(final concentration 1 μM) for the test compound. Nonspecific binding was less than 10% of total binding under these conditions. Specific binding was defined as the difference in binding in the presence and absence of a large excess of nonradioactive benzodiazepine. Data were expressed as percent inhibition of specific binding, and IC_{50} values were estimated from semilogarithmic plots (see Figure 1 in ref 10). Inhibitory constants of compounds under study were calculated by the equation $K_i = IC_{50}/(1 + [L]/K_D)$, where [L] is the ligand concentration (2 nM), and the K_D for [^{3}H]diazepam was estimated to be 5.6 ± 0.34 nM in thrice washed cerebral cortical membranes.[40]

Acknowledgment. We thank Frank Laib and Judith Siegrist for their very able technical assistance.

Registry No. **1b**, 33522-62-2; **1c**, 63-84-3; **2**, 88980-04-5; **2a**, 79815-19-3; **2b**, 88932-16-5; **2b**·HCl, 88932-15-4; **2c**, 88980-05-6; **3a**, 27104-73-0; **3b**, 88932-17-6; **3c**, 88932-18-7; **4**, 645-35-2; **5a**, 88980-06-7; **5b**, 88932-19-8; **6a**, 82523-07-7; **6b**, 82523-11-3; **7a**, 88980-07-8; **7b**, 88980-08-9; **8a**, 88980-09-0; **8b**, 88980-10-3; **12a**, 65284-99-3; **12b**, 60702-98-9; **13a**, 479-43-6; **13b**, 84133-31-3; **14a**, 74214-62-3; **14b**, 69954-48-9; **15**, 82596-93-8; **16**, 88932-13-2; **17**, 88932-14-3.

α-Adrenoreceptor Reagents. 2. Effects of Modification of the 1,4-Benzodioxan Ring System on α-Adrenoreceptor Activity

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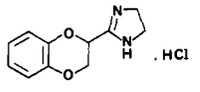
Modification of the 1,4-benzodioxan ring present in RX 781094 (1) has not previously been considered. This paper describes a number of analogues of this ring system, including compounds in which one of the oxygen atoms has been replaced by a methylene group and also those in which the ring size has been changed to give, for example, furan and thiophene derivatives. The dihydrobenzofuranylimidazoline compound **7** is the only analogue possessing presynaptic antagonist potency and selectivity comparable to that of **1**. In view of this result, a number of derivatives was prepared to determine the structure–activity relationships within this series. Many derivatives, as well as the parent compound **7**, were found to possess presynaptic α_2-adrenoreceptor antagonist and postsynaptic α_1-adrenoreceptor partial agonist properties. Two of the selective presynaptic antagonists, **13** and **14**, possess greater potency and selectivity than that possessed by **1**. The 5-chloro derivative **25** is twice as potent as **1** after oral administration but only about half as potent when given intravenously.

The rational design of idazoxan (**1**, RX 781094), a new

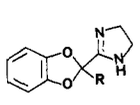


(1) Idazoxan (RX 781094)

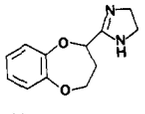
potent and selective antagonist of α_2-adrenoreceptors, has been described, and the effects of substituents on the aromatic or imidazoline ring, as well as modification of the imidazoline moiety, have been discussed.[1] Such modifications resulted in a reduction or loss of both the selectivity and potency of the parent compound **1** and in some examples lead to a change in profile. Modification of the 1,4-dioxan ring present in **1** has not been previously considered, and we discuss here the synthesis of a number of analogues of this ring system.

Chemistry. The preparation of the imidazoline products was carried out following one of the routes shown in Scheme I by using the intermediate ester or acid chloride **2**. The analogues were obtained as described in the following paragraphs.

Variation of Ring Size. The benzodioxole **3b** was



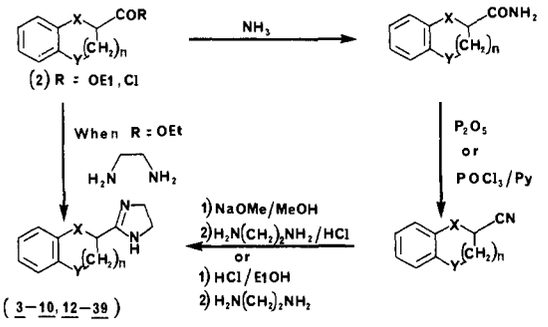
(3) a) R = H
b) R = CH_3



(4)

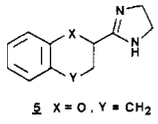
isolated by the procedure first described in the patent[2] to

Scheme I



Olin Mathieson Chemical Corp., which claimed the "benzodioxan ring–idazoxan structure".[3] The corresponding demethylbenzodioxole **3a** and the seven-membered ring analogue **4** were prepared from catechol and the appropriate dihalo esters via the intermediates **2** (n = 0; R = OEt; X = Y = O)[4] and **2** (n = 2; R = OEt; X = Y = O),[5] respectively (Scheme I).

Replacement of One Oxygen Atom by a Methylene Group. The two isomeric chromans **5** and **6** were prepared



5 X = O, Y = CH_2
6 X = CH_2, Y = O

(1) Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Doxey, J. C., Roach, A. G.; Smith, C. F. C. *J. Med. Chem.* **1983**, *26*, 823.
(2) Krapcho, J.; Lott, W. A. U.S. Patent 2979511.
(3) Chapleo, C. B.; Myers, P. L. *Tetrahedron Lett.* **1981**, *22*, 4839. Chapleo, C. B.; Myers, P. L. British Patent 2068476.
(4) Christiansen, W. G.; Dolliver, M. A. *J. Am. Chem. Soc.* **1944**, *66*, 312.
(5) Geigy, J. R. Belgium Patent 613210.

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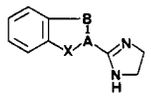
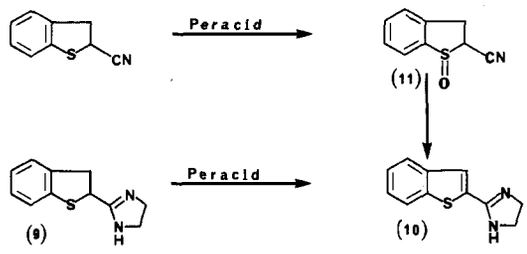
Table I



no.	X	A—B	mp, °C	recrystn solvent	formula
7	O	CH_2—CH_2	204-210[a]	EtOH	$C_{11}H_{12}N_2O\cdot HCl\cdot {}^1/_2H_2O$[b]
8	O	CH=CH	290-340[a]	EtOH	$C_{11}H_{10}N_2O\cdot HCl\cdot {}^1/_4H_2O$
9	S	CH_2—CH_2	178-183	*i*-PrOH/Et_2O	$C_{11}H_{12}N_2S\cdot HCl$
10	S	CH=CH	295-315	EtOH	$C_{11}H_{10}N_2S\cdot HCl\cdot {}^1/_2H_2O$[c]

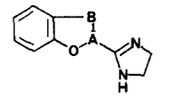
[a] Decomposition temperature. [b] C: calcd, 56.53; found, 56.09. [c] H: calcd, 4.88; found, 4.43.

Scheme II



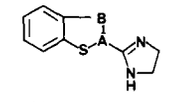
from the intermediate chroman-2-carboxylic acid[6] and 3-cyano-Δ^3-chromene,[7] by using standard procedures.

Furan and Thiophene Analogues. In addition to the structures described above the corresponding furan and thiophene analogues **7–10** (Table I) were designated as



(7) A–B = CH–CH_2

(8) A–B = C=CH



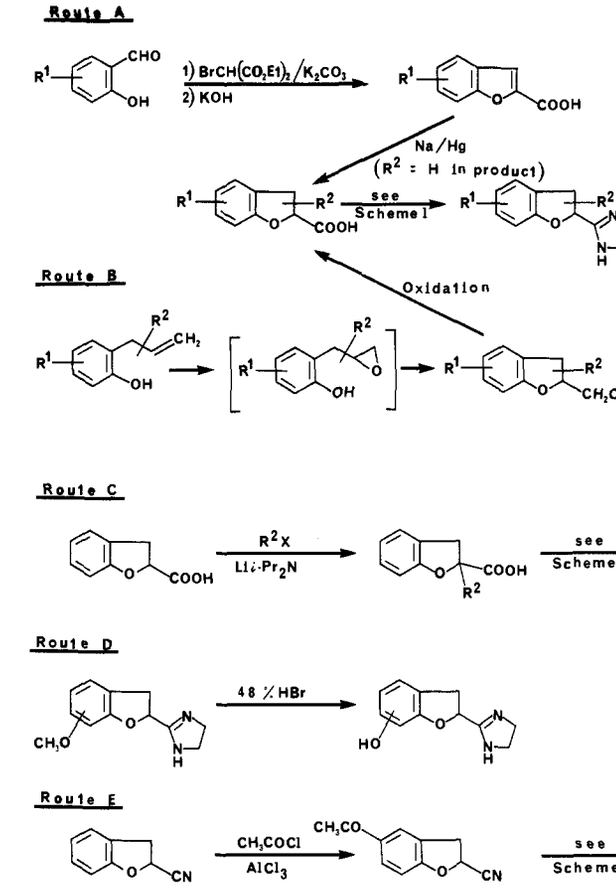
(9) A–B = CH–CH_2

(10) A–B = C=CH

desirable target compounds. In particular, the dihydrobenzofuran structure when incorporated into nonselective α-adrenergic antagonists (originally investigated as antihypertensives) showed activity (albeit with reduced potency) similar to that of their corresponding benzodioxan counterparts.[8] It was obviously of interest if a similar "carry-over" effect could be observed between **1** and, for example, the saturated compound **7**. The four compounds **7–10** were prepared from the corresponding unsaturated carboxylic acids; reduction of the double bond was achieved with sodium amalgam.[9] Attempts were made to prepare the sulfoxide derivative of **9** (Scheme II). Oxidation of **9** with *m*-chloroperbenzoic acid surprisingly gave the unsaturated compound **10**, which was also obtained from the sulfoxide **11** during the conversion of the nitrile group to the imidazoline ring.

As a result of the interesting level of biological activity possessed by the dihydrobenzofuran **7**, the synthesis of a number of derivatives **12–39** was undertaken (Table II) by

Scheme III



the routes shown in Scheme III.

Biological Results and Discussion

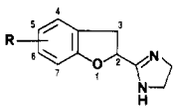
All compounds were examined for α-adrenoreceptor agonist and antagonist properties. The results are summarised in Tables III and IV. The compounds were tested on isolated tissues for presynaptic α_2 (mouse vas deferens) and postsynaptic α_1 (rat anococcygeus) adrenoreceptor agonist activity.[10] The 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 presynaptic α_2 and postsynaptic α_1 antagonist activity.[11] In this case the values are quoted as potencies relative to **1**.[12]

The primary objective of this synthetic program was to define the areas of chemical modification around the benzodioxan ring system, which would give antagonists with comparable or greater selectivity for the presynaptic site while retaining the potency inherent in **1**. An examination of Table III shows quite clearly that the dihydrobenzofuran **7** is the only analogue possessing presynaptic antagonist potency comparable to that of **1**. In view of this result, a number of derivatives (Table IV) were prepared in order to determine the structure–activity relationships within this series.

A wide range of presynaptic antagonist potency was encountered within the dihydrobenzofuran series, with compounds **7**, **13**, **14**, **19**, **20**, **23**, and **30** being equipotent

(6) Witiak, D. T.; Stratford, E. S.; Nazareth, R.; Wagner, G.; Feller, D. F. *J. Med. Chem.* **1971**, *14*, 758.
(7) Rene, L.; Royer, R. *Eur. J. Med. Chem. Chim. Ther.* **1975**, *10*, 72. Rene, L.; Royer, R. *Bull. Soc. Chim. Fr.* **1975**, *9–10*, 2345.
(8) Druey, J.; Tripod, J. *Med. Chem. (Academic)* **1967**, *7*.
(9) Witiak, D. T.; Carr, J. B.; Mersmann, H. J. U.S. Patent 2 007 973.
(10) Doxey, J. C. *Eur. J. Pharmacol.* **1979**, *54*, 185.
(11) Doxey, J. C.; Smith, C. F. C.; Walker, J. M. *Br. J. Pharmacol.* **1977**, *60*, 91.
(12) Chapleo, C. B.; Doxey, J. C.; Myers, P. L.; Roach, A. G. *Br. J. Pharmacol.* **1981**, *74*, 842P.

Table II



no.	R	method[a]	mp, °C	recrystn solvent	formula
12	2-Me	B or C	268-270	$EtOH/Et_2O$	$C_{12}H_{14}N_2O\cdot HCl\cdot {}^1/_4H_2O$
13	2-Et	C	247-250	$EtOH/Et_2O$	$C_{13}H_{16}N_2O\cdot HCl$
14	2-*n*-Pr	C	246-249	$EtOH/Et_2O$	$C_{14}H_{18}N_2O\cdot HCl\cdot {}^1/_8H_2O$
15	2-*n*-pentyl	C	221-224	$EtOH/Et_2O$	$C_{16}H_{22}N_2O\cdot HCl$
16	$2\text{-}(CH_2)_2Ph$	C	209-211	$EtOH/Et_2O$	$C_{19}H_{20}N_2O\cdot HCl$
17	3-Me	B	213-216	$EtOH/Et_2O$	$C_{12}H_{14}N_2O\cdot HCl\cdot {}^1/_8H_2O$
18	4-Me	A	237-238	$EtOH/Et_2O$	$C_{12}H_{14}N_2O\cdot HCl\cdot {}^1/_4H_2O$
19	4-Cl	A	233-237	$EtOH/Et_2O$	$C_{11}H_{11}ClN_2O\cdot HCl\cdot H_2O$
20	5-Me	A	214-224	$EtOH/Et_2O$	$C_{12}H_{14}N_2O\cdot HCl\cdot {}^3/_4H_2O$
21	5-OMe	A	209-211	$EtOH/Et_2O$	$C_{12}H_{14}N_2O_2\cdot HCl\cdot {}^1/_4H_2O$
22	5-OH	D	231-235	$EtOH/Et_2O$	$C_{11}H_{12}N_2O_2\cdot HBr\cdot {}^1/_4H_2O$
23	5-F	A	215-222	$CHCl_3/Et_2O$	$C_{11}H_{11}FN_2O\cdot HCl\cdot H_2O$
24	5-Br	B	216-246[b]	$EtOH/Et_2O$	$C_{11}H_{11}BrN_2O\cdot HCl\cdot {}^1/_2H_2O$
25	5-Cl	A	225-250[b]	$EtOH/Et_2O$	$C_{11}H_{11}ClN_2O\cdot HCl\cdot {}^1/_2H_2O$
26	$5\text{-}C(=O)CH_3$	E	249-251	$EtOH/Et_2O$	$C_{13}H_{14}N_2O_2\cdot HCl\cdot {}^1/_4H_2O$
27	6-Me	A	230-240	$EtOH/Et_2O$	$C_{12}H_{14}N_2O\cdot HCl\cdot {}^1/_2H_2O$
28	6-OMe	A	224-228	$EtOH/Et_2O$	$C_{12}H_{14}N_2O_2\cdot HCl\cdot H_2O$
29	6-OH	D	249-254	$EtOH/Et_2O$	$C_{11}H_{12}N_2O_2\cdot HBr\cdot {}^1/_4H_2O$
30	7-Me	A	271-274	MeOH	$C_{12}H_{14}N_2O\cdot HCl$
31	7-OMe	A	230-250[b]	$EtOH/Et_2O$	$C_{12}H_{14}N_2O_2\cdot HCl$
32	7-OH	D	234-241	$EtOH/Et_2O$	$C_{11}H_{12}N_2O_2\cdot HBr$
33	7-Cl	B	220-270[b]	$EtOH/Et_2O$	$C_{11}H_{11}ClN_2O\cdot HCl$
34	$4,7\text{-}Me_2$	A	254-257	$EtOH/Et_2O$	$C_{13}H_{16}N_2O\cdot HCl\cdot {}^1/_4H_2O$
35	$5,6\text{-}Me_2$	A	215-216	$EtOH/Et_2O$	$C_{13}H_{16}N_2O\cdot HCl\cdot {}^3/_4H_2O$
36	$5,7\text{-}Me_2$	A	230-253[b]	$EtOH/Et_2O$	$C_{13}H_{16}N_2O\cdot HCl\cdot {}^1/_8H_2O$
37	5-Cl, 7-Me	B	245-266[b]	$EtOH/Et_2O$	$C_{12}H_{13}ClN_2O\cdot HCl$
38	$5,7\text{-}Cl_2$	B	279-281	$EtOH/Et_2O$	$C_{11}H_{10}Cl_2N_2O\cdot HCl$
39	$6,7\text{-}Cl_2$	B	308-310	Et_2O[c]	$C_{11}H_{10}Cl_2N_2O\cdot HCl$

[a] Preparative routes (Scheme III): A, bromomalonate route; B, Claisen rearrangement route; C, alkylation of intermediate carboxylic acid; D, dealkylation of methoxy precursor; E, Friedel-Crafts acylation of intermediate nitrile. [b] Decomposition temperature. [c] Obtained by dissolving the free base in Et_2O; addition of ethereal HCl caused precipitation of the product as its salt.

Table III[a]

no.	presynaptic[b] agonist potency (clonidine = 1)[d]	presynaptic[b] antagonist potency (1 = 1)[e]	postsynaptic[b] agonist potency (phenylephrine = 1)[f]	postsynaptic[c] antagonism concn giving DR = 2 vs. phenylephrine potency (1 = 1)[g]	presynaptic selectivity ratio of antagonists (1 = 1): pre/post
3a	IA	0.001	0.005	IA	
3b	IA	0.001	0.05	0.01	0.1
4	IA	0.04	<0.0005	Ag	
5	IA	0.01	IA	1.0	0.01
6	IA	0.01	IA	1.0	0.01
7	IA	1.70	0.01	0.16	10.6
8	<0.0003	0.01	<0.001	Ag	
9	0.001	0.1	IA	0.69	0.14
10	IA	0.001	IA	0.05	0.02

[a] Results are expressed as potencies, which were compared directly with that of the standard in the same experiment: IA = inactive; Ag = agonist; DR = dose response. [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] Clonidine $IC_{40} = 3.68 \pm 0.32$ nm. [e] 1 pre-$pA_2 = 7.98$. [f] Phenylephrine $IC_{50} = 78 \pm 21$ nm. [g] 1 post-$pA_2 = 6.30$.

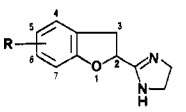
or more potent than 1. However, most of these compounds were found to be postsynaptic agonists; this property was not always detected in the in vitro test situation and was only observed when the compounds were tested in vivo.[13] It can be seen (Table IV) that within this series, agonist properties are evident in a number of compounds, and in most cases this agonism is selective for the postsynaptic site. Generally, it appears that compounds possessing alkyl groups (i.e., **18**, **30**, and **34–36**) and halogen atoms (i.e., **19**, **38**, and **39**) in positions 4 and 7 and the hydroxylated derivatives (i.e., **22**, **29**, and **32**) are associated with this agonism. These results are very similar to those observed[1] in the aromatic substituted derivatives of **1**.

In contrast, the 2-substituted dihydrobenzofurans appear to be pure antagonists possessing good selectivity for the presynaptic site. However, the size of the alkyl sub-

(13) For procedure, see: Doxey, J. C.; Everitt, J. *Br. J. Pharmacol.* **1977**, *61*, 559. See also: Roach, A. G.; Doxey, J. C.; Berridge, T. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1983**, *42*, 636.

(14) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol. Chemother.* **1959**, *14*, 48.

Table IV[a]



no.	R	presynaptic[b] agonist potency (clonidine = 1)[d]	presynaptic[b] antagonist potency (1 = 1)[e]	postsynaptic[b] agonist potency (phenylephrine = 1)[f]	postsynaptic[c] antagonism concn giving DR = 2 vs. phenylephrine potency (1 = 1)[g]	presynaptic selectivity ratio of antagonists (1 = 1): (pre/post)
7	H	IA	1.70	0.01[h]	0.16	10.6
12	2-Me	0.002	0.25	IA	0.35	0.71
13	2-Et	IA	1.8	IA	0.3	6.0
14	2-*n*-Pr	IA	1.9	IA	1.0	1.9
15	2-*n*-pentyl	IA	0.44	IA	1.0	0.44
16	2-$(CH_2)_2$Ph	IA	0.07	IA	0.07	1.0
17	3-Me	IA	0.03	IA	0.1	0.3
18	4-Me	0.2	0.1	1.3	Ag	
19	4-Cl	IA	2.0	1.0	Ag	
20	5-Me	IA	1.0	IA	2.25	0.44
21	5-OMe	IA	0.12	IA	0.023	5.20
22	5-OH	0.02	0.02	0.25	Ag	
23	5-F	IA	1.07	IA[h]	5.6	0.20
24	5-Br	<0.001	0.2	0.026	Ag	
25	5-Cl	IA	0.53	IA[i]	0.35	1.50
26	5-C(=O)CH_3	IA	0.003	0.02	Ag	
27	6-Me	IA	0.46	IA	2.25	0.20
28	6-OMe	IA	0.07	IA	0.35	0.20
29	6-OH	0.02	0.04	1.5	Ag	
30	7-Me	IA	1.6	IA[h]	0.67	2.4
31	7-OMe	IA	0.07	0.3	Ag	
32	7-OH	IA	0.04	0.24	Ag	
33	7-Cl	IA	0.64	IA[h]	1.0	0.64
34	4,7-Me_2	0.14	0.03	0.5	Ag	
35	5,6-Me_2	IA	0.7	IA	0.9	0.80
36	5,7-Me_2	IA	0.3	0.03	Ag	
37	5-Cl, 7-Me	IA	0.5	1.0	Ag	
38	5,7-Cl_2	<0.0001	0.06	0.14	Ag	
39	6,7-Cl_2	0.03	0.12	0.001	Ag	

[a-g] See corresponding footnotes in Table III. [g] Shown in an in vivo test situation to be a postsynaptic agonist. [h] Confirmed in an in vivo test situation as possessing no postsynaptic activity.

stitutent is a crucial factor in determining the potency within this particular series. Potency increases appreciably on going from methyl (12) to propyl (14) but decreases dramatically with further lengthening of this side chain [e.g., pentyl (15)]. The 2-position is close to the imidazoline ring, which is possibly bound to the receptor via one of the nitrogen atoms, and, hence, this position would be expected to be subject to a significant steric constraint.

Table V shows the pA_2 values and selectivities of 1[12] and some of the more potent and/or selective compounds obtained in the dihydrobenzofuran series. Only two (13 and 14) of the selective presynaptic antagonists are more potent than 1, although a number of the analogues do possess good selectivity for the α_2-receptor (i.e., 12, 15, 16, 21, 25, and 35). In addition to these two compounds, the 5-chloro derivative 25 is of interest as a selective antagonist. It was examined as an antagonist of guanoxabenz-induced mydriasis in the anesthetized rat.[15] Interestingly, 25 was found to be twice as potent as 1 after oral administration but only about half as potent when given intravenously.[16]

In summary, a number of dihydrobenzofuran analogues of idazoxan (1) have been prepared that retain the selectivity inherent in 1, although with reduced potency. Of these, the 5-chloro compound 25 is of particular interest because of its potentially superior oral bioavailability. The 2-ethyl (13) and 2-propyl (14) compounds are the only ones possessing greater potency and selectivity than that possessed by 1. Some derivatives were found to possess presynaptic α_2-antagonism with postsynaptic α_1-agonism.

Table V. α_2- and α_1-Adrenoreceptor pA_2 Values.[a] In Vitro Experiments

antagonist	mouse vas deferens: α_2 pA_2 value against clonidine	rat anococcygeus: α_1 pA_2 value against noradrenaline	α_2/α_1 selectivity ratio[b]
yohimbine	7.98 (7.94-8.00)	6.52 (6.47-6.58)	29
1	7.98 (7.88-8.11)	6.30 (6.27-6.34)	50
7	8.35 (8.24-8.50)	partial agonist	
13	8.32 (8.20-8.50)	5.91 (5.83-6.00)	258
14	8.63 (8.52-8.78)	6.39 (6.37-6.41)	175
15	7.97 (7.89-8.07)	6.47 (6.34-6.60)	32
25	7.80 (7.64-8.01)	7.05 (7.00-7.11)	5.6
30	8.22 (8.11-8.35)	partial agonist	
33	7.64 (7.58-7.71)	partial agonist	

[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.

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 and Varian

(15) For procedure, see: Berridge, T. L.; Gadie, B.; Roach, A. G.; Tulloch, I. F. *Br. J. Pharmacol.* **1983**, *78*, 507.
(16) Tulloch, I. F., unpublished result.

Associates T-60 and LKB-2091 instruments, respectively, and were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

2-(2-Methyl-1,3-benzodioxol-2-yl)-2-imidazoline Hydrochloride (3b). This compound was isolated following the procedure[2] that claimed the benzodioxan ring–idazoxan (1) structure. The reaction of ethylenediamine with the intermediate carboxylic acid **2** (n = 0; R = OH; X = Y = O) has since been shown to give **3b**:[3] yield 8%; mp 243–245 °C dec; NMR (Me_2SO) δ 11.2 (2 H, s, NH and HCl exchanged in D_2O), 7.0 (4 H, s, aryl H), 3.95 (4 H, s, NCH_2CH_2N), 2.15 (3 H, s, CH_3). Anal. ($C_{11}H_{12}N_2O_2$·HCl) C, H, N.

2-(1,3-Benzodioxol-2-yl)-2-imidazoline Hydrochloride (3a). A stirred mixture of ethyl 1,3-benzodioxole-2-carboxylate[4] (26 g, 134 mmol) and ethylenediamine (38.64 g, 643 mmol) was heated under reflux for 18 h. At this point, some distillate (~10 mL) was collected to remove water, and more ethylenediamine (10 mL) was added. The mixture was then refluxed for an additional 8 h and then concentrated by dissolution. The residue was fractionated to give a viscous oil, bp 150–170 °C (0.2 mmHg). The oil was dissolved in dichloromethane/ethyl acetate (300 mL, 1:1 mixture), and the solution was treated with an excess of ethereal HCl. The small amount of solid was collected and discarded. The filtrate was treated with ether (1000 mL) and stored at 0 °C for 24 h. The white solid was collected (1.5 g) and recrystallized from 2-propanol/ether to give **3a**: yield 0.6 g (3%); mp 204–206 °C; IR (Nujol) ν_{max} 1620 cm^{-1}; NMR (Me_2SO) δ 11.9 (2 H, s, NH and HCl exchanged in D_2O), 7.26 (1 H, s, CH), 7.02 (4 H, m, aryl H), 3.94 (4 H, s, NCH_2CH_2N). Anal. ($C_{10}H_{10}N_2O_2$·HCl) H, N; C: calcd, 52.99; found, 52.53.

2-(1,5-Benzodioxepin-2-yl)-2-imidazoline Hydrochloride (4). An excess of ammonia gas was passed through a solution of ethyl 1,5-benzodioxepin-2-carboxylate[5] (6.5 g, 29.5 mmol) in ethanol (200 mL). Water was then added to give an oil, which slowly solidified on standing. The solid was collected and triturated with ether to leave the carboxamide: yield 0.85 g (15%). A solution of the carboxamide (0.8 g, 4.1 mmol) in pyridine (10 mL) was treated with phosphorus oxychloride (2 g, 13 mmol) with cooling (0 °C). The solution was heated under reflux for 2.5 h prior to removal of solvent under reduced pressure. The residue was partitioned between dichloromethane and dilute HCl. The aqueous layer was extracted with dichloromethane, and the combined extracts were then washed with 10% aqueous NaCl, dried, and evaporated to leave the nitrile as a yellow oil: yield 0.7 g (96%). A solution of the nitrile (0.7 g, 4 mmol) in methanol (10 mL) was treated with a catalytic amount of sodium methoxide (0.01 g, 0.2 mmol). After 2 h, TLC indicated the starting material had been consumed. The solution was cooled to 0–5 °C, and a solution of ethylenediamine (0.3 g, 4.9 mmol) in methanol (2 mL) was added. After an additional 0.25 h, a solution of methanolic HCl (containing 0.16 g of HCl, 4.4 mmol) was added dropwise. The solution was maintained at 0 °C for 24 h. A small amount of insoluble material (0.1 g of ethylenediamine dihydrochloride) was removed by filtration. The volume of the filtrate was reduced by 50% and stored at 0 °C for 24 h. The solid was collected by filtration to give the imidazoline hydrochloride **4**: yield 0.25 g (25%); mp 165–170 °C dec; mass spectrum, m/e 218 (M^+). Anal. ($C_{12}H_{14}N_2O_2$·HCl) C, H, N.

2-Chromanyl-2-imidazoline Hydrochloride (5). A solution of chroman-2-carboxylic acid[6] (8.7 g, 49 mmol) and thionyl chloride (4.25 mL, 59 mmol) in anhydrous benzene (90 mL) was heated under reflux for 2.5 h. The solution was evaporated to dryness, more benzene (50 mL) was added, and the solution was reevaporated. This process was repeated to leave the carbonyl chloride as a brown oil: yield 8.8 g (100%). A solution of chroman-2-carbonyl chloride (8.8 g, 45 mmol) in dioxane (10 mL) was added dropwise to a stirred cooled (0 °C) solution of ammonia (30 mL, 0.88 solution; 450 mmol). After completion of the addition, the mixture was allowed to warm to room temperature, and stirring was continued for an additional 2 h. Water was then added, and the solid was collected by filtration. The solid was washed with water (200 mL) and dried to leave the carboxamide as a white powder: yield 7.0 g (88%). A mixture of the carboxamide (6.9 g, 39 mmol), phosphorus pentoxide (27.7 g, 195 mmol), and anhydrous toluene (70 mL) was heated under reflux for 2 h and then allowed to stand at room temperature for 16 h. The mixture was filtered and evaporated to dryness, and the residue partitioned between dichloromethane and water. The organic layer was collected, dried, and evaporated to leave 2-cyanochroman as an oil: yield 3.7 g (60%). A steady stream of gaseous hydrogen chloride was bubbled through a stirred, cooled solution of the above nitrile (3.59 g, 23 mmol) in anhydrous ether (35 mL) and ethanol (1.38 g, 24 mmol) for 2.5 h, maintaining the reaction temperature at <10 °C. After an additional 24 h at 0–10 °C, the solid was collected, washed with anhydrous ether, and dried to give the intermediate ethyl 2-chromanimidoate hydrochloride: yield 4.9 g (90%). A solution of ethylenediamine (2 mL, 30 mmol) in ethanol (5 mL) was added dropwise to a stirred, cooled (0–10 °C) solution of the imidoate (4.85 g, 20 mmol) in ethanol (40 mL). After an additional 24 h at 0–10 °C, the precipitated ethylenediamine dihydrochloride was removed, and the filtrate was treated with an excess of ethereal HCl. The resulting solid (4.35 g) was collected and recrystallized from 2-propanol to give **5**: yield 2.3 g (48%); mp 255–260 °C; NMR (Me_2SO + D_2O) δ 6.8–7.4 (4 H, m, aryl H), 5.30 (1 H, dd, J = 4 and 10 Hz, CH), 3.92 (4 H, s, NCH_2CH_2N), 2.1–3.0 (4 H, m, CH_2CH_2). Anal. ($C_{12}H_{14}N_2O$·HCl) C, H, N.

3-Chromanyl-2-imidazoline Hydrochloride (6). To a solution of 3-cyano-Δ^3-chromene[7] (4 g, 25 mmol) in ethyl acetate (80 mL) was added 10% palladium on carbon (0.08 g). Hydrogenation was carried out at 60 psi at 65–70 °C. After 24 h, the mixture was filtered, and the filtrate was evaporated to dryness. The residue was chromatographed on silica (Kieselgel 60; 70–230 mesh), eluting with chloroform, to give recovered starting material (2.1 g) and 3-cyanochroman: yield 0.95 g (49% based on recovered starting material). The cyano compound was converted to the imidazoline hydrochloride **6** by procedures already described: yield 14%; mp 184–186 °C; NMR (Me_2SO/D_2O) δ 6.7–7.3 (4 H, m, aryl H), 4.4 (2 H, m, OCH_2), 3.82 (4 H, s, NCH_2CH_2N), 3.0–3.7 (3 H, m, CH_2CH). Anal. ($C_{12}H_{14}N_2O$·HCl) C, H, N.

2-(2-Benzofuranyl)-2-imidazoline (8) was prepared following the literature method[17] and then converted to its hydrochloride salt: decomposition temperature 290–340 °C. Anal. ($C_{11}H_{10}N_2O$·HCl·$^1/_4H_2O$) C, H, N.

2-(2-Benzothiophene-yl)-2-imidazoline Hydrochloride (10). Benzothiophene-2-carboxylic acid[18] was converted, via methods already described, to the imidazoline hydrochloride **10**: overall yield 12%; mp 295–315 °C; NMR (Me_2SO/D_2O) δ 8.0–8.4 (2 H, m, aryl H), 7.5–7.8 (2 H, m, aryl H), 4.06 (4 H, s, NCH_2CH_2N). Anal. ($C_{11}H_{10}N_2S$·HCl·$^1/_2H_2O$) C, N; H: calcd, 4.88; found, 4.43.

2-(2,3-Dihydro-2-benzothiophene-yl)-2-imidazoline Hydrochloride (9). Compound **9** was obtained from 2,3-dihydrobenzothiophene-2-carboxylic acid[19] by procedures already described: overall yield 20%; mp 178–183 °C; NMR (Me_2SO/D_2O) δ 7.0–7.4 (4 H, m, aryl H), 5.08 (1 H, t, J = 7 Hz, CH), 3.84 (4 H, s, NCH_2CH_2N), 3.70 (2 H, d, J = 7 Hz, CH_2). Anal. ($C_{11}H_{12}N_2S$·HCl) C, H, N.

Attempted Preparation of the Sulfoxide Derivative of Compound 9. A cooled (0 °C) solution of 2-cyano-2,3-dihydrobenzothiophene (intermediate in preparation of **7**) (2.7 g, 16.8 mmol) in dichloromethane (30 mL) was treated with a solution of *m*-chloroperbenzoic acid (2.9 g, 16.9 mmol) in dichloromethane (50 mL). On completion of the addition, the mixture was allowed to warm to room temperature and poured onto a mixture of aqueous Na_2SO_3 and aqueous $NaHCO_3$. The organic layer was separated, washed with water, dried, and evaporated to leave impure 2-cyano-2,3-dihydrobenzothiophene 1-oxide (**11**) as an oil, which solidified on standing: yield 2.6 g (88%); mass spectrum, m/e 177 (M^+). The nitrile **11** was reacted with ethylenediamine, following initial reaction with sodium methoxide. The product isolated was identified as 2-(2-benzothiophene-yl)-2-imidazoline hydrochloride (**10**): yield 13%. The sample was identical (NMR and mp) with that already described.

Oxidation of 2-(2,3-Dihydro-2-benzothiophene-yl)-2-imidazoline Hydrochloride (9). The dihydro compound **9** was

(17) Rao, C. S.; Taneja, V. *Indian J. Chem.* **1979**, *18B*, 254.
(18) Shirley, D. A.; Cameron, M. D. *J. Am. Chem. Soc.* **1950**, *72*, 2788; **1952**, *74*, 664.
(19) Fredga, A. *Acta Chem. Scand.* **1955**, *9*, 719.

oxidized by the procedure described in the preparation of 11. The only isolable product (19% yield) was 2-(2-benzothiopheneyl)-2-imidazoline hydrochloride (10) (identical with the sample mentioned above).

Synthesis of Dihydrobenzofuran Compounds 7 and 12–39. Route A. 2-(5-Fluoro-2,3-dihydro-2-benzofuranyl)-2-imidazoline Hydrochloride (23). 5-Fluorosalicylaldehyde (4.4 g, 31.4 mmol), diethyl bromomalonate (11.3 g, 47.3 mmol) and methyl ethyl ketone (36 mL) were stirred together at room temperature. Anhydrous potassium carbonate (8.7 g, 63 mmol) was added, and the mixture was heated under reflux for 4 h. Excess 2 N H_2SO_4 was added, and the mixture was extracted with ether. The combined extracts were washed with water, dried, and evaporated to leave an oil, which was treated with 10%, w/v, ethanol/KOH (60 mL) and heated under reflux for 0.75 h. The solvent was evaporated, the residue was treated with excess 2 N H_2SO_4, and the solution was heated briefly on a steam bath. After the solution was cooled, the crude acid was filtered off. Recrystallization from ethyl acetate/ethanol gave 5-fluorobenzofuran-2-carboxylic acid: yield 1.1 g (19%); mp 261–266 °C. The carboxylic acid (2.4 g, 13.2 mmol) was added to aqueous NaOH solution (3.3 g, NaOH, 82.5 mmol, in 50 mL of water). Sodium amalgam was added, with stirring, over 20 min (prepared from 1.1 g of sodium and 42 g of mercury). After an additional 2.5 h, the solution was allowed to stand over the amalgam overnight. The mercury was separated, the solution was filtered, and the filtrate was treated with excess 4 M H_2SO_4. 5-Fluoro-2,3-dihydrobenzofuran-2-carboxylic acid was collected by filtration and dried: yield 1.5 g (62%). The acid was converted to the imidazoline hydrochloride **23** by procedures already described: yield 24%; mp 215–222 °C; NMR (Me_2SO) δ 11.4 (2 H, s, NH and HCl exchanged in D_2O), 6.8–7.3 (3 H, m, aryl H), 5.92 (1 H, dd, J = 7 and 9 Hz, CH), 3.94 (4 H, s, NCH_2CH_2N), 3.74 (1 H, d, J = 9 Hz, 1 H of CH_2), 3.56 (1 H, d, J = 7 Hz, 1 H of CH_2). Anal. ($C_{11}H_{11}FN_2O\cdot HCl\cdot H_2O$) C, H, N. Compounds **18–21**, **25**, **27**, **28**, **30**, **31**, and **34–36** were also prepared by the procedures described above (see Table II).

2-(2,3-Dihydro-2-benzofuranyl)-2-imidazoline Hydrochloride (7). Compound **7** was prepared from 2,3-dihydrobenzofuran-2-carboxylic acid: yield 31%; mp 204–210 °C dec. Anal. ($C_{11}H_{12}N_2O\cdot HCl\cdot {}^1/_2H_2O$) H, N; C: calcd, 56.53; found, 56.09.

Route B. 2-(5,7-Dichloro-2,3-dihydro-2-benzofuranyl)-2-imidazoline Hydrochloride (38). A mixture of 2,4-dichlorophenol (25.0 g, 153 mmol), allyl bromide (20.6 g, 170 mmol), potassium carbonate (23.2 g, 168 mmol), and anhydrous dimethylformamide (150 mL) was stirred for 3 h. Stirring was continued for an additional 3 h at 60–65 °C. The mixture was allowed to stand overnight at room temperature and then poured into water. The product was extracted with ether, and the extracts were then washed with water, dried, and evaporated to leave 3-(2,4-dichlorophenoxy)prop-1-ene as an oil: yield 30.1 g (97%). The ether (30.1 g, 148 mmol) was heated at 245–250 °C for 10 min. An exothermic reaction commenced at 220 °C. After cooling, the reaction mixture was taken up in dichloromethane and extracted with aqueous 2 N NaOH. The base extracts were washed with water and then acidified with aqueous 2 N HCl, and the product was reextracted with dichloromethane. These latter extracts were washed with water and brine, dried, and evaporated to leave 3-(2-hydroxy-3,5-dichlorophenyl)prop-1-ene as a brown oil: yield 27.6 g (92%). A solution of *m*-chloroperbenzoic acid (30.5 g, 177 mmol) in dichloromethane (450 mL) was added dropwise over 2.5 h to a stirred solution of this latter ether (27.6 g, 136 mmol) in dichloromethane (200 mL) at 10–20 °C. The mixture was stirred for an additional 24 h and then filtered to remove *m*-chlorobenzoic acid. The filtrate was washed successively with a 10%, w/v, aqueous Na_2SO_3 solution, saturated aqueous $NaHCO_3$ solution, and, finally, saturated brine. The organic phase was dried and evaporated to give 1-(2-hydroxy-3,5-dichlorophenyl)-2,3-epoxypropane: yield 24.3 g (82%). A mixture of the epoxide (24.3 g, 111 mmol) and silica (Kieselgel 60; 70–230 mesh) (100 g) in dichloromethane (200 mL) was stirred at room temperature for 24 h. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was chromatographed on silica (Kieselgel 60; 70–230 mesh) eluting with ether–light petroleum (40–60 °C) (1:2) to give 2-(hydroxymethyl)-5,7-dichloro-2,3-dihydrobenzofuran: yield 17.6 g (72%). To a cooled (0 °C), stirred solution of the hydroxymethyl compound (17.6 g, 80 mmol) in acetone (300 mL) was added dropwise an excess of freshly prepared Jones' reagent[20] (58 mL) at such a rate that the temperature did not exceed 20 °C. After 48 h at room temperature, the mixture was filtered, and the filtrate was evaporated to dryness. The residue was partitioned between ether and 2 N NaOH solution. The aqueous extracts were washed with more ether and then acidified with concentrated HCl. The product was extracted with dichloromethane, and the extracts were washed with water and brine, dried, and evaporated to leave 5,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid as a brown solid [yield 12.0 g (64%)], which was converted to the imidazoline hydrochloride **38**: yield 38%; mp 279–281 °C. Anal. ($C_{11}H_{10}Cl_2N_2O\cdot HCl$) C, H, N.

Compounds **12**, **17**, **24**, **33**, **37**, and **39** were also prepared by the procedures described above (see Table II).

Route C. 2-(2-Phenethyl-2,3-dihydro-2-benzofuranyl)-2-imidazoline Hydrochloride (16). A dry, argon-filled flask was charged with diisopropylamine (8.1 g, 80.2 mmol; freshly distilled from calcium hydride) and anhydrous tetrahydrofuran (100 mL). The stirred solution was cooled to −78 °C, *n*-butyllithium (64 mL of 1.25 M solution in hexane, 80 mmol) was added dropwise, and the mixture was allowed to return to room temperature. On recooling to −78 °C, a solution of 2,3-dihydrobenzofuran-2-carboxylic acid (3.28 g, 20 mmol) in tetrahydrofuran (35 mL) was added dropwise with the immediate formation of an orange–red solution. After 0.5 h, phenethyl bromide (7.4 g, 40 mmol) was added, and stirring was continued for an additional 1 h. The solution was then allowed to warm to room temperature, and the color gradually faded (pale yellow solution). The aqueous layer was acidified with dilute HCl and reextracted with ether. These ether extracts were dried and evaporated to give impure 2-phenethyl-2,3-dihydrobenzofuran-2-carboxylic acid (yield 4.5 g), which was converted to the imidazoline hydrochloride **16**: overall yield 7%; mp 209–211 °C. Anal. ($C_{19}H_{20}N_2O\cdot HCl$) C, H, N.

Compounds **12–15** were also prepared by the procedures described above (see Table II).

Route D. 2-(5-Hydroxy-2,3-dihydro-2-benzofuranyl)-2-imidazoline Hydrobromide (22). The free base generated from 2-(5-methoxy-2,3-dihydro-2-benzofuranyl)-2-imidazoline hydrochloride (**21**; 1.5 g, 5.9 mmol) was treated with 48%, w/v, 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 ethanol/ether to yield the imidazoline hydrobromide **22**: yield 0.5 g (30%); mp 231–235 °C. Anal. ($C_{11}H_{12}N_2O_2\cdot HBr\cdot {}^1/_4H_2O$) C, H, N.

Compounds **27** and **30** were also prepared by the procedure described above (see Table II).

Route E. 2-(5-Acetyl-2,3-dihydro-2-benzofuranyl)-2-imidazoline Hydrochloride (26). To a well-stirred solution of 2-cyano-2,3-dihydrobenzofuran (1.19 g, 8.2 mmol) and acetyl chloride (1.6 g, 20.4 mmol) in dichloromethane (100 mL) was added portionwise aluminum chloride (2.66 g, 20 mmol) at room temperature. After 1 h, the mixture was heated under reflux for an additional 4 h. On cooling, the mixture was poured cautiously onto ice/water (200 mL) and concentrated HCl (20 mL). The product was extracted with chloroform, and the extracts were washed with aqueous 2 N NaOH, dried, and evaporated to leave 2-cyano-5-acetyl-2,3-dihydrobenzofuran as a solid: yield 1.1 g (72%), which was converted to the imidazoline hydrochloride **26**: mp 249–251 °C. Anal. ($C_{13}H_{14}N_2O_2\cdot HCl\cdot {}^1/_4H_2O$) C, H, N.

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 of 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 of 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 con-

(20) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

tractions 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 under an initial tension of 0.5 g. The tissue was bathed in Krebs solution, which 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 the test compound 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 compound was then removed from the bathing fluid, and the responsiveness of the tissue to clonidine 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 idazoxan in the same tissue. Presynaptic α_2-adrenoreceptor antagonist potency was therefore expressed with respect to idazoxan 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 test compounds 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 idazoxan or one of the test compounds. From the dose ratios produced was calculated the concentration of agonist producing a dose ratio, and, thus, the α_1-antagonist potency relative to idazoxan was determined.

Determination of pA_2 Values for Competitive Antagonists. The pA_2 values of selected compounds were determined at presynaptic α_2-adrenoreceptors and postsynaptic α_1-adrenoreceptors. Antagonism of the inhibitory effects of clonidine on the vas deferens and antagonism of noradrenaline contractions on the anococcygeus muscle were used to determine pA_2 values at presynaptic α_2-adrenoreceptors and postsynaptic α_1-adrenoreceptors, respectively. pA_2 is 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. **2** (n = 0; R = OH; X = Y = O), 3663-80-7; **3a**, 89197-24-0; **3a**·HCl, 89197-23-9; **3b**, 89197-25-1; **3b**·HCl, 79944-57-3; **4**, 89197-26-2; **4**·HCl, 89196-91-8; **5**, 89197-27-3; **5**·HCl, 89196-92-9; **6**, 89197-68-2; **6**·HCl, 89196-93-0; **7**, 89197-28-4; **7**·HCl, 89196-94-1; **8**, 72583-92-7; **8**·HCl, 89196-95-2; **9**, 89197-29-5; **9**·HCl, 89196-96-3; **10**, 89197-30-8; **10**·HCl, 89196-97-4; **11**, 89196-98-5; **12**, 89197-31-9; **12**·HCl, 89196-99-6; **13**, 89197-32-0; **13**·HCl, 89197-00-2; **14**, 89197-33-1; **14**·HCl, 89197-01-3; **15**, 89197-34-2; **15**·HCl, 89197-02-4; **16**, 89197-35-3; **16**·HCl, 89197-03-5; **17**, 89197-36-4; **17**·HCl, 89197-04-6; **18**, 89197-37-5; **18**·HCl, 89197-05-7; **19**, 89197-38-6; **19**·HCl, 89197-06-8; **20**, 89197-39-7; **20**·HCl, 89197-07-9; **21**, 89197-40-0; **21**·HCl, 89197-08-0; **22**, 89197-41-1; **22**·HBr, 89197-09-1; **23**, 89197-42-2; **23**·HCl, 89197-10-4; **24**, 89197-43-3; **24**·HCl, 89197-11-5; **25**, 89197-45-5; **25**·HCl, 89210-18-4; **26**, 89197-44-4; **26**·HCl, 89197-12-6; **27**, 89210-21-9; **27**·HCl, 89210-17-3; **28**, 89197-46-6; **28**·HCl, 89197-13-7; **29**, 89197-47-7; **29**·HBr, 89197-14-8; **30**, 89210-22-0; **30**·HCl, 89210-19-5; **31**, 89197-48-8; **31**·HCl, 89197-15-9; **32**, 89197-49-9; **32**·HBr, 89197-16-0; **33**, 89197-50-2; **33**·HCl, 89197-17-1; **34**, 89197-51-3; **34**·HCl, 89197-18-2; **35**, 89197-52-4; **35**·HCl, 89197-19-3; **36**, 89197-53-5; **36**·HCl, 89197-20-6; **37**, 89197-54-6; **37**·HCl, 89197-21-7; **38**, 89210-23-1; **38**·HCl, 89210-20-8; **39**, 89197-55-7; **39**·HCl, 89197-22-8; ethylenediamine, 107-15-3; 1,5-benzodioxepin-2-carboxamide, 89197-56-8; 1,5-benzodioxepin-2-nitrile, 89197-57-9; chroman-2-carboxylic acid, 51939-71-0; chroman-2-carbonyl chloride, 77039-78-2; chroman-2-carboxamide, 3990-58-7; 2-cyanochroman, 89197-58-0; ethyl 2-chromanimidoate hydrochloride, 89197-59-1; 3-cyano-Δ^3-chromene, 57543-66-5; 3-cyanochroman, 89197-60-4; benzothiophene-2-carboxylic acid, 6314-28-9; 2,3-dihydrobenzothiophene-2-carboxylic acid, 27916-82-1; 2-cyano-2,3-dihydrobenzothiophene, 89197-61-5; 5-fluorosalicyaldehyde, 347-54-6; diethyl bromomalonate, 685-87-0; 5-fluorobenzofuran-2-carboxylic acid, 89197-62-6; 5-fluoro-2,3-dihydrobenzofuran-2-carboxylic acid, 89197-63-7; 2,3-dihydrobenzofuran-2-carboxylic acid, 1914-60-9; 2,4-dichlorophenol, 120-83-2; allyl bromide, 106-95-6; 3-(2,4-dichlorophenoxy)prop-1-ene, 5441-16-7; 3-(2-hydroxy-3,5-dichlorophenyl)prop-1-ene, 19182-95-7; 1-(2-hydroxy-3,5-dichlorophenyl)-2,3-epoxypropane, 89197-64-8; 2-(hydroxymethyl)-5,7-dichloro-2,3-dihydrobenzofuran, 89197-65-9; 5,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid, 50635-27-3; phenethyl bromide, 103-63-9; 2-phenethyl-2,3-dihydrobenzofuran-2-carboxylic acid, 89197-66-0; 2-cyano-2,3-dihydrobenzofuran, 24889-97-2; 2-cyano-5-acetyl-2,3-dihydrobenzofuran, 89197-67-1; ethyl 1,3-benzodioxole-2-carboxylate, 831-45-8.