

unknown. The transition from full to partial agonism or antagonism has been related to increased size of the terminal group as monitored by the  $|PC_1|$  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.

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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 discussions. 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).

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## $\alpha$ -Adrenoreceptor Reagents. 1. Synthesis of Some 1,4-Benzodioxans as Selective Presynaptic $\alpha_2$ -Adrenoreceptor Antagonists and Potential Antidepressants

Christopher B. Chapleo,\* Peter L. Myers, Richard C. M. Butler, John C. Doxey, Alan G. Roach, and Colin F. C. Smith

Departments of Medicinal Chemistry and Pharmacology, Reckitt and Colman Ltd., Kingston upon Hull, HU8 7DS, United Kingdom. Received September 10, 1982

The rational design of RX 781094, 2-(1,4-benzodioxan-2-yl)-2-imidazoline hydrochloride (5), a new potent and selective antagonist of  $\alpha_2$ -adrenoreceptors, is discussed. A compound that acts as an antagonist at presynaptic  $\alpha_2$ -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  $\alpha_2$ -adrenoreceptor antagonist and postsynaptic  $\alpha_1$ -adrenoreceptor partial agonist properties were also obtained, and these derivatives could be considered as potential antimigraine agents.

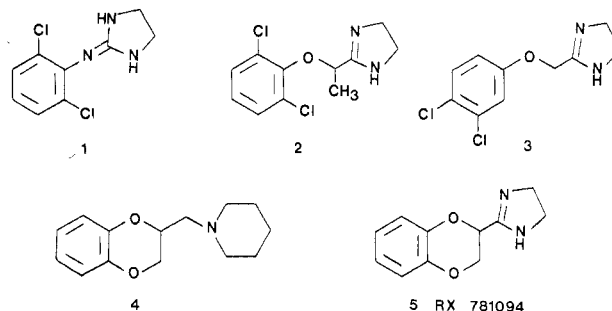
According to the catecholamine hypothesis of affective disorders, a relative deficiency of the transmitter norepinephrine at receptor sites within the central nervous system is responsible for the symptoms of the disease. Support for this hypothesis is provided by drugs that are clinically effective 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  $\alpha$ -adrenoreceptors (negative-feedback mechanism<sup>1</sup>). It was proposed that these presynaptic  $\alpha$ -adrenoreceptors should be designated the prefix  $\alpha_2$  in order to differentiate them from postsynaptic  $\alpha$ -adrenoreceptors, which were themselves designated  $\alpha_1$ . However, recent evidence suggests that  $\alpha_1$ - and  $\alpha_2$ -adrenoreceptors are general subtypes, and the term  $\alpha_2$  should not be limited to presynaptic receptor sites.<sup>2</sup>

Recently, it has been proposed that a common underlying mechanism of action of antidepressants may be an ability to alter  $\alpha_2$ -adrenoreceptor sensitivity.<sup>3</sup> Thus, in depression these receptors ( $\alpha_2$ ) are considered to be supersensitive, hence, turning off release of norepinephrine. It has been suggested<sup>3</sup> that a feature of antidepressant

therapy is a gradual reduction in the sensitivity of central  $\alpha_2$ -adrenoreceptors: such a subsensitivity would gradually increase norepinephrine levels. Therefore, it can be proposed that if central  $\alpha_2$ -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  $\alpha_2$ -adrenoreceptor antagonist, but its lack of specificity limits clinical application.

Clonidine (1) is an  $\alpha_2$ -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  $\alpha_2/\alpha_1$  selectivity and agonist and antagonist character.<sup>4</sup> It

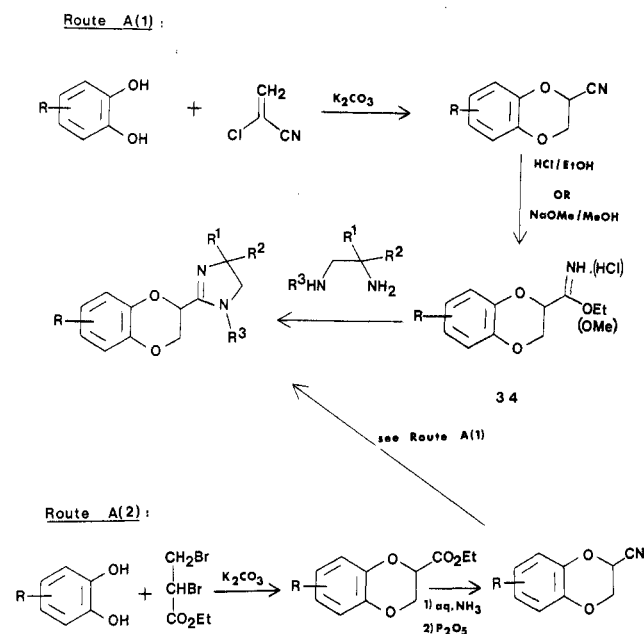
(1) Langer, S. Z. *Biochem. Pharmacol.* 1974, 23, 1763; *Br. J. Pharmacol.* 1977, 60, 481.

(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.

## Scheme I

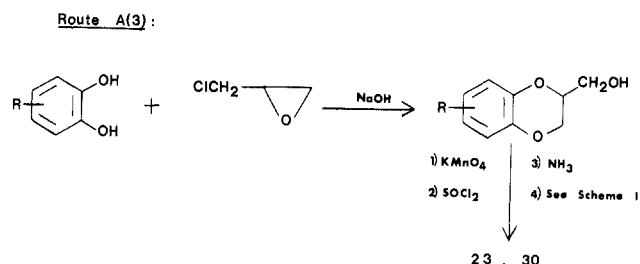


was found that aromatic substitution influenced  $\alpha_2/\alpha_1$  selectivity, and, in addition,  $\alpha_2$ -adrenoreceptor antagonist properties became apparent in some cases. It was also obvious that the aminoimidazoline linkage previously considered to be essential for  $\alpha_2$  agonist activity was not, in fact, necessary, since lofexidine (2), in particular, was a potent  $\alpha_2$  agonist with high affinity for this receptor site. Fenmetazole (3) has been claimed<sup>5</sup> to possess antidepressant properties, and profiling of this compound revealed that, unlike lofexidine (2), it was an  $\alpha_2$ -adrenoreceptor antagonist, albeit of low potency (pre- $\alpha_2$  pA<sub>2</sub> against clonidine =  $6.6 \pm 0.2$ ).<sup>6</sup> 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)  $\alpha$ -adrenoreceptor antagonist piperoxan (4) to give the benzodioxan 5 (RX 781094).<sup>7</sup> We report here the synthesis and pharmacological testing of the title compound and its derivatives.

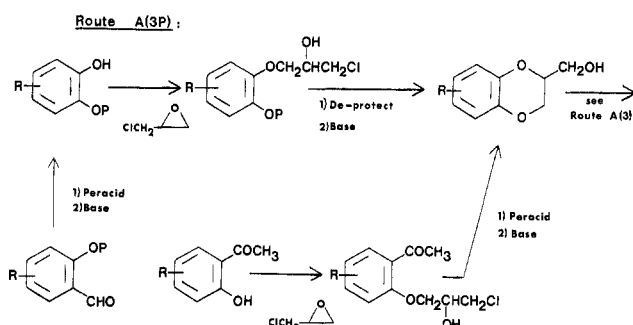
**Chemistry.** For convenience, the synthesis and structure-activity relationships are discussed under three main headings, with each section being discussed in turn.

(1) **Aromatic Substitution (Table I, Compounds 6–33).** The unsubstituted compound (5) was prepared<sup>7</sup> 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

## Scheme II



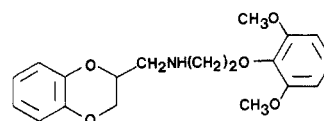
## Scheme III



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.<sup>8</sup> 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<sup>9</sup> 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.<sup>8</sup> Compound 44 was prepared as a direct structural analogue of WB 4101 (51), a postsynaptic  $\alpha_1$ -adrenoreceptor antagonist.<sup>10</sup>



51

(5) *Drugs Future* 1976, 1, 239.

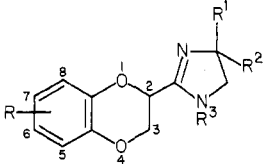
(6) Doxey, J. C., Reckitt and Colman, Ltd., unpublished results.


(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.

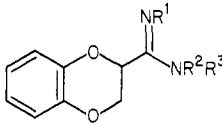
Table I




no.	R <sup>a</sup>	method <sup>b</sup>	mp, °C	recrystn solvent	formula
5	H	A(1)	207-208	<i>i</i> -PrOH	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
6	5-CH <sub>3</sub>	A(3P)	243-246	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
7	6-CH <sub>3</sub>	A(3P)	196-198	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl <sup>c</sup>
8	7-CH <sub>3</sub>	A(3P)	215-217	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
9	8-CH <sub>3</sub>	A(3P)	224-226	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
10	6(and/or 7)- <i>t</i> -Bu	A(1)	197-198	EtOH/Et <sub>2</sub> O	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
11	5(and/or 8)- <i>i</i> -Pr	A(1)	213-214	EtOH/Et <sub>2</sub> O	C <sub>14</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
12	5-OCH <sub>3</sub>	A(2)	187-189	<i>i</i> -PrOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
13	6-OCH <sub>3</sub>	A(3P)	185-186	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
14	7-OCH <sub>3</sub>	A(3P)	201-203	EtOH	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
15	8-OCH <sub>3</sub>	A(2)	196-198	<i>i</i> -PrOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
16	5-OH	A(2), B	206-208	<i>i</i> -PrOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> ·HBr
17	6-OH	A(3P), B	215-217	EtOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> ·HBr
18	7-OH	A(3P), B	168-172	<i>i</i> -PrOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> ·HBr·0.25H <sub>2</sub> O
19	8-OH	A(2), B	226-232	EtOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> ·HBr·0.25H <sub>2</sub> O
20	6(and/or 7)-Cl	D	211-213	EtOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub> ·HCl <sup>d</sup>
21	6(and/or 7)-Br	D	216-218	<i>i</i> -PrOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>11</sub> BrN <sub>2</sub> O <sub>3</sub> ·HCl <sup>e</sup>
22	6(and/or 7)-F	A(1)	249-251	EtOAc/Et <sub>2</sub> O	C <sub>11</sub> H <sub>11</sub> FN <sub>2</sub> O <sub>3</sub> ·HCl·0.25H <sub>2</sub> O
23	8-Cl	A(3), C	215-224 <sup>f</sup>	EtOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub> ·HCl·0.25H <sub>2</sub> O
24	6-NO <sub>2</sub>	A(3P)	202-206	EtOH	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub> ·HCl·0.5H <sub>2</sub> O
25	8-NO <sub>2</sub>	A(3P)	230-240	EtOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub> ·HCl <sup>g</sup>
26	5,8-(CH <sub>3</sub> ) <sub>2</sub>	A(1)	238-240	EtOH	C <sub>13</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·0.25H <sub>2</sub> O
27	6,7-(CH <sub>3</sub> ) <sub>2</sub>	A(1)	210-213	EtOH/Et <sub>2</sub> O	C <sub>13</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·0.25H <sub>2</sub> O
28	6,7-(OCH <sub>3</sub> ) <sub>2</sub>	A(2)	230-232	EtOH	C <sub>13</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> ·HCl·0.25H <sub>2</sub> O
29	6,7-(OH) <sub>2</sub>	A(2), B	250-260 <sup>f</sup>	MeOH	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub> ·HBr
30	5,8-Cl <sub>2</sub>	A(3)	230-240	EtOH	C <sub>11</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
31	6,7-Cl <sub>2</sub>	D	271-273	MeOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
32	6,7-Br <sub>2</sub>	D	278-280	EtOH	C <sub>11</sub> H <sub>10</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
33	6,7- 	A(1)	229-232	EtOH/Et <sub>2</sub> O	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
35	R = H; R <sup>3</sup> = CH <sub>3</sub>	A(1)	164-165	<i>i</i> -PrOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·0.5H <sub>2</sub> O
36	R = H; R <sup>1</sup> = CH <sub>3</sub>	A(1)	187-188	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·0.25H <sub>2</sub> O
37	R = H; R <sup>1</sup> = R <sup>2</sup> = CH <sub>3</sub>	A(1)	201-203	EtOH/Et <sub>2</sub> O	C <sub>13</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·0.25H <sub>2</sub> O

<sup>a</sup> Unless specified otherwise, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> = H. <sup>b</sup> 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. <sup>c</sup> Contains 0.33 mol of diethyl ether. <sup>d</sup> C: calcd, 48.02; found, 48.75. <sup>e</sup> C: calcd, 41.34; found, 40.74. <sup>f</sup> Decomposition temperature. <sup>g</sup> N: calcd, 14.71; found, 13.98.

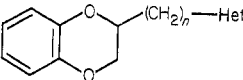
Table II



no.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	method <sup>a</sup>	mp, °C	recrystn solvent	formula
38	H	H	H	I	188-189	EtOH/Et <sub>2</sub> O	C <sub>9</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
39	H	H	OH	N	130-132	EtOH/Et <sub>2</sub> O	C <sub>9</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub>
40	H	H	CH <sub>2</sub> CO <sub>2</sub> H	I	210-212	H <sub>2</sub> O	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub> ·0.75H <sub>2</sub> O
41	H	H	(CH <sub>2</sub> ) <sub>2</sub> OMe	I	141-143	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
42	H	H	(CH <sub>2</sub> ) <sub>2</sub> Ph	I	197-201	EtOH/Et <sub>2</sub> O	C <sub>17</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
43	H	H	(CH <sub>2</sub> ) <sub>3</sub> OH	N <sup>b</sup>	168-169	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
44	H	H	(CH <sub>2</sub> ) <sub>2</sub> O-C <sub>6</sub> H <sub>3</sub> (2,6-MeO)	I	229-231	EtOH/Et <sub>2</sub> O	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub> ·HCl
45	H	H		N	139-141	<i>i</i> -PrOH	C <sub>12</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S
46	H	H	<i>c</i> -NC <sub>5</sub> H <sub>10</sub>	I	93-94	EtOH/H <sub>2</sub> O	C <sub>14</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub>
47	H	H	<i>c</i> -N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> O	I	154-156	EtOH/H <sub>2</sub> O	C <sub>13</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>
48	H	-(CH <sub>2</sub> ) <sub>5</sub> -		I	69-71	Et <sub>2</sub> O/petrol	C <sub>14</sub> H <sub>19</sub> N <sub>2</sub> O <sub>3</sub> ·HCl <sup>c</sup>
49	<i>n</i> -Bu	H	<i>n</i> -Bu	I	121-122	EtOH/Et <sub>2</sub> O	C <sub>17</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub> ·HCl

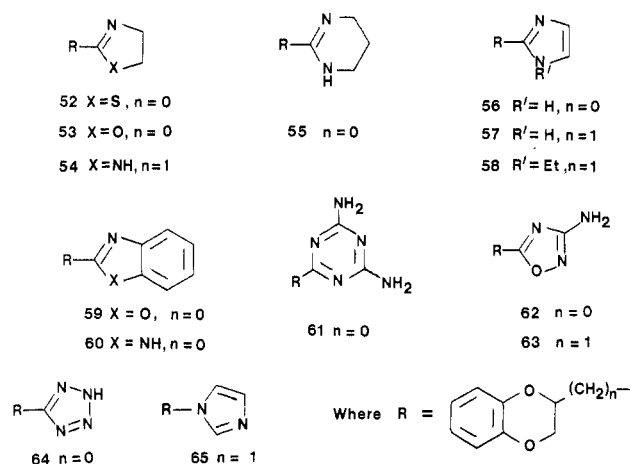
<sup>a</sup> Preparative method: N = nitrile 50 plus amine; I = imidate 34 plus amine. <sup>b</sup> The nitrile was converted to the *S*-methylthioronium salt, via the thio amide prior to reaction with aminopropanol. <sup>c</sup> C: calcd, 68.27; found, 67.58.

Table III

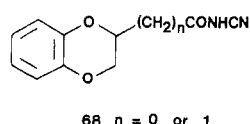
				
no.	reactants	mp, °C	recrystn solvent	formula
52	50 + H <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> SH	142-146	MeOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>11</sub> NO <sub>2</sub> S·HCl
54	see ref 11	228-229	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·HCl
55	34 + H <sub>2</sub> N(CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	188-192	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·HCl·0.5H <sub>2</sub> O
56	34 + H <sub>2</sub> NCH <sub>2</sub> CH(OMe) <sub>2</sub>	248-249	EtOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> ·HCl
57	see ref 11	215-225	<i>i</i> -PrOH	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> ·HCl
58	57 + EtI	172-174	<i>i</i> -PrOH/Et <sub>2</sub> O	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> ·HCl
59	34 + <i>o</i> -C <sub>6</sub> H <sub>4</sub> (OH)NH <sub>2</sub>	88-89	Et <sub>2</sub> O/hexane	C <sub>15</sub> H <sub>11</sub> NO <sub>3</sub>
60	34 + <i>o</i> -C <sub>6</sub> H <sub>4</sub> (NH <sub>2</sub> ) <sub>2</sub>	199-203	EtOH	C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> ·HCl
61	67 + biguanide	208-210	MeOH	C <sub>11</sub> H <sub>11</sub> N <sub>5</sub> O <sub>2</sub> ·0.5H <sub>2</sub> O
62	68 ( <i>n</i> = 0) + NH <sub>2</sub> OH	134-136	Et <sub>2</sub> O/petrol	C <sub>16</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub>
63	68 ( <i>n</i> = 1) + NH <sub>2</sub> OH	119-120	Et <sub>2</sub> O/petrol	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> O <sub>3</sub>
64	50 + NaN <sub>3</sub>	163-165	EtOH/H <sub>2</sub> O	C <sub>9</sub> H <sub>8</sub> N <sub>4</sub> O <sub>2</sub>
65	69 + imidazole	141-143	EtOH/Et <sub>2</sub> O	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> ·HCl
66	see Scheme IV <sup>a</sup>	173-174	EtOH/Et <sub>2</sub> O	C <sub>11</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·HCl <sup>b</sup>

<sup>a</sup> Nitrile was first converted to the corresponding imide. <sup>b</sup> 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

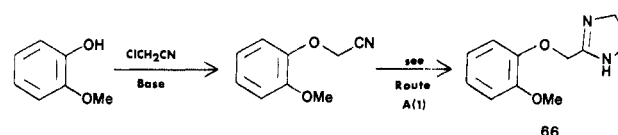


replaced by different heterocyclic rings, were prepared by various methods (Table III). Compounds 52 and 54-60 were readily available from the reaction of imide 34 or the intermediate nitriles with the appropriately substituted amine. Imidazoles 57 and 58 have recently been described<sup>11</sup> as being selective  $\alpha_2$ -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.  $\alpha_2$ - and  $\alpha_1$ -Adrenoreceptor pA<sub>2</sub> Values<sup>a</sup>

antagonist	in vitro experiments		
	vas deferens: anococcygeus		$\alpha_2/\alpha_1$ selectivity ratio <sup>b</sup>
	$\alpha_2$ pA <sub>2</sub> value against clonidine	$\alpha_1$ pA <sub>2</sub> value against norepinephrine	
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

<sup>a</sup> pA<sub>2</sub> values were calculated according to Arunlakshana and Schild<sup>14</sup> and are the means plus or minus SEM of, in each case, a minimum of six experiments. <sup>b</sup> Antilog of the difference between the pA<sub>2</sub> values at  $\alpha_2$ - and  $\alpha_1$ -adrenoreceptors

of clonidine-like analogues recently patented.<sup>12</sup> 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).<sup>11</sup> The imidazole 65 was prepared from the reaction of 2-(bromomethyl)-1,4-benzodioxan (69) with imidazole.

### Biological Results and Discussion

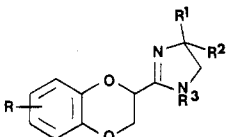
In the present study the presynaptic and postsynaptic  $\alpha$ -adrenoreceptor antagonist properties of prazosin, phentolamine, rauwolscine, piperoxan, and yohimbine were also studied and compared with those of 5. The results obtained are shown in Table IV. It can be seen that 5 was the most potent and selective antagonist at presynaptic  $\alpha_2$ -adrenoreceptors. These observations were confirmed in vivo (pithed rat) and have been reported elsewhere.<sup>13</sup>


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Table V<sup>a</sup>


no.	R <sup>b</sup>	presynaptic agonist potency (clonidine = 1) <sup>c</sup>	presynaptic antagonist potency (5 = 1) <sup>c</sup>	postsynaptic agonist potency (phenyl- ephrine = 1) <sup>c</sup>	postsynaptic antagonism concn giving DR = 2 vs. potency (5 = 1) <sup>d</sup>	presynaptic selectivity ratio of antagonists (5 = 1) (pre/post)
5	H	IA	1.0	IA	1.0	1.0
6	5-CH <sub>3</sub>	0.1	0.13	1.0	Ag	
7	6-CH <sub>3</sub>	IA	0.08	IA	0.4	0.21
8	7-CH <sub>3</sub>	IA	0.08	0.004	0.8	0.14
9	8-CH <sub>3</sub>	0.01	0.5	2.1	Ag	
10	6(and/or 7)- <i>t</i> -Bu	IA	0.01	IA	0.1	0.1
11	5(and/or 8)- <i>i</i> -Pr	0.1	IA	0.5	1.0	
12	5-OCH <sub>3</sub>	IA	0.001	5.0	IA	
13	6-OCH <sub>3</sub>	IA	0.006	0.005	NT	
14	7-OCH <sub>3</sub>	IA	0.02	IA	0.225	0.09
15	8-OCH <sub>3</sub>	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 <sub>2</sub>	IA	<0.0003	IA	<0.02	
25	8-NO <sub>2</sub>	IA	0.02	IA	0.09	0.22
26	5,8-(CH <sub>3</sub> ) <sub>2</sub>	0.19	0.005	2.5	Ag	
27	6,7-(CH <sub>3</sub> ) <sub>2</sub>	IA	0.06	IA	0.64	0.1
28	6,7-(OCH <sub>3</sub> ) <sub>2</sub>	IA	0.015	IA	0.05	0.3
29	6,7-(OH) <sub>2</sub>	0.0006	IA	0.018	>6.0	
30	5,8-Cl <sub>2</sub>	0.02	0.26	0.55	Ag	
31	6,7-Cl <sub>2</sub>	IA	0.003	IA	0.3	0.01
32	6,7-Br <sub>2</sub>	IA	0.001	0.02	0.1	0.01
33	6,7- 	IA	0.001	IA	0.01	0.1
35	R = H; R <sup>3</sup> = CH <sub>3</sub>	IA	0.0003	IA	0.1	0.003
36	R = H; R <sup>1</sup> = CH <sub>3</sub>	IA	0.003	IA	1.0	0.003
37	R = H; R <sup>1</sup> = R <sup>2</sup> = CH <sub>3</sub>	IA	0.0001	IA	0.01	0.01

<sup>a</sup> 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. <sup>b</sup> Unless specified otherwise, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> = H. <sup>c</sup> 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. <sup>d</sup> 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  $\alpha$ -adrenoreceptor agonist and antagonist properties. The results are summarized in Tables V-VII. The compounds were tested on isolated tissues for presynaptic  $\alpha_2$  (rat or mouse vas deferens) and postsynaptic  $\alpha_1$  (rat anococcygeus) adrenoreceptor agonist activity.<sup>15</sup> The values are given in terms of potency relative to clonidine ( $pD_2 = 8.8$ ) ( $\alpha_2$ ) and phenylephrine ( $pD_2 = 6.54$ ) ( $\alpha_1$ ). 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<sup>16</sup> (in vitro). In this case,

the values are quoted as potencies relative to 5.

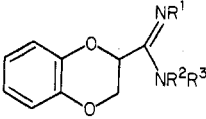
The primary objective of this synthetic program was to define the areas of chemical modification around 5 that would give antagonists with comparable or greater selectivity for the presynaptic site while retaining the potency inherent in 5. Quite clearly, none of the derivatives or analogues examined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

Recently,  $\alpha_2$ -adrenoreceptor antagonism has been demonstrated in a series of imidazole compounds,<sup>11</sup> including 58, which proved to be the most selective compound studied. Our results also show that 58 possesses some selectivity for the  $\alpha_2$ -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*-

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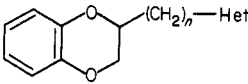
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Table VI<sup>a</sup>


no.	presynaptic agonist potency (clonidine = 1) <sup>b</sup>	presynaptic antagonist potency (5 = 1) <sup>b</sup>	postsynaptic agonist potency (phenylephrine = 1) <sup>b</sup>	postsynaptic antagonist concn giving DR = 2 vs. phenylephrine potency (5 = 1) <sup>c</sup>	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 <sup>d</sup>	NT	NT	NT	NT	
46 <sup>d</sup>	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

<sup>a</sup> 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. <sup>b</sup> 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. <sup>c</sup> 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. <sup>d</sup> Compound could not be tested because of solubility problems.

Table VII<sup>a</sup>


no.	presynaptic agonist potency (clonidine = 1) <sup>b</sup>	presynaptic antagonist potency (5 = 1) <sup>b</sup>	postsynaptic agonist potency (phenylephrine = 1) <sup>b</sup>	postsynaptic antagonist concn giving DR = 2 vs. phenylephrine potency (5 = 1) <sup>c</sup>	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 <sup>d</sup>	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	

<sup>a</sup> 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. <sup>b</sup> 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. <sup>c</sup> 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. <sup>d</sup> 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  $\alpha_1$ -adreno-receptor (under our test conditions), and consequently, its selectivity is less than that previously reported.<sup>11</sup> 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  $\alpha_2$ -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.  $\alpha_2$ - and  $\alpha_1$ -Adrenoreceptor  $pA_2$  Values<sup>a</sup>

antagonist	in vitro experiments		
	vas deferens: $\alpha_2$ $pA_2$ value against clonidine	anococcygeus: $\alpha_1$ $pA_2$ value against nor- epinephrine	$\alpha_2/\alpha_1$ selectivity ratio <sup>b</sup>
5	8.56 $\pm$ 0.05	6.10 $\pm$ 0.05	288
7	7.56 $\pm$ 0.31	6.17 $\pm$ 0.18	30
8	7.10 $\pm$ 0.20	5.87 $\pm$ 0.24	17
58	6.98 $\pm$ 0.02	4.85 $\pm$ 0.07	135

<sup>a</sup>  $pA_2$  values were calculated according to Arunlakshana and Schild<sup>14</sup> and are the means plus or minus SEM of, in each case, a minimum of six experiments. <sup>b</sup> Antilog of the difference between the  $pA_2$  values at  $\alpha_2$ - and  $\alpha_1$ -adreno-receptors.

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  $\alpha_2$  agonists clonidine and lofexidine (2). However, it is interesting to note that the lofexidine analogue 66, unlike lofexidine (2) itself, is a selective postsynaptic  $\alpha_1$ -adrenoreceptor agonist.

Finally, a number of compounds possess presynaptic  $\alpha_2$ -adrenoreceptor antagonist and postsynaptic  $\alpha_1$ -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  $\alpha$ -adrenoreceptors.<sup>6</sup> 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  $\alpha$ -adrenoreceptor antagonist properties seen with this series could contribute to an enhanced antimigraine effect. It has been shown recently<sup>17</sup> that human platelets aggregate in response to presynaptic  $\alpha_2$ -adrenoreceptor agonists and that this aggregation is inhibited by presynaptic  $\alpha_2$  antagonists. In view of the altered character of platelets in patients with migraine,<sup>18</sup> 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  $\alpha_2$ -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  $\alpha_2$  antagonism with postsynaptic  $\alpha_1$  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  $\pm 0.4\%$  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<sup>19</sup> (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<sub>3</sub>)  $\delta$  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)  $\nu_{\max}$  1620 cm<sup>-1</sup>; NMR (Me<sub>2</sub>SO)  $\delta$  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<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>·HCl·0.25H<sub>2</sub>O) C, H, N.

In some cases 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;<sup>20</sup> 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)  $\nu_{\max}$  1670, 1595 cm<sup>-1</sup>.

**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)  $\nu_{\max}$  1625, 1590 cm<sup>-1</sup>; mass spectrum,  $m/e$  204 (M<sup>+</sup>), 174 (100%); NMR (Me<sub>2</sub>SO)  $\delta$  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<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>·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<sup>21</sup> (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)  $\nu_{\max}$  1700 cm<sup>-1</sup>. 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

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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. ( $C_{13}H_{16}N_2O_4 \cdot HCl \cdot 0.25H_2O$ ) C, H, N.

Compounds 12 and 15 were obtained from the corresponding methoxycarboxamides<sup>22</sup> 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<sup>23</sup> (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. ( $C_{11}H_{10}Cl_2N_2O_2 \cdot HCl$ ) 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. ( $C_{11}H_{12}N_2O_3 \cdot HBr \cdot 0.5H_2O$ ) 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<sup>9</sup> (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. ( $C_{11}H_{11}ClN_2O_2 \cdot HCl \cdot 0.25H_2O$ ) 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. Etheral 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. ( $C_{11}H_{11}ClN_2O_2 \cdot HCl$ ) 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 etheral 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. ( $C_{11}H_{10}Cl_2N_2O_2 \cdot HCl$ ) 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 etheral 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. ( $C_{11}H_{10}Br_2N_2O_2 \cdot HCl$ ) 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. ( $C_{11}H_{11}BrN_2O_2 \cdot HCl$ ) 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; 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

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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/etheral hydrogen chloride to give the thiazoline compound 52: yield 0.31 g (6%); mp 142–146 °C. Anal. ( $C_{11}H_{11}NO_2 \cdot S \cdot HCl$ ) C, H, N.

Compounds 54 and 56–58 were prepared by literature procedures.<sup>11</sup> Standard literature procedures were used to prepare the novel compounds 61, 62 and 63<sup>12</sup> 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  $\alpha_2$ -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  $\alpha_2$ -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  $\alpha_2$ -Adrenoreceptor Antagonist Properties. Vas Deferens.** Tissues taken from either the rat or mouse were used to determine presynaptic  $\alpha_2$ -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  $\alpha_2$ -adrenoreceptor antagonist potency was therefore expressed with respect to 5 as the standard.

**Postsynaptic  $\alpha_1$ -Adrenoreceptor Agonist Activity. Rat Anococcygeus.** Postsynaptic  $\alpha_1$ -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  $\alpha_1$ -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  $\alpha_1$  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  $\alpha_2$ - and postsynaptic  $\alpha_1$ -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  $\alpha_2$ - and postsynaptic  $\alpha_1$ -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.