70 ± 6	−9 755 ± 50	3900 ± 200	−7370 ± 30	0.73 ± 0.20	−12 460 ± 170
43	120 ± 8	−9 440 ± 40	3200 ± 200	−7500 ± 40	7.80 ± 0.31	−11 050 ± 20

Table VI. In Vivo α,β-Adrenoceptor Antagonism in the Anesthetized Dog

compd	no. of dogs	antagonism of phenylephrine-induced increase in arterial pressure: α ED_{50}, μg/kg, iv	antagonism of isoproterenol-induced tachycardia: β_1 ED_{50}, μg/kg, iv
27	4	753	6.9
33	2	950	3
34	2	1000	7
28	4	1700	6.9
40	2	1090	1
41	2	3950	66
42	3	1360	5
43	3	3000	81
2	4	1900	120

trometry. The complete experimental details of these assays have been previously published.[14,19]

Nonlinear regression analysis was used on the resulting sets of specific radioligand binding vs. test compound concentration to obtain estimates of the IC_{50} concentrations. Inhibition constants were then calculated from the Cheng–Prussof relationship[20]

$$K_I = IC_{50}/(1 + [C]/K_d)$$

where [C] is the fixed concentration of radioligand, and K_d is the radioligand–receptor dissociation constant. Binding determinations were done twice if the resulting K_I values agreed within the error limits determined from the nonlinear regression analysis or three times in case of lack of agreement.

β-Adrenergic Receptor Binding Assays. The binding of [^{3}H]dihydroalprenolol (DHA) to β-adrenoceptors in rat cortical membranes was performed according to the method of Bylund and Snyder.[21] Rat cerebral cortices were homogenized in 10 vol of ice-cold 0.32 M sucrose with a Teflon–glass homogenizer with 12 complete passes at 500 rpm. The homogenate was centrifuged at 1000g for 10 min at 4 °C, and the resultant supernatant was centrifuged at 27000g for 20 min to produce a crude synaptosomal (P_2) pellet. The pellet was resuspended in 10 vol/original wet weight of ice-cold 50 mM Tris-HCl (pH 8.0) and homogenized with a Polytron (setting = 6.0 for 10 s). The homogenate was washed twice in buffer and resuspended in 16.8 vol of ice-cold buffer to give a final protein concentration of approximately 1 mg/mL.

Binding assays were carried out in polypropylene tubes in a final volume of 1 mL. To each assay tube was added 0.1 mL of 10 nM [^{3}H]dihydroalprenolol (DHA) (specific activity = 50 Ci/mmol), 0.1 mL of 10 μM (−)-alprenolol, 0.1 mL of buffer containing the drug being evaluated or 0.1 mL of buffer to determine nonspecific binding, drug-dependent binding, and total binding, respectively. The reaction was initiated by the addition of 0.8 mL of the tissue suspension and continued for 20 min at room temperature. The reaction was terminated by placing the assay tubes on ice and adding 4.0 mL of ice-cold incubation buffer. Bound radioactivity was isolated by vacuum filtration on Whatman GF/B glass-fiber filters, and excess unbound radioactivity was removed from the filters by 3 × 4 mL washes with ice-cold buffer. Following vacuum filtration and washing of the glass-fiber filters, they were placed in scintillation vials to which were added 10 mL of Aquassure 2′ (New England Nuclear Corp.) liquid scintillation cocktail. The vials were capped and mechanically shaken for 30 min at room temperature. After equilibration, bound radioactivity was determined at an efficiency of approximately 38–40% in a Packard liquid scintillation spectrometer.

All determinations were conducted in triplicate. Total and nonspecific binding were determined for each binding assay, and specific binding was obtained as the difference between the two. This represented 100% binding. Specific binding was then calculated in the presence of each of three or more concentrations of the test agent and expressed as a percentage of the total specific binding. IC_{50}'s were then determined by linear regression analysis (Hewlett Packard HP-97 SD 03A program) of the log concentration vs. percent probit inhibition of binding, and K_I's were calculated by the relationship $K_I = IC_{50}/(1 + [C]/K_d)$,[20] where [C] is the concentration of radioligand used and K_d is the dissociation constant.

Differential α/β-Adrenoceptor Blockade in Anesthetized Dogs. Mongrel dogs of either sex weighing 8–13 kg were anesthetized with vinbarbital (50 mg/kg iv). The vagi were cut, and blood pressure was recorded through a femoral artery catheter (PE 50). Drug injections were made through a femoral vein catheter. Body temperature was maintained within a range of 37–38 °C with a telethermometer-controlled heating pad. The dogs were artificially respired via an endotracheal tube throughout the experiment with a Harvard Equipment mechanical respirator. Physiological responses were recorded from tracings generated by a Honeywell Instruments physiological recorder system. Heart rate was derived electronically from the blood-pressure pulse. Phenylephrine (30 μg/kg iv) and isoproterenol (0.5 μg/kg iv) were injected at 10-min intervals, and the change in mean arterial blood pressure and heart rate was recorded. Test drugs were administered intravenously in a cumulative manner. Following each dose of the test compound, the cardiovascular responses to isoproterenol and phenylephrine were obtained, and the next larger dose of the test compound was administered until at lease four doses had been given to the dog. The percent antagonism of each of the agonists on the two cardiovascular parameters was computed, and an ED_{50} was computed by linear regression analysis by the method of least squares.

Antihypertensive Activity in Spontaneously Hypertensive Rats. The compounds, administered as a saline solution or as a suspension in 1% methylcellulose, were evaluated for their effect on mean arterial pressure in unanesthetized, Wistar-Okamoto, spontaneously hypertensive rats purchased from Charles River/Lakeview Laboratories (Wilmington, MA). Only male rats of 290 to 350 g body weight and 30 to 40 weeks of age were used. Catheters were implanted under ether anesthesia. The caudal artery was cannulated (approximately 1 cm beyond the anus) with PE-10 tubing. The rostral end of the catheter was placed in the abdominal aorta just below the left renal artery. A PE-10 tubing flare and one end of a 20-gauge needle connector (anchor) were buried in the caudal groove of the tail, and the fascia and skin were sutured. PE-60 tubing with a tubular spring guard was fastened to a 20-gauge needle connector (anchor) and subsequently to a water-tight swivel (above the rat cage). The swivel, in turn, was connected to a P-23G Statham pressure transducer. Associated with the pressure transducer was a three-way stopcock and adjustable needle valve system, which permitted a continuous,

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sterile, pyrogen-free, 0.225% saline infusion. One day was allowed for recovery from surgery before the start of drug treatments. Arterial pressure was recorded continuously through Statham P-23Gb transducers on a Honeywell 906C Visicorder. Mean arterial pressure and heart rate data were printed at 0.5 h intervals through a data acquisition system (Data Graphics Corp., San Antonio, TX) by means of ASR-33 teletype units. Mean arterial pressure was recorded 0.5, 1, 2, 4, 8, 12, and 18 h after treatment.

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Registry No. (*S*)-**5**, 69500-51-2; (*RS*)-**5**, 69470-18-4; (*R*)-**5**, 69500-52-3; **7** [R = HC≡C(CH$_3$)$_2$C], 84945-38-0; **7** (R = HC≡CCH$_2$), 84945-39-1; **7** [R = (CH$_3$)$_2$CHCH$_2$CH$_2$], 84945-40-4; **7** (R = cyclohexyl), 84945-41-5; **7** (R = cyclooctyl), 84945-42-6; **7** (R = 1-adamantyl), 84945-43-7; **7** (R = 1,4-dimethylcyclohexyl), 84945-44-8; **7** (R = 4,4-dimethylcyclohexyl), 84945-45-9; **7** (R = 2,3-dihydro-1,4-benzodioxin-2-ylmethyl), 84945-46-0; **7** (R = 1-indanyl), 84945-47-1; **7** [R = PhCH$_2$CH$_2$(CH$_3$)$_2$C], 75561-37-4; **10**, 84945-48-2; **10** free base, 84945-49-3; **11**, 84945-50-6; **11** free base, 84945-51-7; **12**, 84945-52-8; **12** free base, 84945-53-9; **13**, 84945-55-1; **14**, 84945-57-3; **15**, 84945-58-4; **15** free base, 84945-59-5; **16**, 84945-60-8; **16** free base, 84945-61-9; **17**, 84945-62-0; **17** free base, 85026-17-1; **18**, 84945-63-1; **18** free base, 84945-64-2; **19**, 84945-65-3; **19** free base, 84945-66-4; **20**, 84945-67-5; **21**, 74944-03-9; **22**, 84945-68-6; **22** free base, 84945-69-7; **23**, 84945-70-0; **23** free base, 84945-71-1; **24**, 84945-72-2; **24** free base, 84945-73-3; **25**, 84945-74-4; **25** free base, 84945-75-5; **26**, 85026-19-3; **27**, 84945-76-6; **28**, 84945-77-7; **29**, 84945-78-8; **30**, 75598-87-7; **30** free base, 84945-79-9; **31**, 84945-80-2; **31** free base, 75561-41-0; **32**, 85026-21-7; **33**, 75561-54-5; **35**, 84945-81-3; **35** free base, 84945-82-4; **36**, 84945-83-5; **36** free base, 84945-84-6; **37**, 84945-86-8; **38**, 84945-87-9; **38** free base, 84945-88-0; **39**, 84945-90-4; **40**, 84945-92-6; **41**, 84945-94-8; **42**, 84945-96-0; **43**, 84945-98-2; 2-methyl-2-butanamine, 594-39-8; 4-(1,1-dimethylethyl)cyclohexanamine, 5400-88-4; 2-methoxybenzeneethanamine, 2045-79-6; 1,1-dimethyl-2-(4-hydroxyphenyl)ethylamine, 51706-55-9; 3,4-dimethoxy-2,2-dimethylbenzeneethanamine, 75561-47-6; 1,1-dimethyl-3-phenylpropylamine, 43052-72-8; (±)-2-methylbenzenepropanamine, 22148-77-2; 1-phenoxy-2-propanamine, 35205-54-0; 4-methoxy-2,2-dimethylbenzeneethanamine, 56490-94-9; α-methyl-1,3-benzodioxole-5-propanamine, 40742-32-3; 3,4-dimethoxy-2-methylbenzenepropanamine, 27487-78-1; 4-methoxy-α-methylbenzenepropanamine, 51062-15-8; 4-chloro-α-methylbenzenepropanamine, 74697-68-0; 3-(trifluoromethyl)-α-methylbenzenepropanamine, 73839-94-8; α-methylbenzeneethanamine, 60-15-1; 2-chloro-3-cyanopyridine, 6602-54-6; (*R*)-α-methylbenzenepropanamine, 937-52-0; (*S*)-α-methylbenzenepropanamine, 4187-57-9.

Synthesis and Antihypertensive Activity of 4′-Substituted Spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-ones[1]

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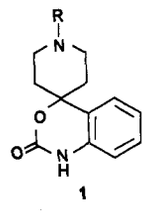
A series of 4′-substituted spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-ones was prepared and evaluated for antihypertensive activity in the spontaneously hypertensive rat (SHR). The basic ring system was prepared in one step by condensation of dilithiated (*tert*-butoxycarbonyl)aniline (**3**) with (*tert*-butoxycarbonyl)piperidinone. Deprotection afforded **6**, which was condensed with expoxides or alkyl halides to furnish the title compounds. The most active compound was *dl-erythro*-4′-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (**9**), and various modifications of this compound were made in order to elucidate the structure–activity relationships in the series. Preliminary indications are that **9** may act by both central and peripheral mechanisms.

We recently described the synthesis and antihypertensive activity of a series of 8-substituted 1-oxa-3,8-diazaspiro[4.5]decan-2-ones[2] and a series of 9-substituted 1-oxa-4,9-diazaspiro[5.5]undecan-3-ones.[3] We now describe related work on spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-ones **1**. Whereas the most active compounds of the two previous series exerted their antihypertensive effects predominantly through peripheral α_1-adrenoceptor blockade, the most interesting compound of the present series (**9**) appears to act by a more complex mechanism that may involve both peripheral and central sites of action. It should be recognized that **9** is structurally related to **2** (Janssen R 28935),[4] a centrally active antihypertensive agent that has been of considerable interest due to its complex and as yet not well understood mechanism(s) of action.[4,5]



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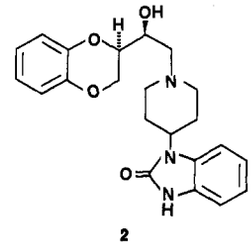

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[†] Institute of Organic Chemistry.
[‡] Institute of Pharmacology and Metabolism.

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