unknown. The transition from full to partial agonism or antagonism has been related to increased size of the terminal group as monitored by the $|PC_t|$ value. To speculate, this could arise from the ability of a partial agonist to bind both to a site furnishing the activity and to a null or antagonist site. The extent of the partitioning between the two sites would depend on the relative binding constants, a function of chain length, and other parameters, such as stereochemistry, hydrophobicity, etc., of the terminal group. Antagonists then, are drugs that are too large to fit into the active site and that bind entirely, and indeed strongly, to the null site.

Acknowledgment. J.M.S. thanks Professors H. Weinstein and S. Maayani for providing much background information, encouragement, and shared insights on structure–activity relationships in this area and also thanks Professor J. P. Green and the Department of Pharmacology at Mount Sinai for their hospitality during a sabbatical year in which this work was begun. Professors T. Mittag and L. A. Barker are acknowledged for several helpful discussons. This work was supported, in part, by grants-in-aid from the CUNY Research Foundation and the Committee on Research Computing, as well as by a grant to Queens College from the General Research Support Branch, NIH (5-S05-RR07064).

Registry No. a, 51-84-3; b, 55-92-5; c, 21408-92-4; (*S*)-e, 84863-70-7; g, 300-54-9; h, 58316-49-7; i, 14172-53-3; (*R*)-QNAMe, 82264-25-3; MSDQ, 84863-71-8.

α-Adrenoreceptor Reagents. 1. Synthesis of Some 1,4-Benzodioxans as Selective Presynaptic α_2-Adrenoreceptor Antagonists and Potential Antidepressants

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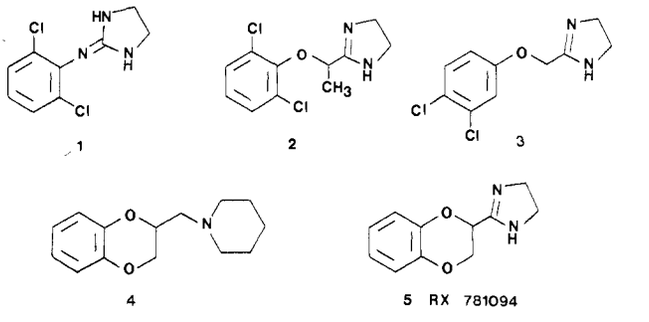
The rational design of RX 781094, 2-(1,4-benzodioxan-2-yl)-2-imidazoline hydrochloride (**5**), a new potent and selective antagonist of α_2-adrenoreceptors, is discussed. A compound that acts as an antagonist at presynaptic α_2-adrenoreceptors could be an effective and novel treatment of depression because of its ability to increase the concentration of norepinephrine at central receptor sites. The effects of substituents in the aromatic and imidazoline rings have been examined, as well as the replacement of the imidazoline ring by an amidine function or by other heterocyclic ring systems. None of these derivatives are as potent or selective as **5**, although some do display a degree of selectivity as antagonists. Some derivatives were found to possess agonist properties that, with the exception of **23**, favored the postsynaptic site. Compounds **9**, **12**, **16**, **21**, **30**, and **51** possessing presynaptic α_2-adrenoreceptor antagonist and postsynaptic α_1-adrenoreceptor partial agonist properties were also obtained, and these derivatives could be considered as potential antimigraine agents.

According to the catecholamine hypothesis of affective disorders, a relative deficiency of the transmitter norepinephrine at receptor sites within the central nervous system is responsible for the symptoms of the disease. Support for this hypothesis is provided by drugs that are clinically effective antidepressants and that increase the concentration of norepinephrine at central receptor sites.

In the early 1970's the accepted concepts of noradrenergic transmission were challenged by a hypothesis that proposed that the release of norepinephrine was regulated by presynaptic α-adrenoreceptors (negative-feedback mechanism[1]). It was proposed that these presynaptic α-adrenoreceptors should be designated the prefix α_2 in order to differentiate them from postsynaptic α-adrenoreceptors, which were themselves designated α_1. However, recent evidence suggests that α_1- and α_2-adrenoreceptors are general subtypes, and the term α_2 should not be limited to presynaptic receptor sites.[2]

Recently, it has been proposed that a common underlying mechanism of action of antidepressants may be an ability to alter α_2-adrenoreceptor sensitivity.[3] Thus, in depression these receptors (α_2) are considered to be supersensitive, hence, turning off release of norepinephrine. It has been suggested[3] that a feature of antidepressant therapy is a gradual reduction in the sensitivity of central α_2-adrenoreceptors: such a subsensitivity would gradually increase norepinephrine levels. Therefore, it can be proposed that if central α_2-adrenoreceptor subsensitivity is a prerequisite for onset of antidepressant effect, then a compound that acts as an antagonist at these receptors could be an effective and novel treatment of depression. At present, yohimbine is used pharmacologically as a selective α_2-adrenoreceptor antagonist, but its lack of specificity limits clinical application.

Clonidine (**1**) is an α_2-adrenoreceptor agonist used clinically as an antihypertensive. Clonidine and a series of aminoimidazolines, differing only in the choice of aromatic substituents, were previously profiled in vitro for α_2/α_1 selectivity and agonist and antagonist character.[4] It



(1) Langer, S. Z. *Biochem. Pharmacol.* **1974**, *23*, 1763; *Br J. Pharmacol.* **1977**, *60*, 481.
(2) A note on terminology for presynaptic receptors: Starke, K.; Langer, S. Z. *Adv. Biosci.* **1979**, *18*, 1–3.
(3) Crews, F. T.; Smith, C. B. *Science* **1979**, *202*, 322; *J. Pharmacol. Exp. Ther.* **1980**, *215*, 143.
(4) Chapleo, C. B.; Doxey, J. C.; Myers, P. L.; Roach, A. G.; Smith, S. E. *Br. J. Pharmacol.* **1981**, *73*(1), 280P.

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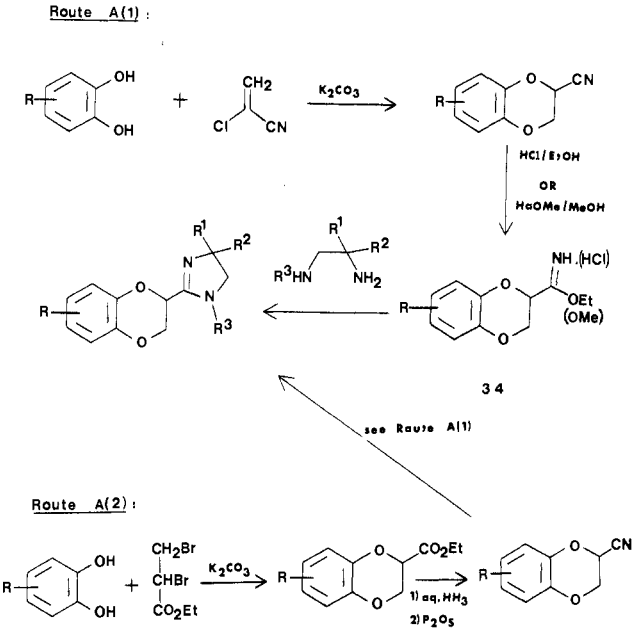
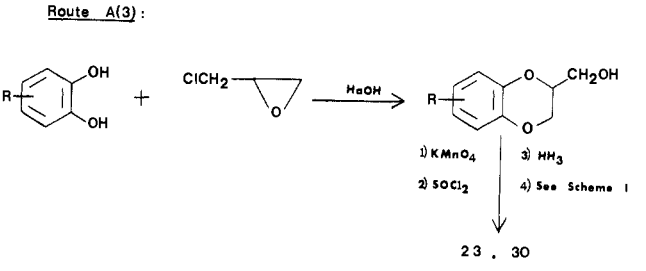
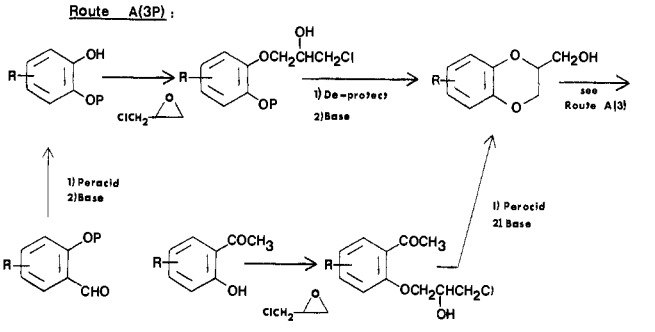
Scheme I



Scheme II



Scheme III



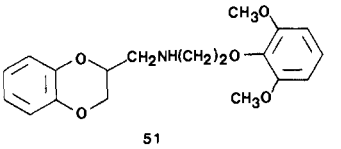
was found that aromatic substitution influenced α_2/α_1 selectivity, and, in addition, α_2-adrenoreceptor antagonist properties became apparent in some cases. It was also obvious that the aminoimidazoline linkage previously considered to be essential for α_2 agonist activity was not, in fact, necessary, since lofexidine (**2**), in particular, was a potent α_2 agonist with high affinity for this receptor site. Fenmetazole (**3**) has been claimed[5] to possess antidepressant properties, and profiling of this compound revealed that, unlike lofexidine (**2**), it was an α_2-adrenoreceptor antagonist, albeit of low potency (pre-α_2 pA_2 against clonidine = 6.6 ± 0.2).[6] In an attempt to improve the affinity of this compound, it was decided to combine its structural features with those of the high-affinity (but nonselective) α-adrenoreceptor antagonist piperoxan (**4**) to give the benzodioxan **5** (RX 781094).[7] We report here the synthesis and pharmacological testing of the title compound and its derivatives.

Chemistry. For convenience, the synthesis and structure–activity relationships are discussed under three main headings, with each section being discussed in turn.

(1) Aromatic Substitution (Table I, Compounds 6–33). The unsubstituted compound (**5**) was prepared[7] by route A(1) shown in Scheme I. Two general problems were encountered in the synthesis of monosubstituted aromatic analogues **6–25**. Firstly, some of the substituted catechols failed to react directly with either 2-chloroacrylonitrile or ethyl 2,3-dibromopropionate [Scheme I, routes A(1) and A(2)]. This problem was overcome by alternative reaction with epichlorohydrin [Scheme II, route A(3)], followed by further chemical elaboration of the resulting alcohol to the intermediate nitrile compound and, hence, to the imidazoline. Secondly, due to lack of directional control of most monosubstituted catechols in any one of the reactions discussed above, mixtures of the two possible isomers resulted that, in general, were difficult to separate. This necessitated starting with suitably monoprotected catechols (e.g., Scheme III). Dealkylation of the methoxy and dimethoxy compounds with HBr readily gave the corresponding phenols **16–19** or catechol **29** (route B); in particular, **17** and **18** were synthesized as possible metabolites of **5**, as there is preliminary evidence to suggest that this may be a primary mode of metabolism in rats.[8] The most difficult compounds to prepare unequivocally were the monohalogenated analogues, such as **23**, due to the inaccessibility of the corresponding monochlorinated catechols. The 8-chloro derivative **23** was synthesized from 2-(hydroxymethyl)-8-nitro-1,4-benzodioxan[9] by reduction and Sandmeyer reaction (route C). Symmetrically disubstituted derivatives **26–30** were obtained from the corresponding catechols by using routes A(1–3) (see Table I). Certain 6,7-dihalogenated derivatives (**31** and **32**) were prepared by direct bromination or chlorination of the unsubstituted compound, **5** (route D). It was also possible to isolate bromo (**21**) or chloro (**20**) derivatives by this method but only as a mixture of 6- and 7-isomers of unknown composition.

(2) Modification of the Imidazoline Ring. (a) The reaction of the key intermediate, the imidate **34**, with *C*- and *N*-methyl-substituted analogues of ethylenediamine gave the corresponding derivatives **35–37** (Table I) substituted in the imidazoline ring (Scheme I).

(b) A range of suitably substituted amidines (**38–49**) was also prepared for evaluation from the imidate **34** or 2-cyano-1,4-benzodioxan (**50**) and the appropriate amine (Table II). In particular, amidines **38** and **40** were synthesized because of evidence that they may be metabolites of **5**.[8] Compound **44** was prepared as a direct structural analogue of WB 4101 (**51**), a postsynaptic α_1-adrenoreceptor antagonist.[10]



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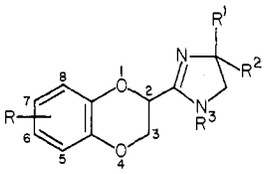
(5) *Drugs Future* **1976**, *1*, 239.
(6) Doxey, J. C., Reckitt and Colman, Ltd., unpublished results.
(7) Chapleo, C. B.; Myers, P. L., *Tetrahedron Lett.* **1981**, *22*, 4839. Mouille, P.; Dabire, H.; Fournier, B.; Schmitt, H. *Eur. J. Pharmacol.* **1981**, *73*, 367. See also ref 11.
(8) Drug Metabolism Department, Reckitt and Colman, Ltd., unpublished results.
(9) Augstein, J.; Green, S. M.; Monro, A. M., Potter, G. W. H.; Worthing, C. R.; Wrigley, T. I. *J. Med. Chem.* **1965**, *8*, 446.

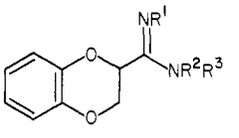
Table I



no.	R[a]	method[b]	mp, °C	recrystn solvent	formula
5	H	A(1)	207-208	*i*-PrOH	$C_{11}H_{12}N_2O_2 \cdot HCl$
6	5-CH_3	A(3P)	243-246	EtOH/Et_2O	$C_{12}H_{14}N_2O_2 \cdot HCl$
7	6-CH_3	A(3P)	196-198	EtOH/Et_2O	$C_{12}H_{14}N_2O_2 \cdot HCl$[c]
8	7-CH_3	A(3P)	215-217	EtOH/Et_2O	$C_{12}H_{14}N_2O_2 \cdot HCl$
9	8-CH_3	A(3P)	224-226	EtOH/Et_2O	$C_{12}H_{14}N_2O_2 \cdot HCl$
10	6(and/or 7)-*t*-Bu	A(1)	197-198	EtOH/Et_2O	$C_{15}H_{20}N_2O_2 \cdot HCl$
11	5(and/or 8)-*i*-Pr	A(1)	213-214	EtOH/Et_2O	$C_{14}H_{18}N_2O_2 \cdot HCl$
12	5-OCH_3	A(2)	187-189	*i*-PrOH/Et_2O	$C_{12}H_{14}N_2O_3 \cdot HCl$
13	6-OCH_3	A(3P)	185-186	EtOH/Et_2O	$C_{12}H_{14}N_2O_3 \cdot HCl$
14	7-OCH_3	A(3P)	201-203	EtOH	$C_{12}H_{14}N_2O_3 \cdot HCl$
15	8-OCH_3	A(2)	196-198	*i*-PrOH/Et_2O	$C_{12}H_{14}N_2O_3 \cdot HCl$
16	5-OH	A(2), B	206-208	*i*-PrOH/Et_2O	$C_{11}H_{12}N_2O_3 \cdot HBr$
17	6-OH	A(3P), B	215-217	EtOH/Et_2O	$C_{11}H_{12}N_2O_3 \cdot HBr$
18	7-OH	A(3P), B	168-172	*i*-PrOH/Et_2O	$C_{11}H_{12}N_2O_3 \cdot HBr \cdot 0.25H_2O$
19	8-OH	A(2), B	226-232	EtOH/Et_2O	$C_{11}H_{12}N_2O_3 \cdot HBr \cdot 0.25H_2O$
20	6(and/or)7-Cl	D	211-213	EtOH/Et_2O	$C_{11}H_{11}ClN_2O_2 \cdot HCl$[d]
21	6(and/or)7-Br	D	216-218	*i*-PrOH/Et_2O	$C_{11}H_{11}BrN_2O_2 \cdot HCl$[e]
22	6(and/or)7-F	A(1)	249-251	EtOAc/Et_2O	$C_{11}H_{11}FN_2O_2 \cdot HCl \cdot 0.25H_2O$
23	8-Cl	A(3), C	215-224[f]	EtOH/Et_2O	$C_{11}H_{11}ClN_2O_2 \cdot HCl \cdot 0.25H_2O$
24	6-NO_2	A(3P)	202-206	EtOH	$C_{11}H_{11}N_3O_4 \cdot HCl \cdot 0.5H_2O$
25	8-NO_2	A(3P)	230-240	EtOH/Et_2O	$C_{11}H_{11}N_3O_4 \cdot HCl$[g]
26	5,8-$(CH_3)_2$	A(1)	238-240	EtOH	$C_{13}H_{16}N_2O_2 \cdot HCl \cdot 0.25H_2O$
27	6,7-$(CH_3)_2$	A(1)	210-213	EtOH/Et_2O	$C_{13}H_{16}N_2O_2 \cdot HCl \cdot 0.25H_2O$
28	6,7-$(OCH_3)_2$	A(2)	230-232	EtOH	$C_{13}H_{16}N_2O_4 \cdot HCl \cdot 0.25H_2O$
29	6,7-$(OH)_2$	A(2), B	250-260[f]	MeOH	$C_{11}H_{12}N_2O_4 \cdot HBr$
30	5,8-Cl_2	A(3)	230-240	EtOH	$C_{11}H_{10}Cl_2N_2O_2 \cdot HCl$
31	6,7-Cl_2	D	271-273	MeOH/Et_2O	$C_{11}H_{10}Cl_2N_2O_2 \cdot HCl$
32	6,7-Br_2	D	278-280	EtOH	$C_{11}H_{10}Br_2N_2O_2 \cdot HCl$
33	6,7- 	A(1)	229-232	EtOH/Et_2O	$C_{15}H_{14}N_2O_2 \cdot HCl$
35	R = H; R^3 = CH_3	A(1)	164-165	*i*-PrOH/Et_2O	$C_{12}H_{14}N_2O_2 \cdot HCl \cdot 0.5H_2O$
36	R = H; R^1 = CH_3	A(1)	187-188	EtOH/Et_2O	$C_{12}H_{14}N_2O_2 \cdot HCl \cdot 0.25H_2O$
37	R = H; R^1 = R^2 = CH_3	A(1)	201-203	EtOH/Et_2O	$C_{13}H_{16}N_2O_2 \cdot HCl \cdot 0.25H_2O$

[a] Unless specified otherwise, R^1, R^2, and R^3 = H. [b] Preparative routes: A, direct reaction of the appropriately substituted catechol with (1) 2-chloroacrylonitrile, (2) ethyl 2,3-dibromopropionate, (3) epichlorohydrin, or (3P) epichlorohydrin with monoprotected catechol, hydroxyacetophenone, or salicylaldehyde; B, dealkylation of methoxy precursor; C, reduction of nitro precursor, followed by Sandmeyer reaction; D, direct halogenation of 5. [c] Contains 0.33 mol of diethyl ether. [d] C: calcd, 48.02; found, 48.75. [e] C: calcd, 41.34; found, 40.74. [f] Decomposition temperature. [g] N: calcd, 14.71; found, 13.98.

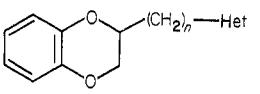
Table II



no.	R^1	R^2	R^3	method[a]	mp, °C	recrystn solvent	formula
38	H	H	H	I	188-189	EtOH/Et_2O	$C_9H_{10}N_2O_2 \cdot HCl$
39	H	H	OH	N	130-132	EtOH/Et_2O	$C_9H_{10}N_2O_3$
40	H	H	CH_2CO_2H	I	210-212	H_2O	$C_{11}H_{12}N_2O_4 \cdot 0.75H_2O$
41	H	H	$(CH_2)_2OMe$	I	141-143	EtOH/Et_2O	$C_{12}H_{16}N_2O_3 \cdot HCl$
42	H	H	$(CH_2)_2Ph$	I	197-201	EtOH/Et_2O	$C_{17}H_{18}N_2O_2 \cdot HCl$
43	H	H	$(CH_2)_3OH$	N[b]	168-169	EtOH/Et_2O	$C_{12}H_{16}N_2O_3 \cdot HCl$
44	H	H	$(CH_2)_2O$-C_6H_3(2,6-MeO)	I	229-231	EtOH/Et_2O	$C_{19}H_{22}N_2O_5 \cdot HCl$
45	H	H		N	139-141	*i*-PrOH	$C_{12}H_{13}N_3O_2S$
46	H	H	c-NC_5H_{10}	I	93-94	EtOH/H_2O	$C_{14}H_{19}N_3O_2$
47	H	H	c-$N(CH_2CH_2)_2O$	I	154-156	EtOH/H_2O	$C_{13}H_{17}N_3O_3$
48	H	—$(CH_2)_5$—		I	69-71	Et_2O/petrol	$C_{14}H_{18}N_2O_2 \cdot HCl$[c]
49	*n*-Bu	H	*n*-Bu	I	121-122	EtOH/Et_2O	$C_{17}H_{26}N_2O_2 \cdot HCl$

[a] Preparative method: N = nitrile 50 plus amine; I = imidate 34 plus amine. [b] The nitrile was converted to the *S*-methylthioronium salt, via the thio amide prior to reaction with aminopropanol. [c] C: calcd, 68.27; found, 67.58.

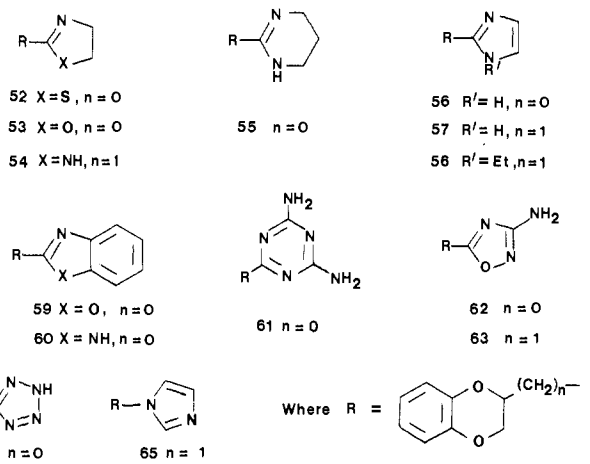
Table III



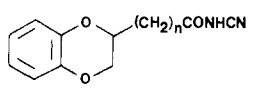
no.	reactants	mp, °C	recrystn solvent	formula
52	50 + $H_2N(CH_2)_2SH$	142-146	$MeOH/Et_2O$	$C_{11}H_{11}NO_2S\cdot HCl$
54	see ref 11	228-229	$EtOH/Et_2O$	$C_{12}H_{14}N_2O_2\cdot HCl$
55	34 + $H_2N(CH_2)_3NH_2$	188-192	$EtOH/Et_2O$	$C_{12}H_{14}N_2O_2\cdot HCl\cdot 0.5H_2O$
56	34 + $H_2NCH_2CH(OMe)_2$	248-249	$EtOH/Et_2O$	$C_{11}H_{10}N_2O_2\cdot HCl$
57	see ref 11	215-225	*i*-PrOH	$C_{12}H_{12}N_2O_2\cdot HCl$
58	57 + EtI	172-174	*i*-PrOH/Et_2O	$C_{14}H_{16}N_2O_2\cdot HCl$
59	34 + *o*-$C_6H_4(OH)NH_2$	88-89	Et_2O/hexane	$C_{15}H_{11}NO_3$
60	34 + *o*-$C_6H_4(NH_2)_2$	199-203	EtOH	$C_{15}H_{12}N_2O_2\cdot HCl$
61	67 + biguanide	208-210	MeOH	$C_{11}H_{11}N_5O_2\cdot 0.5H_2O$
62	68 (n = 0) + NH_2OH	134-136	Et_2O/petrol	$C_{10}H_9N_3O_3$
63	68 (n = 1) + NH_2OH	119-120	Et_2O/petrol	$C_{11}H_{11}N_3O_3$
64	50 + NaN_3	163-165	$EtOH/H_2O$	$C_9H_8N_4O_2$
65	69 + imidazole	141-143	$EtOH/Et_2O$	$C_{12}H_{12}N_2O_2\cdot HCl$
66	see Scheme IV[a]	173-174	$EtOH/Et_2O$	$C_{11}H_{14}N_2O_2\cdot HCl$[b]

[a] Nitrile was first converted to the corresponding imidate. [b] C: calcd, 54.44; found, 53.94.

(3) Miscellaneous. A variety of compounds (**52** and **54–66**), including those in which the imidazoline ring was



replaced by different heterocyclic rings, were prepared by various methods (Table III). Compounds **52** and **54–60** were readily available from the reaction of imidate **34** or the intermediate nitriles with the appropriately substituted amine. Imidazoles **57** and **58** have recently been described[11] as being selective α_2-adrenoreceptor antagonists. Attempts to prepare the oxazoline **53** were unsuccessful, as this compound was much more unstable than the thiazoline **52**, which itself hydrolyzed readily to the corresponding amide under aqueous conditions. The *s*-triazine **61** was obtained by reacting biguanide with ethyl 1,4-benzodioxan-2-carboxylate (**67**). The oxadiazoles **62** and **63** were formed from the reaction of the cyanamide **68** with



hydroxylamine hydrochloride. The latter compounds, **62** and **63**, were of particular potential interest since the aminooxadiazole ring appears to confer similar antihypertensive activity to that of the imidazoline moiety in a series

Scheme IV

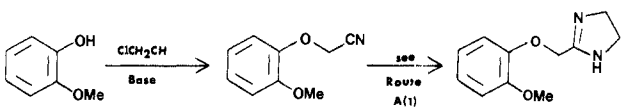


Table IV. α_2- and α_1-Adrenoreceptor pA_2 Values[a]

	in vitro experiments		
antagonist	vas deferens: α_2 pA_2 value against clonidine	anococcygeus α_1 pA_2 value against norepinephrine	α_2/α_1 selectivity ratio[b]
RX 781094 (5)	8.56 ± 0.05	6.10 ± 0.05	288.4
yohimbine	8.14 ± 0.05	6.49 ± 0.06	44.7
piperoxan	7.72 ± 0.03	6.61 ± 0.08	13.0
rauwolscine	7.86 ± 0.06	7.02 ± 0.11	6.9
phentolamine	8.38 ± 0.09	7.70 ± 0.17	4.8
prazosin	5.94 ± 0.10	8.18 ± 0.11	0.0057

[a] pA_2 values were calculated according to Arunlakshana and Schild[14] and are the means plus or minus SEM of, in each case, a minimum of six experiments. [b] Antilog of the difference between the pA_2 values at α_2- and α_1-adrenoreceptors

of clonidine-like analogues recently patented.[12] The tetrazole **64** was formed from the reaction of nitrile **50** with sodium azide.

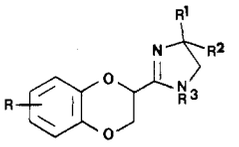
Two obvious chemical variations of the RX 781094 structure lead to the synthesis of compound **66**, the open-chain analogue (Scheme IV), and 2-(1,4-benzodioxan-2-ylmethyl)imidazoline (**54**).[11] The imidazole **65** was prepared from the reaction of 2-(bromomethyl)-1,4-benzodioxan (**69**) with imidazole.

Biological Results and Discussion

In the present study the presynaptic and postsynaptic α-adrenoreceptor antagonist properties of prazosin, phentolamine, rauwolscine, piperoxan, and yohimbine were also studied and compared with those of **5**. The results obtained are shown in Table IV. It can be seen that **5** was the most potent and selective antagonist at presynaptic α_2-adrenoreceptors. These observations were confirmed in vivo (pithed rat) and have been reported elsewhere.[13]

(10) Green, P. N., Shapero, M.; Wilson, C. *J. Med. Chem.* **1969**, *12*, 326.
(11) Michel, A. G., Whiting, R. L. *Br. J. Pharmacol.* **1981**, *74*, 255P. Caroon, J. M.; Clark, R. D.; Kluge, A. F.; Olah, R.; Repke, D. B.; Unger, S. H.; Michel, A. D.; Whiting, R. L. *J. Med. Chem.* **1982**, *25*, 666.
(12) Cohnen, E. German Offen. 2 843 887.
(13) Chapleo, C. B.; Doxey, J. C.; Myers, P. L.; Roach, A. G. *Brit. J. Pharmacol.* **1981**, *74*, 842P.

Table V[a]



no.	R[b]	presynaptic agonist potency (clonidine = 1)[c]	presynaptic antagonist potency (5 = 1)[c]	postsynaptic agonist potency (phenylephrine = 1)[c]	postsynaptic antagonism concn giving DR = 2 vs. phenylephrine potency (5 = 1)[d]	presynaptic selectivity ratio of antagonists (5 = 1) (pre/post)
5	H	IA	1.0	IA	1.0	1.0
6	5-CH_3	0.1	0.13	1.0	Ag	
7	6-CH_3	IA	0.08	IA	0.4	0.21
8	7-CH_3	IA	0.08	0.004	0.8	0.14
9	8-CH_3	0.01	0.5	2.1	Ag	
10	6(and/or 7)-*t*-Bu	IA	0.01	IA	0.1	0.1
11	5(and/or 8)-*i*-Pr	0.1	IA	0.5	1.0	
12	5-OCH_3	IA	0.001	5.0	IA	
13	6-OCH_3	IA	0.006	0.005	NT	
14	7-OCH_3	IA	0.02	IA	0.225	0.09
15	8-OCH_3	IA	0.12	IA	0.9	0.14
16	5-OH	IA	0.018	0.017	Ag	
17	6-OH	0.015	0.017	0.55	Ag	
18	7-OH	0.15	0.036	1.1	Ag	
19	8-OH	IA	0.04	IA	0.2	0.2
20	6(and/or 7)-Cl	IA	0.01	0.005	1.0	0.01
21	6(and/or 7)-Br	IA	0.01	0.05	IA	
22	6(and/or 7)-F	IA	0.01	IA	0.1	0.1
23	8-Cl	0.67	0.49	0.4	Ag	
24	6-NO_2	IA	<0.0003	IA	<0.02	
25	8-NO_2	IA	0.02	IA	0.09	0.22
26	5,8-$(CH_3)_2$	0.19	0.005	2.5	Ag	
27	6,7-$(CH_3)_2$	IA	0.06	IA	0.64	0.1
28	6,7-$(OCH_3)_2$	IA	0.015	IA	0.05	0.3
29	6,7-$(OH)_2$	0.0006	IA	0.018	>6.0	
30	5,8-Cl_2	0.02	0.26	0.55	Ag	
31	6,7-Cl_2	IA	0.003	IA	0.3	0.01
32	6,7-Br_2	IA	0.001	0.02	0.1	0.01
33	6,7- 	IA	0.001	IA	0.01	0.1
35	R = H; R^3 = CH_3	IA	0.0003	IA	0.1	0.003
36	R = H; R^1 = CH_3	IA	0.003	IA	1.0	0.003
37	R = H; R^1 = R^2 = CH_3	IA	0.0001	IA	0.01	0.01

[a] IA = inactive; NT = not tested; Ag = agonist; DR = dose-response. Results are expressed as potencies that were compared directly with that of the standard in the same experiment. [b] Unless specified otherwise, R^1, R^2, and R^3 = H. [c] Dose-response curves of the standards were obtained before and after the dose-response curve of the analogue. There was no significant difference between the two dose-response curves of the standards. [d] A minimum of five dose-response curves were obtained for phenylephrine alone, followed by a minimum of four dose-response curves in the presence of the analogue.

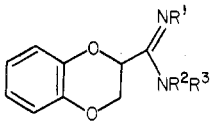
In view of the high potency and selectivity of **5** and the theoretical implications of its profile, the compound is being investigated further. Consequently, a large number of derivatives of **5** were examined for α-adrenoreceptor agonist and antagonist properties. The results are summarized in Tables V–VII. The compounds were tested on isolated tissues for presynaptic α_2 (rat or mouse vas deferens) and postsynaptic α_1 (rat anococcygeus) adrenoreceptor agonist activity.[15] The values are given in terms of potency relative to clonidine (pD_2 = 8.8) (α_2) and phenylephrine (pD_2 = 6.54) (α_1). The ability of compounds to antagonize the inhibitory effect of clonidine on the vas deferens and the contractile effect of phenylephrine on the anococcygeus was used to assess respective pre- and postsynaptic antagonist activity[16] (in vitro). In this case, the values are quoted as potencies relative to **5**.

The primary objective of this synthetic program was to define the areas of chemical modification around **5** that would give antagonists with comparable or greater selectivity for the presynaptic site while retaining the potency inherent in **5**. Quite clearly, none of the derivatives or analogues examined are as potent or as selective as the parent compound **5**, although some do possess some margin of selectivity as antagonists.

Recently, α_2-adrenoreceptor antagonism has been demonstrated in a series of imidazole compounds,[11] including **58**, which proved to be the most selective compound studied. Our results also show that **58** possesses some selectivity for the α_2-adrenoreceptor (53% selectivity of **5**), albeit of very low potency (2% potency of **5**). Table VIII shows the pA_2 values and selectivities of **5**, the *N*-

(14) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol. Chemother.* **1959**, *14*, 48.
(15) Doxey, J. C. *Eur. J. Pharmacol.* **1979**, *54*, 185.
(16) Doxey, J. C.; Smith, C. F. C.; Walker, J. M. *Br. J. Pharmacol.* **1977**, *60*, 91.

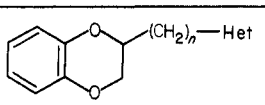
Table VI[a]



no.	presynaptic agonist potency (clonidine = 1)[b]	presynaptic antagonist potency (5 = 1)[b]	postsynaptic agonist potency (phenylephrine = 1)[b]	postsynaptic antagonism concn giving DR = 2 vs. phenylephrine potency (5 = 1)[c]	presynaptic selectivity ratio of antagonists (5 = 1) (pre/post)
38	IA	0.01	0.05	IA	
39	IA	0.001	0.05	0.01	0.1
40	IA	<0.0003	IA	<0.023	
41	IA	IA	IA	0.1	
42	IA	0.0003	IA	0.03	0.01
43	IA	<0.001	IA	0.024	
44	0.0001	0.001	IA	0.1	0.01
45[d]	NT	NT	NT	NT	
46[d]	NT	NT	NT	NT	
47	IA	IA	IA	IA	
48	IA	0.0001	IA	0.01	0.01
49	IA	0.001	IA	0.1	0.01

[a] IA = inactive; NT = not tested; DR = dose-response. Results are expressed as potencies that were compared directly with that of the standards in the same experiment. [b] Dose-response curves of the standards were obtained before and after the dose-response curve of the analogue. There was no significant difference between the two dose-response curves of the standards. [c] A minimum of five dose-response curves were obtained for phenylephrine alone, followed by a minimum of four dose-response curves in the presence of the analogue. [d] Compound could not be tested because of solubility problems.

Table VII[a]



no.	presynaptic agonist potency (clonidine = 1)[b]	presynaptic antagonist potency (5 = 1)[b]	postsynaptic agonist potency (phenylephrine = 1)[b]	postsynaptic antagonism concn giving DR = 2 vs. phenylephrine potency (5 = 1)[c]	presynaptic selectivity ratio of antagonists (5 = 1) (pre/post)
52	IA	IA	IA	IA	
54	IA	0.045	IA	0.14	0.33
55	IA	0.01	IA	0.1	0.1
56	IA	0.001	IA	0.01	0.1
57	IA	0.004	IA	0.25	0.016
58	IA	0.02	IA	0.036	0.53
59[d]	NT	NT	NT	NT	NT
60	IA	0.0003	IA	<0.02	
61	IA	IA	IA	IA	
62	0.0001	IA	IA	IA	
63	IA	<0.0003	IA	<0.023	
64	IA	IA	IA	IA	
65	IA	0.013	IA	<0.023	
66	0.001	IA	10	IA	

[a] IA = inactive; NT = not tested; DR = dose-response; het = heterocyclic ring. Results are expressed as potencies that were compared directly with that of the standard in the same experiment. [b] Dose-response curves of the standards were obtained before and after the dose-response curve of the analogue. There was no significant difference between the two dose-response curves of the standards. [c] A minimum of five dose-response curves were obtained for phenylephrine alone, followed by a minimum of four dose-response curves in the presence of the analogue. [d] Compound could not be tested because of solubility problems.

ethylimidazole compound **58**, and the two most selective and potent antagonists from the aromatic derivatives (**7** and **8**). Contrary to previous findings, we were able to demonstrate that **58** possesses affinity for the α_1-adrenoreceptor (under our test conditions), and consequently, its selectivity is less than that previously reported.[11] This result has been confirmed in vivo (pithed rat) and will be reported elsewhere.

From an examination of the tables, it can be stated that, generally, substitution on the imidazoline ring (**35–37**) or replacement of the imidazoline ring by an amidine function (**38–49**) or by other heterocyclic ring systems (**52** and **54–65**) results in a loss of both the selectivity and potency of **5** and can also lead to a change in profile (see below).

In the chemical modification program, it was realized that compounds with a completely different profile and therapeutic potential could be generated. Thus, the structural similarity of **5** to lofexidine (**2**) suggested that it would be possible to produce presynaptic α_2-adrenoreceptor agonists possessing clonidine-like activity. It can be seen that within the aromatic-substituted derivatives, agonist properties at the pre- and/or postsynaptic site are evident in a number of compounds. In particular, compounds possessing alkyl groups (**6**, **9**, **11**, and **26**) and chlorine atoms (**23** and **30**) in positions 5 and 8 and oxygenated derivatives (**12**, **13**, **16–18**, and **29**) are associated

Table VIII. α_2- and α_1-Adrenoreceptor pA_2 Values[a]

	in vitro experiments		
antagonist	vas deferens: α_2 pA_2 value against clonidine	anococcygeus: α_1 pA_2 value against norepinephrine	α_2/α_1 selectivity ratio[b]
5	8.56 ± 0.05	6.10 ± 0.05	288
7	7.56 ± 0.31	6.17 ± 0.18	30
8	7.10 ± 0.20	5.87 ± 0.24	17
58	6.98 ± 0.02	4.85 ± 0.07	135

[a] pA_2 values were calculated according to Arunlakshana and Schild[14] and are the means plus or minus SEM of, in each case, a minimum of six experiments. [b] Antilog of the difference between the pA_2 values at α_2- and α_1-adrenoreceptors.

with this agonism, which, with the exception of **23**, is selective for the postsynaptic site. The 8-chloro compound **23** is the most potent presynaptic agonist, which is perhaps not too surprising considering the 2,6-dichloro-substitution pattern in the α_2 agonists clonidine and lofexidine (**2**). However, it is interesting to note that the lofexidine analogue **66**, unlike lofexidine (**2**) itself, is a selective postsynaptic α_1-adrenoreceptor agonist.

Finally, a number of compounds possess presynaptic α_2-adrenoreceptor antagonist and postsynaptic α_1-adrenoreceptor partial agonist properties, i.e., compounds **9**, **12**, **16**, **21**, **30**, and **38**. Although there are differences in potencies, the profiles of these compounds are similar to that of ergotamine at postsynaptic α-adrenoreceptors.[6] This partial agonist activity at postsynaptic sites appears to be relevant to the antimigraine action of ergotamine. It is also interesting to speculate whether the additional presynaptic α-adrenoreceptor antagonist properties seen with this series could contribute to an enhanced antimigraine effect. It has been shown recently[17] that human platelets aggregate in response to presynaptic α_2-adrenoreceptor agonists and that this aggregation is inhibited by presynaptic α_2 antagonists. In view of the altered character of platelets in patients with migraine,[18] it is possible that compounds with such a profile could prevent the initiation of migraine attacks.

In summary, RX 781094 (**5**) is a potent selective presynaptic α_2-adrenoreceptor antagonist and may represent a novel class of potential antidepressants. A number of derivatives have been prepared that retain some of the selectivity inherent in **5**, although with reduced potency. Some derivatives show different profiles, and those possessing presynaptic α_2 antagonism with postsynaptic α_1 partial agonism could be considered as potential antimigraine agents.

Experimental Section

Chemistry. Melting points were determined in a Buchi apparatus in glass capillary tubes and are uncorrected. IR, NMR, and MS spectra were recorded on Perkin-Elmer 700, Varian Associates T-60, and Varian Associates LKB-2091 instruments, respectively, and were consistent with the assigned structures. Petrol refers to the light petroleum fraction of bp 40–60 °C. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values. The term "dried" refers to the use of anhydrous sodium sulfate. A general description of the synthetic procedure is given where applicable.

(1) **Aromatic Substitution (Table I). Route A(1). 2-(6,7-Dimethyl-1,4-benzodioxan-2-yl)-2-imidazoline Hydrochloride** (**27**). A stirred mixture of 4,5-dimethylcatechol[19] (1.75 g, 12.7 mmol), 2-chloroacrylonitrile (1.10 g, 12.7 mmol), and anhydrous potassium carbonate (5.25 g, 38 mmol) in acetone (30 mL) was heated at reflux for 18 h. The solvent was removed in vacuo, water (100 mL) was added to the residue, and the mixture was extracted with methylene chloride. The combined extracts were washed with brine and dried, and the solvent was removed at reduced pressure to give a solid (1.6 g), which was recrystallized from diethyl ether/petrol to yield 2-cyano-6,7-dimethyl-1,4-benzodioxan: yield 1.10 g (46%); NMR ($CDCl_3$) 6.75 (2 H, s), 5.06 (1 H, t, J = 3 Hz), 4.34 (2 H, d, J = 3 Hz), 2.20 (6 H, s). A suspension of this nitrile (1.0 g, 5.3 mmol) in methanol (12 mL) was treated with sodium methoxide (15 mg, 0.28 mmol), and the mixture was stirred at room temperature for 4.5 h (solution after 2 h). The solution was cooled to 0 °C and ethylenediamine (0.38 g, 6.4 mmol) was added, followed by a solution of HCl in methanol (0.22 g, 6.4 mmol). After 24 h at 0 °C, the solid was collected (310 mg). Concentration of the filtrate, followed by addition of diethyl ether, gave more solid (300 mg). Recrystallization of the combined solids from ethanol/diethyl ether gave the imidazoline compound **27**: yield 0.44 g (31%); mp 210–213 °C; IR (Nujol) ν_{max} 1620 cm^{-1}; NMR (Me_2SO) δ 11.5 (2 H, s), 6.82 (1 H, s), 6.74 (1 H, s), 5.60 (1 H, t, J = 4 Hz), 4.60 (2 H, d, J = 4 Hz), 3.92 (4 H, s), 2.15 (6 H, s). Anal. ($C_{13}H_{16}N_2O_2 \cdot HCl \cdot 0.25H_2O$) C, H, N.

In some examples the conversion of the cyano compound to the imidazoline product was carried out via a two stage process involving the isolation of the intermediate imidoate hydrochloride, e.g., **34**.

Ethyl (1,4-Benzodioxan-2-yl)imidoate Hydrochloride (**34**). A steady stream of gaseous hydrogen chloride was bubbled through a stirred, cooled solution of 2-cyano-1,4-benzodioxan (**50**;[20] 88 g, 646 mmol) in anhydrous diethyl ether (1 L) and ethanol (30.8 mL; 546 mmol) for 4.5 h, maintaining the reaction temperature at <10 °C. After an additional 24 h at 0–10 °C, the resultant solid was collected, washed with anhydrous diethyl ether, and dried to give the imidoate hydrochloride **34**: yield 110 g (83%); IR (Nujol) ν_{max} 1670, 1595 cm^{-1}.

2-(1,4-Benzodioxan-2-yl)-2-imidazoline Hydrochloride (**5**). A solution of ethylenediamine (16.7 mL, 226 mmol) in ethanol (50 mL) was added over 1 h to a stirred and cooled (0–10 °C) solution of the above imidoate hydrochloride **34** (50 g, 206 mmol) in ethanol (200 mL). After an additional 24 h at 0–10 °C, any precipitated ethylenediamine dihydrochloride was removed, and the volume of filtrate was reduced (to 50 mL). More ethylenediamine dihydrochloride was then removed by filtration, and the remaining filtrate was treated with an excess of a solution of hydrogen chloride in diethyl ether. Addition of a further amount of diethyl ether gave a precipitate of the crude product (44 g), which was recrystallized from 2-propanol to give a white, crystalline solid, **5**: yield 34 g (68%); mp 207–208 °C; IR (Nujol) ν_{max} 1625, 1590 cm^{-1}; mass spectrum, m/e 204 (M^+), 174 (100%); NMR (Me_2SO) δ 11.4 (2 H, s), 6.95 (4 H, s), 5.6 (1 H, t, J = 4 Hz), 4.6 (2 H, d, J = 4 Hz), 3.9 (4 H, s). Anal. ($C_{11}H_{12}N_2O_2 \cdot HCl$) C, H, N.

Compounds **10**, **11**, **22**, **26**, and **33** were also prepared by the procedures described above (see Table I).

Route A(2). 2-(6,7-Dimethoxy-1,4-benzodioxan-2-yl)-2-imidazoline Hydrochloride (**28**). A steady stream of gaseous ammonia was bubbled through a stirred, cooled (0 °C) solution of ethyl 6,7-dimethoxy-1,4-benzodioxan-2-carboxylate[21] (28 g, 104 mmol) in ethanol (500 mL) until saturated. The solution was allowed to stand at room temperature overnight and was then evaporated to dryness to leave a semisolid. Trituration of this solid with ethyl acetate gave the carboxamide: yield 16.5 g (59%); IR (Nujol) ν_{max} 1700 cm^{-1}. A mixture of the crude carboxamide (15 g, 72 mmol), phosphorus pentoxide (50 g, 362 mmol), and anhydrous toluene (1 L) was heated under reflux for 3 h. The cooled solution was decanted off, and the residue was washed well with additional toluene. The combined toluene fractions were

(17) Grant, J. A.; Scrutton, M. C. *Nature (London)* **1979**, *277*, 659.
(18) Hannington, E. *Lancet* **1978**, *2*, 501.
(19) Bruce, M. J.; Sutcliffe, F. K. *J. Chem. Soc.* **1956**, 3824.
(20) Cook, M. J.; Katritsky, A. R.; Sewell, M. J. *J. Chem. Soc. B* **1970**, 1207. Martin, A. R.; Mallick, S. K.; Caputo, J. F. *J. Org. Chem.* **1974**, *39*, 1808.
(21) Wanzlick, H. W., Jahnke, U. *Chem. Ber.* **1968**, *101*, 3744. Cole, E. R.; Crank, G.; Haiminh, H. T. *Aust. J. Chem.* **1980**, *33*, 527. Koo, J.; Avakian, S.; Martin, G. J. *J. Am. Chem. Soc.* **1955**, *77*, 5373.

washed with water, dried, and evaporated to leave 2-cyano-6,7-dimethoxy-1,4-benzodioxan as an off-white solid: yield 6.7 g (49%). The crude cyano compound was converted, by the method described in section 1 route A(1), for the preparation of **27**, to the corresponding imidazoline hydrochloride **28**, mp 230–232 °C. Anal. ($C_{13}H_{16}N_2O_4$·HCl·0.25H_2O) C, H, N.

Compounds **12** and **15** were obtained from the corresponding methoxycarboxamides[22] by the methods described above.

Route A(3). 2-(5,8-Dichloro-1,4-benzodioxan-2-yl)-2-imidazoline Hydrochloride (30). A stirred mixture of 3,6-dichlorocatechol[23] (14.8 g, 83 mmol), epichlorohydrin (19.3 mL, 248 mmol), sodium hydroxide (3.31 g, 83 mmol), and water (33 mL) was heated at 100 °C for 3 h. On cooling, the product was extracted with diethyl ether. The combined extracts were washed with aqueous 1 N sodium hydroxide, water, and brine, dried, and evaporated to leave an oil. Distillation gave the 2-(hydroxymethyl)-5,8-dichloro-1,4-benzodioxan: yield 12.3 g (63%); bp 121–142 °C (0.1 mmHg). To a cooled (10 °C), stirred mixture of the alcohol (12.3 g, 52 mmol), potassium hydroxide (3.5 g, 85% purity, 52 mmol), and water (90 mL) was added, portionwise, potassium permanganate (12.5 g, 78 mmol). During the addition the temperature was maintained in the range 10–20 °C. After an additional 20 h, the mixture was filtered, and the solid was extracted with methylene chloride, which lead to the recovery of some starting hydroxymethyl compound (4.2 g). The filtrate was acidified with sulfuric acid, and the product was extracted with methylene chloride. The desired acid was obtained by washing the extracts with saturated sodium bicarbonate solution, which was then acidified (pH 2) with concentrated hydrochloric acid. Extraction of the acidic aqueous phase with methylene chloride lead to the isolation of the corresponding 2-carboxylic acid as a white solid: yield 4.0 g (47%). To a solution of the acid (3.9 g, 15.7 mmol) in anhydrous toluene (30 mL) was added a solution of thionyl chloride (6.7 g, 31.4 mmol) in anhydrous toluene (30 mL). The mixture was heated at 90–100 °C with stirring for 2 h, and then the solvent and excess thionyl chloride were removed in vacuo to leave the crude 2-carbonyl chloride as an oil: yield 4 g (100%). A solution of the acid chloride (4 g, 15 mmol) in anhydrous dioxane (20 mL) was added dropwise to a stirred, cooled (0–10 °C) solution of ammonia (18 mL, *d* 0.88). After completion of the addition, the mixture was allowed to warm to room temperature over 0.5 h, and water (200 mL) was added. The solid was collected by filtration to give the impure 2-carboxamide: yield 3 g (80%). The carboxamide was converted [see route A(2)] to the corresponding imidazoline hydrochloride **30** decomposition temperature 230–240 °C. Anal. ($C_{11}H_{10}Cl_2N_2O_2$·HCl) C, H, N.

Route A(3P). Compounds **7**, **9**, **24**, and **25** were prepared by the routes described in the text.

Route B. 2-(7-Hydroxy-1,4-benzodioxan-2-yl)-2-imidazoline Hydrobromide (18). The free base generated from 2-(7-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline hydrochloride (**14**; 1.5 g, 5.6 mmol) was treated with an excess of 48% hydrobromic acid solution (15 mL), and the mixture was heated at 100 °C for 7 h with stirring. Evaporation of the solvent gave a solid residue, which was recrystallized from 2-propanol/diethyl ether to yield the imidazoline hydrobromide **18**: yield 0.95 g (54%). Anal. ($C_{11}H_{12}N_2O_3$·HBr·0.5H_2O) C, H, N.

Compounds **16**, **17**, **19**, and **29** were also prepared from the corresponding methoxy compounds by the procedure as described above.

Route C. 2-(8-Chloro-1,4-benzodioxan-2-yl)-2-imidazoline Hydrochloride (23). A mixture of 2-(hydroxymethyl)-8-nitro-1,4-benzodioxan[9] (919.5 g, 92 mmol), cyclohexane (217 mL), and 10% palladium on charcoal (200 mg) was heated under reflux with stirring for 44 h. Ethanol (100 mL) was added, and the mixture was heated under reflux for an additional 2 h. After the mixture was cooled, the catalyst was filtered off. The filtrate was evaporated to leave an oil, which solidified on addition of toluene. The solid was collected and washed with cyclohexane to leave the crude 8-amino compound: yield 13.5 g (81%). A mixture of the amine (12.6 g, 69.6 mmol) and concentrated hydrochloric acid (30.5 mL) was cooled to 0 °C and treated with a solution of sodium nitrite (4.9 g, 71 mmol) in water (14 mL). The temperature was maintained in the range 0–5 °C during the addition. After 0.5 h, a cold, freshly prepared solution of cuprous chloride in concentrated hydrochloric acid [prepared from, 21.8 g (87 mmol) of hydrated copper sulfate and 35 mL of concentrated hydrochloric acid] was added rapidly. The mixture was allowed to warm to room temperature, and stirring was continued for 2.5 h before heating briefly at 70 °C. After cooling, the mixture was extracted with methylene chloride. The combined extracts were washed with water, aqueous 1 N sodium hydroxide, and brine, dried, and evaporated to leave an oil (10.6 g). Distillation gave the 8-chloro compound, bp 113–114 °C (0.35 mmHg), which slowly crystallized to a white solid: yield 7.7 g (42% overall from nitro compound); mp 45–47 °C. This intermediate was converted, by the methods described in route A(3), to the corresponding imidazoline hydrochloride **23**, decomposition temperature 215–224 °C. Anal. ($C_{11}H_{11}ClN_2O_2$·HCl·0.25H_2O) C, H, N.

Route D. 2-[6(and/or 7)-Chloro-1,4-benzodioxan-2-yl]-2-imidazoline Hydrochloride (20). A solution of **5** (4.82 g, 20 mmol) in acetic acid (50 mL) was treated with fuming nitric acid (2.6 mL, 40 mmol) at room temperature with stirring. After 48 h, the solvent was removed under reduced pressure, and the residue was partitioned between aqueous sodium bicarbonate and diethyl ether. The combined extracts were dried, and the volume was reduced to 20 mL. Ethereal hydrogen chloride was added, and the precipitated solid was collected (1.4 g). Recrystallization from ethanol/diethyl ether gave the chloroimidazoline compound **20**: yield 0.1 g (2%); mp 211–213 °C. Anal. ($C_{11}H_{11}ClN_2O_2$·HCl) H, N; C: calcd, 48.02; found, 48.75.

2-(6,7-Dichloro-1,4-benzodioxan-2-yl)-2-imidazoline Hydrochloride (31). To a solution of the free base of **5** (2.04 g, 10 mmol, obtained from 2.4 g of **5**) in chloroform (100 mL) was added ferric chloride (1 g, 16.2 mmol) and a crystal of iodine. A solution of chlorine in carbon tetrachloride [2.13 g (30 mmol) of Cl_2; in 70 mL] was added, and the resultant solution was allowed to stand for 72 h. The precipitated solid (4 g) was collected and partitioned between aqueous sodium bicarbonate and chloroform. The combined extracts were dried and evaporated to dryness. The residue was dissolved in methanol and treated with ethereal hydrogen chloride to give a solid (0.34 g). Recrystallization from methanol/diethyl ether gave the dichloroimidazoline compound **31**: yield 0.12 g (4%); mp 271–273 °C. Anal. ($C_{11}H_{10}Cl_2N_2O_2$·HCl) C, H, N.

Bromination of 2-(1,4-Benzodioxan-2-yl)-2-imidazoline Hydrochloride (5). A solution of **5** (1.2 g, 5 mmol) in acetic acid (25 mL) was treated with a solution of bromine (1.6 g, 10 mmol) in acetic acid (20 mL) at room temperature. After 24 h, the solution was evaporated to dryness to leave a solid residue, which was dissolved in ethanol (10 mL). Addition of ethereal hydrogen chloride to this solution precipitated a white solid, which was collected (0.15 g). The volume of the filtrate was reduced to 5 mL, and diethyl ether was then added, causing the precipitation of the more soluble component of the product mixture (0.71 g). Recrystallization of the more insoluble component (0.15 g) from ethanol gave **2-(6,7-dibromo-1,4-benzodioxan-2-yl)-2-imidazoline hydrochloride (32)**: yielded 0.05 g (3%); mp 278–280 °C. Anal. ($C_{11}H_{10}Br_2N_2O_2$·HCl) C, H, N.

Recrystallization of the more soluble component (0.71 g) from 2-propanol/diethyl ether gave **2-[6(and/or 7)-bromo-1,4-benzodioxan-2-yl]-2-imidazoline hydrochloride (21)**: yield 0.22 g (14%); mp 216–218 °C. Anal. ($C_{11}H_{11}BrN_2O_2$·HCl) H, N; C: calcd, 41.34; found, 40.74.

(2) Modification of the Imidazoline Ring. (a) Compounds **35–37** were prepared by reacting the imidate **34** with the corresponding *C*- and *N*-methyl-substituted derivatives of ethylenediamine (Aldrich Chemical Co.) by the procedure described in Section 1, route A(1), for the preparation of **5**.

(b) Amidines **38–49** were prepared from the reaction of imidate **34** with the appropriate amine by the procedure described in section 1, route A(1).

(3) Miscellaneous. 2-(1,4-Benzodioxan-2-yl)-2-thiazoline Hydrochloride (52). A mixture of 2-cyano-1,4-benzodioxan (**50**;[20] 3 g, 18.6 mmol), cysteamine hydrochloride (2.25 g, 20.5 mmol), and ethanol (60 mL) was heated under reflux with stirring under an atmosphere of nitrogen for 30 h. Evaporation of the solvent

(22) Mills, H.; Valley, G.; Rothburn, R. C., U.S. Patent 2 922 744.
(23) Nishizawa, K.; Satoh, J. Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2215.

gave a semisolid residue, which was chromatographed on silica eluting with chloroform. The early fractions yielded a mixture of the required product and an acid-insoluble component (0.77 g). This mixture was partitioned between aqueous sodium bicarbonate and chloroform. The organic layer was then extracted with dilute hydrochloric acid, and these extracts were then basified with aqueous sodium bicarbonate and reextracted with chloroform. The chloroform extracts were dried and evaporated to leave a solid (0.43 g), which was recrystallized from methanol/ethereal hydrogen chloride to give the thiazoline compound **52**: yield 0.31 g (6%); mp 142–146 °C. Anal. ($C_{11}H_{11}NO_2S$·HCl) C, H, N.

Compounds **54** and **56–58** were prepared by literature procedures.[11] Standard literature procedures were used to prepare the novel compounds **61**, **62** and **63**[12] and **64–66**. Compounds **55** and **59** and **60** were prepared from the imidate **34** and the appropriate amine by the procedure described in section 1, route A(1).

Pharmacology. Preparations. Rat Vas Deferens. Vasa deferentia were removed from male Sprague–Dawley rats weighing 200–250 g. The prostatic half of the vas deferens was cleaned of connective tissue and suspended under an initial tension of 0.5 g in an organ bath at 8–10-mL capacity. The tissue was bathed in Krebs solution (NaCl, 118 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM, KH_2PO_4, 1.2 mM; $MgSO_4$, 0.6 mM, $NaHCO_3$, 25 mM; dextrose, 11.1 mM), which was gassed with 95% O_2 and 5% CO_2 and maintained at a temperature 30 °C. The intramural nerves of the vas deferens were stimulated by rectangular pulses of 3-ms duration, 40 V, at a frequency of 0.1 Hz, and the resultant contractions of the tissue were recorded isometrically.

Mouse Vas Deferens. Vasa deferentia from adult male mice (MFI >30 g) were set up under an initial tension of 0.5 g in an organ bath of 50-mL capacity that contained magnesium-free Krebs solution. The physiological solution was maintained at 30 °C and gassed with 95% O_2 and 5% CO_2. The preparations were field stimulated between platinum electrodes at 0.1 Hz with rectilinear pulses of 3-ms duration. The voltage (100–140 V) was adjusted to give a twitch response of approximately 100-mg tension. Contractions of the tissue were recorded isometrically.

Rat Anococcygeus Muscle. The anococcygeus muscles of male Sprague–Dawley rats weighing 200–250 g were removed and suspended in a 50-mL organ bath using an initial tension of 0.5 g. The tissue was bathed in Krebs solution that was gassed with 95% O_2 and 5% CO_2 and maintained at 30 °C.

In Vitro Screening. Presynaptic α_2-Adrenoreceptor Agonist Activity. Vas Deferens. Either the mouse or rat vas deferens was used in these studies. Repeated cumulative concentration–response curves were constructed to the presynaptic α_2-adrenoreceptor agonist clonidine until consistent ID_{50} values were obtained. The effect of an analogue of **5** was then examined, and if inhibition of the twitch was obtained, an ID_{50} value was determined; i.e., presynaptic potency of the new analogue was compared directly with that of clonidine in the same experiment. The analogue of **5** was then removed from the bathing fluid, and the responsiveness of the tissue to clonidine was reassessed.

Presynaptic α_2-Adrenoreceptor Antagonist Properties. Vas Deferens. Tissues taken from either the rat or mouse were used to determine presynaptic α_2-adrenoreceptor antagonist potency. Contractions of the vas deferens were inhibited by including clonidine (110 nM) in the Krebs solution. The concentration of compound required to produce 50% reversal of the inhibitory effects of clonidine was determined and compared with the value determined for **5** in the same tissue. Presynaptic α_2-adrenoreceptor antagonist potency was therefore expressed with respect to **5** as the standard.

Postsynaptic α_1-Adrenoreceptor Agonist Activity. Rat Anococcygeus. Postsynaptic α_1-adrenoreceptor agonist activity was determined on the rat anococcygeus muscle. Cumulative concentration–response curves to the contractile effects of phenylephrine were constructed until the responses were reproducible. The effects of analogues of **5** were then studied, and the potencies of compounds with agonist activity were compared directly with that of phenylephrine in the same tissue.

Postsynaptic α_1-Adrenoreceptor Antagonist Properties. Rat Anococcygeus. Cumulative concentration–response curves to phenylephrine were constructed in the absence and presence of a fixed concentration of **5** or one of its analogues. From the dose ratios produced, the concentration of agonist producing a dose ratio was calculated, and thus the α_1 antagonist potency relative to **5** was determined.

Determination of pA_2 Values for Competitive Antagonists. The pA_2 values of selected compounds were determined at presynaptic α_2- and postsynaptic α_1-adrenoreceptors. Antagonism of the inhibitory effects of clonidine on the vas deferens and antagonism of norepinephrine contractions on the anococcygeus muscle were used to determine pA_2 values at presynaptic α_2- and postsynaptic α_1-adrenoreceptors, respectively. pA_2 is defined as the negative log of the antagonist concentration required to maintain a constant response when the concentration of the agonist is doubled.

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Registry No. **5**·HCl, 79944-56-2; **6**·HCl, 85084-11-3; **7**·HCl, 85084-12-4; **8**·HCl, 85084-13-5; **9**·HCl, 85084-14-6; **10**·HCl, 85084-08-8; **11**·HCl, 85084-09-9; **12**·HCl, 85084-15-7; **13**·HCl, 85084-16-8; **14**·HCl, 85084-17-9; **15**·HCl, 85084-18-0; **16**·HBr, 85084-19-1; **17**·HBr, 85084-20-4; **18**·HBr, 85084-21-5; **19**·HBr, 85084-22-6; **20**·HCl, 85084-10-2; **21**·HCl, 85097-03-6; **22**·HCl, 85097-04-7; **23**·HCl, 85084-23-7; **24**·HCl, 85084-24-8; **25**·HCl, 85084-25-9; **26**·HCl, 85084-26-0; **27**·HCl, 85084-27-1; **28**·HCl, 85097-05-8; **29**·HCl, 85084-28-2; **30**·HCl, 85084-29-3; **31**·HCl, 85084-30-6; **32**·HCl, 85084-31-7; **33**·HCl, 85084-32-8; **34**·HCl, 79944-55-1; **35**·HCl, 85084-33-9; **36**·HCl, 85084-34-0; **37**·HCl, 85084-35-1; **38**·HCl, 85084-36-2; **39**, 85084-37-3; **40**, 85084-38-4; **41**·HCl, 85084-39-5; **42**·HCl, 85084-40-8; **43**·HCl, 85084-41-9; **44**·HCl, 85084-42-0; **45**, 85084-43-1; **46**, 85084-44-2; **47**, 85084-45-3; **48**·HCl, 85084-46-4; **49**·HCl, 85084-47-5; **50**, 1008-92-0; **51**, 613-67-2; **52**·HCl, 85084-48-6; **53**, 85084-49-7; **54**·HCl, 81167-30-8; **55**·HCl, 85084-50-0; **56**·HCl, 81167-18-2; **57**·HCl, 81167-19-3; **58**·HCl, 81167-22-8; **59**, 85084-51-1; **60**·HCl, 85084-52-2; **61**, 85084-53-3; **62**, 85084-54-4; **63**, 85084-55-5; **64**, 85084-56-6; **65**·HCl, 85084-57-7; **66**·HCl, 68960-51-0; **67**, 4739-94-0; **68** (n = 0), 85084-66-8; **68** (n = 1), 85084-67-9; **69**, 2164-34-3; 4,5-dimethylcatechol, 2785-74-2; 2-chloroacrylonitrile, 920-37-6; 2-cyano-6,7-dimethyl-1,4-benzodioxan, 85084-58-8; ethylenediamine, 107-15-3; ethyl 6,7-dimethoxy-1,4-benzodioxan-2-carboxylate, 85084-59-9; 6,7-dimethoxy-1,4-benzodioxan-2-carboxamide, 85084-60-2; 2-cyano-6,7-dimethoxy-1,4-benzodioxan, 85084-61-3; 3,6-dichlorocatechol, 3938-16-7; epichlorohydrin, 106-89-8; 2-(hydroxymethyl)-5,8-dichloro-1,4-benzodioxan, 85084-62-4; 2-carboxy-5,8-dichloro-1,4-benzodioxan, 85084-63-5; thionyl chloride, 7719-09-7; 2-carboxamido-5,8-dichloro-1,4-benzodioxan, 85084-64-6; 2-(hydroxymethyl)-8-nitro-1,4-benzodioxan, 2271-71-8; 2-(hydroxymethyl)-8-amino-1,4-benzodioxan, 85097-06-9; 2-(hydroxymethyl)-8-chloro-1,4-benzodioxan, 85084-65-7; 2-aminoethanethiol, 156-57-0; *N*-methylethylenediamine, 109-81-9; 1,2-diaminopropane, 78-90-0; 1-methyl-1,2-diaminopropane, 811-93-8; glycine, 56-40-6; 2-methoxyethylamine, 109-85-3; phenethylamine, 64-04-0; 3-aminopropanol, 156-87-6; 2-[(2,6-dimethoxyphenyl)oxy]ethanamine, 40515-98-8; 4,5-dihydro-2-thiazolamine, 1779-81-3; ethyl 2,3-dibromopropionate, 3674-13-3; 4-aminomorpholine, 4319-49-7; 1-aminopiperidine, 2213-43-6; 1,3-propanediamine, 109-76-2; 2-aminophenol, 95-55-6; 1,2-benzenediamine, 95-54-5.