α-Adrenoreceptor Reagents. 4.[1-3] Resolution of Some Potent Selective Prejunctional α_2-Adrenoreceptor Antagonists

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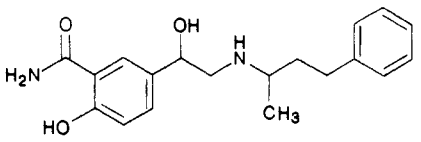
The resolution of three 2-substituted derivatives of idazoxan is described. The enantiomers show large separations in activity in a variety of in vitro and in vivo tests, and the active isomers are all potent and selective antagonists at the α_2-adrenoreceptor. The significance of these results in relation to those published on the enantiomers of idazoxan and to those on optically active α_2-adrenoreceptor agonists is discussed.

It has long been recognized[4] that many receptor systems are highly isomerically selective, and it is therefore important that when drug–receptor interactions are being investigated, compounds possessing chiral centers should be resolved so that the configuration of the active isomer may be established. The advent of sophisticated molecular modeling techniques that are being used to probe the topography of receptors emphasizes this requirement. The importance of working with pure enantiomers is highlighted by two recent examples in which isomeric pairs were found to interact with totally different receptor species. The (*R*,*R*) enantiomer of the antihypertensive agent labetalol[5] (**1**) is almost entirely responsible for its



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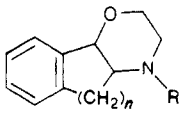
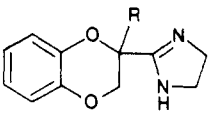


2 (n = 1, 2)

β-blocking activity whereas the (*S*,*R*) isomer antagonizes predominantly the α_1-adrenoreceptor. A second example is provided by the two series of benzocycloalkyl-1,4-oxazines (**2**), which were recently the subject of patent applications.[6,7] The (*R*,*R*) enantiomers in both series exhibit dopaminergic activity whereas the (*S*,*S*) enantiomers demonstrate α_2-adrenergic antagonism.

In addition to these rather special cases there are many instances[4] in which the enantiomers of compounds that interact with only one receptor species have widely differing affinities for that receptor. We have had a particular interest in compounds that have been shown to be antagonists at the α_2-adrenoreceptor, and in a recent paper[3] we briefly described the pharmacological screening of the (+)-*S* enantiomer (**5**) of 2-(2-methoxy-1,4-benzodioxan-2-



3, R = H (idazoxan)
4, R = OCH_3
7, R = CH_3
10, R = $C(=CH_2)CH_3$

yl)-2-imidazoline (**4**). We now report in more detail the resolution of compound **4** together with other potent and selective α_2-adrenoreceptor antagonists based on the 1,4-benzodioxan ring system.[2]

Chemistry. As in any program of resolution a large number of optically active acids were used in an attempt to prepare highly crystalline diastereoisomeric salts. In two of the cases presented here (**4**, **10**) dibenzoyltartaric acid proved the most useful, the third compound (**7**) was resolved by using mandelic acid; the degree of resolution was assessed with the use of ^{1}H NMR by using the chiral shift reagent tris[(trifluoroacetyl)camphorato]europium. To the limits of NMR detection, all three derivatives were fully resolved, and the pharmacological results support this.

The compounds were tested as either the free base (**11**, **12**) or the hydrochloride salts (**5**, **6**, **8**, **9**). The bases were prepared by partitioning the diastereoisomeric salts in a two-phase system consisting of dichloromethane and saturated sodium hydrogen carbonate or potassium carbonate solutions. Hydrochloride salts were formed by treating the free base with ethereal HCl.

Recently, work has been published[8-10] that describes the results of pharmacological testing on the enantiomers of the parent compound in this series, idazoxan (**3**); it is clear that there is a much lower separation of α_2-adrenoreceptor antagonist potencies between the active and "inactive" isomers than those described here for the 2-substituted derivatives. We suspected that a contributory factor to this difference might be that the isomers of idazoxan suffered partial racemization during the testing procedures, and we have therefore investigated the lability of the proton at C-2 in idazoxan using deuterium-exchange techniques. The results of these experiments show that this proton is indeed labile, and at 35 °C in a phosphate buffer maintained at pH 7.4, the half-life for deuterium exchange at C-2 is approximately 3 h. It is possible therefore that some racemization of the enantiomers of

(1) Part 1: Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Doxey, J. C.; Roach, A. G.; Smith, C. F. C. *J. Med. Chem.* **1983**, *26*, 823.
(2) Part 2: Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Davis, J. A.; Doxey, J. C.; Higgins, S. D.; Myers, M.; Roach, A. G.; Smith, C. F. C.; Stillings, M. R.; Welbourn, A. P. *J. Med. Chem.* **1984**, *27*, 570.
(3) Part 3: Stillings, M. R.; Chapleo, C. B.; Butler, R. C. M.; Davis, J. A.; England, C. D.; Myers, M.; Myers, P. L.; Tweddle, N.; Welbourn, A. P.; Doxey, J. C.; Smith, C. F. C. *J. Med. Chem.* **1985**, *28*, 1054.
(4) For a recent review see: Ariens, E. J.; Sondiju, W.; Timmermans, P. B. M. W. M. *Stereochemistry and Biological Activity of Drugs*; Blackwell Scientific: Oxford, 1983.
(5) Clifton, J. W.; Collins, I.; Hallett, P.; Hartley, D.; Lunto, L. H. C.; Wicks, P. D. *J. Med. Chem.* **1982**, *25*, 670.
(6) Jones, J. H.; McClure, D. E.; Grenda, V. J. European Patent Application 821 104 09.8, 1982.
(7) Jones, J. H.; McClure, D. E. European Patent Application 821 104 11.4, 1982.
(8) Dabiré, H.; Mouille, P.; Schmitt, H. *Eur. J. Pharmacol.* **1983**, *86*, 83.
(9) Floch, A.; Advenier, C. *J. Pharmacol. (Paris)* **1985**, *16*, 291.
(10) Dabiré, H.; Mouille, P.; Schmitt, H. *J. Cardiovasc. Pharmacol.* **1985**, *7*(Suppl. 6), S127.

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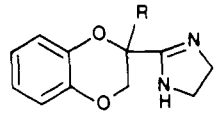
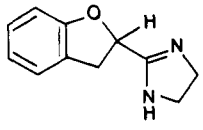
Table I. Physical Properties of Compounds 4–12



no.	R	mp, °C	formula	anal.	$[\alpha]^{21}_D$, deg
4	OCH_3 (±)	90–91	$C_{12}H_{14}N_2O_3$	C, H, N	
5	OCH_3 (+)	283–285	$C_{12}H_{14}N_2O_3 \cdot HCl$	C, H, N	+96.2
6	OCH_3 (−)	283–285	$C_{12}H_{14}N_2O_3 \cdot HCl$	C, H, N	−96.2
7	CH_3 (±)	258–261	$C_{12}H_{14}N_2O_2 \cdot HCl \cdot H_2O$	C, H, N	
8	CH_3 (+)	266–268	$C_{12}H_{14}N_2O_2 \cdot HCl \cdot H_2O$	C, H, N	+93.5
9	CH_3 (−)	266–268	$C_{12}H_{14}N_2O_2 \cdot HCl \cdot H_2O$	C, H, N	−89.8
10	$CH_3C{=}CH_2$ (±)	285–287	$C_{14}H_{16}N_2O_2 \cdot HCl$	C, H, N	
11	$CH_3C{=}CH_2$ (+)	86–88	$C_{14}H_{16}N_2O_2 \cdot H_2O$	C, H, N	+75.3
12	$CH_3C{=}CH_2$ (−)	86–88	$C_{14}H_{16}N_2O_2 \cdot H_2O$	C, H, N	−73.9

idazoxan occurs during pharmacological testing, and this then may be a factor in some of the complications that have been described.[10] Interestingly, similar exchange studies on the structurally related α_2-adrenoreceptor antagonist **13**[2] revealed a much longer deuterium exchange half-life of 33.5 h while the α_2-agonist lofexidine (**14**)[11] showed no exchange after several days under the same conditions.[12]



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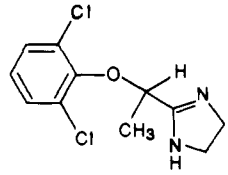

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Results and Discussion

All compounds were examined for α_1- and α_2-adrenoreceptor antagonist properties by using standard in vitro testing procedures.[1-3] The results are summarized in Table II, with the antagonist values being quoted as potencies relative to idazoxan. Table II also gives details of receptor binding at α_2- and α_1-adrenoreceptor sites, and it is clear that there is a good correlation between these two sets of data.

The in vitro results show very clearly that the resolutions were successful, as in each case, one of the isomers is virtually inactive whereas its optical antipode is more potent than the racemate. These findings are supported by the binding data that again demonstrate that one isomer in each case binds very weakly at both the α_2- and α_1-adrenoreceptor.

Further evidence for the enantioselectivity of the α_2-adrenoreceptor for the antagonist molecules in this series is provided by the in vivo results presented in Table III that show the significant separation in the potency of the isomers in the reversal of the inhibitory effects of clonidine in the vas deferens of the pithed rat. Table IV describes the results of a more detailed investigation of the isomers (**5**,**6**) of the most potent member of the series, compound **4**. The effects of the two isomers and the racemate were studied at peripheral prejunctional α_2-adrenoreceptors in the vas deferens and postjunctional α_2- and α_1-adrenoreceptors in the vasculature of pithed rats and at central α_2-adrenoreceptors. The large separation in the activities of the enantiomers is demonstrated in all three peripheral systems and at central α_2-adrenoreceptors. (Some of these data have appeared elsewhere.)[13]

Our findings therefore demonstrate both the marked stereoselective nature of both α_2- and, to a lesser extent, α_1-adrenoreceptors for these antagonist molecules, and the results also confirm the pharmacological similarity between central and peripheral α_2-adrenoreceptors in rats recently described by other authors.[14]

These results are in contrast to those [illegible]birré et al.[8,10] who have studied the activities of the [illegible]t compound in this series, idazoxan (**3**). Only a 3-fol[illegible]ration in the antagonist potencies of the enantior[illegible]as noted at prejunctional α_2-adrenoreceptors in t[illegible]ated rat vas deferens. The discovery[8] of a larger s[illegible]n with idazoxan isomers against α_2-mediated sec[illegible]chicks lead to the suggestion that the central α_2-a[illegible]ceptor may be different from the peripheral α_2-a[illegible]ceptor. Our results clearly do not support this vi[illegible]

The unique structural feature presen[illegible]e compounds described here, the 2-substituent, is p[illegible]ly the major factor responsible for the significant in[illegible]ease in isomer potency ratio over that of the parent compound. However, as previously mentioned, the lability of the proton at C-2 in idazoxan may also contribute to the low and varying enantiomeric potency ratios seen in some test situations. The large difference in the potency ratios in these compounds is also in marked contrast with results obtained with chiral imidazoline-containing agonists at the α_2-adrenoreceptor. Isomeric activity differences for these imidazolines, when they occur, are typically low and rarely exceed 10–20-fold,[15-18] although the enantiomers of a recently published[19] example, lofexidine (**14**), did exhibit potency ratios of up to 30-fold in some pharmacological tests. It would appear therefore that the steric demands of the α_2-adrenoreceptor are much more stringent for the imidazoline-containing antagonists in this series than any imidazoline-containing agonist so far disclosed.

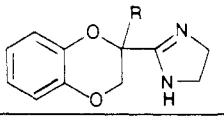
The derivatives of idazoxan described here exhibit no detectable agonist activity at either α_2- or α_1-adrenoceptors, and this, together with their enhanced potency, selectivity, and stability, would suggest that they are more suitable than the isomers of the parent compound for the continued investigation of the α_2-adrenoreceptor.

Experimental Section

Melting points were determined in a Buchi apparatus in glass capillary tubes and are uncorrected. NMR were recorded on all compounds on a Varian Associates T-60 and were consistent with the assigned structures. Deuterium-exchange studies were carried

(11) Baganz, H.; May, H. J. British Patent 1 181 356, 1970.
(12) Hearfield, R. (Reckitt and Colman plc), unpublished results.
(13) Berridge, T. L.; Gadie, B.; Lane, A. C.; Roach, A. G.; Strachan, D. A.; Tulloch, I. F.; Welbourn, A. P. *Br. J. Pharmacol.* **1985**, *4*(Proc. Suppl.), 193P.
(14) Doxey, J. C.; Gadie, B.; Lane, A. C.; Tulloch, I. F. *Br. J. Pharmacol.* **1983**, *80*, 155.
(15) Ruffolo, R. R.; Yaden, E. L.; Waddell, J. E.; Dillard, R. D. *J. Pharmacol. Exp. Ther.* **1980**, *214*, 535.
(16) Fuder, H.; Nelson, W. L.; Miller, D. D.; Patil, P. N. *J. Pharmacol. Exp. Ther.* **1981**, *217*, 1.
(17) Ruffolo, R. R.; Patil, P. N.; Miller, D. D. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1983**, *323*, 221.
(18) Ruffolo, R. R.; Rice, P. J.; Patil, P. N.; Hamada, A.; Miller, D. D. *Eur. J. Pharmacol.* **1983**, *86*, 471.
(19) Wilffert, B.; Mathy, M. J.; Batink, H. D.; de Jong, A.; Thoolen, M. J. M. C.; Prop, G.; Graf, E.; Timmermans, P. B. M. W. M.; Van Zwieten, P. A. *Arch. Int. Pharmacodyn.* **1985**, *273*, 18.

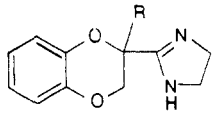
Table II. In Vitro Pharmacological Screening Results[a] and Binding Studies



no.	R	prejunct α_2 rat vas deferens: antag[b] pot.	isom pot. ratio	postjunct α_1 rat anococcygeus: antag[c] pot.	isom pot. ratio	receptor binding: K_i,[d] nm [^{3}H]idazoxan	isom ratio	K_i,[d] nm [^{3}H]prazosin	isom ratio
4	OCH_3 (±)	11.0		4.0		0.8 ± 0.05		66 ± 16	
5	OCH_3 (+)	15.5	419	16.0	>160	0.36 ± 0.07	711	27 ± 8.2	250
6	OCH_3 (−)	0.037		<0.1		256 ± 59		6763 ± 573	
7	CH_3 (±)	0.67		0.28		4.4 ± 0.4		449 ± 90	
8	CH_3 (+)	1.3	260	0.09	>3.9	2.4 ± 0.3	202	285 ± 64	47
9	CH_3 (−)	0.005		<0.023		487 ± 53		13329 ± 3311	
10	$CH_3C{=}CH_2$ (±)	0.4		0.07		16.3 ± 1.8		1794 ± 185	
11	$CH_3C{=}CH_2$ (+)	0.0003	2666	0.03	20	8734 ± 683	1092	46439 ± 11131	31.5
12	$CH_3C{=}CH_2$ (−)	0.8		0.6		8.0 ± 0.91		1473 ± 107	

[a] None of the compounds tested exhibited agonist activity at either the α_2- or α_1-adrenoreceptor. [b] Ability of the compound to antagonize the inhibitory activity of clonidine, relative to idazoxan (1). [c] Ability of the compound to antagonize the inhibitory effect of phenylephrine, relative to idazoxan (1). [d] Ability of test compound to displace radioligand from saturable binding sites on rat brain cerebral cortex.

Table III. In Vivo Pharmacological Screening Results



no.	R	AD_{50} (vs. clonidine),[a] μg/kg	isom pot. ratio
4	OCH_3 (±)	2.68 ± 0.31	
5	OCH_3 (+)	2.25 ± 0.30	349
6	OCH_3 (−)	786 ± 95.6	
7	CH_3 (±)	52.7 ± 13.1	
8	CH_3 (+)	25.8 ± 6.6	99
9	CH_3 (−)	2567 ± 53.0	
10	$CH_3C{=}CH_2$ (±)	71.2	
11	$CH_3C{=}CH_2$ (+)	>14444	>268
12	$CH_3C{=}CH_2$ (−)	53.9 ± 10.5	

[a] Pithed rat vas deferens preparation AD_{50} (50% reversal of maximal inhibitory effects of clonidine at 100 μg/kg, iv).

out on a JEOL FX90Q instrument. Where analysis is indicated only by symbols of the elements, results obtained are within ±0.4% of the theoretical values. Rotations were carried out in methanol at 21° with a concentration of 10 mg/mL with a wavelength of 589 nM on a Perkin-Elmer 141 polarimeter.

Table V describes the methods used for resolving each of the three compounds. As an example, the resolution of compound 4 will be described.

Resolution of 2-(2-Methoxy-1,4-benzodioxan-2-yl)-2-imidazoline (4). To a hot solution of (+)-dibenzoyltartaric acid (14.08 g, 0.0376 mol) in acetone (250 mL) was added a hot solution of compound 4[3] (8.8 g, 0.0376 mol) in acetone (250 mL). This gave a colorless solution that was allowed to cool to room temperature. The white solid that had separated was filtered off, washed with ether, and dried: 19.2 g; $[\alpha]^{21}_D$ +81.63°. The solid was crystallized from a mixture of hot methanol (250 mL) and ethyl acetate (500 mL) to give a white solid that was filtered and dried: 11.5 g; $[\alpha]^{21}_D$ +99.8°. This was recrystallized to constant rotation, which required two further crystallizations from methanol to give the (+)-2-(2-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline dibenzoyltartrate salt: 4.5 g; $[\alpha]^{21}_D$ +114.2°.

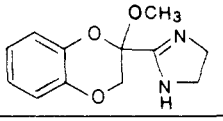
A mixture of the diastereoisomerically pure salt (3.9 g), potassium carbonate (30.0 g), water (100 mL), and dichloromethane (150 mL) was stirred rapidly at room temperature for 30 min. The organic layer was separated off, and the aqueous layer was washed twice with dichloromethane. The combined organic layers were dried by passing through absorbent cotton wool and evaporated to give (+)-2-(2-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline: 1.2 g; $[\alpha]^{21}_D$ +101.4°; mp 102–104 °C. The degree of resolution was assessed by ^{1}H NMR using $CDCl_3$ with the addition of the chiral shift reagent Eu[(tfac)cam]$_3$. In the racemic mixture, increasing concentrations of the shift reagent caused a splitting of the methoxy protons at δ 4.48 and caused a movement of their chemical shifts to δ 3.85 and 3.95. In a repeat study using the (+) isomer described above, no evidence of splitting was observed.

A solution of the free base (0.3 g) in dry ether (50 mL) was added to ethereal HCl (100 mL, 5 M), and the precipitated solid was filtered off and washed with ether. The solid was dried to give **5**: yield 0.24 g; mp 283–285 °C; $[\alpha]^{21}_D$ +96.2°. Anal. ($C_{12}H_{14}N_2O_3$·HCl) C, H, N.

An identical technique using (−)-dibenzoyltartaric acid was employed to provide the (−) isomer (**6**) [see Table I].

Deuterium-Exchange Experiment. Idazoxan hydrochloride (0.049 28 g) was dissolved in a buffer solution (0.5 mL) [made by adding a solution of potassium dihydrogen orthophosphate (0.045 598 g in 5 mL of D_2O) to a solution of disodium hydrogen orthophosphate (0.094 655 g in 10 mL of D_2O) until pH 7.4]

Table IV. Secondary Evaluation of Compound 4 and Its Enantiomers



receptor syst	test	antagonist potency: ±	+	−	stereoselect
prejunctional α_2[a]	vas deferens (pithed rat)	1.9 ± 0.5	1.0 ± 0.2	544 ± 168	544
postjunctional α_2[b]	diastolic bp (pithed rat)	8.0 ± 2.4	4.7 ± 1.4	972 ± 453	203
postjunctional α_1[c]	diastolic bp (pithed rat)	176 ± 19	58.9 ± 11.5	12792 ± 1735	217
central α_2[d]	hypotension	5.9 ± 0.4	2.9 ± 0.5	1620 ± 160	559
central α_2[d]	mydriasis	5.0 ± 0.5	2.0 ± 0.03	1836 ± 119	918

[a] Potency determined as the dose (μg/kg, iv) required to produce a 2-fold shift (DR2) of the dose–response curve to the agonist UK-14,304 on the twitch response of the rat vas deferens. [b] On diastolic blood pressure. [c] Cirazoline on diastolic blood pressure. [d] The cumulative dose (μg/kg, iv) reversing by 50% (AD_{50}) the effects of 20 and 300 μg/kg, iv, UK-14,304 on diastolic blood pressure and mydriasis, respectively.

Table V. Conditions for Resolution

no.	opt pure acid	solvent for salt formn	purification	salt rotations: $[\alpha]^{21}_D$, deg	rel of free base	free-base rotation: $[\alpha]^{21}_D$, deg	salt formn for pharmacolog screening and rotation: $[\alpha]^{21}_D$, deg
4	dibenzoyl-tartaric acid	acetone	recryst from methanol/ethyl acetate 1×, methanol 2×	+114.2, −111.8	$K_2CO_3/H_2O/CH_2Cl_2$/30 min	+101.4, −100.9	HCl salt: +96.2, −96.2
7	mandelic acid	ethanol/petroleum ether (bp 40–60, °C)	recryst from ethanol/ether 5×	−109.5, +108.7	$NaHCO_3/H_2O/CH_2Cl_2$/30 min	−69.0, +72.4	HCl salt: −89.8, +93.5
10	dibenzoyl-tartaric acid	acetone	recryst from methanol/acetone 2×	−102.8, +97.7	$K_2CO_3/H_2O/CH_2Cl_2$/3 h	+75.3, −73.9	free base used

containing a trace amount of 3-(trimethylsilyl)propanesulfonic acid sodium salt as internal standard. The solution was transferred to an NMR tube, and spectra were then recorded at 35 °C on a JEOL FX90Q instrument at 0, 20, 30, 50, 70, 90, 100, 120, and 240 min after solution. Measurements of the integration values of the C-2 proton triplet at δ 5.48 compared to that of the aromatic multiplet centered at δ 7.04 were made at each time point, and the decay of the triplet signal was plotted against time. The $t_{1/2}$ for deuterium exchange was calculated as 3 h.

Pharmacology. Details of in vitro screening procedures are presented in Part 3 of this series.[3]

Activity at Peripheral α_1- and α_2-Adrenoreceptors in Vivo. The effects of the two isomers **5** and **6** and the racemic mixture **4** were studied at prejunctional α_2-adrenoreceptors in the vas deferens and postjunctional α_2- and α_1-adrenoreceptors in the vasculature of pithed rats. Antagonist potencies were determined as the dose (μg/kg, iv) required to produce a 2-fold shift (DR2) of the dose–response curve to UK-14,304[20] on the twitch response of the vas deferens (pre α_2-activity) and diastolic blood pressure (post α_2-activity) or cirazoline on diastolic blood pressure (post α_1-activity).[21] The antagonist potencies of the isomers and compound **4** at the three receptors were determined in separate groups of pithed rats (n = 6 minimum). The effects of all racemates and enantiomers were also tested at peripheral α_2-adrenoreceptors in the pithed rat by measuring AD_{50} values (50% reversal of the maximal inhibitory effects of clonidine at 100 μg/kg, iv) using a minimum of six rats per group.

Activity of Central α_2-Adrenoreceptors—Functional Studies. The antagonist potencies of the (+) and (−) enantiomers **5** and **6** and the racemate **4** at central α_2-adrenoceptors were assessed against the maximal hypotensive and mydriatic responses produced by the selective α_2-adrenoceptor agonist UK-14,304 in pentobarbitone-anaesthetized rats. Antagonist potency was determined as the cumulative dose reversing by 50% (AD_{50}, μg/kg, iv) the effects of 20 and 300 μg/kg, iv, UK-14,304 on diastolic blood pressure and pupil diameter, respectively. Diastolic blood pressure was measured from a cannulated carotid artery and pupil diameter measured according to the method described in the literature.[22] After a maximal effect was achieved with UK-14,304 (after about 10 min for both parameters), antagonist doses were given iv (via a jugular or tail vein) at approximate 5-min intervals (when the reversal effect of the previous dose had reached a plateau). Experiments were performed in separate groups of five to six rats.

Activity at Central α_1- and α_2-Adrenoreceptors—Radioligand Binding Studies. The affinities (K_i, nM) of the two isomers and racemic mixture were determined from their ability to displace the saturable binding of [^{3}H]prazosin and [^{3}H]idazoxan from α_1- and α_2-adrenoreceptor sites prepared from rat cerebral cortical membranes.[23]

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Registry No. (±)-**4**, 89150-52-7; (+)-**4**·(*d*-dibenzoyl tartrate), 89253-79-2; (+)-**4**·HBr, 89195-33-5; (−)-**4**·(*l*-dibenzoyl tartrate), 103532-84-9; **5**, 89195-32-4; **5** (free base), 89195-31-3; **6**, 103532-79-2; **6** (free base), 89195-34-6; (±)-**7**, 94342-74-2; (±)-**7** (free base), 89150-62-9; (+)-**7**·(*S*-mandelate), 103532-88-3; (−)-**7**·(*R*-mandelate), 103532-86-1; **8**, 103532-80-5; **8** (free base), 103532-81-6; **9**, 103532-81-6; **9** (free base), 103532-85-0; (±)-**10**, 94342-76-4; (±)-**10** (free base), 103532-91-8; (+)-**10**·(*d*-dibenzoyl tartrate), 103532-90-7; (−)-**10**·(*l*-dibenzoyl tartrate), 103532-89-4; **11**, 103532-82-7; **12**, 103532-83-8.

Supplementary Material Available: Details of the X-ray crystallographic determination of (+)-(*S*)-2-(2-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline (**5**), listings of atomic coordinates, thermal parameters, bond angles, and bond distances, and a structure of the HBr salt showing hydrogen atoms (6 pages). Ordering information is given on any current masthead page.

(20) Cambridge, D. *Eur. J. Pharmacol.* **1981**, *72*, 413.
(21) Doxey, J. C.; Roach, A. G.; Strachan, D. A.; Virdee, N. K. *Br. J. Pharmacol.* **1983**, *79*(Proc. Suppl.), 311P.
(22) Berridge, T. L.; Gadie, B.; Roach, A. G.; Tulloch, I. F. *Br. J. Pharmacol.* **1983**, *78*, 507.
(23) Doxey, J. C.; Lane, A. C.; Roach, A. G.; Virdee, N. K. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1984**, *325*, 136.